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The Additional Diagnostic Value of Electrocardiogram and Strain Patterns in Transplanted Patients

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Abstract: Background: Transplanted patients are frail individuals who may be affected by diastolic dysfunction, leading to a decrease in exercise tolerance. Previous studies have reported that certain ECG and echocardiographic parameters (such as the P-wave interval, PQ interval, P-wave dispersion, Tend-P interval, QTc interval, and strain) can support the diagnosis of diastolic dysfunction when the ejection fraction is preserved. This study aimed to examine the potential diagnostic contribution of specific ECG and deformation parameters in transplanted recipients, who are at a high risk of heart failure. Materials and Methods: A group of 33 transplanted subjects (17 renal and 16 liver) were categorized using two scores for heart failure with preserved ejection fraction (HFpEF). Additionally, they underwent evaluation based on ECG parameters (P-wave interval, PQ interval, Pwave dispersion, and Tend-P QTc) and echocardiographic deformation parameters (strain and twist). The Student's t-test was used for statistical analysis. Results: The two scores identified different numbers of excludable and not excludable subjects potentially affected by HFpEF. The not excludable group presented ECG parameters with significantly higher values (P-wave, PQ interval, posterior wall diastole, and Tend-P, all with $p \leq 0.05$) and significantly lower 4D strain and twist values ($p < 0.05$) Conclusions: There is evidence for a significant diagnostic contribution of additional ECG and echo strain parameters in an early phase of diastolic dysfunction in subjects potentially affected by HFpEF.

Keywords: HFpEF; organ transplantation; H2FPEF; HFA-PEF; exercise prescription

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1. Introduction

Transplanted subjects are a specific group of patients in whom reduced exercise tolerance can be present, especially in cases of HFpEF [1,2]. Some transplanted subjects, especially if asymptomatic, are included in exercise prescription programs, considering the importance of physical exercise [3]. Two scores, derived from algorithms known as H2FPEF and HFA-PEFF, are currently available in the literature for identifying HFpEF [4,5]. However, at the present state of the art, classification criteria for heart disease with conserved EF classification do not include ECG parameters. Additionally, discrepancies in clinical application [6] have been reported, and the evaluation of brain natriuretic peptide (BNP), proposed in the HFA-PEFF score, may pose further challenges in an ambulatory setting. More recently, the literature has suggested some ECG and echocardiographic deformation parameters to support the diagnosis of potential diastolic dysfunction in post transplanted subjects [7,8]. Nevertheless, there is a strong interest in conducting proper cardiological screening in this patient group before initiating an exercise prescription program [3].

Among ECG parameters, some characteristics are described as particularly important and indicative of possible diastolic dysfunction, such as "electrical dissynchrony", the duration and dispersion of the P wave, the PQ interval, age-related TP/PQ interval duration, the QTc interval, QT dispersion, and left and right intraventricular conduction disturbances [7,8].

Furthermore, specific echocardiographic data are relevant to establishing the grade of diastolic dysfunction, such as the E/e′ strain rate ratio, which has already been studied in transplanted subjects [9]. None of these parameters are actually included in the scores dedicated to HFpEF diagnosis.

Additional information, provided by several parameters, could potentially enhance the inclusion of a greater number of subjects in exercise prescription programs, particularly in the initial phase of myocardial dysfunction. The main purpose of this study was to evaluate ECG parameters' impact in the definition of an includible group of solid organs-transplanted subjects previously classified using the two well-known algorithms developed by the ESC and AHA, namely HFA-PEFF and H2FPEF, respectively.

2. Materials and Methods

A group of 33 adult transplant recipients (>18 years old; 16 kidney and 17 liver transplants) were evaluated at our unit between 2020 and 2022. All patients had undergone transplantation at least 1 year prior to evaluation. All subjects included in this study were clinically stable and met the following inclusion criteria: LVEF > 50% and mild LV diastolic dysfunction [10]. Based on major and minor functional and morphological criteria of the HFA-PEFF algorithm, groups were categorized as HFpEF high probability (≥5 points), lower probability but not excludable (2–4 points), and not includible (≤1 point) [6]. Considering the ambulatorial setting, no data regarding BNP levels were obtained. In addition, patients were asymptomatic at rest. In this study, no subjects were categorized as HFpEF, and none had a score > 4. Furthermore, subjects were categorized according to H2FPEF scores into 3 groups: certainly affected (≥5 points), not excludable (2–5 points), and absolutely not includible (≤1 point). None of the subjects scored higher than 3 points. Some participants were affected by mild or moderate hypertension. They were treated with specific drugs, such as calcium channel blockers, beta-blockers, ACE inhibitors, or ARBs. Immunosuppressive therapy was also assumed; it included drugs such as calcineurin inhibitors (ciclosporin or tacrolimus) in combination with mycophenolate or everolimus and steroids (methylprednisolone). All subjects had a BMI > 25. None of the participants had major arrhythmias in the months preceding the study. A suitable acoustic window for the acquisition of echocardiographic parameters was also essential. Comorbidities, such as diabetes, arterial hypertension, or other metabolic diseases, were not a reason for exclusion. The physical exercise program consisted of mixed physical activity (aerobics and counter-resistance) at least 3 times a week, for 30 min of aerobics. The intensity was approximately 60% of the maximal heart rate for each individual, eventually using the Karvonen formula, modified in the case of patients using beta-blockers [11]. The main cause of liver transplantation was preceding HCV liver cirrhosis, while in other cases it was autoimmune biliary cirrhosis. In the kidney transplantation group, polycystic kidney disease, pyelonephritis, post-glomerulonephritis, Berger's nephropathy, and solitary kidney were reasons for surgical treatment. Measurements were obtained under resting conditions, and the data interpretation followed ECG guidelines [12], including recent ECG parameters [7,8], traditional echocardiography guidelines [13], and the new indications for transplanted subjects [9]. Data were obtained by repeating measurements at least three times, with a few minutes interval.

2.1. ECG Parameters

Subjects were examined using a 12-lead surface ECG. Measurements were performed in the morning after 5 min of rest conditions using a Mortara electrocardiograph (Milwaukee, WI, USA). The printed ECG trace was obtained at a speed of 25 mm/s. The filter band was set at 40 Hz. In cases with artifacts, the ECG was repeated. Rhythm and other basic parameters of the standard ECG interpretation were analyzed. In addition, the Sokolow–Lyon indices for the diagnosis of cardiac hypertrophy and the following indices of diastolic dysfunction were considered, including the duration and morphology of the P wave (measured using a limit value of 110 msec); the dispersion of the P wave (PWD), calculated by withdrawing the minimum duration from maximum duration of the P wave; and the duration of the PQ interval (measured using a maximum threshold of 200 msec). Finally, the Tend-P/(PQ x age) electrocardiographic index was used using the following values of normality: Tend-P ($\geq$311 ms), Tend-Q ($\geq$455 ms), and Tend-P/(PQ x age) $\geq$ 0. 0333, modified by age. In accordance with the literature, the QTc interval was also taken into account.

2.2. Echocardiographic Evaluation

A transthoracic echocardiographic exam was performed using the MyLABX8 Esaote-Genova–Italy echocardiograph equipped with a 2.5 MHz probe. Two certified cardiologists acquired the images.

According to the ASE guidelines, the standard systo-diastolic parameters were obtained. The following parameters were considered: diameters and thicknesses of the left ventricle, left ventricular mass, indexed left atrial volume, pulmonary pressure, mitral inflow pattern (wave E/A ratio, deceleration time), annular mitral septal, and lateral TDI with E/e′ ratio. Diastolic function was categorized as normal or abnormal on the basis of impaired relaxation (grade 1), pseudo-normal (grade 2), or restrictive (grade 3) results. In cases of valvular heart disease, severity was evaluated according to the ASE 2015 guidelines [13]. For strain parameters, including rotation and twisting, one-cycle clip images from 4C, 2C, and 3C, and 1 cycle from parasternal short axis projections on the mitral and apical planes were acquired. The analysis of intracardiac vortices using HyperDoppler sw release F110102 was obtained using a clip of 3 cycles from the 3C projection, with the color Doppler at a maximum FR of 21 HZ. The post processing analysis provided relative geometric and energetic parameters.

2.3. Strain

All subjects were evaluated in this study of myocardial deformation parameters, which included the global longitudinal Sstrain (GLS) measured in two-chamber, three-chamber, and four-chamber views, the 4D strain, and the twisting of the left ventricular chamber, obtained as the net difference between the basal rotation vs. the apical rotation. Xstrain TM SW F110102 (ESAOTE, Genova, Italy) was used to analyze the myocardial deformation. According to the EACVI/ASE consensus document, images were acquired in full cycle and at a high-frame rate. For diastolic function, the early myocardial deformation, as the early strain rate (eSR), was also calculated, and subsequently expressed as the ratio of E/e′ strain rate. The E1/eSR ratio was considered in order to evaluate the grade of the diastolic dysfunction as reported in the literature [9].

2.4. HyperDoppler

Vortex analysis was obtained via HyperDoppler sw F110102 using the MyLab X8 echo scanner (ESAOTE -Genova-Italy)with a cardiac probe. Image acquisition was performed using conventional examinations, with subjects in the left lateral decubitus position, as previously described [14,15].

A standard apical 3C view of 3 cardiac cycles in cine-loop was optimized by including the aortic tract in order to include as much of the LV cavity and the LV outflow tract (LVOT) as possible within the corner of the color Doppler sector. The depth and width of the sector were set to achieve a color Doppler frame rate of 21 fps. The repetition frequency of the color Doppler pulse was 4.4 MH.

Clips were acquired at the end of expiration (Figure 1).

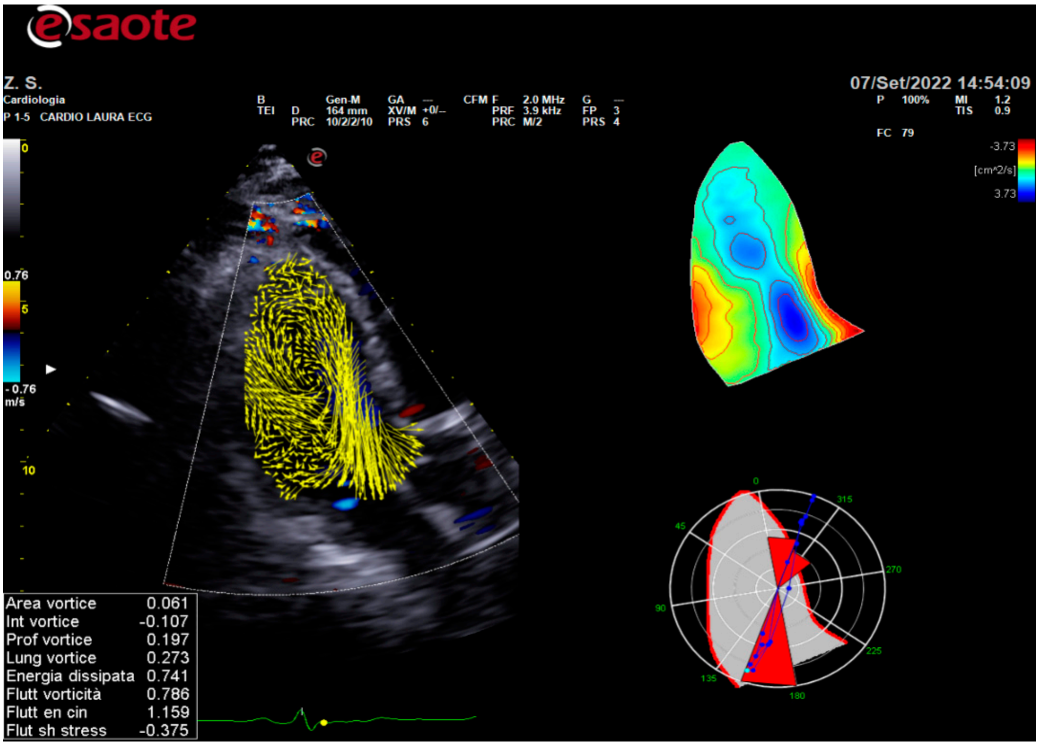

Figure 1. Example of vortex parameters obtained from a 3C view using HyperDoppler analysis.

2.5. Statistical Analysis

Data are expressed as the mean ± standard deviation. Regarding continuous variables, a Student's t-test was used. A p-value < 0.05 was considered statistically significant.

3. Results

A group of 33 solid organ transplanted subjects with a mean age of 55 years (16 kidney transplants, including 9 men and 7 women, and 17 liver transplants, including 13 men and 4 women) was studied.

LV function was normal for all participants, while the "not excludible" subjects showed a diastolic pattern compatible with grade II diastolic dysfunction, as indicated by an E′ value < 0.07 and E/e′ in the range of 9–10 [16]. None of the subjects had a value >4 for the H2FPEF algorithm or >3 points for the HFA-PEFF algorithm.

As expected, the results of the two scores were discordant. The number of subjects identified as potentially affected by HFpEF, or not affected, was different for each of the two scores (excludable: 6 HFA-PEFF vs. 14 H2FPEF; not excludable: 27 HFA-PEFF vs. 19 H2FPEF), as shown in Table 1. The BNP was not considered during classification. Therefore, there is evidence of a grey zone for subjects who were not excludable for HFpEF, but were not definitively affected. The H2FPEF score appears to have a higher sensitivity for a larger recruitment. All values were normal and in agreement with the diagnosis of HFpEF. In particular, the EF was normal >50%, and grades 1–3 diastolic dysfunction were present (Table 2).

Table 1. Comparison between HFA-PEFF and H2FPEF scores by range points.

	HFA-PEFF			H2FPEF		
	Excludable (n = 6)	*Not Excludable (2–4)* (n = 27)	*p*	*Excludable* (n = 14)	*Not Excludable (2–5)* (n = 19)	*p*
Age (years)	59 ± 10	57 ± 9.6	0.07	51 ± 9.4	61 ± 7.21	0.005
Hypertension	9%	57%	-	33%	36%	-
BMI (kg/m^2)	24 ± 2	25 ± 1.6	0.5	24.1 ± 2	25.4 ± 3	0.2
E/e′	8 ± 1.24	9 ± 3.2	0.4	7 ± 1.5	10 ± 3.6	0.01
AF	0	0	-	0	0	-
PVAT (ms)	119.1 ± 13.1	121 ± 17.3	0.7	120 ± 16	121 ± 16	0.8
e′ septal (mm/s)	0.09 ± 0.01	0.07 ± 0.02	**0.04**	0.08 ± 0.02	0.06 ± 0.01	<0.001
e′ lateral (mm/s)	0.11 ± 0.02	0.14 ± 0.19	0.6	0.13 ± 0.12	0.13 ± 0.15	0.8
GLS%	−17.4 ± 2	−16.9 ± 2	0.7	−16.9 ± 2	−17.13 ± 3.4	0.8
LAVI (mL/m^2)	23.7 ± 3.2	26 ± 8	0.4	22.7 ± 5.6	28.9 ± 7.8	0.01
LVMI (g/m^2)	83.7 ± 16.4	104.4 ± 20.5	**0.02**	94.3 ± 21.3	106.8 ± 19.8	0.09
RWT	0.3 ± 0.04	0.3 ± 0.05	0.6	0.3 ± 0.06	0.3 ± 0.03	0.4
IVS.d (mm)	9.25 ± 0.8	10.1 ± 1.2	0.09	9.5 ± 0.9	10.4 ± 1.4	0.04
Functional criteria	6	27		-	-	
Morphological criteria	24	9		-	-	
Clinical criteria	-	-		14	19	

Legend: Data are expressed as M ± SD or n (%), as appropriate. Statistical significance = $p < 0.05$. BMI (body mass index), E/e′ ratio (ratio between E peak wave and septal e′), AF (atrial fibrillation), PVAT (pulmonary velocity acceleration time), GLS (global longitudinal strain), LAVI (indexed left atrial volume), LVMI (left ventricular mass index), RWT (relative wall thickness), IVS.d (interventricular septum in diastole).

Table 2. General echocardiographic parameters.

	All Subjects (n = 33)		**All Subjects (n = 33)**
Systolic function		*Diastolic function/Vortex*	
IVSd (mm)	9.95 ± 1.21	E/A	0.99 ± 0.33
PWd (mm)	9.47 ± 1.18	DTc (ms)	217.24 ± 51.13
LVSD (mm)	30.98 ± 4.13	E/e′	8.80 ± 2.87
LVDD (mm)	50.49 ± 4.60	(PVAT) (ms)	120 ± 16.14
LVMI (g/m^2)	100.02 ± 21.02	Vortex Area	0.20 ± 0.05
RWT	0.38 ± 0.05	Vortex Depth	0.31 ± 0.08
EF (%)	60.94 ± 4.72	Vortex Length	0.55 ± 0.11
MAPSE (mm)	17.63 ± 2.20	Vortex Intensity	−0.22 ± 0.17
TAPSE (mm)	23.62 ± 3.64	Energetic Dissipation	0.79 ± 038
Aortic Root (mm)	26.58 ± 4.64	Kinetic Energy Fluctuation	0.96 ± 0.11
Ascending Aorta (mm)	33.05 ± 3.6	Vorticity Fluctuation	0.81 ± 0.075
LAVI (mL/m^2)	25.59 ± 7.20	Shear Stress Fluctuation	−0.38 ± 0.31

Legend: IVSd (interventricular septum in diastole), PWd (posterior wall diastole), LVSD (ventricular diameter in systole), LVDD (ventricular diameter in diastole), LVMI (left ventricular mass index), RWT (relative wall thickness), EF (ejection fraction), MAPSE (excursion of the mitral annular plane), TAPSE (excursion of the tricuspid annular plane), LAVI (indexed left atrial volume), DTc (deceleration time), E/e′ ratio (ratio between E peak wave and septal e′), PVAT (pulmonary velocity acceleration time).

In view of the discrepancy emerging from the two scores, the introduction of additional electrocardiographic and echocardiographic parameters (shown in Tables 3 and 4) highlighted significant differences between the two groups obtained from each score. The evaluation of QTc showed no statistical differences. All myocardial deformation values (4D strain and twist) were normal compared to the parameters present in the literature. Regarding the behavior of the deformation parameters, significant differences were observed within the excludable and not excludable groups. These parameters confirmed the diagnosis of HFpEF, despite the different results of the two scores. All parameters collected in Tables 3 and 4 showed statistically significant differences when comparing HFA-PEFF and H2FPEF scores, except for QTc.

Table 3. ECG parameters classification based on the range point of the two scores.

ECG	HFA-PEFF			H2FPEF		
	Excludable (n = 7)	*Not Excludable (2–4)* (n = 26)	*p*	*Excludable* (n = 18)	*Not Excludable (2–5)* (n = 15)	*p*
P wave interval	92.8 ±14.9	105.7 ± 13.9	**0.03**	97.7 ± 15.1	109.3 ± 12.2	0.02
Interval PQ	165.7 ± 17.1	171.5 ± 24.4	0.5	161.8 ± 21.8	180.4 ± 20.8	0.01
PWD	35.7 ± 17.1	48.8 ± 20.06	0.1	38.3 ± 19.1	55.3 ± 17.2	0.01
Tend-P/(PQxAge)	0.03 ± 0.01	0.03 ± 0.01	0.7	0.04 ± 0.02	0.02 ± 0.009	0.008
QTc	396.57 ± 7.66	413.27 ± 26.69	0.12	405.11 ± 26.52	415.27 ± 22.21	0.25

Legend: Data are expressed as M ± SD. Statistical significance: $p < 0.05$. PWD (P wave dispersion).

Table 4. Echocardiographic parameters.

Strain	HFA-PEFF			H2PFEF		
	Excludable (n = 7)	*Not Excludable (2–4)* (n = 26)	*p*	*Excludable* (n = 18)	*Not Excludable (2–5)* (n = 15)	*p*
E/e′ strain rate	0.73 ± 0.28	0.62 ± 0.25	0.2	0.61 ± 0.22	0.68 ± 0.27	0.4
Twisting	11.2 ± 4.3	6.8 ± 2.8	**0.003**	9.2 ± 4.3	6.1 ± 1.7	0.01
4D strain	−16.8 ± 2.11	15.3 ± 2.03	0.1	−16.8 ± 1.8	−15 ± 2.2	0.08

Data are expressed as M ± SD. Significance = $p < 0.05$.

4. Discussion

This study focused on a special population of patients with a history of solid organ transplantation who were asymptomatic, at least in at-rest conditions. Sports medicine has been recently involved in the evaluation of certain categories using ECG and echocardiographic parameters [7,9,17,18]. A wide range of subjects with non-communicable diseases started participating in structured physical activity programs known as "exercise prescription". For transplanted subjects, the potential presence of cardiac systo-diastolic dysfunction is relevant in terms of prognostic outcomes and customizing an exercise regimen [3].

Considering the potential discrepancies of using two well-known scores normally used in a larger general population [6], the role of additional parameters from ECG and echocardiographic evaluations can be proposed, especially in categories where ambulatory management is the most common setting for evaluating exercise prescription models.

The literature supports the use of certain instrumental parameters derived from echocardiography and electrocardiography to detect HFpEF in transplanted subjects [9]; the use of these parameters has not yet been routinely investigated. The goal is, therefore, to identify a larger group of subjects potentially included in an exercise program. The early phase of myocardial dysfunction, particularly if diastolic dysfunction is present with normal systolic function, can be challenging to diagnose. This aspect can contribute to a reduction in the number of recruitable subjects potentially involved in exercise programs. Our data, especially ECG parameters, seem to have improved this approach. Additionally, the evaluation of deformation parameters, which focuses on both systolic and diastolic myocardial function (twisting), showed a difference ($p < 0.001$) concerning excludable vs. not excludable groups estimated using HFA-PEF and H_2PEFF. This integrated approach could be used to investigate the grey zone of diastolic dysfunction, when the E/e′ value is in the range of 8–15 and symptoms are not evident. No evidence of a major contribution has been observed from HyperDoppler analysis, at least in this study.

5. Conclusions

Post-transplantation is a frail condition that offers several points of clinical interest. Few experiences are reported in the literature regarding this category of subjects, especially regarding exercise prescription indications. This is the major cause of the poor availability of useful data for the clinical management of post-transplant syndrome. Long-term exposure to regular immune-suppressive therapy and persistent inflammation could be responsible for "post-transplant syndrome", which sustains a high cardiovascular risk profile potentially oriented towards heart dysfunction and early involvement of the diastolic function before the systolic function. Moreover, diastolic dysfunction, and therefore HFpEF, has a similar recognized impact on the outcome of patients, although sports medicine is particularly interested in systolic function, mainly regarding prescribing physical exercise. Given the data we obtained, it seems desirable to suggest considering the role of additional ECG and echocardiographic deformations parameters routinely acquired in the ambulatory setting. To promote physical exercise as therapy for patients with chronic metabolic diseases, the role of a non-invasive score that uses instrumental multi-parameters is advisable.

Regarding the potential vortex analysis contribution, no significant data was obtained. The restricted number of subjects studied, and continued inadequate knowledge regarding the method, did not facilitate the collection of additional information [19].

More studies will be necessary in the future.

6. Limitations of the Study

This study, despite being original in its specific context, had some limitations. First, a small sample size was investigated. However, the literature reports evidence that few experiences (exclusively in specialist and dedicated settings) have been presented, particularly regarding the involvement of renal-transplanted subjects in an exercise prescription program [20–24]. These studies all reported no more than 40 patients. In addition, this study focuses on a highly selective population, and no other data were available, particularly for ECG parameters. In other words, no other studies investigated this specific aspect in the context of an exercise program. Another potential limit is that this study was conducted in a single center, and the measurements were taken by a single expert sonographer. Although these factors limited variability, they also enhanced the statistical power of the study. Another point is the missing BNP assessment. A BNP assessment was not included in this study's inclusion criteria, but is included as a second level test in the HFA–PEFF score, and can be especially useful for outpatients, such as our study population. However, natriuretic peptides assessment is often missing in the clinical setting, as also noted in the HF Long-Term Registry [20]. The missing BNP made it impossible to determine the actual number of patients who fulfilled the 2016 ESC HFpEF in our study [25,26].

These aspects limit the clinical impact of this investigation, especially because the findings cannot be generalized to a larger population at this time. To address this limitation, it is worth noting that clinical experience with the post-transplant population is limited to a few sports medicine centers, as reported in the literature [3,22]. Although an invasive evaluation of HFpEF cannot be proposed in an ambulatorial setting, an adequate evaluation of this protocol in a general population of non-transplanted subjects, in order to test diagnostic parameters in the general population with proven HFpEF (diagnosed using invasive cardiac catheterization) could be helpful. More studies and larger samples are necessary to validate the results presented here.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each patient for data analysis. Specific Ethical Committee approval was not applicable for this study, as data were collected in the database of the clinical institute. This study followed the principles of the Committee on Publication Ethics (COPE) according to Horizon 2020 Programme Guidance (https://ec.europa.eu/research/participants/docs/h2020-funding-guide/index_en.htm).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study and to publish this paper.

Data Availability Statement: Data were anonymized in a way that required "excessive efforts to be re-identified" so that data cannot be considered "personal data" anymore.

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