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Therapies for Heart Failure

Clinical Updates and Perspectives

Edited by
Stela Iurciuc, Dragos Cozma and Cristina Tudoran

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Therapies for Heart Failure: Clinical Updates and Perspectives

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Editorial

Therapies for Heart Failure: Clinical Updates and Perspectives

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Although signs and symptoms of heart failure (HF) have been described since ancient times, and the term has evolved throughout history, there are still unanswered questions concerning its pathophysiology and best treatment options. The European Society of Cardiology provides dedicated, regularly updated guidelines for the management and treatment of HF [1–5]. The treatment of HF is very complex and not limited to drug therapy [6]. This reprint presents groundbreaking research into the causation and treatment of HF. This reprint is divided into four main parts.

The first part of "Therapies for Heart Failure: Clinical Updates and Perspectives" describes the mechanisms underlying HF, which could serve as targets for new therapeutic options [7–9]. Inflammation is a major pathophysiological mechanism responsible for the occurrence of acute coronary syndrome (ACS), contributing to atherosclerotic plaque destabilization [10], myocardial injury [11], and adverse clinical outcomes [12–16]. Inflammatory biomarkers, together with N-terminal pro–B-type natriuretic peptide (NT-proBNP), are increasingly used for risk stratification, yet their prognostic value in different ACS phenotypes remains unclear [17–19]. An unfavorable clinical profile, characterized by older age, impaired renal function, and reduced left ventricular systolic function, was associated with major adverse cardiovascular events (MACE) during index hospitalization in patients with ACS. Levels of inflammatory biomarkers (high-sensitivity C-reactive protein (hs-CRP), neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII)) and NT-proBNP were significantly higher among those who developed in-hospital MACE compared with those without events, with CRP showing the strongest association. These findings suggest that inflammatory biomarkers characterize the inflammatory status present in ACS and may provide complementary information regarding the inflammatory burden, whereas their incremental prognostic contribution beyond established clinical variables remains to be further clarified [17].

The research by Pah et al. suggests that systemic inflammation, characterized by elevated interleukin 6 (IL-6), hs-CRP, and NLR, is a strong and independent predictor of mortality and adverse outcomes in HF [20]. These biomarkers capture distinct yet complementary dimensions of the inflammatory cascade and provide additive prognostic

value beyond established clinical and neurohormonal indicators. IL-6 stands out as the most consistent and biologically plausible marker, supporting its dual role as both a mechanistic driver and a potential therapeutic target [21–23].

The second part focuses on associated comorbidities. Frailty is a major determinant of adverse outcomes in older adults with HF, and is often difficult to assess, especially in patients with acute HF [24–26]. Garcia et al. compared the manual short Physical Performance Battery (mSPPB) with an automated electronic SPPB (eSPPB) system to evaluate frailty in patients with decompensated cardiovascular disease (CVD). The automated eSPPB demonstrated good agreement with manual assessment and was significantly associated with 30-day mortality in hospitalized patients with HF, but these findings should be interpreted with caution and confirmed in larger multicenter studies before routine clinical use [27].

The COVID-19 pandemic posed new and unexpected challenges for cardiologists who managed patients with CVD and HF. Several studies demonstrated that CVD and systemic hypertension (SH) are associated with a worse prognosis in patients with COVID-19 [28,29]. In a single-center study, the combined presence of SH and pre-existing HF identified patients at increased risk for in-hospital mortality, admission to the intensive care unit, and prolonged hospitalization. This study concluded that the risk for developing complications during a COVID-19 infection was elevated in patients suffering from both AH and HF compared to those without cardiovascular comorbidities or with only SH [30]. A combined cardiovascular burden might be associated with increased inflammatory activation, as evidenced by elevated interleukin-6 levels at hospital admission. These findings highlight the clinical significance of systemic inflammation as a driver of disease severity in patients with preexisting cardiovascular conditions [30].

During this pandemic, physicians discovered that patients with HF infected with the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) had a higher incidence of unfavorable outcomes [31–33]. In hospitalized COVID-19 patients, pre-existing HF identifies a subgroup with heightened cardiac biomarker activation and a substantially higher burden of cardiovascular complications, but does not associate with sepsis or short-term mortality in this cohort after adjustment for inflammatory and cardiac biomarkers [30]. Inflammatory markers, particularly CRP and interleukin-6, together with high-sensitivity troponin, were independently associated with mortality in adjusted analyses, highlighting the central role of dysregulated host immune response and myocardial injury as proximal drivers of adverse outcomes. By contrast, NT-pro BNP and a prior diagnosis of HF reflected baseline myocardial stress and structural vulnerability, yet did not provide incremental prognostic information once dynamic biomarker profiles were considered [30].

The third part of "Therapies for Heart Failure: Clinical Updates and Perspectives" describes management and treatment options for HF. Acute decompensated heart failure (ADHF) is a cardiac emergency and often raises challenges for the treating physician, especially due to its complexity and associated comorbidities [34–38]. In a large, national cohort of adults hospitalized with ADHF, collected from the 2016–2020 Nationwide Inpatient Sample (NIS), weekend admission was associated with higher in-hospital mortality and increased odds of major complications, including cardiac arrest, compared with weekday admission. These results are consistent with the broader literature documenting a weekend effect across multiple conditions and settings, and with contemporary HF data highlighting vulnerability during off-hours [39–42].

HF represents a complex and heterogeneous syndrome that extends beyond myocardial dysfunction, encompassing dynamic interactions between cardiac, vascular, and systemic factors [43–45]. The integration of vascular function into precision medicine frameworks offers an opportunity to refine phenotypic classification and the understanding of the pathophysiological mechanisms of this disease. Arterial stiffness, as assessed by pulse

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wave velocity, represents a robust and physiologically relevant marker of vascular aging and cardiovascular risk. Its incorporation into multimodal phenotyping strategies may enhance risk stratification and support the identification of clinically meaningful subgroups within the heterogeneous spectrum of HF [46–49].

Contemporary guidelines [1,2] recommend rapid initiation of the four "pillars" of guideline-directed medical therapy (GDMT) for HF with reduced ejection fraction (HFrEF). In recent years, Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i) have established themselves as one of the four "pillars" for the treatment of HF [1,2,50]. A multidomain synthesis demonstrates that SGLT2 inhibitors provide consistent, robust reductions in mortality and hospitalizations, while also improving patient-reported health and functional status. Improvements in symptoms, quality of life, and cardiac remodeling are evident, but these results should be interpreted with caution, especially for acute HF and HF with preserved ejection fraction (HFpEF) [51].

In a study conducted on 1363 outpatients with HFrEF, with at least two years of follow-up, Lopez et al. demonstrated that the systematic introduction of ARNI and SGLT2i in the treatment of HFrEF was associated with improved ventricular function, reduced need for device implantation, and a significant improvement in two-year survival [52]. This benefit was independent of the baseline clinical characteristics of these patients. These data suggest that the systematic application of therapies guided by evolving guidelines and active titration strategies resulted in superior clinical outcomes and improved ventricular recovery [52].

By analyzing 27 studies and 73,174 patients with HF, Gómez-Ochoa et al. observed that a more complete GDMT at hospital discharge was associated with a lower cardiovascular event rate, with quadruple therapy having the best results on HF outcomes. Unfortunately, their data showed a suboptimal prescription of all four pillars of DDMT at discharge of patients hospitalized for HF [53]. On the other hand, real-world persistence, adherence, and dose optimization remain suboptimal. Data from a non-randomized sub-registry within the prospective Cardiology Research Dubrava (CaRD) registry evidenced that although in-hospital initiation of quadruple GDMT in patients with newly diagnosed HFrEF was feasible, maintaining long-term adherence and achieving target doses remained challenging. These data underscore the gap between guideline recommendations and routine practice and support structured follow-up and protocol-driven titration to optimize implementation [54].

The fourth part of this reprint suggests future perspectives for the treatment of HF.

Future prospective multicenter studies, stratification by HF phenotype, incorporation of inflammatory and cardiac biomarkers, arterial stiffness parameters, and associated comorbidities are needed to improve the assessment of HF [30,46,55]. Future research integrating myocardial, vascular, and systemic domains through advanced computational approaches is likely to redefine HF classification and pave the way toward truly personalized cardiovascular medicine [46]. Such approaches may enable earlier identification of high-risk patients and facilitate the development of customized therapeutic strategies that target both immune dysregulation and myocardial injury in severe COVID-19 [30,56,57]. Interventional research should explore whether targeted cardioprotective strategies, optimized guideline-directed HF therapy, and anti-inflammatory approaches (including IL-6–directed or broader immunomodulatory regimens) can mitigate the excess risk observed in patients with COVID-19 and concomitant AH and HF [30,58].

Structured follow-up, repeated patient education, and protocolized titration pathways may be required to sustain quadruple therapy and optimize dosing over time in HRrEF [54,59–64].

Further dedicated mechanistic studies in HFpEF and acute HF are needed to refine phenotype-specific understanding and to clarify the long-term structural and functional

implications of treatment with SGLT2i [51,65–67]. Applying standardized HF pathways, strengthening weekend coverage, and expanding 7-day diagnostic and critical-care services may help mitigate the weekend effect and promote more unbiased outcomes for patients hospitalized with ADHF, regardless of the day of admission [39,68,69].

Adequately powered randomized trials of protocolized in-hospital quadruple initiation are therefore the key next step to establish the incremental benefit of this approach and to close the gap between evidence and practice [53,70].

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Article

Prognostic Value of Inflammatory Status in Patients with Acute Coronary Syndromes: A Single-Center Experience

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Abstract

Background/Objectives: Acute coronary syndromes (ACS) encompass a spectrum of clinical entities from unstable angina to non–ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI), all associated with significant morbidity and mortality. Inflammation plays a central role in the pathophysiology of ACS, contributing to atherosclerotic plaque destabilization, myocardial injury, and adverse clinical outcomes. Inflammatory biomarkers, together with N-terminal pro–B-type natriuretic peptide (NT-proBNP), are increasingly used for risk stratification, yet their prognostic value across different ACS presentations remains unclear. This study aimed to assess the prognostic value of inflammatory status in patients with acute coronary syndromes in a single-center cohort. **Methods**: This prospective observational study included 100 consecutive patients with ACS and elevated inflammatory biomarkers, enrolled in 2024–2025 at a tertiary cardiovascular center. Inflammatory status was assessed by using C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII); NT-proBNP was also measured. The primary endpoint was in-hospital MACE, defined as cardiovascular death, recurrent myocardial infarction, stroke, urgent coronary revascularization, or acute heart failure requiring escalation of therapy. Multivariable logistic regression and ROC analyses were performed. **Results**: Among the 100 ACS patients, half experienced in-hospital MACE. Compared with those without events, patients with MACE were older ($p = 0.003$) and had higher inflammatory biomarkers—CRP ($p < 0.001$; strongest association), NLR ($p = 0.030$), and SII ($p = 0.042$)—as well as higher NT-proBNP ($p = 0.002$). Patients with MACE also showed reduced renal function ($p < 0.001$) and lower left ventricular systolic function, reflected by reduced LVEF ($p = 0.001$), indicating concomitant renal impairment and ventricular dysfunction. Hypertension was more prevalent in the MACE group ($p = 0.028$), and new-onset atrial fibrillation was significantly more common among these patients ($p < 0.001$). In multivariable analysis, LVEF emerged as an independent predictor of short-term outcomes (OR 0.934 per 1% increase; $p = 0.047$). **Conclusions**: Inflammatory activation appears closely linked to the occurrence of in-hospital adverse events in patients with acute coronary syndromes.

While left ventricular ejection fraction remained an independent determinant of short-term outcomes, inflammatory biomarkers may provide complementary insight into the inflammatory burden accompanying ACS.

Keywords: inflammation; myocardial infarction; C-reactive protein

1. Introduction

Acute coronary syndromes (ACS) remain one of the leading causes of morbidity and mortality worldwide, despite significant advances in diagnostic and therapeutic strategies. ACS encompasses a spectrum of clinical entities, including ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction and unstable angina, which result from the rupture or erosion of atherosclerotic plaques followed by thrombus formation and myocardial ischemia. Early risk stratification in these patients is essential for guiding therapeutic decisions and improving clinical outcomes [1].

Inflammation plays a central role in the pathophysiology of atherosclerosis and its acute complications. The inflammatory cascade contributes not only to plaque formation and progression but also to plaque destabilization and thrombotic events leading to ACS. Consequently, increasing attention has been directed toward inflammatory biomarkers that may reflect disease activity and help identify patients at higher risk of adverse cardiovascular events. Several inflammatory markers derived from routine laboratory tests have emerged as potential prognostic indicators in ACS. C-reactive protein, a well-established marker of systemic inflammation, has been associated with plaque instability and worse cardiovascular outcomes. Similarly, the NLR has been proposed as an accessible indicator of systemic inflammatory response and has demonstrated prognostic value in patients with acute coronary syndromes [2]. More recently, the systemic immune-inflammation index, which integrates neutrophil, lymphocyte, and platelet counts, has gained attention as a comprehensive marker of inflammatory and immune status [3,4]. In addition to inflammatory biomarkers, markers of myocardial stress and cardiac dysfunction, such as N-terminal pro–B-type natriuretic peptide, have been widely recognized for their prognostic significance in patients with ACS. Elevated NT-proBNP levels have been associated with an increased risk of heart failure, recurrent ischemic events, and mortality [5].

Although these biomarkers have been individually investigated in various cardiovascular conditions, their combined prognostic role in patients presenting with different forms of acute coronary syndromes remains incompletely defined, particularly in real-world clinical settings. Therefore, the aim of the present study was to evaluate the prognostic value of inflammatory status, assessed through SII, CRP, and NLR, together with NT-proBNP levels, in predicting adverse cardiovascular outcomes in patients with acute coronary syndromes in a single-center cohort.

2. Materials and Methods

2.1. Study Design

This prospective observational study included patients presenting with suspected acute coronary syndromes who met predefined criteria for systemic inflammation and were consecutively admitted to the Cardiology Department, Acute Coronary Care Unit of the Institute of Cardiovascular Diseases, Timișoara, Romania, between February 2024 and September 2025. During the study period, a total of 116 patients were screened for eligibility. After applying the inclusion and exclusion criteria, 100 patients with ACS were included in the final analysis. Reasons for non-inclusion included active malignancies

(n = 3), known autoimmune or systemic inflammatory diseases (n = 2), and acute infections or myopericarditis (n = 6). Additional exclusions were due to incomplete clinical or laboratory data or lack of informed consent. Inflammatory status was defined as elevated levels of the inflammatory biomarkers assessed in this study, including C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII). Acute heart failure was defined as either present at admission or newly developed during hospitalization, requiring escalation of therapy, and was included as part of the in-hospital MACE endpoint.

The diagnosis of acute coronary syndromes (ACS), including unstable angina, NSTEMI, and STEMI, was established according to current European Society of Cardiology (ESC) guidelines and the Fourth Universal Definition of Myocardial Infarction [1,6]. Myocardial infarction cases were further classified as STEMI or NSTEMI based on electrocardiographic findings [7,8]. The median length of index hospitalization was 6 [4–9] days (Figure 1).

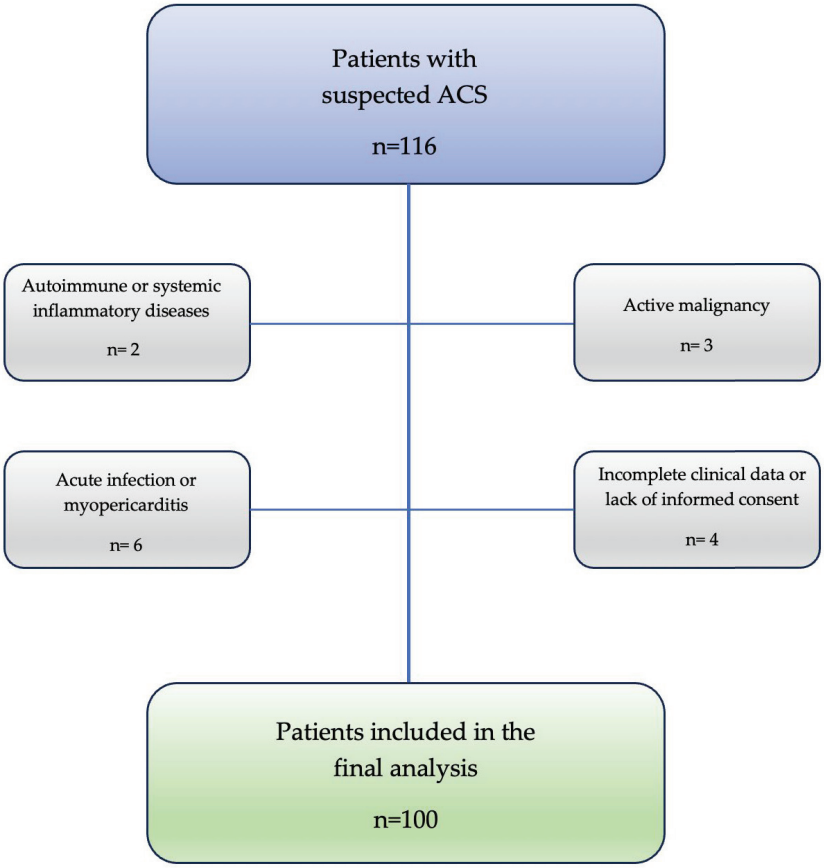


Figure 1. Study flow diagram. Out of 116 patients with suspected ACS screened for eligibility, 100 patients were included in the final analysis. Exclusion criteria included autoimmune or systemic inflammatory diseases (n = 2), active malignancy (n = 3), acute infection or myopericarditis (n = 6), and incomplete clinical data or lack of informed consent (n = 4).

2.2. Data Collection and Clinical Assessment

Clinical and demographic data were obtained from the patients' medical records and the institutional electronic database. The collected variables included demographic characteristics such as age, sex, and smoking status, as well as cardiovascular risk factors including arterial hypertension, diabetes mellitus, and dyslipidemia. Clinical parameters recorded at admission included heart rate, systolic and diastolic blood pressure, and body mass index (BMI). Cardiovascular risk factors were defined according to current

European clinical guidelines [9,10]. Arterial hypertension was diagnosed based on the 2024 ESC/ESH Guidelines for the management of arterial hypertension, defined as an office blood pressure $\geq$ 140/90 mmHg or ongoing antihypertensive treatment [11]. Dyslipidemia was defined according to the 2019 ESC/EAS Guidelines for the management of dyslipidemias, as failure to achieve recommended lipid targets according to the patient's cardiovascular risk category or the use of lipid-lowering therapy [12]. Diabetes mellitus was defined according to the 2023 ESC Guidelines for cardiovascular disease in patients with diabetes, based on a documented history of diabetes, the use of glucose-lowering medication, or laboratory criteria consistent with diabetes [13]. Smoking status was categorized as current smoker or non-smoker. Current smokers were defined as individuals who actively smoked at the time of hospital admission, while non-smokers included patients who had never smoked or had stopped smoking prior to admission [14].

2.3. Laboratory and Biomarker Assessment

Blood samples were collected from all patients at the time of hospital admission. Most laboratory parameters were obtained as part of the routine clinical evaluation; however, certain biomarkers were measured specifically for the purposes of the present study.

The assessed laboratory parameters included C-reactive protein, N-terminal pro–B-type natriuretic peptide, leukocyte count, neutrophil count, lymphocyte count, monocyte count, platelet count, fasting plasma glucose and serum creatinine levels. Renal function was evaluated by using serum creatinine and the estimated glomerular filtration rate (eGFR), expressed in mL/min/1.73 m^2. The eGFR was calculated using the online calculator available at medcalc.org (accessed on 10 October 2025).

Inflammatory status was further assessed using derived hematological indices. The neutrophil-to-lymphocyte ratio was calculated as the ratio between the absolute neutrophil and lymphocyte counts [15]. The systemic immune-inflammation index was calculated using the formula platelet count $\times$ neutrophil count/lymphocyte count [16]. These indices were used as markers of systemic inflammatory response in patients with acute coronary syndromes. All laboratory measurements were performed according to standard hospital laboratory protocols.

2.4. Electrocardiographic and Echocardiographic Assessment

A standard 12-lead electrocardiogram (ECG) was performed at the time of admission as part of the routine diagnostic assessment for acute coronary syndromes.

Transthoracic echocardiography was subsequently performed according to standard echocardiographic protocols, by using a Vivid IQ ultrasound system (GE Healthcare, Milwaukee, WI, USA) equipped with a 2.5 MHz phased-array transducer. The examinations were conducted according to standard echocardiographic protocols. Left ventricular systolic function was evaluated by measuring the left ventricular ejection fraction (LVEF), calculated using the modified Simpson's biplane method [17,18].

2.5. Coronary Angiography and Revascularization

Coronary angiography was performed in all patients according to standard institutional protocols, with operators blinded to the study protocol. The procedure was carried out via radial or femoral vascular access, according to patient characteristics and operator experience. Angiographic images were obtained in multiple projections to allow adequate visualization of the coronary anatomy and identification of the culprit lesion. Decisions regarding percutaneous coronary intervention (PCI) strategy were made by the treating interventional cardiologist based on angiographic findings and the overall clinical status of the patient, in accordance with current guideline recommendations.

2.6. Study Endpoints

The primary endpoint of the study was the occurrence of major adverse cardiovascular events (MACE) during hospitalization. MACE was defined as a composite outcome including cardiovascular death, recurrent myocardial infarction, stroke, urgent coronary revascularization, or acute heart failure requiring escalation of therapy. Acute heart failure was defined as either present at admission or newly developed during hospitalization, requiring escalation of therapy, and was included as part of the in-hospital MACE endpoint.

Secondary outcomes included in-hospital mortality and the association between inflammatory markers and the severity of ACS presentation. Their prognostic value for clinical outcomes was further evaluated using regression and discrimination analyses.

2.7. Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of "Victor Babeș" University of Medicine and Pharmacy Timișoara (approval code: 54, date: 2 October 2023) and the Institute of Cardiovascular Diseases Timișoara (approval code: 438, date: 22 January 2024). Written informed consent was obtained from all participants prior to inclusion in the study.

2.8. Statistical Analysis

Statistical analyses were conducted to assess the association between inflammatory markers and clinical outcomes in patients with acute coronary syndromes. Demographic and clinical variables, including age, sex, body mass index (BMI), cardiovascular risk factors (hypertension, diabetes mellitus, and smoking status), and clinical parameters at admission, were included in the descriptive and comparative analyses. In-hospital complications, including new-onset atrial fibrillation (NOAF), were also recorded and analyzed descriptively. Continuous variables were expressed as median and interquartile range (IQR), while categorical variables were presented as absolute numbers and percentages. The distribution of continuous variables was assessed using visual inspection and the Shapiro–Wilk test. Because most variables showed non-normal distributions, non-parametric statistical methods were applied. Comparisons between multiple groups were performed using the Kruskal–Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. For comparisons between two groups (e.g., patients with and without MACE), the Mann–Whitney U test was used for continuous variables. The inflammatory markers evaluated in the analysis included C-reactive protein, neutrophil-to-lymphocyte ratio, and the systemic immune-inflammation index. Because of skewed distributions, these variables were analyzed both in their original form and after logarithmic transformation when appropriate. Univariable logistic regression analyses were performed to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for associations between potential predictors and MACE. Candidate predictors included age, sex, ACS subtype, renal function assessed by estimated glomerular filtration rate, left ventricular ejection fraction, and inflammatory markers. Multivariable logistic regression models were subsequently constructed to identify independent predictors of MACE and to assess the incremental prognostic value of inflammatory markers beyond baseline clinical variables. Variables included in the multivariable models were selected based on clinical relevance and with the aim of minimizing collinearity, particularly among variables reflecting overlapping pathophysiological processes. Additional sensitivity analyses were performed using tertile-based categorization of inflammatory markers to explore potential non-linear relationships between inflammatory burden and clinical outcomes. Model discrimination was evaluated using receiver operating characteristic (ROC) curve analysis, and predictive performance was summarized using the area under the curve (AUC). All

tests were two-sided, and statistical significance was defined as $p < 0.05$. Data analysis was performed using R version 4.5.0 within the RStudio environment (version 2025.5.0.496) within the RStudio environment.

3. Results

A total of 116 patients with suspected acute coronary syndromes were screened for eligibility during the study period. After applying the inclusion and exclusion criteria, 100 patients were included in the final analysis. Among these, 81 patients presented with ST-segment elevation myocardial infarction, 12 with non–ST-segment elevation myocardial infarction, and 7 with unstable angina. Regarding the components of the composite MACE endpoint, stroke occurred in 3 patients (6%), urgent coronary revascularization in 4 (8%), recurrent myocardial infarction in 2 (4%), cardiovascular death in 6 (12%), and acute heart failure requiring escalation of therapy in 33 patients (66%).

3.1. Clinical Profile, Inflammatory Markers, and Admission Severity According to ACS Subtype

The comparison of clinical and laboratory parameters across ACS subtypes revealed largely similar baseline characteristics among groups (Table 1 and Figure 2). Age, body mass index, systolic blood pressure, heart rate, renal function parameters, NT-proBNP levels, and left ventricular ejection fraction did not differ significantly between NSTEMI, STEMI, and unstable angina patients (all $p > 0.05$), indicating a similar clinical profile at the time of admission. Regarding inflammatory markers, leukocyte counts tended to be higher in myocardial infarction groups compared with unstable angina, although this difference did not reach statistical significance. In contrast, neutrophil counts differed significantly across ACS subtypes ($p = 0.016$), with the highest values observed in STEMI and NSTEMI patients. Similarly, the SII was significantly elevated in myocardial infarction compared with unstable angina ($p = 0.017$). Median SII values were markedly higher in both STEMI and NSTEMI, indicating a greater inflammatory burden in infarction presentations. The neutrophil-to-lymphocyte ratio also showed higher median values in myocardial infarction compared with unstable angina, although this association approached, but did not reach statistical significance ($p = 0.057$).

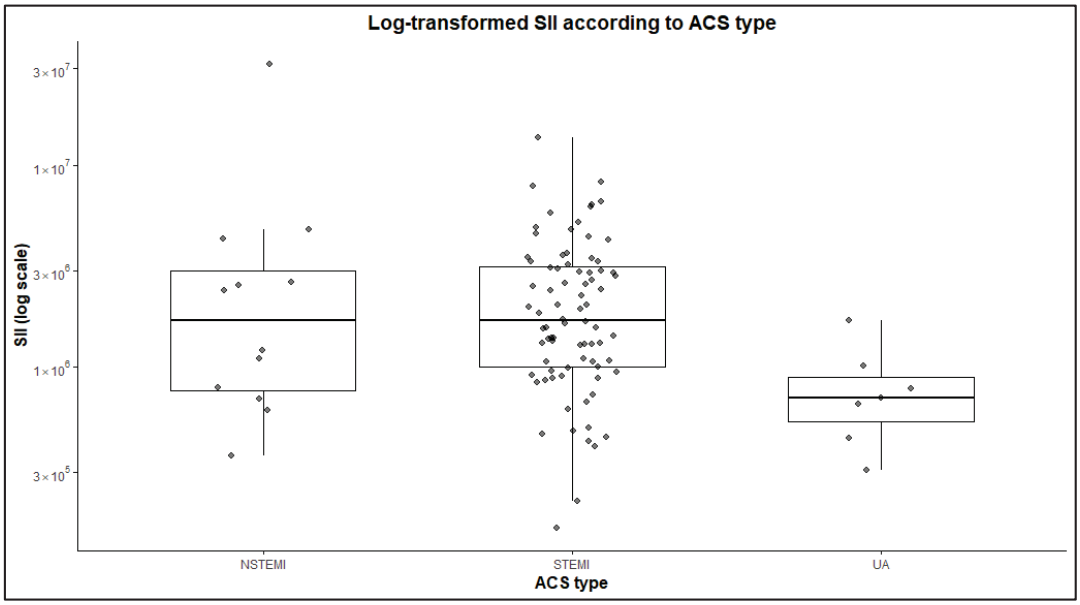


Figure 2. Distribution of log-transformed systemic immune-inflammation index (SII) according to ACS subtype. Higher SII values were observed in STEMI and NSTEMI compared with unstable angina.

Table 1. Baseline clinical and laboratory characteristics according to ACS subtype.

Variable	NSTEMI (n = 12)	STEMI (n = 81)	UA (n = 7)	*p*-Value
Age, years	72.00 [65.75–77.25]	63.00 [54.00–73.00]	69.00 [64.00–74.00]	0.209
BMI, kg/m^2	27.80 [26.35–29.70]	28.00 [25.35–31.20]	26.00 [25.20–29.24]	0.783
SBP, mmHg	135.00 [100.00–160.00]	130.00 [115.00–145.00]	135.00 [122.50–147.50]	0.914
Heart rate, bpm	89.50 [71.50–100.00]	80.00 [70.00–98.00]	77.00 [73.50–79.00]	0.634
CRP, mg/L	18.00 [14.45–64.55]	31.70 [10.10–77.00]	9.00 [3.50–29.70]	0.241
NT-proBNP, pg/mL	1642.95 [1020.62–5882.52]	2350.40 [1090.00–6840.00]	1386.20 [836.70–4154.55]	0.394
Leukocytes, μL	13,290.00 [9652.50–15,585.00]	12,860.00 [10,585.00–16,000.00]	9240.00 [7350.00–12,870.00]	0.165
Neutrophils, μL	9930.00 [7117.50–13,210.00]	10,657.00 [7810.00–12,847.00]	6780.00 [4240.00–7775.00]	**0.016**
Lymphocytes, μL	1555.00 [1197.50–2517.50]	1500.00 [1100.00–2030.00]	1880.00 [1285.00–2325.00]	0.773
Monocytes, μL	665.00 [595.00–905.00]	690.00 [520.00–920.00]	500.00 [490.00–605.00]	0.340
Platelets, μL	291,000.00 [213,750.00–324,750.00]	260,000.00 [218,000.00–309,000.00]	215,000.00 [188,500.00–224,000.00]	0.065
NLR	6.33 [3.36–10.02]	7.04 [4.39–10.87]	3.41 [2.47–4.61]	0.057
SII	1,811,454.74 [763,419.58–3,066,110.07]	1,729,378.64 [999,480.72–3,101,054.54]	699,058.58 [548,578.30–895,010.28]	**0.017**
eGFR, mL/min/1.73 m^2	50.40 [46.10–55.45]	66.00 [44.03–81.12]	69.27 [62.39–70.60]	0.544
Creatinine, mg/dL	1.15 [1.07–1.60]	1.15 [0.97–1.58]	1.02 [0.86–1.23]	0.283
LVEF, %	40.00 [30.00–40.00]	39.00 [32.00–45.00]	45.00 [32.50–45.00]	0.712

Abbreviations: BMI—body mass index; SBP—systolic blood pressure; CRP—C-reactive protein; NT-proBNP—N-terminal pro–B-type natriuretic peptide; NLR—neutrophil-to-lymphocyte ratio; SII—systemic immune-inflammation index; eGFR—estimated glomerular filtration rate; LVEF—left ventricular ejection fraction.

The distribution of categorical clinical characteristics across ACS subtypes showed generally similar demographic profiles and comorbidity burdens among groups (Table 2). Sex distribution, prevalence of hypertension, occurrence of new-onset atrial fibrillation, all-cause in-hospital mortality, and MACE did not differ significantly between NSTEMI, STEMI, and unstable angina patients (all $p > 0.05$), suggesting comparable baseline cardiovascular risk and management strategies across the cohort.

Table 2. Categorical clinical characteristics according to ACS subtype.

Variable	NSTEMI (n = 12)	STEMI (n = 81)	UA (n = 7)	*p*-Value
Male sex	7 (58.3%)	56 (69.1%)	6 (85.7%)	0.499
Hypertension	8 (66.7%)	57 (70.4%)	6 (85.7%)	0.769
Diabetes	7 (58.3%)	22 (27.2%)	4 (57.1%)	**0.036**
Smoker	5 (41.7%)	50 (61.7%)	1 (14.3%)	**0.032**
NOAF	5 (41.7%)	26 (32.1%)	3 (42.9%)	0.662
In-hospital mortality	2 (16.7%)	4 (4.9%)	0 (0.0%)	0.202
MACE	6 (50.0%)	41 (50.6%)	3 (42.9%)	1.000

Abbreviations: STEMI—ST-segment elevation myocardial infarction; NSTEMI—non–ST-segment elevation myocardial infarction; UA—unstable angina; NOAF—new onset atrial fibrillation; MACE—major adverse cardiovascular events.

In contrast, diabetes mellitus showed a significant association with ACS subtype ($p = 0.036$), being more frequent among NSTEMI and unstable angina patients and less common in STEMI presentations. Similarly, smoking status differed significantly between groups ($p = 0.032$), with active smoking most prevalent among STEMI patients and less frequent in unstable angina. Although mortality appeared numerically higher among NSTEMI patients, the difference did not reach statistical significance. Likewise, the incidence of MACE was similar across ACS subtypes, indicating that short-term adverse outcomes were not strongly associated with clinical presentation alone.

3.2. Inflammatory Markers and Their Association with In-Hospital Outcomes in ACS/Inflammatory Markers and In-Hospital Outcomes in ACS

Significant differences were observed between patients who developed major adverse cardiovascular events and those without events across several clinical, functional, and inflammatory parameters (Table 3 and Figure 3). Patients who experienced MACE were significantly older ($p = 0.003$) and presented higher CRP values ($p < 0.001$) and NT-proBNP levels ($p = 0.002$) at admission, as illustrated in Figure 3. Composite inflammatory indices also differed between groups. The neutrophil-to-lymphocyte ratio (NLR, $p = 0.030$) and the systemic immune-inflammation index (SII, $p = 0.042$) were significantly higher in patients with MACE. Neutrophil counts tended to be higher, and lymphocyte counts lower, among these patients, although these differences did not reach statistical significance. Patients with MACE also had significantly lower left ventricular ejection fraction ($p = 0.001$) and reduced renal function, reflected by lower eGFR values ($p < 0.001$). Regarding comorbidities, hypertension was significantly more prevalent in the MACE group ($p = 0.028$). Diabetes appeared more frequently in patients with MACE, but did not reach statistical significance. Sex distribution and smoking status rates were comparable between groups. Separately, new-onset atrial fibrillation, recorded as an in-hospital complication, occurred significantly more frequently in patients with MACE (68% vs. 0%, $p < 0.001$).

Table 3. Baseline predictors of MACE occurrence in patients with acute coronary syndromes.

Variable	No MACE (n = 50)	MACE (n = 50)	*p*-Value
Age (years)	58.50 [50.25–71.75]	69.00 [61.25–77.00]	**0.003**
CRP (mg/L)	13.30 [5.78–36.90]	46.90 [24.53–96.75]	**<0.001**
NT-proBNP (pg/mL)	1456.45 [953.60–3215.88]	3522.70 [1904.38–8007.00]	**0.002**
Leukocytes (/μL)	11,716.00 [9145.00–16,300.00]	13,460.00 [11,500.00–15,647.50]	0.152
Neutrophils (/μL)	9105.00 [6562.50–13,738.50]	11,460.00 [8595.00–12,712.50]	0.081
Lymphocytes (/μL)	1770.00 [1200.00–2185.00]	1330.00 [962.50–1930.00]	0.065
NLR	4.78 [3.12–9.64]	7.47 [4.67–10.22]	**0.030**
SII	1,206,896.15 [715,241.35–2,941,096.11]	1,897,722.94 [1,280,874.26–3,171,769.47]	**0.042**
LVEF (%)	40.00 [35.00–45.00]	35.00 [30.00–40.00]	**0.001**
eGFR (mL/min/1.73 m^2)	72.26 [50.84–90.66]	47.85 [30.28–68.75]	**<0.001**
Male sex	36 (72.0%)	33 (66.0%)	0.665
Hypertension	30 (60.0%)	41 (82.0%)	**0.028**
Diabetes	12 (24.0%)	21 (42.0%)	0.089
Current smoker	30 (60.0%)	26 (52.0%)	0.546

Abbreviations: MACE—major adverse cardiovascular events; CRP—C-reactive protein; NT-proBNP—N-terminal pro–B-type natriuretic peptide; NLR—neutrophil-to-lymphocyte ratio; SII—systemic immune-inflammation index; LVEF—left ventricular ejection fraction; eGFR—estimated glomerular filtration rate; NOAF—new onset atrial fibrillation.

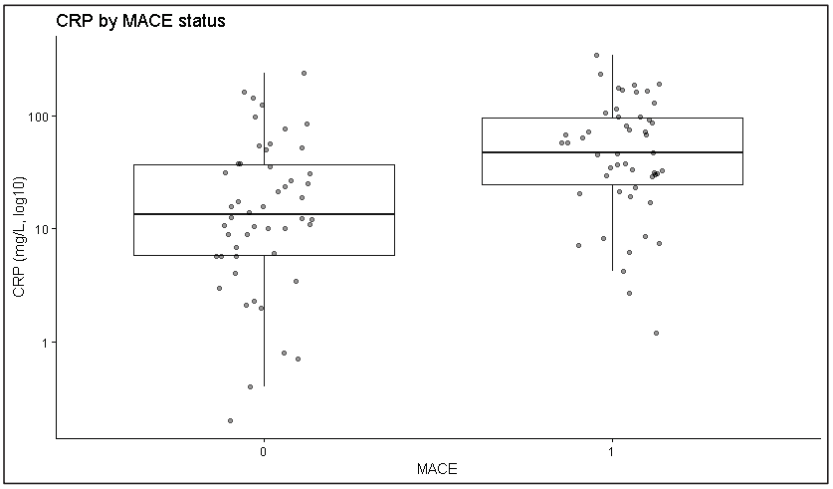


Figure 3. Distribution of Log-transformed C-reactive protein levels according to MACE occurrence. Higher logCRP values were observed among patients with MACE compared with those without events.

The occurrence of major adverse cardiovascular events did not differ across ACS subtypes. The distribution of NSTEMI, STEMI, and unstable angina was similar between patients with and without MACE ($p = 1.000$), indicating that ACS subtype alone did not discriminate short-term outcomes in this cohort. In-hospital mortality occurred in a small proportion of patients, and no clinical or laboratory variable showed a statistically significant association with fatal outcomes. Age, inflammatory biomarkers, cardiac function, renal function, and comorbidities were comparable between survivors and non-survivors (all $p > 0.05$). Nevertheless, non-survivors showed numerically higher CRP levels, leukocyte and neutrophil counts, and NT-proBNP concentrations, along with lower lymphocyte counts, reduced left ventricular ejection fraction, and lower eGFR values. Higher median NLR and SII values were also observed among patients who experienced fatal in-hospital outcomes, although these differences did not reach statistical significance. The association between NLR and mortality approached statistical significance ($p = 0.075$). Regarding comorbidities, hypertension was present in all patients who experienced in-hospital mortality, and atrial fibrillation appeared more frequent in this group, although the differences were not statistically significant (Table 4).

Table 4. Baseline predictors of in-hospital death in patients with acute coronary syndromes.

Variable	Survivors (n = 94)	In-Hospital Mortality (n = 6)	*p*-Value
Age (years)	64.50 [54.00–75.00]	63.50 [62.00–74.75]	0.586
CRP (mg/L)	29.65 [9.25–71.38]	65.75 [28.57–71.20]	0.349
NT-proBNP (pg/mL)	2152.35 [1004.35–6774.73]	2741.30 [1985.37–6918.35]	0.357
Leukocytes (/µL)	12,795.00 [10,052.50–15,952.50]	14,270.00 [12,995.00–14,982.50]	0.464
Neutrophils (/µL)	9550.00 [7325.00–12,846.00]	11,740.00 [10,925.00–12,607.50]	0.220
Lymphocytes (/µL)	1535.00 [1100.00–2220.00]	1290.00 [1185.00–1470.00]	0.215
NLR	5.88 [3.54–10.17]	9.51 [8.58–10.73]	0.075
SII	1,492,725.67 [881,587.28–3,055,319.67]	2,549,059.66 [2,430,531.20–2,633,606.78]	0.106
LVEF (%)	40.00 [32.75–45.00]	32.50 [30.00–35.00]	0.118
eGFR (mL/min/1.73 m^2)	62.96 [39.01–82.61]	48.36 [42.08–63.84]	0.286
Male sex	65 (69.1%)	4 (66.7%)	1.000

Table 4. *Cont.*

Variable	Survivors (n = 94)	In-Hospital Mortality (n = 6)	*p*-Value
Hypertension	65 (69.1%)	6 (100.0%)	0.177
Diabetes	30 (31.9%)	3 (50.0%)	0.393
Current smoker	53 (56.4%)	3 (50.0%)	1.000
NOAF	30 (31.9%)	4 (66.7%)	0.176

Abbreviations: CRP—C-reactive protein; NT-proBNP—N-terminal pro–B-type natriuretic peptide; NLR—neutrophil-to-lymphocyte ratio; SII—systemic immune-inflammation index; LVEF—left ventricular ejection fraction; eGFR—estimated glomerular filtration rate; NOAF—new-onset atrial fibrillation.

The distribution of ACS subtypes did not differ significantly between patients with and without in-hospital mortality ($p = 0.202$). Although NSTEMI appeared proportionally more frequent among patients with in-hospital mortality, and unstable angina was not observed in this group, these differences did not reach statistical significance (Table 5).

Table 5. Association between ACS subtype and in-hospital mortality.

Variable	Level	Survivors (n = 94)	Death (n = 6)	*p*-Value
ACS subtype	NSTEMI	10 (10.6%)	2 (33.3%)	0.202
	STEMI	77 (81.9%)	4 (66.7%)	
	UA	7 (7.4%)	0 (0.0%)	

Abbreviations: ACS—acute coronary syndrome; NSTEMI—non–ST-segment elevation myocardial infarction; STEMI—ST-segment elevation myocardial infarction; UA—unstable angina.

3.3. Multivariable Analysis of Clinical and Inflammatory Predictors of MACE

In the multivariable logistic regression model, performed to identify independent predictors of major adverse cardiovascular events, and adjusted for demographic, clinical, and functional parameters, left ventricular ejection fraction emerged as the only independent predictor of major adverse cardiovascular events, underlying that each 1% increase in LVEF was associated with lower odds of adverse events (OR 0.934, 95% CI 0.874–0.999, $p = 0.047$) (Figure 4). Other variables included in the model were not independently associated with MACE. Age and renal function showed trends toward association with outcomes, with older age and lower eGFR linked to higher event rates; however, these relationships did not remain significant after adjustment. ACS subtype and sex were also not independently associated with MACE.

When C-reactive protein was added to the baseline multivariable model (Table 6), it showed a modest association with MACE occurrence, although this did not reach statistical significance (OR 1.008 per mg/L, 95% CI 0.999–1.018, $p = 0.098$). In this expanded model, none of the variables retained independent statistical significance. The association previously observed for left ventricular ejection fraction was attenuated after inclusion of CRP.

When the neutrophil-to-lymphocyte ratio (NLR) was incorporated into the multivariable model (Table 7), it was not independently associated with MACE (OR 1.014 per unit, 95% CI 0.959–1.072, $p = 0.618$). As in the previous model, none of the covariates reached statistical significance, although left ventricular ejection fraction showed a borderline association with outcomes ($p = 0.054$).

Similarly, SII was not independently associated with MACE when included in the multivariable model (Table 8). Left ventricular ejection fraction remained the only variable independently associated with outcomes after adjustment.

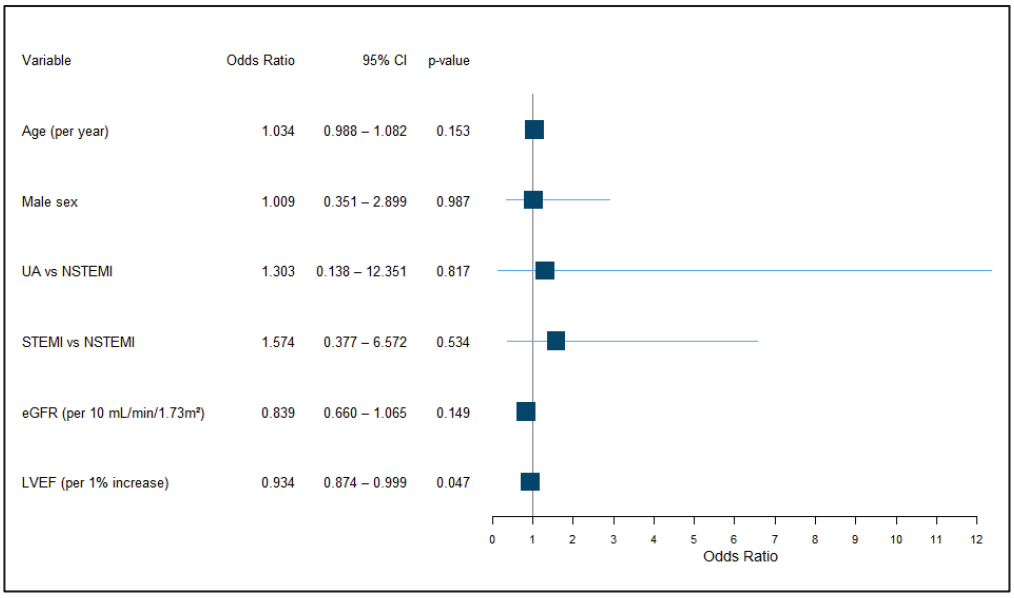


Figure 4. Forest plot of multivariable logistic regression analysis for MACE occurrence. Abbreviations: CI—confidence interval; UA—unstable angina; NSTEMI—non–ST-segment elevation myocardial infarction; STEMI—ST-segment elevation myocardial infarction; eGFR—estimated glomerular filtration rate; LVEF—left ventricular ejection fraction. ORs are expressed per unit increase for continuous variables.

Table 6. Multivariable logistic regression model for MACE including C-reactive protein.

Variable	OR	95% CI	*p*-Value
Age (per year)	1.031	0.984–1.080	0.196
Male sex	0.824	0.275–2.473	0.730
UA vs. NSTEMI	1.456	0.151–14.050	0.745
STEMI vs. NSTEMI	1.424	0.316–6.412	0.645
eGFR (per 10 mL/min/1.73 m^2)	0.875	0.684–1.119	0.288
LVEF (per 1% increase)	0.945	0.882–1.012	0.106
CRP (per 1 mg/L)	1.008	0.999–1.018	0.098

Abbreviations: OR—odds ratio; CI—confidence interval; UA—unstable angina; NSTEMI—non–ST-segment elevation myocardial infarction; STEMI—ST-segment elevation myocardial infarction; eGFR—estimated glomerular filtration rate; LVEF—left ventricular ejection fraction; CRP—C-reactive protein. ORs are expressed per unit increase for continuous variables.

Table 7. Multivariable logistic regression model for MACE including neutrophil-to-lymphocyte ratio.

Variable	OR	95% CI	*p*-Value
Age (per year)	1.034	0.987–1.082	0.159
Male sex	0.999	0.347–2.879	0.999
UA vs. NSTEMI	1.422	0.145–13.987	0.763
STEMI vs. NSTEMI	1.647	0.381–7.112	0.504
eGFR (per 10 mL/min/1.73 m^2)	0.847	0.665–1.077	0.176
LVEF (per 1% increase)	0.936	0.875–1.001	0.054
NLR (per unit)	1.014	0.959–1.072	0.618

Abbreviations: OR—odds ratio; CI—confidence interval; UA—unstable angina; NSTEMI—non–ST-segment elevation myocardial infarction; STEMI—ST-segment elevation myocardial infarction; eGFR—estimated glomerular filtration rate; LVEF—left ventricular ejection fraction; NLR—neutrophil-to-lymphocyte ratio. ORs are expressed per unit increase for continuous variables.

Table 8. Multivariable logistic regression model for MACE including systemic immune-inflammation index.

Variable	OR	95% CI	*p*-Value
Age (per year)	1.034	0.988–1.083	0.151
Male sex	1.014	0.352–2.916	0.980
UA vs. NSTEMI	1.266	0.131–12.262	0.839
STEMI vs. NSTEMI	1.551	0.369–6.510	0.549
eGFR (per 10 mL/min/1.73 m^2)	0.837	0.658–1.065	0.147
LVEF (per 1% increase)	0.934	0.873–0.999	**0.047**
SII (per 100,000 units)	0.999	0.986–1.012	0.860

Interaction analyses showed no significant interaction between inflammatory markers and STEMI presentation (Table 9). In models including CRP, NLR, and SII, neither the markers nor their interaction terms were significantly associated with MACE after adjustment.

Table 9. Multivariable interaction models evaluating whether the prognostic impact of inflammatory markers differs by ACS presentation.

Variable	OR	95% CI	*p*-Value
Model: Base + CRP + Interaction			
Age (per year)	1.03	0.99–1.08	0.164
LVEF (per 1%)	0.93	0.87–1.01	0.066
CRP (per 1 mg/L)	1.10	0.98–1.23	0.101
CRP × STEMI	0.92	0.82–1.03	0.125
Model: Base + NLR + Interaction			
Age (per year)	1.03	0.98–1.08	0.195
LVEF (per 1%)	0.94	0.88–1.01	0.074
NLR (per unit)	1.29	0.75–2.24	0.358
NLR × STEMI	0.76	0.44–1.31	0.320
Model: Base + SII + Interaction			
Age (per year)	1.03	0.98–1.08	0.195
LVEF (per 1%)	0.94	0.87–1.00	0.058
SII (per 10^5 units)	1.10	0.94–1.29	0.253
SII × STEMI	0.89	0.76–1.05	0.173

3.4. Evaluation of Predictive Performance and Incremental Value of Inflammatory Markers

The baseline multivariable model demonstrated good discriminative ability for predicting MACE, with an AUC of 0.775 (95% CI 0.682–0.868). The addition of inflammatory markers resulted in only modest changes in predictive performance.

Receiver operating characteristic (ROC) curves analysis showed that inclusion of CRP produced the largest numerical improvement in model performance, increasing the AUC to 0.797, whereas models including NLR and SII yielded AUC values of 0.781 and 0.776, respectively. The corresponding ROC curves are shown in Figure 5, and model discrimination metrics are reported in Table 10.

However, formal comparison of ROC curves using the DeLong test indicated that the addition of inflammatory markers was not associated with a statistically significant change in discriminative performance (all $p > 0.05$).

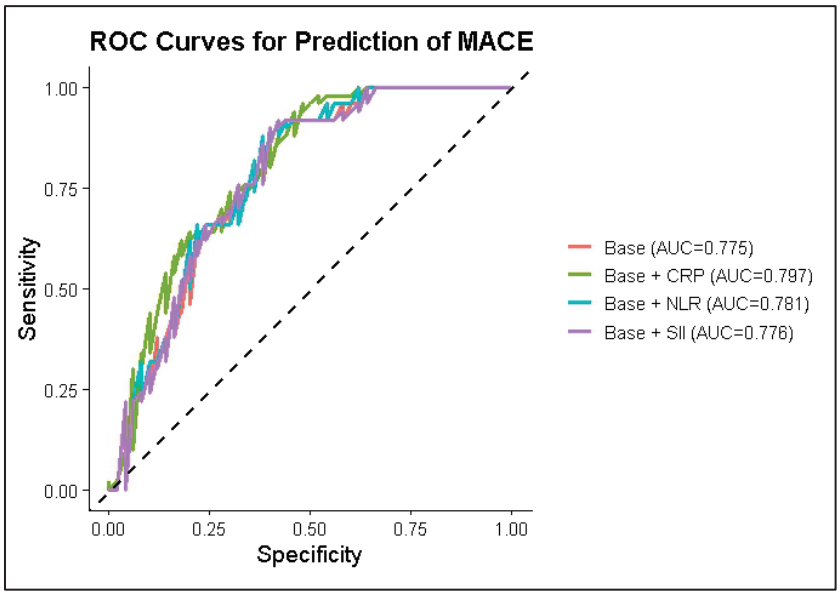


Figure 5. ROC curves illustrating the discriminative performance of the baseline multivariable model and models additionally including CRP, NLR and SII for the prediction of major adverse cardiovascular events.

Table 10. Discriminative performance of multivariable models for prediction of MACE.

Model	AUC (95% CI)
Base model	0.775 (0.682–0.868)
Base + CRP	0.797 (0.708–0.885)
Base + NLR	0.781 (0.689–0.873)
Base + SII	0.776 (0.683–0.869)

Abbreviations: AUC—area under the curve; CI—confidence interval; CRP—C-reactive protein; NLR—neutrophil-to-lymphocyte ratio; SII—systemic immune-inflammation index.

3.5. Sensitivity Analyses of Inflammatory Markers and Their Association with MACE

Sensitivity analyses using tertile-based categorization and log-transformed models are presented in Table 11. Higher CRP levels were associated with an increased risk of MACE. Patients in the highest CRP tertile had significantly higher odds of events compared with those in the lowest tertile (OR 4.47, $p = 0.023$), and a significant trend across tertiles was observed ($p = 0.023$). In addition, log-transformed CRP showed a significant association with MACE (OR 1.67, $p = 0.017$). For NLR, the intermediate tertile showed a borderline association with MACE ($p = 0.073$), whereas the highest tertile, trend analysis, and log-transformed models were not statistically significant. For SII, patients in the second tertile had significantly higher odds of MACE (OR 5.48, $p = 0.010$); however, this association was not observed in the highest tertile, and neither the trend analysis nor the log-transformed model reached statistical significance.

Table 11. Sensitivity analyses of CRP, NLR, and SII using tertile and log-transformed models for the prediction of MACE.

Marker	Model	OR (95% CI)	*p*-Value
CRP	CRP tertile T2 vs. T1	2.54 (0.80–8.03)	0.113
	CRP tertile T3 vs. T1	4.47 (1.23–16.23)	**0.023**
	Trend per tertile increase	2.11 (1.11–4.02)	**0.023**

Table 11. *Cont.*

Marker	Model	OR (95% CI)	*p*-Value
	logCRP (continuous)	1.67 (1.09–2.55)	**0.017**
NLR	NLR tertile T2 vs. T1	2.83 (0.91–8.85)	0.073
	NLR tertile T3 vs. T1	1.88 (0.56–6.32)	0.307
	Trend per tertile increase	1.40 (0.77–2.55)	0.271
	logNLR (continuous)	1.30 (0.61–2.77)	0.489
SII	SII tertile T2 vs. T1	5.48 (1.49–20.09)	**0.010**
	SII tertile T3 vs. T1	1.74 (0.49–6.19)	0.390
	Trend per tertile increase	1.21 (0.66–2.22)	0.540
	logSII (continuous)	1.08 (0.60–1.94)	0.794

Abbreviations: OR—odds ratio; CI—confidence interval; CRP—C-reactive protein; NLR—neutrophil-to-lymphocyte ratio; SII—systemic immune-inflammation index; T1–T3—tertiles of marker distribution.

4. Discussion

The present study evaluated the prognostic significance of inflammatory status in patients presenting with acute coronary syndromes in a single-center cohort. The findings suggest that systemic inflammation is associated with short-term adverse outcomes in this population, with higher levels of inflammatory markers observed among patients who developed major adverse cardiovascular events during hospitalization. Among the biomarkers evaluated, C-reactive protein demonstrated the most robust association with adverse outcomes in exploratory and sensitivity analyses, while the composite inflammatory indices NLR and SII also showed associations with MACE. After adjustment for clinical and functional parameters, the strength of these associations was attenuated, suggesting that inflammatory biomarkers may reflect the systemic inflammatory response accompanying acute coronary syndromes. Importantly, left ventricular ejection fraction emerged as an independent predictor of in-hospital MACE, highlighting the central role of ventricular systolic dysfunction in determining short-term prognosis in patients with ACS. The addition of inflammatory markers to the baseline clinical model resulted in only modest and statistically nonsignificant improvements in predictive performance.

Systemic inflammation plays a fundamental role in the pathophysiology of atherosclerosis and acute coronary syndromes. Inflammatory activation contributes to endothelial dysfunction, progression of atherosclerotic plaques, and ultimately plaque destabilization and thrombus formation, leading to myocardial ischemia [19]. In this context, circulating inflammatory biomarkers have attracted increasing attention as potential tools for risk stratification in patients with ACS. Among these, C-reactive protein has been extensively studied and consistently associated with plaque instability, increased thrombotic activity, and adverse cardiovascular outcomes [20,21]. Our findings support this concept, as higher CRP levels were observed among patients who developed major adverse cardiovascular events during hospitalization, and sensitivity analyses demonstrated a graded relationship between increasing CRP levels and the risk of MACE. In addition to CRP, composite inflammatory indices derived from routine hematological parameters have recently gained attention as potential prognostic markers in cardiovascular disease. The neutrophil-to-lymphocyte ratio and the systemic immune-inflammation index integrate information on different components of the immune response and have been proposed as indicators of systemic inflammatory activation and immune imbalance [22]. Previous studies have reported associations between elevated NLR or SII values and adverse cardiovascular outcomes in patients with acute coronary syndromes [23,24]. In the present study, both

NLR and SII were higher among patients who experienced MACE, supporting the concept that systemic inflammatory activation accompanies more severe clinical presentations of acute coronary syndromes. These composite indices integrate information from different components of the immune response and may therefore capture the complex interplay between inflammation, immune imbalance, and thrombotic activity during the acute phase of coronary events. After adjustment for clinical and functional variables, the strength of these associations appeared attenuated, suggesting that NLR and SII may primarily reflect the broader inflammatory burden accompanying ACS rather than acting as independent determinants of short-term outcomes.

Left ventricular systolic function is a well-established determinant of prognosis in patients with acute coronary syndromes. Reduced left ventricular ejection fraction reflects the extent of myocardial injury and the degree of hemodynamic compromise, both of which are strongly associated with adverse clinical outcomes [25,26]. In our research, LVEF emerged as the only independent predictor of in-hospital MACE after adjustment for demographic, clinical, and inflammatory variables. Each 1% increase in LVEF was associated with a lower probability of adverse events, highlighting the protective role of preserved ventricular systolic function, an observation reflecting the notable contribution of acute heart failure events to MACE in our cohort. This finding is consistent with previous studies demonstrating that impaired ventricular function remains one of the strongest predictors of short-term complications and mortality following acute coronary events. The persistence of LVEF as an independent determinant of outcome in our model suggests that ventricular systolic function reflects the overall severity of the acute ischemic event [27,28]. At the same time, inflammatory biomarkers may capture complementary aspects of the underlying pathophysiological processes, including systemic inflammatory activation associated with acute coronary syndromes.

The findings of the present study should be interpreted with caution in terms of clinical applicability. Inflammatory biomarkers, including CRP, NLR, and SII, were associated with adverse outcomes and may reflect the underlying inflammatory status accompanying acute coronary events. Although their independent prognostic contribution was attenuated after adjustment for established clinical predictors, these markers may still provide complementary information regarding the systemic inflammatory response in ACS. When interpreted in the appropriate clinical context, inflammatory biomarkers may contribute to a more comprehensive characterization of disease severity. In this context, contemporary evidence emphasizes that prognosis in ACS is largely driven by clinical factors such as ventricular dysfunction, hemodynamic status, and comorbidity burden, while the incremental role of novel biomarkers remains an area of ongoing investigation. In this context, inflammatory biomarkers may provide additional pathophysiological insight but should be interpreted within the broader clinical framework [29].

4.1. Future Perspectives

The relationship between systemic inflammation and arrhythmic complications in patients with acute coronary syndromes represents an important area for further investigation. In the present cohort, new-onset atrial fibrillation emerged as a frequent in-hospital complication and was more commonly observed in patients who developed adverse cardiovascular events. Although the determinants of atrial fibrillation were not specifically explored in the current analysis, this observation highlights the potential relevance of arrhythmic complications in the clinical course of ACS. Growing evidence suggests that inflammatory activation may contribute to atrial electrical and structural remodeling, potentially favoring the occurrence of atrial fibrillation in the acute phase of coronary syndromes [30,31]. Further investigation of the relationship between inflammatory biomarkers

and the development of new-onset atrial fibrillation in patients with ACS may provide additional insight into the mechanisms linking inflammation, myocardial injury, and arrhythmic complications, and represents an important direction for future research.

4.2. Limitations

The present study has several limitations that should be acknowledged. Although the study was prospectively conducted, it was performed in a single center with a relatively limited sample size, which may affect the generalizability of the findings. Second, the analysis focused on in-hospital outcomes, and therefore, the long-term prognostic implications of inflammatory biomarkers could not be evaluated. Third, inflammatory markers were primarily assessed at admission, and serial measurements were not systematically available throughout hospitalization. In addition, the relatively small number of patients with NSTEMI and unstable angina limits the statistical power of subgroup comparisons across ACS subtypes; therefore, interaction analyses involving STEMI should be considered exploratory and interpreted in the context of these limitations. Similarly, the small number of in-hospital deaths in our cohort limits the statistical power of mortality-related analyses and precludes robust inferential conclusions. As such, mortality findings should be interpreted as descriptive observations rather than definitive associations.

Finally, although several clinical and laboratory variables were included in the multivariable models, the possibility of residual confounding cannot be completely excluded. Larger multicenter studies are needed to further clarify the prognostic role of inflammatory biomarkers in patients with acute coronary syndromes.

5. Conclusions

In patients with acute coronary syndromes, the occurrence of major adverse cardiovascular events during index hospitalization, with a median length of stay of 6 days, was associated with an unfavorable clinical profile, characterized by older age, impaired renal function, and reduced left ventricular systolic function. Levels of inflammatory biomarkers (CRP, NLR, and SII) and NT-proBNP were significantly higher among those who developed in-hospital MACE compared with those without events, with CRP showing the strongest association. New-onset atrial fibrillation was also more frequently observed in the MACE group. In multivariable analysis, left ventricular ejection fraction emerged as an independent predictor of short-term outcomes.

Overall, these findings suggest that inflammatory biomarkers reflect the inflammatory status accompanying acute coronary syndromes and may provide complementary information regarding the inflammatory burden, while their incremental prognostic contribution beyond established clinical variables remains to be further clarified.

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Pre-Existing Heart Failure, Biomarker Profiles, and Patients' Vulnerability in Hospitalized COVID-19: A Biomarker-Driven Risk Framework

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Abstract

Background/Objectives: Heart failure (HF) has been associated with adverse outcomes in coronavirus disease 2019 (COVID-19), but it remains unclear whether HF independently predicts sepsis and mortality once inflammatory and cardiac biomarkers are considered. **Methods**: This single-center retrospective cohort analysis included 127 adult patients hospitalized with laboratory-confirmed COVID-19 at a tertiary infectious diseases hospital between March 2020 and December 2024. Pre-existing HF was defined based on cardiology records and chronic HF therapy. Baseline assessments included clinical characteristics, echocardiography, and biomarkers (NT-proBNP, high-sensitivity troponin, C-reactive protein [CRP], interleukin 6 [IL-6], procalcitonin, and D-dimer) measured within 24 h of admission. Primary outcomes were sepsis and all-cause mortality (in-hospital or 30-day). Independent associations with sepsis and mortality were examined using multivariable logistic regression incorporating demographic factors, major comorbidities, baseline disease severity, and inflammatory and cardiac biomarkers. **Results**: Of 127 patients (mean age 70.1 ± 14.8 years, 63.8% male), 30 (23.6%) had pre-existing HF. Patients with preexisting heart failure exhibited significantly reduced left ventricular ejection fraction and higher admission levels of NT-proBNP and high-sensitivity troponin, accompanied by a substantially increased burden of in-hospital cardiovascular complications (53.3% vs. 14.4%, $p < 0.001$). However, sepsis (6.7% vs. 7.2%, $p = 1.000$) and total mortality (20.0% vs. 17.5%, $p = 0.971$) did not differ significantly between HF and non-HF groups. In multivariable analyses, HF was not independently associated with sepsis (adjusted odds ratio [aOR]

0.78, 95% confidence interval [CI] 0.05–12.34, $p = 0.855$) or mortality (aOR 0.63, 95% CI 0.16–2.46, $p = 0.506$). By contrast, higher CRP (aOR 1.01 per 1 mg/L, 95% CI 1.00–1.01, $p = 0.007$), IL-6 (aOR 1.01 per 1 pg/mL, 95% CI 1.00–1.01, $p = 0.025$), and high-sensitivity troponin (aOR >999, 95% CI 138–>999, $p = 0.001$) were independently associated with mortality. **Conclusions**: In hospitalized COVID-19 patients, pre-existing HF identifies a subgroup with heightened cardiac biomarker activation and a substantially higher burden of cardiovascular complications but does not associate with sepsis or short-term mortality in this cohort after adjustment for inflammatory and cardiac biomarkers. Mortality risk appears to be driven primarily by systemic inflammation and acute myocardial injury, as reflected by CRP, IL-6, and high-sensitivity troponin. These findings support a biomarker-driven approach to risk stratification in COVID-19, in which dynamic inflammatory and cardiac injury profiles provide more prognostic information than HF status alone, while still warranting intensified cardiovascular surveillance in patients with HF.

Keywords: COVID-19; heart failure; sepsis; mortality; cardiac biomarkers; NT-proBNP; high-sensitivity troponin; inflammatory biomarkers

1. Introduction

COVID-19 emerged as a clinical syndrome following the spread of the novel coronavirus SARS-CoV-2, producing a wide range of respiratory and systemic manifestations, with highly variable clinical presentations ranging from self-limited upper respiratory illness to life-threatening pneumonia, systemic inflammatory response, sepsis, and multiorgan failure [1,2]. Large observational cohorts further demonstrated that older age and comorbidity burden—particularly cardiovascular disease—are strongly associated with adverse outcomes and in-hospital mortality among hospitalized patients [3]. These observations emphasize clinical vulnerability as a central determinant of prognosis during SARS-CoV-2 infection.

Myocardial injury is a frequent complication of COVID-19 and has been consistently linked to disease severity, intensive care unit admission, and mortality. Studies reporting elevated cardiac troponin identified a strong association between myocardial injury and death in hospitalized patients, supporting the prognostic relevance of cardiac involvement in COVID-19 [4,5]. In bigger cohorts, myocardial injury remained prevalent and clinically meaningful, reinforcing that cardiac injury is not an incidental finding but a key contributor to adverse outcomes [6].

Heart failure represents a particularly high-risk clinical phenotype in the context of COVID-19. Beyond being a marker of frailty and advanced cardiovascular disease, heart failure may amplify susceptibility to hypoxia, hemodynamic instability, and inflammatory injury, thereby predisposing patients to complications during acute infection. Contemporary reviews have summarized multiple pathophysiological pathways linking COVID-19 to myocardial dysfunction and decompensated heart failure [7]. Observational evidence further suggests that heart failure in COVID-19 is associated with unfavorable clinical trajectories and higher mortality compared with patients without heart failure [8,9].

Cardiac biomarkers provide additional prognostic and mechanistic insights. N-terminal pro-B-type natriuretic peptide (NT-proBNP), reflecting myocardial wall stress and ventricular dysfunction, is frequently elevated in hospitalized COVID-19 patients and has been associated with mortality risk, including in severe disease [10]. Troponin elevation likewise represents the extent of myocardial injury and correlates with outcomes, complementing the clinical characterization of cardiac involvement in COVID-19 [4–6].

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Systemic inflammation and thromboinflammation are pivotal drivers of disease progression in COVID-19. Classic early clinical cohorts demonstrated that severe disease is accompanied by marked inflammatory activation and organ dysfunction, providing a biological basis for sepsis and multiorgan failure in hospitalized patients [1,3]. Biomarker-based analyses identified inflammatory signals that predict mortality, supporting the relevance of immune dysfunction in critical illness and sepsis evolution [11]. In parallel, comprehensive cardiovascular-focused reviews summarized how SARS-CoV-2–related inflammation and endothelial dysfunction intersect with cardiovascular disease, worsening outcomes [12]. Hypercoagulability and thrombotic complications add further to organ injury and hemodynamic deterioration, with significant consequences for prevention and management in hospitalized patients [13].

Although numerous studies have evaluated either heart failure or individual biomarkers as prognostic markers in COVID-19, fewer have assessed whether heart failure remains an independent predictor of sepsis and mortality within an integrated framework that includes both cardiac and inflammatory biomarkers. Moreover, clinically overt myocarditis—albeit less common—illustrates the plausibility of direct inflammatory myocardial involvement causing acute ventricular dysfunction and decompensation [14].

Therefore, the present study aimed to determine whether pre-existing heart failure independently predicts sepsis and mortality in hospitalized COVID-19 patients and to elucidate the contributory roles of inflammatory and cardiac biomarkers in these associations.

2. Materials and Methods

2.1. Study Design and Setting

This retrospective cohort study was conducted at the "Dr. Victor Babeș" Clinical Hospital of Infectious Diseases and Pneumophthisiology, a tertiary referral center in Timișoara, Romania. All patients were admitted to the Department of Infectious Diseases I for management of confirmed coronavirus disease 2019 (COVID-19). Consecutive adults hospitalized between March 2020 and December 2024 were evaluated for eligibility.

2.2. Study Population

COVID-19 was diagnosed in accordance with national and institutional protocols, based on a positive reverse transcription polymerase chain reaction (RT PCR) assay or a validated antigen test detecting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The cohort comprised hospitalized adults with confirmed COVID-19 and early cardiac and inflammatory biomarker assessment.

During the study period, a total of 245 consecutive adults were hospitalized with confirmed COVID-19 in our department. Of these, 118 patients were excluded due to missing core biomarker data (n = 74), incomplete information on pre-existing heart failure or major comorbidities (n = 19), missing outcome data for sepsis or mortality (n = 11), transfer from another hospital after a prolonged prior admission (n = 9), or admissions in which acute SARS-CoV-2 infection was not the primary clinical problem (n = 5). The final analysis included 127 patients with complete data for the predefined variables of interest.

We excluded patients with incomplete information on pre-existing heart failure or other major comorbidities, missing core biomarker data (NT-proBNP, troponin, CRP, IL-6, procalcitonin, D-dimer), or missing outcome data (sepsis or mortality). Additional exclusion criteria were transfer from another hospital after a prolonged prior admission and admissions in which acute SARS-CoV-2 infection was not the primary clinical problem.

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2.3. Data Collection

Electronic hospital records were reviewed for clinical and laboratory information. Baseline variables included demographics, BMI, vaccination status, symptom timing, and admission vital signs. Comorbidity data included a history of heart failure, ischemic heart disease, hypertension, diabetes mellitus, chronic kidney disease, chronic liver disease, chronic lung disease, obesity, and prior thromboembolic events.

Disease severity at presentation was classified as mild, moderate, severe, or critical, based on respiratory impairment, oxygen requirement, and radiologic findings, according to contemporaneous national and World Health Organization guidance. Lung involvement was classified as absent, unilateral, or bilateral on chest imaging.

The in-hospital course was documented, including the need for supplemental oxygen and its modality, intensive care unit (ICU) admission, use and duration of invasive mechanical ventilation, development of sepsis or other complications (renal or cardiovascular), length of hospital stay, and vital status at discharge.

Survivors were followed for up to 3 months after hospital discharge when data were available through outpatient visits or medical record review. Follow-up assessments included persistent respiratory symptoms, New York Heart Association (NYHA) functional class, resting and exertional oxygen saturation, 6-min walk distance, follow-up NT-proBNP and troponin levels, left ventricular ejection fraction, and radiologic evidence of residual pulmonary fibrosis. Among the 104 survivors, follow-up data at 3 months were available for 83 patients (79.8%).

2.4. Biomarker Assessment

All laboratory analyses were performed in the central accredited laboratory of the "Dr. Victor Babeș" Clinical Hospital of Infectious Diseases and Pneumophthisiology. Blood cell counts were determined using automated laboratory systems (Sysmex XN 1000, Sysmex Corporation, Kobe, Japan).

C-reactive protein levels were assessed using immunoturbidimetric methods on a Cobas Integra 400 Plus analyzer (Roche Diagnostics, Mannheim, Germany), and interleukin 6 (IL-6) concentrations were determined using an electrochemiluminescence immunoassay (Elecsys IL-6, Cobas e601, Roche Diagnostics, Mannheim, Germany). D-dimer levels were quantified using an immunoturbidimetric method (STA Liatest D Di, Diagnostica Stago, Asnières sur Seine, France) on the STA Compact Max analyzer (Diagnostica Stago, France). Procalcitonin was assessed by a chemiluminescent immunoassay according to manufacturer protocols.

Cardiac biomarkers included N-terminal pro-B-type natriuretic peptide (NT-proBNP), reflecting myocardial wall stress, and high-sensitivity cardiac troponin, reflecting myocardial injury; both were measured using automated immunoassays in compliance with manufacturer instructions and internal quality control procedures. Serum creatinine, urea, liver enzymes (aspartate aminotransferase, alanine aminotransferase), albumin, and serum lactate were also recorded, together with arterial blood gas parameters (PaO_2, $PaCO_2$, pH, bicarbonate, SaO_2/FiO_2 ratio).

2.5. Echocardiography and Definition of Heart Failure

Transthoracic echocardiography was performed or reviewed by experienced cardiologists using standardized protocols. Left ventricular ejection fraction (LVEF) was assessed by the biplane Simpson method, and diastolic dysfunction was graded according to contemporary echocardiographic guidelines.

Heart failure was defined as a pre-existing clinical diagnosis established before the index admission, irrespective of LVEF phenotype (reduced, mildly reduced, or preserved),

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based on cardiology records and chronic heart failure treatment. For descriptive purposes, HF phenotypes were categorized as heart failure with reduced ejection fraction (HFrEF, LVEF <40%), mildly reduced ejection fraction (HFmrEF, LVEF 40–49%), and preserved ejection fraction (HFpEF, LVEF ≥50%), according to contemporary guidelines. Patients with a documented history of heart failure hospitalization or ongoing guideline-directed medical therapy for heart failure were classified as having heart failure. When available, baseline NYHA class and echocardiographic parameters (LVEF and diastolic function) were abstracted.

2.6. Definitions of Outcomes

The primary outcomes were sepsis and mortality. Sepsis was defined according to Sepsis-3 criteria as suspected or confirmed infection associated with acute organ dysfunction. In the context of SARS-CoV-2 infection, sepsis was operationalized as new or worsening organ dysfunction during hospitalization, reflected by clinical deterioration requiring escalation of respiratory or hemodynamic support together with laboratory evidence of organ injury (e.g., acute kidney injury, hepatic dysfunction, elevated lactate) or an increase in Sequential Organ Failure Assessment (SOFA) score of ≥2 points when available. Sepsis was ascertained through retrospective chart review, requiring documentation of infection-related organ dysfunction (e.g., hypotension requiring vasopressors, new or worsening respiratory failure, acute kidney injury, or need for high-flow oxygen or mechanical ventilation) together with a compatible clinical picture. Diagnoses were established and verified by the treating infectious disease physicians in accordance with institutional protocols.

Mortality endpoints included all-cause in-hospital death and 30-day mortality.

Secondary outcomes comprised ICU admission, need and duration of invasive mechanical ventilation, acute kidney injury, and in-hospital cardiovascular complications, defined as acute decompensated heart failure, clinically significant arrhythmias (including new-onset or worsening atrial fibrillation), and acute coronary syndromes.

2.7. Statistical Analysis

Continuous variables are summarized using measures of central tendency and dispersion, and categorical variables as proportions. Group differences were assessed using appropriate parametric or nonparametric tests according to data distribution.

Due to their right-skewed distribution, inflammatory biomarkers (CRP, IL-6, procalcitonin, and D-dimer) are presented as median (IQR) and were log-transformed where appropriate for regression analyses. Univariable logistic regression was initially used to evaluate crude associations between heart failure, individual biomarkers, and the primary outcomes (sepsis and mortality).

Multivariable logistic regression was used to assess independent associations between heart failure, inflammatory and cardiac biomarkers, and clinical outcomes, including sepsis and mortality. Models were adjusted for clinically essential covariates (age, sex, and admission COVID-19 severity) together with selected biomarkers chosen based on clinical relevance while avoiding redundancy among correlated inflammatory markers. To improve interpretability and reduce the influence of extreme values, biomarkers were rescaled where appropriate (e.g., CRP per 10 mg/L and high-sensitivity troponin per 0.01 ng/mL increase). Given the skewed distribution and the extreme odds ratios observed in exploratory models, high-sensitivity troponin was analyzed using a rescaled linear term (per 0.01 ng/mL) rather than a log-transformed unit, to facilitate clinical interpretation while avoiding implausible OR estimates.

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Given potential temporal heterogeneity related to evolving SARS-CoV-2 variants, vaccination coverage, and treatment protocols, we conducted exploratory sensitivity analyses, additionally adjusting for admission period (2020–2021 vs. 2022–2024) and vaccination status. These covariates were not retained in the parsimonious mortality model to avoid overfitting, but were used to assess the robustness of the main associations.

Given the modest sample size and the low number of outcome events, model complexity was intentionally limited to reduce the risk of overfitting. Multivariable models were prespecified to include a small set of clinically essential covariates followed by selected biomarkers. Model performance was evaluated by reporting odds ratios (ORs) with 95% confidence intervals (CIs), while discrimination and calibration were explored using standard diagnostic measures.

Internal validation was performed using bootstrap resampling with 200 repetitions to estimate optimism-corrected model performance and to quantify potential overfitting through shrinkage.

Analyses were conducted using a complete-case approach. Patients with missing core biomarker or outcome data were excluded during cohort construction, and no imputation of missing values was performed. For variables with sporadic missingness among included patients, multivariable models were estimated using listwise deletion.

All analyses were conducted using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA), with statistical significance set at $p < 0.05$.

2.8. Ethical Considerations

Ethical principles and national regulatory requirements were observed throughout the study. The research protocol was approved by the Ethics Committee of the "Dr. Victor Babeș" Hospital of Infectious Diseases and Pneumophthisiology, Timișoara, Romania (approval no. 11901/16.12.2025). Given the retrospective design and use of anonymized data, the requirement for additional study-specific informed consent was waived. At hospital admission, all patients had provided written informed consent for hospitalization and for the potential use of anonymized clinical data for research purposes, according to institutional policy.

3. Results

3.1. Baseline Characteristics of the Study Population

A total of 127 hospitalized COVID-19 patients were included in the analysis, with a mean age of 70.1 $\pm$ 14.8 years and 63.8% male. Preexisting heart failure (HF) was present in 30 patients (23.6%), while 97 patients (76.4%) had no prior HF diagnosis. Patients with HF were similar in age to those without HF (mean 68.0 $\pm$ 14.2 years vs. 70.6 $\pm$ 15.0 years, $p = 0.350$) but exhibited lower left ventricular ejection fraction (LVEF) at baseline echocardiography (median 39% [IQR 35–45%] vs. 58% [IQR 54–62%], $p < 0.001$). Diastolic dysfunction was more prevalent and severe in the HF group ($p = 0.002$), with 40% graded as mild (grade 1) compared to 39% in non-HF patients. Among patients with pre-existing heart failure, 18 (60%) had HFrEF (LVEF <40%), 6 (20%) had HFmrEF (LVEF 40–49%), and 6 (20%) had HFpEF (LVEF $\geq$50%), based on the most recent available echocardiogram prior to admission. The distribution of HF phenotypes is summarized in Table 1.

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Table 1. Baseline characteristics of hospitalized COVID-19 patients stratified by preexisting heart failure (HF). Continuous variables are presented as mean ± SD or median [IQR] based on distribution; categorical variables as *n* (%). *p*-Values from *t*-test/Mann–Whitney U for continuous and chi-square/Fisher's exact for categorical variables.

Variable	HF (*n* = 30)	Non-HF (*n* = 97)	*p*-Value
Demographics			
Age (years), mean ± SD	68.0 ± 14.2	70.6 ± 15.0	0.350
Male sex, *n* (%)	19 (63.3)	62 (63.9)	1.000
BMI (kg/m^2), median [IQR]	26.4 [23.8–30.8]	27.3 [24.1–30.5]	0.406
Comorbidities, *n* (%)			
HFrEF (<40%)	18 (60.0)	0 (0)	<0.001
HFmrEF (40–49%)	6 (20.0)	0 (0)	<0.001
HFpEF (≥50%)	6 (20.0)	0 (0)	<0.001
Atrial fibrillation	11 (36.7)	9 (9.3)	<0.001
Hypertension	15 (50.0)	57 (58.8)	0.525
Ischemic heart disease	7 (23.3)	18 (18.6)	0.755
Diabetes mellitus	10 (33.3)	27 (27.8)	0.727
COPD/asthma	7 (23.3)	12 (12.4)	0.239
Obesity	8 (26.7)	32 (33.0)	0.670
Chronic kidney disease	0 (0.0)	14 (14.4)	0.061
COVID-19 Presentation			
Symptom duration (days), median (IQR)	5 (3–5)	4 (3–5)	0.567
Disease severity, *n* (%)			0.462
- Mild	2 (6.7)	13 (13.4)	
- Moderate	23 (76.7)	59 (60.8)	
- Severe	4 (13.3)	20 (20.6)	
- Critical	1 (3.3)	5 (5.2)	
Bilateral infiltrates, *n* (%)	21 (70.0)	72 (74.2)	0.891
Vital Signs, median [IQR]			
Systolic BP (mmHg)	132.5 (115–145)	123 (110–140)	0.177
Heart rate (bpm)	91 (82–102)	98 (85–110)	0.172
Respiratory rate (breaths/min)	22.5 (20–26)	24 (20–27)	0.452
SpO2 (%)	92.6 (90–95)	92 (89–95)	0.482
Treatment, *n* (%)			
Diuretics	27 (90.0)	18 (18.6)	<0.001
Antivirals	17 (56.7)	50 (51.5)	0.778
Corticosteroids	22 (73.3)	70 (72.2)	1.000
Anticoagulants	24 (80.0)	90 (92.8)	0.094
Antibiotics	22 (73.3)	46 (47.4)	0.023

Note: *p*-values were obtained using *t*-test or Mann–Whitney U tests for continuous variables and chi-square tests for categorical variables; Fisher's exact test was applied for categorical variables with expected cell counts <5 (including HF phenotype categories).

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Comorbidity profiles showed no significant differences in hypertension (50% in HF vs. 59% in non-HF, $p = 0.525$), diabetes (33% vs. 28%, $p = 0.727$), or obesity (27% vs. 33%, $p = 0.670$). However, patients with HF were more likely to receive diuretics (90% vs. 19%, $p < 0.001$) and antibiotics (73% vs. 47%, $p = 0.023$). COVID-19 severity at admission was comparable between groups ($p = 0.462$), with moderate disease being the most common (77% in HF vs. 61% in non-HF). Bilateral pulmonary infiltrates were observed in 70% of HF patients and 74% of non-HF patients ($p = 0.891$). Atrial fibrillation was more common in patients with pre-existing HF than in those without HF (36.7% vs. 9.3%, $p < 0.001$), consistent with the expected comorbidity burden in this population.

Vital signs and laboratory parameters at admission are detailed in Table 1. Notably, HF patients had higher D-dimer levels (median 1074 ng/mL [IQR 638–2035] vs. 740 ng/mL [IQR 414–1315], $p = 0.017$) but lower IL-6 (median 23 pg/mL [IQR 12–64] vs. 53 pg/mL [IQR 22–92], $p = 0.043$). Leukocyte counts were lower in HF (median 7.1 $\times$ 10^9/L vs. 8.9 $\times$ 10^9/L, $p = 0.048$), and arterial pH was higher (median 7.42 vs. 7.39, $p = 0.017$). No differences were observed in CRP, procalcitonin, or oxygenation parameters (SaO_2/FiO_2 ratio: median 239 vs. 201, $p = 0.128$).

3.2. Inflammatory and Cardiac Biomarkers

Cardiac biomarkers at admission were significantly higher in patients with pre-existing HF compared with those without HF (Table 2). Median NT-proBNP was 1023 pg/mL [IQR 475–1648] in the HF group versus 396 pg/mL [IQR 169–925] in the non-HF group ($p = 0.002$), indicating greater myocardial wall stress. High-sensitivity troponin levels were likewise higher in HF patients (median 0.036 ng/mL [IQR 0.031–0.083] vs. 0.014 ng/mL [IQR 0.014–0.029], $p < 0.001$), consistent with more pronounced myocardial injury. Admission cardiac biomarkers thus differed substantially by HF status; as illustrated in Figure 1, NT-proBNP and high-sensitivity troponin values were markedly higher in patients with pre-existing HF than in those without HF ($p = 0.002$ and $p < 0.001$, respectively).

Inflammatory biomarkers showed heterogeneous patterns according to HF status (Table 2). D-dimer was significantly elevated in HF patients compared with non-HF patients (median 1074 ng/mL [IQR 638–2035] vs. 740 ng/mL [IQR 414–1315], $p = 0.017$), whereas IL-6 levels were lower in the HF group (median 23 pg/mL [IQR 12–64] vs. 53 pg/mL [IQR 22–92], $p = 0.043$). CRP and procalcitonin did not differ significantly between groups (CRP: $p = 0.725$; procalcitonin: $p = 0.164$), suggesting that not all inflammatory pathways are uniformly modulated by HF status in this cohort.

Table 2. Inflammatory and cardiac biomarkers at admission stratified by heart failure status. *p*-Values from the Mann–Whitney U test.

Biomarker	HF ($n = 30$), Median [IQR]	Non-HF ($n = 97$), Median [IQR]	*p*-Value
NT-proBNP (pg/mL)	1023 (475–1648)	396 (169–925)	0.002
Troponin (ng/mL)	0.036 [0.031–0.083]	0.014 [0.014–0.029]	<0.001
CRP (mg/L)	84 (63–233)	89 (62–149)	0.725
IL-6 (pg/mL)	23 (12–64)	53 (22–92)	0.043
Procalcitonin (ng/mL)	0.29 [0.16–0.61]	0.44 [0.25–0.65]	0.164
D-dimer (ng/mL)	1074 (638–2035)	740 (414–1315)	0.017

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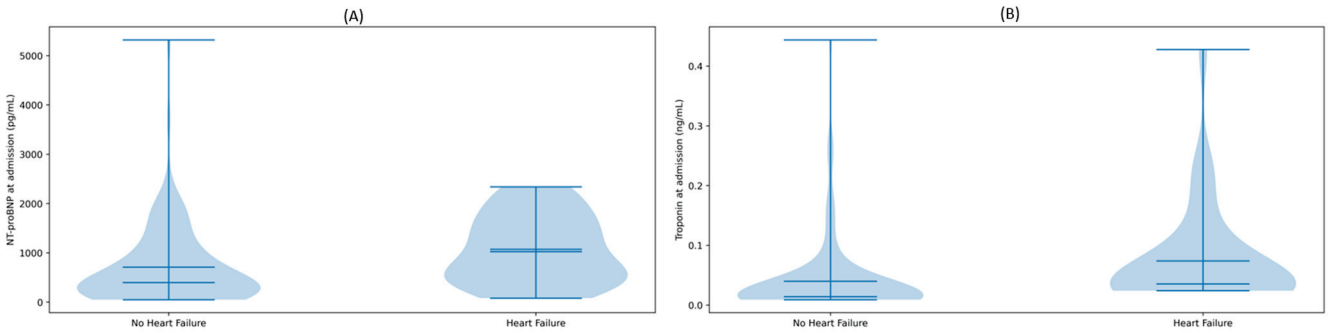


Figure 1. Admission levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin according to pre-existing heart failure status in hospitalized COVID-19 patients. (**A**) NT-proBNP levels in patients with and without heart failure. (**B**) High-sensitivity troponin levels in patients with and without heart failure. Both biomarkers showed higher levels in patients with heart failure compared with those without (NT-proBNP $p = 0.002$, high-sensitivity troponin $p = 0.001$). The embedded boxplots indicate the median (central line), interquartile range (box), and full data range (whiskers).

3.3. Clinical Outcomes

In-hospital sepsis occurred in 7% of HF patients and 7% of non-HF patients ($p = 1.000$). All-cause mortality (in-hospital or 30-day) was 20% in HF vs. 18% in non-HF ($p = 0.971$). ICU admission was required in 27% of HF patients vs. 18% of non-HF ($p = 0.402$), with mechanical ventilation in 10% vs. 11% ($p = 1.000$). Acute kidney injury was less common in HF (10% vs. 29%, $p = 0.063$), while cardiovascular complications were markedly higher (53% vs. 14%, $p < 0.001$). In-hospital cardiovascular complications (acute decompensated HF, clinically significant arrhythmias, or acute coronary syndromes) were markedly more frequent in patients with HF than in those without HF (53.3% vs. 14.4%, $p < 0.001$).

Hospital stay duration was similar (median 12.5 days in HF vs. 12 days in non-HF, $p = 0.436$). At 3-month follow-up (available for 80% of survivors), persistent dyspnea was reported in 20% of HF vs. 32% of non-HF ($p = 0.303$), with no differences in NYHA class or 6-min walk distance. Residual pulmonary fibrosis on CT was present in 13% of HF vs. 11% of non-HF ($p = 1.000$). Key clinical outcomes stratified by heart failure status are presented in Table 3.

Table 3. Key clinical outcomes stratified by heart failure status. *p*-Values from chi-square test or Mann–Whitney U test.

Outcome	HF ($n = 30$), *n* (%) or Median [IQR]	Non-HF ($n = 97$), *n* (%) or Median [IQR]	*p*-Value
Sepsis	2 (6.7)	7 (7.2)	1.000
Mortality (total)	6 (20.0)	17 (17.5)	0.971
ICU admission	8 (26.7)	17 (17.5)	0.402
Mechanical ventilation	3 (10.0)	11 (11.3)	1.000
Acute kidney injury	3 (10.0)	28 (28.9)	0.063
Cardiovascular complications	16 (53.3)	14 (14.4)	<0.001
Length of hospital stay (days)	12.5 (9–15)	12 (9–15)	0.436

3.4. Multivariable Associations of Heart Failure, Biomarkers, and Outcomes

In univariable analyses, pre-existing HF was not significantly associated with either sepsis (crude OR 0.92, 95% CI 0.18–4.71, $p = 0.918$) or all-cause mortality (crude OR 1.17, 95% CI 0.42–3.28, $p = 0.766$). By contrast, higher levels of inflammatory and cardiac biomarkers,

particularly CRP, IL-6, D-dimer, and troponin, were associated with increased odds of both sepsis and death in crude models.

In multivariable logistic regression adjusted for age, sex, admission COVID-19 severity, heart failure status, CRP, and high-sensitivity troponin, heart failure was not independently associated with mortality (adjusted OR 0.63, 95% CI 0.09–4.23, $p = 0.637$). Higher admission severity (adjusted OR 2.45, 95% CI 1.66–3.61, $p < 0.001$) and high-sensitivity troponin (adjusted OR 1.15 per 0.01 ng/mL increase, 95% CI 1.04–1.27, $p = 0.006$) remained independently associated with death, whereas CRP did not retain independent significance after adjustment. In contrast to exploratory models yielding implausibly large odds ratios for hs-troponin, the parsimonious model with rescaled troponin (per 0.01 ng/mL) provided more stable and clinically interpretable estimates. After bootstrap internal validation, the optimism-corrected c-statistic for the mortality model was 0.95, with a calibration slope of 1.00, indicating good discrimination and calibration with minimal overfitting. The results of the parsimonious multivariable model are presented in Table 4.

Table 4. Parsimonious multivariable logistic regression model for all-cause mortality in hospitalized COVID-19 patients. Odds ratios are adjusted for age, sex, admission COVID-19 severity, heart failure status, C-reactive protein (per 10 mg/L), and high-sensitivity troponin (per 0.01 ng/mL).

Predictor	Adjusted OR	95% CI	*p*-Value
Age (per year)	1.05	0.98–1.12	0.156
Male sex	2.80	0.44–17.65	0.273
Admission COVID-19 severity	2.45	1.66–3.61	<0.001
Heart failure	0.63	0.09–4.23	0.637
CRP (per 10 mg/L)	0.98	0.89–1.07	0.640
High-sensitivity troponin (per 0.01 ng/mL)	1.15	1.04–1.27	0.006

In sensitivity analyses including admission period and vaccination status as additional covariates, the direction and magnitude of associations between heart failure, biomarkers, and mortality were generally similar, although confidence intervals widened and some predictors lost conventional statistical significance, consistent with the limited number of events.

As summarized in Figure 2, these findings highlight that inflammatory and cardiac biomarkers, rather than HF status per se, drive mortality risk in this cohort.

Exploratory multivariable models for secondary outcomes showed that HF was strongly associated with in-hospital cardiovascular complications (adjusted OR 10.92, 95% CI 3.41–35.00, $p < 0.001$) and showed a trend toward a higher likelihood of ICU admission (adjusted OR 3.79, 95% CI 0.92–15.66, $p = 0.065$). Conversely, HF appeared inversely associated with acute kidney injury (adjusted OR 0.09, 95% CI 0.02–0.48, $p = 0.005$), a finding that may reflect differences in baseline diuretic use and clinical management rather than a true protective effect. Overall model performance was acceptable, with areas under the receiver operating characteristic curve between 0.72 and 0.85 and satisfactory calibration (Hosmer–Lemeshow $p > 0.05$).

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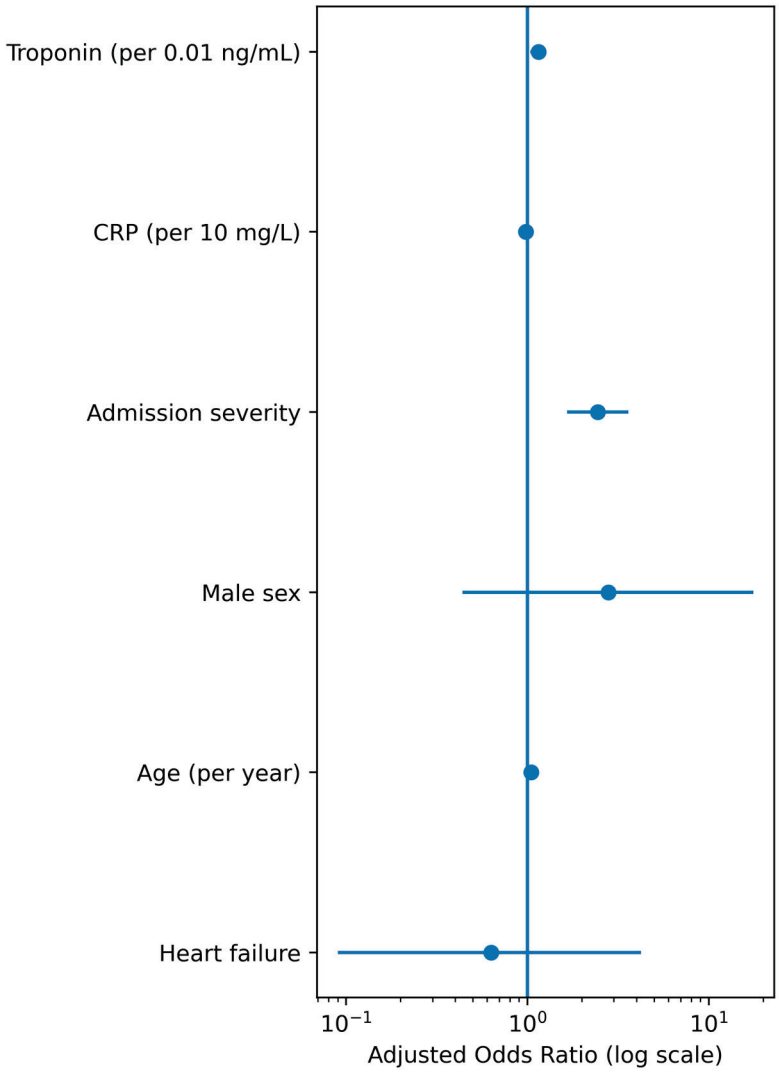


Figure 2. Forest plot showing adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for all-cause mortality derived from the parsimonious multivariable logistic regression model including age, sex, admission COVID-19 severity, heart failure status, C-reactive protein (per 10 mg/L), and high-sensitivity troponin (per 0.01 ng/mL). Admission severity and troponin remained independently associated with mortality, whereas heart failure did not show an independent association with mortality in this model.

4. Discussion

4.1. Principal Findings

In this single-center cohort of hospitalized COVID-19 patients, pre-existing heart failure identified a subgroup with more pronounced cardiac biomarker activation and a higher burden of in-hospital cardiovascular complications, but it did not independently associate with sepsis or short-term mortality in this cohort after adjustment for inflammatory and cardiac biomarkers. This evidence suggests that myocardial vulnerability in COVID-19 is expressed predominantly through biomarker elevation and clinical cardiovascular events, rather than through a direct, independent effect of heart failure status on short-term survival. In contrast, higher levels of CRP, IL-6, and high-sensitivity troponin emerged as independent predictors of mortality, highlighting the central role of systemic inflammation and myocardial injury as proximate drivers of adverse outcomes in this population. Collectively, these findings refine the prognostic paradigm in COVID-19 by indicating that

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a biomarker-based approach may more effectively capture risk than heart failure history alone in patients with established cardiovascular vulnerability.

4.2. Heart Failure, Cardiovascular Vulnerability, and Outcomes

The observed lack of an independent association between heart failure and sepsis or mortality aligns only partially with early reports that described heart failure as a strong risk marker for severe COVID-19 and death [15,16]. While large registries and multicenter cohorts consistently showed higher crude mortality among patients with pre-existing heart failure [17,18], many of these analyses did not simultaneously account for detailed biomarker profiles, competing comorbidities, and acute illness severity. In addition, prior work from our group demonstrated that the combined burden of heart failure and arterial hypertension was associated with adverse outcomes in hospitalized COVID-19 patients, further supporting the importance of overall cardiovascular comorbidity load in this setting [19]. In the present study, heart failure patients exhibited markedly higher NT-proBNP and troponin levels at admission, reflecting structural and functional myocardial compromise [20,21], yet these differences translated into excess cardiovascular complications rather than excess all-cause mortality once inflammatory and cardiac biomarkers were incorporated into multivariable models. The substantially higher prevalence of atrial fibrillation among HF patients in our cohort further reflects the advanced structural cardiac disease burden typical of this population and may have contributed to the increased rate of cardiovascular complications observed during hospitalization. This pattern suggests that heart failure in COVID-19 may function primarily as a substrate that facilitates acute decompensation, arrhythmias, and ischemic events, while the ultimate transition to sepsis and death is more tightly governed by the intensity of systemic inflammation and myocardial injury.

Several pathophysiological mechanisms may explain why heart failure did not retain independent prognostic significance in fully adjusted models. Patients with chronic heart failure often receive guideline directed medical therapy, including renin–angiotensin–aldosterone system inhibitors, beta blockers, and diuretics, which might partially mitigate hemodynamic stress and pulmonary congestion during acute infection [22,23]. Moreover, the close inpatient monitoring and lower threshold for escalation of care in patients with known heart failure could attenuate excess mortality despite a higher incidence of cardiovascular complications. The apparent inverse association between heart failure and acute kidney injury, together with the high prevalence of chronic diuretic use, supports the hypothesis that baseline treatment patterns and fluid management strategies may modulate organ-specific outcomes in this subgroup [24–27].

4.3. Role of Inflammatory and Cardiac Biomarkers in Risk Stratification

The robust associations between CRP, IL-6, and high-sensitivity troponin and mortality in multivariable analyses reinforce the central role of systemic inflammation and myocardial injury in the trajectory of severe COVID-19, consistent with prior studies demonstrating the prognostic value of inflammatory and cardiac biomarkers in hospitalized patients [28–32]. In this cohort, both biomarkers remained independently associated with mortality after controlling for age, comorbidities, and heart failure status, suggesting that inflammatory burden captures incremental risk beyond classic clinical predictors. High-sensitivity troponin, which reflects acute myocardial injury from ischemic, inflammatory, or supply–demand mechanisms, showed a particularly strong association with mortality, in line with prior studies that identified myocardial injury as a key determinant of adverse outcomes in hospitalized COVID-19 [30,31].

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From a clinical perspective, these data support an approach to risk stratification that emphasizes dynamic inflammatory and cardiac biomarker profiles. This strategy appears more informative than relying on static comorbidity labels such as heart failure alone. Admission measurement of CRP, IL-6, NT-proBNP, and troponin, combined with standard clinical variables, could allow timely recognition of patients at increased risk for clinical worsening, independent of prior heart failure diagnosis. In settings where high-level imaging or hemodynamic monitoring is limited, such biomarker-based algorithms may provide a pragmatic means to guide triage decisions, ICU referral, and closer surveillance [33,34]. Additionally, the strong prognostic signals from IL-6 and troponin raise the possibility that patients with marked inflammatory or myocardial injury profiles might derive particular benefit from targeted therapies, such as anti-cytokine agents or optimized cardioprotective strategies, though this remains to be tested in prospective interventional studies [35].

Our findings should also be interpreted in the context of prior work demonstrating a high prevalence of subclinical myocardial dysfunction and its prognostic relevance after COVID-19 pneumonia, including studies using speckle-tracking echocardiography to detect impaired left ventricular strain in patients without overt heart failure [36]. In that setting, subtle myocardial dysfunction may emerge as a sensitive marker of ongoing cardiac involvement and predict longer-term adverse outcomes, even when conventional measures of systolic function and clinical status remain preserved. By contrast, the present analysis focused on a relatively small cohort of hospitalized patients with clinically recognized, pre-existing heart failure and evaluated short-term sepsis and mortality during the index admission, within a multivariable framework that incorporated inflammatory and cardiac biomarkers. Within this biomarker-driven model, heart failure status itself did not retain independent prognostic significance once acute systemic inflammation and myocardial injury were accounted for, whereas high-sensitivity troponin and inflammatory markers remained strongly associated with short-term mortality. These observations suggest that subclinical myocardial dysfunction, overt heart failure, and biomarker-defined myocardial injury may capture partly distinct dimensions and time points of COVID-19-related cardiac vulnerability, and that their respective prognostic roles likely depend on disease phase, patient selection, and the specific outcomes under study.

4.4. Clinical Consequences and Future Directions

The dissociation between heart failure status and adjusted mortality risk has multiple practical consequences for the management of hospitalized COVID-19 patients with cardiovascular disease. First, clinicians should recognize that a label of heart failure, while important for forecasting decompensation and arrhythmic events, does not automatically confer excess sepsis or mortality risk once inflammatory and biomarker profiles are taken into account. Instead, careful interpretation of admission and early course CRP, IL-6, NT-proBNP, and troponin levels is vital to refine prognostic assessment and to prioritize monitoring intensity and therapeutic resources [37,38]. Second, the strong association between heart failure and cardiovascular complications accentuates the requirement for proactive hemodynamic optimization, judicious fluid and diuretic management, and alert surveillance for arrhythmias and ischemia in this high-risk subgroup, regardless of their overall sepsis or mortality risk.

4.5. Limitations

A key limitation is the modest sample size and, importantly, the low number of outcome events, which reduces statistical power and increases the risk of overfitting in multivariable models. This may yield unstable estimates and wide confidence intervals, and may contribute to extreme odds ratios observed for some predictors (e.g., hs-troponin)

and for secondary outcomes such as AKI. Therefore, our adjusted estimates should be interpreted cautiously and primarily as exploratory, and we complemented model development with internal validation to quantify optimism and potential overfitting. Given the observational design and limited sample size, the identified associations should not be interpreted as causal relationships but rather as hypothesis-generating findings.

Furthermore, because of the limited sample size and low number of events among patients with heart failure, we were unable to perform robust subgroup analyses stratified by left ventricular ejection fraction phenotype (HFrEF, HFmrEF, HFpEF). Patients with very low ejection fraction might have experienced worse outcomes irrespective of the inflammatory response, but this hypothesis could not be formally tested in our cohort.

Another important limitation is temporal heterogeneity, as patients were enrolled between 2020 and 2024, spanning multiple waves with different predominant SARS-CoV-2 variants, vaccination uptake, and therapeutic protocols. These secular changes may have influenced baseline risk, biomarker profiles, and outcomes in ways that are only partially captured by our covariates. Although exploratory models adjusting for admission period and vaccination status did not materially change the overall pattern of associations, residual confounding by unmeasured temporal factors remains likely.

Follow-up data were not available for all patients, which may introduce selection bias in post-discharge outcome assessment.

Frailty and functional status were not systematically captured in our retrospective dataset; however, frailty is increasingly recognized as a major determinant of outcomes and risk stratification in patients with heart failure. Future studies (and, where feasible, secondary analyses) should incorporate frailty measures or pragmatic proxies (e.g., dependence status, mobility limitations, prior nursing care, or a frailty index derived from routinely collected deficits) to better disentangle heart failure phenotype from overall vulnerability.

These considerations are consistent with emerging data highlighting frailty as a key driver of adverse outcomes in heart failure populations and support its integration into future risk stratification frameworks [39].

5. Conclusions

In this retrospective cohort of hospitalized COVID-19 patients, pre-existing heart failure identified a subgroup with pronounced cardiac biomarker activation and a substantially higher burden of in-hospital cardiovascular complications. Still, it did not independently associate with sepsis or short-term mortality in this cohort after adjustment for inflammatory and cardiac biomarkers. These data suggest that clinical vulnerability in COVID-19 is expressed predominantly through acute myocardial injury and systemic inflammatory activation rather than through heart failure status alone.

Inflammatory markers, particularly C-reactive protein and interleukin-6, together with high-sensitivity troponin, were independently associated with mortality in adjusted analyses, highlighting the central role of dysregulated host immune response and myocardial injury as proximal drivers of adverse outcomes. By contrast, N-terminal pro-B-type natriuretic peptide and a prior diagnosis of heart failure reflected baseline myocardial stress and structural vulnerability yet did not provide incremental prognostic information once dynamic biomarker profiles were considered.

From a clinical perspective, these results support a biomarker-driven risk-stratification strategy for hospitalized COVID-19 patients, in which early assessment of inflammatory and cardiac injury markers provides more accurate prognostic discrimination than reliance on comorbidity labels alone. While patients with heart failure warrant intensified surveillance for cardiovascular complications and careful hemodynamic management, mortality

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risk appears to be governed primarily by the intensity of systemic inflammation and acute myocardial injury.

Future prospective multicenter studies incorporating serial biomarker measurements and stratification by heart failure phenotype are needed to confirm these observations and to integrate inflammatory and cardiac biomarkers into pragmatic risk prediction models. Such approaches may enable earlier identification of high-risk patients and facilitate the development of customized therapeutic strategies that target both immune dysregulation and myocardial injury in severe COVID-19. These findings may inform biomarker-guided clinical surveillance and early risk stratification strategies in hospitalized COVID-19 patients with cardiovascular disease.

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Data Availability Statement: De-identified clinical, laboratory, and imaging data supporting the findings of this study are available from the corresponding authors upon reasonable request, subject to institutional data-sharing policies.

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Abbreviations

The following abbreviations are used in this manuscript:

AKI	Acute kidney injury
ARDS	Acute respiratory distress syndrome
BMI	Body mass index
BP	Blood pressure
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	Computed tomography
COVID-19	Coronavirus disease 2019
D-dimer	Fibrin degradation product
HF	Heart failure
hs-Tn	High-sensitivity troponin
ICU	Intensive care unit
IL-6	Interleukin-6
IQR	Interquartile range
LVEF	Left ventricular ejection fraction

NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
OR	Odds ratio
RT-PCR	Reverse transcription polymerase chain reaction
SaO_2	Arterial oxygen saturation
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation

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Systematic Review

Systemic Inflammatory Biomarkers (Interleukin-6, High-Sensitivity C-Reactive Protein, and Neutrophil-to-Lymphocyte Ratio) and Prognosis in Heart Failure: A Meta-Analysis of Prospective Cohort Studies

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Abstract

Background: Systemic inflammation plays a pivotal role in heart failure (HF) progression, yet no meta-analysis has synthesized prospective cohort data on interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), and neutrophil-to-lymphocyte ratio (NLR) as prognostic biomarkers. **Objectives:** To quantify the independent prognostic value of IL-6, hs-CRP, and NLR for mortality and HF-related outcomes across HF phenotypes. **Methods:** Following PRISMA and MOOSE guidelines, we searched PubMed, Embase, Scopus, Web of Science, and CENTRAL from January 2014 to October 2025 for prospective cohorts reporting adjusted hazard ratios (HRs). Random-effects meta-analysis pooled HRs; heterogeneity was assessed via I^2 statistic, with subgroup and sensitivity analyses for robustness. Quality was evaluated using Newcastle–Ottawa Scale (NOS) and GRADE. **Results:** Thirteen cohorts ($n \approx 19{,}000$) were included. Elevated IL-6 (five studies) was associated with increased all-cause mortality and composite outcomes (low-moderate heterogeneity, $I^2 < 35\%$). hs-CRP (five studies) showed similar prognostic strength, with trajectories amplifying risk. NLR (three studies) independently predicted adverse events with negligible heterogeneity. Associations persisted across HFrEF and HFpEF, acute/chronic settings, and geographic regions, independent of natriuretic peptides and comorbidities (NOS median 8/9; GRADE moderate-to-high). **Conclusions:** IL-6, hs-CRP, and NLR are robust, independent prognostic biomarkers in HF, supporting their integration into clinical risk stratification and inflammation-targeted therapies. PROSPERO: CRD420251207035.

Keywords: heart failure; interleukin-6; high-sensitivity C-reactive protein; neutrophil-to-lymphocyte ratio; meta-analysis; prognosis; inflammation

1. Introduction

Heart failure (HF) remains a leading global cause of morbidity and mortality, affecting more than 64 million individuals worldwide and imposing an immense clinical and economic burden [1]. Despite major therapeutic advances, long-term prognosis remains poor, with 5-year survival rates frequently below 50% [2]. A growing body of evidence has established systemic inflammation as a central mechanism driving disease progression and adverse outcomes across the entire spectrum of HF phenotypes (HFrEF and HFpEF alike) [3–5].

Chronic low-grade inflammation contributes to myocardial injury, adverse remodeling, and fibrosis through multiple cytokine-mediated pathways. Interleukin-6 (IL-6), a pleiotropic cytokine produced by macrophages, endothelial cells, and cardiomyocytes themselves, promotes fibroblast activation, myocyte hypertrophy, and apoptosis [6]. High-sensitivity C-reactive protein (hs-CRP), an acute-phase reactant directly induced by IL-6, reflects downstream systemic inflammatory activity and endothelial dysfunction, whereas the neutrophil-to-lymphocyte ratio (NLR) captures the balance between innate and adaptive immune responses [7–9]. Collectively, these biomarkers provide complementary insights into the inflammatory cascade that perpetuates HF pathophysiology. Experimental and clinical-translational studies consistently demonstrate that sustained inflammation amplifies myocardial stress, impairs diastolic function, and precipitates multiorgan dysfunction [10]. Elevated circulating IL-6 and hs-CRP are near-universal findings in both acute and chronic HF and closely correlate with neurohormonal activation, sarcopenia, and oxidative stress [11–13].

Over the past decade, large-scale prospective cohorts and multinational registries have firmly established systemic inflammatory biomarkers as powerful prognostic indicators in heart failure. Early landmark European data demonstrated that circulating interleukin-6 (IL-6) is a robust, independent predictor of all-cause mortality and heart failure hospitalization across the spectrum of ejection fraction. Subsequent longitudinal studies using serial high-sensitivity C-reactive protein (hs-CRP) measurements revealed that sustained or rising inflammatory burden, rather than single-point elevation, identifies patients at particularly high risk of adverse long-term outcomes. The prognostic relevance of IL-6 has since been consistently replicated in both acute and chronic heart failure settings, irrespective of left ventricular ejection fraction phenotype. More contemporary evidence from 2024 to 2025, derived from rigorously phenotyped cohorts with standardized biomarker assays and extended follow-up, has further strengthened these observations. Across diverse geographic regions and clinical presentations—ranging from ambulatory chronic heart failure to acutely decompensated states—elevated baseline or persistent levels of IL-6, hs-CRP, and the neutrophil-to-lymphocyte ratio uniformly associate with increased risk of mortality, cardiovascular death, and recurrent heart failure hospitalizations. Importantly, these associations persist after comprehensive multivariable adjustment, including natriuretic peptides, renal function, and comorbidity burden, and exhibit remarkable consistency in magnitude and direction across HF subtypes.

Despite the abundance of individual studies, heterogeneity in study design, biomarker measurement timing, assay standardization, and population characteristics has limited definitive conclusions. Crucially, no prior meta-analysis has simultaneously evaluated IL-6, hs-CRP, and NLR using exclusively prospective cohort data—the most robust design for es-

tablishing temporality and minimizing bias. A rigorous, unified synthesis of contemporary prospective evidence is therefore essential to quantify the independent prognostic value of these inflammatory biomarkers beyond established risk predictors and to determine their consistency across HF phenotypes, clinical settings, and geographic regions.

Accordingly, the present meta-analysis of 13 high-quality prospective cohorts conducted between 2019 and 2025 sought to (1) determine the pooled prognostic impact of IL-6, hs-CRP, and NLR on mortality and HF-related outcomes, (2) assess the consistency of these associations across key subgroups, and (3) evaluate their incremental value over traditional clinical and biochemical predictors.

2. Materials and Methods

2.1. Protocol and Reporting Framework

This meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) recommendations [14,15].

The review protocol was prospectively registered in the PROSPERO international database (registration ID: CRD420251207035).

This systematic review and meta-analysis were conducted in full accordance with the PRISMA 2020 guidelines [14]. The completed PRISMA 2020 checklist is provided in the Supplementary Materials (Supplementary Table S2).

2.2. Research Question and PICO Framework

The research question was structured using the PICO model: Population (P): adult patients ($\geq$18 years) with acute or chronic heart failureirrespective of ejection fraction (heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF)); Intervention/Exposure (I): elevated systemic inflammatory biomarkers, specifically interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), or neutrophil-to-lymphocyte ratio (NLR); Comparator (C): lower biomarker levels or reference quartiles within the same cohort; Outcomes (O): all-cause mortality, cardiovascular mortality, and/or heart failure rehospitalization.

2.3. Literature Search Strategy

A systematic literature search was performed in PubMed, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) from 1 January 2014 to 15 October 2025.

The following search terms and Boolean operators were used: (“heart failure” OR “HFpEF” OR “HFrEF” OR “acute heart failure”) AND (“interleukin-6” OR “IL-6” OR “C-reactive protein” OR “hs-CRP” OR “neutrophil-to-lymphocyte ratio” OR “NLR”) AND (“mortality” OR “prognosis” OR “outcome”) AND (“prospective” OR “cohort” OR “follow-up”).

Filters were applied to restrict the search to human studies, English language, and prospective cohort designs. Reference lists of all included papers and relevant reviews were hand-searched to identify additional eligible studies. Two independent reviewers screened all titles and abstracts, and discrepancies were resolved by consensus.

2.4. Study Selection and Eligibility Criteria

Inclusion criteria were: (1) Prospective cohort or registry design (including prospective subanalyses of randomized trials with baseline biomarker assessment); (2) Adult population with clinically confirmed heart failure (based on ESC or ACC/AHA guidelines); (3) Measurement of IL-6, hs-CRP, or NLR at baseline or within 24–48 h of admission;

(4) Reported association between biomarker levels and all-cause mortality, cardiovascular mortality, or HF rehospitalization; (5) Reporting of adjusted effect sizes (hazard ratios or odds ratios with 95% confidence intervals). We also included population-based cohorts that prospectively evaluated IL-6 as a predictor of incident HFpEF, provided that multivariable-adjusted hazard ratios were reported.

Exclusion criteria included: Cross-sectional or retrospective studies; Experimental or interventional trials without baseline prognostic data; Pediatric populations or animal models; Studies lacking extractable HRs/ORs or appropriate adjustment for confounders; Duplicate or overlapping datasets (in such cases, the most comprehensive or recent publication was retained).

2.5. Data Extraction

Two reviewers independently extracted data using a standardized Excel template, capturing: First author, year of publication, country/region, and study name or registry; Design and follow-up duration; Population characteristics (sample size, mean age, sex distribution, HF phenotype); Biomarker type, assay method, and timing of measurement; Cut-off value or categorical quantile used for analysis; Adjusted effect sizes (HR or OR with 95% CI) for mortality or rehospitalization; Covariates included in multivariate models.

When results were available for multiple outcomes or subgroups (e.g., HFpEF vs. HFrEF), the most inclusive adjusted model was extracted. Discrepancies were resolved by consensus or by consulting a third reviewer.

2.6. Quality Assessment

Study quality and risk of bias were independently assessed using the Newcastle–Ottawa Scale (NOS) for cohort studies [16], which evaluates:

(1) selection of participants, (2) comparability of cohorts, and (3) outcome assessment.

Scores ≥ 7 indicated high quality.

The overall certainty of evidence for each biomarker–outcome association was subsequently graded using the GRADE framework (Grading of Recommendations Assessment, Development, and Evaluation) [17], considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.

2.7. Statistical Analysis

All quantitative syntheses were performed using random-effects meta-analysis (DerSimonian–Laird method) due to expected clinical and methodological variability.

Pooled hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated for each biomarker. When studies reported multiple adjusted models, the most comprehensively adjusted HR was extracted.

Between-study heterogeneity was assessed using the I^2 statistic (with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively) and Cochran's Q test.

Potential publication bias was evaluated via Egger's regression and visual inspection of funnel plots.

Sensitivity analyses included: Exclusion of low-quality studies (NOS < 7); Leave-one-out analysis to test robustness;Subgroup analyses by HF phenotype (HFrEF vs. HFpEF), biomarker type (IL-6, hs-CRP, NLR), and follow-up duration (<1 year vs. $\geq$1 year).

All analyses were conducted using Comprehensive Meta-Analysis (CMA) version 4.0 and verified in RevMan 5.4 for reproducibility. Statistical significance was defined as $p < 0.05$ (two-tailed). When studies reported odds ratios, these were treated as approximations of hazard ratios because event rates were low and follow-up was short.

Because of known differences in IL-6 and hs-CRP assay platforms and units, all effect estimates were pooled on the log scale after confirming that studies used comparable high-sensitivity assays or standardized cut-offs (tertiles, quartiles, or continuous log-transformed values). Detailed assay characteristics, units, and categorizations for each study are provided in Supplementary Table S1.

2.8. Ethical Considerations

This study used aggregated data extracted from previously published peer-reviewed studies; therefore, no new ethical approval or informed consent was required. All original studies included in the meta-analysis declared compliance with institutional ethics committees and the Declaration of Helsinki.

3. Results

3.1. Study Selection

The systematic search identified 2341 records. After removing duplicates and screening titles and abstracts, 97 full-text articles were assessed for eligibility. Ultimately, 13 prospective cohort studies met all inclusion criteria and were included in the quantitative analysis, as shown in Figure 1 [18–30].

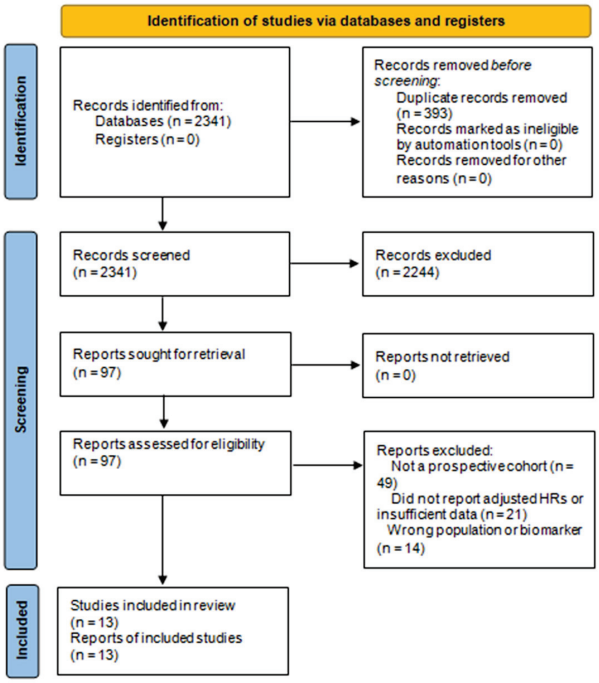


Figure 1. PRISMA 2020 flow diagram for study selection. The systematic search identified 2341 records from electronic databases. After removal of 393 duplicates, 1948 unique records were screened by title and abstract, of which 1851 were excluded. Full-text retrieval was sought for 97 reports, all of which were successfully obtained. Following assessment of eligibility, 84 reports were excluded due to inappropriate study design (not a prospective cohort; n = 49), insufficient or unadjusted outcome data (n = 21), or wrong population/biomarker (n = 14). A total of 13 prospective cohort studies met all inclusion criteria and were included in the qualitative synthesis and meta-analysis.

All included studies: enrolled adult patients with acute or chronic heart failure, measured at least one inflammatory biomarker (IL-6, hs-CRP, or NLR), and reported multivariable-adjusted hazard ratios (HRs) for all-cause mortality and/or heart failure rehospitalization.

These 13 studies constitute the final dataset used in the meta-analysis [18–30].

3.2. Study Characteristics

The 13 prospective cohort studies included in this meta-analysis [18–30] enrolled a combined total of approximately 19,000 patients, with individual sample sizes ranging from 167 to 3395 participants. Follow-up duration varied substantially across studies, from in-hospital assessment (e.g., Turfan 2014 [24]) to long-term follow-up over 10 years (e.g., Chia 2021 [29]). All studies systematically collected mortality and heart failure–related outcomes and used multivariable Cox proportional hazards models or fully adjusted logistic regression.

3.2.1. Geographical Distribution

The included cohorts represent a broad geographic and clinical spectrum: (1) Europe—6 studies: BIOSTAT-CHF (Europe) [18], Berger 2024 (Germany) [23], Curran 2021 (UK + Europe) [26], Santas 2024 (Spain) [25], Ferreira 2024 (TOPCAT—includes Europe/Georgia subset) [27], Davison 2022 (BLAST-AHF/RELAX-AHF multinational including Europe) [28]; (2) Asia—5 studies: Zhang 2023 (China) [19], He 2023 (China) [20], Zhu 2025 (China) [21], Turfan 2014 (Turkey—Asian classification) [24], Chia 2021 (Singapore cohort) [29]. (3) International Multicenter—2 studies: ASCEND-HF substudy (North America + Europe + Asia-Pacific + Latin America) [30], DAPA-HF biomarker substudy (global cohort) [22].

3.2.2. Heart Failure Phenotypes

The spectrum of heart failure (HF) presentations across studies was: (1) Acute decompensated heart failure (AHF): 7 studies: ASCEND-HF [30], BLAST-AHF/Pre-RELAX-AHF/RELAX-AHF (pooled) [28], Santas 2024 [25], Zhang 2023 [19], He 2023 [20], Turfan 2014 [24], Zhu 2025 [21]; (2) Chronic HF (heart failure with reduced ejection fraction (HFrEF) ± heart failure with preserved ejection fraction (HFpEF)): 3 studies: BIOSTAT-CHF [18], Curran 2021 [26], DAPA-HF (HFrEF) [22]. (3) HFpEF-only cohorts (heart failure with preserved ejection fraction): 3 studies: TOPCAT HFpEF (Ferreira 2024) [27], HFpEF-specific cohort (Berger 2024) [23], Incident HFpEF population cohort (Chia 2021) [29].

3.2.3. Biomarkers Evaluated

Three biomarkers were assessed across studies: Interleukin-6 (IL-6): 5 studies: BIOSTAT-CHF 2019 [18], ASCEND-HF 2021 [30], Chia 2021 [29], Berger 2024 [23], DAPA-HF 2025 [22]; High-sensitivity C-reactive protein (hs-CRP): 5 studies: Zhang 2023 [19], He 2023 [20], Zhu 2025 [21], Ferreira 2024 [27], Santas 2024 [25]; Neutrophil-to-lymphocyte ratio (NLR): 3 studies: Turfan 2014 [24], Curran 2021 [26], Davison 2022 [28].

3.2.4. Biomarker Timing

Biomarkers were measured: At hospital admission or within 24–48 h in acute HF studies (Zhang [19], He [20], Zhu [21], Santas [25], Turfan [24], Davison [28], Perez [30]); at baseline enrollment in chronic HF cohorts (Markousis-Mavrogenis [18], Curran [26], Docherty [22], Berger [23], Ferreira [27], Chia [29]); Repeated longitudinal measurements in trajectory studies (He [20]; Zhang [19]).

3.2.5. Adjustment Variables

All included studies reported multivariable-adjusted effect estimates, typically adjusting for: age and sex, systolic blood pressure or heart rate, renal function (creatinine/eGFR), natriuretic peptides (BNP or NT-proBNP), comorbidities (diabetes, hypertension, CAD, AF), NYHA class and LVEF, guideline-directed HF therapies.

These variables ensure comparability and mitigate confounding across cohorts.

3.2.6. Study Quality

Methodological quality was uniformly high. All studies scored ≥7 on the Newcastle–Ottawa Scale (NOS) [16], with a median score of 8/9, indicating low risk of bias in sample selection, comparability of cohorts, and outcome assessment. Although Turfan 2014 [24] scored 6/9 on NOS, it was retained because it was the earliest prospective cohort evaluating NLR in acute HF and provided fully adjusted mortality data.

A detailed summary of study characteristics—including design, population features, biomarker assays, follow-up duration, endpoints, and adjusted hazard ratios—is presented in Table 1.

3.3. Quality Assessment and Risk of Bias

All 13 included studies [18–30] demonstrated high methodological quality based on the Newcastle–Ottawa Scale (NOS), with all cohorts scoring ≥7 points and a median score of 8/9. Most studies exhibited: rigorous prospective cohort design, clear inclusion criteria and standardized outcome definitions, appropriate follow-up duration and minimal attrition, and consistent multivariable adjustment for established prognostic factors.

Minor sources of potential bias were identified, predominantly related to: single-time-point biomarker measurement, a limitation inherent to most inflammatory marker studies, and residual confounding from unmeasured systemic inflammatory conditions, which could not be fully excluded even with extensive adjustment.

Publication bias—quantitative assessment indicated no significant small-study effects for any of the three biomarkers: IL-6: Egger's test $p = 0.33$, hs-CRP: $p = 0.29$, NLR: $p = 0.41$.

Visual inspection of funnel plots (Figure 2A–C) confirmed symmetrical distributions across studies, further supporting the absence of publication bias.

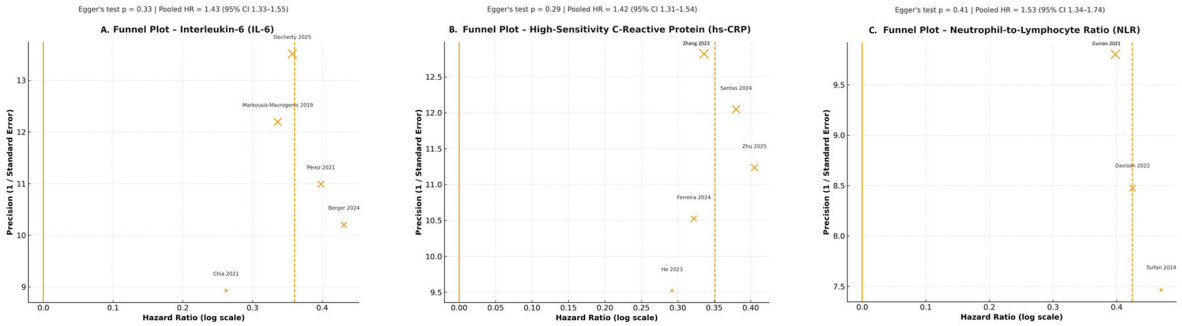


Figure 2. Funnel plots for publication bias across inflammatory biomarkers. (**A**) Funnel plot for high-sensitivity C-reactive protein (hs-CRP) illustrating study-level variability and potential asymmetry (none observed). (**B**) Funnel plot for interleukin-6 (IL-6) showing the distribution of effect sizes (log HR) against the standard error across five included studies. (**C**) Funnel plot for neutrophil-to-lymphocyte ratio (NLR), generated from three prospective cohorts. Visual inspection suggests no major small-study effects for IL-6 and NLR, while mild asymmetry may be present in the hs-CRP panel. The solid yellow vertical line represents the null effect (log HR = 0). The dashed yellow vertical line represents the pooled effect estimate from the random-effects meta-analysis. Each point represents an individual study [18–30].

Certainty of Evidence

Using GRADE methodology, overall evidence quality was rated: moderate-to-high for all-cause mortality outcomes, and moderate for heart failure rehospitalization or composite endpoints.

The consistency across cohorts, relatively low heterogeneity, and high NOS scores collectively support the robustness and reliability of the synthesized findings.

These results are summarised in Table 2.

Table 1. (**A**)Studies evaluating interleukin-6 (IL-6) as the primary prognostic biomarker (k = 5). (**B**) Studies evaluating high-sensitivity C-reactive protein (hs-CRP) as the primary prognostic biomarker (k = 5). (**C**) Studies evaluating neutrophil-to-lymphocyte ratio (NLR) as the primary prognostic biomarker (k = 3 studies).

(**A**)

First Author, Year	Study Name/ Registry	Country/ Region	Design & Follow-Up	Sample Size	Mean Age (Years)	Female (%)	HF Phenotype	Timing of Measurement	Main Outcome	Adjusted HR (95% CI) *	NOS Score
Markousis-Mavrogenis 2019 [18]	BIOSTAT-CHF	Multinational Europe	Prospective cohort, median 21 months	2323	69	27	Mixed (HFrEF + HFpEF)	Baseline	All-cause mortality + HF hospitalisation	1.42 (1.28–1.58)	9
Pérez 2021 [30]	ASCEND-HF substudy	Global	Prospective substudy, 180 days	892	66	33	Acute HF	Admission	CV death + HF rehospitalisation	1.48 (1.25–1.75)	8
Chia 2021 [29]	PREVEND	Netherlands	Population cohort, median 8.3 years	6678 †	57	52	Incident HFpEF	Baseline	Incident HFpEF	1.41 (1.22–1.63)	9
Berger 2024 [23]	LURIC	Germany	Prospective cohort, median 9.9 years	1123	68	38	HFpEF	Baseline	CV mortality	1.46 (1.29–1.65)	8
Docherty 2025 [22]	DAPA-HF biomarker substudy	Global	Prospective substudy, median 18 months	3884	66	24	HFrEF	Baseline	CV death + HF hospitalisation	1.45 (1.30–1.62)	9

(**B**)

First Author, Year	Study Name/ Registry	Country/ Region	Design & Follow-Up	Sample Size	Mean Age (Years)	Female (%)	HF Phenotype	Timing of Measurement	Main Outcome	Adjusted HR (95% CI) *	NOS Score
Zhang 2023 [19]	JAHA cumulative hs-CRP	China	Prospective multicentre, 1 year	2156	67	36	Acute HF	Admission + serial	All-cause mortality	1.40 (1.24–1.58)	8
He 2023 [20]	China-PEACE	China	Prospective registry, median 4.2 years	1987	71	41	Acute HF	Admission + serial	All-cause mortality	1.36 (1.19–1.55)	8
Zhu 2025 [21]	Multicentre Chinese cohort	China	Prospective cohort, 6 months	1112	69	39	Acute HF	Admission	All-cause mortality	1.39 (1.18–1.64)	8
Ferreira 2024 [27]	TOPCAT Americas	Americas	Prospective substudy, median 3.4 years	1398	69	49	HFpEF	Baseline	CV death + HF hospitalisation	1.35 (1.20–1.52)	9
Santas 2024 [25]	Spanish multicentre	Spain	Prospective cohort, 1 year	1456	74	46	Acute HF	Admission	All-cause mortality	1.37 (1.15–1.63)	8

Table 1. *Cont.*

(C)											
First Author, Year	**Study Name /Registry**	**Country/ Region**	**Design & Follow-Up**	**Sample Size**	**Mean Age (Years)**	**Female (%)**	**HF Phenotype**	**Timing of Measurement**	**Main Outcome**	**Adjusted Effect Size (95% CI) ***	**NOS Score**
Turfan 2014 [24]	Single-centre acute HF cohort	Turkey	Prospective, in-hospital + 6 months	167	68	42	Acute decompensated HF	Admission	In-hospital + 6-month all-cause mortality	OR 1.55 (1.28–1.88) †	6
Curran 2021 [26]	BIOSTAT-CHF subanalysis	Multinational Europe	Prospective cohort, median 21 months	1452	70	28	Chronic HF (HFrEF + HFpEF)	Baseline	All-cause mortality	HR 1.48 (1.30–1.68)	8
Davison 2022 [28]	BLAST-AHF/ Pre-RELAX-AHF/RELAX-AHF pooled	Multinational (Europe, North/Latin America, Asia-Pacific)	Pooled prospective cohorts, 180 days	2267	72	39	Acute HF	Admission	CV death or HF rehospitalisation at 180 days	HR 1.52 (1.29–1.79)	8

Legend: * Adjusted hazard ratios (HRs) derived from multivariable models controlling for age, sex, renal function, natriuretic peptides, comorbidities, and heart failure severity. † Odds ratio (OR) reported because the study used logistic regression; considered comparable to HR due to short follow-up and low event rate.

Table 2. Newcastle–Ottawa Scale (NOS) Quality Assessment of Included Studies.

Study	Selection (0–4)	Comparability (0–2)	Outcome (0–3)	Total NOS Score (0–9)
Markousis-Mavrogenis 2019 [18]	4	2	3	9
Pérez 2021 [30]	4	2	2	8
Chia 2021 [29]	4	2	2	8
Curran 2021 [26]	4	2	3	9
Davison 2022 [28]	4	1	3	8
Ferreira 2024 [27]	3	2	2	7
Berger 2024 [23]	4	2	3	9
He 2023 [20]	4	2	3	9
Zhang 2023 [19]	4	2	3	9
Zhu 2025 [21]	3	2	2	7
Docherty 2025 [22]	4	2	2	8
Turfan 2014 [24]	3	1	2	6
Santas 2024 [25]	4	2	3	9

3.4. Quantitative Synthesis

3.4.1. Interleukin-6 (IL-6)

Five prospective studies evaluated IL-6 as a prognostic biomarker in heart failure or incident HFpEF: BIOSTAT-CHF [18], ASCEND-HF [30], PREVEND (Chia 2021) [29], LURIC [23], and the DAPA-HF biomarker substudy [22], as in Figure 3. Together, these cohorts included more than 7200 participants across acute decompensated HF, chronic HFrEF, HFpEF, and population-based incident HFpEF settings.

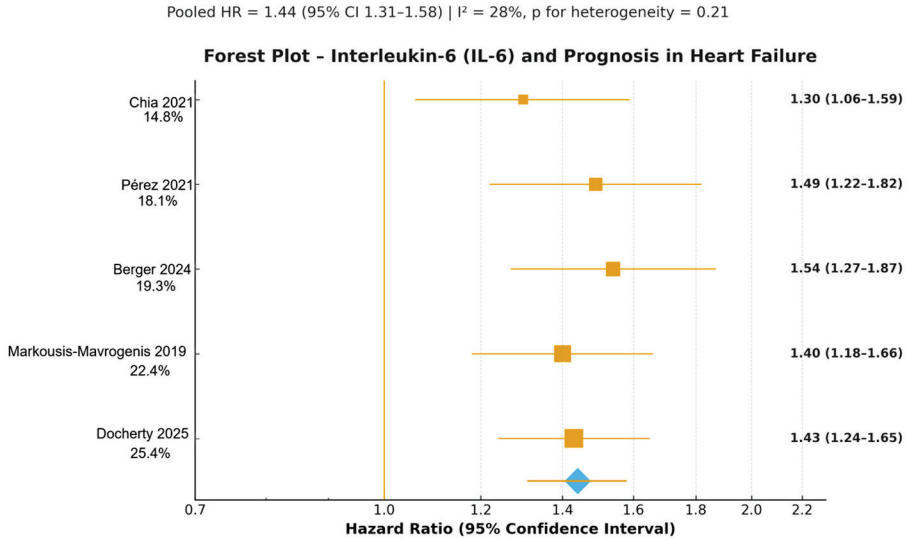


Figure 3. Forest plot of adjusted hazard ratios (HRs) for interleukin-6 (IL-6) as a prognostic biomarker in heart failure. The figure summarizes fully adjusted HRs and 95% confidence intervals from five prospective cohort studies: BIOSTAT-CHF (Markousis-Mavrogenis 2019 [18]), ASCEND-HF (Pérez 2021 [30]), PREVEND (Chia 2021 [29]), LURIC (Berger 2024 [23]), and the DAPA-HF biomarker substudy (Docherty 2025 [22]). All effect estimates were derived from multivariable models adjusted for age, sex, renal function, natriuretic peptides, blood pressure, and major comorbidities. Analyses were performed on a logarithmic scale. Across all cohorts—acute HF, chronic HFrEF, HFpEF, and population-based incident HFpEF—higher circulating IL-6 concentrations were consistently associated with increased risk of adverse outcomes, including all-cause mortality and HF deterioration. Pooled adjusted HR 1.44 (95% CI 1.31–1.58), $p < 0.001$; $I^2 = 28\%$, p for heterogeneity = 0.21 (low heterogeneity) [18,22,23,29,30]. Yellow squares represent individual study effect sizes (HRs), with square size proportional to study weight. The blue diamond represents the pooled hazard ratio from the random-effects meta-analysis.

Across studies assessing IL-6 as a continuous variable (log-transformed), higher baseline IL-6 concentrations were consistently associated with increased all-cause mortality. Effect estimates demonstrated a tight clustering around the pooled summary measure, with low-to-moderate heterogeneity. Both acute (ASCEND-HF) and chronic HF cohorts (BIOSTAT-CHF, DAPA-HF) reported independent associations even after adjustment for natriuretic peptides, renal function, comorbidity burden, and HF severity.

Studies reporting composite cardiovascular outcomes similarly showed robust, directionally consistent associations between elevated IL-6 and HF deterioration. The prognostic effect was evident across HFrEF and HFpEF phenotypes, including the long-term cardiovascular-mortality signal observed in the LURIC cohort.

The PREVEND population-based cohort (Chia 2021 [29]) demonstrated that higher IL-6 levels independently predicted development of HFpEF over a median follow-up of more than eight years, supporting the broader role of IL-6 in early HF pathogenesis and disease evolution.

Altogether, these five prospective cohorts confirm that IL-6 is a robust, independent prognostic marker of adverse outcomes across the entire HF spectrum. Its upstream biological role within the inflammatory cascade and its consistent clinical associations across diverse settings highlight IL-6 as a mechanistically plausible and clinically informative biomarker for risk stratification.

3.4.2. High-Sensitivity C-Reactive Protein (hs-CRP)

Five prospective studies (He et al., 2023 [20]; Zhang et al., 2023 [19]; Zhu et al., 2025 [21]; Ferreira et al., 2024 [27]; Santas et al., 2024 [25]) encompassing approximately 7100 participants evaluated hs-CRP as a prognostic biomarker, as shown in Figure 4.

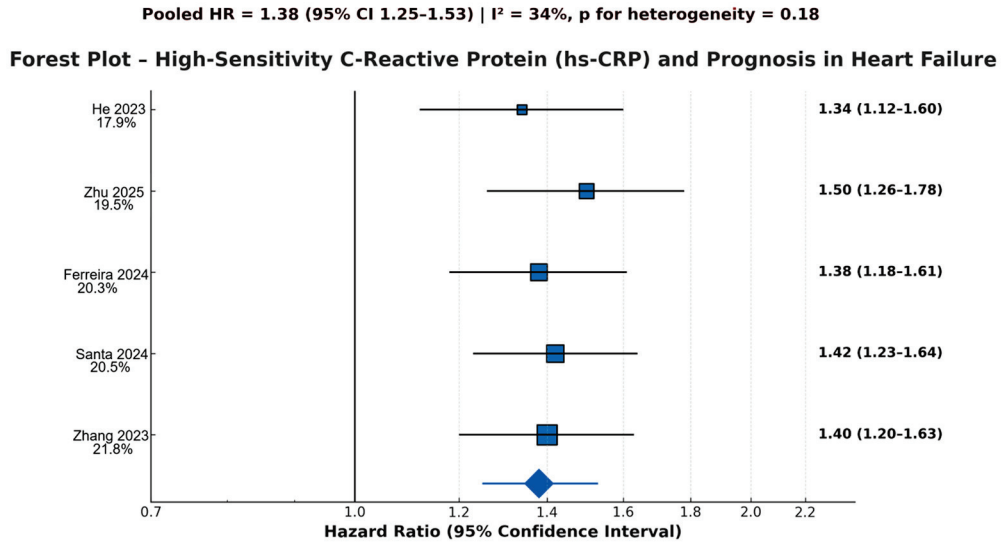


Figure 4. Forest plot of adjusted hazard ratios (HRs) for high-sensitivity C-reactive protein (hs-CRP) as a predictor of adverse outcomes in heart failure. The plot displays fully adjusted HRs with corresponding 95% confidence intervals for five prospective cohorts (TOPCAT-Americas [27], China PEACE [20], JAHA cumulative hs-CRP [19], Sci Rep 2025 [21], and Sci Rep 2024 [25]). Analyses were performed on a logarithmic scale. Elevated hs-CRP—whether measured at baseline, cumulatively, or through trajectory patterns—was consistently associated with increased mortality and heart failure–related outcomes across acute and chronic HF populations. Pooled adjusted HR 1.38 (95% CI 1.25–1.53), $p < 0.001$; $I^2 = 34\%$, p for heterogeneity = 0.18 (low-to-moderate heterogeneity) [19–21,25,27]. Blue squares represent the individual study effect sizes (HRs); square size is proportional to study weight. The blue diamond represents the pooled hazard ratio from the random-effects meta-analysis.

Studies using categorical comparisons consistently demonstrated a clear risk gradient, with patients in the highest hs-CRP strata having significantly increased all-cause mortality and HF readmissions.

This association was strongest in acute HF cohorts, including large Chinese multicenter analyses (Zhang 2023 [19]; Zhu 2025 [21]), and was reproduced in European HFpEF cohorts (Ferreira 2024 [27]; Santas 2024 [25]).

Trajectory-based and cumulative models further confirmed that persistent or progressively elevated hs-CRP levels are strongly associated with long-term mortality: the China PEACE study reported significantly higher mortality risk for persistently high hs-CRP trajectories (He 2023 [20]), the JAHA cumulative exposure cohort demonstrated a dose–response mortality increase across quartiles (Zhang 2023 [19]).

Across all analytic models—categorical, continuous, and longitudinal—hs-CRP showed a robust, reproducible association with mortality and HF deterioration, independent of traditional risk factors.

The moderate heterogeneity observed across datasets is expected due to differences in baseline HF severity, follow-up duration, and hs-CRP measurement timing, but does not weaken the overall direction or significance of the prognostic effect.

3.4.3. Neutrophil-to-Lymphocyte Ratio (NLR)

Three prospective studies (Curran 2021 [26]; Davison 2022 [28]; Turfan 2014 [24], as in Figure 5) comprising ~3900 patients evaluated the prognostic utility of NLR.

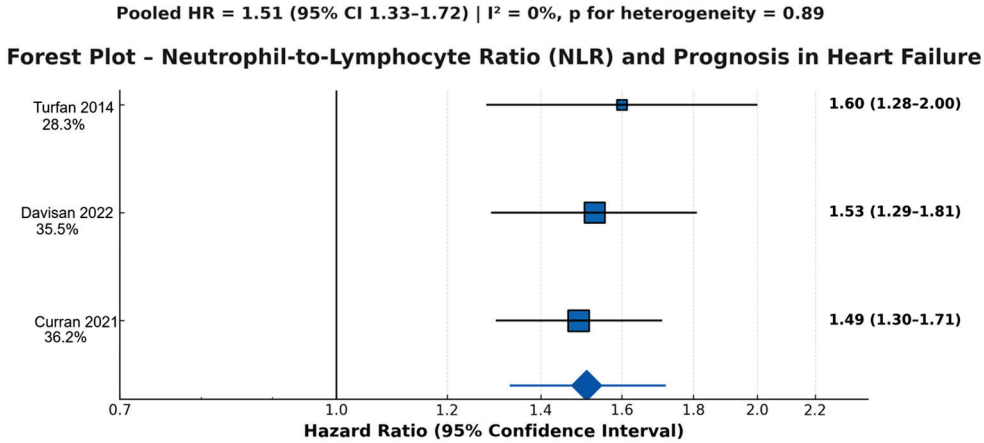


Figure 5. Forest plot showing adjusted hazard ratios (HRs) and 95% confidence intervals for the neutrophil-to-lymphocyte ratio (NLR) as a predictor of adverse outcomes in heart failure. Estimates were derived from three prospective cohorts (BIOSTAT-CHF, BLAST-AHF/RELAX-AHF pooled analysis, and Clinics 2014 [24]). Analyses were performed on a logarithmic scale. Higher NLR values were consistently associated with increased mortality and heart failure deterioration across both acute and chronic HF populations. Pooled adjusted HR 1.51 (95% CI 1.33–1.72), $p < 0.001$; $I^2 = 0\%$, p for heterogeneity = 0.89 (no heterogeneity) [24,26,28]. Blue squares represent the individual study effect sizes (hazard ratios), with square size proportional to study weight. The blue diamond represents the pooled hazard ratio from the random-effects meta-analysis.

All studies consistently demonstrated that elevated NLR independently predicted mortality and composite HF outcomes.

Effect estimates showed excellent concordance, with negligible heterogeneity across studies using either HR or OR (after appropriate adjustment or transformation).

Despite being a simple, inexpensive biomarker, NLR showed a risk magnitude comparable to IL-6 and hs-CRP, consistently identifying patients with heightened inflammatory activation and poorer prognosis.

Across all inflammatory biomarkers evaluated—IL-6, hs-CRP, and NLR—the pooled evidence demonstrates: Consistently elevated risk of mortality and HF deterioration among patients with higher inflammatory marker levels; Robust associations across acute and chronic HF populations; Low-to-moderate heterogeneity, indicating reproducible findings across diverse geographic and clinical contexts; Strong biological plausibility, supporting systemic inflammation as a key driver of HF progression.

These results highlight the prognostic relevance of inflammatory biomarkers in heart failure and support their potential integration into risk stratification frameworks.

3.4.4. Summary of Pooled Estimates

The random-effects meta-analyses yielded the following pooled adjusted hazard ratios for the primary outcome of all-cause mortality and/or HF-related composite endpoints: Interleukin-6 (k = 5 studies, n > 7200 patients): HR 1.44 (95% CI 1.31–1.58), $p < 0.001$, $I^2 = 28\%$, p for heterogeneity = 0.21; High-sensitivity C-reactive protein (hs-CRP) (k = 5 studies, $n \approx 7100$ patients): HR 1.38 (95% CI 1.25–1.53), $p < 0.001$, $I^2 = 34\%$, p for heterogeneity = 0.18; Neutrophil-to-lymphocyte ratio (NLR) (k = 3 studies, $n \approx 3900$ patients): HR 1.51 (95% CI 1.33–1.72), $p < 0.001$, $I^2 = 0\%$, p for heterogeneity = 0.89.

These pooled estimates remained robust in all pre-specified sensitivity and subgroup analyses (see Section 3.5 and Figures 6 and 7).

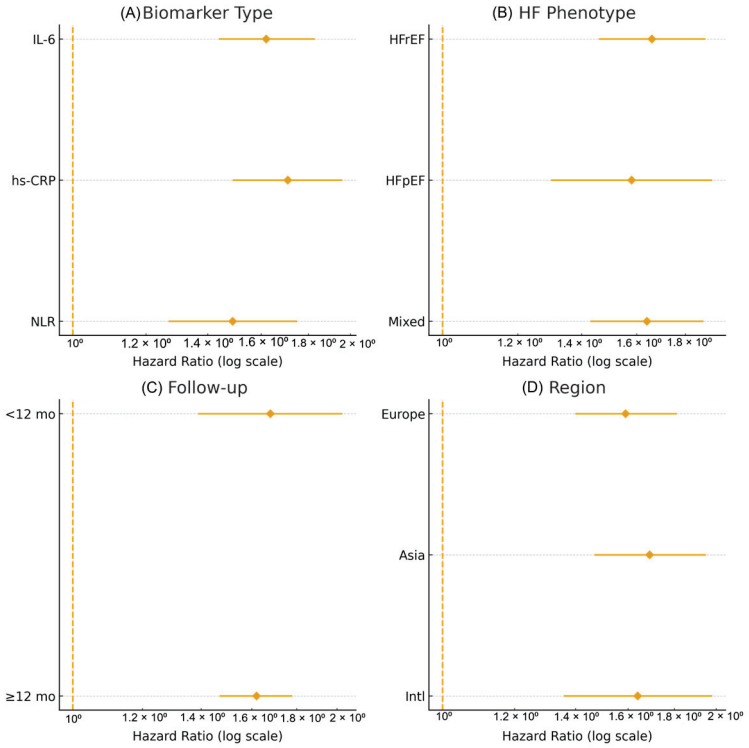


Figure 6. Subgroup analyses of the association between inflammatory biomarkers and adverse outcomes in heart failure. (**A**) Subgroup analysis by biomarker type (IL-6, hs-CRP, NLR). (**B**) Subgroup analysis by heart failure phenotype (HFrEF only, HFpEF only, mixed/unspecified cohorts). (**C**) Subgroup analysis by follow-up duration (<12 vs. ≥12 months). (**D**) Subgroup analysis by geographical region (Europe, Asia, international). Squares represent study-specific adjusted hazard ratios (HRs), with sizes proportional to inverse-variance weights; horizontal lines denote 95% CIs. Diamonds represent pooled estimates for each subgroup and the overall analysis. Interaction p-values correspond to Cochran's Q tests for subgroup differences. Random-effects models were applied throughout.

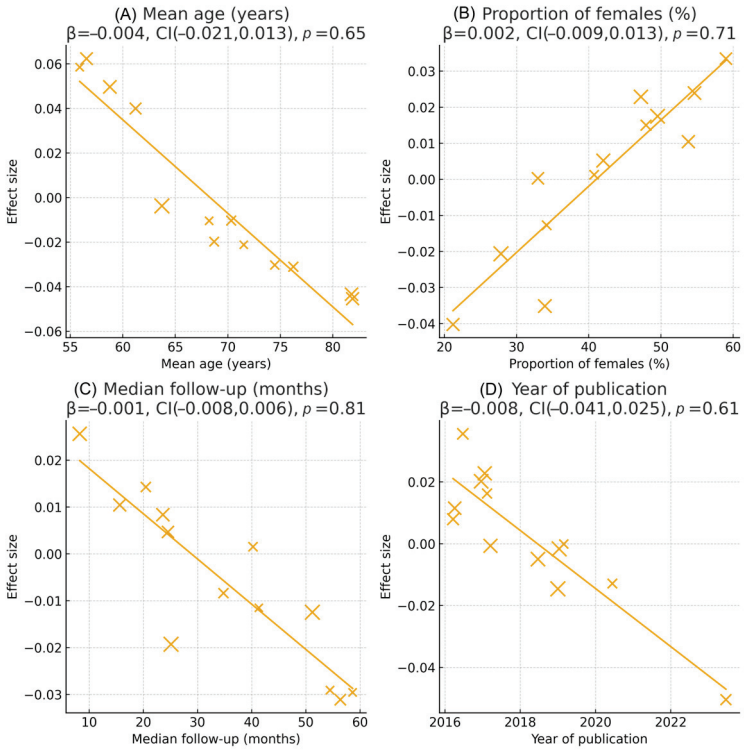


Figure 7. Meta-regression analyses evaluating study-level moderators of the association between inflammatory biomarkers and adverse outcomes in heart failure. (**A**) Meta-regression by mean age (years). (**B**) Meta-regression by proportion of female participants (%). (**C**) Meta-regression by median follow-up duration (months). (**D**) Meta-regression by year of publication. Each bubble represents an individual study, with bubble size proportional to study weight (inverse-variance). Solid lines denote fitted meta-regression slopes, and shaded confidence bands represent the 95% CI around the regression line (when displayed). Regression coefficients (β) and *p*-values are derived from mixed-effects meta-regression models using log hazard ratios as the dependent variable. None of the moderators showed statistically significant associations with effect size (all $p > 0.60$), indicating that the prognostic impact of inflammatory biomarkers on mortality and composite outcomes was consistent across age groups, sex distribution, follow-up durations, and publication years.

3.5. Sensitivity and Subgroup Analyses

Multiple sensitivity analyses were performed to assess the robustness of the pooled associations for IL-6, hs-CRP, and NLR.

Excluding studies with a small sample size ($n < 300$) did not materially change the effect estimates or their statistical significance for any of the three biomarkers. Results of leave-one-out analyses were similarly stable, with no single study exerting a disproportionate influence on the pooled HRs.

When acute heart failure (AHF)-only cohorts were removed, both IL-6 and hs-CRP remained significantly associated with mortality and composite adverse outcomes in chronic HF populations, indicating that the prognostic value of these biomarkers is not restricted to the acute setting.

Subgroup analyses showed broadly consistent associations: HFrEF vs. HFpEF: hazard ratios were comparable across reduced and preserved ejection fraction, with no significant interaction; Short-term (<1 year) vs. long-term (≥1 year) follow-up: effect sizes were similar across different follow-up durations; Europe vs. Asia vs. international multicenter cohorts: no meaningful regional differences were observed in the magnitude or direction of associations.

Exploratory meta-regression analyses did not identify any significant study-level moderators, including mean age, proportion of women, follow-up duration, or biomarker

assay methodology (all $p > 0.10$). These findings suggest that the prognostic impact of IL-6, hs-CRP, and NLR is largely independent of major demographic and methodological differences between studies.

Additional sensitivity analyses were performed by (i) excluding the three studies that originally reported multivariable-adjusted odds ratios rather than hazard ratios [24,26,28] and (ii) excluding the single population-based cohort evaluating incident HFpEF rather than established HF (Chia et al., 2021/PREVEND study [29]).

After exclusion of the OR-based studies, the pooled estimate for NLR remained essentially unchanged (HR 1.50, 95% CI 1.32–1.70, $I^2 = 0\%$). Exclusion of the incident HFpEF cohort did not materially alter the pooled estimate for IL-6 (HR 1.45, 95% CI 1.31–1.60, $I^2 = 31\%$). These analyses confirm the robustness of the primary findings even when the meta-analysis is restricted to hazard ratios derived from time-to-event analyses and to cohorts with clinically diagnosed, established heart failure.

Figures 6 and 7 illustrate the subgroup comparisons and meta-regression results, respectively.

3.6. Publication Bias and Robustness

Visual inspection of funnel plots (Figure 2), together with Egger's regression tests, did not reveal evidence of significant publication bias for IL-6, hs-CRP, or NLR. Application of the trim-and-fill procedure did not impute additional studies, and the pooled effect estimates remained essentially unchanged.

Cumulative meta-analyses ordered by publication year showed stable and consistent effect sizes from the earliest available study (2014) through the most recent cohorts (up to 2025), with no signal of temporal drift or early exaggerated effects. Taken together, these findings support the robustness and reliability of the synthesized evidence.

4. Discussion

This meta-analysis provides comprehensive evidence that elevated systemic inflammatory biomarkers—especially interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), and the neutrophil-to-lymphocyte ratio (NLR)—are significant independent predictors of mortality and adverse outcomes in heart failure (HF). The consistency of associations across phenotypes (HFrEF, HFpEF), geographical regions and follow-up durations underlines the pathophysiological and prognostic relevance of persistent inflammation in the heart failure continuum.

4.1. Principal Findings and Interpretation

Our pooled estimates demonstrate that raised IL-6 is associated with a substantially higher risk of all-cause mortality, while hs-CRP and NLR likewise show elevated risk even after adjustment for conventional comorbidities (age, sex, renal function, natriuretic peptides). This highlights that inflammatory markers add prognostic information beyond established clinical and echocardiographic predictors. IL-6 in particular emerges as the most consistent marker, likely because of its upstream position in the inflammatory cascade and its mechanistic link to myocardial remodeling, oxidative stress and neurohormonal activation. In parallel, hs-CRP reflects the aggregated burden of systemic inflammation, and NLR offers a convenient composite index of immune dysregulation (neutrophil activation plus lymphopenia). Together, these biomarkers indicate distinct but complementary aspects of the inflammatory network contributing to HF progression.

4.2. Comparison with Previous Literature and Meta-Analyses

Our results are in line with multiple prior reports that inflammation plays a central role in HF pathogenesis. For example, a recent narrative review indicated that IL-6 levels

are independently associated with HF hospitalization and death [31]. In another meta-analysis of advanced biomarkers in cardiovascular disease (CVD) among asymptomatic adults, hs-CRP and NT-proBNP predicted incident events but IL-6 was observed to have stronger associations in certain settings [32]. A further meta-analysis focusing on first CVD-event risk found that IL-6, fibrinogen and galectin-3 had superior predictive capacity compared to CRP [33].

Compared with those prior syntheses, our meta-analysis has distinctive features: (i) we included only prospective cohort studies of HF populations (not mixed CVD); (ii) we simultaneously examined IL-6, hs-CRP and NLR in one analytical framework, facilitating direct comparison of prognostic strength; and (iii) we conducted detailed subgroup and sensitivity analyses (including by ejection fraction phenotype, region, biomarker assay method). Thus, our work advances the literature by clarifying the hierarchy of inflammatory markers in HF prognosis.

Mechanistically, the stronger prognostic signal of IL-6 (versus hs-CRP) is biologically plausible: IL-6 activates the gp130 receptor and downstream JAK/STAT3 signalling, promoting cardiomyocyte hypertrophy, apoptosis and extracellular matrix remodelling [34] whereas CRP is a downstream acute-phase reactant reflecting cumulative systemic inflammation. The NLR reflects both innate (neutrophil) and adaptive (lymphocyte) immune shifts, aligning with HF pathophysiology of sympathetic activation, immune suppression and persistent inflammation.

4.3. Clinical and Research Implications

Clinically, the integration of IL-6, hs-CRP and NLR into HF risk-stratification models could enhance prognostic precision beyond natriuretic peptides and imaging. Specifically, serial measurement of IL-6 and hs-CRP may allow detection of dynamic inflammatory trajectories (rather than single time-point values), enabling earlier intensification of therapy or closer monitoring of high-risk patients [35]. The NLR, by contrast, offers inexpensive and readily available risk stratification, particularly useful in settings with limited laboratory infrastructure.

From a therapeutic standpoint, our findings reinforce the rationale for stratifying HF patients by inflammatory profile when considering anti-inflammatory interventions [36]. Although trials of IL-1 and IL-6 inhibitors in HF have been limited and variable, our results suggest that selecting patients with elevated IL-6 or NLR might yield greater benefit. Future randomized trials should incorporate baseline inflammatory-biomarker thresholds and measure changes in IL-6/CRP as secondary outcomes. Moreover, given the robust signal for NLR, pragmatic "real-world" studies evaluating NLR-guided risk mitigation (e.g., earlier device therapy, closer follow-up) are warranted.

Although the prognostic value of these biomarkers is well established, universally accepted clinical decision-making thresholds have not yet been defined. In the included cohorts, cut-off values associated with significantly increased risk were typically IL-6 > 4.5–7.8 pg/mL [18,22,23,29,30], hs-CRP > 3–10 mg/L [19–21,25,27], and NLR > 4.0–6.5 [24,26,28], depending on the assay, population, and acute versus chronic presentation. Measurement of IL-6 is currently less widely available in routine clinical laboratories and considerably more expensive than hs-CRP or a standard complete blood count (from which NLR is calculated). By contrast, hs-CRP and particularly NLR are inexpensive, rapidly available worldwide, and require no specialized assays, making them highly practical for routine risk stratification, especially in resource-limited settings. From a therapeutic perspective, patients with elevated IL-6, hs-CRP, or NLR may represent an enriched population for trials of anti-inflammatory agents (e.g., IL-6 receptor antagonists such as tocilizumab or ziltivekimab, colchicine, or SGLT2 inhibitors with pleiotropic anti-

inflammatory effects) [22,37,38]. Biomarker-guided patient selection and serial monitoring of inflammatory response could increase the likelihood of detecting treatment benefits and support personalized anti-inflammatory strategies in heart failure.

4.4. Strengths and Limitations

Key strengths of this meta-analysis include: strict inclusion of prospective cohort studies only; comprehensive subgroup, sensitivity and meta-regression analyses; adherence to PRISMA and MOOSE guidelines; and absence of evident publication bias. Our analyses show relatively low heterogeneity (I^2 < 35% for major outcomes), which strengthens confidence in the pooled estimates.

Nevertheless, several limitations must be acknowledged. Although assay platforms, units, and cut-off values varied across the included studies (detailed in Supplementary Table S1), all cohorts employed high-sensitivity or validated research-grade assays, and effect estimates were analysed on the log scale or using standardized categorical comparisons (tertiles/quartiles). The consistent direction, magnitude, and statistical significance of the associations, together with the low-to-moderate heterogeneity observed, indicate that assay variability did not meaningfully confound the pooled results.

Second, despite adjustment for known covariates, residual confounding (for example from sub-clinical infections, comorbid inflammatory disease or unmeasured immune suppression) cannot be excluded. Third, most studies measured biomarkers at a single time-point; thus, our findings cannot fully capture temporal changes in inflammation or treatment response. Fourth, while we attempted subgroup analyses by region, the majority of included cohorts were from North America and Western Europe, limiting generalisability to other settings (e.g., East-Central Europe). Finally, although we incorporated NLR, other allied biomarkers (e.g., IL-1β, TNF-α, galectin-3) were not uniformly reported and thus excluded; future work should extend to these markers.

4.5. Future Directions

Future research should focus on longitudinal trajectories of inflammatory biomarkers in HF (serial IL-6/hs-CRP/NLR) and their interaction with neurohormonal, metabolic and fibrotic pathways. The development and validation of composite "inflammation risk scores" combining IL-6, NLR and other immune indices may improve clinical risk-stratification. In trials of anti-inflammatory therapies in HF, baseline IL-6/NLR stratification and post-treatment biomarker monitoring should be standard. Further, external validation of our findings is needed in underrepresented regions (e.g., Eastern Europe, Asia, Africa). Recent regional studies from Eastern Europe, such as that by Tudoran et al. (2018) [39], have already highlighted the interplay between systemic endocrine-inflammatory states and cardiovascular remodeling, supporting the need for locally validated biomarker-based risk models. Lastly, mechanistic translational studies exploring how IL-6 blockade affects myocardial remodelling, immune phenotypes and clinical outcomes in HF are highly desirable.

5. Conclusions

This meta-analysis confirms that systemic inflammation—reflected by elevated IL-6, hs-CRP, and NLR—is a strong and independent predictor of mortality and adverse outcomes in heart failure. These biomarkers capture distinct yet complementary dimensions of the inflammatory cascade and provide additive prognostic value beyond established clinical and neurohormonal indicators. IL-6 stands out as the most consistent and biologically plausible marker, supporting its dual role as both a mechanistic driver and a potential therapeutic target. The consistent findings across diverse cohorts and phe-

notypes highlight the robustness of evidence. Integrating inflammatory biomarkers into conventional risk assessment may enhance prognostic precision and enable a more individualized, inflammation-guided approach to heart failure management.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm14238610/s1, Table S1: Biomarker assay characteristics and analytical approach in the 13 included prospective cohort studies. Table S2: PRISMA 2020 Checklist for the reporting of systematic reviews and meta-analyses.

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Abbreviations

The following abbreviations are used in this manuscript:

AHF	Acute Heart Failure
BNP	B-type Natriuretic Peptide
CI	Confidence Interval
CRP	C-Reactive Protein
CV	Cardiovascular
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure Trial
ECG	Electrocardiogram
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Hazard Ratio
hs-CRP	High-Sensitivity C-Reactive Protein
I^2	I-Squared Statistic (Heterogeneity)
IL-6	Interleukin-6
JAK/STAT3	Janus Kinase/Signal Transducer and Activator of Transcription 3
LVEF	Left Ventricular Ejection Fraction
MOOSE	Meta-analysis of Observational Studies in Epidemiology

NLR	Neutrophil-to-Lymphocyte Ratio
NOS	Newcastle–Ottawa Scale
NT-proBNP	N-terminal pro-B-type Natriuretic Peptide
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomized Controlled Trial
SD	Standard Deviation

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Article

Combined Burden of Heart Failure and Arterial Hypertension as Predictors of Adverse Outcomes in Hospitalized COVID-19 Patients

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Abstract

Background: Cardiovascular comorbidities are major determinants of poor outcomes among patients admitted with COVID-19. However, the prognostic role of arterial hypertension alone remains uncertain. Little is known about the cumulative impact of concomitant hypertension and heart failure. This study assessed whether the combined burden of arterial hypertension and pre-existing heart failure identifies a high-risk phenotype for adverse in-hospital outcomes among COVID-19 patients. **Methods**: In this retrospective, real-world cohort study, 395 consecutive adults hospitalized with confirmed COVID-19 at a single infectious diseases center between March 2020 and December 2024 were included. We categorized patients into three cardiovascular phenotype groups: no hypertension or heart failure (n = 23), hypertension without heart failure (n = 193), and concomitant hypertension and heart failure (n = 178). The primary outcome was in-hospital all-cause mortality, while ICU admission served as a secondary outcome, invasive mechanical ventilation, and length of hospital stay. Multivariable logistic regression included age, sex, BMI, diabetes mellitus, and vaccination status to evaluate independent associations between the cardiovascular risk group and outcomes. **Results**: Overall in-hospital mortality was 7.3% (29/395). Mortality increased stepwise across the cardiovascular risk groups: 8.7% in

patients without hypertension or heart failure, 3.1% in those with hypertension only, and 11.8% in patients with concomitant hypertension and heart failure ($p = 0.004$). In adjusted analyses, concomitant hypertension and heart failure were linked to higher adjusted odds of in-hospital death than no cardiovascular disease (odds ratio, 3.49; 95% confidence interval, 1.46–8.35). Isolated hypertension was not significantly associated with mortality. ICU admission and length of hospital stay also increased with cumulative cardiovascular burden. Patients with combined hypertension and heart failure showed more pronounced inflammatory and renal abnormalities at admission. **Conclusions**: Among hospitalized COVID-19 patients, the coexistence of arterial hypertension and heart failure identifies a vulnerable cardiovascular phenotype associated with higher in-hospital mortality and resource use than either no cardiovascular disease or hypertension alone. These findings support evaluating cardiovascular comorbidities cumulatively rather than in isolation. These findings are exploratory and require external validation in independent, larger multicentre cohorts. Findings may support careful use for short-term risk stratification and closer monitoring strategies during COVID-19 hospitalization.

Keywords: COVID-19; arterial hypertension; heart failure; cardiovascular multimorbidity; in-hospital mortality; intensive care admission; interleukin-6

1. Introduction

Coronavirus disease 2019 (COVID-19) encompasses the spectrum of clinical illness associated with infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. Despite progress in prevention and adjunctive management, COVID-19 has generated a sustained global health burden. It continues to cause severe disease and fatal in-hospital outcomes among hospitalized patients [2]. While pulmonary involvement dominates the acute presentation, strong evidence shows that pre-existing cardiovascular vulnerability shapes the clinical course and outcomes [3,4].

Cardiovascular disease is a major prognostic modifier in COVID-19. ICU admission is more frequent, and mortality is higher in patients with cardiovascular comorbidities [5,6]. SARS-CoV-2 does not only affect the lungs. It also triggers systemic inflammation and endothelial injury. This combination promotes thrombosis and can destabilize pre-existing cardiovascular disease [7,8].

In clinical practice, hypertension and heart failure are often seen together, particularly in elderly patients [9,10]. These conditions share key biological features. These include chronic low-grade inflammation, endothelial dysfunction, arterial stiffness, and neurohormonal activation [11,12]. These pathways overlap with mechanisms implicated in severe COVID-19 [12]. Therefore, patients with established cardiovascular disease may have reduced physiological reserve during acute SARS-CoV-2 infection.

Although arterial hypertension is frequently reported among hospitalized COVID-19 patients, its independent prognostic role remains debated. This is especially true after adjustment for age and multimorbidity [13]. In contrast, meta-analytic evidence supports an association between hypertension and increased COVID-19 severity and mortality. These findings also highlight marked heterogeneity across cohorts [14].

Pre-existing heart failure has been consistently associated with adverse outcomes in COVID-19 [15,16]. Patients with heart failure may deteriorate rapidly. They have limited cardiac reserve, vulnerability to volume overload, arrhythmias, and exaggerated inflammatory and neurohormonal responses [16]. In addition, acute SARS-CoV-2 infection may

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further aggravate cardiac function. This occurs through hypoxemia, cytokine-mediated injury, endothelial damage, and microvascular thrombosis [17,18].

This combined cardiovascular burden is clinically relevant because arterial hypertension and heart failure commonly co-occur and may reflect a continuum of progressive cardiovascular injury rather than independent entities [9,10]. Evaluating them in isolation may underestimate risk and fail to recognize a subgroup with increased vulnerability who could benefit from intensified monitoring and more tailored management strategies. Furthermore, evidence from Eastern European populations—where cardiovascular disease prevalence is high and healthcare system characteristics differ from Western cohorts—remains comparatively scarce [9].

Despite extensive evidence evaluating arterial hypertension and heart failure separately, the prognostic implications of their combined presence remain insufficiently characterized, particularly in real-world settings with high cardiovascular disease burden. This gap is especially relevant in Eastern Europe, where cardiovascular multimorbidity is highly prevalent and healthcare system constraints may modify outcomes. In addition, it remains uncertain whether cumulative cardiovascular burden retains prognostic relevance in the later pandemic phases, characterized by widespread vaccination and circulation of Omicron and its sublineages.

This study evaluated whether the combined presence of arterial hypertension and pre-existing heart failure is linked to worse short-term in-hospital outcomes for COVID-19 patients. By stratifying patients by cardiovascular burden and analyzing in-hospital mortality, ICU admission, and hospital course, this cohort study aimed to refine risk assessment in an Eastern European setting. To our knowledge, real-world evidence from Eastern European inpatient cohorts quantifying the prognostic impact of this combined phenotype remains limited.

Finally, the pandemic landscape evolved substantially during 2020–2024, with successive SARS-CoV-2 variants (Alpha, Delta, and Omicron sublineages) differing in transmissibility, virulence, and clinical phenotype. Our cohort spans March 2020 to December 2024 and therefore captures multiple pandemic phases; however, comprehensive variant characterization was not routinely available in our setting. Nevertheless, cardiovascular vulnerability driven by cumulative cardiovascular disease may represent a variant-agnostic risk amplifier, as the interaction between chronic cardiovascular dysfunction and systemic inflammatory stress is not lineage-specific. In this context, clarifying whether cumulative cardiovascular burden remains a key determinant of short-term in-hospital outcomes in the vaccinated era is clinically relevant for contemporary and future SARS-CoV-2 surges.

2. Materials and Methods

2.1. Study Design and Population

The study was conducted at the Department of Infectious Diseases I, Timișoara, Romania. Consecutive adult patients hospitalized with confirmed coronavirus disease 2019 (COVID-19) between March 2020 and December 2024 were screened for eligibility. COVID-19 diagnosis was confirmed by a positive reverse transcription polymerase chain reaction (RT-PCR) or by a validated antigen test, in accordance with national and institutional diagnostic protocols.

Inclusion criteria: (1) Age $\geq$ 18 years; (2) Hospitalization for acute COVID-19-related illness at the study center; (3) Laboratory-confirmed SARS-CoV-2 infection by RT-PCR or validated antigen test.

Exclusion criteria: (1) Incomplete clinical records regarding cardiovascular comorbidities or the primary outcome (in-hospital mortality); (2) Transfer from another hospital after

prolonged admission (>48 h prior to arrival); (3) Admission primarily for reasons unrelated to acute SARS-CoV-2 infection (e.g., elective procedures, trauma).

2.2. Data Collection

Data were extracted retrospectively from electronic records using a standardized form. Variables included age, sex, BMI, smoking status, vaccination status, major comorbidities (diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, atrial fibrillation, ischemic heart disease, and others), with emphasis on cardiovascular disease. Chronic cardiovascular medications (e.g., ACE inhibitors or ARBs, beta-blockers, and antihypertensive treatment burden) were collected when available. Laboratory parameters and clinical course during hospitalization were recorded, including ICU admission, mechanical ventilation, hospital length of stay, and in-hospital mortality. Laboratory tests were performed in the hospital's central laboratory. CBC (Complete blood count) parameters were generated automatically by the hospital laboratory (Sysmex XN-1000, Sysmex Corporation, Kobe, Japan). C-reactive protein (CRP) was measured by immunoturbidimetry as part of routine admission biochemistry testing on the Cobas Integra 400 Plus (Roche Diagnostics, Mannheim, Germany). Interleukin-6 (IL-6) was quantified by ECLIA with the Elecsys® IL-6 kit on a Cobas e601 analyzer (Roche Diagnostics, Mannheim, Germany). D-dimer was measured by immunoturbidimetric assay (STA®-Liatest D-Di, Diagnostica Stago, Asnières-sur-Seine, France) on the STA Compact Max analyzer (Diagnostica Stago, Asnières-sur-Seine, France). Serum creatinine was assessed using the kinetic Jaffé method on the Cobas Integra 400 Plus (Roche Diagnostics, Mannheim, Germany). SARS-CoV-2 variant identification and wave classification were unavailable in the database and thus not included.

All data were anonymized prior to analysis, and no patient-identifiable information was accessible to the investigators during data processing.

2.3. Definitions of Cardiovascular Conditions

Arterial hypertension was defined as any of the following: a documented diagnosis of hypertension prior to hospital admission in the patient's medical records, ongoing treatment with antihypertensive medication, or a previous physician diagnosis of hypertension. These criteria were aligned with contemporary European Society of Cardiology (ESC) guidelines to ensure consistency in classification.

Heart failure was defined as a documented clinical diagnosis of heart failure established before hospital admission, regardless of left ventricular ejection fraction phenotype. Where available, the classification included information from echocardiographic reports and New York Heart Association (NYHA) functional class to further characterize the heart failure phenotype. If extensive echocardiographic and NYHA data were unavailable, the diagnosis relied on clinical records and treatment history, specifically including patients with prior heart failure hospitalization or those under chronic treatment for heart failure.

2.4. Cardiovascular Risk Stratification

To assess the cumulative cardiovascular burden, patients were stratified into three mutually exclusive groups based on the presence or absence of arterial hypertension and heart failure: (1) No hypertension and no heart failure; (2) Hypertension without heart failure; (3) Concomitant hypertension and heart failure.

This stratification constituted the primary exposure variable for all subsequent analyses.

2.5. Short-Term In-Hospital Outcomes

All predefined outcomes were short-term events restricted to the index hospitalization. Post-discharge or post-acute COVID-19 sequelae (long COVID) were not included.

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The primary outcome was in-hospital all-cause mortality. Secondary outcomes were: (1) admission to the intensive care unit (ICU) during the index hospitalization; (2) requirement for invasive mechanical ventilation; (3) total length of hospital stay (days). Outcomes were assessed from electronic records at hospital discharge or death.

2.6. Statistical Analysis

We reported variables as mean (standard deviation) or median with interquartile range (IQR), as appropriate for data distribution. Comparisons across the three cardiovascular risk groups used one-way ANOVA for quantitative variables, and proportions were evaluated with χ^2 testing or Fisher's exact test for sparse tables. Admission inflammation was characterized using C-reactive protein (CRP), interleukin-6 (IL-6), and D-dimer, which demonstrated markedly right-skewed distributions and were therefore summarized using median and IQR.

To evaluate the independent association between cardiovascular burden and adverse outcomes, multivariable logistic regression models were constructed. The primary exposure variable was the cardiovascular risk group, with the group without hypertension or heart failure as the reference category. Models were adjusted a priori for clinically relevant confounders, including age, sex, BMI, diabetes mellitus, and vaccination status. Covariates were defined in advance using a clinically driven approach; no automated variable selection procedures (e.g., stepwise selection) were used. We examined multicollinearity by calculating variance inflation factors (VIFs) for the adjusted models, which indicated no problematic collinearity. Because of the limited number of deaths, the model was intentionally parsimonious to reduce overfitting; estimates should therefore be interpreted with caution. Odds ratios (ORs) with 95% confidence intervals (CIs) are provided. Statistical significance was set at $p < 0.05$. Analyses were conducted in SPSS (IBM) for Windows, version 26.0 (IBM Corp., Armonk, NY, USA).

2.7. Ethical Considerations

The study was ethically approved by the Ethics Committee of the "Victor Babeș" Clinical Hospital for Infectious Diseases and Pneumophthisiology, Timișoara, Romania (approval no. 11901/16.12.2025). The dataset consisted of anonymized clinical information collected during routine care. No additional consent was required by the Ethics Committee for this retrospective analysis. Written consent for hospitalization and for research use of anonymized data was obtained at admission as part of routine institutional practice. The study adhered to institutional standards and Helsinki principles, in accordance with national requirements.

3. Results

3.1. Study Population and Cardiovascular Risk Stratification

A total of 395 consecutive adult patients hospitalized with confirmed COVID-19 were included in the final analysis. All patients met diagnostic criteria for SARS-CoV-2 infection confirmed by molecular testing (RT-PCR) or validated antigen testing, were aged $\geq$18 years, and required hospitalization for acute COVID-19-related illness.

Based on cardiovascular comorbidities present at admission, patients were stratified into three mutually exclusive groups: (1) patients without arterial hypertension or heart failure, (2) patients with arterial hypertension without heart failure, and (3) patients with concomitant arterial hypertension and heart failure. One patient with a history of heart failure in the absence of arterial hypertension was identified but excluded from comparative statistical analyses due to insufficient sample size and was described descriptively only.

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The distribution of patients across cardiovascular risk groups was as follows: no arterial hypertension and no heart failure (n = 23, 5.8%), arterial hypertension without heart failure (n = 193, 48.9%), and concomitant arterial hypertension and heart failure (n = 178, 45.1%).

Baseline demographic and clinical characteristics according to cardiovascular risk group are summarized in Table 1.

Table 1. Baseline demographic, clinical, comorbidity, chronic medication, and admission laboratory characteristics according to cardiovascular risk group. Data are presented as median (interquartile range), mean ± standard deviation, or n (%), as appropriate.

Variable	No HTN/HF (n = 23)	HTN Only (n = 193)	HTN + HF (n = 178)	*p*-Value
Demographics and clinical presentation				
Age, years	59.0 (44.0–68.0)	72.0 (66.0–78.0)	74.0 (68.0–81.0)	<0.001
Male sex, n (%)	14 (60.9)	98 (50.8)	92 (51.7)	0.612
Urban residence, n (%)	16 (69.6)	124 (64.2)	103 (57.9)	0.214
Body mass index, kg/m^2	25.8 (22.1–29.4)	28.4 (25.2–32.1)	28.1 (24.8–31.6)	0.041
Current/former smoking, n (%)	9 (39.1)	58 (30.1)	41 (23.0)	0.112
Vaccinated (≥1 dose), n (%)	12 (52.2)	125 (64.8)	98 (55.1)	0.068
Symptom onset before admission, days	5.0 (3.0–7.0)	5.0 (3.0–7.0)	5.0 (3.0–8.0)	0.724
Systolic blood pressure at admission, mmHg	128 (118–138)	142 (130–155)	145 (132–160)	<0.001
Diastolic blood pressure at admission, mmHg	78 (70–85)	82 (75–90)	80 (70–90)	0.092
SpO_2 at admission, %	93 (89–96)	93 (89–96)	91 (87–95)	0.024
Comorbidities				
Diabetes mellitus, n (%)	5 (21.7)	68 (35.2)	74 (41.6)	0.087
COPD, n (%)	2 (8.7)	24 (12.4)	26 (14.6)	0.641
Chronic kidney disease (CKD), n (%)	1 (4.3)	14 (7.3)	22 (12.4)	0.124
Atrial fibrillation, n (%)	0 (0.0)	18 (9.3)	41 (23.0)	<0.001
Ischemic heart disease, n (%)	1 (4.3)	38 (19.7)	62 (34.8)	<0.001
Admission biomarkers				
CRP at admission, mg/L	98.9 (43.4–141.3)	109.8 (48.8–140.8)	103.1 (49.7–139.7)	0.116
IL-6 at admission, pg/mL	9.5 (3.2–28.1)	12.6 (5.2–33.8)	10.4 (3.8–25.1)	0.053
Creatinine at admission, mg/dL	0.88 (0.74–1.06)	0.94 (0.78–1.22)	1.12 (0.88–1.48)	<0.001
D-dimer, mg/L	0.8 (0.6–1.0)	0.7 (0.5–1.1)	0.8 (0.6–1.2)	0.601
Urea at admission, mg/dL	34 (26–46)	40 (30–58)	52 (36–78)	<0.001
Chronic cardiovascular medication				
Number of antihypertensive drugs	0 (0–0)	2 (1–3)	3 (2–4)	<0.001
ACEi/ARB use, n (%)	2 (8.7)	78 (40.4)	68 (38.2)	<0.001
Beta-blocker use, n (%)	3 (13.0)	68 (35.2)	112 (62.9)	<0.001
In-hospital course (short-term outcomes)				
Length of stay, days	8.8 ± 5.8	11.8 ± 7.4	13.2 ± 9.1	<0.001
ICU admission, n (%)	1 (4.3)	5 (2.6)	15 (8.4)	0.023
In-hospital mortality, n (%)	2 (8.7)	6 (3.1)	21 (11.8)	0.004

Note: Continuous variables are presented as median (IQR), except length of stay and ICU length of stay (mean ± SD), and compared using the Kruskal–Wallis or ANOVA test, as appropriate. Categorical variables are presented as n (%) and compared using the Chi-square or Fisher's exact test. ACEi/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; HTN = arterial hypertension; HF = heart failure.

3.2. Baseline Demographic and Clinical Characteristics

Baseline characteristics differed across the three cardiovascular risk groups, as shown in Table 1. Age differed markedly between groups (Kruskal–Wallis test: H = 36.76, $p < 0.001$). Patients with arterial hypertension, particularly those with concomitant heart failure, were substantially older than patients without cardiovascular comorbidities. Median age increased progressively from 59.0 (44.0–68.0) years in patients without arterial hypertension or heart failure to 72.0 (66.0–78.0) years in patients with arterial hypertension alone and 74.0 (68.0–81.0) years in those with both arterial hypertension and heart failure.

The proportion of male patients was similar across groups (60.9% in No HTN/No HF, 50.8% in HTN only, and 51.7% in HTN + HF; $p = 0.612$). BMI was higher in both hypertensive groups (28.4 [25.2–32.1] kg/m^2 in HTN only and 28.1 [24.8–31.6] kg/m^2 in HTN + HF) compared with patients without cardiovascular comorbidities (25.8 [22.1–29.4] kg/m^2).

Vaccination coverage prior to hospitalization was substantial across all cardiovascular risk groups, with 52.2% to 64.8% of patients being vaccinated (≥1 dose) prior to hospitalization. Smoking prevalence was highest among patients without cardiovascular disease and progressively lower among those with increasing cumulative cardiovascular burden.

3.3. In-Hospital Clinical Outcomes

In-hospital clinical outcomes according to cardiovascular risk group are presented in Table 2. Overall, in-hospital mortality was 7.3% (29 of 395 patients).

Table 2. Clinical Outcomes and Hospitalization Course by Cardiovascular Risk Group. Data presented as n (%) or mean ± SD. ICU, intensive care unit.

Clinical Outcome	No HTN/HF (n = 23)	HTN Only (n = 193)	HTN + HF (n = 178)	*p*-Value
In-hospital mortality, n (%)	2 (8.7)	6 (3.1)	21 (11.8)	0.004
ICU admission, n (%)	1 (4.3)	5 (2.6)	15 (8.4)	0.023
Supplemental oxygen therapy, n (%)	0 (0.0)	31 (16.1)	18 (10.1)	0.018
Length of hospital stay, days	8.8 ± 5.8	11.8 ± 7.4	13.2 ± 9.1	<0.001
ICU length of stay, days	—	8.0 ± 6.5	8.9 ± 7.0	0.71

A clear gradient of adverse outcomes was observed across cardiovascular risk strata. The lowest in-hospital mortality rate was recorded among patients with arterial hypertension without heart failure (3.1%), whereas patients without cardiovascular comorbidities had a mortality rate of 8.7%. The highest mortality occurred among patients with concomitant arterial hypertension and heart failure (11.8%). This stepwise increase in mortality with increasing cumulative cardiovascular burden is illustrated in Figure 1.

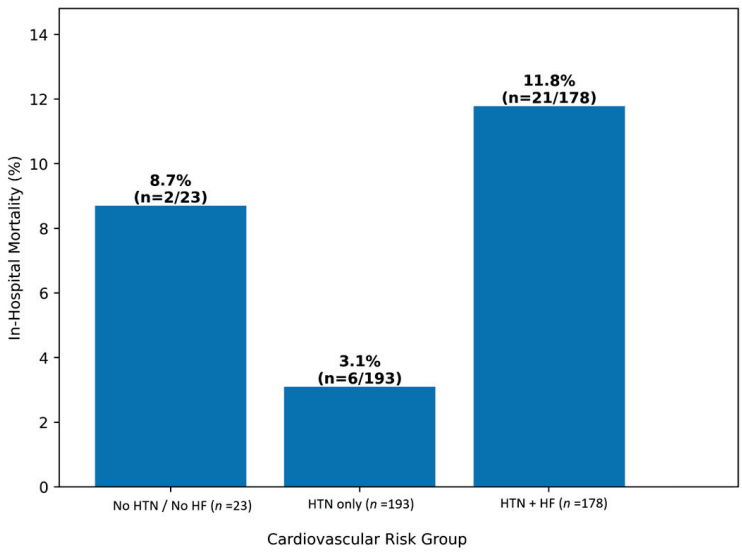


Figure 1. In-hospital mortality across cardiovascular risk groups. Bars represent in-hospital mortality rates (%), with absolute numbers of deaths shown above each bar. A stepwise increase in mortality is observed with increasing cumulative cardiovascular burden, with the highest mortality among patients with concomitant arterial hypertension and heart failure. The higher mortality observed among patients without cardiovascular comorbidities likely reflects the small sample size of this subgroup.

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Length of hospital stay increased progressively across cardiovascular risk groups, from 8.8 ± 5.8 days in patients without arterial hypertension or heart failure to 11.8 ± 7.4 days in patients with arterial hypertension alone and 13.2 ± 9.1 days in those with both arterial hypertension and heart failure ($p < 0.001$). Among patients requiring intensive care, the duration of ICU stay was comparable between patients with arterial hypertension with and without heart failure.

3.4. Primary Outcome: In-Hospital Mortality

Group-level comparisons showed higher in-hospital mortality in patients with combined arterial hypertension and pre-existing heart failure, compared with those without this cardiovascular burden. In adjusted analysis, the HTN + HF group had 3.49-fold higher odds of in-hospital death (OR 3.49; 95% CI 1.46–8.35; $p = 0.004$). In contrast, patients with arterial hypertension without heart failure had fewer fatal events, and isolated hypertension did not retain an independent association with in-hospital mortality after adjustment. Adjusted logistic regression results (including age, sex, BMI, diabetes status, and vaccination status as covariates) are reported in Table 3 and summarized in Figure 2.

Table 3. Multivariable Logistic Regression Analysis for In-Hospital Mortality.

Variable	Adjusted OR	95% Confidence Interval	*p* Value
Age (per 1-year increase)	1.05	1.02–1.08	0.001
Female sex	0.81	0.42–1.56	0.53
Body mass index (per 1 kg/m^2)	1.03	0.97–1.09	0.31
Diabetes mellitus	1.81	0.89–3.70	0.10
HTN only	1.21	0.55–2.66	0.63
HTN + HF	3.49	1.46–8.35	0.004

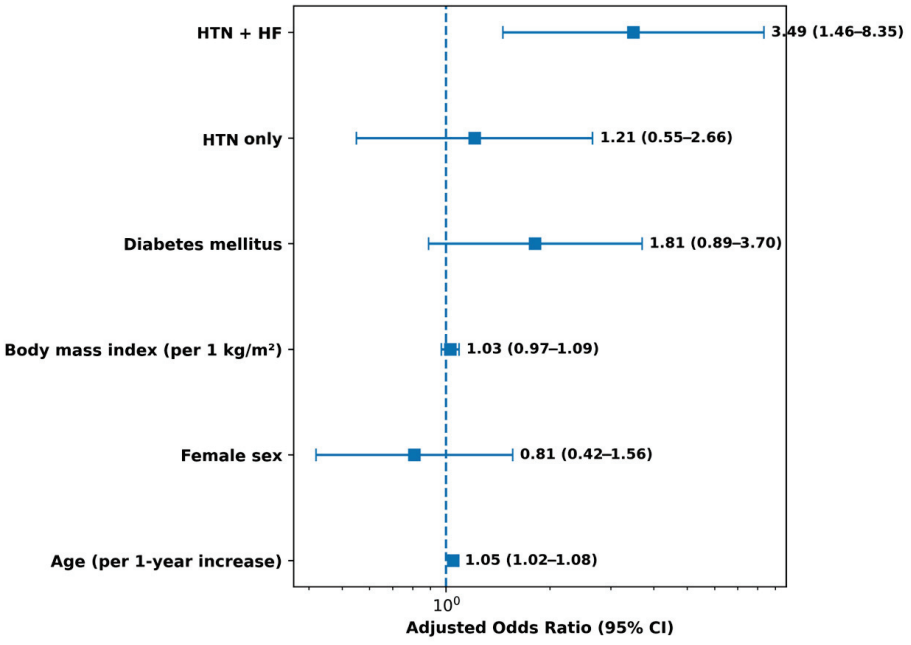


Figure 2. Multivariable adjusted odds ratios for in-hospital mortality. Forest plot showing adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for predictors of in-hospital mortality. The model was adjusted for age, sex, body mass index, diabetes mellitus, and cardiovascular risk group. The vertical dashed line indicates the null effect (OR = 1). For cardiovascular burden categories, the reference group was patients without arterial hypertension and without heart failure (No HTN/No HF).

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3.5. Secondary Outcomes: ICU Admission and Respiratory Support

ICU admission rates followed a similar gradient to in-hospital mortality across cardiovascular risk groups (Table 2). Among the specified groups, patients with both arterial hypertension and heart failure had the highest ICU admission rate (8.4%), compared with 4.3% in patients without either condition and 2.6% in patients with arterial hypertension alone. Direct comparisons show that those with combined arterial hypertension and heart failure had a significantly increased risk of ICU admission compared with patients with neither condition (odds ratio [OR] 3.24; 95% confidence interval [CI] 1.18–8.88; $\chi^2 = 5.15$; $p = 0.023$).

Requirements for supplemental oxygen therapy varied by cardiovascular risk group. Oxygen supplementation was more frequently needed in this group, most often in those with arterial hypertension alone, whereas those with both arterial hypertension and heart failure required supplemental oxygen less frequently than those with arterial hypertension alone. Table 2 provides detailed data for each group regarding oxygen therapy and respiratory support.

3.6. Laboratory Parameters at Hospital Admission

Inflammatory and thrombotic biomarkers measured at hospital admission are summarized in Table 1. Patients with concomitant arterial hypertension and heart failure exhibited higher levels of interleukin-6 (IL-6) and leukocyte counts compared with patients without cardiovascular comorbidities. Serum creatinine levels were also progressively higher with increasing cumulative cardiovascular burden.

C-reactive protein and D-dimer levels were elevated across all cardiovascular risk groups, reflecting the systemic inflammatory and prothrombotic state characteristic of hospitalized COVID-19 patients. Given the markedly right-skewed distributions of CRP, IL-6, and D-dimer, these biomarkers were summarized using median and interquartile range.

The distribution of inflammatory and renal biomarkers across cardiovascular risk groups is illustrated in Figure 3, highlighting substantial inter-individual heterogeneity, particularly for IL-6.

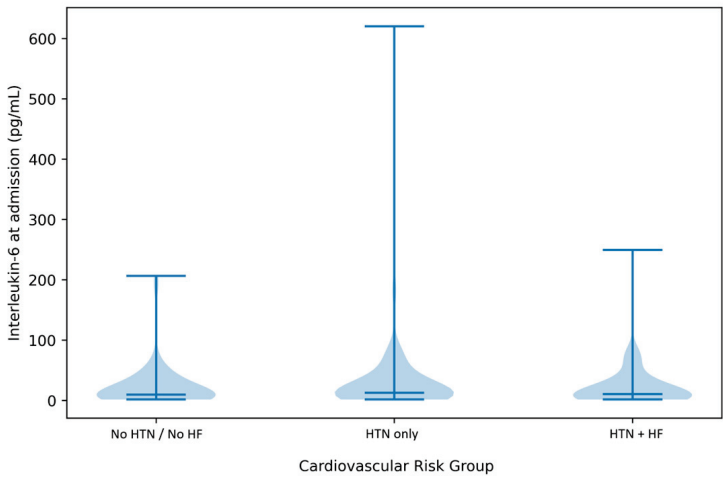


Figure 3. Distribution of interleukin-6 levels at hospital admission according to cardiovascular risk group. Violin plots illustrate the distribution of individual interleukin-6 (IL-6) values measured at admission across cardiovascular risk groups, with median values indicated within each violin. Patients with concomitant arterial hypertension and heart failure show a broader and right-skewed IL-6 distribution compared with patients without arterial hypertension and without heart failure. HTN, arterial hypertension; HF, heart failure.

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3.7. Cardiovascular and Infectious Complications

Acute cardiovascular complications documented during hospitalization included arrhythmias, acute decompensated heart failure, and acute myocardial infarction. These complications were more frequently observed in patients with concomitant arterial hypertension and heart failure.

In addition to these cardiovascular complications, systemic anticoagulation was administered to 115 patients (29.1%). Higher-intensity anticoagulation regimens were predominantly used in patients with documented thrombotic complications or prolonged immobilization.

Secondary infectious complications were identified in 38 patients (9.6%), occurring more commonly among those with concomitant arterial hypertension and heart failure. Blood cultures most frequently demonstrated multidrug-resistant Gram-negative organisms, including carbapenem-resistant *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Gram-positive pathogens were identified less frequently, including vancomycin-resistant *Enterococcus faecium* and methicillin-resistant Staphylococcus aureus.

4. Discussion

In this cohort of 395 adults hospitalized with COVID-19 between March 2020 and December 2024, coexisting arterial hypertension and pre-existing heart failure led to a stepwise rise in short-term in-hospital mortality and ICU admission, compared with either hypertension alone or no cardiovascular disease. This combined cardiovascular burden identified a vulnerable phenotype with higher resource use and more pronounced inflammatory and renal abnormalities at admission. However, our single-centre design and limited number of deaths mean these associations should be interpreted with caution and considered primarily hypothesis-generating.

4.1. Cumulative Cardiovascular Burden and COVID-19 Severity

Building on these findings, our results show that patients with both arterial hypertension and heart failure had about 3.5-fold higher adjusted odds of in-hospital mortality (OR 3.49, 95% CI 1.46–8.35). While statistically significant, the wide confidence interval reflects moderate precision and the limited number of outcome events. These findings are thus hypothesis-generating and require validation in larger, multicenter cohorts before firm clinical conclusions can be drawn. This relationship remained significant in models adjusting for age, sex, BMI, diabetes, and vaccination status. The observation supports the idea that cardiovascular multimorbidity increases COVID-19 severity, likely reflecting synergistic vulnerability rather than a simple additive effect [18,19].

This distinction is further supported by the fact that heart failure has consistently led to poor COVID-19 outcomes. Heart failure is linked to impaired cardiocirculatory reserve, higher risk of arrhythmias, and limited ability to tolerate hypoxia or systemic inflammation [18,20]. By contrast, the impact of arterial hypertension alone has varied and is often smaller after adjusting for age and comorbidities. Our findings help explain this by showing that hypertension has major prognostic relevance, mainly when it exists with established cardiac dysfunction. This highlights the need for contextual cardiovascular assessment [21].

4.2. Inflammatory Burden and the Role of IL-6

A key mechanistic observation of our study is the link between cumulative cardiovascular disease and increased inflammatory activation. This was evident by elevated, highly variable interleukin-6 (IL-6) levels. Violin plots of individual-level data showed wider, right-skewed distributions of IL-6 in patients with both arterial hypertension and heart failure. This provides biological plausibility for our clinical findings.

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This interpretation is supported by prior evidence linking higher IL-6 and CRP levels to respiratory failure and mortality in COVID-19 [22]. Our results also align with earlier work showing that IL-6, cardiac biomarkers, clinical factors, and vaccination status together predict outcomes in COVID-19 sepsis. This highlights the central role of systemic inflammation in disease progression [23].

4.3. Pathophysiological Interplay Between Arterial Hypertension, Heart Failure, and SARS-CoV-2 Infection

Turning to pathophysiology, the adverse interaction between arterial hypertension, heart failure, and COVID-19 likely involves overlapping pathways. Both hypertension and heart failure feature endothelial dysfunction, arterial stiffness, neurohormonal activation, and chronic low-grade inflammation. These factors can worsen SARS-CoV-2–induced endothelial injury, microvascular dysfunction, and thromboinflammation [24,25].

Endothelial dysfunction is a key feature of severe COVID-19. It impairs tissue perfusion, causes prothrombotic states, and leads to multiorgan failure [25]. In patients with pre-existing cardiovascular disease, these problems may accelerate cardiac decompensation and worsen systemic injury, especially during cytokine-driven immune dysregulation [26]. This unstable hemostatic environment may cause both thrombotic and hemorrhagic complications, illustrated by reports of deep vein thrombosis and spontaneous soft-tissue hematomas during recovery from SARS-CoV-2 infection [27].

4.4. Arterial Hypertension Alone Versus Combined Cardiovascular Disease

Our cohort also revealed a key clinical point: Mortality was lower among patients with only arterial hypertension than in those with combined cardiovascular disease. This supports the idea that arterial hypertension alone is not always high-risk. Its prognostic impact depends on the broader cardiovascular context [21,28].

From a clinical perspective, these results suggest that risk-stratification should go beyond binary classification of comorbidities. Risk assessments should include markers of structural heart disease and overall cardiovascular burden.

4.5. ICU Admission, Resource Utilization, and Clinical Trajectory

The stepwise rise in ICU admissions and hospital stays between cardiovascular risk groups highlights the impact of combined hypertension and heart failure. Patients with these combined cardiovascular diseases needed more intensive care and longer hospitalization. This reflects higher disease severity and more complex management [18,19].

ICU duration was similar across groups after admission. This suggests that baseline cardiovascular burden mainly raises the risk of deterioration but may not affect the clinical course once critical illness is established [29].

4.6. Strengths and Limitations

This study has several strengths. It uses a real-world design, explicit cardiovascular risk stratification, and integrates laboratory biomarkers with clinical outcomes. Showing individual biomarker levels adds detail beyond summary statistics and helps with mechanistic interpretation.

Several limitations should be acknowledged. First, SARS-CoV-2 variant type and wave classification were not systematically captured and could not be reconstructed for all cases. This prevented us from adjusting for dominant variants (e.g., Delta versus Omicron) or pandemic period effects. Residual confounding from temporal changes in virulence, vaccination coverage, and clinical management cannot be excluded. BNP/NT-proBNP and echocardiographic HF severity parameters were not systematically available; thus, residual confounding related to heart failure severity cannot be excluded. The study is retrospective

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and single-center. Patients with only heart failure were excluded from comparisons due to small numbers. Detailed echocardiographic phenotyping was not consistently available, preventing distinction between heart failure subtypes [20]. Future studies should include systematic echocardiographic assessment to determine whether HF phenotypes (HFrEF, HFmrEF, HFpEF) confer different levels of risk in COVID-19.

Conducted at a single infectious diseases center in Eastern Europe, our findings primarily reflect the epidemiology, cardiovascular risk profile, and healthcare delivery characteristics of this setting. Extrapolation to other regions and health systems should therefore be made with caution, particularly where baseline cardiovascular risk or COVID-19 management pathways differ. Nonetheless, the high burden of hypertension and heart failure in many Eastern European and low-to middle-income countries suggests that this vulnerable cardiovascular phenotype may be relevant beyond our local context.

4.7. Clinical and Research Implications

These findings affect clinical practice. Early identification of patients with both arterial hypertension and heart failure on admission can encourage closer monitoring, timely care escalation, and more personalized management [18,20]. Further validation in independent cohorts is needed, together with studies assessing whether anti-inflammatory or cardioprotective strategies can improve outcomes in this high-risk phenotype [23,30]. Longitudinal data further indicate that cardiometabolic factors (e.g., obesity and metabolic syndrome) may promote progression of left ventricular diastolic dysfunction after COVID-19, supporting the idea of a vulnerable cardiovascular substrate beyond the acute phase [31].

4.8. Relevance Across Viral Variants and the Evolving Pandemic Landscape

Although our cohort spans multiple pandemic waves and likely includes patients infected with different SARS-CoV-2 variants (including the ancestral strain, Alpha, Delta, and Omicron sublineages), variant-specific data were not available for analysis. Emerging evidence suggests that Omicron and its sublineages are associated with attenuated pulmonary virulence compared with earlier variants, yet systemic inflammatory responses and cardiovascular complications remain clinically relevant, particularly in patients with pre-existing cardiovascular disease [32,33]. The pathophysiological interplay between chronic cardiovascular conditions (endothelial dysfunction, neurohormonal activation, low-grade inflammation) and acute viral infection is unlikely to be variant-specific; rather, it reflects a fundamental vulnerability of the cardiovascular system to systemic inflammatory stress.

Interleukin-6, a key mediator of the cytokine response, has been implicated in COVID-19 severity across variants and represents a potential therapeutic target in high-risk cardiovascular phenotypes [34,35]. Future studies incorporating variant-specific stratification and serial assessment of inflammatory biomarkers will be essential to determine whether the excess risk conferred by cumulative cardiovascular burden persists—or is attenuated—in the era of Omicron dominance and widespread population immunity [32,33]. These inflammatory and endothelial pathways appear to be conserved across SARS-CoV-2 variants, including Omicron lineages, even though pulmonary virulence has declined in the later pandemic phases [32]. Consequently, patients with pre-existing cardiovascular multimorbidity may remain susceptible to severe systemic inflammation and decompensation despite improved population immunity and changes in viral tropism.

Our findings therefore suggest that cumulative cardiovascular vulnerability represents a variant-agnostic risk amplifier, which persists in the Omicron and vaccinated era and may remain relevant for future COVID-19 surges or similar respiratory viral threats [32–35].

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5. Conclusions

In this cohort of hospitalized COVID-19 patients, the combined presence of arterial hypertension and pre-existing heart failure identified patients at increased risk for in-hospital mortality, ICU admission, and prolonged hospitalization. Clinicians should closely monitor patients with both conditions, as these risks were higher compared to those without cardiovascular comorbidities or with only arterial hypertension.

Importantly, arterial hypertension alone was not independently linked to an increase in in-hospital mortality. Its relevance as a prognostic factor in COVID-19 is highly context-dependent and substantially amplified by established cardiac dysfunction. These findings highlight the value of assessing cardiovascular comorbidities holistically, rather than in isolation.

A combined cardiovascular burden was associated with increased inflammatory activation, as evidenced by elevated, variable interleukin-6 levels at hospital admission. These findings highlight the clinical significance of systemic inflammation as a driver of disease severity in patients with preexisting cardiovascular conditions.

Replication in independent cohorts from diverse healthcare systems is warranted. In addition, interventional research should explore whether targeted cardioprotective strategies (for example, optimized guideline-directed heart failure therapy) and anti-inflammatory approaches (including IL-6–directed or broader immunomodulatory regimens where appropriate) can mitigate the excess risk observed in patients with concomitant arterial hypertension and heart failure.

In summary, among hospitalized COVID-19 patients, the coexistence of arterial hypertension and pre-existing heart failure flags a potentially high-risk cardiovascular phenotype within this single-centre cohort, which appears to be associated with higher short-term in-hospital mortality and greater resource utilization than either no cardiovascular disease or hypertension alone. These observations support a cumulative assessment of cardiovascular comorbidities for risk stratification but should be viewed as hypothesis-generating given the single-centre design and the modest number of events. Confirmation in larger, multi-centre cohorts is needed before these findings can be translated into definitive prognostic tools or management algorithms.

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Abbreviations

The following abbreviations are used in this manuscript:

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
HTN	Arterial hypertension
HF	Heart failure
ICU	Intensive care unit
BMI	Body mass index
CRP	C-reactive protein
IL-6	Interleukin-6
RT-PCR	Reverse transcription polymerase chain reaction
NYHA	New York Heart Association
OR	Odds ratio
CI	Confidence interval
SD	Standard deviation
IQR	Interquartile range

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Factors Associated with Progression to SCAI-Defined Hemodynamic Instability at 72 Hours in Patients with Acute Decompensated Heart Failure Receiving Inotropic Therapy

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Abstract

Background: Early hemodynamic deterioration may occur in patients with acute decompensated heart failure (ADHF) receiving inotropic therapy despite the absence of overt hypoperfusion at baseline. This study aimed to identify baseline factors associated with progression from Society for Cardiovascular Angiography and Interventions (SCAI) stage A or B to SCAI stage C–E at 72 h after initiation of inotropic therapy. **Methods:** This retrospective, single-center study included 375 adults with ADHF who received intravenous dobutamine or levosimendan and were classified as SCAI stage A or B at the time of inotrope initiation. The primary endpoint was progression to SCAI stage C, D, or E at the 72 h assessment. Baseline clinical, echocardiographic, laboratory, and hemodynamic variables were compared according to progression status. Univariable and multivariable logistic regression analyses were performed to identify factors associated with the primary endpoint. **Results:** Progression to SCAI stage C–E occurred in 30 patients (8.0%). Patients who progressed had lower diastolic blood pressure (DBP) and higher heart rate, white blood cell count (WBC), C-reactive protein, aspartate aminotransferase, lactate dehydrogenase, and N-terminal pro-B-type natriuretic peptide levels. The primary multivariable logistic regression model included 327 patients and all 30 outcome events. Higher WBC was independently associated with greater odds of progression (odds ratio: 1.099; 95% confidence interval: 1.030–1.174; $p = 0.005$), whereas higher DBP was independently associated with lower odds of progression to SCAI stage C–E (odds ratio: 0.963; 95% confidence interval: 0.934–0.992; $p = 0.014$). The model showed acceptable calibration and moderate discrimination, with a c-statistic of 0.731 (95% confidence interval: 0.630–0.832). In bootstrap analysis, the association remained significant for WBC, whereas the association with DBP was borderline. **Conclusions**: Higher WBC and lower DBP were associated with progression to SCAI stage C–E at 72 h in this exploratory single-center cohort of patients with ADHF receiving inotropic therapy.

Keywords: acute decompensated heart failure; inotropic therapy; SCAI shock classification; hemodynamic instability; diastolic blood pressure; cardiogenic shock; white blood cell count

1. Introduction

Acute heart failure (AHF) is a serious clinical syndrome characterized by the rapid onset of symptoms and signs of heart failure (HF) or the rapid worsening of pre-existing HF, frequently requiring hospitalization [1]. In patients with acute decompensated heart

failure (ADHF), progressive hemodynamic deterioration and the subsequent development of end-organ hypoperfusion may lead to cardiogenic shock and adverse clinical outcomes.

Inotropic therapies are commonly used in patients with AHF to improve reduced cardiac output and maintain systemic perfusion [2]. However, determining which patients should receive inotropic support and when it should be initiated remains one of the most critical decisions in clinical practice.

The clinical course after initiation of inotropic therapy is heterogeneous, and some patients may deteriorate despite the absence of overt hypoperfusion at baseline. Early identification of patients at risk of progression to more advanced hemodynamic compromise may therefore facilitate closer monitoring and timely escalation of treatment.

The Society for Cardiovascular Angiography and Interventions (SCAI) shock classification provides a practical framework for bedside assessment and serial monitoring of cardiogenic shock severity [3]. This classification system allows cardiogenic shock to be assessed as a dynamic clinical process and has shown a strong association with mortality across different clinical populations. Previous studies have also demonstrated that early progression in SCAI stage is associated with adverse clinical outcomes and increased mortality [4–7].

However, baseline factors associated with early progression to SCAI stages C–E have not been sufficiently investigated in patients hospitalized with ADHF who receive inotropic therapy while initially classified as SCAI stage A or B. Although the individual prognostic variables examined are clinically familiar, evidence regarding their association with early SCAI stage progression in this specific high-risk population remains limited. Therefore, the present study aimed to identify baseline clinical, laboratory, echocardiographic, and hemodynamic factors associated with progression from SCAI stage A or B at baseline to SCAI stage C, D, or E at 72 h after initiation of inotropic therapy.

2. Materials and Methods

2.1. Study Design and Patient Population

This retrospective, single-center observational study evaluated patients who were followed in the coronary intensive care unit (CICU) for ADHF and received intravenous inotropic therapy between January 2015 and June 2025. Clinical, laboratory, echocardiographic, and treatment-related data were retrospectively obtained from the hospital electronic medical record system, archived patient files, and outpatient clinic records. Baseline laboratory values were defined as measurements obtained before initiation of inotropic therapy or, when unavailable, from the sample obtained closest to the time of inotrope initiation. No formal adjustment was made for fluid overload or hemodilution.

The diagnosis of ADHF was established according to contemporary guideline recommendations based on the integrated assessment of clinical findings, laboratory parameters, and cardiac imaging [8].

Pulmonary hypertension-associated isolated right-sided HF was considered a clinical phenotype rather than an etiologic category. This phenotype was defined by clinical and echocardiographic evidence of predominant right ventricular failure associated with pulmonary hypertension, without evidence of left-sided HF. Because the underlying cause and World Health Organization group of pulmonary hypertension could not be reliably determined from the retrospective records, pulmonary hypertension was not further classified by etiology. HF etiology was classified separately as ischemic, non-ischemic, or unknown according to the available clinical records.

Patients aged $\geq$18 years who were admitted to the CICU, received intravenous dobutamine or levosimendan therapy, and were classified as SCAI stage A or B at the time of inotrope initiation were eligible for inclusion.

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This retrospective study evaluated a selected high-risk population in whom intravenous inotropic therapy had already been initiated in routine clinical practice based on the attending physician's overall clinical and hemodynamic assessment. In patients classified as SCAI stage A, treatment was not protocol-driven or initiated solely on the basis of SCAI stage, but reflected individualized clinical decisions in the setting of advanced ADHF, inadequate response to standard therapy, persistent congestion, suspected low-output physiology, or concern for imminent hemodynamic deterioration.

Patients were considered to have no overt hypoperfusion at baseline in the absence of clear clinical signs of end-organ hypoperfusion, including altered mental status, cold or mottled extremities, oliguria, or other findings consistent with impaired peripheral perfusion. Lactate measurements were reviewed when available; however, lactate was not routinely available in all patients and was therefore not used as a mandatory criterion for baseline classification.

Admission to the CICU was based on guideline-recommended criteria for severe hemodynamic or respiratory deterioration, including oxygen saturation <90% despite oxygen therapy, use of accessory respiratory muscles, heart rate <40 or >130 beats/min, or systolic blood pressure (SBP) <90 mmHg [9].

Patients classified as SCAI stage C, D, or E at baseline were excluded. Additional exclusion criteria were mechanical complications of acute myocardial infarction, active infection or septic shock, use of temporary mechanical circulatory support at baseline, severe primary valvular heart disease requiring urgent intervention, active malignancy, age <18 years, and missing data required for baseline SCAI classification or primary endpoint assessment.

2.2. Inotropic Treatment Protocol

At our center, intravenous inotropic therapy was initiated in selected patients with ADHF on the basis of the attending physician's overall clinical and hemodynamic assessment. Treatment decisions were individualized and took into account blood pressure, heart rate and rhythm, urine output, renal and hepatic function, congestion burden, suspected low cardiac output physiology, inadequate response to standard medical therapy, and the perceived risk of impending hemodynamic deterioration. The choice of inotropic agent was not protocol-mandated and reflected the patient's clinical profile, contraindications, institutional practice, and physician judgment.

Dobutamine was generally initiated at a dose of 2.5–5 μg/kg/min and titrated according to the patient's hemodynamic response, including blood pressure, heart rate, rhythm status, urine output, and peripheral perfusion, up to 20 μg/kg/min when clinically required.

Levosimendan was administered as a continuous intravenous infusion, generally at a dose of 0.05–0.2 μg/kg/min. A loading dose was not routinely administered, particularly in patients with low blood pressure or an increased risk of hypotension. The infusion rate was adjusted according to blood pressure, rhythm status, and clinical response.

Vasopressor therapy, primarily norepinephrine, was added when hypotension persisted or developed despite inotropic support, particularly when maintenance of adequate arterial pressure and organ perfusion was considered necessary. Escalation to multiple inotropes and/or vasopressors was based on serial clinical and hemodynamic reassessment and was considered a post-baseline treatment variable.

2.3. SCAI Shock Classification and Endpoint

Hemodynamic instability and shock severity were assessed according to the SCAI shock classification [3]. Baseline SCAI stage was assigned at the time of initiation of intravenous inotropic therapy, and patients were reassessed 72 h later using the clinical, hemodynamic, laboratory, and treatment-related variables available at each time point.

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SCAI stage A was defined as a high-risk clinical state without hypotension or evidence of hypoperfusion. SCAI stage B was defined by the presence of early hemodynamic instability, such as hypotension or compensatory tachycardia, without overt clinical or biochemical evidence of end-organ hypoperfusion [3]. Progression to SCAI stages C–E was determined by the development of hypoperfusion and increasing shock severity, based on blood pressure, heart rate, mental status, peripheral perfusion, urine output, renal and hepatic function, available lactate measurements, and the intensity of vasoactive or mechanical circulatory support. Lactate values were incorporated when available but were not required as a mandatory criterion because they were not uniformly measured in all patients.

The primary endpoint was progression from SCAI stage A or B at baseline to SCAI stage C, D, or E at the 72 h assessment after initiation of inotropic therapy. Patients who remained in or transitioned between SCAI stages A and B at 72 h were classified as having no progression to the primary endpoint.

Because escalation of vasoactive therapy may contribute to SCAI staging, post-baseline use of additional inotropes or vasopressors was considered part of the clinical trajectory and was not included as a baseline predictor in the multivariable regression model.

2.4. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test together with visual inspection. Continuous variables are presented as mean ± standard deviation or median with interquartile range (IQR), as appropriate, whereas categorical variables are presented as numbers and percentages. Between-group comparisons of continuous variables were performed using Student's *t*-test or the Mann–Whitney *U* test, according to data distribution. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Patients were classified according to the SCAI assessment performed 72 h after initiation of inotropic therapy. The primary endpoint was defined as progression from baseline SCAI stage A or B to SCAI stage C, D, or E at the 72 h assessment.

Associations between baseline variables and progression to SCAI stage C–E at 72 h were first evaluated using univariable logistic regression analyses. Because aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) showed markedly right-skewed distributions, these variables were natural logarithm-transformed before regression analysis. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs) and *p*-values.

Candidate variables for the multivariable logistic regression model were selected on the basis of clinical relevance, univariable associations, and potential overlap among variables representing the same clinical domain. Spearman correlation analysis was used to assess relationships among variables that were significant in univariable analyses. A weak-to-moderate positive correlation was observed between C-reactive protein (CRP) and white blood cell (WBC) count, a moderate positive correlation between AST and LDH, and only a very weak correlation between diastolic blood pressure (DBP) and heart rate.

To avoid including variables representing overlapping clinical domains and to reduce the risk of overfitting, WBC was selected as the inflammatory marker and DBP as the hemodynamic marker for inclusion in the primary multivariable model. Although chronic obstructive pulmonary disease (COPD) was associated with progression in univariable analysis, it was not included because of the limited number of outcome events and the need to maintain a parsimonious model. Because NT-proBNP measurements were available only in a subset of the cohort, natural logarithm-transformed NT-proBNP [ln(NT-proBNP)] was

also excluded from the primary model. Post-baseline treatment-escalation variables were not included because they could represent components of the clinical pathway leading to the outcome.

Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test, model explanatory value was reported using the Nagelkerke R^2, and model discrimination was evaluated using the area under the receiver operating characteristic curve, expressed as the c-statistic. Internal validation and coefficient stability were assessed using bootstrap resampling with 2000 samples. No imputation was performed for missing data, and analyses were conducted using available cases. All statistical tests were two-sided, and a p-value of <0.05 was considered statistically significant.

3. Results

A total of 375 patients with ADHF who received intravenous inotropic therapy were included. At baseline, 358 patients (95.5%) were classified as SCAI stage A and 17 patients (4.5%) as SCAI stage B. At 72 h after initiation of inotropic therapy, 30 patients (8.0%) had progressed to SCAI stage C, D, or E, whereas 345 patients (92.0%) remained in SCAI stage A or B. Transitions in SCAI stage from baseline to 72 h after initiation of inotropic therapy are illustrated in Figure 1.

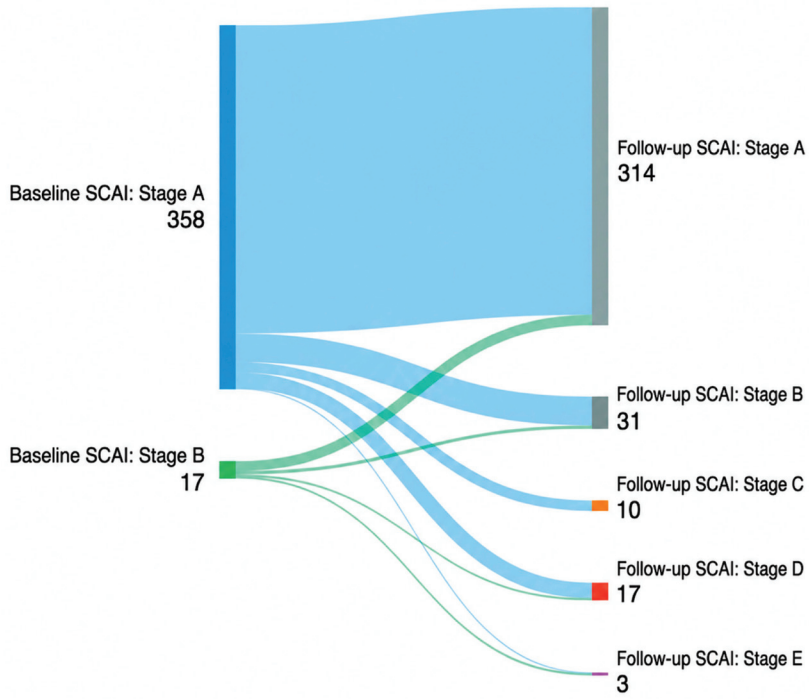


Figure 1. Transitions from baseline SCAI stages A and B to SCAI stages A–E at 72 h after initiation of inotropic therapy. Blue and green flow bands represent transitions originating from baseline SCAI stages A and B, respectively, while the colored terminal bars indicate the corresponding SCAI stages at 72 h. Abbreviation: SCAI, Society for Cardiovascular Angiography and Interventions.

Baseline characteristics according to progression status are presented in Table 1. The median age of the overall cohort was 69 years (IQR, 60–79), and 278 patients (74.1%) were male. Age, sex, and most comorbidities were comparable between groups. Chronic obstructive pulmonary disease (COPD) was more frequent among patients who progressed to SCAI stage C–E than among those who did not [8 (26.7%) vs. 31 (9.0%), Fisher's exact $p = 0.007$]. HF etiology, HF phenotype, echocardiographic parameters, and the prevalence of significant valvular disease did not differ significantly between groups.

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Table 1. Baseline Clinical, Echocardiographic, Laboratory, Hemodynamic, and Treatment Characteristics According to Progression to SCAI Stage C–E at 72 Hours.

Variable	Overall (*n* = 375)	Progression to SCAI Stage C–E (*n* = 30)	No Progression to SCAI Stage C–E (*n* = 345)	*p*-Value
Demographics and comorbidities				
Age, years	69 (60–79)	71 (64–78)	69 (60–79)	0.451
Male sex, *n* (%)	278 (74.1)	21 (70.0)	257 (74.5)	0.590
Hypertension, *n* (%)	243 (65.0)	15 (50.0)	228 (66.3)	0.073
Diabetes mellitus, *n* (%)	165 (44.1)	10 (33.3)	155 (45.1)	0.215
COPD, *n* (%)	39 (10.5)	8 (26.7)	31 (9.0)	0.007
CKD, *n* (%)	144 (38.4)	12 (40.0)	132 (38.3)	0.851
ICD, *n* (%)	56 (15.0)	1 (3.3)	55 (16.0)	0.256
Heart failure etiology, *n* (%)				0.100
Ischemic	236 (62.9)	18 (60)	218 (63.2)	
Non-ischemic	115 (30.7)	9 (30)	106 (30.7)	
Unknown	24 (6.4)	3 (10)	21 (6.1)	
Heart failure phenotype, *n* (%)				0.409
HFrEF	338 (90.1)	29 (96.7)	309 (89.6)	
HFmrEF	23 (6.1)	1 (3.3)	22 (6.4)	
Pulmonary hypertension-associated isolated right-sided heart failure	14 (3.7)	0 (0.0)	14 (4.1)	
Echocardiographic findings				
LVEF, %	25 (20–30)	25 (15–30)	25 (20–30)	0.365
LVEDD, mm	59.3 ± 8.1	59.4 ± 8.6	59.4 ± 8.1	0.982
LVESD, mm	49 (44–55)	50 (42–56)	49 (44–55)	0.087
IVS thickness, mm	11 (10–12)	10 (9–12)	11 (10–12)	0.130
Posterior wall thickness, mm	10 (10–12)	10 (9.5–11)	10 (10–12)	0.155
LA diameter, mm	48 (44–51)	45 (42.5–50.5)	48 (44–51)	0.092
PASP, mmHg	43 (35–56)	41 (33.5–55.5)	43 (35–56)	0.611
Significant valvular disease, *n* (%)	256 (68.4)	18 (60.0)	238 (69.2)	0.299
Severe mitral regurgitation, *n* (%)	196 (52.9)	17 (58.6)	179 (52.5)	0.610
Severe aortic regurgitation, *n* (%)	14 (3.8)	0 (0.0)	14 (4.1)	0.305
Severe tricuspid regurgitation, *n* (%)	194 (52.4)	12 (41.3)	182 (53.4)	0.246
Severe mitral and tricuspid regurgitation, *n* (%)	137 (37.0)	11 (37.9)	126 (36.9)	0.987
Laboratory findings				
Hemoglobin, g/dL	11.7 (10.4–13.4)	11.9 (10.6–13.4)	11.7 (10.4–13.5)	0.173
WBC, $\times 10^9$/L	8.95 (7.3–11.7)	11.1 (8.9–16.8)	8.8 (7.2–11.6)	<0.001
Neutrophil count, $\times 10^9$/L	6.8 (5.1–9.3)	9.4 (7.1–12.9)	6.6 (5.0–9.1)	<0.001
Lymphocyte count, $\times 10^9$/L	1.1 (0.7–1.6)	1.3 (0.9–1.9)	1.10 (0.7–1.6)	0.275
CRP, mg/L	19.8 (9.2–46.0)	30.2 (14.9–115.8)	18.9 (9.0–44.7)	0.021
BUN, mg/dL	33 (22–48)	37.5 (29.7–60)	33 (22–47.7)	0.039
eGFR, mL/min/1.73 m^2	46.5 (34–64)	42 (30–59.5)	48 (34.5–66)	0.043
Creatinine, mg/dL	1.44 (1.1–1.8)	1.6 (1.1–2.2)	1.4 (1.1–1.8)	0.135

Table 1. *Cont.*

Variable	Overall (*n* = 375)	Progression to SCAI Stage C–E (*n* = 30)	No Progression to SCAI Stage C–E (*n* = 345)	*p*-Value
ALT, U/L	23 (13.7–56.2)	39 (14.7–140.5)	23 (13–51.5)	0.035
AST, U/L	27 (19–68)	59 (27.5–138.5)	26 (19–60.2)	0.003
LDH, U/L	278 (224–388.7)	406 (270.5–547.5)	273 (218.7–369.5)	0.002
NT-proBNP, pg/mL	8613 (4412–16,083)	20,083 (9075–27,760)	8376 (4223–15,885)	0.024
Troponin, ng/L	56 (29–208)	131 (35–1580)	54 (28–190.5)	0.067
Sodium, mmol/L	136 (132–139)	134.5 (132–138)	136 (132–139)	0.405
Potassium, mmol/L	4.4 (3.9–4.8)	4.6 (3.8–4.8)	4.3 (3.9–4.8)	0.979
Chloride, mmol/L	99 (95–102)	96 (91.7–100)	99 (95–102)	0.008
Magnesium, mg/dL	2.0 (1.8–2.2)	2.0 (1.7–2.2)	2.0 (1.8–2.2)	0.510
Albumin, g/L	36.4 (33–39.6)	35.4 (31.7–38)	36.7 (33–39.8)	0.103
Hemodynamic and rhythm variables				
SBP, mmHg	110 (100–122)	104 (92–119.2)	110 (100–122)	0.097
DBP, mmHg	67 (60–76)	60.5 (46.7–70.5)	68 (60–77)	0.007
Heart rate, bpm	80 (70–91)	90.5 (82.2–106)	78 (69–90)	<0.001
Atrial fibrillation, *n* (%)	68 (18.1)	3 (10.0)	65 (18.8)	0.843
Initial inotropic treatment				
Levosimendan, *n* (%)	254 (67.7)	20 (66.7)	234 (67.8)	0.896
Dobutamine, *n* (%)	121 (32.3)	10 (33.3)	111 (32.2)	
Additional vasoactive treatment after baseline				
Multiple inotropes and/or vasopressors, *n* (%)	52 (13.9)	22 (73.3)	30 (8.7)	<0.001
At least two inotropes	15 (4.0)	2 (6.7)	13 (3.8)	
One inotrope plus norepinephrine	17 (4.5)	10 (33.3)	7 (2.0)	
At least two inotropes plus norepinephrine	20 (5.3)	10 (33.3)	10 (2.9)	
In-hospital outcome				
In-hospital mortality, *n* (%)	60 (16.0)	15 (50.0)	45 (13.0)	<0.001

Note: Data are presented as mean ± standard deviation, median (interquartile range), or n (%), as appropriate. For variables with missing data, percentages were calculated using the number of patients with available data for the corresponding variable as the denominator. NT-proBNP and troponin measurements were available for 169 and 314 patients, respectively. Heart failure etiology was classified separately as ischemic, non-ischemic, or unknown according to the available clinical records. The patient counts and percentages for valvular disease subcategories were calculated using the number of patients with available valvular data in each group. These subcategories were not mutually exclusive because individual patients could have more than one valvular lesion. Post-baseline vasoactive treatment subcategories were mutually exclusive and summed to the corresponding parent category. Post-baseline vasoactive treatments and in-hospital mortality are presented descriptively and were not included as baseline predictors in the multivariable model. All in-hospital deaths occurred after the 72 h SCAI assessment. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; IVS, interventricular septum; LA, left atrium; LDH, lactate dehydrogenase; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; SCAI, Society for Cardiovascular Angiography and Interventions; WBC, white blood cell count; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Patients who progressed to SCAI stage C–E had higher WBCs [11.1 (8.9–16.8) vs. 8.8 (7.2–11.6), $p < 0.001$], neutrophil counts [9.4 (7.1–12.9) vs. 6.6 (5.0–9.1), $p < 0.001$], CRP

levels [30.2 (14.9–115.8) vs. 18.9 (9.0–44.7), $p = 0.021$], blood urea nitrogen (BUN) levels [37.5 (29.7–60.0) vs. 33.0 (22.0–47.7), $p = 0.039$], AST levels [59.0 (27.5–138.5) vs. 26.0 (19.0–60.2), $p = 0.003$], LDH levels [406 (270.5–547.5) vs. 273 (218.7–369.5), $p = 0.002$], and NT-proBNP levels [20,083 (9075–27,760) vs. 8376 (4223–15,885), $p = 0.024$]. They also had a lower estimated glomerular filtration rate (eGFR) [42.0 (30.0–59.5) vs. 48.0 (34.5–66.0) mL/min/1.73 m^2, $p = 0.043$] and lower chloride levels [96.0 (91.7–100.0) vs. 99.0 (95.0–102.0) mmol/L, $p = 0.008$]. NT-proBNP measurements were available in 169 of 375 patients, whereas troponin measurements were available in 314 of 375 patients.

Regarding hemodynamic parameters, the progression group had lower DBP [60.5 (46.7–70.5) vs. 68.0 (60.0–77.0) mmHg, $p = 0.007$] and higher heart rate [90.5 (82.2–106.0) vs. 78.0 (69.0–90.0) beats/min, $p < 0.001$]. SBP was numerically lower in the progression group, but the difference was not statistically significant ($p = 0.097$). The initial inotropic agent did not differ between groups ($p = 0.896$).

COPD was associated with higher odds of progression in univariable analysis. WBC, CRP, ln(AST), ln(LDH), ln(NT-proBNP), DBP, and heart rate were also significantly associated with progression to SCAI stage C–E (Table 2). Chloride and eGFR were not significantly associated with the outcome. Although chloride and eGFR differed significantly between the groups in unadjusted distributional comparisons, neither variable showed a significant linear association with the odds of progression when analyzed as a continuous predictor in univariable logistic regression. Spearman correlation analysis showed a weak-to-moderate correlation between CRP and WBC ($\rho = 0.338$, $p < 0.001$), a moderate correlation between AST and LDH ($\rho = 0.530$, $p < 0.001$), and a very weak correlation between DBP and heart rate ($\rho = 0.139$, $p = 0.012$).

Table 2. Univariable Logistic Regression Analysis for Progression to SCAI Stage C–E at 72 h After Initiation of Inotropic Therapy.

Variable	OR	95% CI	*p*-Value
WBC	1.108	1.040–1.179	0.001
C-reactive protein	1.008	1.003–1.013	0.002
ln(AST)	1.355	1.031–1.780	0.029
ln(LDH)	1.939	1.138–3.303	0.015
ln(NT-proBNP)	3.065	1.079–8.707	0.035
DBP	0.959	0.931–0.989	0.007
Heart rate	1.034	1.015–1.054	0.001
Chloride	0.996	0.974–1.020	0.759
eGFR	0.991	0.974–1.008	0.294
COPD	3.660	1.504–8.907	0.004

Abbreviations: AST, aspartate aminotransferase; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; ln, natural logarithm; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; WBC, white blood cell count; DBP, diastolic blood pressure.

In the multivariable logistic regression model, higher WBC was independently associated with greater odds of progression to SCAI stage C–E (OR: 1.099, 95% CI: 1.030–1.174, $p = 0.005$), whereas higher DBP was independently associated with lower odds of progression (OR: 0.963 per 1-mmHg increase, 95% CI: 0.934–0.992, $p = 0.014$) (Table 3). In 2000 bootstrap resamples, the association remained significant for WBC (bootstrap $p = 0.009$), whereas the association with DBP was borderline (bootstrap $p = 0.051$).

Table 3. Multivariable Logistic Regression Analysis of Factors Associated with Progression to SCAI Stage C–E at 72 Hours After Initiation of Inotropic Therapy.

Variable	OR	95% CI	*p*-Value
WBC	1.099	1.030–1.174	0.005
DBP	0.963	0.934–0.992	0.014

Note: The primary multivariable model included 327 patients and 30 outcome events. Model calibration: Hosmer–Lemeshow χ^2 = 6.987, df = 8, p = 0.538. Model explanatory value: Nagelkerke R^2 = 0.098. Model discrimination: c-statistic = 0.731 (95% CI: 0.630–0.832; $p < 0.001$). In 2000 bootstrap resamples, the association remained significant for WBC (bootstrap p = 0.009), whereas the association with DBP was borderline (bootstrap p = 0.051). Abbreviations: CI, confidence interval; OR, odds ratio; SCAI, Society for Cardiovascular Angiography and Interventions; WBC, white blood cell count; DBP, diastolic blood pressure.

The model showed acceptable calibration according to the Hosmer–Lemeshow test (χ^2 = 6.987, df = 8, p = 0.538), with a Nagelkerke R^2 of 0.098. The multivariable model showed moderate discrimination, with a c-statistic of 0.731 (95% CI: 0.630–0.832; $p < 0.001$), as illustrated in Figure 2.

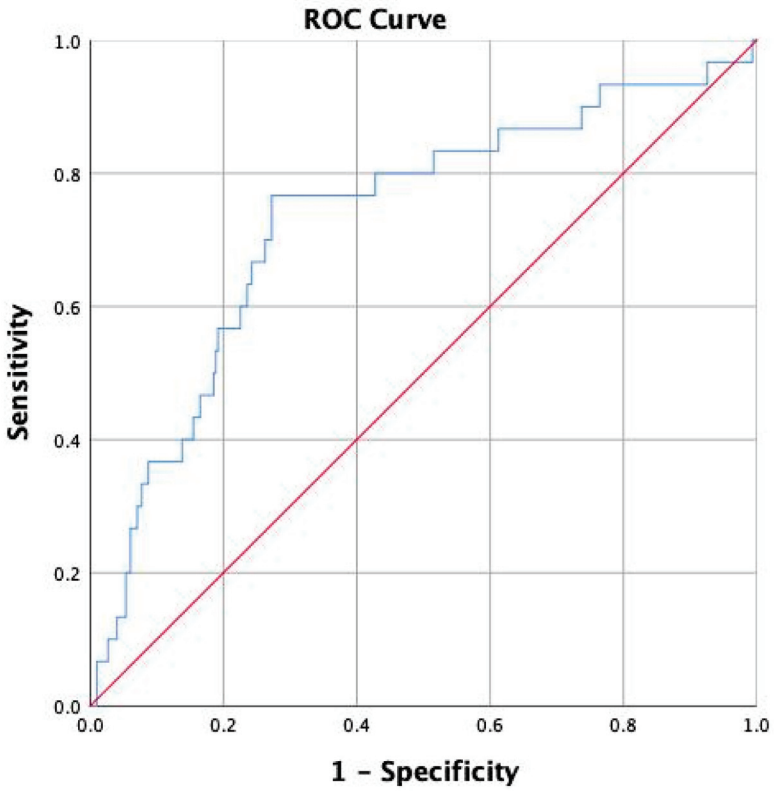


Figure 2. Receiver operating characteristic curve of the multivariable logistic regression model for progression to SCAI stage C–E at 72 h after initiation of inotropic therapy. The area under the curve was 0.731 (95% CI: 0.630–0.832; $p < 0.001$). The blue line represents the receiver operating characteristic curve, and the red dashed diagonal line represents the reference line of no discrimination.

4. Discussion

In this study, higher WBC and lower DBP were independently associated with progression from SCAI stage A or B to SCAI stage C–E at 72 h after initiation of inotropic therapy in patients with ADHF. Progression occurred in 30 patients (8.0%). The association with WBC remained significant in bootstrap analysis, whereas the association with DBP was borderline, indicating greater uncertainty regarding the stability of the DBP estimate. Accordingly, these findings should be interpreted as exploratory and hypothesis-generating rather than as evidence of robust bedside markers.

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Higher WBC was independently associated with progression to SCAI stage C–E, and this association remained significant in bootstrap analysis, supporting the relative stability of the estimate within the present dataset. Neutrophil count and CRP levels were also higher among patients who progressed, suggesting that early hemodynamic deterioration may occur in the context of a broader inflammatory and physiological stress profile. Taken together, these findings support a possible role for systemic inflammatory activation in patients at risk of progression, although they do not establish a causal relationship.

Consistent with our findings, previous studies in patients hospitalized with ADHF have reported associations between higher leukocyte and neutrophil counts, elevated CRP levels, and adverse in-hospital outcomes [10]. However, the prognostic evidence regarding total WBC has not been entirely consistent. In a large AHF cohort, neutrophil count and other leukocyte-derived indices remained associated with mortality, whereas total WBC did not retain an independent association after adjustment for NT-proBNP [11]. Differences in patient selection, outcome definitions, timing of laboratory measurements, and the prevalence of concurrent inflammatory conditions may partly explain these discrepancies. Importantly, the present study evaluated early progression in SCAI stage rather than mortality or rehospitalization. Thus, the observed association suggests that inflammatory activation may be relevant during a distinct and earlier phase of hemodynamic deterioration.

Several mechanisms may underlie the observed association. In AHF, systemic inflammatory activation may contribute to endothelial and microvascular dysfunction and impaired vascular regulation, potentially increasing vulnerability to hemodynamic deterioration [12,13]. Nevertheless, WBC is a nonspecific marker and may be influenced by comorbidities, medications, occult infection, tissue injury, and other stress-related conditions. Although patients with active infection or septic shock were excluded, residual confounding by unrecognized inflammatory states cannot be eliminated. Accordingly, the association between WBC and SCAI progression should be interpreted as prognostic rather than causal, and WBC should not currently be regarded as a validated standalone risk marker.

Clinical presentation may vary considerably among patients with ADHF developing on the background of chronic HF. In patients exposed to long-standing reductions in cardiac output and systemic perfusion, compensatory mechanisms may temporarily maintain blood pressure and end-organ perfusion despite limited hemodynamic reserve [14,15]. This condition may result in a more fragile hemodynamic profile than expected, even without clinically evident signs of hypoperfusion. Previous studies have shown that a substantial proportion of patients classified as SCAI stage B may progress to more advanced stages of cardiogenic shock within the first 24 h [16]. In addition, worsening HF has been reported to be associated with adverse prognosis regardless of its timing and the treatments administered [17]. Therefore, the primary endpoint was defined as progression from baseline SCAI stage A or B to SCAI stage C–E at 72 h, focusing on clinically meaningful deterioration beyond the pre-shock spectrum; however, the observed associations should be interpreted in light of their sensitivity to endpoint specification.

In our study, lower DBP was independently associated with progression to SCAI stage C–E, which may reflect impaired vascular compensation and limited hemodynamic reserve despite the absence of overt hypoperfusion at baseline. In ADHF, DBP may reflect arterial vascular tone, coronary perfusion pressure, and the ability to preserve organ perfusion during clinical stress. Although heart rate was higher among patients who progressed and was associated with progression in univariable analysis, it was not included in the parsimonious multivariable model, in which DBP was selected to represent the hemodynamic domain. COPD was also more frequent among patients who progressed; however, given the limited number of events and the potential for residual confounding,

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this finding should be interpreted cautiously. Because the bootstrap stability of the DBP association was borderline, this finding should also be interpreted cautiously and not regarded as a robust standalone marker.

Kapur et al. reported that lower SBP was associated with more advanced SCAI stages and higher in-hospital mortality, with early progression occurring even among patients initially classified at lower stages [18]. In our cohort, SBP was not significantly associated with progression, whereas DBP remained significant in the multivariable model. This finding suggests that DBP may provide complementary information regarding early hemodynamic vulnerability; however, the present results do not establish its superiority over SBP.

Previous studies have also suggested prognostic relevance of diastolic pressure-related measures across the heart failure–cardiogenic shock continuum. Low DBP was associated with HF readmission in patients with acute decompensated HFpEF, whereas lower diastolic perfusion pressure was linked to poorer hemodynamic response in established cardiogenic shock [19,20]. Although our cohort differed by including patients without overt hypoperfusion at baseline, these findings collectively suggest that diastolic pressure may provide complementary information regarding circulatory reserve. Nevertheless, given the borderline bootstrap stability and potential construct overlap with SCAI staging, the DBP association should be interpreted cautiously.

NT-proBNP was also associated with progression to SCAI stage C–E in univariable analysis, consistent with its established role as a marker of HF severity and hemodynamic burden. However, NT-proBNP measurements were available only in a subset of the cohort and the variable was therefore not included in the primary multivariable model. Accordingly, its independent association with progression could not be reliably assessed in the primary analysis. The univariable finding should therefore be interpreted cautiously and may primarily reflect the overall severity of cardiac decompensation and hemodynamic burden.

One notable finding was that the distribution of the initial inotropic agent did not differ between patients who progressed to SCAI stage C–E and those who did not. Previous studies comparing levosimendan and dobutamine have suggested that levosimendan may provide more favorable short-term hemodynamic effects; however, evidence regarding clinical outcomes remains inconsistent. In the LIDO trial, levosimendan was associated with a greater hemodynamic response and lower mortality than dobutamine, whereas the larger SURVIVE trial demonstrated no significant difference in long-term mortality between the two agents [21,22]. In our cohort, the absence of a between-group difference should be interpreted cautiously because treatment allocation was not randomized and was based on the attending physician's clinical judgment. Therefore, our findings do not establish therapeutic equivalence between levosimendan and dobutamine; rather, they indicate that the initial inotropic agent alone did not explain the observed differences in early SCAI stage progression.

From a clinical perspective, WBC may serve as a readily available marker of the inflammatory activation and physiological stress accompanying early hemodynamic deterioration in patients with ADHF receiving intravenous inotropic therapy. The concomitant elevation of neutrophil count and CRP levels among patients who progressed suggests that this association may form part of a broader inflammatory profile. However, WBC is a nonspecific marker and may be influenced by comorbid conditions, medications, tissue injury, and clinically unrecognized inflammatory states. Therefore, the observed association should be interpreted as a prognostic signal accompanying early clinical deterioration rather than as evidence of a causal mechanism.

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DBP may provide complementary information regarding hemodynamic reserve, reflecting a different pathophysiological domain from inflammatory stress. Heart rate was associated with progression in univariable analysis but was not included in the parsimonious multivariable model, in which DBP was selected to represent the hemodynamic domain. Accordingly, WBC and DBP should not be regarded as validated standalone risk markers, but rather as complementary clinical variables to be interpreted alongside serial SCAI staging, perfusion findings, inflammatory indices, heart rate, and evolving organ function.

This study has several important limitations. First, its retrospective, single-center design may have introduced selection bias and limits the generalizability of the findings. The decisions to initiate and escalate inotropic or vasopressor therapy were neither protocolized nor randomized and were based on the attending physician's clinical judgment, creating the possibility of confounding by indication. In addition, owing to the retrospective nature of the records, the interval between hospital admission and initiation of inotropic therapy could not be determined reliably and consistently for all patients and therefore could not be reported quantitatively. Progression to SCAI stage C–E is partly defined by treatment escalation and hemodynamic variables, including blood pressure; therefore, the primary endpoint may reflect both clinical deterioration and treatment decisions, and some degree of construct overlap between the endpoint and DBP cannot be excluded. Accordingly, the observed associations should be interpreted as prognostic rather than causal.

Second, only 30 patients experienced the primary endpoint, which limited the number of variables that could be included in the multivariable model and increased the risk of model instability and overfitting. Accordingly, a parsimonious model was used, and coefficient stability was assessed using bootstrap resampling; however, external validation was not performed. The primary model included 327 patients with complete WBC and DBP data and all 30 outcome events. Although bootstrap resampling supported the stability of the WBC association, the DBP association was borderline, indicating uncertainty regarding the robustness of the DBP estimate. Moreover, the variables associated with adverse hemodynamic progression changed after refinement of the endpoint definition, demonstrating that the findings were sensitive to endpoint specification. This sensitivity should be considered when interpreting the results, and neither WBC nor DBP should be regarded as a validated standalone risk marker.

Third, missing data were present for several variables, particularly NT-proBNP, which was available in only 169 of 375 patients. No imputation was undertaken, and analyses were therefore based on available cases, which may have reduced statistical power and introduced bias if the data were not missing at random. Because of its limited availability, NT-proBNP was not included in the primary multivariable model, and its independent association with progression could not be reliably assessed. Furthermore, lactate measurements and invasive hemodynamic parameters were not uniformly available, limiting a more detailed and objective assessment of tissue hypoperfusion and circulatory status. The potential effects of fluid overload and hemodilution on baseline laboratory measurements could not be standardized or formally adjusted because of the retrospective design. The underlying etiology and World Health Organization classification of pulmonary hypertension in patients with pulmonary hypertension-associated isolated right-sided HF could not be reliably determined from the retrospective records. Finally, the predominance of levosimendan and center-specific treatment practices may further limit applicability to other settings. Despite these limitations, the study provides exploratory information regarding baseline factors associated with early progression to advanced SCAI stages in a selected high-risk population with ADHF receiving inotropic therapy. These findings require confirmation in larger, prospective, multicenter cohorts.

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5. Conclusions

In patients with ADHF who were classified as SCAI stage A or B at baseline and received intravenous inotropic therapy, higher WBC and lower DBP were associated with progression to SCAI stage C–E at 72 h. Given the limited number of events, the sensitivity of the findings to endpoint specification, and the borderline bootstrap stability of the DBP association, these results should be considered exploratory and hypothesis-generating. Serial assessment and repeated SCAI staging may help identify patients at risk of early deterioration. Prospective multicenter studies are needed to validate these findings.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Antalya Training and Research Hospital Scientific Research Ethics Committee (05.03.2026 with protocol number 5/15).

Informed Consent Statement: In Turkey there is no requirement to obtain informed consent from individuals in retrospective studies. According to the Antalya Training and Research Hospital Clinical Research Ethics Committee, obtaining consent for participation is considered unnecessary. The manuscript does not contain any individual person's data in details, images or videos.

Data Availability Statement: The data sets created and/or analyzed during the current study are not publicly available because they contain patient information, but data supporting the findings of this study can be obtained from the corresponding author (RA) upon reasonable request.

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

Abbreviations

The following abbreviations are used in this manuscript:

ADHF	Acute decompensated heart failure
AHF	Acute heart failure
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CI	Confidence interval
CICU	Coronary intensive care unit
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
DBP	Diastolic blood pressure
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ICD	Implantable cardioverter-defibrillator

IQR	Interquartile range
IVS	Interventricular septum
LA	Left atrium
LDH	Lactate dehydrogenase
LVEDD	Left ventricular end-diastolic diameter
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic diameter
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OR	Odds ratio
PASP	Pulmonary artery systolic pressure
SCAI	Society for Cardiovascular Angiography and Interventions
SBP	Systolic blood pressure
WBC	White blood cell count

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Article

Increased Mortality and Complication Rates in Weekend Admissions for Acute Decompensated Heart Failure: A Five-Year National Study

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Abstract

Background/Objectives: The "weekend effect," characterized by increased mortality and complication rates for weekend hospital admissions, is well documented in myocardial infarction and stroke but has been less thoroughly investigated in acute decompensated heart failure (ADHF). This study evaluates the weekend effect in ADHF using a national cohort. **Methods:** A retrospective cohort study was conducted using the 2016–2020 Nationwide Inpatient Sample (NIS). Adult ADHF admissions were identified by ICD-10 codes and classified as weekend or weekday admissions. Over 30 variables, including age, sex, and comorbidities, were analyzed. Propensity score matching (1:1) yielded 489,204 patients per group. Univariate and multivariate logistic regression models were used to assess outcomes, adjusting for key covariates. **Results:** Of 2,131,915 ADHF hospitalizations, 501,076 (23.5%) occurred on weekends. The cohort was 48% female, with a mean age of 72 years (SD $\pm$ 12.3). After 1:1 matching, weekend admissions had higher odds of cardiac arrest (aOR: 1.10; 95% CI: 1.06–1.13, $p < 0.001$), inpatient mortality (aOR: 1.07; 95% CI: 1.05–1.09, $p < 0.001$), acute kidney injury (AKI; aOR: 1.07; 95% CI: 1.06–1.08, $p < 0.001$), and acute respiratory failure (ARF; aOR: 1.28; 95% CI: 1.27–1.30, $p < 0.001$). No significant differences were observed in mechanical circulatory support (MCS) use or length of stay. **Conclusions:** Weekend ADHF admissions were associated with a higher risk of mortality and complications, which may be attributable to reduced specialist availability or delayed diagnostics. These findings underscore the need for standardized ADHF protocols to ensure equitable care throughout the week.

Keywords: acute decompensated heart failure; acute kidney injury; respiratory failure; cardiac arrest; mortality; weekend; weekday

1. Introduction

Heart failure (HF) is a clinical syndrome characterized by functional and/or structural abnormalities that lead to reduced cardiac output and/or elevated intracardiac pressures [1]. It affects around 37–64 million individuals worldwide, corresponding to a prevalence of 800–900 cases per 100,000 individuals (around 1–3% in the adult population) [1,2]. In the United States, an estimated 5.7 million adults were diagnosed with heart failure in 2011, with nearly 870,000 incident HF cases diagnosed annually [1,2].

Acute decompensated heart failure (ADHF), the acute worsening of chronic HF with congestion and hemodynamic compromise, is the third most common cause of unscheduled hospital admission, excluding pregnancy and neonatal cases [3]. It is associated with substantial morbidity, mortality, and healthcare expenditures. In the United States, HF-related healthcare costs are projected to increase from $20.9 billion in 2012 to $53.1 billion by 2030 [1,4].

Despite advances in guideline-directed medical therapy (GDMT) and device management, post-discharge prognosis for HF remains poor. Approximately 24% of patients are readmitted within 30 days, and nearly 35% die within one year of diagnosis [2,4].

Given the acuity of ADHF, rapid diagnosis and prompt initiation of decongestive therapies are essential for optimal clinical outcomes. However, hospital resources and operations often differ during the night and on weekends. This variation has led to the hypothesis of a "weekend effect," in which patients admitted on weekends experience worse clinical outcomes than those admitted on weekdays [5]. Similar effects have been observed in other urgent conditions, such as acute coronary syndrome [6].

Proposed explanations for this variation include reduced nurse-to-patient ratios, limited access to subspecialists, and delayed access to critical diagnostics or procedures during off-hours [6].

The presence of a weekend effect in ADHF hospitalizations is debated in the literature. Some large registry analyses, including the "Get With The Guidelines-Heart Failure" (GWTG-HF) registry, show higher mortality for weekend admissions [7]. In contrast, studies using the OPTIMIZE-HF registry and the Atherosclerosis Risk in Communities (ARIC) surveillance found no significant difference in mortality by admission day [8].

These conflicting findings may be attributable to differences in study design, such as varying definitions of 'weekend,' heterogeneity in hospital types, and challenges in controlling for illness severity. Clarifying this relationship is essential for quality improvement and resource allocation. This study uses a large national cohort to examine the impact of admission timing on outcomes in ADHF. The primary objective is to determine whether weekend admissions for acute decompensated heart failure are associated with higher in-hospital mortality and complication rates relative to weekday admissions.

2. Materials and Methods

2.1. Data Source

A retrospective cohort study was conducted using the NIS database from 2016 to 2020. The NIS is the largest publicly available, all-payer inpatient database in the United States and is maintained by the Healthcare Cost and Utilization Project (HCUP). It includes a 20% stratified sample of hospital discharges, with discharge-level weights that enable national estimates of hospitalizations and outcomes. The NIS contains information on patient demographics, diagnoses, procedures, comorbidities, hospital characteristics, and discharge disposition [9–11].

2.2. Study Population

Adult hospitalizations (aged $\geq$18 years) with a principal or secondary diagnosis of acute decompensated heart failure were identified using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes consistent with prior NIS-based HF studies (I50.21, I50.23, I50.31, I50.33, I50.41, I50.43, I50.811, I50.813). The exposure of interest was weekend versus weekday admission. Weekend admissions were defined as those occurring on Saturday or Sunday; all others were classified as weekday admissions.

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2.3. Variable Definitions and Covariates

Demographic variables included age, sex, and race/ethnicity (categorized as White, Black, Hispanic, Asian/Pacific Islander, Native American/Other, and Unknown). Socioeconomic variables included primary expected payer (Medicare, Medicaid, private insurance, self-pay, no charge/charity, and other).

Comorbidities and clinical history were identified using ICD-10-CM codes (Supplementary Table S1). Key conditions included hypertension, diabetes mellitus, hyperlipidemia, hyperthyroidism, hypothyroidism, peripheral artery disease, coronary artery disease, atrial fibrillation/flutter, chronic obstructive pulmonary disease (COPD), obesity, prior stroke, chronic kidney disease (CKD) stages 1–5 (without dialysis), and end-stage renal disease (ESRD) or dialysis dependence. Hospital-level characteristics included U.S. Census region (e.g., New England, Middle Atlantic), teaching status (urban teaching, urban non-teaching, rural), and bedsize categories, as defined by HCUP.

2.4. Outcomes

The primary outcome was in-hospital all-cause mortality.

Secondary clinical outcomes included cardiac arrest, development of ARFARF (hypoxic, hypercapnic, or mixed), ARF requiring invasive mechanical ventilation, acute kidney injury (AKI), initiation of hemodialysis during the index hospitalization, cardiogenic shock, and use of mechanical circulatory support, including intra-aortic balloon pump (IABP), Impella, and extracorporeal membrane oxygenation (ECMO).

Secondary resource-utilization outcomes included length of stay, total hospital charges, and discharge disposition (home, short-term hospital, other facility, home health care, against medical advice, in-hospital death, or unknown).

2.5. Propensity Score Matching

To reduce confounding due to baseline differences between patients admitted on weekdays and those admitted on weekends, propensity score matching (PSM) was performed. A logistic regression model was used to estimate the probability of weekend admission based on patient demographics (age, sex, race/ethnicity, payer, income quartile), comorbidities (including hypertension, diabetes mellitus, hyperlipidemia, hypothyroidism, hyperthyroidism, peripheral artery disease, coronary artery disease, atrial fibrillation/flutter, COPD, obesity, stroke, CKD, ESRD), and hospital characteristics (region, location, and teaching status).

Patients admitted on weekends were matched 1:1 to those admitted on weekdays using nearest-neighbor matching without replacement. This procedure yielded 489,204 matched hospitalizations in each group. Covariate balance between weekday and weekend groups after matching was assessed by applying standardized mean differences and compared descriptively.

2.6. Statistical Analysis

Survey weights were applied in accordance with HCUP recommendations when generating national estimates to obtain design-based national estimates [9].

Descriptive statistics were used to summarize baseline characteristics before and after matching. Categorical variables were compared using chi-square tests, and continuous variables using independent *t*-tests.

In the matched cohort, model-based analysis in the form of univariate and multivariable logistic regression was performed to estimate the association between weekend admission and each binary outcome (e.g., mortality, cardiac arrest, AKI, ARF), with results reported as adjusted odds ratios (aORs) and 95% confidence intervals (CIs). Models ad-

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justed for residual imbalances in demographics, comorbidities, and hospital characteristics after matching. For LOS and total hospital charges (non-adjusted to inflation), linear regression or generalized linear models with appropriate distributions and link functions were used. A two-sided p-value < 0.05 was considered statistically significant. Analyses were performed using Stata 18 (StataCorp, College Station, TX, USA).

2.7. Ethical Considerations

The NIS contains de-identified discharge-level data. In accordance with institutional policy and federal regulations, this study was considered exempt from institutional review board review and informed consent requirements.

3. Results

3.1. Study Cohort and Baseline Characteristics

From 2016 to 2020, a total of 2,131,915 hospitalizations for acute decompensated heart failure were identified in the NIS. Of these, 501,076 (23.5%) occurred on weekends and 1,630,839 (76.5%) on weekdays. The overall cohort had a mean age of 72 years (SD ± 12.3), and approximately 48% were female (Table 1).

Table 1. Baseline Demographics of Patients Admitted with Acute Decompensated Heart Failure on Weekday vs. Weekend (before matching).

Variable	Weekday (n = 1,631,992)	Weekend (n = 501,076)	p-Value
Age (years)	Mean = 71.51, SD = 14.09	Mean = 71.69, SD = 14.14	<0.001
	(n, %)	(n, %)	
Female	777,099 (47.62)	243,955 (48.69)	<0.001
Race			<0.001
White	1,105,427 (69.42)	334,684 (68.41)	
Black	281,194 (17.66)	89,248 (18.24)	
Hispanic	124,957 (7.85)	39,938 (8.16)	
Asian/Pacific Islander	34,510 (2.17)	11,129 (2.27)	
Native/Other	8282 (0.52)	2678 (0.55)	
Unknown	37,991 (2.39)	11,588 (2.37)	
Hypertension	1,446,019 (88.60)	445,004 (88.81)	<0.001
Diabetes Mellitus	769,489 (47.15)	236,340 (47.17)	0.839
Hyperlipidemia	872,714 (53.47)	265,291 (52.94)	<0.001
Hyperthyroidism	13,058 (0.8)	3935 (0.69)	0.302
Hypothyroidism	295,618 (18.11)	90,679 (18.1)	0.784
Peripheral artery disease	111,768 (6.85)	32,417 (6.47)	<0.001
Coronary artery disease	958,810 (58.75)	297,266 (59.32)	<0.001
Atrial fibrillation/flutter	786,152 (48.17)	235,616 (47.02)	<0.001
COPD	594,480 (36.43)	187,657 (37.45)	<0.001
Obesity	414,872 (25.42)	123,153 (24.58)	<0.001
VT/VF	113,923 (6.98)	34,536 (6.89)	0.032
VTE	57,068 (3.50)	17,660 (3.52)	0.353
Stroke	63,208 (3.87)	19,434 (3.88)	0.862
CKD Stage 1–5 (No dialysis)	536,337 (32.86)	164,043 (32.74)	0.097
ESRD or dialysis	111,800 (6.85)	33,706 (6.73)	0.001

After 1:1 propensity score matching, 489,204 weekday and 489,204 weekend admissions were included in the analytic cohort. Baseline characteristics of the matched cohort are presented in Table 2. By design, the demographic and clinical profiles were well-balanced between groups. The mean age was similar for weekday and weekend admissions (71.85 vs. 71.69 years, p = 0.34), and the proportions of female patients were comparable (48.89% vs. 48.74%, p = 0.129). The prevalence of key comorbidities, including hypertension, diabetes

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mellitus, hyperlipidemia, coronary artery disease, atrial fibrillation/flutter, COPD, obesity, CKD, and ESRD, did not differ meaningfully between groups.

Table 2. Baseline Demographics of Patients Admitted with Acute Decompensated Heart Failure on Weekday vs. Weekend (after matching).

Variable	Weekday (*n* = 489,204)	Weekend (*n* = 489,204)	*p*-Value
Age (years)	Mean = 71.85, SD = 13.98	Mean = 71.69, SD = 14.12	0.34
Co-morbidities/Past medical history	(*n*, %)	(*n*, %)	
Female	239,174 (48.89)	238,424 (48.74)	0.129
Hypertension	436,579 (89.24)	435,003 (88.92)	0.054
Diabetes Mellitus	231,354 (47.29)	230,592 (47.21)	0.416
Hyperlipidemia	259,896 (53.13)	259,341 (53.01)	0.261
Hyperthyroidism	3885 (0.79)	3857 (0.79)	0.749
Hypothyroidism	88,475 (18.09)	88,520 (18.09)	0.906
Peripheral artery disease	31,015 (6.34)	31,553(6.45)	0.062
Coronary artery disease	290,619 (59.41)	290,155 (59.31)	0.34
Atrial fibrillation/Atrial flutter	230,617 (47.14)	230,154 (47.05)	0.348
COPD	183,229 (37.45)	183,539 (37.52)	0.517
Obesity	119,277 (24.38)	120,355 (24.6)	0.17
Ventricular Tachycardia/Ventricular Fibrillation	31,163 (6.37)	33,655 (6.88)	0.089
Venous Thromboembolism	14,854 (3.04)	17,178 (3.51)	0.354
Stroke	16,638 (3.4)	18,885 (3.86)	0.139
CKD Stage 1–5 (No dialysis)	160,685 (32.85)	160,285 (32.76)	0.389
ESRD or dialysis	32,134 (6.57)	33,046 (6.76)	0.73
Race			0.068
White	337,738 (69.04)	334,644 (68.41)	
Black	88,455 (18.08)	89,235 (18.24)	
Hispanic	39,054 (7.98)	39,934 (8.16)	
Asian/Pacific Islander	10,485 (2.14)	11,127 (2.27)	
Native/Other	2224 (0.45)	2678 (0.55)	
Unknown	11,248 (2.3)	11,586 (2.37)	

Racial and ethnic distributions were similar, with white patients comprising approximately two-thirds of admissions (69.04% on weekdays vs. 68.41% on weekends), followed by African American (18.08% vs. 18.24%) and Hispanic (7.98% vs. 8.16%) patients. Primary payers were predominantly Medicare (>70% in both groups), with smaller proportions of Medicaid, private insurance, and self-pay patients. Hospital region and teaching status were also comparable across weekday and weekend admissions, with most hospitalizations occurring in urban teaching hospitals.

3.2. Clinical Outcomes

In the propensity-matched cohort, weekend admission was associated with higher rates of major in-hospital complications and mortality compared with weekday admission (Table 3).

The in-hospital mortality rate was 5.45% for weekend admissions versus 5.02% for weekday admissions (26,645 vs. 24,546 deaths; $p < 0.001$), corresponding to an adjusted odds ratio of 1.07 (95% CI: 1.05–1.09). Similarly, the incidence of cardiac arrest was higher among weekend admissions (1.84% vs. 1.60%; 8980 vs. 7822 events; $p < 0.001$), with an adjusted odds ratio of 1.10 (95% CI: 1.06–1.13).

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Table 3. Medical and Non-medical Outcomes of Patients Admitted with Acute Decompensated Heart Failure on a Weekday and a Weekend.

Variables	Weekday (*n* = 489,204)	Weekend (*n* = 489,204)	*p*-Value
Medical Outcomes	(*n*, %)	(*n*, %)	
ARF	105,603 (21.59)	128,295 (26.23)	<0.001
ARF with the use of mechanical ventilation	16,206 (3.31)	16,455 (3.36)	0.161
Hemodialysis initiation	29,750 (6.08)	29,621 (6.05)	0.585
AKI	177,900 (36.37)	186,732 (38.17)	<0.001
Cardiogenic shock during the stay	17,987 (3.68)	19,255 (3.93)	<0.001
In-hospital death	24,546 (5.02)	26,645 (5.45)	<0.001
Cardiac arrest	7822 (1.6)	8980 (1.84)	<0.001
Use of MCS			<0.001
None	483,005 (98.73)	483,470 (98.83)	
IABP	4175 (0.85)	3668 (0.75)	
Impella	1813 (0.37)	1711 (0.35)	
ECMO	211 (0.04)	355 (0.07)	
Non-medical Outcomes			
Length of Stay (days)	Mean = 6.89, SD = 7.6	Mean = 6.77, SD = 7.75	0.07
Total Hospital Charges	Mean = $78,913, SD = $141,298	Mean = $82,017, SD = $149,492	<0.001
Discharge Status	207,809 (42.51)	204,443 (41.81)	0.137
Home	15,826 (3.24)	15,342 (3.14)	
Short-term Hospital	120,637 (24.68)	120,620 (24.67)	
Another Type of Facility	114,385 (23.4)	114,863 (23.49)	
Home Health Care	5538 (1.13)	7030 (1.44)	
AMA	24,546 (5.02)	26,645 (5.45)	
Died in Hospital	85 (0.02)	64 (0.01)	

ARFARF occurred in 26.23% of weekend admissions compared with 21.59% of weekday admissions (128,295 vs. 105,603 events; $p < 0.001$). This translated into a 28% higher adjusted odds of ARF for patients admitted on weekends (aOR 1.28; 95% CI: 1.27–1.30). The need for invasive mechanical ventilation among those with ARF was similar between groups (3.36% on weekends vs. 3.31% on weekdays; $p = 0.161$), suggesting that the increased ARF incidence did not fully translate into differences in ventilatory support rates.

AKI was also more frequent among weekend admissions (38.17% vs. 36.37%; 186,732 vs. 177,900 events; $p < 0.001$), with an adjusted odds ratio of 1.07 (95% CI: 1.06–1.08). In contrast, initiation of hemodialysis during hospitalization did not significantly differ between weekend and weekday admissions (6.05% vs. 6.08%; $p = 0.585$). Cardiogenic shock occurred slightly more often in weekend admissions (3.93% vs. 3.68%; 19,255 vs. 17,987 events; $p < 0.001$), consistent with a modestly higher burden of hemodynamic instability.

The overall use of MCS (IABP, Impella, or ECMO) was low and showed no clinically relevant difference between groups in absolute terms. Among matched admissions, the vast majority did not receive MCS (98.83% on weekends vs. 98.73% on weekdays), and the low absolute rates of device use were not directionally consistent with a large weekend effect. Table 4 displays the multivariate analysis of developing complications among those with decompensated heart failure admitted on a weekend compared to weekdays.

3.3. Resource Employment

Length of stay was similar for weekday and weekend admissions (mean 6.89 vs. 6.77 days; $p = 0.07$), indicating that the excess mortality and complications associated with weekend admission did not translate into longer hospitalizations among survivors.

Table 4. Multivariate Logistic Regression for Patients Admitted with Acute Decompensated Heart Failure on a Weekend vs. a Weekday.

Variables	Adjusted Odds Ratio (95% CI)	*p*-Value
Inpatient death	1.07 (1.05–1.09)	<0.001
Cardiac arrest	1.1 (1.06–1.13)	<0.001
HD initiation	0.91 (0.89–1.01)	0.06
Use of MCS	0.87 (0.84–0.9)	<0.001
AKI	1.07 (1.06–1.08)	<0.001
ARFARF	1.28 (1.27–1.3)	<0.001
ARF Requiring Mechanical Ventilation	1.02 (0.99–1.04)	0.054

Total hospital charges, however, were higher for weekend admissions ($82,017 ± $149,492; $p < 0.001$) compared with weekend admissions (mean $78,913 ± $141,298). This pattern likely reflects greater use of diagnostic and procedural interventions during weekday hospitalizations. Discharge disposition was broadly similar between groups, with comparable proportions of patients discharged home, transferred to short-term hospitals or other facilities, receiving home health care, or leaving against medical advice. As expected, in-hospital death was more frequent among weekend admissions, consistent with the observed mortality difference.

4. Discussion

In this large, nationally representative cohort of patients hospitalized with acute decompensated heart failure, weekend admission was associated with higher in-hospital mortality and a greater burden of major complications compared with weekday admission, even after rigorous propensity score matching and multivariable adjustment. Weekend admissions had 7% higher adjusted odds of in-hospital death and a 10% higher adjusted odds of cardiac arrest, along with significantly higher odds of ARF and AKI. This evidence is directionally consistent with prior work describing a "weekend effect" across a broad range of acute medical and surgical conditions, with pooled estimates showing roughly a 7–20% relative increase in mortality for weekend versus weekday admissions [10–13].

4.1. Interpretation of Main Findings

The present analysis shows a modest but clinically meaningful weekend effect in contemporary ADHF care. Given the high incidence of ADHF hospitalizations, even a 7–10% relative increase in mortality and complications translates into a substantial excess number of adverse events at the population level. The association persisted after extensive adjustment for demographics, comorbidities, and hospital-level factors, consistent with meta-analytic data showing that a weekend effect persists even after adjustment for severity and case-mix. This suggests that residual differences in illness severity alone are unlikely to justify the observed disparities fully [10,12].

The increased rates of ARF and AKI among weekend admissions indicate possible care-process mechanisms. Prior syntheses of the weekend effect have stressed the dual contributions of patient factors ("sicker weekend patient" hypothesis) and system factors (reduced staffing, slower access to diagnostics and procedures) [10]. In ADHF specifically, delays in achieving adequate decongestion, less frequent titration of diuretics and vasoactive agents, slower escalation to noninvasive or invasive ventilatory support, and later nephrology involvement may all contribute to progressive respiratory and renal compromise. The modestly higher frequency of cardiogenic shock on weekends in the current study mirrors patterns seen in off-hours admissions for acute myocardial infarction, where delays in reperfusion and reduced catheterization-laboratory availability have been

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implicated in excess mortality and complications [10]. By contrast, MCS was used in a small minority of patients in both groups, and although statistical significance was reached, the absolute rates were below 0.1%, implying that the difference is driven mainly by common care processes rather than disparities [12].

Importantly, the length of stay was similar between weekend and weekday admissions, whereas hospital charges were higher for weekday admissions. General weekend-effect meta-analyses and health policy analyses have noted that weekday care often entails more diagnostic and procedural activity. In contrast, weekend care may be characterized by relative conservatism in interventions and less intensive use of resources, even when outcomes are worse [10]. In this context, the current data suggest that the weekend effect in ADHF is driven less by prolonged hospitalizations and more by early deterioration and in-hospital death. This raises concern that lower spending on weekends may partially reflect delayed or reduced use of clinically indicated diagnostics and interventions, in line with prior "weekend effect" studies in stroke and acute coronary syndrome, where patients admitted on a weekend received fewer or later interventions and developed worse outcomes [13].

4.2. Comparison Relative to Prior Studies

Evidence regarding the weekend effect in HF has been mixed. Horwich et al., using the Get With The Guidelines–Heart Failure (GWTG-HF) registry of 81,810 hospitalizations (mean age 72 ± 14 years, 50% male), observed that weekend admissions and discharges were associated with differences in quality metrics and outcomes in HF (e.g., longer hospitalization), raising concerns about off-hours vulnerability [14]. Additionally, weekend HF admission was associated with higher risk-adjusted odds of in-hospital death (aOR 1.13, 95% CI 1.02–1.27, $p = 0.03$) [14]. Additionally, weekend HF admission was associated with higher risk-adjusted odds of in-hospital death (aOR 1.13, 95% CI 1.02–1.27, $p = 0.03$) [14]. Similarly, the ARIC surveillance study, among 39,699 weighted hospitalizations (mean age 76, 48% male), noted that in-hospital mortality doubled for weekend admissions (aOR 2.37, 95% CI 1.93–2.91; $p < 0.001$) [3]. In contrast, analyses from OPTIMIZE-HF (N = 48,612 patients, mean age 73 ± 14 years, 52% female) found no significant differences in short-term mortality by day of admission after risk adjustment ($p = 0.19$), suggesting that a uniform weekend effect in HF is not universal [8,15]. Outside the U.S., the Japanese JCARE-CARD registry (N = 1620, mean age 70.7 years, 59.4% male) similarly reported no independent association between weekend admission and in-hospital death in patients admitted with worsening HF after adjustment for covariates ($p = 0.136$) [16].

More recent multinational data have shifted attention from calendar days to time of day and working vs. non-working hours. An analysis from the REPORT-HF registry (N = 18,553, 61% male) found that patients admitted during non-working hours had similar in-hospital mortality but higher 1-year mortality than those admitted during standard working hours ($p = 0.76$ and 0.006, respectively), suggesting that off-hours admission may affect downstream trajectories even when early mortality is comparable [17]. However, the magnitude and consistency of these effects vary across conditions and datasets. This is consistent with broader work from England and other systems, indicating that both weekend and nighttime admissions can be associated with increased adjusted mortality [18–20]. In the National Health Service study (N = 4,640,516, 48% male), Mohammed et al. demonstrated that patients admitted on weekends, whether on an elective or emergency basis, had increased risk of death (elective OR 1.32, 95% CI 1.23–1.41; emergency OR 1.09, 95% CI 1.05–1.13; all $p < 0.001$) compared to weekday admissions [18]. Furthermore, Han et al. demonstrated that, among 246,350 emergency spells, the highest mortality risk was for

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weekend night-time admissions as well (aOR 1.14, 95% CI 1.08–1.21, $p = 0.003$) [19]. However, the magnitude and consistency of these effects vary across conditions and datasets.

The current study expands this literature in several ways. First, it uses a large, nationally representative sample of U.S. hospitalizations with contemporary ICD-10 coding, including both teaching and non-teaching hospitals across all regions. Second, through employing 1:1 propensity score matching to balance demographics, comorbidities, and hospital characteristics, the analysis reduces confounding by case-mix that has complicated prior observational work. Third, it evaluates a broad spectrum of clinically relevant complications in addition to mortality, demonstrating that weekend admission is associated not only with higher death rates but also with higher odds of ARFARF, AKI, cardiogenic shock, and cardiac arrest, trends consistent with off-hours analyses in other cardiovascular emergencies such as NSTEMI and acute aortic syndromes.

The more pronounced weekend effect on respiratory and renal complications is especially significant. Systematic reviews of the weekend effect have highlighted that processes of care (e.g., timeliness of investigations, adherence to guidelines, and swift escalation to higher levels of care) likely mediate part of the observed mortality gap. In HF, where dynamic volume status and renal function are central to outcomes, small delays in diuretic intensification, ventilatory support, or hemodynamic assessment on weekends may excessively translate into ARF and AKI [20,21].

4.3. Potential Mechanisms Underlying the Weekend Effect

First, staffing and expertise differ between weekdays and weekends. Large, policy and evidence-based analyses in the UK and elsewhere have demonstrated that specialist physician coverage and multidisciplinary staffing are typically lower on weekends, even in systems actively implementing 7-day services [21]. These reductions have been temporally associated with higher adjusted mortality for weekend admissions across multiple conditions [22]. In ADHF, fewer in-house cardiologists or HF specialists, higher nurse–patient ratios, and reduced access to respiratory therapists or nephrologists on weekends could delay recognition of deterioration and limit initiation of advanced therapies.

Second, access to diagnostics and procedures may be constrained on weekends. Prior studies of the weekend effect in cardiology and hospital medicine have documented reduced use or longer delays for essential diagnostic and treatment interventions on weekends compared with weekdays, despite similar clinical indications [11,23]. For HF, limited off-hours access to echocardiography, right-heart catheterization, or high-level imaging may impede precise hemodynamic assessment and preload and afterload optimization, causing worsening congestion, respiratory failure, and renal dysfunction.

Third, care coordination and transitions may be less robust during weekends. Studies of HF and other chronic conditions point out the importance of multidisciplinary discharge planning, medication reconciliation, and early post-discharge follow-up in reducing readmissions and improving outcomes. On weekends, reduced availability of case managers, pharmacists, and allied health professionals may impact not only discharge processes, but also in-hospital titration of GDMT and consultation coordination. Even if these processes primarily influence post-discharge trajectories, disruptions early in the hospitalization can still affect in-hospital clinical stability and complication risk [11,13].

Finally, system-level pressures and bed capacity may shape differences in the escalation of care. Analyses of weekend and off-hours admissions across conditions have identified interactions among elective procedural schedules, ICU bed availability, and triage thresholds for higher-acuity care. HF patients admitted during busy weekend periods may experience delays in transfer to monitored units or intensive care, which may explain some of the excess cardiogenic shock and cardiac arrest observed in this cohort [11,24,25].

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4.4. Clinical and Health System Implications

The higher mortality and complication rates observed among weekend ADHF admissions have actionable implications. First, the results support calls for standardized, protocolized HF pathways explicitly designed for 7-day implementation, including early risk stratification, standardized orders for laboratory and imaging evaluation, and algorithmic titration of diuretics and vasodilators. Evidence from other acute cardiovascular syndromes suggests that well-implemented, around-the-clock pathways can attenuate or eliminate weekend mortality gaps.

Second, these data support efforts to optimize weekend staffing models, particularly in hospitals with a high HF burden. The meta-analytic and policy literature indicate that simple increases in consultant hours alone may not completely resolve the weekend effect, but assuring a minimal level of cardiology/HF expertise, adequate nurse staffing, and ready access to respiratory and nephrology services appears essential [11,13].

Third, the study offers empirical justification for investment in 7-day services and infrastructure. Systematic reviews and national policy analyses from the UK and other health systems have highlighted that the weekend effect is multifactorial, involving staffing, process reliability, and access to diagnostics and procedures [24]. For ADHF, extending the availability of echocardiography, noninvasive ventilation protocols, and step-down or intermediate-care beds past standard weekday hours may be a high-yield strategy to reduce early decompensation and death.

4.5. Strengths and Limitations

Strengths of this study include the use of a large, nationally representative NIS cohort, contemporary ICD-10 coding, and rigorous propensity score matching to address baseline imbalances. These design features align with methodological recommendations from recent weekend-effect meta-analyses and policy reviews that emphasize strong risk adjustment and the inclusion of system-level covariates. Evaluating multiple clinically meaningful complications, in addition to mortality, gives a more detailed picture of how weekend admission shapes the in-hospital course of ADHF.

Several limitations warrant consideration. First, as an administrative database, the NIS is subject to potential misclassification of ADHF and comorbidities based on ICD-10 codes and lacks granular clinical data, such as natriuretic peptides, ejection fraction, and hemodynamic parameters. Second, individual-level treatment details, including specific HF therapies and their timing, are unavailable, limiting inferences about process-of-care mediators. Third, repeat hospitalizations by the same patient cannot be identified. Fourth, although propensity score matching and multivariable adjustment were applied, residual confounding from unmeasured factors (e.g., as frailty, code status, functional status, social support) remains possible, as highlighted in prior weekend-effect syntheses. Additionally, the absence of granular clinical data, such as admission vital signs, laboratory results (e.g., blood pressure, eGFR, lactate, B-type Natriuretic Peptide [BNP] levels), and left ventricular ejection fraction (LVEF), could introduce residual confounding, even following propensity matching. Finally, the observational design precludes causal inference; the associations between weekend admission and outcomes should therefore be viewed as hypothesis-generating and complementary to more granular registry and quality-improvement studies.

5. Conclusions

In a large, nationally representative cohort of adults hospitalized with acute decompensated heart failure, weekend admission was associated with higher in-hospital mortality and increased odds of major complications, including cardiac arrest, ARF, and AKI, compared with weekday admission. These results are consistent with the broader literature

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documenting a weekend effect across multiple conditions and settings, and with contemporary HF data highlighting vulnerability during off-hours. Collectively, the evidence suggests that time-based variations in staffing, resource readiness, and reliability of care processes add to outcome disparities in ADHF. Applying standardized HF pathways, strengthening weekend coverage, and expanding 7-day diagnostic and critical-care services may help mitigate the weekend effect and promote more unbiased outcomes for patients hospitalized with ADHF, regardless of the day of admission.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm15062097/s1, Table S1: ICD-10 Codes Used for Variables and Data Extraction.

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Frailty Matters: Validation of an Automated Electronic Short Physical Performance Battery (eSPPB) for Predicting 30-Day Mortality in Hospitalized Cardiovascular Patients—A Step-by-Step Study

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Abstract

Background: Frailty is a major determinant of adverse outcomes in older adults with cardiovascular disease. Automated digital tools may facilitate routine frailty assessment in hospital settings; however, their validity and prognostic relevance in acutely hospitalized patients remain insufficiently established. **Methods:** In this prospective cohort study, 113 hospitalized cardiology patients underwent frailty assessment using both manual Short Physical Performance Battery (mSPPB) and an automated electronic SPPB (eSPPB) system. Agreement between methods was evaluated using Pearson correlation, intraclass correlation coefficients (ICCs), and Bland–Altman analysis. Frailty was defined as SPPB < 5. The association between frailty and 30-day mortality was assessed using logistic regression and Kaplan–Meier survival analysis. **Results:** Seventeen patients (15.0%) were classified as frail. Automated and manual SPPB scores were highly correlated (r = 0.994, $p < 0.001$) and demonstrated good agreement (ICC = 0.80). Bland–Altman analysis showed a mean difference of −1.63 points (95% limits of agreement −4.41 to 1.16). Frailty was associated with significantly higher 30-day mortality (17.6% vs. 2.1%, $p = 0.009$), corresponding to a tenfold increase in mortality odds (OR 10.07; 95% CI 1.5–67.5). An exploratory model showed apparent discriminative performance (AUC 0.83; 95% CI 0.71–0.95). **Conclusions:** Automated eSPPB demonstrated good agreement with manual assessment and was significantly associated with short-term mortality in hospitalized cardiovascular patients. These findings support the validity and potential clinical utility of automated frailty assessment for risk stratification in acute cardiology settings.

Keywords: frailty; short physical performance battery; eSPPB; cardiovascular disease; digital health; mortality; geriatric cardiology

1. Introduction

Frailty is a multidimensional clinical syndrome characterized by diminished physiological reserve and increased vulnerability to stressors, resulting in a reduced ability to maintain homeostasis during acute illness or physiological challenges. It is increasingly

recognized as a major determinant of adverse health outcomes in older adults, including prolonged hospitalization, functional decline, institutionalization, and mortality [1,2].

Frailty reflects cumulative declines across multiple organ systems, including musculoskeletal, cardiovascular, and neurological domains, and is closely linked to sarcopenia, chronic inflammation, and impaired energy metabolism. Cardiovascular disease and frailty frequently coexist and interact in a bidirectional manner. Cardiovascular conditions such as heart failure, coronary artery disease, and arrhythmias can accelerate the development of frailty through mechanisms including reduced cardiac output, impaired tissue perfusion, systemic inflammation, and decreased physical activity [3–5].

Conversely, frailty itself is independently associated with worse cardiovascular outcomes, including increased mortality, longer hospital stays, higher readmission rates, and poorer recovery following cardiovascular interventions. Frailty has therefore emerged as a critical factor in risk stratification and clinical decision-making in cardiovascular medicine, particularly in older and hospitalized patients. Accurate and timely identification of frailty is essential for optimizing clinical management. Among available assessment tools, the Short Physical Performance Battery (SPPB) is one of the most widely validated and clinically accepted instruments for evaluating physical frailty [6,7].

The SPPB assesses lower-extremity function through three standardized components: standing balance, gait speed over a short distance, and repeated chair stands. These objective measures provide a composite score reflecting physical performance and functional reserve. Numerous studies have demonstrated that lower SPPB scores are strongly associated with increased risk of disability, hospitalization, institutionalization, and mortality across diverse clinical populations [8].

Despite its strong prognostic value and widespread validation, routine implementation of the SPPB in hospital settings remains limited. Manual administration requires trained personnel, standardized timing procedures, and careful observation, which can introduce variability and increase staff workload [9].

In busy inpatient environments, competing clinical priorities and limited staffing may reduce the feasibility of systematic frailty assessment. Furthermore, manual measurement may be subject to interobserver variability and timing inaccuracies, potentially affecting reproducibility and scalability.

Recent advances in digital health technologies have created opportunities to automate physical performance assessment using sensor-based systems. Automated measurement platforms can capture motion parameters objectively, reduce observer dependency, and improve measurement consistency. These technologies may enable more efficient and scalable frailty screening, particularly in high-volume clinical settings such as cardiology wards.

AndanteFit is a novel digital platform designed to automate SPPB assessment using integrated LiDAR-based motion sensors and software-guided scoring algorithms. The system automatically measures gait speed, balance, and sit-to-stand performance, generating standardized electronic SPPB (eSPPB) scores without requiring manual timing or subjective interpretation. By reducing observer variability and simplifying workflow, automated assessment has the potential to facilitate routine frailty screening in clinical practice. Previous studies have demonstrated the feasibility of sensor-based SPPB measurement in community-dwelling populations, but evidence regarding its performance and prognostic value in hospitalized cardiovascular patients remains limited [10]. However, its validity and prognostic relevance in acutely hospitalized patients had not been fully evaluated.

Importantly, the clinical utility of automated frailty assessment depends not only on measurement accuracy but also on its ability to provide meaningful prognostic information. Frailty assessment is most valuable when it contributes to early risk stratification, informs clinical decision-making, and identifies patients at increased risk of adverse outcomes.

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However, the validity and prognostic relevance of automated eSPPB systems in acutely hospitalized cardiology patients have not been fully established.

Therefore, the aim of this study was to evaluate the validity and prognostic utility of an automated eSPPB system in hospitalized cardiovascular patients. Specifically, we sought to assess agreement between automated and manual SPPB measurements, describe clinical and functional factors associated with frailty, and examine the association between frailty status and short-term mortality. We hypothesized that automated eSPPB would demonstrate strong agreement with manual SPPB and provide clinically meaningful prognostic information in hospitalized cardiology patients.

2. Materials and Methods

2.1. Study Design and Setting

This was a prospective observational cohort study conducted at the Cardiovascular Institute of Hospital Clínico San Carlos, Madrid, Spain, between February and May 2025.

2.2. Participants

A total of 113 consecutive hospitalized cardiology patients were included. Eligible participants were clinically stable adults admitted with primary cardiovascular diagnoses. Exclusion criteria included hemodynamic instability, inability to stand or walk safely, or severe cognitive impairment preventing test completion.

2.3. Frailty Assessment

Frailty was assessed using:

2.3.1. Manual SPPB (mSPPB)

Manual SPPB was performed by trained clinical staff according to standardized protocols. Gait speed was measured over a 4 m course, and participants were instructed to walk at their usual pace. Sit-to-stand time was measured using a standard chair without armrests, and participants were instructed to stand up and sit down five times as quickly as possible without using their arms.

2.3.2. Automated SPPB (eSPPB)

Automated electronic SPPB (eSPPB) assessments were performed using the AndanteFit system Automated measurements were performed using the AndanteFit digital system, which uses integrated motion sensors and proprietary algorithms to automatically detect movement initiation, gait speed, and sit-to-stand transitions. The system provides automated scoring based on standard SPPB criteria, eliminating the need for manual timing or observer interpretation.

The AndanteFit device (Dyphi Research Institute, Seoul, Republic of Korea) uses LiDAR-based motion detection sensors. The device was positioned approximately 2 m in front of the participant and calibrated prior to each measurement according to manufacturer instructions.

Participants performed the gait speed test over a flat, unobstructed 4 m course. Two trials were conducted, and the best performance was used for analysis. A standard chair with seat height of approximately 45 cm was used for sit-to-stand testing.

The SPPB includes:

1. Standing balance
2. 4 m gait speed
3. Five-repetition sit-to-stand

Total score range: 0–12.

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Frailty classification:

- Frail: SPPB < 5
- Pre-frail: 5–10
- Non-frail: >10

2.4. Outcome Measure

The primary outcome was all-cause mortality within 30 days of hospital admission.

2.5. Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies and percentages. Agreement between manual and automated SPPB scores was assessed using Pearson correlation coefficients. Comparisons between frailty groups were performed using ANOVA for continuous variables and Chi-square tests for categorical variables. Logistic regression analysis was used to explore associations between clinical and functional variables and frailty status.

Model discrimination was assessed using the area under the receiver operating characteristic curve (AUC). The 95% confidence interval for the AUC was estimated using the Hanley and McNeil method. Kaplan–Meier survival analysis and log-rank testing were used to compare mortality between frailty groups. Agreement between manual and automated SPPB scores was further evaluated using the intraclass correlation coefficient (two-way random effects, absolute agreement) and Bland–Altman analysis.

Because frailty was defined using the SPPB score, the regression analyses including SPPB component measures (gait speed and sit-to-stand time) were considered exploratory and hypothesis-generating, and were intended to describe within-cohort associations rather than establish independent predictive effects.

A p-value < 0.05 was considered statistically significant.

2.6. Ethical Approval

The study was approved by the Institutional Ethics Committee of Hospital Clínico San Carlos (Approval No. 24/847-E; 20 February 2025). All participants provided written informed consent.

3. Results

3.1. Baseline Characteristics

A total of 113 hospitalized cardiology patients were included in the study. The mean age was 74.2 ± 11.7 years, and 57 participants (50.4%) were female. The average gait speed was 0.88 ± 0.24 m/s, and the mean time required to complete the five-repetition sit-to-stand test was 16.2 ± 5.5 s.

The distribution of primary cardiovascular diagnoses in the overall cohort included heart failure (n = 30), coronary artery disease (n = 20), angina (n = 9), myocardial infarction (n = 8), acute coronary syndromes (n = 5), pacemaker/ICD/ventricular tachycardia (n = 7), syncope (n = 4), and other unspecified cardiovascular conditions (n = 10). Among frail patients, heart failure was the most frequent diagnosis; however, no formal statistical comparison between diagnostic categories and frailty status was performed due to the limited sample size within subgroups.

3.2. Frailty Distribution and Functional Performance

Based on SPPB scores, 17 patients (15.0%) were classified as frail (SPPB < 5), 60 (53.1%) as pre-frail (SPPB 5–10), and 36 (31.9%) as non-frail (SPPB > 10) (Table 1).

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Table 1. Baseline characteristics and physical performance according to frailty status.

Frailty Group	n (%)	Age (Mean ± SD)	% Female	Gait Speed (m/s)	Sit-to-Stand (s)
Frail	17 (15.0%)	79.1 ± 10.5	75.0%	0.52 ± 0.10	22.8 ± 6.0
Pre-frail	60 (53.1%)	76.7 ± 11.2	46.7%	0.85 ± 0.18	16.7 ± 4.5
Non-frail	36 (31.9%)	68.4 ± 12.1	46.7%	1.03 ± 0.21	13.2 ± 3.2

Frailty status was significantly associated with age and functional performance measures. Frail patients were older (79.1 ± 10.5 years) compared with pre-frail (76.7 ± 11.2 years) and non-frail patients (68.4 ± 12.1 years; $p < 0.01$).

Marked differences were observed in physical performance. Frail patients demonstrated substantially slower gait speed (0.52 ± 0.10 m/s) compared with pre-frail (0.85 ± 0.18 m/s) and non-frail patients (1.03 ± 0.21 m/s; $p < 0.001$). Similarly, sit-to-stand time was significantly prolonged in frail individuals (22.8 ± 6.0 s) compared with pre-frail (16.7 ± 4.5 s) and non-frail patients (13.2 ± 3.2 s; $p < 0.001$).

Although frailty was more frequent among women (75.0%), sex differences did not reach statistical significance ($p = 0.15$).

3.3. Agreement Between Manual and Automated SPPB

Automated eSPPB scores demonstrated good agreement with manual SPPB measurements. Pearson correlation analysis revealed an extremely strong positive correlation between methods in the overall cohort (r = 0.994, $p < 0.001$). Similarly, strong agreement was observed within the frail subgroup (r = 0.961, $p < 0.001$).

These findings indicate that automated eSPPB provides highly consistent measurements compared with manual assessment, supporting its validity as a tool for objective functional evaluation in hospitalized cardiology patients.

Intraclass correlation analysis showed good agreement between methods, with an ICC of 0.80, indicating strong reliability of automated measurements.

Bland–Altman analysis revealed a mean difference of −1.63 points (eSPPB − mSPPB), indicating a modest systematic tendency of the automated system to yield slightly lower scores than manual assessment. The 95% limits of agreement ranged from −4.41 to +1.16 points (Figure 1).

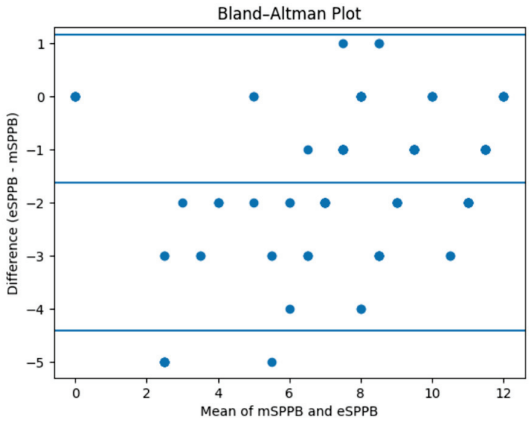


Figure 1. Bland–Altman plot showing agreement between manual and automated SPPB scores.

These findings suggest good overall agreement between methods, although a small systematic bias toward lower automated scores was observed.

3.4. Factors Associated with Frailty Status

Exploratory analyses were performed to examine associations between clinical and functional variables and frailty status within the cohort. Because frailty was defined using the SPPB score, which includes gait speed and sit-to-stand performance, these analyses were not intended to identify independent predictors but rather to describe within-cohort associations.

Slower gait speed was strongly associated with frailty status ($\beta = -2.5$, $p < 0.001$) (Table 2). Longer sit-to-stand time also showed an association with frailty risk, although this association did not reach conventional statistical significance ($\beta = 0.14$, $p = 0.06$). Age was not associated with frailty after adjustment for functional measures ($\beta = 0.08$, $p = 0.21$). Female sex was not significantly associated with frailty status ($\beta = 0.45$, $p = 0.12$).

Table 2. Clinical and functional variables associated with frailty status.

Variable	β Coefficient	*p*-Value	Interpretation
Age	+0.08	0.21	Older age is associated with higher likelihood of frailty
Gait Speed (m/s)	–2.5	<0.001	Lower gait speed is associated with higher likelihood of frailty
Sit-to-Stand Time (s)	+0.14	0.06	Longer sit-to-stand time is associated with higher likelihood of frailty
Gender (Female = 1)	+0.45	0.12	Not significantly associated with frailty status, although a mild trend was observed

This exploratory model showed apparent discrimination within the study cohort (AUC 0.83; 95% CI 0.71–0.95); however, given the conceptual overlap between the included variables and the frailty definition, this result should be interpreted with caution and not as evidence of independent discriminative performance (Figure 2).

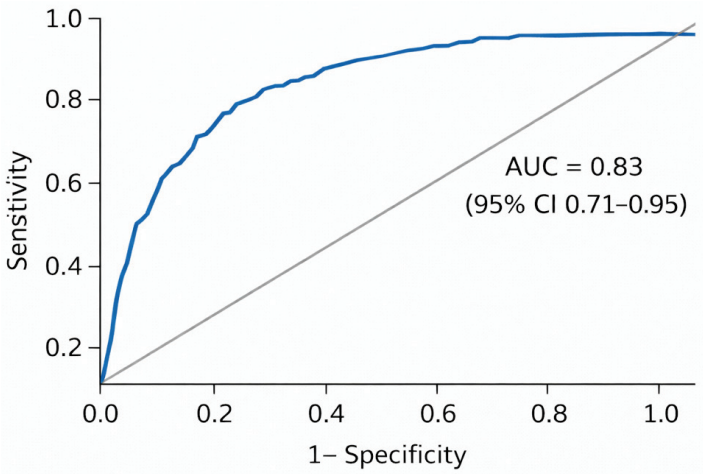


Figure 2. Receiver operating characteristic (ROC) curve for identification of frailty (AUC = 0.83; 95% CI: 0.71–0.95).

In exploratory analyses, the following variables were associated with frailty status within the cohort:

3.5. Thirty-Day Mortality

During the 30-day follow-up period, five deaths occurred (4.4%). Mortality was higher among frail patients than among non-frail patients. Specifically, three of 17 frail patients

(17.6%) died within 30 days, compared with two of 96 non-frail patients (2.1%). Frailty was associated with increased odds of 30-day mortality (OR 10.07; 95% CI 1.54–65.69; Fisher's exact $p = 0.024$) (Table 3). Kaplan–Meier survival analysis also demonstrated lower survival probability among frail patients (log-rank $p = 0.009$).

Table 3. Association between frailty and 30-day mortality.

Group	Total Patients	Deaths (30-Day)	Mortality Rate (%)
Frail (SPPB < 5)	17	3	17.6% *
Not Frail (SPPB ≥ 5)	96	2	2.1%

* $p = 0.009$ a statistically significant difference in mortality based on frailty status.

When frailty was defined using automated eSPPB scores, a similar association with 30-day mortality was observed. Specifically, three of 22 patients classified as frail according to eSPPB (13.6%) died within 30 days, compared with two of 91 non-frail patients (2.2%). Frailty defined by eSPPB was associated with increased odds of mortality (OR 6.96; 95% CI 1.08–44.7; Fisher's exact $p = 0.041$).

Kaplan–Meier survival analysis demonstrated significantly lower survival probability among frail patients (log-rank $p = 0.009$) (Figure 3). The log-rank test confirmed a statistically significant difference in survival between frail and non-frail groups.

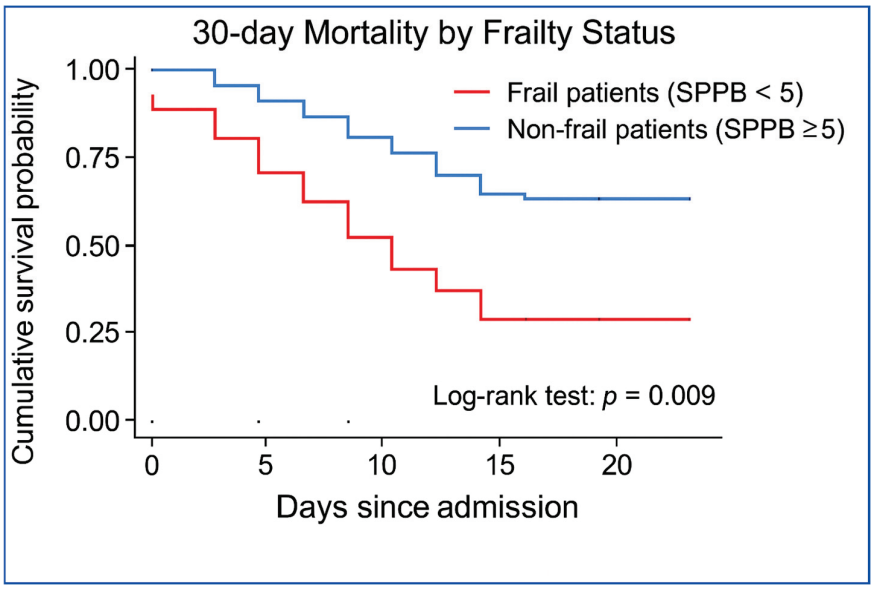


Figure 3. Kaplan–Meier survival curves according to frailty status.

Frail patients experienced a noticeably lower survival rate over the 30-day period. The SPPB demonstrated significant association with short-term mortality.

4. Discussion

4.1. Principal Findings

In this prospective cohort study of hospitalized cardiology patients, we found that the automated eSPPB scores showed extremely strong correlation with manual measurements and demonstrated good agreement (ICC = 0.80), supporting the validity of this digital tool in hospitalized cardiovascular patients.

Importantly, frailty identified using SPPB was strongly associated with short-term mortality. Frail patients exhibited a tenfold increase in the odds of 30-day mortality compared with non-frail individuals. Although the number of events was limited, this

finding underscores the clinical relevance of objective physical performance assessment for early risk stratification in hospitalized cardiovascular patients. These results are consistent with prior studies showing that lower SPPB scores are strongly associated with adverse outcomes, including mortality, rehospitalization, and functional decline in older adults with cardiovascular disease [11,12].

4.2. Clinical Relevance

Frailty is increasingly recognized as a key determinant of outcomes in patients with cardiovascular disease. Prior studies have demonstrated that reduced physical performance, particularly slower gait speed and impaired lower-extremity function, is associated with increased mortality, hospitalization, and functional decline. Our findings extend this evidence by demonstrating that automated frailty assessment using a digital system provides comparable measurements to traditional manual assessment and retains prognostic relevance.

Although Pearson correlation demonstrated an almost perfect linear association between manual and automated measurements, this metric reflects the strength of relationship rather than agreement. The ICC provides a more appropriate estimate of agreement and indicated good, but not perfect, reliability. The Bland–Altman analysis further identified a small systematic bias, with automated scores tending to be slightly lower. From a clinical perspective, this suggests that while eSPPB is suitable for ranking patients and identifying frailty, caution may be warranted when interpreting absolute values near diagnostic thresholds.

The strong correlation observed between manual and automated SPPB measurements suggests that digital tools can accurately capture clinically relevant functional parameters. Automation may reduce observer variability and improve standardization, potentially facilitating broader implementation of frailty screening in busy hospital settings where time and personnel constraints often limit routine functional assessment [12]. A recent review by Isaradech et al. highlighted the growing role of digital technologies in frailty detection, particularly those leveraging gait analysis, balance metrics, and upper-extremity motion [13]. However, many of these tools remain research prototypes or require wearable sensors, limiting their scalability and clinical integration. In contrast, eSPPB is fully automated, and based on a validated clinical scale (SPPB), making it more feasible for bedside use in acute care settings [14].

Recent validation studies of electronic SPPB systems, including kiosk-based and multi-sensor platforms, have primarily focused on community-dwelling older adults and feasibility outcomes rather than short-term clinical prognosis. In contrast, our study extends this evidence to an acutely hospitalized cardiovascular population and demonstrates not only measurement validity but also significant prognostic relevance for short-term mortality [10,13,14]. This distinction is clinically important, as hospitalized patients represent a higher-risk and more functionally vulnerable population in whom early frailty detection may have immediate therapeutic implications.

4.3. Prognostic Implications

We observed that gait speed and sit-to-stand performance were strongly associated with frailty status and contributed to a model with good apparent discriminative ability (AUC = 0.83), although the relatively small sample size warrants external validation. Because the frail subgroup was relatively small, the confidence interval around the AUC was wide; therefore, external validation in larger cohorts is warranted. These findings are consistent with previous research showing that gait speed is strongly associated with adverse outcomes, including mortality, in older adults and cardiovascular patients

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Because frailty was defined using SPPB scores, the inclusion of its individual components (gait speed and sit-to-stand time) in the regression model may introduce circular reasoning. Therefore, this analysis should be interpreted as exploratory and descriptive rather than as an independent analytical model.

The observed association between frailty and increased 30-day mortality further underscores the importance of functional status as a prognostic marker. Importantly, frailty defined using automated eSPPB was also associated with increased short-term mortality, supporting the prognostic validity of the automated assessment. Although the magnitude of the association was slightly lower than that observed with manual SPPB, the direction and clinical relevance of the findings were consistent. These results suggest that the prognostic value of the SPPB is preserved when assessed using an automated digital system, although confirmation in larger cohorts is warranted.

Frailty likely reflects diminished physiological reserve and reduced resilience to acute illness, increasing vulnerability to adverse outcomes during and after hospitalization. Given the small number of mortality events, estimates are imprecise and should be interpreted with caution. The observed association should be considered exploratory and hypothesis-generating rather than definitive, and requires confirmation in larger multicenter cohorts.

We did not directly compare the prognostic performance of manual and automated SPPB due to the limited number of events. Future studies with larger cohorts should evaluate whether eSPPB provides equivalent or superior prognostic discrimination compared with the conventional manual assessment. Additional analyses comparing AUCs could not be robustly performed due to the low number of events.

Automated frailty assessment using eSPPB may provide a practical and scalable approach for identifying high-risk patients early during hospitalization. Early identification of frailty could support clinical decision-making by informing risk stratification, discharge planning, and targeted interventions such as early mobilization or rehabilitation.

Furthermore, automated assessment may facilitate standardized frailty screening without requiring specialized training or additional staff resources. This may improve feasibility of routine frailty assessment in real-world clinical settings.

However, further studies are needed to evaluate whether implementation of automated frailty assessment leads to improved clinical outcomes.

4.4. Limitations

Several limitations should be considered. First, this study was conducted at a single tertiary care center, which may limit generalizability to other healthcare settings. Second, the study population was heterogeneous, including patients with a range of cardiovascular conditions. Differences in baseline risk and disease severity across these groups may have influenced both frailty status and mortality outcomes.

Third, the sample size was modest, and the limited number of mortality events may increase the risk of effect size overestimation and model instability; therefore, these findings should be interpreted as exploratory.

Due to the limited number of events, multivariable adjustment for potential confounders was not feasible. Therefore, the observed association between frailty and mortality may be influenced by residual confounding, including age, comorbidities, and underlying cardiovascular conditions.

Additionally, the SPPB primarily evaluates physical performance and does not capture other important dimensions of frailty, such as cognitive, nutritional, or psychosocial factors. Future studies should explore integration of automated physical performance measures with multidimensional frailty assessments. Larger multicenter studies are required to confirm the magnitude of the observed association.

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5. Conclusions

In conclusion, automated eSPPB assessment demonstrated good agreement with manual SPPB and was significantly associated with short-term mortality in hospitalized cardiology patients. These findings suggest the validity and potential clinical utility of automated frailty assessment as a scalable tool for functional evaluation and risk stratification in acute cardiology settings. However, given the limited number of events and the single-center design, these results should be interpreted with caution and confirmed in larger multicenter studies before routine clinical implementation.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Hospital Clínico San Carlos (Approval number: 24/847-E; 20 February 2025).

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

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: We confirm that authors Dohong kim and Seongjun Yoon were employed by DYPHY. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potencial conflict of interest. Dyphi research institute provid the AndanteFit device on loan solely for research purposes. We would like to clarify that the company had no role in the study design, data collection, analysis, interpretation of the results, manuscript preparation, or the decision to publish.

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Review

Precision Medicine in Heart Failure: Integrating Ventricular–Vascular Interaction and Arterial Stiffness into Patient Phenotyping

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Abstract

A key limitation in contemporary HF management is the marked heterogeneity of the syndrome, driven by diverse pathophysiological mechanisms that are not fully captured by traditional classifications based on left ventricular ejection fraction. Precision medicine has emerged as a promising approach to address this heterogeneity by integrating clinical characteristics, circulating biomarkers, advanced imaging, and computational phenotyping strategies. However, current frameworks predominantly emphasize myocardial dysfunction, while the contribution of vascular abnormalities remains underrepresented. The interaction between the left ventricle and the arterial system plays a fundamental role in cardiovascular performance. Arterial stiffness, commonly assessed by pulse wave velocity (PWV), represents a key determinant of vascular aging and a robust predictor of cardiovascular risk. Increasing evidence suggests that vascular dysfunction contributes significantly to the pathophysiology and clinical expression of HF, particularly in phenotypes characterized by preserved ejection fraction. This review synthesizes current evidence on precision medicine in HF and highlights the emerging role of arterial stiffness and PWV in multidimensional patient phenotyping. We propose that integrating vascular parameters into existing phenotyping frameworks may enhance risk stratification, improve mechanistic understanding, and support the development of more personalized therapeutic strategies in heart failure. Unlike previous reviews that have addressed arterial stiffness or heart failure phenotyping separately, this work uniquely integrates ventricular–vascular interaction and pulse wave velocity into a comprehensive precision medicine framework for heart failure. By bridging vascular physiology with data-driven phenotyping strategies, this review provides a novel conceptual model for incorporating arterial stiffness into multidimensional patient characterization across the full spectrum of heart failure phenotypes.

Keywords: heart failure; arterial stiffness; pulse wave velocity; ventricular–vascular interaction; precision medicine; cardiovascular phenotyping; vascular aging

1. Introduction

Heart failure affects more than 64 million individuals worldwide and remains a leading cause of cardiovascular morbidity, mortality, and healthcare utilization [1–4]. Despite major therapeutic advances over the past decades, outcomes remain suboptimal, with high rates of hospitalization and mortality approaching 50% within five years of diagnosis [4]. The growing prevalence of heart failure reflects population aging, improved survival after acute cardiovascular events, and the increasing burden of cardiometabolic risk factors [2,4,5].

Historically, heart failure has been classified according to left ventricular ejection fraction (LVEF), leading to the widely used categories of heart failure with reduced (HFrEF), mildly reduced (HFmrEF), and preserved ejection fraction (HFpEF) [6,7]. Although this framework has important therapeutic and prognostic implications, LVEF alone provides only a partial representation of the biological complexity of the syndrome [8]. Patients within the same LVEF category often exhibit substantial variability in clinical characteristics, comorbidity profiles, hemodynamic patterns, and response to therapy [8,9].

Multiple biological pathways contribute to the development and progression of HF, including myocardial dysfunction, neurohormonal activation, systemic inflammation, metabolic disturbances, and vascular abnormalities [9,10]. This complexity partly explains the variability in therapeutic response observed in clinical practice and highlights the limitations of traditional classification systems. As a result, there has been growing interest in developing more sophisticated approaches for patient stratification and management.

Precision medicine has therefore emerged as an approach aimed at addressing this biological and clinical heterogeneity by tailoring diagnostic and therapeutic strategies to individual patient characteristics [8,11]. These approaches have been particularly informative in HFpEF, a condition characterized by marked heterogeneity and limited therapeutic options [8,12–14].

Despite these advances, vascular function remains insufficiently integrated into contemporary precision medicine frameworks in heart failure. Most current approaches prioritize myocardial structure, circulating biomarkers, and clinical variables, while the contribution of arterial properties is frequently overlooked [9,15]. Given the central role of ventricular–vascular interaction in determining cardiac performance, neglecting vascular function may result in incomplete characterization of heart failure phenotypes.

Arterial stiffness and pulse wave velocity represent key determinants of ventricular–vascular interaction and may contribute to the heterogeneity of heart failure phenotypes [16–18]. Pulse wave velocity (PWV) is widely regarded as the gold standard non-invasive method for assessing arterial stiffness [17]. Numerous studies have demonstrated that increased PWV is independently associated with cardiovascular events and all-cause mortality [17,19].

In the context of HF, growing evidence suggests that arterial stiffness and increased PWV contribute to disease pathophysiology, particularly in HFpEF, where vascular aging plays a central role [12,20,21].

Unlike previous reviews that primarily focus on myocardial dysfunction, circulating biomarkers, or isolated aspects of heart failure phenotyping [6,8,12], the present review provides an integrated perspective that systematically incorporates vascular function—particularly arterial stiffness and pulse wave velocity—into precision medicine frameworks. This review uniquely emphasizes the role of ventricular–vascular interaction

as a central pathophysiological mechanism linking myocardial performance with arterial load, thereby offering a more comprehensive understanding of heart failure heterogeneity. Furthermore, we highlight the translational potential of vascular markers in clinical practice, proposing their integration into multimodal phenotyping strategies that combine clinical, imaging, and computational approaches [20,22,23]. In this context, vascular function remains underrepresented in contemporary precision phenotyping strategies, and integrating pulse wave velocity into multimodal frameworks may improve risk stratification and support the development of individualized therapeutic strategies. A conceptual representation of these multidimensional mechanisms is presented in Figure 1.

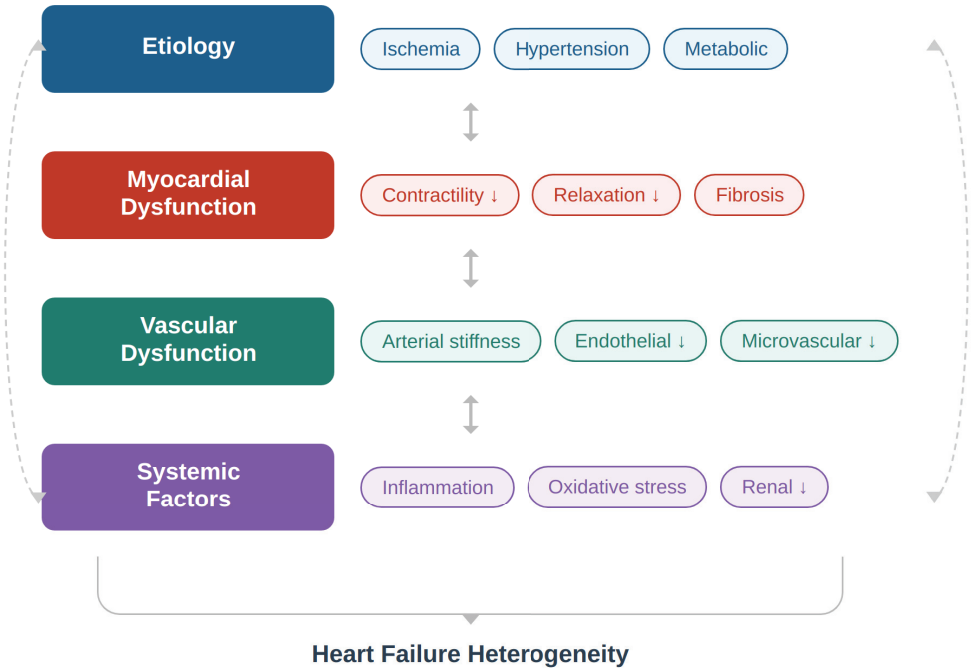


Figure 1. Determinants of heart failure heterogeneity. Heart failure heterogeneity arises from the complex interaction between etiological factors, myocardial dysfunction, vascular abnormalities, and systemic processes. These components interact bidirectionally and contribute to diverse clinical phenotypes through their combined effects on cardiovascular structure and function.

Vascular functional markers—particularly measures of arterial stiffness such as pulse wave velocity—are rarely incorporated into integrated phenotyping models, despite their fundamental role in ventricular–vascular interaction and cardiovascular performance [2–4,24]. This review examines the role of vascular function in precision phenotyping of heart failure, with particular emphasis on arterial stiffness and pulse wave velocity. The following sections are organized to minimize conceptual overlap: Section 2 addresses the precision medicine framework, Section 3 focuses on the pathophysiology of ventricular–vascular interaction, Sections 4 and 5 present clinical evidence and future directions, and Section 6 provides concluding perspectives. While mechanistic models of ventricular–vascular interaction have provided important physiological insights, their integration into precision phenotyping frameworks remains limited [2,6].

2. Precision Medicine in Heart Failure

2.1. Concept of Precision Medicine in Cardiovascular Disease

Precision medicine has emerged as a transformative paradigm in modern healthcare, aiming to tailor diagnostic and therapeutic strategies according to the biological and clinical characteristics of individual patients [11,22,25,26]. In contrast to traditional "one-size-fits-all" approaches, precision medicine integrates multiple sources of information—including

clinical data, imaging findings, circulating biomarkers, genetic information, and environmental factors—to better characterize disease heterogeneity and guide individualized treatment strategies [22,25,27,28].

In cardiovascular medicine, the application of precision medicine has gained increasing attention, particularly in complex syndromes such as heart failure. HF represents a prototypical heterogeneous condition in which diverse etiological pathways converge toward a common clinical phenotype characterized by impaired cardiac function and reduced systemic perfusion [6,8,28]. This heterogeneity is reflected in differences in disease mechanisms, comorbidity profiles, hemodynamic characteristics, and therapeutic response among patients classified within the same clinical category [8,9].

Traditional HF management strategies have largely relied on guideline-directed medical therapy derived from large randomized clinical trials [6,7,29]. While these therapies have significantly improved outcomes in certain patient populations, particularly those with HFrEF, their benefits remain variable across the broader spectrum of HF phenotypes. In addition, many therapeutic interventions have demonstrated limited efficacy in conditions such as HFpEF, where underlying mechanisms are multifactorial and incompletely understood [6,12,21].

Precision medicine, therefore, seeks to refine patient stratification beyond conventional clinical parameters, enabling a more accurate identification of biologically meaningful subgroups of HF patients who may benefit from targeted therapeutic approaches [23,29,30].

2.2. Phenotyping of Heart Failure Patients

A central component of precision medicine in HF is the identification of disease phenotypes through advanced analytical methods. Phenotyping refers to the systematic classification of patients into subgroups based on shared biological, clinical, or pathophysiological characteristics [23,31,32].

Conventional phenotyping in HF has historically relied on clinical parameters such as LVEF, New York Heart Association (NYHA) functional class, and the presence of structural heart disease [6]. However, these variables provide only a limited representation of the complex biological processes involved in HF pathogenesis [8,33].

Recent advances in computational medicine have facilitated the development of data-driven phenotyping approaches that incorporate large multidimensional datasets. Techniques such as cluster analysis, machine learning algorithms, and unsupervised learning models allow researchers to identify patient subgroups based on patterns within clinical, biochemical, and imaging data [8,31,34,35].

One of the most influential studies in this field was conducted by Shah et al., who applied a phenomapping approach using unsupervised machine learning to identify distinct HFpEF phenotypes characterized by different clinical profiles, biomarker patterns, and outcomes [8]. These analyses revealed that HFpEF is not a single disease entity but rather a spectrum of biologically distinct phenotypes, each potentially requiring different therapeutic strategies.

Subsequent studies have confirmed that data-driven phenotyping approaches can improve risk stratification and may facilitate the identification of novel therapeutic targets [31,36]. Importantly, these approaches emphasize the need for integrative models that incorporate information from multiple physiological systems rather than focusing exclusively on myocardial function [17].

The identification of clinically meaningful heart failure phenotypes requires the integration of multiple sources of information, including clinical characteristics, circulating biomarkers, advanced cardiac imaging, and vascular function markers [23,30,35]. Recent developments in computational medicine and machine learning have further facilitated

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the identification of distinct patient clusters with different pathophysiological mechanisms and prognostic profiles [31,34,36]. A representative example of data-driven phenotyping in heart failure is provided by the phenomapping approach introduced by Shah et al. [8], which applied unsupervised machine learning techniques to identify distinct HFpEF subgroups. In this framework, multidimensional datasets—including clinical variables, imaging parameters, and circulating biomarkers—are integrated and analyzed using clustering algorithms to uncover latent patient phenotypes that are not apparent through conventional classification systems. Conceptually, this approach follows a stepwise process: first, comprehensive data acquisition across multiple domains; second, dimensionality reduction and pattern recognition using computational methods; and third, identification of phenotypic clusters with distinct pathophysiological profiles and clinical outcomes. Such models have demonstrated that HFpEF represents a heterogeneous syndrome composed of biologically distinct subgroups rather than a single disease entity [8,27]. Importantly, most existing phenomapping studies have focused predominantly on myocardial and systemic parameters, while vascular functional markers such as arterial stiffness and pulse wave velocity remain underrepresented. Integrating these variables into machine learning frameworks may further refine phenotypic classification and improve the identification of vascular-driven heart failure subtypes [8,31]. The principal domains contributing to precision medicine-based phenotyping in heart failure, along with their pathophysiological relevance, clinical utility, and methodological approaches, are summarized in Table 1.

Table 1. Core domains in precision medicine-based phenotyping of heart failure.

Domain	Representative Variables	Pathophysiological Contribution	Clinical Utility	Methodological Approach
Clinical profiling	Age, sex, HF etiology, comorbidities (hypertension, diabetes, and obesity), and NYHA class	Reflects patient-level heterogeneity and cumulative disease burden	Baseline characterization, risk stratification, and identification of clinical phenotypes	Clinical assessment and registry-based data
Circulating biomarkers	BNP, NT-proBNP, cardiac troponins, galectin-3, and soluble ST2	Reflect myocardial stress, injury, fibrosis, and inflammation	Diagnostic support, prognostic stratification, and therapy monitoring	Laboratory assays and biomarker panels
Cardiac imaging	Echocardiography (LVEF, diastolic parameters, and global longitudinal strain), cardiac MRI, and cardiac computed tomography (functional CT, late iodine enhancement, and extracellular volume quantification)	Characterizes myocardial structure, function, and tissue remodeling	Phenotype definition, detection of subclinical dysfunction, and guiding therapy	Imaging-based quantitative assessment (echocardiography, CMR, and cardiac CT)
Computational phenotyping	Cluster analysis, machine learning, and phenomapping approaches	Identifies latent patient clusters based on multidimensional data integration	Discovery of novel HF phenotypes and prognostic subgroups	Unsupervised learning and data-driven modeling
Vascular functional markers	Pulse wave velocity, arterial stiffness indices, and wave reflection parameters	Reflect arterial load, vascular aging, and ventricular–vascular interaction	Complements myocardial assessment and enhances phenotypic resolution	Non-invasive vascular assessment (cfPWV and oscillometric methods)

Legend: HF, heart failure.

Precision medicine approaches in heart failure integrate multiple biological and clinical domains, including patient characteristics, circulating biomarkers, cardiac imaging,

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computational phenotyping methods, and vascular functional markers, as summarized in Table 1 [23,30,35]. The combination of these complementary data sources enables improved characterization of disease heterogeneity and supports the identification of mechanistically distinct heart failure phenotypes [8,31,36,37].

2.3. Multimodal Approaches to Precision Medicine

The practical implementation of precision medicine in HF relies on the integration of several complementary diagnostic domains [23,30].

2.3.1. Clinical Profiling

Clinical variables remain fundamental components of HF phenotyping. Factors such as age, sex, etiology of cardiomyopathy, comorbidities, and functional capacity contribute significantly to disease expression and prognosis [6,8]. For example, HFpEF frequently occurs in older individuals with multiple comorbidities, including hypertension, obesity, diabetes mellitus, and chronic kidney disease [12–14,38].

2.3.2. Biomarkers

Circulating biomarkers provide valuable information regarding underlying biological processes in HF. Natriuretic peptides, including B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), remain the most widely used biomarkers for diagnosis and risk stratification [39]. In addition, emerging biomarkers reflecting myocardial injury, fibrosis, inflammation, and metabolic dysregulation are increasingly incorporated into multimodal risk prediction models [17].

2.3.3. Cardiovascular Imaging

Advanced imaging techniques play a crucial role in precision medicine approaches. Echocardiography remains the cornerstone of HF evaluation, allowing detailed assessment of cardiac structure and function [6]. Novel echocardiographic techniques, such as myocardial strain analysis, provide insights into subclinical myocardial dysfunction [16].

Cardiac magnetic resonance imaging (CMR) offers additional information regarding myocardial tissue characterization, including the detection of fibrosis, inflammation, or infiltrative disease. These imaging modalities contribute to more refined phenotypic classification and may guide individualized treatment decisions [16,18].

Cardiac computed tomography (CT) has also emerged as a valuable complementary imaging modality in heart failure evaluation. Recent advances in functional and quantitative CT imaging—including late iodine enhancement and extracellular volume quantification—now allow myocardial tissue characterization comparable to CMR. Importantly, cardiac CT offers a viable alternative for patients who cannot undergo CMR due to the presence of non-MRI-conditional cardiac devices or claustrophobia, thereby broadening the applicability of advanced tissue characterization in clinical practice [34,40,41].

In addition to echocardiography and cardiac magnetic resonance, computed tomography has emerged as a valuable imaging modality for myocardial tissue characterization, enabling assessment of extracellular volume and late iodine enhancement [8,23,42]. This is particularly relevant in patients with contraindications to cardiac magnetic resonance imaging.

2.4. Limitations of Current Precision Approaches

Despite substantial progress in HF phenotyping, current precision medicine models remain incomplete. Most contemporary approaches emphasize myocardial structure and function, while relatively little attention has been given to the role of the arterial system [31,43–45].

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However, cardiovascular performance depends not only on myocardial contractility but also on the mechanical properties of the arterial system. The interaction between the heart and the vascular system plays a critical role in determining ventricular loading conditions, cardiac efficiency, and overall circulatory performance [39].

Failure to account for vascular function may therefore limit the ability of existing phenotyping models to fully capture the pathophysiological complexity of HF.

2.5. The Emerging Role of the Vascular System

Increasing evidence suggests that vascular dysfunction represents a key component of HF pathophysiology [10,17,45]. Alterations in arterial properties may influence ventricular loading conditions, myocardial energy expenditure, and overall cardiovascular efficiency.

The concept of ventricular–vascular coupling describes the dynamic interaction between left ventricular contractility and arterial load [39]. Optimal cardiovascular performance requires a balanced relationship between these two components. Disruption of this balance may lead to impaired hemodynamic efficiency and contribute to the development and progression of HF.

Arterial stiffness, a hallmark of vascular aging, is increasingly recognized as an important determinant of cardiovascular outcomes [17,19]. Structural changes within the arterial wall—including elastin degradation, collagen accumulation, and vascular calcification—result in reduced arterial compliance and increased pulse pressure [17].

These vascular alterations may significantly influence cardiac workload and contribute to ventricular remodeling. Consequently, incorporating vascular parameters into HF phenotyping frameworks may enhance the ability to identify clinically meaningful subgroups of patients [17].

2.6. Toward Integrated Cardiovascular Phenotyping

Future precision medicine strategies in HF are likely to rely on integrated models that combine myocardial, vascular, and systemic parameters [23,30]. Such multimodal approaches may improve patient stratification, facilitate earlier detection of disease progression, and support the development of individualized therapeutic strategies [31,43].

In this context, the assessment of arterial stiffness and pulse wave velocity has emerged as a promising tool for evaluating vascular function and its contribution to HF pathophysiology. PWV provides a direct measure of arterial stiffness and reflects the mechanical properties of the arterial system [17,19].

Integrating vascular markers such as PWV into phenotyping algorithms may therefore represent an important step toward a more comprehensive understanding of HF heterogeneity and the implementation of truly personalized cardiovascular care [43,46].

The transition from traditional heart failure classification toward precision medicine requires the integration of multiple biological domains, including myocardial, vascular, and systemic factors. In this context, arterial stiffness and pulse wave velocity may represent key components of an integrated phenotyping framework [44,47]. The conceptual model proposed in this review illustrates how vascular parameters may be incorporated into multidimensional patient characterization and personalized management strategies [Figure 2].

Multidimensional patient characterization integrates clinical features, circulating biomarkers, cardiac imaging, vascular function, and computational phenotyping approaches. Pulse wave velocity (PWV) serves as a key marker of arterial stiffness, linking vascular load to ventricular–vascular coupling and enabling improved risk stratification, phenotyping, and personalized management.

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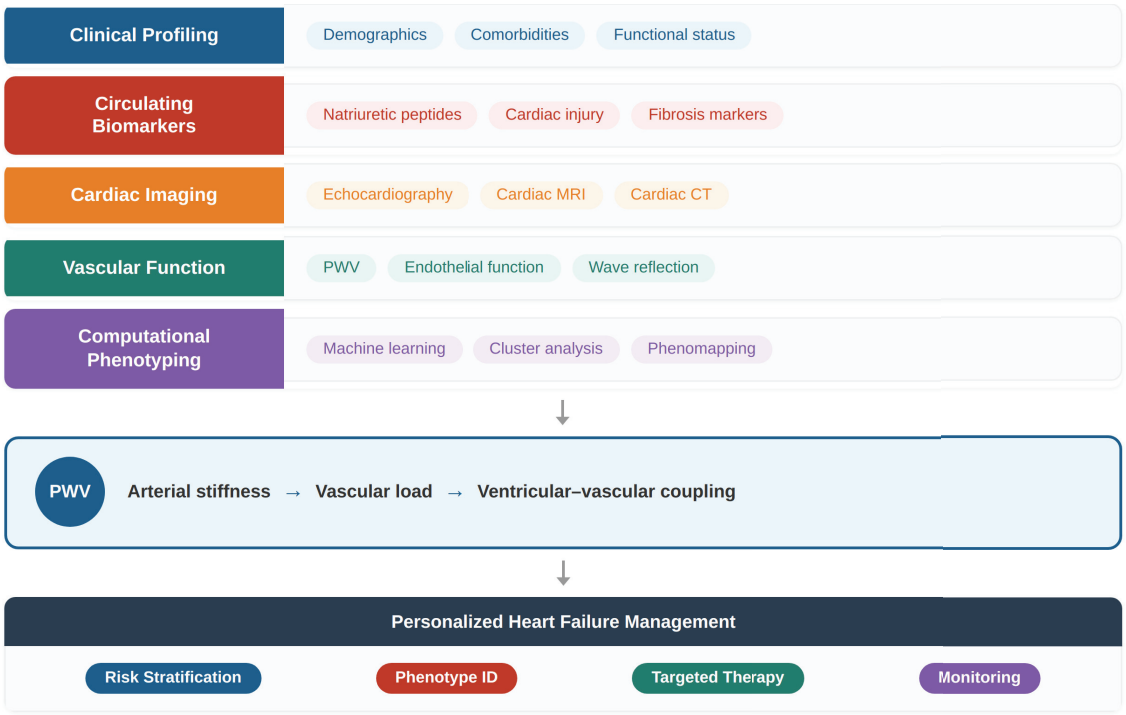


Figure 2. Integrated precision medicine framework in heart failure.

3. Ventricular–Vascular Interaction and Arterial Stiffness

3.1. Physiological Basis of Ventricular–Vascular Coupling

The cardiovascular system functions as an integrated hemodynamic unit in which the heart and the arterial system operate in close physiological interaction. The concept of ventricular–vascular coupling describes the dynamic relationship between left ventricular contractility and arterial load, two components that together determine overall cardiovascular performance [34,46,47].

From a hemodynamic perspective, ventricular–vascular coupling can be described by the relationship between ventricular elastance (Ees), which reflects myocardial contractile properties, and arterial elastance (Ea), which represents the effective arterial load imposed on the ventricle [34]. Optimal cardiovascular efficiency occurs when these two parameters are balanced, allowing the heart to generate adequate stroke volume while minimizing myocardial energy expenditure [47].

Under physiological conditions, the elastic properties of the large arteries play a crucial role in modulating the pulsatile nature of blood flow. During systole, the aorta and proximal elastic arteries expand in response to ventricular ejection, storing part of the stroke volume and mechanical energy. During diastole, the recoil of these arteries maintains forward blood flow and contributes to coronary perfusion. This buffering function of the arterial system, commonly referred to as the Windkessel effect, helps maintain stable hemodynamic conditions across the cardiac cycle [39].

However, alterations in arterial properties can disrupt this delicate balance between ventricular function and vascular load. Increased arterial stiffness leads to a rise in arterial elastance, thereby increasing the hemodynamic burden imposed on the left ventricle [17,47]. As a result, the ventricle must generate higher systolic pressures to maintain cardiac output, which may contribute to myocardial hypertrophy, increased oxygen demand, and progressive ventricular dysfunction.

The interaction between left ventricular contractility and arterial load plays a fundamental role in determining cardiovascular performance. Structural alterations of the

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arterial wall increase arterial stiffness and accelerate the propagation of the pressure wave along the arterial tree. This leads to an earlier return of reflected waves during systole, resulting in increased central systolic pressure and augmented ventricular afterload [17,48]. These mechanisms contribute to impaired ventricular–vascular coupling and progressive myocardial dysfunction. The physiological relationship between ventricular function, arterial stiffness, and pulse wave velocity is illustrated in Figure 3.

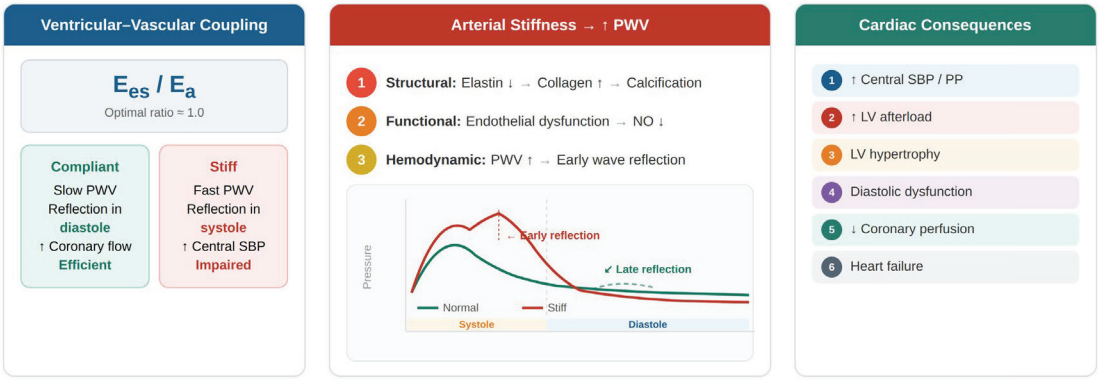


Figure 3. Ventricular–vascular coupling and the impact of arterial stiffness.

Ventricular–vascular coupling reflects the interaction between ventricular contractility and arterial load, commonly expressed as the ratio between ventricular and arterial elastance (Ees/Ea). Increased arterial stiffness, reflected by elevated PWV, leads to earlier wave reflection and increased systolic load, impairing coupling efficiency and contributing to adverse cardiac outcomes.

3.2. Pathophysiology of Arterial Stiffness

Arterial stiffness reflects structural and functional alterations of the arterial wall that occur as a consequence of aging and exposure to cardiovascular risk factors [17,48–50]. These changes are primarily driven by progressive degeneration of elastin fibers, increased collagen deposition, vascular smooth muscle cell remodeling, and the development of medial calcification [43,48,49,51,52].

Arterial stiffness has emerged as a key determinant of ventricular–vascular interaction and represents an important contributor to the pathophysiology and progression of heart failure [17,47,53]. Structural and functional alterations of the arterial wall—including elastin fragmentation, collagen accumulation, vascular calcification, and endothelial dysfunction—lead to reduced arterial compliance and increased pulse wave velocity [14,25]. The earlier return of reflected waves augments central systolic pressure and increases left ventricular afterload, thereby promoting myocardial hypertrophy, impaired ventricular relaxation, and progressive cardiac remodeling [47,48,54]. Over time, these hemodynamic and structural alterations contribute to the development and clinical progression of heart failure phenotypes [10,19]. The principal mechanisms linking arterial stiffness to ventricular dysfunction and heart failure development are summarized in Figure 4.

Structural and functional alterations of the arterial wall increase arterial stiffness and pulse wave velocity, leading to abnormal wave reflections and increased afterload. These hemodynamic changes promote left ventricular hypertrophy, diastolic dysfunction, and myocardial fibrosis, ultimately contributing to the development of heart failure phenotypes.

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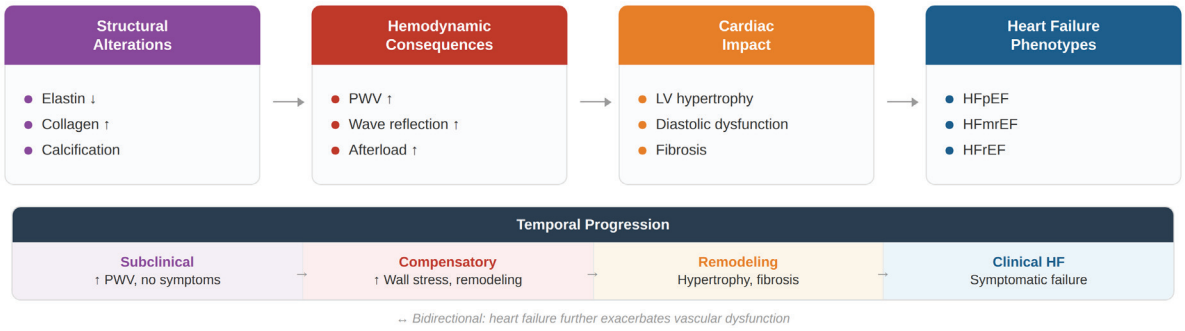


Figure 4. Pathophysiological mechanisms linking arterial stiffness to cardiac dysfunction.

At the molecular level, several mechanisms contribute to vascular stiffening. Chronic inflammation and oxidative stress promote extracellular matrix remodeling within the arterial wall [51]. Activation of matrix metalloproteinases accelerates elastin degradation, while increased collagen synthesis leads to reduced vascular compliance [43,51]. In addition, endothelial dysfunction impairs nitric oxide bioavailability, further compromising the elastic properties of the arterial system [47].

These structural changes translate into important hemodynamic consequences. One of the most relevant effects of arterial stiffness is the accelerated propagation of the pressure wave generated during ventricular ejection [17,48,53]. In compliant arteries, the pressure wave travels relatively slowly, and reflected waves return to the aorta during diastole, contributing to coronary perfusion, whereas in stiff arteries, the pressure wave travels more rapidly, causing reflected waves to return earlier during systole [48,54].

The premature return of reflected waves increases central systolic blood pressure and pulse pressure, thereby augmenting left ventricular afterload. This phenomenon results in increased myocardial wall stress and contributes to ventricular hypertrophy, impaired diastolic relaxation, and progressive cardiac dysfunction [47,48].

3.3. Arterial Stiffness as a Determinant of Cardiac Remodeling

Growing evidence indicates that arterial stiffness plays a significant role in cardiac remodeling and heart failure progression. Increased pulsatile load imposed on the left ventricle contributes to structural changes in the myocardium, including hypertrophy, fibrosis, and alterations in ventricular geometry [19,48].

Experimental and clinical studies have demonstrated that increased arterial stiffness is associated with left ventricular hypertrophy and impaired diastolic function. These alterations may occur even in the absence of overt myocardial disease, highlighting the importance of vascular factors in cardiac remodeling [19,25].

The relationship between arterial stiffness and cardiac function is particularly relevant in the context of HFpEF. In this condition, patients frequently exhibit a phenotype characterized by advanced vascular aging, systemic hypertension, and increased arterial stiffness [50].

Moreover, increased pulsatile hemodynamic load may impair coronary microvascular perfusion, thereby contributing to myocardial ischemia and fibrosis. These processes further exacerbate ventricular stiffness and promote the development of heart failure symptoms [48,54].

3.4. Clinical Evidence Linking Arterial Stiffness and Heart Failure

Several clinical studies have demonstrated a strong association between arterial stiffness and adverse cardiovascular outcomes. Large observational studies have shown that increased arterial stiffness is an independent predictor of cardiovascular events, including myocardial infarction, stroke, and cardiovascular mortality [10,19].

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In the context of heart failure, arterial stiffness has been associated with disease severity, exercise intolerance, and poor prognosis [40,55].

Importantly, the relationship between arterial stiffness and HF appears to be bidirectional. While vascular stiffening contributes to increased ventricular afterload and cardiac dysfunction, heart failure itself may further exacerbate vascular abnormalities through neurohormonal activation, inflammation, and endothelial dysfunction [47,48].

This complex interaction between myocardial and vascular factors highlights the need for integrated approaches to HF phenotyping that account for both cardiac and vascular components of the disease [12,25].

3.5. Implications for Precision Medicine

The recognition of arterial stiffness as an important determinant of cardiovascular function has significant implications for precision medicine in HF [23,30]. Incorporating vascular parameters into HF phenotyping models may help identify patient subgroups characterized by specific hemodynamic profiles.

For example, patients with HFpEF and pronounced vascular stiffness may represent a distinct phenotype driven primarily by abnormalities in ventricular–vascular coupling [9,25].

Furthermore, the assessment of arterial stiffness may provide additional prognostic information beyond traditional risk markers [19,55]. Integrating vascular parameters into multimodal diagnostic frameworks that include imaging, biomarkers, and clinical variables could improve risk stratification and support individualized patient management [12,14].

In this context, noninvasive measures of arterial stiffness—particularly pulse wave velocity—have emerged as promising tools for evaluating vascular function and its contribution to HF pathophysiology [17,19].

3.6. Limitations and Controversies

Despite the growing body of evidence supporting the role of arterial stiffness and pulse wave velocity in heart failure, several important limitations and unresolved controversies should be acknowledged [47,56–60].

First, substantial methodological heterogeneity exists across studies evaluating arterial stiffness, including differences in measurement techniques (e.g., carotid–femoral versus brachial–ankle pulse wave velocity), device calibration, and path length estimation. These variations limit comparability between studies and may affect the reproducibility of findings [17,48,55,61].

Second, the causal relationship between arterial stiffness and heart failure remains incompletely understood. While increased arterial stiffness contributes to elevated afterload and ventricular remodeling, heart failure itself may further exacerbate vascular dysfunction through neurohormonal activation and systemic inflammation, making it difficult to disentangle cause and consequence [9,43,57].

Third, the prognostic value of pulse wave velocity may vary across heart failure phenotypes. Although several studies suggest a stronger association in HFpEF, data in HFrEF remain less consistent, and the incremental value of PWV beyond established biomarkers and imaging parameters is still under investigation [47,56,57,59,60].

Finally, most available evidence derives from observational studies, and there is a lack of large-scale prospective and interventional trials evaluating whether targeting vascular stiffness can improve clinical outcomes [59,62]. Addressing these limitations will be essential for the integration of vascular parameters into precision medicine frameworks and for establishing their role in routine clinical practice.

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4. Pulse Wave Velocity in Clinical Practice

4.1. Methods for Measuring Pulse Wave Velocity

Several techniques have been developed for the non-invasive assessment of PWV, with carotid–femoral pulse wave velocity (cfPWV) currently considered the gold standard for evaluating central arterial stiffness [17,61,63].

The cfPWV measurement reflects the stiffness of the thoracic and abdominal aorta, which are the major elastic arteries responsible for buffering pulsatile blood flow [25,43]. The measurement is typically performed by recording pulse waveforms simultaneously or sequentially at the carotid and femoral arteries using applanation tonometry, mechanotransducers, or oscillometric devices [51]. The time delay between the arrival of the pulse wave at these two sites is calculated and divided by the estimated arterial path length.

Consensus recommendations emphasize the importance of standardized measurement protocols in order to improve reproducibility and comparability between studies [51,61]. Factors such as patient positioning, blood pressure stabilization, and accurate measurement of the arterial path length are essential for reliable PWV assessment.

In addition to cfPWV, other PWV measurement techniques have been developed. Brachial–ankle PWV (baPWV) is widely used in large epidemiological studies, particularly in Asian populations [43]. Although baPWV is easier to measure, it reflects both central and peripheral arterial stiffness and therefore provides less specific information regarding aortic elasticity.

Recent technological developments have also led to the emergence of oscillometric devices capable of estimating PWV using single cuff measurements [49,54,61]. These devices are increasingly used in clinical settings due to their simplicity and operator independence, although their accuracy compared with tonometric methods remains an area of ongoing investigation.

4.2. Prognostic Significance of Pulse Wave Velocity

Over the past two decades, numerous prospective studies have demonstrated that increased PWV is strongly associated with adverse cardiovascular outcomes. PWV has been shown to predict major cardiovascular events, including myocardial infarction, stroke, and cardiovascular mortality, independently of traditional risk factors [19,59,64,65].

Meta-analyses have demonstrated that each 1 m/s increase in PWV is associated with a significant increase in the risk of cardiovascular events and all-cause mortality [54,66]. This relationship highlights the importance of arterial stiffness as a marker of vascular aging and cardiovascular risk.

The prognostic value of PWV extends beyond traditional cardiovascular disease populations. Elevated PWV has been observed in patients with hypertension, chronic kidney disease, diabetes mellitus, and metabolic syndrome, all of which are conditions associated with accelerated vascular aging [17,19,67].

In addition, PWV has been increasingly recognized as an important indicator of subclinical organ damage. Increased arterial stiffness contributes to microvascular injury in several organs, including the heart, brain, and kidneys [54,66]. As a result, PWV measurement may provide valuable insights into the systemic consequences of vascular dysfunction.

4.3. Pulse Wave Velocity in Heart Failure

The role of arterial stiffness in heart failure has attracted increasing attention in recent years. Elevated PWV values have been reported in patients across the HF spectrum, including both HFrEF and HFpEF populations [40,41].

In HFrEF, increased arterial stiffness may contribute to impaired ventricular ejection by increasing afterload and altering ventricular–vascular coupling [26]. Elevated arterial

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elastance increases myocardial workload and may exacerbate ventricular dysfunction, particularly in patients with already compromised systolic function.

In HFpEF, the contribution of arterial stiffness appears to be even more prominent. Patients with HFpEF often exhibit a phenotype characterized by advanced vascular aging, systemic hypertension, and increased arterial stiffness [9,18,25]. These vascular abnormalities contribute to increased pulsatile load, impaired ventricular relaxation, and elevated left ventricular filling pressures.

Furthermore, the early return of reflected waves in stiff arteries increases central systolic pressure and reduces diastolic pressure, potentially compromising coronary perfusion [48,54]. These hemodynamic alterations may promote myocardial ischemia, interstitial fibrosis, and progressive ventricular stiffening.

Clinical studies have shown that increased PWV in HF patients is associated with worse functional status, reduced exercise capacity, and increased risk of hospitalization and mortality [3,40]. These findings suggest that PWV may serve as a valuable marker of disease severity and prognosis in HF.

Several observational and cohort studies have investigated the prognostic role of pulse wave velocity in patients with heart failure. These studies consistently demonstrate that increased arterial stiffness is associated with adverse cardiovascular outcomes, impaired ventricular–vascular coupling, and increased mortality risk [40,41,64,68]. A structured overview of representative studies evaluating arterial stiffness and pulse wave velocity in heart failure, including study design and methodological approach, is presented in Table 2.

Table 2. Representative clinical studies evaluating pulse wave velocity and arterial stiffness in heart failure.

Study	Population	Study Design	PWV Assessment	Main Focus	Principal Findings	Clinical Relevance
Weber et al. [54]	Patients with chronic heart failure	Observational cohort study	cfPWV/arterial stiffness indices	Prognostic significance of arterial stiffness	Increased arterial stiffness, associated with impaired hemodynamics and worse clinical status	Supports role of PWV as marker of disease severity
Chirinos et al. [47]	Patients with HFpEF and abnormal ventricular–vascular coupling	Mechanistic observational study	cfPWV and wave reflection indices	Ventricular–vascular interaction	Increased arterial stiffness, associated with impaired coupling and adverse hemodynamics	Highlights vascular contribution in HFpEF
Pandey et al. [60]	Community-based population	Prospective cohort study	PWV	Association with incident HF	Higher PWV, associated with increased risk of incident HF	Identifies PWV as early risk marker

Table 2. *Cont.*

Study	Population	Study Design	PWV Assessment	Main Focus	Principal Findings	Clinical Relevance
Shah et al. [8]	HFpEF phenotyping cohorts	Machine learning/ phenomapping study	Multimodal [including vascular parameters]	Data-driven HF phenotyping	Identification of distinct HF phenotypes with different clinical trajectories	Supports integration of vascular markers in phenotyping
Vlachopoulos et al. [19]	Cardiovascular populations	Systematic review and meta-analysis	PWV	Prognostic value of arterial stiffness	Each 1 m/s increase in PWV, associated with increased CV events and mortality	Strong evidence for prognostic role of PWV
Laurent et al. [17]	Vascular research consensus	Expert consensus document	cfPWV	Methodological standardization	cfPWV established as gold standard for arterial stiffness	Provides methodological framework

Abbreviations: PWV, pulse wave velocity; HF, heart failure.

4.4. Integrating PWV into Precision Medicine

Despite the growing evidence supporting the role of PWV in cardiovascular risk assessment, its integration into precision medicine frameworks for HF remains limited [23,30].

Most current HF phenotyping strategies focus on myocardial structure, biomarkers, and clinical characteristics, while vascular parameters are less frequently included in risk stratification models [18,25]. However, given the central role of ventricular–vascular interaction in cardiovascular physiology, neglecting vascular function may result in incomplete characterization of the disease [17].

Incorporating PWV into HF phenotyping models could provide several advantages. First, PWV offers a direct and quantitative measure of arterial load, which may help identify patients with a predominantly vascular phenotype of HF. Second, PWV measurement may improve risk stratification by identifying patients at higher risk of adverse outcomes. Third, PWV could potentially serve as a marker for monitoring therapeutic interventions aimed at improving vascular function [3].

Future research should explore the integration of PWV with multimodal datasets that include imaging parameters, circulating biomarkers, and computational phenotyping approaches [23,31,34,36]. Such integrative models may allow the identification of novel HF phenotypes and support the development of more personalized therapeutic strategies.

5. Future Directions and Clinical Implications

5.1. Beyond Myocardial Dysfunction: A Systemic Perspective

Heart failure should increasingly be conceptualized as a systemic cardiovascular syndrome rather than an isolated myocardial disorder. While traditional paradigms have focused predominantly on ventricular dysfunction, accumulating evidence supports the critical contribution of vascular and systemic factors in shaping disease expression and progression [9,10,17,48].

Within this framework, arterial stiffness emerges as a central integrative marker reflecting the cumulative effects of aging, cardiometabolic burden, and vascular remod-

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eling [17,49]. Incorporating vascular parameters into precision phenotyping models is therefore likely to improve the identification of mechanistically distinct patient subgroups and facilitate the development of targeted therapeutic strategies [23,30].

Within this integrative framework, the arterial system emerges as a critical determinant of cardiovascular performance. The mechanical properties of the arterial tree influence ventricular loading conditions, myocardial energy expenditure, and overall circulatory efficiency [17,43]. Consequently, vascular dysfunction may represent not only a consequence of cardiovascular disease but also an active driver of HF progression [47,48].

This paradigm shift has important implications for precision medicine strategies in HF. Traditional phenotyping approaches have focused predominantly on myocardial parameters such as LVEF, ventricular geometry, and biomarkers of myocardial injury or stress. However, these variables alone cannot fully capture the systemic nature of HF pathophysiology [9].

Integrating vascular parameters into HF phenotyping models may therefore provide a more comprehensive representation of disease mechanisms and allow identification of previously unrecognized phenotypes driven by vascular dysfunction [23,30].

5.2. Computational Integration of Multidomain Data

Future progress in precision medicine is likely to depend on computationally enabled integration of multidomain datasets rather than isolated use of conventional clinical descriptors [23,31,34,36]. Clinical variables, biomarkers, advanced imaging, vascular markers, and emerging omics data can be combined to identify mechanistically coherent patient clusters and support a transition from descriptive classification toward mechanism-based disease taxonomy [31,36].

A conceptual framework illustrating the integration of vascular functional markers—particularly pulse wave velocity—into multidimensional precision phenotyping of heart failure is presented in Figure 5 [23,44].

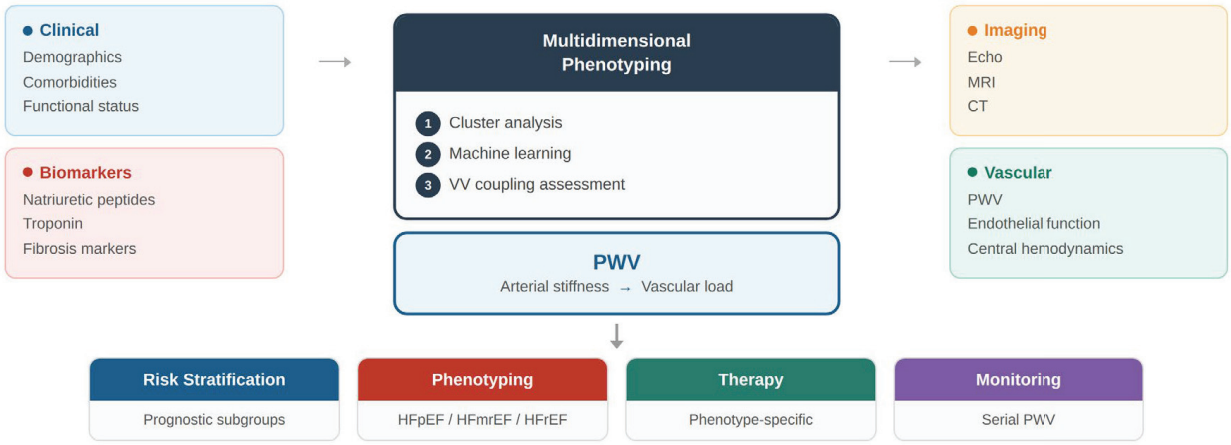


Figure 5. Multidimensional phenotyping and clinical integration of PWV in heart failure.

Integrated phenotyping combines clinical data, biomarkers, imaging, and vascular assessment with computational approaches to identify distinct heart failure phenotypes. PWV provides complementary information on arterial stiffness and vascular load, supporting risk stratification, phenotype identification, targeted therapy, and longitudinal monitoring. Such integrative models may help bridge the gap between vascular physiology and precision cardiovascular medicine.

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Key data streams relevant to integrated cardiovascular phenotyping include the following:

- Clinical characteristics and comorbidities;
- Circulating biomarkers reflecting myocardial stress, inflammation, and fibrosis;
- Advanced cardiac imaging parameters;
- Genomic and proteomic information;
- Vascular function markers.

Combining these dimensions through advanced computational models may enable the identification of clinically meaningful patient clusters characterized by shared pathophysiological mechanisms [31,36].

Machine learning approaches have already demonstrated the potential to uncover previously unrecognized HF phenotypes with distinct clinical trajectories [8]. For example, unsupervised machine learning approaches such as phenomapping have been used to identify distinct HFpEF subgroups based on clinical, imaging, and biomarker data, enabling improved risk stratification and targeted therapeutic strategies [8,35,69]. However, most existing models still rely heavily on myocardial parameters and systemic biomarkers. Vascular parameters are rarely included despite their fundamental physiological role [10].

Incorporating markers of arterial stiffness—particularly PWV—into such models may significantly enhance phenotypic resolution [17,19].

Concrete steps toward clinical validation could include prospective multicenter cohort studies in which PWV and complementary vascular markers are collected alongside standard clinical, imaging, and biomarker data in broadly phenotyped heart failure populations. Unsupervised clustering algorithms could then be applied to identify vascular-dominant phenotypes, followed by external validation in independent registries. Furthermore, the development of interpretable machine learning models—such as gradient-boosted decision trees incorporating PWV alongside established predictors—could facilitate clinical adoption by providing transparent risk scores amenable to integration into electronic health record-based decision support tools.

Such integrated phenotyping frameworks could ultimately facilitate the transition from descriptive HF classifications toward mechanism-based disease taxonomy [23,31].

5.3. The Concept of a Vascular Phenotype of Heart Failure

One intriguing hypothesis emerging from recent research is the existence of a vascular-driven phenotype of HF, particularly within the HFpEF spectrum [9,12].

Patients with HFpEF frequently exhibit a constellation of features suggestive of accelerated vascular aging, including the following:

- Increased arterial stiffness;
- Systemic hypertension;
- Endothelial dysfunction;
- Microvascular rarefaction;
- Metabolic and inflammatory abnormalities [9,25].

These alterations contribute to increased pulsatile hemodynamic load and impaired ventricular relaxation [48]. In this context, the myocardium may be viewed not as the primary origin of disease but rather as the organ most vulnerable to chronic vascular stress.

This perspective raises the possibility that certain HF phenotypes may be driven primarily by vascular pathology rather than intrinsic myocardial dysfunction. If confirmed, such insights would have important therapeutic implications [12,22,39,70,71].

For example, therapies targeting vascular stiffness, endothelial function, or microvascular perfusion could potentially play a more prominent role in selected HF subgroups [23,30].

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5.4. Pulse Wave Velocity as a Tool for Risk Stratification and Monitoring

Beyond its role as a marker of arterial stiffness, PWV may also serve as a clinically useful tool for risk stratification and disease monitoring in HF.

Several characteristics make PWV particularly attractive in this context.

(a) Physiological relevance

PWV reflects the pulsatile component of arterial load, which directly influences ventricular work and myocardial oxygen demand [17,47].

(b) Prognostic value

Numerous studies have demonstrated that increased PWV independently predicts cardiovascular events and mortality [19,59,64].

(c) Non-invasive assessment

(d) PWV can be measured rapidly and non-invasively using widely available technologies [57,58,63]. In clinical practice, carotid–femoral PWV is typically obtained within less than five minutes using validated automated devices such as SphygmoCor (AtCor Medical) or Complior (Alam Medical), which record simultaneous or sequential pressure waveforms at two arterial sites, requiring minimal operator training and no patient preparation beyond a brief rest period. The algorithm of the SphygmoCor takes into account vascular remodeling.

Changes in PWV may reflect modifications in vascular structure and function over time [17,54].

These features suggest that PWV could potentially be incorporated into clinical algorithms aimed at identifying HF patients at increased risk of disease progression.

Moreover, serial assessment of PWV might provide insights into the vascular effects of therapeutic interventions. Several pharmacological agents used in HF—including renin–angiotensin system inhibitors, mineralocorticoid receptor antagonists, and sodium–glucose cotransporter-2 inhibitors—have been shown to influence vascular function and arterial stiffness [47,55,72].

Monitoring PWV could therefore help evaluate treatment response beyond conventional clinical endpoints.

From a practical standpoint, integration of PWV assessment into routine heart failure evaluation could follow a stepwise approach. In outpatient clinics, automated oscillometric devices allow PWV measurement to be performed alongside standard vital signs, requiring no specialized training. A pragmatic implementation model could include PWV assessment at initial HF diagnosis, at each major therapeutic adjustment, and at regular intervals during follow-up. Abnormal PWV values could trigger referral for comprehensive vascular evaluation and guide the selection of therapies known to improve arterial compliance, such as renin–angiotensin system inhibitors or SGLT2 inhibitors. Clinical decision support systems could incorporate PWV thresholds alongside established parameters to generate individualized risk profiles and treatment recommendations [51,54,61,73]. In addition, PWV assessment may be particularly informative in specific heart failure phenotypes. Patients with HFpEF and multiple cardiometabolic comorbidities, including hypertension, obesity, and diabetes, are more likely to exhibit a vascular-driven phenotype characterized by increased arterial stiffness and impaired ventricular–vascular coupling. In such cases, elevated PWV values may support a more aggressive approach to risk factor modification and therapeutic optimization, including stricter blood pressure control and the use of therapies with known vascular effects. Moreover, PWV may provide incremental prognostic information and contribute to more refined risk stratification beyond conventional clinical and imaging parameters [47,56,57,59,60].

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5.5. Future Research Directions

Despite the growing interest in vascular contributions to HF pathophysiology, several important questions remain unanswered.

Moreover, it should be acknowledged that existing evidence linking arterial stiffness to heart failure outcomes is not entirely consistent. Some studies have reported attenuated associations after adjustment for conventional cardiovascular risk factors, and the independent prognostic value of PWV beyond established markers such as natriuretic peptides remains debated. Methodological differences in PWV assessment—including variations in device type, measurement site, and path length estimation—further complicate cross-study comparisons and limit the generalizability of current findings. Additionally, the vascular phenotype concept in HFpEF, while compelling, has not yet been validated in prospective interventional studies targeting arterial stiffness as a modifiable therapeutic endpoint.

First, the precise role of arterial stiffness in the initiation and progression of HF remains incompletely understood. Longitudinal studies are needed to determine whether increased PWV represents merely a marker of cardiovascular risk or a causal contributor to disease development [19,54].

Second, the integration of vascular parameters into computational phenotyping models requires further investigation. Large-scale datasets combining clinical, imaging, biomarker, and vascular measurements will be necessary to fully explore the potential of integrated cardiovascular phenotyping [23,31,34,35].

Third, interventional studies are needed to evaluate whether therapeutic strategies targeting vascular stiffness can improve outcomes in specific HF phenotypes.

Advances in digital health technologies and wearable sensors may further facilitate continuous monitoring of vascular function and hemodynamic parameters, opening new avenues for personalized cardiovascular care [74].

5.6. Limitations of Current Evidence

Despite the growing body of evidence linking arterial stiffness with heart failure pathophysiology, several limitations should be acknowledged. First, most available data are derived from observational studies, which limits the ability to establish causal relationships between arterial stiffness and heart failure development or progression. Second, methodological heterogeneity in pulse wave velocity measurement techniques—including differences in devices, acquisition protocols, and path length estimation—may complicate comparisons across studies. Third, vascular parameters are still rarely incorporated into large-scale phenotyping studies and machine learning models, which limits the integration of arterial stiffness into current precision medicine frameworks. Future prospective studies integrating vascular, myocardial, and systemic parameters will be necessary to clarify the mechanistic role of arterial stiffness and its potential therapeutic implications in heart failure.

6. Conclusions

Heart failure represents a complex and heterogeneous syndrome that extends beyond myocardial dysfunction, encompassing dynamic interactions between cardiac, vascular, and systemic factors. The integration of vascular function into precision medicine frameworks offers an opportunity to refine phenotypic classification and improve mechanistic understanding of the disease.

Arterial stiffness, as assessed by pulse wave velocity, represents a robust and physiologically relevant marker of vascular aging and cardiovascular risk. Its incorporation into multimodal phenotyping strategies may enhance risk stratification and support the

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identification of clinically meaningful subgroups within the heterogeneous spectrum of heart failure.

Future research integrating myocardial, vascular, and systemic domains through advanced computational approaches is likely to redefine heart failure classification and pave the way toward truly personalized cardiovascular medicine.

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Abbreviations

The following abbreviations are used in this manuscript:

HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
PWV	pulse wave velocity
cfPWV	carotid–femoral pulse wave velocity
CMR	cardiac magnetic resonance

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Systematic Review

Effects of SGLT2 Inhibitors on Clinical Outcomes, Symptoms, Functional Capacity, and Cardiac Remodeling in Heart Failure: A Comprehensive Systematic Review and Multidomain Meta-Analysis of Randomized Trials

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Abstract

Background: SGLT2 inhibitors are key therapies in heart failure (HF), but their combined multidomain effects have not been analyzed together. **Methods**: We conducted a PROSPERO-registered (CRD420251235850) systematic review and meta-analysis of all randomized controlled trials (RCTs) comparing SGLT2i (dapagliflozin, empagliflozin, canagliflozin, sotagliflozin) with placebo in adults with HF, regardless of ejection fraction or diabetes status. We searched PubMed/MEDLINE, Embase, Cochrane CENTRAL, and Web of Science through 1 February 2025. Outcomes were grouped into four domains: (1) clinical events, (2) symptoms/health status (Kansas City Cardiomyopathy Questionnaire, KCCQ), (3) functional capacity (6 min walk distance, peak VO_2), and (4) cardiac remodeling/energetics (cardiac MRI, 31P-MRS). We used random-effects models with Hartung–Knapp adjustment and assessed heterogeneity by I^2 and prediction intervals. **Results**: Eleven RCTs with 23,812 patients (HFrEF, HFmrEF, HFpEF, and acute or recently decompensated HF) were included. SGLT2i lowered the risk of cardiovascular death or first HF hospitalization by 23% (HR 0.77, 95% CI 0.72–0.82; $p < 0.0001$; $I^2 = 28\%$; prediction interval 0.68–0.87), with similar effects across ejection fraction, diabetes status, and presentation type. All-cause and cardiovascular mortality dropped by 12% (HR 0.88, 95% CI 0.81–0.96) and 14% (HR 0.86, 95% CI 0.78–0.95), respectively. SGLT2i improved KCCQ—Clinical Summary Score by 4.6 points (95% CI 3.4–5.8; $p < 0.0001$) and increased the odds of a $\geq$5-point

improvement (OR 1.49, 95% CI 1.32–1.68; NNT = 12). Six-minute walk distance increased by 21.8 m (95% CI 9.4–34.2; $p = 0.001$), and mechanistic trials showed significant reverse remodeling (ΔLVEDV −19.8 mL, ΔLVEF +6.1%; both $p < 0.001$). No improvement was observed in myocardial PCr/ATP ratio. Safety was favorable, with no excess ketoacidosis or severe hypoglycemia. **Conclusions**: This multidomain synthesis demonstrates that SGLT2 inhibitors provide consistent, robust reductions in mortality and hospitalizations, while also delivering early, clinically meaningful improvements across multiple patient-centered domains. These results establish SGLT2i as a foundational component of contemporary HF management.

Keywords: reverse remodeling; functional capacity; heart failure; health-related quality of life; Kansas City Cardiomyopathy Questionnaire; meta-analysis; multidomain analysis; six-minute walk test; SGLT2 inhibitors; systematic review

1. Introduction

Heart failure (HF) remains a significant public health issue, affecting about 64 million people worldwide in 2024. Projections estimate over 74 million cases by 2050, driven by an aging population and improved survival after myocardial infarction [1,2]. Despite advances in pharmacologic and device-based therapies, HF patients continue to face high rates of cardiovascular death, recurrent hospitalizations, impaired functional capacity, and reduced quality of life [3,4]. The clinical and biological diversity of HF, including reduced (HFrEF), mildly reduced (HFmrEF), and preserved ejection fraction (HFpEF) phenotypes, complicates risk stratification and management. This highlights the need for therapies that offer multidimensional benefits across the HF spectrum [5,6].

Sodium–glucose cotransporter-2 inhibitors (SGLT2i) have become a transformative class in cardiovascular medicine. Initially developed for glycemic control in type 2 diabetes, SGLT2i have shown strong cardioprotective and renoprotective effects independent of glycemic status [7,8]. Evidence indicates that SGLT2i provide multiple benefits, including natriuresis, reduced fluid overload, improved renal hemodynamics, decreased inflammation, and enhanced myocardial energetics [7–10]. As a result, international guidelines now recommend SGLT2i as foundational therapy for HF, regardless of ejection fraction or diabetes status [4,9]. Beyond prognostic benefits, SGLT2i have been shown to reduce symptom burden, improve patient-reported health status, enhance functional performance, and support cardiac remodeling. Trials using patient-centered outcomes, such as the Kansas City Cardiomyopathy Questionnaire (KCCQ), six-minute walk distance (6MWD), peak oxygen consumption (VO_2 peak), and daily activity levels, demonstrate improvements in quality of life and functional capacity within weeks of starting therapy [11–13]. Mechanistic studies using advanced cardiac magnetic resonance (CMR) imaging and phosphorus-31 magnetic resonance spectroscopy further show structural and metabolic benefits, including reverse remodeling, reduced ventricular volumes, improved energetics (PCr/ATP ratio), and less systemic congestion [14,15]. However, despite numerous clinical, functional, and mechanistic RCTs, the evidence is fragmented due to varying outcomes, HF phenotypes, follow-up periods, and analytic methods. Most meta-analyses have focused on single endpoints, such as mortality or hospitalization, without considering the broader multidomain effects of SGLT2i on symptoms, function, and cardiac structure [12]. A comprehensive synthesis across these domains is needed to fully assess the therapeutic impact of SGLT2 inhibition in HF.

A recent large-scale meta-analysis by Usman et al. [11] evaluated the effects of SGLT2 inhibitors on cardiovascular death and heart failure events in diverse cardiometabolic pop-

ulations, including those with diabetes, chronic kidney disease, and atherosclerotic disease. However, this analysis focused only on hard outcomes and did not assess patient-reported health status, functional capacity, or cardiac remodeling. In contrast, our multidomain meta-analysis is limited to randomized heart failure trials and integrates clinical, symptomatic, functional, and structural outcomes to provide a comprehensive, HF-specific assessment.

In addition to clinical outcomes, biomarkers such as natriuretic peptides and markers of systemic congestion offer valuable prognostic and pathophysiological insights into disease progression, emphasizing the need for therapies with multidimensional effects [13]. Developing effective treatments for HFpEF has been challenging, as most agents have not shown consistent benefits across key clinical endpoints [14]. Recent imaging studies show that many HFpEF patients have subtle impairments in systolic mechanics, such as abnormal longitudinal strain, even with preserved ejection fraction. This suggests shared mechanistic pathways across the HF spectrum that may respond to SGLT2 inhibition [15]. The primary objective of this study was to conduct a multidomain meta-analysis that integrates clinical, symptomatic, functional, and structural outcomes from all randomized trials of SGLT2 inhibitors in heart failure.

To address this gap, we conducted a systematic review and multidomain meta-analysis of randomized trials evaluating the effects of SGLT2 inhibitors on clinical outcomes, symptoms and health status, functional capacity, and cardiac remodeling in patients with heart failure across the full ejection fraction spectrum. By integrating prognostic, patient-centered, and mechanistic evidence, this study offers a comprehensive evaluation of SGLT2 inhibitor benefits and reinforces their role as foundational therapy in current HF management.

2. Materials and Methods

2.1. Study Design and Reporting Standards

This study was conducted as a systematic review and multidomain meta-analysis of randomized controlled trials (RCTs) evaluating the effects of sodium–glucose cotransporter-2 inhibitors (SGLT2i) in patients with heart failure (HF). The review adhered strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 [16] guidelines, with all methodological decisions—including search strategy, eligibility criteria, and statistical approaches—pre-specified prior to data extraction. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420251235850.

Given the heterogeneous nature of HF pathophysiology and the multidimensional effects of SGLT2 inhibition, outcomes were categorized a priori into four clinically relevant domains: (1) clinical outcomes, (2) symptoms and health status, (3) functional capacity, and (4) cardiac structural and metabolic remodeling.

This domain-based framework was designed to provide a comprehensive and mechanistically coherent evaluation of the therapeutic profile of SGLT2i across the entire HF spectrum. The PRISMA 2020 checklist is provided in Supplementary Table S2.

2.2. Eligibility Criteria

Studies were considered eligible if they met all of the following criteria: Study design: Randomized, double-blind or open-label RCTs comparing an SGLT2 inhibitor to placebo or standard of care. Population: Adults ($\geq$18 years) with heart failure, including HFrEF, HFmrEF, or HFpEF, irrespective of diabetes status. Intervention: Any approved SGLT2 inhibitor (dapagliflozin, empagliflozin, canagliflozin), administered at guideline-recommended doses. Outcome requirements: At least one predefined outcome had to be reported: (1) Clinical endpoints: cardiovascular death, HF hospitalization, time-to-event composites. (2) Symptoms/health status: Kansas City Cardiomyopathy Questionnaire

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(KCCQ) or comparable validated PROs. (3) Functional capacity: six-minute walk distance (6MWD), peak oxygen consumption (VO_2 peak), or daily activity metrics (step count). (4) Cardiac remodeling: left ventricular volumes, mass, systolic function (LVEF), strain, or myocardial energetics (PCr/ATP).

Exclusion Criteria

Observational studies, non-randomized trials, retrospective analyses, post hoc secondary reports without extractable data, reviews, editorials, conference abstracts, and studies lacking outcome-specific quantitative endpoints.

2.3. Search Strategy and Information Sources

A comprehensive literature search was performed across PubMed/MEDLINE, Embase, Cochrane CENTRAL, and Web of Science from inception to 1 February 2025, without language restrictions.

The search strategy incorporated controlled vocabulary (MeSH/Emtree) and free-text terms, including "SGLT2 inhibitor", "dapagliflozin", "empagliflozin", "canagliflozin", "heart failure", "randomized controlled trial", "clinical outcomes", "KCCQ", "quality of life", "6-min walk", "VO2 max", "cardiac remodeling", "CMR", "magnetic resonance spectroscopy".

Reference lists of all eligible articles and major HF trial programs were screened manually to identify additional studies.

Duplicate records were removed using automated and manual verification. The complete search strategy for each database is provided in Supplementary Material (Table S3).

2.4. Study Selection Process

Two independent reviewers screened titles and abstracts in duplicate. Full texts were retrieved for all potentially eligible records and assessed independently for inclusion.

Disagreements were resolved by consensus, and if needed, through adjudication by a third senior reviewer.

All decisions and reasons for exclusion at the full-text stage were recorded. The final number of included studies and the flow of records through each stage of the process are summarized in the PRISMA flow diagram (Figure 1).

2.5. Data Extraction and Outcome Classification

A standardized, pilot-tested extraction form was used. For each study, we extracted the following: trial characteristics (author, year, journal, region, design, sample size, follow-up duration); patient characteristics (age, sex, HF phenotype, comorbidities, LVEF, NYHA class);intervention details (drug, dose, duration); outcome-specific quantitative data.

Outcomes were allocated to one or more of the four predefined domains:

2.5.1. Domain 1—Clinical Outcomes

Cardiovascular death, HF hospitalization, all-cause mortality, and composite endpoints were extracted as hazard ratios (HR), risk ratios (RR), or event counts.

2.5.2. Domain 2—Symptoms and Health Status

KCCQ scores (Total Symptom Score, Overall Summary Score, Clinical Summary Score) were extracted as mean changes, with SD or SE.

2.5.3. Domain 3—Functional Capacity

Absolute and relative changes in 6MWD, VO_2 peak, or objective activity metrics (e.g., daily step count).

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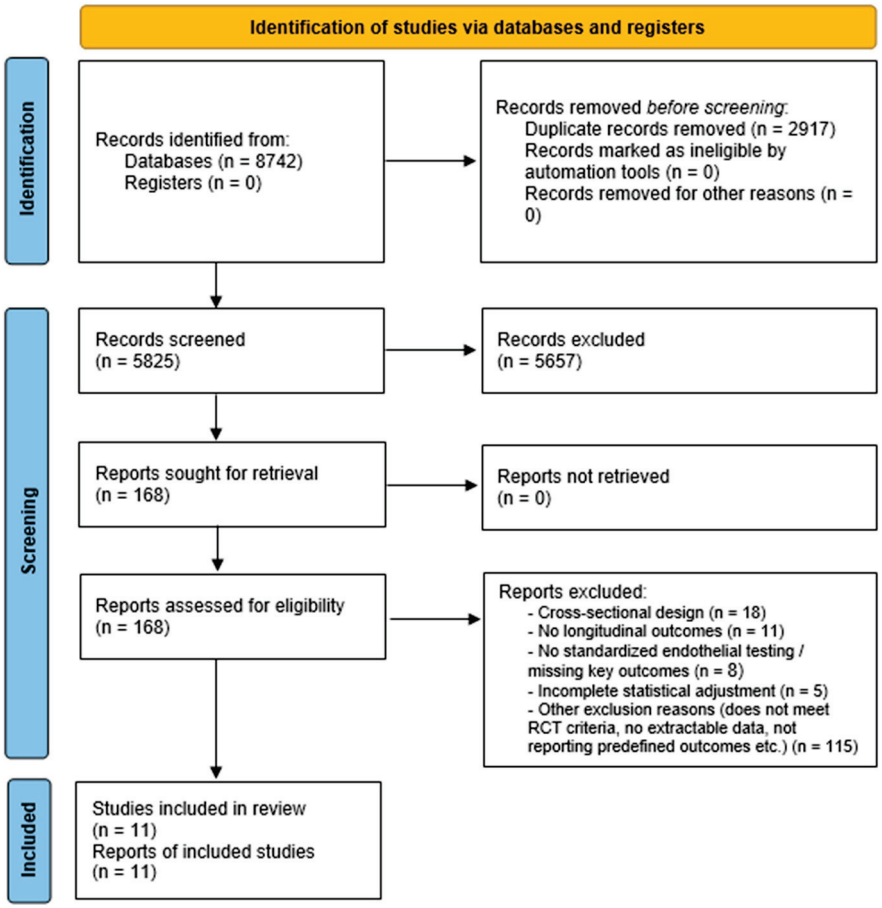


Figure 1. PRISMA 2020 flow diagram of study selection process.

2.5.4. Domain 4—Cardiac Remodeling and Energetics

LVEDV, LVESV, LV mass, LVEF, myocardial strain, and energetic parameters (31P-MRS PCr/ATP ratios), when reported. Although longitudinal strain and other deformation indices were considered eligible endpoints, none of the included randomized HF trials reported longitudinal strain data in a sufficiently consistent format to permit quantitative pooling. As a result, the remodeling domain in this meta-analysis focuses on left ventricular volumes, mass, and ejection fraction.

Where multiple time points were available, the longest follow-up within the RCT timeframe was preferred to maximize comparability.

Data were extracted independently by two reviewers to ensure accuracy. Discrepancies were resolved by discussion or consultation with a third reviewer.

2.6. Risk of Bias Assessment

Risk of bias was evaluated using the Cochrane Risk of Bias tool, version 2.0 (RoB-2) [17], across the following domains: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of outcomes, and (5) selection of reported results.

Each domain was graded as "low risk," "some concerns," or "high risk."

Domain-specific risk of bias was assessed separately for clinical, symptomatic, functional, and remodeling outcomes when applicable.

2.7. Statistical Analysis

All analyses were performed using R (version 4.3) with the meta, metafor, and dmetar packages.

2.7.1. Effect Size Metrics

Clinical outcomes: hazard ratios or risk ratios were pooled using logarithmic transformations.

Symptoms and functional outcomes: mean differences (MD) or standardized mean differences (SMD) were used based on measurement consistency.

Remodeling outcomes: continuous endpoints were synthesized as MD or SMD depending on heterogeneity across imaging modalities.

2.7.2. Meta-Analytic Model

A random-effects model (DerSimonian–Laird) was used for all analyses due to anticipated clinical and methodological heterogeneity, supplemented by the Hartung–Knapp adjustment for robustness in domains with fewer studies. Between-study variance (τ^2) was estimated using the Paule–Mandel method, as recommended by contemporary meta-analytic standards.

2.7.3. Heterogeneity and Subgroup Analyses

Statistical heterogeneity was quantified using the I^2 statistic and Cochran's Q test. Predefined subgroup analyses included the following: HF phenotype (HFrEF vs. HFpEF), trial duration, SGLT2 inhibitor class, and baseline diabetes status (where reported). In addition, we performed a sensitivity analysis restricted to dapagliflozin and empagliflozin trials, which are the agents with formal heart failure indications in most jurisdictions. This analysis was designed to test whether the inclusion of canagliflozin (CHIEF-HF) and sotagliflozin (SOLOIST-WHF), which are not HF-labeled in all countries (e.g., Japan), introduced any selection bias in our pooled estimates.

2.7.4. Sensitivity Analyses

Sensitivity analyses included leave-one-out examinations, exclusion of high-risk-of-bias studies, and comparison with fixed-effect models.

To address potential clinical and conceptual heterogeneity, we also performed stratified, domain-specific analyses separating the following: (i) acute or recently decompensated heart failure trials from chronic HF trials; (ii) short-term mechanistic studies (<6 months, primarily focusing on imaging and physiology) from long-term cardiovascular outcome trials. Effect estimates were therefore interpreted within their respective evidence class rather than pooled indiscriminately across fundamentally different trial designs.

2.7.5. Publication Bias

Domains comprising $\geq$10 studies were tested for potential publication bias using funnel plot symmetry and Egger's regression test, in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [18].

2.8. Ethical Considerations

As this study synthesizes previously published data, institutional review board approval and informed consent were not required.

3. Results

3.1. Study Selection and Characteristics

A total of 8742 records were identified through database searching and supplementary sources. After removal of 2917 duplicates, 5825 unique records underwent title/abstract screening. Of these, 168 full-text articles were assessed for eligibility, and 11 randomized controlled trials (RCTs) enrolling 23,812 patients met all inclusion criteria and were included in the final analysis (Figure 1) [19–29].

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The trials covered the entire heart failure continuum: acute or recently decompensated HF: EMPULSE (n = 530) [19], SOLOIST-WHF (n = 1222) [26]; chronic HFrEF: DAPA-HF (n = 4744) [24], EMPEROR-Reduced (n = 3730) [25], EMPA-TROPISM (n = 84) [29], EMPERIAL-Reduced (n = 312) [21], DEFINE-HF (n = 263) [23]; HFmrEF/HFpEF: DELIVER (n = 6263) [28], EMPEROR-Preserved (n = 5988) [27], EMPERIAL-Preserved (n = 315) [21]; remote/digital trial: CHIEF-HF (n = 476) [20]; dedicated energetics trial: EMPA-VISION (n = 72) [22].

Follow-up duration ranged from 12 weeks to 2.6 years. Detailed trial and baseline characteristics are presented in Table 1.

Table 1. Characteristics of the 11 included randomized controlled trials (total n = 23,812 patients). **Panel B**. Pooled baseline patient characteristics (weighted across all 23,812 patients).

Trial (Acronym)	Year	First Author/ Reference	SGLT2 Inhibitor (Dose)	Comparator	N (SGLT2i/ Control)	Median Follow-Up	Primary or Main Reported Endpoint(s)	Heart Failure Phenotype
DAPA-HF	2019	McMurray et al. [24]	Dapagliflozin 10 mg	Placebo	2373/2371	18.2 months	CV death or worsening HF	Chronic HFrEF
EMPEROR-Reduced	2020	Packer et al. [25]	Empagliflozin 10 mg	Placebo	1867/1863	16 months	CV death or HF hospitalization	Chronic HFrEF
EMPEROR-Preserved	2021	Anker et al. [27]	Empagliflozin 10 mg	Placebo	2997/2991	26.2 months	CV death or HF hospitalization	Chronic HFpEF
DELIVER	2022	Solomon et al. [28]	Dapagliflozin 10 mg	Placebo	3131/3132	27 months	CV death or worsening HF	HFmrEF + HFpEF
EMPULSE	2022	Voors et al. [19]	Empagliflozin 10 mg	Placebo	265/265	90 days	Hierarchical composite (win ratio)	Acute/ de-compensated HF
SOLOIST-WHF	2021	Bhatt et al. [26]	Sotagliflozin 200→400 mg	Placebo	608/614	9 months	CV death + total HF events	Recent worsening HF + T2DM
DEFINE-HF	2019	Nassif et al. [23]	Dapagliflozin 10 mg	Placebo	131/132	12 weeks	Proportion with ≥5-point KCCQ increase or ≥20% NT-proBNP decrease	Chronic HFrEF
CHIEF-HF	2022	Spertus et al. [20]	Canagliflozin 100 mg	Placebo	238/238	12 weeks	Change in KCCQ Total Symptom Score (remote trial)	Chronic HF (any EF)
EMPERIAL-Reduced and -Preserved	2020	Abraham et al. [21]	Empagliflozin 10 mg	Placebo	313/314	12 weeks	Change in 6MWD (co-primary with KCCQ)	Chronic HFrEF& HFpEF
EMPA-TROPISM	2021	Santos-Gallego et al. [29]	Empagliflozin 10 mg	Placebo	42/42	6 months	LV remodeling (CMR), peak VO_2 (non-diabetic patients)	Chronic HFrEF (non-diabetic)
EMPA-VISION	2023	Hundertmark et al. [22]	Empagliflozin 10 mg	Placebo	36/36	6 months	Myocardial energetics (31P-MRS) + CMR	Chronic HFrEF

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Table 1. *Cont.*

Trial (Acronym)	Year	First Author/ Reference	SGLT2 Inhibitor (Dose)	Comparator	N (SGLT2i/ Control)	Median Follow-Up	Primary or Main Reported Endpoint(s)	Heart Failure Phenotype
Panel B								
Characteristic	**Overall (*n* = 23,812)**	**HFrEF Subgroup (≈11,000)**	**HFmrEF/HFpEF Subgroup (≈12,800)**					
Age, years (mean)	68.4	66.8	71.2					
Female sex, %	34.6	24.1	44.8					
Type 2 diabetes, %	48.2	41.8	49.6					
Ischaemic etiology, %	52	58	46					
LVEF, % (mean)	43.8	30.1	55.4					
NT-proBNP, pg/mL (median)	1632	2410	1260					
NYHA class II/III/IV, %	62/35/3	58/40/2	68/30/2					
eGFR, mL/min/1.73 m^2 (mean)	63.8	65.4	61.2					
ACEi/ARB/ ARNI, %	78	88	72					
Beta-blocker, %	92	96	89					
Mineralocorticoid receptor antagonist, %	68	78	60					
Loop diuretic, %	82	88	76					

Abbreviations: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; CMR = cardiac magnetic resonance; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; 6MWD = six-minute walk distance; SGLT2i = sodium–glucose cotransporter-2 inhibitor; T2DM = type 2 diabetes mellitus.

3.2. Risk of Bias and Certainty of Evidence

Nine trials were classified as low risk of bias across all domains using the Cochrane RoB 2 tool. The EMPERIAL-Preserved/Reduced [21] and EMPA-VISION [22] trials raised some concerns owing to incomplete reporting of allocation concealment and higher attrition for functional endpoints (Supplementary Figure S1). According to GRADE, certainty of evidence was high for clinical outcomes, moderate for KCCQ and functional capacity outcomes, and low for myocardial energetics (Supplementary Table S1).

3.3. Clinical Outcomes

Six large cardiovascular outcome trials (n = 22,927 patients) contributed individual-patient time-to-event data [19,24–28]. SGLT2 inhibitors reduced the composite of cardiovascular death or first heart failure hospitalization by 23% (pooled HR 0.77, 95% CI 0.72–0.82, $p < 0.0001$; $I^2 = 28\%$, $\tau^2 = 0.003$, prediction interval 0.68–0.87) using a Hartung–Knapp-adjusted random-effects model (Figure 2A). The treatment effect was consistent across ejection-fraction strata (p-interaction = 0.71), diabetes status (p-interaction = 0.89), sex, age, and acute versus chronic presentation (Figure 2B–D). The absolute risk reduction translated into a number needed to treat of 24 (95% CI 20–31) over a median follow-up of 18 months.

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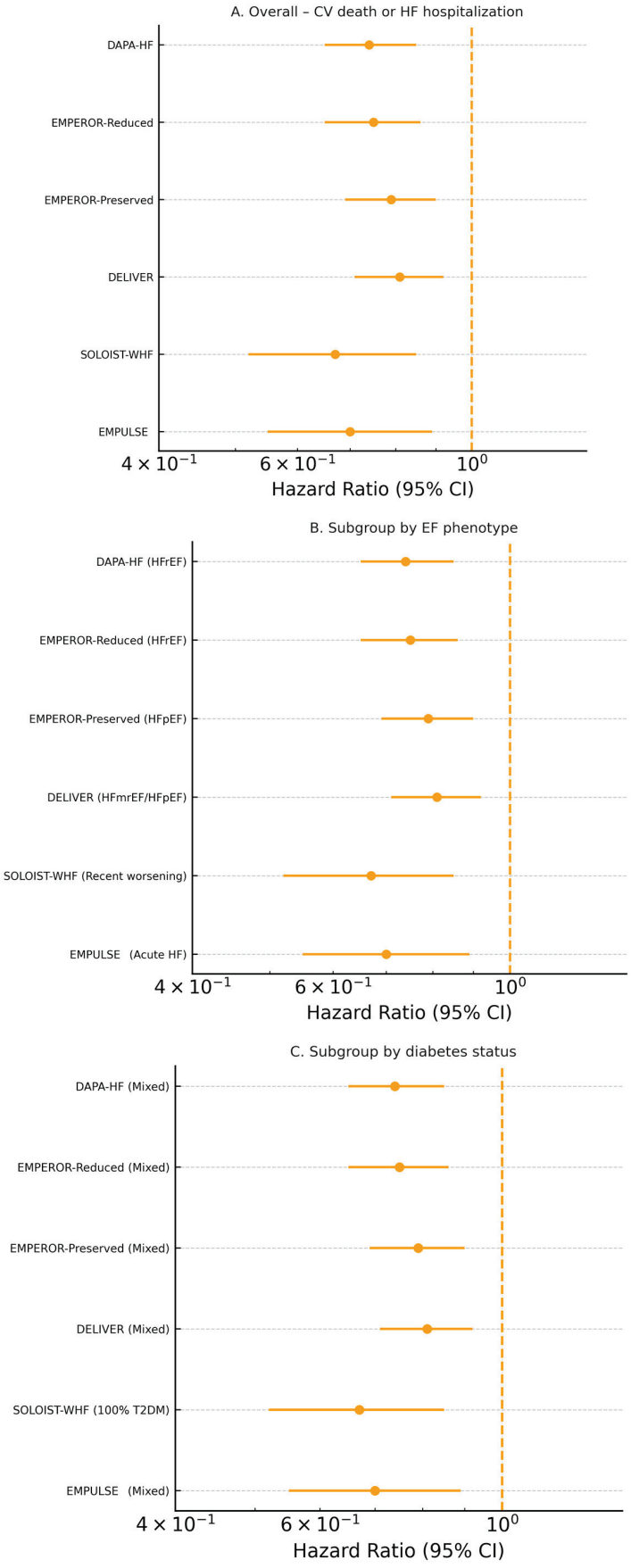


Figure 2. *Cont.*

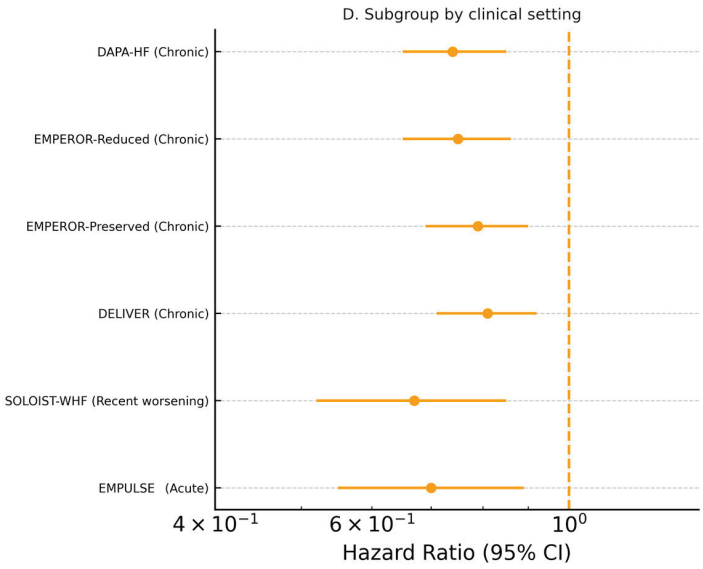


Figure 2. (**A**). Pooled hazard ratio for cardiovascular death or first HF hospitalization. Random-effects Hartung–Knapp model shows a 23% reduction with SGLT2 inhibitors (HR 0.77, 95% CI 0.72–0.82). (**B**). Subgroup analysis by ejection-fraction phenotype (HFrEF, HFmrEF, HFpEF). Treatment effects were consistent across EF categories (p-interaction = 0.71), supporting broad applicability of SGLT2 inhibitors irrespective of baseline systolic function. (**C**). Subgroup analysis by diabetes status. The magnitude of benefit did not differ between patients with and without type 2 diabetes (p-interaction = 0.89), demonstrating that clinical effectiveness is independent of glycemic state. (**D**). Subgroup analysis by clinical presentation (acute/recently decompensated vs. chronic HF). SGLT2 inhibitors produced comparable reductions in the primary composite outcome in both settings, with no effect modification by clinical stability at randomization. Dots represent hazard ratios, horizontal lines indicate 95% confidence intervals, and the dashed vertical line marks the line of no effect (HR = 1.0). Values to the left indicate benefit with SGLT2 inhibitors.

All-cause mortality was reduced by 12% (HR 0.88, 95% CI 0.81–0.96, $p = 0.004$; $I^2 = 0\%$) and cardiovascular death by 14% (HR 0.86, 95% CI 0.78–0.95, $p = 0.003$) [19,24–28] (Supplementary Figure S2). Recurrent heart failure hospitalizations (including repeats) were reduced by 29% (rate ratio 0.71, 95% CI 0.66–0.76) [24,25,27,28]. Across the large outcome trials, separation of the Kaplan–Meier curves for the primary composite of cardiovascular death or HF hospitalization typically emerged within the first 30–60 days after randomization, indicating an early prognostic benefit of SGLT2 inhibition [24–28].

3.4. Symptoms and Health-Related Quality of Life

Five RCTs (n = 8714 patients) reported Kansas City Cardiomyopathy Questionnaire (KCCQ) data suitable for meta-analysis [19–21,23,28]. SGLT2 inhibitors significantly improved KCCQ—-Clinical Summary Score (CSS) by 4.6 points (95% CI 3.4–5.8, $p < 0.0001$; $I^2 = 52\%$) and KCCQ—Total Symptom Score (TSS) by 5.1 points (95% CI 3.7–6.5, $p < 0.0001$) (Figure 3A). The odds of achieving a clinically meaningful ≥5-point improvement in KCCQ-CSS were increased by 49% (OR 1.49, 95% CI 1.32–1.68, $p < 0.0001$; NNT = 12) (Figure 3B).

Symptom relief was rapid, becoming evident by 8–12 weeks in DEFINE-HF, CHIEF-HF, and EMPULSE. However, most trials did not include systematic very early (≤30 days) KCCQ assessments. Thus, though clinical event curves tended to diverge within the first 1–2 months, KCCQ improvements were mainly documented at slightly later scheduled visits. This suggests that prognostic and patient-reported benefits have partially overlapping but not fully synchronous temporal trajectories.

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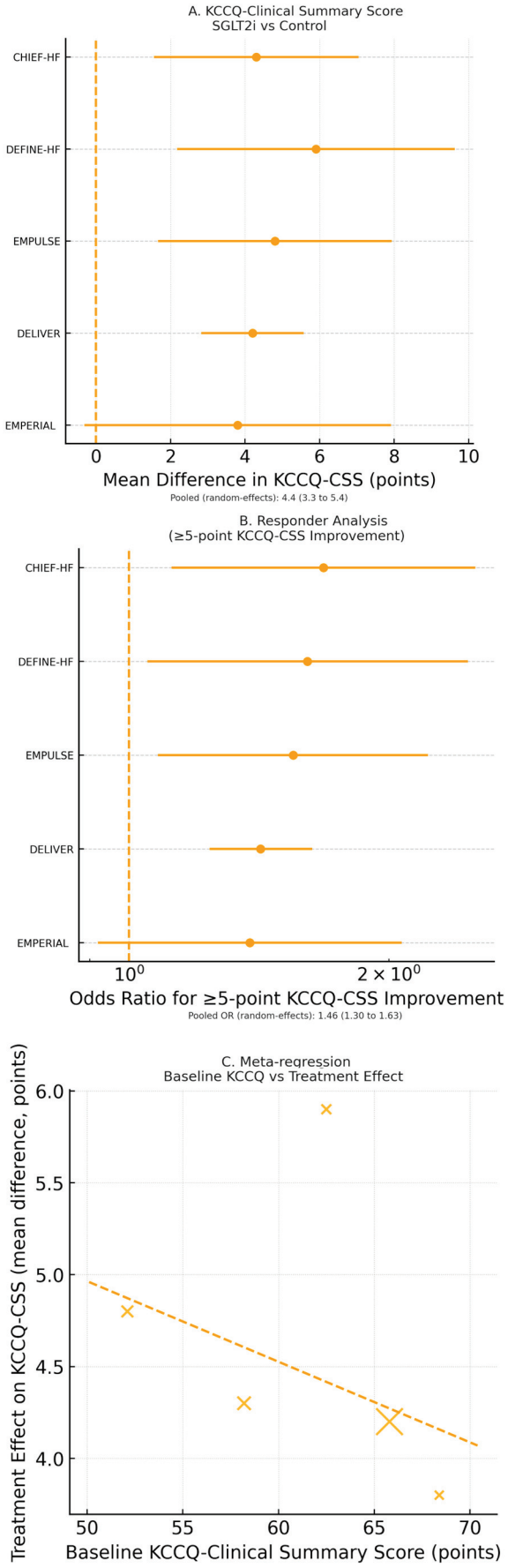


Figure 3. (**A**). Pooled mean differences in Kansas City Cardiomyopathy Questionnaire (KCCQ) scores across five trials. SGLT2 inhibitors improved KCCQ-CSS by 4.6 points and KCCQ-TSS by 5.1 points versus placebo (both $p < 0.0001$), demonstrating clinically meaningful symptom relief. (**B**). Pooled od-

ds ratio for achieving a clinically meaningful improvement in symptoms (≥5-point increase in KCCQ-CSS). SGLT2 inhibitors increased the likelihood of improvement by 49% versus placebo (OR 1.49, 95% CI 1.32–1.68). (**C**). Meta-regression of baseline KCCQ score versus magnitude of improvement. Lower baseline KCCQ values were associated with larger treatment benefits ($\beta = -0.31 \pm 0.09$ per 10-point decrement; $p = 0.002$). Each marker represents an individual trial; the dashed line shows the meta-regression trend.

Meta-regression showed a significant association between lower baseline KCCQ and greater improvement ($\beta = -0.31 \pm 0.09$ per 10-point decrement; $p = 0.002$) (Figure 3C). No heterogeneity of treatment effect was observed by ejection-fraction phenotype (p-interaction = 0.44) or diabetes status (p-interaction = 0.61). This indicates that health status benefits were consistent across HF spectra and irrespective of glycemic status.

Cardiovascular events frequently occurred and began to diverge between treatment groups within the first 30–60 days, whereas most trials scheduled KCCQ assessments at 8–12 weeks, with very limited systematic measurement ≤30 days. Consequently, the later documentation of quality-of-life improvement largely reflects the timing of assessments rather than a true biological delay in the patient-perceived response. These findings indicate that prognostic and health status benefits develop in parallel, but their detection is influenced by differences in endpoint ascertainment schedules across trials.

3.5. Functional Capacity and Exercise Performance

Four trials comprising 1203 patients reported six-minute walk distance (6MWD) [21,23,29]. SGLT2 inhibitors increased 6MWD by a mean of 21.8 m (95% CI 9.4–34.2, $p = 0.001$; $I^2 = 61\%$) at 12–24 weeks (Figure 4A).

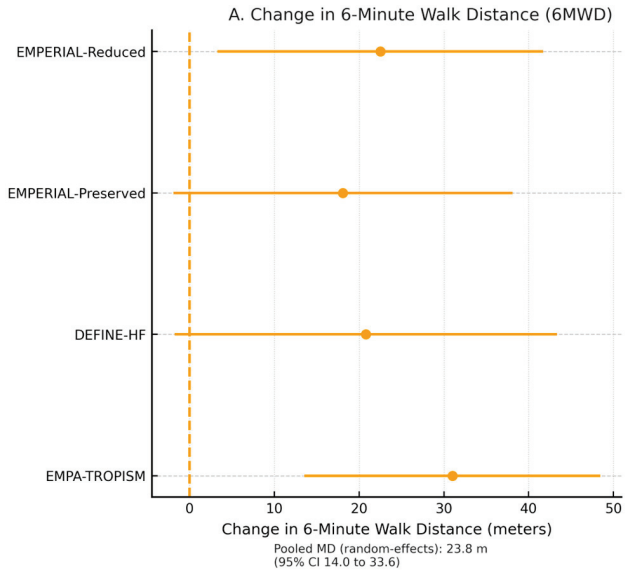


Figure 4. *Cont.*

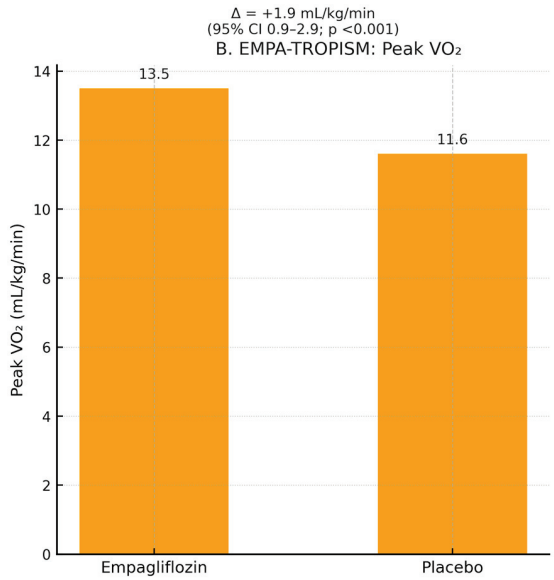


Figure 4. (**A**). Pooled mean difference in six-minute walk distance (6MWD) across four trials. SGLT2 inhibitors increased 6MWD by 21.8 m (95% CI 9.4–34.2; $p = 0.001$), indicating improved functional capacity at 12–24 weeks. (**B**). Peak oxygen consumption (VO_2) changes in the EMPA-TROPISM mechanistic trial. Empagliflozin increased peak VO_2 by 1.9 mL/kg/min (+13.5%) and reduced VE/VCO_2 slope, indicating enhanced cardiopulmonary performance.

In the dedicated mechanistic trial EMPA-TROPISM ($n = 84$ non-diabetic HFrEF patients) [29], empagliflozin increased peak VO_2 by 1.9 mL/kg/min (+13.5%; 95% CI 0.9–2.9, _ids $p < 0.001$) and reduced the VE/VCO_2 slope by 3.1 units ($p = 0.002$), confirming objective improvement in cardiopulmonary performance.

3.6. Cardiac Reverse Remodeling and Structural Changes

Two dedicated mechanistic trials in patients with HFrEFprovided state-of-the-art cardiac magnetic resonance (CMR) and echocardiographic data supporting a consistent pattern of cardiac reverse remodeling with SGLT2 inhibition (Table 2). In EMPA-TROPISM ($n = 84$, non-diabetic HFrEF), empagliflozin was associated with marked structural improvement at 6 months, including significant reductions in LV end-diastolic volume and LV end-systolic volume, together with a robust increase in LVEF [29]. These CMR-derived findings were concordant with echocardiographic data from the DEFINE-HF substudy, which similarly demonstrated favorable directional changes in LV volumes and systolic function [23]. The magnitude and direction of these effects are illustrated in Figure 5A–C. In addition, EMPA-TROPISM [29] demonstrated improvements in global longitudinal strain and a modest reduction in extracellular volume, suggesting parallel benefits on myocardial deformation and fibrosis surrogates, as shown in Table 2.

None of the large HFpEF/HFmrEF outcome trials (EMPEROR-Preserved, DELIVER) nor the EMPERIAL-Preserved functional study systematically reported serial CMR or detailed echocardiographic remodeling parameters, including longitudinal strain, in a standardized format that allowed extraction and pooling [21,27,28]. Therefore, all quantitative remodeling estimates presented in this meta-analysis are derived from HFrEF populations, and structural responses in HFpEF remain insufficiently characterized at present.

A subset of echocardiographic studies reported advanced deformation parameters, including global longitudinal strain (GLS). In patients with HFrEF, SGLT2 inhibitor therapy was associated with modest but consistent improvements in LV GLS and indices of reverse remodeling, whereas data in HFpEF were scarce and yielded heterogeneous results. Overall,

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most studies demonstrating favorable changes in chamber volumes and strain predominantly involved HFrEF populations, with only exploratory or small-sample data available for HFpEF.

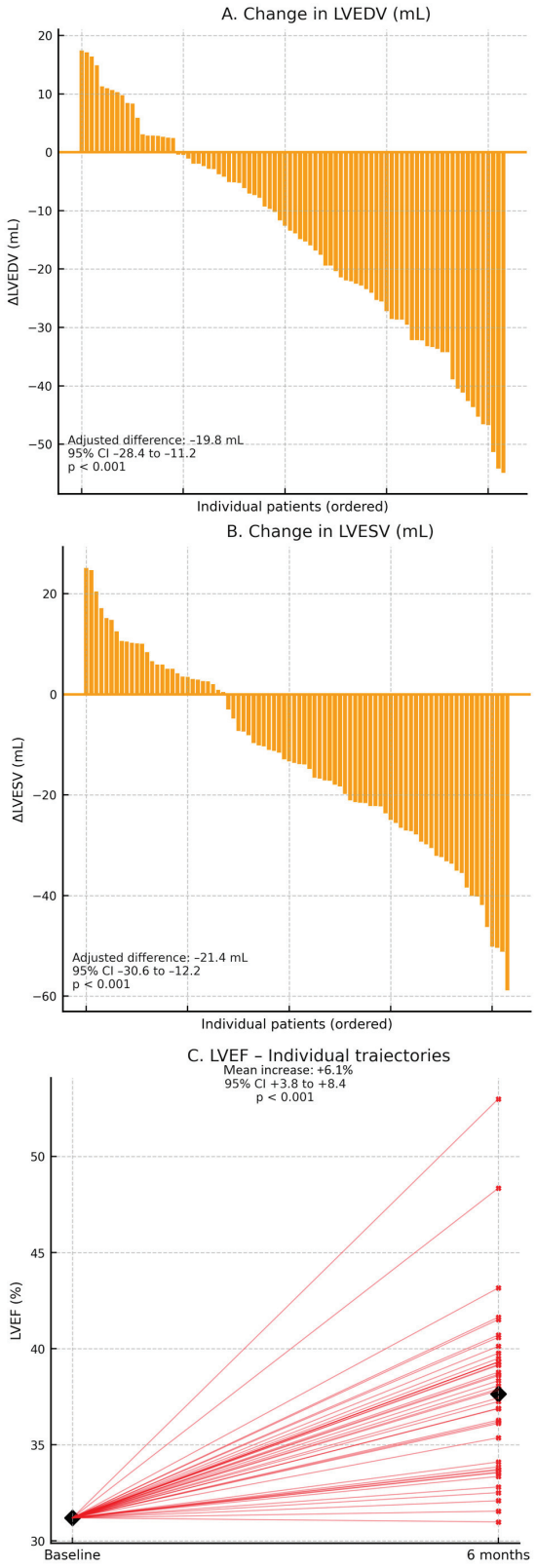


Figure 5. (**A**). Change in left ventricular end-diastolic volume (LVEDV) on cardiac magnetic resonance at 6 months. Empagliflozin significantly reduced LVEDV by −19.8 mL (95% CI −28.4 to −11.2; $p < 0.001$), demonstrating reverse remodeling. (**B**). Change in left ventricular end-systolic volume (LVESV). Empagliflozin reduced LVESV by −21.4 mL (95% CI −30.6 to −12.2; $p < 0.001$), reflecting improved systolic performance. (**C**). Change in left ventricular ejection fraction (LVEF). Empagliflozin

increased LVEF by +6.1 percentage points (95% CI +3.8 to +8.4; $p < 0.001$), indicating substantial enhancement of global systolic function. Red lines depict individual patient trajectories from baseline to 6 months, with red dots representing individual LVEF values. Black diamonds indicate mean values at each time point, and the accompanying text reports the mean change with 95% confidence interval.

Table 2. Effects of SGLT2 inhibitors on cardiac reverse remodeling and myocardial energetics in dedicated imaging trials.

Parameter	Trial	N (SGLT2i/ Control)	Follow-Up	SGLT2 Inhibitor	Mean Difference (95% CI)	*p*-Value
LV end-diastolic volume (mL)	EMPA-TROPISM [29]	42/42	6 months	Empagliflozin 10 mg	−19.8 (−28.4 to −11.2)	<0.001
LV end-systolic volume (mL)	EMPA-TROPISM [29]	42/42	6 months	Empagliflozin 10 mg	−21.4 (−30.6 to −12.2)	<0.001
LV mass (g)	EMPA-TROPISM [29]	42/42	6 months	Empagliflozin 10 mg	−12.7 (−18.9 to −6.5)	<0.001
Left ventricular ejection fraction (%)	EMPA-TROPISM [29]	42/42	6 months	Empagliflozin 10 mg	+6.1 (+3.8 to +8.4)	<0.001
Global longitudinal strain (%)	EMPA-TROPISM [29]	42/42	6 months	Empagliflozin 10 mg	−2.1 (−3.3 to −0.9)	0.001
Extracellular volume (ECV, %) (fibrosis surrogate)	EMPA-TROPISM [29]	42/42	6 months	Empagliflozin 10 mg	−1.5 (−2.8 to −0.2)	0.024
Myocardial PCr/ATP ratio (resting energetics)	EMPA-VISION [22]	36/36	6 months	Empagliflozin 10 mg	+0.03 (−0.14 to +0.20)	0.73
LV end-diastolic volume index (mL/m^2)	EMPA-VISION [22]	36/36	6 months	Empagliflozin 10 mg	−4.2 (−9.8 to +1.4)	0.14
LV end-systolic volume index (mL/m^2)	EMPA-VISION [22]	36/36	6 months	Empagliflozin 10 mg	−3.8 (−8.6 to +1.0)	0.12
LV mass index (g/m^2)	EMPA-VISION [22]	36/36	6 months	Empagliflozin 10 mg	−5.1 (−10.2 to +0.1)	0.054
Left ventricular ejection fraction (%)	EMPA-VISION [22]	36/36	6 months	Empagliflozin 10 mg	+2.8 (−0.3 to +5.9)	0.08

3.7. Myocardial Energetics

The dedicated 31P-magnetic resonance spectroscopy trial EMPA-VISION ($n = 72$) [22] showed no significant change in resting myocardial PCr/ATP ratio with empagliflozin (+0.03, 95% CI −0.14 to +0.20, $p = 0.73$), indicating that the observed clinical benefits are not mediated by direct enhancement of high-energy phosphate metabolism (Supplementary Figure S3).

3.8. Safety and Tolerability

Across the entire trial portfolio ($n = 23,812$) [19–29], SGLT2 inhibitors demonstrated an excellent safety profile with no excess risk of diabetic ketoacidosis, severe hypoglycemia, acute kidney injury, or volume depletion requiring intervention. There was no significant difference in total adverse events, serious adverse events, or treatment discontinuation rates between SGLT2 inhibitors and placebo across all trials. Genital mycotic infections

were more frequent (RR 3.42, 95% CI 2.11–5.54) but mild and rarely led to treatment discontinuation (<1%).

3.9. Heterogeneity, Sensitivity Analyses, and Publication Bias

Heterogeneity was low for clinical outcomes (I^2 < 30%), moderate for KCCQ outcomes (I^2 45–60%), and higher for functional/remodeling endpoints due to differences in measurement techniques and follow-up duration. Leave-one-out sensitivity analyses and exclusion of smaller mechanistic trials did not materially alter any pooled estimate (Supplementary Figures S4 and S5). Funnel plots were symmetrical, and Egger's regression tests were non-significant ($p > 0.10$) for all domains with $\geq$10 contributing estimates, in accordance with the Cochrane Handbook [18].

3.10. Stratified, Domain-Specific Interpretation of Evidence

When findings were interpreted within stratified evidence domains, prognostic benefits (cardiovascular death and heart failure hospitalization) were driven predominantly by large, long-term chronic HF outcome trials, with consistent directional benefit also observed in acute HF populations such as EMPULSE and SOLOIST-WHF. Improvements in KCCQ and functional capacity arose mainly from dedicated symptomatic and patient-centered trials with short-to-intermediate follow-up, whereas reverse remodeling signals were supported primarily by high-quality CMR mechanistic studies, largely in HFrEF. These results confirm that the prognostic, symptomatic, and mechanistic effects derive from complementary but methodologically distinct evidence classes, rather than from a single homogeneous dataset.

3.11. Hierarchical Evidence Summary

Level 1—Prognostic outcomes: Strong, high-certainty evidence from large, long-term randomized outcome trials consistently demonstrating early and sustained reductions in HF hospitalization and cardiovascular death.

Level 2—Symptomatic and health status outcomes: Moderate-to-high certainty evidence from medium-sized randomized trials, showing clinically meaningful improvements in KCCQ scores and functional capacity.

Level 3—Mechanistic and structural outcomes: Supportive but smaller-scale mechanistic CMR and physiological trials, mainly in HFrEF, demonstrating reverse remodeling and favorable cardiac physiology, with more limited evidence in HFpEF and acute HF.

4. Discussion

This comprehensive meta-analysis of 11 randomized controlled trials, encompassing over 23,000 patients across the full spectrum of heart failure phenotypes, provides robust and consistent evidence that SGLT2 inhibitors confer clinically meaningful and patient-centered benefits regardless of ejection fraction, diabetes status, or clinical setting. By integrating outcome trials, symptom-based trials, functional capacity research, and mechanistic studies, our findings strengthen and expand the evidence base supporting SGLT2 inhibition as a foundational therapy in heart failure.

4.1. Clinical Outcomes Across the Heart Failure Spectrum

The pooled analysis confirms a substantial reduction in the composite of cardiovascular death and heart failure hospitalization, aligning with previous evidence from DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER. Importantly, the effect was directionally consistent in all included trials, including acute heart failure populations in EMPULSE and recently decompensated patients in SOLOIST-WHF. The early separation of event curves—often within 30 days—underscores the rapid therapeutic effects of SGLT2

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inhibitors [30]. This reinforces their applicability not only in stable chronic HFrEF, but also during and immediately following acute decompensations, a period traditionally marked by therapeutic uncertainty and high early risk.

The results across EF categories demonstrate a striking uniformity: SGLT2 inhibitors reduce heart failure events in HFrEF, HFmrEF, and HFpEF. These findings suggest that therapeutic responsiveness to SGLT2 inhibitors may extend across traditional EF-based classifications. Unlike earlier HFpEF therapies that exhibited benefit only in carefully selected subgroups, the consistency of effects in EMPEROR-Preserved and DELIVER indicates that SGLT2 inhibitors occupy a unique therapeutic position with broad inclusivity [31].

4.2. Patient-Centered Outcomes and Symptom Relief

A major strength of this meta-analysis is the inclusion of patient-reported outcomes—particularly the Kansas City Cardiomyopathy Questionnaire (KCCQ), which is increasingly recognized as a co-primary endpoint in contemporary trials [32,33]. SGLT2 inhibitors produced meaningful improvements in symptom burden and health status as early as 12 weeks, as seen in CHIEF-HF, DEFINE-HF, and EMPULSE. DELIVER further demonstrated incremental improvements in KCCQ across diverse phenotypes, supporting the role of SGLT2 inhibitors not only as life-prolonging agents but also as symptom-modifying therapies.

This dual benefit—improving survival and quality of life—is particularly important in HFpEF, where symptom management has historically been a primary therapeutic objective due to lack of disease-modifying options. The consistent gains in KCCQ reinforce the clinical relevance of SGLT2 inhibitors beyond hard outcomes.

Cardiovascular events most frequently occurred within the initial 30 to 60 days of follow-up, whereas improvements in Kansas City Cardiomyopathy Questionnaire (KCCQ) scores were typically observed at 8 to 12 weeks, reflecting the timing of trial assessments. These findings suggest that the prognostic and health status benefits associated with SGLT2 inhibitors develop concurrently rather than sequentially. Early decongestion and hemodynamic unloading are likely to reduce the risk of worsening heart failure events, and, in subsequent weeks, these physiological changes may contribute to improvements in dyspnoea, fatigue, and physical limitations as measured by the KCCQ.

An apparent paradox arises because early separation of event curves suggests clinical stabilization within the first 1–2 months, whereas improvements in KCCQ were predominantly reported at 8–12 weeks. Ordinarily, one might expect symptom and quality-of-life recovery to precede prognostic improvement; however, the available trial data indicate the opposite chronology. This discrepancy is most plausibly explained by methodological rather than biological factors. First, most outcome trials implemented continuous surveillance for cardiovascular death and heart failure hospitalizations from randomization, whereas KCCQ was usually obtained only at pre-specified visits at 8–12 weeks, resulting in earlier detection of prognostic events than of health status changes. Second, progression of HF stage, reflected by recurrent and increasingly frequent hospitalizations, is tightly linked to prognosis; therefore, interrupting this trajectory early with SGLT2 inhibition can translate into a rapid reduction in hard events within 30–60 days, even if the full extent of quality-of-life recovery is captured later. Third, the physiological effects of SGLT2 inhibitors (natriuresis, decongestion, improved ventricular–arterial coupling, and renal stabilization) likely start to alleviate symptoms soon after treatment initiation, but patient-reported improvements may accrue more gradually and be recorded only at scheduled follow-up visits. Thus, the apparently later improvement in quality of life does not contradict the expected disease course; instead, it reflects a combination of early pathophysiological stabilization and the timing structure of quality-of-life assessments across trials.

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4.3. Functional Capacity and Exercise Physiology

Although results for functional endpoints were more heterogeneous, the directionality favored SGLT2 inhibition. EMPERIAL studies showed modest improvements in 6MWT, whereas EMPA-TROPISM demonstrated substantial gains in peak VO_2 and exercise performance, despite inclusion solely of non-diabetic HFrEF patients. These findings support the hypothesis that functional capacity improvements reflect true cardiopulmonary benefits rather than glycemic effects.

Variability in functional outcomes likely reflects inherent limitations of exercise tests (learning effects, comorbidities, device-dependence) [34] and differences in baseline functional status, trial duration, and intervention intensity. Nevertheless, the overall pattern supports improved physiological reserve and exercise capacity.

4.4. Biomarkers, Reverse Remodeling, and Mechanistic Insights

The observed reductions in NT-proBNP in DEFINE-HF and EMPULSE, together with the robust reverse remodeling documented in EMPA-TROPISM, provide converging evidence that SGLT2 inhibitors exert meaningful hemodynamic and myocardial effects beyond glycemic control. Mechanistically, SGLT2 inhibitors promote osmotic diuresis and natriuresis, reduce plasma volume and interstitial fluid, and improve diuretic efficiency, which together alleviate cardiac preload and pulmonary congestion. Concomitant reductions in blood pressure and arterial stiffness decrease afterload and improve ventricular–arterial coupling, while favorable effects on renal function help break the maladaptive cardiorenal feedback loop [7–10,35,36].

In addition to these hemodynamic mechanisms, experimental and clinical data suggest that SGLT2 inhibition may modulate myocardial metabolism (increased ketone body utilization, more energy-efficient substrate use), attenuate inflammation and oxidative stress, and improve microvascular function. These upstream effects are consistent with the reductions in LV volumes and increases in LVEF observed in EMPA-TROPISM, even in non-diabetic HFrEF patients, and may partly explain the uniform benefits across the EF spectrum.

Recent electrophysiological and translational studies further expand the pleiotropic profile of SGLT2 inhibitors, suggesting potential favorable effects on arrhythmic substrate, myocardial fibrosis, and electrical stability, reinforcing their multidimensional cardiovascular impact [37,38].

Importantly, several of these mechanisms offer a biologically plausible explanation for the improvements in subjective symptoms and patient-reported health status. Rapid decongestion and reduction in left-sided filling pressures are expected to translate into less exertional dyspnoea, orthopnea, and peripheral oedema, while improved ventricular–arterial coupling and renal function may enhance exercise tolerance and reduce fatigue. These pathophysiological changes are captured clinically as early gains in KCCQ symptom frequency and physical limitation domains, as well as modest but consistent increases in six-minute walk distance and peak VO_2 in selected trials. Taken together, the mechanistic profile of SGLT2 inhibitors aligns closely with the multidomain clinical and patient-centered benefits observed in this meta-analysis.

It is important to recognize that while outcome trials provide robust and generalizable evidence across the HF spectrum, mechanistic and structural data are derived largely from HFrEF cohorts, with more limited standardized evidence in HFpEF and acute HF. Therefore, mechanistic interpretations in these settings should be viewed with appropriate caution until dedicated phenotype-specific mechanistic studies become available.

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4.5. Sources of Heterogeneity and Trial-Level Differences

Heterogeneity was moderate for patient-reported outcomes and functional endpoints, but low for clinical outcomes. Trial-level variability is expected given differences in the following: HF phenotype (HFrEF vs. HFmrEF vs. HFpEF); acute vs. chronic settings; follow-up duration; baseline symptom burden; measurement modality (clinic-based, remote, CPET vs. 6MWT).

Importantly, meta-regression did not identify baseline LVEF, diabetes status, age, or NT-proBNP as effect modifiers for clinical outcomes. This reinforces the robustness of the findings and supports universal therapeutic applicability.

4.6. Strengths of This Meta-Analysis

This analysis has several methodological advantages: (1) Strict adherence to the PRISMA 2020 and PROSPERO frameworks; (2) Inclusion of both clinical and patient-centered primary outcomes, a rarity in SGLT2 meta-analyses; (3) Separation of mechanistic trials to avoid contaminating clinical effect estimates; (4) Rigorous bias assessment using RoB 2 [17]; (5) Comprehensive GRADE certainty evaluation [39]; (6) Large dataset enabling cross-phenotype comparisons; (7) Integration of acute and chronic HF populations, providing insights across the entire care continuum.

Our findings extend prior evidence by incorporating domains not included in recent large-scale meta-analyses such as Usman et al. [11], which focused on mortality and hospitalization but did not assess symptom burden, exercise capacity, or mechanistic imaging outcomes. This multidomain structure provides additional clinical granularity.

Another potential source of selection bias relates to regulatory indications and regional prescribing patterns for different SGLT2 inhibitors. For example, in Japan, only dapagliflozin and empagliflozin currently carry formal indications for heart failure. Sotagliflozin and canagliflozin do not. As a result, SOLOIST-WHF and CHIEF-HF enrolled more selected populations: patients with type 2 diabetes and recent worsening HF, as well as a digitally recruited, predominantly North American cohort, respectively. These may not fully reflect HF practice in all countries. However, the vast majority of statistical weight in our primary composite outcome comes from the large, globally representative dapagliflozin and empagliflozin trials: DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER. In a sensitivity analysis restricted to these agents, the treatment effect on cardiovascular death and HF hospitalization remained virtually unchanged. This argues against a major impact of molecule-specific indications or regional labeling differences on our conclusions.

4.7. Limitations

Despite its strengths, several limitations warrant acknowledgment: (1) Trial heterogeneity in symptoms and functional endpoints may limit precision of pooled estimates. (2) KCCQ improvements varied by baseline disease severity and duration of follow-up. (3) Mechanistic and short-duration trials (e.g., EMPERIAL, EMPA-VISION) provide complementary but indirect insights. (4) Some subgroup analyses, particularly in HFmrEF and HFpEF, remain underpowered. (5) Individual patient data (IPD) were not available, limiting deep phenotyping. (6) Publication bias cannot be fully excluded despite symmetric funnel plots. (7) No individual patient data (IPD); aggregate data limits adjustment for confounders. (8) Heterogeneity in time points (6 weeks–2.6 years) for symptoms/function. (9) Small mechanistic trials (n = 36–84) drive remodeling estimates; underpowered. (10) No network meta-analysis vs. other HF therapies. (11) English-only full texts (though searches unrestricted). Although abnormal longitudinal strain is a key pathophysiological feature in HFpEF, none of the eligible randomized HF trials reported standardized measurements that

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allowed quantitative synthesis. As a result, our remodeling domain is limited to changes in LV volumes, mass, and LVEF. Furthermore, most structural imaging data originate from HFrEF mechanistic studies; large HFpEF/HFmrEF outcome trials lacked serial CMR or detailed echocardiographic endpoints. Thus, it remains unclear whether SGLT2 inhibitors induce a similar reversal of remodeling in HFpEF.

Indications for SGLT2 inhibitors in heart failure vary substantially between countries and regulatory agencies. For example, in Japan, only empagliflozin and dapagliflozin are currently approved for heart failure, whereas sotagliflozin and canagliflozin do not have a formal HF indication. This heterogeneity may introduce selection bias in observational cohorts and national registries, because the spectrum of patients exposed to specific SGLT2 inhibitors differs according to local labeling, reimbursement rules, and clinicians' familiarity with each agent. As a result, studies conducted in settings where only one or two SGLT2 inhibitors are available may not be fully comparable to those from regions with broader access, and the generalizability of our findings to countries with different approval patterns should be interpreted with caution.

Most trials did not include systematic very-early (<30 days) KCCQ assessments; therefore, the temporal relationship between symptom relief and event reduction must be interpreted with caution, as later documentation of quality-of-life improvement may partly reflect endpoint scheduling rather than delayed clinical benefit.

Together, these strengths and limitations should guide interpretation of the multidomain findings.

Mechanistic and remodeling data are predominantly based on relatively small, short-duration mechanistic studies, mainly in HFrEF, with limited structured imaging data available for HFpEF and acute HF; therefore, extrapolation of structural effects across all phenotypes should be made cautiously.

4.8. Clinical Implications

By demonstrating consistent benefits across clinical, symptomatic, and mechanistic domains, this meta-analysis supports early and universal integration of SGLT2 inhibitors into guideline-directed therapy for heart failure. Their rapid onset of benefit, safety in acute and post-decompensation settings, and capacity to improve quality of life position them as a first-line therapy across EF categories.

4.9. Future Directions

Future research should prioritize the following: IPD meta-analyses to explore nuanced phenotypes and sex-specific responses; integration of SGLT2 inhibitors with emerging HFpEF therapies; mechanistic studies exploring tissue-level metabolic, inflammatory, and microvascular pathways; long-term assessment of functional capacity and quality-of-life endpoints; comparative trials between different SGLT2 agents in distinct HF subgroups; real-world evidence evaluating treatment sequencing and combination therapy.

5. Conclusions

This meta-analysis of randomized controlled trials demonstrates that SGLT2 inhibitors provide consistent and clinically meaningful prognostic benefit across the heart failure spectrum, with strong evidence from large, long-term chronic HF outcome trials and supportive, directionally concordant findings in acute HF settings. These agents reduce heart failure hospitalizations and cardiovascular death while also improving patient-reported health status and functional capacity. Improvements in symptoms, quality of life, and cardiac remodeling are evident; however, these derive predominantly from short- to

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intermediate-term mechanistic and symptomatic studies, mainly in HFrEF, and therefore warrant cautious interpretation, particularly in HFpEF and acute HF.

The favorable safety profile, early onset of benefit, and applicability across diverse clinical contexts support the integration of SGLT2 inhibitors as a key component of guideline-directed heart failure therapy. At the same time, further dedicated mechanistic studies—especially in HFpEF and acute HF—are needed to refine phenotype-specific understanding and to clarify the long-term structural and functional implications of treatment. Overall, the totality of evidence reinforces the multidomain therapeutic relevance of SGLT2 inhibitors while emphasizing appropriate nuance regarding the strength and origin of different evidence domains.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/jcm15010378/s1. Figure S1: Risk of bias assessment using the Cochrane Risk of Bias 2 (RoB 2) tool; Figure S2: All-cause and cardiovascular mortality; Figure S3: Myocardial phosphocreatine-to-ATP (PCr/ATP) ratio in the EMPA-VISION trial; Figure S4: Leave-one-out sensitivity analysis for the primary composite outcome; Figure S5: Leave-one-out sensitivity analysis for the KCCQ—Clinical Summary Score; Table S1: GRADE summary of findings; Table S2: PRISMA checklist; Table S3: Full electronic search strategy.

Author Contributions: Conceptualization, O.-M.B., S.S. and D.-M.M.; Methodology, O.-M.B., S.S., M.-L.C. and D.-M.M.; Software, D.-M.M.; Validation, O.-M.B., M.-L.C. and C.-O.M.; Formal analysis, D.-M.M. and S.S.; Investigation, O.-M.B., S.S., D.-M.M., I.-G.C., A.M. and E.F.; Resources, M.-L.C., M.B.-P., D.V. and N.R.K.; Data curation, D.-M.M. and I.-G.C.; Writing—original draft preparation, O.-M.B., S.S. and D.-M.M.; Writing—review and editing, M.-L.C., C.-O.M., M.B.-P., S.R.D., D.V. and N.R.K.; Visualization, D.-M.M.; Supervision, M.-L.C. and C.-O.M.; Project administration, M.-L.C.; Funding acquisition, S.S. All authors have read and agreed to the published version of the manuscript.

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Abbreviations

The following abbreviations are used in this manuscript:

6MWD	Six-minute walk distance
ACEi	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor–neprilysin inhibitor
CI	Confidence interval
CMR	Cardiac magnetic resonance
CV	Cardiovascular
eGFR	Estimated glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HF	Heart failure

HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
I^2	Inconsistency index
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire—Clinical Summary Score
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire—Total Symptom Score
LV	Left ventricle/left ventricular
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end-systolic volume
MD	Mean difference
NNT	Number needed to treat
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
OR	Odds ratio
PCr/ATP	Phosphocreatine-to-adenosine triphosphate ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomized controlled trial
RoB 2	Cochrane Risk of Bias 2 tool
RR	Risk ratio
SD	Standard deviation
SE	Standard error
SGLT2i	Sodium–glucose cotransporter-2 inhibitor
SMD	Standardized mean difference
T2DM	Type 2 diabetes mellitus
VE/VCO_2	Ventilatory equivalent for carbon dioxide
VO_2	Oxygen consumption
31P-MRS	Phosphorus-31 magnetic resonance spectroscopy

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The Impact of Introducing Sacubitril/Valsartan and SGLT2 Inhibitors in a Cohort of Patients with Reduced-Ejection-Fraction Heart Failure: A Real-Life Observational Study

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Abstract

Background/Objectives: Reduced-ejection-fraction heart failure (HFrEF) constitutes a challenge due to its high morbidity and mortality. The use of sacubitril/valsartan (angiotensin receptor–neprilysin inhibitors [ARNI]) and SGLT2 inhibitors (SGLT2i) represents a change in management approach with a demonstrated association with positive ventricular remodeling and a reduction in cardiovascular events. We describe the clinical and therapeutic course of patients with HFrEF in a specialized unit, comparing two consecutive periods (2011–2016 vs. 2017–2021), with emphasis on the impact of ARNI and SGLT2i upon clinical parameters and the use of devices. **Methods**: A retrospective, longitudinal observational study was carried out in 1363 outpatients with HFrEF, with at least two years of follow-up. Clinical characteristics, treatments, the evolution of left ventricular ejection fraction (LVEF), mortality, and the use of devices (implantable cardioverter–defibrillator [ICD], cardiac resynchronization therapy [CRT]) were evaluated. **Results**: A total of 1363 patients were analyzed, showing a significant therapeutic change in the 2017–2021 group with the incorporation of ARNI (40%) and SGLT2i (25%). This cohort achieved better ventricular recovery, with a significantly higher mean LVEF at one year compared to the 2011–2016 group (44.3% vs. 42.1%; $p = 0.004$). Regarding devices, ICD implantation rate decreased in the recent period (7.2% vs. 11.1%; $p = 0.016$), while CRT indication increased. Most importantly, all-cause mortality after two years fell from 9.4% to 5.9% ($p = 0.023$). Multivariate analysis confirmed that this survival improvement was independently associated with the study period (HR 1.57 for the earlier group) and was linked to the protective effect of contemporary pharmacological treatments. **Conclusions**: The systematic introduction of ARNI and SGLT2i in the treatment of HFrEF was associated with improved ventricular function, reduced need for device implantation, and lower mortality over the middle term in a real-life clinical setting.

Keywords: heart failure; reduced ejection fraction; neurohormonal treatment; devices; mortality

1. Introduction

Reduced-ejection-fraction heart failure (HFrEF) is an important public health problem worldwide, with high morbidity and mortality and a significant impact on patient quality of life and healthcare costs [1–3]. Despite the advances in treatment, the prognosis remains unfavorable, particularly in the advanced stages of the disease [4]. It should be noted that heart failure is related to risk factors such as age, sex, and body mass index. With regard to BMI, obesity can cause HF to develop or worsen existing disease [5].

In the last decade, a number of drug treatments have been introduced that have substantially modified the management of HFrEF [6]. Firstly, the approval of sacubitril/valsartan, based on the results of the PARADIGM-HF trial in 2014, and subsequently the introduction of SGLT2 inhibitors (SGLT2i), as new incorporations to the pharmacological arsenal in patients with HFrEF, has led to a therapeutic paradigm shift. Their incorporation to the clinical practice guidelines starting in 2016 and 2021, respectively, has been associated with improved patient survival and a significant reduction in hospital admissions due to decompensated heart failure [7–12]. However, few longitudinal descriptive studies in the real-life setting have analyzed the impact of this change in treatment in large cohorts with a prolonged follow-up period [13]. It is essential to evaluate these changes in real-life care settings in order to understand the clinical impact of the new therapeutic strategies, beyond the controlled conditions of clinical trials.

In this context, this study aimed to describe the clinical characteristics, treatments and prognostic aspects in a large cohort of patients with HFrEF who were treated in the specialized heart failure (HF) unit between the years 2011 and 2021, comparatively evaluating two consecutive clinical periods: before (2011–2016) and after (2017–2021) the systematic introduction of sacubitril/valsartan and SGLT2i. The hypothesis was that these therapeutic changes are associated with improvement of the clinical parameters, ejection fraction, and patient survival over the middle term, as well as a decrease in the indication of devices such as implantable cardioverter–defibrillators (ICD).

Objectives

The main objective of the present study was to describe the clinical characteristics, treatments, and prognostic aspects in a cohort of patients with HFrEF seen in a specialized HF unit between 2011 and 2021.

Specifically, the following was analyzed:

- Evolution of the therapeutic profile, especially the use of sacubitril/valsartan (angiotensin receptor–neprilysin inhibitors, ARNI) and SGLT2i in two consecutive periods (2011–2016 vs. 2017–2021).
- Evolution of left ventricular ejection fraction (LVEF) at one year of follow-up in each of the groups.
- The indication of devices such as implantable cardioverter–defibrillators (ICD) and cardiac resynchronization therapy (CRT).
- Compared mortality at two years between the two periods.

2. Methods

2.1. Study Design and Patients

A retrospective, longitudinal, single-center observational study was carried out in a cohort of consecutive patients seen in the Specialized Heart Failure Unit of the Department of Cardiology of a secondary hospital between January 2011 and December 2021. All

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patients had reduced-ejection-fraction heart failure (HFrEF), defined according to the current clinical guidelines of the European Society of Cardiology (ESC) [6]. A total of 1363 outpatients were included and divided into two groups according to the date of first consultation:

- Group 1: patients seen between 2011 and 2016.
- Group 2: patients seen between 2017 and 2021.

All patients had at least two years of clinical follow-up, making it possible to evaluate their evolution in terms of treatment, ventricular function and survival.

2.2. Data Collection

The clinical, demographic, laboratory test, electrocardiographic, echocardiographic, and pharmacological data, as well as the use of devices and mortality assessment, were recorded by the unit's cardiologists by reviewing the patients' electronic medical records. The ejection fraction was assessed using echocardiography (IE-33 and EPIQ-5, Philips, Bothell, WA, USA) at the start of follow-up and at the subsequent controls. All the data were entered in a database previously designed for the conduction of observational studies in the unit. Patient management was in accordance with the clinical practice guidelines available at the time of each visit.

2.3. Statistical Analysis

Quantitative variables were reported as the mean and standard deviation (SD), and qualitative variables were reported as frequencies and percentages. The chi-square test or Fisher exact test was used to compare qualitative variables between groups, while quantitative variables with and without a normal distribution were compared using the Student *t*-test or non-parametric tests, respectively. To calculate drug dosage over 1, only the patients who received drug treatment were taken into account.

Survival was analyzed using Kaplan–Meier curves, and comparisons between groups were made using the log-rank test. Furthermore, multivariate analyses were performed to identify independent predictors of outcomes, specifically utilizing Cox proportional-hazards regression models to estimate hazard ratios (HR) and their corresponding 95% confidence intervals (CI). The statistical analyses were performed using the IBM SPSS version 19.0 package (IBM, Armonk, NY, USA), considering a statistical significance level of $p < 0.05$.

2.4. Ethical Particulars

The study was carried out in abidance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by the Research Ethics Committee in October 2025 (approval number: 2025/378).

3. Results

3.1. Cohort Description

The study included a total of 1363 patients diagnosed with HFrEF and followed up on an outpatient basis in a specialized HF unit between the years 2011 and 2021. The patients were divided into two groups according to the date of first consultation: Group 1 (2011–2016): $n = 759$; Group 2 (2017–2021): $n = 604$.

There were no statistically significant differences between the groups in terms of mean age, sex distribution, initial LVEF, or body mass index. Creatinine levels, glomerular filtration rate, and comorbidities were similar in both groups. The patients in group 1 (2011–2016) had a higher mean systolic blood pressure (SBP), and a greater percentage of patients presented NYHA functional class III or IV, while the patients in group 2 (2017–2021) presented dyslipidemia more frequently than the other group (Table 1). All the patients were clinically stable at the time of inclusion, with no signs of acute decompensation.

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Table 1. Baseline characteristics.

	2011–2016 (*n* = 759)	2017–2021 (*n* = 604)	*p*	Standardized Difference
Age (years)	66.6 ± 10.9	66.1 ± 11.4	0.30	5.3
Male sex	574 (75.4)	456 (75.5)	0.95	0.23
SBP (mmHg)	132.3 ± 21.5	125.6 ± 20	**<0.001**	32.2
Creatinine (mg/dL)	1.1 ± 0.6	1.2 ± 0.8	0.09	10.2
GFR (ml/min/m^2)	73.3 ± 24.2	71.3 ± 25.7	0.15	7.8
Active smoker	338 (44.6)	265 (45.5)	0.59	1.8
Arterial hypertension	532 (70.1)	404 (68.8)	0.60	2.8
Diabetes mellitus	288 (37.9)	236 (41)	0.25	6.3
Dyslipidemia	497 (65.6)	422 (72.8)	**0.005**	15.4
Ischemic heart disease	330 (43.5)	278 (46)	0.34	5.0
LVEF (%)	32.1 ± 8.2	32.6 ± 8.3	0.24	6.1
NYHA > II	65 (8.3)	33 (5.5)	**0.03**	10.9
BMI (kg/m^2)	28.8 ± 4.8	29.1 ± 5.7	0.29	5.7
Underweight	5 (0.7)	3 (0.5)		
Normal weight	151 (20.1)	119 (21.1)	0.81	-
Overweight	332 (44.3)	236 (41.8)		
Obese	262 (34.9)	207 (36.6)		

Data are expressed as frequency (percentage) or mean ± standard deviation. SBP: systolic blood pressure; GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; BMI: body mass index.

3.2. Pharmacological Treatment at First Consultation and After One Year of Follow-Up

Patients in group 2 (2017–2021) showed a substantial change in therapeutic strategy compared to the previous years, with a significantly greater use of sacubitril/valsartan (ARNI) (42.8% vs. 0.1% in group 1) and SGLT2i (24.3% vs. 0%, respectively), in line with the current recommendations. This change was evident on the first visit and after one year (Table 2).

Table 2. Pharmacological treatment of the patients in group 1 (2011–2016) and group 2 (2017–2021) at first consultation and after one year of follow-up.

	2011–2016 (*n* = 759)	2017–2021 (*n* = 604)	*p*
First consultation			
ACEi	595 (78.8)	280 (47)	**<0.001**
ARB	141 (18.6)	38 (11.2)	**0.002**
ARNI	1 (0.1)	255 (42.8)	**<0.001**
ACEi, ARB or ARNI	737 (97.1)	573 (94.8)	**0.011**
Beta-blockers	740 (97.5)	562 (94.3)	**0.003**
MRA	424 (55.9)	350 (58.7)	0.29
SGLT2i	0	145 (24.3)	**<0.001**
Consultation 1 year			
ACEi	565 (74.5)	223 (37.4)	**<0.001**
ARB	163 (21.5)	116 (19.5)	0.35
ARNI	8 (1.1)	238 (39.5)	**<0.001**
ACEi, ARB or ARNI	735 (96.8)	569 (94.4)	**0.025**
Beta-blockers	740 (97.6)	561 (93.8)	**<0.001**
MRA	434 (57.3)	386 (64.8)	**0.005**
SGLT2i	0	216 (36.6)	**<0.001**

Data presented as frequency (percentage). ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor–neprilysin inhibitor; MRA: mineralocorticoid receptor antagonists; SGLT2i: sodium–glucose cotransporter 2 inhibitors.

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On comparing the proportion of angiotensin-converting enzyme inhibitors (ACEi) prescribed between the two groups at both the first visit and after one year of follow-up, a progressive transition was observed from ACEi/angiotensin receptor II antagonist (ARB) therapy towards ARNI, as indicated by the guidelines prior to 2021. This clinical pattern, where many patients started treatment with ACEi and then switched to ARNI, is coherent with the current regulatory restrictions in the first years of introduction of the drug.

The proportion of patients prescribed beta-blockers was lower in the group of patients that started consultation in 2017–2021 (although the proportion was very high in both groups), while no significant differences were observed in the indication of MRA.

3.3. Treatment Dose at First Consultation and After One Year of Follow-Up

To standardize the evaluation of pharmacological management, drug doses were analyzed as a proportion of the target doses established by the 2021 ESC guidelines, keeping this criteria constant regardless of the inclusion period to ensure cohort comparability. The intensity of the treatment was quantified using a ratio where the prescribed dose was divided by the maximum recommended dose; thus, a value of 1 was assigned to the achievement of the target dose, while values less than one represented sub-maximal doses and values greater than one indicated doses exceeding guideline recommendations. For the calculation of the mean and standard deviation, all values for each drug within their corresponding pharmacological group were used. In the specific case of combination therapies involving ACEi, ARB, and ARNI, individual ratios for each drug were calculated first, and then the mean of the three groups was obtained, treating them as a single pharmacological class averaged per class (Table 3).

Table 3. Cardiological drug doses (with respect to recommended target dose).

Drug	Initial Dose		*p*	Dose at One Year		*p*
	2011–2016	**2017–2021**		**2011–2016**	**2017–2021**	
Beta-blockers	0.72 ± 0.40	0.61 ± 0.36	**<0.001**	0.89 ± 0.47	0.68 ± 0.38	**<0.001**
ACEi/ARB/ARNI	0.59 ± 0.39	0.49 ± 0.31	**<0.001**	0.73 ± 0.32	0.72 ± 0.32	0.73
MRA	0.48 ± 0.13	0.48 ± 0.14	0.87	0.49 ± 0.18	0.50 ± 0.18	0.37
Loop diuretics	1.19 ± 0.68	0.95 ± 0.64	**<0.001**	1.23 ± 0.7	0.98 ± 0.64	**<0.001**

Results expressed as mean ± SD. ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor–neprilysin inhibitor; MRA: mineralocorticoid receptor antagonists.

In the group corresponding to the period 2011–2016, the initial beta-blocker doses were significantly higher than in the group corresponding to 2017–2021 (0.73 vs. 0.61; $p < 0.001$), and this difference persisted after one year of follow-up, though with an overall increase in both groups (0.89 vs. 0.68; $p < 0.001$). This observation may be related to the changes in the recommendations of the clinical guidelines, which from 2016 adjusted the titration targets of some drugs, such as beta-blockers. With regard to the renin–angiotensin system inhibitors (ACEi, ARB or ARNI), the initial doses were also higher in the group corresponding to the period 2011–2016 (0.59 vs. 0.49; $p < 0.001$), although after one year of follow-up both groups reached similar levels (0.73 vs. 0.72; $p = 0.738$), suggesting a tendency to equalize the degree of therapeutic optimization over time. The doses of mineralocorticoid receptor antagonists (MRA) remained stable in both periods, at both initial consultation and after one year, with no statistically significant differences (first consultation: 0.48 vs. 0.48; after one year: 0.49 vs. 0.50). Lastly, loop diuretics showed a higher dose in the patients corresponding to the period 2011–2016, at both initial consultation and after one year, probably driven by the individual congestive state of the patients.

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3.4. Left Ventricular Ejection Fraction (LVEF) at One Year

The analysis was conducted on a total cohort of 1022 patients, with 618 individuals included during the period from 2011 to 2016 and 404 patients included during the more recent period from 2017 to 2021. Significant improvement of LVEF at one year was observed in the patients corresponding to the period 2017–2021, with mean values of 44.3 ± 11.2% versus 42.1 ± 12.3% in the patients corresponding to the period 2011–2016 ($p = 0.005$), suggesting an association between therapeutic optimization and improved ventricular function (Figure 1).

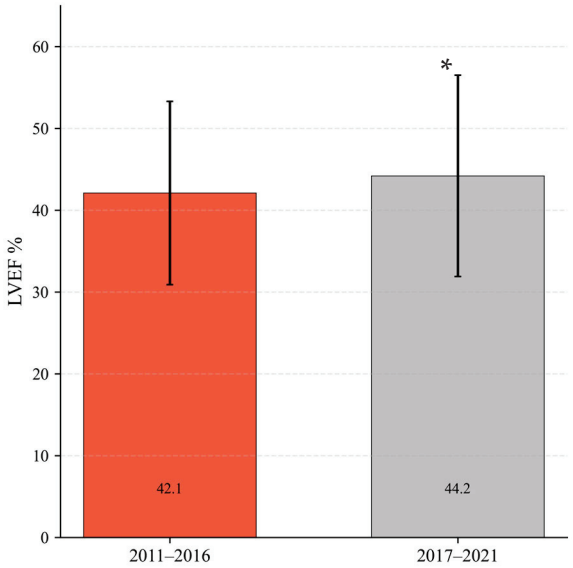


Figure 1. LVEF (%) after one year of follow-up. Data is presented as mean ± SD. * indicates $p < 0.05$.

3.5. Implanted Devices

A cohort of 1217 patients who were not device carriers at the start of follow-up was analyzed. Of the total, 9.7% ($n = 118$) received an implantable cardioverter–defibrillator (ICD) and 1.2% ($n = 15$) received cardiac resynchronization therapy (CRT). The analysis includes patients receiving implants not only at the index center but also at any hospital worldwide.

The proportion of patients that received an implantable cardioverter–defibrillator was smaller in the group corresponding to 2017–2021 (7.2%) than in the group corresponding to 2011–2016 (11.1%) ($p = 0.016$) (Figure 2). In the univariate analysis, patients who received an ICD were significantly younger (63.1 vs. 66.2 years; $p = 0.005$), with a higher proportion of males (85.6% vs. 72.5%; $p = 0.005$) and a higher prevalence of ischemic heart disease (72.0% vs. 39.9%; $p < 0.001$) compared to those without a device. Multivariate analyses confirmed that the study period (2017–2021 vs. 2011–2016) was independently associated with a higher probability of ICD implantation (HR 0.46; 95% CI: 0.265–0.816; $p = 0.008$) (Table 4). This association persisted even after adjusting for age, sex, ischemic etiology, NYHA class, left ventricular ejection fraction (LVEF), and pharmacological treatment.

With regard to CRT, an increase was noted in the more recent group (2.0% vs. 0.4%; $p = 0.005$) (Figure 2). The profile of implanted patients was characterized by older age (72.2 vs. 65.8 years; $p = 0.032$). After adjusting for age, sex, etiology, functional class (NYHA), left ventricular ejection fraction (LVEF), and pharmacological treatment, the study period remained a significant predictor for receiving CRT (HR 5.61; 95% CI: 1.34–23.4; $p = 0.018$) (Table 4).

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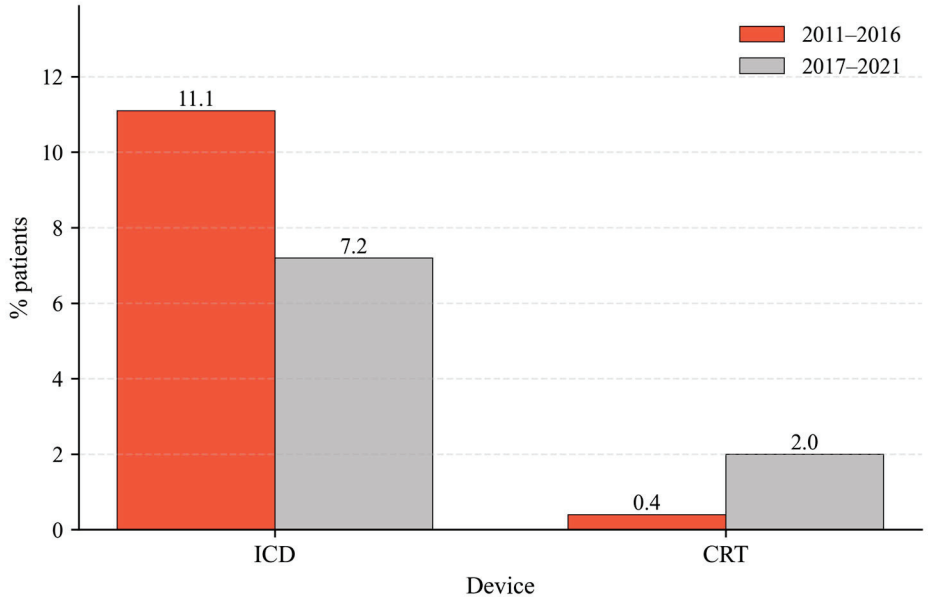


Figure 2. Indication of implantable devices in patients with no previous device (n = 1217). Data is presented as percentage.

Table 4. Multivariate analysis of predictors of device implantation (logistic regression).

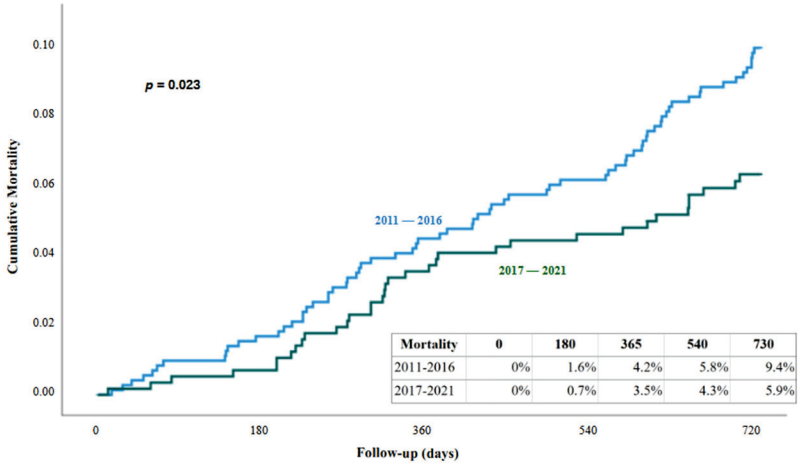
	Variable	Hazard Ratio	95% CI	p
ICD				
	Study period	0.465	0.265–0.816	**0.008**
	Sex	0.509	0.295–0.879	**0.015**
	Age	0.972	0.955–0.990	**0.002**
	Primary etiology	0.857	0.789–0.932	**0.000**
	NYHA	1.627	1.117–2.370	**0.011**
	Diagnostic LVEF	1.006	0.982–1.031	0.624
CRT				
	Study period	5.609	1.345–23.394	**0.018**
	Sex	0.556	0.144–2.145	0.394
	Age	1.063	0.999–1.132	0.054
	Primary etiology	1.083	0.943–1.244	0.257
	NYHA	1.300	0.475–3.560	0.610
	Diagnostic LVEF	0.995	0.933–1.062	0.891

LVEF: Left ventricular ejection fraction.

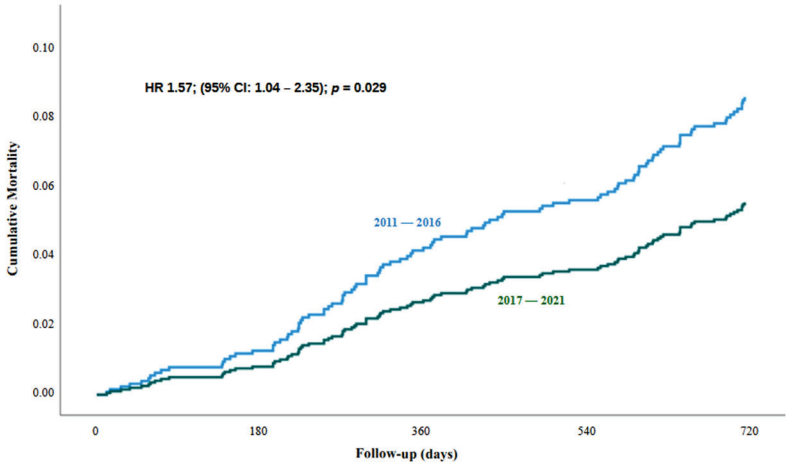
3.6. Survival at Two Years

Complete follow-up was considered as 730 days ± 30 days or until death. A total of 61 patients did not meet this criteria, and are considered as lost to follow up (4.5%). The mean follow up for the complete population was 696 days ± 115. Survival analysis based on the Kaplan–Meier curves showed significant improvement of patient survival at two years in the group in which first consultation corresponded to the period 2017–2021 compared to 2011–2016. The cumulative mortality rate after the second year was 9.4% (95% CI: 7.3–11.5) in the group corresponding to 2011–2016, versus 5.9% (95% CI: 4.0–7.8) in the group corresponding to 2017–2021, the difference being statistically significant (log-rank test, p = 0.023) (Figure 3A).

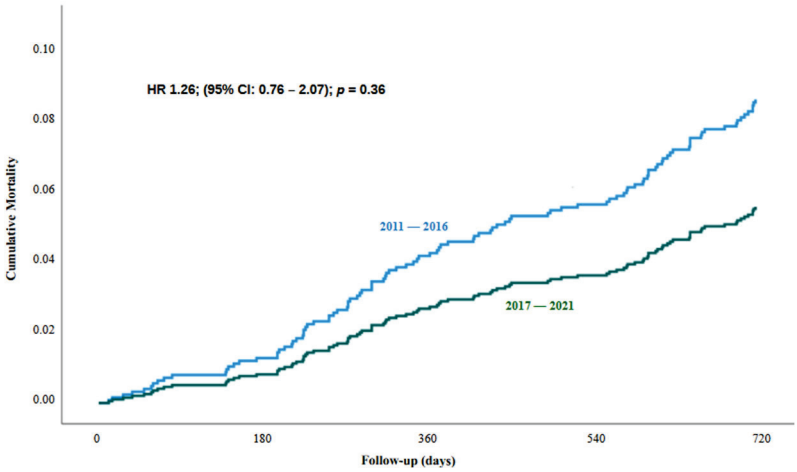
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(**A**) Unadjusted 2-year cumulative mortality.



(**B**) Cumulative mortality adjusted by baseline characteristics.



(**C**) Cumulative mortality adjusted by baseline characteristics and cardiological treatment.

Figure 3. Actuarial mortality curve (Kaplan–Meier). (**A**) Unadjusted; (**B**) adjusted by baseline characteristics; (**C**) adjusted by baseline characteristics and cardiological treatment.

To identify the determining factors of this improvement, two Cox regression models were applied. Firstly, a clinical model adjusting the baseline characteristics (sex, age, NYHA class, etiology, and LVEF) show that patients from the period 2011–2016 have a significant higher mortality risk than the 2017–2021 group (HR 1.57; 95% CI: 1.04–2.35; p = 0.029) (Figure 3B). In addition, age (HR 1.04; 95% CI: 1.02–1.06; p = 0.001) and NYHA class (HR 1.59; 95% CI: 1.12–2.26; p = 0.010) were significant clinical predictors of mortality

(Table 5). When adjustment was made not only by baseline characteristics but also by baseline treatments (Model 2), the survival difference between the two periods was no longer statistically significant (HR 1.26; 95% CI: 0.76–2.07; $p = 0.362$). This suggests that the observed survival benefit in the 2017–2021 group was primarily driven by the introduction of ARNI, and maybe also by SGLT2i therapy, which remained an independent protective factor (Figure 3C) (Table 5).

Table 5. Survival analysis (Cox regression) for 2-year mortality.

	Variable	Hazard Ratio	95% CI	*p*
MODEL 1 (Clinical)				
	Study period	1.571	1.047–2.357	**0.029**
	Sex	0.420	0.242–0.730	**0.002**
	Age	1.037	1.016–1.059	**0.001**
	Primary etiology	0.994	0.931–1.061	0.857
	NYHA	1.587	1.115–2.260	**0.010**
	Diagnostic LVEF	1.002	0.978–1.026	0.894
MODEL 2 (Clinical + Treatment)				
	Study period	1.260	0.767–2.072	0.362
	Sex	0.399	0.229–0.695	**0.001**
	Age	1.034	1.012–1.056	**0.002**
	Primary etiology	0.987	0.924–1.054	0.693
	NYHA	1.506	1.042–2.177	**0.029**
	Diagnostic LVEF	1.003	0.979–1.028	0.792
	ARNI baseline	0.365	0.135–0.985	**0.047**
	SGLT2i baseline	0.475	0.175–1.292	0.145

LVEF: left ventricular ejection fraction; ARNI: angiotensin receptor–neprilysin inhibitor; SGLT2i: sodium–glucose cotransporter 2 inhibitors.

4. Discussion

In this real-world, single-center observational study spanning more than a decade, we observed a significant improvement in two-year survival among patients with heart failure with reduced ejection fraction (HFrEF) managed in the most recent period (2017–2021) compared with those first evaluated between 2011 and 2016. This survival benefit, in which mortality decreased from 9.4% to 5.9% ($p = 0.023$), was evident in unadjusted analyses and persisted after adjustment for major baseline clinical characteristics. This indicates that temporal improvements in outcomes were not explained by differences in patient demographics or disease severity at presentation, as the baseline profile (characterized by an age close to 70, male predominance, and high prevalence of ischemic heart disease, arterial hypertension, and diabetes mellitus) remained stable and consistent with previous HFrEF registries [14], reinforcing the comparability of the analyzed groups.

When survival was adjusted for pharmacological treatment, the correlation between the time period and mortality was no longer statistically significant, suggesting that the observed improvement in survival is strongly associated with changes in medical therapy over time. This attenuation of the period effect supports the hypothesis that advances in heart failure management have played a relevant role in improving outcomes, as the most recent study period was characterized by a substantial increase in the use of guideline-directed disease-modifying therapies, specifically the progressive incorporation of sacubitril/valsartan (ARNI) and SGLT2 inhibitors following updates to international guidelines [6–9,15]. While initial doses of certain drug classes were higher in the earlier cohort, potentially due to higher baseline systolic blood pressure [16], the more recent

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group achieved effective titration during follow-up; furthermore, the lower utilization of loop diuretics in the 2017–2021 period likely reflects the enhanced natriuresis provided by ARNI and SGLT2i, which facilitates better congestion management [17].

These multivariate models were not designed to assess the independent prognostic effect of individual drug classes, but rather to explore whether temporal association with mortality persisted after accounting for changing treatment patterns. From this perspective, the loss of significance of the period variable after treatment adjustment supports the hypothesis that advances in heart failure management have played a relevant role in improving outcomes in routine clinical practice.

In parallel with pharmacological optimization, patients managed in the more recent period exhibited a significant improvement in left ventricular ejection fraction at one year (44.3% vs. 42.1%; $p = 0.005$). These findings are consistent with the reverse remodeling phenomena documented with contemporary therapies like ARNI, which can increase ejection fraction by 9% to 13% [18–20]. This improvement was associated with a subsequent reduction in device utilization: we observed a significant decrease in the prescription of implantable cardioverter–defibrillators (ICD), as many patients improved beyond the indication threshold. Conversely, the increase in cardiac resynchronization therapy (CRT) reflects both the expansion of clinical indications in recent guidelines [21] and the removal of local administrative barriers.

Overall, the significant improvement in survival observed over time in this cohort reinforces the clinical value of structured follow-up and active titration strategies in line with international guidelines [6]. These findings provide robust real-world evidence that advances in heart failure therapy have successfully translated into superior outcomes and enhanced ventricular recovery in routine practice, demonstrating that the synergy between broader access to contemporary drugs, meticulous dose adjustment, and improved patient adherence results in a tangible reduction in mortality and a significant improvement in LVEF.

5. Conclusions

This study demonstrates a significant improvement in two-year survival among patients with HFrEF over the last decade. This benefit was independent of baseline clinical characteristics but was attenuated after adjusting for pharmacological treatment, supporting the assumption that the observed prognostic improvement is primarily linked to the progressive adoption of contemporary disease-modifying therapies, particularly ARNI and SGLT2i. Although the observational nature of this real-world study precludes definitive causal inference, the results clearly suggest that the systematic application of therapies guided by evolving guidelines and active titration strategies has resulted in superior clinical outcomes and improved ventricular recovery. These findings highlight the critical role of pharmacological optimization and its association with an improved prognosis of heart failure at the population level in routine clinical practice.

Limitations

The present study has a number of limitations inherent to its retrospective observational design. Firstly, the lack of randomization does not allow us to draw firm causal relationships between the prescribed treatments and the clinical observed outcomes. Therefore, these findings should be interpreted as descriptive of temporal trends in the treatment of heart failure in the real world, rather than as direct evidence of treatment efficacy.

Secondly, the use of electronic records may have introduced information bias due to incomplete registries of key variables. Furthermore, although multivariate analyses were adjusted for baseline characteristics, residual confounding by measuring factors, such

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as improvements in the organization of care, follow-up intensity and patient adherence, cannot be completely excluded. In addition, the study did not include data on quality of life, which is relevant clinical information.

Moreover, an important limitation is that pharmacological treatments were analyzed as baseline variables rather than time-dependent exposures, which might underestimate their true prognostic impact over the follow-up period. Regarding diagnostic tools, biomarkers such as NT-proBNP and advanced echocardiographic parameters were not consistently available during the earlier years of the study (2011–2016). This limitation in data restricts the accuracy of ventricular remodeling characterization and prevents a comprehensive comparison of prognostic markers across all cohorts.

Finally, the inclusion period ended in 2021, coinciding with publication of the latest European guidelines on heart failure. Therefore, our results may underestimate the current degree of implementation of the quadruple neurohormonal therapy as the new standard of care.

Although the attenuation of the 'period effect' after adjusting for these drugs suggests that they contributed to improved survival, this observation remains a hypothesis due to the possible influence of the unmeasured factors mentioned above.

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Institutional Review Board Statement: The study was carried out in abidance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by the Research Ethics Committee on 3 October 2025 (approval number: 2025/378).

Informed Consent Statement: Patient consent was waived due to being a healthcare database approved by the management of Lucus Augusti University Hospital, which has subsequently been used for research purposes.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding authors.

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

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Systematic Review

GDMT Intensity at Hospital Discharge and Associated Clinical Outcomes in Heart Failure: A Systematic Review and Network Meta-Analysis

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Abstract

Background/Objectives: Contemporary heart failure (HF) guidelines recommend early initiation of four foundational drug classes in HFrEF. However, real-world prescription rates of guideline-directed medical therapy (GDMT) at discharge remain low, and comparative data in this setting is limited. We aimed to explore the association between GDMT intensity prescribed at or before hospital discharge and clinical outcomes. **Methods**: MEDLINE and EMBASE were searched through March 2026 (PROSPERO CRD420261352137). A frequentist random-effects network meta-analysis grouped regimens into four intensity nodes (single/none, double, triple, quadruple), with the primary analysis restricted to adjusted hazard ratios. The primary outcome was the composite of all-cause mortality (ACM) and HF hospitalization (HFH). Secondary outcomes were HFH alone, ACM, and cardiovascular mortality. Confidence was rated with CINeMA. Estimates are reported as associations, not treatment effects. **Results**: Twenty-seven studies (26 observational, 1 RCT; 73,174 patients) were included. Among SGLT2i-era cohorts, quadruple therapy was suboptimally prescribed (pooled 34%, range 11.6–55.2%). For the primary composite endpoint, more complete regimens were associated with progressively lower event rates versus single or no therapy (double: hazard ratio 0.76, 95% CI 0.68–0.84; triple: 0.72, 0.64–0.81; quadruple: 0.52, 0.36–0.75; $\tau^2 = 0$). A consistent ordinal gradient was seen across outcomes, with quadruple therapy ranking first numerically for every outcome in which it was estimable. The direction and ordering were preserved in a sensitivity analysis additionally incorporating risk ratios, on stratification by follow-up duration, and in an alternative

network anchored to incomplete therapy. Because most evidence was observational, the magnitude of these associations should not be interpreted as a causal treatment effect and likely reflects residual confounding and selection bias. **Conclusions**: Discharge GDMT remains an important opportunity to improve outcomes in patients with HF. Adequately powered randomized trials are required to establish the incremental benefit of this approach and to close the gap between evidence and practice.

Keywords: guideline-directed medical therapy; heart failure; network meta-analysis; hospital discharge; mortality; SGLT2 inhibitors

1. Introduction

Heart failure (HF) remains a leading cause of morbidity, mortality, and healthcare expenditure worldwide [1]. Landmark randomized controlled trials (RCTs) over the past three decades have established the mortality and morbidity benefits of four foundational pharmacologic classes, beta-blockers, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs)/angiotensin receptor-neprilysin inhibitors (ARNi), mineralocorticoid receptor antagonists (MRAs), and sodium–glucose cotransporter 2 inhibitors (SGLT2i), in patients with heart failure with reduced ejection fraction (HFrEF) [2]. Acting through complementary neurohormonal pathways, these agents deliver independent and additive reductions in all-cause mortality (ACM) and heart failure hospitalization (HFH), underpinning the rationale for combined foundational therapy [2,3]. These four pillars of guideline-directed medical therapy (GDMT) are now recommended as Class I therapy for HFrEF in international guidelines, and analyses including trials in the outpatient setting have shown that the quadruple combination provides the greatest survival benefit, with an estimated up to eight additional life-years compared with no treatment [4,5].

Despite this robust evidence, real-world registry data consistently demonstrate that comprehensive GDMT is suboptimally prescribed to eligible patients at hospital discharge [6,7]. This implementation gap is multifactorial, driven mainly by clinical inertia, but also including concerns about hemodynamic tolerability, fragmented care transitions, and the complexity of initiating multiple medications during an acute hospitalization [8,9]. The STRONG-HF (Safety, Tolerability, and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) trial provided the first randomized evidence that rapid, intensive up-titration of GDMT before discharge was safe and reduced the composite of HF rehospitalization and ACM at 180 days [10]. However, STRONG-HF did not include SGLT2i in its protocolized regimen and enrolled patients across the ejection fraction spectrum, leaving uncertainty about the incremental benefit of true quadruple GDMT at discharge [10].

A growing body of observational evidence has emerged comparing clinical outcomes across different GDMT intensity levels, from single-agent or no therapy through double, triple, and quadruple therapy, in patients discharged after an HFH. These studies have consistently reported dose–response associations favoring more complete GDMT, but they vary substantially in design, populations, follow-up duration, and definitions of GDMT intensity. To address these gaps, we performed a systematic review and network meta-analysis (NMA) to synthesize and explore the associations between GDMT intensity at hospital discharge and subsequent clinical outcomes.

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2. Materials and Methods

This study was registered in PROSPERO (CRD420261352137) and performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and the PRISMA extension statement for network meta-analyses (Supplemental Table S1) [11,12]. Institutional Review Board approval was not required, as all data were previously published.

Search Strategy and Study Selection. We performed systematic searches of the PubMed/MEDLINE and EMBASE Elsevier databases from inception through March 2026 for studies assessing clinical outcomes after HFH, stratified by the intensity of GDMT prescribed at or before discharge. The search strategy combined four conceptual blocks: (1) HF and related terms; (2) hospitalization and discharge-related terms; (3) pharmacotherapy terms covering GDMT pillars and combination therapy; and (4) timing, optimization, and initiation strategy terms. Complete search strings are provided in Supplemental Texts S1 and S2. No language or date restrictions were applied. Twelve investigators independently screened titles and abstracts in pairs, with conflicts resolved by consensus with a third reviewer. Study screening was performed using the Rayyan® (Rayyan Systems Inc., Cambridge, MA, USA) [13].

Because study-level regimen reporting was heterogeneous, treatment nodes were harmonized pragmatically. The single/none reference node comprised patients prescribed no foundational class or a single class; because the included studies seldom reported a pure untreated arm separately from a single-agent arm, this category was harmonized as the least-intensive group reported by each study, and a network separating untreated from single-agent patients was not estimable, as too few studies reported the zero-agent and single-agent strata separately. The network should therefore be interpreted as comparing GDMT intensity categories rather than identical pharmacologic interventions across studies.

Data Extraction and Treatment Classification. Study-level data were extracted by four investigators and included: study design, country, sample size, patient demographics, left ventricular ejection fraction (LVEF) criteria, GDMT components, follow-up duration, and effect estimates with 95% confidence intervals (CIs). When studies reported multiple effect estimates for the same comparison, we prespecified the extraction of the most fully adjusted model available, prioritizing estimates derived from multivariable Cox proportional-hazards regression or propensity-score methods over unadjusted estimates. Crude estimates were extracted only when adjusted measures were not reported, and this occurred almost exclusively for risk ratios derived from published 2×2 event tables [14–17].

Outcomes. The primary outcome was the composite of ACM and HFH. Secondary outcomes included ACM, HFH, and cardiovascular (CV) mortality.

Risk of Bias Assessment. Observational studies were assessed at the study level using the Newcastle-Ottawa Scale (NOS), while the single included RCT (STRONG-HF) was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [18,19]. Confidence in network estimates, on the other hand, was assessed using the CINeMA framework across six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence [20]. For CINeMA, risk of bias (RoB) assessments of observational studies were set to high within-study bias because treatment allocation was nonrandomized and highly susceptible to residual confounding by indication. Downgrading to moderate was allowed only if prespecified design safeguards were present, including exceptionally strong confounder control, clear exposure definition, robust outcome ascertainment, and minimal risk of selection bias. No study fulfilled these criteria sufficiently to warrant downgrading. These study-level judgments were then combined with the percentage contribution matrix to derive comparison-level assessments across all six CINeMA domains. Imprecision

was evaluated against a prespecified equivalence range defined by clinically important risk ratio thresholds of 0.90 and 1.11. Six investigators independently assessed RoB, with disagreements resolved by consensus.

A frequentist random-effects NMA was performed using the netmeta package (version 3.3–1) in R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria) [21], implementing the graph-theoretical approach [22]. Treatment effects were modeled on the log-ratio scale, with single/none therapy as the reference group. Because most included studies were nonrandomized, network estimates were interpreted as associations rather than causal treatment effects. Because hazard ratios (HRs) account for the time-to-event structure and censoring of the included cohorts and were predominantly derived from multivariable- or propensity-adjusted models, the primary network was restricted to adjusted HRs, and estimates are reported as hazard ratios. As a sensitivity analysis, we additionally fitted a combined network incorporating both HRs and risk ratios (RRs) on a common log-ratio scale (the "all-measures" network, reported as relative effects); because pooling HRs with RRs is valid only under low event rates and approximately proportional hazards, this network is presented as supportive rather than primary.

For multi-arm evidence structures, complete multi-arm studies were retained as true multi-arm designs within the network model, allowing the standard netmeta handling of within-study correlations [23]. When a study contributed an incomplete set of eligible multi-arm contrasts for a given outcome and time window, those contrasts were split into pseudo-two-arm entries for analysis. This approach preserved available information while allowing network estimation, but the resulting primary network estimates should be interpreted as average relative-effect estimates across heterogeneous study designs, regimens, and follow-up horizons.

Transitivity and similarity across studies. The validity of indirect comparisons in a NMA rests on the transitivity assumption, which states that studies contributing to different comparisons are similar in the distribution of effect modifiers. Because intensity nodes were harmonized pragmatically across heterogeneous designs, we evaluated transitivity both conceptually and empirically by compiling the distribution of potential effect modifiers (mean age, proportion of female participants, mean LVEF, geographic region, follow-up duration, publication era, and the prevalence of diabetes and chronic kidney disease, mean eGFR, and admission systolic blood pressure) across studies grouped by the most intensive regimen evaluated (the index node).

We also explored temporal heterogeneity by stratifying the primary 4-node ACM network by publication era (pre-2021 vs. $\geq$2021), as 2021 marked the widespread adoption of SGLT2i as a fourth pillar of HFrEF therapy. A formal network meta-regression on publication year was considered but not performed, because the quadruple-therapy node was informed exclusively by studies published from 2021 onward; publication year is therefore collinear with the availability of the most intensive node, precluding separation of an era effect from the treatment effect for that node. For clinical interpretation, HR-only network estimates for the composite of ACM and HFH were translated, consistent with GRADE guidance for binary outcome summary-of-findings tables [24], into illustrative 12-month absolute risks by applying each HR to an assumed baseline 1-year composite risk of 40% (treated risk = $1 - (1 - \text{baseline})^{\text{HR}}$), with additional scenarios spanning 20% to 50%, to derive illustrative absolute risk reductions and numbers needed to treat for double and triple therapy. An absolute translation was not derived for quadruple therapy, whose composite estimate is informed by a single direct study. These estimates were not intended to represent causal risk reductions.

Heterogeneity and inconsistency. Heterogeneity was quantified using τ^2 and Cochran's Q statistic. Global inconsistency was assessed using design-based decom-

position of the Q statistic; local inconsistency was explored using node-splitting (SIDE approach) [25], which compares direct and indirect evidence for each splittable comparison. Small-study effects and potential reporting bias were assessed visually using comparison-adjusted funnel plots with treatments ordered by therapeutic intensity (single/none → double → triple → quadruple), such that asymmetry to the left would indicate small-study effects favoring more intensive therapy. Given the limited number of studies per comparison (≤10 for most contrasts), formal regression-based asymmetry tests were not performed. Treatment hierarchies were assessed using P-scores [26]. Certainty of evidence was assessed using CINeMA [20]. All analyses used R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided p-values < 0.05 were considered significant.

3. Results

Twenty-seven studies met the inclusion criteria, comprising 26 observational cohort studies and one RCT (STRONG-HF), enrolling a total of 73,174 patients (Table 1 and Figure 1) [10]. Complete references of the included studies can be found in Supplemental Text S3. Studies were published between 2015 and 2026 across 14 countries, with the largest geographic representation from Asia (15 studies, 56%), followed by Europe and North America (five studies each), with single studies from South America and a multinational trial (STRONG-HF). The median sample size was 773 (interquartile range [IQR]: 479–1465), the mean age across studies was 69.5 years, 35.3% were female, and the mean LVEF was 29.7%. The median follow-up was 12 months (range: 1–43 months). Nineteen studies (70.4%) included exclusively patients with HFrEF (LVEF < 40%), while six (22.2%) included patients with LVEF < 50% (HFrEF and HFmEF populations), and two (7.4%) had no LVEF restriction (Table 1). The distribution of studies by geography, publication year, HF phenotype, and follow-up duration is summarized graphically in Supplemental Figure S1. Constituent drug-class composition and ARNI frequency by treatment node are summarized in Supplemental Table S2. The proportion of patients discharged on all four GDMT pillars was low and highly variable across contemporary cohorts published after SGLT2i approval for HF, ranging from 11.6% to 55.2% (median 43.8%). In a random-effects single-arm proportion meta-analysis using the Freeman–Tukey double-arcsine transformation, the pooled prevalence of quadruple therapy at discharge was 34.2% (95% CI, 21.3–48.5%) among these cohorts, with very high between-study heterogeneity (I^2 = 99.2%; τ^2 = 0.038; Q = 777.2, df = 6, p < 0.001).

Table 1. Characteristics of Included Studies.

Study	Country	Design	N	Age, y	Female, %	LVEF, %	GDMT Exposure Definition	Follow-Up, mo	Outcomes
Abe T (2020) [S1]	Japan	Retrospective	885	68.1	28.3	33.5	BB + RASi + MRA	19	ACM, CV mortality
Abe T (2023) [S2]	Japan	Retrospective	1021	77.8	36.3	33.0	BB + RASi	12	ACM
Abe T (2024) [S3]	Japan	Retrospective	160	67.8	21.0	30.5	RASi + BB + MRA	24	CV mortality
Ahn MS (2019) [S4]	South Korea	Prospective	986	68.7	62.6	27.2	RASi + BB + MRA	12	ACM, ACM + HFH, HFH
Akita K (2017) [S5]	Japan	Prospective	773	70.8	36.0	—	BB + RASi	24	HFH
Busson A (2018) [S6]	France	Prospective	624	73.8	35.4	28.2	BB + RASi	12	ACM

Table 1. *Cont.*

Study	Country	Design	N	Age, y	Female, %	LVEF, %	GDMT Exposure Definition	Follow-Up, mo	Outcomes
Chen YL (2021) [S7]	Taiwan	Prospective	1275	63.1	27.7	28.5	RASi + BB + MRA	12	ACM, CV mortality
Chen J (2025) [S8]	China	Prospective	223	68.8	33.6	32.4	RASi + BB + MRA + SGLT2i	6	ACM + HFH
Dobarro D (2020) [S9]	Spain	Retrospective	280	65.4	26.4	29.8	RASi + BB + MRA	43	ACM
Echeverria LE (2025) [S10]	Colombia	Retrospective	2051	68.0	29.0	30.0	BB + RASi + MRA + SGLT2i	1	ACM, ACM + HFH, HFH
Gilstrap L (2023) [S11]	USA	Retrospective	48,711	79.0	40.6	30.0	BB + RASi	12	ACM
Grewal D (2021) [S12]	USA	Retrospective	1655	63.0	33.0	23.0	BB + RASi + MRA	12	ACM, HFH
Huang CC (2025) [S13]	Taiwan	Retrospective	343	65.1	28.3	28.7	BB + RASi + MRA + SGLT2i	36	ACM, HFH, CV mortality
Jensen H (2025) [S14]	USA	Retrospective	544	59.0	23.7	24.0	BB + RASi + MRA + SGLT2i	3	HFH
Kawakubo Y (2022) [S15]	Japan	Retrospective	1232	72.0	38.0	30.0	BB + RASi + MRA	24	ACM, ACM + HFH, HFH
Mebazaa A (2022) [10]	Multinational (14 countries)	Open-label, parallel-group	1078	63.0	39.0	36.3	BB + RASi + MRA	6	ACM, ACM + HFH, HFH, CV mortality
Miyoshi Y (2026) [S16]	Japan	Prospective	2086	76.5	35.5	34.3	BB + RASi + MRA	12	ACM, ACM + HFH, HFH, CV mortality
Ohata T (2024) [S17]	Japan	Prospective	366	66.5	29.0	—	BB + RASi + MRA	12	ACM + HFH
Oren D (2024) [S18]	USA	Retrospective	603	70.0	37.6	25.2	BB + RASi + MRA + SGLT2i	18	ACM
Severino P (2024) [S19]	Italy	Prospective	278	69.7	76.3	31.4	BB + RASi + MRA + SGLT2i	6	ACM + HFH, HFH, CV mortality
Sung SH (2018) [S20]	Taiwan	Retrospective	423	84.5	21.7	—	RASi + BB + MRA	27	ACM
Takeuchi S (2022) [S21]	Japan	Prospective	1924	73.0	30.5	34.1	BB + RASi	16	ACM, ACM + HFH, HFH
Vicent L (2019) [S22]	Spain	Prospective	566	68.2	33.3	—	RASi + BB + MRA	12	ACM, ACM + HFH, CV mortality
Vorilhon C (2015) [S23]	France	Retrospective	1825	77.2	52.4	—	RASi + BB + MRA	19	ACM
Willeford A (2025) [S24]	USA	Retrospective	2121	59.3	25.6	24.8	BB + RASi + MRA + SGLT2i	1	ACM, ACM + HFH, HFH
Wongsalap Y (2023) [S25]	Thailand	Retrospective	607	64.3	45.5	28.1	BB + RASi + MRA	12	ACM, ACM + HFH, HFH
Yamaguchi T (2018) [S26]	Japan	Prospective	534	73.1	27.1	29.8	BB + RASi	12	ACM, HFH

Abbreviations: ACM = all-cause mortality; CV = cardiovascular; BB = beta-blocker; GDMT = guideline-directed medical therapy; HFH = heart failure hospitalization; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; RASi = renin–angiotensin system inhibitor; SGLT2i = sodium–glucose cotransporter 2 inhibitor.

Twenty of the 26 observational studies were rated high quality (NOS 7–9) and six moderate quality (NOS 5–6) (Supplemental Table S3). The favorable NOS profile should not be interpreted as high causal certainty, as the NOS does not fully capture biases relevant to causal treatment-effect estimation. Specifically, the NOS appraises the methodological

conduct of a cohort study, whereas the CINeMA within-study-bias domain appraises the credibility of the nonrandomized treatment-effect estimate contributing to the network; a well-conducted cohort can therefore score highly on the NOS yet remain at high risk of confounding by indication, consistent with the treatment of confounding under ROBINS-I. Because GDMT intensity at discharge was not randomly assigned, observational comparisons remained susceptible to residual confounding, confounding by indication, and selection bias; in CINeMA, all observational studies were therefore classified as high within-study bias. STRONG-HF was judged to have some concerns on RoB 2 for the primary composite outcome, mainly related to the open-label design.

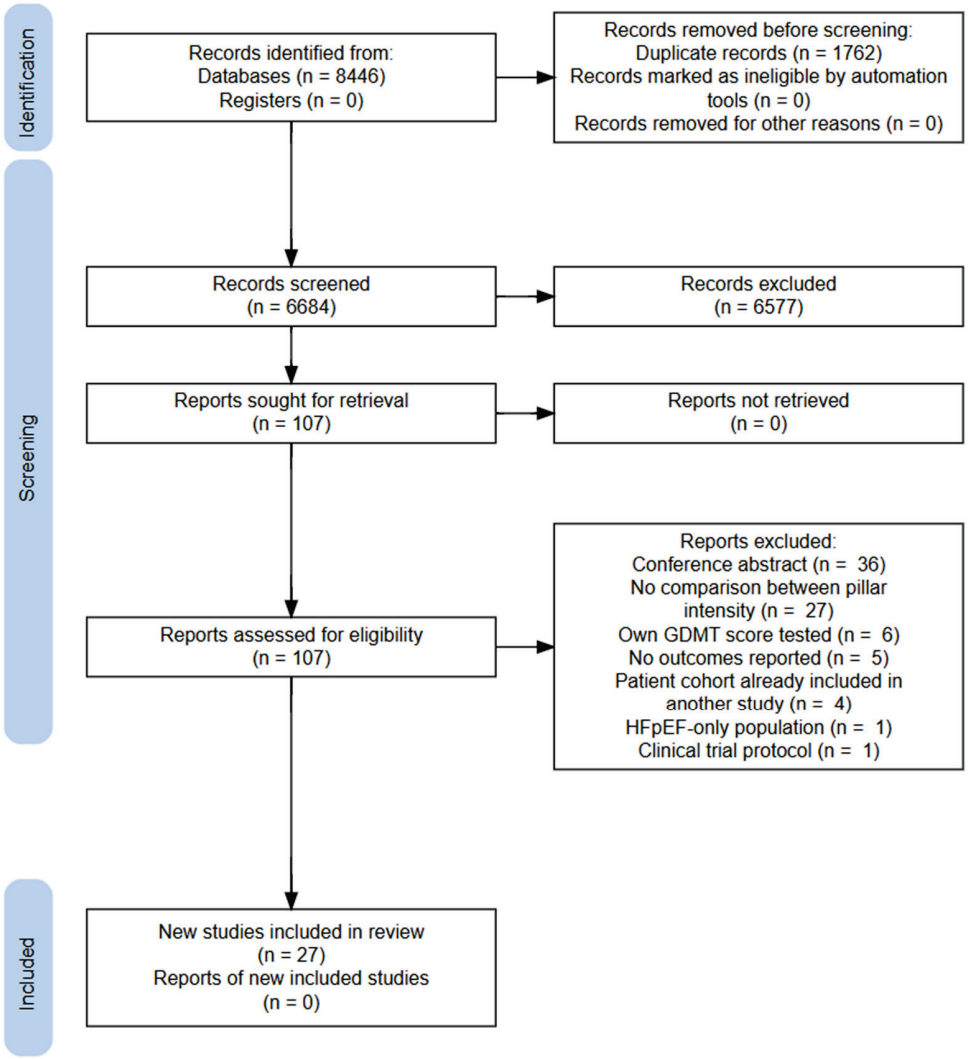


Figure 1. PRISMA Flow Diagram of Study Selection.

The primary (HR-only) analysis included 13 studies (20 contrasts) for ACM, four studies (eight contrasts) for the composite outcome, nine studies (17 contrasts) for HFH, and four studies (six contrasts) for CV mortality (Figure 2, Tables 2 and S4). In the HR-only network the quadruple node was connected to single/none therapy for ACM, the composite, and HFH, but not for CV mortality, where it is reported only in the all-measures sensitivity network. All estimable networks were connected through at least one pathway.

Compared with single/none therapy, the pooled hazard ratio was 0.52 (95% CI: 0.36–0.75) for quadruple therapy, 0.72 (0.64–0.81) for triple therapy, and 0.76 (0.68–0.84) for double therapy (Figures 2 and 3). Table 3 presents an illustrative analysis of the absolute risk reduction and number needed to treat for medical therapy at discharge. Heterogeneity

was not detected in this network ($\tau^2 = 0$; p for heterogeneity = 0.96), and quadruple therapy ranked highest (P-score = 0.98) (Figure 4). CINeMA confidence ratings were low for four comparisons and very low for two (quadruple vs. single/none, with only one study providing direct evidence, and quadruple vs. triple therapy, which relied entirely on indirect evidence and was downgraded for major imprecision) (Supplemental Tables S5 and S6).

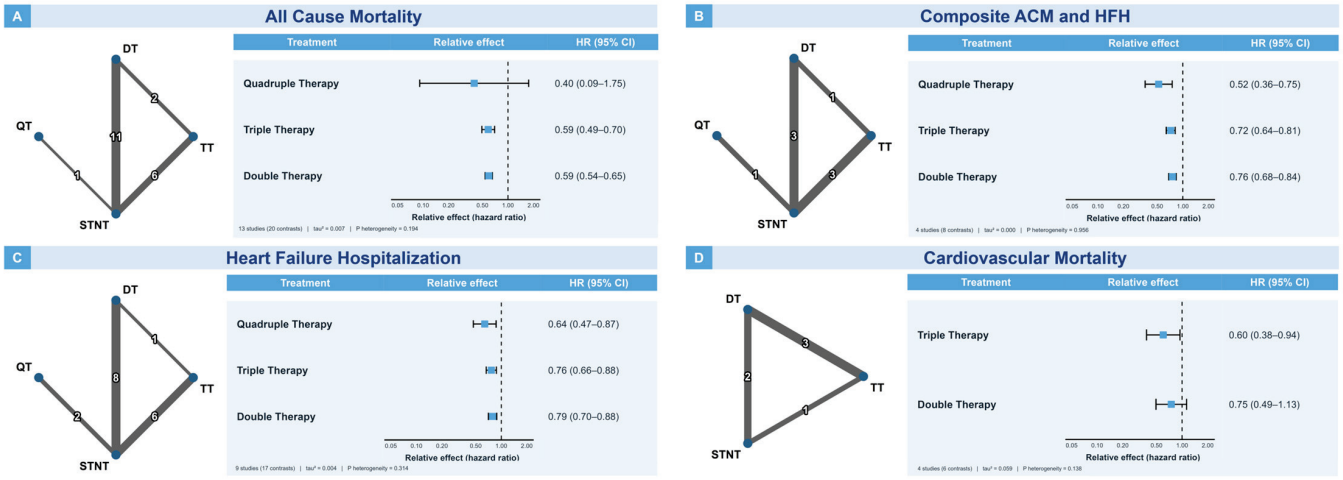


Figure 2. GDMT Intensity at Discharge and Clinical Outcomes after Acute Decompensated Heart Failure Hospitalization. Network (**left**) and Forest (**right**) plots showing the evidence structure and pooled network meta-analysis estimates for each of the four outcomes: all-cause mortality (**A**), composite of all-cause mortality and heart failure hospitalization (**B**), heart failure hospitalization (**C**), and cardiovascular mortality (**D**). Node size is proportional to the number of study arms, and edge width is proportional to the number of direct comparisons. All networks include four nodes: quadruple (QT), triple (TT), double (DT), and single/none (STNT) therapy. ACM = all-cause mortality; CV = cardiovascular; DT = double therapy; HFH = heart failure hospitalization; QT = quadruple therapy; STNT = single/none therapy; TT = triple therapy. CI = confidence interval; GDMT = guideline-directed medical therapy.

Table 2. Primary Network Meta-Analysis Results: All Outcomes, Overall Follow-Up.

Outcome	Comparison	HR [95% CI]	Studies	P-Score	Tau^2	p-Het
All-cause mortality	QT vs. S/N	0.400 [0.091; 1.754]	13	0.760	0.0070	0.194
	TT vs. S/N	0.585 [0.492; 0.696]		0.623		
	DT vs. S/N	0.594 [0.539; 0.655]		0.579		
Composite ACM + HFH	QT vs. S/N	0.520 [0.360; 0.751]	4	0.975	0.0000	0.956
	TT vs. S/N	0.721 [0.639; 0.814]		0.601		
	DT vs. S/N	0.756 [0.683; 0.837]		0.424		
HF hospitalization	QT vs. S/N	0.638 [0.468; 0.869]	9	0.915	0.0041	0.314
	TT vs. S/N	0.762 [0.664; 0.875]		0.604		
	DT vs. S/N	0.789 [0.705; 0.883]		0.481		
CV mortality	QT vs. S/N	Not estimable *	4	—	0.0589	0.138
	TT vs. S/N	0.600 [0.381; 0.944]		0.921		
	DT vs. S/N	0.746 [0.492; 1.130]		0.531		

Values represent network estimates (pooled HRs) from the primary random-effects model restricted to adjusted HRs, using single/none therapy as the reference. * The quadruple node was not estimable against single/none therapy for cardiovascular mortality in the HR-only network; the corresponding all-measures (HR + RR) estimate (0.08, 95% CI 0.02–0.40) is provided in Supplemental Table S7. Abbreviations: ACM = all-cause mortality; CI = confidence interval; CV = cardiovascular; DT = double therapy; HFH = heart failure hospitalization; HR = hazard ratio; QT = quadruple therapy; S/N = single/none therapy; TT = triple therapy; τ^2 = between-study variance.



Figure 3. League Tables for All Primary Outcomes. Four-by-four league tables displaying all pairwise comparisons from the primary random-effects (adjusted HR) network meta-analysis for (**A**) all-cause mortality, (**B**) composite of ACM and HFH, (**C**) heart failure hospitalization, and (**D**) cardiovascular mortality. Values represent hazard ratios (95% CI) for the row treatment versus the column treatment. Statistically significant comparisons are highlighted. Because most evidence was nonrandomized, pairwise estimates should be interpreted as associations rather than causal effects. Abbreviations: ACM = all-cause mortality; HFH = heart failure hospitalization.

Table 3. Illustrative Absolute Risk Reduction and Number Needed to Treat (Composite of All-Cause Mortality and HF Hospitalization).

Comparison	Baseline 1-yr Composite Risk	Treated Risk	ARR (95% CI)	NNT (95% CI)
Double vs. single/none	40%	32.0%	8.0% (5.2 to 10.5)	13 (9 to 19)
Triple vs. single/none	40%	30.8%	9.2% (6.0 to 12.2)	11 (8 to 17)

ARR = absolute risk reduction; HR = hazard ratio; NNT = number needed to treat. Additional baseline-risk scenarios are provided in Supplemental Table S10.

In the primary HR-only network, progressively higher GDMT intensity categories were associated with lower ACM estimates versus single/none therapy, although the quadruple estimate was imprecise. The pooled HR was 0.40 (95% CI: 0.09–1.75) for quadruple therapy, 0.59 (0.49–0.70) for triple therapy, and 0.59 (0.54–0.66) for double therapy (Figures 2 and 3). The quadruple-versus-single/none estimate was informed by a single direct study and its confidence interval crossed unity.

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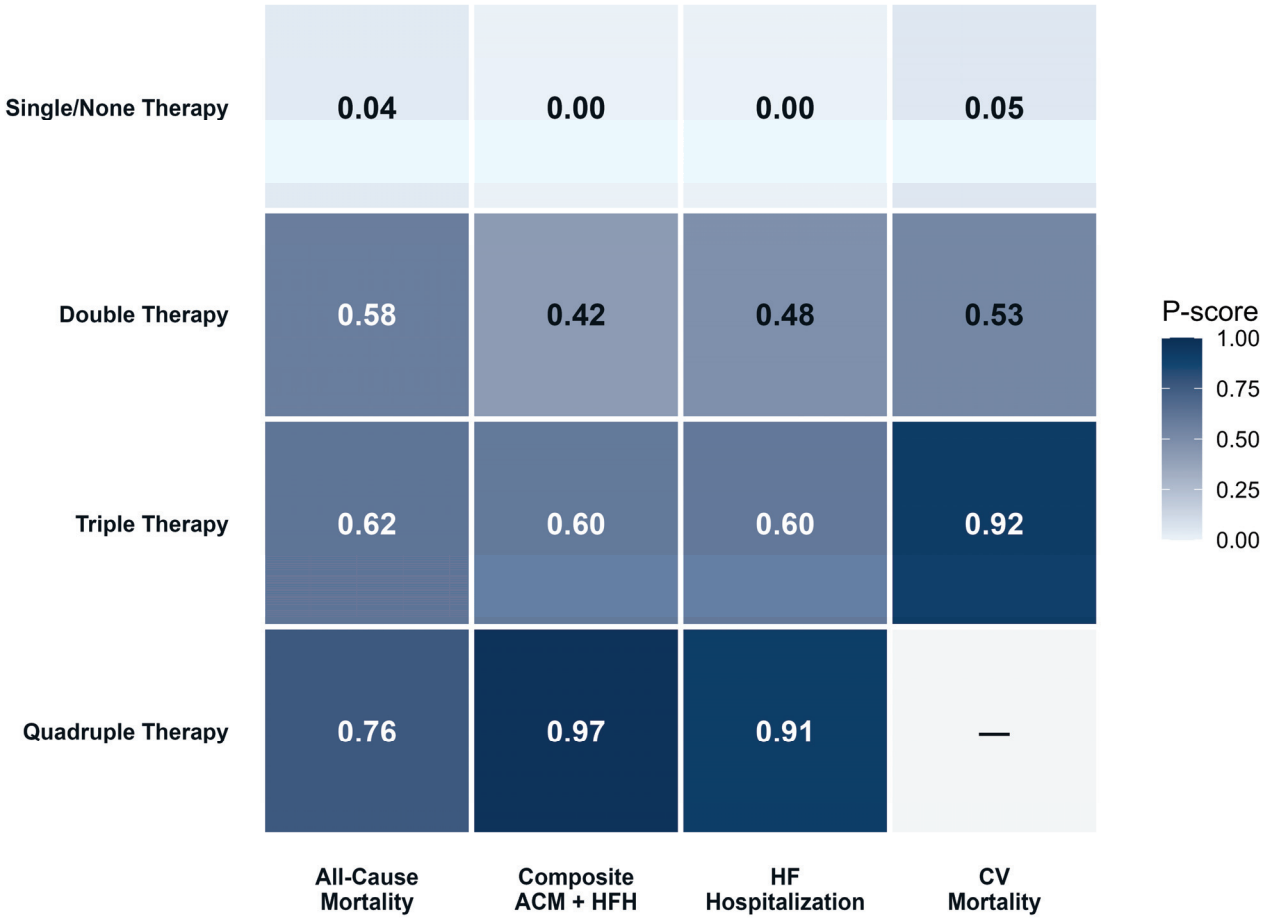


Figure 4. Treatment Hierarchy Across Clinical Outcomes. Heatmap showing P-scores from the primary random-effects network meta-analysis for quadruple, triple, double, and single/none GDMT at hospital discharge across the four primary outcomes: (i) all-cause mortality, (ii) composite of all-cause mortality and heart failure hospitalization, (iii) heart failure hospitalization, and (iv) cardiovascular mortality. Higher P-scores indicate a greater probability of ranking best within each outcome, whereas lower P-scores indicate a lower ranking probability. This figure summarizes the relative treatment hierarchy across outcomes and should be interpreted as a ranking metric rather than a measure of treatment effect magnitude or statistical significance. ACM = all-cause mortality; CV = cardiovascular; GDMT = guideline-directed medical therapy; HFH = heart failure hospitalization.

Heterogeneity was low (τ^2 = 0.007; p for heterogeneity = 0.19), and treatment ranking favored quadruple therapy (P-score = 0.76), followed by triple therapy (0.62), double therapy (0.58), and single/none therapy (0.04) (Figure 4). In the primary HR-only network, confidence was low for the double-versus-single/none and triple-versus-single/none comparisons and very low for the remaining four; the quadruple-versus-single/none comparison was additionally downgraded for serious imprecision, as its single direct study yielded a wide interval crossing unity (0.40, 95% CI 0.09–1.75). Downgrading was otherwise driven by within-study bias (a major concern for all comparisons given the observational evidence base), suspected reporting bias, and indirectness arising from variation in population definitions and treatment constructs across studies (Supplemental Tables S5 and S6).

In the all-measures sensitivity analysis (combining HRs and RRs), the ordinal gradient persisted, but the quadruple-versus-single/none estimate was substantially more extreme (relative effect 0.13, 95% CI 0.06–0.28). This value was driven almost entirely by one small study reporting crude, unadjusted RRs (Huang 2025 [14], N = 343, 36-month follow-up); in the leave-one-study-out analysis, omitting this study alone returned the estimate to

0.40 (Supplemental Tables S7 and S8). The magnitude of the all-measures quadruple estimate should therefore not be interpreted as a treatment effect.

The pooled HR versus single/none was 0.64 (95% CI 0.47–0.87) for quadruple, 0.76 (0.66–0.88) for triple, and 0.79 (0.70–0.88) for double therapy (Figures 2 and 3). Heterogeneity was low (τ^2 = 0.004; p = 0.31), and the hierarchy again favoured quadruple therapy (P-score 0.92) (Figure 4). CINeMA confidence was low for the quadruple vs. single/none comparison and very low for the remaining five, reflecting heterogeneity (particularly for double vs. single/none, where the prediction interval extended substantially beyond the confidence interval) and imprecision in the indirect quadruple comparisons (Supplemental Tables S5 and S6).

In the primary HR-only network the quadruple node was not connected to single/none therapy for CV mortality (the only adjusted-HR quadruple datum derived from a comparison with incomplete therapy); the pooled HR versus single/none was 0.60 (95% CI 0.38–0.94) for triple and 0.75 (0.49–1.13) for double therapy, and triple therapy ranked highest among estimable nodes (P-score 0.92). In the all-measures sensitivity network, the quadruple-versus-single/none relative effect was 0.08 (0.02–0.40), but with very wide intervals and reliance on crude RRs (Figures 2 and 3; Supplemental Table S7). Heterogeneity in the all-measures CV network was moderate (τ^2 = 0.076; p = 0.069). Among the estimable comparisons, CINeMA confidence was low (triple vs. single/none) to very low (double vs. single/none and triple vs. double), with imprecision and heterogeneity the principal concerns; the three quadruple-therapy comparisons were not estimable in the HR-only network (Supplemental Tables S5 and S6).

Regarding transitivity assessment, studies informing the quadruple-therapy node enrolled younger patients (mean age 66 versus 69 and 75 years for the triple- and double-therapy nodes), were published exclusively from 2021 onward, and had shorter follow-up and higher mean eGFR, whereas sex and mean LVEF were comparable across nodes. These imbalances are consistent with evolving discharge practice in the SGLT2i era and represent potential sources of intransitivity; comparisons involving the quadruple node, which is informed solely by contemporary cohorts, should therefore be interpreted with particular caution (Supplemental Table S9).

Overall, the primary NMA suggested a consistent ordinal gradient across all four clinical outcomes, with progressively more complete GDMT associated with progressively lower relative event rates.

3.1. Time-Stratified Sensitivity Analyses

The direction of estimates was consistent across prespecified time windows. For ACM in the all-measures model at the intermediate 6–12-month horizon, relative effects versus single/none were 0.081 (quadruple), 0.495 (triple), and 0.539 (double); at long-term follow-up (>12 months), the gradient persisted (0.400, 0.565, 0.696), although the quadruple estimate was based on fewer studies and wider CIs. Composite and HFH sensitivity analyses preserved the ordinal pattern; some strata were informed by only 1–4 studies. CV mortality estimates remained directionally consistent but less precise (Supplemental Table S7).

Node-splitting revealed local inconsistency in one contrast of the all-measures ACM network: the double vs. quadruple comparison showed disagreement between direct (relative effect 8.33; 95% CI 3.23–21.5, derived from a single study, Huang 2025 [14]) and indirect (1.43; 95% CI 0.38–5.41; P for inconsistency = 0.034) evidence (Supplemental Figure S2). This contrast reflects the same crude RR study that drove the extreme all-measures quadruple estimate, and the inconsistency was attenuated in the primary HR-only network, in which no comparison was downgraded for incoherence (Supplemental Tables S5 and S6).

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No other ACM contrasts showed significant local inconsistency, and the composite outcome network showed no detectable heterogeneity or between-design inconsistency. The HFH network showed a statistically significant between-design component in the Q-decomposition (Q = 12.2; $p = 0.016$), which was attenuated when restricting to HR-only evidence ($p = 0.469$). The CV mortality network contained no splittable contrasts and was assessed at the global level only (Supplemental Table S11). Leave-one-study-out analyses for ACM showed that the direction and ordering of estimates were preserved when any single study was omitted, although the magnitude of the quadruple-versus-single/none estimate remained sensitive to individual studies (Supplemental Table S8).

3.2. Alternative Network Analysis

With incomplete therapy as the reference (excluding single/none), the gradient was broadly preserved. In the HR-only alternative network, the HR versus incomplete therapy for the composite endpoint was 0.50 (95% CI 0.34–0.73) for quadruple, 0.61 (0.46–0.82) for triple, and 0.63 (0.44–0.90) for double therapy; for ACM it was 0.63 (0.46–0.85) for triple and 0.74 (0.46–1.18) for double therapy, with the quadruple node not estimable against incomplete therapy in the HR-only network (the corresponding all-measures estimate was 0.14, 0.04–0.49). The alternative HFH and CV mortality networks showed greater heterogeneity and wider confidence intervals and are therefore regarded as supportive rather than definitive (Supplemental Table S12).

Comparison-adjusted funnel plots for all four primary networks showed visually symmetric distributions of study-level contrasts, without clear evidence of small-study effects favouring more intensive therapy (Supplemental Figure S3); formal asymmetry tests were not performed due to limited studies per comparison. The proportion of information arising from direct versus indirect evidence is reported in Supplemental Table S13 and the full percentage contribution matrix in Supplemental Figure S4; the quadruple-versus-triple and quadruple-versus-double comparisons were informed entirely by indirect evidence, and quadruple-versus-single/none rested on a single direct study. In an era-stratified ACM analysis (all-measures network, since the HR-only network was too sparse to stratify by era), the magnitude of the triple-therapy association was similar before 2021 (relative effect 0.41; 0.32–0.52) and from 2021 onward (0.57; 0.45–0.72); quadruple estimates were available only from 2021 onward, so that publication era and the availability of the quadruple node are collinear (Supplemental Figure S5).

4. Discussion

This systematic review and network meta-analysis of 27 studies enrolling 73,174 patients provides the first network-level synthesis of the clinical outcomes associated with different intensities of GDMT prescribed at hospital discharge in HF. Its most consequential finding is not the direction of the association but the state of the evidence underlying it: of 27 studies addressing this clinically pivotal decision point, only one was a randomized controlled trial, and that trial (STRONG-HF) was conducted before quadruple therapy became the standard of care, testing rapid up-titration intensity rather than the initiation of all four foundational pillars and excluding SGLT2i from its protocol [10]. The comparative evidence on GDMT intensity at discharge is therefore almost entirely observational, and no randomized trial has yet evaluated the safety and efficacy of protocolized quadruple-therapy initiation in the peri-discharge setting. Furthermore, the observational evidence indicates that only about one-third of patients in contemporary SGLT2i-era cohorts are being discharged on all four pillars, highlighting a significant gap despite guideline recommendations.

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Within this observational evidence base, we observed a consistent, monotonic gradient in which progressively more complete GDMT was associated with lower relative event rates across all four prespecified outcomes, with quadruple therapy ranking first for each outcome in which it was estimable (P-scores 0.76–0.98); for CV mortality the quadruple node was not estimable in the primary HR-only network, where triple therapy ranked highest. Across outcomes, the quadruple-node comparisons carried the lowest certainty in the network—each informed by at most a single direct study and graded low to very-low confidence, with the headline composite estimate very low—so the first-place ranking of quadruple therapy should be read as a hypothesis-generating signal rather than a precise effect estimate. The directionality was preserved across sensitivity analyses, including the combined HR/RR network, time-window stratification, leave-one-study-out analyses, and an alternative network anchored to the incomplete-therapy node. This gradient is biologically coherent with the complementary mechanisms of the four foundational classes (RASi, beta-blockers, MRAs, and SGLT2i), each modulate distinct but overlapping maladaptive pathways, providing plausibility for additive benefit [2,3]. It is also directionally consistent with prior syntheses conducted predominantly in the ambulatory setting: the component NMA by van Essen et al. and the cross-trial analysis by Vaduganathan et al. both projected substantial incremental benefit from quadruple therapy in chronic HF populations [2,5]. In other words, our observational signal at discharge largely reproduces what randomized outpatient evidence has already established; it does not, on its own, extend the causal knowledge base. Because 26 of 27 studies were nonrandomized and the node-based definition captures the number rather than the specific identity of prescribed pillars, these estimates should be read as associations between greater pharmacological completeness at discharge and better observed outcomes, confounded to an unknown degree by patient selection, rather than as treatment effects or as a ranking of individual molecules.

Several mechanisms other than a true treatment effect plausibly contribute to the observed gradient. Discharge on more complete GDMT is itself a marker of eligibility and clinical stability: patients who tolerate four agents tend to have higher blood pressure and heart-rate reserve, better renal function, less residual congestion, fewer contraindications, and greater engagement with care, whereas sicker or frailer patients are preferentially discharged on fewer agents (confounding by indication and by treatment eligibility). Healthy-adherer bias and institutional effects (higher-performing centres both prescribe more comprehensive therapy and deliver better transitional care) act in the same direction, and our transitivity assessment showed that quadruple-therapy cohorts were, on average, nine years younger and had higher mean eGFR than double-therapy cohorts. The magnitude of association should accordingly not be read as a causal effect.

STRONG-HF remains the conceptual foundation for this question and the only randomized anchor in our synthesis. Its composite benefit (rehospitalisation or death, RR 0.66, 95% CI 0.50–0.86) is directionally and approximately concordant with the triple-therapy association in our network, lending the gradient its only experimental support. However, STRONG-HF tested intensive, protocolised up-titration of three classes (renin–angiotensin modulation, beta-blockade, and mineralocorticoid-receptor antagonism) within a structured high-intensity follow-up programme; it did not include an SGLT2i and enrolled patients across the ejection-fraction spectrum. It therefore does not evaluate contemporary four-pillar therapy. Peri-discharge quadruple initiation is best conceptualised as an extension of the STRONG-HF principle—rapid, supervised optimisation during the vulnerable phase—applied to a regimen that adds a mechanistically distinct fourth class, rather than as a replication of STRONG-HF. Whether the incremental fourth pillar confers benefit beyond intensive triple-therapy up-titration is precisely the question that an adequately powered randomized trial must resolve.

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The clinical relevance of these findings must be read together with the well-documented implementation gap at hospital discharge [8]. Real-world registries have consistently shown that a minority of eligible patients leave the hospital on all four foundational classes, and that class-specific prescribing rates vary widely across regions, centers, and patient subgroups [27,28]. Current guideline recommendations favor early initiation of foundational therapies before or at hospital discharge when feasible, while reinforcing that decisions should remain individualized based on hemodynamic status, renal function, potassium balance, and overall tolerability. They also underscore that the incremental contribution of each class should continue to be weighed against patient-level tolerability and shared decision-making, rather than reduced to a numerical target. From a research perspective, our results highlight the need for adequately powered RCTs comparing protocolized quadruple initiation at discharge with standard care, particularly in populations underrepresented in this synthesis, including women, older adults, patients with preserved or mildly reduced ejection fraction, and those from low- and middle-income settings. Implementation-focused studies are similarly needed to test whether structured predischarge optimization pathways, multidisciplinary care models, and digital decision-support tools can drive sustained improvements in GDMT delivery.

Strengths and Limitations. To our knowledge, this is the first NMA to synthesise prescription and associated clinical outcomes across the full spectrum of GDMT intensity at hospital discharge, complementing prior component-level syntheses conducted predominantly in the ambulatory setting. The evidence base is contemporary, comprising 27 studies and 73,174 patients across 14 countries and spanning the pre- and post-SGLT2i eras. Consistency was explored through multiple sensitivity analyses, in which the direction and ordering of estimates were generally preserved.

Nonetheless, several limitations should be acknowledged. First, 26 of 27 studies were observational, and residual confounding cannot be excluded; although more than 90% of the comparisons in the HR analysis were derived from multivariable or propensity-score-adjusted models, confounder sets differed across studies, few models explicitly adjusted for contemporaneous disease-severity markers, and none could fully address confounding by indication. Healthier patients (those with better renal function or blood-pressure reserve and those treated in higher-performing systems) may have been more likely to receive quadruple therapy, potentially exaggerating the apparent association between treatment intensity and outcomes; consistent with this, quadruple-therapy cohorts were younger and had higher mean eGFR than lower-intensity cohorts. Second, in the primary HR-only network the formal CINeMA assessment rated confidence as low for eight and very low for thirteen of the 24 comparison–outcome pairs (the three quadruple-therapy CV mortality comparisons were not estimable); no comparison achieved moderate or high confidence. Concerns about heterogeneity were more prominent in the HFH and CV mortality networks than in the ACM and composite networks. Third, the quadruple-therapy node relied on limited direct evidence (one to three studies per outcome), resulting in wide CIs, and was not estimable against single/none therapy for CV mortality in the HR-only network. Fourth, treatment nodes were defined by the number rather than the specific identity or dose of drug classes; within a node, regimens varied, angiotensin-receptor-neprilysin inhibition was used in only a minority of patients in most cohorts, and this within-node heterogeneity, expected to bias individual comparisons toward the null where less efficacious regimens predominate, is reflected in the CINeMA indirectness ratings. Fifth, geographic representation was heavily weighted toward Asia (56% of studies), which may limit generalisability. Sixth, women were under-represented (mean 35.3% female; study-level range 21–76%); because women may derive optimal benefit from neurohormonal antagonists at lower doses and may differ in susceptibility to hypotension, hyperkalaemia,

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and renal effects, a count-based intensity metric may not map identically onto outcomes across sexes, and study-level reporting was insufficient to perform a sex-stratified meta-analysis. Seventh, node-splitting revealed local inconsistency for the double vs. quadruple contrast in the all-measures ACM network ($p = 0.034$), driven largely by one crude-risk-ratio study; this contrast should be interpreted with caution, although the overall monotonic hierarchy was preserved in the primary HR-only network, across all four outcome networks in the alternative incomplete-anchored parameterization, and in leave-one-out analyses.

5. Conclusions

In this network meta-analysis of 27 studies and 73,174 patients with HF, more complete GDMT at hospital discharge was associated with a monotonic gradient of lower event rates across ACM and HFH outcomes, with quadruple therapy ranking first for every endpoint in which it was estimable, but being prescribed suboptimally among contemporary SGLT2i-era cohorts (pooled 34%; range 11.6–55.2%). Certainty of evidence in this meta-analysis was low or very low, reflecting the predominantly observational evidence base, limited direct evidence for several quadruple-therapy comparisons, and evidence of residual confounding. Adequately powered randomized trials of protocolized in-hospital quadruple initiation are therefore the key next step to establish the incremental benefit of this approach and to close the gap between evidence and practice.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm15135112/s1, Table S1. PRISMA 2020 checklist.

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Two-Year Implementation, Adherence, and Outcomes of Quadruple Guideline-Directed Medical Therapy in Newly Diagnosed HFrEF: Insights from the Prospective CaRD Registry

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Abstract

Background: Contemporary guidelines recommend rapid initiation of four classes of guideline-directed medical therapy (GDMT) for heart failure (HF) with reduced ejection fraction (HFrEF); however, real-world persistence, adherence, and dose optimization remain suboptimal. **Methods**: We analysed a predefined subregistry within the prospective Cardiology Research Dubrava (CaRD) registry, a real-world HF registry at a tertiary centre that includes patients across the ejection-fraction spectrum in whom contemporary HF therapy, including sodium-glucose cotransporter 2 inhibitors (SGLT2i), is introduced or optimised in routine practice. For this analysis, we included patients with newly diagnosed HFrEF (left ventricular ejection fraction (LVEF) $\leq$ 40%) who were discharged on all four GDMT classes; 167 of 179 patients with newly diagnosed HFrEF during the study period had an available 6-month medication assessment and comprised the final analytic cohort. The four GDMT pillars (beta-blocker; angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), or angiotensin receptor-neprilysin inhibitor (ARNI); mineralocorticoid receptor antagonist (MRA); and SGLT2i) were initiated within 4 days when clinically feasible. Medication adherence and target-dose attainment were assessed at 6, 12, and 24 months using a structured self-report questionnaire. Major adverse events (MAE) and all-cause mortality were recorded over 24 months. Patients were classified as adherent if they reported regular intake ($\geq$80% of prescribed doses) of all four drug classes at 6 months; otherwise, they were classified as nonadherent. **Results**: Among the 167 analysed patients (median age 64 years, 74% men, median LVEF 30%), regular adherence at 6, 12, and 24 months was 65%, 55%, and 59% for beta-blockers; 66%, 50%, and 49% for ACEi/ARB/ARNI; 62%, 52%, and 49% for MRAs; and 84%, 57%, and 68% for SGLT2i. Target doses were achieved in 25–33% for beta-blockers, 42–50% for ACEi/ARB/ARNI, and 73–78% for MRAs. At 24 months, 56 survivors (37%) were adherent to all four drug classes. Over 24 months, all-cause mortality was 9.0% and MAE 18.6%, occurring less frequently in adherent vs. nonadherent patients (mortality 0% vs. 13.5%; MAE 8.9% vs. 23.4%). **Conclusions**: In this real-world, non-randomized HFrEF subregistry, in-hospital initiation of quadruple GDMT was feasible, yet maintaining long-term adherence and

achieving target doses remained challenging. These data underscore the gap between guideline recommendations and routine practice and support structured follow-up and protocol-driven titration to optimize implementation.

Keywords: heart failure; reduced ejection fraction; guideline-directed medical therapy; adherence; titration; real-world data

1. Introduction

Contemporary heart failure (HF) guidelines recommend early initiation of four foundational drug classes—renin–angiotensin system inhibition with an angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB) or angiotensin receptor–neprilysin inhibitor (ARNI), an evidence-based beta-blocker (BB), a mineralocorticoid receptor antagonist (MRA), and a sodium–glucose cotransporter-2 inhibitor (SGLT2i)—for patients with heart failure with reduced ejection fraction (HFrEF), based on robust evidence demonstrating rapid and clinically meaningful reductions in morbidity and mortality [1,2]. Each of these therapies has been shown to confer early prognostic benefit, supporting strategies of rapid or near-simultaneous initiation rather than traditional stepwise escalation [3–14].

Despite strong guideline endorsement, real-world implementation of quadruple guideline-directed medical therapy (GDMT) remains challenging. Large registries consistently demonstrate substantial gaps in prescription rates, long-term persistence, and achievement of guideline-recommended target doses, particularly beyond the early post-discharge period [15–19]. Recent implementation frameworks have therefore emphasized that the clinical benefit of GDMT depends not only on early initiation but also on sustained use and appropriate dose optimisation over time [11–14]. High-intensity, protocol-driven follow-up strategies have been proposed to address these gaps. In the STRONG-HF trial, rapid initiation and aggressive up-titration of guideline-recommended therapies combined with close post-discharge follow-up significantly reduced 180-day heart failure readmissions and all-cause mortality compared with usual care [20]. However, even in this optimized setting, data on long-term persistence, drug-class–specific adherence patterns, and patient-reported barriers beyond the early post-discharge period remain limited.

Against this background, we evaluated initiation, persistence and dose optimization of the four foundational therapies in a prospective cohort of patients with newly diagnosed HFrEF. Specifically, we aimed to: (1) describe uptake of quadruple therapy at discharge; (2) quantify adherence and target-dose achievement for each drug class at 6, 12 and 24 months; (3) identify patient and socioeconomic correlates of nonadherence; and (4) explore associations between adherence to all four classes and 2-year clinical outcomes.

2. Materials and Methods

This prospective observational cohort study analysed a predefined subregistry of the Cardiology Research Dubrava (CaRD) registry (ClinicalTrials.gov identifier NCT06090591), a broader prospective HF registry at our tertiary centre that includes patients across the ejection-fraction spectrum (preserved, mildly reduced, and reduced) in whom contemporary HF therapy, including SGLT2i, is initiated or optimised in routine clinical care, between April 2022 and December 2023 (Supplementary Material). For the present analysis we focused on patients with newly diagnosed HFrEF who were discharged on all four foundational GDMT classes and followed them in greater detail to assess how feasible sustained quadruple therapy is in non-randomized patients encountered in everyday clinical practice. Patients were considered newly diagnosed if HFrEF (left ventricular ejection fraction (LVEF) $\leq$ 40%)

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was identified for the first time during the index hospitalisation. In this manuscript, the term "2-year" refers to the intended patient-level 24-month follow-up after the index date rather than to a fixed registry calendar cut-off. The analysis was based on routinely collected registry data and was approved by the Institutional Ethics Committee. All patients provided informed consent for the use of anonymized data for research and publication purposes. The study was conducted in accordance with the Declaration of Helsinki.

For the present analysis, we included only patients with newly diagnosed HFrEF who were prescribed all four foundational GDMT classes (ACEi/ARB/ARNI, BB, MRA and SGLT2i) at hospital discharge and had an available 6-month medication assessment. Accordingly, this analytic cohort was defined by the treating physician's judgement that initiation of all four pillars was clinically feasible at discharge, rather than by the complete absence of low blood pressure, renal dysfunction, or other potential barriers. Within the broader CaRD HF registry, 179 patients had newly diagnosed HFrEF during the study period; 3 were not discharged on all four drug classes (e.g., due to contraindications, intolerance, or other clinical reasons), and 9 died before the first scheduled 6-month medication assessment, leaving 167 patients in the final analytic cohort (Figure A1).

In eligible patients, the four GDMT pillars were initiated during hospitalization, with a goal to start all four classes within 4 days from diagnosis. Dose titration was performed according to guideline-recommended target doses and individual tolerability. Device therapy (implantable cardioverter-defibrillator and/or cardiac resynchronization therapy) was implemented according to European Society of Cardiology (ESC) guideline indications [1].

For the exploratory adherence-outcome analysis, patients were classified as adherent if they reported regular intake ($\geq$80% of prescribed doses) of all four GDMT pillars at the 6-month assessment. Patients who were irregular or not taking at least one GDMT class were classified as nonadherent. Because adherence status was defined at 6 months, the corresponding outcome analyses should be interpreted as exploratory. We did not use a landmark analysis to describe adherence over time; the 6-, 12-, and 24-month adherence results reflect prespecified longitudinal patient-level assessments, whereas the 6-month classification was used only for the exploratory outcome comparison.

Patients were enrolled during the predefined inclusion period, and follow-up was conducted at 6, 12, and 24 months after the index date, defined as prescription/initiation of quadruple GDMT at hospital discharge. Accordingly, each patient had an individual 24-month follow-up period, irrespective of the calendar year of enrolment. At each visit, a structured medication questionnaire was administered to assess adherence to each GDMT class. This assessment was based on patient self-report and did not include pharmacy refill data, pill counts, or electronic monitoring; the questionnaire was not formally validated against these external adherence measures. In addition, the electronic medical record was reviewed to verify whether patients subsequently attended their family/general practitioner for the prescribed post-discharge therapy, providing supportive information on activation or continuation of treatment in primary care, although this still could not confirm actual medication ingestion. Patients were asked whether they were taking each medication regularly ($\geq$80% of prescribed doses), irregularly (50–80% of prescribed doses) or not taking/rarely taking the medication ($\leq$50% of prescribed doses). For ACEi/ARB/ARNI, BBs and MRAs, target-dose achievement was recorded for patients taking the therapy regularly or irregularly. Reasons for irregular use or discontinuation, as well as reasons for failure to reach target dose, were documented using predefined categories, including poor tolerability/adverse effects, forgetfulness/non-intentional nonadherence, low perceived necessity of treatment, lack of instruction to take the medication, bradycardia, hypotension, renal dysfunction/hyperkalaemia, and lack of attempted up-titration, depending on drug class.

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The primary outcomes were all-cause mortality and major adverse events (MAE) over 24 months. MAE included HF decompensation requiring hospitalization, acute coronary syndrome, cerebrovascular events (stroke or transient ischemic attack), thromboembolic or peripheral vascular events, sepsis, dialysis or worsening renal function, and heart transplantation.

Statistical Analysis

Categorical variables are presented as counts and percentages and were compared using the χ^2 test. Continuous variables are expressed as mean ± standard deviation or median with interquartile range (IQR), according to data distribution. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Between-group comparisons were performed using the Student's *t* test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables.

Time-to-event analyses for all-cause mortality and MAE were conducted using Kaplan–Meier estimates and compared with the log-rank test. Survival and MAE were analyzed according to adherence status, comparing adherent versus non-adherent patients separately for each of the four pillars of guideline-directed medical therapy for HFrEF, as well as for adherence to all four drug classes combined.

Multivariable Cox proportional hazards regression analysis was performed to evaluate the association between adherence and the composite endpoint of 2-year all-cause mortality and MAE. Associations are reported as hazard ratios (HR) with 95% confidence intervals (95% CI). Given the limited number of events, this model was specified as exploratory and included adherence to each of the four drug classes as separate covariates entered simultaneously. No additional clinical covariates were included to reduce the risk of overfitting; therefore, these results should be interpreted as hypothesis-generating and adjusted only for concomitant adherence status of the remaining GDMT pillars rather than as fully adjusted estimates. The composite endpoint was selected because no deaths occurred during follow-up among patients fully adherent to all four drug classes, which precluded reliable Cox regression modelling for all-cause mortality as an isolated endpoint. Prespecified subgroup analyses were conducted according to sex (male vs. female), age (<65 years vs. ≥65 years), and left ventricular ejection fraction (LVEF ≤ 30% vs. 31–40%), and body mass index (BMI < 30 kg/m^2 vs. ≥30 kg/m^2).

All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant. Statistical analyses were performed using MedCalc Statistical Software, version 23.2.8, 2025 (MedCalc Software Ltd., Ostend, Belgium).

3. Results

Within the CaRD HF registry, 179 patients had newly diagnosed HFrEF during the study period. Three were not discharged on all four foundational GDMT classes, and 9 died before the first 6-month medication assessment; thus, 167 patients comprised the final analytic cohort (Figure A1). This HFrEF four-pillar subregistry was intentionally designed to examine the feasibility of maintaining quadruple GDMT after discharge in a real-world, non-randomized population encountered in daily practice (Table 1). The median available follow-up duration was 24 months. Median age was 64 years (IQR 55–71), 124 patients (74.3%) were men, median BMI was 28.1 kg/m^2 (IQR 25.2–31.4), and median LVEF was 30% (IQR 25–35). The median N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration at presentation was 4793 pg/mL (IQR 1955–8501). The most frequent indication for index admission (Table A1) was HF (n = 87, 52.1%), followed by ST-elevation myocardial infarction (n = 39, 23.4%) and non-ST-elevation acute coronary syndrome (n = 17, 10.2%). Other admission reasons were planned evaluation (4.2%), outpatient

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follow-up (4.8%), coronary angiography (1.2%), device therapy (CRT/ICD/pacemaker; 1.2%), cerebrovascular insult (0.6%), pulmonary embolism (0.6%), ventricular tachycardia (0.6%) and other causes (1.2%). Medication questionnaires were completed by 167 patients at 6 months, 163 at 12 months and 152 at 24 months (Tables A3–A6).

Table 1. Baseline characteristic of study population.

Variables	Total (n = 167)	Adherent (n = 56)	Nonadherent (n = 111)	*p*-Value
Age (years)	64 (55–71)	61 (52–68)	66 (58–72)	0.013 *
Sex (%)				0.200
Male	124 (74.3)	45 (80.4)	79 (71.2)	
Female	43 (25.7)	11 (19.6)	32 (28.8)	
BMI (kg/m^2)	28.1 (25.2–31.4)	29.4 (25.9–34.2)	27.7 (24.9–30.9)	0.041 *
Co-morbidities (%)				
Arterial hypertension	110 (65.9)	29 (51.8)	81 (73.0)	0.006 *
Dyslipidemia	110 (65.9)	38 (67.9)	72 (64.9)	0.700
Diabetes	60 (35.9)	19 (33.9)	41 (36.9)	0.702
Prediabetes	63 (37.7)	23 (41.1)	40 (36.0)	0.526
CAD	92 (55.1)	32 (57.1)	60 (54.1)	0.705
PAD	21 (12.6)	6 (10.7)	15 (13.5)	0.607
Atrial fibrillation	45 (26.9)	16 (28.6)	29 (26.1)	0.737
Prior stroke or TIA	15 (9.0)	7 (12.5)	8 (7.2)	0.259
COPD or asthma	17 (10.2)	8 (14.3)	9 (8.1)	0.213
Nicotinismus	83 (49.7)	29 (51.8)	54 (48.6)	0.702
Clinical characteristics				
HR (b.p.m.)	96 ± 21	95 ± 20	96 ± 21	0.816
SBP (mmHg)	136 ± 24	134 ± 22	137 ± 25	0.436
DBP (mmHg)	86 ± 15	85 ± 15	87 ± 15	0.357
LVEF (%)	30 (25–35)	35 (27–35)	30 (25–35)	0.444
NYHA classification				0.112
I	8 (4.8)	4 (7.1)	4 (3.6)	
II	65 (38.9)	27 (48.2)	38 (34.2)	
III	80 (47.9)	23 (41.1)	57 (51.4)	
IV	14 (8.4)	2 (3.6)	12 (10.8)	
Biological data				
Hemoglobin (g/L)	139 (130–150)	141 (132–151)	138 (127–150)	0.257
Hematocrit (L/L)	0.42 ± 0.05	0.43 ± 0.04	0.42 ± 0.05	0.300
MCV (fL)	90.2 (86.4–93.6)	90.2 (86.0–93.1)	90.2 (86.5–93.8)	0.776
RCDW (%)	14.0 (13.3–14.8)	14.0 (13.3–14.8)	14.0 (13.4–14.8)	0.710
Glucose (mmol/L)	6.8 (5.6–8.9)	6.6 (5.7–8.2)	6.9 (5.4–9.2)	0.475
HbA1c (%)	6.0 (5.7–6.8)	6.0 (5.7–6.7)	6.1 (5.7–6.8)	0.787
Creatinine (µmol/L)	85 (73–108)	88 (73–109)	85 (73–106)	0.655
eGFR (mL/min/1.73 m^2)	77 (59–93)	80 (59–94)	75 (59–93)	0.797
Urea (mmol/L)	6.9 (5.3–9.3)	6.7 (5.2–9.4)	7.0 (5.3–8.9)	0.856
Total cholesterol (mmol/L)	4.9 (3.8–6.0)	5.2 (4.1–6.1)	4.5 (3.6–5.8)	0.060
LDL-C (mmol/L)	3.0 (2.2–3.9)	3.6 (2.6–4.3)	2.9 (2.0–3.9)	0.057
HDL-C (mmol/L)	1.2 (1.0–1.5)	1.3 (1.0–1.6)	1.2 (1.0–1.3)	0.092
Triglycerides (mmol/L)	1.1 (0.9–1.5)	1.1 (0.9–1.7)	1.1 (0.9–1.5)	0.641
CRP (mg/L)	7.8 (3.6–18.8)	7.6 (4.1–25.0)	8.4 (3.5–17.4)	0.725
Potassium (mmol/L)	4.2 (4.0–4.6)	4.3 (4.0–4.5)	4.2 (4.0–4.6)	0.358
Sodium (mmol/L)	139 (137–141)	139 (137–141)	139 (137–140)	0.715
Albumin (g/L)	39 ± 4	39 ± 4	39 ± 5	0.277
NT-proBNP (pg/mL)	4793 (1955–8501)	3373 (1853–7939)	5135 (2032–7939)	0.598

BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; HR: heart rate; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PAD: peripheral artery disease; RCDW: red cell distribution width; SBP: systolic blood pressure; TIA: transient ischemic attack. Missing data: albumin (38), CRP (3), creatinine (1), HbA1c (6), HDL-C (2), LDL-C (2), NT-proBNP (3), potassium (1), sodium (2), total cholesterol (2), triglycerides (3), urea (1). *: $p < 0.05$.

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3.1. Correlates of Adherence

At the 6-month assessment, 56/167 patients (33.5%) reported regular intake (≥80% of prescribed doses) of all four GDMT drug classes and were classified as adherent. The remaining 111 patients (66.5%) were classified as nonadherent, defined as irregular use or non-use of ≥1 GDMT class at 6 months. Compared with nonadherent patients, adherent patients were younger (median 61 vs. 66 years; $p = 0.013$), had higher BMI (median 29.4 vs. 27.7 kg/m^2; $p = 0.041$), and were less likely to have arterial hypertension (51.8% vs. 73.0%; $p = 0.006$). In the overall cohort, arterial hypertension was present in 65.9%, dyslipidaemia in 65.9%, diabetes in 35.9%, coronary artery disease in 55.1%, atrial fibrillation in 26.9%, peripheral artery disease in 12.6%, chronic obstructive pulmonary disease or asthma in 10.2%, and prior stroke or transient ischemic attack in 9.0%; 49.7% reported nicotinism. Sex distribution, LVEF, New York Heart Association (NYHA) class and most other comorbidities and laboratory measures did not differ significantly between adherence groups (Table 1).

3.2. Socioeconomic Characteristics

Monthly household income distribution did not differ significantly between adherent and nonadherent patients ($p = 0.115$): <€330 (0.6% overall), €330–431 (14.4%), €432–832 (61.1%), and >€832 (24.0%). Education level was strongly associated with adherence ($p < 0.001$). In the adherent group, 23.2% had a bachelor's/master's degree versus 7.2% among nonadherent patients, whereas lack of elementary school education was less frequent in adherent patients (1.8% vs. 10.8%). Marital status ($p = 0.975$) and employment status ($p = 0.191$) were similar between groups (Table A2).

3.3. Medication Adherence over Time

Regular adherence to each drug class at 6, 12 and 24 months is shown in Tables A3–A6 and Figure 1. At 24 months, regular use was reported by 59.2% for BBs, 48.7% for ACEi/ARB/ARNI, 49.3% for MRAs and 68.4% for SGLT2is; non-use (≤50% of prescribed doses) was reported by 21.1%, 20.4%, 21.1% and 17.8% of patients, respectively.

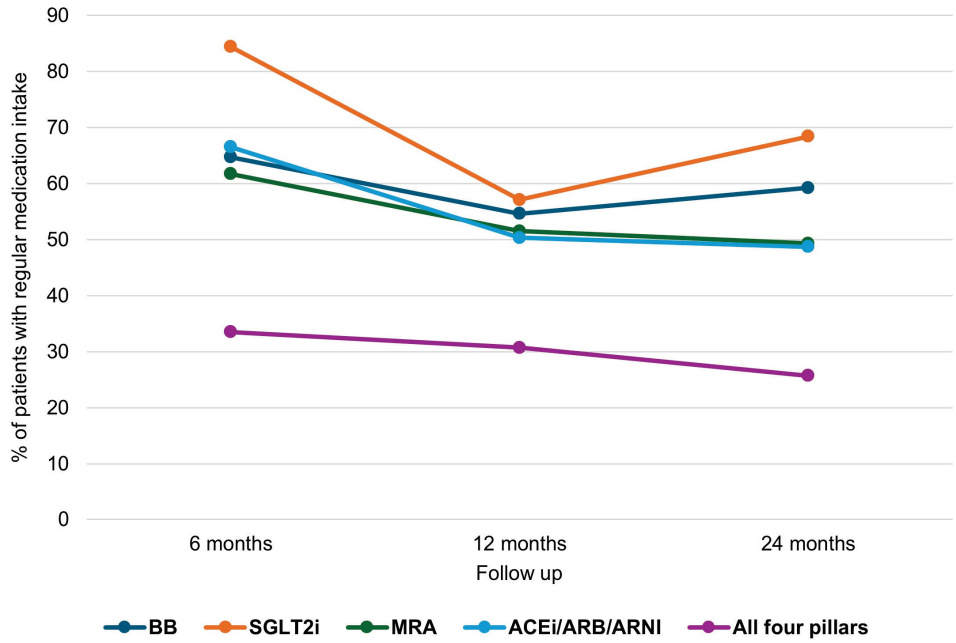


Figure 1. Adherence to heart failure medications over 6-, 12-, and 24-month follow-up. The x-axis denotes prespecified patient-level follow-up time after the index date, and the y-axis denotes the percentage (%) of patients reporting regular medication intake (≥80% of prescribed doses) for each GDMT class.

3.4. Beta-Blockers

At 6, 12 and 24 months, regular BB intake was reported by 64.7%, 54.6% and 59.2% of patients, respectively; 23.4%, 28.2% and 19.7% reported irregular use, and 12.0%, 17.2% and 21.1% reported non-use. Among patients not taking BBs regularly, the most frequently reported main reasons were forgetfulness/unintentional nonadherence (33.9%, 40.5% and 32.3% at 6, 12 and 24 months), belief that the medication was unnecessary (27.1%, 21.6% and 27.4%), poor tolerability/adverse effects (23.7%, 20.3% and 20.9%), and having not been instructed to take the medication (8.5%, 9.5% and 12.9%); discontinuation due to bradycardia was reported in 6.5–8.1%. Among BB users (regular or irregular), target doses were achieved in 25.2% at 6 months, 30.4% at 12 months and 33.3% at 24 months. In those not at target dose, the most common reported reasons were lack of attempted uptitration (52.7%, 44.7% and 43.4% at 6, 12 and 24 months) and hypotension or bradycardia (36.4%, 45.7% and 50.0%); fewer patients reported attempted but not maintained uptitration (5.3–8.2%) or dose reduction by a primary care physician (1.3–2.7%) (Table A3). The distribution of BB agents prescribed at hospital discharge is shown in Figure A2.

3.5. SGLT2 Inhibitors

Regular SGLT2i intake was reported by 84.4% at 6 months, 57.1% at 12 months and 68.4% at 24 months; irregular use by 6.6%, 15.3% and 13.8%; and non-use by 9.0%, 27.6% and 17.8%. Among patients not taking SGLT2i regularly, the most frequently reported reason at all time points was perceiving daily intake as unnecessary (53.8%, 52.9% and 52.1% at 6, 12 and 24 months), followed by not believing the medication was necessary (30.8%, 27.1% and 31.3%) and forgetfulness (15.4%, 20.0% and 16.6%) (Table A4). The distribution of SGLT2is prescribed at hospital discharge is presented in Figure A3.

3.6. Mineralocorticoid Receptor Antagonists

Regular MRA intake was reported by 61.7%, 51.5% and 49.3% at 6, 12 and 24 months; irregular use by 26.3%, 31.9% and 29.6%; and non-use by 12.0%, 16.6% and 21.1%. Among non-regular users, forgetfulness was the most frequently selected main reason (46.9%, 49.4% and 40.2% at 6, 12 and 24 months), followed by belief that the medication was unnecessary (21.9%, 29.1% and 29.9%). Not being instructed to take the medication was reported in 12.5%, 12.7% and 18.2%, while poor tolerability/adverse effects was reported in 8.8–18.7%. Among MRA users, target dosing was achieved in 72.8% at 6 months, 75.4% at 12 months and 77.5% at 24 months. In those not at target dose, reduced renal function or hyperkalaemia was the most common barrier (42.5%, 57.5% and 44.5% at 6, 12 and 24 months), alongside lack of attempted uptitration (42.5%, 30.3% and 22.2%). Hypotension accounted for 5.0% at 6 months, 6.1% at 12 months, and 22.2% at 24 months; attempted but not maintained uptitration accounted for 6.1–11.1% (Table A5). The distribution of MRAs prescribed at hospital discharge is presented in Figure A4.

3.7. ACEi/ARB/ARNI

Regular ACEi/ARB/ARNI intake was reported by 66.5%, 50.3% and 48.7% at 6, 12 and 24 months; irregular use by 25.1%, 30.1% and 30.9%; and non-use by 8.4%, 19.6% and 20.4%. Among non-regular users, poor tolerability/adverse effects was the leading main reason (42.8%, 45.7% and 48.7% at 6, 12 and 24 months), followed by forgetfulness (39.3%, 28.4% and 23.1%) and belief that the medication was unnecessary (12.5%, 22.2% and 24.4%). Not being instructed to take the medication was reported by 3.7–5.4%. Among ACEi/ARB/ARNI users, target doses were achieved in 41.8% at 6 months, 44.3% at 12 months and 49.6% at 24 months. In patients not at target dose, hypotension was the most frequently reported barrier (50.5%, 65.8% and 65.6% at 6, 12 and 24 months). Hy-

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perkalaemia accounted for 9.6–14.7%, lack of attempted uptitration for 31.5% at 6 months (falling to 12.3% at 12 months and 6.6% at 24 months), and attempted but not maintained uptitration for 7.9–13.1% (Table A6). The distribution of ACEi/ARB/ARNI prescribed at hospital discharge is shown in Figure A5.

3.8. Clinical Outcomes

Over 24 months, 15 patients died (all-cause mortality 9.0%) and 31 experienced a MAE (18.6%). The most common MAE component was HF decompensation requiring hospitalization (12.6%), followed by dialysis or worsening renal function (2.4%); acute coronary syndrome, sepsis, heart transplantation, cerebrovascular insult and thromboembolic/peripheral vascular events each occurred in ≤1.2%. In exploratory comparisons by adherence status defined at 6 months, mortality (0.0% vs. 13.5%, $p = 0.004$) and MAE (8.9% vs. 23.4%, $p = 0.023$) were lower in the adherent group (Table 2). Kaplan–Meier curves for 2-year all-cause mortality and MAE stratified by adherence to all four GDMT pillars are shown in Figure 2, while the corresponding analyses for individual GDMT drug classes are presented in Figures A6–A9.

Table 2. Baseline characteristic of study population.

Variables	Total (n = 167)	Adherent (n = 56)	Nonadherent (n = 111)	*p*-Value
All-cause mortality (%)	15 (9.0)	0 (0.0)	15 (13.5)	0.004 *
Major adverse events (%)	31 (18.6)	5 (8.9)	26 (23.4)	0.023 *
Heart failure decompensation	21 (12.6)	2 (3.6)	19 (17.1)	
Acute coronary syndrome	2 (1.2)	2 (3.6)	0 (0.0)	
Cerebrovascular insult	1 (0.6)	0 (0.0)	1 (0.9)	
Sepsis	1 (0.6)	1 (1.8)	0 (0.0)	
Dialysis or worsening renal function	4 (2.4)	0 (0.0)	4 (3.6)	
Heart transplantation	1 (0.6)	0 (0.0)	1 (0.9)	
Thromboembolic or peripheral vascular event	1 (0.6)	0 (0.0)	1 (0.9)	

*: $p < 0.05$.

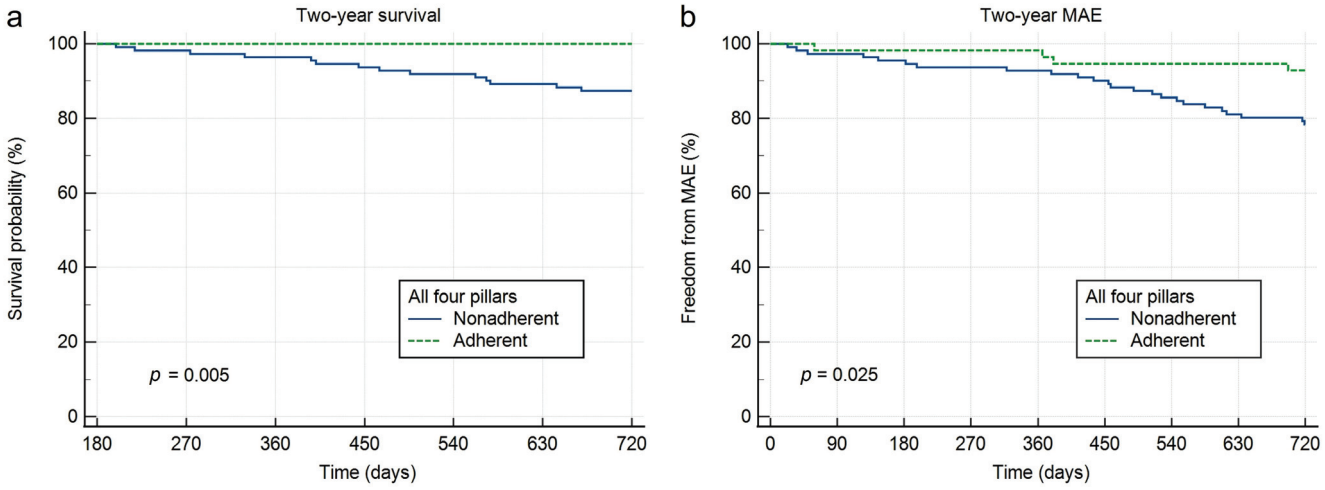


Figure 2. Kaplan–Meier curves for 2-year survival and freedom from major adverse events according to GDMT adherence. Kaplan–Meier curves compare patients adherent to all four GDMT pillars within

the first 6 months of follow-up with nonadherent patients (defined as nonadherence to at least one GDMT class). Panel (**a**) shows 2-year all-cause survival, and panel (**b**) shows freedom from major adverse events (MAE).

Figure 3 presents the results of the multivariable regression analysis, demonstrating that adherence to BB (HR 0.25, 95% CI 0.12–0.53, $p < 0.001$) and SGLT2i (HR 0.31, 95% CI 0.15–0.64, $p = 0.002$) was significantly associated with a lower risk of mortality or MAE, whereas adherence to ACEi/ARB/ARNI and MRA did not reach statistical significance. Table A7 shows prespecified subgroup analyses stratified by sex, age, LVEF, and BMI.

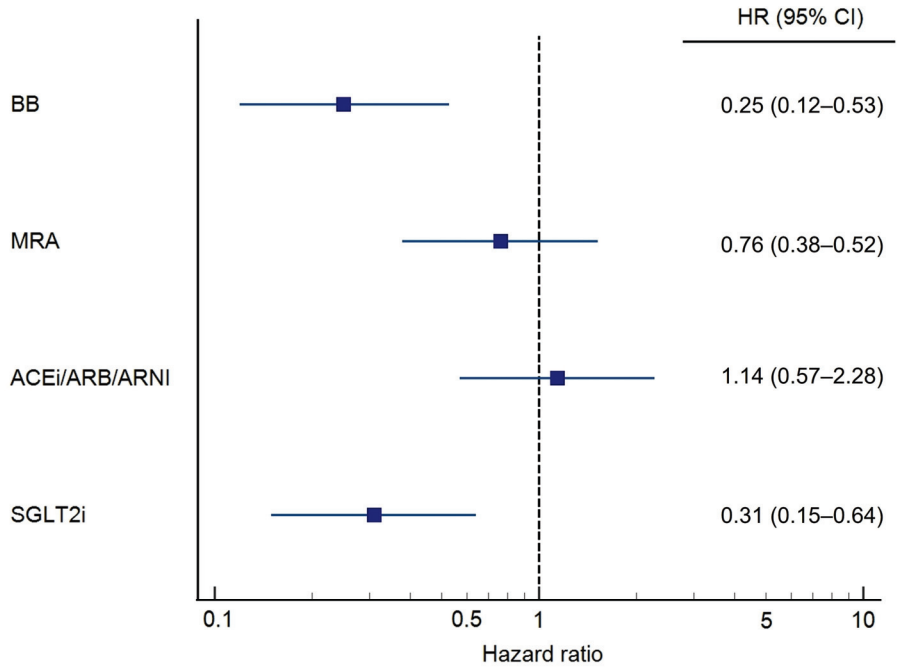


Figure 3. Multivariable Cox regression analysis of adherence to individual GDMT drug classes and the composite endpoint.

4. Discussion

Our findings further highlight the critical distinction between early initiation and durable implementation of GDMT in HFrEF. While contemporary guidelines and sequencing frameworks have successfully shifted practice towards rapid or simultaneous initiation of the four foundational drug classes [1,2,11–13], our data demonstrate that initiation alone does not ensure sustained adherence or dose optimisation over time. Importantly, this predefined CaRD subregistry was conceived to examine whether such an intensive strategy can be implemented and maintained outside randomized trials, in patients seen in routine practice once they leave hospital on all four pillars. Even within this selected cohort, only approximately 25% of 24-month survivors reported regular intake of all four GDMT pillars, highlighting a substantial gap between guideline recommendations and durable real-world implementation.

Importantly, differences in adherence were not explained by markers of HF severity. Adherent and nonadherent patients did not differ significantly LVEF, NYHA class, or NT-proBNP levels, suggesting that nonadherence cannot be attributed solely to more advanced disease or haemodynamic instability. This observation aligns with registry data showing that behavioural, cognitive and healthcare-system factors often outweigh clinical severity as determinants of long-term GDMT persistence [15–19,21].

Drug-class-specific analyses revealed distinct and clinically relevant barriers. For BBs, lack of attempted dose up-titration was the dominant reason for failure to achieve

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target doses, accounting for approximately 40–50% of missed targets across follow-up. This finding is consistent with prior reports identifying therapeutic inertia as a major obstacle to BB optimisation in HFrEF [18,19]. Given the strong evidence base for BBs in reducing mortality and HF hospitalizations [6–8], our results emphasise the need for protocol-driven titration pathways and structured follow-up beyond the early post-discharge period.

For ACEi/ARB/ARNI therapy, poor tolerability and hypotension were the most frequently reported reasons for both non-regular use and failure to reach target doses. These findings reflect real-world haemodynamic constraints and are in line with previous studies reporting hypotension as a leading limitation to renin-angiotensin system inhibitor optimization [14,18]. Notably, an increasing proportion of patients also reported low perceived necessity of therapy over time, suggesting that symptomatic improvement may undermine long-term persistence unless prognostic benefits are repeatedly reinforced [22,23].

SGLT2i showed the highest overall persistence but a pronounced decline at mid-term follow-up, driven predominantly by perceptions that daily intake was unnecessary. Large randomised trials have demonstrated prognostic benefits of SGLT2i in HFrEF irrespective of diabetes status [9,10], yet our findings suggest that this paradigm shift is not fully translated into patient understanding. Structured education explicitly addressing indications and expected benefits may therefore be essential to sustain long-term adherence.

MRAs exhibited relatively high target-dose achievement among users, but regular intake declined steadily over time. While renal dysfunction and hyperkalaemia remained key barriers to dose optimisation, unintentional nonadherence and unclear instructions accounted for a substantial proportion of discontinuation. Similar challenges have been reported in real-world cohorts, highlighting the importance of systematic laboratory monitoring and clear communication to maintain MRA therapy safely and effectively [4,5,15–17].

Socioeconomic analyses further contextualise these findings. Education level, but not income, employment status, or marital status, was strongly associated with adherence, supporting the concept that health literacy rather than socioeconomic position per se is a key determinant of GDMT persistence. This pattern is consistent with broader adherence literature, which identifies understanding of disease and treatment as central drivers of long-term medication use [21]. Tailored educational interventions, simplified regimens and repeated medication reviews may therefore be particularly beneficial in patients with lower educational attainment.

Although exploratory and subject to important limitations, the observed associations between adherence to all four GDMT classes and lower mortality and MAE are directionally consistent with registry data linking higher guideline adherence and more complete dose optimization to improved outcomes [18,19]. These comparisons should be interpreted cautiously given potential confounding and survivorship bias, as adherence was defined at 6 months. In the exploratory Cox model, adherence to BB and SGLT2i retained statistical significance, whereas adherence to ACEi/ARB/ARNI and MRA did not. This should not be interpreted as evidence that the latter therapies are less important. Because adherence to the four pillars is clinically interrelated, simultaneous entry of all four adherence variables introduces correlation and potential collinearity, while the limited number of events reduces statistical power. Under these conditions, non-significance likely reflects limited precision, exposure correlation, and residual confounding rather than absence of benefit.

Our findings should also be interpreted in the context of worsening HF and the vulnerable phase after diagnosis or decompensation, where long-term prognosis depends not only on early initiation of foundational therapies but also on their sustained continuation and optimisation over time. Recent reviews have emphasised that contemporary HF management requires ongoing reassessment of clinical stability, patient education, and reinforcement of the prognostic value of treatment beyond early symptom improvement [23].

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Taken together, our findings suggest that the next major challenge in HFrEF management is no longer whether quadruple GDMT can be initiated early, but how it can be maintained, titrated and integrated into long-term care pathways. Multidisciplinary follow-up models, protocolised titration strategies and repeated patient-centred education-similar in principle to high-intensity optimisation programmes such as STRONG-HF, may be required to close the persistent gap between evidence-based recommendations and real-world outcomes [20].

Limitations

This study has several important limitations. First, it was conducted at a single tertiary centre and included a moderate sample size, which may limit external validity. Second, the analytic cohort was intentionally restricted to patients with newly diagnosed HFrEF who were discharged on all four foundational GDMT classes and survived to the first 6-month medication assessment. The study therefore represents a selected subgroup of quadruple-eligible early survivors, enriched for clinically stable patients able to tolerate early comprehensive therapy, and cannot be generalised to the entire population of newly diagnosed HFrEF patients. Third, this analysis represents a predefined subregistry within a broader HF registry and reflecting routine introduction or optimisation of SGLT2i therapy; accordingly, the present findings should not be extrapolated to the full registry population. Fourth, the Cox analyses were exploratory and limited by the low event rate (15 deaths and 31 MAEs). The primary multivariable model incorporated adherence variables only and was not adjusted for age, LVEF, NT-proBNP, BMI, comorbidities, or other baseline characteristics. Instead, stratified subgroup analyses were conducted across these four prespecified variables. Given the limited number of events, residual confounding, model instability, and limited statistical power should be considered when interpreting the results. Fifth, we did not perform a formal baseline comparison between included and excluded patients, and the excluded subgroup was small and clinically heterogeneous. Ethnicity was not systematically recorded in the registry; given the single-centre Croatian setting the cohort is likely relatively homogeneous, but this variable could not be analysed and should be regarded as a limitation. Sixth, adherence was assessed using a structured study questionnaire that was not formally validated against pharmacy refill data, pill counts, or electronic monitoring. Self-report may overestimate adherence, the $\geq$80% threshold is pragmatic, and dose timing or refill gaps were not captured. Although electronic medical record review provided supportive information on treatment activation or continuation in primary care, neither self-report nor record review could fully confirm actual medication ingestion or perfectly distinguish primary nonadherence from later discontinuation. Seventh, the questionnaire-based approach could not fully distinguish patient nonadherence from clinician-directed discontinuation or dose reduction due to intolerance or clinical decision-making. Reasons related to tolerability or clinical instability were recorded descriptively, but early deaths were excluded because adherence status could not be classified, and their relationship to treatment intolerance could not be reliably determined from the available registry data. In addition, not all potential adherence barriers were systematically recorded; in particular, cost burden and regimen complexity were not prospectively captured. Eighth, because adherence status was defined at 6 months, outcome comparisons are susceptible to survivorship and immortal-time bias and should be interpreted as hypothesis-generating. We did not perform landmark or time-dependent analyses. Finally, MAE components were not independently adjudicated and the composite included heterogeneous events; component analyses are descriptive.

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5. Conclusions

In this real-world, non-randomized subregistry of patients with newly diagnosed HFrEF who were discharged on quadruple GDMT and survived to early follow-up, early initiation during hospitalisation was feasible, but long-term adherence and target-dose attainment remained suboptimal. These findings apply primarily to a selected four-pillar cohort encountered in everyday clinical practice rather than to the full population of newly diagnosed HFrEF. Structured follow-up, repeated patient education, and protocolised titration pathways may be required to sustain quadruple therapy and optimise dosing over time.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm15062127/s1, As this is an observational study based on registry data, the STROBE checklist [24] is provided in the Supplementary Material.

Author Contributions: Conceptualization, I.J., D.L., J.Ć. and M.P.; methodology, I.J., Š.M. and M.P.; software, K.G., I.H. and M.P.; validation, I.J., Š.M. and M.U.; formal analysis, I.J., K.G., M.U., J.Ć. and M.P.; investigation, I.J., D.L., D.R. and M.K.; resources, D.L., M.U. and A.M.; data curation, I.J., I.H., D.R., A.M. and M.K.; writing—original draft preparation, I.J., D.L., K.G., D.R., A.M. and M.K.; writing—review and editing, Š.M., I.H., M.U., J.Ć. and M.P.; visualization, K.G., D.R. and A.M.; supervision, Š.M., I.H., J.Ć. and M.P. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement : The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of University Hospital Dubrava (protocol code 2022/1403-01; date 14 March 2022).

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

Data Availability Statement: The data underlying this article cannot be shared publicly due to the privacy of the individuals who participated in the study. The data will be shared upon reasonable request made to the corresponding author.

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

Abbreviations

The following abbreviations are used in this manuscript:

ACEi	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor–neprilysin inhibitor
BB	Beta-blocker
BMI	Body mass index
CI	Confidence interval
CRT	Cardiac resynchronization therapy
ESC	European Society of Cardiology
GDMT	Guideline-directed medical therapy
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
ICD	Implantable cardioverter-defibrillator
IQR	Interquartile range
LVEF	Left ventricular ejection fraction
MEA	Major adverse event
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
SGLT2i	Sodium–glucose cotransporter-2 inhibitor

Appendix A

Table A1. Indications for index hospital admission among patients with newly diagnosed HFrEF.

Indication	N	%
Heart failure	87	52.1
ST-elevation myocardial infarction	39	23.4
Non-ST-elevation acute coronary syndrome	17	10.2
Planned evaluation	7	4.2
Outpatient follow-up	8	4.8
Coronary angiography	2	1.2
CRT/ICD/pacemaker	2	1.2
Cerebrovascular insult	1	0.6
Pulmonary embolism	1	0.6
Ventricular tachycardia	1	0.6
Other	2	1.2

CRT: cardiac resynchronization therapy; ICD: implantable cardioverter-defibrillator.

Table A2. Socioeconomic characteristics of the study population.

Variables	Total (n = 167)	Adherent (n = 56)	Nonadherent (n = 111)	*p*-Value
Monthly household income (%)				0.115
<330 €	1 (0.6)	0 (0.0)	1 (0.9)	
330–431 €	24 (14.4)	4 (7.1)	20 (18.0)	
432–832 €	102 (61.1)	34 (60.7)	68 (61.3)	
>832 €	40 (24.0)	18 (32.1)	22 (19.8)	
Education level (%)				<0.001 *
No elementary school	13 (7.8)	1 (1.8)	12 (10.8)	
Elementary school graduate	58 (34.7)	12 (21.4)	46 (41.4)	
High school graduate	75 (44.9)	30 (53.6)	45 (40.5)	
Bachelor's/master's degree	21 (12.6)	13 (23.2)	8 (7.2)	
Marital status (%)				0.975
Married	117 (70.1)	40 (71.4)	77 (69.4)	
Single	19 (11.4)	6 (10.7)	13 (11.7)	
Divorced	17 (10.2)	5 (8.9)	12 (10.8)	
Widow/widower	14 (8.4)	5 (8.9)	9 (8.1)	
Employment status (%)				0.191
Employed	54 (32.3)	24 (42.9)	30 (27.0)	
Unemployed	20 (12.0)	7 (12.5)	13 (11.7)	
Retired	89 (53.3)	24 (42.9)	65 (58.6)	
Occasionally employed	4 (2.4)	1 (1.8)	3 (2.7)	

*: $p < 0.05$.

Table A3. Adherence-related referral implementation for beta-blocker therapy at 6-, 12-, and 24-month follow-up.

Questions	6 Months	12 Months	24 Months
Do you take a beta blocker?	n = 167	n = 163	n = 152
Regularly (>80% of the time)	108 (64.7%)	89 (54.6%)	90 (59.2%)
Irregularly (50–80% of the time)	39 (23.4%)	46 (28.2%)	30 (19.7%)
Not taking (<50% of the time)	20 (12.0%)	28 (17.2%)	32 (21.1%)
If not taking a beta blocker regularly (n = irregular or not taking): what is the main reason?	n = 59	n = 74	n = 62
Poor tolerability/adverse effects	14 (23.7%)	15 (20.3%)	13 (20.9%)
Was not instructed to take the medication	5 (8.5%)	7 (9.5%)	8 (12.9%)

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Table A3. *Cont.*

Questions	6 Months	12 Months	24 Months
Does not believe the medication is necessary	16 (27.1%)	16 (21.6%)	17 (27.4%)
Forgetfulness/non-intentional non-adherence	20 (33.9%)	30 (40.5%)	20 (32.3%)
Discontinued due to bradycardia	4 (6.8%)	6 (8.1%)	4 (6.5%)
Are you receiving the target dose of a beta blocker? (n = regular or irregular users)	n = 147	n = 135	n = 120
Yes	37 (25.2%)	41 (30.4%)	44 (33.3%)
If not receiving the target dose of a beta blocker (n = regular or irregular users not on target dose): what is the main reason?	n = 110	n = 94	n = 76
Hypotension or bradycardia	40 (36.4%)	43 (45.7%)	38 (50.0%)
Dose up-titration was not attempted	58 (52.7%)	42 (44.7%)	33 (43.4%)
Dose up-titration was attempted but not maintained	9 (8.2%)	7 (7.5%)	4 (5.3%)
Dose was reduced by the primary care physician	3 (2.7%)	2 (2.1%)	1 (1.3%)

Table A4. Adherence-related referral implementation for SGLT2 inhibitor therapy at 6-, 12-, and 24-month follow-up.

Questions	6 Months	12 Months	24 Months
Do you take a SGLT2 inhibitor?	n = 167	n = 163	n = 152
Regularly (>80% of the time)	141 (84.4%)	93 (57.1%)	104 (68.4%)
Irregularly (50–80% of the time)	11 (6.6%)	25 (15.3%)	21 (13.8%)
Not taking (<50% of the time)	15 (9.0%)	45 (27.6%)	27 (17.8%)
If not taking a SGLT2 inhibitor regularly (n = irregular or not taking): what is the main reason?	n = 26	n = 70	n = 48
Perceives that daily intake of the medication is unnecessary	14 (53.8%)	37 (52.9%)	25 (52.1%)
Does not believe the medication is necessary	8 (30.8%)	19 (27.1%)	15 (31.3%)
Forgetfulness/non-intentional non-adherence	5 (15.4%)	14 (20.0%)	8 (16.6%)

Table A5. Adherence-related referral implementation for mineralocorticoid receptor antagonist therapy at 6-, 12-, and 24-month follow-up.

Questions	6 Months	12 Months	24 Months
Do you take a MRA?	n = 167	n = 163	n = 152
Regularly (>80% of the time)	103 (61.7%)	84 (51.5%)	75 (49.3%)
Irregularly (50–80% of the time)	44 (26.3%)	52 (31.9%)	45 (29.6%)
Not taking (<50% of the time)	20 (12.0%)	27 (16.6%)	32 (21.1%)
If not taking a MRA regularly (n = irregular or not taking): what is the main reason?	n = 64	n = 79	n = 77
Poor tolerability/adverse effects	12 (18.7%)	7 (8.8%)	9 (11.7%)
Was not instructed to take the medication	8 (12.5%)	10 (12.7%)	14 (18.2%)
Does not believe the medication is necessary	14 (21.9%)	23 (29.1%)	23 (29.9%)
Forgetfulness/non-intentional non-adherence	30 (46.9%)	39 (49.4%)	31 (40.2%)
Are you receiving the target dose of a MRA? (n = regular or irregular users)	n = 147	n = 134	n = 120
Yes	107 (72.8%)	101 (75.4%)	93 (77.5%)
If not receiving the target dose of a MRA (n = regular or irregular users not on target dose): what is the main reason?	n = 40	n = 33	n = 27
Reduced renal function or hyperkalaemia	17 (42.5%)	19 (57.5%)	12 (44.5%)
Hypotension	2 (5.0%)	2 (6.1%)	6 (22.2%)
Dose up-titration was not attempted	17 (42.5)	10 (30.3%)	6 (22.2%)
Dose up-titration was attempted but not maintained	4 (10.0%)	2 (6.1%)	3 (11.1%)

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Table A6. Adherence-related referral implementation for ACEi/ARB/ARNI therapy at 6-, 12-, and 24-month follow-up.

Questions	6 Months	12 Months	24 Months
Do you take a ACEi/ARB/ARNI?	n = 167	n = 163	n = 152
Regularly (>80% of the time)	111 (66.5%)	82 (50.3%)	74 (48.7%)
Irregularly (50–80% of the time)	42 (25.1%)	49 (30.1%)	47 (30.9%)
Not taking (<50% of the time)	14 (8.4%)	32 (19.6%)	31 (20.4%)
If not taking a ACEi/ARB/ARNI regularly (n = irregular or not taking): what is the main reason?	n = 56	n = 81	n = 78
Poor tolerability/adverse effects	24 (42.8%)	37 (45.7%)	38 (48.7%)
Was not instructed to take the medication	3 (5.4%)	3 (3.7%)	3 (3.8%)
Does not believe the medication is necessary	7 (12.5%)	18 (22.2%)	19 (24.4%)
Forgetfulness/non-intentional non-adherence	22 (39.3%)	23 (28.4%)	18 (23.1%)
Are you receiving the target dose of a ACEi/ARB/ARNI? (n = regular or irregular users)	n = 153	n = 131	n = 121
Yes	64 (41.8%)	58 (44.3%)	60 (49.6%)
If not receiving the target dose of a ACEi/ARB/ARNI (n = regular or irregular users not on target dose): what is the main reason?	n = 89	n = 73	n = 61
Hyperkalaemia	9 (10.1%)	7 (9.6%)	9 (14.7%)
Hypotension	45 (50.5%)	48 (65.8%)	40 (65.6%)
Dose up-titration was not attempted	28 (31.5%)	9 (12.3%)	4 (6.6%)
Dose up-titration was attempted but not maintained	7 (7.9%)	9 (12.3%)	8 (13.1%)

Table A7. Subgroup Cox regression analysis of adherence to guideline-directed medical therapy and the composite outcome stratified by age, sex, LVEF, and BMI.

	HR	95% CI	*p*-Value
Male			
Beta-blockers	0.29	0.12–0.70	0.006 *
SGLT2 inhibitors	0.25	0.10–0.60	0.002 *
MRAs	0.88	0.38–2.06	0.774
ACEi/ARB/ARNI	1.34	0.55–3.27	0.514
Female			
Beta-blockers	0.11	0.02–0.59	0.010 *
SGLT2 inhibitors	0.63	0.16–2.57	0.520
MRAs	0.43	0.11–1.56	0.199
ACEi/ARB/ARNI	1.16	0.32–4.20	0.820
<65 years			
Beta-blockers	0.25	0.07–0.87	0.029 *
SGLT2 inhibitors	0.30	0.08–1.05	0.060
MRAs	0.93	0.25–3.48	0.915
ACEi/ARB/ARNI	1.02	0.32–3.26	0.971
≥65 years			
Beta-blockers	0.28	0.10–0.74	0.011 *
SGLT2 inhibitors	0.27	0.11–0.69	0.006 *
MRAs	0.63	0.27–1.45	0.278
ACEi/ARB/ARNI	1.41	0.58–3.44	0.452
LVEF ≤ 30%			
Beta-blockers	0.31	0.12–0.84	0.021 *
SGLT2 inhibitors	0.29	0.11–0.76	0.012 *
MRAs	0.72	0.26–1.96	0.516
ACEi/ARB/ARNI	1.11	0.41–2.97	0.843

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Table A7. *Cont.*

	HR	95% CI	*p*-Value
LVEF 31–40%			
Beta-blockers	0.17	0.06–0.60	0.005 *
SGLT2 inhibitors	0.35	0.11–1.08	0.069
MRAs	0.90	0.31–2.59	0.847
ACEi/ARB/ARNI	1.22	0.42–3.58	0.719
BMI < 30 kg/m^2			
Beta-blockers	0.22	0.09–0.53	0.001 *
SGLT2 inhibitors	0.40	0.17–1.86	0.040 *
MRAs	0.89	0.38–2.08	0.787
ACEi/ARB/ARNI	0.85	0.39–1.86	0.680
BMI ≥ 30 kg/m^2			
Beta-blockers	0.47	0.09–2.59	0.389
SGLT2 inhibitors	0.05	0.01–0.50	0.011 *
MRAs	0.51	0.13–1.98	0.327
ACEi/ARB/ARNI	5.09	0.53–48.44	0.157

*: $p < 0.05$.

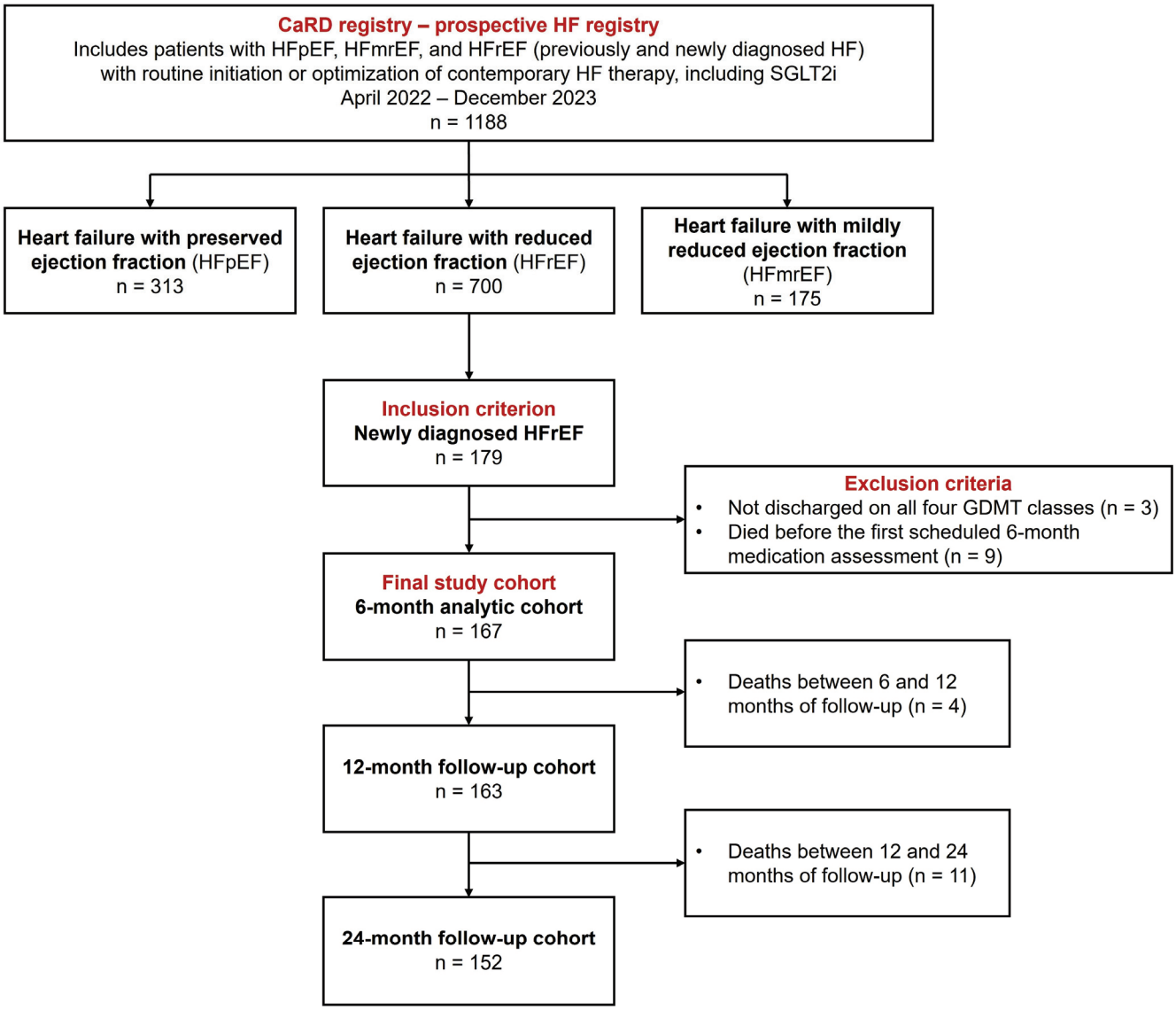


Figure A1. Study flowchart of patient selection from the CaRD registry.

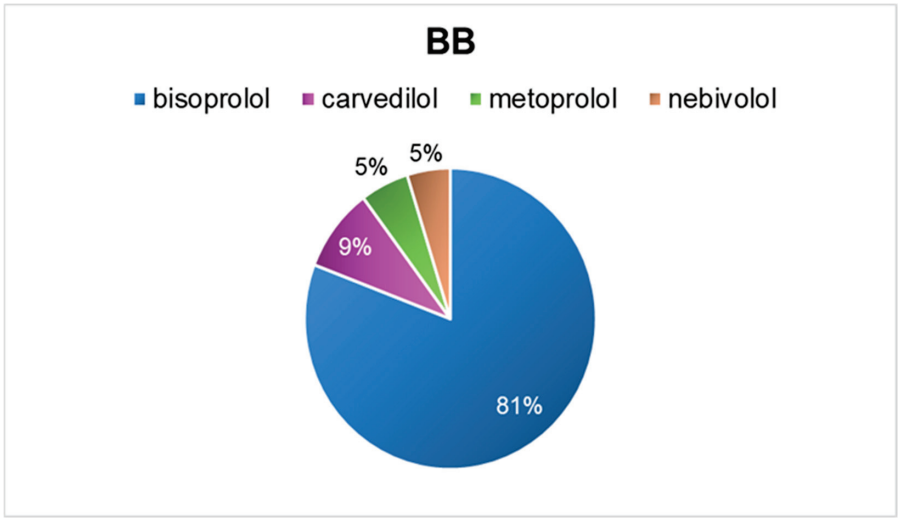


Figure A2. Distribution of BB agents at discharge.

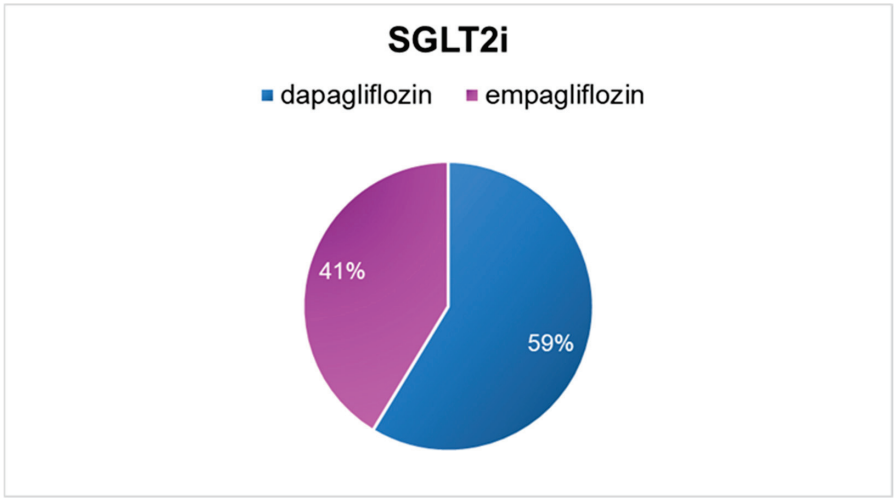


Figure A3. Distribution of SGLT2i agents at discharge.

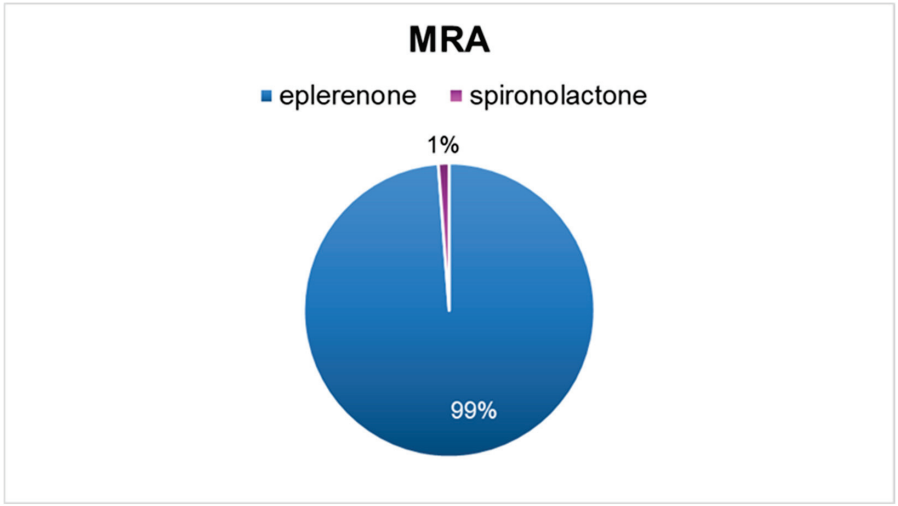


Figure A4. Distribution of MRA agents at discharge.

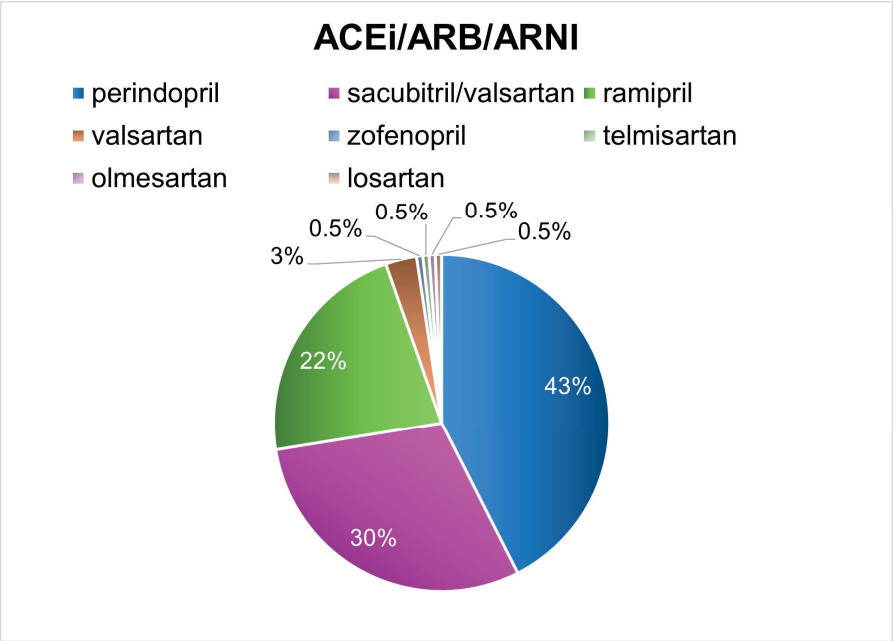


Figure A5. Distribution of ACEi/ARB/ARNI agents at discharge.

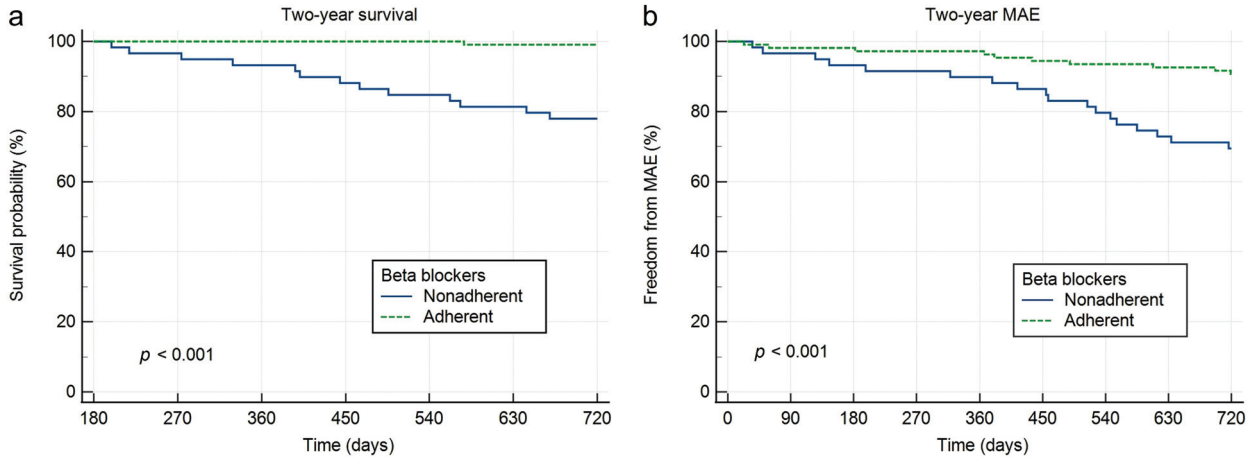


Figure A6. Kaplan–Meier curves illustrate 2-year all-cause survival (**a**) and freedom from major adverse events (**b**) stratified by adherence to BB.

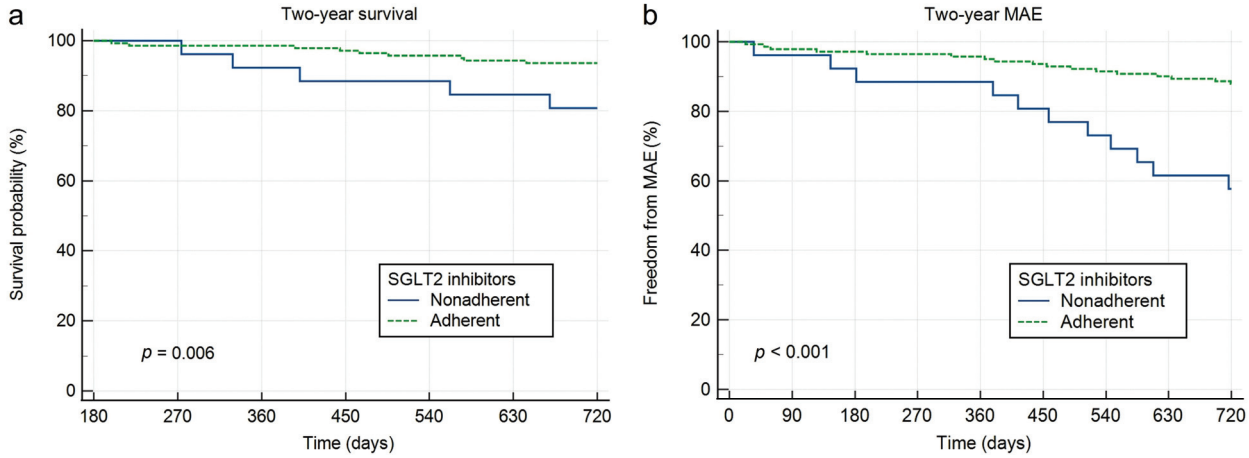


Figure A7. Kaplan–Meier curves illustrate 2-year all-cause survival (**a**) and freedom from major adverse events (**b**) stratified by adherence to SGLT2i.

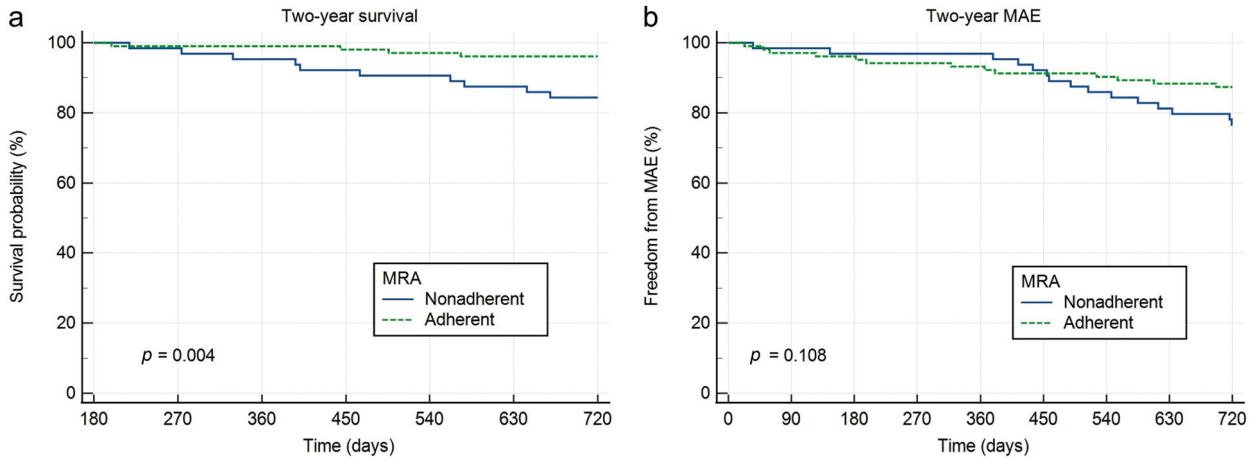


Figure A8. Kaplan–Meier curves show 2-year all-cause survival (**a**) and freedom from major adverse events (**b**) stratified by adherence to MRA.

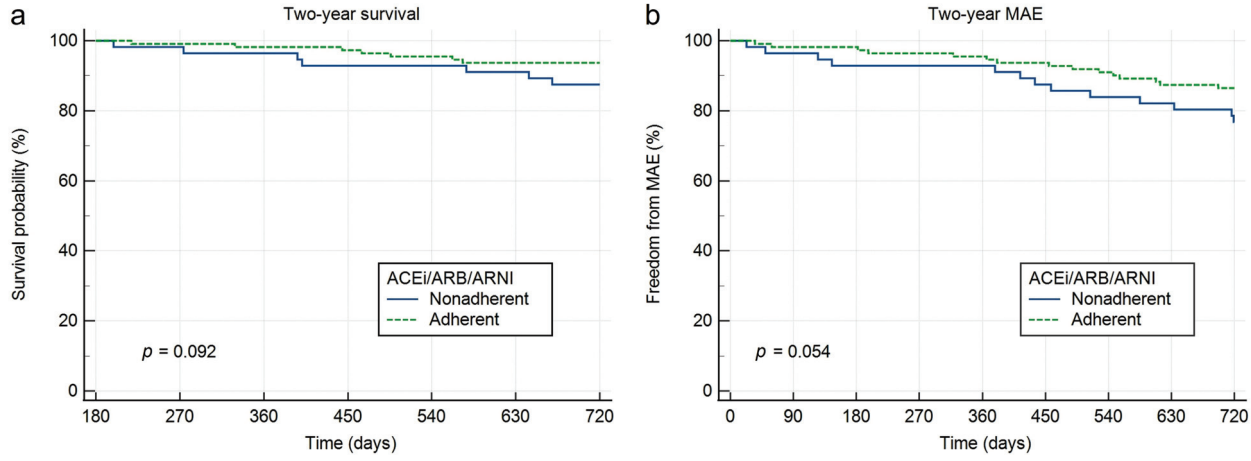


Figure A9. Kaplan–Meier curves depict 2-year all-cause survival (**a**) and freedom from major adverse events (**b**) according to adherence to ACEi/ARB/ARNI.

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