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Special Issue Reprint

Acute and Chronic Heart Failure

Pathophysiology and New Therapeutic
Developments, 2nd Edition

Edited by
Serafino Fazio and Valentina Mercurio

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**Acute and Chronic Heart Failure:
Pathophysiology and New Therapeutic
Developments, 2nd Edition**

Acute and Chronic Heart Failure: Pathophysiology and New Therapeutic Developments, 2nd Edition

Guest Editors

Serafino Fazio

Valentina Mercurio



Basel • Beijing • Wuhan • Barcelona • Belgrade • Novi Sad • Cluj • Manchester

Guest Editors

Serafino Fazio

Department of Internal Medicine

Federico II University

Naples

Italy

Valentina Mercurio

Department of Translational

Medical Sciences

Federico II University

Naples

Italy

Editorial Office

MDPI AG

Grosspeteranlage 5

4052 Basel, Switzerland

This is a reprint of the Special Issue, published open access by the journal *Biomedicines* (ISSN 2227-9059), freely accessible at: https://www.mdpi.com/journal/biomedicines/special_issues/51T64T2NV0.

For citation purposes, cite each article independently as indicated on the article page online and as indicated below:

Lastname, A.A.; Lastname, B.B. Article Title. <i>Journal Name</i> Year , Volume Number, Page Range.
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ISBN 978-3-7258-8915-0 (Hbk)

ISBN 978-3-7258-8916-7 (PDF)

<https://doi.org/10.3390/books978-3-7258-8916-7>

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About the Editors

Serafino Fazio

Serafino Fazio was born in Naples, Italy, on February 5, 1950. He began his academic career in June of 1968, and obtained his Master's degree in medicine and surgery from the Federico II University of Naples, Faculty of Medicine and Surgery, on December 21, 1974, specializing in internal medicine and cardiology. He first worked as a university researcher and, subsequently, as Associate Professor of internal medicine at the Federico II University of Naples, Faculty of Medicine and Surgery, from July 1975 to July 2012. He carried out clinical activities in the cardiology department with an attached coronary unit from August 1975 to May 1997, and subsequently transferred to the internal medicine department of the Federico II University Hospital, working there from June 1997 to August 2012. Throughout his career, he has distinguished himself through his clinical insight, excellent relationships with patients, and strong leadership skills. He is now retired. He is the author of over 190 articles published in prestigious journals, among which are *New England Journal of Medicine*, *Nature Medicine*, *Annals of Internal Medicine*, *Circulation*, *International Journal of Cardiology*, and *The Journal of Clinical Endocrinology and Metabolism*. He has been particularly interested in the interaction between hormones and the heart, the treatment of heart failure, metabolic syndrome, nutraceutical substances, and, recently, the pathophysiology and treatment of COVID-19. For over 10 years, he has been studying insulin resistance and the hyperinsulinemia associated with heart diseases. His H-index, according to Google Scholar, is 49. He participated in and organized numerous medical conferences. Among these, the last one was on February 7th, 2026, in Naples, Italy, entitled "Prevention and longevity in health". He is also an Associate Editor of the medical journals *Biomedicines* and *Frontiers in Cardiovascular Medicine*, as well as a reviewer for numerous medical journals.

Valentina Mercurio

Valentina Mercurio is an Assistant Professor of Medicine (tenure-track) at the Department of Translational Medical Sciences, University of Naples Federico II, Italy, and an attending physician at the Cardio-Pulmonary Immuno-Oncology Unit of the Federico II University Hospital. Her clinical and research activity focuses on heart failure, pulmonary hypertension, and cardio-oncology, with particular expertise in non-invasive cardiovascular imaging and right ventricular function. She obtained her MD degree *summa cum laude*, did a clinical fellowship in internal medicine, and completed a PhD in clinical and experimental medicine at the University of Naples Federico II. Dr. Mercurio has held international research positions, including a postdoctoral research fellowship in pulmonary and critical care medicine at Johns Hopkins University (Baltimore, MD, USA), where she conducted research on pulmonary arterial hypertension and advanced echocardiographic assessment. She is an active member of several international scientific societies, including the European Society of Cardiology and the Heart Failure Association, and serves in leadership roles within the Italian Society of Cardiology. She is also involved in international guideline development (Guidelines for the Echocardiographic Assessment of the Right Heart in Adults and Special Considerations in Pulmonary Hypertension: Recommendations from the American Society of Echocardiography) and scientific committees in the field of cardio-oncology and pulmonary hypertension. Dr. Mercurio has authored over 120 peer-reviewed publications with an H-index of 30 and has received multiple international awards and research grants. Her work contributes to advancing risk stratification and therapeutic strategies in the field of pulmonary vascular disease.



Editorial

Screening and Treatment Intervention for Insulin Resistance/Hyperinsulinemia in the General Population to Prevent Heart Failure or Slow Its Worsening

Serafino Fazio ^{1,*}, Flora Affuso ², Valeria Fazio ³ and Valentina Mercurio ⁴

¹ Department of Internal Medicine, Federico II University, 80131 Naples, Italy

² Independent Researcher, 80129 Naples, Italy; flora.affuso70@gmail.com

³ Cardiologia, Ospedale Santa Maria delle Grazie, 80078 Pozzuoli, Italy; valeria.fazio1986@gmail.com

⁴ Dipartimento di Scienze Mediche Traslazionali, Federico II University, 80131 Naples, Italy; valentina.mercurio@unina.it

* Correspondence: fazio0502@gmail.com

† This author has retired.

Despite significant progress in the prevention and treatment of cardiovascular diseases in recent decades, they remain the leading causes of death worldwide [1]. In particular, heart failure, the common endpoint of most heart diseases, affects between 1 and 3% of the adult population worldwide, but increases to approximately 10% in adults over 70 years of age, and exceeds 20% in those over 80–85 years of age [2,3]. HF is the leading cause of hospital admissions in Italy, accounting for approximately 2% of total hospital admissions, with high rehospitalization rates and very high healthcare costs [3]. In recent years, cases of HFpEF have been increasing steadily, particularly in women, and have now exceeded 50% of HF cases. It is well known that HFrEF and HFpEF have completely different causes and pathophysiological mechanisms, and that their therapies differ accordingly. In fact, while HFrEF has well-defined treatments according to guidelines, HFpEF has no clearly defined therapies [4]. Important recognized causes of HF, particularly HFpEF, are cardiometabolic diseases. Among these, insulin resistance, with associated hyperinsulinemia, is very prevalent in the general population of developed and developing countries [5,6]. It is the principal cause of type 2 diabetes, preceding its development by many years—even 15 or more [7,8]. In the meantime, hyperinsulinemia produces significant damage to the cardiovascular system, to the extent that individuals with type 2 diabetes are treated, according to guidelines, as if they had already experienced a cardiovascular event [9]. It has been shown that hyperinsulinemia associated with insulin resistance is also linked to concentric left ventricular remodeling and diastolic dysfunction, main features of HFpEF [10–13].

Therefore, to reduce hospitalizations, deaths, and healthcare costs resulting from HF, we believe that it would be extremely important to implement a more thorough cardiovascular disease prevention plan, particularly by intervening early in the recognition and treatment of insulin resistance in the general population, and finding treatments that more effectively block or slow the worsening progression of HF.

Conflicts of Interest: The authors declare no conflict of interest.

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Article

Evaluation of Body Position Association with Diuretic Response and Neurohormonal Activation in Patients with Acutely Decompensated Heart Failure

Mateusz Guzik ^{1,2,*} and Rafał Tymków ^{1,2}¹ Institute of Heart Diseases, Faculty of Medicine, Wrocław Medical University, 50-556 Wrocław, Poland² Department of Cardiology, Wrocław Medical University Hospital, 50-556 Wrocław, Poland

* Correspondence: mateuszguzik23@gmail.com

Abstract

Background/Objectives: Hemodynamic and neurohormonal factors, including renal perfusion and venous pressure, may affect diuretic response, which may be modulated by body position. This study aimed to assess whether supine versus upright positioning influences diuretic efficacy and neurohormonal activation during early decongestion in patients with AHF and reduced ejection fraction (HFrEF). **Methods:** This single-center, prospective, pilot randomized study enrolled 12 hospitalized patients with decompensated HFrEF receiving guideline-directed medical therapy. Participants were randomized (1:1) to remain in either the supine or upright/seated position during intravenous furosemide administration (1 mg/kg; half of the dose administered as a bolus, half as a 2-h infusion). Serial measurements of urine volume, electrolyte excretion, and neurohormonal biomarkers (renin, aldosterone, catecholamines) were performed at baseline, 2, and 6 h after diuretic administration. **Results:** No significant differences were found between supine and upright groups in total urine output, urine dilution, sodium excretion, or weight change after 6 h. There were no statistically significant differences in renin and aldosterone levels across subsequent timepoints; however, renin concentration tended to be higher in upright than in supine individuals. Interestingly, supine participants demonstrated greater urinary adrenaline concentration after furosemide administration, alone and after adjustment for urinary creatinine. **Conclusions:** No clinically meaningful differences were found between supine versus upright position patients with AHF, receiving neurohormonal blockade.

Keywords: congestion; diuretic response; neurohormonal activation; RAAS; natriuresis; acute heart failure; body position

1. Introduction

The diuretic response is influenced by a range of factors, including renal perfusion and neurohormonal activity. Key regulatory systems such as the sympathetic nervous system, the renin–angiotensin–aldosterone system (RAAS), and vasopressin pathways modulate both vascular tone and intrinsic renal function, thereby affecting whole-body volume status [1–8].

In heart failure with reduced ejection fraction (HFrEF), pharmacologic agents targeting neurohormonal blockade constitute the cornerstone of evidence-based therapy. These interventions have been shown to improve outcomes; consequently, optimizing their modulatory effects on neurohormonal systems appears to be an important determinant

of effective decongestion [9,10]. Adequate organ perfusion represents another critical determinant of diuretic efficacy, as urine formation depends not only on arterial pressure but also on venous pressure and vascular resistance [11]. Even in the presence of apparently satisfactory arterial blood pressure and relatively low systemic vascular resistance, elevated venous pressure can significantly reduce the renal perfusion gradient, leading to impaired renal function. In the setting of heart failure, diminished cardiac output results in reduced renal arterial flow, eliciting a compensatory increase in intrarenal vascular resistance aimed at preserving perfusion [12–14]. This phenomenon constitutes part of the so-called “stressed volume”—the intravascular volume responsible for generating pressure exceeding the mean circulatory filling pressure [12]. Beyond sympathetic activation, which induces fluid shifts and vasoconstriction, hydrostatic pressure also contributes to vascular dynamics depending on body position. Under physiological conditions, the hydrostatic component adds approximately 20 mmHg to the pressure at the level of the renal vein in the upright position relative to the right atrium. This may exert an unfavorable effect on renal vascular afterload and thereby reduce the renal perfusion gradient. Consequently, patients in the supine position are expected to be free from this adverse hydrostatic influence. This theory is supported by the results of a study conducted on an animal model (monkeys), which indicates that the head-up tilt from a supine position can alter the difference between the renal vein and the right atrium [15].

The clinical relevance of improving renal perfusion pressure in the context of diuretic therapy is underscored by ongoing investigations employing the Doraya catheter, designed to reduce renal venous pressure and thereby enhance renal perfusion [16]. Moreover, mechanistic observational studies conducted in diverse patient groups (hepatic cirrhosis, nephrotic syndrome, heart failure) indicated a tendency toward a better diuretic response, greater natriuresis, and lower plasma renin activity in patients who remained in a supine position compared with those who were standing during the study [17,18].

The introduction of drugs affecting the renin–angiotensin–aldosterone system provided some indications of mitigating the effect of body position on treatment response; however, the data have so far remained inconclusive [19,20]. Based on these pathophysiological considerations, we have designed a study to assess whether body position (supine vs. upright) influences the diuretic response in patients with acute heart failure.

2. Materials and Methods

The study was a single-center, prospective, pilot trial conducted from September to December 2024 at the Institute of Heart Diseases in Wrocław, Poland. The study population consisted of patients hospitalized due to acute decompensation of chronic heart failure with reduced left ventricular ejection fraction (HFrEF) who required diuretic therapy, provided written informed consent to participate, and met all inclusion criteria without fulfilling any exclusion criteria. The study protocol was approved by the Bioethics Committee of the Wrocław Medical University (approval no. 243/2024).

Inclusion criteria:

- Exacerbation of chronic heart failure symptoms;
- Stable, guideline-directed medical therapy (beta-blocker, ACEI/ARB/ARNI, MRA, SGLT2 inhibitor) for at least 3 months;
- Clinical signs of tissue congestion;
- Peripheral edema extending to at least the lower one-third of the shank.

Exclusion criteria:

- De novo acute heart failure;
- Pulmonary edema or cardiogenic shock;
- Severe tricuspid regurgitation;

- Chronic kidney disease with $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$.

2.1. Study Protocol

After enrollment, baseline demographic and clinical data were collected for all participants, including comorbidities, current pharmacotherapy, and physical signs of fluid overload. Each patient underwent urinary catheterization to accurately measure urine output.

Participants were randomized in a 1:1 ratio to either the supine or upright/seated position groups during diuretic treatment. Randomization was performed using a computer-generated random number sequence before study initiation. To account for circadian variations in neurohormonal parameters and to minimize inter-individual variability secondary to these rhythms, all study procedures were initiated at 8:00 AM. Furosemide was administered at 12:00 PM, and urine collection was completed at 6:00 PM.

All participants were instructed on the day before the study began to remain in the supine position for at least 4 h without leaving the bed prior to the start of the study. The first baseline samples were then obtained. Afterwards, half of the patients remained supine, while the other half changed to the upright position according to randomization. After this period, blood and urine samples were collected again for biochemical analyses. Subsequently, furosemide was administered at a dose of 1 mg/kg body weight—half as an intravenous bolus and half as a 2-h continuous infusion.

Hourly urine output was measured for 6 h following loop diuretic administration. Additional blood and urine samples were collected at 2 h and 6 h for further biochemical evaluation.

Throughout the study period, all patients adhered to a fluid restriction protocol and received hospital-prescribed meals in accordance with the standard heart failure diet.

Urine dilution was defined as urinary creatinine in baseline to urinary creatinine in subsequent timepoints. This parameter was designed to present the degree of water excretion changes in relation to baseline [21]. To adjust urine output for eGFR and to assess fractional sodium excretion (FeNa), baseline serum creatinine and sodium concentrations were used at all time points, assuming they remained constant.

2.2. Statistical Analysis

Quantitative data were expressed as mean $\pm$ standard error of mean (SEM). Qualitative data were presented as absolute numbers and percentages. Normality of distribution was assessed using the Shapiro–Wilk test, and homogeneity of variance was verified using Levene’s test. Statistical assessment of differences between groups was performed using Student’s *t*-test, with Welch’s correction applied in cases of unequal variances. For non-normally distributed variables, the Mann–Whitney U test was used.

All statistical analyses were performed using Statistica 13 (StatSoft, Inc., Tulsa, OK, USA). Graphs were generated using GraphPad Prism 9.5.0. The graphical abstract was created in BioRender (Biegus, J. (2026) <https://BioRender.com/jw4tomi>).

3. Results

3.1. Patients’ Characteristics

The study group included 12 patients, predominantly men (10 (83%)), with a mean age of 74 ± 4 years, with HFrEF. The mean ejection fraction was $28 \pm 2\%$, NT-proBNP $15,162 \pm 4490 \text{ pg/mL}$. The pre-diuretic urine output was $310 \pm 83 \text{ mL}$ ($77 \pm 21 \text{ mL/h}$), while cumulative 6-h diuresis after furosemide administration was $1855 \pm 368 \text{ mL}$, ($309 \pm 61 \text{ mL/h}$). After adjustment for eGFR the mean hourly urine output in pre- and post- diuretic periods were: 1.29 ± 0.27 and $4.64 \pm 0.69 \text{ mL/h per mL/min/1.72 m}^2$ of eGFR, respectively. The mean furosemide dose administered during the study was

84 ± 5 mg. After 6 h of intensive diuretic treatment the weight change was −0.9 ± 0.4 kg. The comprehensive study group characteristic was presented in Table 1.

Table 1. Characteristics of the general population and comparison of the supine and upright groups.

Parameter	General Population	Supine	Upright	<i>p</i> -Value
Sex, men N (%)	10 (83%)	5 (83%)	5 (83%)	1.00
Age, years	74 ± 4	72 ± 8	76 ± 2	0.57
Concomitant diseases				
Hypertension, N (%)	10 (83%)	5 (83%)	5 (83%)	1.00
Diabetes mellitus, N (%)	7 (58%)	3 (50%)	4 (67%)	0.56
Chronic kidneys disease, N (%)	7 (58%)	2 (33%)	5 (83%)	0.08
COPD/Asthma, N (%)	2 (17%)	1 (17%)	2 (17%)	1.00
Myocardial infarction in past, N (%)	6 (50%)	2 (33%)	4 (67%)	0.35
Echocardiography				
LVDD, cm	65 ± 3	69 ± 3	62 ± 3	0.16
LVEF, %	28 ± 2	28 ± 3	28 ± 2	0.83
TAPSE, cm	14 ± 1	15 ± 1	12 ± 1	0.11
S' TV, cm/s	7.0 ± 0.9	8.4 ± 1.5	5.9 ± 0.8	0.21
E/E'	26.5 ± 5.1	32.6 ± 13.1	22.8 ± 3.4	0.53
Serum biochemical assessment				
Leukocytes, 10 ³ /μL	7.16 ± 0.51	6.61 ± 0.74	7.72 ± 0.68	0.29
Hemoglobin, g/dL	11.5 ± 0.5	10.8 ± 0.6	12.2 ± 0.8	0.18
Hematocrit, %	36 ± 2	34 ± 2	38 ± 2	0.27
Platelet count, 10 ³ /μL	194 ± 17	187 ± 17	201 ± 32	0.72
Bilirubin, mg/dL	1.4 ± 0.2	1.5 ± 0.2	1.4 ± 0.3	0.71
AST, IU/L	39 ± 12	29 ± 4	49 ± 24	1.00
ALT, IU/L	25 ± 5	21 ± 1	30 ± 10	0.33
GGTP, IU/L	82 ± 20	58 ± 20	99 ± 29	0.46
Urea, mg/dL	70 ± 14	40 ± 7	100 ± 21	0.03
Creatinine, mg/dL	1.4 ± 0.2	1.0 ± 0.1	1.7 ± 0.3	0.03
Sodium, mmol/L	138 ± 1	139 ± 1	138 ± 1	0.72
Potassium, mmol/L	4.0 ± 0.1	3.9 ± 0.1	4.1 ± 0.2	0.49
Chloride, mmol/L	103 ± 2	101 ± 2	105 ± 2	0.18
NT-proBNP, pg/mL	15,162 ± 4490	9015 ± 2946	21,309 ± 8056	0.39
Aldosterone, ng/dL	18.1 ± 4.5	19.1 ± 8.6	17.2 ± 4.2	0.69
Renin, μIU/mL	123.3 ± 56.4	74.6 ± 66.9	172.1 ± 93.1	0.42
Baseline urine biochemical assessment				
Urea, mg/dL	1096 ± 152	1050 ± 264	1142 ± 178	0.94
Creatinine, mg/dL	63.7 ± 13.1	70.9 ± 25.2	56.5 ± 9.7	0.70
Sodium, mmol/L	74.6 ± 10.2	74.5 ± 15.7	74.7 ± 15	0.99
Potassium, mmol/L	38.3 ± 4.6	44.3 ± 8.5	32.2 ± 2.8	0.23
Chloride, mmol/L	73 ± 11	70 ± 19	76 ± 14	0.81
Adrenaline, μg/mL	0.008 ± 0.001	0.008 ± 0.001	0.009 ± 0.003	0.73
Noradrenaline, μg/mL	0.056 ± 0.013	0.058 ± 0.023	0.055 ± 0.014	0.92

3.2. The Comparison of Urine Output Between Groups

There were no differences between supine and upright patients regarding urine output in both pre-diuretic (94 ± 37 vs. 60 ± 19 mL/h; *p* = 0.37) and post-diuretic periods (343 ± 88 vs. 275 ± 91 mL/h; *p* = 0.58), respectively. Moreover, when adjusted for eGFR, there were no differences between supine and upright patients in both pre-diuretic (1.19 ± 0.43 vs.

1.40 ± 0.35 mL/h per mL/min/ 1.73 m^2 of eGFR; $p = 0.69$) and post-furosemide periods (3.81 ± 0.62 vs. 5.52 ± 1.20 mL/h per mL/min/ 1.73 m^2 of eGFR; $p = 0.47$). Naturally, it was not reflected in differences in weight change during 6 h of diuretic treatment between supine and upright individuals (-0.6 ± 0.4 vs. -1.1 ± 0.7 kg; $p = 0.81$). Moreover, when comparing cumulative urine output per 40 mg administered furosemide, the values of adjusted urine volume did not differ between each other (933 ± 192 vs. 835 ± 306 mL/40 mg furosemide; $p = 0.69$). However, patients randomized to the supine group presented a more dynamic diuretic response, reflected in a tendency to more diluted urine in 2nd hour after the diuretic dose. The urinary output and dilution trajectories were presented in Figure 1A,B.

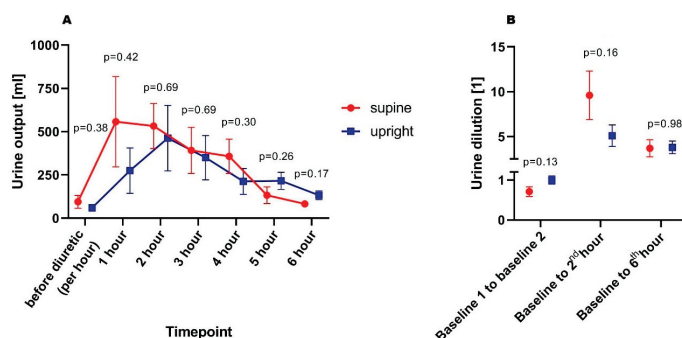


Figure 1. Urine output (A) and degree of urine dilution (B) in subsequent timepoints.

3.3. Diuretic Response Biochemical Parameters Between Supine and Upright Patients

The trajectory of urine sodium concentration and excretion was similar in both supine and upright groups prior to loop diuretic dose and post-loop diuretic administration. Nevertheless, the slightly non-significant tendency for greater sodium fractional and total excretion prior to the loop-diuretic dose was observed (8.4 ± 4.6 vs. 2.8 ± 0.5 mmol/h; $p = 0.26$) in supine patients was observed. Moreover, there were no significant differences in fractional sodium excretion across all timepoints. The trajectories of urea and chloride excretion were parallel, with no significant differences across subsequent timepoints. The trajectories of the abovementioned parameters were presented on Figure 2A–E.

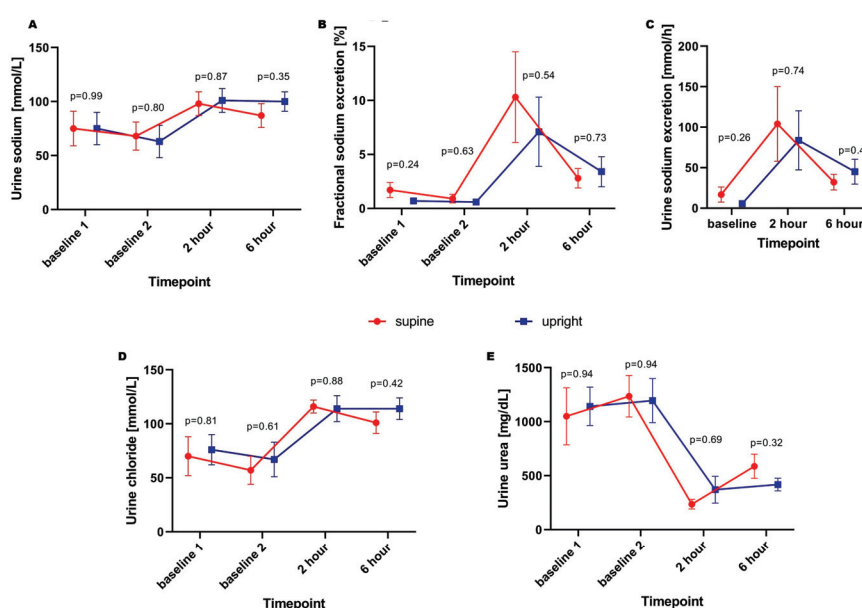


Figure 2. Spot urine sodium concentration (A), fractional (B) and total (C) excretion, urine chloride concentration (D), and urine urea concentration (E) in subsequent timepoints.

3.4. Neurohormonal Patterns in Supine and Upright Patients

No statistically significant differences in aldosterone concentrations were found at subsequent time points. A similar pattern was observed for renin; however, despite the lack of statistical significance, there was a trend toward higher values in patients who remained in the upright position (Figure 3A,B). Regarding markers of adrenergic activity, higher urinary epinephrine concentrations were observed at 2nd hour (0.006 ± 0.001 vs. 0.002 ± 0.001 $\mu\text{g/mL}$; $p = 0.02$) and 6th hour (0.007 ± 0.001 vs. 0.002 ± 0.001 mL/h ; $p < 0.01$) in supine patients compared to those in the upright position, while baseline concentrations were similar. Furthermore, this difference was preserved after adjustment for urinary creatinine concentration as a marker of renal filtration capacity. No significant differences were found with respect to norepinephrine—a similar pattern of changes was observed in both groups (Figure 4A–D).

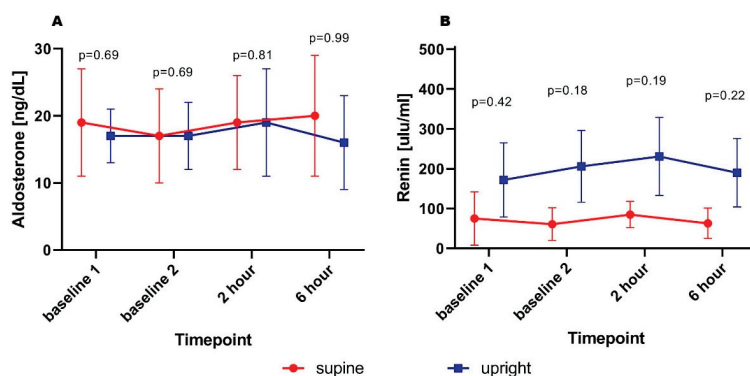


Figure 3. Serum aldosterone (A) and renin (B) concentration in subsequent timepoints.

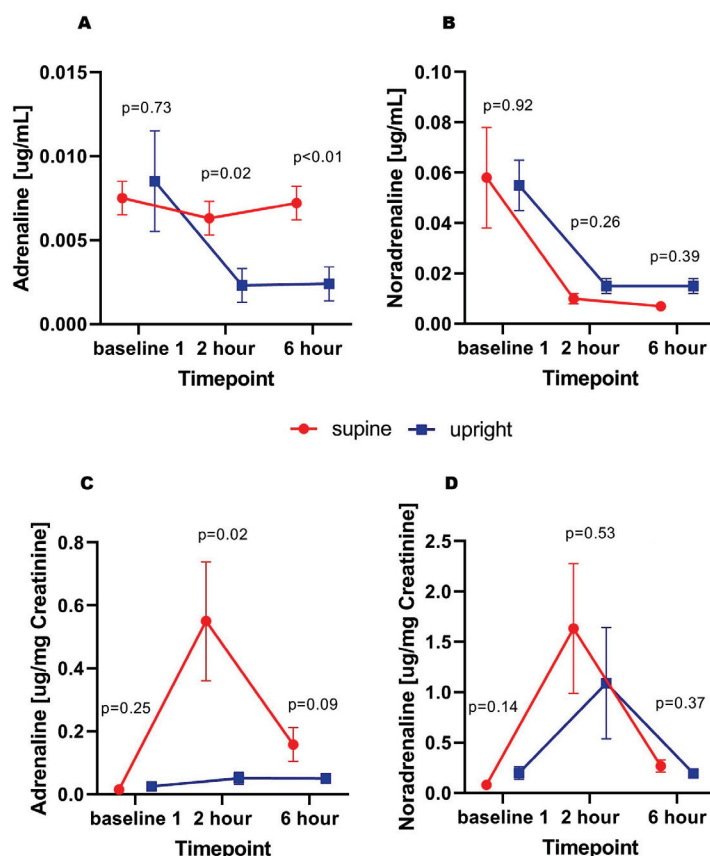


Figure 4. Adrenaline (A), noradrenaline (B) concentration; adrenaline (C) and noradrenaline concentration adjusted for urinary creatinine (D) in subsequent timepoints.

4. Discussion

The presented study demonstrates several findings regarding the pathophysiology of the diuretic response in heart failure. Given the nature of the data obtained, as described in detail in the limitations discussion below, the study primarily reflects a descriptive tendency toward changes observed in patients rather than establishing direct causality:

1. No significant differences were found between the groups in terms of total urine output. Interestingly, those in the supine position presented a (non-significant) tendency to a more dynamic diuretic response.
2. Urinary sodium concentration, total and fractional sodium excretion were comparable between the groups at all (pre- and post-diuretic) timepoints. However, total sodium excretion in supine patients before furosemide administration showed a tendency (non-significant) for being higher.
3. Patients in both groups had similar aldosterone concentrations before and after diuretic administration. Likewise, no significant differences in renin secretion were observed; however, upright patients showed a trend toward higher renin levels than those in the supine position.
4. Interestingly, patients who remained in the supine position exhibited higher urinary adrenaline concentrations after diuretic administration. This effect was particularly evident after adjustment for urinary creatinine, reflecting glomerular filtration function.

In studies of a similar design conducted before the era of neurohormonal blockade, in different patient populations (e.g., with nephrotic syndrome or severe hypoalbuminemia), a significantly higher urine output and urinary sodium excretion were observed both at baseline and after diuretic administration in patients allocated to supine position group. Additionally, the fractional sodium excretion was higher between baseline measurements in the supine versus upright positions, with no post-diuretic differences [17].

A comparable effect—greater diuresis and sodium excretion (associated with higher eGFR)—was observed in a randomized trial administering 1 mg bumetanide to patients with liver cirrhosis or heart failure (analyzed as a single study group). Furthermore, plasma concentrations of noradrenaline, renin, and aldosterone tended to be higher in patients who remained upright during diuretic therapy [18].

Importantly, in heart failure patients treated with enalapril 10 mg twice daily, no significant differences in urine output or sodium excretion were observed between the supine and upright positions, whereas this effect was observed in patients receiving furosemide alone. Moreover, ACEI-treated patients exhibited higher plasma renin activity with a relatively large standard deviation across timepoints, while angiotensin II concentrations were significantly lower, confirming effective pharmacological blockade [19,20].

The changes observed between these populations following the introduction of ACEI therapy, supported by the findings of our study, suggest that the altered diuretic response profile between upright and supine patients may be a consequence of neurohormonal blockade. Its influence on renal function—most likely by (1) modulating vascular resistance—appears to diminish the role of pressure gradients in driving urine production under the strong stimulus of loop diuretic administration, and (2) in sodium avidity regulation during decongestion.

Despite a lack of clinically significant effect (no difference in urine output, urine dilution and natriuresis), the results have shown potential different mechanisms of this condition. On the one hand, high renin excretion in those being in the upright position (with potentially higher venous pressure at the kidneys' level), and on the other hand, adrenergic drive in patients being supine, with potentially better right ventricle preload, and diminished hydrostatic pressure impact on venous pressure gradients.

Another issue should be noted: patients who remained in the supine position showed a more dynamic trajectory of urine excretion, which, in conjunction with the trend toward higher renin concentrations, may have contributed to the observed tendency toward urine concentration relative to baseline, as compared with upright patients (who exhibited a more “flat” diuretic response pattern). It was also reflected in (non-significant) higher urine dilution despite higher tendency for baseline urinary creatinine concentration. Nonetheless, the lack of statistical significance in these parameters potentially could be diluted due to the limited study population (which was discussed below).

Additionally, although the difference did not reach statistical significance, total sodium excretion tended to be higher before loop diuretic administration in patients assigned to the supine group, but spot urine sodium concentration remained highly similar. Notably, at baseline 1, supine patients also showed a tendency toward higher FeNa, with a diminished difference at baseline 2. Because all participants were initially in the supine position, this particular finding is more likely attributable to better renal function—reflected by higher serum creatinine and urea—in the supine in relation to the upright.

The study was subject to several limitations. First, the study group was small, resulting in limited statistical power. Therefore, the results should be interpreted with caution and considered exploratory and hypothesis-generating rather than definitive. Consequently, it increases the likelihood that meaningful associations may not have been detected, resulting in type 2 error. The extension of the study population was not possible due to the study’s financial limitations. Second, although the study was randomized, it was not blinded to the investigator, which may have introduced a certain degree of assessment bias. Third, the patient cohort was highly selected (with strict inclusion/exclusion criteria), which limits the generalizability of the findings to the broader population of patients with HFrEF; however, its role was to mechanistically show the pathophysiological patterns of diuretic response in relation to patients’ body position. Fourth, despite the lack of significant differences in urine output or natriuresis between groups adjusted for eGFR, the worse renal in upright patients could potentially confound the interpretation of the results. Fifth, total body water (including intravascular volume) was not objectively assessed prior to the study. Volume status and congestion were determined by the physician based on physical examination. Finally, the use of covariate or regression analyses was severely limited, preventing the exclusion of potential confounders (e.g., age, sex, kidneys’ function parameters) when evaluating diuretic response.

5. Conclusions

No clinically meaningful differences were observed between supine and upright AHF patients receiving neurohormonal blockade, although trends in renin and urinary adrenaline were noted. Further adequately powered studies are needed to confirm these findings.

Author Contributions: Conceptualization, M.G.; methodology, M.G.; formal analysis, M.G., R.T.; investigation, M.G.; writing—original draft preparation, M.G., R.T.; writing—review and editing, M.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by Wroclaw Medical University subsidy no.: SUBK.A460.24.053.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethical Committee of Wroclaw Medical University; No. 243/2024, approval date 18 April 2024.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw datasets generated during this study may be obtained from the corresponding author upon request under restrictions related to patient confidentiality, ethical approval, and data protection regulations.

Conflicts of Interest: The authors declare no conflicts of interest.

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Article

Integrated Model for Predicting Cancer Therapy-Related Cardiac Dysfunction in Non-Hodgkin Lymphoma

Daniela Bursacovschi ^{1,*}, Oleg Arnaut ^{2,3,4}, Viorica Ochisor ⁵, Georgeta Mihalache ⁵, Ruslan Baltaga ^{6,7}, Vladimir Iacomi ⁸, Maria Robu ⁹ and Valeriu Revenco ⁵

¹ Department of Heart Failure, Public Healthcare Institution—Institute of Cardiology, MD-2025 Chisinau, Moldova

² Department of Human Physiology and Biophysics, Nicolae Testemitanu State University of Medicine and Pharmacy, MD-2004 Chisinau, Moldova; oleg.arnaut@usmf.md

³ Bioinformatics and Computational Medicine Laboratory, Nicolae Testemitanu State University of Medicine and Pharmacy, MD-2004 Chisinau, Moldova

⁴ National Cancer Registry, Public Healthcare Institution—Oncological Institute, MD-2025 Chisinau, Moldova

⁵ Department of Cardiology, Nicolae Testemitanu State University of Medicine and Pharmacy, MD-2004 Chisinau, Moldova

⁶ Department of Anesthesiology and Intensive Care Nr. 1, Nicolae Testemitanu State University of Medicine and Pharmacy, MD-2004 Chisinau, Moldova; ruslan.baltaga@usmf.md

⁷ Public Healthcare Institution—Oncological Institute, MD-2025 Chisinau, Moldova

⁸ Department of Pediatrics, Hematology Clinic, Nicolae Testemitanu State University of Medicine and Pharmacy, MD-2004 Chisinau, Moldova; vladimir.iacomi@usmf.md

⁹ Department of Hematology, Nicolae Testemitanu State University of Medicine and Pharmacy, MD-2004 Chisinau, Moldova; maria.robust@usmf.md

* Correspondence: daniela.bursacovschi@gmail.com

Abstract

Background/Objectives: Cancer Therapy-Related Cardiac Dysfunction (CTRCD) is a major complication in patients with non-Hodgkin lymphoma (NHL), potentially leading to heart failure and other severe cardiovascular events. Early identification of patients at risk is crucial for timely interventions. **Methods:** A prospective analytical cohort study was conducted on 127 adult NHL patients to evaluate chemotherapy-related cardiac dysfunction over a 6-month period, with the aim of assessing early adverse cardiac effects. Assessments included echocardiography, cardiorespiratory exercise testing, 24-h Holter monitoring, and measurement of cardiac-specific biomarkers (troponin I and NT-proBNP) to identify early subclinical cardiac changes. **Results:** A predictive model for CTRCD was developed using clinical, serological, echocardiographic, cardiopulmonary, and treatment-related parameters in patients with non-Hodgkin lymphoma. The model demonstrated high overall accuracy (94.2%) and strong discriminative ability (AUC 0.95; precision-sensitivity AUC 0.824) for 6-month cardiotoxicity. SHAP analysis identified the most influential predictors as baseline SDNNi, mean daily heart rate, total doxorubicin dose, NT-proBNP, QT corrected interval, hemoglobin, age, left atrial volume, and diastolic function indices (E/e' , E/A). Lower cardiopulmonary reserve was also associated with increased risk. **Conclusions:** The predictive model developed in this study serves as a practical and robust tool for assessing the risk of cancer therapy-related cardiac dysfunction.

Keywords: chemotherapy-related cardiac dysfunction; heart failure; cancer treatment; prediction model

1. Introduction

Cardiovascular diseases remain a major contributor to mortality among individuals diagnosed with malignant conditions. Contemporary data indicate that the most substantial increase in cardiovascular risk occurs within the first year following the identification of a malignant process [1]. Although the underlying cancer accounts for the majority of deaths in oncology, cardiovascular complications consistently represent the second leading cause of mortality [2]. This pattern has likewise been observed in the therapeutic management of non-Hodgkin lymphoma (NHL). Nevertheless, the timely recognition and early detection of cardiovascular toxicity during NHL treatment continue to pose a significant and persistent clinical concern [3]. Non-Hodgkin lymphomas are neoplasms of lymphoid tissue arising from mature B or T lymphocytes and their precursors, with B-cell-derived subtypes being predominant. NHL represents the most common hematologic malignancy in adults [4]. Following oncologic treatment, a considerable proportion of cancer survivors are exposed to an elevated risk of cardiovascular complications [5,6]. For cardiac injury, cardiomyopathy, and heart failure, current cardio-oncology guidelines recommend the use of the term cancer therapy-related cardiac dysfunction. Despite advances in the treatment of hematologic malignancies, heart failure remains a clinical syndrome characterized by persistent symptoms that impair patients' quality of life, with a high mortality rate reaching approximately 50% at five years after diagnosis [7]. The incidence of heart failure continues to rise dynamically following treatment regimens including anthracyclines and trastuzumab, reaching approximately 20.1% at five years after therapy. The quality of life of patients with heart failure is closely correlated with New York Heart Association functional class, being superior in those with lower functional class impairment [8].

The early detection of cancer therapy-related cardiac dysfunction facilitates timely initiation of treatment strategies, thereby mitigating the likelihood of developing heart failure and other major cardiovascular complications. Transthoracic echocardiography remains the gold standard for evaluating left ventricular performance, owing to its broad accessibility and cost-efficiency. Moreover, advanced imaging modalities, including tissue Doppler imaging and speckle-tracking echocardiography, allow for the identification of subtle alterations in myocardial mechanics that are not yet evident with conventional assessment techniques [9]. Cardiopulmonary exercise testing provides an integrated assessment of cardiovascular and respiratory function; however, its role in predicting CTRCD has not been fully elucidated. Some studies have reported promising results for CPET-derived parameters, such as peak VO_2 and the ventilatory efficiency slope (VE/VCO_2), in the early identification of patients at risk for CTRCD [10]. Within the setting of chemotherapy-associated cardiotoxicity, continuous 24-h Holter electrocardiographic monitoring permits the detection of subtle disturbances in cardiac rhythm and electrical conduction that may precede clinically apparent myocardial dysfunction. Holter recordings are particularly valuable for uncovering silent ischemic episodes and asymptomatic arrhythmic events, thereby aiding in patient-specific risk assessment and guiding individualized therapeutic strategies [11]. However, the precise correlation between rhythm abnormalities identified on Holter monitoring and the subsequent emergence of heart failure or other cardiovascular complications remains to be fully elucidated. Complementary assessment through cardiac biomarkers, including troponins and natriuretic peptides, offers critical insights into subclinical myocardial injury. Elevations in these biochemical markers can reveal early cardiac involvement prior to the manifestation of overt clinical symptoms [12]. Even though a standardized protocol encompassing all these monitoring modalities has not yet been established, the implementation of an integrated surveillance strategy—including periodic echocardiographic assessments, cardiopulmonary exercise stress evaluation, ambulatory ECG monitoring, and evaluation of myocardial injury markers might become an

integral part of the clinical protocol for patients undergoing cardiotoxic cancer therapy. This multidisciplinary approach holds the potential to facilitate early detection of CTRCD, enabling prompt interventions and real-time treatment adjustments. Such a strategy has the potential to significantly lower cardiovascular risk while promoting better long-term clinical outcomes for patients with malignancies.

The Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) risk assessment tool is one of the most widely cited frameworks for CTRCD prediction. It incorporates clinical risk factors, treatment-related variables, and baseline cardiac function to stratify patients into low, medium, and high-risk categories. Although endorsed in guidelines, its discriminative power is moderate and primarily validated in breast cancer populations receiving HER2-targeted therapies [13]. Emerging predictive models for cancer therapy-related cardiac dysfunction include AI-based ECG approaches, machine learning cohort models, and nomogram-based tools. AI-CTRCD models leverage baseline ECGs with transfer learning, achieving AUCs ~ 0.78 , offering early detection and accessibility, but their performance across diverse populations and regimens remains unvalidated and requires high-quality ECG input [14]. Machine learning models using longitudinal clinical, imaging, and laboratory data report AUROC ~ 0.80 , benefiting from multi-modal integration, yet are limited by single-center design and retrospective biases [15]. Nomogram-based models in breast cancer cohorts combining clinical, biomarker, and echocardiographic data show AUCs 0.79–0.82, but external validation is lacking and applicability to other cancers is uncertain [16]. Collectively, these studies highlight the potential of predictive modeling for CTRCD while emphasizing the need for broader validation and adaptable frameworks across cancer types.

2. Materials and Methods

The study was prospectively conducted in collaboration between the “Institute of Oncology,” which provided randomly selected patients, and the “Institute of Cardiology” in Chisinau, Republic of Moldova, where they underwent assessment. The study population consisted of 127 adult patients (≥ 18 years) diagnosed with NHL who provided written informed consent. Enrollment took place between 2022 and 2024, following approval from the Ethics Committee of the State University of Medicine and Pharmacy “Nicolae Testemitanu” (approval no. 7/28 December 2021). The study adhered to the principles of the Declaration of Helsinki. Exclusion criteria included a history of other malignancies, previous oncological therapies (chemotherapy, immunotherapy, or radiotherapy), and underlying cardiovascular disorders, including coronary artery disease, previous myocardial infarction, chronic ischemic heart conditions, various cardiomyopathies, or post-inflammatory/infiltrative myocardial abnormalities. Individuals with moderate to severe valvular heart disease (encompassing at least moderate stenosis or regurgitation) or advanced heart failure (NYHA class III–IV) were likewise excluded from the study. At baseline, patients completed a structured questionnaire regarding cardiovascular risk factors—including diabetes mellitus, hypertension, dyslipidemia, and smoking—as well as comorbidities such as chronic kidney disease, proteinuria, chronic obstructive pulmonary disease, and thyroid disorders. Clinical data regarding lymphoma characteristics and administered treatments, including specific chemotherapy or immunotherapy regimens and cumulative doxorubicin dose at 6 months, were systematically recorded. Participants underwent two comprehensive evaluations: prior to initiation of antitumor therapy and at a 6-month follow-up according to the study design. According to the diagnostic criteria established by the 2022 cardio-oncology guidelines, cancer therapy-related cardiac dysfunction was identified in 18 (14.2%) patients at the 6-month follow-up evaluation [7].

Assessments included transthoracic echocardiography, cardiopulmonary exercise testing, and laboratory analyses. Serological measurements focused on troponin I and NT-proBNP levels, obtained both at baseline and after 6 months of therapy. Echocardiographic examinations were performed by a single experienced cardiologist using a General Electric Vivid E95 system (GE VINGMED ULTRASOUND A/S, Horten, Norway). Cardiac chamber dimensions and function were evaluated according to the 2015 recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [17]. Twenty-four-hour Holter ECG monitoring was performed using the ECGpro Holter system (2021), with automated analysis followed by manual verification for accuracy. Key parameters included mean, minimum, and maximum heart rate, rhythm classification (sinus rhythm, atrial fibrillation), and the total number of supraventricular and ventricular ectopic beats. Episodes of sustained supraventricular or nonsustained ventricular tachycardia were identified based on standard criteria [18]. Heart rate variability metrics analyzed included SDNN, SDANN, and SDNNi, reflecting autonomic modulation and myocardial function, with reductions indicating increased cardiovascular risk [18,19]. Corrected QT interval (QTc, Fridericia formula: $QTc = QT / \sqrt[3]{RR}$) and PQ intervals were measured continuously, with QTc ≥ 480 ms or sex-specific intermediate thresholds (men: 450–480 ms; women: 460–480 ms) flagged as potential arrhythmic risk. ST-T segment changes were classified as ischemic if ST depression ≥ 1 mm persisted ≥ 1 min but ≤ 20 min, separated by ≥ 1 min from other episodes. PQ intervals between 120 and 200 ms were considered normal. Patients were familiarized with the cardiopulmonary exercise testing equipment (Quark CPET, Cosmed, Rome, Italy), utilizing equipment such as a cycle ergometer along with devices for assessing respiratory parameters, with participants directed to perform exercise at maximal intensity, discontinuing if they experienced symptoms like chest discomfort, palpitations, or lightheadedness. CPET was performed according to the 2019 American Thoracic Society and 2020 European Society of Cardiology guidelines for cardiopulmonary exercise testing and exercise in cardiovascular patients [20,21], with continuous 12-lead ECG, blood pressure, and oxygen saturation monitoring. A symptom-limited, incremental protocol was applied, progressing every minute through rest, unloaded cycling, progressive exercise, and recovery phases. Key CPET parameters analyzed included hemodynamics (baseline and peak heart rate, systolic/diastolic blood pressure, oxygen saturation), peak VO_2 , VO_2 at anaerobic threshold, % VO_2 at threshold, VO_2 pulse, VO_2 /work rate, ventilatory efficiency (VE/VCO_2), minute ventilation, ventilatory reserve, end-tidal CO_2 , and oxygen uptake efficiency slope. A peak $VO_2 < 14$ mL/kg/min was considered indicative of reduced aerobic capacity and higher cardiovascular risk, while $VE/VCO_2 > 30$ reflected ventilatory inefficiency and predicted increased long-term heart failure severity, hospitalizations, and mortality [22]. The study design is presented in Figure 1.

Statistical Analysis

The main dataset was processed and examined using RStudio (v. 2024.09.1+394, <https://www.rstudio.com/>) and Python (v. 3.12.3, <https://www.python.org/>), ensuring that the entire statistical workflow could be fully reproduced. For numerical variables, descriptive statistics were calculated, including minimum, maximum, mean, standard deviation, median, and interquartile range. Differences between groups for numerical data were assessed using the Mann–Whitney U test. For categorical variables, both absolute counts and percentages were calculated, with percentages reported alongside their 95% confidence intervals. Associations between categorical variables were evaluated using Pearson’s Chi-squared test, applying the Monte Carlo method with 100,000 simulations. A significance level of 0.05 ($\alpha = 0.05$) was used for all statistical tests. The predictive performance of the model for CTRCD was evaluated using the area under the receiver

operating characteristic curve. Feature contributions were interpreted with SHAP (SHapley Additive exPlanations) analysis, with descriptive statistics of SHAP values calculated for each feature. Visualizations, including summary and dependence plots, were used to illustrate the relative importance and interactions of the predictors.

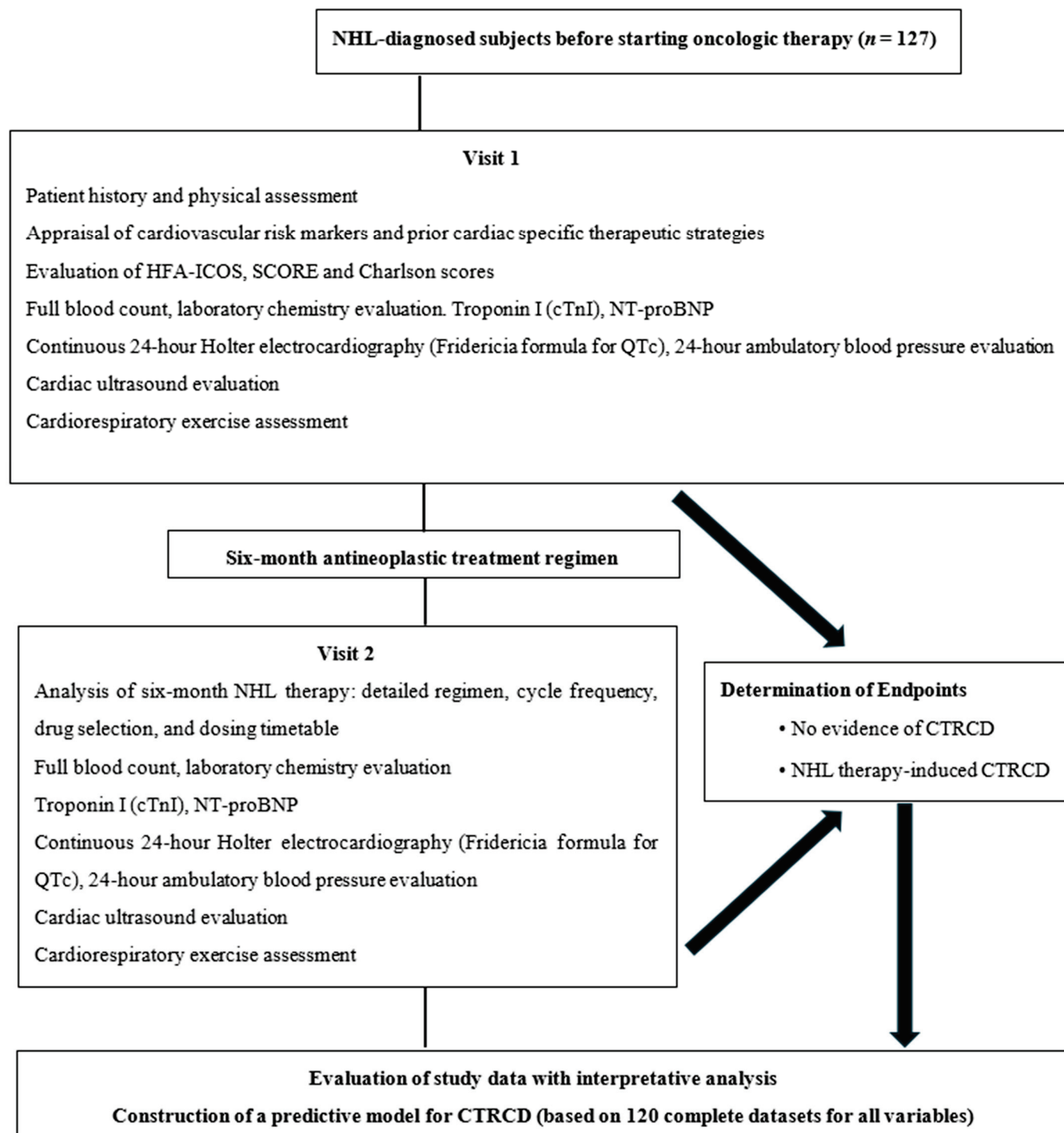


Figure 1. Study design.

3. Results

3.1. Demographic Profile, Comorbidities, and Treatment Features in Patients with Non-Hodgkin Lymphoma

The study cohort comprised 127 patients diagnosed with non-Hodgkin lymphoma, of whom 72 were men (56.7%, 95% CI: 48–65) and 55 were women (43.3%, 95% CI: 35–52). In terms of place of residence, 66 individuals lived in city settings (52.0%, 95% CI: 43–61), while 61 lived in village settings (48.0%, 95% CI: 39–57). The median body mass index was 25.9 kg/m² (IQR = 7.0), ranging from 18.6 to 48.7 kg/m². According to BMI categories, 59 subjects (46.5%, 95% CI: 38–55) were eutrophic, 37 (29.1%, 95% CI: 21–37) were overweight, 21 (16.5%, 95% CI: 10–23) had class I obesity, 7 (5.5%, 95% CI: 1.5–9.5) had class II obesity, and 3 subjects (2.4%, 95% CI: 0.0–5.0) presented with class III obesity. Eighty-four patients exhibited dyslipidemia (66.1%, 95% CI: 58–74), while metabolic syndrome was documented in 18 subjects (14.2%, 95% CI: 8.1–20). The most frequent concurrent medical condition was arterial hypertension, identified in about 50 individuals (39.3%). Among these, grade II hypertension was the most common, observed in 35 patients (27.6%, 95% CI: 20–35), followed by grade III hypertension in 11 patients (8.7%, 95% CI: 3.8–14) and grade I hypertension in 4 cases (3.1%, 95% CI: 0.11–6.2). A history of chronic obstructive pulmonary disease was present in 27 patients (21.3%, 95% CI: 14–28). Pre-existing chronic kidney disease was documented in 14.9% of patients. According to the KDIGO 2020 classification, 14 patients (11.0%, 95% CI: 5.6–16) had CKD stage G1–G2, and 5 patients (3.9%, 95% CI: 0.55–7.3) had stage G3 disease. No cases of more advanced CKD or other severe decompensated comorbidities were reported. Considering the identified comorbidities and the individual characteristics of the patients, the entire study cohort was assessed using the Charlson Comorbidity Index. Based on this tool, three risk categories were defined: 17 patients (13.4%, 95% CI: 7.5–19) were classified as low risk, reflecting a generally good health status and a relatively low probability of major adverse events or long-term mortality. A substantially larger proportion of 54 patients (42.5%, 95% CI: 34–51) fell into the moderate-risk category, suggesting the presence of concurrent conditions that may influence disease progression. In contrast, 56 individuals (44.1%, 95% CI: 35–53) were identified as high risk, indicating a considerable burden of serious comorbidities that may significantly compromise overall health status and require more intensive management. Cardiovascular risk according to the SCORE algorithm was estimated in line with the most recent 2021 ESC Guidelines on cardiovascular disease prevention. Patients were distributed across three categories: low-to-moderate cardiovascular risk in 13 cases (10.2%, 95% CI: 5.0–16), high cardiovascular risk in 30 cases (23.6%, 95% CI: 16–31), and very high cardiovascular risk in 84 patients (66.1%, 95% CI: 58–74). Subsequently, all patients were assessed using the HFA-ICOS risk stratification model for cardiotoxicity in oncology. According to this model, 44 patients (34.6%, 95% CI: 26–43) were identified as having a low risk of cardiotoxicity, 31 patients (24.4%, 95% CI: 17–32) were classified as moderate risk, and 5 patients (3.9%, 95% CI: 0.55–7.3) were categorized as high or very high risk. Importantly, in 47 patients (37.0%, 95% CI: 29–45), risk assessment could not be performed because they had not received anthracycline-based therapy within their treatment regimen. Table 1 outlines the baseline and clinical profiles of the cohorts with and without CTRCD.

The indolent form represented the predominant subtype, being identified in 78 patients (61.4%, 95% CI: 53–70), and was associated with a more protracted and less aggressive clinical evolution. Precursor B-lymphoblastic lymphoma accounted for the overwhelming majority of diagnoses—123 cases (96.9%, 95% CI: 94–100). In terms of disease staging, stage IV was the most frequently encountered, recorded in 89 individuals (70.1%, 95% CI: 62–78). This was followed by stage III in 18 patients (14.2%, 95% CI: 8.1–20), stage II in 16 cases (12.6%, 95% CI: 6.8–18), while stage I was uncommon, observed in only 4 patients (3.1%,

95% CI: 0.11–6.2). As for the primary tumor site, peripheral lymph node involvement predominated (94 patients, 74.1%, 95% CI: 46–98). Splenic origin was reported in 11 cases (8.7%, 95% CI: 3.8–14), abdominal involvement in 9 cases (7.1%, 95% CI: 2.1–11), while hepatic (2 cases, 1.6%, 95% CI: −0.59–3.7) and thyroidal localization (1 case, 0.8%, 95% CI: −0.75–2.3) were rare.

Table 1. Baseline demographic and clinical data for patients with/without CTRCD.

	Group I (CTRCD, n = 18) ¹	CI ² 95%	Group II (Without CTRCD, n = 109) ¹	CI ² 95%	Statistic Test	p ³
Age (years)	65.3 (11.9) 69.5 (16.5) 35.0, 83.0	59, 71	60.9 (10.0) 62.0 (13.0) 34.0, 80.0	59, 63	1243	0.071
Sex					1.3	0.3
Male	8 (44.4)	21, 67	64 (58.7)	49, 68		
Female	10 (55.6)	33, 79	45 (41.3)	32, 51		
BMI (kg/m ²)	28.2 (5.1) 28.7 (8.3) 18.6, 36.8	26, 31	26.6 (5.6) 25.2 (6.6) 19.2, 48.7	26, 28	1217	0.10
BMI > 30 kg/m ²	8 (44.4)	21, 67	23 (21.1)	13, 29	4.6	0.043
AC (cm)	88.7 (20.7) 93.5 (33.8) 59.0, 124.0	78, 99	83.9 (17.8) 78.0 (20.0) 57.0, 139.0	80, 87	1108	0.4
Worsened anamnesis	7 (38.9)	16, 61	16 (14.7)	8.0, 21	6.1	0.022
Smoking	4 (22.2)	3.0, 41	26 (23.9)	16, 32	0.02	>0.9
Hypertension grade					24	<0.001
gr.I	2 (11.1)	−3.4, 26	2 (1.8)	−0.68, 4.4		
gr.II	6 (33.3)	12, 55	29 (26.6)	18, 35		
gr.III	6 (33.3)	12, 55	5 (4.6)	0.66, 8.5		
Diabetes mellites	5 (27.8)	7.1, 48	13 (11.9)	5.8 18	3.2	0.13
CKD					9.0	0.029
CKD G1/2	2 (11.1)	−3.4, 26	12 (11.0)	5.1, 17		
CKD G3	3 (16.7)	−0.55, 34	2 (1.8)	−0.68, 4.4		
Chronic bronchitis	5 (27.8)	7.1, 48	22 (20.2)	13, 28	0.53	0.5
Thyroid pathology	1 (5.6)	−5.0, 16	8 (7.3)	2.4, 12	0.07	>0.9

Note: ¹ mean (SD), median (IQR), minimum, maximum; n (%) ² confidence interval (CI), ³ Kruskal–Wallis test, Pearson Chi-Square test with estimated p-value.

With respect to treatment patterns, the majority of patients received combined chemoimmunotherapy (114 cases, 89.8%, 95% CI: 84–95). Chemotherapy alone was administered to 7 patients (5.5%, 95% CI: 1.5–9.5), immunotherapy alone to 5 patients (3.9%, 95% CI: 0.55–7.33), and one patient (0.8%, 95% CI: 0–2.3) received a combination of chemotherapy, immunotherapy, and radiotherapy. Anthracycline-based regimens (doxorubicin) were given to 80 patients (63.0%, 95% CI: 55–71), while 47 patients (37.0%, 95% CI: 29–45) did not receive doxorubicin-containing protocols. The median cumulative doxorubicin dose at treatment completion was 250 mg/m² (IQR = 410.0), with a maximum dose of 735 mg/m². High-dose cyclophosphamide (≥150 mg/kg) was administered in 16 cases (12.6%, 95% CI: 6.8–18). Nearly all patients (122 cases, 96.1%, 95% CI: 93–99) received vincristine. The median number of chemotherapy cycles was 6.0 (IQR = 2.0), ranging from 1 to 8 cycles over a 6-month period.

3.2. Development of a Multimodal Model to Predict Cardiac Dysfunction Related to Antitumor Therapy in Non-Hodgkin Lymphoma

To identify potential predictors, we selected parameters derived from the cardiovascular profile and cardiovascular risk factors, alongside serological markers, echocardiographic parameters, variables obtained from cardiopulmonary exercise testing, 24-h Holter ECG

monitoring, and ambulatory blood pressure monitoring (ABPM). In addition, we considered parameters specific to non-Hodgkin lymphoma and its treatment. Within the cardiovascular risk profile, the assessed clinical indicators encompassed age, the presence of obesity ($\text{BMI} > 30 \text{ kg/m}^2$), active smoking, dyslipidemia, arterial hypertension, type 2 diabetes mellitus, chronic kidney disease, the calculated SCORE cardiovascular risk, as well as the Charlson comorbidity index. Indices obtained from 24-h Holter ECG or ABPM prior to initiation of antitumor therapy included: 24-h ABPM, SDNNi index, mean heart rate over 24 h, and mean corrected QT interval ($\text{QTc}/24\text{h}$). Echocardiographic parameters included: left atrial volume indexed to body surface area, left ventricular end-diastolic volume, left ventricular Tei index, E/A ratio, E/Vp ratio, E/e' ratio, and right ventricular Tei index. The CPET parameters analyzed for their potential predictive value regarding cancer therapy-related cardiac dysfunction were: peak $\text{VO}_2 < 14 \text{ mL/kg/min}$, VO_2 at the anaerobic threshold, and VO_2 pulse. Serological parameters included: baseline hemoglobin, troponin I, and NT-proBNP levels. Treatment- and disease-related variables analyzed for their potential impact on CTRCD prediction after 6 months of therapy comprised: NHL stage, cumulative doxorubicin dose, rituximab administration, and chemotherapy regimens (COP, R-COP, R-CHOP, or other treatment schemes). When analyzing relative and absolute frequencies for predictive model development, it was observed that CTRCD occurred in 14.2% of patients. Since this rate exceeds 10%, standard classification methods could be applied for predictive modeling. The prediction model was developed using data from 120 respondents. Model performance in predicting 6-month cardiotoxicity was evaluated using a binary confusion matrix (2×2 table). The overall model accuracy was 94.2%. Specifically, the model correctly predicted the occurrence of cardiotoxicity in 11 patients who developed the complication, while it failed to predict CTRCD in 6 patients. Among patients who did not develop cardiotoxicity, 102 were correctly classified at 6-month follow-up, with only one false-positive case misclassified as developing therapy-related cardiac dysfunction when in fact it did not occur (Figure 2).

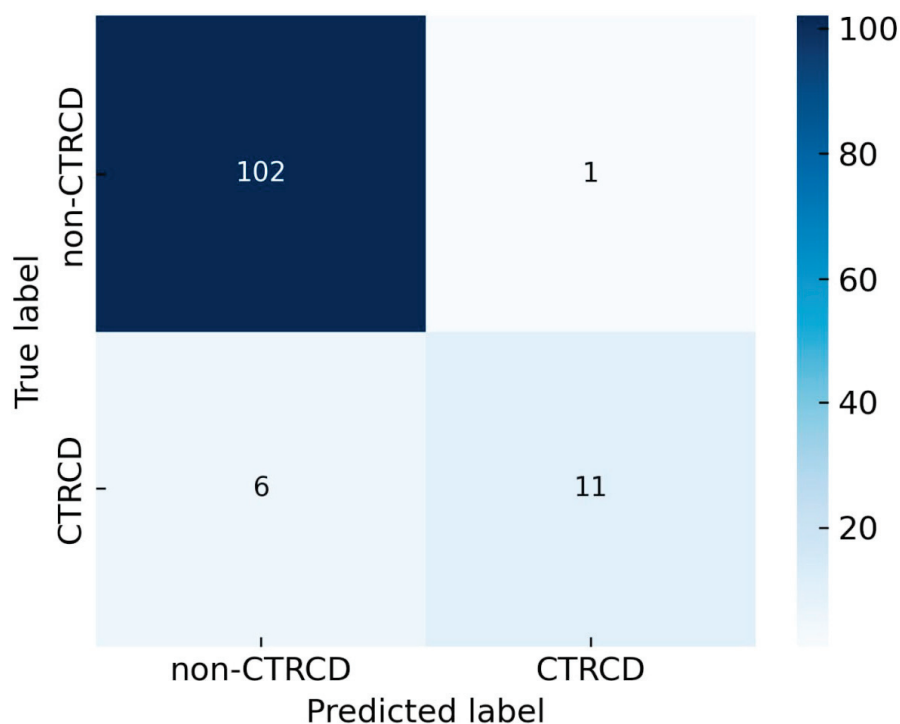


Figure 2. Assessment of the predictive accuracy of the model for identifying CTRCD.

Figure 3 displays the precision-recall curve, illustrating the association between the true positive rate on the Y-axis and the false positive rate on the X-axis. A visual assessment of the curve shows a tendency to approach the upper left corner of the plot, suggesting a high level of discrimination. This indicates that the model successfully identifies the majority of true positive cases (patients who develop CTRCD) while minimizing misclassification of negative cases (patients who do not develop CTRCD). The area under the curve (AUC) value of 0.95, obtained from the predictive model analysis for cardiotoxicity, reflects strong performance in distinguishing between patients who subsequently develop cardiotoxicity and those who do not. This value indicates that the model can accurately detect 95% of positive cases (patients who experience cardiotoxicity) while considering false positive rates, highlighting its substantial clinical relevance. Moreover, an AUC of 0.95 signifies that, for any randomly selected pair of patients, the model has a 95% likelihood of assigning a higher risk score to the individual who will develop cardiotoxicity compared to one who will not. This finding demonstrates not only efficiency but also reliability, which is essential for supporting informed clinical decision-making.

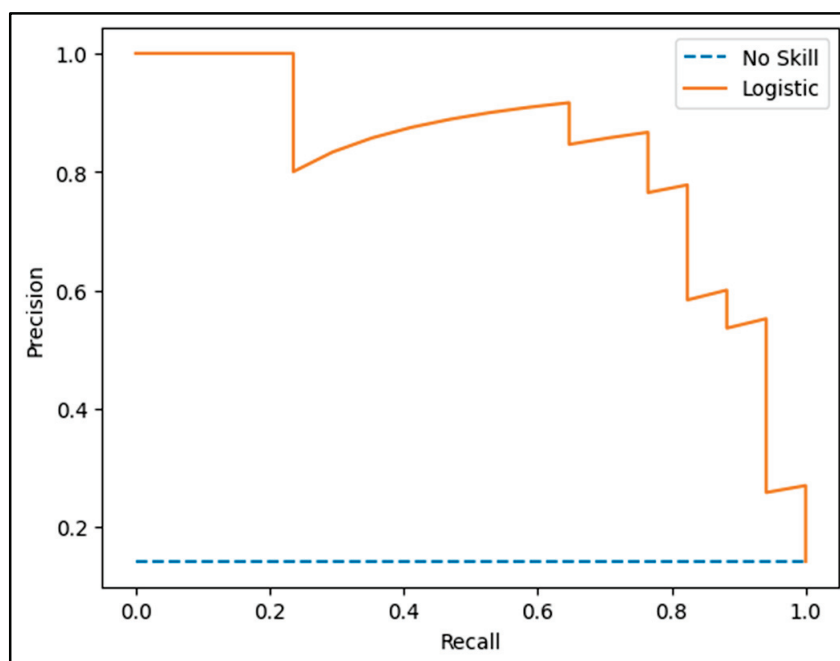


Figure 3. Performance analysis of the CTRCD prediction model through the precision-recall curve.

After the initial ROC curve assessment of the CTRCD prediction model, a further evaluation was carried out using precision and sensitivity metrics. This methodology offered an alternative perspective on model performance, enabling a more comprehensive appraisal of the trade-off between correctly identifying true positive cases and limiting misclassification errors. The ROC curve derived from this precision–sensitivity analysis demonstrated an AUC of 0.824, indicative of robust discriminative capability. These results suggest that the model reliably identifies patients at risk of developing cardiotoxicity within six months of therapy. Furthermore, an AUC of 0.824 indicates that, on average, the model correctly classifies patients with an 82.4% probability relative to random assignment (Figure 4).

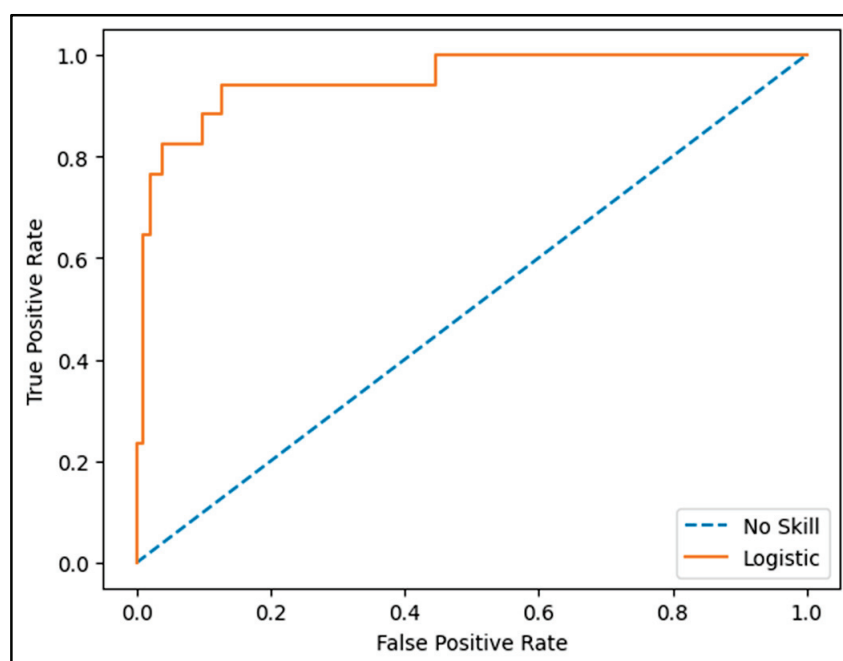


Figure 4. Evaluation of the accuracy and sensitivity of the CTRCD prediction model.

Following the evaluation of model performance via ROC curves, an analysis based on additive explanations using Shapley values (SHAP analysis) was performed to gain a deeper understanding of each variable's contribution to the cardiotoxicity prediction model. The resulting SHAP plot illustrates how each feature influences the model's predictions. In Figure 5, SHAP values indicate the extent to which each component affects the predictive outcome. Baseline values from the first visit of SDNNi and mean heart rate obtained from 24-h Holter ECG exhibited the strongest influence on the model. Higher values of these parameters were associated with an increased predicted risk of subsequent CTRCD. Cumulative doxorubicin dose also emerged as a major contributing variable, with higher total doses substantially increasing predicted risk, reflecting the known association between anthracycline exposure and cardiotoxicity. Baseline hemoglobin levels had a considerable impact as well; lower hemoglobin values were associated with a reduced predicted risk, whereas higher values correlated with a less favorable prediction, potentially indicating patients with more complex medical conditions (e.g., compensatory polycythemia). Prolonged QTc intervals increased the likelihood of adverse outcomes, suggesting that QTc prolongation serves as an important prognostic marker in this model. Elevated baseline NT-proBNP levels were strongly associated with increased cardiotoxicity risk. Age, particularly higher values, was another significant predictor, contributing substantially to an increased predicted risk. Echocardiographic assessment highlighted left atrial volume indexed to body surface area and the E/e' ratio as key determinants. Higher indexed left atrial volumes were moderately associated with an increased predicted risk. Elevated E/e' ratios (red) were associated with a greater likelihood of developing therapy-induced cardiac dysfunction. The E/A ratio also contributed modestly, with higher values slightly increasing predicted risk, consistent with its association with more severe diastolic dysfunction or increased ventricular stiffness. Cardiopulmonary functional reserve, assessed by VO_2 at the anaerobic threshold and peak $\text{VO}_2 < 14 \text{ mL/kg/min}$, provided insight into cardiopulmonary capacity, with lower values corresponding to higher predicted CTRCD risk, reflecting patients' functional limitations.



Figure 5. The contribution of clinical variables in the CTRCD prediction model.

The contribution of each variable to the model was evaluated by measuring the reduction in predictive accuracy following randomization or permutation of that variable's values (Figure 6). Based on this analysis, SDNNi had the greatest numerical contribution to the model prediction (+0.12), with diminished heart rate variability strongly correlating with an elevated risk of developing CTRCD. Following SDNNi, the variables with the next highest influence were increased mean heart rate on 24-h Holter ECG and cumulative doxorubicin dose at six months, succeeded by baseline NT-proBNP, mean QTc over 24 h, and baseline hemoglobin, which demonstrated comparable effects on the model. In contrast, factors such as rituximab administration and various chemotherapy protocols (R-CHOP, COP, R-COP) showed lesser impact, indicating that although these variables may be clinically relevant in specific contexts, they are not among the strongest predictors of CTRCD within this predictive framework.

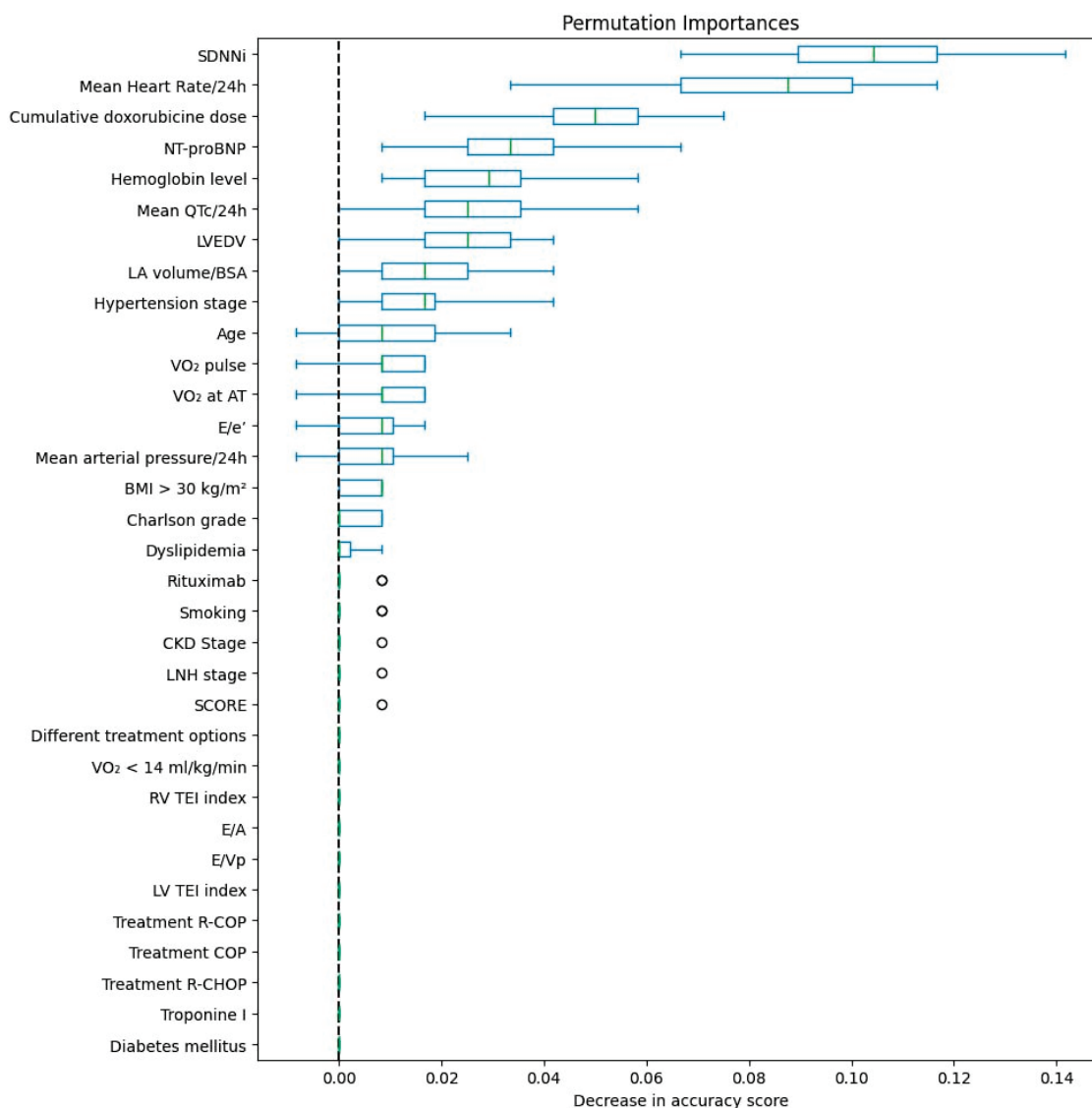


Figure 6. Impact of variables through permutation and SHAP mean values for the CTRCD prediction model.

4. Discussion

Early identification of patients at high risk for CTRCD is essential to prevent irreversible cardiac dysfunction. In this regard, a number of studies have introduced multi-modal predictive frameworks that combine clinical, imaging, and biometric parameters, with some employing artificial intelligence-based methodologies. One study proposed a CTRCD prediction model using clinical and echocardiographic variables [23]. Other analyses have focused on incorporating data from electrocardiograms. For example, one study demonstrated that artificial intelligence-based algorithms are capable of analyzing ECG recordings to detect subclinical cardiac alterations prior to the emergence of overt heart failure symptoms [14]. In a similar vein, another predictive model emphasized the value of baseline ECG assessments for estimating the risk of CTRCD in patients receiving anthracycline therapy [24]. These observations underscore the growing potential of non-invasive approaches in routine clinical practice. In patients with HER2-positive breast cancer, trastuzumab treatment is commonly linked to cardiotoxic events. A recent investigation proposed a personalized risk prediction model incorporating demographic and echocardiographic parameters, which can assist in optimizing therapeutic decision-making [25]. Additionally, heart rate variability has been explored as an early indicator of

cardiotoxicity, with evidence suggesting that reductions in variability may precede measurable changes in left ventricular ejection fraction. Taken together, these studies highlight the substantial promise of multimodal predictive frameworks, particularly those enhanced by AI, for the early identification of CTRCD and the implementation of tailored cardiac monitoring strategies in oncology patients.

Other tools for evaluating heart failure risk aim to combine various clinical and demographic factors into an overall risk estimate; however, the best approach to predicting heart failure in cancer survivors remains unresolved. The HFA-ICOS score, developed by the Heart Failure Association in collaboration with the International Cardio-Oncology Society, is currently the only HF risk assessment tool specifically designed for adults with cancer. It incorporates variables related to cancer and its treatment, but since it was created for use at the start of chemotherapy, its effectiveness in predicting HF events in routine primary care or over long-term follow-up is still uncertain [26,27]. In general, non-cancer populations have relied on risk scores such as the ARIC-HF (Atherosclerosis Risk in Communities) and the modified Pooled Cohort Equations to Prevent Heart Failure (PCP-HF) to anticipate incident HF [26,27]; however, their accuracy and applicability in cancer survivor populations have not yet been fully determined. In comparative analyses, both HFA-ICOS and ARIC-HF demonstrated superior performance relative to PCP-HF across cancer and non-cancer cohorts, although all three instruments exhibited only modest discriminative ability for incident heart failure in clinical practice. This highlights the potential value of a cancer-specific heart failure risk assessment tool, which could improve early identification of high-risk individuals and support targeted preventive strategies among cancer survivors [28].

In our study, the model integrated variables from clinical, serological, and instrumental diagnostic domains. The model was constructed employing SHAP analysis, which prioritizes variables based on their relative contribution to the model's performance. Such an approach can be incorporated into existing medical systems to automatically estimate patient status regarding the risk of therapy-related cardiac dysfunction, potentially guiding clinical interventions. The model's multivariate design effectively supports binary prediction, determining the potential occurrence of the adverse event. Its clinical integration allows early identification of patients undergoing antitumor therapy who may develop CTRCD. This strategy enables early and targeted intervention, optimizing both clinical monitoring and resource allocation.

5. Limitations

The study may be affected by unaccounted interactions between different chemotherapy regimens due to the limited sample size, which could influence outcomes. Additionally, the impact of cardiovascular risk factors on CTRCD development might be underestimated. The lack of comparison with healthy controls or non-CTRCD patients limits the contextual understanding of therapy-related cardiac effects. Future studies with larger cohorts and stratified analyses are needed to address these issues. One limitation of this study is the moderate class imbalance between patients with and without CTRCD (18 of 127, $\approx 14\%$). Although this proportion does not represent an extreme imbalance ($<10\%$), it may still bias model performance. The limited number of positive cases can restrict the model's ability to learn discriminative patterns for CTRCD and may lead to optimistic overall accuracy but reduced sensitivity for the minority class.

Author Contributions: Conceptualization, D.B.; data curation, D.B. and G.M.; formal analysis, D.B. and V.I.; investigation, D.B., M.R. and V.O.; methodology, D.B. and O.A.; resources, V.R., V.O. and R.B.; supervision, V.R.; visualization, D.B. and V.R.; writing—original draft, D.B. and V.I.; Writing—

review and editing, D.B. and R.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the State University of Medicine and Pharmacy “Nicolae Testemitanu” (approval number 7/28 December 2021).

Informed Consent Statement: Informed consent was obtained from all the subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: The authors thank their department for the support in this research.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ABPM	ambulatory blood pressure monitoring
ARIC-HF	Atherosclerosis Risk in Communities—Heart Failure
AUC	area under the curve
BMI	body mass index
CI	confidence interval
CKD	chronic kidney disease
CO ₂	carbon dioxide
COP	cyclophosphamide, vincristine, prednisone
CPET	cardiopulmonary exercise testing
CTRCD	cancer therapy-related cardiac dysfunction
ECG	electrocardiogram
HER2	human epidermal growth factor receptor 2
HFA-ICOS	Heart Failure Association—International Cardio-Oncology Society
IQR	interquartile range
LVEF	left ventricular ejection fraction
NHL	non-Hodgkin lymphoma
OUES	oxygen uptake efficiency slope
PCP-HF	Prediction of Cardiovascular events in Primary Care—Heart Failure
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
R-COP	rituximab, cyclophosphamide, vincristine, prednisone
RER	respiratory exchange ratio
ROC	receiver operating characteristic curve
SDANN	standard deviation of the averages of NN intervals
SDNN	standard deviation of all normal-to-normal intervals
SDNNi	standard deviation of the normal-to-normal intervals index
SHAP	Shapley additive exPlanations analysis
VCO ₂	volume of carbon dioxide
VE/VCO ₂	ventilatory equivalent for carbon dioxide
VO ₂	volume of oxygen
VO ₂ peak	peak oxygen uptake
VO ₂ pulse	volume of oxygen per heart rate
VO ₂ /WR	volume of oxygen per work rate

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Article

Mitral Annular Disjunction and Arrhythmic Risk: Case Series and State of the Art

Marisa Varrenti ^{1,*}, Eleonora Bonvicini ², Leandro Fabrizio Milillo ¹, Iaria Garofani ^{1,3}, Lorenzo Gigli ¹, Matteo Baroni ¹, Alberto Preda ¹, Marco Carbonaro ¹, Roberto Menè ¹, Giulia Colombo ¹, Antonio Frontera ¹, Raffaele Falco ¹, Federica Giordano ¹, Sara Vargiu ¹, Fabrizio Guarracini ¹, Patrizia Pedrotti ¹, Cristina Giannattasio ^{1,3} and Patrizio Mazzone ¹

¹ De Gasperis Cardio Center, Niguarda Hospital, 20162 Milan, Italy; leandrofabrizio.milillo@ospedaleniguarda.it (L.F.M.); ilaria.garofani@ospedaleniguarda.it (I.G.); raffaele.falco@ospedaleniguarda.it (R.F.)

² Department of Cardiology, Santa Chiara Hospital, 38122 Trento, Italy

³ School of Medicine and Surgery, University of Milano-Bicocca, 20126 Milan, Italy

* Correspondence: marisa.varrenti@ospedaleniguarda.it

Abstract

Background: Mitral annular disjunction (MAD) is an anatomical abnormality associated with an increased risk of major arrhythmic events, regardless of the presence of mitral valve prolapse. Cardiac magnetic resonance (CMR) plays a key role in diagnosing MAD and identifying myocardial fibrosis, a marker of arrhythmic vulnerability. **Aim:** This study reports the experience of the De Gasperis Cardiology Centre at Niguarda Hospital (Milan, Italy) in managing high-risk MAD patients who underwent implantable cardioverter-defibrillator (ICD) implantation and describes their main clinical characteristics. **Methods:** Between January 2020 and April 2025, five patients with MAD who received ICDs were identified and monitored remotely. Although the small sample size limits generalizability, the objective was to characterize factors associated with arrhythmic susceptibility. **Results:** Four patients exhibited documented ventricular arrhythmias: two with non-sustained and two with sustained ventricular tachycardia. Notably, CMR did not reveal myocardial fibrosis in two symptomatic cases, suggesting that arrhythmic vulnerability may precede detectable structural abnormalities. The observed coexistence of MAD with arrhythmogenic cardiomyopathies and channelopathies underscores the relevance of comprehensive genetic evaluation in these patients. **Conclusions:** MAD should be considered a potential arrhythmogenic substrate rather than a benign anatomical variant. A multimodal diagnostic approach and individualized risk stratification—potentially integrating genetic findings—are essential for optimal patient management.

Keywords: mitral; annular disjunction; arrhythmic risk; sudden cardiac death; case reports

1. Introduction and Definition

In 1981 Bharati et al. [1] performed histological identification and description of mitral annular disjunction (MAD) as “the mitral valve anchored completely on the atrial side with an elongated annulus in a floppy mitral valve”. In 1986, Hutchins et al. [2] described a separation between the left atrioventricular junction and the left ventricular (LV) free wall in a cohort of patients using the term ‘disjunction’, which was also observed in normal hearts. In contemporary medical literature, the term “mitral annular disjunction (MAD)” is defined as a separation between the mitral valve (MV) annulus and the left ventricle (LV)

myocardium. This condition is distinguished from “pseudo MAD,” a condition in which the MV leaflet is in close proximity to the atrial wall, resulting in a similar appearance without the presence of a distinct separation between the atrioventricular junction and the LV myocardium. Pseudo MAD is most often observed in diastole, when the measured distance may appear increased despite the absence of true disjunction. Unlike MAD, pseudo-MAD is not associated with significant leaflet prolapse or curling, and it shows no correlation with late gadolinium enhancement (LGE) or myocardial fibrosis. Historically, MAD has been regarded as an uncommon occurrence. However, recent studies utilizing the analysis of cardiac magnetic resonance (CMR) or computer tomography (CT) images demonstrated a prevalence of MAD reaching up to 96% in the general population [3,4].

Mitral valve prolapse (MVP) has been identified as the most prevalent valve condition in Western countries [5]. It is characterized by the displacement of the leaflets in the left atrium during systole, with fibro myxomatous degeneration and fibroelastic deficiency being the most frequent responsible alterations. With the exception of cases of mitral regurgitation (MR) and left ventricular (LV) modifications, mitral valve prolapse (MVP) has a predominantly favourable outcome. Nonetheless, the likelihood of sudden cardiac death (SCD) in patients with mitral valve prolapse (MVP) has been estimated to be 1.75–2.3 times higher than in the general population [6]. In a recent study, the yearly incidence of severe ventricular arrhythmias (VAs) was approximately 4% in patients with MVP and no previous severe events [7,8], but only a small number of cases have been linked to poor prognosis [9].

The identification of a MVP phenotype associated with an increased risk of VAs has been proposed. This phenotype is characterized by mitral annular disjunction (MAD), which has been demonstrated to be one of the strongest arrhythmic risk factors [9].

The presence of left ventricular wall myocardial fibrosis, as documented on cardiac MRI, is another key factor in determining arrhythmic risk in patients with MVP. A study of 474 patients with MVP demonstrated that the presence of myocardial fibrosis predicts major events such as syncope, sustained ventricular tachycardia, and sudden cardiac death. In reference to the presence of MAD, Figliozzi et al. demonstrate how, with comparable documentation of MAD in the two groups with LGE+ vs. LGE−, the length of MAD was greater in patients with LGE+, hypothesizing that this feature may impact the occurrence of fibrosis and thus increased arrhythmic risk [10,11].

The correlation between MVP and MAD is unclear. The prevalence of MAD in patients with MVP varies between 16% and 32.6% [9,12–15] and the prevalence of MVP in patients with MAD is 78% [16]. Although MAD in MVP is a recognized risk factor for ventricular arrhythmias, the exact correlation between MVP, MAD and arrhythmias remains a point of discussion. Indeed, while Verhulst et al. [17] demonstrated that mitral valve abnormalities increase the arrhythmic risk in MAD patients, Dejgaard et al. [16] identified an independent correlation between MAD and more severe arrhythmias in patients with MAD but without MVP. However, it has been noted that ventricular arrhythmias increase over time in MAD patients, and mortality does not increase in the first 10 years after diagnosis, but only when VAs are detected [9].

In 2022, the European Society of Cardiology published a consensus document defining Arrhythmogenic Mitral Valve Prolapse (AMVP) as MVP (with or without MAD) combined with frequent and/or complex ventricular arrhythmia in the absence of any other well-defined arrhythmic substrate (e.g., primary cardiomyopathy, channelopathy, active ischemia, or ventricular scarring due to another defined etiology), regardless of mitral regurgitation severity.

It is currently recognized that MAD may be preceded by phenotypes not yet associated with overt arrhythmias, but which are considered ‘at risk’ of developing malignant arrhythmias [5].

This study reports the experience of the De Gasperis Cardiology Centre at Niguarda Hospital (Milan, Italy) in managing patients diagnosed with mitral annular disjunction (MAD) who were considered at high risk for arrhythmias and underwent implantable cardioverter–defibrillator (ICD) implantation. The aim was to describe the clinical and individual characteristics of this patient population. Table 1 shows the main characteristics of the clinical cases reported below.

Table 1. Main Characteristics of Patients with Mitral Annular Disjunction (MAD) and High Arrhythmic Risk.

Age	Gender	Symptoms	ECG	Arrhythmias	CMR	MVP	Mitral Regurgitation	LVEF	Therapy	EPS
50	M	Pre-Syncope after exercise		SVT	- 4 mm MAD - No fibrosis	Present	MODERATE	55%	Bisoprolol	Performed, negative
58	M	Syncope	Negative T waves in inferior leads	- NSVT	- 5 mm MAD - No fibrosis	Present	MILD	55%	No	Not performed
43	F	-	- Low peripheral voltages - Negative T waves in inferior leads	- NSVT	- 7 mm MAD - Infero-lateral papillary muscle LGE	Present	MILD	44%	Bisoprolol	Not performed
34	F	-	Spontaneous type 1 Brugada pattern	- None	- 6 mm MAD - 4 mm TAD - Posterior medial papillary muscle LGE	Present	MILD	55%	No	Performed, positive for VF
70	M	-		- SVT	- 8 mm MAD - Septal LGE	Present	MILD	50%	No	Performed, Negative

CMR = Cardiac Magnetic Resonance, SVT = Sustained Ventricular Tachycardia, NSVT = Non-Sustained Ventricular Tachycardia, VF = Ventricular Fibrillation, MAD = Mitral Annular Disjunction, TAD = Tricuspid Annular Disjunction, LGE = Late Gadolinium Enhancement, EPS = Electrophysiological Study, MVP = Mitral Valve Prolapse, LVEF = Left Ventricular Ejection Fraction.

Patients were identified through the institutional database of individuals who received ICD implantation between January 2020 and April 2025 and were subsequently followed up via the remote monitoring system of the Electrophysiology Department of our Centre.

2. Case Series

2.1. Case 1

A 50-year-old male patient with no significant comorbidities and no family history of sudden cardiac death or cardiovascular disease presented with a pre-syncope episode during exertion in January 2023.

A 24 h Holter ECG revealed rare single monomorphic ventricular extrasystoles and three runs of non-sustained ventricular tachycardia (NSVT) lasting up to four beats. A transthoracic echocardiogram was performed, which revealed mild to moderate mitral regurgitation, with biventricular systolic function found to be at the lower limits of normal. He underwent an exercise test, which was interrupted at 83% of the maximum theoretical frequency due to the onset of asymptomatic ventricular bigeminy, which regressed spontaneously during recovery. Cardiac magnetic resonance imaging (MRI) showed mitral valve prolapse, with 4 mm MAD and preserved biventricular systolic function (Figure 1). No evidence of enhancement, edema or areas of fat replacement was observed. The patient was initiated on beta-blocker therapy (bisoprolol 1.25 mg/day), which effectively controlled symptoms until May 2024, when the patient experienced recurrent exertional pre-syncope without angina or palpitations. A physical examination was conducted, which revealed adequate hemodynamic compensation. However, electrocardiographic (ECG) analysis revealed sinus bradycardia, with indications of early left ventricular overload and QRS

fragmentation in leads D3 and aVF. As recorded in the 24 h Holter monitoring results, two episodes of rapid monomorphic ventricular tachycardia were documented, with each episode lasting approximately 25 s. These episodes were found to correlate with symptomatic presyncope. The patient was subsequently admitted for coronary angiography, a procedure which ruled out the presence of coronary artery disease. Echocardiography revealed that the biventricular function had been preserved, and this finding confirmed the presence of mild-to-moderate mitral regurgitation, which was due to anterior mitral valve prolapse. Due to the considerable ventricular arrhythmic burden, the patient underwent catheter ablation targeting the arrhythmic focus originating from the anterolateral papillary muscle (Figure 2), followed by implantation of an extracardiac implantable cardioverter-defibrillator (ICD). There were no defibrillator interventions and no significant arrhythmic recurrences in the annual follow-up.

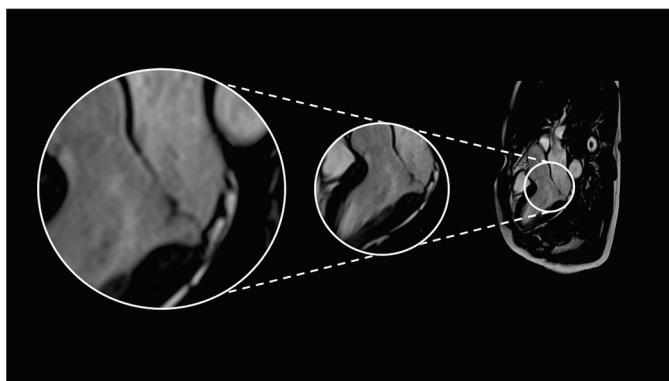


Figure 1. Cardiac magnetic resonance imaging (long-axis three-chamber view) demonstrates mildly redundant, prolapsing mitral-valve leaflets with a mitral annular disjunction (MAD) measuring 4 mm. Cine CMR sequences further reveal curling of the basal inferolateral and anterolateral left-ventricular walls, accompanied by mild mitral regurgitation.

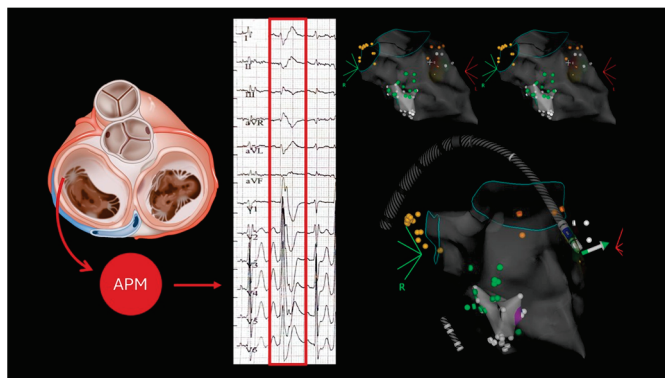


Figure 2. Surface ECG analysis suggested a probable origin of the clinical ventricular ectopy from the anterolateral papillary muscle (ALPM). A combined retrograde transaortic and transseptal approach was used to access the left ventricle. During electroanatomical mapping, mechanically induced premature ventricular contractions (PVCs), showing a morphology consistent with the clinical pattern (positive concordant right bundle branch block and intermediate axis), were observed, confirming the ALPM as the site of origin. Radiofrequency catheter ablation (RFCA) was successfully performed at this location via the retrograde aortic route, resulting in resolution of the PVCs.

2.2. Case 2

The second case concerns a 58-year-old male patient. The patient's medical history included systemic arterial hypertension, type II diabetes mellitus, a body mass index in the overweight category, a previous deep vein thrombosis of the right upper limb with MTHFR mutation, and hyperhomocysteinemia. In the absence of prodromal symptoms, a syncopal

episode was experienced, subsequently accompanied by palpitations and dizziness. The patient presented to the emergency department. The electrocardiogram (ECG) revealed symptomatic non-sustained ventricular tachycardia (NSVT) (heart rate (HR) 300 beats per minute (bpm), duration 8 s) with inverted T waves in leads DIII and aVF. A detailed echocardiographic examination revealed mild mitral valve prolapse, with the potential for MAD. Following the attainment of arrhythmic stability, a coronary angiogram was conducted, which revealed the absence of coronary artery disease. Cardiac magnetic resonance imaging revealed normal biventricular size and function, confirming MAD measuring 5 mm in the inferior region without associated prolapse. The evaluation for myocardial edema, fatty infiltration, and fibrosis yielded negative results. Consequently, a defibrillator was implanted, and beta-blocker therapy was initiated.

2.3. Case 3

The third case concerns a 43-year-old female patient with a medical history of essential thrombocythemia, who was treated with acetylsalicylic acid. A recent cardiological evaluation revealed frequent ventricular extrasystoles (11,000 in 24 h), primarily isolated but occasionally occurring in pairs or triplets. Echocardiography revealed a left ventricle that was above the upper limits of normal size, indicating left ventricular dysfunction due to diffuse hypokinesia. Additionally, mild mitral regurgitation was observed, attributed to prolapse. In contrast, the right heart chambers were found to be within normal limits. The therapeutic approach was initiated with a dosage of metoprolol 50 mg administered twice daily. A cardiac MRI was performed, which documented mild LV dilatation (DTD 61 mm, VTD 94 mL/m²) with preserved wall thickness, except for the mid-apical lateral wall, which appeared dyskinetic and thinned. Septal dyssynchrony was also noted, with an ejection fraction of 41%. No late gadolinium enhancement (LGE) indicative of myocardial fibrosis was detected. STIR sequences were negative, ruling out the presence of myocardial edema, and both T1 and T2 mapping values were within normal limits, suggesting the absence of active inflammation. A mild pericardial effusion was also observed. Furthermore, the right ventricle exhibited mild dysfunction, characterized by an ejection fraction of 44%. The findings, when considered collectively, suggest a picture consistent with dilated cardiomyopathy.

A 24 h Holter ECG was conducted, which confirmed a high ventricular arrhythmic burden. This included 19,759 polymorphic ventricular ectopic beats (18.5%), comprising 715 couplets and 6 triplets. The baseline ECG exhibited sinus rhythm at a rate of 61 beats per minute (bpm), with a PQ interval of 178 milliseconds (ms). The QRS voltages in all peripheral leads were low, with fragmentation observed in leads D3, aVL, and aVF (in the inferior-lateral region). In contrast, the voltages in the precordial leads remained stable, and the QRS duration fell within the normal range. The presence of negative T waves in the inferior leads, in conjunction with biventricular bigeminy exhibiting right bundle branch block morphology, was duly noted. The medical therapy was intensified with the addition of eplerenone and dapagliflozin.

The patient was admitted for further diagnostic procedures. A subsequent cardiac MRI revealed a mild reduction in biventricular systolic function, mild mitral regurgitation due to valve prolapse, and mitral annular disjunction (MAD) measuring 7 mm. Late gadolinium enhancement (LGE) was observed at the apex of the inferolateral papillary muscle.

Due to the ventricular arrhythmic profile exhibited by the patient, who was diagnosed with cardiomyopathy in conjunction with mitral valve prolapse and MAD, in addition to the presence of left ventricular free wall (LGE) involving the inferolateral papillary muscle, the

decision was to proceed with the implantation of an implantable cardioverter–defibrillator (ICD) as a primary prevention measure.

2.4. Case 4

The fourth case refers to a 34-year-old female patient who was referred following the electrocardiographic detection of a type 1 Brugada pattern during a period of hospitalization for fever and chest pain. The echocardiogram revealed a normal left ventricle size, kinesis, and biventricular systolic function, accompanied by mild atrioventricular valve insufficiency. The ECG findings were used to inform genetic testing, which revealed the p.51573G variant in the SCN5A gene. This variant was also identified in both the father and son. An endocardial electrophysiological study (EPS) was conducted, which revealed ventricular fibrillation (drive 500 ms, double extrastimulus at 220 ms). The ventricular fibrillation was effectively cardioverted with a single DC shock at 200 J.

Subsequent cardiac magnetic resonance imaging revealed normal cavity dimensions and preserved global biventricular systolic function. No evident areas of myocardial edema or adipose infiltration were detected. The mitral valve leaflets appeared slightly redundant and prolapsed, with a 6 mm MAD, accompanied by curling of the basal segments of the inferolateral and anterolateral walls of the left ventricle, and mild mitral regurgitation. Subsequent to the administration of contrast media, subsequent imaging revealed focal enhancement lesions in the posteromedial papillary muscle. Furthermore, tricuspid annular disjunction (TAD) measuring 4 mm was observed.

In view of the results of the electrocardiogram (ECG) and the patient's clinical history, an extravascular implantable cardioverter–defibrillator (ICD) was implanted (see Figure 3).

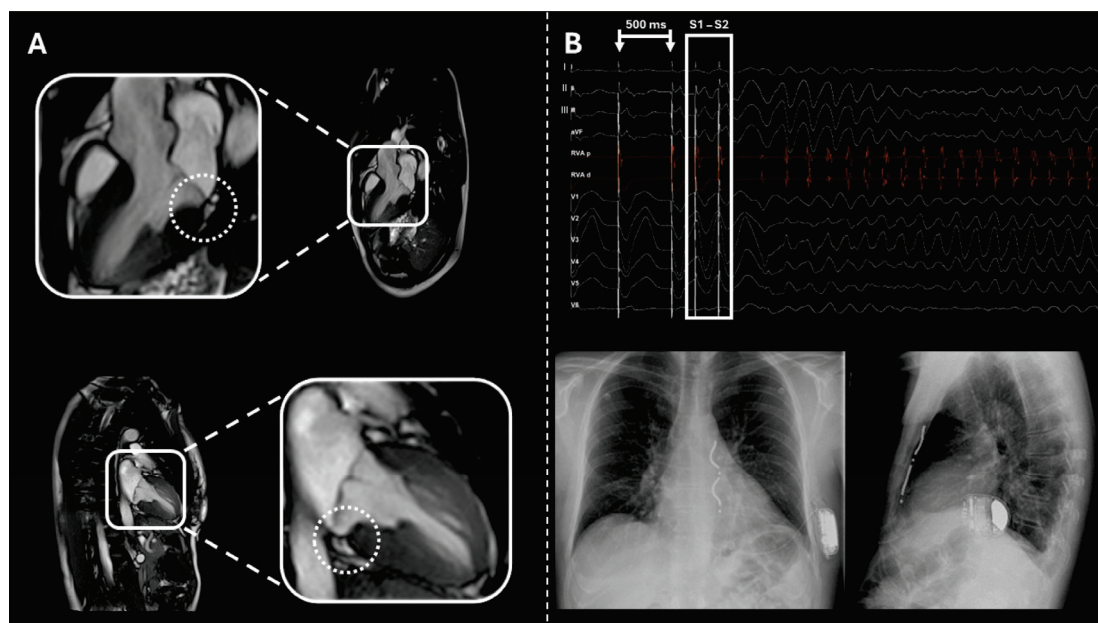


Figure 3. (A) Cardiac magnetic resonance imaging in the three-chamber view (upper panel) and two-chamber view (lower panel) demonstrating a mitral annular disjunction (MAD) measuring 6 mm, evident as a separation between the posterior mitral annulus and the basal inferolateral left ventricular myocardium during systole. (B) Upper section: Intracardiac electrophysiological study performed using a drive train of 8 stimuli at a cycle length of 500 ms, followed by 2 ventricular extrastimuli (S1–S2) at a coupling interval of 220 ms, resulting in the induction of ventricular fibrillation (VF). The arrhythmia was promptly terminated with a single 200 J external biphasic defibrillation shock, restoring sinus rhythm. Lower section: Anteroposterior and lateral chest radiographic views following implantation of an extravascular implantable cardioverter–defibrillator (EV-ICD), demonstrating appropriate lead and device placement.

2.5. Case 5

The final case involves a 70-year-old male patient with a history of mitral valve prolapse, who was referred to our centre following the completion of a 24 h Holter ECG that documented sustained ventricular tachycardia lasting 42 beats. The diagnosis of coronary artery disease was excluded by coronary CT. Cardiac magnetic resonance imaging revealed mitral valve prolapse associated with an 8 mm MAD and intramyocardial late gadolinium enhancement in the mid-basal septum. The patient was then admitted for defibrillator implantation in prevention of sudden cardiac death.

3. Discussion

We selected five cases of patients with mitral annular disjunction (MAD) who underwent ICD implantation. This could be considered a limitation of the study; however, our aim was to describe cases with a high arrhythmic risk in order to analyze their characteristics and identify factors contributing to increased arrhythmic vulnerability.

The presence of MAD—whether or not associated with mitral valve prolapse, myocardial fibrosis, or electrocardiographic abnormalities—was found to significantly influence arrhythmic risk and, consequently, the decision regarding protection from sudden cardiac death.

The documentation of ventricular arrhythmias is a recognized risk factor for major arrhythmic events and supports the identification of patients who may benefit from preventive strategies against sudden cardiac death. In our case series, four out of five patients had documented arrhythmias: two with non-sustained ventricular tachycardia and two with sustained ventricular tachycardia.

Baseline ECG abnormalities also appear to be useful for arrhythmic risk assessment in patients with MAD. In two of the five cases, the patients demonstrated negative T waves in the inferior leads. Although not always correlated with fibrosis, these findings may help identify patients requiring closer clinical follow-up.

Cardiac magnetic resonance imaging (CMR) plays a key role in detecting myocardial fibrosis, which is associated with increased arrhythmic risk. However, no fibrosis was observed in the first two cases despite the presence of syncope-inducing symptoms. This suggests that arrhythmic risk may precede the phenotypic expression of myocardial stress, as evidenced by fibrosis.

Moreover, the correlation between MAD and cardiomyopathies with an arrhythmic phenotype—as well as channelopathies, exemplified by the case of a young female patient without fibrosis—highlights the need for comprehensive genetic evaluation in this population. Current knowledge in this field remains limited, emphasizing the importance of further research.

3.1. Mechanisms of Arrhythmias

The presence of MAD has been shown to result in excessive mobility of the mitral annulus, which in turn leads to an abnormal systolic curling of the myocardium in the posterior mitral ring [18]. This process is likely to cause isolated and asymmetrical left ventricular (LV) hypertrophy, which is localized in the basal inferolateral segment [19]. The phenomenon of hypertrophy of the papillary muscles (PMs) has also been documented, a likely consequence of altered mechanical load and forces acting upon them [19]. Increased wall stress in this region has been observed to result in repetitive microtrauma and subsequent fibrotic replacement, as evidenced by histological studies and LGE on CMR imaging in vivo subjects [20]. This fibrotic substrate has been shown to be proarrhythmic [21], and the associated mechanical stretch of the mitral annulus may facilitate the development of ventricular arrhythmias. Fibrosis has been shown to induce repolarisation abnormalities,

while mechanical stretch has been demonstrated to shorten the action potential duration and lower the resting diastolic potential. This, in turn, has been shown to promote early after-depolarisations and triggered activity [22]. Mechanical stretching of cardiac cells activates stretch-activated channels (SACs), which are voltage-sensitive ion channels permeable to cations such as Na^+ , Ca^{2+} , and K^+ . Activation of SACs can depolarize the cell membrane, increasing cellular excitability. This depolarization can lead to a shortening of the action potential duration (APD) and a reduction in the diastolic resting potential. These electrophysiological changes enhance the likelihood of abnormal electrical activity, thereby promoting arrhythmogenesis [23]. It is important to consider that not all MAD cases are associated with fibrosis [9], suggesting that the development of tissue alterations and consequently the arrhythmic risk may be progressive.

3.2. Arrhythmic Risk Stratification

In patients diagnosed with MVP, the stratification of arrhythmic risk has been a subject of extensive debates, with the aim of identifying patients who are at elevated risk of SCD. While it is widely accepted that MAD is a significant arrhythmic risk factor in patients with MVP, the precise stratification of arrhythmic risk in MAD patients with or without MVP remains a subject of ongoing research.

The existing literature suggests that younger age is associated with an increased risk of arrhythmia in MAD [16], the role of female sex as a predictor factor remains a subject of debate [20,24]. Furthermore, presyncope and unexplained syncope have been identified as indicators of patients with a higher arrhythmic risk in comparison to isolated palpitations and asymptomatic status [16,25].

Electrocardiography and ambulatory ECG monitoring are recognized as essential tools for arrhythmic risk stratification. Abnormal repolarisation, consequent to unbalance forces that act upon the myocardium and PMs, is revealed on the surface ECG through T wave inversions (TWI) or biphasic T waves, predominantly in the inferior and lateral leads. These have been demonstrated to be independently associated with malignant arrhythmias [6,9]. In our case series, two patients demonstrated inferior T-wave inversions on baseline ECG. In one patient, cardiac MRI additionally revealed evidence of myocardial fibrosis, whereas the other showed no such findings. Both patients had documented TVNS on ECG monitoring. Of note, one of these patients was symptomatic with syncope.

However, it should be noted that not all reports concur with this assertion, and the existence of a direct association with increased mortality remains a subject of debate [20]. Finally, Kaya et al. [26] proposed that fragmented QRS could predict VAs in MVP patients, although further data are needed to validate this hypothesis. Premature ventricular contractions (PVCs) and non-sustained ventricular tachycardia (NSVT) originating from the PMs, the mitral annulus and the basal portion of the left ventricle (LV) are frequently observed. Although a history of NSVT is associated with increased arrhythmic risk, the question of whether the burden of PVCs has the same prognostic value remains the subject of debate [16,27].

Multimodality imaging, incorporating echocardiography and CMR, is of crucial importance in the diagnosis and risk stratification of this disease. In the domain of 2D echocardiography, MAD is typically identified and quantitated in the parasternal long-axis view during the late systolic phase of the cardiac cycle. CMR is also useful for a more detailed characterization of the extension and localization of the MAD and overall for the differential diagnosis with pseudo-MAD. It is imperative that both imaging techniques are employed in order to assess the dimensions and function of the left ventricle (LV), the size of the left atrium (LA), the morphology of the mitral valve, and the degree of mitral regurgitation. The accurate evaluation of the extension and localization of MAD has been

demonstrated to have a major impact on arrhythmic risk stratification. In two cohorts of idiopathic ventricular fibrillation (IVF) patients [17,28], inferolateral MAD was observed to be significantly more prevalent than other localizations. In such cases, the length of the MAD did not demonstrate a correlation with the risk of arrhythmia. However, Carmo et al. [29] found that a MAD length greater than 8.5 mm was able to predict NSVT. The present findings are consistent with those reported in other studies [3,15]. Associations between MAD length, myocardial fibrosis, and cardiac death have also been described [19].

Myocardial fibrosis, secondary to mechanical stress, has been proposed as a predictor of arrhythmic risk. LGE on CMR, an indirect marker of fibrosis, has typically been identified as patchy areas in the infero-basal LV and mid-wall of the PMs [15]. Perazzolo Marra et al. [19] reported that LGE is more frequently present in patients with MAD than in those with isolated MVP, and that it increases with the length of MAD [10]. Several studies have confirmed the association between LGE and ventricular arrhythmias in MVP patients [10,11,30], although data on isolated MAD remain limited [9,16,31]. However, research has demonstrated that arrhythmia focuses in MAD are known to originate from fibrotic areas [19,20]. The hypothesis that T1 mapping may have a role in arrhythmic stratification in MVP has been advanced [30]. Moreover, recent data suggest a potential link between basal inferolateral hypertrophy and an elevated risk of SCD [32].

In addition to myocardial modifications, the presence of MAD and MVP has been linked to electromechanical dyssynchrony. The calculation of left ventricular mechanical dispersion (MD) through strain analysis has been utilized in both ischemic and non-ischemic cardiomyopathies to quantify electromechanical dyssynchrony, and has been demonstrated to correlate with arrhythmic risk [33]. Increased MD has also been found in MVP with increased arrhythmic risk [34], but specific studies for MAD has not been conducted yet. Similarly, post-systolic shortening has been associated with arrhythmogenesis in MVP, though evidence specific to MAD is limited [35].

Although MAD and MVP are likely distinct pathophysiological entities, the two diseases are diagnosed together and MAD has been recognized as the most important predictor of arrhythmic events in MVP. Consequently, when MAD co-exists with MVP, classical MVP-related risk markers must also be taken into account [6,9]. These risk markers include, but are not limited to, bileaflet prolapse, myxomatous degeneration, mitral regurgitation, and LA or LV dilation.

Dejgaard et al. [16] observed that MVP patients with MAD may have less severe arrhythmias, potentially due to earlier diagnosis and treatment compared to isolated MAD cases.

It has been hypothesized that a genetic predisposition may underlie non-syndromic MVP [36,37]. However, the correlation between MAD and genetically determined arrhythmic predisposition remains hypothetical [2]. Furthermore, the assessment of biomarkers has not yet yielded results in this regard. Given the heterogeneity of MAD manifestations—ranging from incidental findings without fibrosis or ventricular arrhythmias to overlapping channelopathies or cardiomyopathies—a pragmatic, multimodal risk assessment is warranted. Clinicians should begin with a detailed history of symptoms, focusing on palpitations, syncope, or exercise intolerance. This should be complemented by a 12-lead ECG and an extended Holter monitor or implantable loop recorder to evaluate the burden of PVCs, polymorphic ectopy, or nonsustained ventricular tachycardia. Echocardiography remains essential for assessing MVP, leaflet redundancy, and the presence of MAD, while cardiac magnetic resonance imaging (CMR) adds further value by quantifying the extent of MAD and identifying both the presence and degree of fibrosis. A family history of sudden cardiac death or inherited arrhythmic syndromes should prompt heightened vigilance. Taken together, these data points can be integrated into a practical risk profile (see Figure 4):

- Low risk: asymptomatic, short MAD segments, no arrhythmia.
- Intermediate risk: MAD with mild arrhythmic expression.
- High risk: syncope, complex ventricular arrhythmias, or extensive LGE.

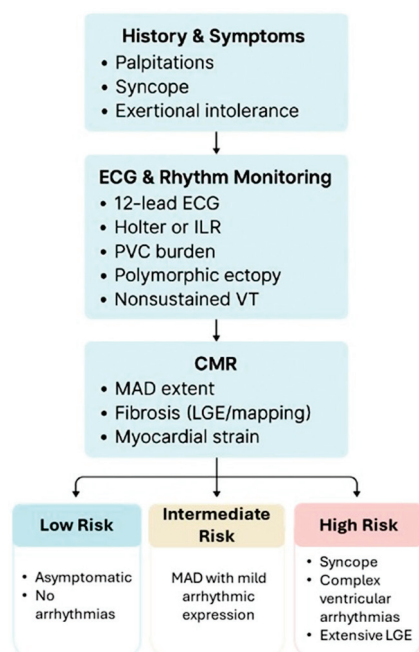


Figure 4. Possible flow chart for arrhythmic risk stratification in patients with MAD.

Further research is needed on this topic, particularly to clarify the genetic aspects in this group of patients.

3.3. Therapeutic Considerations

The current literature on arrhythmia management, especially in patients with MVP, is limited, and information regarding patients with MAD is extremely limited. While pharmacological therapy has been shown to alleviate symptoms and improve quality of life, there is no evidence to suggest that it has an impact on mortality [27]. Of all the anti-arrhythmic drugs, flecainide has produced encouraging results [7]. Current ESC guidelines for ventricular arrhythmias recommend ICD implantation for primary and secondary prevention [38], have suggested that ICD implantation should be considered for MVP patients presenting with unexplained syncope and non-sustained ventricular tachycardia (NSVT) likely arising from the mitral apparatus, or for patients presenting with unexplained syncope or NSVT and exhibiting two or more phenotypic risk features (e.g., T wave inversion in the inferior leads, repetitive polymorphic premature ventricular complexes (PVCs), MAD, redundant mitral valve (MV) leaflets, an enlarged left atrium, an ejection fraction of $\leq 50\%$, or late gadolinium enhancement (LGE) within the mitral apparatus. Catheter ablation is also performed according to general guidelines for ventricular arrhythmias [38]. Specific data on VA ablation in MAD are currently lacking. However, a case series involving 14 patients with mitral valve prolapse (MVP) who underwent catheter ablation reported a procedural success rate of 98% [39]. Surgical correction of severe mitral regurgitation (MR) has been shown to restore life expectancy in patients without VAs and reduce VAs in patients with MVP [9,24]. However, it is unclear whether this correction alone is sufficient to eliminate the need for ICD implantation in patients with arrhythmia.

4. Conclusions

It is evident that prospective studies incorporating larger case series are imperative to further delineate the arrhythmic risk in patients with MAD, with or without concomitant mitral prolapse, with the objective of identifying those who are predisposed to major arrhythmic events.

In conclusion, MAD should be regarded not only as an anatomic variant but also as a potential arrhythmogenic heart disease that necessitates multimodal evaluation and individualized risk assessment. A more comprehensive understanding of its pathophysiology and correlation with possible genetic variants is imperative to enhance patient outcomes through early diagnosis and targeted therapies.

Author Contributions: Data curation and conceptualization, M.V., E.B., S.V., L.G., M.C., A.P. and I.G.; methodology and analysis M.V., M.B. and F.G. (Federica Giordano); software, L.F.M., G.C. and A.F.; validation P.P., C.G. and P.M.; writing—original draft preparation, M.V., E.B. and L.F.M.; writing—review and editing, P.P., C.G., P.M., R.M., F.G. (Fabrizio Guarracini) and R.F.; supervision, P.P., C.G. and P.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Informed consent to participate in the clinical research was obtained from all subjects at admission.

Data Availability Statement: Data are contained within the article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

CMR	Cardiac Magnetic Resonance
EPS	Electrophysiological Study
LGE	Late Gadolinium Enhancement
MAD	Mitral Annular Disjunction
MVP	Mitral valve prolapse
NSVT	Non-Sustained Ventricular Tachycardia
SVT	Sustained Ventricular Tachycardia
VF	Ventricular Fibrillation
TAD	Tricuspid Annular Disjunction

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Article

A Mid-Term Follow-Up in Patients with Symptomatic Moderate to Severe and Severe Degenerative Mitral Valve Regurgitation After Transapical NeoChord Implantation

Argyro Kalompatsou ¹, Dimitris Tousoulis ^{1,*}, Yannis Dimitroglou ¹, Eirini Beneki ^{1,2}, Panagiotis Theofilis ¹, Konstantinos Tsioufis ¹, Constantina Aggeli ¹ and Vasilis Lozos ¹

¹ First Department of Cardiology, “Hippokration” General Hospital, National and Kapodistrian University of Athens, 11527 Athens, Greece; iro.kalompatsou@gmail.com (A.K.); dimiyann@hotmail.com (Y.D.); e.beneki@hotmail.com (E.B.); panos.theofilis@hotmail.com (P.T.); ktsioufis@gmail.com (K.T.); dina.aggeli@gmail.com (C.A.); lozosvasilis@yahoo.com (V.L.)

² Department of Cardiology, Lausanne University Hospital and University of Lausanne, 1011 Lausanne, Switzerland

* Correspondence: drtousoulis@hotmail.com

Abstract

Background: The transapical off-pump NeoChord procedure is a recognized minimally invasive surgical approach for the treatment of severe degenerative mitral regurgitation. This study aims to report the initial Greek experience with the NeoChord procedure, presenting mid-term clinical and echocardiographic outcomes from a single cardiothoracic surgical center, with a median follow-up duration of 20 months. **Methods:** In this study, 42 symptomatic patients with moderate to severe and severe primary mitral regurgitation underwent mitral valve repair with the NeoChord procedure between March 2018 and December 2024. All patients were evaluated clinically and echocardiographically by the Heart team preoperatively, after 1 month, and at the last follow-up (end of 2024). The primary endpoint was established as the presence of a major clinical event (all-cause mortality, re-intervention due to deterioration of MR, and cardiac-related rehospitalization). **Results:** The median age of patients was 69 [61.75–79.25] years, and 69% of patients were men. The median EuroScore II was 1.79 [1.32–2.48], and the STS-PROM MV repair score was 3.18 [2.28–4.66]. Regarding the preprocedural mitral valve anatomical evaluation, 35 patients had type A (83.3%), 4 had type B (9.5%), whereas only two patients had type C and 1 with type D anatomy. The median of LAI was 1.2 [1.15–1.25], whereas the CI was 4 [2.15–5]. More than two neochordae were implanted in 34 patients (81%). MR severity improved at 1-month (<moderate:92.85%) and at the last follow-up (<moderate:92.1%). NYHA class decreased within 1 month (I + II: 95.23%) after the procedure and was maintained at the last follow-up (I + II: 94.73%). The median left ventricular ejection fraction (LVEF) before the procedure was 63 [58–67]%, which significantly decreased to 57 [53–61]% at the 1-month follow-up (2-sided $p < 0.001$). At the final follow-up, LVEF increased to 65 [60–68]%, however, this change was not statistically significant compared to the preprocedural value. During the follow-up period, four deaths were documented—three due to non-cardiac and one attributable to a cardiac cause. Two cases proceeded to reoperation for surgical valve implantation due to recurrent mitral valve regurgitation 6 months and 8 months after the NeoChord procedure. **Conclusions:** Transapical off-pump NeoChord implantation offers a minimally invasive alternative to conventional surgery for symptomatic patients with moderate-to-severe or severe primary mitral regurgitation. Among patients with suitable mitral valve anatomy, the procedure has demonstrated a favorable safety profile and promising mid-term outcomes, in terms of cardiac mortality, as well as freedom from reoperation and rehospitalization.

Keywords: mitral valve repair; NeoChord implantation; primary mitral valve regurgitation

1. Introduction

Mitral regurgitation (MR) is the most common valve disease in the general population. It is divided into primary, which is characterized by lesions of one or more components of the mitral valve (MV) apparatus, or secondary, as a disease of the left ventricle or atrium resulting from an imbalance between closing and tethering forces. According to the European Society of Cardiology (ESC) guidelines [1], patients with severe primary MR should undergo mitral valvuloplasty by an experienced surgical team to keep the integrity of the MV anatomy as well as the subvalvular apparatus. Additionally, MV valvuloplasty should be the first option defined by the Heart Team in cases with high expectations for surgical success and preservation of the results. Mitral valve repair has arisen as the best treatment option for patients with primary MR, due to long-term outcomes, low risk of recurrence and reoperation, and low mortality rate [1,2].

Mitral valve repair mainly consists of annuloplasty, leaflet resection, and prosthetic chordae repair [3]. While surgical mitral valve repair is associated with favorable long-term outcomes, it necessitates thoracotomy and the use of extracorporeal circulation, rendering it a highly invasive intervention. Conversely, minimally invasive interventional repair techniques can be performed on a beating heart without the need for extracorporeal support, thereby reducing surgical trauma and facilitating a more rapid postoperative recovery. For patients with severe primary mitral regurgitation who are deemed ineligible for surgery or present with a high operative risk, transapical mitral valve neochoord implantation under transesophageal guidance provides a safe and effective therapeutic alternative [1,4,5].

The NeoChord transapical off-pump MV repair is an established minimally invasive surgical procedure for reducing MR in patients with favorable MV anatomy [2–9]. The NeoChord procedure was performed using the NeoChord DS1000 Artificial Chordae Delivery System (NeoChord, Inc., St. Louis Park, MN, USA), guided by real-time two-dimensional and three-dimensional transesophageal echocardiographic imaging. By obtaining transapical access, three or more expanded polytetrafluoroethylene (ePTFE) chordae are positioned to the mitral valve. Notably, the accurate positioning, optimal neochoordae length, and appropriate tensioning of the prolapsing leaflets are effectively achieved through three-dimensional transesophageal echocardiographic guidance [3–7].

The study aimed to present the first Greek experience of transapical NeoChord procedure, providing a mid-term follow-up in 20 [11.75–39] months in a single center of cardiothoracic surgery.

2. Materials and Methods

2.1. Patient Population

In the current study, 43 symptomatic patients with moderate to severe and severe degenerative mitral valve regurgitation, who underwent MV repair with the NeoChord procedure at the Hippokration General Hospital of Athens between March 2018 and December 2024, were enrolled. One patient was excluded from the study due to the occurrence of left atrial posterior wall dissection during the procedure. The Surgical Team decided to convert the initial surgical plan to MV replacement, and the procedure was completed successfully [10]. Exclusion criteria included the pleural disease, active endocarditis, coexistence of other valve disease, and unfavorable anatomy of the mitral valve, defined as extensive valve calcification or leaflet perforation [11–14].

2.2. Preoperative Evaluation

All patients underwent preoperative transthoracic echocardiography (TTE) and trans-esophageal echocardiography (TEE) to depict the anatomical data of the mitral valve apparatus. Moreover, the 3D-TEE offered more accurate information regarding the precise anatomy, the origin, and the direction of MR jet(s). The patients' surgical risk was determined using the EuroScore II and the Society of Thoracic Surgeons Predicted Risk of Mortality Mitral Valve repair score (STS-PROM MV repairscore) for mitral valve repair [8,9]. Clinical assessment of patients' symptomatic profile was evaluated with the New York Heart Association (NYHA) functional class grading system. All patients received the optimal guideline-directed medical therapy. The severity and mechanism of MR have been analyzed by TTE and TEE using Philips echo machine EPIQ 7 system (X5-1c, X8-2t probes) (Philips, Eindhoven, The Netherlands). The patient population was categorized based on the preprocedural 3D TEE study of MV morphology:

- Type A, isolated central posterior leaflet prolapse/flail;
- Type B, posterior multi-segment prolapse/flail;
- Type C, anterior or bileaflet prolapse/flail; and
- Type D, paracommissural prolapse/flail, or any disease with significant leaflet/annular calcifications [9].

The most important TEE echocardiographic parameter for patient selection is the leaflet-to-annulus index (LAI) ratio, which comprises the sum of posterior mitral leaflet (PML) and anterior mitral leaflet (AML) lengths divided by the antero-posterior diameter (AP) [(PML + AML):AP]. LAI measurements were obtained during mid-systole at the A2/P2 scallops level, using the mid-esophageal long-axis view. Patients with an LAI greater than 1.2 were considered to have sufficient leaflet tissue to achieve effective coaptation following the repair procedure [10–16]. An LAI value of ≥ 1.2 indicates that the combined leaflet length is approximately 20% greater than the AP. This redundant leaflet tissue serves as a potential coaptation surface, which can be effectively utilized following restoration of posterior leaflet mobility through the NeoChord repair procedure [12]. A value greater than 1.2 has been shown to be significantly correlated, maintaining favorable one-year outcomes [16]. Additionally, the coaptation index (CI) is defined as the ratio of the sum of PML and AML length minus AP divided by 2: $[(PML + AML) - AP]:2$ [11–16]. The coaptation length index is a reliable predictor of sufficient tissue overlap to attain a postoperative coaptation length ranging from 3 to 5 mm. CI value > 5 mm indicates optimal anatomy of the mitral valve and offers supplementary insight into the feasibility and potential success of the technique [14–18].

2.3. Technical Description of NeoChord Implantation

The technical part of the procedure has been described in our previous publication [13]. MV repair was conducted under general anaesthesia via a left minithoracotomy approach, lateral to the apex. The NeoChord device was introduced into the left ventricle (LV) using 3D TEE guidance and the precise leaflet capture as well as the optimization of chordal length was performed appropriately (Figure 1). Procedural success was defined as the implantation of at least two neochordae and the reduction of MR to trivial-mild and mild to moderate at the end of the procedure.

2.4. Post-Procedural Follow-Up of the Study Population

All patients received guideline-directed medical therapy in accordance with the European Society of Cardiology guidelines. Clinical and echocardiographic assessments were performed at 1, 3, 6, and 12 months, and annually thereafter, either at Hippokration Hospital or at another institution based on patient preference. Both the initial and

final follow-up visits were conducted in our department. The median follow-up for the study population was 20 [12–39] months. MR severity was evaluated during follow-up as trivial-mild, mild-moderate, moderate-severe, and severe. The primary endpoint was defined as the occurrence of major clinical events (all-cause mortality, reintervention due to deterioration of MR, and cardiac-related rehospitalizations).

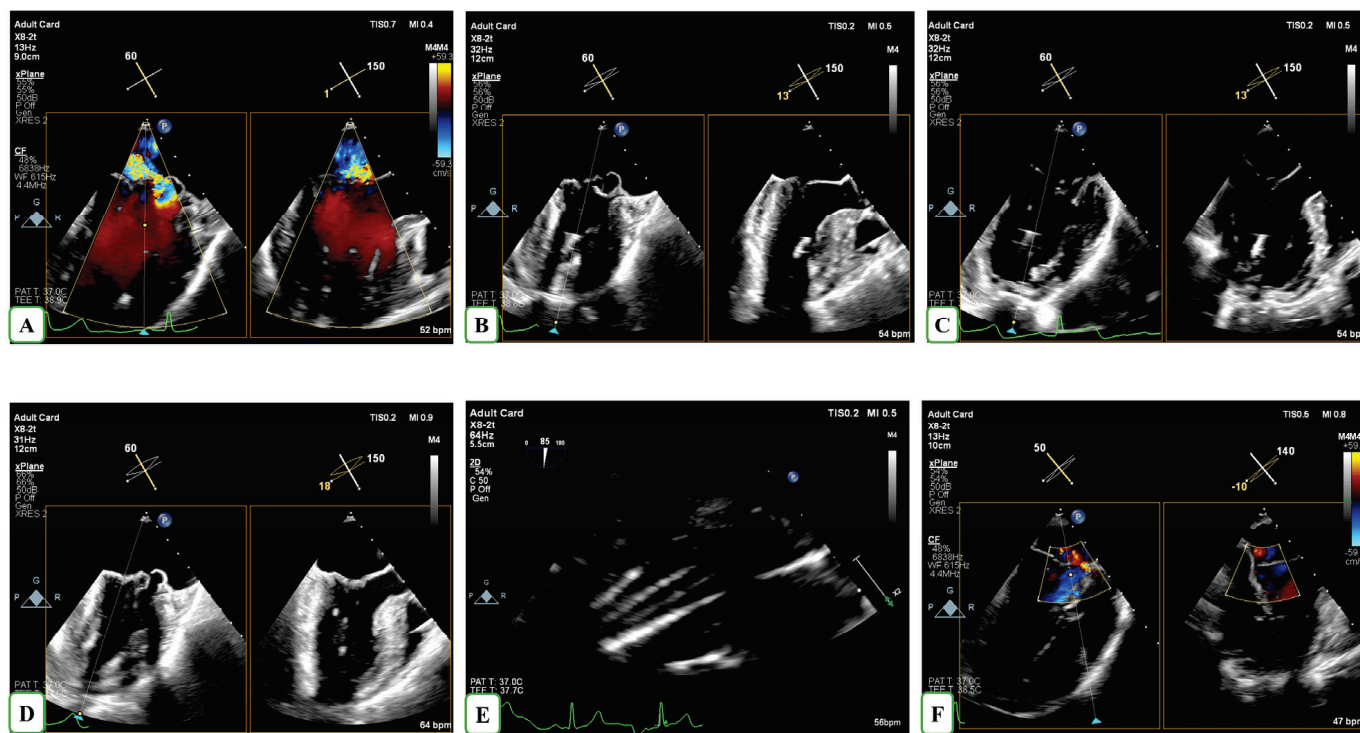


Figure 1. TEE-guided insertion of the NeoChord device through the left ventricular apex in a patient with severe MR (A). The TEE-guided procedure is illustrated in panels (B–D) using X-Plane modality to acquire the bicommissural and 3-chamber views. Four neo-chordae were implanted on the posterior leaflet, as visualized using the transgastric echocardiographic view (E). Color Doppler revealed residual trivial mitral regurgitation following NeoChord implantation (F).

2.5. Statistical Analysis

Data were analyzed using the SPSS software (SPSS, IBM SPSS Statistics, version 29.0.2.0, Armonk, NY, USA). Demographic and baseline variable data are reported as frequency (%), while continuous variables are summarized using medians and interquartile ranges (IQR, 25th to 75th percentiles). Comparisons of continuous variables were performed using the Wilcoxon signed-rank test. For all analyses, a two-sided $p < 0.05$ was statistically significant. We also conducted a post hoc power analysis, which showed that all statistically significant variables achieved a power greater than 0.95. The event-free survival curve was estimated using the Kaplan–Meier method.

2.6. Ethics

Written informed consent was obtained from all participants prior to their inclusion in the study. The research was conducted in full compliance with the ethical principles of the Declaration of Helsinki and followed all institutional guidelines to protect patient confidentiality and ensure data security. The study was approved by the ethical committee of Hippokration General Hospital of Athens (Protocol Code: 22532/19-12-2023, Approval Date: 21 December 2023). The authors declare no conflicts of interest. The study was not supported by any external funding sources that could have affected its design or analysis.

3. Results

The median age of patients was 69 [61.75–79.25] years, and 69% of patients were men. Demographic data were summarized in Table 1. Patient population surgical risk for MV replacement was defined as Euroscore II 1.79 [1.32–2.48] and STS-PROM MV repair score was 3.18 [2.28–4.66]. Eighteen patients had known coronary artery disease, whereas only one patient had had a previous MV valvuloplasty.

Table 1. Demographic and preoperative data of the patient population.

Parameters	Median [IQR] or n (%)
Age, years	69 [61.75–79.25]
Male, n (%)	29 (69)
BMI (kg/m ²)	26 [24.50–27.92]
BSA (m ²)	1.96 [1.82–2.06]
EuroSCORE II (%)	1.79 [1.32–2.48]
STS-PROM MV Repair Score (%)	3.18 [2.28–4.66]
Previous mitral valve surgery, n (%)	1 (2.3)
Know history of CAD, n (%)	18 (42.90)
Dyslipidemia, n (%)	30 (71.40)
Diabetes mellitus type 2, n (%)	8 (19)
Arterial hypertension, n (%)	30 (71.40)
COPD, n (%)	2 (4.80)
AF, n (%)	13 (31)
Smoking, n (%)	16 (38.10)
GFR (mL/min)	70.50 [57.75–83.97]

IQR: InterQuartile range; BMI: body mass index; BSA: body surface area; STS-PROM MV repair Score: Society of Thoracic Surgeons predicted risk of mortality mitral valve repair score; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; GFR: glomerular filtration rate.

The preprocedural anatomical MV parameters are illustrated in Table 2. Most of the patients had type A (83.3%) and B anatomy (9.5%), whereas only two patients had type C and 1 with type D. More than two neochordae were implanted in the majority of patients (81%). The median of LAI was 1.2 [1.15–1.25], and the CI was 4 [2.15–5] mm.

Table 2. Preprocedural mitral valve echo analysis and number of implanted chords.

Parameters	Median [IQR] or n (%)
LAI	1.2 [1.15–1.25]
CI (mm)	4 [2.15–5]
Types of anatomy of the mitral valve	
Type A	35 (83.30)
Type B	4 (9.50)
Type C	2 (4.80)
Type D	1 (2.40)
Number of implanted chords	
2	8 (19)
3	20 (47.6)
4	13 (31)
5	1 (2.40)

IQR: InterQuartile range; LAI: leaflet to annulus index; CI: coaptation index.

In all cases, the grade of MR was successfully reduced postoperatively. All patients were discharged within two to three days following the procedure. Before the intervention, nine patients had moderate-to-severe mitral regurgitation (MR), while 33 patients presented with severe MR. At the one-month follow-up, 27 patients exhibited trivial-to-mild MR,

12 had mild-to-moderate MR, and three showed moderate to severe residual MR. Of the 42 patients, 38 were alive during the last follow-up. The favorable MR outcomes were sustained, with 23 patients showing trivial-to-mild MR, 12 exhibiting mild-to-moderate MR, and three presenting with moderate-to-severe residual MR (Figure 2).

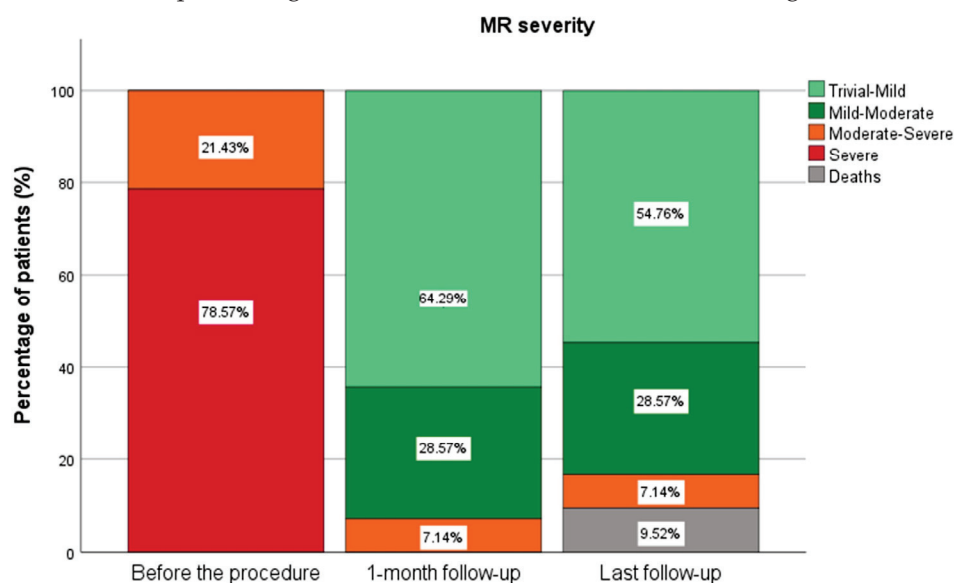


Figure 2. MR severity grade before the procedure, one-month follow-up, and the last follow-up.

Similarly, NYHA class was improved immediately after the NeoChord implantation, and these results were preserved during mid-term follow-up. Before the procedure, nine patients were classified as NYHA class II, 23 as NYHA class III, and 10 as NYHA class IV. At the one-month follow-up, 18 patients were NYHA I, 22 were NYHA II, and two remained NYHA III. At the time of the final follow-up, 15 patients were classified as NYHA class I, 21 as class II, and two patients as class III (Figure 3). The median of left ventricular ejection fraction (LVEF) before the procedure was 63 [58–67]%, which significantly decreased to 57 [53–61]% at the one-month follow-up. At the final follow-up, LVEF increased significantly to 65 [60–68]%, however, this change was not statistically significant compared to the preprocedural (Figure 4).

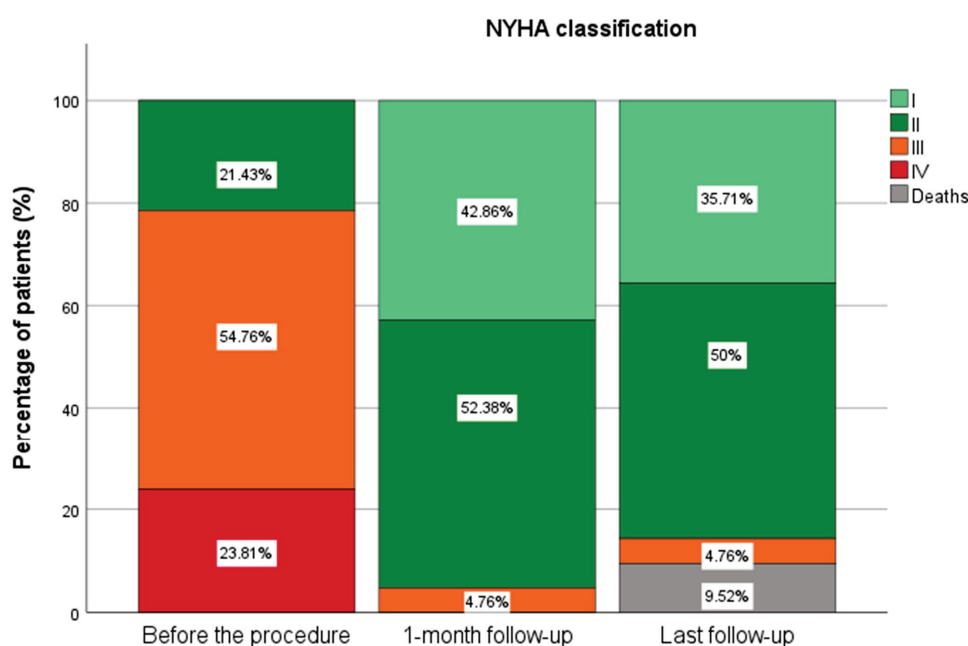


Figure 3. NYHA classification before the procedure, one-month follow-up, and the last follow-up.

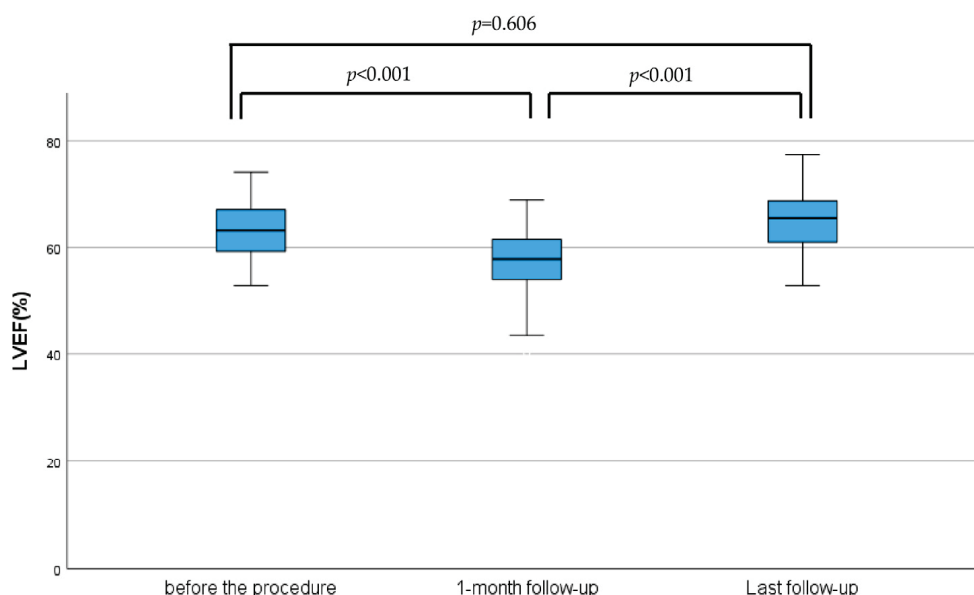


Figure 4. Medians of left ventricular ejection fraction (LVEF) before the procedure, one-month follow-up, and at last follow-up.

The overall survival and incidence of cardiovascular events were depicted using a Kaplan-Meier survival curve (Figure 5). From March 2018 to December 2024, four patient deaths were recorded, three of which were attributed to non-cardiac causes. Two 80-year-old men and one 82-year-old woman died 11 months and 10 months after the procedure, respectively. The causes of death were sepsis in the first two cases and an embolic event in the third. The cardiac death referred to a 69-year-old man with multiple comorbidities. Two months after the NeoChord procedure, the patient was diagnosed with MV endocarditis and died during the reoperation procedure for MV replacement.

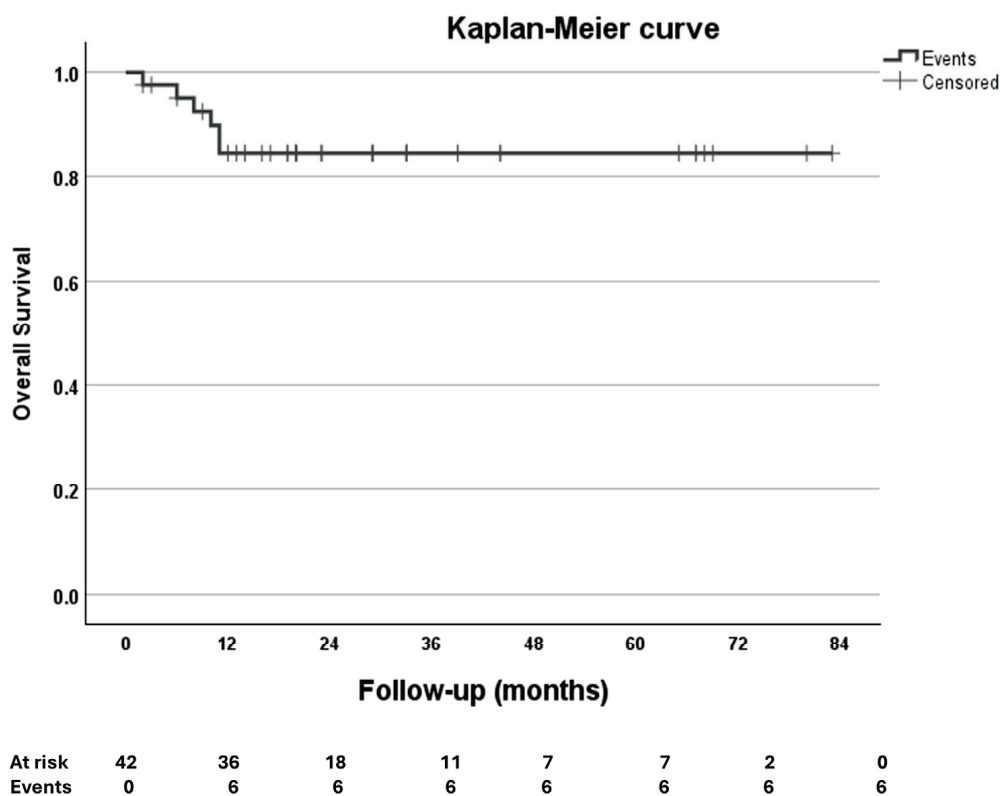


Figure 5. Kaplan–Meier event-free survival curve.

Furthermore, during follow-up, two cases proceeded to reoperation, surgical valve implantation due to recurrent mitral valve regurgitation six months and eight months after the NeoChord implantation, respectively. The first patient had no ideal MV anatomy for the NeoChord procedure. The LAI index was calculated as 1.1 (lower than 1.2), and the coaptation index was small (2 mm), whereas, posterior mitral annulus calcification was detected (type C). Moreover, the second one had complex MV anatomy of the posterior leaflet with P2a, P2b scallops, and an indentation between them. The anterior leaflet also demonstrated a pseudoprolapse part. This case was classified as a Type B candidate for the NeoChord treatment (P1-P2-P3 involvement). Due to the presence of multi-segmental disease, the LAI and coaptation index could not be reliably calculated. A newly ruptured chord originating from the anterior leaflet was identified during the subsequent surgical procedure. Despite the stability of the four previously implanted chords, the reoperative procedure necessitated the implantation of a prosthetic valve, tricuspid annuloplasty ring placement, and atrial fibrillation ablation. Interestingly, while the four implanted chords remained stable, the reoperation procedure included a prosthetic valve and tricuspid ring implantation as well as atrial fibrillation ablation.

4. Discussion

The follow-up data concerning the results of minimally invasive procedures such as transapical NeoChord implantation are limited. This study presented the first Greek experience of the mid-term follow-up of 42 symptomatic patients with moderate to severe and severe degenerative MR. While the first experience of transapical NeoChord implantation began in 2018, the enrollment of patients was significantly delayed during the COVID-19 pandemic. According to the current study results, elderly patients with moderate surgical risk successfully underwent the NeoChord procedure with favorable mid-term follow-up data. Even though the specific echocardiographic parameters in our population were not ideal as expressed by LAI and CI, the MR severity as well as the NYHA class improved significantly one month and at the last follow-up.

Furthermore, the LVEF decreased immediately after the procedure and improved during the most recent follow-up assessment. The initial decrease in LVEF is attributable to both a reduction in preload and an increase in afterload. The decrease of LVEF at the one-month follow-up and the increase of LVEF at the last follow-up were statistically significant.

According to the results of the current study, during follow-up, one cardiac related death was observed, two cases of rehospitalizations and three non-cardiac deaths occurred. As illustrated in Figure 4, all remaining patients experienced no major adverse events.

Interestingly, both patients who required surgical valve implantation for recurrent mitral regurgitation exhibited anatomically unfavorable mitral valve apparatus anatomy. In the first case, the anatomical criteria were suboptimal, with an LAI index of 1.1—below the ideal cutoff of 1.2—and a markedly reduced coaptation index. A short CI was predictive of suboptimal leaflet coaptation following the procedure. Additionally, the presence of posterior mitral annular calcification represented an adverse morphological parameter (type C anatomy). For the aforementioned reasons, the Heart Team initially recommended mitral valve replacement as the preferred treatment option, however, the patient declined. After thorough discussion, transapical NeoChord implantation was proposed as an alternative, albeit with limited expectations for a favorable outcome. The second patient had a complex MV anatomy, characterized by the presence of P2a and P2b scallops with an indentation. Moreover, the A2 and A3 segments appeared as pseudoprolapsed regions, resulting from inadequate support provided by the P2 and P3. Two distinct MR jets were observed: one central (a flail part of the posterior leaflet) and the other eccentric, directed. Although the patient was classified as a Type B candidate for

the NeoChord procedure, multiple mitral valve segments were involved. As presented in the Section 3, the LAI and CI could not be reliably calculated due to the involvement of multiple segments (P2a, P2b, A2, and A3). The mitral valve was replaced with a new prosthetic valve, tricuspid ring implantation as well as atrial fibrillation ablation. It is worth emphasizing that clinical outcomes are determined not only by the type of MV but also by the complexity of the MV anatomy structure.

It is noteworthy that within the study population, a 61-year-old patient had previously undergone mitral valvuloplasty (MV ring and two chords implantation) and Percutaneous Coronary Intervention (PCI), two years and six months prior to the Neochords procedure, respectively. The new deterioration of MR was attributed to the rupture of previously implanted chordae. There is great interest in the Cardiothoracic Community concerning the role of transapical chord implantation in this specific population of patients with a previous mitral valvuloplasty as a Redo procedure. Three neochordae were implanted successfully, and the patient remained NYHA II class during the last follow-up.

It is worth highlighting that our initial experience, including immediate and short-term follow-up at six months, was previously published in 2020 in the *Hell J Cardiol* [13]. According to those initial results, patients who underwent transapical NeoChord implantation demonstrated excellent immediate and short-term (six-month) outcomes, with notable improvement in both NYHA functional class and mitral regurgitation severity.

Colli et al. [8] presented a large series of patients who had received neochordae implantation and analyzed the possible mechanisms of recurrent MR. Among the key points responsible for recurrent regurgitation, patient selection (17.3%), technical issues (28.8%), progression of baseline disease (15.4%), left ventricle reverse remodeling (1.9%), excessive over-tensioning (35.8%), and PML curling (30.8%) were identified. According to those results, the main problem was the unfavorable mitral valve anatomy based on mitral annular calcification as well as the fragile leaflets, leading to possibly poorly calculated LAI. Furthermore, in published studies, cases of neochordae rupture were reported [14–19]. The potential causes are primarily attributed to prolonged friction between dissimilar materials (ePTFE, polypropylene, pledgets), excessive over-tensioning, and inadvertent neochordae damage during intraoperative handling. Nevertheless, robust data that definitively substantiate these assumptions remain unavailable at present.

Another critical intraoperative consideration was the degree of neochordal tension applied during the procedure. In accordance with the extensive experience of Colli et al. as well as our own clinical experience, the overtensioning of implanted neochordae represents a critical consideration that requires careful attention and expertise from the operating surgeon [11–15]. It is essential to take into account left ventricular remodeling during the follow-up period. In such cases, positive remodeling is expected to result in the relaxation of the neochordae. Conversely, the remodeling of the annulus, particularly in the absence of calcification, plays a crucial role [12,15,18–23].

The morphology of the mitral annulus and the extent of calcification are key determinants in the successful implantation of NeoChord. The mitral valve annulus is not rigid; therefore, positive left ventricular remodeling may also contribute to annular remodeling. Therefore, the initial theoretical limitation regarding the absence of a combined technique (involving both leaflets and annulus) may not be accurate. The positive LV remodeling and the flexible mitral ring should contribute to favorable MR results. Positive annular remodeling has been observed as a strong impact on patient heart function. However, the role of annular stabilization remains a topic of ongoing debate, as it has been proposed as a predictor of repair durability in conventional surgical procedures. In our view, this remains a significant concern, and further studies are required to validate the impact of NeoChord implantation on predicting favorable patient outcomes.

The first Canadian Clinical experience derived by a single Cardiothoracic Center [16]. Among 10 patients (mean age 76 years), the procedure was successfully completed in 9 patients, with an average of 3 chords implanted. The procedure was converted to an open surgery with mitral valve replacement. At the 6-week follow-up assessment, the majority of patients demonstrated either no or trivial MR, and two patients had moderate MR. It is noteworthy that the study population included two patients with a history of prior MV valvuloplasty.

Even with conventional surgical repair techniques, a certain proportion of patients experience recurrence. Recently, Kemin Liu et al. [21] published a study focusing on the outcomes following surgical repair of anterior, posterior, or bileaflet mitral valve prolapse. In a large cohort of 1192 patients with a mean age of 55 years, the majority (60.6%) presented with posterior leaflet prolapse. The 10-year cumulative survival and reoperation incidences among AML, PML, and bileaflet repairs were not significantly different. However, AML repair exhibited a higher cumulative incidence of recurrent mitral regurgitation compared to PML repair. These findings highlight the significance of leaflet involvement, particularly the AML, which is associated with a worse prognosis.

A novel ePTFE chordal implantation device, E-Chord (Med-Zenith Medical, Beijing, China), was recently developed in China. This study reported the initial results of this device in a porcine model [22]. Interestingly, the clinical evaluation should be very interesting as a different approach to mitral valve leaflets should be added. Smaller device that punctures the leaflets without insertion of the device (T shape) into the left atrium.

Limitations

The results are based on a small cohort of consecutive patients managed in a single cardiothoracic center, limiting the generalizability of the study and the extrapolation of the findings to all patients with degenerative mitral regurgitation and suitable anatomical characteristics. The sample size limited the statistical power of the study, particularly with regard to detecting rare complications or performing reliable subgroup analyses. In addition, only the initial and final follow-up assessments were performed at our department, while all other evaluations were conducted at institutions chosen by the patients. Consequently, comprehensive annual echocardiographic follow-up data were not consistently available. On the other hand, a notable strength of this study is that the same experienced cardiothoracic surgical team, in conjunction with a dedicated cardiovascular imaging group specializing in this technique, established a coordinated and systematic approach during that period, which facilitated consistent interdisciplinary collaboration and longitudinal patient follow-up. The Heart Team thoroughly evaluated all clinical and anatomical data both prior to and during the procedure, and subsequently conducted follow-up for each patient. Given the anatomical variability among patients, it is essential that the Heart Team possesses the necessary knowledge and expertise to determine the most appropriate and individualized treatment strategy for each case. The specific characteristics of patients with primary MR pose challenges in designing large multicenter studies, which are essential to overcome the limitations of the current research protocol and enhance the generalizability of the findings to a broader MR patient population.

5. Conclusions

Transapical off-pump heart neochordae implantation is a minimally invasive alternative to conventional surgery in symptomatic patients with moderate to severe or severe primary MR. Regarding patients who had favorable MV anatomy for neochords implantation, the procedure has been demonstrated to be safe and to provide good mid-term outcomes for up to 20 [12–39] months in terms of cardiac mortality and freedom from reoperation and rehospitalization.

Author Contributions: Methodology, Y.D., E.B. and P.T.; Investigation, A.K.; Supervision, D.T., K.T., C.A. and V.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Hippokration General Hospital of Athens (Protocol Code: 22532/19-12-2023, Date of approval: 21 December 2023).

Informed Consent Statement: Informed consent was obtained from all patients involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to patient privacy.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

MR	Mitral Regurgitation
NYHA	New York Heart Association
MV	Mitral Valve
2D	Two-dimensional
3D	Three-dimensional
TTE	Transthoracic Echocardiography
TEE	Transesophageal Echocardiography
LAI	Leaflet to Annulus Index
CI	Coaptation Index
AML	Anterior Mitral Leaflet
PML	Posterior Mitral Leaflet
AP	Anteroposterior diameter
LVEF	Left Ventricular Ejection Fraction
ESC	European Society of Cardiology
PCI	Percutaneous Coronary Intervention
STS-PROM MV repair score	Society of Thoracic Surgeons Predicted Risk of Mortality Mitral Valve repair score
ePTFE	Expanded polytetrafluoroethylene

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Article

Left Ventricular Assist Device (LVAD)-Related Major Adverse Events Account for a Low Number of Emergency Room Admissions in HeartMate 3™ Patients—A 10-Year Retrospective Study

Christoph Salewski, Christian Jörg Rustenbach *, Spiros Lukas Marinos, Rodrigo Sandoval Boburg, Christian Schlensak and Medhat Radwan

Department of Thoracic and Cardiovascular Surgery, University Hospital Tuebingen, Hoppe-Seyler-Strasse 3, 72076 Tuebingen, Germany; christoph.salewski@med.uni-tuebingen.de (C.S.); spiros.marinos@med.uni-tuebingen.de (S.L.M.); rodrigo.sandoval@med.uni-tuebingen.de (R.S.B.); medhat.radwan@med.uni-tuebingen.de (M.R.)

* Correspondence: christian.rustenbach@med.uni-tuebingen.de

Abstract

Background: The yearly number of left ventricular assist device (LVAD) implantations is approximately twice the number of heart transplantations (HTX) in Germany. As the number of patients with an LVAD installed grows, so does the likelihood of their presentation to the emergency room (ER). Due to uneasiness in identifying their primary complaint, ER personnel are often likely to overlook important clues in the treatment of patients with an LVAD. **Methods:** To assess the urgency of patients' conditions and their relationship with LVADs, we retrospectively examined the ER admissions of patients with HeartMate 3™ (HM 3) LVADs installed between 2014 and 2024 at our university medical center. We counted referrals to the peripheral ward (minor) and to the intensive care unit (ICU, major). Relation to LVAD relation was also recorded. The survival was analyzed with respect to the severity of the cause of admission (minor/major) and the relationship to the LVAD therapy. **Results:** We observed 100 presentations to the emergency department. Of these, 77 were minor and 23 were major. The majority (92) was not related to the LVAD. Of the eight admissions related to the LVAD, two were major adverse events, accounting only for 2% of the total cases. **Conclusions:** An ER presentation of a patient with an HM 3 is very likely to have a medical cause not related to the LVAD. LVAD-related causes were mostly minor and could be treated on the ward.

Keywords: LVAD; HeartMate3™; emergency room; acute adverse events

1. Introduction

The yearly number of left ventricular assist device (LVAD) implantations is approximately twice the number of heart transplantations (HTX) in Germany. As the number of patients with an LVAD installed grows, so does the likelihood of their presentation to the emergency room (ER). The Abbott HeartMate 3™ (HM 3) is a third-generation fully magnetically levitated centrifugal LVAD for patients with end-stage heart failure. The first in-human HM 3 implantation was performed in Hannover, Germany in 2014 [1]. Our center of thoracic and cardiovascular surgery performed its first implantation of this device shortly thereafter. For ER personnel, patients with an LVAD form a particular and rare

group of patients. ER staff are often uneasy identifying their primary complaint. They focus on the LVAD, and are therefore likely to overlook important clues. To see whether this aversion is justified, we seek to assess the ER presentations of patients with LVADs and identify their underlying causes. Our objective is to determine whether patients with an LVAD constitute a high-risk group when they arrive at the ER. Our investigation is focused on a cohort that uses HM 3.

2. Materials and Methods

At the Department for Thoracic and Cardiovascular Surgery of the University Hospital of Tübingen, Germany, we conducted a single-center retrospective study examining the reasons for the presentation to ERs of patients with an HM 3 LVAD and their survival between 2014 and 2024.

2.1. Study Design

Over the 10-year course of this retrospective study, 72 patients received an LVAD. Five received the HM II, including one reinstallation. Eleven patients received an HVAD. Overall, 56 patients were implanted with an HM 3 LVAD, non-consecutively. The flow chart for patient inclusion is shown in Figure 1. Eight patients died during the early postoperative period. A total of 48 were discharged and entered the follow-up period.

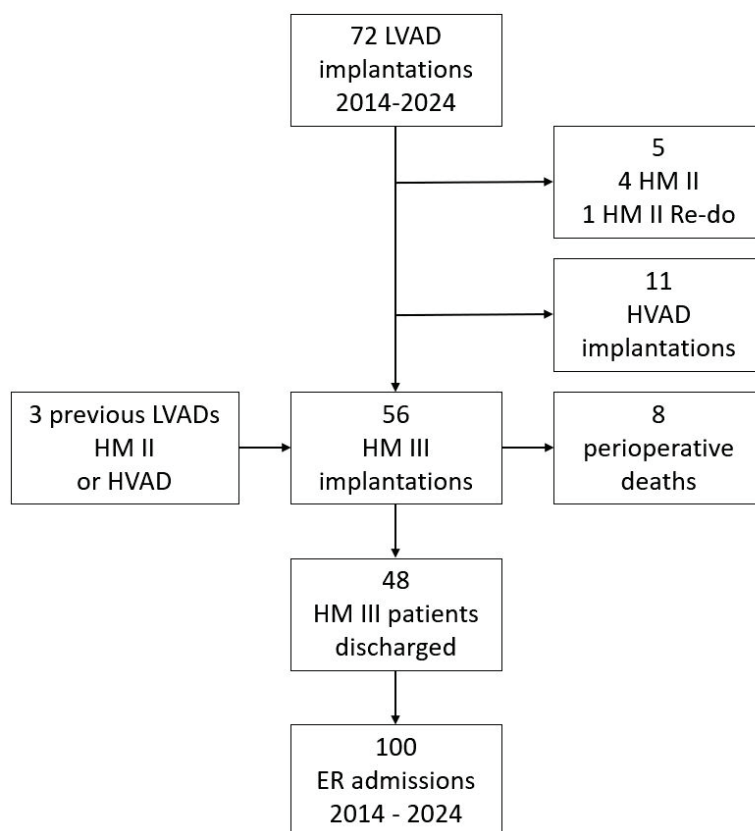


Figure 1. HM 3 implantations between 2014 and 2024 at University Medical Center Tübingen, Germany.

2.2. Metrics

Emergency room admissions were counted during the follow-up period and reported as minor (treated on the ward) or major (referred to the intensive care unit, ICU). From the ER point of view, a minor cause for admission could be transferred to the ward, while a major cause was referred to the ICU. It was recorded whether the presentation was related to LVAD therapy. The clinical courses could differ and deteriorate in the ward or improve

on the ICU. The initial referral from the ER was crucial. Baseline parameters (age, sex, implant age, indication, and therapy objective) were recorded. The follow-up time, the time until the first admission to the ER, and survival were calculated.

2.3. Statistics

Data are presented as counts, ratios, and percentages in tables and bar charts. Survival analyzes and inferential statistics were performed by means of SPSS 28.0[®], IBM[®], and presented as Kaplan–Meier diagrams.

3. Results

We present the baseline characteristics, number and causes of admissions to the emergency department, their relation to LVAD therapy, non-presentation-free survival in the emergency department, general survival, and survival with respect to minor and major events.

3.1. Baseline Characteristics

A total of 56 patients received an HM 3 LVAD, 45 of whom were male (80.3%). The mean age at implantation was 56.8 $\pm$ 10.9 years and the mean age was 61.2 $\pm$ 11.1 on the day of the last living contact. The mean follow-up time and therefore duration on the LVAD was 4.3 $\pm$ 2.7 years (min, 85 days; max, 9.1 years, range, 8.9 years). Of these, 15 (31.25%) died during the follow-up period. Two patients received heart transplants and spent 2.04 and 4.77 years on HM 3 prior to their transplant. Until 31 December 2024, the 31 (65.6%) ongoing patients spent 4.5 $\pm$ 3.2 years on the device and counting. This does not include the time on other LVADs for the three patients who received an HM 3 as a second LVAD. One patient spent 7.02 years on an HM II until a critical drive line cable defect occurred. Since then, he has been on the HM 3 for 2.2 years and counting. A second patient had an HM II for 2.8 years before suffering a direct device infection. He spent 5.8 more years on an HM 3 until he died of non-LVAD-related sepsis. The third patient spent 3.07 years on an HVAD before experiencing multiple pump thromboses. He has been active on an HM 3 for the last 2.7 years and counting. The last documented patient contact before 31 December 2024 was counted. The study population consisted of 48 (100%) patients, 40 (83%) of whom were male (see Table 1). During the follow-up period, we observed 210 LVAD patient years.

Table 1. Group demographics and therapy objectives. Counts and % or means $\pm$ SD.

Parameter	n = 48
Gender [m]	40 (83.3%)
Age [y]	61.2 $\pm$ 11.1
Implant age [y]	56.8 $\pm$ 10.9
Follow-up [y]	4.3 $\pm$ 2.7
Indication	
Ischemic cardiomyopathy	24 (50%)
Dilative cardiomyopathy	20 (41.7%)
Myocarditis	4 (8.3%)
Therapy objective	
Bridge to transplant	33 (68.75%)
Destination therapy	11 (22.92%)
Bridge to decision	3 (6.25%)
Bridge to recovery	1 (2.08%)

3.2. Emergency Room Admissions

In the follow-up period, 37 patients with an HM 3 (77%) presented to the emergency room and 100 admissions occurred. Of these, 77 were minor events that were managed on the ward. Only six of the minor events were related to LVAD therapy. The same cohort suffered 23 major adverse events, but only two were attributed to their LVAD. In other words, of the 100 admissions to the emergency department, only 8 were related to the LVAD and 92 were medical (see Table 2). Of the 100 admissions, 94% could be discharged after treatment. Six patients died after being admitted with major causes that needed referral to the ICU (accounting for 12.5% of patients and 6% of ER admissions). None of the deaths were LVAD-related. However, patients with an LVAD-related reason for presentation to the ER had a higher likelihood of being transferred to the ICU (odds ratio: 1.127).

Table 2. ER admissions within the follow-up period.

LVAD Relation	Minor	Major	Σ LVAD Relation
No	71	21	92
Yes	6	2	8
Σ severity	77	23	100

The leading cause of overall admissions was arrhythmia. The total of 24 arrhythmic events were traced back to only 11 patients, 1 of whom had 9 presentations, another patient had 5, and another had 2 presentations. Infections were the second most common reason for admission. The 15 infections were traced to 10 patients, 2 of whom were admitted 3 times, 1 was admitted 2 times, and 7 were admitted only once. Gastrointestinal complaints were the third most common reason for admission. The 13 GI complaints were suffered by eight patients. Specifically, there were four patients with gall bladder infections, three admissions with diarrhea, one with appendicitis, one with a hernia, one with nausea and vomiting, and three cases of unspecific abdominal pain. In half of the reasons for admission, patients visited the ER multiple times or at least twice for the same reason. The causes of admission are listed in Table 3.

Table 3. Most frequent reasons for ER admission.

Cause	Counts	Patients
Arrhythmia	24	11
Infection	15	10
Gastrointestinal	13	8
Bleeding	7	7
Drive Line Infection	7	6
Neurologic	6	6
Metabolic	5	3
Musculoskeletal	5	4
Trauma	5	4
Heart Failure	4	4
Oncologic	2	2
Urologic	2	2
Acute coronary syndrome	1	1
COVID-19	1	1
Pain	1	1
Psychiatric	1	1
Unknown	1	1
Sum	100	72

Furthermore, we analyzed where the HM 3 patients were referred and treated. An infection could have been a minor cause and treated conservatively on the ward or a major cause with the need for ICU monitoring and/or surgical treatment. The most common minor causes were arrhythmia (21 cases) and GI bleeding (11 cases). The most common major reasons were infection (six cases) and bleeding (four cases). Driveline infections accounted for most of the minor causes related to LVADs (five cases). In two cases, driveline infections led to systemic inflammation, resulting in sepsis. These were counted as major cases related to LVADs. Table 4 presents the causes of admissions, categorized according to their severity and relation to LVADs.

Table 4. Causes for ER admission with respect to severity (minor/major) and relation to LVAD.

ER Presentation Causes	Non-LVAD-Related	LVAD-Related	Sum
Minor	71	6	77
Arrhythmia	21		21
Gastrointestinal	10	1	11
Infection	9		9
Drive Line Infection		5	5
Metabolic	5		5
Musculoskeletal	5		5
Trauma	5		5
Neurologic	4		4
Bleeding	3		3
Heart Failure	2		2
Oncologic	2		2
Urologic	2		2
COVID-19	1		1
Pain	1		1
Psychiatric	1		1
Major	21	2	23
Infection	6		6
Bleeding	4		4
Arrhythmia	3		3
Drive Line Infection		2	2
Gastrointestinal	2		2
Heart Failure	2		2
Neurologic	2		2
Acute coronary syndrome	1		1
Unknown	1		1
Sum	92	8	100

3.3. Survival and Freedom from Emergency Room Admission

In our cohort, 33 (68.8%) of the patients are still alive. The mean survival time was 6.9 years (95% CI: 6.0–7.8 years). The probability of survival is shown in Figure 2a. The probability of living longer than 1568 days (4.3 years) was 80.6%. The probability of living longer than 2355 days (6.5 years) was 51.1%. The longer patients were followed up, the more likely they were to be admitted to the emergency room. Figure 2b shows the estimated time of admission-free survival to the ER as a Kaplan–Meier diagram. The probability of being free from admission to the emergency room for 500 days (1.37 years) is approximately 60%, and probability of remaining free from admission for 1500 days (4.1 years) is slightly above 30%. We then looked at the ER presentations of all 15 deceased patients: when distinguishing between minor and major causes for ER admission, the LVAD patient group with major reasons for admission had a significantly higher probability of dying. This is

shown in Figure 2c. The Kaplan–Meier survival estimator was 2047 ± 153 days for LVAD patients with minor ER admissions, while it was only 1295 ± 235 days for LVAD patients with major ER admissions. This difference was significant, as the log-rank Mantel–Cox test showed ($\chi^2 = 3.869, p = 0.049$).

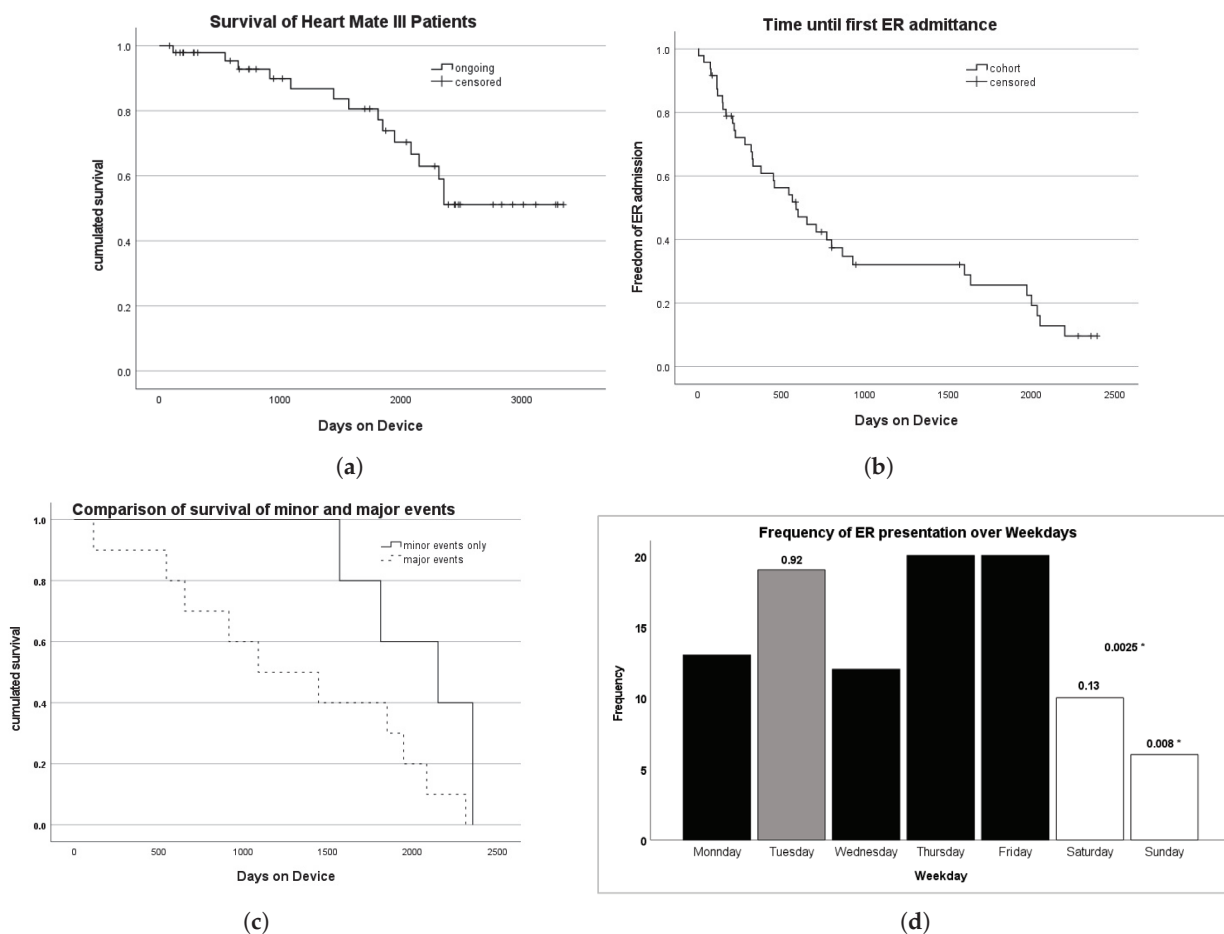


Figure 2. (a) Probability of survival with an HM 3 based on our study cohort between 2014 and 2024. The probability of living longer than 1568 days (4.3 years) is 80.6%. The probability of living longer than 2355 days (6.5 years) is 51.1%. (b) Probability of ER-admission-free survival with an HM 3 based on our study cohort between 2014 and 2024. Staying free from ER admissions for 500 days had a 60% probability, while staying free from ER admissions for 1500 days had a 30% probability. (c) The probability of survival of all 15 deceased patients with respect to minor and major ER admission causes is depicted in a Kaplan–Meier diagram. The dark line represents the group with only minor reasons for ER admission, while the dashed line represents the group with major ER admissions, respectively. LVAD patients with minor reasons for ER admissions had a 100% probability of a 500-day survival, whereas LVAD patients with major reasons had only an 80% probability of survival for the same duration. To live 1500 days with minor ER admission reasons only had a 80% probability, whereas this probability was only 40% for the group with major reasons for ER admission for the same duration. (d) Frequency of ER admissions over weekdays. The LVAD outpatient clinic takes place on Tuesdays. On Tuesdays, 19 out of 100 presentations occurred. A binomial distribution analysis showed no fewer presentations in the ER when there was an LVAD outpatient clinic the same day ($p = 0.92$). * Significantly fewer patients presented on Sundays compared to other days ($p = 0.008$). Fewer patients presented on weekends than on weekdays ($p = 0.0025$).

3.4. LVAD-Related Admissions to the Emergency Room

3.4.1. Causes of Death

General Causes of All Deaths

Of the cohort of 48 patients with an HM 3 LVAD, 15 died during the follow-up period. The most common cause was sepsis (four patients). Three patients had an oncologic complication (one had glioblastoma, one had pancreatic cancer, and one had bladder carcinoma). Two patients had a severe intracranial hemorrhage. A patient developed severe aortic insufficiency and therefore circulatory failure. One patient had pneumonia, while two patients suffered right ventricular failure. One patient developed complicated appendicitis and died of peritonitis. Only a fraction of these patients presented to the ER prior to their death. In some cases, patients had ongoing chronic diseases and decided against further treatment. In other cases, patients were referred from another hospital.

Death After Emergency Room Admittance

Five patients died during the clinical course after referral from the ER to the ICU. Therefore, all causes were considered major reasons for admission. None of the causes were related to LVADs. The mean hospital stay from admission to the ER until death was 34.5 days (min, 0 days; max, 84 days). The first patient was admitted with heart failure symptoms as a primary complaint. He was referred to the ICU for his circulatory instability. He had massive aortic regurgitation and died 30 days later. The second patient presented with abdominal pain to the ER. He was diagnosed with appendicitis. However, he suffered peritonitis and died of sepsis. The third patient was admitted with arrhythmia and died 56 days later from right ventricular failure. The fourth patient suffered intracranial hemorrhage and was referred from the ER to the ICU. The bleeding was severe, so the LVAD therapy was discontinued. The fifth patient was referred from the ER to the ICU with pneumonia. Coincidentally, he had severe intracranial bleeding 7 days later, so the LVAD therapy was discontinued.

4. Discussion

In our study of 100 admissions to the emergency department of our 48 LVAD patients during the study period, we recorded the causes and severity of the underlying medical condition.

4.1. Principal Findings and Clinical Interpretation

This retrospective analysis indicates that LVAD-related presentations to the ER were rare—only 8% of the total admissions of patients with an LVAD—and the major adverse events related to LVADs were exceedingly rare (2%). These figures challenge the assumption that the presence of an LVAD implies a high probability of mechanical failure or an urgent intervention related to the device itself. Most admissions were due to typical health complaints such as arrhythmias, infections, and gastrointestinal disorders, common issues in the cardiac population. This suggests that the presence of an LVAD should not distract clinicians from standard diagnostic routines. Instead, attention should remain focused on the primary complaint.

As could be observed, 92 out of 100 ER presentations of LVAD patients were not related to their LVAD. This should calm ER staff when they are informed of an incoming patient with LVAD. Only 2 of the 23 major cases were related to the LVAD. Patients with major events have a higher likelihood of mortality; however, this is rarely related to the LVAD. ER admissions are equally frequent on weekdays, regardless of the presence of an outpatient LVAD clinic.

Patients with LVAD-related presentations had a slightly higher likelihood of being referred to the ICU (OR 1.127), but LVAD-related causes did not correlate with increased mortality. This highlights that although emergency department personnel may perceive patients with LVADs as high-risk, this assumption should be tempered with clinical judgment and objective findings.

4.2. Role of LVAD Clinics and Temporal Presentation Patterns

We investigated whether the availability of an outpatient LVAD clinic influenced ER presentation patterns. We assumed that outpatient clinics for LVAD reduced the number of spontaneous presentations of LVAD patients in the ER department on that day. There was no significant reduction in emergency room visits on clinic days. So, structured outpatient follow-up does not reduce acute presentations for other reasons. However, timing and frequency may not adequately cover periods of vulnerability. However, when there was no LVAD-specialized nurse or perfusionist on duty, such as on weekends, the presentation of LVAD patients in the emergency room was less likely ($p = 0.008$). This may reflect behavioral barriers rather than clinical need. The presentation counts and a binomial analysis are shown in Figure 2d. We encourage emergency room personnel to assess patients with an LVAD in their local standard way, as if there were no LVAD. We advise contacting the local LVAD reference center and informing them of your patient's admission to the ER if they have an LVAD—if out of hours, at least do this the next day. They will have standard operating procedures in general or patient-specific advice; they can consult over the telephone or take over the patient, if applicable.

4.3. Integration with Existing Literature

Patients with LVADs, especially the HeartMate 3, have better survival than those treated with optimal medical therapy [2,3]. Our findings align with the published data from the MOMENTUM3 trial [4], which demonstrated superior survival and fewer adverse events in patients with the HeartMate 3 compared to earlier devices. Similarly, the ELEVATE registry supports the low incidence of device-related complications in the post-market setting [5]. Our study adds evidence that can reassure emergency room personnel: although LVADs remain an important component of heart failure patient therapy, most emergency room presentations are not device-related and can be treated accordingly. Finch et al. examined a 5-year period and found 290 ER presentations of 107 LVAD patients in two adjunct centers in Minnesota and Florida. Overall, 7.9 % were related to the LVAD therapy [6]. Our data comply with these findings, but in a smaller cohort (8% of $n = 100$ over 10 years). The Heart Failure Association of the European Society of Cardiology curated a position paper for healthcare providers that do not profit from an LVAD center and highlighted bleeding, stroke, and pump thrombosis. They identified bleeding with 0.35–0.65 events per patient year. Neurological events, especially stroke, can occur in 10% of patients during their first year of support, and stroke remains the primary cause of death within the first 6–24 months. Finally, during pump thrombosis, stabilization of the patient is key. Secondary, the location of the thrombus needs to be identified. Medical treatment is available for thrombi in both the inflow and outflow cannula. Surgical options for excision or pump exchange exist [7]. Reza et al. found no significant sex differences in presentation to the ER for device complications, stroke, infection, or heart failure. Women with LVADs presented more frequently with obesity and depression. In addition, respiratory, genitourinary, and gynecological reasons for admission were more frequent. Women form up to 20–25% of the LVAD patient population [8]. In pediatric patients, the percentage of discharges to the outpatient setting post LVAD implantation is much lower than in adults. So, as a non-transplant/non-LVAD center, it is rare to encounter a pediatric LVAD patient

in the ER. However, in their study, Pokrajac et al. described that 80% of their 30 discharged patients presented to the ER, with vomiting, abdominal pain, fever, and headache being the most common primary complaints. The mean age of the pediatric patients was 13.5 years, and their study period was 10 years [9]. We advocate for a paradigm shift in emergency care for LVAD patients—from a device-centric to a patient-centric approach. Clinicians should prioritize standard assessment protocols, thoroughly evaluate primary complaints, and then only consider LVAD-specific interventions or consultations. However, centers of reference for LVAD patients would be glad to be informed of the hospitalization of one of their LVAD patients.

4.4. Recommendations for Emergency Care

1. Do not assume an LVAD-related pathology; initial evaluation should follow standard emergency workups.
2. Mental status, vital signs, and primary complaints should guide triage decisions.
3. Contact the LVAD patient reference center when necessary, but avoid unnecessary delays in treatment.
4. Check for anticoagulation, battery status, and LVAD alarms.
5. Standard operating procedures (SOPs) from reference centers can improve decision making (e.g., Royal Brompton Protocol [10] or [11,12], online [13], and for Germany [14,15]).

4.5. Limitations and Future Directions

This is a single-center retrospective study, which limits generalization. Also, we categorized admissions as “minor” and “major” based on ER disposition; some clinical courses evolved post-admission and did not reflect initial severity. Our center provides specially trained LVAD nursing staff from 8 a.m. to 4 p.m. on weekdays and a staff of perfusionists on call 24/7. In addition, we operate an outpatient LVAD clinic once a week and see every LVAD patient every three months. All of the mentioned cases were strictly attributed to actual admissions and presentations to the emergency department. We explicitly focused on ER presentations because centers of the basic level of care do not provide an LVAD patient clinic in the same way as we do. Future multi-center prospective studies could explore whether specific risk factors predict ER utilization in this population and whether enhanced patient education or digital monitoring can further reduce unnecessary presentations.

Author Contributions: Conceptualization, C.S. (Christoph Salewski), M.R. and C.S. (Christian Schlensak); methodology, C.S. (Christoph Salewski) and M.R.; software, C.S. (Christoph Salewski); validation, C.J.R., S.L.M. and R.S.B.; formal analysis, R.S.B.; investigation, C.S. (Christoph Salewski); resources, C.S. (Christian Schlensak); data curation, C.S. (Christian Schlensak); writing—original draft preparation, C.S. (Christoph Salewski); writing—review and editing, M.R.; visualization, C.S. (Christoph Salewski); supervision, C.S. (Christian Schlensak). All authors have read and agreed to the published version of the manuscript.

Funding: The Article Processing Charge was supported by the Open Access Publication Fund of the University Library from the University of Tübingen, in addition to a supplementary contribution from the Medical Library of the Eberhard-Karls-University Tübingen.

Institutional Review Board Statement: The ethics committee of the Tübingen University Hospital approved this project (Project nr. 194/2020BO2, 15 April 2020).

Informed Consent Statement: Patient consent was waived due to the retrospective data analysis of this study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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Article

Paradox of Low CA-125 in Patients with Decompensated Congestive Heart Failure

Raquel López-Vilella ^{1,2,3}, Borja Guerrero Cervera ^{2,*}, Víctor Donoso Trenado ^{1,2}, Julia Martínez-Solé ^{1,2}, Sara Huélamo Montoro ², Valero Soriano Alfonso ², Franco Appiani ², Luis Martínez Dolz ^{2,3} and Luis Almenar-Bonet ^{1,2,3}

¹ Unit of Heart Failure and Transplant, Hospital Universitari i Politècnic La Fe, 46026 Valencia, Spain; cune10@hotmail.com (R.L.-V.); vdonoso@outlook.com (V.D.T.); juliamsole@gmail.com (J.M.-S.); lualmenar@gmail.com (L.A.-B.)

² Cardiology Department, Hospital Universitari i Politècnic La Fe, 46026 Valencia, Spain; huelamo_sar@gva.es (S.H.M.); valero1996@gmail.com (V.S.A.); fappiani@gmail.com (F.A.); luismartinezdolz@gmail.com (L.M.D.)

³ Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III, 28029 Madrid, Spain

* Correspondence: borja_vlc95@hotmail.com

Abstract

Background/Objectives: Patients diagnosed with decompensated congestive heart failure (HF) often have elevated CA-125 levels, attributed to systemic congestion. However, a subgroup of patients presents with normal CA-125 levels. The primary objective of this study was to characterize the clinical, analytical, and echocardiographic profiles of patients admitted for decompensated congestive HF according to their CA-125 levels. The secondary objective was to analyze mortality after discharge. **Methods:** We conducted a retrospective study of patients hospitalized for a decompensated congestive HF episode. Recruitment was consecutive over more than 4 years (December 2019–June 2024), with 3151 patients recruited. Scheduled admissions, transfers from other hospitals, pulmonary congestion patterns, mixed patterns, and low output were the exclusion criteria. The final number of patients included was 166, all with an isolated systemic congestion pattern: CA-125 ≤ 50 U/mL: 38, and CA-125 > 50 U/mL: 128. **Results:** The comparative analysis between the groups showed that patients with CA-125 ≤ 50 U/mL were more often women ($p < 0.05$). They also had lower bilirubin and GOT/AST levels ($p < 0.05$). The percentage of patients with a preserved left ventricular ejection fraction ($\geq 50\%$) was higher in the CA-125 ≤ 50 U/mL group ($p < 0.05$). The right ventricular (RV) size and inferior vena cava (IVC) were enlarged in both groups but with no significant differences ($p < 0.05$). However, the degree of RV dysfunction was greater in the CA-125 > 50 U/mL group, while the proportion of patients with inspiratory collapse of the IVC was higher in the CA-125 ≤ 50 U/mL group ($p < 0.05$). Survival curves differed from the first month and throughout the follow-up, with higher mortality in the CA-125 > 50 U/mL group. Thus, the probability of being alive at the end of the follow-up was over 50% in the CA-125 ≤ 50 U/mL group, while in the CA-125 > 50 U/mL group, it was around 25% ($p < 0.05$). **Conclusions:** The proportion of patients with decompensated congestive HF and systemic congestion who present with a low CA-125 level is close to 25%. These patients are mostly women with a preserved ejection fraction and inspiratory collapse of the IVC of $> 50\%$. Moreover, they have a higher survival rate, so a low CA-125 could help identify a subgroup of patients with a better prognosis.

Keywords: heart failure; systemic congestion; CA-125; clinical profiles; survival

1. Introduction

Heart failure (HF) is a global disease that reduces both the life expectancy and quality of life of patients who suffer from it [1]. It generally follows a chronic course, with exacerbations that occur more or less frequently, necessitating visits to the emergency room and/or hospitalization, which, in turn, increases morbidity and mortality [2]. Among hospitalized patients with acute heart failure, there are different clinical congestion profiles, each with varying prognoses depending on the hemodynamic situation and the location of the congestion [3]. Among these profiles, studies show that the clinical picture of decompensated systemic congestion, although not the most frequent, has the worst prognosis over five years [4].

Carbohydrate antigen 125 (CA-125) is a high-molecular-weight protein synthesized in the serous membranes, primarily used as an analytical control marker for ovarian cancer, and is also elevated in patients with acute HF and congestion [5]. Its elevation depends on the degree and location of the congestion, with systemic congestion presenting the highest levels (3,4). However, even in patients hospitalized with this pattern, normal values can be found, a fact that remains unclear in the scientific literature, creating confusion in the clinical research on this novel biomarker [6,7].

The hypothesis for this study was that in patients hospitalized for decompensated HF with systemic congestion, a low CA-125 level would be associated with a specific profile that could have prognostic implications regarding survival.

This study aimed to characterize the clinical profiles of patients hospitalized for decompensated congestive HF based on their CA-125 levels. The secondary objective was to compare the mean survival times between the study groups.

2. Materials and Methods

This is a retrospective study based on a database of patients consecutively admitted for an episode of decompensated HF in the Cardiology Department of a tertiary care hospital. Information was gathered during patient admission and extracted and stored by a team of cardiologists specializing in HF. Recruitment was consecutive over more than four years (December 2019–June 2024), with 3151 patients recruited. Scheduled admissions (n: 1018), transfers from other hospitals (n: 752), a pulmonary congestion pattern (n: 822), pulmonary and systemic congestion (n: 320), and a low-output pattern (n: 73) were the exclusion criteria. The final number of patients included in the study was 166, among which all had a systemic congestion pattern, 38 had normal CA-125 levels, and 128 had elevated CA-125 levels (Figure 1).

The diagnosis of acute HF with predominant decompensated systemic congestion was defined as the presence of fluid retention manifesting as a significant increase in weight, reduced diuresis, and severe edema, without evidence of orthopnea or signs of low cardiac output. Furthermore, the absence of pulmonary congestion was required, confirmed by the absence of crackles on lung auscultation and no signs of congestion on chest X-ray. In cases of doubt, patients were evaluated by a multidisciplinary team to ensure correct classification according to the established criteria.

CA-125 was considered normal up to 50 U/mL. The maximum normal value is not defined in HF. For ovarian cancer suspicion, this limit is usually 35 U/mL, although it may vary by laboratory [6,8].

The variables of interest included clinical (medical history and baseline characteristics), echocardiographic (functional assessment of both ventricles and the inferior vena cava), therapeutic (medications at the time of admission), and analytical (standard parameters for these patients based on a pre-configured analytical profile for decompensated HF) variables [9,10]. Survival time was also analyzed in both study groups.

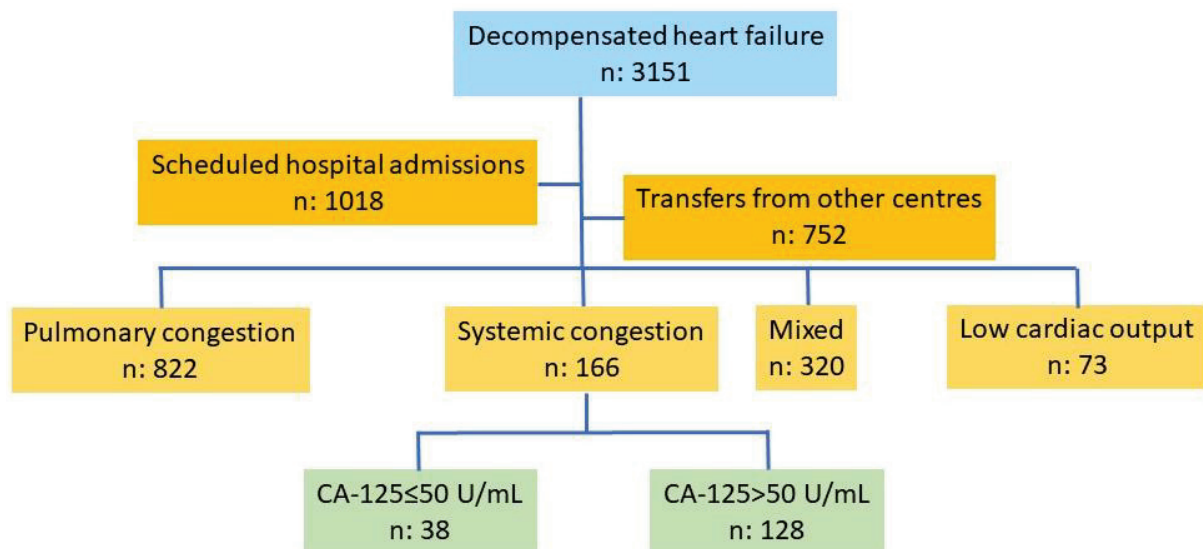


Figure 1. Flow chart of patient selection. Abbreviations: CA-125: carbohydrate antigen 125.

The study was conducted in accordance with the Declaration of Helsinki. The research project was approved by the Biomedical Research Ethics Committee of La Fe University and Polytechnic Hospital, Valencia (Registration No.: 2024-0925-1, Protocol Code/ Acronym: HF-125, approval date 20/11/2024).

Statistical Analysis

Categorical variables are expressed as numbers and percentages, and numerical variables as means and standard deviations or medians and interquartile ranges, depending on the normality distribution (Kolmogorov–Smirnov test).

Comparisons between groups for qualitative variables were performed using the Pearson Chi-squared test with exact bilateral significance, and corrected with Fisher’s exact statistic when any of the expected frequencies in the 2×2 table were less than 5. For comparisons of quantitative variables, Student’s t-test or a Mann–Whitney U test was used for non-normal distributions of independent variables.

For Kaplan–Meier survival curves, comparisons were made using the Log Rank method. Mortality tables were used to analyze the number and percentage of deaths within 365 days by study group. The Wilcoxon statistic (Gehan) was used for statistical tests.

A p -value of <0.05 was considered statistically significant. The statistical software used included IBM SPSS Statistics Version 27[®] and Stata[®] Statistics/Data Analysis 16.1. Graphs were created using Power Point version 2505 and SPSS version 27.

3. Results

3.1. Clinical Data

The comparative analysis between the two groups showed that patients with $CA-125 \leq 50$ U/mL included a higher proportion of women ($p < 0.05$), with some trends indicating a higher proportion of patients with a valvular etiology of HF ($p < 0.1$) (Table 1). The baseline characteristics related to functional class, cause of decompensation, number

of hospital days, and length of stay were similar between the groups ($p > 0.05$) (Table 2). The percentage of patients receiving cardioactive drugs upon admission was similar between groups. The mean number of diuretics prescribed was 1.3 ± 0.9 . Loop diuretics were the most commonly prescribed at admission ($>80\%$), followed by thiazides ($>30\%$). There were no statistically significant differences between any pharmacological groups ($p > 0.05$) (Table 3).

Table 1. Baseline characteristics of patients.

	CA-125 $\leq$ 50 U/mL n: 38	CA-125 $>$ 50 U/mL n: 128	<i>p</i>	Total n: 166
Age (years) #	70 $\pm$ 11	69 $\pm$ 12	0.683	70 $\pm$ 12
Sex (male)	16 (42)	94 (73)	0.001	110 (66)
Baseline heart disease:				
HT	6 (16)	16 (13)	0.599	22 (13)
Ischemic	8 (21)	37 (29)	0.339	45 (27)
IDCM	3 (8)	14 (11)	0.811	17 (10)
Valvular	16 (42)	35 (27)	0.083	51 (31)
Other	5 (13)	26 (20)	0.320	31 (19)
Previous CVS	10 (26)	36 (28)	0.807	46 (28)
HT	32 (84)	93 (73)	0.199	125 (75)
Dyslipidemia	18 (47)	79 (62)	0.135	97 (58)
Diabetes mellitus	14 (38)	55 (43)	0.706	69 (42)
Active smoking *	14 (38)	59 (47)	0.354	73 (44)
Active drinking	3 (8)	6 (5)	0.428	9 (6)
COPD	2 (5)	14 (11)	0.367	16 (10)
SAHS	5 (13)	13 (16)	0.537	18 (11)
Obesity	7 (18)	22 (17)	0.860	29 (17)
Renal failure	16 (42)	55 (43)	0.994	71 (43)
Hypothyroidism	5 (13)	11 (10)	0.533	16 (10)
Atrial fibrillation	22 (58)	82 (65)	0.452	104 (63)
Stroke	2 (5)	14 (11)	0.352	16 (10)
PVD	2 (5)	6 (5)	0.898	8 (7)
Peritoneal dialysis	1 (3)	3 (2)	0.929	4 (4)

Kolmogorov–Smirnov < 0.05 . Median and interquartile range. The rest of the values are expressed as absolute numbers and percentages (in parentheses). * Active smoker or ex-smoker < 1 year. Abbreviations: CA-125: carbohydrate antigen 125; COPD: chronic obstructive pulmonary disease; CVS: cardiovascular surgery; HT: hypertension; IDCM: idiopathic dilated cardiomyopathy; PVD: peripheral vascular disease; SAHS: sleep apnea-hypopnea syndrome.

Table 2. Clinical profiles of patients.

	CA-125 $\leq$ 50 U/mL n: 38	CA-125 $>$ 50 U/mL n: 128	<i>p</i>	Total n: 166
De novo HF	4 (11)	19 (15)	0.601	13 (14)

Table 2. Cont.

Functional class (NYHA)				
I	1 (3)	7 (5)	0.251	8 (5)
II	25 (65)	65 (51)		90 (54)
III, IV	12 (32)	56 (44)		68 (41)
Cause of decompensation				
Disease progression	21 (55)	76 (59)	0.707	97 (58)
Infections	4 (11)	11 (9)		15 (9)
Arrhythmias	6 (16)	14 (11)		20 (12)
Unknown	2 (5)	8 (6)		10 (6)
Other	5 (13)	19 (15)		24 (15)
Number of previous admissions #	2.7 ± 2.2	2.7 ± 2.6	0.972	2.7 ± 2.5
Days of admission #	9.6 ± 6.4	10.0 ± 9.1	0.822	9.9 ± 8.5
Size (cm) #	164 ± 8	163 ± 11	0.390	163 ± 10
Weight (Kg) #	78 ± 17	80 ± 21	0.401	80 ± 20
SBP (mmHg) #	123 ± 26	125 ± 25	0.628	125 ± 25
DBP (mmHg) #	69 ± 13	75 ± 21	0.093	74 ± 19
Heart rate (bpm) #	81 ± 12	85 ± 24	0.325	84 ± 21

All values are those at admission. # Kolmogorov–Smirnov > 0.05. Mean and standard deviation. The rest of the values are expressed as absolute numbers and percentages (in parentheses). Abbreviations: CA-125: carbohydrate antigen 125; DBP: diastolic blood pressure; HF: heart failure; NYHA: New York Heart Association; SBP: systolic blood pressure.

Table 3. Treatment prior to admission.

	CA-125 ≤ 50 U/mL n: 38	CA-125 > 50 U/mL n: 128	<i>p</i>	Total n: 166
ACEI/ARB/ARNI	19 (50)	54 (42)	0.458	73 (44)
Beta-blockers	21 (55)	76 (59)	0.669	97 (58)
MRA	17 (46)	64 (50)	0.711	81 (49)
SGLT2i	5 (13)	33 (26)	0.126	38 (23)
Loop diuretic	31 (82)	108 (84)	0.802	139 (84)
Thiazides	10 (27)	43 (34)	0.550	53 (32)
Tolvaptan	2 (5)	12 (9)	0.738	14 (8)
Acetazolamide	5 (5)	10 (8)	0.891	15 (9)
Number of diuretics #@	1.2 ± 0.8	1.4 ± 0.9	0.419	1.3 ± 0.9

Kolmogorov–Smirnov > 0.05. Mean and standard deviation. The rest of the values are expressed as absolute numbers and percentages (in parentheses). @ Excluding ARM and iSGLT2. Abbreviations: ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ARNI: angiotensin receptor and neprilysin inhibitor; CA-125: carbohydrate antigen 125; MRA: mineralocorticoid receptor antagonist; SGLT2i: Sodium–glucose cotransporter 2 inhibitor.

3.2. Analytical and Echocardiographic Data

When comparing analytical parameters upon admission between the two groups, few significant differences were found. Bilirubin and aspartate aminotransferase (GOT/AST) levels were lower in the low-CA-125 group ($p < 0.05$). The median CA-125 level in the study group was 23 with an interquartile range of 20, while in the CA-125 > 50 U/mL group, it was 209 with an interquartile range of 275 ($p: 0.0001$) (Table 4).

Table 4. Blood tests on admission.

	CA-125 $\leq$ 50 U/mL n: 38	CA-125 > 50 U/mL n: 128	<i>p</i>	Total n: 166
Urea (mg/dL)	66 (69)	80 (84)	0.443	73 (78)
Creatinine (mg/dL)	1.6 (1.5)	1.6 (1.1)	0.426	1.6 (1.1)
Glomerular filtration rate (mL/min/1.73 m ²)	38 (31)	42 (36)	0.473	42 (34)
Bilirubin (mg/dL)	0.7 (0.5)	1.2 (1.2)	0.003	1.0 (1.1)
GOT/AST (U/L)	18 (12)	25 (15)	0.037	24 (14)
GPT/ALT (U/L)	14 (10)	18 (15)	0.139	17 (14)
usTnT (ng/L)	43 (36)	58 (52)	0.145	52 (44)
NT-proBNP (pg/mL)	5770 (4685)	5902 (6058)	0.193	5836 (5494)
Sodium (mEq/L)	139 (7)	136 (11)	0.160	138 (9)
Potassium (mEq/L)	4.1 (0.9)	4.0 (1.1)	0.867	4.0 (1.1)
Hemoglobin (g/dL)	11.0 (3.2)	12.9 (2.3)	0.772	12.5 (2.8)
Hematocrit (%)	34 (8)	41 (9)	0.439	39 (11)
Platelets (μ L, $\div$ 100)	168 (92)	210 (81)	0.378	201 (82)
Uric acid (mg/dL)	8.4 (3.5)	8.6 (2.7)	0.593	8.6 (2.8)
TSAT (%)	22 (12)	18 (11)	0.452	19 (12)
Ferritin (ng/mL)	136 (322)	165 (340)	0.565	161 (337)
CA-125 (U/mL)	23 (20)	209 (275)	0.0001	148 (270)

Median and interquartile range. The rest of the values are expressed as absolute numbers and percentages (in parentheses). Abbreviations: ALT (GPT), alanine aminotransferase; AST (GOT), aspartate aminotransferase; CA-125: carbohydrate antigen 125; TSAT: transferrin saturation; NT-proBNP: N-terminal pro-B-type natriuretic peptide; usTnT: ultrasensitive troponin.

Significant differences were found in some echocardiographic parameters between the study groups. The percentage of patients with a preserved left ventricular ejection fraction (LVEF) ($\geq 50\%$) was higher in the normal-CA-125 group. Right ventricular (RV) size was increased in both groups but without significant differences ($p > 0.05$). However, right ventricular dysfunction was more common in the CA-125 > 50 U/mL group ($p < 0.05$). Inferior vena cava (IVC) dilation was present in both groups, but more patients in the normal-CA-125 group showed greater than 50% inspiratory collapse ($p < 0.05$) (Table 5).

Table 5. Echocardiographic evaluation.

	CA-125 $\leq$ 50 U/mL n: 38	CA-125 > 50 U/mL n: 128	<i>p</i>	Total n: 166
Preserved LVEF ($\geq 50\%$)	22 (58)	51 (40)	0.038	73 (44)
Dilated LV (LV-EDD > 56 mm)	12 (32)	46 (36)	0.450	58 (35)
LVH (>12 mm)	23 (61)	64 (50)	0.170	87 (52)
Severe left atrial dilatation (≥ 50 mm)	14 (37)	52 (41)	0.765	66 (40)
Significant valvulopathies *				
AoR	1 (3)	4 (3)	0.663	5 (3)

Table 5. Cont.

	CA-125 $\leq$ 50 U/mL n: 38	CA-125 $>$ 50 U/mL n: 128	<i>p</i>	Total n: 166
AoS	3 (8)	7 (5)	0.702	10 (6)
MR	7 (18)	19 (15)	0.620	26 (16)
MS	0 (0)	4 (3)	0.573	4 (2)
TR	15 (39)	44 (34)	0.565	59 (36)
RV function (TAPSE) @				
Normal	18 (46)	53 (41)	0.004	71 (43)
Mild dysfunction	13 (36)	17 (14)		30 (18)
Moderate dysfunction	5 (13)	31 (24)		36 (22)
Severe dysfunction	2 (5)	27 (21)		29 (17)
Dilated RV (basal diameter $>$ 40 mm)	27 (71)	83 (65)	0.471	110 (66)
Inferior vena cava (mm) #	23 (7)	23 (4)	0.085	23 (5)
Vena cava collapse $\geq$ 50%	20 (53)	23 (18)	0.001	43 (26)
PH (PAsP $\geq$ 50 mmHg)	19 (50)	88 (69)	0.102	107 (64)

Median and interquartile range. The rest of the values are expressed as absolute numbers and percentages (in parentheses). * moderate–severe + severe. @ TAPSE intervals: Normal: TAPSE $\geq$ 17 mm; Mild dysfunction: TAPSE 13–16 mm; Moderate dysfunction: TAPSE 10–12 mm; Severe dysfunction: TAPSE $<$ 10 mm. Abbreviations: AoS: aortic stenosis; AoR: aortic regurgitation; CA-125: carbohydrate antigen 125; LV-EDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; MS: mitral stenosis; MR: mitral regurgitation; PH: pulmonary hypertension; LVH: left ventricular hypertrophy; PAsP: pulmonary artery systolic pressure; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation. # Kolmogorov–Smirnov $<$ 0.05.

3.3. Survival

Survival analysis showed high mortality rates among these patients from admission and throughout the follow-up period of more than four years. The survival probability differed starting from the first month after hospitalization, with a significant trend towards higher mortality in the CA-125 $>$ 50 U/mL group (0.07). After the first month, the differences were consistently significant ($p <$ 0.05) (Table 6).

Table 6. Survival probability at follow-up.

	CA-125 $\leq$ 50 U/mL n: 38	CA-125 $>$ 50 U/mL n: 128	<i>p</i>	Total n: 166
30 days	97	91	0.074	93
1 year	88	63	0.0001	69
2 years	79	47	0.0001	54
3 years	53	24	0.0001	31
4 years	53	24	0.0001	31

The values represent survival percentages. Abbreviations: CA-125: carbohydrate antigen 125.

The survival curves showed significant differences, particularly at four years of follow-up. The probability of being alive in the study group was above 50%, while in the CA-125 $>$ 50 U/mL group, it was around 25% ($p <$ 0.05) (Figure 2). Figure 3 illustrates the different mortality proportions between the two groups from hospitalization and through-

out follow-up, showing that the elevated-CA-125 group had higher mortality at all stages analyzed ($p < 0.05$). We have included a Graphical Abstract summarizing the results.

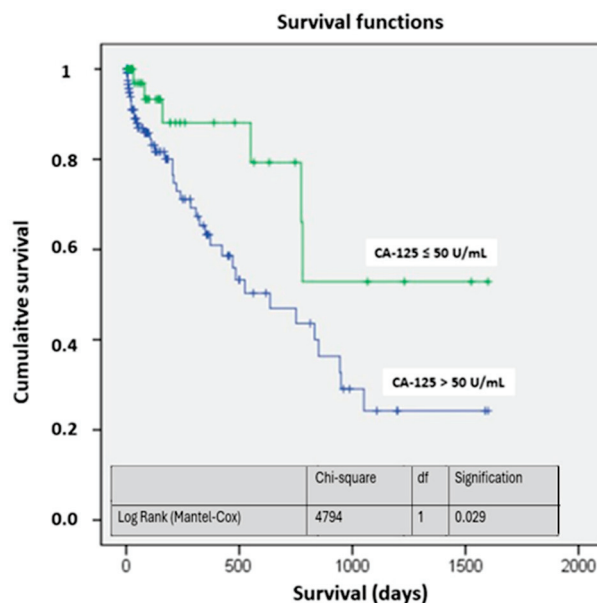


Figure 2. Survival based on CA-125. Abbreviations: CA-125: carbohydrate antigen 125; df: degrees of freedom.

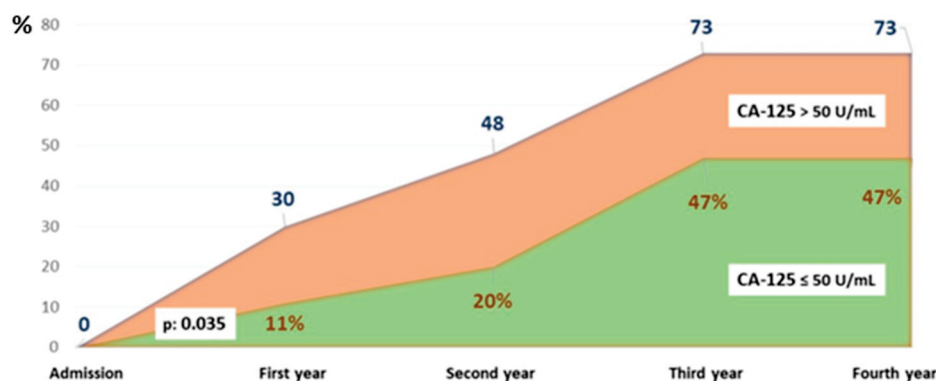


Figure 3. Cumulative percentage of patients who died by group and year of follow-up. Abbreviations: CA-125: carbohydrate antigen 125.

4. Discussion

CA-125 is a novel biomarker that has been linked to congestion. Of the various congestion patterns described [3], the one associated with higher CA-125 values is systemic congestion [4,5,11]. However, there is a group of patients who do not develop this elevation, which remains unexplained in the current scientific literature [6,7,12]. The aim of this study was to analyze patients admitted consecutively for decompensated congestive HF to compare whether a $CA-125 \leq 50$ U/mL is associated with certain clinical characteristics and echocardiographic findings and whether it has implications for survival. It has been shown that normal CA-125 levels are more common in women with a preserved left ventricular ejection fraction (LVEF), a right ventricle (RV) with normal function or mild dysfunction, and the presence of inspiratory collapse of $> 50\%$ in the inferior vena cava (IVC) [6,7,12]. Additionally, it has a clear prognostic relationship, so it could enable the identification of a subgroup of patients with a better prognosis.

Regarding the chosen cutoff point (50 U/mL), it should be noted that the maximum normal value is not defined in heart failure, with the value commonly used in ovarian can-

cer being 35 U/mL [8,13]. Only one study analyzed cutoff points in acute HF (<23 U/mL); however, this cutoff was established based on a retrospective cohort analysis with a validation cohort including patients only up to 2018, and the timing of CA-125 measurement differed slightly between the two cohorts [14]. The 50 U/mL threshold helps reduce variability by excluding smaller elevations that may not be clinically significant, ensuring that only cases with a relevant increase in CA-125 are considered. In this sense, standardizing and homogenizing the diagnostic tests performed on patients admitted for HF decompensation would contribute to establishing better knowledge of this molecule and improved clinical management of patients, as CA-125 is still not routinely requested in many centers [9,10]. To achieve this, the use of pre-configured analytical profiles that systematically include this biomarker is essential [10].

In this study, 23% of the patients had low CA-125 levels despite being admitted for acute HF with clear systemic congestion. There are factors that have not been clarified, which explain why normal CA-125 values are found in populations that typically present elevated levels. In the BIOSAT-CHF cohort (1583 patients with acute congestive heart failure), 34.6% of the patients had CA-125 levels below 35 U/mL [15]. Even in women with advanced serous ovarian cancer, which represents the paradigm of elevated CA-125, some series report up to 10–20% of patients with normal levels [16,17].

In our series, patients admitted for acute HF with low CA-125 levels at admission were more frequently women. Other baseline characteristics showed no significant differences between the groups. In other published series, the female sex has also been described as an independent predictor of low CA-125 [6]. Atrial fibrillation (AF) and its recurrence after ablation have been linked to elevated plasma levels [18,19], although we did not find this relationship in this study of patients with acute congestive HF.

Regarding pharmacological treatment, up to one-third of patients in our series were receiving treatment with three diuretic drugs, with sequential nephron blockade being the usual strategy employed in congestive patients [3]. Many patients with reduced-ejection-fraction heart failure (HFrEF) are already treated with mineralocorticoid receptor antagonists as part of HF treatment [20]. The low number of patients treated with sodium–glucose cotransporter type 2 inhibitors (SGLT2is) is notable, but it should be considered that patient recruitment started in 2019 when their level of recommendation in heart failure guidelines was not yet established. One study evaluated the effect of dapagliflozin on CA-125 levels in the short term in chronic HFrEF, finding that this drug was associated with a significant reduction in CA-125 [21]; however, this has not been analyzed in acute HF, for which the literature is scarce.

From an analytical perspective, it is common for patients with congestive heart failure to have renal impairment and develop cardiorenal syndrome [22–24]. In this series, no differences were found in renal function, ions, hemograms, or amino-terminal fragment of the brain natriuretic peptide (NT-proBNP). The absence of a relationship between CA-125 and renal function is an expected finding, as it has been demonstrated that this biomarker is not affected by renal function [25]. In contrast, some studies have found a direct association between CA-125 and NT-proBNP levels [6,7]. Patients with low CA-125 had lower levels of bilirubin and liver enzymes (AST). Since bilirubin and transaminases are especially elevated in right ventricular failure, it is justified that higher levels of these biomarkers are associated with elevated CA-125 levels [4,26]. Bilirubin and AST are primarily elevated in response to hepatic congestion and hypoperfusion, while alanine aminotransferase (ALT) is more specific for pure hepatocellular damage and less sensitive to hypoxia [27]. One possible hypothesis for the lack of significant differences in NT-proBNP levels between groups is that both groups had a similarly high baseline risk and comparable degrees of congestion at admission. Lower AST and bilirubin levels are associated with less systemic

congestion and better prognosis in the context of HF [28], although in the specific scenario of congestion with low CA-125, this correlation has not been specifically studied.

From an echocardiographic perspective, patients with CA-125 < 50 U/mL were more likely to have preserved LVEF, along with normal or mildly depressed RV function. Other echocardiographic parameters showed no significant differences, nor did the size of the IVC. However, in the group with CA-125 < 50 U/mL, half of the patients had inspiratory collapse of the IVC of >50%. The relationship between CA-125 levels and echocardiographic parameters has shown contradictory results in some studies. In several studies in patients with congestive heart failure, CA-125 levels did not correlate with LVEF or the left ventricular end-diastolic diameter [29,30]. However, other groups described a positive correlation between CA-125 levels and pulmonary systolic pressure and a negative correlation with the ejection fraction [31]. The size of the IVC, part of the VEXUS (Venous Excess Ultrasound) score, was also not associated with higher CA-125 levels in the present study. It is important to remember that VEXUS is not yet validated in all settings and may be affected by frequent alterations in patients with HF, such as the degree of tricuspid regurgitation [23,24]. Regarding the collapse of the IVC, there are no studies that analyze the collapse and its size separately with CA-125. However, it has been described that there is a greater (inverse) correlation between the percentage of IVC collapse and the degree of venous congestion (measured using central venous pressure (CVP)), compared to the direct correlation between CVP and IVC diameter [32,33].

As for survival, the curves differ since admission, and the probability of survival shows significant differences at one year, which become more pronounced at 3–4 years. Other observational studies analyzing two-year survival based on CA-125 and NT-proBNP levels in acute HF have also reproduced these results, with CA-125 being an independent prognostic factor for survival, and with higher levels being associated with higher mortality [34]. Mansour IN et al. analyzed survival according to CA-125 levels at admission, divided into quartiles, in decompensated heart failure. Patients in the highest quartile with CA-125 levels >50.6 U/mL had a 46% mortality rate at 40 months, compared to the group with levels below 8.3 U/mL, which had a mortality rate of 13.6% [35].

The high 4-year mortality in the group with congestive HF and elevated CA-125 levels is striking. This group has been shown to have the worst prognosis in some series, even worse than patients with low-output heart failure [4,36]. This could be justified because patients with systemic congestion more often have poorer renal function and RV function, both independent predictors of poorer survival [37].

Thus, CA-125 is a recently used clinical biomarker in HF, associated with congestion and with prognostic value, especially in a chronic outpatient context [38]. However, it is a biomarker that is not heart-specific and can be elevated in oncological or inflammatory diseases [3,5], and a significant percentage of patients, nearly 25% in our series, may present normal values of this biomarker despite congestive heart failure decompensation. Furthermore, its cutoff point is not fully validated in HF, with the value commonly used being that for ovarian cancer (35 U/mL) [8,14], and the cutoff points in HF come from retrospective cohorts [15]. It still does not have the same validity as other biomarkers used in cardiology, such as troponins or NT-proBNP. NT-proBNP is widely validated, organ-specific, and part of the heart failure diagnostic algorithm in clinical practice guidelines [22]. Therefore, in the context of acute HF, CA-125 should still be considered an experimental biological marker, and more basic and clinical studies are needed to help standardize it. Future studies should aim to better understand the interaction between systemic inflammation, venous congestion, and serosal activation, which might explain CA-125 fluctuations.

This is a retrospective, single-center study based on a database compiled upon patient discharge. Other causes that might elevate this biomarker were not analyzed, although in

some cases, a gynecologist was consulted to perform tumor screening tests, all of which were negative. A value of 50 was chosen to balance the groups, as there is no recommended value in the literature specifically for heart failure, and the values established are related to ovarian neoplasia. On the other hand, a value of 50 helps avoid giving importance to minor elevations without clinical significance. CA125 was not assessed at discharge despite the average hospital stay being nearly 10 days. However, the series is consecutive, which lends reliability to the results, and was completed by the team of cardiologists in the Heart Failure Unit. Additionally, all data were verified by a single cardiologist, who is also part of the team, before inclusion in the database.

5. Conclusions

Based on this study's results, it can be concluded that the relationship of patients with HF and decompensated systemic congestion requiring hospitalization and presenting low CA-125 is 1:4. These patients are mostly women with preserved LVEF, normal or slightly reduced RV function, and inspiratory collapse of the inferior vena cava of >50%. Moreover, they have a better survival rate, so a low CA-125 at admission in this cohort of patients could identify a subgroup with a better prognostic evolution.

Author Contributions: Conceptualization, L.A.-B.; methodology, L.A.-B.; validation, L.A.-B.; formal analysis, L.A.-B.; investigation, L.A.-B. and R.L.-V.; resources, L.A.-B. and R.L.-V.; data curation, L.A.-B., R.L.-V., B.G.C., V.S.A., V.D.T., J.M.-S., S.H.M. and F.A.; writing—original draft preparation, L.A.-B., R.L.-V. and B.G.C.; writing—review and editing, L.A.-B., R.L.-V. and B.G.C.; supervision, L.A.-B.; project administration, L.A.-B.; review of final draft, R.L.-V., B.G.C., V.D.T., J.M.-S., S.H.M., V.S.A., F.A., L.M.D. and L.A.-B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and approved by the Instituto de Investigación Sanitaria La Fe (Registration No.: 2024-0925-1, Protocol Code/ Acronym: HF-125, approval date: 20 November 2024).

Informed Consent Statement: Patient consent was waived due to the retrospective and observational nature of the study.

Data Availability Statement: The dataset is available upon request to the authors.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ALT	Alanine aminotransferase
CA-125	Carbohydrate antigen 125
CVP	Central venous pressure
GOT/AST	Aspartate aminotransferase
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
IVC	Inferior vena cava
LVEF	Left ventricular ejection fraction
NTproBNP	Amino-terminal fragment of the brain natriuretic peptide
RV	Right ventricle
SGLT2i	Sodium–glucose cotransporter type 2 inhibitor
VEXUS	Venous Excess Ultrasound

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Article

Myocardial Damage Patterns in Patients with Left Ventricular Systolic Dysfunction with and Without Coronary Artery Disease Referred for Cardiac Magnetic Resonance[†]

Justyna M. Sokolska ^{1,2,*}, Katarzyna Logoń ³, Magdalena Pszczółowska ³ and Wojciech Kosmala ^{1,2}

¹ Department of Cardiovascular Imaging, Institute of Heart Diseases, Faculty of Medicine, Wrocław Medical University, 50-556 Wrocław, Poland; wojciech.kosmala@umw.edu.pl

² Institute of Heart Diseases, Jan Mikulicz-Radecki University Hospital, 50-556 Wrocław, Poland

³ Institute of Heart Diseases, Faculty of Medicine, Student Scientific Club of Transplantology and Advanced Therapies of Heart Failure, Wrocław Medical University, 50-556 Wrocław, Poland; katarzyna.logon@student.umw.edu.pl (K.L.); magdalena.pszczolowska@gmail.com (M.P.)

* Correspondence: justyna.sokolska@umw.edu.pl

[†] This article is a revised and expanded version of a paper entitled “The aetiology of myocardial damage in patients with left ventricular systolic dysfunction with and without coronary artery disease referred for cardiac magnetic resonance”, which was presented at the Heart Failure 2023 and the World Congress on Acute Heart Failure, Prague, Czechia, 20–23 May 2023.

Abstract

Background: Cardiac magnetic resonance (CMR) is widely used to determine the underlying cause of left ventricular (LV) systolic dysfunction. Patients with ischemic disease are less frequently referred for CMR, as the underlying disease is often presumed to explain LV systolic dysfunction. However, various etiologies of myocardial impairment may coexist. Late gadolinium enhancement (LGE) is a technique used for tissue characterization, particularly visualization of myocardial fibrosis. **Objectives:** The aim of this study was to assess the prevalence of LGE patterns suggesting ischemic or non-ischemic etiology of myocardial damage in patients with LV systolic dysfunction with and without known coronary artery disease (CAD). **Methods:** 131 patients (76% male, 55 ± 15 years old) with LV ejection fraction (LVEF) $\leq 50\%$ in echocardiography underwent CMR between December 2021 and November 2022. Patients were divided according to the known history of CAD. Regional subendocardial and transmural LGE was interpreted as ischemic etiology, whereas midmyocardial and subepicardial LGE was non-ischemic. **Results:** The mean LVEF assessed in CMR was $35 \pm 10\%$. A total of 122 patients underwent CMR with LGE sequence. LGE was detected in 62% of patients: 34% had a non-ischemic pattern, 16% ischemic, and 11% mixed. LGE patterns did not differ between patients with and without CAD. In every third patient with CAD and almost every second patient without CAD, no myocardial fibrosis was detected. A completely normal CMR study was found in 6% of patients without CAD and 1% of patients with CAD (all p NS). **Conclusions:** The LGE patterns suggesting ischemic or non-ischemic myocardial damage are similarly prevalent in patients with and without known CAD. The diagnosis based solely on clinical information may be unreliable, as LV dysfunction might have multifactorial origins. The absence of local myocardial fibrosis is relatively common in patients with LV dysfunction, irrespective of its etiology.

Keywords: magnetic resonance imaging; late gadolinium enhancement; cardiomyopathy; heart failure; ischemic heart disease

1. Introduction

Heart failure (HF) is a clinical syndrome that stems from cardiac structural and functional abnormalities leading to impairment in myocardial contractility and/or ventricular filling. HF is one of the biggest challenges in modern medicine. Each year, it is the reason for over 1 million hospitalizations in North America and Europe [1], making HF a huge concern for the healthcare system.

Cardiovascular magnetic resonance (CMR) has become a widely used tool for diagnosing the etiology of HF and determining whether its character is ischemic, non-ischemic, or mixed. CMR imaging provides precise information on tissue characterization, cardiac chamber volumes, and myocardial mass, and allows for the detection of even small local myocardial damage [2,3]. The distribution and extension of late gadolinium enhancement (LGE) obtained with contrast administration can provide etiology-focused data on myocardial injury.

LGE enables the visualization of increased extracellular spaces in conditions such as fibrosis, fibrofatty tissue, or edema. The patterns of LGE help to differentiate between ischemic and non-ischemic myocardial injury. Specific LGE distribution is useful in distinguishing between non-ischemic etiologies of LV systolic dysfunction such as hypertrophic cardiomyopathy, sarcoidosis, myocarditis, amyloidosis, and Fabry disease [4,5].

In recent years, CMR has evolved considerably, with improvements in both imaging sequences and hardware [6]. New methods such as parametric mapping and four-dimensional flow are now being more commonly used in clinical practice. While CMR offers valuable diagnostic information, it also presents certain limitations, particularly long image processing times. Emerging artificial-intelligence-based algorithms have the potential to reduce processing times [7]. Functional CMR has been investigated as a method to evaluate myocardial viability and perfusion. It can assess regional tissue contractility through techniques like MRI tagging, which has been shown to reveal early manifestations of subclinical cardiac dysfunction that typically precede reductions in EF [8].

The purpose of this study was to investigate the consistency of LGE patterns in CMR, suggesting ischemic and non-ischemic etiology of myocardial damage, with the diagnosis of CAD established on the basis of clinical data.

2. Materials and Methods

2.1. Study Population

This retrospective study was performed in a tertiary cardiology center in Poland. The records of all in- and outpatients who underwent CMR between December 2021 and November 2022 were reviewed. Inclusion criteria were age ≥ 18 years and reduced LV ejection fraction ($LVEF \leq 50\%$), based on the transthoracic echocardiography, and an unknown HF etiology as the reason for referral for CMR. This article is a revised and expanded version of a paper entitled “The aetiology of myocardial damage in patients with left ventricular systolic dysfunction with and without coronary artery disease referred for cardiac magnetic resonance”, which was presented at the Heart Failure 2023 and the World Congress on Acute Heart Failure, Prague, Czechia, 20–23 May 2023 [9].

After inclusion, information such as demographics, clinical history, comorbidities, and present treatment was collected. For further analysis, the studied population was divided into two groups according to the known history of CAD, including history of ischemic coronary disease diagnosed by the referring cardiologist (based on coronary computed tomography angiography or invasive coronary angiography), past acute coronary syndromes, and revascularization procedures.

The study was conducted in accordance with the Declaration of Helsinki, and authorization to perform this study was obtained from the Wroclaw Medical University Ethical

Committee (approval number: 19-285A). All data used for this study were acquired for clinical purposes. Due to the retrospective design of the study, the requirement for written informed consent was waived by the University Ethical Committee. Data processing was performed anonymously and in strict confidence.

2.2. Laboratory Measurements

For all inpatients, routine venous blood samples were taken during hospitalization. The following laboratory measurements were performed using standard methods: (i) hematology: hemoglobin, hematocrit, leucocytes, platelets; (ii) renal function tests: creatinine (with a calculation of the estimated glomerular filtration rate (eGFR)); (iii) plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP); (iv) glucose. Outpatients did not have additional venous blood samples taken.

2.3. Cardiac Magnetic Resonance Imaging

CMR imaging was performed during breath holding at end-expiration using a 1.5 Tesla MRI scanner (Siemens Magnetom Sola Cardiovascular Edition, Siemens Healthineers, Erlangen, Germany) to assess myocardial tissue characteristics and evaluate left and right ventricular diameters, volumes, and function. For all patients, the CMR protocol included cine imaging with a balanced steady-state free precession sequence for cardiac volume assessment (short-axis stack covering the entire left ventricle; two-, three-, and four-chamber views) and LGE imaging to evaluate myocardial scar tissue. LGE imaging was applied in the same orientations as cine images to identify myocardial fibrosis, with Phase-Sensitive Inversion Recovery (PSIR) sequences acquired approximately 10–15 min after the administration of 1.5 mL of gadolinium contrast per kilogram of body weight (gadobutrol, Gadovist 1.0, Bayer Schering Pharma, Zurich, Switzerland). The LGE pattern acquired in CMR with contrast administration was used to determine the possible etiology of myocardial dysfunction in the studied population. Regional subendocardial and transmural LGE was interpreted as of ischemic etiology, whereas midmyocardial and subepicardial LGE was of non-ischemic origin [10] (see Figure A1). CMR images were evaluated using the commercially available CVI42 software (version 5.17, Circle Cardiovascular Imaging, Calgary, AB, Canada).

2.4. Statistical Analysis

Statistical analysis was performed using Statistica (StatSoft Polska, version 13.3). Continuous variables were presented as mean with standard deviation (SD). The assumption of normality was tested using the Kolmogorov–Smirnov test. Categorical variables were expressed as counts and percentages. Differences between blood and CMR parameters were assessed by unpaired *t*-tests or respective non-parametric tests if data were not normally distributed. A *p* value equal to or less than 0.05 was considered statistically significant.

3. Results

3.1. Patient Characteristics

Of 647 CMR studies performed between December 2021 and November 2022, 131 patients (20%) satisfying the inclusion criteria were enrolled. The average age was 55 ± 15 years, 76% were men, the average LVEF assessed by echocardiography was 35%, and 62% of the studied patients had a known CAD history. Previous acute coronary syndrome was diagnosed in 12% of the total studied population, with previous myocardial infarction affecting every tenth person. Regarding co-morbidities, lipid disorders and/or hypertension were present in over half of the studied population, 12% of patients had a history of acute heart failure, and every fifth patient suffered from diabetes. Twenty-three

percent of the studied population had at least moderate valve disease, most commonly significant mitral regurgitation (15%) and tricuspid regurgitation (9%). Atrial fibrillation was present in one-third of patients, and 8% had implanted cardiac devices. Among the study participants, 43% were smokers. The most commonly used medications were beta-blockers, SGLT-2 inhibitors, aldosterone antagonists, and statins. Detailed baseline characteristics of the study population are presented in Table 1.

Table 1. Baseline characteristics of the study population and studied subgroups.

Parameters	Studied Population n = 131	Patients Without CAD n = 50 (38%)	Patients with CAD n = 81 (62%)	p
Demographics				
Age (years)	55 ± 15	55 ± 16	55 ± 15	0.90
Male sex, n (%)	100 (76)	38 (76)	62 (77)	0.94
LVEF, % (echocardiography)	35 ± 10	39 ± 9	33 ± 10	0.006 *
Clinical data				
Known coronary artery disease (CAD), n (%); including previous acute coronary syndromes (UA and/or MI), n (n%)	81 (62); 18 (14)	0 0	81 (100) 18 (22)	<0.001 *
Hypertension, n (%)	66 (54)	21 (48)	45 (57)	0.32
Atrial fibrillation, n (%)	42 (34)	17 (39)	25 (32)	0.43
Significant (moderate or severe) valve disease, n (%)	28 (23)	9 (20)	19 (24)	0.58
Chronic kidney disease, n (%)	23 (19)	8 (18)	15 (19)	0.91
Liver diseases, n (%)	13 (11)	6 (14)	7 (9)	0.04 *
Chronic obstructive pulmonary disease/asthma, n (%)	4 (3)	4 (9)	0	0.02 *
Number of comorbidities, n (%)	2.9 ± 1.8	1.9 ± 1.3	3.4 ± 1.8	<0.001 *
Basic laboratory parameters				
Hemoglobin (g/dL)	14.4 ± 2.0	14.6 ± 1.9	14.2 ± 2.0	0.69
Platelets (10 ³ /μL)	225 ± 69	203 ± 53	237 ± 74	0.01 *
Creatinine (mg/dL)	1.24 ± 1.22	1.15 ± 1	1 ± 1	0.55
NTproBNP (pg/L)	3433 ± 8131	2639 ± 5683	3782 ± 9011	0.51
Treatment				
Loop diuretics, n (%)	66 (57)	19 (45)	47 (64)	0.06
ACEI/ARB, n (%)	43 (37)	17 (41)	26 (35)	0.53
Sacubitril + valsartan, n (%)	44 (38)	17 (41)	27 (36)	0.63
Beta-blockers, n (%)	100 (86)	38 (90)	62 (83)	0.25
Aldosterone antagonists, n (%)	81 (69)	28 (67)	53 (71)	0.65
SGLT-2 inhibitors, n (%)	78 (67)	27 (64)	51 (68)	0.68
Statins, n (%)	69 (59)	25 (60)	44 (59)	0.93
Acetylsalicylic acid, n (%)	27 (23)	6 (14)	21 (28)	0.09
P2Y12 inhibitors (clopidogrel/prasugrel/ticagrelor), n (%)	12 (10)	0	12 (16)	0.006 *
Dual antiplatelet therapy, n (%)	9 (7)	0	9 (11)	0.003 *

Results are presented as numbers with a percentage or an average number with standard deviation. Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; * A p value of 0.05 or lower was considered significant.

3.2. Studied Subgroups

The studied group was divided into 2 subgroups: patients with and without known CAD in their medical history, accounting for 62% and 38% of the population, respectively.

Among comorbidities, significant differences between studied subgroups were observed in liver diseases and asthma, which were more common in the group without CAD. In this group, aortic regurgitation in a moderate/severe state was observed significantly more often than in those with CAD (9 vs. 1%, $p = 0.04$).

In 117 patients, venous blood samples were taken. Regarding the laboratory findings, the number of blood platelets was significantly higher in the group with CAD.

There were no differences between the two groups in terms of medications used, except P2Y12 inhibitors, which were used by 16% of the patients with CAD and no patients without known CAD. Furthermore, 20% of the CAD subgroup had previous acute coronary syndromes, including myocardial infarction with/without ST elevation in 16% of this subgroup. Detailed baseline characteristics of the study subgroups are presented in Table 1.

3.3. CMR Findings

A total of 122 (93%) patients underwent CMR study with contrast administration and were included into further analysis of LGE presence and patterns, whereas in 9 patients, contrast was not administered due to chronic kidney disease/dialysis ($n = 5$), or because the study was interrupted as there were non-diagnostic cine images with severe artifacts coming from implanted devices (ICD $n = 3$, CRT-D $n = 1$).

Patients with CAD had lower LVEF, more dilated left ventricles, and higher LV mass than those without CAD. There were no relevant differences in the right ventricle between the studied subgroups (Table 2).

Table 2. Cardiac magnetic resonance characteristics in the studied population.

Parameters	Studied Population n = 131	Patients Without CAD n = 50	Patients with CAD n = 81	p
Left ventricle and atrium				
IVSd (mm)	10 ± 2	10 ± 2	10 ± 2	0.87
LVEDd (mm)	65 ± 9	62 ± 8	67 ± 9	0.004 *
LVESd (mm)	52 ± 12	49 ± 9	55 ± 12	0.01 *
LVEDVi (mL/m ²)	124 ± 37	115 ± 28	130 ± 42	0.04 *
LVESVi (mL/m ²)	80 ± 37	70 ± 27	88 ± 42	0.01 *
LVEF (%)	38 ± 12	41 ± 11	35 ± 12	0.004 *
LV-CO (mL/min)	6 ± 6	7 ± 5	6 ± 6	0.54
LVMassEDi (g/m ²)	72 ± 19	69 ± 17	73 ± 20	0.2
LAVI (mL/m ²)	50 ± 19	50 ± 2	50 ± 19	0.88
Right ventricle and atrium				
RVEDVi (mL/m ²)	89 ± 27	89 ± 22	89 ± 30	0.96
RVESVi (mL/m ²)	47 ± 26	48 ± 25	46 ± 27	0.74
RVEF (%)	50 ± 11	49 ± 10	50 ± 12	0.88
RAVI (mL/m ²)	44 ± 19	47 ± 21	42 ± 18	0.18

Abbreviations: CAD, coronary artery disease; IVSd, interventricular septum end-diastolic diameter; LAVI, left atrial volume index; LV-CO, left ventricular cardiac output; LVEDd, left ventricular end-diastolic diameter; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESd, left ventricular end-systolic diameter; LVESVi, left ventricular end-systolic volume index; LVMassEDi, left ventricular end-diastolic mass index; RAVI, right atrial volume index; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction. * A p value of 0.05 or lower was considered significant.

CMR revealed that LGE was present in the majority of the studied HF population. Subepicardial and/or midmyocardial LGE, suggesting non-ischemic myocardial damage, was found in half of the studied group, whereas subendocardial LGE, indicating ischemic

myocardial damage, was found in almost every third patient. Every tenth patient had both patterns of myocardial damage (Table 3, Figure 1).

Table 3. Cardiac magnetic resonance—late gadolinium enhancement characteristics in the studied population.

Parameters	Studied Population n = 131	Patients Without CAD n = 50	Patients with CAD n = 81	p
LGE sequence, n (%)	122 (93)	47 (94)	75 (93)	0.76
Presence of LGE, n (%)	75 (61)	26 (55)	49 (65)	0.14
Subendocardial and transmural pattern of LGE, n (%)	34 (28)	10 (21)	24 (32)	0.20
Cardiac segments with subendocardial and transmural LGE, n	1.0 ± 2.1	0.6 ± 1.3	1.2 ± 2.5	<0.001 *
Subepicardial pattern of LGE, n (%)	9 (7)	5 (11)	4 (5)	0.28
Cardiac segments with subepicardial LGE, n	0.3 ± 1.3	0.4 ± 1.3	0.3 ± 1.3	0.92
Midmyocardial pattern of LGE, n (%)	52 (43)	19 (40)	36 (44)	0.70
Cardiac segments with midmyocardial LGE, n	1.4 ± 2.3	1.5 ± 2.9	1.3 ± 1.8	<0.001 *
Subepicardial and midmyocardial pattern of LGE, n (%)	55 (45)	21 (45)	34 (45)	0.94
Interpretation of myocardial damage				
Isolated ischemic myocardial damage, n (%)	20 (16)	5 (11)	15 (20)	0.17
Isolated non-ischemic myocardial damage, n (%)	41 (34)	16 (34)	25 (33)	0.94
Mixed myocardial damage, n (%)	14 (11)	5 (11)	9 (12)	0.82
Normal CMR findings (LVEF ≥ 51% in men and >52% in women)	4 (3)	3 (6)	1 (1)	0.12

Abbreviations: CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; * A *p* value of 0.05 or lower was considered significant.

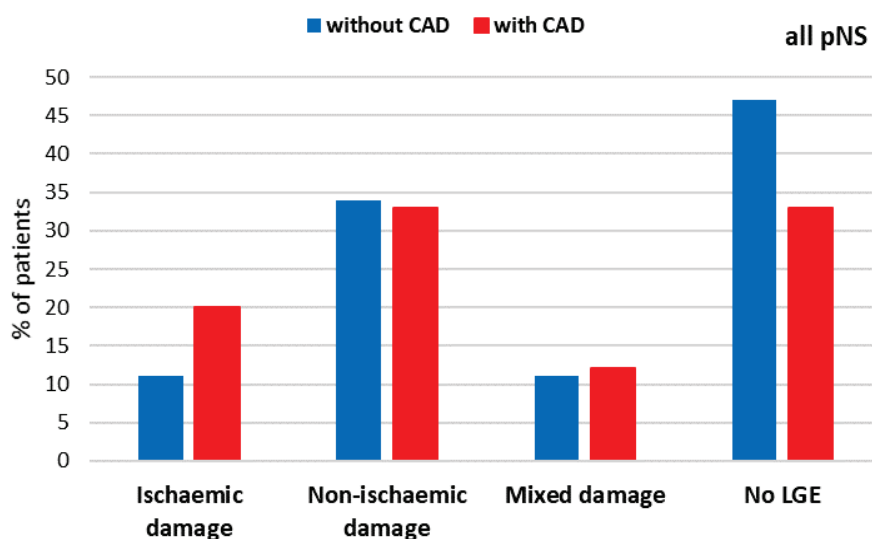


Figure 1. Distribution of myocardial damage based on LGE interpretation in patients with LVEF ≤ 50%.

There were no differences between subgroups with and without known CAD in the frequency of LGE patterns. However, patients with known CAD had, on average, twice as many cardiac segments with subendocardial scarring as those without a previous diagnosis of CAD. The number of segments with midmyocardial LGE was significantly higher among subjects without CAD (Table 3). Among patients with a history of acute coronary syndromes and/or revascularization procedures, the most common LGE pattern was ischemic, observed in 44% of cases. A mixed pattern was present in 22% of patients, while a non-ischemic pattern was present in 17%. In one patient, no myocardial fibrosis was detected. A summary of CMR findings, together with a study flowchart, is presented in Figure 2.

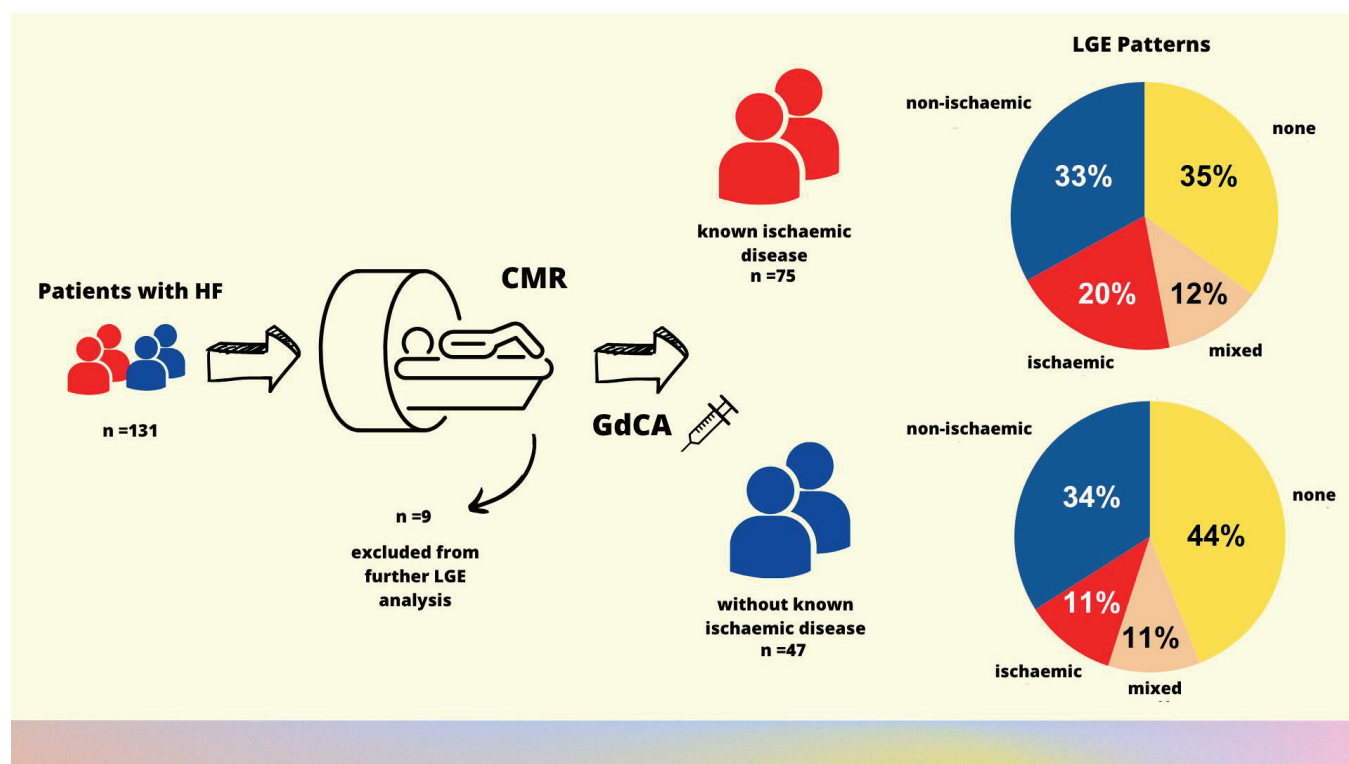


Figure 2. Graphical abstract. Study flowchart and the main study findings showing the distribution of etiology of myocardial damage based on LGE patterns in CMR in patients with heart failure.

4. Discussion

This study uniquely demonstrates that the CMR-derived LGE patterns, typically used to distinguish ischemic from non-ischemic etiologies of myocardial injury, are equally prevalent in patients with and without known CAD. This finding highlights the limitations of relying solely on clinical history or LGE distribution in determining the etiology of LV systolic dysfunction, underscoring the multifactorial nature of heart failure and advocating for a more comprehensive diagnostic approach.

The study showed that myocardial fibrosis may not correspond to the previous history of CAD. The most common type of myocardial damage was non-ischemic, which was present in every third studied patient. Ischemic pattern was observed less often, whereas coexistence of both etiologies was found only in every ninth patient. Importantly, no differences in LGE patterns were found between patients with and without known CAD. The presence of both ischemic and non-ischemic LGE among patients with and without known CAD suggests the contribution to LV impairment from different etiological factors. This highlights the importance of considering a range of reasons for cardiac impairment in clinical decision making, irrespective of past medical information.

In the cohort of patients with HF, two-thirds were previously diagnosed with coronary artery disease (CAD), which is consistent with previous studies, demonstrating CAD to be the most common etiological factor in HF [11–13]. In patients with known CAD, only one-fifth had isolated ischemic scars, whereas many patients had non-ischemic patterns of myocardial damage, suggesting the presence of mixed etiology. It is an important finding as non-ischemic fibrosis was found to be associated with a poorer outcome than fibrosis attributable to myocardial infarction [14]. In all-cause mortality analysis, both ischemic and non-ischemic LGE patterns were associated with worse survival than the reference group. However, in the adjusted analysis, only major non-ischemic LGE (defined as well-

established, classic patterns associated with myocarditis, infiltrative cardiomyopathies, or myocardial hypertrophy) was associated with an elevated risk of mortality [14].

There was no significant difference in LGE patterns between patients with and without known CAD. Interestingly, in patients without a history of CAD, LGE patterns associated with ischemic scars are found as frequently as in patients with known CAD. Every fifth patient without CAD presented with a subendocardial LGE pattern, associated with ischemic scars. This finding suggests a possible ischemic etiology of HF with previously undetected myocardial infarction in these subjects. Results from this study are consistent with a previous report [15].

In a large proportion (39%) of the currently studied population, no imaging findings of replacement myocardial fibrosis were detected. However, only a few patients had no other pathologies detected in CMR.

4.1. Clinical Implications

This study provides evidence that patient management strategy should not focus solely on previous medical findings and highlights that LV dysfunction might have multifactorial origins, even in the presence of established CAD. Comprehensive management of all underlying conditions is essential for achieving better clinical outcomes.

The pattern and extent of myocardial fibrosis predict adverse outcomes in new-onset HFrEF [16], the development of LV dysfunction [17], and the need for heart transplantation, regardless of the presence of CAD [18]. Therefore, the detection of fibrosis by CMR can provide additional prognostic information and improve risk stratification. This is crucial in view of a recent meta-analysis demonstrating the prognostic importance of unrecognized myocardial infarctions [19,20].

4.2. Limitations of the Study

This study has several limitations that should be acknowledged. First, the possible presence of asymptomatic CAD was not excluded by computed tomography or coronary angiography in all patients from the non-CAD group. Second, the retrospective design and cross-sectional character of the study inherently limit the ability to establish causality. Third, the single-center study design constrains the generality of our findings, as variations in clinical practice, patient demographics, and local healthcare systems could influence the outcomes. Fourth, the relatively small sample size may have contributed to the limited ability to detect certain intergroup differences, particularly in the frequency of the isolated ischemic LGE pattern. Fifth, while the analysis of the underlying etiology was based on widely accepted interpretations of LGE patterns, this approach may have introduced interpretative bias, particularly if subtle variations in LGE patterns were not adequately captured or if there were inconsistencies in the imaging protocol. Sixth, the reliance on imaging findings without histopathologic confirmation further limits the reliability of conclusions, as LGE patterns, although informative, are not definitive indicators of specific pathologies. The lack of histopathologic correlation means that some diagnoses might have been inaccurately classified, potentially affecting the validity of the results. Lastly, incomplete or missing information for some patients might have impacted the robustness of our findings.

Future research should aim to address these limitations by utilizing a prospective, multicenter design, incorporating histopathologic validation, and including a more comprehensive analysis of potential confounding factors to strengthen the validity and generalizability of findings.

5. Conclusions

LGE patterns suggesting ischemic or nonischemic etiology of LV systolic dysfunction are similarly prevalent in patients with and without a known history of CAD. Therefore, establishing the diagnosis of LV damage based on clinical information alone may be unreliable. The ischemic LGE patterns in patients without known CAD suggest the possibility of undiagnosed myocardial infarctions contributing to LV dysfunction. Non-ischemic or mixed LGE patterns in patients with CAD indicate additional contributing factors of LV dysfunction besides CAD. The absence of replacement myocardial fibrosis is a quite common finding in patients with LV dysfunction, irrespective of its etiology.

Author Contributions: Conceptualization, J.M.S.; methodology, J.M.S.; validation, J.M.S., K.L., M.P. and W.K.; formal analysis, J.M.S., K.L. and M.P.; investigation, J.M.S., K.L. and M.P.; resources, K.L. and M.P.; data curation, J.M.S., K.L. and M.P.; writing—original draft preparation, J.M.S., K.L. and M.P.; writing—review and editing, J.M.S. and W.K.; visualization, J.M.S., K.L. and M.P.; supervision, W.K. All authors have read and agreed to the published version of the manuscript.

Funding: Publication fee was financed from the subsidy for science and teaching by Wroclaw Medical University, Wroclaw, Poland.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Wroclaw Medical University Ethical Committee (987/2022, 4 January 2023).

Informed Consent Statement: Patient consent was waived due to a retrospective design of the study.

Data Availability Statement: The data underlying this article will be shared upon reasonable request to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

CMR	Cardiac magnetic resonance
LV	Left ventricle
CAD	Coronary artery disease
LVEF	Left ventricular ejection fraction
LGE	Late gadolinium enhancement
HF	Heart failure
PSIR	Phase-sensitive inversion recovery

Appendix A

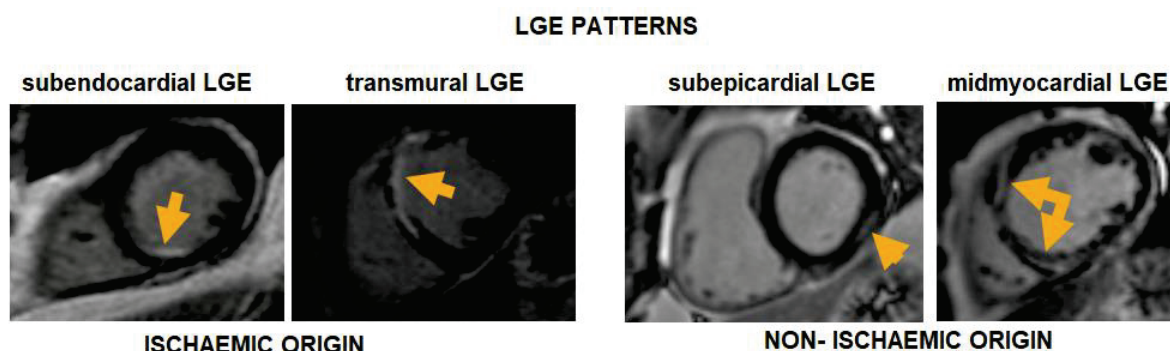


Figure A1. Representative examples of late gadolinium enhancement (LGE) patterns and their interpretation in cardiac magnetic resonance in patients with LVEF $\leq 50\%$ included in the study.

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Article

Initial Low-Density Lipoprotein Cholesterol and Inflammation Status Predicts Long-Term Mortality in Patients with Acute Coronary Syndrome in the Chinese Population

Yanqiao Lu ^{1,2,†}, Yujun Sun ^{1,3,†}, Yutong Miao ^{1,†}, Zhitong Liu ¹, Lan Shen ^{4,*} and Ben He ^{1,*}

¹ Department of Cardiology, Shanghai Chest Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200030, China; luyanqiao2013@live.com (Y.L.); yujunsun@icloud.com (Y.S.); miaoyutong8128@163.com (Y.M.); lzt_gdgz@sjtu.edu.cn (Z.L.)

² Department of Cardiology, Shanghai Sixth People's Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200233, China

³ Cardiac Center, Shanghai Jiahui International Hospital, Shanghai 200000, China

⁴ Medical Center, Harrisburg Hospital, University of Pittsburgh, Pittsburgh, PA 17050, USA

* Correspondence: shenl7@upmc.edu (L.S.); heben@sjtu.edu.cn (B.H.)

† These authors contributed equally to this work.

Abstract

Background: Low-density lipoprotein cholesterol (LDL-C) is considered an important risk factor for acute coronary syndrome (ACS). Recent studies have revealed high mortality in ACS patients with low LDL-C levels. However, the association between spontaneously very low LDL-C levels and the prognosis in ACS remains unknown. **Methods:** A total of 1882 consecutive statin-null ACS patients were analyzed and categorized into four groups according to their on-admission LDL-C level: very low <70 mg/dL, low 70–99 mg/dL, high 100–129 mg/dL, and very high ≥ 130 mg/dL. In-hospital mortality and 3-year mortality were assessed. Among them, 1009 patients were further grouped according to the hs-CRP value (<2 mg/L and ≥ 2 mg/L). **Results:** Over one-third of the patients had an initially lower LDL-C concentration. Higher in-hospital mortality (9.7%, 4.5%, 2.7%, and 3.5%, $p = 0.001$), long-term mortality (20.8%, 13.1%, 8.0%, and 7.8%, $p < 0.001$), and lower survival rate (KM: HR = 3.15, 95% CI 1.40–7.12, $p < 0.001$; Cox: HR = 2.09, 95% CI 1.30 to 3.36) were observed in the very low LDL-C group compared with other groups. Patients in the low LDL-C high CRP subgroup had the worst prognosis compared with other subgroups (in-hospital: 7.7%, 1.2%, 0.5%, and 4.3%, $p = 0.031$; long-term: 15.5%, 1.2%, 2.6%, and 9.4%, $p = 0.018$). Lower LDL-C levels were accompanied by higher CRP levels ($p = 0.003$). The CRP–LDL-C ratio had good predictive ability on short-term and long-term outcomes (AUC: 0.630 and 0.738). **Conclusions:** Spontaneously very low LDL-C level was independently associated with poor long-term survival in patients with ACS. Lower LDL-C level was related to higher CRP level, while the CRP–LDL-C ratio may be a potential risk prediction factor.

Keywords: acute coronary syndrome; hyperlipidemia; CRP; risk assessment; LDL-C

1. Introduction

What is already known on this topic—A low LDL level is regarded as a protective factor in ACS, while some studies show patients with lower LDL to have a poorer prognosis. Few researchers have studied the role of LDL and inflammation in statin-null patients until now.

What this study adds—We found that low LDL concentrations were related to more short-term and long-term outcomes in statin-null ACS patients and tended to have higher hs-CRP levels. The CRP–LDL ratio has good predictive ability on short-term and long-term outcomes. More attention and aggressive treatments should be added to those spontaneously very low LDL ACS patients with high CRP in clinical practice.

Currently, ischemic heart disease is the leading cause of death, causing heart failure and cardiac death [1]. It imposes heavy burdens on the affected families and society [2]. Several risk factors have been identified during the development and progression of acute coronary syndrome (ACS). Among these factors, lipid level is considered to be one of the most important predictive factors for the prognosis of ACS, and a high lipid level is related to poor prognosis [3]. Low-density lipoprotein (LDL) is a key lipoprotein involved in cholesterol transport [4,5]. It carries cholesterol, which is then measured as low-density lipoprotein cholesterol (LDL-C) in plasma. Our study assessed LDL-C levels and their association with clinical endpoints. Epidemiological studies have demonstrated the contribution of LDL-C-lowering therapy to better outcomes in patients with ACS, which further supported the concept of “the lower the better” [6–8]. However, in recent years, several cohort studies have shown associations between low on-admission LDL-C levels and increased mortality in ACS patients [9,10]. This phenomenon is known as the “Lipid paradox”. Until now, the complex role of LDL-C in the progression of ACS remains unclear.

Recent studies imply that lipid-driven inflammation is important during the occurrence and development of atherosclerosis [11]. LDL-C adheres to the vascular wall and activates the downstream inflammatory response [12]. Oxidized LDL induces pyroptosis and inflammation mediated by GSDME [13]. However, the statin therapy history of ACS patients may have complex effects on spontaneous LDL-C levels and anti-inflammation effects independent of lowering the LDL-C. Few studies explored the inflammation status in low-LDL-C ACS patients without statin therapy. High-sensitivity C-reactive protein (hs-CRP) is a common marker of acute inflammation reaction, which is relevant to cardiovascular outcomes [14,15]. Thus, our research aimed to explore the association between CRP and LDL-C levels in the statin-null ACS population.

2. Materials and Methods

2.1. Study Population

From 1 January 2010 to 31 December 2014, the complete clinical data of 2493 consecutive patients admitted to the cardiac care unit of the Department of Cardiology in Shanghai Renji Hospital with an accurate discharge diagnosis of ACS, including ST-elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS), was subjected to careful screening.

We excluded patients reporting home statin use or for whom information on pre-admission statin prescriptions was not available. To reduce bias and more accurately detect the effect of LDL-C, the on-admission cholesterol profile was strictly limited to within the first 24 h after admission. Patients who had been transferred from other hospitals more than 24 h after the most recent ischemic symptoms, before the initial presentation, and whose current admission was for repeat angiography or selective percutaneous coronary intervention (PCI) for the last ischemic events were also excluded.

Among the total of 2493 patients, 40 patients were excluded due to missing information on pre-hospital statin use, 148 patients were excluded due to the absence of a lipid profile within 24 h after admission, 255 patients were excluded due to transfer-time criteria and repeat angiography or selective PCI, and 168 patients were excluded for self-reported home statin use. Thus, a total of 1882 patients were ultimately included in the assessment. Among these patients, 1009 of them had the hs-CRP test on-admission and were further

analyzed. The patients were divided into four groups according to their initial LDL-C level: very low, <70 mg/dL; low, 70–99 mg/dL; high, 100–129 mg/dL and very high, ≥ 130 mg/dL. In addition, hs-CRP ≥ 2 mg/L was defined as a high-CRP group while hs-CRP < 2 mg/L was defined as a low-CRP group according to multiple large-scale clinical studies on myocardial infarction [16–18].

2.2. Patient and Public Involvement

Patients, investigators, and statisticians were involved in the design and management of this research. The comprehensible language was used to obtain the patients' understanding. To improve the cooperation and satisfaction degree of patients, we received suggestions from several patient representatives about follow-up plans. Participants will be informed of the main results of this study.

2.3. Data Collection

For all the eligible patients, information on demographics, medical history, clinical characteristics, therapeutic medication, and procedural intervention was extracted from the electronic medical records system of the hospital. In-hospital events and long-term follow-ups were determined from hospital discharge records or by telephone interviews, and were verified by consulting the Social Security Death Certificate Registries.

2.4. Statistical Analysis

Statistical analyses to identify risk factors were performed using SPSS19.0 for Windows (SPSS, Chicago, IL, USA). Categorical variables were compared with the χ^2 test. α continuous variables were compared with the Student's *t*-test. Survival curves were produced with the Kaplan–Meier method and compared with the log-rank test. Cox regression analysis was used for multivariate analyses via a stepwise selection process. Age, sex, diabetes mellitus history, PCI surgery, in-hospital treatments, and medications (unfractionated heparin, low molecular weight heparin, beta blocker, ACEI/ARB, statin, and high-dose statins) were included in the model. ROC curves were used to evaluate the prediction ability of the in-hospital and long-term outcomes. $p < 0.05$ was considered statistically significant.

3. Results

In 2493 patients, a total of 1882 statin-null patients with ACS were included in the study. The hs-CRP tests were detected in 1009 of them. After guideline treatment, in-hospital death occurred in 42 patients and long-term deaths occurred in 87 patients. The flow chart of this study is shown in Figure 1. A total of 1714 patients (94.9%) completed the 3-year follow-up. The median follow-up time was 32 months (IQR: 17–47).

3.1. Baseline Characteristics in Statin-Null ACS Patients with Different LDL-C Level

The baseline characteristics of all the enrolled statin-null patients were summarized in Table 1. The median age of the population was 62 years, and 20.4% of patients were female. We divided the 1882 patients into 4 groups according to their on-admission LDL-C level: very low, <70 mg/dL (N = 144); low, 70–99 mg/dL (N = 551); high, 100–129 mg/dL (N = 639); and very high, ≥ 130 mg/dL (N = 548). Over one-third of the patients had an initial LDL-C concentration lower than 100 mg/dL. Patients who presented with lower LDL-C levels were more likely to be older (median ages of 66, 63, 62, and 62 years, $p = 0.004$), male (84.7%, 83.8%, 80.1%, and 73.5%, $p < 0.001$), and had a lower BMI index (23.9, 24.1, 24.5, and 24.7). However, there was little difference among the four groups in the history of prior myocardial infarction (MI) (7.6%, 3.8%, 3.1%, and 3.1%, $p = 0.058$), prior PCI (6.9%, 4.7%, 3.0%, and 3.3%, $p = 0.086$) and prior heart failure (4.2%, 2.2%, 1.4%, and 1.3%, $p = 0.094$).

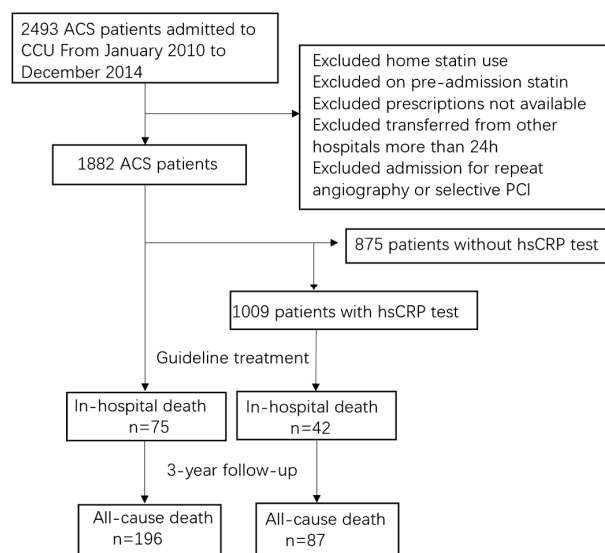


Figure 1. The study flowchart.

Table 1. Baseline, treatment, and outcome characteristics of the study population by LDL-C level.

	All Patients (N = 1882)	LDL-C Level at Presentation (mg/dL)				p Value
		<70 (N = 144)	70–99 (N = 551)	100–129 (N = 639)	≥130 (N = 548)	
Demographics						
Age, median (IQR), y	62 (55–72)	66 (57–75)	63 (56–73)	62 (56–72)	62 (54–71)	0.004
Female sex, n (%)	383 (20.4)	22 (15.3)	89 (16.2)	127 (19.9)	145 (26.5)	<0.001
Cardiac risk factors, n (%)						
Current smoker	845 (44.9)	69 (47.9)	256 (46.5)	270 (42.3)	250 (45.6)	0.392
Hypertension	1161 (61.7)	86 (59.7)	336 (61.0)	399 (62.4)	340 (62.0)	0.911
Diabetes mellitus	462 (24.5)	43 (29.9)	151 (27.4)	135 (21.1)	133 (24.3)	0.034
Family history of CAD	91 (4.8)	6 (4.2)	24 (4.4)	35 (5.5)	26 (4.7)	0.802
Prior stroke	217 (11.5)	18 (12.5)	70 (12.7)	74 (11.6)	55 (10.0)	0.556
Prior MI	69 (3.7)	11 (7.6)	21 (3.8)	20 (3.1)	17 (3.1)	0.058
Prior PCI	73 (3.9)	10 (6.9)	26 (4.7)	19 (3.0)	18 (3.3)	0.086
Prior heart failure	34 (1.8)	6 (4.2)	12 (2.2)	9 (1.4)	7 (1.3)	0.094
BMI (kg/m ²)	24.4 (3.2)	23.9 (3.4)	24.1 (3.2)	24.5 (3.1)	24.7 (3.2)	0.037
Diagnosis						
STEMI	1284 (68.2)	91 (63.2)	363 (65.9)	447 (70.0)	383 (69.9)	0.230
NSTE-ACS	598 (31.8)	53 (8.9)	188 (31.4)	192 (32.1)	165 (27.6)	
In-hospital treatment						
Cardiac catheterization	1783 (94.7)	131 (91.0)	518 (94.0)	614 (96.1)	520 (94.9)	0.071
PCI	1640 (87.1)	115 (79.9)	457 (82.9)	574 (89.8)	494 (90.1)	<0.001
Thrombolytic therapy	170 (9.0)	9 (6.3)	41 (7.4)	66 (10.3)	54 (9.9)	0.186
Heparin administration						
IV unfractionated	1417 (75.3)	106 (73.6)	391 (71.0)	491 (76.8)	429 (78.3)	0.026
Low molecular weight	1289 (68.5)	82 (56.9)	398 (72.2)	445 (69.6)	364 (66.4)	0.003
Medications w/in 24 hours						
Aspirin	1863 (99.0)	140 (97.2)	546 (99.1)	634 (99.2)	543 (99.1)	0.318
Beta-blocker	937 (49.8)	55 (38.2)	253 (45.9)	330 (51.6)	299 (54.6)	0.001
ACEI/ARB	1142 (60.7)	66 (45.8)	329 (59.7)	413 (64.6)	334 (60.9)	0.001
Statin	1817 (96.5)	133 (92.4)	525 (95.3)	621 (97.2)	538 (98.2)	0.003
Intensive statin	104 (19.0)	16 (11.1)	82 (14.9)	105 (16.4)	104 (19.0)	0.088

Continuous values are expressed as the mean ± standard deviation or median (with 25th and 75th percentiles); categorical values are expressed as total number and proportion of the global population (in parentheses). CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; IV, intravenous; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index.

In the treatment and procedural characteristics, we found that statin-null ACS patients with lower initial LDL-C levels were less likely to receive PCI therapy (Table 1, $p < 0.001$) during the procedure. The rate of early prescription (within 24 h) of guideline-recommended medications, beta-blockers ($p = 0.001$), angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB) ($p = 0.001$), and statins ($p = 0.003$) decreased in the lower LDL-C groups, while the rate of aspirin and intensive statin did not show any difference (Table 1). Similarly, discharge prescriptions of guideline-recommended medications (aspirin, clopidogrel, beta-blockers, ACEI/ARB, statins, and intensive statins) were less frequent in the lower LDL-C groups (Supplementary Table S1).

3.2. LDL-C Paradox in the Prognosis of Statin-Null ACS Patients

To evaluate the incidence of short-term and long-term outcomes in ACS patients with different initial LDL-C levels, we compared the in-hospital mortality, in-hospital MACE, and long-term mortality in patients with different initial LDL-C levels. As shown in Table 2, we found that patients with very low and low LDL-C levels had higher in-hospital mortality compared to patients with high and very high LDL-C levels (9.7%, 4.5%, 2.7%, 3.5%, $p = 0.001$). Similarly, lower LDL-C level patients also had more in-hospital MACE events (38.9%, 42.3%, 34.3%, 36.7%, $p = 0.037$) and long-term mortality (20.8%, 13.1%, 8.0%, 7.8%, $p < 0.001$). To further understand the long-term survival of patients in each LDL-C group, Kaplan–Meier survival curves were plotted and the statistical differences were analyzed through log-rank analysis. We found that the probability of survival was significantly lower in the very low LDL-C group compared to the high LDL-C group (Figure 2A, $p < 0.001$) or the very high LDL-C group (Figure 2A, $p < 0.001$). Moreover, patients with low LDL-C levels also had a poorer probability of survival compared with patients with very high LDL-C levels (Figure 2A, $p = 0.005$). All these results showed that the ACS patients with low LDL-C levels had poorer short-term and long-term prognoses, which was contrary to our previous lipid regulation belief that lower LDL-C level is better. Then, Cox’s regression analysis was used for the multivariate analyses as implemented with a stepwise selection process (Table 3). Multivariate analysis was performed while accounting for baseline differences in demographics, additional risk factors, and in-hospital treatment. The results showed that very low LDL-C (<70 mg/dL) (HR = 2.09, 95% CI 1.30–3.36) was associated with significantly higher mortality than LDL ≥ 130 mg/dL (Table 3). Age, diabetes, diagnosis of STEMI, and presentation of heart failure were independent risk factors of long-term survival. Patients who underwent PCI therapy had a lower long-term mortality than those treated with conservative therapy. The early prescription of ACEI/ARB and statin in the first 24 h contributed to better survival.

Table 2. The short-term and long-term outcomes between different LDL-C patients.

	LDL-C Level at Presentation (mg/dL)				<i>p</i> Value
	<70 (N = 144)	70–99 (N = 551)	100–129 (N = 639)	≥ 130 (N = 548)	
In-hospital mortality, <i>n</i> (%)	14 (9.7)	25 (4.5)	17 (2.7)	19 (3.5)	0.001
In-hospital MACE, <i>n</i> (%)	56 (38.9)	233 (42.3)	219 (34.3)	201 (36.7)	0.037
Long-term mortality, <i>n</i> (%)	30 (20.8)	72 (13.1)	51 (8.0)	43 (7.8)	<0.001

Values are expressed as numbers (percentage). LDL-C: low-density lipoprotein cholesterol; MACE: major adverse cardiovascular events.

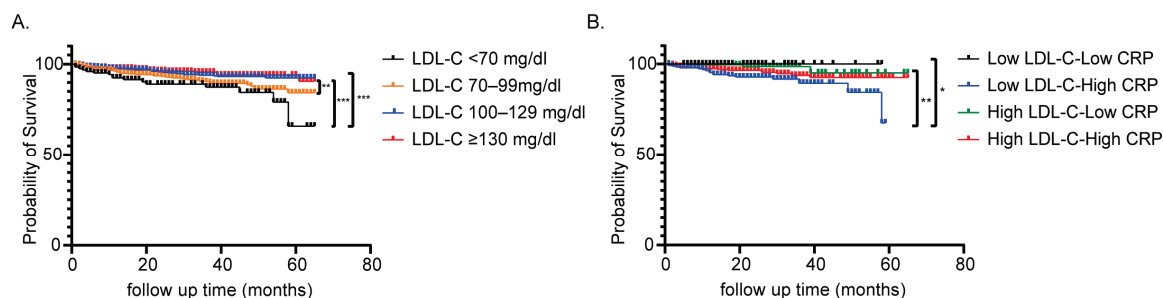


Figure 2. Kaplan–Meier analysis of overall survival in ACS patients. (A) Kaplan–Meier analysis of overall survival in 1882 ACS patients by different LDL-C level. (B) Kaplan–Meier analysis of overall survival in 1009 ACS patients by different LDL-C and CRP level. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 3. Cox’s proportional hazard regression model of long-term mortality in 1882 ACS patients.

Parameter	<i>p</i> Value	HR	95% CI	
			Lower	Upper
On-admission LDL-C level				
<70 mg/dL	0.002	2.09	1.30	3.36
70–89 mg/dL	0.169	1.31	0.89	1.91
90–129 mg/dL	0.382	0.83	0.55	1.26
≥130 mg/dL		Reference		
Demographics				
Age	<0.001	1.07	1.05	1.09
Cardiac risk factors				
Diabetes mellitus	0.008	1.50	1.11	2.02
Clinical presentation				
Heart failure	<0.001	2.29	1.69	3.11
Diagnosis				
STEMI	0.007	1.59	1.14	2.23
In-hospital treatment				
PCI	<0.001	0.28	0.21	0.38
ACEI/ARB in first 24 h	0.003	0.65	0.48	0.87
Statin in first 24 h	0.001	0.42	0.25	0.70

LDL-C, low-density lipoprotein cholesterol; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers. HR: hazard ratio.

3.3. Heterogeneity of CRP Level in Low LDL-C Group Explained for Lipid Paradox

To explore the mechanism of the LDL-C paradox, we further divided the patients with lower LDL-C levels or higher LDL-C levels into different subgroups according to the inflammatory indicators hs-CRP. First, we compared the baseline difference between patients with or without hs-CRP tests to understand the representation of these 1009 patients with hs-CRP tests. As shown in Supplementary Table S2, most of the characteristics were the same except for current smoking rate, total cholesterol level, high-density lipoprotein cholesterol (HDL-C), LDL-C level, peak CK level, in-hospital ACEI/ARB use, and in-hospital intensive statin use. Fewer patients were diagnosed as STEMI in the patients with hs-CRP tests (65.9% vs. 70.9%, $p = 0.020$). Then, these 1009 patients with hs-CRP were further divided into low LDL-C low CRP (LDL-C < 100 mg/dL, hs-CRP < 2 mg/L), low LDL-C high CRP (LDL-C < 100 mg/dL, hs-CRP ≥ 2 mg/L), high LDL low CRP (LDL ≥ 100 mg/dL, hs-CRP < 2 mg/L), high LDL-C high CRP groups (LDL-C ≥ 100 mg/dL, hs-CRP ≥ 2 mg/L). We found that low LDL-C high CRP patients were older (65.3 vs. 60.8, $p = 0.002$) and had less statin/intensive statin use (statin: 91.9% vs. 98.8, $p = 0.025$; intensive statin: 9.6% vs. 17.9%, $p = 0.041$) compared with low LDL-C low CRP patients (Supplementary Table S3). High LDL-C high CRP patients had higher hypertension history (66.4% vs. 53.9%, $p = 0.002$), prior MI history (4.3% vs. 1.0%,

$p = 0.026$) and prior heart failure history (2.6% vs. 0.0%, $p = 0.044$) compared with high LDL-C low CRP patients (Supplementary Table S3). Lower HDL-C level (1.16 vs. 1.23, $p = 0.005$) was found in high LDL-C high CRP patients (Supplementary Table S3).

Interestingly, we found the patients with low LDL-C high CRP had significantly higher in-hospital mortality (7.7% vs. 1.2%, $p = 0.030$) and in-hospital MACE (46.2% vs. 22.6%, $p < 0.001$) compared with the low LDL-C low CRP group (Table 4). Similarly, patients with low LDL-C high CRP also had significantly higher long-term mortality (15.5% vs. 1.2%, $p = 0.001$) compared with the low LDL-C low CRP group (Table 4). These results implied that inflammation status predicted the short-term and long-term outcomes in low LDL-C patients, which might explain the LDL-C paradox. In high LDL-C level patients, high hs-CRP levels were also related to high in-hospital mortality (4.3% vs. 0.5%, $p = 0.009$, Table 4), in-hospital MACE (35.8% vs. 23.0%, $p < 0.001$, Table 4) and long-term mortality (9.4% vs. 2.6%, $p = 0.002$, Table 4). Kaplan–Meier survival curves of these four groups indicated that low LDL-C high CRP patients had a poorer long-term prognosis compared to low LDL-C low CRP patients and high LDL-C low CRP patients ($p = 0.023$, $p = 0.003$, Figure 2B).

Table 4. The short-term and long-term outcomes between different CRP-level groups in spontaneously low LDL patients.

	Low LDL-C < 100		<i>p</i> Value	High LDL-C ≥ 100		<i>p</i> Value
	Low CRP (<2)	High CRP (≥2)		Low CRP (<2)	High CRP (≥2)	
In-hospital mortality	1 (1.2)	20 (7.7)	0.030	1 (0.5)	20 (4.3)	0.009
In-hospital MACE	19 (22.6)	120 (46.2)	<0.001	47 (23.0)	165 (35.8)	<0.001
Long-term mortality	1 (1.2)	39 (15.5)	0.001	5 (2.6)	42 (9.4)	0.002

LDL-C, low-density lipoprotein cholesterol; CRP, c-reactive protein; MACE, major adverse cardiovascular events.

3.4. The Predictive Ability of the CRP–LDL-C Ratio in Prognosis

To figure out the relationship between hs-CRP and LDL-C levels, the scatter plot of hs-CRP and LDL-C was drawn (Figure 3A). The levels of hs-CRP and LDL-C showed a weak negative correlation, which meant that patients with lower LDL-C levels tended to have higher hs-CRP levels (Pearson: -0.074 , $p = 0.018$, Figure 3A). Then, we calculated the average hs-CRP level in different LDL-C level groups (very low, low, high, and very high LDL-C groups). As shown in Figure 3B, the mean value of hs-CRP in very low, low, high, and very high LDL-C groups is 30.15, 23.1, 17.42, and 16.70 mg/L, respectively. The hs-CRP level in very low LDL-C patients was significantly higher than it was in high LDL-C patients ($p = 0.0074$, Figure 3B) and very high LDL-C patients ($p = 0.003$, Figure 3B). Similarly, the hs-CRP level in low LDL-C patients was also higher than it was in high LDL-C patients ($p = 0.0539$, Figure 3B) and very high LDL-C patients ($p = 0.025$, Figure 3B). Thus, we calculated the CRP–LDL-C ratio of every patient. The ratio of CRP–LDL-C had a great prediction ability in the in-hospital MACE (AUC under ROC curve: 0.630, 95% CI: 0.593–0.666, $p < 0.001$, Figure 4A) and long-term mortality (AUC under ROC curve: 0.738, 95% CI: 0.684–0.792, $p < 0.001$, Figure 4B).

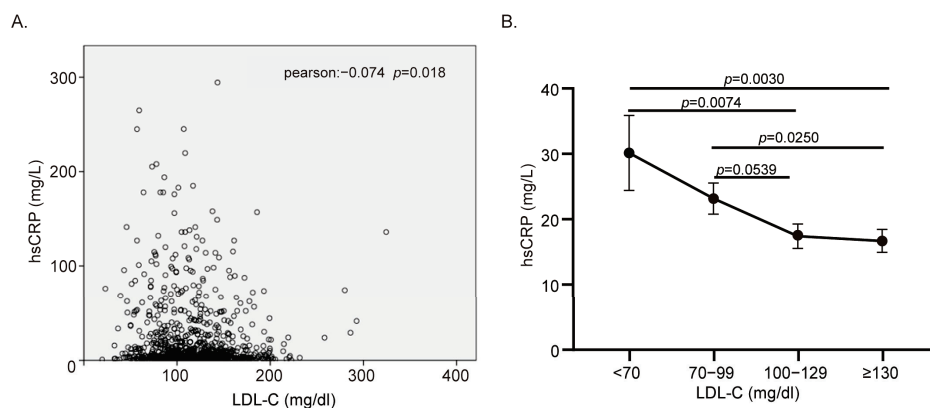


Figure 3. The correlation between the LDL-C and CRP level. **(A)** The scatter plot of LDL-C level and hs-CRP level. (Pearson: -0.074 , $p = 0.018$); **(B)** the average hs-CRP level in different grade of LDL-C groups. Data were shown as mean (black dot) and SEM (black lines).

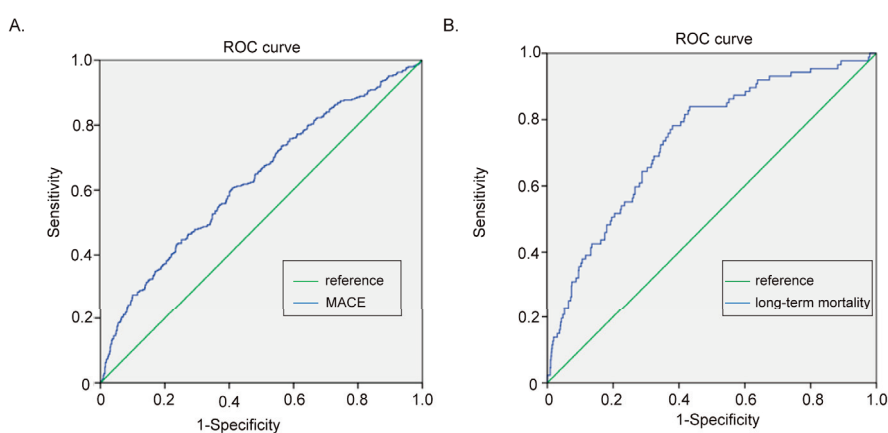


Figure 4. The prediction of prognosis of CRP–LDL–C ratio in 1882 ACS patients. **(A)** ROC curve of CRP–LDL–C ratio in the prediction of in-hospital MACE. AUC: 0.630, 95% CI (0.593–0.666), $p < 0.001$. **(B)** ROC curve of CRP–LDL–C ratio in the prediction of long-term mortality. AUC: 0.738, 95% CI (0.684–0.792), $p < 0.001$.

4. Discussion

In the present study, about 37% of patients were divided into the very low and low LDL-C group, which indicated that the proportion of spontaneously low LDL-C was high in statin-null ACS patients. While 29.1% of patients were divided into a very high LDL-C group. Similarly, in the CRUSADE Registry, which excluded home statin-used patients, 35.3% of patients had very low and low LDL-C concentrations; the very high group accounted for nearly one-third of the population [19]. LDL-C lowering has been reported as an acute phase response to myocardial infarction [20–23]. However, this phenomenon often occurs over several days rather than in the first 24 h. Our lipid profiles were obtained within the first 24 h after admission; thus, an acute change in LDL-C level is unlikely to be responsible for the differences observed in the present study.

The Honolulu Heart Program first reported the relationship between low cholesterol and high mortality in the 20-year follow-up of lipid concentration in the elderly [24]. Subsequently, several studies indicated that low LDL-C was associated with worse outcomes in patients with STEMI, NSTEMI, and heart failure [9,19,25,26]. Patients with very low LDL-C who were treated with statins have been found to have better outcomes than corresponding patients who were not treated with statins despite the low cholesterol level [26,27]. Until now, the mechanism of the “LDL-C paradox” has been controversial. The most common concept is that it is related to confounding factors associated with survival. The KAMIR Registry found evidence of this paradox, but after adjusting for

baseline characteristics, LDL-C level was no longer an independent predictor of mortality [28]. Patients with low LDL-C in the CRUSADE Registry were older than patients with high LDL-C and had more comorbidities, including hypertension, diabetes, and heart failure [19]. In our study, patients in the lower LDL-C categories also had a greater burden of risk factors. Nevertheless, the prognostic effect of spontaneously very low LDL-C remained valid after adjustment for other clinical characteristics. Unlike KAMIR, the present study excluded patients with reported pre-admission statin therapy, allowing the effect of initial LDL-C level without the pleiotropic function of statins to be determined. In addition, in the Münster Heart Study, the increase in mortality at low levels of LDL-C was only observed in smokers and was explained by an increase in smoking-related cancer deaths [20]. However, in the present cohort, there was no difference in current smoking among the LDL-C groups. An age-dependent reduction in LDL-C was observed in a previous study, which used to be considered an effect of poor health status [22]. The multivariate analyses of the present study revealed the independent prognostic values of age and spontaneously very low LDL-C levels. Thus, these two factors play important roles in the development and onset of ACS.

In terms of drug treatment, our patients with lower LDL-C levels tended to be older and had more comorbidities, which may have contributed to poorer drug tolerance and medication adherence during treatment. In our database, individuals with lower LDL-C levels also had lower rates of PCI therapy and medication use. Similarly, Yang et al. reported that patients with lower LDL-C levels received less PCI therapy and had lower usage rates of statins, oral anticoagulants, beta-blockers, and ACEI/ARBs [29]. Treatment decisions are influenced by various factors, including socioeconomic status, patient compliance, and disease assessment. Further research will be targeted at including those confounding factors. The localization of myocardial infarction should also be analyzed to better understand the characteristics of coronary angiography in those statin-naïve patients, which may influence treatment decisions. Our patients benefited from early initiation of ACEI/ARB and statin, but early prescription of beta-blockers did not contribute to higher survival. The restricted use of beta-blockers in the acute phase might explain this finding. Many of the patients were unstable and could not tolerate this medication, especially in the first 24 h. The protective effect of beta-blockers is more likely due to their early titration and long-term administration [30,31], which was not evaluated in the current study. In the present study, low LDL-C reduced the rate of optimal medical therapy at discharge, particularly the prescription of statins, with the rate ranging from 88.3% to 97.6%. Thus, further studies and improvements to standard treatments in this special ACS population are needed.

Due to the importance of anti-inflammatory therapy and lipid-lowering therapy in AMI, we tried to further figure out the role of inflammation in the “LDL-C paradox”. The study reported that on-treatment CRP but not LDL-C was correlated with outcomes under 24 months of potent statin therapy [32]. Another study investigated the combined utility of hemoglobin level and neutrophil-to-lymphocyte ratio in patients with STEMI undergoing primary PCI [33]. These findings indicated that inflammation might be an important driver of residual cardiovascular risk in patients with coronary artery disease despite aggressive statin therapy. In the subgroup analysis of the present cohort, low LDL-C high CRP group patients had the highest short-term and long-term mortality. Similarly, the newest collaborative analysis of three randomized trials also found that CRP level can predict cardiovascular events [18]. In addition, they found that the predictive value of residual cholesterol risk was neutral compared with residual inflammatory risk [18] which was different from our results. Compared with our cohort, they enrolled high atherosclerotic disease risk patients with current statin treatment, while our study enrolled ACS patients without statin treatment history, which may contribute to the different conclusions. Thus,

our study was the first to investigate the relationship between CRP and LDL-C in statin-null ACS patients. The severe inflammation status might be a mechanism contributing to the poor prognosis of patients with spontaneously very low LDL-C levels. We found that spontaneously very low LDL-C levels were associated with a higher probability of inflammation, which may be due to the function of cholesterol in the acute state. Since statins have anti-inflammatory effects, primary and secondary prevention strategies in this unique population require further study.

5. Conclusions

In patients with ACS, spontaneously low LDL-C levels on-admission are independently associated with high short-term and long-term mortality, suggesting that improved treatments are needed in this unique population. Spontaneously lower LDL-C patients tended to have higher hs-CRP levels, which could increase the short-term and long-term events. The CRP–LDL-C ratio may be a potential method for predicting the ACS prognosis.

6. Limitations

This study has some limitations. First, the retrospective study design might have led to selection bias, treatment bias, and unequal distributions of baseline comorbidities among the groups. Second, although we performed multivariate analysis and included as many baseline variables as possible, we could not account for all possible confounding characteristics and treatment effects. For example, the lack of cancer and cachexia information may induce bias. However, BMI is also a common indicator of cachexia [34]. BMI < 20 kg/m² is sufficient for cachexia if weight loss cannot be recorded [35]. The mean (SD) BMI of our patients was 24.4 (3.2) kg/m², suggesting that cachexia was uncommon in our cohort. For another, our study cannot include all the chronic diseases. Thus, we have included chronic diseases associated with a high risk of heart disease such as hypertension, diabetes, heart failure history, stroke history, and MI history to reduce bias. Other chronic diseases such as connective diseases, COPD, hematological or oncological diseases, are also becoming a hotspot in the prognosis studies of cardiovascular diseases. Further studies are needed to make the conclusion more accurate. Third, we recorded only from discharge information, while information on therapies during follow-up, whose effects on outcomes are not clear, was not available. Additionally, our patient cohort was enrolled between 2010 and 2014, which may introduce treatment bias due to subsequent advances in therapy. Finally, although we compared the baseline between patients with or without hs-CRP tests, the prognostic value of the CRP–LDL-C ratio requires validation with a larger data set. The current conclusions were limited to the Chinese population. These conclusions need to be further confirmed in a larger cohort of patients with a uniform therapeutic approach in subsequent studies.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/biomedicines13071534/s1>. Supplementary Table S1. Discharge treatment by LDL level, Supplementary Table S2. The difference of baseline characteristics between patients with or without hs-CRP tests, Supplementary Table S3. The baseline characteristics of the patients with Low and High CRP level.

Author Contributions: Y.L. and Y.S. contributed to the design of the study, data analysis and the first draft. Y.M. contributed to the data analysis. Y.M. and Z.L. revised the manuscript. L.S. provided the conception, interpreted the data, supervised the progress, revised the manuscript. B.H. contributed to the revision of the manuscript, interpreted the data, supervised the progress, funding acquisition, and approved the final version for publication. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the National Natural Science Foundation of China (grant numbers: 82130012, 81830010 and 81900308), Clinical Research Plan of SHDC (grant number: SHDC2020CR1039B), SINO-German Mobility Program (grant number: M-0526).

Institutional Review Board Statement: The studies were approved by the Ethical Committee at Shanghai Renji Hospital and Shanghai Chest Hospital (approval code: 2015 [111], approval date: 29 December 2015; approval code: KS(Y) 1867, approval date: 13 April 2018).

Informed Consent Statement: The data is anonymous and informed consent was waived.

Data Availability Statement: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments: All the patients, investigators, and statisticians involved in this research deserve our sincere thanks. The authors also would like to thank all the grants for the support. In addition, we are grateful to Shanghai Renji Hospital for the data acquisition.

Conflicts of Interest: The authors declare that they have no competing interests.

Abbreviations

The following abbreviations are used in this manuscript:

LDL-C	Low-density lipoprotein cholesterol
ACS	Acute coronary syndrome
hs-CRP	High-sensitivity C-reactive protein
STEMI	ST-elevation myocardial infarction
NSTE-ACS	Non-ST-segment elevation acute coronary syndrome
PCI	Percutaneous coronary intervention
HDL-C	High-density lipoprotein cholesterol
ACEI	Angiotensin-converting enzyme inhibitors
ARB	Angiotensin II receptor blockers

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Article

Effects of SGLT2 Inhibitors on Sleep Apnea Parameters and Cheyne–Stokes Respiration in Patients with Acute Decompensated Heart Failure: A Prospective Cohort Study

Petar Kalaydzhiev ^{1,2,*}, Tsvetelina Velikova ³, Yanitsa Davidkova ⁴, Gergana Voynova ², Angelina Borizanova ^{1,2}, Natalia Spasova ^{1,2}, Neli Georgieva ², Radostina Ilieva ^{1,2}, Elena Kinova ^{1,2} and Assen Goudev ^{1,2}

¹ Department of Emergency Medicine, Medical University—Sofia, 1000 Sofia, Bulgaria; borizanowa@abv.bg (A.B.); spasova.natalia@gmail.com (N.S.); radostilieva@yahoo.com (R.I.); kinova.e@abv.bg (E.K.); agoudev@abv.bg (A.G.)

² Cardiology Department, University Hospital “Tsaritsa Yoanna—ISUL”, 1000 Sofia, Bulgaria; gerivoinova@gmail.com (G.V.); ngeorgieva87@gmail.com (N.G.)

³ Medical Faculty, Sofia University St. Kliment Ohridski, 1407 Sofia, Bulgaria; tsvelikova@medfac.mu-sofia.bg

⁴ Department of Clinical Hematology, Specialized Hospital of Active Treatment of Hematological Diseases, 1000 Sofia, Bulgaria; yani.tihomirova@gmail.com

* Correspondence: pkalaidzhiev@gmail.com

Abstract: Background: Sleep-disordered breathing (SDB), particularly Cheyne–Stokes respiration (CSR), is highly prevalent among patients hospitalized with acute decompensated heart failure (ADHF) and is associated with worse clinical outcomes. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have demonstrated cardiorenal benefits in heart failure, but their effects on nocturnal respiratory parameters remain underexplored. **Objectives:** This study aims to evaluate the impact of SGLT2i therapy on key respiratory and cardiac indices including CSR burden, oxygenation, and right heart function in patients with ADHF and reduced left ventricular ejection fraction. **Methods:** In this single-center prospective cohort study, 60 patients with ADHF, LVEF < 40%, and a baseline apnea–hypopnea index (AHI) > 5 were assessed before and three months after the initiation of SGLT2i therapy. Sleep respiratory parameters were measured using home polygraphy (ApneaLink™), while cardiac and renal indices were evaluated by echocardiography, NT-proBNP, and the estimated glomerular filtration rate (eGFR). Structural and functional echocardiographic changes were analyzed both at baseline and following the 3-month treatment period. Patient-reported outcomes were assessed using the Epworth Sleepiness Scale (ESS) and Kansas City Cardiomyopathy Questionnaire (KCCQ). **Results:** After 3 months of SGLT2i therapy, significant improvements were observed in daytime sleepiness (ESS: −2.68 points; $p < 0.001$), CSR index (−5.63 events/h; $p < 0.001$), AHI (−3.07 events/h; $p < 0.001$), ODI (−6.11 events/h; $p < 0.001$), and mean nocturnal SpO₂ (+1.95%; $p < 0.001$). KCCQ scores increased by 9.16 points ($p < 0.001$), indicating improved quality of life. Cardiac assessments revealed reductions in NT-proBNP (−329.6 pg/mL; $p < 0.001$) and E/e′ ratio (−1.08; $p < 0.001$), with no significant change in LVEF or chamber dimensions. Right ventricular function improved, as evidenced by the increased TAPSE/sPAP ratio (+0.018; $p < 0.001$). Renal function remained stable, with a non-significant upward trend in eGFR. **Conclusions:** This exploratory study suggests that SGLT2 inhibitors may be associated with the attenuation of Cheyne–Stokes respiration and an improvement in right heart function in patients with ADHF, warranting further investigation in controlled trials. These findings highlight the potential of SGLT2is to address overlapping cardio-respiratory dysfunction in this high-risk population.

Keywords: SGLT2 inhibitors; acute decompensated heart failure; Cheyne–Stokes respiration; sleep apnea; right ventricular function

1. Introduction

ADHF frequently coexists with SDB, notably sleep apnea and Cheyne–Stokes respiration, both of which exacerbate cardiovascular strain and diminish patient quality of life. Sleep apnea in patients with ADHF contributes to intermittent nocturnal hypoxemia, enhanced sympathetic nervous system activity, and ventilatory instability, accelerating the progression of heart failure. CSR, characterized by cyclic fluctuations between hyperpnea and apnea, is a particularly common form of respiratory instability in this population and has been associated with poor prognosis, increased arrhythmogenic potential, and impaired sleep architecture [1,2].

A critical link between heart failure and sleep apnea is the pathophysiological impact of fluid redistribution. During recumbency, intravascular volume shifts rostrally toward the thoracic and peripharyngeal regions, predisposing patients to airway narrowing and altered respiratory mechanics [3]. This overnight rostral fluid shift plays a major role in the pathogenesis of sleep apnea in heart failure and has been identified as a potential therapeutic target [4,5]. The resulting pulmonary congestion and stimulation of vagal afferents contribute to periodic breathing and CSR, a phenomenon amplified by heightened chemoreflex sensitivity and autonomic dysregulation [6].

In recent years, SGLT2is have emerged as a class of cardioprotective agents with effects that extend far beyond glycemic control. In heart failure, SGLT2is promote natriuresis and osmotic diuresis, leading to reduced plasma volume, improved hemodynamic status, and attenuation of left ventricular filling pressures [7,8]. These effects may favorably influence SDB by limiting pulmonary congestion and mitigating fluid shifts during sleep [9–11]. Furthermore, SGLT2is have demonstrated the ability to reduce sympathetic overactivation, modulate chemoreceptor responsiveness, and potentially stabilize respiratory control networks involved in the generation of CSR [12–14]. Their emerging role in fluid management and nocturnal respiratory stabilization has positioned SGLT2is as promising candidates for targeting both cardiac and respiratory dysfunction in patients with ADHF [15].

Considering these factors, the present investigation was undertaken to elucidate the impact of SGLT2i therapy on nocturnal respiratory dynamics in patients admitted with ADHF and impaired left ventricular systolic function. Over the three-month treatment period, we systematically assessed changes in the incidence and severity of CSR, mean nocturnal oxygen saturation, and the overall burden of sleep apnea. These evaluations were accompanied by assessments of daytime somnolence and health-related quality of life, providing a comprehensive overview of the clinical impact of SGLT2 inhibition in this high-risk population.

2. Materials and Methods

This single-center, prospective cohort study was conducted at the Cardiology Department of University Hospital “Tsaritsa Yoanna—ISUL” in Sofia, Bulgaria, between January 2021 and December 2023. The study protocol was approved by the Ethics Committee of the Medical University of Sofia (Protocol 2145 from 27 April 2021), and all the patients provided written informed consent in accordance with the Declaration of Helsinki.

A total of 195 consecutively admitted patients with ADHF and LVEF < 40% were screened for eligibility. The inclusion criteria comprised NT-proBNP > 900 pg/mL and AHI > 5, as measured by the ApneaLinkTM system during hospitalization. Patients with

NYHA class IV symptoms, end-stage renal failure, severe respiratory insufficiency, or COPD were excluded. Of the screened population, 73 patients met all the eligibility criteria and were enrolled in the study. Among the remaining 122 patients, 81 did not meet the inclusion criteria, while 14 were excluded due to comorbidities or unstable clinical condition. Additionally, 27 patients declined participation. After enrollment, 13 patients did not complete follow-up: 7 were lost to follow-up, 4 withdrew consent, and 2 died before the 3-month assessment. Thus, a total of 60 patients were included in the final analysis. Figure 1 illustrates the study screening and enrollment process.

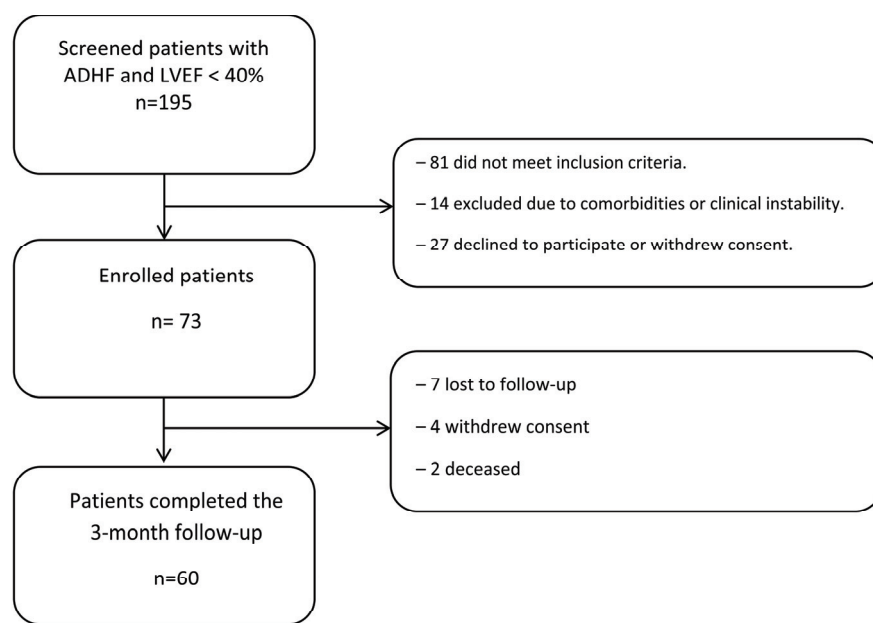


Figure 1. Study flow diagram. Of 195 ADHF patients (LVEF < 40%) screened, 73 were enrolled; 13 were excluded during the 3-month follow-up, leaving 60 for final analysis. ADHF—acute decompensated heart failure; LVEF—left ventricular ejection fraction.

SDB was assessed using ApneaLink™ (ResMed® San Diego, CA, USA), a validated home respiratory polygraphy device that records nasal airflow, thoracic movements, pulse rate, and peripheral oxygen saturation (SpO₂). ApneaLink™ has demonstrated high diagnostic agreement with polysomnography and is widely used in real-world sleep apnea screening [16]. Derived parameters included the apnea-hypopnea index (AHI), oxygen desaturation index (ODI), presence of CSR, and average and minimum nocturnal SpO₂.

Echocardiographic evaluation and NT-proBNP measurements were performed at baseline and at the 3-month follow-up. Functional outcomes were assessed using the Epworth Sleepiness Scale (ESS) and the Kansas City Cardiomyopathy Questionnaire (KCCQ). The ESS is a standardized and validated instrument used to quantify subjective daytime sleepiness, with strong internal consistency and test–retest reliability [17]. The KCCQ is a disease-specific health status questionnaire that evaluates symptoms, physical limitations, quality of life, and social functioning in patients with heart failure. It has shown high sensitivity to clinical change and is considered a robust tool for measuring patient-reported outcomes in this population [18].

Descriptive statistics were used for baseline characterization. Continuous variables were expressed as mean ± standard deviation (SD). Normality was tested using the Kolmogorov–Smirnov test. Within-group comparisons between baseline and follow-up values were conducted using the paired-samples t-test. Given the exploratory design and limited sample size, multivariable regression analyses were not conducted in order to avoid overfitting and unstable estimates. Paired comparisons were prioritized to evaluate

within-subject changes over time. A p -value < 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics, version 24.

3. Results

3.1. Baseline Characteristics

The cohort comprised predominantly male patients in their seventh decade of life, with non-ischemic etiology, atrial fibrillation, and type 2 diabetes mellitus each affecting a substantial proportion—hallmarks of the complex comorbidity profile in ADHF. Guideline-directed therapies were broadly implemented: most patients received β -blockers, ACEI/ARB, ARNi, MRAs, and loop diuretics. SGLT2i initiation—either dapagliflozin or empagliflozin—occurred in roughly half of the population, with dosing tailored to individual clinical needs. Among the patients with type 2 diabetes ($n = 34$), 21 (61.8%) were treated with metformin, 8 (23.5%) with insulin, 6 (17.6%) with DPP-4 inhibitors, and 2 (5.9%) with sulfonylureas. No patients received GLP-1 receptor agonists or thiazolidinediones. Throughout the 3-month follow-up, no symptomatic hypoglycemia, hyperglycemic crises, or cases of ketoacidosis were reported. These baseline features mirror those of contemporary heart failure trials and real-world registries, supporting the external validity of our findings (Table 1).

Table 1. Baseline characteristics of the study cohort ($N = 60$).

Characteristic	Value, n (%)
Age, years	69.3 $\pm$ 9.4 (45–86)
Sex, n (%)	
Female	19 (31.7)
Male	41 (68.3)
Non-ischemic etiology, n (%)	38 (63.3)
Atrial fibrillation, n (%)	43 (71.7)
Diabetes mellitus type 2, n (%)	34 (56.7)
Medications, n (%)	
Beta-blockers	54 (90.0)
ACEI/ARB	44 (73.3)
ARNi	33 (55.0)
MRA	26 (43.3)
Loop diuretics	52 (86.7)
Antidiabetic therapy among patients with DM2	
Dapagliflozin 5 mg	10 (16.7)
Dapagliflozin 10 mg	26 (43.3)
Empagliflozin 5 mg	3 (5.0)
Empagliflozin 10 mg	21 (35.0)
Metformin	21 (61.8%)
DPP-4 inhibitors	6 (17.6%)
Insulin (basal and/or bolus)	8 (23.5%)
Sulfonylureas	2 (5.9%)

Continuous data are presented as mean $\pm$ SD (range); categorical data as n (%). Abbreviations: ACEI—angiotensin-converting enzyme inhibitor; ARB—angiotensin II receptor blocker; ARNi—angiotensin receptor–neprilysin inhibitor; MRA—mineralocorticoid receptor antagonist; DM2—type 2 diabetes mellitus; DPP-4 inhibitors—dipeptidyl peptidase-4 inhibitors; SD—standard deviation.

3.2. Sleep-Related Respiratory Outcomes

Following three months of SGLT2i therapy, the patients demonstrated a significant attenuation of SDB, as detailed in Table 2. Subjective daytime sleepiness, quantified by the ESS, decreased appreciably, coinciding with a reduction in the frequency of apnea–hypopnea events per hour (AHI). The measures of nocturnal oxygenation improved, with a lower oxygen desaturation index and higher mean overnight SpO₂, while the prevalence and duration of the Cheyne–Stokes respiration cycles declined. These respiratory improvements were paralleled by enhanced health-related quality of life, reflected in a marked increase in KCCQ overall scores, indicating relief of heart failure-related symptoms and functional impairment (Table 2).

Table 2. Sleep-related and patient-reported outcomes at baseline and 3-month follow-up.

Parameter	Baseline	Follow-Up	Δ (Follow-Up – Baseline)	<i>p</i> -Value
ESS	10.72 ± 1.61	8.04 ± 2.27	−2.68	<0.001
KCCQ overall score	62.87 ± 5.73	72.03 ± 6.99	+9.16	<0.001
CSR index (events/h)	32.63 ± 11.05	27.01 ± 9.61	−5.63	<0.001
AHI (events/h)	21.18 ± 4.82	18.11 ± 4.64	−3.07	<0.001
ODI (events/h)	24.35 ± 6.66	18.24 ± 5.83	−6.11	<0.001
Mean nocturnal SpO ₂ (%)	89.98 ± 2.85	91.93 ± 2.58	+1.95	<0.001
Lowest nocturnal SpO ₂ (%)	80.91 ± 5.55	81.69 ± 5.26	+0.78	0.206

Data are mean ± SD; Δ indicates absolute change from baseline to follow-up. ESS—Epworth Sleepiness Scale; KCCQ—Kansas City Cardiomyopathy Questionnaire; CSR—Cheyne–Stokes respiration; AHI—apnea–hypopnea index; ODI—oxygen desaturation index; SpO₂—peripheral oxygen saturation.

3.3. Cardiac and Functional Parameters

Concomitant cardiac assessments revealed neurohormonal and hemodynamic stabilization without a compromise of ventricular systolic performance. NT-proBNP concentrations fell, consistent with reduced ventricular wall stress, and the E/e' ratio improved, indicating lower left ventricular filling pressures. The left ventricular ejection fraction remained unchanged, and the chamber dimensions—left ventricular end-diastolic volume and left atrial volume index—exhibited minimal variation, suggesting that structural reverse remodeling was not yet pronounced. The right heart evaluation showed a modest decrease in RVOT diameter with a stable right atrial area, whereas TAPSE increased, denoting improved right ventricular contractile function; the relationship between TAPSE and systolic pulmonary artery pressure is illustrated in Figure 2. Renal function, as assessed by both eGFR and serum creatinine, remained preserved throughout the study period, with a slight but non-significant decrease in serum creatinine. Additionally, a significant reduction in body mass index (BMI) was observed. These favorable changes likely reflect the effective decongestive therapy achieved during hospitalization and follow-up, contributing to improved volume status and metabolic profile.

All the findings are detailed in Table 3.

Table 3. Cardiac, renal, and echocardiographic parameters at baseline and 3-month follow-up.

Parameter	Baseline	Follow-Up	Δ (Follow-Up – Baseline)	<i>p</i> -Value
NT-proBNP (pg/mL)	1780.9 ± 882.8	1451.3 ± 923.4	−329.64	<0.001
E/e'	14.55 ± 2.76	13.48 ± 2.65	−1.08	<0.001

Table 3. Cont.

Parameter	Baseline	Follow-Up	Δ (Follow-Up – Baseline)	<i>p</i> -Value
LVEF (%)	35.06 $\pm$ 4.65	35.16 $\pm$ 4.85	+0.10	0.490
LVEDV (mL)	191.76 $\pm$ 19.20	189.78 $\pm$ 17.97	−1.98	0.094
LAVi (mL/m ²)	45.58 $\pm$ 4.20	45.47 $\pm$ 4.24	−0.11	0.239
eGFR (mL/min/1.73 m ²)	61.87 $\pm$ 9.42	62.37 $\pm$ 9.56	+0.50	0.210
Serum creatinine, μ mol/L	108 $\pm$ 9.1	103 $\pm$ 8.2	−5	0.081
BMI, kg/m ²	29.2 $\pm$ 2.6	27.8 $\pm$ 2.5	−1.4	0.011
RVOT diameter (mm)	39.44 $\pm$ 4.18	38.53 $\pm$ 3.91	−0.92	0.001
RA area (cm ²)	21.93 $\pm$ 3.15	21.99 $\pm$ 3.04	+0.06	0.728
TAPSE/s-PAP (mm/mmHg)	0.455 $\pm$ 0.108	0.474 $\pm$ 0.107	+0.018	<0.001

Data are mean $\pm$ SD; Δ indicates absolute change from baseline to follow-up. NT-proBNP—N-terminal pro-B-type natriuretic peptide; E/e'—ratio of early mitral inflow velocity to mitral annular early diastolic velocity; LVEF—left ventricular ejection fraction; LVEDV—left ventricular end-diastolic volume; LAVi—left atrial volume index; eGFR—estimated glomerular filtration rate; RVOT—right ventricular outflow tract; RA—right atrium; TAPSE—tricuspid annular plane systolic excursion; s-PAP—systolic pulmonary artery pressure; BMI—body mass index.

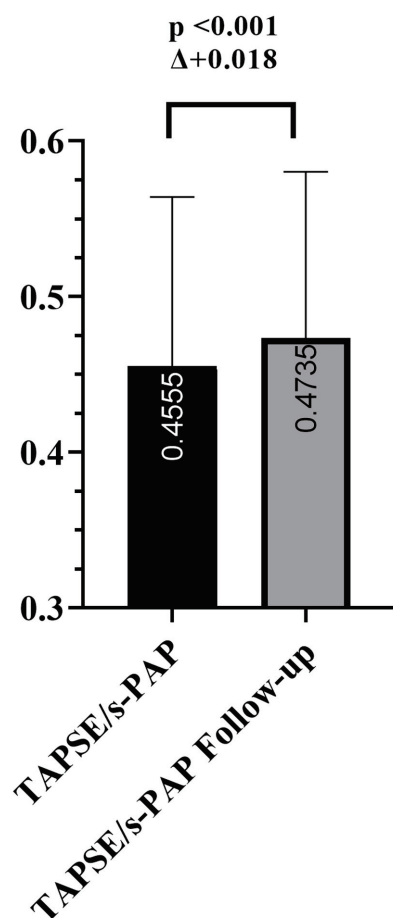


Figure 2. Change in TAPSE/sPAP ratio following 3 months of SGLT2i therapy. Bar chart illustrating the increase in the TAPSE/sPAP ratio—an integrated echocardiographic marker of right ventricular–pulmonary arterial coupling—between baseline and 3-month follow-up in patients with acute decompensated heart failure. The observed improvement reflects enhanced right ventricular systolic function relative to pulmonary arterial pressure.

4. Discussion

The interplay between ADHF and SDB, particularly CSR, is rooted in a complex pathophysiological framework involving chronic hyperventilation, prolonged circulatory delay, and enhanced chemoreceptor sensitivity [19]. Our study supports this model by identifying a high prevalence of CSR in a cohort of ADHF patients with reduced LVEF. One of the central mechanisms likely underpinning this relationship is the rostral fluid shift during recumbency, which facilitates pulmonary congestion, upper airway narrowing, and cyclical apnea–hyperpnea patterns that typify CSR [20,21]. These dynamics are not merely mechanical but are further compounded by autonomic instability and arrhythmogenic substrates. In this context, autonomic dysregulation and coexisting AF act synergistically to exacerbate ventilatory instability, creating a self-reinforcing loop of nocturnal hypoxemia, sympathetic activation, and progressive cardiac decompensation [22]. These interrelated processes reinforce the emerging concept that CSR is not merely a by-product of heart failure but represents a modifiable pathophysiological target with both prognostic and therapeutic implications. Recent data further support this interplay, highlighting the potential of both SGLT2 inhibitors and GLP-1 receptor agonists to mitigate cardiovascular risk and reduce OSA severity through pleiotropic, multi-organ effects [23].

Although autonomic modulation and fluid redistribution are biologically plausible mechanisms through which SGLT2is may attenuate CSR, our study did not include direct assessments of sympathetic activity or fluid volume status. Thus, the mechanistic basis of these observations remains to be elucidated in future studies designed to evaluate these physiological domains more directly.

Simultaneously, the demographic and clinical profile of our cohort provides essential context for the interpretation of our findings. It reflects a representative phenotype of patients with ADHF and reduced LVEF, aligning with those observed in pivotal heart failure trials and large observational registries. The predominance of elderly males, the high prevalence of AF and T2DM, and a majority non-ischemic etiology enhance the generalizability of our findings [24–26]. From a therapeutic standpoint, all the patients were initiated on SGLT2i therapy upon discharge, and dosing strategies were tailored to clinical status and comorbidity profile. Lower doses were predominantly prescribed to T2DM patients already receiving combination antihyperglycemic agents such as metformin or DPP-4 inhibitors, and to those with advanced age or a higher risk for intravascular volume depletion. This approach is consistent with real-world prescribing behaviors and reflects a precision-based strategy in the implementation of guideline-directed medical therapy for HFrEF [27–29].

Consistent with this optimized pharmacological regimen, the three-month follow-up revealed substantial improvements in multiple parameters of sleep-disordered breathing. Specifically, the ESS scores decreased significantly, indicating the amelioration of daytime somnolence, while reductions in both AHI and ODI underscored improvements in nocturnal respiratory stability and oxygenation. These changes were accompanied by a meaningful rise in mean overnight SpO₂, albeit without a statistically significant shift in nadir saturation. The improvements observed across these objective and subjective domains underscore the potential role of SGLT2is in modulating nocturnal breathing patterns. Of particular relevance is that the CSR index declined by more than five events per hour, consistent with emerging data that suggest SGLT2is mitigate respiratory instability through hemodynamic modulation and the attenuation of sympathetic tone [30,31]. The clinical importance of these improvements is further substantiated by a marked increase in KCCQ scores, indicating enhanced patient-reported symptom burden and quality of life. These findings are in agreement with results from the DAHOS study and the meta-analysis by Polecka et al., both of which demonstrated the consistent benefits of SGLT2is for sleep

quality, ventilatory parameters, and functional outcomes in HF patients with coexisting SDB [31].

The cardiac biomarker and echocardiographic data further reinforced the systemic benefits of SGLT2i in this high-risk cohort. The significant reduction in NT-proBNP, coupled with a decrease in E/e' , suggests effective LV unloading and improved diastolic filling pressures. These effects are mechanistically in line with the known natriuretic and vasodilatory actions of SGLT2is and mirror the findings of Correale et al., who observed similar improvements in patients undergoing combination therapy with SGLT2is and ARNis [32]. Similarly, Jaffuel et al. [33] investigated ARNi-based therapy optimization in patients with reduced systolic function and re-evaluated sleep-disordered breathing parameters after three months. They also reported significant reductions in central apneas and Cheyne–Stokes respiration, along with improved nocturnal oxygen saturation. These findings reinforce the importance of optimizing pharmacological treatment according to current guidelines before initiating positive airway pressure therapy for sleep apnea at home. While LVEF remained stable over the observation period, modest changes in LVEDV and LAVi suggest the possibility of early reverse remodeling, which may become more evident with longer treatment duration. This is consistent with prior studies indicating that functional improvements often precede structural adaptation during SGLT2i therapy [34]. In addition, beyond their cardiorenal effects, SGLT2 inhibitors may influence chemoreflex sensitivity and autonomic tone, potentially modulating central respiratory drive. Their emerging antiarrhythmic and sympathoinhibitory properties may further stabilize ventilatory patterns, particularly in patients with underlying autonomic imbalance or atrial fibrillation [35].

Complementing the left-sided findings, additional insights were obtained from the assessment of right ventricular function. An increase in TAPSE, along with a reduction in RVOT diameter and stable RA area, suggests improved RV contractile performance. Furthermore, the observed rise in the TAPSE/sPAP ratio reflects enhanced RV–PA coupling, an integrated echocardiographic indicator of right ventricular adaptation to afterload. Notably, while this improvement occurred in parallel with attenuation of CSR burden, the relationship should be interpreted as associative rather than causal. This parameter has gained recognition as a strong independent prognostic marker in patients with HF, particularly in the presence of pulmonary hypertension and SDB [36,37]. Given the mechanistic link between RV dysfunction and CSR, our findings further support the notion that improvement in RV–PA coupling may mediate some of the observed respiratory benefits [38].

Renal function was also closely monitored, given the well-established nephroprotective effects of SGLT2is. eGFR remained stable throughout the observation period, with a non-significant trend toward improvement. This trajectory mirrors the expected biphasic renal response to SGLT2i therapy, wherein an early and transient rise in serum creatinine attributed to afferent arteriolar vasoconstriction is followed by the functional stabilization or recovery of glomerular filtration [39]. Although SGLT2 inhibitors are associated with an initial decline in eGFR during the first weeks of therapy, previous studies have demonstrated a subsequent recovery phase. In our cohort, the modest improvement in eGFR observed after 3 months may reflect both this physiological rebound and the effects of optimized heart failure therapy during the post-decompensation period. Importantly, no adverse renal events were observed, which further supports the safety and tolerability of SGLT2is in this clinically fragile population.

5. Limitations

While this study contributes valuable insights into the intersection of heart failure and sleep-disordered breathing, a few limitations should be acknowledged. Being conducted at

a single center, the findings may not fully capture the diversity of patient populations or practice patterns in other settings. The sample size, though adequate for evaluating overall treatment effects, was not large enough to explore subgroup differences or interactions, such as those based on heart failure etiology or the initial severity of CSR. Additionally, the use of portable respiratory polygraphy, while practical and validated, offers a limited view of sleep architecture and does not distinguish central from obstructive events with the granularity of full polysomnography. We did not record or control for patients' sleeping position, which may have influenced the detection and severity of sleep-disordered breathing events. We did not assess acid–base status or systematically exclude noncardiac causes of CSR, such as uremia, CNS pathology, or medication-induced effects. The three-month follow-up period, although sufficient to detect early physiological responses, may not reflect the full trajectory of long-term cardiac or renal adaptation. Moreover, the lack of multivariate modeling represents a limitation, as it precludes adjustment for potential confounders such as age, baseline disease severity, and comorbidities. Our findings generate hypothesis-supporting evidence that SGLT2 inhibitors may influence respiratory and cardiac parameters in patients with ADHF. However, due to the limitations of the study design, these observations should be interpreted with caution.

6. Conclusions

This prospective cohort study suggests that SGLT2i therapy in patients with ADHF and reduced LVEF may be associated with early improvements in SDB, RV function, and markers of decongestion. The favorable trends observed in both the respiratory parameters and patient-reported outcomes support the hypothesis that SGLT2is exert pleiotropic benefits beyond glycemic control. While promising, these findings should be interpreted cautiously due to the limited sample size, lack of a comparator arm, and short follow-up. Future studies with larger cohorts are needed to enable more robust statistical control.

Author Contributions: Conceptualization, P.K., E.K., and A.G.; methodology, P.K. and G.V.; software, P.K., N.S. and R.I.; validation, P.K., E.K., N.G. and T.V.; formal analysis, T.V.; investigation, P.K., A.B. and G.V.; resources, T.V. and Y.D.; data curation, R.I.; writing—original draft preparation, P.K.; writing—review and editing, T.V., Y.D. and E.K.; visualization, P.K., N.S. and R.I.; supervision, A.G.; project administration, P.K.; funding acquisition, P.K. All authors have read and agreed to the published version of the manuscript.

Funding: This study is financed by the European Union-NextGenerationEU through the National Recovery and Resilience Plan of the Republic of Bulgaria, project BG-RRP-2.004-0004-C01 “Strategic research and innovation program for development of Medical University—Sofia”.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Medical University of Sofia, protocol code 2145, from 27 April 2021.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data cannot be shared for ethical/privacy reasons. The data underlying this article cannot be shared publicly due to ethical reasons. The data contain sensitive information and are associated with questionnaires completed by patients. The data will be shared upon reasonable request to the corresponding author, after any sensitive information has been removed.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ACE	Angiotensin-Converting Enzyme
ADHF	Acute Decompensated Heart Failure
AF	Atrial Fibrillation
AHI	Apnea–Hypopnea Index
ARB	Angiotensin II Receptor Blocker
ARNi	Angiotensin Receptor–Neprilysin Inhibitor
CSR	Cheyne–Stokes Respiration
DPP-4i	Dipeptidyl Peptidase-4 Inhibitor
eGFR	Estimated Glomerular Filtration Rate
ESS	Epworth Sleepiness Scale
HFrEF	Heart Failure with Reduced Ejection Fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAVi	Left Atrial Volume Index
LVEDV	Left Ventricular End-Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
MRA	Mineralocorticoid Receptor Antagonist
NT-proBNP	N-terminal pro-B-type Natriuretic Peptide
NYHA	New York Heart Association
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnea
RA	Right Atrium
RV	Right Ventricle
RVOT	Right Ventricular Outflow Tract
RV-PA	Right Ventricular–Pulmonary Arterial
SDB	Sleep-Disordered Breathing
SD	Standard Deviation
SGLT2i	Sodium–Glucose Cotransporter 2 Inhibitor
SpO ₂	Peripheral Oxygen Saturation
SPSS	Statistical Package for the Social Sciences
T2DM	Type 2 Diabetes Mellitus
TAPSE	Tricuspid Annular Plane Systolic Excursion
TAPSE/sPAP	Ratio of TAPSE to Systolic Pulmonary Artery Pressure

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Article

A Word of Caution—Potential Limitations of Pulmonary Artery Pressure Monitoring in Detecting Congestion Caused by Right-Sided Heart Failure

Ester Judith Herrmann ¹, Eva Herrmann ^{2,3}, Khodr Tello ⁴, Kathleen Mantzsch ⁵, Meaza Tekeste ⁵, Stephan Fichtlscherer ⁵, Christian W. Hamm ^{1,2} and Birgit Assmus ^{1,2,5,*}

¹ Department of Medicine I, Cardiology and Angiology, University Hospital Giessen and Marburg, 35392 Giessen, Germany; ester.herrmann@innere.med.uni-giessen.de (E.J.H.); christian.hamm@innere.med.uni-giessen.de (C.W.H.)

² German Center for Cardiovascular Research, DZHK, Partner Site Frankfurt Rhine-Main, 61231 Bad Nauheim, Germany; herrmann@med.uni-frankfurt.de

³ Institute of Biostatistics and Mathematical Modeling, Goethe University Frankfurt, 60590 Frankfurt am Main, Germany

⁴ Department of Medicine II, Internal Medicine, Pneumology, University Hospital Giessen and Marburg, 35392 Giessen, Germany; khodr.tello@innere.med.uni-giessen.de

⁵ Department of Medicine III, Cardiology, University Hospital Frankfurt am Main, 60590 Frankfurt am Main, Germany; kmantzsch@yahoo.de (K.M.); tekeste@med.uni-frankfurt.de (M.T.); fichtlscherer@em.uni-frankfurt.de (S.F.)

* Correspondence: birgit.assmus@innere.med.uni-giessen.de

Abstract: Background/Objectives: Patients with New York Heart Association (NYHA) class III heart failure (HF) suffer from frequent hospitalizations. Non-invasive pulmonary artery pressure (PAP) sensor-guided HF care has been shown to reduce hospitalizations. However, it is unknown whether the PAP changes prior to hospitalization differ between clinical right, left or global cardiac decompensation. **Methods:** Sensor-derived PAP data and HF hospitalization records from 41 patients with NYHA class III HF were classified retrospectively into predominantly left, right or global decompensation. Linear mixed-effect regression models were used for statistical evaluations of the PAP in selected hospitalizations for which admission was at least 28 days after the last admission and 14 days after the last hospital discharge and with readings in between. **Results:** During 24.4 months of follow-up, 127 hospitalizations in 38 patients were evaluated. The global cardiac decompensation ($n = 13$) had the highest PAP before hospitalization, followed by left-sided ($n = 20$) decompensation. Patients with right-sided decompensation ($n = 9$) had comparable PAP values before hospitalization to the cohort without any cardiac decompensation ($n = 85$). The diastolic PAP showed a significant increase of 0.035 mmHg/day ($p = 0.0097$) in left-sided decompensation and of 0.13 mmHg/day ($p < 0.0001$) in global cardiac decompensation, whereas no significant change in the diastolic PAP occurred prior to the right-sided decompensation. The baseline right ventricular function and right ventricle–pulmonary arterial coupling (TAPSE/PASP ratio) were impaired in patients with subsequent global cardiac decompensation. **Conclusion:** PAP telemonitoring-guided therapy can reliably detect early signs of left and global cardiac decompensation but may be limited in detecting right-sided cardiac congestion. The routine assessment of RV–PA coupling may improve the detection of global cardiac decompensation, as severe impairments could indicate impending deterioration. In contrast, monitoring the RV contractility may aid in identifying isolated right-sided congestion and imminent decompensation.

Keywords: chronic heart failure; remote monitoring; pulmonary artery pressure; right-sided decompensation

1. Introduction

Heart failure (HF) affects approximately 1–2% of the adult population in developed countries, and the incidence and prevalence are increasing due to the growing life expectancy [1,2]. More than 75% of acute HF hospitalizations occur in people with pre-existing chronic HF [3], so that hospitalization for acute HF is a major contributor to the economic burden of HF [4]. Moreover, every cardiac decompensation is associated with a further deterioration of myocardial function, which favors disease progression [5]. Although initial decongestion is clinically successful in the vast majority of admitted patients, 34% of acute HF patients are readmitted to hospital for the recurrence of acute HF within 3 months after discharge [6]. Consequently, there is a need for improved strategies for the early detection of HF decompensation. The monitoring of blood pressure, heart rate and weight changes as well as intrathoracic impedance as single or combined measures of congestion status were shown to have limited effectiveness in reducing hospitalization rates for HF [7,8]. However, a structured remote patient management intervention, when used in a well-defined HF population, was shown to reduce the number of days lost due to unplanned cardiovascular hospital admissions as well as all-cause mortality [9]. Likewise, results from trials with implantable hemodynamic pulmonary artery pressure (PAP) monitoring demonstrated that HF management supported by the monitoring of outpatient PAP values, as provided by the CardioMEMSTM system, was associated with a significant and profound reduction in the HF hospitalization rate in New York Heart Association (NYHA) functional class III patients in the US [10,11]. More recently, the GUIDE-HF hemodynamic monitoring trial provided mixed results with a non-significant reduction in the primary endpoint in a broader patient cohort from NYHA class II–IV, which was most likely due to a significant impact on event rates by the SARS CoV-2 pandemic. In addition, the MEMS-HF trial demonstrated a significant reduction in PAP irrespective of an additional underlying precapillary component to postcapillary pulmonary hypertension (PH) [12]. More recently, the MONITOR-HF trial showed that hemodynamic monitoring substantially improved quality of life and reduced HF hospitalizations in patients with moderate-to-severe HF treated according to contemporary guidelines, which was the first large-scale randomized European study [13]. Thus, the potential of monitoring PAP to reduce HF hospitalizations is well recognized and has led to the implementation of hemodynamic telemedical care in numerous centers.

During the PAP-supported HF care of patients at our HF center, it was noticed that some patients were admitted to hospital with cardiac decompensation although there was no meaningful increase in PAP readings prior to the cardiac decompensation.

Therefore, the present case study was designed to investigate these episodes with no PAP increase prior to hospitalization for decompensation with respect to the hypothesis that the right ventricular (RV) contractility may be greater and the RV systolic function and right ventricular–pulmonary artery (RV–PA) coupling may be less impaired in these patients, compared to patients with hospitalizations with a prior increase in PAP. In addition, none of the previously published hemodynamic monitoring trials in HF have thus far provided any data with respect to RV function, contractility or RV–PA coupling.

2. Materials and Methods

Patients with chronic HF in NYHA functional class III and a cardiac decompensation event within the last 12 months were offered implantation of the PAP sensor (CardioMEMS™, Abbott, Sylmar, CA, USA) and participation in a single-center telemonitoring registry. A total of 43 patients underwent implantation of the PAP sensor between 2015 and 2019, received PAP-guided HF management and were repeatedly trained in HF self-care by a European Society of Cardiology (ESC)-certified HF nurse. For the present analyses, one patient with an LVAD implantation and one patient with newly diagnosed constrictive pericarditis and surgery were excluded, leaving a total of 41 patients with regular data transmission of PAP values at least 5 times per week. Hospitalization was defined as an in-hospital stay ≥ 24 h (Figure 1).

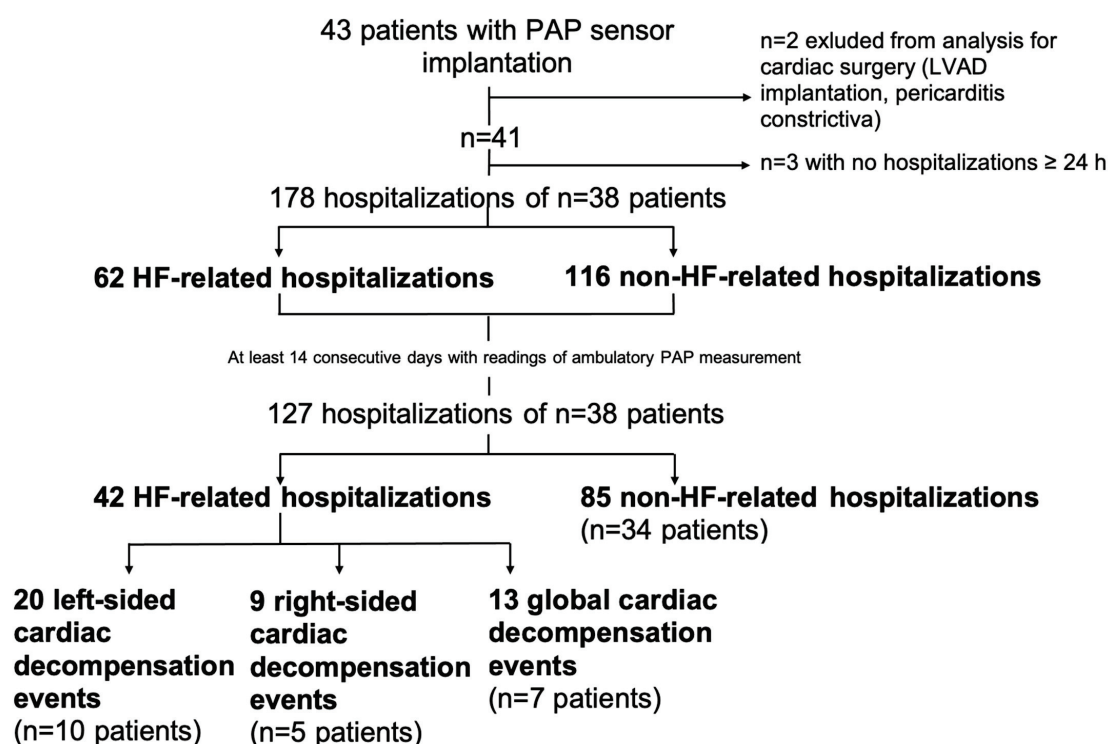


Figure 1. Flowchart of hospitalization analysis.

The hospitalizations were retrospectively classified by a HF specialist based on available hospital records with clinical, imaging and laboratory criteria in order to discriminate cardiac decompensation from other reasons for hospitalization and to decide about elective and urgent cause for hospital admission. The hospitalizations for cardiac decompensation were further classified according to clinical signs and symptoms into predominately left-sided (pulmonary congestion on chest X-ray or presence of B-lines, but no peripheral congestion with edema or ascites), right-sided (peripheral edema and/or ascites, no pulmonary congestion on chest X-ray and no B-lines) or globally decompensated (evidence of pulmonary congestion on chest X-ray or B-lines and peripheral congestion with edema and/or ascites).

The outpatient routine follow-up in our Heart Failure Center took place at the defined periods of 3, 6, 12 and 24 months after PAP sensor implantation, but additional outpatient visits were possible.

RV–PA coupling was non-invasively assessed by echocardiography using the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure (TAPSE/PASP) ratio method, as described previously [14]. In addition, the corresponding sensor-derived

systolic PAP was used for ratio calculation. Associations between the different methods of non-invasive coupling assessment are shown in Supplemental Figures S1 and S2.

Furthermore, mean pulse pressure (PP) has been calculated as average of the difference in systolic PAP and diastolic PAP and mean proportional PP is the proportion of mean PP to systolic arterial blood pressure [15].

All patients who were implanted with the CardioMEMSTM sensor provided written informed consent for participation in the single-center registry (NCT03020043). This study was approved by the local ethics committee and complied with the principles laid out in the Declaration of Helsinki.

Statistical Analysis

This case study is a descriptive comparison of four different types of hospitalizations (without cardiac decompensation event, decompensation with predominantly left-sided, right-sided and global cardiac decompensation). Baseline characteristics were compared with the non-parametric Mann–Whitney U-test. The association between TAPSE/PASP ratio (echocardiogram) and TAPSE/PASP ratio (systolic PAP derived from CardioMEMSTM pressure sensor, Abbott, Sylmar, CA, USA) was analyzed by linear mixed-effect regression (Supplemental Figures S1 and S2).

Linear mixed-effect models were applied for statistical evaluations of PAP and variation in PAP within the individual patients and for differentiating between the type of hospitalization in selected hospitalizations for admissions at least 28 days after the last admission, 14 days after the last hospital discharge; this left 127 hospitalizations for further analysis with respect to PAP changes (Figure 1; corresponding monitoring times prior to hospitalization are shown in Supplemental Figure S3). For illustration of the time course of PAP readings, non-parametric smoothing methods were applied (kernel smoothing with the R package lokern). Thus, for the group comparisons of time-dependent, hospitalization-based variables, intra-patient dependence was considered with the mixed-effect modeling.

Statistical significance was assumed if $p < 0.05$, and all reported p -values are two-sided. Statistical analysis was carried out with the software packages SPSS (Version 23.0, SPSS Inc., IBM Corp., Armonk, NY, USA) and R (Version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline Characteristics

The hemodynamic patient cohort comprised a total of 38 patients with NYHA class III chronic HF. The mean patient age was 74 ± 2 years, 84.2% were male and 78.9% suffered from ischemic cardiomyopathy. HF with reduced ejection fraction (HFrEF) was present in 92.1% of patients. Twenty-six of thirty-eight patients (68.4%) had PH (PAPmean >20 mmHg), and of those, twenty patients presented with a combined pre- and postcapillary PH phenotype with a PVR > 2 WU, according to the ESC 2022 Guidelines [16].

During an average follow-up (with at least five PAP measurements per week) of 24.4 ± 1.3 months (range from 2 to 49 months), a total of 178 hospitalizations occurred in 38 patients (62 hospitalizations for cardiac decompensation, 116 hospitalizations for other reasons; Figure 1). Three patients in our cohort did not have any hospitalizations, thus leaving thirty-eight patients with 178 hospitalizations for further assessment. Due to the focus on the PA pressure course prior to hospitalization, we further required at least 14 days of outpatient PA pressure measurements prior to hospitalization, resulting in 127 hospitalizations in 38 patients for further evaluation (Supplementary Figure S3).

These hospitalizations included 42 hospitalizations for HF in 16 patients, which were further sub-classified as predominantly left-sided ($n = 20$), right-sided ($n = 9$) or global

(n = 13) cardiac decompensation events. A total of 85 hospitalizations occurred without cardiac decompensation (Figure 1).

Eleven patients died during the follow-up period, with eight patients experiencing cardiac death, but no patient died within 30 days after hospital admission (Figure 2 and Supplementary Table S1).

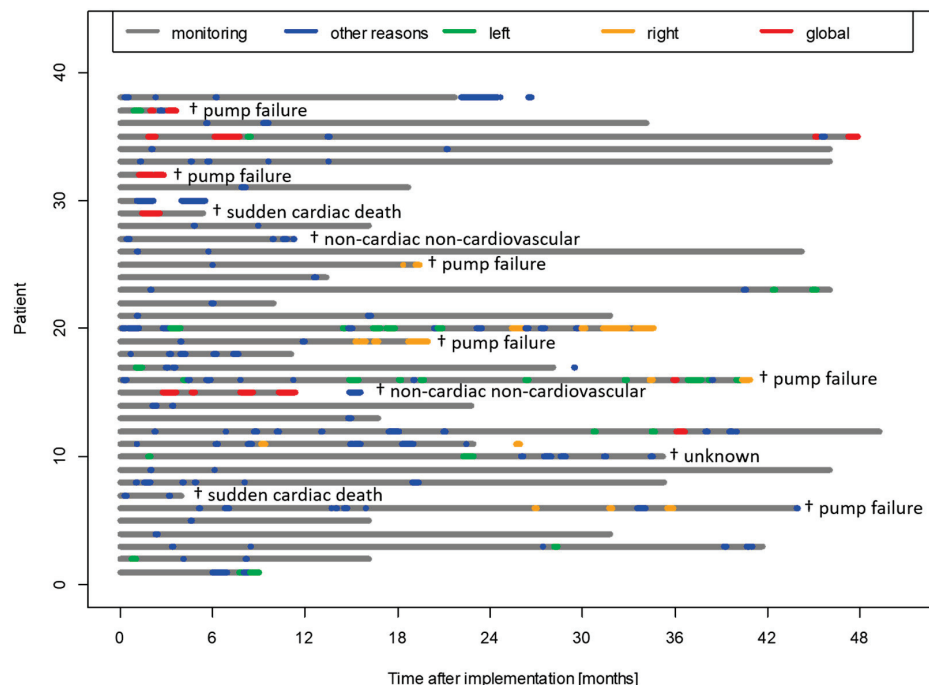


Figure 2. Graphical display of monitoring of patients with decompensation events (n = 38), including cause of death (n = 11).

The analysis of the association of a later cardiac decompensation event with patient baseline characteristics revealed that these events are associated with higher creatinine levels and a more impaired RV–PA coupling, as assessed non-invasively by the TAPSE/PASP ratio at the time of the PAP sensor implantation (Table 1). With respect to the hemodynamics of HF, the cardiac index of the cohort with cardiac decompensation was comparable to that of the group without cardiac decompensation, although the PAP was elevated in the former group. The pulmonary arterial wedge pressure was similarly elevated in the two groups, and the pulmonary vascular resistance was pathologically elevated in 52% of the hospitalizations.

Table 1. Patient baseline characteristics analyzed per hospitalization at the time of the sensor implantation.

Variables	Hospitalizations Without Cardiac Decompensation (n = 85;%)	Hospitalizations with Cardiac Decompensation (n = 42;%)	p-Value	Left-Sided Decompensation (n = 20;%)	Right-Sided Decompensation (n = 9;%)	Global Cardiac Decompensation (n = 13;%)	p-Values ^{1,2,3} p-Values ^{a,b,c}
Clinical characteristics							
Age, years	74 ± 1	79 ± 1	0.098	76 ± 2	80 ± 1	81 ± 1	0.614/0.283/0.738 0.381/0.283/0.940
Etiology of CHF							
HFpEF	2; 8%	2; 6%	0.546	1; 9%	0; 0%	1; 20%	0.456/0.989/0.589
HFrEF	83; 92%	40; 94%		19; 91%	9; 100%	12; 80%	0.992/0.739/0.984
NYHA class							
IIIA	83; 94%	36; 88%	0.079	19; 87%	8; 80%	9; 75%	0.509/0.301/0.670
IIIB	2; 6%	6; 12%		1; 13%	1; 20%	4; 25%	0.595/0.174/0.059
Body Mass Index (kg/m ²)	26 ± 0.3	27 ± 0.4		27 ± 0.7	26 ± 0.8	27 ± 0.7	
Systolic blood pressure, mmHg	114 ± 2	112 ± 2	0.149	111 ± 4	110 ± 4	109 ± 3	0.622/<0.001/0.729 0.339/0.252/0.903

Table 1. Cont.

Variables	Hospitalizations Without Cardiac Decompensation (n = 85;%)	Hospitalizations with Cardiac Decompensation (n = 42;%)	p-Value	Left-Sided Decompensation (n = 20;%)	Right-Sided Decompensation (n = 9;%)	Global Cardiac Decompensation (n = 13;%)	p-Values ^{1,2,3} p-Values ^{a,b,c}
Laboratory parameters							
Creatinine, mg/dl	1.44 ± 0.04	1.79 ± 0.10	0.021	1.75 ± 0.12	1.40 ± 0.09	2.27 ± 0.21	0.204/0.698/0.086
Log-NT-proBNP, pg/mL	3.2 ± 0.07	3.5 ± 0.08	0.079	3.2 ± 0.07	3.6 ± 0.13	3.5 ± 0.19	0.337/0.030/0.219 0.403/0.046/0.551 0.006/0.007/<0.001
Medication at baseline							
ACEI/ATRB	70; 78%	41; 92%	0.085	20; 100%	9; 100%	12; 86%	0.995/0.997/0.966 1.000/0.983/0.987
ARNI	15; 20%	1; 2%	0.085	0; 0%	0; 0%	1; 14%	0.987/0.98/0.965 1.000/0.997/0.999
ACEI/ARB/ARNI	85; 100%	42; 100%	1.000	20; 100%	9; 100%	13; 100%	1.000/1.000/1.000 1.000/1.000/1.000
Beta-blockers	83; 97%	40; 91%	0.470	18; 92%	9; 100%	13; 100%	0.200/0.998/0.976 0.982/1.000/1.000
MRA	57; 81%	30; 69%	0.468	15; 70%	9; 100%	6; 40%	0.922/0.969/0.511 0.991/0.218/0.911
Loop diuretics	77; 92%	42; 100%	0.996	20; 100%	9; 100%	13; 100%	0.972/0.997/0.989 1.000/1.000/1.000
Torsemide, dose equivalent in mg	22 ± 2	26 ± 2	0.447	26 ± 3	23 ± 4	30 ± 4	0.494/0.901/0.680 0.661/0.734/0.550
Furosemide, dose equivalent in mg	88 ± 8	104 ± 8		104 ± 12	92 ± 16	120 ± 16	
Echocardiography							
LVEF, %	26 ± 1	25 ± 2	0.598	28 ± 3	24 ± 3	29 ± 3	0.688/0.380/0.781 0.324/0.731/0.079
TAPSE, mm	18 ± 1	17 ± 1	0.070	16 ± 1	21 ± 2	13 ± 1	0.080/0.154/<0.001 0.161/0.014/0.157
RV fractional area change, %	39 ± 1.1	38 ± 2.4	0.131	41 ± 3.2	48 ± 6.9	36.2 ± 9.9	0.001/0.277/0.712 0.894/0.201/0.476
TAPSE/PASP ratio, mm/mmHg (Echo)	0.52 ± 0.04	0.42 ± 0.03	0.190	0.42 ± 0.05	0.37 ± 0.08	0.28 ± 0.09	0.334/0.578/0.099 0.140/0.807/0.454
TAPSE/PASP ratio, mm/mmHg (CardioMEMS™)	0.50 ± 0.03	0.35 ± 0.03	0.007	0.36 ± 0.05	0.40 ± 0.05	0.26 ± 0.04	0.060/0.351/0.045 0.626/0.211/0.038
Association TAPSE/PASP ratio (Echo vs. CardioMEMS™)	p = 0.0012	p = 0.0014	-	p = 0.423	p < 0.001	p = 0.228	-
Invasive hemodynamics							
Cardiac index, l/min/m ²	2.0 ± 0.1	2.0 ± 0.2	0.687	2.6 ± 0.3	2.2 ± 0.5	1.8 ± 0.1	0.206/0.636/0.768 0.760/0.197/0.062
PAP systolic, mmHg	44 ± 2	53 ± 2	0.002	53 ± 4	54 ± 4	54 ± 5	0.030/0.169/0.564 0.940/0.422/0.754
PAP mean, mmHg	27 ± 1	34 ± 2	0.013	33 ± 3	34 ± 3	34 ± 3	0.099/0.262/0.667 0.879/0.495/0.804
PAP diastolic, mmHg	17 ± 1	22 ± 1	0.031	20 ± 2	23 ± 2	22 ± 2	0.261/0.194/0.608 0.561/0.418/0.901
PCWP mean, mmHg	17 ± 1	18 ± 1	0.524	19 ± 2	16 ± 3	18 ± 2	0.870/0.396/0.958 0.396/0.897/0.483
PVR, Wood unit	3.5 ± 0.3	2.7 ± 0.2	0.017	3.1 ± 0.4	3.0 ± 0.7	2.4 ± 0.2	0.238/0.386/0.625 0.796/0.170/0.074
cpcPH, n, %	43; 51%	23; 55%	-	14; 70%	6; 67%	3; 23%	-

Values represent the mean ± standard error or n (%) from linear or logistic mixed-effect regression models accounting for multiple hospitalizations in single patients. First *p*-values are for the association with the type of cardiac decompensation with the reference group of hospitalizations without cardiac decompensation (¹ *p*-value: no cardiac decompensation vs. left, ² *p*-value: no cardiac decompensation vs. right and ³ *p*-value: no cardiac decompensation vs. global), and reported *p*-values are two-sided and not corrected for multiple comparisons. Second *p*-values are for the association with different types of cardiac decompensation (^a *p*-value: left vs. right, ^b *p*-value: left vs. global and ^c *p*-value: right vs. global), and *p*-values are two-sided and not corrected for multiple comparisons. The association between the TAPSE/PASP ratio (echocardiogram) and TAPSE/PASP ratio (CardioMEMS™) was also analyzed with a mixed-effect regression model, and the R² is the proportion of variations explained by the fixed effect factors, and *p*-values are two-sided. Baseline medication: ACEI-I, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor blocker neprilysin inhibitor; ATRB, angiotensin receptor blocker; and MRA, mineralocorticoid antagonist. Other abbreviations: CHF, chronic heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal fragment of pro-brain natriuretic protein; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricular; PASP, systolic pulmonary artery pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; and cpcPH, combined post- and precapillary pulmonary hypertension.

The length of hospital stays was longer in all types of cardiac decompensation than in the hospitalizations without cardiac decompensation (left-sided: 8.0 ± 2.7 days; $p = 0.046$, right-sided: 5.3 ± 1.6 days; $p = 0.731$, global: 14.8 ± 3.14 days; $p = 0.083$, vs. without cardiac decompensation event: 4.5 ± 0.6 days). Hospitalizations for the global cardiac decompensation had the longest duration of hospitalization (Table 2).

Table 2. Clinical characteristics and echocardiographic and laboratory parameters pre-decompensation without cardiac decompensation vs. pre-decompensation per hospitalization for all cardiac decompensation events and for those classified as left-sided, right-sided and global cardiac decompensation.

Variables	Hospitalizations Without Cardiac Decompensation (n = 85;%)	Hospitalizations with Cardiac Decompensation (n = 42;%)	p-Value	Left-Sided Decompensation (n = 20;%)	Right-Sided Decompensation (n = 9;%)	Global Cardiac Decompensation (n = 13;%)	p-Values ^{1,2,3} p-Values ^{a,b,c} p-Values ^{*,§,§}
Clinical characteristics							
NYHA class							
IIA	18; 12%	15; 19%	0.0788	9; 18%	4; 40%	2; 30%	
IIB	4; 3%	0; 0%		0; 0%	0; 0%	0; 0%	0.186 ¹ / 0.236 ² / 0.208 ³
IIIA	61; 80%	23; 67%		10; 72%	4; 50%	9; 58%	0.559 ^a / 0.572 ^b / 0.927 ^c
IIIB	2; 6%	4; 13%		1; 10%	1; 10%	2; 12%	
Echocardiographic parameters							
TAPSE, mm	19.1 $\pm$ 0.6	17.0 $\pm$ 1.1	0.010	18.1 $\pm$ 1.3	17.7 $\pm$ 0.7	14.2 $\pm$ 1.5	0.272 ¹ / 0.357 ² / <0.001 ³ 0.686 ^a / 0.014 ^b / 0.235 ^c
TAPSE/PASP ratio, mm/mmHg (Echo)	0.53 $\pm$ 0.04	0.42 $\pm$ 0.05	0.030	0.47 $\pm$ 0.06	0.41 $\pm$ 0.04	0.28 $\pm$ 0.04	0.333 ¹ / 0.137 ² / 0.057 ³ 0.336 ^a / 0.030 ^b / 0.360 ^c
TAPSE/PASP ratio, mm/mmHg (CardioMEMS™)	0.53 $\pm$ 0.04	0.37 $\pm$ 0.06	0.014	0.39 $\pm$ 0.08	0.37 $\pm$ 0.05	0.31 $\pm$ 0.04	0.159 ¹ / 0.114 ² / 0.028 ³ 0.642 ^a / 0.098 ^b / 0.352 ^c
Association TAPSE/PASP ratio (Echo vs. CardioMEMS™)	$p < 0.001$	$p < 0.001$	-	$p = 0.894$	$p = 0.999$	$p = 0.981$	-
RV fractional area change, %	37 $\pm$ 1	34 $\pm$ 2	0.066	36 $\pm$ 2	35 $\pm$ 2	30 $\pm$ 2	0.491 ¹ / 0.502 ² / 0.219 ³ 0.620 ^a / 0.034 ^b / 0.463 ^c
Laboratory parameters							
Creatinine, mg/dl	1.61 $\pm$ 0.08; # $p < 0.001$	2.40 $\pm$ 0.45; & $p = 0.025$	0.021	2.51 $\pm$ 0.74	1.91 $\pm$ 0.21	3.07 $\pm$ 0.90	0.345 ¹ / 0.241 ² / 0.319 ³ 0.922 ^a / 0.187 ^b / 0.482 ^c 0.176 ^a / 0.142 ^b / 0.231 ^c
Rel. Creatinine, %	17% $\pm$ 3%	33% $\pm$ 16%	0.310	33% $\pm$ 26%	35% $\pm$ 13%	40% $\pm$ 33%	0.953 ¹ / 0.095 ² / 0.877 ³ 0.391 ^a / 0.836 ^b / 0.867 ^c 0.870 ¹ / 0.067 ² / 0.310 ³
Log-NT-proBNP, pg/ml	3.2 $\pm$ 0.08; # $p = 0.172$	3.6 $\pm$ 0.13; & $p = 0.228$	0.015	3.2 $\pm$ 0.13	3.6 $\pm$ 0.19	3.7 $\pm$ 0.25	0.024 ^a / 0.012 ^b / 0.861 ^c 0.305 ^a / 0.414 ^b / 0.478 ^c
Δ log-NT-proBNP, pg/ml	-0.06 $\pm$ 0.04	0.12 $\pm$ 0.10	0.098	0.16 $\pm$ 0.14	0.07 $\pm$ 0.08	0.16 $\pm$ 0.21	0.318 ¹ / 0.404 ² / 0.016 ³ 0.623 ^a / 0.945 ^b / 0.487 ^c
Urgent admission, n; %	60; 78%; 23; 22%	22; 67%; 16; 33%	0.311	10; 70%; 10; 30%	5; 60%; 4; 40%	7; 67%; 2; 33%	0.291 ¹ / 0.498 ² / 0.931 ³ 0.860 ^a / 0.283 ^b / 0.692 ^c
Length of hospitalization, days	4.5 $\pm$ 0.6	11.0 $\pm$ 1.8	0.003	8.0 $\pm$ 2.7	5.3 $\pm$ 1.6	14.8 $\pm$ 3.14	0.046 ¹ / 0.731 ² / 0.083 ³ 0.437 ^a / 0.073 ^b / 0.292 ^c

Values represent the mean $\pm$ standard error or n (%). The last available observation before hospitalization is reported. First p -values are for the association of the type of cardiac decompensation with the reference group of hospitalizations without cardiac decompensation (¹ p -value: no cardiac decompensation vs. left, ² p -value: no cardiac decompensation vs. right, ³ p -value: no cardiac decompensation vs. global) using a mixed-effect logistic regression analysis; reported p -values are two-sided and not corrected for multiple testing. Second p -values are for the association of the types of cardiac decompensation (^a p -value: left vs. right, ^b p -value: right vs. global, ^c p -value: left vs. global) using a mixed-effect logistic regression analysis; p -values are two-sided and are not corrected for multiple testing. Third p -values are for the comparison from the baseline versus pre-hospitalization within the different types of hospitalization (baseline vs. pre-hospitalization: # p -value for hospitalizations without cardiac decompensation events; & p -value for all cardiac decompensation events; * p -value for left-sided decompensation events; § p -value for right-sided decompensation events; and § p -value for global cardiac decompensation events) using linear logistic regression for log ratios. The last observation and relative change from baseline and to the last observation in laboratory parameters prior to hospitalization. The association between the TAPSE/PASP ratio (echocardiogram) and TAPSE/PASP ratio (CardioMEMS™) was also analyzed with a mixed-effect regression model, and p -values are two-sided. Further characteristics of the hospitalization and the outcome per hospitalization. Mean and standard errors or proportions from a corresponding linear or logistic random effect regression estimate. For abbreviations see Table 1.

The comparison of baseline variables between the different clinical types of cardiac decompensation revealed that clinical and functional parameters were worse in cases with

global cardiac decompensation events. For example, patients with a right-sided or global cardiac decompensation during follow-up tended to be older, had higher levels of the N-terminal fragment of the pro-brain natriuretic peptide (NT-proBNP) and worse kidney function than patients with left-sided cardiac decompensation events (Table 1). The RV–PA coupling at baseline, measured as the TAPSE/PASP ratio, was significantly impaired in global versus right-sided cardiac decompensation (TAPSE/PASP ratio 0.40 ± 0.05 in right-sided decompensation versus 0.26 ± 0.04 in global decompensation events, $p = 0.038$). The RV–PA coupling in patients with global cardiac decompensation was also numerically lower in comparison to left-sided cardiac decompensation, although the difference was not significant (TAPSE/PASP ratio 0.36 ± 0.05 in left-sided decompensation versus 0.26 ± 0.04 in global decompensation events, $p = 0.211$). When the TAPSE/PASP ratio was calculated using both the echocardiographic- and sensor-derived systolic PAP, the latter value was associated with numerically more cases due to limitations in echocardiographic assessments. However, the two calculated ratios showed a highly significant positive association with each other (at baseline: $R^2 = 0.33$, $p = 0.001$, and at last visit prior to hospitalization: $R^2 = 0.34$, $p < 0.001$; Supplementary Figures S1 and S2).

3.2. Association of Follow-Up Characteristics with Subsequent Decompensation Events

The impact of more recent clinical, laboratory and echocardiographic data, which were obtained at the follow-up visits, was assessed with respect to the impending cardiac decompensation event. These analyses showed that the pattern of differences obtained at baseline persisted during the follow-up. For example, NT-proBNP levels remained significantly lower in patients with left-sided cardiac decompensation than in those with right-sided or global cardiac decompensation (left-sided 3.3 ± 0.13 pg/mL versus global 3.7 ± 0.25 pg/mL, $p = 0.012$, left-sided versus right-sided 3.6 ± 0.19 pg/mL, $p = 0.024$), and the kidney function was worse in patients with global cardiac decompensation (Table 2). Likewise, in comparison with the baseline, there was no change in the RV–PA coupling pattern or RV function in the left-sided or global cardiac decompensation groups and just a slight deterioration of the RV function prior to right-sided decompensation events. However, a limitation of this analysis is that there are different time frames between the last observation obtained at the follow-up visit and the impending cardiac decompensation event.

3.3. PAP Course Prior to Different Types of Cardiac Decompensation

Based on the course of the outpatient PAP values in the 30 days prior to a non-cardiac hospitalization event, there was a significant decrease in the systolic PAP and mean PAP of (mean $\pm$ standard error) 0.037 ± 0.01 mmHg/day ($p = 0.0013$) and 0.022 ± 0.008 mmHg/day ($p = 0.0074$). In contrast, there was a significant increase in the diastolic PAP of 0.035 ± 0.01 mmHg/day ($p = 0.0104$) in patients with predominantly left-sided decompensation and a significant increase in the systolic PAP, diastolic PAP and mean PAP of 0.14 ± 0.03 mmHg/day ($p < 0.0001$), 0.12 ± 0.02 mmHg/day ($p < 0.0001$) and 0.12 ± 0.02 mmHg/day ($p < 0.0001$), respectively, in patients with global decompensation. However, no significant changes in PAP values occurred prior to predominantly right-sided decompensation events (0.003 ± 0.02 ($p = 0.90$)). Notably, the models account for a slightly but significantly reduced standard deviation in patients with right-sided decompensation by 25% ($p < 0.0001$), 20% ($p = 0.0005$) and 24% ($p < 0.0001$) in the systolic PAP, diastolic PAP and mean PAP, respectively. The graphical representations (Figure 3top) show the smoothed PAP curves for the time course.

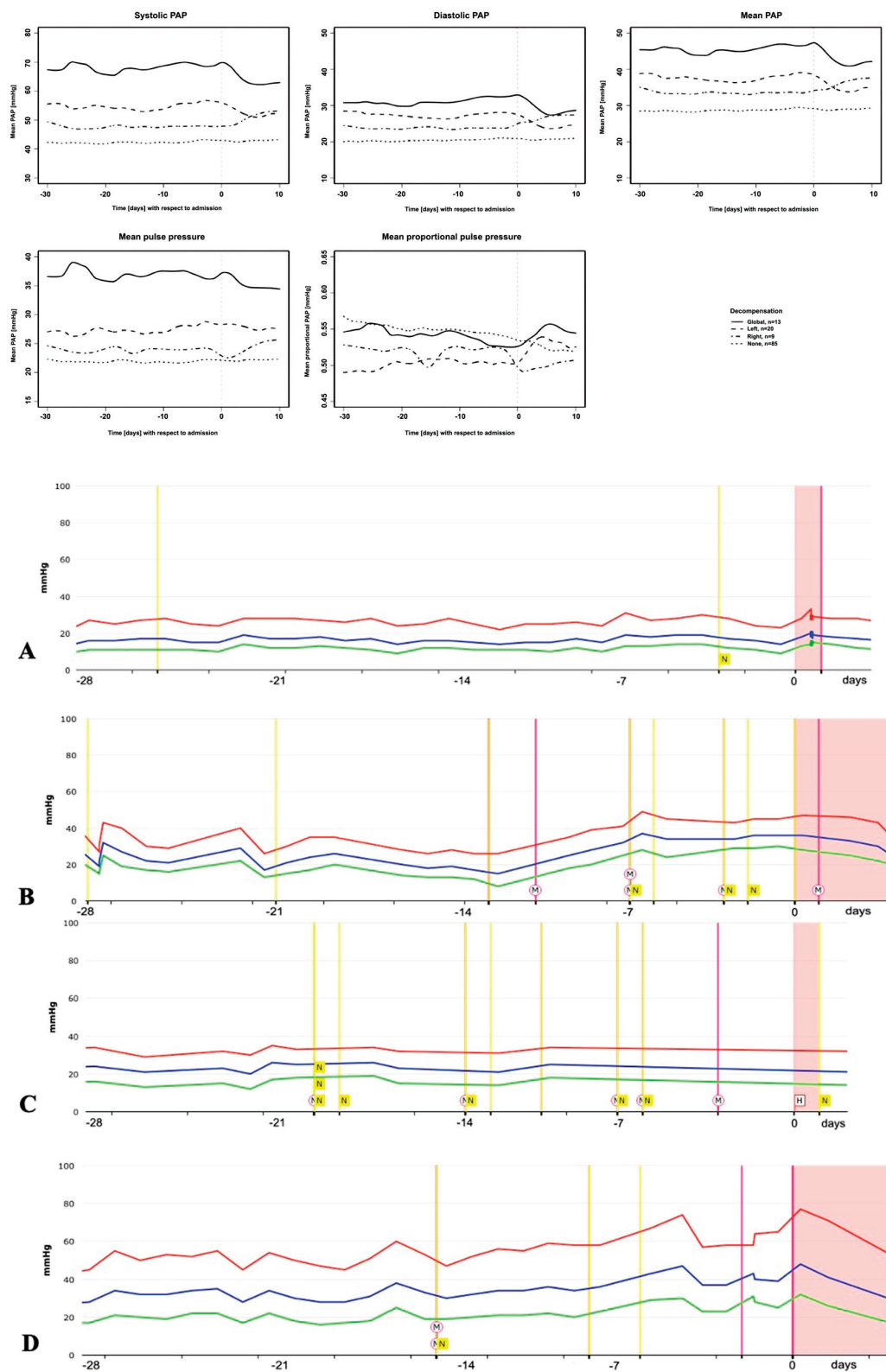


Figure 3. (Top) the time course of pulmonary artery pressure (PAP) values in the 30 days prior to hospitalization. The graphical representation shows smoothed mean curves for the time course. (Bottom) examples of patients' PAP course (raw data) prior to hospitalization. (A): hospitalization for non-cardiac decompensation; (B): predominantly left-sided decompensation; (C): predominantly right-sided decompensation; and (D): global cardiac decompensation. Day 0 = day of hospitalization. Red line, systolic PAP. Blue line, mean PAP. Green line, diastolic PAP. Pink bar with circled "M", medication adjustment. Yellow bar with "N", denotes telephone contact with patient.

The mean PP in left-sided and global cardiac decompensation was higher compared to no cardiac decompensation ($p = 0.006$ and $p < 0.0001$ for left and global, respectively), while there were no significant differences for the mean proportional PP. Furthermore, there was a significant decrease in the mean PP of 0.03 ± 0.01 mmHg/day ($p = 0.0011$) but not in the mean proportional PP in patients without cardiac decompensation. Again, models account for a significantly reduced standard deviation in patients with right-sided decompensation, by 19% ($p = 0.0011$) and 71% ($p < 0.0001$) for the mean PP and mean proportional PP, respectively. In all other cases, there was no significant trend.

Exemplarily, the course of PAP values 30 days prior to hospitalization is shown for the four different types of hospitalization as a single case study in Figure 3bottom.

4. Discussion

The present retrospective analysis is, to our knowledge, the first report to investigate the different clinical types of cardiac decompensation in a patient cohort of NYHA class III HF managed by PAP-supported HF care. Our case study confirms that PAP telemonitoring can reliably detect early signs of left and global cardiac decompensation but suggests that it may be less effective in detecting predominately right-sided congestion followed by decompensation events because there may be a lack of a PAP increase prior to cardiac decompensation in these patients.

Notably, we detected a significantly reduced standard deviation as an expression of a reduced variability of the PA pressure, mean PP and mean proportional PP only in patients with right-sided decompensation events but not in patients with left-sided or global cardiac decompensation. This has not yet been described previously and might represent a marker of a reduced RV stroke volume and contractility, aligning with the interpretation of proportional PP as a surrogate marker for RV function proposed by Mazimba et al. [16].

In patients with HF, the presence of secondary PH is associated with a reduced exercise capacity and worse prognosis [17–20]. This might be explained if one considers that PH reflects more advanced HF, leading to a more upstream transmission of the increased pulmonary artery wedge pressure to PAP, which in turn favors the development of afterload-induced RV failure. As we know that RV afterload consists of a static (PVR) and a combined static and dynamic pulsatile (pulmonary arterial capacitance as a ratio of the stroke volume over pulmonary PP) component [21,22], therefore, it could be anticipated that there might be differences in the clinical presentation between the types of cardiac decompensation depending on which component of the RV afterload is predominantly affected.

However, PA pressure monitoring can successfully be used in patients with type 1 PH, as demonstrated by Benza et al. [23]. In this group with NYHA functional class III-IV symptoms, the cardiac index was not markedly reduced, and separate data on the RV function or RV–PA coupling were not reported. Nevertheless, since RV function is exquisitely sensitive to afterload, afterload-reducing treatments and management, like the present PAP-guided HF treatment, could provide substantial benefits in different types of PH. Notably, a subgroup analysis of the MEMS-HF registry demonstrated that patients without PH, but also those with isolated PH and even patients with combined pre-and postcapillary PH, derived similar benefits from PAP-guided HF care [12].

Interestingly, a recent study by Nies et al of 114 patients with paradoxical low-flow, low-gradient aortic stenosis demonstrated that right ventricular dysfunction (RVD) and impaired RV–PA coupling were present in 50% of cases and independently associated with increased post-transcatheter aortic valve replacement (TAVI) mortality [24]. These findings support our observations by underscoring the prognostic relevance of the RV function and

RV–PA coupling, even in patient populations where the left ventricular function appears preserved. Together, they highlight the need for comprehensive biventricular evaluations in heart failure management and reinforce the value of RV dysfunction and RV–PA coupling as a prognostic marker across different cardiovascular pathologies.

The prevention of RV functional deterioration and RV–PA uncoupling might be an additional mechanism by which PAP-guided HF management may improve outcomes in heart failure patients. It might therefore be interesting to serially assess the RV function and contractility in future trials with hemodynamically guided HF treatments. In our small case study, the routinely performed echocardiographic assessments during follow-up showed no changes in the RV function and RV–PA coupling in predominantly right-sided decompensation. But, we observed a significantly reduced day-to-day variation in the PAP and of the mean PP and mean proportional PP prior only to the right-sided decompensation, which may be an indirect sign for a reduced right ventricular contractility, distensibility and pulmonary arterial capacitance (PAC) [15]. Thus, predominantly right-sided decompensation events might rather reflect a decrease in RV contractility than an impairment of the systolic RV function and RV–PA uncoupling. Whether additional assessments of RV contractility can help to prevent hospitalization in cases of right-sided decompensation without a corresponding rise in PAP should be investigated in future studies.

However, a reduced TAPSE/PASP ratio and TAPSE, even at the baseline and prior decompensation, was identified as a possible surrogate parameter for pending global cardiac decompensation. Importantly, the TAPSE/PASP ratio seemed to provide more impact if calculated with the hemodynamically obtained PAP, which may be related to better accuracy. In line with our findings, Boehm et al. showed in an experimental, sham controlled study, that isolated RV pressure overload induced by pulmonary artery banding induces RV–PA uncoupling and reduces the systolic RV function and even RV hypercontractility [25]. Therefore, we hypothesize that a predominantly right-sided decompensation might rather be a result of a reduced RV contractility, thus without an increase in PAP, and a predominantly global cardiac decompensation may rather possibly be a result of a longer-term increase in PAP with a subsequent RV–PA uncoupling and deterioration of RV function. However, this indeed needs further investigations in larger trials.

In general, the development of RV dysfunction and failure is regarded as a turning point in the natural course of heart failure and is associated with a worse outcome [26]. Most of the previous work related to adaptive and maladaptive RV remodeling and failure has been conducted in the setting of pulmonary arterial hypertension (Group 1 PH), whereas most patients with PH suffer from left-sided heart disease (Group 2 PH). The presence of early RV dysfunction is challenging to detect in the routine clinical settings. While Gruenig et al. [27] proposed an exercise-induced increase in systolic PAP as a surrogate marker of the RV contractile reserve, a more recent analysis proposed to use an exercise RV ejection fraction to non-invasively detect occult RV dysfunction [28]. In a further analysis of the CHAMPION trial, a low proportional PP identified patients with low forward flow (stroke volume) and a low PA PP (RV contractility and distensibility) [15]. However, the most sensitive and precise way to measure the RV contractile reserve is RV–PA coupling [29–31]. RV–PA coupling is defined by $RV\ E_{ES}/E_a$, or the ratio of the RV end-systolic elastance (E_{ES}) to the PA effective arterial elastance (E_a). $RV\ E_{ES}$ is a load-independent method to measure intrinsic RV contractility, whereas E_{ES}/E_a measures the right-sided ventriculo-arterial coupling. The optimal E_{ES}/E_a ratio is between 1.5 and 2.0. RV–PA coupling in PH has considerable reserve, and the E_{ES}/E_a threshold at which uncoupling occurs is estimated to be approximately 0.7 [31]. The gold-standard method for measuring RV–PA coupling is the conductance catheter-based multi-beat assessment. However, Tello et al. showed that the non-invasive, echocardiographic TAPSE/PASP ratio

could be used for the assessment of RV–PA coupling in patients with severe pulmonary arterial hypertension [14]. More recently, this ratio was incorporated into the updated ESC guidelines for PH, specifically into the echocardiographic risk stratification of patients with Group 1 PH [16]. Although the groundbreaking work was performed in Group 1 PH patients, numerous trials have shown that the TAPSE/PASP ratio also provides important information about the right ventricle, RV remodeling and prognosis in left-sided heart disease. For example, in a retrospective cohort study of 228 patients after a MitraClip® application for severe mitral regurgitation, a TAPSE/PASP ratio below the median value of 0.35 mm/mmHg was associated with post-intervention adverse events like HF hospitalization and all-cause mortality [32]. In a larger cohort of 1.149 cardiology patients from Leiden University with moderate to severe secondary tricuspid regurgitation, the median TAPSE/PASP ratio was 0.35 mm/mmHg at the time of the diagnosis of significant secondary tricuspid regurgitation [33]. During a 5-year follow-up, RV–PA uncoupling, defined as a TAPSE/PASP ratio < 0.31 mm/mmHg, was the only echocardiographic parameter independently associated with all-cause mortality. Interestingly, most patients in our cohort who experienced cardiac decompensation also had a TAPSE/PASP ratio < 0.35 mm/mmHg, indicating an increased risk and advanced HF, especially the group of patients with global cardiac decompensation. In contrast, hospitalizations without cardiac decompensation had normal RV–PA coupling (0.50 ± 0.03 mm/mmHg). Thus, the routine measurement of RV–PA coupling could be used for pending global cardiac decompensation.

Moreover, in contrast to other studies, we calculated the TAPSE/PASP ratio by two methods, using the traditional TAPSE as well as either the routine echocardiography-derived PASP value or the directly measured sensor-derived systolic PAP. Thus, the PAP could therefore be obtained immediately prior to the cardiac decompensation event, for a “de novo” TAPSE/PASP ratio during follow-up. However, although a significant positive association between the traditional pure echocardiographic and the hemodynamic-supported TAPSE/PASP ratio persisted, there were no substantial changes between the first baseline-derived TAPSE/PASP ratio and the follow-up TAPSE/PASP ratio, which may be related to the fact that the TAPSE values were collected at pre-defined time points with variable time intervals to the pending cardiac decompensation event.

Finally, the ultimate goal of measuring congestion is obviously not yet achieved by using a hemodynamic sensor for measuring pressure as a surrogate of resistance and volume. Nonetheless, clinically established alternatives are rare, and the recently presented CAVA-ADHF-DZHK10 trial (ESC 2023) could not demonstrate that the ultrasound-guided imaging of the inferior Vena cava to guide decongestion in ADHF patients was superior to the standard treatment [34]. Thus, the optimal assessment of congestion remains to be determined. Experimentally, it has been shown that the filling pressure cannot always be used as a specific parameter for the evaluation of the intravascular volume [35], which might be of specific interest in the context of right-sided HF. A recent report demonstrated a lack of correlation between different types of congestion markers in acute decompensated HF [36], which underlines the difficulties of the early detection of right heart decompensation.

5. Limitations

The limitations of the case study, in addition to it being a retrospective analysis, are the small patient cohort and the limited number of hospitalizations. The classification of the type of HF decompensation event was performed by a single HF-experienced clinician based on the medical report of clinical, imaging and laboratory data. Most importantly, patients were treated for increasing PAP values to avoid cardiac decompensation, and we cannot exclude that other potentially pending right-sided or global cardiac decompensations had elevations in PAP that triggered treatment and, thereby, that hospitalization could

be prevented. Prior to the predominantly left-sided decompensation, there were 15 down-titrations of diuretics and 3 of the guideline-directed medical therapy (GDMT), compared to 27 up titrations of diuretics and 3 of GDMT. Prior to the global cardiac decompensations, we identified eight down-titrations of diuretics and two of GDMT, compared to sixteen up-titrations of diuretics and one of GDMT. In the cases of predominantly right-sided decompensation, there have been just two down-titrations of diuretics and one of GDMT, compared to seven up-titrations of diuretics and zero of GDMT (Supplementary Figure S4). Thus, the analyzed cardiac decompensation events occurred despite the telemedical advice for ambulatory medical treatment changes, which may be an indicator for advanced HF requiring even more intense treatment, such as the intravenous administration of diuretics.

In addition, the follow-up measurements were collected at the defined dates after the PAP sensor implantation; thus, the last available date of assessments prior to hospitalization varied.

6. Conclusions

Our case study shows that outpatient daily PAP-guided HF therapy can reliably detect early signs of impending left and global ventricular decompensation but may have limitations in detecting predominately right-sided decompensation.

The variability of the PA pressure, PP and proportional PP was profoundly reduced in these patients; however, whether this can be used as a predictive additive tool for the identification of the impending deterioration of RV contractility and decompensation was beyond the scope of this analysis. Future studies with a prespecified RV contractility analysis, echocardiographic parameters (e.g., TAPSE; TAPSE/PASP ratio, RV-FAC) and machine learning will provide more insight.

Furthermore, patients could profit from an additional routine measurement of RV–PA coupling, because a severely impaired RV–PA coupling might be a hint of pending global cardiac decompensation. PAP sensor trials, like the ongoing PASSPORT trial in Germany, routinely collect data on RV function; thus, more detailed insights into the value of the PA pulse pressure and RV–PA coupling for hemodynamic HF care, but also for standard nurse-based care, will be available upon the trial's completion.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/biomedicines13061469/s1>: Figure S1: Scatter plot and fixed effect regression line from a mixed-effect regression analysis of baseline TAPSE/PASP ratio derived from CardioMEMS™ and echocardiogram for the different types of hospitalization; Figure S2: Scatter plot and fixed effect regression line from a mixed-effect regression analysis of pre-hospitalization TAPSE/PASP ratio derived from CardioMEMS™ and echocardiogram for the different types of hospitalization; Figure S3: Criteria for selecting hospitalizations. Hospitalizations were selected to be analyzed if the interval between the previous admission and the next admission is at least 28 days and if the interval between the last hospital discharge and the next hospitalization is at least 14 days; Figure S4: Medication changes within the different types of decompensations. Blue, changes in diuretics. Red, changes in guideline-directed medical therapy; and Table S1: Type of death.

Author Contributions: Conceptualization, B.A.; methodology, B.A. and E.J.H.; formal analysis, E.H. and E.J.H.; investigation, B.A., S.F. and E.J.H.; data curation, B.A., E.J.H., K.M. and M.T.; original draft preparation, E.J.H.; revision, review and editing, B.A., E.J.H., K.T., E.H. and C.W.H.; visualization, B.A.; supervision, B.A.; project administration, B.A.; funding acquisition, B.A. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the LOEWE Center for Cell and Gene Therapy Frankfurt funded by Hessisches Ministerium für Wissenschaft und Kunst, funding reference number III L 4-518/17.004 (2010): EUR 50.000, and by the Deutsche Forschungsgemeinschaft DFG SFB 1213, Project B09: EUR 7500.

Institutional Review Board Statement: This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Goethe University, Frankfurt, Germany, (protocol number 253/16; 22 June 2016).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study. Written informed consent was provided by the patients to publish the results of this study.

Data Availability Statement: The data are combined together and analyzed within the single-center registry (NCT03020043) and can be obtained by a written request.

Acknowledgments: We thank the catheterization laboratory team for their excellent study support.

Conflicts of Interest: BA reports having received consulting fees and an unrestricted research grant from St Jude Medical, which is now Abbott, and lecture fees from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Meyers Squibb, Edwards, Novartis, Pfizer and CSL Vifor. EJH reports receiving lecture fees from Bayer and CSL Vifor.

Abbreviations

The following abbreviations are used in this manuscript:

ACEI-I	angiotensin-converting enzyme inhibitor
ARNI	angiotensin receptor blocker neprilysin inhibitor
ATRB	angiotensin receptor blocker
CHF	chronic heart failure
cpPH	combined post- and precapillary pulmonary hypertension
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LVEF	left ventricular ejection fraction
MRA	mineralocorticoid antagonist
NYHA	New York Heart Association
NT-proBNP	N-terminal fragment of pro-brain natriuretic protein
PASP	systolic pulmonary artery pressure
PAP	pulmonary artery pressure
PCWP	pulmonary capillary wedge pressure
TAPSE	tricuspid annular plane systolic excursion
RV	right ventricular
PVR	pulmonary vascular resistance

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Article

Sex-Specific Impact of 17 β -Estradiol and Testosterone Levels on Inflammation and Injury in Acute Myocardial Infarction—Preliminary Results

Niya E. Semerdzhieva ^{1,*}, Adelina D. Tsakova ^{2,3} and Vesela V. Lozanova ⁴

¹ Clinic of Internal Medicine, University Emergency Medicine Hospital ‘Pirogov’, 1606 Sofia, Bulgaria

² Department of Clinical Laboratory, Medical University, 1431 Sofia, Bulgaria

³ Clinical Laboratory, University Hospital ‘Sofamed’, 1797 Sofia, Bulgaria; adelina_d@abv.bg

⁴ Department of Chemistry and Biochemistry, Medical University, 1431 Sofia, Bulgaria; vlozanova@medfac.mu-sofia.bg

* Correspondence: niaemilova@yahoo.com

Abstract: Background: Estrogens play a protective role during the early stages of life. However, endogenous 17 β -estradiol (E2) can accelerate atherosclerosis progression. **Aim:** The purpose of this study was to test for the significance of the sex-specific associations of gonadal hormones with the extent of the inflammatory response, myocardial damage, and ventricular arrhythmia risk in acute myocardial infarction (MI). **Materials and Methods:** Study design: single-center cohort study. Blood samples for the assessment of sex steroids (E2, total testosterone [T]), oxidized low-density lipoproteins, high-sensitivity C-reactive protein (CRP), white blood cell (WBC) counts, and cardiac enzymes were collected 48 h after the onset of symptoms (and within 6 h after PCI) from 111 patients (37% women) with acute MI. Coronary disease severity, left ventricular systolic function (LV), and indices of ventricular repolarization were assessed using coronary angiography, echocardiography, and a conventional electrocardiogram, respectively. **Results:** In men with acute MI, peak cardiac enzyme levels were predicted by post-percutaneous coronary intervention (PCI) E2 plasma levels, peak WBC count, and peak CRP plasma levels. T levels and the E2/T ratio were associated with post-PCI CRP in these men. For women, peak WBC count was a marker of highest testosterone, and only WBC count was a significant indicator of myocardial injury extent. The incidence of acute ventricular tachycardia detected in AMI was significantly associated with left ventricular ejection fraction and with peak WBC count (as a tendency) regardless of sex. A longer duration of cardiac repolarization prior to PCI was predicted by lower ejection fractions in men and by age, CRP, and testosterone levels in female patients. **Conclusions:** During acute MI, elevated endogenous estradiol levels in men and increased leukocytes in women indicate acute myocardial damage. Post-PCI plasma inflammatory markers are sex-specific confounding factors for acute endogenous E2 levels, T levels, and the E2/T ratio. LV systolic function in men and, characteristically, the acute inflammatory response and testosterone levels in women are predictors of longer ventricular repolarization and arrhythmia risk.

Keywords: 17 β -estradiol; total testosterone; oxidized low-density lipoproteins; C-reactive protein; acute myocardial infarction; ventricular tachycardia

1. Introduction

Low plasma concentrations of endogenous 17 β -estradiol in early life correlate with an atherogenic lipid profile and endothelial dysfunction in men [1,2], as well as with an

increased risk of cardiovascular disease and, in particular, acute myocardial infarction (AMI) in women [3,4]. Furthermore, diseases characterized by hyperandrogenemia in women (e.g., polycystic ovary syndrome) and hypogonadism (low testosterone) in young men are predisposing factors for premature and extensive coronary artery disease [5,6].

In contrast, in cohorts with established cardiovascular disease, high serum estradiol levels in both men and women [7,8] and low serum testosterone in men predict the severity of coronary atherosclerosis [7,9]. The ratio of endogenous estradiol to testosterone (E2/T)—used as a surrogate marker of aromatase activity—indicates an adverse prognosis in older women with known cardiovascular disease [10]. An allele variant of the enzyme aromatase converts testosterone to estradiol in various tissues and is a risk indicator for mortality in men with acute coronary syndrome [11]. Aromatase activity varies throughout life, especially during acute illnesses (e.g., acute myocardial infarction), leading to increased endogenous estradiol concentrations [10,12–14]. The clinical implications of these fluctuations in endogenous sex hormone concentrations and aromatase activity in acute coronary disease remain uncertain.

Animal research indicates that bilateral ovariectomy increases ischemia–reperfusion (MI/R) injury of the myocardium. Estrogen treatment can mitigate this by inhibiting endoplasmic reticulum stress, reducing cardiomyocyte apoptosis, and resulting in smaller infarcts [15,16]. However, animal models do not adequately represent the extent of atherosclerosis in older humans, limiting their relevance. Studies involving human participants suggest that men with low serum testosterone levels undergoing primary percutaneous coronary intervention (PCI) for MI with ST elevation experience inferior myocardial reperfusion and myocardial systolic function [17]. Conversely, elevated endogenous estradiol levels independently correlate with the risk of no-reflow in postmenopausal women [18].

The regional inhomogeneities in ventricular refractoriness have been demonstrated to increase during myocardial ischemia and to decrease with the reversal of the ischemic state following successful angioplasty [19]. Higher values of dispersion in ventricular repolarization are related to an increased incidence of ventricular arrhythmias and nonfatal myocardial infarction [19]. In general, the sex-related differences in repolarization duration and dispersion can be explained by the cellular effects of sex steroids on action potential duration and autonomic control of the heart rate [20,21].

Our hypothesis is that the change in endogenous sex hormone concentrations and aromatase activity in acute MI is associated with myocardial damage, the inflammatory response to injury in the myocardium, and ventricular repolarization.

Purpose

The purpose of this study was to test for the significance of the sex-specific associations of gonadal hormones with the extent of the inflammatory response, myocardial damage, and ventricular arrhythmia risk in acute myocardial infarction (MI).

2. Materials and Methods

This single-center cohort study included 111 patients (37% women) diagnosed with AMI and admitted to the Clinic of Cardiology, University Hospital “Alexandrovska,” Sofia, between July 2011 and December 2013. Blood samples were drawn 48 h after symptom onset to measure the levels of sex steroids (total 17 β -estradiol [E2], total testosterone [T], dehydroepiandrosterone sulfate), oxidized low-density lipoproteins (oxLDL), high-sensitivity C-reactive protein (hsCRP), white blood cell (WBC) counts, and cardiac enzymes (creatinine kinase [CK], Muscle–Brain fraction of CK [CPK-MB], and high-sensitivity troponin T [hsTnT]). To measure coronary disease severity, we calculated the SYNTAX score for each patient with angiographically defined coronary atherosclerosis. The levels of E2

and T, as well as those of cardiac enzymes and inflammatory markers (CRP and WBC), were measured within six hours of PCI. In the group without catheter revascularization, hormones, enzymes, and inflammatory markers were measured within 48 h of symptom onset. If re-evaluated, the highest values were used for analysis. All the patients underwent standard echocardiography. Echocardiographic studies were performed in accordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging using the Sonos 5500 (Hewlett-Packard, Palo Alto, CA, USA) and Aloka ProSound 10 (Hitachi Aloka Medical, Hitachinaka, Japan) ultrasound systems. LV ejection fraction (EF) was measured using Simpson's method.

We compared the E2 and T of the patients with AMI with the E2 and T of 15 men and women with stable coronary disease in order to test the hypothesis that endogenous E2 and T plasma concentrations change in the acute phase of myocardial infarction in parallel with the levels of inflammatory markers. Eighteen men and women of similar age as the studied cohort with coronary disease excluded via coronary angiography served as the control group.

Patients diagnosed with secondary hypogonadism or diseases of the adrenal and pituitary glands were excluded. Other exclusion criteria included acute infectious disease, chronic inflammatory disease, known or suspected neoplastic processes, surgical procedures, and trauma within two weeks before hospital admission. The participants had not used hormone or immunoreactive therapies six months before or during this study.

We adhered to the Declaration of Helsinki and received approval from the ethics committee of the Medical University of Sofia. All the participants provided written informed consent. This study was retrospectively registered in the UK's Clinical Study Registry (ISRCTN) with study registration number ISRCTN62480360.

After a 12 h fast, venous blood samples were collected into EDTA sample tubes, centrifuged at 12,000 rpm for 20 min, and stored at -20°C until analysis. The hsCRP concentrations were determined using a latex-enhanced immunoturbidimetric assay (Roche Diagnostics GmbH, Mannheim, Germany) on the COBAS INTEGRA 700 analyzer. We assessed the levels of steroid hormones and hsTNT using an electrochemiluminescent immunoassay with Roche Diagnostics reagents on the Elecsys 2010 analyzer. These methods have been detailed elsewhere [22,23]. Plasma levels of oxLDL were quantified using the OxiSelect Human Oxidized LDL immunosorbent assay (ELISA; MDA-LDL) kit (Cell Biolabs, San Diego, CA, USA) and a sandwich ELISA [24].

2.1. ECG Analysis

Standard 12-lead ECGs were recorded at a paper speed of 25 mm/s and a gain of 10 mm/mV. The QT interval was measured using a standardized technique and corrected with Bazett's formula. Corrected QT dispersion was calculated as the difference between the maximum and minimum corrected QT intervals [19] assessed using surface body electrocardiography (ECG).

2.2. Statistical Analysis

We checked variable distributions using the Kolmogorov–Smirnov and Shapiro–Wilk tests. We explored the associations between variables using both parametric (independent-samples *t*-test) and non-parametric (χ^2 test, Fisher's exact tests, and Mann–Whitney U test) methods, further validated by Cox proportional regression and univariate and multivariate analyses. The multivariable model which explored the predictors of the highest cardiac enzyme levels included estradiol, testosterone, the estradiol-to-testosterone ratio, white blood cell count, C-reactive protein, the extent and severity of coronary atherosclerotic plaques measured using the Syntax score, and age. The multivariable model testing the

significance of the predictors of the highest levels of hormones and E2/T included white blood cell count, C-reactive protein, the extent and severity of coronary atherosclerotic plaques measured using the Syntax score, left ventricular (LV) ejection fraction (EF) as a measure of LV systolic function, and the age. The analyses were conducted using IBM SPSS Statistics for Windows, Version 19.0. (IBM Corp: Armonk, NY, USA). A two-tailed *p*-value less than 0.05 was deemed significant.

3. Results

A flowchart showing the steps in the enrollment of the patients studied is presented in Figure 1.

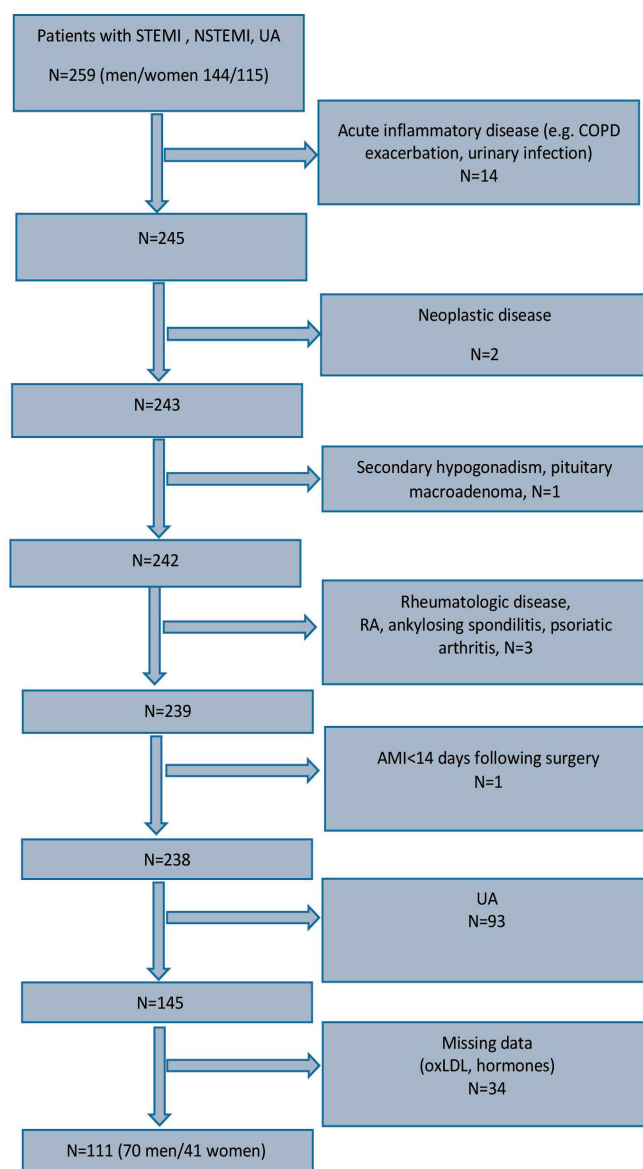


Figure 1. Patient group; inclusion and exclusion criteria. Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, myocardial infarction without ST elevation; UA, unstable angina; COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis; AMI, acute myocardial infarction; oxLDL, oxidized low-density lipoprotein.

Female patients were, on average, older than male patients (Table 1) and had lower C-reactive protein (CRP) and cardiac enzyme levels. During the acute phase of MI, E2 levels were higher in male patients, while the E2-to-T ratio (E2/T) was lower in female

patients (Table 1). The groups did not differ substantially according to MI localization or atherosclerotic involvement of coronary arteries. Women were leaner than men but of similar BMI (Table 1).

Table 1. Patient characteristics compared by sex.

Variables	Men (n = 70)	Women (n = 41)	p-Value
Age, years	62.8 ± 12.7	70.7 ± 10	0.001
Hypertension, n %	66 (94)	40 (97)	NS
Dyslipidemia, n %	58 (83)	38 (93)	NS
Diabetes mellitus, n %	24 (34)	18 (43)	0.320
oxLDL, mg/mL	10.4 ± 7.3	8.1 ± 4.9	0.099
CRP, mg/L	27.7 ± 52	16.9 ± 21.7	0.032
WBC, ×10 ⁹ L	10.3 ± 3.8	9.8 ± 3.3	0.662
STEMI, n %	38 (34)	19 (17)	1.000
NSTEMI, n %	31 (28)	22 (19)	
Anterior MI, n %	28 (25)	22 (19)	0.527
Inferior MI, n %	22 (19)	12 (12)	
Lateral MI, n %	12 (11)	4 (4)	
Non-obstructive CAD, n %	2 (2)	3 (2)	0.519
1-vessel CAD, n %	15 (13)	12 (11)	
2-vessel CAD, n %	28 (26)	13 (12)	
3-Vessel CAD, n %	23 (21)	14 (10)	
Syntax score	14.1 ± 10.6	11.2 ± 9.2	0.027
EF, %	53.6 ± 10	52.4 ± 12.9	0.606
BMI, kg/m ²	28.4 ± 4.3	27.4 ± 5.3	0.330
Weight, kg	85.9 ± 13.6	67.6 ± 10	<0.0001
CK, U/L	1178.9 ± 1486.4	474 ± 722.4	0.001
CK-MB, U/L	116.1 ± 146	63.6 ± 82.1	0.057
hsTnT, ng/mL	2.5 ± 3.4	1.4 ± 2.5	0.036
E2, pmol/L	155.8 ± 69.6	108.7 ± 126.9	<0.0001
T, nmol/L	13.4 ± 5.2	1.7 ± 3	<0.0001
E2/T	0.02 ± 0.03	0.23 ± 0.51	<0.0001
β-blocker, n %	19 (27)	18 (36)	0.571
ACE-I/ARB, n %	18 (41)	23 (59)	0.197
Statin, n %	1 (2)	2 (5)	NS
Antiplatelet, n %	22 (32)	13 (32)	1.000

Abbreviations: oxLDL, oxidized low-density lipoprotein; CRP, C-reactive protein; WBC, white blood cell; EF, ejection fraction; BMI, body mass index; CK, creatine kinase; CK-MB, MB fraction of CK; hsTnT, high-sensitivity troponin T; E2, endogenous 17β-estradiol; T, total testosterone; E2/T, ratio of plasma 17β-estradiol to total testosterone concentrations.

A total of 86% of the patients underwent PCI. Among the remaining 14%, some were diagnosed with non-obstructive coronary disease and were suitable for optimal conservative treatment, and the rest of these patients were diagnosed with three- and multi-vessel disease. The latter group was transferred for aorto-coronary by-pass surgery.

Plasma concentrations of E2 and T were higher in the patients with AMI compared to those with stable coronary disease, except there were no differences in E2 between the men with AMI and men with stable CAD (Table 2). E2 levels were higher and T was lower in male patients with AMI compared to the men in the control group (Table 2). Vice versa associations in E2 and T levels in the women with AMI versus female controls were found (Table 2).

Table 2. Age, E2, and T in patients with AMI, patients with stable CAD, and controls.

Variables	Men		<i>p</i> -Value	Women		<i>p</i> -Value
	AMI	Stable CAD, n = 15		AMI	Stable CAD, n = 15	
Age	62.8 ± 12.7	61.8 ± 14	0.413	70.7 ± 10	74.6 ± 6.4	0.106
E2	155.8 ± 69.6	115.4 ± 33.4	0.007	108.7 ± 126.9	66.3 ± 29.6	0.067
T	15.7 ± 14.7	14.1 ± 8.4	0.875	1.7 ± 3.0	0.8 ± 0.4	0.088
	AMI	Control, n = 18		AMI	Control, n = 18	
Age	62.8 ± 12.7	59.1 ± 13.6	0.179	70.7 ± 10	57.4 ± 15.2	0.050
E2	155.8 ± 69.6	139.2 ± 115.9	0.0001	108.7 ± 126.9	223.7 ± 255.4	<0.0001
T	13.4 ± 5.2	19 ± 9.6	<0.0001	1.7 ± 3	0.6 ± 0.3	<0.0001

Abbreviations: AMI, acute myocardial infarction; CAD, coronary disease; E2, endogenous 17β-estradiol; T, total testosterone.

E2 correlated positively with CRP, WBC count, Syntax score, and QTc in the male patients with AMI, as well as with T, oxLDL, and MI size (peak cardiac enzymes) in the female AMI patients. E2 had a similar inverse correlation with LVEF in both men and women, in addition to showing a weak tendency for inverse association with age in women. T was associated with WBC count, myocardial injury, and lower EF in the female patients. E2/T was related to peak WBC count, peak troponin levels, and low EF among the male patients with AMI; conversely, in the female patients, E2/T was related to higher heart rates at admission and to a tendency towards higher BMI and CRP (Table 3, Figures 2 and 3).

Table 3. E2, T, and E2/T and patient characteristics—correlation analysis.

Variables	Male Patients						Female Patients					
	E2		T		E2/T		E2		T		E2/T	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
T	0.100	0.457					0.345	0.022 *				
BMI	0.087	0.524	0.157	0.248	−0.207	0.123	−0.174	0.297	−0.187	0.262	0.276	0.093 *
Age	−0.043	0.749	−0.103	0.443	0.156	0.242	−0.259	0.094 *	−0.077	0.625	0.096	0.542
oxLDL	−0.010	0.947	−0.093	0.544	0.040	0.793	0.444	0.004 *	0.063	0.697	0.130	0.424
CRP	0.398	0.002 *	−0.340	0.009 *	0.021	0.874	0.488	0.001 *	0.139	0.370	0.254	0.096 *
WBC	0.351	0.008 *	−0.253	0.060 *	0.334	0.012 *	0.299	0.051 *	0.459	0.002 *	−0.195	0.210
Syntax score	0.303	0.021 *	−0.139	0.299	0.156	0.243	0.238	0.125	0.050	0.750	−0.109	0.485
EF	−0.237	0.072 *	0.003	0.983	−0.296	0.024 *	−0.434	0.003 *	−0.439	0.003 *	−0.009	0.951
CK	0.182	0.171	0.018	0.898	0.127	0.335	0.226	0.146	0.776	0.001 *	−0.158	0.307
CK-MB	0.198	0.136	−0.001	0.994	0.107	0.425	0.334	0.027 *	0.612	0.001 *	−0.171	0.267
hsTnT	0.333	0.111	−0.158	0.238	0.521	0.001 *	0.036	0.059 *	0.320	0.029 *	−0.137	0.376
Heart rate	−0.018	0.910	−0.314	0.038 *	−0.067	0.666	0.269	0.112	−0.045	0.793	0.457	0.005 *
QTc	0.337	0.020 *	−0.038	0.879	−0.013	0.932	−0.045	0.791	0.164	0.331	−0.178	0.292

Abbreviations: E2, endogenous 17β-estradiol; T, total testosterone; E2/T, estradiol-to-testosterone ratio; BMI, body mass index; oxLDL, oxidized low-density lipoprotein; CRP, C-reactive protein; WBC, white blood cell; EF, ejection fraction; CK, creatine kinase; CK-MB, MB fraction of CK; hsTnT, high-sensitivity troponin T; * denotes significant or as tendency significant associations.

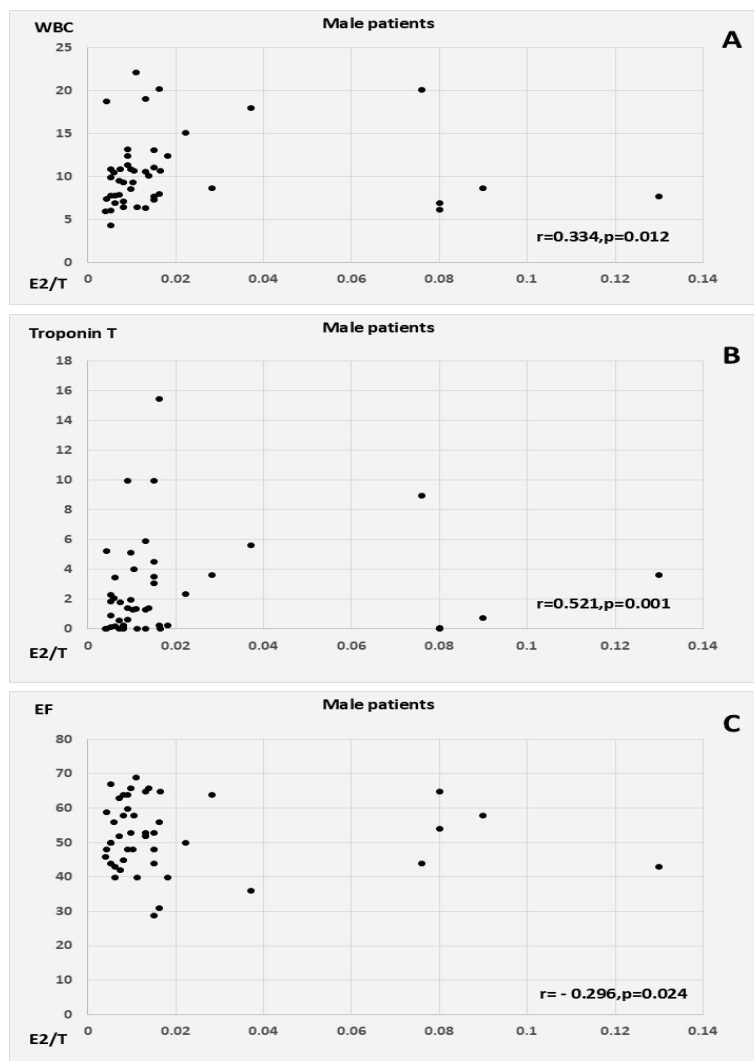


Figure 2. Correlation of E2/T with (A) WBC count, (B) troponin, and (C) ejection fraction in male patients. Abbreviations: WBC, white blood cell; E2/T, ratio of plasma 17β-estradiol to total testosterone concentrations; EF, ejection fraction.

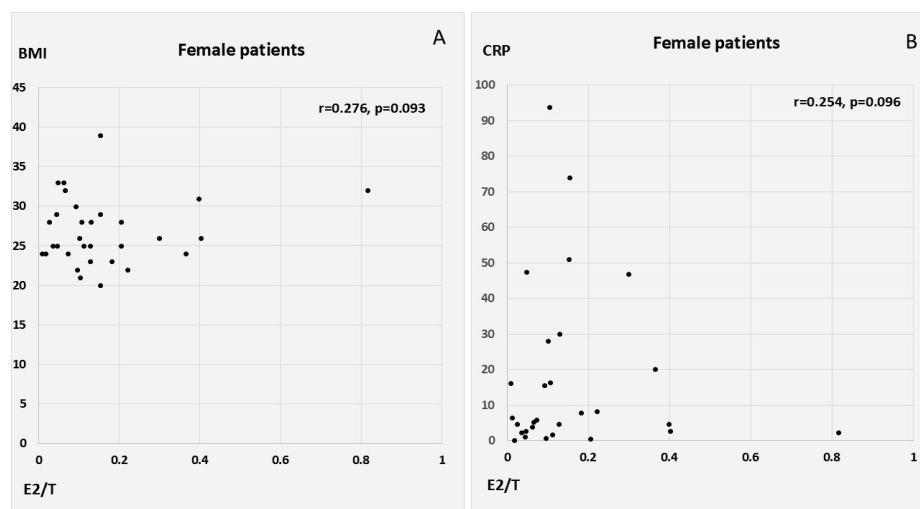


Figure 3. Correlation of E2/T with with heart rate, (A) BMI and (B) CRP in female patients. Abbreviations: CRP, C-reactive protein; BMI, body mass index; E2/T, ratio of plasma 17β-estradiol to total testosterone concentrations.

In the male patients, post-PCI E2, CRP, and WBC counts were predictors of peak cardiac enzyme levels, as determined by a univariable regression analysis. For the female patients, peak WBC count was a significant indicator of myocardial injury (Tables 4–6 and Figure 4).

Table 4. Association of gonadal steroids and inflammatory and oxidative stress markers with peak creatine kinase (CK) activity.

CK	Lowest Tertile	Highest Tertile	p-Value	OR	95% CI	p-Value
Male patients						
oxLDL	10 ± 8.9	10 ± 7.9	0.317	0.985	0.908–1.070	0.725
WBC	8.4 ± 1.9	11.9 ± 4.4	0.002 *	1.487	1.081–2.045	0.015 *
CRP	11.6 ± 20.5	49.5 ± 56.3	0.005 *	1.040	1.003–1.078	0.033 *
Syntax score	15.9 ± 10.8	17.5 ± 10.2	0.301	1.016	0.958–1.077	0.593
17β-estradiol	133.6 ± 54.4	185.6 ± 92.8	0.015 *	1.011	1.000–1.022	0.047 *
Testosterone	14.5 ± 6.2	13 ± 4.6	0.179	0.947	0.843–1.062	0.352
E2/T	0.016 ± 0.016	0.021 ± 0.017	0.156	6.788	0.154–298.9	0.321
Female patients						
oxLDL	9.6 ± 7.9	10.9 ± 7.3	0.314	1.026	1.026–1.134	0.620
WBC	8.6 ± 2.1	11.2 ± 3.3	0.026 *	1.426	1.017–1.998	0.039 *
CRP	10.9 ± 16.8	22.5 ± 25.8	0.170	1.030	0.985–1.078	0.198
Syntax score	10.7 ± 8.1	13.8 ± 9.9	0.395	1.041	0.951–1.141	0.381
17β-estradiol	105.5 ± 109.1	155.6 ± 178.1	0.377	1.033	0.997–1.009	0.383
Testosterone	0.98 ± 1.57	3.23 ± 4.5	0.050	1.346	0.882–2.054	0.169
E2/T	0.39 ± 0.84	0.18 ± 0.21	0.181	0.446	0.063–3.167	0.419

Abbreviations: oxLDL, oxidized low-density lipoprotein; CRP, C-reactive protein; WBC, white blood cell; CK, creatine kinase; CK-MB, MB fraction of CK; E2, endogenous 17β-estradiol; T, total testosterone; * denotes significant or as tendency significant associations.

Table 5. Relationship of estradiol (E2), testosterone (T), inflammation, and oxidative stress with post-PCI activity of CK-MB.

CK-MB	Lowest Tertile	Highest Tertile	p-Value	OR	95% CI	p-Value
Male patients						
oxLDL	10.4 ± 8.3	9.8 ± 7.7	0.794	0.983	0.910–1.074	0.787
WBC	8.2 ± 1.8	12.7 ± 4.7	<0.0001 *	1.709	1.174–2.488	0.005 *
CRP	15.7 ± 27.7	58.4 ± 66.2	0.008 *	1.024	1.002–1.046	0.029 *
Syntax score	15.5 ± 10.2	18.1 ± 9.5	0.370	1.028	0.968–1.092	0.364
17β-estradiol	128 ± 45.9	188.9 ± 90.1	0.003 *	1.018	1.004–1.032	0.013 *
Testosterone	13.8 ± 5.4	12.9 ± 4.5	0.268	0.963	0.856–1.083	0.528
E2/T	0.019 ± 0.021	0.019 ± 0.015	0.470	0.879	0.033–23.517	0.939
Female patients						
oxLDL	8.9 ± 6.6	8.9 ± 3.7	0.993	0.991	0.913–1.076	0.838
WBC	8.3 ± 2.5	11.1 ± 3.3	0.022 *	1.384	1.022–1.875	0.036 *
CRP	11.7 ± 16.3	22.3 ± 25.9	0.195	1.027	0.984–1.072	0.217
Syntax score	13.2 ± 16.3	22.3 ± 25.9	0.195	0.979	0.890–1.076	0.659
17β-estradiol	101.1 ± 106.9	137.9 ± 171.1	0.245	1.002	0.996–1.008	0.489
Testosterone	0.73 ± 0.53	3.1 ± 4.6	0.039	2.115	0.594–7.527	0.248
E2/T	0.36 ± 0.81	0.16 ± 0.20	0.188	0.443	0.057–3.472	0.439

Abbreviations: PCI, percutaneous coronary intervention; oxLDL, oxidized low-density lipoprotein; CRP, C-reactive protein; WBC, white blood cell; CK, creatine kinase; CK-MB, MB fraction of CK; E2, endogenous 17β-estradiol; T, total testosterone. * denotes significant or as tendency significant associations.

For the male patients, high plasma concentrations of E2 and CRP were significant markers for an increase in Troponin T (TnT) levels. Peak WBC count was notably associated with the highest activities of both CK-MB and hs TnT in a multiple regression model (Table 7).

Table 6. Association of hormones and inflammatory and oxidative stress markers with troponin T in acute myocardial infarction (AMI).

Troponin T	Lowest Tertile	Highest Tertile	<i>p</i> -Value	OR	95% CI	<i>p</i> -Value
Male patients						
oxLDL	12.1 ± 8.8	7.9 ± 3.6	0.630	0.868	0.769–1.625	0.161
WBC	8.6 ± 2.2	12.1 ± 4.4	0.003 *	1.391	1.076–1.768	0.012 *
CRP	11.4 ± 16.6	61.3 ± 63.7	0.001 *	1.063	1.017–1.111	0.006 *
Syntax score	14.6 ± 10.8	17.9 ± 8.9	0.258	1.037	0.974–1.103	0.257
17β-estradiol	123 ± 49.9	195.8 ± 89.7	0.001 *	1.019	1.006–1.033	0.005 *
Testosterone	13.9 ± 5.7	11.8 ± 5.5	0.125	0.938	0.840–1.046	0.250
E2/T	0.018 ± 0.021	0.029 ± 0.035	0.107	2.755	0.178–42.656	0.468
Female patients						
oxLDL	8.4 ± 7.0	8.8 ± 3.7	0.410	0.954	0.879–1.035	0.254
WBC	8.8 ± 2.8	11.8 ± 4.1	0.034 *	1.299	1.022–1.685	0.048 *
CRP	12.1 ± 19	23 ± 25.6	0.198	1.025	0.986–1.066	0.213
Syntax score	8.9 ± 8.6	15 ± 9.5	0.089 *	1.081	0.985–1.186	0.099 *
17β-estradiol	101.6 ± 102.9	153.5 ± 179.2	0.172	1.003	0.997–1.009	0.355
Testosterone	0.98 ± 1.57	3.23 ± 4.5	0.050	1.346	0.882–2.054	0.169
E2/T	0.42 ± 0.81	0.12 ± 0.10	0.178	0.067	0.001–5.665	0.233

Abbreviations: AMI, acute myocardial infarction; oxLDL, oxidized low-density lipoprotein; CRP, C-reactive protein; WBC, white blood cell; E2, endogenous 17β-estradiol; T, total testosterone; * denotes significant or as tendency significant associations.

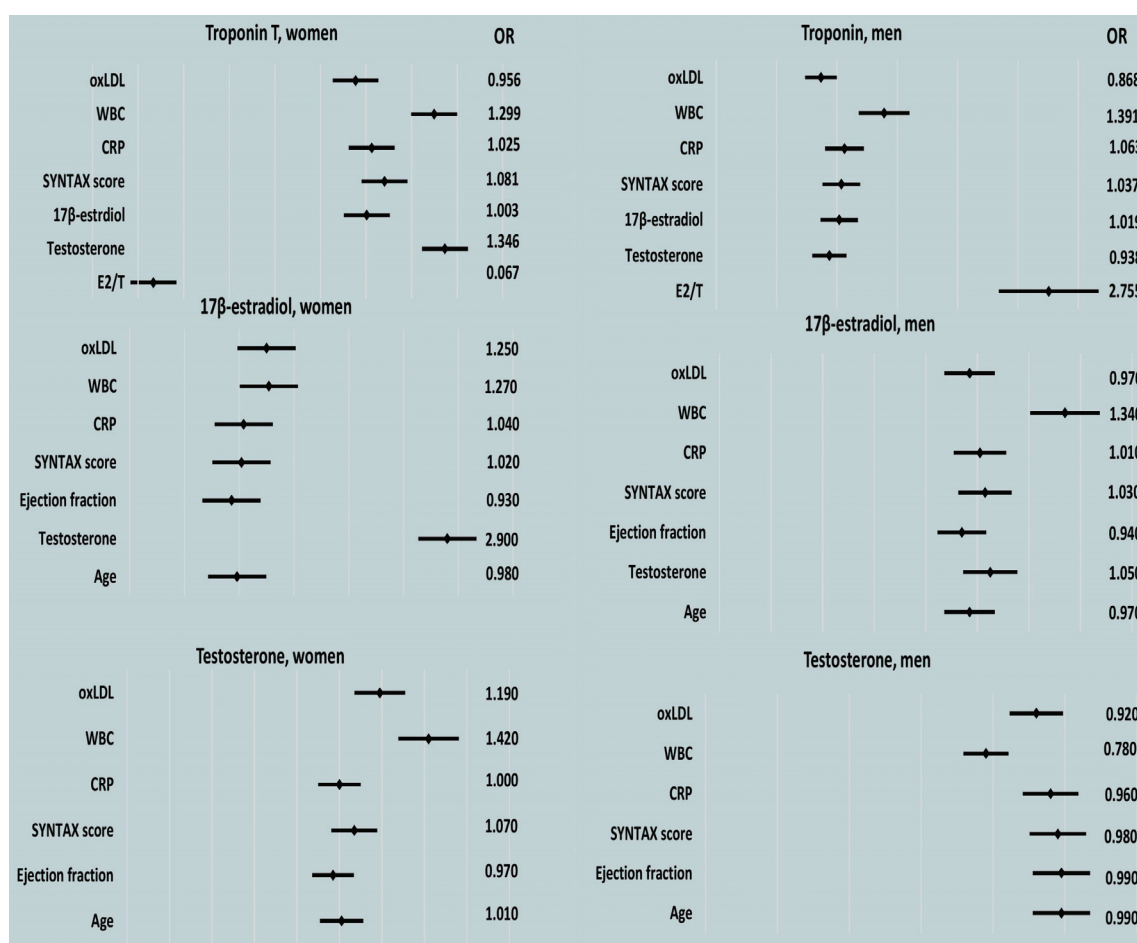


Figure 4. Indicators of troponin T and gonadal steroid hormones in male and female patients assessed using univariable regression analysis. Abbreviations: oxLDL, oxidized low-density lipoprotein; WBC, white blood cell; CRP, C-reactive protein; EF, ejection fraction; T, total testosterone; E2/T, ratio of plasma 17β-estradiol to total testosterone concentrations.

Table 7. CRP and E2 as indicators of myocardial injury in male patients with acute myocardial infarction.

Male Patients			
Troponin T	OR	95% CI	p-Value
17 β -estradiol	1.018	1.001–1.035	0.042 *
CRP	1.048	1.004–1.093	0.031 *
WBC	1.096	0.811–1.480	0.552
CK-MB	OR	95% CI	p-Value
WBC	1.503	1.018–2.217	0.040 *
CRP	1.017	0.994–1.040	0.144
17 β -estradiol	1.014	0.996–1.032	0.129
CK	OR	95% CI	p-Value
WBC	1.301	0.923–1.833	0.133
CRP	1.025	0.992–1.058	0.137
17 β -estradiol	1.005	0.992–1.018	0.426

Abbreviations: CRP, C-reactive protein; WBC, white blood cell; CK, creatine kinase; CK-MB, MB fraction of CK;

* denotes significant or as tendency significant associations.

An analysis of the correlations between gonadal steroid hormones and the E2/T ratio during the acute phase of MI revealed that increases in E2 were predicted by increases in CRP in both men and women. The lowest EFs tended to indicate women with the highest E2 levels in the acute phase of MI (Table 8, Figure 4).

Table 8. Relationship of 17 β -estradiol with oxLDL and inflammatory markers.

17 β -Estradiol	Lowest Tertile	Highest Tertile	p	OR	95% CI	p-Value
Male patients						
Age	71.1 $\pm$ 14.9	66.1 $\pm$ 12.3	0.325	0.970	0.920–1.030	0.313
oxLDL	10 $\pm$ 7.4	8.7 $\pm$ 5.5	0.625	0.970	0.850–1.100	0.614
WBC	8.5 $\pm$ 2.0	11.8 $\pm$ 5.1	0.023	1.340	0.980–1.830	0.066 *
CRP	21.9 $\pm$ 27.5	45 $\pm$ 57.3	0.049	1.010	0.990–1.040	0.209
Syntax score	14.5 $\pm$ 10	18 $\pm$ 11.4	0.373	1.030	0.960–1.110	0.365
EF	53.5 $\pm$ 8.6	48.3 $\pm$ 19.6	0.164	0.940	0.860–1.020	0.134
Testosterone	12.6 $\pm$ 4.8	13.9 $\pm$ 6.4	0.501	1.050	0.920–1.20	0.487
Female patients						
Age	70 $\pm$ 7.8	67.8 $\pm$ 12.9	0.637	0.980	0.900–1.060	0.618
oxLDL	11 $\pm$ 5.8	7.1 $\pm$ 3.6	0.089	1.250	0.950–1.640	0.115
WBC	8.6 $\pm$ 2.5	10.5 $\pm$ 3.3	0.150	1.270	0.920–1.760	0.149
CRP	11 $\pm$ 16	51 $\pm$ 53.5	0.028	1.040	1.000–1.100	0.067 *
Syntax score	12.2 $\pm$ 8.5	14.1 $\pm$ 10.5	0.653	1.020	0.930–1.120	0.635
EF	60.3 $\pm$ 7.8	47.6 $\pm$ 17.8	0.050	0.930	0.860–1.000	0.065 *
Testosterone	0.6 $\pm$ 0.5	2.9 $\pm$ 3.9	0.065	2.90	0.480–17.620	0.247

Abbreviations: oxLDL, oxidized low-density lipoprotein; CRP, C-reactive protein; WBC, white blood cell; EF, ejection fraction; * denotes significant or as tendency significant associations.

In the multivariable model, neither EF nor the maximal elevation of CRP independently predicted peak levels of E2 in the female patients with AMI (EF 0.960, OR 0.890–1.050, $p = 0.379$; CRP 1.040, OR 0.990–1.090, $p = 0.159$).

CRP level and WBC count were tendency markers of a decrease in the plasma levels of total T in the male patients, while WBC count was inversely associated with T in the women with AMI (Table 9). Among the male patients with AMI, peak CRP count showed a trend toward marking the lowest T levels in multivariable analysis (CRP 0.940, OR 0.880–1.000, $p = 0.053$; WBC 1.210, OR 0.700–2.080, $p = 0.501$).

Table 9. Relationship of total testosterone with oxLDL and inflammatory markers.

Testosterone	Lowest Tertile	Highest Tertile	<i>p</i>	OR	95% CI	<i>p</i> -Value
Male patients						
Age	62.9 ± 12.1	62.1 ± 11	0.839	0.990	0.980–1.060	0.832
oxLDL	11.2 ± 7.9	8.5 ± 4.2	0.315	0.920	0.770–1.090	0.335
WBC	11.6 ± 4.6	8.7 ± 2.5	0.048 *	0.780	0.590–1.020	0.072 *
CRP	61.2 ± 65.8	10.3 ± 13.3	0.010 *	0.960	0.910–1.000	0.057 *
Syntax score	18.4 ± 9.6	16.3 ± 9.5	0.550	0.980	0.900–1.060	0.539
EF	50.9 ± 10.5	50 ± 8.3	0.804	0.990	0.910–1.070	0.795
Female patients						
Age	69.7 ± 10.8	71.1 ± 12	0.782	1.010	0.940–1.090	0.769
oxLDL	7.5 ± 4.7	9.9 ± 2.9	0.157	1.190	0.930–1.510	0.160
WBC	8.1 ± 2.3	11.4 ± 4.1	0.024 *	1.420	1.010–1.980	0.044 *
CRP	29 ± 37.8	62.7 ± 32.7	0.929	1.000	0.980–1.020	0.925
Syntax score	8.7 ± 8.1	12.8 ± 8.1	0.236	1.070	0.960–1.190	0.227
EF	50.6 ± 10.9	45.7 ± 14.6	0.377	0.970	0.910–1.040	0.360

Abbreviations: oxLDL, oxidized low-density lipoprotein; CRP, C-reactive protein; WBC, white blood cell; EF, ejection fraction; * denotes significant or as tendency significant associations.

Additionally, a trend suggested that high CRP levels were associated with a higher E2/T ratio (Table 10).

Table 10. Relationship of E2/T with oxLDL and inflammatory markers.

E2/T	Lowest Tertile	Highest Tertile	<i>p</i>	OR	95% CI	<i>p</i> -Value
Male patients						
Age	69.8 ± 12.7	67.2 ± 11.7	0.522	0.980	0.930–1.040	0.509
oxLDL	8.0 ± 3.2	8.5 ± 4.9	0.699	1.031	0.895–1.202	0.692
WBC	9.7 ± 2.8	10.4 ± 4.3	0.494	1.058	0.902–1.242	0.488
CRP	29.1 ± 46.4	57.2 ± 62	0.062 *	1.010	0.999–1.022	0.079 *
Syntax score	14.3 ± 9.5	17.4 ± 10.6	0.270	1.032	0.976–1.090	0.268
EF	50.3 ± 7.9	49.9 ± 11.5	0.901	1.000	0.930–1.070	0.897
Female patients						
Age	74.8 ± 6.7	70.3 ± 10.9	0.293	0.940	0.840–1.050	0.285
oxLDL	8.6 ± 4.6	8.4 ± 6.7	0.857	1.031	0.884–1.162	0.850
WBC	10.3 ± 3.7	8.4 ± 2.0	0.115	0.781	0.565–1.079	0.133
CRP	11.9 ± 16.5	20.2 ± 24.1	0.302	1.021	0.981–1.063	0.300
Syntax score	11.1 ± 7.1	11.2 ± 10.6	0.980	1.001	0.917–1.093	0.979
EF	55.9 ± 13	52.1 ± 15.3	0.555	0.980	0.920–1.050	0.534

Abbreviations: oxLDL, oxidized low-density lipoprotein; CRP, C-reactive protein; WBC, white blood cell; EF, ejection fraction; * denotes significant or as tendency significant associations.

E2 and T were not significantly related to extremely short or long repolarization periods after PCI in either men or women early in the course of MI in this analysis of data. The highest versus the lowest duration of cardiac repolarization at admission showed a relationship with the severity of coronary atherosclerosis, the extent of myocardial injury, and myocardial infarction size (reflected by the levels of cardiac enzymes), as well as with LV systolic function in the subset of male patients with myocardial infarction (Table 11).

Lower ejection fractions of the left ventricle were independently predictive of prolonged repolarization, specifically for the male patients (EF: OR 0.810, 95% CI 0.650–1.010, $p=0.0059$; Syntax score: OR 1.030, $p=0.737$; CK: OR 1.000, $p=0.680$; CK-MB: OR 1.030, $p=0.243$; troponin T OR 1.000, $p=0.998$).

We found a significant, non-sex-specific association between the incidence of ventricular tachycardia (VT, 6.8%, $n=7$) and left ventricular ejection fraction ($43.6\% \pm 12\%$ vs. $53.2\% \pm 10.7\%$, $p=0.018$), as well as a tendency with peak WBC count levels ($9.7 \times 10^9/L \pm 3.7 \times 10^9/L$, $p=0.088$), during the first week of AMI. Gonadal steroids

were not associated with the incidence of VT in an analysis not adjusted for biological sex (E2: 125.9 ± 72.9 pmol/L vs. 131 ± 98.6 pmol/L, $p = 0.886$; T: 9.1 ± 5.6 nmol/L vs. 8.7 ± 7.7 nmol/L, $p = 0.879$; E2/T 0.49 ± 1.32 vs. 0.12 ± 0.3 , $p = 0.975$).

Table 11. Relationship of MI size, extent of coronary atherosclerosis, left ventricular systolic function, and hormones with repolarization period (QTc).

QTc	Lowest Tertile	Highest Tertile	<i>p</i>	OR	95% CI	<i>p</i> -Value
Male patients						
Age	64.8 ± 11.3	63.9 ± 13.9	0.874	1.270	0.800–2.010	0.310
oxLDL	7.8 ± 4.2	11.0 ± 9.0	0.312	1.090	0.920–1.290	0.233
WBC	7.8 ± 1.4	9.8 ± 3.8	0.112	1.360	0.900–2.060	0.142
CRP	14.7 ± 15.3	37.4 ± 63.4	0.240	1.010	0.990–1.040	0.291
Syntax score	11.3 ± 6.1	18.3 ± 12.9	0.099 *	1.090	0.970–1.230	0.099 *
EF	55.8 ± 6.6	48.5 ± 8.3	0.026 *	0.870	0.770–1.000	0.043 *
17 β -estradiol	149.6 ± 36	183.7 ± 89.4	0.233	0.920	0.760–1.120	0.419
Testosterone	15.3 ± 5.2	15.5 ± 6.4	0.917	2.750	0.490–15.360	0.248
E2/T	0.02 ± 0.03	0.01 ± 0.01	0.290	0.080	0.001–14.680	0.309
CK	437.8 ± 555.9	1464.3 ± 146.1	0.033 *	1.000	0.970–1.030	0.064 *
CK-MB	49.9 ± 52.1	146.7 ± 144.8	0.040 *	1.010	1.000–1.020	0.077 *
Troponin T	0.82 ± 1.23	2.93 ± 3.1	0.044 *	1.650	0.980–2.770	0.060 *
Female patients						
Age	72 ± 5.9	63.2 ± 10.3	0.045 *	0.910	0.810–1.020	0.118
oxLDL	6.3 ± 3.1	5.4 ± 2.6	0.530	0.890	0.620–1.270	0.510
WBC	8.4 ± 1.9	8.8 ± 2.3	0.679	1.110	0.690–1.800	0.657
CRP	32.7 ± 54.6	5.6 ± 5	0.054 *	0.880	0.740–1.050	0.169
Syntax score	13.3 ± 11.8	7.7 ± 9.6	0.303	1.100	0.950–1.280	0.190
EF	53.4 ± 14.5	54 ± 15.4	0.937	1.000	0.940–1.070	0.932
17 β -estradiol	83.8 ± 10.2	80.8 ± 56	0.957	1.000	0.990–1.010	0.932
Testosterone	0.68 ± 0.28	1.33 ± 1.86	0.070 *	11.700	0.600–22.7	0.105
E2/T	0.17 ± 0.17	0.13 ± 0.06	0.502	0.050	0.001–38.9	0.295
CK	405.6 ± 94.3	249.3 ± 281.3	0.460	1.000	1.000–1.000	0.434
CK-MB	61.8 ± 94.3	36.1 ± 37.8	0.434	0.990	0.980–1.010	0.432
Troponin T	1.05 ± 1.52	1.38 ± 3.1	0.768	1.060	0.720–1.560	0.754

Abbreviations: QTc, corrected duration of cardiac repolarization; oxLDL, oxidized low-density lipoprotein; CRP, C-reactive protein; WBC, white blood cell; EF, ejection fraction; E2/T, ratio of endogenous 17 β -estradiol to total testosterone; CK, creatine kinase; CK-MB, MB fraction of CK; hsTnT, high-sensitivity troponin T; * denotes significant or as tendency significant associations.

4. Discussion

We found that during the acute phase of MI, the highest levels of endogenous estradiol and CRP were significantly related to the severity of cardiomyocyte necrosis (as evidenced by peak plasma TnT levels) in the male patients. Conversely, peak WBC count emerged as a sex-specific marker for acute myocardial damage in the women. Interestingly, peak plasma T in the women correlated with the rise in WBC count, while in the men with AMI, T was inversely related to the increase in CRP levels. Furthermore, a positive association was observed between CRP and the E2/T ratio in the male patients.

4.1. Sex-Specific Relationship of oxLDL and CRP with E2 and E2/T

According to basic research reports, oxLDL influences estradiol and testosterone production [25,26]. OxLDL, or oxidized low-density lipoprotein, refers to LDL particles that have been modified through oxidation. Oxidized LDL levels can increase after percutaneous coronary intervention, particularly in the acute phase following an MI. The degree of myocardial ischemia acts as a severe cellular stressor, resulting in oxidative stress with increased free radical generation and oxLDL formation. This increase is often transient and may be related to the mechanical disruption of plaque and the release of oxidized lipids during the procedure. However, no significant association of plasma oxLDL levels with inflammatory markers and E2 could be detected in our study, either due to the rapid

immune clearance of oxLDL [27], due to the blood samples being obtained too early, or because of a complex relationship which remained statistically undetectable in our small study group.

Many observational studies highlight the significance of the association between gonadal steroid hormones and markers of ongoing low-grade vascular inflammation in atherosclerosis in male patients with chronic coronary disease [7]. Under nonacute conditions, excess adipose infiltration with macrophages leads to increased aromatase expression and elevated endogenous estradiol levels [28]. Obesity might induce the production of chemokine ligand 2 (an MCP-1 receptor) in adipose tissue, thereby inducing inflammation and local aromatase, and subsequently amplifying estrogen levels [29]. A relationship between certain cytokines (IL-6 and TNF- α) and E2 has been documented in male patients with metabolic syndrome [30]. Notably, pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α), induce the expression of the human aromatase gene in mammary adipose tissue [31].

Recent observational studies show that the effect of exogenous estrogen (hormone replacement therapy) is a predisposing factor for adverse cardiovascular events in women who have had menopausal status for more than ten years [32]. Experimental studies indicate that when atherosclerotic lesions are present, the altered expression of estrogen receptors on the vascular wall further exacerbates arterial wall damage [32,33]. In a low-grade inflammation state, such as established atherosclerosis, E2 can destabilize atherosclerotic plaques by inducing molecules like MCP-1 and matrix metalloproteinases (specifically MMP-2 and MMP-9) in endothelial cells [32]. E2 induces different effects regarding atheromatous plaque instability through different ERs. The overexpression of ER α may result in E2-induced plaque instability by increasing MCP-1 protein expression and MMP-2 activity [32]. In the absence of an inflammatory state, E2, at low concentrations, exerts atheroprotective effects, mainly by decreasing MMP-2 activity and increasing LOX expression via ER β [32].

During acute illness, a surge in aromatase in response to an elevated production of pro-inflammatory cytokines has been described [34]. A critical illness produces endocrine responses, such as hypogonadotropic hypogonadism in male patients, associated with low luteinizing hormone, LH [35]. Also, an increase in adipose aromatase content, decreased serum T levels, and a rise in estrone levels, with a trend toward a rise in E2, has been observed in both men and women [36]. Aromatase expression in adipose tissue is primarily under the control of its promoter, which is regulated by cytokines and the stress-induced glucocorticoid cortisol [36].

Importantly, several human studies have reported fluctuations in E2 and testosterone levels during acute coronary syndrome [12,13]. Persistently elevated E2 and declining testosterone have been associated with changes in hemostatic factors (notably, increased plasminogen activator inhibitor-1, PAI-1) in men with AMI [12]. Elevated cardiac PAI-1 post-myocardial infarction may contribute to tissue remodeling and augmented cardiac fibrosis [37], creating a prothrombotic profile in male AMI patients and in situ microthromboses.

4.2. Relationship of WBC Count with TnT in Female Patients

For the male AMI patients, the peak systemic inflammatory mediators predicted plasma 17 β -estradiol levels and E2 correlated with infarct size, while testosterone levels did not emerge as a significant marker of myocardial injury. In contrast, WBC count was associated with T levels and myocardial injury severity specifically in the group of female patients.

According to observational data, in middle-aged women, a higher WBC count indicates an underlying inflammatory state associated with obesity, hyperandrogenemia, and

polycystic ovary syndrome (PCOS) [38]. Moreover, testosterone has been directly linked to increased platelet thromboxane A receptor density and maximal platelet aggregation [39]. In particular conditions in which tissue factor biological action is crucial, such as acute myocardial infarction, the neutrophil count increases substantially [40]. Tissue factor is expressed by endothelial cells, platelets, and neutrophils [40]. Inflammatory molecules such as P-selectin and TNF- α share the ability to induce tissue factor synthesis on the neutrophil surface [40]. A testosterone-rich environment may intensify platelet–leukocyte interactions, potentially leading to increased fibrin deposition and extensive coronary thrombus formation, which could be a potential source of distal embolization. Testosterone’s associations with thrombin generation parameters (like fibrinogen, factor VIIc, PAI-1) have been documented in young women with PCOS [41] and middle-aged women [42].

4.3. Lack of Overt Relationship of E2 with Myocardial Injury in Women with AMI

Interestingly, only E2 emerged as a predictor of myocardial injury in our study, and specifically in the men. In contrast, for the female AMI patients, troponin levels were associated with higher WBC counts. Notably, earlier population-based studies have proved that the plasma concentration of estradiol and its production rate were significantly higher in healthy men than in age-matched postmenopausal women without cardiovascular disease [43]. The levels of E2 and T measured in our study coincided in time with peak plasma levels of inflammatory and myocardial injury markers (measured within six hours of PCI). Also, E2 and E2/T were significantly associated with the inflammatory response in the acute phase of MI and, in the case of E2, also with myocardial damage, suggesting a potential significance of E2 as a male-specific marker of myocardial injury in small AMI cohorts.

4.4. Lack of Significant Association of E2/T and E2 with Body Mass Index

Most E2 production in men arises from the extragonadal aromatization of adrenal androgens and testosterone in muscle and adipose tissues. The rate of testosterone conversion to estradiol is lower than that of androstenedione aromatization to estrone [10,44]. However, the estradiol/testosterone ratio is accepted as a measure of the aromatization of T into E2 in large studies of male patients [45]. The aromatization of C19 steroids in peripheral tissues (adipose and skin fibroblasts) by enzyme aromatase is the primary mechanism for estrogen formation in postmenopausal women [10]. The androstenedione-to-estrone ratio is used as a marker of aromatase enzyme activity in postmenopausal women [10]. Nevertheless, the median value of estrone-to-androstenedione concentrations correlated significantly with the estradiol/testosterone ratio in postmenopausal women [10].

Our analysis revealed that body mass index (BMI) did not significantly correlate with the levels of gonadal steroid hormones, E2/T, or inflammatory markers. Other studies have emphasized a stronger relationship between abdominal adipose tissue thickness (rather than BMI) and the levels of inflammatory mediators and sex hormones [46]. Inflammatory pathways are activated soon after high-fat diet consumption, leading to inflammatory macrophage accumulation in white adipose tissue even before overt obesity manifests [47]. The association of sex hormones and inflammatory markers with BMI as a measure of overall adiposity is obviously far too weak compared to the correlation of abdominal adipose tissue thickness with inflammatory mediators and sex hormones.

4.5. Association of QTc with EF in Male Patients and of QTc with CRP and Testosterone in Female Patients

The incidence of ventricular tachycardia detected until the end of the first week of AMI was non-sex-specifically associated with left ventricular ejection fraction and, as a tendency, with peak WBC count. In the male patients, the longer duration of cardiac repolarization (QTc) prior to PCI was related to the severity of coronary disease, infarction

size (peak cardiac enzymes), and EFs. Specifically in the male patients, the reduction in LV systolic function showed a significant independent relationship with longer QTc in the multivariable model. In the subset of female patients with AMI, QTc showed a trend for association with younger age, lower CRP, and higher total testosterone levels but was not independently predicted by any of these variables. These results showed that regarding the women with acute MI, factors, such as higher endogenous plasma T levels, might be implicated in the predisposition to ventricular arrhythmia via mechanisms not directly involving acute myocardial injury.

Among the possible mechanisms involved in the deleterious actions of supraphysiological doses of testosterone in female individuals are unfavorable changes in the lipid profile, procoagulatory effects, activation of the sympathetic nervous system and renin–angiotensin–aldosterone system, and insulin resistance. These indirect actions of testosterone can affect the vasculature. Among its direct effects, the stimulation of pro-inflammatory enzymes in the vasculature [e.g., thromboxane synthase, cyclooxygenase-1 (COX-1), and COX-2] and reactive oxygen species generation in vascular smooth muscle cells may decrease nitric oxide (NO) bioavailability and lead to increased vasoconstriction, increased blood pressure, and renal dysfunction [48].

In women, low testosterone levels may be linked to an increased risk of ventricular arrhythmias, including sudden cardiac death by prolonging ventricular repolarization [48]. However, oxidative stress can also elevate the risk of arrhythmias in both sexes. Testosterone upregulates the expression of NADP oxidase (NOX4) and increases oxidative stress [48]. Increased levels of mitochondrial NOX4 during aging lead to a higher inducibility of self-limiting ventricular arrhythmias [49]. Transgenic mice with mitochondria-targeted Nox4 overexpression showed a significantly higher incidence of pacing-induced VT, associated with shorter action potential duration due to increased transient outward potassium currents. Fractional sarcoplasmic reticulum Ca^{2+} release and Ca^{2+} leak remained intact despite these changes [49].

4.6. Significance and Limitations

The results of this study contribute to scientific theory beyond the pathophysiology of coronary disease. Incomplete gonadal hormone suppression is involved in resistance to adjuvant therapy in different hormone-sensitive neoplasms (breast cancer and prostate cancer). The knowledge that variations in endogenous 17β -estradiol, testosterone, and E2/T associated with systemic increases in inflammatory markers can occur in pathologic settings (e.g., acute myocardial infarction) is important for discerning resistant malignancies and for developing optimal protocols for therapy, including adjuvant antitumor therapy.

This study has some limitations. First, the hormone levels were measured once. The changes in hormone levels after the infarction are likely to better characterize the observed relationships of inflammatory markers with E2 and E2/T. Second, estrone levels are higher than estradiol in postmenopausal women, and the ratio of androstenedione to estrone (not the E2/T ratio) directly characterizes aromatase activity. Third, we did not have any measurement of fat mass except BMI. The thickness of abdominal adipose tissue measured by ultrasound indicates the effects of obesity with higher accuracy. Finally, in up to 14% of the patients, PCI was not performed, mainly because of non-obstructive coronary disease. In these patients, the peak levels of cardiac enzymes, and thus the size of the infarction, may not have been precisely evaluated due to the blood samples being obtained too early.

5. Conclusions

During acute MI, elevated endogenous estradiol levels in men and increased leukocytes in women indicate acute myocardial damage. Post-PCI plasma inflammatory markers

are sex-specific confounding factors for acute endogenous E2 levels, T levels, and the E2/T ratio. LV systolic function in men and the acute inflammatory response and testosterone levels characteristically for women are predictors of longer ventricular repolarization and arrhythmia risk.

Author Contributions: Conceptualization, N.E.S. and A.D.T.; methodology, V.V.L. and A.D.T.; software, N.E.S.; validation, V.V.L.; formal analysis, N.E.S.; investigation, N.E.S., V.V.L. and A.D.T.; resources, N.E.S.; data curation, N.E.S.; writing—original draft preparation, N.E.S.; writing—review and editing, N.E.S., V.V.L. and A.D.T.; visualization, N.E.S.; supervision, A.D.T.; project administration, N.E.S.; funding acquisition, N.E.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Medical University of Sofia; grant numbers: 5-D/2012 and 5-D/2013 (project No 35-D/2012 and 6-D/2013).

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Sofia (protocol codes: 81/5 May 2012 and 262/7 May 2013).

Informed Consent Statement: Informed consent was obtained from all the subjects involved in this study.

Data Availability Statement: Data is available from the corresponding author; details regarding data supporting the reported results can be sent to editors and reviewers upon request.

Acknowledgments: N.S. wishes to thank Z.R., M.R., M.S., N.E., and P.E. for their contribution to validating the results of this study. We thank Servier Medical Bulgaria for their financial support, which was spent on a reagent used in this study.

Conflicts of Interest: The authors declare no conflicts of interest.

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Article

Three-Dimensional Speckle-Tracking Echocardiography-Derived Left Ventricular Global Longitudinal Strain and Mitral Annular Plane Systolic Excursion Are Associated in Healthy Adults—Insights from the MAGYAR-Healthy Study

Attila Nemes *, Nóra Ambrus and Csaba Lengyel

Department of Medicine, Albert Szent-Györgyi Medical School, University of Szeged, P.O. Box 427, 6725 Szeged, Hungary; ambrusnora@gmail.com (N.A.); lecs@in1st.szote.u-szeged.hu (C.L.)

* Correspondence: nemes.attila@med.u-szeged.hu; Tel.: +36-62-545220; Fax: +36-62-544568

Abstract: Introduction: Mitral annular plane systolic excursion (MAPSE) is a quantitative feature of left ventricular (LV) function that can be easily measured by M-mode echocardiography. The more recent LV strains represent LV contractility, and they can be determined for the three main directions in the radial (RS), longitudinal (LS), and circumferential (CS) directions. Three-dimensional (3D) speckle-tracking echocardiography (3DSTE) seems to be ideal for the simultaneous assessment of all LV strains from the same acquired 3D dataset. Their associations, however, have not been fully analyzed in clinical settings in healthy volunteers yet. Therefore, the present study aimed to find associations between MAPSE and 3DSTE-derived LV strains in healthy circumstances. **Methods:** The present study consisted of 106 healthy adult volunteers (mean age 28.1 ± 6.3 years, 48 men). Complete two-dimensional Doppler echocardiography with MAPSE assessment and 3DSTE-derived LV strain measurements were performed in all cases. **Results:** Tendentiously reduced LV volumes with preserved LV ejection fraction were present in the case of mean MAPSE as compared to decreased/increased MAPSE. Global and regional LV-RS and LV-CS did not differ if MAPSE was increased, mean or decreased. Global LV-LS was reduced in the case of decreased MAPSE, mainly due to tendentiously higher apical LV-LS. MAPSE did not differ if global LV-RS and LV-CS were increased, mean or decreased. MAPSE was tendentiously increased in the presence of increased global LV-LS. **Conclusions:** Only 3DSTE-derived global LV-LS and MAPSE are associated in healthy adults; LV global strains in other directions show no relationship with MAPSE.

Keywords: left ventricular; mitral annular plane systolic excursion; strain; three-dimensional echocardiography; healthy

1. Introduction

In recent decades, echocardiography has undergone enormous technical development. While old well-established methods have remained in clinical practice, new ones have spread rapidly and become everyday practice. There are several echocardiographic parameters used to characterize left ventricular (LV) systolic function [1]. The up-and-down motion of the mitral annular (MA) plane during the cardiac cycle is a quantitative feature of LV longitudinal function that can be measured using M-mode echocardiography (MME) [2–7]. The method is simple, easy to implement, and validated, and the parameter is called MA plane systolic excursion (MAPSE). In other words, MAPSE refers to LV longitudinal shortening, MA motion,

left atrioventricular plane displacement, or mitral ring displacement, which can be affected earlier than LV ejection fraction (EF). MAPSE is known for its significant prognostic power as well [2–7]. The more recent LV strains as quantitative representatives of LV contractility are to be determined by echocardiography as well in the three main directions of the space in the radial (RS), longitudinal (LS), and circumferential (CS) directions [8]. Three-dimensional (3D) speckle-tracking echocardiography (STE) seems to be ideal for the simultaneous assessment of LV strains using virtually created LV models from the same acquired 3D dataset [9–12]. On the one hand, it may seem that partially similar and interchangeable parameters can be calculated with both methods. On the other hand, both methods have their own advantages and disadvantages. Furthermore, the associations between MAPSE and 3DSTE-derived strains have not been fully analyzed in clinical settings even in healthy volunteers yet. Therefore, the present study aimed to find associations between MAPSE as assessed by MME and 3DSTE-derived LV strains in healthy circumstances. It was also examined whether the relationship between these parameters shows differences depending on whether they are average or smaller/larger.

2. Materials and Methods

Subjects. The present study consisted of 106 healthy adult volunteers (mean age: 28.1 ± 6.3 years, 48 men) who were involved in the present study between 2011 and 2017. All participants were considered to be healthy due to the fact that their medical history did not contain any known disorder or other condition that could theoretically affect the findings. No one was obese, a professional athlete, pregnant, or a smoker at the time of enrollment. In all cases, physical examination, a laboratory test, electrocardiography (ECG), and two-dimensional (2D) Doppler echocardiography were performed with a negative result. 3DSTE was performed at the time of the enrollment with 3D echocardiographic data acquisition, and their analysis was performed at a later date. The present retrospective study is an analysis from the ‘Motion Analysis of the heart and Great vessels by three-dimensional speckle-tracking echocardiography in Healthy subjects’ (MAGYAR-Healthy) Study. This study was partly organized for physiologic studies to compare 3DSTE-derived parameters in healthy individuals among others (‘Magyar’ means ‘Hungarian’ in the Hungarian language). This study was performed in accordance with the Helsinki Declaration (revised in 2013); it was approved by the Institutional and Regional Biomedical Research Committee of the University of Szeged (number 71/2011), and informed consent was given by all participants.

Two-dimensional Doppler echocardiography. A Toshiba Artida™ cardiac ultrasound device (Toshiba Medical Systems, Tokyo, Japan) was used in all tests attached to a PST-30BT (1–5 MHz) phased-array transducer. In all individuals being in the left lateral decubitus position, the transducer was placed on their chest in typical parasternal and apical positions by the observer. In all cases, LA and LV were quantified, and Simpsons’s LV-EF measurement was carried out. Significant valvular stenosis and regurgitation were excluded by Doppler echocardiography. LV diastolic function was assessed by measuring transmitral flow E and A velocities and their ratio by pulsed Doppler. MAPSE was measured in the apical long-axis view as the movement of the lateral MA edge towards the apex of the LV in systole by MME (Figure 1) [2].

Three-dimensional speckle-tracking echocardiography. The same echocardiographic tool was used for 3DSTE after changing the transducer to a PST-25SX matrix phased-array transducer [9–12]. Then, 3D echocardiographic datasets were acquired from the apical window. To reach optimal image quality, 6 subvolumes within 6 cardiac cycles during a breathhold were acquired. Version 2.7 of 3D Wall Motion Tracking software (Ultra Extend, Toshiba Medical Systems, Tokyo, Japan) was used for the analysis of the auto-created

merged 3D full-volume dataset. Apical four-chamber (AP4CH) and two-chamber (AP2CH) long-axis views and 3 cross-sectional views were automatically created, and then septal and lateral edges of the LV-MA and the endocardial surface of the LV apex were determined by the observer. Following automatic contour detection and sequential analysis, a virtual 3D model of the LV was created, and the following global and basal, midventricular, and apical regional unidirectional/unidimensional LV strains were calculated as a mean of segmental ones (Figure 2) [1,2,8–12]:

- Radial (RS) representing the thickening/thinning of the LV;
- Circumferential (CS) representing the narrowing/widening of the LV;
- Longitudinal strain (LS) representing the shortening/lengthening of the LV.

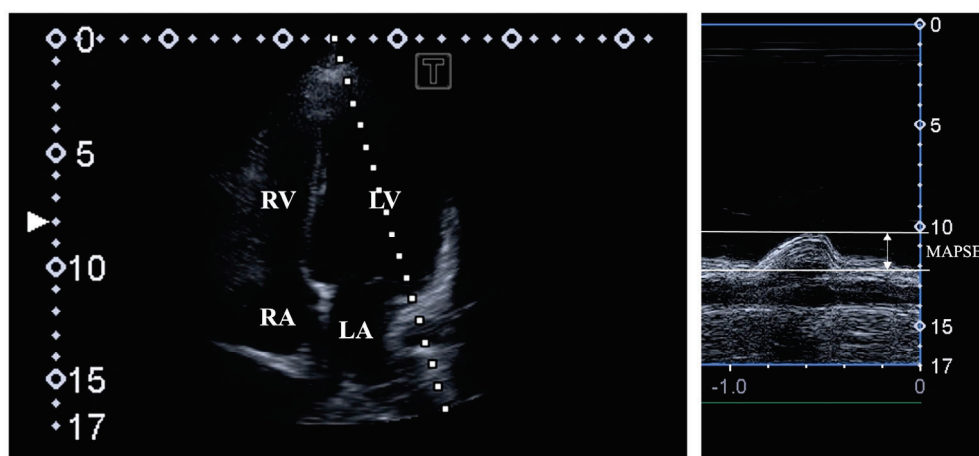


Figure 1. Assessment of mitral annular plane systolic excursion (MAPSE) by M-mode echocardiography in apical four-chamber view. Abbreviations: LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; MAPSE = mitral annular plane systolic excursion.

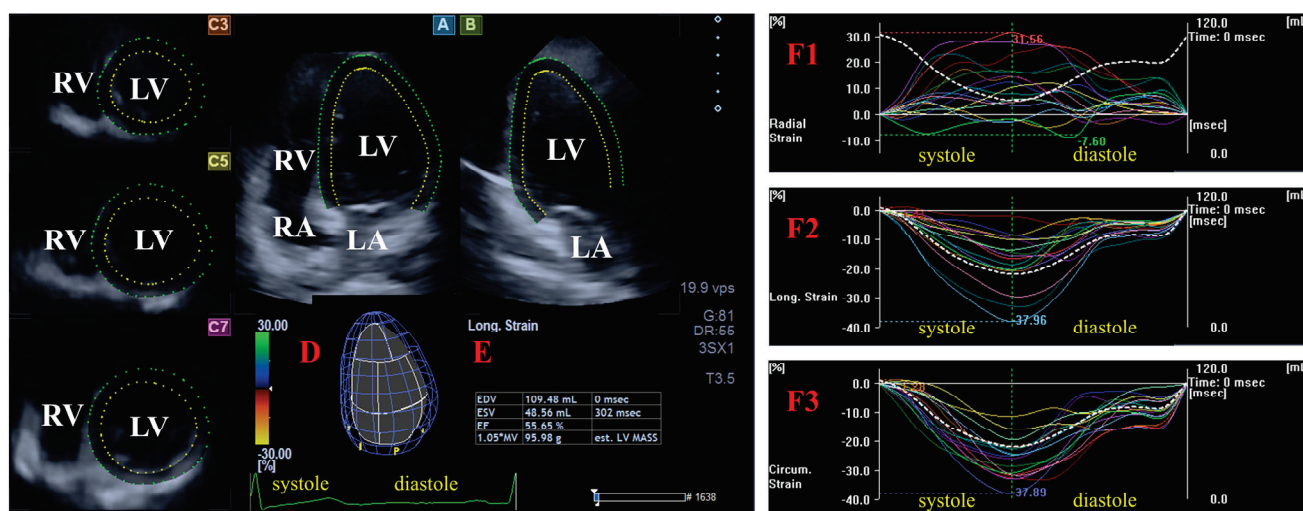


Figure 2. Assessment of the left ventricular (LV) strains by three-dimensional (3D) speckle-tracking echocardiography. Apical four-chamber (A) and two-chamber (B) long-axis views and short-axis views at the basal (C3), midventricular (C5), and apical levels (C7) of the LV are presented together with a 3D cast of the LV (D) and the LV volumetric data calculated (E). Curves of time—global and segmental radial (F1), longitudinal (F2), and circumferential (F3) LV strains (white and colored lines) and time—change in the LV volume (dashed white line) during the cardiac cycle are shown together. Abbreviations: LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction.

Statistical analysis. All continuous variables were represented in mean $\pm$ standard deviation (SD) format together with the median (in bracket). Statistical significance was considered to be present in the case of a p of less than 0.05. Data were analyzed by the analysis of variance (ANOVA) test for normal distribution data and the Kruskal–Wallis H test for non-normal distribution data. Pearson’s correlation coefficients were calculated between MAPSE and global and regional LV strains. Non-parametric tests alongside parametric methods were used where appropriate (e.g., Spearman rank correlation). Correlations between MAPSE and the global and regional LV strain were assessed using linear regression analysis as well. SPSS software version 22 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

3. Results

Clinical data. Routine clinical data including systolic and diastolic blood pressures (122.3 ± 3.2 mmHg and 83.3 ± 2.1 mmHg, respectively), heart rate (71.0 ± 1.8 1/s), height (169.3 ± 9.8 cm), weight (72.9 ± 14.3 kg), and body surface area (1.84 ± 0.33 m²) were in normal ranges in all healthy subjects.

Two-dimensional Doppler echocardiography. Echocardiographic measures including LA diameter (37.2 ± 3.6 mm), LV end-diastolic diameter and volume (48.0 ± 3.6 mm and 106.7 ± 22.7 mL, respectively), LV end-systolic diameter and volume (32.1 ± 3.2 mm and 37.9 ± 9.2 mL, respectively), interventricular septum and LV posterior wall (9.1 ± 1.2 mm and 9.4 ± 1.5 mm, respectively), LV-EF ($64.5 \pm 3.7\%$), and early and late mitral inflow velocities (78.8 ± 16.7 and 59.3 ± 14.5 cm, respectively) were within the normal reference ranges. Larger than grade 1 valvular regurgitation or significant valvular stenosis could not be found in case of any valves in any cases.

Classification of subjects. The group of healthy subjects was classified according to the following: mean $\pm$ SD of MAPSE, global LV-RS, LV-CS, and LV-LS were calculated, and then three subgroups were created based on the lower (11 mm, 15.7%, -22.5% , and -13.9% , respectively) and upper (17 mm, 35.5%, -32.1% , and -18.7% , respectively) values of these parameters.

LV strains in MAPSE subgroups. Tendentiously reduced LV volumes were present in the case of mean MAPSE as compared to decreased/increased MAPSE. Global and regional LV-RS and LV-CS did not differ in the MAPSE subgroups. Global LV-LS was reduced in case of decreased MAPSE, mainly due to tendentiously higher apical LV-LS (Table 1, Figure 3).

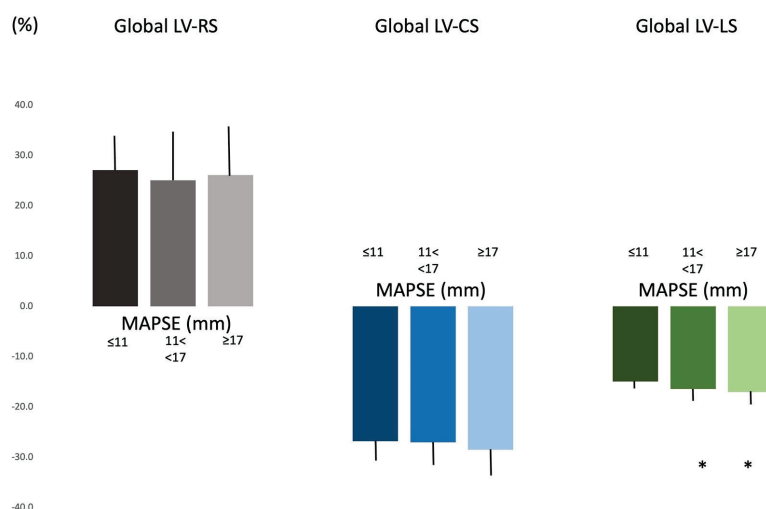


Figure 3. Left ventricular global strains in different mitral annular plane systolic excursion groups. * $p < 0.05$ vs. MAPSE ≤ 11 mm. Abbreviations: LV = left ventricular, RS = radial strain, CS = circumferential strain, LS = longitudinal strain, MAPSE = mitral annular plane systolic excursion.

Table 1. Mitral annular plane systolic excursion and left ventricular volumes and strains in different mitral annular plane systolic excursion groups.

	All Subjects (<i>n</i> = 106)	MAPSE ≤ 11 mm (<i>n</i> = 15)	11 mm < MAPSE < 17 mm (<i>n</i> = 70)	MAPSE ≥ 17 mm (<i>n</i> = 21)
LV-EDV (mL)	83.9 ± 21.3 (83.2)	90.9 ± 26.0 (84.4)	80.5 ± 19.4 (80.8)	90.0 ± 21.0† (90.5)
LV-ESV (mL)	36.0 ± 9.5 (35.1)	39.9 ± 12.2 (38.3)	34.9 ± 8.4 (34.9) *	36.8 ± 10.2 (32.2)
LV-EF (%)	57.4 ± 5.3 (56.5)	56.3 ± 3.5 (56.0)	57.1 ± 5.4 (56.4)	59.1 ± 5.7 (58.1)
LV mass (g)	162.2 ± 31.7 (166.0)	166.9 ± 35.3 (179.0)	161.7 ± 28.9 (169.3)	160.5 ± 37.1 (154)
global LV-RS (%)	25.6 ± 9.9 (24.7)	27.1 ± 7.1 (28.8)	25.1 ± 10.3 (24.2)	26.1 ± 9.9 (23.0)
basal LV-RS (%)	32.2 ± 12.9 (32.7)	34.6 ± 8.2 (36.5)	31.5 ± 12.9 (32.8)	32.6 ± 15.2 (30.2)
midventricular LV-RS (%)	29.8 ± 11.2 (28.1)	30.5 ± 8.7 (28.8)	29.5 ± 12.2 (27.7)	30.5 ± 8.7 (28.1)
apical LV-RS (%)	17.9 ± 9.2 (16.3)	17.5 ± 9.3 (17.8)	17.7 ± 9.4 (16.2)	18.9 ± 8.1 (17.2)
global LV-CS (%)	−27.3 ± 4.8 (−26.6)	−26.8 ± 4.2 (−26.5)	−27.0 ± 4.8 (−26.6)	−28.5 ± 5.2 (−27.0)
basal LV-CS (%)	−25.3 ± 4.6 (−25.6)	−26.8 ± 3.9 (−28.5)	−25.1 ± 4.8 (−25.0)	−25.1 ± 3.8 (−25.6)
midventricular LV-CS (%)	−29.2 ± 5.6 (−28.5)	−28.8 ± 3.9 (−28.7)	−28.8 ± 5.7 (−28.0)	−30.7 ± 6.0 (−30.4)
apical LV-CS (%)	−31.3 ± 10.3 (−30.9)	−28.2 ± 11.1 (−28.6)	−31.2 ± 10.0 (−30.9)	−33.8 ± 10.0 (−36.4)
global LV-LS (%)	−16.3 ± 2.4 (−16.3)	−14.9 ± 1.6 (−14.6)	−16.4 ± 2.3 (−16.3) *	−17.0 ± 2.6 (−17.3) *
basal LV-LS (%)	−20.3 ± 4.4 (−20.0)	−19.5 ± 3.6 (−19.6)	−20.2 ± 4.5 (−20.0)	−21.4 ± 4.3 (22.0)
midventricular LV-LS (%)	−13.7 ± 3.5 (−13.5)	−12.5 ± 3.0 (−11.9)	−13.9 ± 3.8 (−13.79)	−14.0 ± 2.9 (−13.9)
apical LV-LS (%)	−17.1 ± 5.8 (−16.8)	−15.2 ± 5.4 (−15.5)	−17.4 ± 5.5 (−16.7)	−17.8 ± 6.5 (−17.9)
MAPSE (mm)	14.2 ± 3.0 (14.4)	9.3 ± 1.8 (10.3)	14.0 ± 1.5 (14.1) *	18.4 ± 1.3 (18.1) *†

* *p* < 0.05 vs. MAPSE ≤ 11 mm, † *p* < 0.05 vs. 11 mm < MAPSE < 17 mm. Abbreviations: LV = left ventricular, EDV = end-diastolic volume, ESV = end-systolic volume, EF = ejection fraction, RS = radial strain, CS = circumferential strain, LS = longitudinal strain, MAPSE = mitral annular plane systolic excursion.

MAPSE in LV strain subgroups. With increasing global LV-RS, a parallel increase in LV-CS and preserved global LV-LS could be detected with the highest LV end-diastolic volume and LV-EF in the case of the highest global LV-RS. With increasing global LV-CS, a parallel increase in LV-RS could be detected with the lowest LV end-systolic volume and the highest LV-EF and global LV-LS at the highest global LV-CS. With increasing global LV-LS, global LV-RS remained unchanged, and LV end-systolic volume was the lowest, while LV-EF and global LV-CS were the highest in the case of the highest global LV-LS. MAPSE did not differ in the global LV-RS and LV-CS subgroups. MAPSE was increased in case of increased global LV-LS (Table 2, Figure 4).

Table 2. Mitral annular plane systolic excursion and left ventricular volumes and strains in different left ventricular strain groups.

	global LV-RS ≤ 15.7% (<i>n</i> = 14)	15.7% < global LV-RS < 35.5% (<i>n</i> = 76)	global LV-RS ≥ 35.5% (<i>n</i> = 16)	global LV-CS ≤ −22.5% (<i>n</i> = 8)	−22.5% < global LV-CS < −32.1% (<i>n</i> = 81)	global LV-CS ≥ −32.1% (<i>n</i> = 17)	global LV-LS ≤ −13.9% (<i>n</i> = 18)	−13.9% < global LV-LS < −18.7% (<i>n</i> = 72)	global LV-LS ≥ −18.7% (<i>n</i> = 16)
LV-EDV (mL)	71.9 ± 11.8 (72.1)	84.2 ± 21.9 (84.0)	92.0 ± 21.0 (91.7) *	73.7 ± 12.5 (76.2)	85.4 ± 22.3 (84.5)	81.6 ± 17.8 (82.8)	86.5 ± 24.0 (79.6)	85.1 ± 19.4 (85.6)	75.4 ± 24.1 (78.4)
LV-ESV (mL)	33.9 ± 5.1 (33.0)	36.4 ± 9.5 (35.9)	35.8 ± 12.2 (33.1)	37.0 ± 5.2 (37.5)	37.7 ± 9.4 (34.0)	27.5 ± 6.9 (25.8) †/††	38.6 ± 11.4 (34.9)	36.4 ± 8.9 (36.8)	31.1 ± 8.3 (27.5) †/††
LV-EF (%)	53.2 ± 4.6 (52.7)	57.3 ± 4.4 (56.5) *	61.6 ± 6.4 (60.2) */**	49.5 ± 2.9 (50.8)	56.3 ± 3.0 † (56.2)	66.3 ± 4.1 (66.4) †/††	55.3 ± 4.6 (55.2)	57.1 ± 5.1 (56.5)	61.0 ± 5.2 (61.2) †/††
LV mass (g)	149.1 ± 29.5 (157.0)	163.5 ± 31.0 (167.5)	167.6 ± 33.7 (179.0)	164.2 ± 25.4 (171.0)	163.3 ± 31.5 (166.0)	155.7 ± 32.2 (162.0)	162.2 ± 33.3 (169.8)	163.9 ± 32.1 (170.0)	154.7 ± 26.6 (156.5)
global LV-RS (%)	11.9 ± 2.9 (12.2)	24.5 ± 5.0 (24.5) *	42.8 ± 7.0 (40.6) */**	18.3 ± 6.5 (20.4)	24.8 ± 8.3† (24.6)	32.7 ± 13.6 (31.0) †/††	24.5 ± 11.7 (20.7)	25.2 ± 9.0 (25.0)	28.4 ± 10.8 (25.7)
global LV-CS (%)	−24.4 ± 4.7 (−23.8)	−27.3 ± 4.4 (−26.7) *	−29.9 ± 5.6 (−28.3) */**	−18.8 ± 2.7 (−18.8)	−26.4 ± 2.5 (−26.4) †	−35.4 ± 2.7 (−34.9) †/††	−26.0 ± 4.5 (−24.8)	−27.1 ± 4.6 (−26.6)	−29.6 ± 4.8 (−28.1) †
global LV-LS (%)	−15.7 ± 2.2 (−15.3)	−16.2 ± 2.4 (−16.5)	−16.2 ± 3.4 (−14.9)	−15.8 ± 1.7 (−15.8)	−16.1 ± 2.2 (−16.2)	−17.4 ± 2.9 (−17.9) †	−13.0 ± 1.1 (−13.4)	−16.3 ± 1.3 † (−16.3)	−20.1 ± 1.2 (−19.7) †/††
MAPSE (mm)	14.2 ± 2.4 (14.0)	14.1 ± 3.2 (14.4)	14.9 ± 2.6 (14.3)	14.0 ± 2.9 (14.4)	13.9 ± 3.1 (14.0)	15.6 ± 2.5 (15.5)	12.7 ± 3.1 (12.3)	14.3 ± 3.1 (14.3) †	15.4 ± 1.9 (15.6) †

* *p* < 0.05 vs. global LV-RS ≤ 15.7%, ** *p* < 0.05 vs. 15.7% < global LV-RS < 35.5%, † *p* < 0.05 vs. global LV-CS ≤ −22.5%, †† *p* < 0.05 vs. −22.5% < global LV-CS < −32.1%, ††† *p* < 0.05 vs. global LV-LS ≤ −13.9%, †††† *p* < 0.05 vs. −13.9% < global LV-LS < −18.6%. Abbreviations: LV = left ventricular, EDV = end-diastolic volume, ESV = end-systolic volume, EF = ejection fraction, RS = radial strain, CS = circumferential strain, LS = longitudinal strain, MAPSE = mitral annular plane systolic excursion.

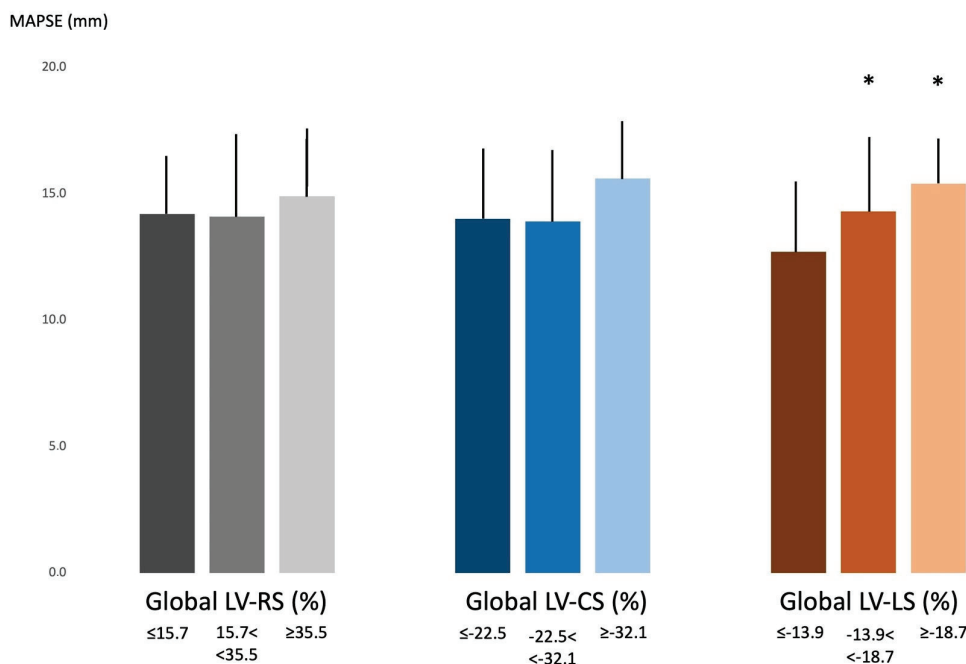


Figure 4. Mitral annular plane systolic excursion in different left ventricular global strain groups. * $p < 0.05$ vs. global LV-LS $\leq -13.9\%$. Abbreviations: LV = left ventricular, RS = radial strain, CS = circumferential strain, LS = longitudinal strain, MAPSE = mitral annular plane systolic excursion.

Correlation and regression analyses. MAPSE did not show correlations with global ($r = 0.04$, $p = 0.66$), basal ($r = 0.01$, $p = 0.91$), midventricular ($r = 0.07$, $p = 0.45$), and apical ($r = 0.07$, $p = 0.49$) LV-RS, global ($p = -0.16$, $p = 0.09$), basal ($r = 0.09$, $p = 0.37$), midventricular ($r = -0.15$, $p = 0.12$), and apical ($r = -0.21$, $p = 0.07$) LV-CS, and basal ($r = -0.14$, $p = 0.16$), midventricular ($p = -0.10$, $p = 0.31$), and apical ($r = -0.18$, $p = 0.07$) LV-LS. Only global LV-LS ($r = -0.27$, $p = 0.004$) showed mild correlations with MAPSE. Linear regression analysis revealed correlations only between global LV-LS and MAPSE ($r = -0.35$, $p = 0.009$).

4. Discussion

In clinical practice, a number of echocardiographic parameters are used to assess the systolic function of the LV in addition to the LV-EF [1]. One of the simplest MME-based parameters is MAPSE, which is defined as the displacement of the lateral MA edge respecting the cardiac cycle [2,3]. MAPSE is widely used in different clinical scenarios and validated, and its significant prognostic power has also been confirmed [2–7,13].

Echocardiography has undergone enormous development in recent decades. One of the most important results of this process is the appearance of STE and the resulting strains being increasingly used in clinical practice [14]. If the strain is defined in a loop fixed in a given plane, then it is 2DSTE, if it is defined in an acquired 3D echocardiographic database, it is called 3DSTE [9–12,14]. The latter one is considered to be the most modern echocardiographic technique since it is able to determine strains in predefined radial (RS), longitudinal (LS), and circumferential (CS) directions simultaneously from a given acquired 3D dataset. Moreover, LV strains featuring the whole LV (global) and its segments (segmental) can be calculated at the same time together with derived regional and mean segmental LV strains [9–12].

The saddle-shaped MA has a fibrotic structure with a dynamic motion throughout the cardiac cycle; its spatial movement depends largely on the musculature of the adjacent heart cavities, like that of LV [15]. Due to the above facts, MAPSE is a functional feature of LV like the strains, which can excellently characterize the spatial contractility of the LV [1–7]. 3DSTE is validated for LV volumetric and strain assessments [16–19]. In recent 3DSTE studies

from the MAGYAR-Healthy Study, observations confirmed several associations between LV volumes and strains after the determination of their normal reference values [20–22]. Therefore, the aim of the present study was to confirm associations between MAPSE and LV strains under healthy conditions by also examining what happens when parameters are lower or larger than the average.

In a previous paper from the MAGYAR-Healthy Study, a similar parameter was measured for the right ventricle (RV), which was calculated for the tricuspid annulus (TA), called TA plane systolic excursion (TAPSE), characterizing the longitudinal function of the RV. Although MAPSE and TAPSE are calculated in the same way, LV and RV are ventricles with different shapes and functional properties, which can partially explain differences in sample size due to exclusions in these studies [23]. Regarding the results of the present study, the expected findings have confirmed that global LV-LS representing longitudinal LV contraction and MAPSE are associated with healthy adults. These results were primarily due to apical longitudinal contraction, represented by (non-significant) changes in regional apical LV-LS. However, it has also been shown that strains representing systolic radial thickening (global LV-RS) and circumferential narrowing (global LV-CS) show no associations with MAPSE. These findings suggest differences between MAPSE and TAPSE; the latter showed associations with global LV-RS in healthy adults [23].

The presented results have several implications. First, although 3DSTE-derived LV-LS and MAPSE are similar features of LV longitudinal function, they are fundamentally different [3–5,9–12]. MAPSE is not only able to assess the LV regional systolic function but also the global LV longitudinal function [4]. Specific LV strains are more complex and seem to be more relevant characteristics of LV contractility in all directions of the space [8–12]. However, LV strain assessment is highly dependent on the operator's experience [24], on the frame rate setting [25], and on the chest wall conformation [26]. For instance, a narrow antero-posterior thoracic diameter may cause an increased intra- and inter-rater reliability in LV-LS assessment [26]. Nevertheless, MAPSE can be successfully used clinically because it can be easily determined with MME [2–4]. Secondly, MAPSE shows associations only with LV-LS; other LV strains have no relationship with it. These findings were expected but could be quantitatively confirmed in the present study. Thirdly, although only tendentious differences could be confirmed, regional apical LV-LS was associated with MAPSE, not regional basal LV-LS. These findings can indicate the importance that associations should be examined in certain pathologies to see what happens in case of the presence of subclinical LV abnormalities. This could be a topic of future investigations, which could help understand the development of early-stage heart failure.

Limitation section. The most important limitations that arose during the study are listed below.

- The most important technical limitation associated with 3DSTE is its lower image quality compared to 2D echocardiography, which may have affected the findings [5–8].
- Although 3DSTE-capable software offers simultaneous assessment of LV rotational parameters, the present study did not aim to determine them due to their complexity. This could be a topic of future investigations.
- 3DSTE offers complex 3D analysis of all other chambers, but analyzing the results would have gone significantly beyond the scope of this communication [9–12].
- 3DSTE-derived determination of LV strains is validated; therefore, the present study did not aim to validate it again [16–19].
- The relatively small sample size may raise certain concerns, which we tried to overcome by applying appropriate statistical methods (non-parametric tests, providing median values, etc.).

Conclusions. Only 3DSTE-derived global LV-LS and MAPSE are associated in healthy adults; LV global strains in other directions show no relationship with MAPSE.

Author Contributions: A.N.: Conceptualization, Methodology, Investigation, Data curation, Writing—original draft. N.A.: Validation, Writing—review and editing. C.L.: Resources, Writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation (Registration No.: 71/2011).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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Article

The Role of the Estimated Plasma Volume Variation in Assessing Decongestion in Patients with Acute Decompensated Heart Failure

Andreea-Maria Grigore ^{1,2}, Mihai Grigore ^{1,3,*}, Ana-Maria Balahura ^{1,3}, Gabriela Uscoiu ^{1,3}, Ioana Verde ¹, Camelia Nicolae ^{1,3}, Elisabeta Bădilă ^{1,2} and Adriana-Mihaela Ilieșiu ^{1,3}

- ¹ Department Cardio-Thoracic Pathology, Carol Davila University of Medicine and Pharmacy, 020021 Bucharest, Romania; andreea-maria.banciu@drd.umfcd.ro (A.-M.G.); ana-maria.balahura@umfcd.ro (A.-M.B.); gabriela.uscoiu@umfcd.ro (G.U.); ioana.verde@umfcd.ro (I.V.); dr_camelia_nicolae@yahoo.com (C.N.); elisabeta.badila@umfcd.ro (E.B.); adriana.iliesiu@umfcd.ro (A.-M.I.)
- ² Cardiology Department, Colentina Clinical Hospital, 020125 Bucharest, Romania
- ³ Internal Medicine and Cardiology Department, “Prof. Th. Burghele” Clinical Hospital, 050653 Bucharest, Romania
- * Correspondence: mihai.grigore@drd.umfcd.ro; Tel.: +40-747669940

Abstract: Introduction and Aim: Assessing decongestion in patients with acute decompensated heart failure (ADHF) is challenging, requiring multiple parameters and often remaining imprecise. The study aimed to investigate the utility of indirectly estimating plasma variation (Δ PVS) for evaluating decongestion in ADHF patients in relation to natriuretic peptides. Materials and Methods: This prospective, observational, single-center study included 111 patients (mean age 74 years, 40% female) hospitalized with ADHF and treated with intravenous diuretics along with optimized medical therapy. Patients were clinically and echocardiographically evaluated at admission, with blood tests performed at both admission and discharge. A decrease of $\geq 30\%$ in NT-proBNP at discharge was considered a marker of decongestion. Δ PVS was calculated using the Strauss formula: Δ PVS (%) = $100 \times [(\text{Hb admission}/\text{Hb discharge}) \times (1 - \text{Hct discharge}) / (1 - \text{Hct admission})] - 100$. A negative Δ PVS ($< 0\%$) at discharge was considered a marker of hemoconcentration. Patients were divided into two groups: G1 (Δ PVS $< 0\%$, 81 patients) and G2 (Δ PVS $\geq 0\%$, 30 patients). Results: Both groups had similar left ventricular ejection fraction (LVEF) values of 46%, mean hemoglobin (Hb) (12 g/dL), and creatinine (1.16 ± 0.65 mg/dL). NT-proBNP decreased in 88% patients in G1 and in 26% patients in G2 ($p < 0.001$). During hospitalization, five patients from G2 died. At 6 months, rehospitalization occurred in 35% of G2 and 21% of G1 ($p = 0.04$), with mortality rates of 37% in G2 and 11% in G1 ($p = 0.012$). Multivariate regression identified Δ PVS as the only significant predictor of NT-proBNP decrease (OR 0.11, 95% CI 0.04–0.33, $p < 0.001$). Conclusions: Indirect estimation of plasma volume and its variation are valuable, accessible, and cost-effective parameters for assessing decongestive treatment in ADHF patients, complementing natriuretic peptides.

Keywords: heart failure; decongestion; plasma volume

1. Introduction

Congestion is the primary cause of hospitalization in patients ADHF [1,2]. It is often underdiagnosed, as detecting congestion remains challenging because its clinical manifestations represent only the final stage of evolving pathophysiological processes [3–5].

The importance of evaluating decongestion stems from its role as one of the most significant negative predictors, influencing the prognosis of heart failure (HF) patients through early rehospitalizations and increased mortality [6]. In patients hospitalized with ADHF, a careful evaluation of congestion before discharge is recommended [7].

However, relying solely on clinical signs may lead to inadequate patient management. Currently, there are several methods for assessing decongestion, such as the ultrasound evaluation of the venous flow in the portal vein or intrarenal veins, but these methods can be time-consuming and require a steep learning curve [8]. Plasma volume variation during decongestive therapy has been proposed as a parameter to monitor a patient's progress toward euvolemia [9].

The gold standard for measuring plasma volume is the radioisotope assay; however, this method is expensive and impractical, as it requires multiple venous blood samples [10].

Non-invasive equations have been validated as alternative methods for Δ ePVS [9]. These equations are based on the assumption that variations in Hb concentrations over time are inversely related to changes in intravascular total blood volume (TBV). Based on these beliefs, changes in Hb concentration are expected to be inversely proportional to changes in TBV [11]. However, there is limited evidence regarding the use of plasma volume to predict outcomes in ADHF, and most studies analyzing Δ ePVS have been retrospective, primarily including patients with chronic HF, with only a few prospective studies focusing on patients with ADHF [9,11].

Several formulas are available for Δ ePVS, but the Strauss formula was the only that has been validated against a radiolabeled gold-standard method and has been consistently used for decades to estimate plasma volume in patients undergoing plasma exchanges [12,13].

The aim of this study is to evaluate Δ ePVS for monitoring decongestion in ADHF patients and to assess its prognostic role.

The study endpoints include in-hospital mortality, six-month mortality, and hospitalization for ADHF.

2. Materials and Methods

This prospective, observational study was conducted at a single center from 1 November 2022 to 1 January 2023. All patients provided informed consent, and the study adhered to the ethical standards outlined in the Declaration of Helsinki (1964) and its subsequent amendments as well as national guidelines for good medical practice. The study received approval from the Hospital's Ethics Committee.

The diagnosis of ADHF was established based on the 2021 European Society of Cardiology guidelines for HF [7].

Inclusion criteria included the following:

- Patients with episodes of decompensated HF, regardless of left ventricular ejection fraction (LVEF).

Exclusion criteria included the following:

- Severe anemia (Hb < 8 g/dL);
- Worsening anemia, defined as a decrease in Hb > 2 g/dL during hospitalization;
- Patients having received a blood transfusion, specifically those with an increase in Hb of more than 3 g/dL from admission to discharge;
- Hyponatremia requiring correction;
- Advanced malignancies with a life expectancy of less than 1 year;
- Septic shock;
- Patients with stage V chronic kidney disease (eGFR < 15 mL/min/1.73 m²) or hemodialysis;
- Any type of surgical intervention;

- Pregnant females.

All patients received intravenous loop diuretics within the first 48 h of admission, with dose adjustments based on clinical and biochemical response. Monitoring included daily weight measurement, renal function tests, and NT-proBNP levels at admission and discharge.

Assessments were conducted at two time points: the first within the first 24 h of admission and the second on the day of discharge.

2.1. Clinical and Laboratory Evaluation

Clinical evaluations were performed at admission, and lower-limb edema was assessed clinically by applying digital pressure to evaluate pitting and swelling. Laboratory analyses were conducted at both admission and discharge, including Hb, Ht, serum creatinine, and estimated glomerular filtration rate (eGFR), calculated using the CKD-EPI formula, as well as serum urea, serum sodium (Na), serum potassium (K), and NT-proBNP. Worsening renal function (WRF) was defined as an increase in creatinine of more than 0.3 mg/dL between the two time points [14]. A significant decrease in NT-proBNP was defined as a reduction $\geq 30\%$ from the initial value [15].

Estimation of Plasma Volume Variation

Multiple formulas are available for estimating plasma volume; however, the Strauss formula was selected due to its validation against a radiolabeled gold-standard method and its long-standing use over decades in estimating plasma volume for patients undergoing plasma exchanges [12,13].

The definitions of hemoconcentration and the Strauss formula are based on the assumption that variations in Hb concentrations over time are inversely related to changes in intravascular TBV. Based on these beliefs, changes in Hb concentration are expected to be inversely proportional to changes in TBV [11].

The Strauss formula is as follows:

$$\Delta ePVS = 100 \times \frac{\text{hemoglobin}(\frac{\text{g}}{\text{dL}})_{\text{admission}}}{\text{hemoglobin}(\frac{\text{g}}{\text{dL}})_{\text{discharge}}} \times \frac{100 - \text{hematocrit}(\%)_{\text{admission}}}{100 - \text{hematocrit}(\%)_{\text{discharge}}} - 100$$

Based on $\Delta ePVS$, patients were divided into two groups:

- Group 1 ($<0\%$)—hemoconcentration;
- Group 2 ($\geq 0\%$)—hemodilution.

$\Delta ePVS$ was chosen for its validated use as a surrogate for plasma volume changes, offering a non-invasive, cost-effective, and widely applicable method based on routine clinical parameters.

2.2. Ultrasound

Echocardiography was performed at admission using a GE Vivid E95 Ultrasound Machine (GE HealthCare, Chicago, IL, USA) with a 1.4–4.6 MHz transducer and simultaneous ECG recording. Several parameters were measured at admission according to the latest European Association of Cardiovascular Imaging recommendations [16], including LVEF, left atrial diameter (LAd), and estimation of E/e' filling pressures. Right-heart parameters such as tricuspid annular plane systolic excursion (TAPSE), lateral tricuspid annulus peak systolic velocity (S'), systolic pulmonary artery pressure (sPAP), and inferior vena cava diameter (IVCd)/collapse for sPAP estimation were also recorded [16]. Images were analyzed and processed using the offline EchoPAC PC v204 software.

Lung ultrasound was performed using a GE Vivid E95 ultrasound machine equipped with a 6.0–13.0 MHz transducer to identify pulmonary congestion, defined by the presence of a minimum of three B-lines in two zones of a hemithorax, and to assess for pleural

effusion, which appears as an anechoic structure located between the pleura and the lung parenchyma [17].

Discharge

Discharge was based on clinical stability, including symptom resolution, improved biochemical parameters, and echocardiographic parameters, as determined by the attending physician.

Follow-up

Patient follow-up was conducted either via telephone or by reviewing hospital records at 180 days.

ADHF hospitalization was defined as an admission where HF was the primary diagnosis, characterized by symptoms and signs of HF that necessitated treatment with intravenous diuretics. We used the same criteria for “HF” as we did for ADHF in the inclusion criteria. Information on these endpoints was gathered through a review of records in local hospital databases, telephone interviews with patients, and consultation of documents from other hospitals.

2.3. Statistical Analysis

The statistical analysis was performed using IBM SPSS software (version 20 for Windows). Descriptive statistics were calculated for all patients. For continuous variables, data are presented as the mean with standard deviation for normally distributed data or as the median and interquartile range (IQR) for non-normally distributed data. The Shapiro–Wilk test was used to assess the normality of the data distribution. Categorical variables are summarized as absolute numbers and percentages.

The relationship between quantitative variables was evaluated using either Pearson’s or Spearman’s correlation tests, depending on the data distribution, while associations between categorical variables were analyzed with the chi-square test. For within-group comparisons over the two time points for non-normally distributed variables, the Friedman test was applied. Comparisons between groups were carried out using the Student’s *t*-test for normally distributed variables and the Mann–Whitney test for non-normally distributed ones.

Receiver operating characteristic (ROC) curve analysis was employed to assess the predictive value of quantitative variables. To identify independent predictors of mortality and readmission, multivariate regression analysis was performed, with results expressed as odds ratios (OR) and 95% confidence intervals (CI).

A *p*-value of less than 0.05 was considered statistically significant for all tests.

3. Results

The patient selection process for the study is detailed in Figure 1. Initially, 131 patients with ADHF were identified; however, 15 patients were excluded due to severe anemia at admission. An additional five patients were excluded because of worsening anemia during hospitalization. As a result, a total of 111 patients were included in the final analysis.

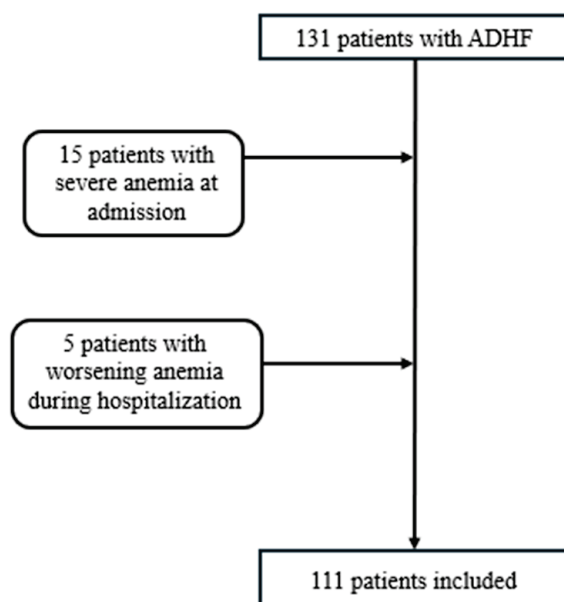


Figure 1. Patient Selection Flowchart.

A total of 111 patients were divided at discharge based on Δ ePVS into two groups: Group 1 with 81 patients and Group 2 with 30 patients. The median age was 73 years in Group 1 and 74 years in Group 2, with no statistically significant difference between the groups ($p = 0.20$) (Table 1). The proportion of female patients was similar, accounting for 40.7% in Group 1 and 36.67% in Group 2 ($p = 0.56$). Body mass index (BMI) was also comparable between the groups, with a median value of 28.57 kg/m² in Group 1 and 30.51 kg/m² in Group 2 ($p = 0.23$) (Table 1).

Comorbidities

Ischemic heart disease was present in 44.44% of patients in Group 1 and 26.67% in Group 2, although this difference was not statistically significant ($p = 0.141$). HTN was observed in 81.48% of Group 1 and 86.67% of Group 2 ($p = 0.49$). DM affected 39.51% of Group 1 and 30% of Group 2 ($p = 0.39$). CKD was more prevalent in Group 2 (73.33%) compared to Group 1 (56.79%), but this did not reach statistical significance ($p = 0.169$). AF was present in 54.32% of Group 1 and 66.67% of Group 2 ($p = 0.30$). COPD was similar in both groups (20.99% in Group 1 vs. 26.67% in Group 2, $p = 0.49$) (Table 1).

Medication at admission

Regarding medication at admission, the use of ACEi was similar between the groups (32.10% in Group 1 vs. 36.67% in Group 2, $p = 0.54$), as was the use of ARB (18.52% in Group 1 vs. 10% in Group 2, $p = 0.33$). ARNI usage was observed in 20.99% of Group 1 and 10% of Group 2 ($p = 0.24$) (Table 1).

The use of beta-blockers at admission was higher in Group 1 (90.12%) compared to Group 2 (70%, $p = 0.06$), although this difference was not statistically significant.

The use of MRA was also significantly higher in Group 1 (79.01%) versus Group 2 (43.33%, $p = 0.0008$). No significant differences were noted in the use of SGLT-2 inhibitors (37.04% in Group 1 vs. 30% in Group 2, $p = 0.47$) (Table 1).

Table 1. Clinical and demographic characteristics of both groups.

Baseline Admission Characteristics	Total (111 Patients)	Groups		<i>p</i> -Value
		Group 1 81 Patients	Group 2 30 Patients	
Age, years, median (IQR)	74 (67–82)	73 (66–82)	74 (70–85)	0.20
Sex, female (%)	39.29	40.7	36.67	0.56
BMI (kg/m ²), median (IQR)	28.71 (24–33)	28.57 (24–45)	30.51 (27–32)	0.23
HR, beats/min, median (IQR)	76 (69–100)	75 (70–100)	76.5 (66–100)	0.66
SBP, mmHg, median (IQR)	130 (110–149)	130 (115–147)	130 (110–150)	0.68
Smoker (%)	41.08	41.98	40	0.59
Comorbidities				
IHD, (%)	39.29	44.44	26.67	0.14
HTN, (%)	82.14	81.48	86.67	0.49
DM (%)	36.61	39.51	30	0.39
CKD (%)	60.71	56.79	73.33	0.16
AF (%)	57.14	54.32	66.67	0.30
COPD (%)	22.32	20.99	26.67	0.49
Medication at admission				
ACEi (%)	33.04	32.10	36.67	0.54
ARB (%)	16.07	18.52	10	0.33
ARNI (%)	17.86	20.99	10	0.24
Beta-blocker (%)	83.93	90.12	70	0.06
MRA (%)	68.75	79.01	43.33	0.0008
SGLT-2 inhibitors (%)	34.82	37.04	30	0.47
CRT (%)	5.40	5	1	0.08

BMI—body mass index; HR—heart rate; SBP—systolic blood pressure; IHD—ischemic heart disease; HTN—hypertension; DM—diabetes mellitus; CKD—chronic kidney disease; AF—atrial fibrillation; COPD—chronic obstructive pulmonary disease; ACEi—angiotensin-converting-enzyme inhibitors; ARB—angiotensin II receptor blockers; ARNI—angiotensin receptor receptor-neprilysin inhibitor; MRA—mineralocorticoid receptor antagonists; CRT—cardiac resynchronization therapy.

3.1. Clinical Congestion Parameters

The assessment of congestion parameters across all 111 patients yielded several findings, as presented in Table 2.

Regarding weight, the mean at admission for the entire cohort was 83 kg (± 18.02). Group 1 reported a mean weight of 83.5 ± 18.82 kg, while Group 2's mean weight was 83.8 ± 15.95 kg, indicating no significant difference between the groups ($p = 0.92$). At discharge, the mean weight for the overall group decreased to 82 kg (± 17.10), with Group 1 showing a mean weight of 80 ± 17.77 kg and Group 2 showing 82 ± 14.55 kg; again, no statistically significant difference was observed ($p = 0.17$).

In terms of lower-limb edema, it was present in 36% of the total cohort at admission, with 31% in Group 1 and 48% in Group 2, but this difference was not statistically significant ($p = 0.28$). By discharge, the prevalence of edema had decreased to 9% overall, with Group 1 showing 7% and Group 2 showing 12%, which also did not reach statistical significance ($p = 0.15$).

Jugular vein distension was observed in 71% of the entire cohort at admission, with Group 1 reporting a similar prevalence of 68% and Group 2 at 75% ($p = 0.38$). At discharge,

the overall prevalence of JVD decreased to 13%, with 11% in Group 1 and 15% in Group 2, again showing no significant difference ($p = 0.29$).

Table 2. Clinical Congestion Parameters at Admission and Discharge.

Parameter	Total (111 Patients)	Group 1 (81 Patients)	Group 2 (30 Patients)	<i>p</i> -Value
Weight (kg)				
Admission, mean	83 ± 18.02	83.5 ± 18.82	83.8 ± 15.95	0.92
Discharge, mean	82 ± 17.10	80 ± 17.77	82 ± 14.55	0.17
Weight difference, median, IQR	2 (0–3)	2 (1–3)	1 (0–2)	0.046
Lower-limb edema (%)				
Admission	36	31	48	0.28
Discharge	9	7	12	0.15
Jugular vein distention (%)				
Admission	71	68	75	0.38
Discharge	13	11	15	0.29

3.2. Echocardiography and Lung Ultrasound

Ultrasound evaluations, including echocardiography and lung ultrasound, were performed for all 111 patients (Table 3).

Table 3. Echocardiographic and Lung Ultrasound Findings at admission.

Parameter	Total 111 Patients	Group 1 (81 Patients)	Group 2 (31 Patients)	<i>p</i> -Value
Echocardiography				
LVEF, mean	46.74 ± 15.08	46.19 ± 15.16	46.03 ± 12.77	0.95
E/e' medial ratio, median	28 (20–37)	28.33 (19–39)	29 (21–32)	0.31
LAd (mm), mean	47 ± 6.99	47 ± 5.8	48 ± 8.9	0.87
TAPSE (mm), mean	17 ± 3.9	17 ± 3.8	16 ± 4.2	0.50
S'RV (cm/s), mean	11 ± 2	11.73 ± 1.9	11.31 ± 2.5	0.49
IVC (mm), mean	22 ± 4.8	22 ± 4.6	21 ± 5.3	0.82
sPAP (mm Hg), mean	49 ± 14.1	49 ± 13	50 ± 16	0.36
Lung Ultrasound				
Pleural fluid (%)	48.65	46.91	53.33	0.45
Signs of pulmonary congestion (%)	87.39	86.42	90	0.54

LVEF—left-ventricular ejection fraction; LAd—left atrium diameter; TAPSE—tricuspid annular plane systolic excursion; S'RV—S' right ventricle; IVC—inferior vena cava; sPAP—systolic pulmonary arterial pressure.

The echocardiographic findings revealed a mean LVEF of 46.74% ± 15.08 for the entire cohort. In Group 1, the mean LVEF was 46.19% ± 15.16, while Group 2 had a mean LVEF of 46.03% ± 12.77, indicating no significant difference between the groups ($p = 0.95$). The median E/e' medial ratio was 28 (IQR 20–37) for the total cohort, with Group 1 showing a median of 28.33 (IQR 19–39) and Group 2 showing 29 (IQR 21–32), which was not statistically significant ($p = 0.31$).

Regarding the LAd, the mean was $47 \text{ mm} \pm 6.99$ across all patients, with Group 1 reporting a mean of $47 \text{ mm} \pm 5.8$ and Group 2 reporting $48 \text{ mm} \pm 8.9$, revealing no significant difference ($p = 0.87$). The TAPSE averaged $17 \text{ mm} \pm 3.9$ for the overall cohort, with Group 1 and Group 2 presenting means of $17 \text{ mm} \pm 3.8$ and $16 \text{ mm} \pm 4.2$, respectively, also showing no significant difference ($p = 0.50$).

The mean S'RV for the total cohort was $11 \text{ cm/s} \pm 2$, with Group 1 at $11.73 \text{ cm/s} \pm 1.9$ and Group 2 at $11.31 \text{ cm/s} \pm 2.5$, again indicating no significant difference ($p = 0.49$). The diameter of the IVC averaged $22 \text{ mm} \pm 4.8$ for all patients, with Group 1 measuring $22 \text{ mm} \pm 4.6$ and Group 2 measuring $21 \text{ mm} \pm 5.3$, which was not statistically significant ($p = 0.82$). The mean sPAP was found to be $49 \text{ mmHg} \pm 14.1$ overall, with Group 1 and Group 2 showing means of $49 \text{ mmHg} \pm 13$ and $50 \text{ mmHg} \pm 16$, respectively ($p = 0.36$).

In terms of lung ultrasound findings, pleural effusion was present in 48.65% of the total cohort, with 46.91% in Group 1 and 53.33% in Group 2, reflecting no significant difference ($p = 0.45$). Signs of pulmonary congestion were noted in 87.39% of the overall patients, with a prevalence of 86.42% in Group 1 and 90% in Group 2, which also did not show a significant difference ($p = 0.54$).

3.3. Biochemical Parameters and Diuretic Treatment

Biochemical and diuretic treatment data were collected at both admission and discharge for all 111 patients (see Table 4).

Table 4. Biochemical Parameters at Admission and Discharge and Diuretic Treatment at admission and during hospitalization.

Baseline	Total (111 Patients)	Group 1 (81 Patients)	Group 2 (30 Patients)	<i>p</i> -Value	Total 111 Patients	Group 1 (81 Patients)	Group 2 (30 Patients)	<i>p</i> -Value
Time	Admission				Discharge			
Biochemical								
Hb (g/dL), mean	12 ± 2.66	12.3 ± 2.68	11.75 ± 2.63	0.90	12.7 ± 2.4	13.4 ±2.34	11.2 ± 2.74	0.33
Ht (%)	37.4 ± 7.7	37.34 ± 7.62	37.8 ± 7.82	0.92	39.1 ± 7.02	40.6 ± 6.79	34.5 ± 9.01	0.33
Creatinine (mg/dL), mean	1.16 ± 0.65	1.08 ± 0.49	1.34 ± 0.57	0.048	1.19 ± 0.43	1.13 ± 0.49	1.32 ± 0.61	0.00418
eGFR, (1.73 mL/min/mp), median	54.50 (41–71)	56 (43–73)	51 (31–61)	0.89	58.89 (44–73)	59.67 (45–74)	55.86 (40–64)	0.86
WRF (%)					42.34	39.51	50	0.27
Serum urea (mg/dL)	56 ± 38.5	54 ± 30	73 ± 55	0.0051	59 ± 37.1	54 ± 34.4	88 ± 53	0.09
K (mmol/L)	4.5 ± 0.56	4.45 ± 0.54	4.72 ± 0.61	0.57	4.17 ± 0.55	4.3 ± 0.56	3.89 ± 0.54	0.66
Na (mmol/L)	139 ± 3.80	139 ± 3.56	139 ± 4.11	0.37	138 ± 13.1	138 ± 16.61	137 ±3.48	0.60
NT-proBNP (pg/dL), median	4060 (1865–7085)	3626 (2456–6254)	4855.5 (1203–14,243)	0.005	1561.5 (1013–2921)	1454 (1002–2741)	1899 (1120–5242)	0.01
Diuretic dose at admission and at discharge								
Furosemide (mg/day), median (IQR)	20 (0–40)	20 (0–35)	20 (0–40)	0.06	60 (40–80)	60 (40–80)	100 (40–120)	0.03
Diuretic dose during hospitalization								
Furosemide (mg/day), median (IQR)	85 (60–110)	75 (50–90)	95 (70–120)	0.03				

Hb—hemoglobin; Ht—hematocrit; eGFR—estimated glomerular filtration rate; WRF—worsening renal function; K—potassium; Na—sodium.

Regarding Hb levels, the mean at admission for the entire cohort was $12 \pm 2.66 \text{ g/dL}$. In Group 1, the mean Hb level was slightly higher at $12.3 \pm 2.68 \text{ g/dL}$, while Group 2 presented a lower mean of $11.75 \pm 2.63 \text{ g/dL}$, with no statistically significant difference observed ($p = 0.90$). At discharge, the overall mean Hb level increased to $12.7 \pm 2.4 \text{ g/dL}$.

Group 1 exhibited a further increase to 13.4 ± 2.34 g/dL, whereas Group 2's mean Hb level decreased to 11.2 ± 2.74 g/dL, again showing no significant difference ($p = 0.33$).

In terms of Ht, the mean at admission for the total population was recorded at $37.4 \pm 7.7\%$. Group 1 had a mean Ht of $37.34 \pm 7.62\%$, while Group 2 reported a mean of $37.8 \pm 7.82\%$, indicating no significant difference ($p = 0.92$). At discharge, the overall mean Ht increased to $39.1 \pm 7.02\%$. Group 1's mean was higher at $40.6 \pm 6.79\%$, while Group 2's mean Ht decreased to $34.5 \pm 9.01\%$, with no statistically significant difference between the groups ($p = 0.33$).

The median furosemide dose at admission was 20 mg/day (IQR 0–40 mg/day) for both groups, with no significant difference between them ($p = 0.06$). At discharge, the median dose increased to 60 mg/day (IQR 40–80 mg/day) for both groups, with Group 2 receiving a higher dose ($p = 0.03$).

The median total furosemide dose during hospitalization was 85 mg/day (IQR 60–110 mg/day) across both groups, with a lower dose in Group 1 [75 mg/day (IQR 50–90 mg/day)] compared to Group 2 [95 mg/day (IQR 70–120 mg/day)].

3.4. Δ ePVS and Renal Function

At admission, the mean creatinine level was significantly different between the groups, with an overall level of 1.16 ± 0.65 mg/dL. Group 1 had a mean creatinine level of 1.08 ± 0.49 mg/dL, while Group 2 reported a higher mean of 1.34 ± 0.57 mg/dL ($p = 0.048$). By discharge, the overall mean creatinine level decreased to 1.19 ± 0.43 mg/dL, with Group 1 showing a level of 1.13 ± 0.49 mg/dL and Group 2 at 1.32 ± 0.61 mg/dL ($p = 0.00418$).

Patients in Group 2, with worsening renal function in contrast to Group 1 without WRF, had a significantly higher risk of in-hospital mortality (OR 1.66, 95% CI 1.10–2.51, $p = 0.02$) and six-month mortality (OR 1.87, 95% CI 1.16–3.01, $p < 0.01$). However, they did not significantly predict the risk of rehospitalization (OR 1.28, 95% CI 0.76–2.15, $p = 0.28$).

The mean serum urea level at admission was significantly higher in Group 2, with a value of 73 ± 55 mg/dL compared to 54 ± 30 mg/dL in Group 1 ($p = 0.0051$). At discharge, the overall mean serum urea level was 59 ± 37.1 mg/dL, with Group 1 at 54 ± 34.4 mg/dL and Group 2 at 88 ± 53 mg/dL; however, this difference was not statistically significant ($p = 0.09$).

Regarding K levels, the mean at admission was 4.5 ± 0.56 mmol/L overall, with Group 1 at 4.45 ± 0.54 mmol/L and Group 2 at 4.72 ± 0.61 mmol/L ($p = 0.57$). By discharge, the overall K levels were 4.17 ± 0.55 mmol/L, with Group 1 showing 4.3 ± 0.56 mmol/L and Group 2 demonstrating lower levels at 3.89 ± 0.54 mmol/L ($p = 0.66$).

Sodium levels remained similar between the groups, with an overall mean of 139 ± 3.80 mmol/L at admission; Group 1 had a mean of 139 ± 3.56 mmol/L, while Group 2 had 139 ± 4.11 mmol/L ($p = 0.37$). At discharge, Na levels were recorded as 138 ± 13.1 mmol/L overall, with Group 1 at 138 ± 16.61 mmol/L and Group 2 at 137 ± 3.48 mmol/L ($p = 0.60$).

3.5. Δ ePVS and NT-proBNP

The median NT-proBNP level at admission was 4060 pg/dL overall, with Group 1 showing a median of 3626 pg/dL and Group 2 showing 4855.5 pg/dL, a statistically significant difference ($p = 0.005$). At discharge, the overall median NT-proBNP level decreased to 1561.5 pg/dL, with Group 1 at 1454 pg/dL and Group 2 at 1899 pg/dL ($p = 0.01$).

The association between Δ ePVS and NT-proBNP indicated a nearly threefold increased risk (OR 2.96, 95% CI 1.61–5.43, $p < 0.008$), suggesting a significant correlation.

Figure 2 illustrates the relationship between Δ ePVS and the proportion of patients who achieved a reduction in NT-proBNP $\geq 30\%$ or more. Patients in Group 1 had a significantly higher likelihood of achieving this reduction (88.9%) compared to those in Group 2, where only 11.1% showed similar results.

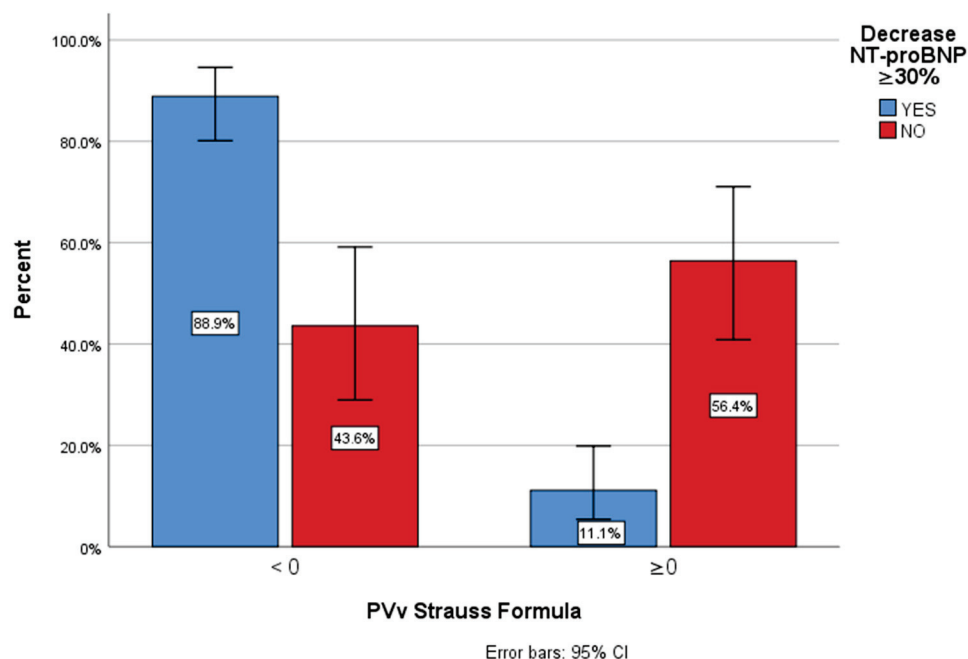


Figure 2. Correlation Between Δ ePVS and NT-proBNP reduction at discharge ($\geq 30\%$).

The ROC curve analysis, evaluating the relationship between NT-proBNP reduction and Δ ePVS, demonstrated a moderate predictive value with an AUC of 0.682 (95% CI 0.533–0.830, $p = 0.008$) (Figure 3).

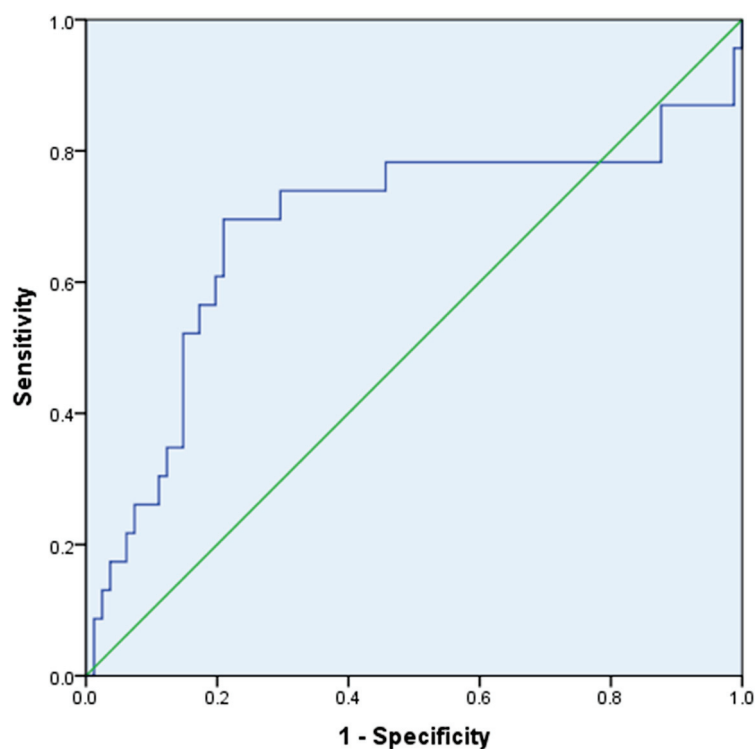


Figure 3. ROC Curve Analysis of NT-proBNP Reduction and Δ ePVS Predictive Value (AUC 0.682, $p = 0.008$).

The multivariate analysis was conducted using multivariate logistic regression model. The independent variables included in the model were LVEF, IVC diameter at discharge, sPAP at discharge, E/e' ratio at discharge, and Δ ePVS. The variables were selected based on their potential association with NT-proBNP reduction. The reduction in NT-proBNP of >30% (used in dichotomous form) at discharge was used as the reference point for assessing decongestion and served as the dependent variable in the regression analysis. The analysis identified Δ ePVS as the only significant predictor of NT-proBNP reduction at discharge (OR 0.11, 95% CI 0.04–0.33, $p < 0.001$).

3.6. Δ ePVS and Clinical Outcomes

The absence of Δ ePVS was linked to a higher risk of in-hospital mortality (OR 1.30, 95% CI 1.07–1.58, $p < 0.01$) and six-month mortality (OR 1.30, 95% CI 1.02–1.66, $p = 0.04$). However, it did not show statistical significance in predicting rehospitalization (OR 1.25, 95% CI 0.82–1.93, $p = 0.25$). During hospitalization, five patients in Group 2 died. At the six-month follow-up, the rehospitalization rate was 35% in Group 2 (10 patients) and 21% in Group 1 (17 patients) ($p = 0.04$). Mortality rates at six months were 37% in Group 2 (11 patients) and 11% in Group 1 (8 patients) ($p = 0.012$).

4. Discussion

It has been proposed that changes in easily accessible parameters, such as Hb and Ht, could serve as surrogates for effective decongestion, aiding in the assessment of therapeutic efficacy in patients with ADHF. This was supported by several large retrospective post hoc studies that demonstrated an association between hemoconcentration (indicated by increased Hb concentrations or Ht levels) and improved clinical outcomes in hospitalized ADHF patients [11].

We analyzed 111 patients with ADHF and, using the Strauss formula, divided them based on Δ ePVS. Subsequently, we assessed clinical, biochemical, and echocardiographic parameters.

Patients in Group 2, who had worse decongestion outcomes, presented with poorer clinical status upon admission compared to Group 1. Specifically, although the weight at admission showed no significant differences between groups, Group 2 had a higher prevalence of lower-limb edema and jugular vein distension, which are indicative of more severe congestion. These clinical findings may reflect the greater diuretic requirement observed in Group 2.

In our study, a borderline statistically significant difference in weight loss was observed between the groups, with Group 1 showing a median weight difference of 2 kg (IQR: 1–3) compared to 1 kg (IQR: 0–2) in Group 2 ($p = 0.046$). This result highlights the limitations of weight changes as a surrogate for decongestion. While weight loss may reflect clinical decongestion, it does not reliably indicate changes in intravascular volume or predict better ADHF outcomes. Patient-to-patient variability in volume status at admission and discharge further complicates its interpretation [18].

No statistically significant differences were identified between the groups regarding age, sex, BMI, BP, HR, or smoking status. There were also no statistically significant differences in comorbidities between the two groups. Group 2 patients received significantly fewer MRAs at admission, and this difference is likely attributable to the more severe renal dysfunction present at admission in this group.

There were also no significant differences regarding SGLT-2 inhibitors between the two groups despite the evidence suggesting that treatment with SGLT-2 inhibitors leads to a 7.3% reduction in measured plasma volume from baseline, with consistent increases

in Ht and Hb levels [19]. This effect is likely more relevant in patients with chronic heart failure rather than acute cases.

Among the clinical parameters for assessing congestion, no statistically significant differences were observed between the two groups, suggesting that the clinical congestion was similar. Regarding echocardiographic data, no statistically significant differences in LVEF were found between the groups. Previous studies have shown that congestion levels are similar regardless of LVEF category [20].

Regarding renal function, Group 2 exhibited higher baseline creatinine levels (1.34 ± 0.57 mg/dL vs. 1.08 ± 0.49 mg/dL in Group 1), likely due to more severe comorbidities such as diabetes and hypertension. These conditions are associated with an increased risk of diuretic resistance, which contributes to poorer outcomes in acute decompensated heart failure.

The analysis of renal function demonstrated that Group 2 patients with WRF had significantly higher in-hospital mortality and six-month mortality compared to Group 1 patients with WRF. These results support prior findings indicating that hemoconcentration, although associated with WRF, does not adversely affect prognosis [21–23]. On the other hand, WRF occurring without hemoconcentration, particularly in the presence of persistent congestion, is associated with significantly poorer outcomes [24,25].

In this study, the significant difference in NT-proBNP levels between Group 1 and Group 2 at admission and discharge highlights the potential role of this biomarker in distinguishing different patient risk profiles. The findings align with the previous work, which similarly identified elevated NT-proBNP levels as a marker for worse prognosis in heart failure patients [15]. The higher baseline and discharge levels in Group 2 suggest a more severe disease state and potentially poorer response to treatment, as reflected by the lower proportion of patients achieving a $\geq 30\%$ NT-proBNP reduction.

The correlation between plasma Δ PVS and NT-proBNP reduction supports the hypothesis that effective decongestion is a key factor in improving patient outcomes. The nearly threefold increased risk associated with Δ PVS indicates that this parameter could be a valuable addition to the clinical assessment of ADHF patients, particularly in settings where biomarkers like NT-proBNP are not routinely available due to cost constraints.

The ROC curve analysis further reinforces the moderate predictive value of Δ PVS for NT-proBNP reduction. Its value lies in complementing other biomarkers and clinical assessments. It provides a simple, dynamic measure of intravascular volume changes, aiding in evaluating decongestion therapy, especially in resource-limited settings. This indicator is best utilized as part of a multimodal approach, integrating clinical and biochemical parameters to enhance patient management.

In this study, multivariate regression analysis identified Δ PVS as the sole significant predictor of NT-proBNP decrease. This emphasizes the importance of monitoring and managing plasma volume, especially since it can be derived from routine blood tests without incurring additional costs. This aspect becomes increasingly relevant in healthcare systems facing resource limitations, as highlighted by the literature [26,27].

In conclusion, while NT-proBNP remains a valuable biomarker for assessing prognosis and guiding therapy in ADHF patients, Δ PVS offers a cost-effective alternative for evaluating decongestion and predicting outcomes. Further studies are needed to validate these findings and explore the integration of plasma volume assessment into standard clinical practice for ADHF management.

Our study demonstrated that the absence of Δ PVS was significantly associated with an increased risk of both in-hospital mortality and six-month mortality. However, it did not show a statistically significant correlation with the risk of rehospitalization (OR 1.25, 95% CI 0.82–1.93, $p = 0.25$). These findings are consistent with the previous

literature. For instance, a study involving 712 patients with ADHF observed that an increase in Strauss-derived estimated plasma volume at discharge was associated with a worse prognosis [28]. Similarly, changes in Δ ePVS have been identified as prognostic indicators for death, ADHF hospitalization, and all-cause mortality in patients with ADHF, as shown in an observational cohort study [9]. Additional evidence from a post hoc analysis of the EVEREST study highlighted that hemoconcentration correlated with improved congestion and reduced mortality in such patients [29].

The exact mechanism through which plasma volume changes influence prognosis in ADHF remains uncertain. However, some studies have challenged the use of Δ ePVS as a reliable clinical indicator. For instance, a study involving 36 patients with congestion monitored estimated and directly measured plasma volume changes, revealing that variations in Hb and Ht did not accurately correspond to the actual changes in plasma volume measured in ADHF patients [11]. These findings indicate that relying on Hb or Hct levels alone may not provide a precise assessment of intravascular volume status in patients with ADHF.

To date, the exact mechanism through which changes in plasma volume impact prognosis remains unclear [30,31].

5. Limitations

Our study has several limitations that should be acknowledged. First, it was a prospective observational cohort study conducted at a single center. The sample size was relatively small, and we included only patients whose primary diagnosis was ADHF, excluding those with ADHF secondary to other conditions. This limits the applicability of Δ ePVS to a broader population of ADHF patients. Furthermore, we were unable to directly measure plasma volume for comparison, relying instead on estimates.

A limitation of our study is the lack of direct quantification of the volume removed at the second plasma volume measurement. While Δ ePVS reflects changes in plasma volume, measuring the removed volume could provide further insights into decongestion dynamics.

Lastly, the unequal distribution of patients between the groups may have impacted the results and limited the strength of the conclusions drawn.

While targeting Δ ePVS $< 0\%$ may guide therapy, it should not be an absolute goal for all patients. This metric is best used alongside clinical assessment to individualize treatment and optimize outcomes.

6. Conclusions

Indirectly Δ ePVS is a cost-effective and accessible parameter for evaluating of decongestive treatment in ADHF patients. Unlike natriuretic peptides, Δ ePVS can be derived from routine blood tests, making it an affordable tool that could be integrated into clinical practice.

Our study suggests that Δ ePVS may predict mortality in ADHF patients post discharge. The simplicity and low cost of this parameter make it a promising tool for risk stratification and targeted treatment. However, further research is necessary to validate its utility in larger and more diverse cohorts of heart failure patients.

Author Contributions: Conceptualization, M.G., A.-M.I., E.B. and A.-M.G.; methodology, M.G., A.-M.B., G.U. and A.-M.G.; software, M.G. and A.-M.G.; validation, A.-M.I. and E.B.; formal analysis, M.G., I.V., G.U. and A.-M.G.; investigation M.G. and A.-M.G.; resources, M.G. and A.-M.G.; data curation, M.G. and A.-M.G.; writing—original draft preparation, M.G. and A.-M.G.; writing—review and editing, M.G. and A.-M.G.; visualization, M.G., C.N. and A.-M.G.; supervision, A.-M.I. and E.B.; project administration, M.G. and A.-M.G.; funding acquisition, A.-M.I. and E.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by Prof. Dr. Th. Burgehele Clinical Hospital's ethics committee (9115/26 September 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study; on admission, all subjects agreed to have their anonymized data available for research purposes.

Data Availability Statement: Data used in this study may be provided by the authors upon reasonable request.

Acknowledgments: Publication of this paper was supported by the Carol Davila University of Medicine and Pharmacy, through the institutional program Publish not Perish.

Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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Article

The Usefulness of Soluble ST2 Concentration in Heart Failure with Reduced Ejection Fraction to Predict Severe Impairment in Exercise Capacity Assessed in Cardiopulmonary Exercise Testing

Magdalena Dudek ^{1,*}, Marta Kałużna-Oleksy ¹, Filip Sawczak ¹, Agata Kukfisz ², Aleksandra Soloch ¹, Jacek Migaj ¹, Maciej Lesiak ¹ and Ewa Straburzyńska-Migaj ¹

¹ 1st Department of Cardiology, Poznan University of Medical Sciences, 61-701 Poznań, Poland; marta.kaluzna@wp.pl (M.K.-O.); fsawczak@gmail.com (F.S.); ola.soloch@gmail.com (A.S.); jacek.migaj@gmail.com (J.M.); maciej.lesiak@usk.poznan.pl (M.L.); ewa.straburzynska-migaj@usk.poznan.pl (E.S.-M.)

² 3rd Department of Cardiology, Silesian Center for Heart Disease, Faculty of Medical University of Silesia, 41-800 Zabrze, Poland; agata.kukfisz@gmail.com

* Correspondence: magdalena.dudek@usk.poznan.pl

Abstract: Background/Objectives: Heart failure (HF) constitutes a complex clinical syndrome that is highly prevalent worldwide, comprises a serious prognosis, and results in a reduced quality of life. Exercise capacity is one of the most significant parameters involved in the prognosis in HF patients. Our objective was to evaluate the relationship between the selected cardiopulmonary exercise testing (CPET) parameters and the concentration of novel biomarker sST2 in a group of patients with heart failure with reduced ejection fraction (HFrEF). **Methods:** A group of 135 patients with HFrEF was enrolled in this prospective cohort study. Patients were in the stable phase of the disease in the prior 4 weeks and received optimal medical treatment. Clinical and biochemical parameters were investigated. All patients performed maximal CPET. **Results:** The mean (SD) concentration of sST2 was 45.5 ± 39.2 ng/mL. Based on the CPET results, the cut-off value (52.377 ng/mL) was established, optimal for the discrimination of relative peakVO₂ < 12 mL/kg/min. Patients were divided into two groups according to sST2 cut-off values determined with an ROC curve (AUC 0.692, 95% CI: 0.567–0.816). The mean relative peakVO₂ in patients with higher sST2 was 14.5 ± 4.6 mL/kg/min, while in the second group, it was 17.6 ± 5.2 ($p = 0.002$). In the sST2 ≥ 52.377 ng/mL group, 55.6% of patients achieved VO₂ < 50%. Subjects with lower sST2 values obtained higher values of PETCO₂ ($p < 0.001$) and higher values of pulse O₂ ($p = 0.01$). VE/VCO₂slope ($p = 0.002$) was higher in patients with increased sST2 concentration. **Conclusions:** The concentration of sST2 protein is substantially associated with the clinical severity of heart failure with reduced left ventricular ejection fraction assessed by functional capacity through CPET.

Keywords: ST2; sST2; biomarker; cardiopulmonary exercise testing; CPET; heart failure; heart failure with reduced ejection fraction; HFrEF

1. Introduction

Heart failure (HF) represents a complex clinical syndrome that is highly prevalent worldwide [1]. The hallmark of chronic heart failure (CHF) is exercise intolerance, i.e., an impaired ability to perform physical activity with accompanying symptoms of significant shortness of breath and fatigue, which is associated with a reduced quality of life and increased mortality [2]. The pathophysiological mechanisms underlying exercise intolerance

in HF are complex and include the impairment of cardiac and pulmonary reserves, as well as a reduced peripheral and respiratory perfusion of skeletal muscles.

Exercise capacity constitutes one of the most vital parameters related to prognosis in HF patients. Peak oxygen uptake (VO_2), measured during maximal progressive physical exertion with the use of cardiopulmonary exercise testing (CPET), is the gold standard for determining exercise capacity in patients with HF [3] and therapy modifications [4]. CPET is a non-invasive, objective simultaneous measurement of cardiovascular and respiratory function during exercise, performed to assess exercise capacity in healthy subjects, as well as in patients with CHF. Multiple CPET parameters are predictors of mortality in HF patients, although several studies indicate that peak VO_2 is the most crucial variable [5,6]. VO_2max may be expressed as absolute values (L/min) and relative to total body mass values (mL/kg/min) [7]. Furthermore, other CPET test parameters have become increasingly emphasized, such as the value of the increased exercise ventilation index (VE/VCO_2 slope), end-expiratory carbon dioxide pressure (PETCO_2) or oxygen pulse. These, in turn, correlate with the prognosis in this group of patients, according to a number of data derived from the analysis of respiratory gases and hemodynamic measurements performed during exercise [6,8]. In terms of evaluating patients with heart failure, a comprehensive assessment of patients using CPET in combination with new biomarkers has recently been greatly highlighted.

According to the 2021 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HF, relative peak $\text{VO}_2 \leq 12 \text{ mL/kg/min}$ defines a severe impairment of exercise capacity with an inability to exercise and represents one of the criteria for diagnosing advanced heart failure [2]. Patients who reached relative peak $\text{VO}_2 \leq 12 \text{ mL/kg/min}$ during CPET should be considered for qualification for heart transplantation [5].

The ST2 (suppression of tumorigenicity 2) protein has been increasingly explored as a potential biomarker in cardiovascular disease. ST2 is involved in the immune response and is secreted in response to the mechanical overload of the myocardium, thus providing information on myocardial remodeling and fibrotic processes [9,10]. Moreover, the IL-33/ST2L system is involved in cardioprotection, preventing fibrosis, hypertrophy and the apoptosis of cardiomyocytes, and it inhibits the inflammatory response [11]. It is of note that the association between sST2 and mortality rates has been confirmed in patients with heart failure with reduced ejection fraction (HFrEF) [10,12,13]. There are single reports available concerning the sST2 biomarker and the evaluation of physical capacity using CPET. Some studies have demonstrated a significant correlation between sST2 protein levels and CPET parameters, such as $\text{VO}_2 \text{ max}$ [14,15]. Nevertheless, studies evaluating the relationship between sST2 and CPET parameters in HF patients are scarce.

The objective of this study was to assess the relationship between the selected CPET parameters and sST2 concentration in a group of patients with HFrEF.

2. Materials and Methods

2.1. Study Population

In this cross-sectional study, patients with heart failure with reduced ejection fraction (HFrEF) who were hospitalized for the evaluation of heart failure in the cardiology department were enrolled. The inclusion criteria were as follows: left ventricular ejection fraction (LVEF) $\leq 40\%$, age ≥ 18 years, stable disease state (no hospitalization due to exacerbation/decompensation or need for intravenous diuretics for HF in the previous 4 weeks), and optimal pharmacological treatment according to the European Society of Cardiology guidelines for heart failure [2]. The exclusion criteria were heart failure caused by a primary valvular defect, hypertrophic cardiomyopathy, end-stage chronic kidney disease requiring

dialysis therapy, inflammatory diseases, severe chronic obstructive pulmonary disease (GOLD 4), and intellectual impairment making cooperation impossible. Additionally, the participants were required to sign the informed consent form. This study was conducted according to the Declaration of Helsinki guidelines and approved by the local Bioethics Committee (approval number 378/19).

2.2. Analyzed Parameters

The collected data included age, gender, comorbidities, etiology of HF, New York Heart Association (NYHA) functional class, prescribed medications, echocardiography assessment and CPET results. We analyzed complete blood count and other laboratory parameters, i.e., sST2, natriuretic peptides, creatinine, aspartate, electrolytes (sodium, potassium), creatinine and high-sensitivity C-reactive protein (hsCRP).

The sST2 concentration from the peripheral blood was performed using the ELISA method using the Presage[®] ST2 Assay (Critical Diagnostics, San Diego, CA, USA) [16]. CPET was conducted using the Vmax29 Sensor Medics measurement module. Patients performed a symptom-limited maximal exercise test on a treadmill, either according to the RAMP protocol (load increment with a change in treadmill incline and speed was 0.5 MET/min), or according to the Bruce protocol modified for HF (an introductory step of 3 min with a treadmill speed of 1.7 km/h and an incline of 5% was added to the standard Bruce protocol). The left ventricular ejection fraction was calculated using the echocardiographic Simpson's method in accordance with the European Society of Cardiology guidelines [17].

2.3. Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation or median (25th percentile of the data—75th percentile of the data), depending on the presence of a normal distribution. Categorical variables are presented as numbers of subjects and corresponding percentages in parentheses. Normal distribution was tested with the Kolmogorov–Smirnov test. Patients were divided according to the optimal cut-off value of sST2 for the prediction of relative peak VO_2 below 12 mL/kg/min. The Student's *t*-test, Mann–Whitney U-test, and χ^2 test (with Yates correction if necessary) were performed where appropriate. Spearman's non-parametric correlations were used to assess the association of sST2 with CPET findings. A Receiver Operator Characteristic (ROC) curve analysis of sST2 was employed to select the optimal cut-off value for the prediction of the relative peak VO_2 below 12 mL/kg/min with the Youden method. A *p*-value of <0.05 was considered significant. All statistical analyses were conducted using STATISTICA 13.3 Tibco Software Inc., Palo Alto, CA, USA.

3. Results

The study involved 135 patients, among whom 91.9% were men. The mean (SD) age was 53.2 ± 10.9 years, and the mean (SD) BMI was 28.5 ± 4.8 kg/m². The most common comorbidities included arterial hypertension (48.2%), atrial fibrillation (AF) (37.8%), diabetes mellitus (28.2%) and chronic kidney disease (14.8%). The mean LVEF was $23.7 \pm 8.1\%$. In the studied group, 67 patients presented with NYHA class III and ambulatory IV (49.6%). Most of the patients were administered the optimal HFrEF treatment at the time they entered the study.

All patients who were enrolled in the study performed symptom-limited CPET, and sST2 concentration was measured in all patients. The mean (SD) concentration of sST2 was 45.5 ± 39.2 ng/mL. For the value of relative peak VO_2 below 12 mL/kg/min sST2 concentration (70.7 ± 57.4 vs. 40.6 ± 32.7 ng/mL, $p < 0.001$) was significantly higher

(Figure 1). Based on the CPET results, the sST2 cut-off value (52.377 ng/mL) optimal for the discrimination of relative peak $\text{VO}_2 < 12 \text{ mL/kg/min}$ was established. Patients were divided into two groups according to the sST2 cut-off value determined with the ROC curve (AUC 0.692, 95% CI: 0.567–0.816) (Figure 2).

Patients in the group with sST2 concentration $\geq 52.377 \text{ ng/mL}$ showed lower LVEF, a higher heart rate (HR) on discharge ($p = 0.002$), and more frequently AF ($p = 0.01$). Moreover, patients with a higher sST2 demonstrated more advanced symptoms of heart failure assessed in NYHA class (NYHA III or ambulatory IV class) (69.4% vs. 42.4%, $p = 0.005$ respectively). There was no significant difference in the HF etiology between the groups. Significantly higher levels of brain natriuretic peptide (BNP) ($p < 0.001$) and N-terminal pro-brain natriuretic peptide (NT-proBNP) ($p < 0.001$) were observed in patients with higher sST2. In addition, in this group, the serum albumin ($p = 0.013$) and sodium concentration were significantly lower ($p = 0.005$), and uric acid concentration was significantly higher ($p = 0.04$) (Table 1).

When dividing patients according to the sST2 level, we found a significantly lower forced vital capacity ($p = 0.012$) and a lower forced expiratory volume in the first second ($p = 0.034$) in patients with an sST2 concentration $\geq 52.377 \text{ ng/mL}$. The mean peak oxygen consumption in the group of patients with higher sST2 was $14.5 \pm 4.6 \text{ mL/kg/min}$, while in the other group it was 17.6 ± 5.2 ($p = 0.002$). In the sST2 $\geq 52.377 \text{ ng/mL}$ group, 55% of patients achieved a VO_2 below 50% of the age- and sex-specific reference value, whereas in the other group, it was equal to 35.4% ($p = 0.035$).

Furthermore, other parameters of CPET differed significantly between the two groups. Patients with lower sST2 protein values obtained higher values of PETCO_2 ($p < 0.001$), and lower values of oxygen pulse were found in the same group ($p = 0.011$). Differences were also demonstrated in the VE/VCO_2 slope ($p = 0.002$), which was significantly higher in subjects with higher sST2 concentration. The participants with lower levels of sST2 presented higher maximum systolic blood pressure ($p = 0.017$) and diastolic blood pressure ($p = 0.04$) during CPET (Table 2).

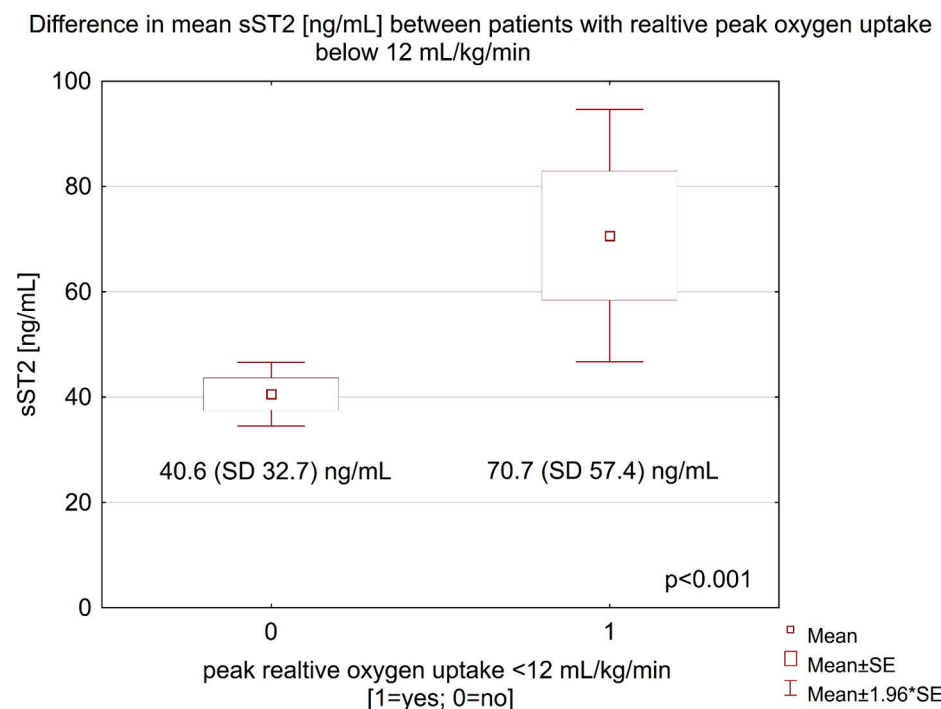


Figure 1. Difference in mean sST2 between patients with relative peak $\text{VO}_2 < 12 \text{ mL/kg/min}$.

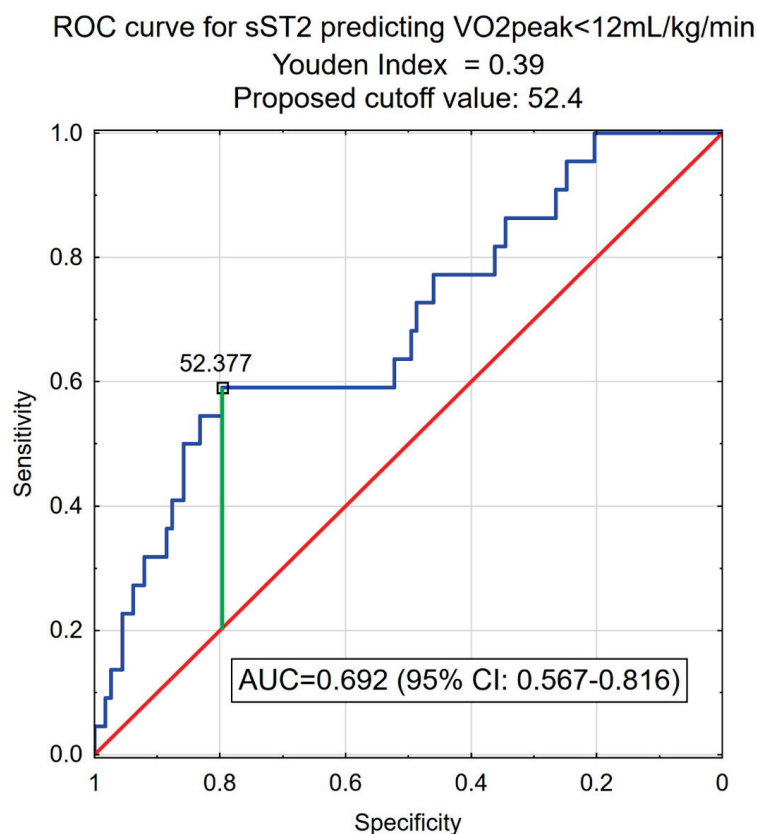


Figure 2. ROC curve for soluble ST2 predicting relative peak $\text{VO}_2 < 12 \text{ mL/kg/min}$. Abbreviations: ST2, suppression of tumorigenicity 2; peak VO_2 , peak oxygen uptake.

Table 1. Baseline characteristics of the studied group. Comparison of the baseline characteristic parameters in two groups according to the sST2 cut-off value (52.377 ng/mL), optimal for the discrimination of relative peak $\text{VO}_2 < 12 \text{ mL/kg/min}$.

Characteristics	All (N = 135) ^a	sST2 < 52.377 ng/mL (N = 99) ^a	sST2 $\geq$ 52.377 ng/mL (N = 36) ^a	<i>p</i> Value
Age, years	53.2 (10.9)	53.4 (10.8)	52.7 (11.3)	0.72
Females	11 (8.1%)	7 (7.1%)	4 (11.1%)	0.69
IHD etiology	68 (50.4%)	50 (50.5%)	18 (50.0%)	0.96
BMI, kg/m^2	28.5 (4.8)	28.7 (4.4)	28.0 (6.0)	0.45
LVEF, %	20.0 (20.0–30.0)	25.0 (20.0–30.0)	20.0 (15.0–25.0)	0.02
Comorbidities				
DM	38 (28.2%)	26 (26.3%)	12 (33.3%)	0.42
COPD	18 (13.3%)	13 (13.1%)	5 (13.9%)	0.86
CKD	20 (14.8%)	12 (12.1%)	8 (22.2%)	0.24
HA	65 (48.2%)	50 (50.5%)	15 (41.7%)	0.36
AF	51 (37.8%)	31 (31.3%)	20 (55.6%)	0.01
NYHA class				
I	4 (3.0%)	4 (4.0%)	0 (0%)	0.52
II	64 (47.4%)	53 (53.5%)	11 (30.6%)	0.02
NYHA class III or IV	67 (49.6%)	42 (42.4%)	25 (69.4%)	0.005

Table 1. Cont.

Characteristics	All (N = 135) ^a	sST2 < 52.377 ng/mL (N = 99) ^a	sST2 ≥ 52.377 ng/mL (N = 36) ^a	p Value
Biochemical parameters				
Hgb, mmol/L	9.06 (0.88)	9.06 (0.75)	9.06 (1.17)	0.43
RBC, ×10 ¹² /L	4.79 (0.51)	4.74 (0.42)	4.93 (0.69)	0.38
BNP, pg/mL	263.7 (109.8–468.0)	203.4 (86.3–367.9)	498.2 (385.5–839.9)	<0.001
NT-proBNP, pg/mL	1466 (492–2526)	921 (403–1798)	2923 (1912–5319)	<0.001
Uric acid, μmol/L	436.5 (117.7)	419.2 (96.1)	485.4 (155.8)	0.04
Creatinine, μmol/L	103.0 (26.2)	100.0 (25.6)	111.3 (26.4)	0.03
eGFR MDRD, mL/min/1.73 m ²	74.3 (22.9)	77.0 (23.4)	66.7 (20.0)	0.02
Serum protein, g/L	73.0 (8.4)	73.4 (9.1)	72.2 (6.3)	0.48
Serum albumin, g/L	41.0 (3.4)	41.5 (3.3)	39.8 (3.5)	0.01
TSH, mIU/L	1.51 (0.84–2.46)	1.51 (0.83–2.41)	1.65 (0.87–2.81)	0.15
Na ⁺ , mmol/L	140 (138–141)	140 (138–141)	138 (136–141)	0.00453
hsCRP, mg/L	2.27 (1.00–4.38)	1.80 (0.90–3.74)	5.05 (2.72–10.5)	<0.001
Fasting glucose, mmol/L	5.97 (5.36–6.57)	5.88 (5.36–6.57)	6.05 (5.38–6.67)	0.70
Medications				
Loop diuretics, %	123 (91.1%)	87 (87.9%)	36 (100%)	0.06
β-blockers, %	133 (98.5%)	98 (99.0%)	35 (97.2%)	0.96
ACEI/ARB, %	110 (81.5%)	83 (83.8%)	27 (75.0%)	0.24
ARNI, %	18 (13.3%)	13 (13.1%)	5 (13.9%)	0.86
MRA, %	120 (88.9%)	86 (86.9%)	34 (94.4%)	0.35

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation (paroxysmal, permanent or persistent); ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; eGFR MDRD, glomerular filtration rate estimated by the Modification of Diet in Renal Disease (MDRD); HA, arterial hypertension; Hgb, hemoglobin; hsCRP, high-sensitivity C-reactive protein; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association Classification; RBC, red blood count; TSH, thyroid-stimulating hormone. ^a Data presented as XX (YY) do not follow a normal distribution (XX—mean, YY—standard deviation), whereas data presented as XX (YY–ZZ) do not follow a standard distribution (XX—median, YY—lower quartile, ZZ—higher quartile).

Table 2. Comparison of cardiopulmonary exercise testing parameters in two groups according to sST2 cut-off value (52.377 ng/mL) optimal for the discrimination of relative peak VO₂ < 12 mL/kg/min.

CPET Parameter	All (N = 135) ^a	sST2 < 52.377 ng/mL (N = 99) ^a	sST2 ≥ 52.377 ng/mL (N = 36) ^a	p Value
%VO ₂ < 50%	55 (40.7%)	35 (35.4%)	20 (55.6%)	0.04
FVC, L	3.72 (0.94)	3.84 (0.97)	3.38 (0.74)	0.01
FEV1, L	2.77 (0.78)	2.86 (0.81)	2.54 (0.64)	0.03
FEV1/FVC	74.9 (10.9)	74.7 (11.0)	75.3 (10.7)	0.77
relative peak VO ₂ , mL/kg/min	16.8 (5.2)	17.6 (5.2)	14.5 (4.6)	0.002
peak VO ₂ , L/min	1.47 (0.51)	1.55 (0.52)	1.24 (0.40)	0.001
relative peak VO ₂ < 12 mL/kg/min, %	22 (16.3%)	9 (9.1%)	13 (36.1%)	<0.001

Table 2. Cont.

CPET Parameter	All (N = 135) ^a	sST2 < 52.377 ng/mL (N = 99) ^a	sST2 ≥ 52.377 ng/mL (N = 36) ^a	p Value
%VO ₂ pred, %	53.5 (16.1)	55.8 (15.6)	47.1 (15.8)	0.005
VE/VCO ₂ slope	33.6 (8.7)	32.3 (7.2)	37.7 (11.2)	0.002
O ₂ pulse, mL/beat	13.0 (10.5–15.9)	13.4 (10.8–16.2)	11.0 (9.5–13.5)	0.01
HR max, beats/min	117.1 (24.6)	118.6 (23.7)	112.7 (26.8)	0.23
SBP at rest, mmHg	110 (100–120)	110 (100–120)	109 (100–120)	0.16
DBP at rest, mmHg	70 (60–80)	70 (60–80)	60 (60–70)	0.07
SBP max, mmHg	140 (120–152)	140 (120–160)	130 (110–140)	0.02
DBP max, mmHg	80 (70–80)	80 (80–85)	77 (70–80)	0.04
PETCO ₂ , mmHg	32.6 (6.9)	34.1 (6.4)	28.4 (6.6)	<0.001

Abbreviations: DBP, diastolic blood pressure; FEV1, forced expiratory volume in 1 s; peak VO₂, oxygen uptake at peak exercise; FVC, forced vital capacity; HR, heart rate; O₂ pulse, oxygen pulse; peak VO₂ < 12 mL/kg/min, percent of patients with oxygen uptake at peak exercise below 12 mL/kg/min; SBP, systolic blood pressure; PETCO₂, end tidal carbon dioxide partial pressure; VE/VCO₂ slope, minute ventilation-to-carbon dioxide output; VE, minute ventilation; %VO₂pred, percent predicted oxygen uptake at peak exercise; %VO₂ < 50%, percent of patients with predicted oxygen uptake at peak exercise below 50% predicted value. ^a Data presented as XX (YY) follow a normal distribution (XX—mean, YY—standard deviation), and data presented as XX (YY–ZZ) do not follow a normal distribution (XX—median, YY—lower quartile, ZZ—higher quartile).

We found significant negative correlations between sST2 and peakVO₂ ($R = -0.249$, $p = 0.004$) (Figure 3), relative and peak VO₂ ($R = -0.219$, $p = 0.011$), oxygen pulse ($R = -0.252$, $p = 0.003$), and PETCO₂ ($R = -0.305$, $p < 0.001$) (Table 3), as well as a positive correlation with the VE/VCO₂ slope ($R = 0.258$, $p = 0.004$) (Figure 4).

Table 3. Spearman nonparametric correlation of sST2 with parameters of cardiopulmonary exercise testing.

CPET Parameter Correlated with sST2	Spearman R	p
%VO ₂ < 50% [%]	0.132	0.127
relative VO ₂ peak [mL/kg/min]	−0.219	0.011
VO ₂ peak [L/min]	−0.249	0.004
relative VO ₂ peak < 12 mL/kg/min [%]	0.246	0.004
%VO ₂ pred [%]	−0.204	0.018
VE/VCO ₂ slope	0.258	0.004
VE [L]	−0.055	0.529
O ₂ pulse [mL/beat]	−0.252	0.003
HR max [beats/min]	−0.061	0.481
SBP at rest [mmHg]	−0.050	0.611
SBP max [mmHg]	−0.134	0.146
PET CO ₂ [mmHg]	−0.305	0.0003

Abbreviations: %VO₂ < 50%—percent of patients with predicted oxygen uptake at peak exercise below 50% prediction value, VO₂peak—oxygen uptake at peak exercise, VO₂peak < 12 mL/kg/min—percent of patients with oxygen uptake at peak exercise below 12 mL/kg/min, %VO₂pred—percent predicted oxygen uptake at peak exercise, VE/VCO₂ slope—minute ventilation-to-carbon dioxide output, VE—minute ventilation, O₂ pulse—oxygen pulse, HR—heart rate, SBP—systolic blood pressure, PET CO₂—end-tidal carbon dioxide partial pressure.

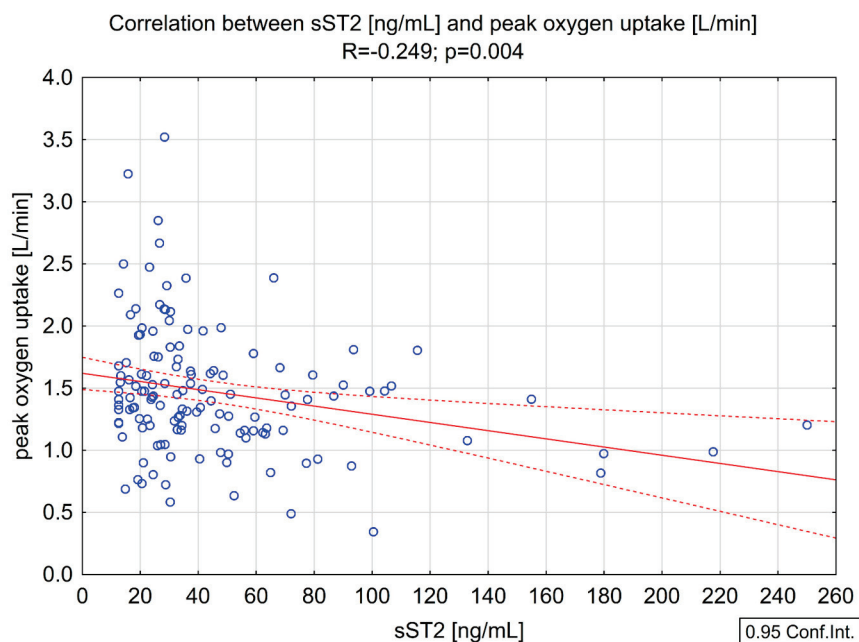


Figure 3. Correlation between sST2 and peakVO₂.

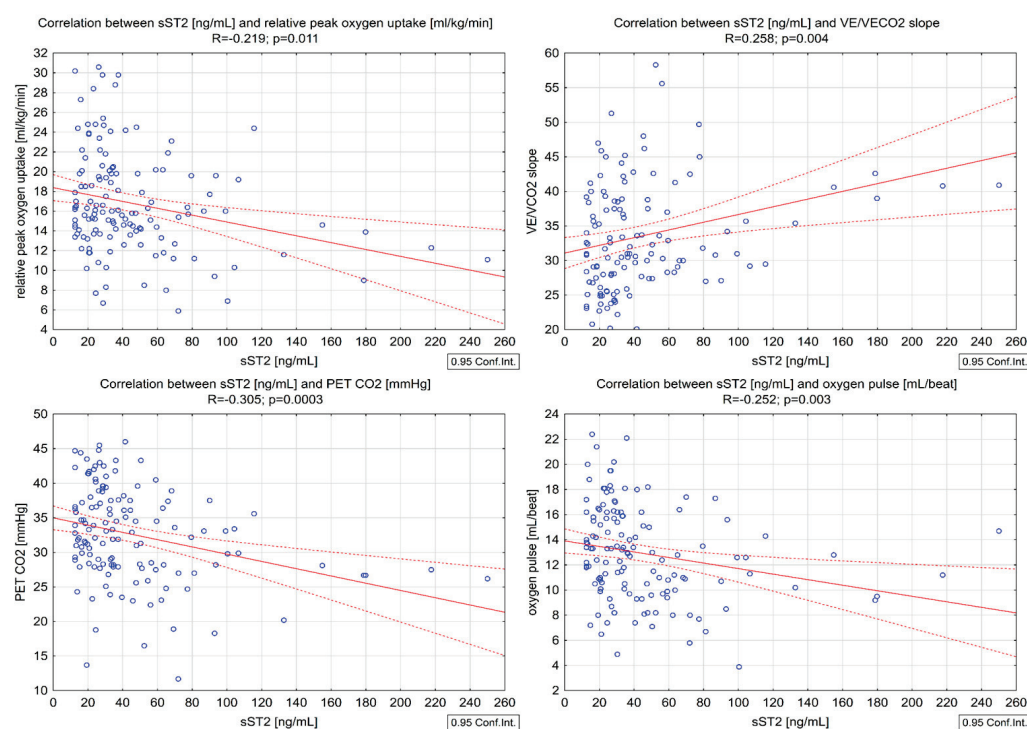


Figure 4. Correlations between sST2 and relative peakVO₂, VE/VCO₂, PETCO₂, and oxygen pulse.

4. Discussion

CPET is an essential tool used to assess the functional capacity of HF patients and in qualifying them for heart transplantation [2,5]. However, it may be difficult to access in the clinical setting, and the majority of scientific papers employ the NYHA scale to assess patients' physical performance, which may be subjective. Felker et al. [15] found a higher NYHA class in subjects with higher sST2 protein concentrations. Our study assessed the relationship between sST2 and physician-assessed functional capacity (NYHA class), and it objectively measured the maximum functional capacity in CPET. To our knowledge, there are very few prospective studies that assess the correlation between sST2 and CPET

parameters. Our study is first to propose a cut-off value for sST2 for prediction of advanced heart failure assessed with CPET.

In the presented study, sST2 was demonstrated to be significantly correlated with CPET parameters in the group of HF patients. Moreover, we also found that patients with a higher sST2 concentration showed a higher NYHA class.

In the analyzed sub-population of the HF-ACTION study [15], a significant correlation was found between the sST2 concentration and both the clinical assessment using the NYHA classification and objective measurements of functional capacity during CPET, which is consistent with our observations. In the current study, as in the study by Felker et al. [15], we found significantly lower values of peak VO_2 and higher values of VE/VCO_2 in patients with higher sST2 concentrations. Although in both studies all patients suffered from HFrEF, it is worth bearing in mind that there were several crucial differences between the study conducted by Felker et al. [15] and our study presented here. The study group in their research was significantly larger ($n = 912$) and primarily consisted of men. Moreover, the patient population of the study by Felker et al. [15] was more diverse in terms of the NYHA classification (NYHA II—63.4%, NYHA III—35.6%, NYHA IV—1%), and patients were older (median 59.2 years, IQR 51.1–68.0) than in our research. We would like to emphasize that in the HF-ACTION study, only two parameters from CPET were analyzed.

The CPET parameters analysis showed differences for forced expiratory volume in 1 s (FEV1) ($p = 0.03$) and forced vital capacity (FVC) ($p = 0.01$) between the groups divided according to sST2 levels; however, no significant difference was found in the FEV1/FVC index. These differences are likely to stem from a more advanced heart failure and the possible coexistence of a restrictive spirometry pattern (RSP) in patients with higher levels of sST2. The Jackson Heart study [18] showed that the baseline RSP was more common in patients who were subsequently hospitalized for HF. Furthermore, a high incidence of restrictive-type ventilation disorders was also observed in patients with HF, which constitutes a predictor of poor prognosis in patients eligible for heart transplant [19].

Only single reports regarding the determination of the sST2 biomarker and the assessment of physical capacity using CPET in patients with CHF are available. These studies retrospectively assessed the association between new biomarkers and exercise capacity as evaluated by CPET in patients with HFrEF and in subjects with heart failure with preserved ejection fraction [20]. They demonstrated a significant correlation between sST2 and only two parameters from CPET—peak VO_2 and VE/VCO_2 slope. Our study also found a significant correlation between sST2 and peak VO_2 ($R = -0.249$, $p = 0.004$), relative peak VO_2 ($R = -0.219$, $p = 0.011$), VE/VCO_2 slope ($R = 0.258$, $p = 0.004$), oxygen pulse ($R = -0.252$, $p = 0.003$) and PETCO_2 ($R = -0.305$, $p < 0.001$).

The relationship between the concentrations of new biomarkers and the parameters of the CPET in patients undergoing rehabilitation was studied by Billebeau et al. [14]. Their study showed higher sST2 concentrations in patients with lower peak VO_2 values. Our analysis presented here is prospective study to confirm the existence of a correlation between the sST2 level and the results of the CPET study and seems to be the first study to propose a cut-off point for sST2 values for the prediction of advanced heart failure assessed as relative peak VO_2 below 12 mL/kg/min. Moreover, we also observed significantly higher VE/VCO_2 slope values in the group with sST2 values ≥ 52.377 ng/mL. Previous studies indicated that the VE/VCO_2 slope values gradually increased with the disease progression [21]. Notably, this parameter allows for assessing the risk of cardiovascular events in patients with HF [22].

In the available sources, no data were found regarding the relationship between the sST2 protein concentration and other parameters of the spiroergometric test except for peak VO_2 or the VE/VCO_2 slope in patients with HFrEF. According to current reports, low

PETCO₂ values achieved in CPET were an independent factor correlating with a poorer prognosis of patients and a higher mortality in CHF patients [23]. In turn, our study showed that PETCO₂ ($p < 0.001$) and oxygen pulse ($p = 0.005$) were significantly lower in the group of patients with a higher concentration of the sST2 biomarker. In the research by Oliveira et al. [24], the values of oxygen pulse for predicting cardiovascular events were analyzed. Age-predicted peak O₂ pulse was demonstrated to be a strong and independent predictor of cardiac mortality and complemented peakVO₂ in risk prediction in HF patients [25].

In comparison to the abovementioned studies, our analysis showed a significant association between the recognized prognostic parameters, the unconventional parameters from the spiroergometric test and the new biomarker sST2. Therefore, it seems that the sST2 protein in combination with measures of cardiopulmonary fitness may represent a valuable tool in the long-term treatment of patients with HF.

Study Limitations

This is a single-center study involving a small patient group, which, nevertheless, was sufficient to demonstrate associations between the parameters of interest. However, the predictive power presented (AUC = 0.692) does not effectively predict CPET outcomes based on this single study, although high sST2 may help to identify patients with poor CPET outcomes. Nevertheless, this is a first step towards conducting further studies in this area on a larger group of patients. Women represented a small percentage of the study group. This was due to the inclusion of only HFrEF patients and the relatively young age of the subjects. In such groups, there is a much higher prevalence of men [26,27]. Females enrolled in high-income or upper middle-income countries in the Global Congestive Heart Failure registry were older than men [28]. Future research involving multi-center collaboration and larger, more diverse participant groups is essential to validate these findings and provide more comprehensive insights.

5. Conclusions

The concentration of the sST2 protein is significantly associated with the clinical severity of heart failure with reduced left ventricular ejection fraction and functional capacity assessed by cardiopulmonary exercise testing. Further studies including a larger number of patients are essential to confirm these data and to explore this important research topic in order to incorporate sST2 protein as a biomarker applied in the daily routine.

Author Contributions: Conceptualization, M.D. and E.S.-M.; methodology, M.D., M.K.-O. and F.S.; software, J.M., validation, M.D., M.K.-O. and F.S.; formal analysis, M.D., M.K.-O., F.S. and A.K.; investigation, M.D. and A.S.; resources, M.D.; data curation, M.D. and J.M.; writing—original draft preparation, M.D.; writing—review and editing, M.D., M.K.-O. and E.S.-M.; visualization, M.D. and A.S.; supervision, E.S.-M. and M.L.; project administration, M.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Poznan University of Medical Sciences (protocol code 378/19, date of approval 07.03.2019).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: This manuscript was developed during Clinical Scholars Research Training Program at Harvard Medical School which was facilitated by the Medical Research Agency (ABM).

Conflicts of Interest: The authors declare no conflicts of interest.

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Review

Advances in Mechanical Circulatory Support (MCS): Literature Review

Jasmine K. Dugal ^{1,*}, Arpinder S. Malhi ¹, Yuvraj Singh ², Rooz Razmi ³, Joshua Vance ⁴ and Divyansh Sharma ⁵

¹ Department of Internal Medicine, Kirk Kerkorian School of Medicine, University of Nevada Las Vegas, Las Vegas, NV 89102, USA; arpinder.malhi@unlv.edu

² Lake Erie College of Osteopathic Medicine (LECOM), Erie, PA 16509, USA; ysingh46067@med.lecom.edu

³ Michigan State University College of Osteopathic Medicine (MSUCOM), East Lansing, MI 48824, USA; razmiroo@msu.edu

⁴ A.T. Still University Kirksville College of Osteopathic Medicine, Kirksville, MO 63501, USA; joshua.vance@atsu.edu

⁵ Department of Cardiology, Kirk Kerkorian School of Medicine, University of Nevada Las Vegas, Las Vegas, NV 89102, USA; divyansh.sharma@unlv.edu

* Correspondence: jasmine.dugal@unlv.edu

Abstract: Heart failure is a heterogeneous disorder that can lead to cardiogenic shock. Mechanical circulatory support (MCS) devices can replace the cardiac function in an attempt to bridge patients to transplant or they can serve as destination therapy to improve overall patient functionality and in turn quality of life. Currently utilized MCS devices include devices such as Left Ventricular Assist Devices (LVADs), Biventricular Assist Devices (BiVADs), Impella, Total Artificial Hearts (TAHs), and extracorporeal membrane oxygenation (ECMO). This literature review examines a range of studies, case reports, and meta-analyses to present current approaches to mechanical circulatory support (MCS), along with the challenges and limitations of existing devices, common complications, and overall survival and long-term outcomes following MCS therapy.

Keywords: heart failure; cardiogenic shock; left-ventricular assist device; Bi-ventricular assist device; impella; total artificial heart; intra-aortic balloon pump; extra-corporeal membrane oxygenation; survival rates; clinical outcomes; MCS complications; bridge to transplant; destination therapy

1. Introduction

1.1. Overview of Heart Failure

Heart failure (HF) is characterized by inefficient myocardial function, impacting ventricular filling and/or ejection of systemic blood flow. As a result of the lack of blood distribution, the body's metabolic demands are not met, leading to several associated symptoms and potentially cardiogenic shock (CS). These symptoms can include, but are not limited to, chest pain, shortness of breath, swelling of the lower extremities, and in later stages, death [1]. HF can be caused by several conditions and factors, all leading to a pathologic circulatory system. HF is a condition that is ubiquitously seen throughout the world, affecting millions of individuals. Globally, HF is a leading cause of hospitalization among individuals aged 65 and older, contributing to increased morbidity and mortality rates. In 2012, HF-related healthcare expenditures in the United States were estimated at \$31 billion, accounting for over 10% of total cardiovascular disease costs. Projections indicate that these costs could increase by 127% by 2030 [2]. Experts describe HF as a global pandemic, affecting 26 million people throughout the world. As the population

ages, healthcare costs and morbidity have increased, presenting an unfortunate fate for those affected [3]. Due to the implications it has on healthcare costs, life quality, and patient life spans, HF is truly a pressing issue in regards to the general health of the entirety of humanity.

1.2. The Role of Mechanical Circulatory Support (MCS)

In modern medicine, methods of HF treatment have developed, which involve technology to aid in the patient's circulatory system. Mechanical Circulatory Support (MCS) involves the use of various devices to monitor and manage cardiac function when in need of HF treatment. These devices replace the ineffective heart's pumping mechanism to support cardiac recovery, stabilize patients awaiting definitive heart transplantation, and maintain proper circulation and symptom relief in patients who cannot maintain functional capacity. MCS technology has evolved from being a cumbersome and short-term circulatory aid to an efficient and permanent HF treatment. As a result of these developments, certain MCS devices now have the potential to perform as long-term alternatives for patients unsuitable for transplantation, having significantly increased clinical indications from what was previously only a temporary form of bridging treatment. MCS technology is now a crucial component of all-encompassing HF care, greatly enhancing clinical results, patient survival, and quality of life.

1.3. Objectives of the Paper

Advancements to MCS in the present have had a net positive effect on the outcomes of patients who suffer from HF. Not only are HF patients who do not qualify for transplantation living longer, but they are also living with a higher quality of life. These positive effects can be attributed to the miniaturization of devices such as Left Ventricular Assist Devices (LVADs), Biventricular Assist Devices (BiVADs), and Total Artificial Hearts (TAHs). Technological innovation results in smaller, more portable MCS systems that allow greater patient mobility and compatibility [4]. Furthermore, through the use of modern materials, the biocompatibility of patients to MCS devices has increased, reducing the risk of complications such as thrombosis and device failures [5]. The future of MCS is set to improve the technology that has been developed via further miniaturization, changes in device design and uses, and the integration of remote monitoring of vitals and conditions. MCS technology is continuing to evolve in the present.

2. Current Approaches in Mechanical Circulatory Support

2.1. Types of MCS Devices

2.1.1. LVADs

LVADs are implanted mechanical pumps that support left ventricular (LV) function in cases of purely or predominantly left-sided HF. In these devices, the primary driver of blood flow is the ventricle, with some assistance from the LVAD. During implantation, an inflow cannula is inserted through the apex of the heart. This directs blood from the left ventricle (LV) to an electric motor, then on through a tube to the aorta. The motor is powered by a drive line connected to a small, external controller, which is, in turn, connected to an external battery. This allowed patients to receive continued hemodynamic support outside of the hospital. Previous iterations of LVADs used pulsatile motors in an attempt to mimic normal physiology; more modern devices, however, use continuous flow (CF-LVADs) with artificial pulsatility, as they tend to be more durable [6].

In patients with irreversible dysfunction with refractory symptoms of HF despite optimized medical therapy, LVADs are the best treatment option besides heart transplantation (HTx) [7]. A recent meta-analysis of patients who received LVADs shows a significant

increase in survival rates at 6, 12, and 18 months compared to other treatment options (OR 1.96) [8]. LVADs are, therefore, often used as a bridge to transplantation (BTT) for HTx. Because of their efficacy, they are sometimes also used as destination therapy (DT) [9].

Despite their benefits, LVADs have several drawbacks. While patients with this device have better survival, they are significantly more likely to be rehospitalized for complications (OR 2.98), including adverse events such as bleeding, infection, stroke, and arrhythmia [8]. Notably, LVADs often provide inadequate support for LV dysfunction due to arrhythmias, and surgical implantation can, indeed, cause arrhythmias. Likewise, while they can reduce symptoms of RH failure secondary to LH failure, LVADs are inadequate in patients with primary RH dysfunction [7].

Notable devices in use include HeartMate 3 and HeartMate II by Abbott and HeartWare HVAD by Medtronic (though HeartWare was removed from the market in 2021) [10].

2.1.2. BiVADs

BiVADs are the configuration of two ventricular assist devices (VADs) for the purpose of supporting both left and right ventricles in the setting of severe dysfunction. The BiVAD configuration is achieved by using both a temporary RVAD and LVAD or by using two LVADs [11]. BiVAD can serve as an important bridge to transplantation (BTT), but it is associated with significant mortality. Where LVADs have a 1-year survival rate of 82%, BiVADs are only 56% at 6 months [12,13]. Part of this is related to the greater iatrogenic damage associated with installing two devices rather than one.

In recent years, there has been a significant shift away from pulsatile VADs to continuous-flow VADs. However, there is currently no on-label continuous-flow RVAD available to treat chronic right heart failure (RHF) aside from Total Artificial Hearts (TAH), discussed below. All other on-label RVADs are temporary devices such as the RP Impella used in isolated RHF. This is a problem for several reasons. Firstly, up to 40% of patients who receive an LVAD subsequently develop RHF [14]. Many of these then require RVAD, which shows significantly greater mortality than when BiVAD is implanted concomitantly [15]. Secondly, the lack of therapy options has led to a variety of methods to modify LVADs for right-sided use [16]. Recent small studies of BiVAD using dual HeartMate3 implants have shown large differences in survival between centers—for instance, one study showed a survival rate of 91% at 18 months, and another showed a rate of roughly 54% [17,18]. The discrepancy may, of course, be ascribed to several confounding variables (e.g., support methods, sample size), but as there is a paucity of randomized controlled trials for BiVADs, the variety of LVAD modification techniques might very well play a part in the poor outcomes associated with BiVAD use.

2.1.3. Impella

Percutaneous MCS, such as the Impella (Abiomed, Danvers, MA, USA) microaxial pump, has been demonstrated to enhance peripheral organ perfusion, lower myocardial oxygen demand, and raise coronary perfusion. Thus, preemptive implantation during high-risk percutaneous coronary intervention (HR-PCI) and emergency use for CS (CS) are among the indications for the Impella device [19]. The Impella is a continuous-flow device that actively translocates oxygenated blood from the LV to the ascending aorta regardless of the cardiac phase and function. Current Impella devices on the market include the Impella 2.5, Impella CP, Impella 5.0 and 5.5, and the Impella RP model for right ventricle (RV) support. Of these, the Impella 2.5 and CP can be inserted percutaneously, while the 5.0 and 5.5 require surgical placement. Similar to how an intra-aortic balloon pump (IABP) is placed, the Impella 2.5 and Impella CP variants are often placed using a retrograde femoral arterial route. An arteriotomy is necessary for the implantation of the larger Impella 5.0

device. By using an end-to-end anastomotic conduit, the Impella 5.0/LD can be inserted straight into the proximal aorta. With the aid of fluoroscopic or echocardiographic guidance, each model is positioned over the aortic valve. The catheter's pigtail design encourages stability and makes it easier to pass the aortic valve. The inlet is placed in the LV, whereas the outlet is placed in the ascending aorta [20]. Although widespread, femoral access is not always feasible, such as in the case of severe peripheral artery disease (PAD), which might restrict access in the lower extremities. Alternatively, axillary access can be used in these situations. By providing LV to aorta support, ventricular load is reduced, cardiac output is improved, coronary perfusion pressure and distal flow are increased, and myocardial recovery is enhanced in CS [21,22].

2.1.4. TAH

The TAH is a mechanical support system that replaces the function of the entire heart. Unlike VADs, which assist the ventricles in their action, the TAH completely replaces the valves and ventricles. It instead has two chambers, each with two valves, that are connected to both atria and the great arteries. The first successful human TAH implantation was performed in 1967 by Christiaan Barnard, and it has been used for decades since [23]. Today, TAH is used significantly less often than LVADs, and, unlike LVADs, TAH is not used as destination therapy (DT) in the United States. However, it is still a viable BTT for patients requiring biventricular support [11]. The 1-year mortality of TAH is similar to that of BiVAD, as is the 1- and 5-year post-transplant survival rate. The device is associated with significant complications, with one study showing that 70% of patients experienced major infections, 23% experienced stroke, and 23% experienced major gastrointestinal hemorrhage while on the device [11]. Significantly, some studies have shown that patients with TAH are more likely to need post-implant hemodialysis than patients with BiVAD or LVAD, though analysis of LDH levels between patients who required no dialysis (pre- and post-implant) were not significantly different than LDH levels of those who required only post-implant dialysis [11].

Only one TAH is currently approved for use by the FDA—the Syncardia Total Artificial Heart (Syncardia Systems, Tucson, AZ, USA). A newer TAH, Aeson (Carmat, Vélizy-Villacoublay, France), is currently being studied for FDA approval.

2.1.5. IABP

The IABP has been one of the most frequently used MCS devices since its invention in the 1960s [24]. It has been used to quickly improve hemodynamic stability in patients with CS by means of counterpulsation. When used, a balloon is inserted through the femoral artery and advanced until it is just distal to the left subclavian artery. The IABP is then rapidly inflated and deflated in time with the cardiac cycle. Its inflation during diastole increases diastolic pressure and coronary artery perfusion. Its deflation during the isovolumetric contraction phase of systole decreases afterload, thereby decreasing myocardial oxygen demand and increasing cardiac output [25].

The device is used as a temporary supportive therapy for several clinical problems, including CS (CS), refractory HF, and supportive therapy after coronary artery bypass grafting (CABG) [26]. IABPs are relatively inexpensive, and in theory, they should offer great support to struggling or recently repaired hearts. Some studies have suggested as much; for one of IABPs' most common uses—hemodynamic support to a patient in CS secondary to MI—one meta-analysis showed that the use of an IABP was associated with lower hospital mortality and lower 30-day mortality compared to no preoperative IABP [26]. Such findings are in the minority, however.

The IABP-Shock II trial, for instance, was a randomized, prospective, multicenter trial that assessed 600 patients for the effects of IABP counterpulsation in the setting of CS with early revascularization. The study showed that IABP use provided no reduction in 30-day, 12-month, or 6-year mortality [27,28]. Another meta-analysis from 2021 analyzed 9 RCTs (1996 patients) comparing the efficacy of IABPs, Impella, and no MCS in the setting of CS or high-risk PCI. They found that there was no difference in 30-day mortality, but that IABP caused increased vascular complications compared to no MCS [29].

Notably, when treating patients with CS using both extracorporeal membrane oxygenation (ECMO) with IABPs, one study showed higher in-hospital survival rates than patients who were treated with ECMO alone (OR = 1.58) [30].

2.1.6. ECMO

ECMO is an MCS device that can be used in different configurations to temporarily support either pulmonary or both pulmonary and circulatory function. ECMO can be performed centrally or peripherally. In peripheral ECMO, both the right femoral artery and the right common femoral vein are cannulated. In central ECMO, the venous cannula is placed in the right atrium, and the arterial cannula is placed in the ascending aorta. ECMO directs blood out of the body and through a membrane oxygenator. The ECMO adds oxygen, removes carbon dioxide, and warms the blood as needed. An extracorporeal pump is also used for circulatory support. In veno-venous ECMO (VV-ECMO), large-bore catheters remove blood from the vena cava and return oxygenated blood to the right heart. Since this method relies on a functioning heart for circulation, it is most often used for cases of reversible respiratory failure. In veno-arterial ECMO (VA-ECMO), the afferent cannula withdraws blood from the vena cava and the right heart, and the efferent cannula returns blood to the aorta, thus bypassing the cardiopulmonary circuit entirely [31].

Despite its use since the 1970s, ECMO has a relative paucity of supportive evidence as to its overall survival benefit. Two of the biggest studies examining ECMO's use in ARDS—CESAR (2009) and EOLIA (2018)—show mixed reviews. A meta-analysis of their combined RCTs showed a reduction in mortality at 90 days from 48% on standard therapy to 36% with early ECMO therapy [32]. The analysis also concluded that patients with early ECMO were alive and out of the ICU on an average of 8 days earlier than patients on standard therapy. It is worth noting, though, that the treatments for control patients in the CESAR study were not standardized, and that the EOLIA study concluded that there was no difference in 60-day mortality between patients who received early ECMO compared to those who received a standard therapy of mechanical ventilation with ECMO as rescue therapy [33,34]. Additionally, neither study used VV-ECMO [32].

Granted, ECMO has most often been used as an adjunct rescue therapy, and the most common cause of death while on ECMO is multiorgan failure [32]. By the time a patient needs this therapy, they may already have several other comorbidities aside from cardiopulmonary issues that could result in an adverse event. It may be for this reason that ECMO seems to have greater success in severe trauma situations than it does in others. For instance, one study found that patients being treated with ECMO for traumatic injury had a survival rate of 64.7% compared to a rate of 23.5% on conventional mechanical ventilation [35].

2.2. Technological Advancements

2.2.1. Enhanced Durability and Reliability

The advancement from pulsatile to continuous flow in LVAD pumps resulted in devices with much greater longevity. Unfortunately, human bodies are designed for pulsatile blood flow, and the use of CF-LVADs resulted in several vascular complications

(most commonly, gastrointestinal bleeding) [36]. Some studies show that continuous flow creates a mechanical shear stress that results in acquired von Willebrand Syndrome [37]. The HeartMate 3 overcame this issue by creating pulsatile flow in its CF-LVADs by quickly alternating the speed of the rotor. Combined with HeartMate 3's magnetically levitated centrifugal motor, this has resulted in a significant reduction in bleeding, stroke, and pump thrombosis [38].

2.2.2. Improved Biocompatibility

An important MCS advancement currently being studied is the Aeson Total Artificial Heart (A-TAH) by Carmat. This device, like Syncardia TAH, is only approved for BTT (in Europe, not the United States). Their ultimate goals for their respective TAHs are approval as DT. The A-TAH, however, has several important features that improve its biocompatibility over older TAHs. Firstly, the A-TAH uses an inner electrohydraulic system to preserve the pulsatility of the native heart, and it uses sensors to adjust heart rate to respond to physiologic demand [39,40]. The pulsatility also helps in the prevention of AVWS [41].

Secondly, the surfaces that contact a patient's blood are made of a hybrid bovine pericardial tissue processed with glutaraldehyde, which allows for fibrin deposition and endothelialization. This matters because elevation of inflammatory markers after LVAD implantation has been associated with increased mortality, but after 12 months of A-TAH implantation, a study found no difference in pre- and post-implantation inflammatory markers [41,42].

The full impact of this device is yet to be determined, and many studies have yet to be performed, but the A-TAH has the potential to greatly improve the lives of patients requiring TAH or BiVAD. Another TAH currently being studied in vitro is SoftHeart (ETH Zurich, Zurich, Switzerland), which is a pneumatic TAH made almost entirely of silicone rubber. This is the only completely soft TAH developed thus far, and it currently has very limited longevity [43–45].

2.2.3. Electrophysiological Impact of MCS

MCS allows for hemodynamic stabilization, particularly in patients in CS due to refractory ventricular arrhythmias and electrical storm. The implantation of MCS devices to ensure end-organ perfusion can partially compensate for the decrease in native cardiac output during arrhythmias. Sometimes, the use of MCS to achieve hemodynamic stabilization may be followed by the spontaneous restoration of sinus rhythm, and other times, electrophysiologic intervention such as catheter ablation is required. Patients with ventricular tachycardia or fibrillation (VT or VF) typically already have reduced left ventricular ejection fraction (LVEF) and lower basal cardiac output, which predispose them to further hemodynamic compromise during catheter ablation due to the anesthesia induction and possible need for recurrent shocks. Through MCS devices, particularly the Impella, essential hemodynamic stabilization can be achieved by maintaining end-organ perfusion, reducing LV wall stress and oxygen consumption, and enabling prolonged mapping during VT episodes [46].

Contrastingly, VT and VF can be seen in the early postoperative period, particularly in the first 30 days after MCS device implantation, and decreasing episodes over the longer term [47]. A retrospective study of 91 patients who underwent LVAD implantation was conducted. Moreover, 35% of patients were noted to have ventricular arrhythmias with de novo monomorphic VT and de novo polymorphic VT or VF after implantation [48]. Interestingly, the risk of ventricular arrhythmias has also been linked to the type of MCS

device being used. Although multiple variables are at play, retrospective studies have shown elevated risk of VT and VF after LVAD compared to bi-VAD recipients [47].

3. Challenges and Limitations of Current MCS Technologies

3.1. Complications

3.1.1. LVADs

Per ESC guidelines, the major nonsurgical complications of LVADs include bleeding, device thrombosis, ischemic and hemorrhagic strokes, renal impairment, multiorgan failure, and infections [49]. Post-LVAD complications can either be early-occurring (<30 days after placement) or late-occurring (>30 days after placement) [49]. The use of antiplatelets and anticoagulants in those with LVAD placement predisposes them to bleeding complications. Early bleeding events within the first 14 days after LVAD placement are typically related to surgery, whereas later bleeding can be caused by the formation of arteriovenous malformations, hepatic dysfunction secondary to right ventricular failure post-LVAD implantation, or even acquired von Willebrand syndrome (AvWS) [50]. Typically, gastrointestinal (GI) bleeding occurs at a median of 33 days from surgery, with the greatest risk being within the first postoperative month [50]. Possible explanations for GI bleeding post-LVAD implantation include the development of angiodysplasia due to increased shear stress and intraluminal pressure or the development of AvWS from red blood cell mechanical damage, causing von Willebrand factor (vWF) deformity [50].

Despite antiplatelet and anticoagulation therapy, thromboembolic events are a common complication of LVAD therapy, with neurologic events being one of the primary causes of death [51]. Pump thrombosis remains the leading cause of device malfunction and embolic strokes. Studies have shown that the target INR of 2.6 is optimal to avoid thrombotic and bleeding complications, supporting the current practice of a target INR range being 2.0 to 3.0 [52].

Infections, another common complication of LVAD implantation, remain the second leading cause of death in patients who survive the first six months of LVAD support. Rates of infections related to LVADs range from 30% to 50%. These infections include pneumonias and sepsis, followed by driveline site infections (DLIs), and pump interior and pocket infections. When comparing HeartWare and HeartMate II, infections are lower in HeartWare patients, likely because this device is implanted within the pericardial space without requiring a pocket pump [53]. Unfortunately, for DLIs, no formal guidelines exist regarding the initial antibiotics to use or the length of antibiotic therapy required for treatment. If initial antibiotic therapy for at least two weeks is not sufficient, then surgical debridement or prolonged intravenous antibiotic therapy may be required. Worsening clinical status despite these therapies may indicate a possible fungal infection for which antifungal therapy should be considered, given the high mortality risk [54].

Aortic insufficiency (AI) is frequently seen in LVAD-supported patients, ranging from 11% to as high as 42%. The pathophysiologic mechanism of LVAD-induced AI occurs from the incorrect angle of blood outflow from the LVAD into the ascending aorta, increasing the risk of aortic root dilation, aortic wall changes due to shear stress, aortic valve injury and degeneration, and overall aortic root weakening. Once AI develops in an LVAD-supported patient, the valvular incompetence lowers the LVAD's pump efficiency, leading to worsening HF [55]. Of note, the development of AI in patients with the HeartMate II LVAD is heavily covered in published studies, which contrasts with the rarity of AI development in patients with HeartWare LVAD [56].

Lastly, right ventricular failure (RVF) can occur after LVAD implantation due to increased cardiac output, which may overwhelm the load-sensitive right ventricle (RV).

The RV body also becomes altered due to the shifting of the interventricular septum once the left intraventricular pressure falls due to the LVAD [57].

3.1.2. BiVADs

Patients requiring BIVAD support are typically more critically ill. Per the INTERMACS database, where adverse events and outcomes were recorded for primary implants of LVADs or BiVADs, patients who required BiVAD therapy experienced a lower survival rate and higher adverse event rate compared to patients supported with LVAD alone. Adverse events were significantly higher in terms of infection, bleeding, neurologic events, and device failure in the BiVAD group compared to the LVAD group [13]. Other adverse event profiles include renal dysfunction and device malfunction, regardless of whether the RVAD was temporary or durable [58].

3.1.3. Impella

Adverse hemorrhagic and ischemic events contribute to the bleeding and vascular complications associated with the Impella. The need for large-bore access sites, anticoagulation, ongoing shock-induced coagulation dysfunction, and device-related hemolysis from mechanical shear forces largely contributes to these complications. The Italian IMP-IT registry found that Impella-related complications were higher in the CS patients receiving Impella therapy in comparison to those with high-risk percutaneous coronary intervention (HR-PCI) [59]. Common complications of Impella use include major bleeding at access sites, limb ischemia, and hemolysis [19].

3.1.4. TAH

A meta-analysis of TAH utilization studying 75 patients from the NIS administration database who underwent TAH (Figure 1) found that the postoperative complication rate was $n = 22$ for death, $n = 52$ for acute renal failure, $n = 21$ for postoperative infections, $n = 11$ for required blood transfusions, $n = 5$ for respiratory complications, and $n = 3$ for stroke/transient ischemic attack (TIA) [60]. Another study identified 453 patients who received TAH in the MAUDE database (Figure 1) and noted that the most common adverse event reported was infection at 20.2% followed by device malfunction at 20.1% [61]. Death was reported in 49.4% of all reported cases ($n = 224/453$), and the most common cause was multiorgan failure $n = 73$, followed by neurologic complications like cerebrovascular accident (CVA) $n = 44$, sepsis $n = 24$, and support withdrawal $n = 20$ [61].

3.1.5. IABP

The most common complications associated with IABP include vascular complications such as stroke and limb ischemia. An incidence of 2.6% for major complications is noted in the benchmark registry [62]. These significant complications include severe limb ischemia, severe bleeding, balloon leaks, or death [62]. However, the overall IABP-associated mortality was about 0.05% [62]. The benchmark registry found that independent risk factors for major complications were female gender, peripheral vascular disease, body surface area less than 1.65 m^2 , and age ≥ 75 years [63]. Additional risk factors to compound the ones listed include duration of required IABP support, size of catheter used, previous history of diabetes mellitus, and a low cardiac index $\leq 2.2 \text{ L/min}$ [63]. The IABP-SHOCK II trial found no significantly higher risk of complications in those receiving IABP compared to the control group [63]. These results are depicted in Figure 2 below.

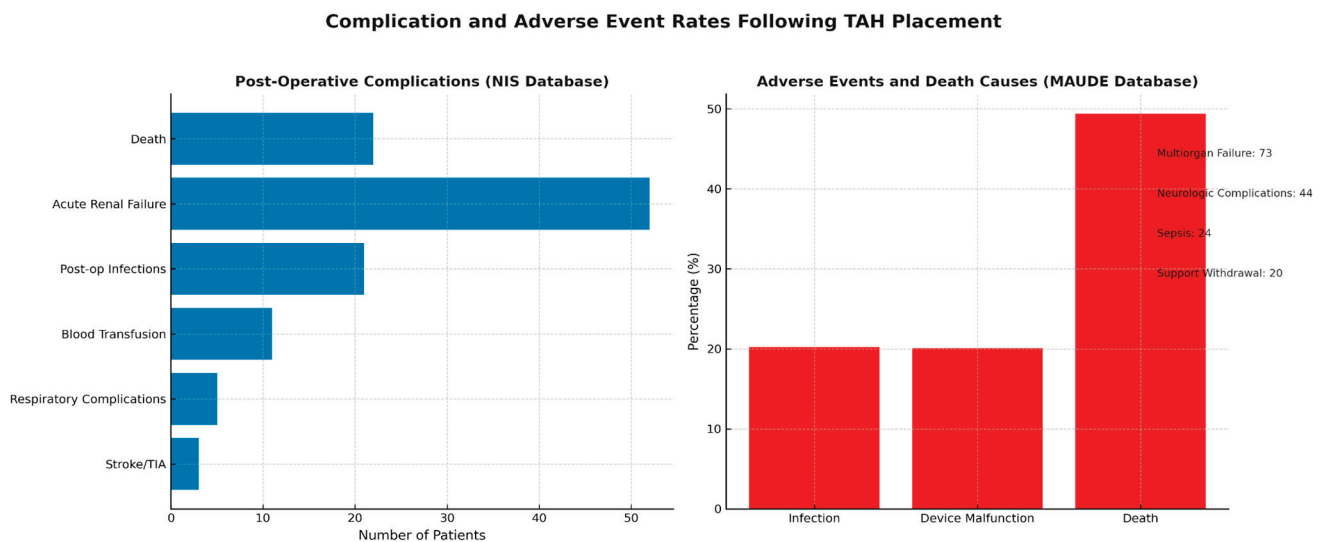


Figure 1. Postoperative and adverse event rates after TAH placement based on NIS and MAUDE database reports.

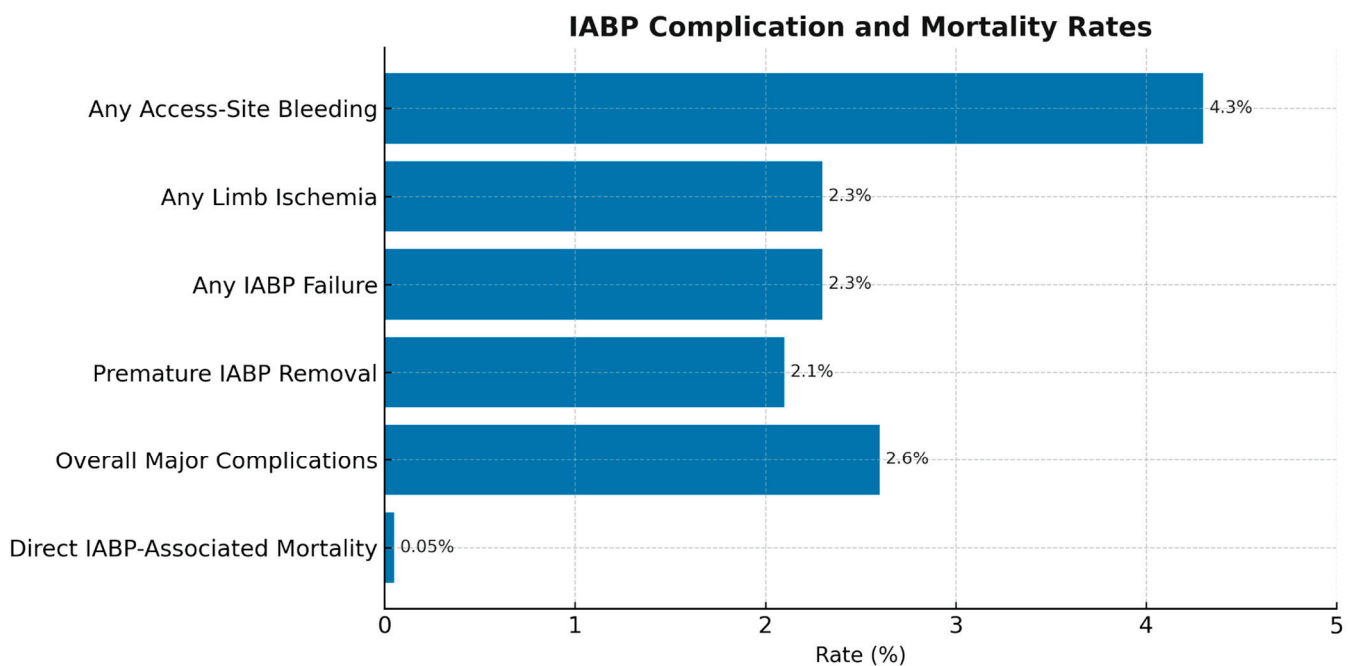


Figure 2. IABP-associated complication and mortality rates. Shown are events with an incidence greater than 2%, the overall major complication rate (2.6%), and direct IABP-related mortality (0.05%). The IABP-SHOCK II trial reported no significant difference in complication rates between IABP and control groups (all $p > 0.05$) [63].

3.1.6. ECMO

Morbidity associated with ECMO use is significantly high, with the most common complications being bleeding, thrombosis, hemolysis, CVA, and limb ischemia. Given the mechanism by which cannulation and oxygenation are performed, there are instances of significant blood contact against foreign objects and surfaces, stasis of blood in the heart, and increased risk of disseminated intravascular coagulation (DIC); the risk and incidence of thrombosis while on VA-ECMO is substantial. These risks warrant therapeutic anticoagulation therapy during ECMO [64]. However, due to consumption of clotting factors and thrombocytopenia, the incidence of bleeding with therapeutic anticoagulation remains high, with about 42% of patients requiring re-exploration surgery [64]. Heparin-

induced thrombocytopenia, in addition to platelet injury throughout the circuit, contributes to the high incidence of bleeding. High-risk bleeding tends to occur in multiple organs, but most commonly at the cannulation sites, the brain, and the gastrointestinal tract. CVA. Similarly, the incidence of CVA is reported to be up to 3.3–17.6% for ischemic stroke and 1.6–5% for hemorrhagic stroke [65]. Limb ischemia can be a major complication of peripheral VA-ECMO, where femoral artery cannulation is used, causing upwards of 10% of cases requiring treatment with fasciotomy and about 5% requiring treatment with amputation [66].

Some complications are specific to VA-ECMO, such as LV distension and Harlequin syndrome. The LV distension develops secondary to the retrograde flow of oxygenated blood in the ascending aorta, which increases the load against which the failing LV has to eject. The strong current of retrograde flow of blood can lead to the development of pulmonary edema and, in some cases, cardiac thrombi [67]. Sometimes, if LV distension and concern for intracardiac stasis are present, an LV vent can be inserted.

Due to the mixing of antegrade ejected deoxygenated blood, such as in the case of respiratory failure, and retrograde flow of oxygenated blood, a mixing cloud or zone forms. This mixing cloud is exposed to the coronary and cerebral circulations. This issue typically arises as a result of LV function recovery, where the mixing cloud is found in the descending aorta, past the cerebral and coronary arterial outflow. Over time, exposure to deoxygenated blood in the vital organs poses increased harm and risk of mortality [68]. Figure 3 below illustrates pooled event rates by different device types.

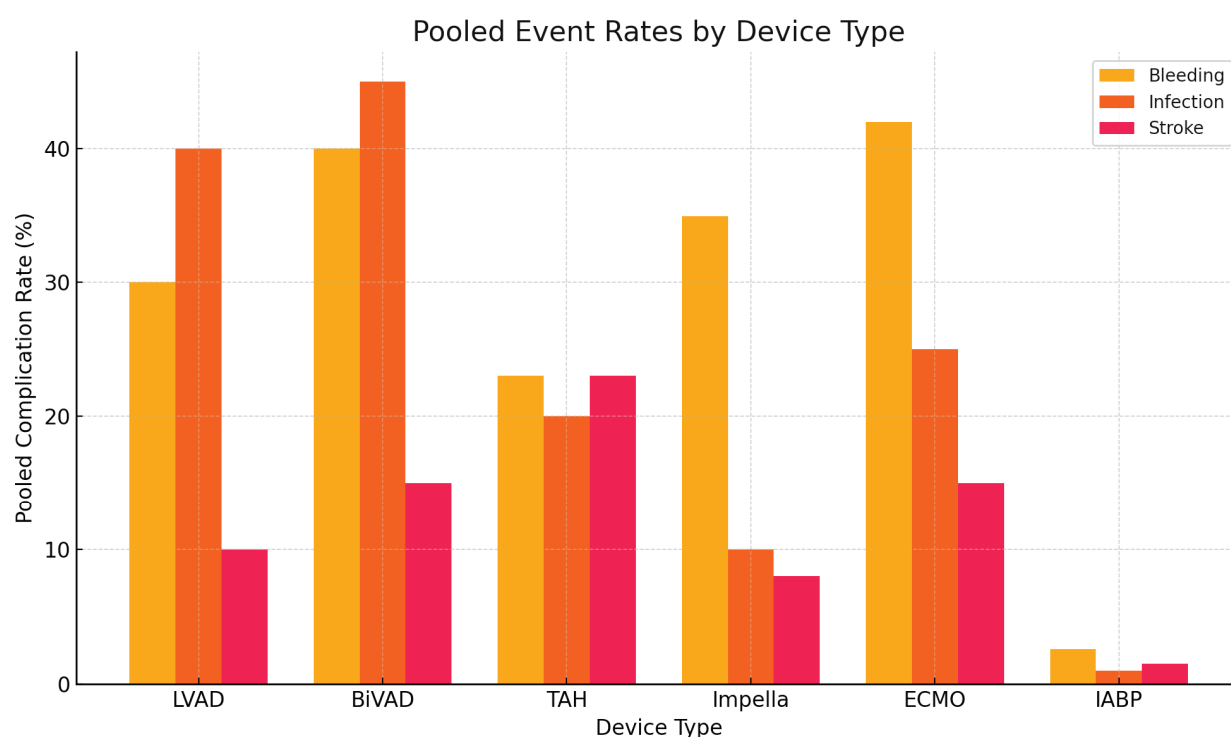


Figure 3. Pooled complication rates for major adverse events associated with mechanical circulatory support (MCS) devices. This figure summarizes pooled rates of bleeding, infection, and stroke for major MCS devices based on data from the review.

3.2. Limited Long-Term Data

3.2.1. LVAD Long-Term Survival Outcomes and Device Performance

Survival with durable MCS has significantly improved over the last two decades. The current 1-year survival rate is about 87%, with an absolute improvement in this rate of about 35% over 18 years. A 2001 study, Randomized Evaluation of Mechanical Assistance

for Treatment of Congestive Heart Failure (REMATCH), found a 1-year survival rate of 52% when compared against medical management alone [69]. A newer study called Multicenter, Study of MagLev Technology in Patients Undergoing MCS Therapy with HeartMate 3 (MOMENTUM 3) found a 1-year and five-year survival rate of 84% and 52% with use of the HeartMate 3 LVAD, respectively, improved from the 1-year and five-year survival rate of 82% and 44% with use of the HeartMate II LVAD, respectively [69]. This can also be seen in Figure 4 below. This study, along with data from the Society of Thoracic Surgeons Intermacs National Database (STS Intermacs) validated the survival benefits of the HeartMate 3 device [70].

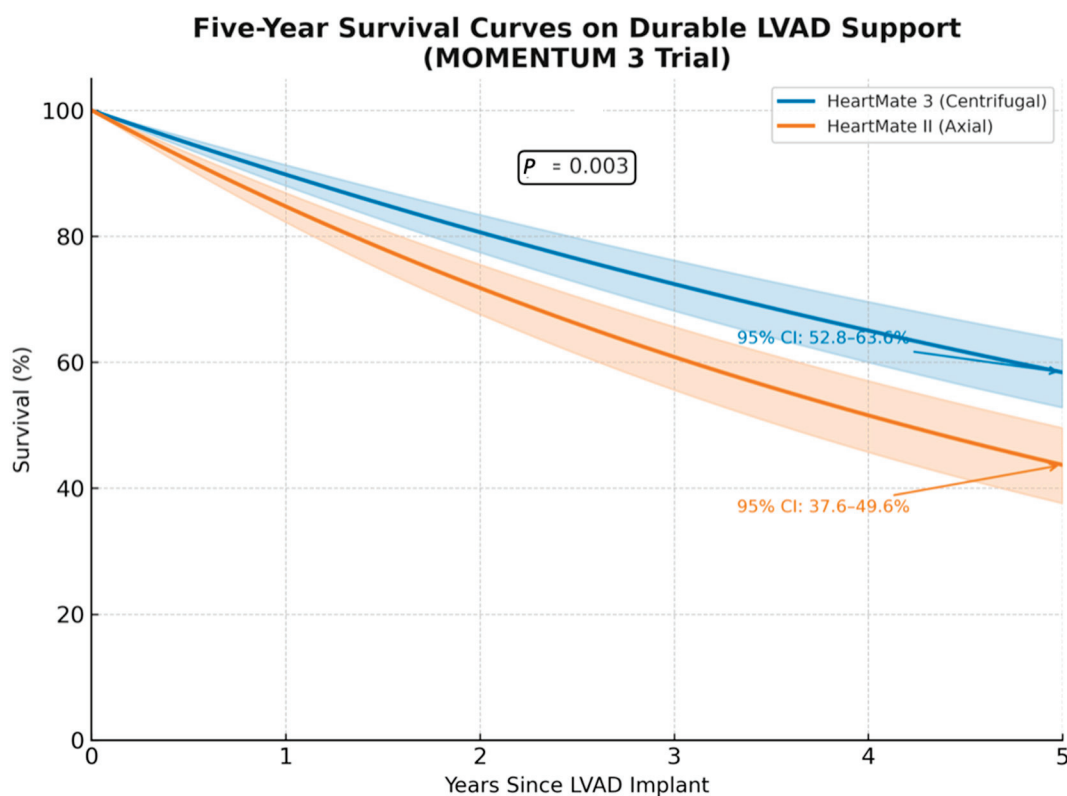


Figure 4. The five-year survival on continuous-flow durable left ventricular assist device (LVAD) support from the MOMENTUM 3 trial. Five-year survival was 58.4% (95% CI: 52.8–63.6) in the centrifugal flow pump group (HeartMate 3) and 43.7% (95% CI: 37.6–49.6) in the axial flow pump group (HeartMate II) [71].

In addition to survivability, improvement in patient-reported outcomes such as quality of life and functional capacity per New York Heart Association (NYHA) functional class was noted with a reduction in anxiety/depression and hospital admissions, proving the impact of durable MCS [69]. MOMENTUM 3 found that 95% of the selected patients for HeartMate 3 were classified as NYHA Class IV before device implantation, and 77% experienced improvement to NYHA Class I or II within six months of MCS therapy. Improvement in the six-minute walk test was evidenced by an overall increase in distance walked from 140 m to 230 m post-device implantation [69].

3.2.2. BIVAD Long-Term Survival Outcomes and Device Performance

Literature demonstrates that the overall 1-year survival in patients supported with BiVAD therapy is significantly lower compared to LVAD-only cohorts at about 50% vs. 83% [58]. The survival of concurrent BiVAD-supported patients was higher than those who received sequential VAD therapy, LVAD placement followed by a separate surgical en-

counter for RVAD placement, at about 56% compared to 42%, respectively [58]. Pre-implant patient characteristics were controlled through a propensity-score matching analysis study and factors studied included age, sex, race, BMI, implant brand, implant year, diagnoses, inotrope status, valvular abnormalities of mitral and tricuspid regurgitation, ECMO usage within 48 h of implant, and various other laboratory values like bilirubin and albumin. This study supports the avoidance of a sequential RVAD placement unless it is necessary [58].

3.2.3. Impella Long-Term Survival Outcomes and Device Performance

A prospective, multicenter observational study evaluating 804 patients receiving Impella for CS found that patients who received Impella 5.5 alone, compared to multiple types of MCS, had an overall favorable in-hospital, six-month, and 12-month survival rate, whether they were bridged to native heart survival or became candidates for Htx [72]. Many small retrospective studies have been performed comparing the Impella to IABP. These include the ISAR-SHOCK trial, which found that Impella improved hemodynamics in patients but not mortality, and the IMPRESS trial, which found that there was no difference in 30-day (48.5% for Impella vs. 46.4% for IABP, $p = 0.64$) or 6-month mortality between CS patients receiving IABP versus Impella [73,74]. Notably, the Impella group experienced higher rates of severe bleeding and peripheral vascular complications [75].

3.2.4. TAH Long-Term Survival Outcomes and Device Performance

A multicenter, retrospective analysis of about 217 patients undergoing TAH implantation between 2014 and 2019 in six different American medical centers studied the survival and adverse event profile. This study found that 63.5% of patients with TAH successfully transitioned to heart transplant, while 34.5% of patients died before heart transplant [76]. Overall patient survival in the TAH-receiving cohort at the 1-year, 2-year, and 5-year mark was 75%, 64%, and 58%, respectively. Of the 63.5% of patients transplanted, the overall survival at the 6-month, one-year, two-year, and five-year mark was 88%, 84%, 79%, and 74%, respectively [76]. This study concluded that nearly two-thirds of the patients receiving TAH could successfully undergo heart transplantation with an acceptable range of overall survival and survival post-transplant among these critically ill individuals [76].

3.2.5. IABP Survival Outcomes and Device Performance

The IABP-SHOCK II multicenter, randomized, open-label trial studying 600 patients with acute STEMI complicated by CS confirmed the lack of benefit of IABP on overall clinical outcomes when comparing mortality at 30 days in the control group. A follow-up retrospective study was performed on data collected from the European Registry on Patients with ST-Elevation MI Transferred for Mechanical Reperfusion, from which 1650 consecutive patients were located in an attempt to reassess IABP-use outcomes in “unselected” patients from the IABP-SHOCK II trial [77]. Notably, 51 patients with CS on initial admission were identified and stratified by IABP use or not during hospital stay. Notably, 30 of the 51 patients elected underwent IABP placement, while the remaining 21 did not receive IABP placement [77]. This study found that even after adjustment for age and sex, there was no difference in short- and long-term mortality between patients treated with and without IABP [77].

RHF significantly worsens the prognosis in patients who do not benefit from IABP therapy. The presence of RVD is associated with higher mortality and highlights the limitations of IABP in managing biventricular failure. Early recognition of RHF and consideration of alternative mechanical support strategies are crucial for improving outcomes in this patient population [78].

3.2.6. ECMO Survival Outcomes and Device Performance

Long-term survival and outcomes after ECMO remain limited in the literature. Per the Extracorporeal Life Support Organization (ELSO) Live Registry Dashboard, in the last five years, of all 111,129 patients undergoing VA or VV-ECMO in the world, 53% survived to transfer or discharge [79]. A single-center, retrospective chart review-based survival analysis over a period of five years was performed in 2023 to evaluate the five-year survival and overall quality of life in patients treated with ECMO, both VV and VA. Notably, 370 patients, 288 on VA-ECMO and 82 on VV-ECMO, found that the over five-year survival was 33% for VA-ECMO patients and 36% for those on VV-ECMO [80]. It was noted that in patients who survived the first 30 days after ECMO initiation, the five-year survival rate significantly improved to 73% on VA-ECMO and 71% on VV-ECMO (Figure 5) [80].

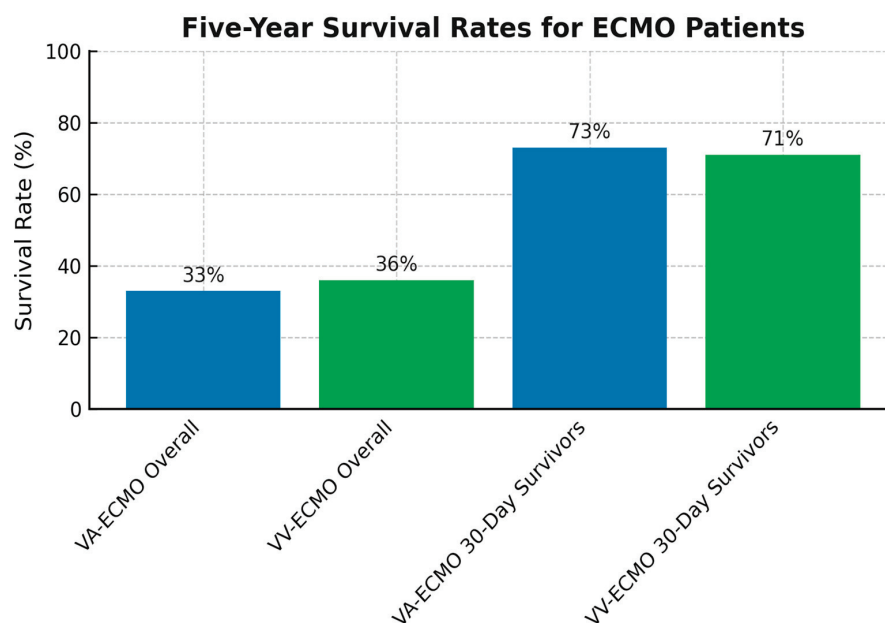


Figure 5. Overall survival beyond five years was slightly higher in the VV-ECMO group (36%) compared to the VA-ECMO group (33%). Patients who survived the first 30 days after ECMO initiation demonstrated markedly improved long-term outcomes in both groups.

About 56% of the patients studied participated in a median follow-up of 4.2 years and 5.7 years after VA-ECMO and VV-ECMO, respectively. Notably, 29% of VA-ECMO survivors and 75% of VV-ECMO survivors reported difficulties with activities of daily living (ADLs). Overall, these findings suggest that among patients who survive the critical early post-ECMO period, long-term survival and functional outcomes are generally acceptable [80]. Comparative data for all the MCS devices can be found below in Table 1.

Table 1. Comparative Summary Table of Mechanical Circulatory Support Devices.

Device	Primary Indications	Common Complications	Survival Outcomes	Typical Patient Population
LVAD	- Refractory left-sided HF - Bridge to transplantation - Destination therapy	- Bleeding (GI, perioperative) - Thrombosis - Stroke - Infection (driveline, pump) - RV failure - Aortic insufficiency	- 1 year: ~84–87% - 5 years: ~52% - Improved QoL (NYHA class, walk test)	- Patients with end-stage HF not eligible for transplant or are awaiting transplant

Table 1. Cont.

Device	Primary Indications	Common Complications	Survival Outcomes	Typical Patient Population
BiVAD	- Biventricular HF - Bridge to transplant	- Higher rate of infection - Bleeding - Neurologic events - Device failure - Renal dysfunction	- 6 months: ~56% - 1 year: ~50% - Concomitant implant is better compared to sequential implant	- Critically ill patients with RHF + LHF, often not candidates for isolated LVAD
TAH	- Replacement for both ventricles - Bridge to transplant (not a destination therapy in U.S.)	- Infection - Device malfunction - Renal failure - Stroke	- 1 year: 75% - 2 years: 64% - 5 years: 58% - 63.5% successfully transitioned to heart transplant	- Patients with end-stage biventricular HF unsuitable for LVAD/BiVAD and awaiting transplant
Impella	- Cardiogenic shock - High-risk PCI	- Bleeding - Hemolysis - Limb ischemia	- 1 month: ~48% - No survival benefit over IABP	- Acute cardiogenic shock patients during/after intervention
IABP	- Cardiogenic shock, especially post-MI - Supportive therapy post-CABG	- Limb ischemia - Stroke - Balloon leak - Bleeding	- Overall, IABP mortality ~0.05%	- Used for transient support in patients with ischemic cardiogenic shock or low output post-surgery
ECMO (VA/VV)	- VA: cardiogenic shock, cardiac arrest - VV: refractory ARDS	- Bleeding - Thrombosis - Stroke - Hemolysis - Limb ischemia - LV distension	- 5 years (overall): ~33% (VA) and ~36% (VV) - 5 years (after first 30-day survival): ~73% (VA) and ~71% (VV)	- Patients in severe respiratory/circulatory failure or multiorgan dysfunction

Summary of all mechanical circulatory support devices along with their indications, complications, survival, and patient population. LVAD: Left ventricular assist device, BiVAD: Biventricular assist device, TAH: Total artificial heart, IABP: Intra-aortic balloon pump, ECMO: Extracorporeal membrane oxygenation, VA: veno-arterial, VV: veno-venous, HF: heart failure, GI: gastrointestinal, RV: right ventricle, QoL: Quality of Life, NYHA: New York Heart Association, RHF: right heart failure, LHF: Left heart failure, PCI: percutaneous coronary intervention, MI: myocardial infarction, CABG: coronary artery bypass graft.

3.3. Cost and Accessibility

Mechanical circulatory support device use comes with a high-cost burden. Significant differences in cost were noted between devices like ECMO and Impella in comparison to IABP. The adjusted median standardized cost of hospitalization was highest with ECMO \$210,383.0 (IQR: \$165,760–\$239,373), followed by Impella \$142,518 (IQR: \$126,845–\$179,938) and IABP \$132,059.7 (IQR: \$113,794–\$160,243.7) [81]. The adjusted cost of hospitalization was also highest amongst patients receiving ECMO support, with a mean of \$210,383 ± \$66,028 [81]. During the research period, it was noted that the cost of IABP and ECMO reduced with time, but the cost associated with Impella remained the same. Unfortunately, a direct relationship was found between cost-adjusted hospitalization amount and device-associated stroke and bleeding. However, a direct relationship between 30-day mortality and overall price-adjusted hospitalization cost was not observed. After adjusting for patient factors, only patients treated at the highest-cost-adjusted hospitals showed a lower 30-day mortality rate [81].

4. Future Directions in Mechanical Circulatory Support

4.1. Next-Generation Devices

4.1.1. Fully Implantable and Wearable Devices

Recent advancements in fully implantable, wearable LVADs have made significant strides in addressing the challenges faced by HF patients requiring long-term mechanical support. These devices offer a substantial benefit by eliminating the need for external

drivelines, which are a major source of infection and complications in conventional models. In fact, driveline infections affect up to 40% of patients with traditional models, presenting a significant obstacle to their long-term success [10]. By fully implanting the device, this risk is minimized, leading to improved patient outcomes. Advances such as the HeartMate 3 have demonstrated improved survival and lower thrombotic complication rates compared to earlier devices, further validating the move toward next-generation designs [10].

However, creating a fully implantable model introduces its challenges. One of the biggest obstacles is ensuring a reliable power supply without external wires. Recent progress in battery technology and wireless power transmission systems has enabled reductions in the size and weight of these devices, though long-term battery durability remains a concern [82]. Furthermore, although these devices aim to replicate natural heart function, they must withstand mechanical stress over prolonged periods. The occurrence of pump thrombosis, in which blood clots form within the pump, remains a significant issue, with an annual incidence of 5 to 10 percent [10]. Long-term durability and the minimization of complications such as device failure and thromboembolic events are vital considerations in the further development of fully implantable circulatory support devices.

4.1.2. Bioengineered and Biological Solutions

One promising development is the integration of bioengineered materials aimed at enhancing biocompatibility, reducing thrombosis, and promoting tissue integration. Research into bioengineered tissues and scaffolds made from natural polymers has shown promise in reducing thromboembolic events and infection rates. These approaches aim to improve endothelialization and device integration with natural tissues, ultimately reducing complications like pump thrombosis. Although pump positioning has been identified as a significant factor influencing thrombosis risk in devices such as the HVAD, the development of bioengineered surfaces offers a complementary strategy to further mitigate thrombosis [83]. Improper positioning of the pump, particularly in HVAD devices, has been associated with a higher incidence of thrombosis, highlighting the role of imaging in long-term management [83].

Advances in tissue engineering have also led to the conceptualization of “living devices,” which combine mechanical support with regenerative capabilities. By using stem cells, scaffolds, and bioactive materials, researchers have developed systems that could stimulate myocardial repair and promote tissue healing. In animal models, stem cell-based devices have been shown to improve myocardial function by reducing fibrosis and promoting regeneration [10]. These bioengineered devices hold promise for providing both mechanical support and biological restoration, potentially improving long-term outcomes.

4.1.3. AI and Machine Learning Integration

Artificial intelligence and machine learning are expected to revolutionize patient care by enabling continuous monitoring and predictive analytics for device performance. Machine learning algorithms can analyze vast amounts of data from device sensors, detecting subtle changes in patient status that could indicate impending complications. A study by Malone et al. found that AI-assisted monitoring can predict the onset of pump thrombosis with a sensitivity of 85% and a specificity of 90% [82]. Early detection capabilities such as these allow for timely interventions, reducing the risk of life-threatening events like stroke or pump failure.

Additionally, AI systems are increasingly used to personalize patient care. Machine learning algorithms can help tailor anticoagulation therapy by predicting optimal anticoagulant dosages based on individual patient profiles [82]. This personalized approach could reduce the incidence of bleeding and thrombotic complications, which remain significant

challenges in LVAD management. By combining continuous monitoring with predictive analytics, AI-driven management strategies may significantly improve survival rates and enhance quality of life for patients [10].

4.2. Stem Cell Therapy and Regenerative Approaches

Recent advancements in regenerative medicine have highlighted the potential of stem cell-derived therapies for heart failure. Li et al. developed a multilayered cardiac tissue using human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) seeded onto a fibrous scaffold [84]. This engineered tissue achieved a thickness of approximately 1 mm and demonstrated enhanced contractile properties and cytokine secretion compared to traditional single-layer constructs. When applied to a rat model of myocardial infarction, the multilayer group showed improved functional recovery and less fibrosis [84]. These results indicated that the appropriate hiPSC-CM dose requires careful evaluation in developing clinical therapy.

These findings underscore the promise of hiPSC-CM-based therapies in cardiac regeneration. However, further large-scale, randomized controlled trials are necessary to validate the long-term safety and effectiveness of these approaches in human patients.

4.3. The Role of Gene Therapy

Gene therapy is emerging as a promising approach for treating heart failure by targeting underlying genetic and molecular mechanisms. Khan et al. investigated the therapeutic potential of adeno-associated virus serotype 9 (AAV9)-mediated delivery of cardiac bridging integrator 1 (cBIN1) in a canine model of chronic heart failure due to ischemic cardiomyopathy [85]. In this study, adult mongrel dogs underwent ligation of the left anterior descending artery to induce heart failure. Once the LVEF dropped below 40%, the animals received a one-time series of endocardial injections of either AAV9-cBIN1 or AAV9-GFP (control). The AAV9-cBIN1-treated group showed significant improvement in LVEF (from $29 \pm 3\%$ to $42 \pm 2\%$; $p = 0.0095$) and global longitudinal strain (from $-7.1 \pm 0.9\%$ to $-12.5 \pm 1.6\%$; $p = 0.0095$) compared to the control group [85]. Additionally, treated animals exhibited improved T-tubule morphology, reduced left ventricular chamber size, favorable plasma biomarker profiles, and enhanced endocardial voltage [85]. Importantly, all animals in the AAV9-cBIN1-treated group survived the study period, highlighting the therapy's potential efficacy and safety [85].

These findings underscore the potential of gene therapy as a transformative treatment for heart failure, offering hope for improved patient outcomes through targeted molecular interventions.

4.4. Combining MCS with Other Therapies

The integration of mechanical circulatory support with adjunctive therapies, such as pharmacological agents and gene therapies, offers a multifaceted approach to optimizing patient outcomes. For instance, combining mechanical support with gene therapies promoting angiogenesis has demonstrated improvements in myocardial perfusion and trends toward better ventricular function [86].

Additionally, targeting immune responses through innovative therapies holds promise for reducing infection rates, a leading cause of morbidity and mortality in LVAD recipients. Fu et al. discussed how immune modulation strategies could decrease infection-related complications, although precise figures regarding infection reduction rates are still under investigation [87].

Another promising avenue is combining mechanical support with novel pharmacological agents. Sodium-glucose cotransporter 2 inhibitors have emerged as effective treatments for HF, improving outcomes and potentially reducing the need for advanced mechanical

support if initiated early [88]. In addition to improving glycemic control, SGLT2 inhibitors have demonstrated cardiovascular benefits even in patients without diabetes [88]. Their mechanisms include reducing myocardial fibrosis, improving ventricular remodeling, and decreasing HF hospitalizations. Early initiation of SGLT2 inhibitors after the diagnosis of HF has been associated with better preservation of cardiac function, highlighting the importance of integrating pharmacologic strategies alongside mechanical circulatory support [88]. As research evolves, these combined strategies may offer synergistic benefits, improving both device longevity and patient quality of life.

4.5. Xenotransplantation

An alternative to cardiac transplantation, xenotransplantation, particularly porcine-to-human heart transplantation, is up and coming. Due to advances in somatic cell nuclear transfer technology (i.e., cloning) and CRISPR/Cas9 gene editing, the removal of immunogenic epitopes and porcine endogenous retroviruses has been enabled, reducing the risk of hyperacute rejection [89]. Specifically, thus far, gene editing has been used to modify 10 genes in a domestic pig, making it a viable alternative to conventional heart transplantation, albeit temporarily. Xenotransplantation may eventually be used as a destination therapy for patients who are not eligible for lasting MCS, as well as a bridge to transplant for patients waiting for human hearts, as bioengineering and immunomodulation progress. Notwithstanding moral and legal challenges, its advancements make it a viable avenue for advanced heart failure treatment in the future.

5. Conclusions

Advances in MCS therapies have expanded the available treatment options for patients with severe HF and CS. These devices have unique roles in providing bridging therapy for recovery, heart transplant, or even long-term support. The overall use of MCS devices is on the rise, particularly the Impella device, followed by ECMO, with LVADs notable for their use as BTT and, due to their efficacy, as destination therapy. Despite an increase in MCS device use, there has not been a significant difference noted in 30-day mortality or hospitalization rates for each device type, which suggests that increased use does not necessarily equate to improved patient outcomes. While strong evidence is available to suggest overall improvement in survival outcomes with MCS therapies like LVADs, Impella, and ECMO in critically ill patients who survive the first 30 days post-implantation of MCS devices, the high rates of complications of bleeding and thrombosis secondary to these therapies remain a significant challenge. Cost considerations and improvement in overall quality of life are important considerations for the use of MCS therapies, highlighting the importance of careful patient selection, a multidisciplinary medical team approach, and long-term follow-up.

Author Contributions: Conceptualization, J.K.D. and A.S.M.; methodology, J.K.D.; software, J.K.D.; validation, J.K.D., Y.S. and R.R.; formal analysis, J.K.D.; investigation, J.K.D.; resources, J.K.D.; data curation, J.K.D.; writing—original draft preparation, J.K.D., J.V., Y.S., R.R., A.S.M. and D.S.; writing—review and editing, J.K.D., J.V., Y.S., R.R., A.S.M. and D.S.; visualization, J.K.D.; supervision, J.K.D.; project administration, J.K.D.; funding acquisition, A.S.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: We thank the University of Nevada, Las Vegas (UNLV) Cardiology and Internal Medicine Departments for their invaluable support and guidance throughout the preparation of this manuscript. Their expertise and encouragement were instrumental in the successful completion of

this work. Additionally, OpenAI's ChatGPT (version 4.0, accessed via ChatGPT Plus, June 2025) was used for generating figures included in this paper.

Conflicts of Interest: The authors declare no conflict of interest.

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Review

The Microbiome Connection: A Common Pathway Linking Cancer and Heart Failure

Ioannis Paraskevaïdis ^{1,2}, Elias Tsougos ² and Christos Kourek ^{1,*}

¹ Medical School of Athens, National and Kapodistrian University of Athens, 15772 Athens, Greece; iparas@otenet.gr

² Department of Cardiology, Hygeia Hospital, 15123 Athens, Greece; tsougos@yahoo.com

* Correspondence: chris.kourek.92@gmail.com

Abstract: In humans, heart failure (HF) and cancer are among the leading causes of morbidity and mortality. A growing body of evidence highlights a bidirectional relationship between these conditions, underpinned by shared risk factors and overlapping pathophysiological pathways. This review aims to explore the emerging role of the intestinal microbiome as a common mechanistic link between HF and cancer. Specifically, we examine how microbial dysbiosis and its metabolic products—such as trimethylamine N-oxide (TMAO), short-chain fatty acids (SCFAs), bile acids, lipopolysaccharides (LPS), and branched-chain amino acids (BCAAs)—contribute to inflammation, immune dysregulation, oxidative stress, and metabolic dysfunction. These mechanisms promote multiorgan impairment and establish a vicious cycle that fuels both tumorigenesis and cardiac deterioration. HF, cancer, and the gut microbiome are not isolated entities but are deeply interconnected through shared biological mechanisms—including chronic inflammation, microbial dysbiosis, immune and neurohumoral modulation, and metabolic derangement. These findings support the concept of a microbiome-centered axis involving the gut, heart, and tumors, which may underlie many chronic disease processes. Understanding these interactions may provide novel insights into disease pathogenesis and uncover promising therapeutic targets that leverage microbiome modulation to prevent or treat HF, cancer, and other systemic diseases.

Keywords: heart failure; cardiovascular disease; cancer; tumors; microbiome

1. Introduction

Heart failure (HF) and cancer are two of the most pressing global health challenges of the 21st century. HF affects over 64 million people worldwide and remains a leading cause of hospitalization and death, particularly among the aging population. Its global burden continues to rise due to increased longevity and improved survival after acute cardiovascular events. One-year mortality rates following hospitalization for acute HF reach 20–30%, and the condition is associated with high readmission rates and reduced quality of life [1].

Cancer is responsible for nearly 10 million deaths annually, with projections estimating over 28 million new cases worldwide by 2040. This increase is driven by aging populations and lifestyle-related risk factors [2]. In Europe, cancer accounts for approximately one in four deaths, making it the second leading cause of death after cardiovascular diseases. In 2020, cancer caused nearly 1.9 million deaths across the continent, representing about 25% of all deaths [3].

Notably, a growing number of patients are being diagnosed with both HF and cancer—either sequentially or concurrently—suggesting shared pathophysiological mechanisms and a potential bidirectional relationship [4]. Patients with HF may develop cancer [4–6], while cancer patients—especially those undergoing antitumor treatments—are at increased risk of developing HF [7,8]. Therefore, long-term follow-up of both groups is recommended [9,10].

These two conditions share common risk factors, including smoking, hypertension, metabolic imbalance, and genetic alterations. They also follow similar pathophysiological mechanisms, such as activation of the neurohumoral system (including the sympathetic and parasympathetic nervous systems and the renin-angiotensin-aldosterone system), heightened inflammation, and increased production of free radicals. Dysregulation of these pathways disrupts homeostasis, impairs structural and functional integrity, and weakens cellular and tissue defense mechanisms.

The term microbiota refers to various microorganisms, including bacteria, viruses, and fungi, that inhabit different parts of the human body, such as the skin, oral and nasal cavities, stomach, and especially the intestines. In contrast, the microbiome encompasses both the microbiota and their interactions with the host [11]. These microorganisms are essential to human health, supporting metabolic, immune, and inflammatory balance, as well as regulating obesity-related disorders [12–14].

In patients with HF and/or cancer, the microbiota and its metabolic products are significantly altered due to an impaired intestinal environment. This disruption, known as dysbiosis, is marked by structural and functional changes and increased intestinal permeability [15,16]. These alterations are not incidental; they are increasingly recognized as active contributors to disease development. The microbiome influences host physiology through immune modulation, metabolic regulation, and communication with the nervous and endocrine systems [17–19]. Many of these pathways such as chronic inflammation, oxidative stress, and immune dysfunction are common to both HF and cancer. Given its regulatory role and ability to affect distant organs through microbial metabolites, the microbiome is emerging as a compelling common link between the two diseases.

Thus, HF, cancer, and an altered microbiome are interconnected, sharing common pathophysiological mechanisms such as systemic inflammation, neurohumoral activation, oxidative stress, insulin resistance, and metabolic dysregulation. These processes are often driven by harmful microbial metabolites, including trimethylamine N-oxide (TMAO), lipopolysaccharides (LPS), branched-chain amino acids (BCAAs), and secondary bile acids, which promote endothelial dysfunction, immune activation, mitochondrial stress, and tissue remodeling. By influencing these shared mechanisms, a disrupted microbiome plays a pivotal role in the onset and progression of both cardiovascular and oncologic diseases.

The objective of this review is to explore the microbiome as a shared mechanistic link between HF and cancer, emphasizing the role of microbial metabolites and common pathophysiological pathways such as inflammation, dysbiosis, immune modulation, and metabolic dysfunction.

2. The Microbiome in Immunological, Metabolic, and Cardiovascular Homeostasis

The gut microbiome is a key regulator of human health, exerting significant influence on immune, metabolic, and cardiovascular homeostasis. It plays a crucial role in educating and modulating the host immune system by promoting the development of gut-associated lymphoid tissue (GALT), maintaining mucosal barrier integrity, and regulating inflammatory responses [20–22]. Commensal microorganisms help maintain immune

tolerance to non-pathogenic antigens while ensuring robust defense mechanisms against harmful pathogens.

From a metabolic perspective, the microbiome enhances nutrient absorption, synthesizes essential vitamins, and produces important metabolites such as short-chain fatty acids (SCFAs), bile acids, and amino acid derivatives [23]. Among SCFAs, butyrate and propionate are particularly notable for their anti-inflammatory properties, ability to improve insulin sensitivity, and role in supporting energy balance [24]. Through these functions, the gut microbiota helps regulate body weight, glucose metabolism, and lipid levels.

Cardiovascular health is also strongly influenced by the microbiome. Microbial metabolites affect endothelial function, vascular tone, and the risk of atherosclerosis [25,26]. SCFAs contribute to vascular protection and help lower blood pressure [27], whereas dysregulated production of other metabolites, such as TMAO, can promote vascular inflammation and atherogenesis [28]. By maintaining metabolic balance, reducing oxidative stress, and modulating systemic inflammation, a healthy microbiome supports cardiovascular resilience.

Understanding these homeostatic functions is essential for appreciating how microbiome disturbances contribute to the development and progression of complex diseases such as HF and cancer.

Although experimental studies have described the role of the gut microbiome in maintaining immune, metabolic, and cardiovascular balance, longitudinal studies in humans remain limited. Future research should aim to characterize microbial profiles across diverse populations and investigate how specific microbiome configurations influence disease risk or resilience over time.

3. The Microbiome Interplay

The microbiome can exert both oncogenic and tumor-suppressive effects. Its oncogenic potential is well documented in several types of cancer. For example, *Helicobacter pylori* is implicated in gastric cancer; hepatitis B and C viruses in liver cancer; human papillomavirus in cervical and vaginal cancers; Epstein-Barr virus in nasopharyngeal carcinoma and lymphoma; and *Escherichia coli* in colorectal cancer, among others [28]. Conversely, some microbiota—such as butyrate-producing bacteria—have demonstrated protective effects by inhibiting the progression of colorectal cancer [29].

Regardless of whether its effects are oncogenic or protective, the microbiome clearly exerts a profound influence on immune cells and inflammatory processes. This is especially relevant given that the gastrointestinal tract contains the majority of the body's immune cells. Moreover, microbial metabolites can have effects beyond the gut by entering the enterohepatic circulation, thereby influencing distant organ systems [28].

In HF, reduced cardiac output leads to gut ischemia and congestion—observed in both HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) [30]. These changes disrupt the intestinal microbiota and increase intestinal permeability [16,31]. The resulting alterations: (a) activate immune and inflammatory responses, and (b) stimulate the neurohumoral axis, which contributes to left ventricular remodeling and myocardial fibrosis [30,32]. Additionally, these changes are linked to insulin resistance, obesity, metabolic syndrome [33], and impaired mitochondrial energy metabolism [15,19].

Taken together, these findings highlight how intestinal dysbiosis—characterized by disruption of the normal microbiota and its metabolic products—affects core pathophysiological mechanisms common to both cancer and HF. These include neurohumoral over-activation, chronic inflammation, and disturbances in metabolism and energy production [31,34].

There is a clear bidirectional relationship between the microbiome, HF, and cancer. Each condition can alter the composition and function of the gut microbiota, which in turn contributes to the development and progression of these diseases, establishing a self-perpetuating cycle (Figure 1).

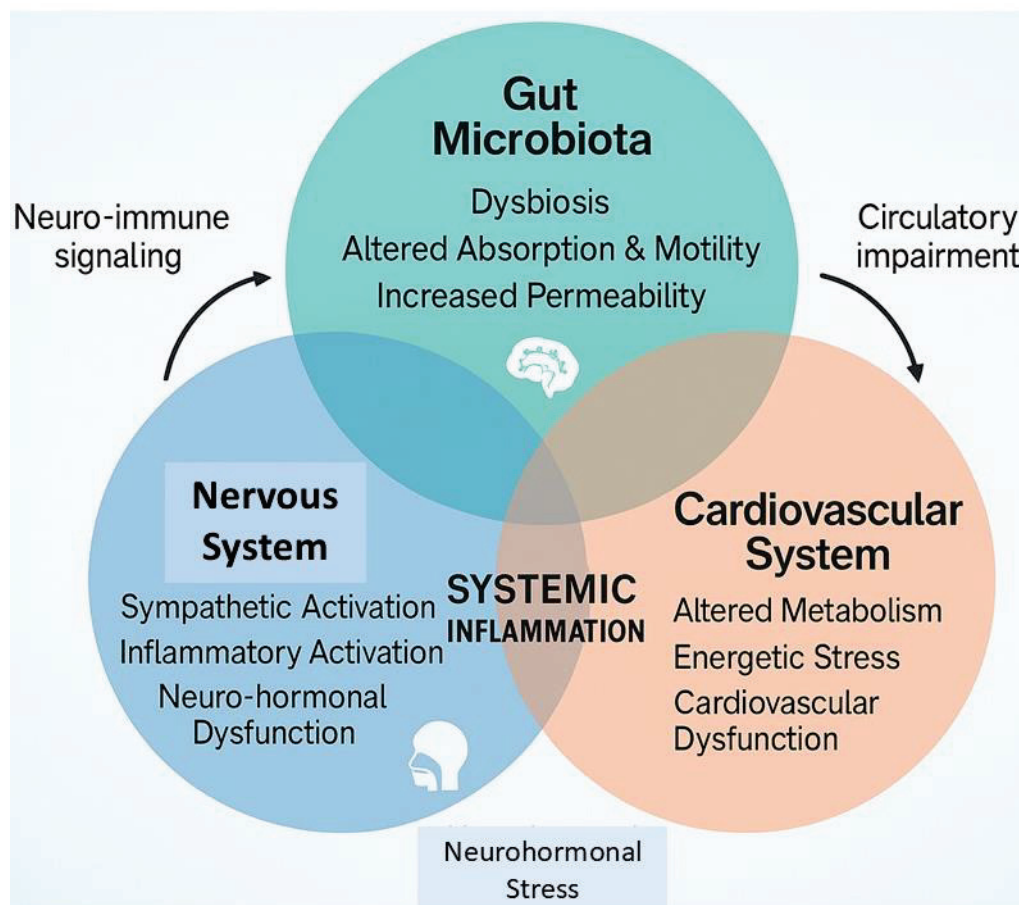


Figure 1. The reciprocal interplay between gut microbiota and the nervous and cardiovascular systems. The altered intestinal homeostatic status initiates neuro-humoral, nervous, and immune system dysfunction, pillars of both cancer and cardiovascular disease pathophysiology.

While compelling evidence links microbiota-derived metabolites to both oncogenesis and cardiovascular dysfunction, much of the current data stems from preclinical studies. Translational research and human interventional trials are urgently needed to validate these causal relationships and to explore strategies for therapeutic modulation of the microbiome.

Table 1 summarizes key microbiome-derived carcinogenic metabolites, their bacterial sources, the pathways they activate, their effects on antitumor immunity, the associated cancer types, and their relationships with cardiovascular dysfunction and heart failure.

Table 1. Microbiome-derived carcinogenic metabolites, responsible bacteria, involved pathways, effects on the immune system, associated cancers, and links with heart failure.

Metabolite	Key Bacteria	Pathways Involved	Effect on Antitumor Immunity	Metabolite	Key Bacteria
Acetaldehyde	<i>Escherichia coli</i> , <i>Klebsiella</i> spp.	DNA damage, ROS generation	DNA adduct formation, immune suppression	Colorectal, esophageal	Promotes systemic oxidative stress and inflammation
Heterocyclic amines (HCAs)	<i>Clostridium</i> spp., <i>Bacteroides</i> spp.	Activation of NF- κ B, CYP450 enzymes	Induces immune evasion via chronic inflammation	Colorectal, pancreatic	Chronic inflammation leads to vascular dysfunction
Secondary bile acids (e.g., deoxycholic acid)	<i>Clostridium</i> spp.	FXR signaling, ROS production	Disruption of immune surveillance, promotes tumor growth	Liver, colorectal	Endothelial dysfunction, promotes cardiac fibrosis
Lipopolysaccharides (LPS)	<i>Enterobacteriaceae</i> , <i>Bacteroides</i> spp.	TLR4 activation, NF- κ B pathway	T-cell exhaustion, macrophage polarization	Multiple (systemic effect)	Drives myocardial inflammation and remodeling
Phenylacetylglutamine (PAGln)	<i>Proteobacteria</i> group	Adrenergic receptor signaling	Enhances pro-tumorigenic adrenergic responses	Breast, prostate	Induces platelet hyperreactivity, promotes HF
Trimethylamine N-oxide (TMAO)	<i>Lachnospiraceae</i> , <i>Enterobacteriaceae</i>	Inflammatory, metabolic pathways	Modulates immune cell metabolism	Colorectal, gastric	Strongly associated with atherosclerosis, HF risk

3.1. Shared Microbial Mechanisms in HF and Cancer

Dysbiosis refers to an imbalance or disruption in the normal composition, diversity, or function of the microbiome. It may involve a reduction in beneficial commensal microbes, an overgrowth of pathogenic species, or a loss of overall microbial diversity. Dysbiosis can be triggered by a variety of factors, including dietary changes, infections, antibiotic use, chronic diseases, and environmental exposures [35,36]. It plays a central role in the pathogenesis of both HF and cancer through shared biological pathways. Dysbiosis is marked by a reduction in beneficial commensals, an overgrowth of pathogenic species, and altered microbial metabolism, which together promote systemic inflammation, oxidative stress, and immune dysfunction [15,35–37].

Key microbial metabolites such as TMAO, LPS, SCFAs, secondary bile acids, BCAAs, and phenylacetylglutamine (PAGln) exert profound systemic effects. For example, TMAO, derived from dietary choline and carnitine by gut bacteria and converted in the liver via flavin-containing monooxygenases, promotes vascular inflammation, endothelial dysfunction, platelet hyperreactivity, and adverse cardiac remodeling [38–46]. It activates inflammatory pathways including NF- κ B and the NLRP3 inflammasome, and has been associated with an increased risk of atherosclerosis, HF, and cancer progression [39,40,43,45].

Similarly, LPS, a product of Gram-negative bacteria such as *Enterobacteriaceae*, crosses a compromised intestinal barrier and enters systemic circulation. It activates Toll-like receptor 4 (TLR4), induces macrophage polarization, and drives the release of proinflammatory cytokines—key processes that contribute to myocardial inflammation, vascular dysfunction, and tumor-promoting immune modulation [37,47–50].

While SCFAs such as butyrate and propionate normally exert anti-inflammatory, antitumor, and insulin-sensitizing effects, their production is often diminished in dysbiotic

states [23,24,51,52]. This reduction in protective metabolites, coupled with an increase in harmful ones, results in immune dysregulation, metabolic disturbance, mitochondrial stress, and chronic low-grade inflammation—all of which are common to both cancer and cardiovascular pathology [12,14,15,19,53–55].

The pathophysiological impact of these metabolites is not unidirectional. In both HF and cancer, impaired intestinal perfusion, systemic inflammation, and the effects of chemotherapeutic or cardiovascular therapies further exacerbate dysbiosis, creating a vicious cycle of mutual reinforcement [16,30–32]. Thus, the gut microbiota is not merely a bystander but an active participant in disease propagation, forming the foundation of a bidirectional, metabolite-driven feedback loop.

This unified perspective underscores the microbiome as a mechanistic bridge between oncologic and cardiovascular disease, and highlights shared therapeutic opportunities. Targeting microbiome-derived metabolites through diet, probiotics, or pharmacological agents may represent a promising strategy to attenuate systemic inflammation, restore metabolic balance, and interrupt disease progression.

While mechanistic pathways involving TMAO, LPS, and SCFAs have been well characterized in preclinical models, their direct causal roles in human disease progression, particularly in the context of concurrent HF and cancer, remain an area of active investigation.

3.2. Metabolic/Energetic Status

The intestinal microbiome plays a critical role in regulating host energy balance, metabolic homeostasis, and nutrient utilization. Under normal conditions, commensal microbes enhance carbohydrate fermentation, producing beneficial SCFAs such as butyrate and propionate. These SCFAs serve as energy substrates, maintain epithelial integrity, and exhibit anti-inflammatory and insulin-sensitizing properties [12,14,23,24,51,52]. The microbiome also participates in bile acid metabolism, modulates glucose and lipid profiles, and influences the bioavailability of micronutrients and neurotransmitters [15,23,56–58].

In dysbiotic states—commonly observed in both HF and cancer—the microbial production of protective SCFAs diminishes, while harmful byproducts such as TMAO, LPS, and BCAAs increase [15,53,59–61]. These changes promote insulin resistance, metabolic inflammation, mitochondrial dysfunction, and impaired oxidative metabolism [15,19,62–64].

Dietary composition significantly shapes the metabolic output of the microbiota. High-fat and high-cholesterol diets favor the generation of LPS and TMAO—metabolites strongly associated with atherosclerosis, cardiac fibrosis, and tumor progression [38–42]. Conversely, fiber-rich diets support SCFA production and metabolic resilience [15,51,52]. The microbiome's metabolic output is also influenced by local factors such as intestinal pH, oxygen levels, and motility, as well as systemic factors including bile and pancreatic secretions, hormonal status, and host genetics [15,65–69].

Thus, the microbiome functions as a metabolic integrator between the gut and peripheral organs. In HF and cancer, its dysregulation contributes to energetic depletion, oxidative stress, and chronic inflammation—hallmarks that accelerate disease progression [15,53–55]. Interventions aimed at modulating microbial metabolism—such as dietary modification, probiotics, or targeted pharmacologic agents—may offer novel strategies to restore systemic metabolic balance.

3.3. Inflammation/Free Radical Production

The gut microbiota closely interacts with the host immune system and plays a critical role in regulating inflammatory responses at both local and systemic levels. Under normal physiological conditions, the microbiome supports the maturation of lymphoid tissues, maintains epithelial barrier integrity, and promotes immune tolerance by modulating T-

cell responses and dendritic cell function [70–73]. Commensal bacteria also stimulate the expansion of cytotoxic CD8⁺ T cells, which possess anti-tumor activity, while preserving mucosal immune homeostasis [74,75].

However, during dysbiosis, pathogenic microbes and their toxic metabolites—such as lipopolysaccharides (LPS) and reactive nitrogen species—can dominate the gut environment. This shift impairs immune defense mechanisms and initiates chronic inflammation. The resulting disruption of mucosal immunity increases cytokine production and promotes abnormal epithelial cell proliferation, contributing to carcinogenesis [76–78]. Dysbiosis has also been linked to the development of cancers beyond the gut through systemic inflammatory pathways and microbial translocation [79–81].

Importantly, microbes originating in the gut have been identified within tumor tissues, forming what is known as the intratumoral microbiota. These microbes, often residing within immune cells, interfere with autophagy and immune surveillance, thereby promoting tumor progression [82–84]. At the same time, inflammation and microbial imbalance trigger systemic endocrine and neurohormonal changes—including insulin resistance, activation of the renin-angiotensin-aldosterone system (RAAS), and increased oxidative stress—all of which are key contributors to the development of both HF and cancer [33,85–88].

Free radicals, including reactive oxygen species (ROS) and reactive nitrogen species (RNS), are major mediators of inflammation and cellular injury. While they serve important roles in signaling and immune defense at low concentrations, excessive production—common in dysbiotic states—results in lipid peroxidation, protein oxidation, and DNA damage [89–91]. In the heart, oxidative stress promotes myocardial cell apoptosis, necrosis, fibrosis, and mitochondrial dysfunction. These changes impair cardiac contractility and drive the progression of HF [91–94]. In cancer, free radicals contribute to genomic instability, damage tumor suppressor genes, and promote a tumor-friendly microenvironment, particularly under hypoxic conditions [95–98].

These interconnected mechanisms—chronic inflammation, immune dysregulation, and oxidative stress—represent a shared pathogenic link between dysbiosis and both cardiovascular and oncologic diseases. Although these associations are supported by both experimental and clinical data, the exact sequence of events and causal relationships remain uncertain. Further longitudinal studies are needed to determine whether targeting the microbiome can reduce oxidative and inflammatory damage in HF and cancer.

Although dysbiosis-induced immune dysregulation and oxidative stress are strongly implicated in preclinical models of both cancer and cardiovascular disease [89–93], the temporal sequence and clinical causality of these processes in humans are not yet fully delineated.

3.4. The Multiciliary Axis

The microbiome plays a regulatory role in neurogenesis, myelination, glial cell function, synaptic pruning, and blood–brain barrier permeability [18]. Communication with the central nervous system (CNS) is bidirectional, involving metabolic, endocrine, neurological, and immune pathways that influence both the onset and progression of various diseases [18,99]. This communication—often referred to as the “gut–brain axis”—occurs via both neural and humoral routes. Microbiome-derived signals reach the brain through stimulation of the enteric nervous system and the vagus nerve [100], or through the systemic circulation, which transports microbial metabolites—both beneficial and harmful—across the blood–brain barrier [101,102] (Figure 2).

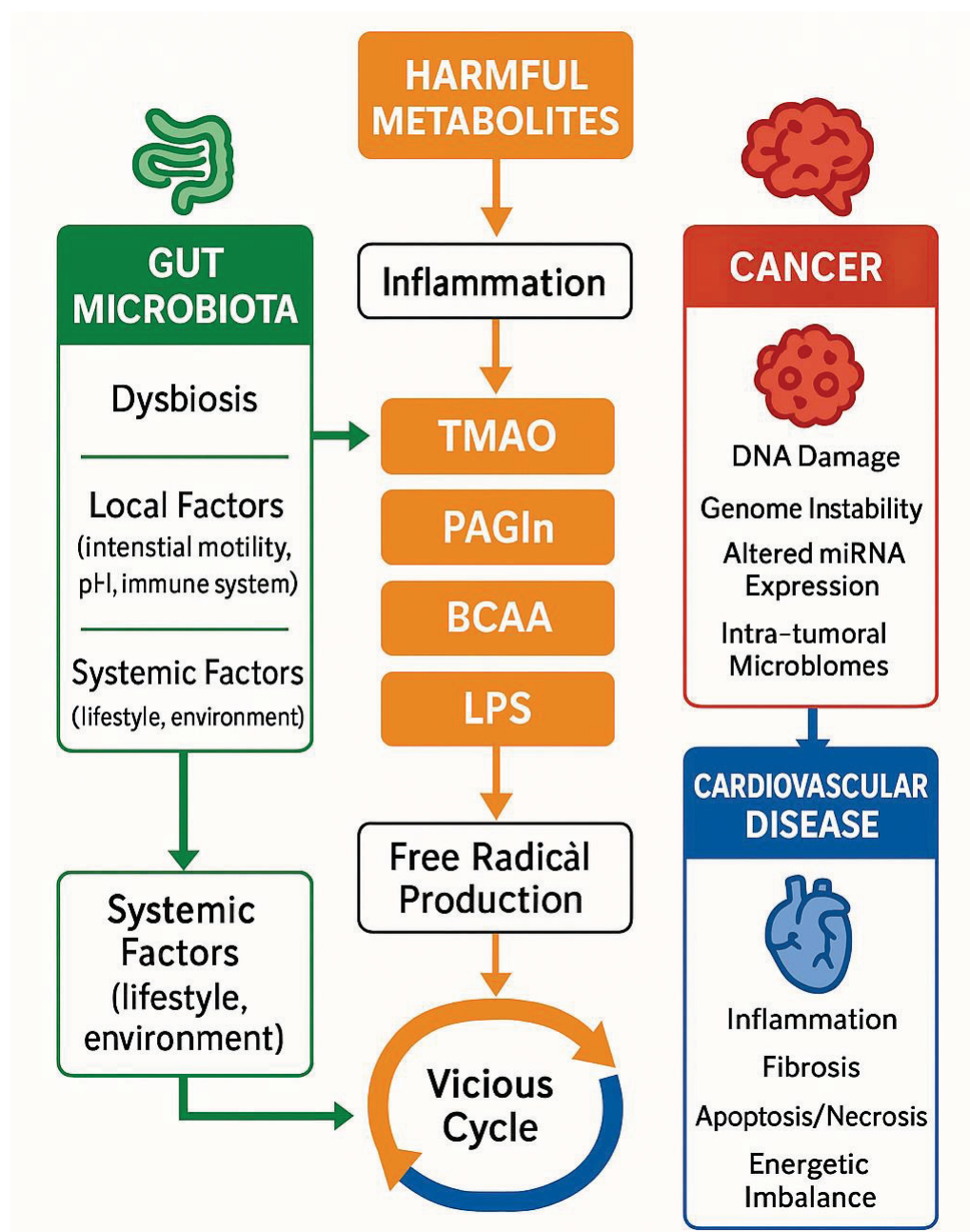


Figure 2. Pathophysiological concepts for microbiome—cancer—cardiovascular diseases interplay. BCAA: branched-chain amino acids, CV: cardiovascular diseases, LPS: lipopolysaccharides, PAGln: phenylacetylglutamine, TMAO: Trimethylamine N-Oxide.

Increased intestinal permeability allows microbial products such as LPS and SCFAs to activate both peripheral and central immune cells, promote cytokine release, and induce neuroinflammation. These processes affect CNS function and contribute to disease pathophysiology. Microbial products, including SCFAs, bile acid derivatives, neurotransmitter agonists, tryptophan metabolites, serotonin, and catecholamines, can modulate host metabolic and inflammatory responses, contributing to the development and progression of both cancer and cardiovascular diseases [103–106]. The inflammatory response triggered by harmful microbial stimuli activates immune cells and promotes cytokine release, which directly impacts CNS function [99]. This axis highlights an indirect mechanism by which the microbiome influences the nervous system and broader human physiology.

According to the International Cancer Microbiome Consortium, there is currently no direct evidence that the human commensal microbiome is a key determinant in the etiology of cancer [107]. While some cancers such as those associated with bacterial vaginosis and co-infection with HIV or human papillomavirus may involve a more direct microbial role, it appears that toxic products from a dysregulated microbiome are the primary contributors to cancer development. These metabolites disrupt host homeostasis, promote systemic inflammation and neurohumoral activation, and drive pathological processes that can facilitate cancer progression even at distant sites.

In HF, the nervous system is also significantly affected. Chronic cerebral hypoperfusion, inflammation, oxidative stress, and overactivation of the RAAS are key factors. RAAS is active in several organs, including the brain, heart, lungs, and intestines, and functions in an integrated manner to regulate homeostatic processes such as glycemic control and electrolyte balance [108]. When the gut microbiota and its metabolic outputs are pathologically altered, these regulatory mechanisms are disrupted. This disruption promotes cardiac fibrosis, cellular apoptosis and necrosis, and ultimately, the progression of HF [109,110] (Figure 3).

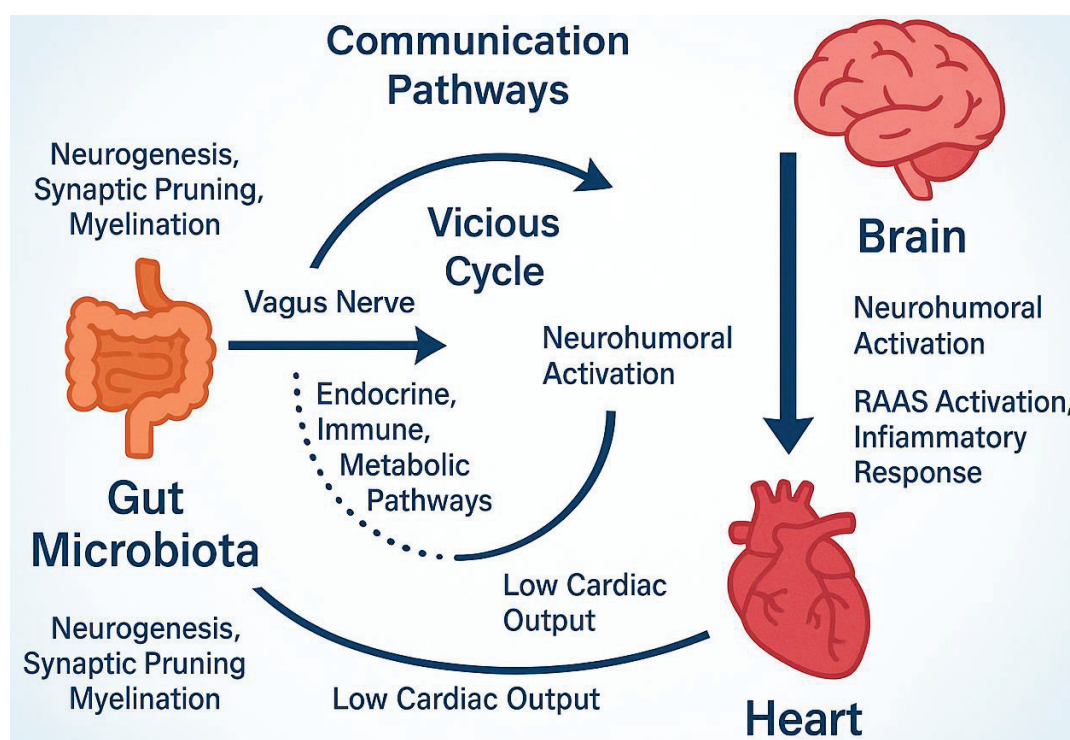


Figure 3. Microbiome nervous system communication through the gut–brain axis. This axis using metabolic, endocrine and other pathways interfere with neurogenesis, myelination etc. The altered microbiota environments activate RAAS system that, in turn, promote free radical production and inflammatory response, the basic concept of HF syndrome. Accordingly, low cardiac output further aggravates these actions and stimulate central nervous system constituting thus a vicious cycle with harmful effects. RAAS; Renin-angiotensin-aldosterone system.

In addition, conditions such as insulin resistance, obesity, and metabolic syndrome [33], which are central to cardiovascular disease pathophysiology [19,31], are frequently present. In HF, reduced cardiac output and venous congestion impair intestinal function and promote dysbiosis. This microbial imbalance leads to excessive LPS production, which further increases intestinal permeability. The resulting endotoxemia drives systemic inflammation and activates immune and neurohumoral pathways [48–50], thereby exacerbating the severity of HF.

Clearly, a vicious cycle exists between the microbiome, HF, and the nervous system. These systems share overlapping pathophysiological mechanisms [100], and their dysfunction contributes to complications such as cognitive impairment [111]. Interestingly, the microbiome can also interact with the host's reward pathways (e.g., the mesolimbic system) and modulate the effects of noradrenaline on the bone marrow, thereby enhancing antitumor immunity. Furthermore, the use of probiotics as adjunctive cancer therapy has shown potential to modulate the microbiome, improve psychological well-being, and slow cancer progression [112,113].

There is little doubt that a dynamic, reciprocal interplay exists among the brain, gut, and heart, forming a regulatory axis that governs nutrient absorption, gut motility, intestinal permeability, and broader biochemical, metabolic, and neurohormonal balance. Disruption of this axis compromises these homeostatic processes and may trigger disorders affecting the brain, gut, heart, and even cancer development [100].

Remarkably, this axis appears to be part of a broader, multicentric regulatory network involving multiple organ systems, including the brain (e.g., anxiety, depression), endocrine system (metabolic and hormonal disorders), cardiovascular system (heart disease, thrombosis), lungs (chronic obstructive pulmonary disease), liver (cirrhosis), pancreas (diabetes), and bones (osteoporosis), among others. Dysregulation within this network contributes to the pathogenesis of a wide range of systemic diseases [15].

Although the role of the gut–brain axis in disease is increasingly recognized, the precise pathways through which microbiome-induced neuroinflammation contributes to cancer and HF remain incompletely understood. Advanced imaging techniques and biomarker-based studies are needed to clarify the temporal and mechanistic aspects of this complex interplay.

Much of the current understanding of the gut–brain–heart axis stems from animal studies and observational human data. The precise pathways through which microbiome-driven neuroinflammation influences cancer and HF progression in humans remain largely hypothetical and warrant further clinical validation.

Is there a connection among these clinical states and genomic alterations?

4. Microbiome Relation to Genomic Mutation and Instability

The connection between cancer and an altered microbiome or metabolic environment, specifically dysbiosis, is well recognized [98,114]. Three key mechanisms explain the interplay between the microbiome, its metabolites, and the initiation and progression of cancer: inflammation, impaired intestinal permeability, and genomic damage. The first two mechanisms have been discussed previously. The third involves direct interactions between the microbiome and host DNA, as dysbiotic microbial communities and their toxic metabolites promote DNA damage, a phenomenon observed in both cancer and cardiovascular diseases.

DNA is a dynamic molecule that constantly undergoes replication and recombination. The fidelity of these processes depends on the cell's ability to detect and repair abnormalities. However, when the frequency or intensity of DNA-damaging factors exceeds the repair capacity, lesions such as base mismatches, single- or double-strand breaks, and DNA adducts can occur. These abnormalities lead to defective sequences and the production of dysfunctional proteins. The accumulation of such DNA damage is a central driver of cellular mutations and, ultimately, tumorigenesis [114,115].

Microbes residing in various organs, especially the gastrointestinal tract, have also been detected within tumors, forming what is known as intratumoral microbiota. These microbial populations are closely associated with cancer development [116]. Intratumoral microbiomes, particularly those located near human leukocyte antigens (HLA-I and HLA-

II), differ significantly from the microbiota of adjacent healthy tissue and vary across different tumor types [117–119].

Microbiota-induced DNA damage can occur either directly, as described, or indirectly through increased production of free radicals [120]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) can modify DNA bases; for instance, through the formation of 8-hydroxy-deoxyguanosine, which results in G→T transversions. These mutations contribute to malignancy by disrupting tumor suppressor genes such as *p53*, stabilizing hypoxia-inducible factors (HIFs), and activating transcription factors like nuclear factor kappa B (NF-κB) and activator protein-1 (AP-1) [121].

Beyond genetic mutations, microbiome dysbiosis can also promote disease through epigenetic modifications. These include chemical alterations to DNA and histones, such as methylation and acetylation, that influence gene expression without altering the DNA sequence itself [122–124]. Certain microbial metabolites, particularly SCFAs (e.g., butyrate) and secondary bile acids, can modify the activity of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), thereby altering DNA methylation patterns [125]. Chronic inflammation and oxidative stress triggered by dysbiosis may promote hypermethylation of tumor suppressor gene promoters or global DNA hypomethylation—both hallmarks of cancer development [126,127]. Changes in histone acetylation can further affect chromatin accessibility and gene transcription, influencing key processes such as cell cycle regulation, apoptosis, and inflammation [127].

Although the role of microbiome-induced epigenetic alterations in HF is less well understood, emerging evidence suggests that oxidative and inflammatory environments driven by dysbiosis can induce epigenetic reprogramming in cardiac tissue. This may contribute to myocardial remodeling, fibrosis, and progression of HF [122,124]. Thus, epigenetic changes represent a crucial mechanistic link between microbiome dysbiosis, oncogenesis, and cardiac dysfunction.

In the context of cardiovascular disease, although the underlying mechanisms remain incompletely defined, gene mutations resulting in abnormal protein expression are increasingly recognized as contributing factors [128,129]. Each individual carries unique genomic variants, including single nucleotide polymorphisms and larger chromosomal abnormalities, which account for approximately 85% of the known genetic variation associated with disease susceptibility [130,131].

These variants can shape disease phenotypes and, conversely, the phenotype may influence microbiome composition. Altered gene expression can directly or indirectly impact microbial populations, which may, in turn, influence disease manifestation. This highlights a strong association between genetic variation and the development of diseases such as cancer and cardiovascular conditions [132].

Notably, associations have been documented between gut microbiota or their metabolites and HF, as well as with its major risk factors, including diabetes, hypertension, myocarditis, myocardial ischemia, arrhythmias, and both hypertrophic and dilated cardiomyopathies [133]. MicroRNAs (miRNAs), small, non-coding RNAs that regulate gene expression by modulating mRNA degradation and translational repression, play vital roles in processes such as cell differentiation, proliferation, and apoptosis [134]. A bidirectional relationship exists between miRNAs and the microbiome: miRNAs can influence microbiome composition and activity, while the microbiome can affect host miRNA expression through its metabolic and inflammatory effects [120,135].

This reciprocal interaction significantly shapes the development of various diseases, including cancer and cardiovascular disorders.

While the epigenetic influence of the microbiome on cancer development is becoming clearer, its role in HF remains underexplored. Future research should focus on elucidating

how microbiome-driven DNA methylation and histone modifications contribute to cardiovascular disease. Epigenome-wide association studies conducted in well-characterized patient cohorts could offer valuable insights.

5. Insulin Resistance, Hyperinsulinemia, and Their Link to the Microbiome

Insulin resistance, characterized by impaired glucose uptake and utilization, is a central feature of metabolic syndrome, which is strongly linked to both cancer and cardiovascular disease [136]. Hyperinsulinemia—resulting from compensatory pancreatic insulin secretion—fosters a pro-inflammatory, pro-oxidant, and pro-growth environment, conducive to tumor progression and myocardial remodeling. Emerging evidence highlights the gut microbiome as a key modulator of insulin sensitivity, through direct and indirect mechanisms involving microbial metabolites, immune activation, and intestinal permeability [137].

The gut microbiota influences systemic metabolism via SCFAs, LPS, TMAO, and BCAAs. For example, SCFAs such as butyrate have anti-inflammatory and insulin-sensitizing properties [138], while BCAAs and LPS are associated with metabolic inflammation and IR [139,140]. In HF, congestion and gut ischemia promote dysbiosis, favoring Gram-negative bacterial overgrowth and LPS translocation, which activates TLR4 signaling and contributes to systemic insulin resistance [141,142].

In cancer, hyperinsulinemia supports tumor growth by activating insulin and IGF-1 receptors, promoting mitogenic signaling via PI3K/Akt and MAPK pathways [143–145]. In parallel, IR impairs mitochondrial efficiency and oxidative metabolism, both of which are disrupted in cancerous and failing myocardial cells. This metabolic derangement is exacerbated by dysbiosis-induced systemic inflammation and oxidative stress, creating a vicious cycle where microbiota, metabolism, and immune responses reinforce disease progression.

Hyperinsulinemia may modulate the tumor microenvironment, impair immune surveillance, and alter drug metabolism—effects that are influenced by microbiota-derived metabolites [146]. For instance, TMAO, produced from dietary choline by gut microbes, is elevated in IR states and is associated with both atherosclerosis and tumor angiogenesis [147].

Intervening on the gut microbiome may attenuate insulin resistance and, by extension, mitigate progression of HF and cancer. Prebiotics, probiotics, and dietary interventions (e.g., Mediterranean diet, fiber-rich intake) have been shown to restore microbial balance and improve insulin sensitivity [148]. Furthermore, emerging strategies such as fecal microbiota transplantation (FMT) and targeted microbial metabolite modulation (e.g., SCFA enhancement, LPS inhibition) may hold promise [149].

Metformin—a cornerstone antidiabetic drug—also exerts microbiome-modulating effects, increasing the abundance of *Akkermansia muciniphila*, a bacterium associated with improved metabolic outcomes [150]. Notably, metformin has shown antitumor effects in epidemiological studies, further linking insulin pathways, microbiota, and cancer biology.

Although associations between dysbiosis and insulin resistance are well-documented, it remains uncertain whether microbiome modulation can consistently reverse insulin resistance in clinical settings. Interventional studies employing probiotics, dietary fiber, or fecal microbiota transplantation are needed to test this therapeutic potential.

6. Microbiome Stabilizing Strategies

Several pharmacological and non-pharmacological interventions are essential in the management of both cancer and cardiovascular diseases. Non-pharmacological strategies, such as exercise training, lifestyle modifications, and adherence to a Mediterranean diet,

have demonstrated beneficial effects on these conditions [151]. While their positive impact is well documented, potential adverse effects have also been reported [152,153]. These interventions can influence the composition and bioavailability of the intestinal microbiome, thereby affecting metabolic processes, immune cell function, and other host responses.

For example, excessive consumption of high-fat foods can increase the levels of harmful microbial metabolites such as TMAO, LPS, PAGIn, and phenylacetylglutamine, all of which are associated with adverse health outcomes [154–158].

Beyond lifestyle interventions, both cardiovascular disease and cancer require pharmacological treatment. However, it is important to recognize that an altered gut microbiome can interfere with drug pharmacokinetics and pharmacodynamics [159–162]. For instance, the effectiveness of β -blockers [162,163], sodium-glucose cotransporter-2 (SGLT2) inhibitors [164,165], and RAAS inhibitors [110,166] may be reduced in the presence of dysbiosis, potentially leading to suboptimal therapeutic outcomes.

A similar phenomenon is observed with many anticancer therapies. The microbiome and its metabolites—through metabolic, immune (both innate and adaptive), epigenetic, and inflammatory pathways—can influence the effectiveness of immunotherapy [167]. As noted, “the gut microbiota may interact with oncogenic pathways, including epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and Kirsten rat sarcoma viral oncogene homolog (KRAS)” [168]. This highlights how gut microbiome alterations can affect not only cancer development and progression but also the response to cancer treatment.

Changes in the microbiome have also been linked to drug resistance. This may occur through mechanisms involving DNA damage, altered drug metabolism, and modifications of the tumor microenvironment [169]. As a result, toxic microbial byproducts may reduce the efficacy of targeted therapies and contribute to tumor growth and progression [170,171]. Specific examples include:

- Irinotecan, a pro-drug used to treat colorectal cancer, is metabolized into the active compound SN-38, a topoisomerase inhibitor. SN-38 can cause DNA damage and severe, potentially life-threatening toxicity [172].
- Gemcitabine, a nucleoside analog used in multiple cancers, can be inactivated by microbial enzymes that convert it into 2',2'-difluorodeoxyuridine, thereby reducing its therapeutic effectiveness [173].
- Cyclophosphamide, a widely used chemotherapeutic agent, exerts some of its effects through immune modulation—a process also influenced by the gut microbiome [174].

The interaction between the microbiome and pharmacological agents is now well established, prompting growing interest in stabilizing the microbiome to optimize drug responses. Notably, different tumor types have been associated with distinct microbial profiles [175,176], emphasizing the need for personalized treatment strategies based on an individual's microbiome composition.

In this context, antibiotic therapy targeting specific bacterial species has shown promise. For example, antibiotics targeting *Bacteroides* species have been linked to improved survival in patients with metastatic renal cell carcinoma receiving first-line VEGF tyrosine kinase inhibitors [177]. However, contradictory results in other cancer types suggest that the broad use of antibiotics may not always be beneficial [178].

An emerging area of interest is the use of probiotics and prebiotics to stabilize the gut microbiota. Probiotics—live microorganisms that support health—can help maintain mucosal integrity, regulate intestinal motility, and suppress pathogenic bacteria [11,179]. For instance:

- Lactobacilli produce antioxidant and anti-angiogenic compounds, reduce DNA damage, and mitigate inflammation [180].

- Bifidobacterium species have demonstrated the ability to activate the innate immune system and exhibit anti-cancer properties, particularly in lung, cervical, and breast cancers [180].
- Inulin and galacto-oligosaccharides (GOS) can stimulate immune responses and have shown anticancer potential [181].

Prebiotics, which promote the growth of beneficial gut bacteria, also exert protective effects by modulating intestinal metabolism [179]. A notable example is GOS, a class of carbohydrates found naturally in breast milk. These compounds enhance the production of beneficial cytokines such as interleukin-8 (IL-8), interleukin-10 (IL-10), and C-reactive protein, while reducing harmful ones such as interleukin-1 β (IL-1 β) [179].

Recent advances in microbiome research highlight the potential benefits of personalizing interventions based on individual microbial profiles to improve the treatment of both cancer and HF. In the context of HF, targeting the gut microbiome may offer an adjunctive strategy to modulate systemic inflammation, improve metabolic parameters, and restore intestinal barrier function. Dietary interventions such as increased fiber intake and adherence to a Mediterranean diet have been associated with enhanced SCFA production, improved endothelial function, and reduced cardiovascular risk [148,151]. Probiotic supplementation, particularly with *Lactobacillus* and *Bifidobacterium* species, has shown promise in small clinical studies by attenuating inflammatory cytokine release and improving left ventricular function [180,182]. Fecal microbiota transplantation, though still experimental in cardiovascular settings, offers a way to re-establish a eubiotic microbial ecosystem and has been shown to reduce insulin resistance and systemic inflammation in metabolic disease models. Integration of these interventions into HF management may be especially relevant for patients with comorbid metabolic syndrome, obesity, or gut-derived inflammation, further helping to attenuate systemic inflammation, improve metabolic profiles, and slow cardiac remodeling [182]. In oncology, specific microbial signatures have been associated with responses to immune checkpoint inhibitors and chemotherapy, suggesting that modulating the microbiome could enhance antitumor immunity and reduce drug resistance [183]. Precision microbiome-based interventions offer the possibility of reducing treatment-related toxicity, enhancing therapeutic efficacy, and preventing disease progression by restoring a balanced host–microbiome interaction tailored to each patient’s unique microbial ecosystem.

Although microbiome-targeted therapies are promising, the optimal strategies for specific patient populations remain undefined. Personalized microbiome interventions, tailored to an individual’s microbial profile and disease phenotype, should be a major focus of future clinical trials.

7. Challenges to Be Addressed and Strengths of the Manuscript

Although numerous studies support a link between the intestinal microbiome environment and both cancer and cardiovascular diseases, several critical challenges remain. There is a pressing need to generate robust, high-quality evidence to better understand this relationship. Specifically, longitudinal studies are required to determine whether alterations in the microbiome are a cause or a consequence of cancer and/or cardiovascular diseases.

To draw such conclusions, advancements in diagnostic techniques for accurately characterizing microbiome composition are essential. Current methods, such as analyzing blood or fecal samples to identify microbial biomarkers, are widely used but carry notable limitations. In order to improve accuracy and interpretation, it is imperative to first establish a clear definition of what constitutes normal microbiota [184], and to further stratify microbiome profiles by sex and age [185]. Additionally, expanding and refining

existing microbiome databases is necessary to overcome current limitations in reference datasets [186].

Although the gut microbiome has been extensively studied in relation to individual disease states such as HF or cancer, its role as a shared pathophysiological bridge between these two major conditions remains underexplored. This review provides a novel and integrative perspective by examining how microbiome-derived metabolites such as TMAO, LPS, and SCFAs, influence common biological pathways including inflammation, immune modulation, metabolic dysfunction, and oxidative stress. We introduce the concept of a “gut–heart–tumor” axis and propose that microbial dysbiosis represents a unifying mechanism driving both cardiac and oncologic disease progression. Furthermore, this review synthesizes emerging evidence on the bidirectional interplay among the gut, heart, and brain, and explores therapeutic opportunities through microbiome modulation. By bridging cardiology, oncology, and microbiome science, our review offers a comprehensive framework that advances current understanding and suggests novel avenues for prevention and treatment in comorbid disease states.

8. Conclusions

In conclusion, HF, cancer, and the gut microbiome are not isolated entities but are deeply interconnected through shared biological mechanisms, including chronic inflammation, microbial dysbiosis, immune and neurohumoral modulation, and metabolic derangement. These findings support the concept of a microbiome-centered axis involving the gut, heart, and tumors, which may underlie many chronic disease processes. Recognizing the microbiome as a dynamic contributor to both cardiac and oncological health opens new frontiers for targeted interventions. Although preclinical studies have established compelling mechanistic links between microbial metabolites and both cardiovascular and oncologic pathology, translation into clinical practice remains in its early stages. Most human data are associative or observational, and causality has not been firmly established. Rigorous longitudinal studies, interventional trials, and multi-omics approaches are essential in order to validate microbiome-derived biomarkers and personalize prevention and treatment strategies in patients with concurrent HF and cancer. Modulating the gut microbiota through diet, probiotics, or pharmacological agents may offer a promising therapeutic avenue to simultaneously address the burden of cancer and cardiovascular disease.

Author Contributions: Conceptualization, I.P.; methodology, I.P. and C.K.; investigation, E.T. and C.K.; original draft preparation, I.P.; writing—review and editing, I.P., C.K. and E.T.; supervision, I.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

AP-1	Activator Protein-1
BCAA	Branched-Chain Amino Acids
CNS	Central Nervous System
EGFR	Epidermal Growth Factor Receptor
GOS	Galacto-Oligosaccharides
HF	Heart Failure
HIF	Hypoxia-Inducible Factors
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigens
IL	Interleukin

KRAS	Kirsten Rat Sarcoma
LPS	Lipopolysaccharides
miRNAs	MicroRNAs
NF-κB	Nuclear Factor Kappa B
PAGIn	Phenylacetylglutamine
RAAS	Renin-Angiotensin-Aldosterone System
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SCFAs	Short-Chain Fatty Acids
SGLT2	Sodium-Glucose Cotransporter-2
TMAO	Trimethylamine N-oxide
VEGF	Vascular Endothelial Growth Factor

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Review

Targeting Inflammation and Iron Deficiency in Heart Failure: A Focus on Older Adults

Daniela Maidana ¹, Andrea Arroyo-Álvarez ¹, Guillermo Barreres-Martín ¹, Andrea Arenas-Lorient ², Pedro Cepas-Guillen ³, Raphaela Tereza Brigolin Garofo ⁴, Pedro Caravaca-Pérez ² and Clara Bonanad ^{1,5,*}

¹ INCLIVA—Biomedical Research Institute, 46010 Valencia, Spain; danumaidana.dm@gmail.com (D.M.); andreastream97@gmail.com (A.A.-Á.); guillbamar@gmail.com (G.B.-M.)

² Cardiology Department, Hospital Clínic Barcelona, 08036 Barcelona, Spain; pecarav86@gmail.com (P.C.-P.)

³ Quebec Heart & Lung Institute, Laval University, Quebec City, QC G1V 4G5, Canada; pedro.cepasguillen@gmail.com

⁴ Cardiology Department, Hospital do Coração, São Paulo 04004-030, Brazil; raphaelagarofa@outlook.com

⁵ Cardiology Department, University Clinical Hospital of Valencia, 46010 Valencia, Spain

* Correspondence: clarabonanad@gmail.com; Tel.: +34-689107071

Abstract: Background/Objectives: Heart failure (HF) is a leading cause of morbidity and mortality worldwide, with a higher prevalence among older adults. Iron deficiency (ID), affecting up to 50% of HF patients, is closely linked to chronic inflammation, exacerbating HF outcomes. This review aims to explore the interplay between inflammation, ID, and HF, focusing on older patients, and to identify therapeutic gaps and emerging treatment strategies. **Methods:** A comprehensive review of the literature was conducted, emphasizing the pathophysiological mechanisms of inflammation and ID in HF, the challenges of current diagnostic criteria, and the limitations of available treatments. Emerging pharmacological and diagnostic approaches were analyzed. **Results:** Chronic inflammation in HF, particularly in older adults, promotes functional ID through elevated hepcidin levels, impairing iron availability and worsening anemia. Current diagnostic criteria, relying heavily on ferritin, often misclassify ID due to inflammation. Intravenous (IV) iron therapy shows clinical benefits in patients with <50% left ventricular ejection fraction (LVEF), but the evidence is limited in heart failure with preserved ejection fraction (HFpEF). Emerging therapies, such as Sodium-Glucose Cotransporter-2 inhibitors (SGLT2is) and prolyl hydroxylase inhibitors like Roxadustat, offer promising avenues to improve iron metabolism and outcomes. **Conclusions:** ID and inflammation significantly impact HF progression, particularly in older adults. Refining diagnostic criteria and exploring innovative therapies are critical to addressing these challenges. Future research should prioritize personalized approaches targeting inflammation and ID, especially in underrepresented populations, such as HFpEF and elderly patients.

Keywords: heart failure; iron deficiency; inflammation; older adults

1. Introduction

Heart failure (HF) remains a leading cause of morbidity and mortality worldwide [1]. The prevalence of HF ranges from 1% to 5%, with significantly higher rates among older adults, and is expected to rise further, driven in part by an aging population [2]. However, these numbers may be underestimated, as HF is often underdiagnosed in older patients due to its overlap with geriatric syndromes such as frailty and multimorbidity [3], reinforcing the importance of addressing HF in these patients. These factors contribute to an increase

in the absolute number of HF hospitalizations, projected to grow by as much as 50% over the next 20 years [4], posing a substantial public health challenge.

In older adults, several aging-related factors, along with traditional risk factors such as hypertension, diabetes, and coronary artery disease, trigger structural and functional changes in the heart, increasing the incidence of HF [5]. One frequently overlooked but crucial aspect is iron deficiency (ID), which affects up to 50% of HF patients [6]. ID is closely linked to chronic low-grade inflammation, a condition commonly associated with aging [7]. The concept of “inflammaging” highlights how persistent inflammatory pathways in older adults contribute to an increased cardiovascular risk. Consequently, aging, chronic inflammation, and ID collectively exacerbate HF [8].

ID has emerged as a significant factor in heart failure with reduced ejection fraction (HFrEF) or heart failure with mildly reduced ejection fraction (HFmrEF), associated with a worse quality of life and a higher risk of adverse events. ID treatment has been shown to improve exercise tolerance and quality of life and reduce hospitalizations and mortality [4]. However, further evidence is needed on managing ID, especially in patients with heart failure with preserved ejection fraction (HFpEF) and older adults [9]. The divergent results from trials evaluating the role of ID in HF underscore the need for further research into the pathophysiology of HF and highlight the necessity of refining current definitions of ID in HF to improve patient outcomes [10,11].

This review aims to provide a comprehensive overview of the main pathophysiological mechanisms driving inflammation and ID in HF, focusing on older patients. We will address the ongoing controversies, the limitations of current treatments, and gaps in our understanding while discussing the latest pharmacological advancements and pivotal studies in this evolving field to improve patient outcomes.

2. Methods

A detailed literature review was conducted to comprehensively understand the interplay between heart failure, inflammation, and iron deficiency. The search included PubMed, Scopus, and Web of Science databases, focusing on articles published between 2010 and 2025, particularly in the last five years. Studies were selected based on their relevance to the relationship between these factors, especially in older adults. Keywords such as ‘heart failure’, ‘inflammation’, ‘iron deficiency’, and ‘older adults’ guided the search to ensure a thorough and focused analysis.

Scope of the Review

This review addresses the ongoing controversies, the limitations of current treatments, and gaps in our understanding while discussing the latest pharmacological advancements and pivotal studies in this evolving field to improve patient outcomes.

3. Pathophysiology of Heart Failure: Role Inflammation and Iron Deficiency

HF represents the final common pathway of numerous cardiovascular pathologies, driven by a complex interplay of hemodynamic, neurohormonal, metabolic, and inflammatory factors contributing to its onset and progression. Inflammation plays a pivotal role in the pathophysiology of HF by regulating key processes like fibrosis and ventricular remodeling [12]. In older patients, chronic low-grade inflammation and immunosenescence, combined with comorbidities, accelerate cardiac dysfunction, a progression that is particularly notable in those patients with ID [13]. In this section, we discuss how inflammation is linked with HF pathophysiology, the role of “inflammaging” in older adults, and the relationship of these processes to ID in this context (Figure 1).

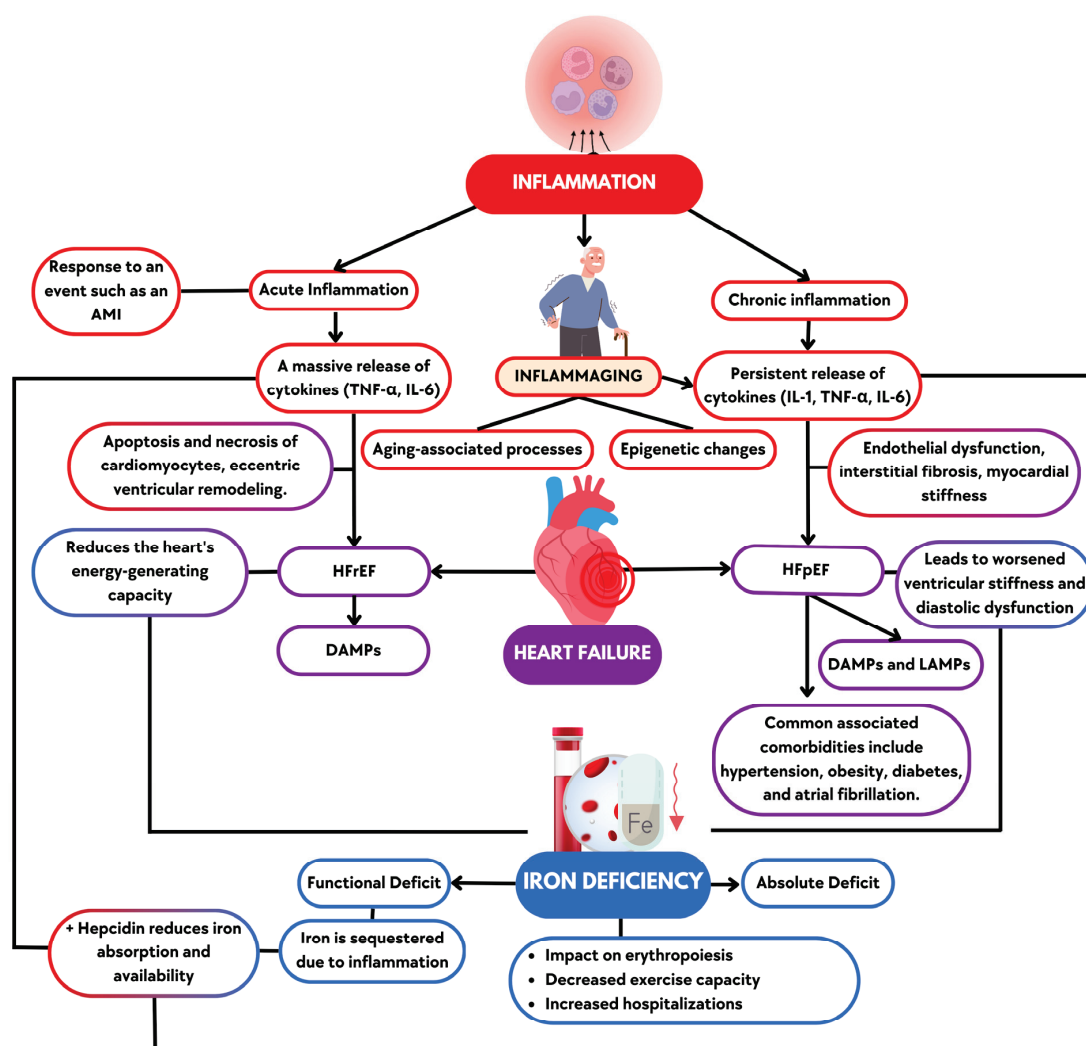


Figure 1. Inflammation and its role in heart failure with preserved and reduced ejection fraction. Acute inflammation, triggered by events such as heart attacks, is more closely associated with the development of heart failure with reduced ejection fraction (HFrEF), while chronic inflammation is more commonly linked to heart failure with preserved ejection fraction (HFpEF). Both types of inflammation, along with their respective forms of HF, contribute to impaired heart function and ID, which further exacerbates cardiac dysfunction. The background colors in the figure indicate specific concepts: blue represents ID, red denotes Inflammation, and purple corresponds to HF. Overlapping areas feature a combination of colors to emphasize the interplay between these conditions. AMI (acute myocardial infarction), DAMPs (damage-associated molecular patterns), HFpEF, HFrEF, IL-1 (Interleukin-1), IL-6 (Interleukin-6), LAMPs (lifestyle-associated molecular patterns), and TNF- α (Tumor Necrosis Factor-alpha). The blue represents Iron Deficiency, the red represents Inflammation, and the purple represents Heart Failure. Additionally, in the overlapping areas, the boxes are divided into two colors to highlight the relationship between these elements.

3.1. Inflammation in Heart Failure

Inflammation in HF can be categorized into acute or chronic [12]. Acute inflammatory episodes, such as those following an acute myocardial infarction (AMI), trigger an intense inflammatory response aimed at repairing tissue damage [14]. However, when this response is prolonged, it contributes to adverse myocardial remodeling, ultimately leading to HF [15]. During AMI, the massive release of proinflammatory cytokines like Tumor Necrosis Factor-alpha (TNF- α) and Interleukin-6 (IL-6) promotes the infiltration of inflammatory cells, which can lead to damage and the loss of cardiomyocytes, as well as fibrosis [16].

Chronic low-grade inflammation is even more insidious, occurring in individuals with comorbidities and closely associated with aging. These conditions create an unresolved inflammatory state involving effectors such as proinflammatory cytokines and components of the innate and humoral immune response, which contribute to the progressive dysfunction of the left ventricle (LV) [17]. Both HFrEF and HFpEF are influenced by inflammation but with distinct mechanisms and outcomes [11].

In HFrEF, the inflammatory process primarily targets cardiomyocytes, leading to their apoptosis and necrosis, which drives the eccentric remodeling of the LV, resulting in ventricular dilation and decreased contractile function [18]. In contrast, HFpEF involves endothelial dysfunction, increasing myocardial stiffness through interstitial fibrosis and impairing diastolic function [18]. HFpEF is now recognized as a systemic syndrome, where inflammation, aging, lifestyle factors, genetic predisposition, and comorbidities such as age, diabetes, hypertension, obesity, and atrial fibrillation play a significant role [19]. All of these factors lead to fibrosis, nitric oxide signaling deficits, and mitochondrial dysfunction, contributing to the structural and functional changes in the heart [20]. Finally, all of these inflammatory processes, affecting cardiomyocytes in HFrEF or endothelial function in HFpEF, are associated with molecular patterns that drive immune responses and contribute to disease progression [21].

The interaction between pathogens, tissue damage, and immune responses in HF can be understood through the concepts of pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), and lifestyle-associated molecular patterns (LAMPs) [22]. PAMPs originate from pathogens, and DAMPs from damaged tissues like after an AMI, while LAMPs are influenced by lifestyle factors like poor diet or inactivity. All of these patterns can dysregulate the immune system, leading to unresolved inflammation, chronic damage, and worsening HF [22]. Table 1 summarizes the main aspects that differentiate inflammation in HF.

Table 1. Differences in inflammatory mechanisms in HFrEF and HFpEF.

Aspect	HFrEF	HFpEF
Type of Inflammation	Primarily acute and chronic low-grade inflammation	Chronic low-grade inflammation
Triggering Events	AMI leading to an intense inflammatory response	Comorbidities and lifestyle factors create an unresolved inflammatory state
Primary Targets	Cardiomyocytes, leading to apoptosis and necrosis	Endothelial cells and interstitial tissue
Mechanism of Action	Proinflammatory cytokines (e.g., TNF- α and IL-6) promote inflammation and cell infiltration	Increased myocardial stiffness and fibrosis due to chronic inflammation
Outcomes of Inflammation	Eccentric remodeling, ventricular dilation, and decreased contractile function	Impaired diastolic function and increased myocardial stiffness
Associated Patterns	PAMPs and DAMPs	DAMPs with LAMPs
Influencing Factors	Focused on myocardial damage and inflammatory cell infiltration	Systemic syndrome influenced by aging, diabetes, hypertension, obesity, and atrial fibrillation

HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; AMI: acute myocardial infarction; TNF- α : Tumor Necrosis Factor-alpha; IL-6: Interleukin-6; DAMPs: damage-associated molecular patterns; LAMPs: lifestyle-associated molecular patterns; PAMPs: pathogen-associated molecular patterns.

3.2. Inflammation in the Older Patient

In older patients, the phenomenon of inflammaging—a chronic, low-grade inflammation that accompanies aging—plays a central role in the progression of HF and the development of ID [23].

Inflammaging involves chronic innate immune activation, leading to the release of inflammatory cytokines as Interleukin-1 (IL-1), TNF- α , and IL-6 that exacerbate HF mechanisms like Nuclear factor kappa B (NF- κ B) activation and NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome formation drive systemic inflammation, oxidative stress, arterial stiffness, and endothelial dysfunction, increasing cardiovascular risk [24]. This creates a cycle of inflammation that accelerates HF progression and adverse outcomes [25]. The upregulation of proinflammatory mediators like Interleukin-1 β (IL-1 β) and Interleukin-18 (IL-18) further exacerbates this, as both are implicated in cardiac fibrosis, hypertrophy, and diastolic dysfunction [26].

Moreover, in patients with HF, elevated levels of reactive oxygen species (ROS) damage cardiomyocytes, while chronic inflammation impairs iron regulation, worsening ID and its impact on HF [27]. In addition, the infiltration of proinflammatory M1 macrophages into the myocardium was observed more prominently in aging women, and reduced the presence of anti-inflammatory M2 macrophages and contributed to cardiac dysfunction. In contrast, male patients with end-stage cardiomyopathy display a higher presence of CD68-positive macrophages, highlighting sex differences in immune responses associated with inflammaging and HF progression [24].

3.3. The Role of Inflammation in Iron Deficiency

The link between inflammation and ID in HF is well-established and especially relevant in older patients [28]. Under conditions of chronic inflammation, as seen in HF and inflammaging, levels of IL-6 increase, which triggers hepcidin production [29]. Hepcidin reduces iron absorption in the intestines and sequesters iron in macrophages and hepatocytes. This primarily leads to functional ID, where iron stores are adequate but unavailable for essential processes such as hemoglobin synthesis and adenosine triphosphate (ATP) production in mitochondria [30]. Several studies have demonstrated the relationship between inflammation and ID [31–33]. Specifically, an international registry including 2329 HF patients found that increased plasma IL-6 concentrations were associated with lower iron, highlighting IL-6's role in the dysregulation of iron metabolism [29]. Inflammatory cytokines also inhibit erythropoiesis by impairing the bone marrow's response to erythropoietin, contributing to anemia [34]. In patients with HF, exacerbated inflammation promotes this state of functional ID. This interaction between inflammation, ID, and anemia increases stress on the heart and exacerbates HF symptoms, including fatigue and exercise intolerance [35].

3.4. Iron Deficiency in Heart Failure

ID is standard in patients with HF, affecting up to 50% of them, regardless of the presence of anemia [36]. According to HF practice guidelines, ID in HF is classified into two primary forms: absolute and functional. Absolute ID occurs when total body iron stores are depleted, while functional ID occurs when iron is sequestered in the body despite adequate stores, usually due to inflammation [27]. Both forms of ID are associated with poorer outcomes in HF patients, including reduced exercise tolerance, higher hospitalization rates, and increased mortality [37].

As previously explained, ID impacts hematopoietic function and directly affects cellular function due to its role in mitochondrial respiration and energy production [27]. In HF patients, ID is associated with reduced functional capacity, decreased quality of life,

and increased hospitalizations and mortality [38]. In HFrEF, ID directly contributes to myocardial dysfunction by reducing the heart's energy consumption. But ID not only impacts HFrEF, it is also prevalent in HFpEF, though the mechanisms by which it impacts cardiac and muscular performance may differ slightly from those observed in HFrEF [39]. Rather than contractility failure, HFpEF patients experience ventricular stiffness and diastolic dysfunction exacerbated by inflammation and ID [40].

4. Impact of Iron Deficiency on Heart Failure in Older Patients

In older adults with HF, a vicious cycle emerges from the interplay of multimorbidity, inflammaging, and inflammation [41]. Chronic inflammation, often driven by comorbidities, elevates hepcidin levels, leading to functional ID. This interaction significantly worsens prognosis, increasing hospitalizations and mortality [4]. The intricate relationship between aging, inflammation, and ID in HF highlights the need for a deeper understanding of these mechanisms to improve patient outcomes.

The Role of Aging and Inflammation in Iron Deficiency

Aging-related changes in immune function, termed immunosenescence and inflammaging, synergistically worsen iron dysregulation in older HF patients [23]. In this population, the inflammatory state becomes even more pronounced, as HF is associated with elevated levels of proinflammatory cytokines.

In this context, hepcidin, a central iron homeostasis regulator, leads to functional ID [42]. As a result, HF patients with ID experience disrupted mitochondrial function, impairing the electron transport chain and reducing oxidative phosphorylation, forcing the heart to rely on glycolysis for energy production [27]. This shift is partly driven by the Hypoxia-Inducible Factor (HIF) pathway, as ID stabilizes HIF by inhibiting prolyl hydroxylases, even in normoxic conditions. The activation of HIF target genes mimics a hypoxic response, further promoting glycolysis over oxidative metabolism. While glycolysis generates energy faster, it is less efficient, leading to diminished ATP production and compromised cardiac contractility, worsening HF outcomes [35].

Furthermore, the combined effects of aging, inflammation, and ID severely impair cardiac function and elevate the risk of hospitalizations in older HF patients [38]. Figure 2 summarizes how the combined impact of inflammation from HF and aging exacerbates ID, leading to increased hospitalizations and a worse overall prognosis.

A systematic review and meta-analysis examined the relationship between anemia and frailty in older adults [43]. The study found that frail individuals are more than twice as likely to present with anemia as their non-frail counterparts, underscoring the close association between these two conditions. The pooled prevalence of frailty among individuals with anemia was 24%, further highlighting the need to consider frailty when assessing OA with anemia [43].

On the other hand, a study involving 208 older hospitalized patients categorized by frailty revealed that inflammation significantly increased the prevalence of anemia, particularly in frail patients [44].

The diagnosis of ID in older patients is essential for improving outcomes. In older adults with multimorbidity, factors like frailty, malnutrition, and chronic diseases often contribute to anemia, making it challenging to differentiate ID related to HF from other causes of anemia. This challenge is especially relevant in frail patients, who are more likely to have elevated markers of inflammation that can obscure ID [45].

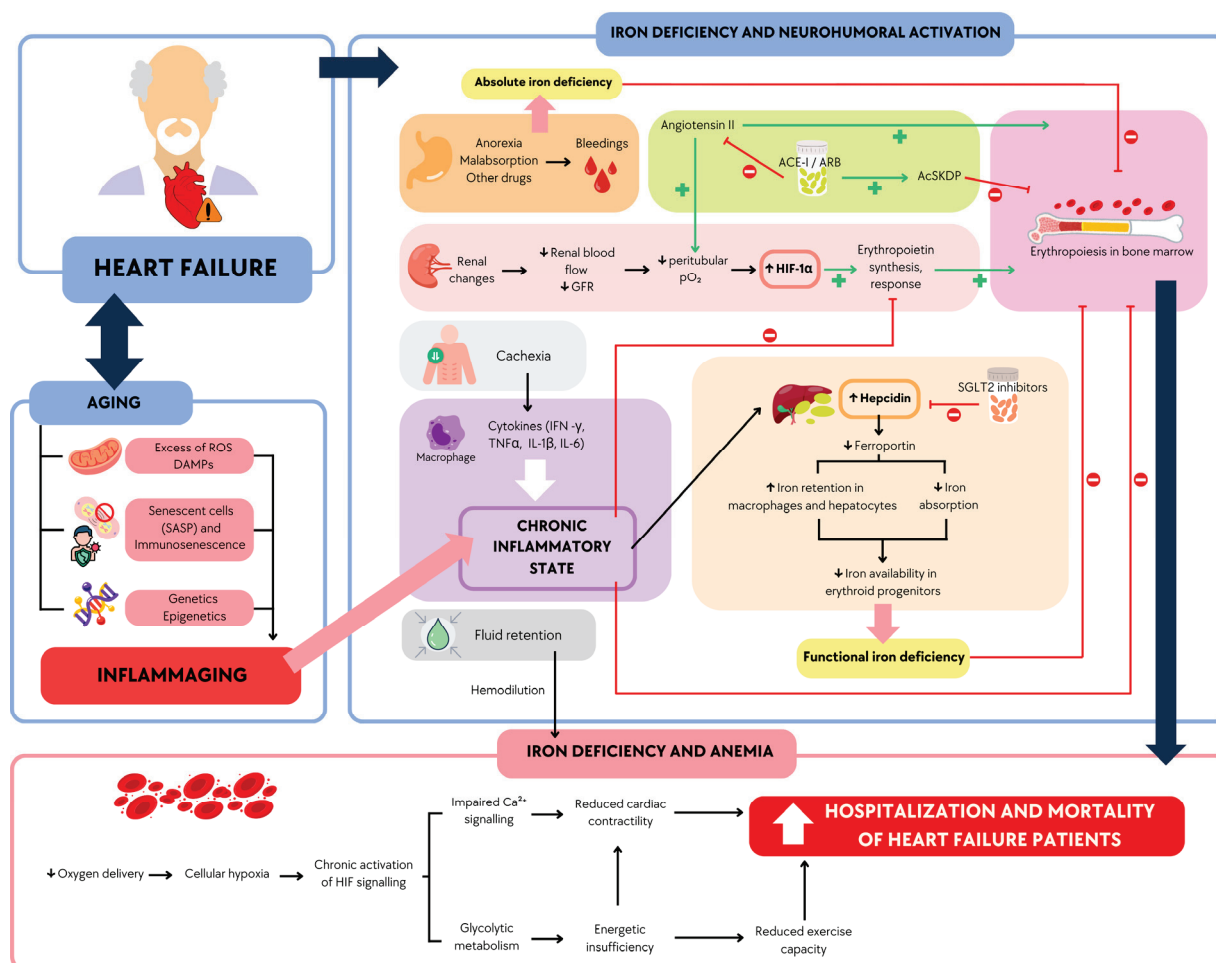


Figure 2. Main effects and interactions associated with HF in older patients: inflammation and iron deficiency. Older patients with HF experience renal changes, fluid retention, anorexia, poor nutrient absorption, cachexia, and immune and cytokine dysregulation, leading to a chronic inflammatory state. Additionally, due to age-related processes, they are affected by factors such as excess reactive oxygen species and cellular senescence, which contribute to systemic and chronic inflammation. Combined with medications used to treat HF, these factors result in anemia and functional iron deficiency, leading to increased mortality and hospitalizations in HF patients. Red lines indicate inhibition, while green lines represent positive stimulation. AcSDKP (N-acetyl-seryl-aspartyl-lysyl-proline), ACE-I (angiotensin-converting enzyme inhibitor), ARB (angiotensin receptor blocker), DAMPs (damage-associated molecular patterns), GFR (glomerular filtration rate), IL-1β (interleukin-1β), IL-6 (interleukin-6), ROS (reactive oxygen species), and SGLT2i (Sodium-Glucose Cotransporter-2 inhibitor).

5. Diagnosis, Treatment, and Therapeutic Challenges

Early diagnosis is critical because treating ID has been shown to improve clinical outcomes, reduce hospitalizations, and enhance the quality of life [4]. A retrospective study of older patients with HF showed that addressing ID early, particularly with intravenous (IV) iron, reduced the incidence of infections and improved functional capacity [46]. Therefore, screening for ID in older patients with HF should be a routine part of clinical care, as these patients are at a higher risk of complications from untreated ID.

The diagnosis of ID in HF patients relies on serum ferritin and transferrin saturation (TSAT) as primary biomarkers. Current guidelines define ID as a ferritin level <100 ng/mL or 100–299 ng/mL with TSAT < 20% [4]. However, this definition has sparked significant controversy due to the distortion of ferritin levels by systemic inflammatory states, commonly seen in older adults and patients with chronic conditions like inflammatory bowel

disease or chronic kidney disease (CKD) [31]. Additionally, as ferritin is an acute-phase reactant, its levels are often elevated in response to inflammation, potentially masking actual ID [47].

Packer et al. highlighted that nearly 25 years ago, the diagnostic threshold for ferritin in patients with HF was significantly increased—by 5- to 20-fold—to promote the use of iron supplements and improve the effectiveness of erythropoiesis-stimulating agents in treating renal anemia [10]. However, this change was driven by clinical necessity rather than studies on total body iron depletion. As a result, this threshold is not a reliable ID indicator in HF patients. He proposes that, in the context of HF, a TSAT threshold of less than 20% should be prioritized over ferritin levels to diagnose ID [10]. This approach emphasizes the need for a more precise ID marker, which helps identify patients who would most benefit from IV iron therapy [10].

Shifting the focus from ferritin to TSAT < 20% could lead to earlier interventions and better outcomes for HF patients, particularly older adults prone to both inflammation and ID [10,28]. This change in diagnostic criteria is particularly relevant in light of the evidence that patients with functional ID (low TSAT but normal ferritin) respond well to IV iron supplementation [10].

5.1. Clinical Trials Supporting Intravenous Iron Therapy

Current guidelines recommend IV iron therapy with ferric derisomaltose or ferric carboxymaltose for patients with HF and <50% left ventricular ejection fraction (LVEF) and ID, supported by evidence from clinical trials outlined in Table 2 [4]. These studies consistently show that IV iron alleviates symptoms, enhances functional capacity, and reduces hospitalizations in this population. However, despite the prevalence of ID and associated symptoms, similar recommendations do not extend to patients with HFpEF, where the evidence is less [40].

Regarding the differences between the use of one type of IV iron versus another, the IRONMAN and AFFIRM-AHF studies evaluated the administration of IV iron in patients with HF and ID, showing similar benefits in reducing hospitalizations. However, no statistical significance was reached in the reduction of cardiovascular mortality. Both studies suggest that IV iron, regardless of the type of complex used, provides a general benefit in these patients.

On the other hand, a study that evaluated the cost-effectiveness of ferric derisomaltose versus ferric carboxymaltose in patients with inflammatory bowel disease and ID anemia found that ferric derisomaltose not only improved patient quality of life but also reduced direct healthcare costs compared to ferric carboxymaltose [48].

Additionally, a systematic review and meta-analysis, which pooled data from four large-scale randomized controlled trials, suggested that ferric isomaltose was associated with a lower incidence of cardiovascular adverse events compared to ferric carboxymaltose in patients with ID anemia of various etiologies [49].

Potential explanations for these differences include the depletion of adenosine triphosphate and 2,3-diphosphoglycerate (critical intermediate metabolites) arising from hypophosphatemia, specifically proposed as a possible mechanism for cardiomyopathy and arrhythmia. It has been observed that ferric carboxymaltose results in a higher incidence of post-infusion hypophosphatemia compared to ferric derisomaltose [50,51]. However, further research is needed to confirm whether this also influences cardiovascular events. Recent studies suggest that ferric isomaltose may be associated with a lower incidence of severe hypersensitivity reactions than ferric carboxymaltose [52].

Table 2. Key clinical trials supporting intravenous iron therapy in heart failure. Evidence from “2023 Focused Update of the 2021 ESC Guidelines for diagnosing and treating acute and chronic heart failure”. ID: iron deficiency; LVEF: left ventricular ejection fraction; T: TSAT, transferrin saturation (%); F: ferritin ($\mu\text{g/L}$); CVM: cardiovascular mortality; HHF: hospitalization for heart failure; IV: intravenous.

Study	Number of Patients (n)	Patient Population and ID Definition	Intervention	Primary Outcomes	Key Findings
IRONMAN (2022) [53]	1137	HF patients (LVEF $\leq 45\%$). TSAT $< 20\%$ + ferritin < 400 or ferritin < 100 .	Ferric derisomaltose vs. usual care	Composite of total HF hospitalizations and cardiovascular mortality (CVM).	RR 0.82 (95% CI 0.66–1.02; $p = 0.070$); significant benefit post-COVID-19 analysis (HR 0.76, $p = 0.047$) in reducing primary endpoint.
Graham et al. (2023) [54]	3373	Meta-analysis of 10 trials; ferritin < 100 or ferritin 100–300 + TSAT $< 20\%$. IRONMAN also allowed TSAT $< 20\%$ with ferritin < 400 .	IV iron therapy vs. standard care	Composite of total hospitalization for heart failure (HHF) and CVM.	IV iron reduced total HHF and CVM (RR 0.75, 95% CI 0.61–0.93; $p < 0.01$), and first HF hospitalization or cardiovascular death (OR 0.72, $p = 0.04$).
AFFIRM-AHF (2020) [55]	1108	HF patients (LVEF $< 50\%$). Ferritin < 100 or TSAT $< 20\%$ + ferritin 100–299.	Ferric carboxymaltose vs. placebo	Total HF hospitalizations and CVM.	Ferric carboxymaltose reduced the risk of first HF hospitalization (RR 0.74; 95% CI 0.58–0.94; $p = 0.013$) and recurrent hospitalizations.
PIVOTAL (2019) [56]	2141	End-stage CKD patients on hemodialysis, with ferritin < 400 and TSAT $< 30\%$, and receiving erythropoiesis-stimulating agents.	High-dose IV iron vs. low-dose iron	First and recurrent HF events.	High-dose IV iron reduced HHF (HR: 0.66; 95% CI: 0.48–0.91; $p = 0.01$) in hemodialysis patients.
CONFIRM-HF (2015) [57]	301	HF patients (LVEF $\leq 45\%$) with ferritin < 100 or TSAT $< 20\%$ + ferritin 100–300.	Ferric carboxymaltose vs. placebo	Change in 6-min walk distance (6MWD) at 24 weeks.	Significant improvement in 6MWD ($+33 \pm 11$ m, $p = 0.002$); reduced HHF. HR 0.39; 95% CI: 0.19–0.82; $p = 0.009$.

5.2. Limitations and Controversies in Iron Supplementation

Although trials like FAIR-HF, CONFIRM-HF, AFFIRM-AHF, and EFFECT-HF (as outlined in Table 2) demonstrated the benefits of IV ferric carboxymaltose in improving symptoms, exercise capacity, and reducing hospitalizations in patients with HF and ID, recent findings from the HEART-FID trial have raised new questions regarding its impact on hard clinical endpoints [58].

In HEART-FID, IV ferric derisomaltose was associated with numerical improvements in all-cause mortality, heart failure hospitalizations, and 6 min walk distance. However, these differences did not reach statistical significance compared to placebo, likely due to the trial’s rigorous methodological design [58]. Unlike previous studies, HEART-FID employed strict inclusion criteria, enrolling a large and heterogeneous population with

detailed stratification by comorbidities and baseline characteristics. Additionally, the study featured an extended follow-up period and comprehensive assessments of patient outcomes, reducing the potential for bias but making it more challenging to demonstrate significant differences in mortality and hospitalizations [58].

These findings highlight the complexity of evaluating iron supplementation in HF populations and suggest that methodological rigor may influence outcome detectability. Moreover, differences in trial design, patient selection, and iron formulations (ferric carboxymaltose vs. ferric derisomaltose) could have contributed to the discrepancies observed across studies. Further research is needed to determine whether specific subgroups of HF patients, particularly those with more severe iron deficiency or a more significant inflammatory burden, may benefit most from iron supplementation. More extensive and longer-duration trials with refined patient stratification are required to fully elucidate the role of IV iron in improving hard clinical endpoints such as mortality and hospitalizations.

5.3. Response in Heart Failure with Preserved Ejection Fraction

While ID is standard in HFpEF patients, the current guidelines do not advocate for routine iron supplementation [4]. This discrepancy is primarily due to the limited evidence regarding the efficacy of iron treatment in this population. For example, the ferric carboxymaltose and exercise capacity in HFpEF and ID: the FAIR-HFpEF trial investigated the impact of IV iron on exercise capacity and the quality of life in patients with HFpEF and serum ferritin < 100 ng/mL or ferritin 100–299 ng/mL with TSAT < 20%. Although some patients experienced improvements, the overall results did not justify a broad recommendation of iron therapy in this group because the trial lacked sufficient power to identify or refute effects on symptoms or quality of life. Consequently, many patients with HFpEF continue to suffer debilitating symptoms, yet there is insufficient evidence to support routine iron supplementation [59].

The Trial of Exercise Training in Patients with Heart Failure and Preserved Ejection Fraction (TRAINING-HF) was a landmark study designed to evaluate the efficacy of structured exercise training in improving functional capacity and quality of life in patients with HFpEF. The trial demonstrated that tailored exercise programs significantly enhance peak oxygen consumption (peak VO₂), functional status, and symptoms in HFpEF patients, providing robust evidence for the role of physical training in this population. Moreover, the findings highlighted the influence of patient-specific factors, such as ID, on the overall response to therapy [60].

Building on these findings, a sub-study of TRAINING-HF by Palau et al. provides additional insights into the specific role of ID in modulating exercise response in HFpEF. This sub-study revealed that patients with ID, defined as ferritin levels < 100 ng/mL or TSAT < 20%, exhibited a markedly poorer response to exercise interventions compared to non-ID patients (p for interaction < 0.001). Specifically, individuals with lower baseline ferritin or TSAT showed less improvement in peak VO₂, a key marker of aerobic capacity and functional status [61]. These findings underscore the importance of evaluating and addressing iron status as part of the pre-exercise assessment in HFpEF patients to optimize therapeutic outcomes.

5.4. Impact of Pharmacologic Treatments on Iron Metabolism

Pharmacologic treatments for HF, such as Angiotensin-Converting Enzyme inhibitors (ACEis) and Angiotensin II Receptor Blockers (ARBs), may influence iron metabolism. ACEis and ARBs may affect iron metabolism by suppressing erythropoietin production [62]. This medication could exacerbate anemia and worsen ID in some patients [63]. Although

these drugs improve cardiovascular outcomes by modulating the Renin–Angiotensin–Aldosterone System (RAAS), their impact on iron regulation needs further exploration.

Conversely, Sodium-Glucose Cotransporter-2 inhibitors (SGLT2is) have shown promise in improving iron homeostasis by reducing hepcidin levels. By lowering hepcidin, SGLT2i may enhance iron mobilization, improving ID and HF outcomes in patients across the ejection fraction spectrum [64].

Finally, ACEis, such as sacubitril/valsartan, may influence iron metabolism. These drugs lower hepcidin and ferritin levels by reducing inflammation, improving iron availability, and promoting erythropoiesis [65]. However, they may also distort the interpretation of iron biomarkers, complicating the diagnosis and management of ID in HF [10]. Similarly, vericiguat has been associated with an increased incidence of anemia, as observed in the VICTORIA trial [66]. However, the underlying pathophysiological mechanism remains unclear due to the lack of ferric metabolism biomarkers collected during the study.

5.5. Clinical Implications and Management

Despite compelling evidence that TSAT < 20% is a more reliable marker of ID than ferritin, current clinical guidelines have not yet fully adopted this approach [4]. It is argued that reliance on ferritin thresholds is outdated, and TSAT is proposed to be prioritized to identify better patients who would benefit from IV iron therapy. This shift would align with the growing evidence showing that patients with hypoferrremia (TSAT < 20%) respond best to iron supplementation [10]. The role of pharmacologic treatments in managing ID also requires careful consideration. As noted, ACEis, ARBs, neprilysin inhibitors, and SGLT2is influence iron metabolism differently. Clinicians should consider these effects when interpreting iron biomarkers and making treatment decisions. For instance, SGLT2is may reduce hepcidin and improve iron availability, while ACEis and ARBs may exacerbate anemia by suppressing erythropoiesis.

Managing ID in HF, particularly in older adults, is essential for improving clinical outcomes. Recent guidelines emphasize the importance of regularly assessing iron status—measuring ferritin and TSAT levels—to identify and treat ID early [4]. While IV iron therapy has emerged as a valuable treatment for patients with symptomatic ID with HF and <50% LVEF, the situation remains unclear for those with HFpEF [59]. Additionally, addressing ID could enhance the effectiveness of exercise-based rehabilitation programs in HFpEF patients [61]. Managing ID may improve exercise tolerance and quality of life, but further research is needed to confirm these benefits [59,61].

High-dose IV iron, ferric carboxymaltose, or ferric derisomaltose can be administered in low-volume infusions. Ferric derisomaltose allows doses of up to 20 mg/kg in a 100 mL infusion over 30 min, enabling complete iron repletion in one session. It is recommended to routinely evaluate hemoglobin and iron status in hospitalized patients with LVEF or HFmrEF or during clinical visits when symptoms are present [28]. According to the AFFIRM-AHF and IRONMAN studies, IV iron should be administered before discharge in cases of ID in these patients [48,50].

Hemoglobin and iron levels should be monitored between 4 weeks and 4 months after the initial dose, followed by one or two annual reviews. If TSAT is below 20%, an additional dose will be necessary. Recurrent iron deficiency could indicate active blood loss. Therefore, testing for occult blood in feces and urine is suggested as a diagnostic measure [28].

The inflammatory burden, combined with ID, complicates the management of HF patients, particularly in older adults who often face concurrent conditions. This complex interplay between immunosenescence and HF-induced inflammation creates a cycle that accelerates disease progression and limits the effectiveness of therapeutic interventions, in-

cluding physical rehabilitation [67]. To achieve better outcomes, clinicians should consider the impact of pharmacologic treatments on iron metabolism and tailor their management strategies accordingly.

5.6. Erythropoiesis-Stimulating Agents (ESAs) in HF: Clinical Considerations and Risks

Erythropoiesis-stimulating agents (ESAs), such as darbepoetin alfa and epoetin alfa, have been explored as potential therapies for anemia in HF, aiming to improve oxygen delivery and exercise capacity [68]. However, their clinical utility remains controversial due to safety concerns and limited efficacy in HF patients [69].

The RED-HF trial, one of the most extensive studies evaluating ESAs in HF, found that darbepoetin alfa effectively increased hemoglobin levels but did not reduce mortality or HF hospitalizations. Additionally, there was a higher incidence of thromboembolic events and stroke in patients receiving ESAs compared to placebo, raising concerns about their safety in this population [70].

From a clinical management perspective, ESAs stimulate erythropoiesis, increasing iron demand, which can lead to functional ID if iron stores are inadequate. This effect highlights the importance of ensuring sufficient iron availability before considering ESAs in HF patients. Moreover, these agents can worsen hypertension, increase blood viscosity, and promote thrombosis, which could offset potential benefits in cardiovascular populations [71].

Given these risks, current guidelines do not support the routine use of ESAs for anemia management in HF [4]. Instead, they recommend prioritizing IV iron supplementation, which has demonstrated excellent safety and efficacy in improving symptoms and reducing hospitalizations. Future research may help identify whether specific low-risk subgroups could benefit from ESA therapy without significant adverse effects [72].

6. Future Directions: Emerging Research and Therapeutic Approaches

Diagnostic criteria for ID in chronic HF patients may be inadequate and potentially misleading, as they rely too heavily on serum ferritin and TSAT thresholds. Ferritin alone may not accurately reflect functional ID, as inflammation and other non-iron-related factors common in HF can be influenced by inflammation. This imprecision may include patients unlikely to benefit from iron supplementation, excluding those who could experience significant clinical improvements. A re-evaluation of these biomarkers is needed to identify better the clinically relevant ID to HF. A refined definition could enable more targeted and effective therapeutic interventions in this population [10].

ID and inflammation play a key role in chronic HF, with distinct inflammatory pathways potentially requiring tailored therapeutic approaches. HFrEF and HFpEF may exhibit different inflammatory profiles, suggesting that a standardized approach to iron supplementation may not be optimal for all patients. This variation underscores the need for targeted research, especially in elderly patients with multiple comorbidities, who are often underrepresented in clinical trials despite constituting a significant portion of the chronic HF population [73]. Ongoing studies aim to address specific ID mechanisms across different HF phenotypes by examining the role of inflammation and its impact on iron metabolism. The ongoing IRON-PATH II (NCT05000853) seeks to elucidate the specific mechanisms of ID across different HF phenotypes by examining the role of inflammation and its impact on iron metabolism. By clarifying these mechanisms, this study hopes to pave the way for more individualized and effective iron repletion strategies that consider the unique inflammatory and iron-handling characteristics of each HF subtype [74].

A promising area of research involves targeting IL-6 to mitigate inflammation in HF patients. Ziltivekimab, a human monoclonal antibody targeting the IL-6 ligand, has

effectively reduced inflammatory biomarkers in patients with chronic kidney disease and elevated hs-CRP levels [75]. The ongoing HERMES trial evaluates the effects of ziltivekimab on morbidity and mortality in patients with HFmrEF or HFpEF and systemic inflammation [76]. Tocilizumab, another IL-6 inhibitor, has been explored in inflammatory conditions such as rheumatoid arthritis and has shown potential in reducing systemic inflammation [77]. While preliminary studies suggest that IL-6 inhibition may play a role in cardiovascular diseases, its specific effects in HF remain to be fully established [78,79]. Further research is necessary to confirm the efficacy and safety of IL-6 targeted therapies in managing inflammation and ID in HF.

Limitations and Controversies in Iron Supplementation

Although trials like FAIR-HF and CONFIRM-HF demonstrated the benefits of IV ferric carboxymaltose in improving symptoms and exercise capacity in HfmrEF, specific analyses revealed no significant differences in hard endpoints such as mortality or hospitalizations when compared to placebo. The limited sample sizes, short follow-up durations, or the inherent heterogeneity of HF populations might explain these discrepancies. Such findings highlight the need for further research to determine whether specific subgroups may derive more pronounced benefits from iron supplementation.

A deeper understanding of iron homeostasis has provided insights into the interrelation of iron biomarkers, presenting new opportunities for improving ID management in HF patients [80]. In this regard, clinical trials are testing agonists and blockers for therapeutic use, mainly testing them for use in hematological diseases [81]. In HF, treatment with an SGLT2i has shown biomarker changes consistent with improved iron utilization by increasing serum transferrin receptors and reduced ferritin, TSAT, and hepcidin. The reduction in plasma hepcidin is consistent with an enhanced capacity for iron absorption and increased mobilization of iron from sequestered stores [82]. A post hoc analysis of the IRONMAN trial revealed a trend to a more significant increase in hemoglobin with ferric derisomaltose in ID patients taking an SGLT2i at baseline, as compared with those not taking one [82].

Additionally, findings from the Randomized Trial of Empagliflozin in Nondiabetic Patients with Heart Failure and Reduced Ejection Fraction (EMPA-TROPISM trial) suggest that empagliflozin, an SGLT2i, reversed cardiac remodeling and increased physical capacity in stable nondiabetic patients with HFrEF [67]. A post hoc study explores whether treatment effects in this cohort, comprising patients with a high ID prevalence, were related to iron metabolism. The analysis indicated that empagliflozin might positively influence iron metabolism in HF patients by reducing inflammation and influencing hepcidin levels and iron homeostasis [83]. These results align with the observed hepcidin-lowering effects of SGLT2i, supporting their potential to improve iron mobilization and utilization in patients with HF with ID by enhancing the release of iron from storage sites and facilitating its availability for erythropoiesis [83]. Sub-analyses from studies such as DAPA-HF suggest a modest rise in hemoglobin and hematocrit in patients with anemia, even though this was not a primary outcome [66].

The hepcidin modulation capability by dapagliflozin, an SGLT2i, is under investigation in the ADIDAS trial (NCT04707261), a study conducted on a large cohort of anemic HF patients [84]. Further studies are needed to elucidate whether SGLT2is can contribute to restoring iron balance and could be positioned as potentially beneficial drugs and another tool for treating ID [84]. Available evidence indicates that, although most studies on correcting ID in HF use IV iron, data suggest that SGLT2i indirectly improves iron homeostasis—primarily by reducing hepcidin and thereby increasing serum iron. While no specific clinical trials are focusing on correcting ID in older adults with HF through SGLT2is, an increasing number of reports show a partial improvement of chronic (functional) anemia

in patients with HF and type 2 diabetes under these medications, reinforcing a potentially beneficial interaction between SGLT2i, iron availability, and hematological parameters [82].

Exacerbated inflammation contributes to functional ID by increasing hepcidin levels, which restricts iron availability and exacerbates anemia [31]. Therefore, addressing inflammation with anti-inflammatory therapies is crucial in improving iron homeostasis in this scenario. Recently, the COLICA trial demonstrated a significant reduction in inflammation markers in acute HF patients treated with colchicine [85]. However, despite these changes in biomarkers, the study did not observe significant improvements in hard clinical endpoints, such as mortality or hospital readmission rates. These findings suggest that colchicine effectively reduces inflammation, but its broader clinical impact on HF remains uncertain. There is potential value in the further investigation of anti-inflammatory therapies specifically designed to address the unique inflammatory mechanisms at play in HF with ID. We can develop more targeted anti-inflammatory strategies that enhance iron mobilization and patient outcomes by refining our understanding of inflammation's role in iron metabolism across different HF phenotypes, including HFrEF and HFpEF and acute versus chronic presentations [70].

Emerging therapies such as Roxadustat, a Prolyl Hydroxylase inhibitor, represent a promising future direction for addressing anemia and iron metabolism disorders in HF. Roxadustat has shown the ability to reduce hepcidin levels and enhance iron absorption, effectively improving iron availability. While its current focus lies in nephrology, its application in HF populations could open new avenues for managing anemia and functional ID, especially in patients with concurrent CKD. Future trials in HF patients will be essential to evaluate its efficacy and safety within this context [86,87].

Future directions should focus on developing specific recommendations for iron therapy in HFpEF, as there is currently a lack of evidence-based studies supporting its use in this population despite the high prevalence of ID [9]. While IV iron therapy is well-supported for patients with HFrEF, the clinical complexity of HFpEF patients, most frequently presented in older people who often present with additional comorbidities and distinct inflammatory profiles, warrants further investigation. Ongoing and future clinical trials addressing the unique characteristics of HFpEF and interaction with ID will be crucial to determine whether iron supplementation could provide meaningful clinical benefits and establish more effective, tailored treatment strategies for this population [40,59].

7. Conclusions

ID and chronic inflammation are critical factors exacerbating the burden of HF, especially in older adults. The interplay between inflammaging, multimorbidity, and functional ID significantly worsens HF outcomes, leading to higher rates of hospitalizations and mortality. While IV iron therapy has demonstrated benefits in improving symptoms and quality of life and reducing hospitalizations in patients with HFrEF, its role in HFpEF remains uncertain due to limited evidence.

Current diagnostic criteria for ID in HF, primarily based on serum ferritin and TSAT, may not adequately reflect iron status in chronic inflammation. Emerging data suggest prioritizing TSAT thresholds over ferritin to more accurately identify patients who could benefit from iron supplementation. Additionally, novel therapies targeting inflammation and iron homeostasis, such as SGLT2i, show promise in improving iron mobilization and HF outcomes.

Future research should focus on refining diagnostic biomarkers for ID, exploring anti-inflammatory strategies, and conducting robust clinical trials to establish evidence-based recommendations for iron therapy in HFpEF and older adults with HF. Personalized

treatment approaches addressing the unique inflammatory and iron-handling profiles of HF subtypes and patient populations are essential to optimize clinical outcomes.

Author Contributions: D.M. conceived and designed the review. The manuscript was drafted by D.M., A.A.-L., P.C.-G. and R.T.B.G., with contributions to the figures by A.A.-Á., G.B.-M., P.C.-P., P.C.-G. and C.B. reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This work was conducted within the framework of the Spanish Health Research and Development Program (I+D+I) and the Juan Rodés (JR) program.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article as it is a review of existing literature.

Acknowledgments: The authors would like to express their gratitude to the JR team at the Hospital Clínico de Valencia, including administrative staff and nurses, for their invaluable support throughout this project. Their dedication and assistance have been essential to the completion of this review.

Conflicts of Interest: The authors declare no conflicts of interest.

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ISBN 978-3-7258-8916-7