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Differences in Clinical Features, Hemodynamic Findings and Clinical Outcomes of Ischemic and Non-ischemic Cardiomyopathy in End-Stage Heart Failure

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ABSTRACT

Introduction: The aim of this study was to investigate the effect of heart failure (HF) etiology on clinical, echocardiographic, and hemodynamic findings, right ventricular (RV) function, and outcomes in patients with end-stage HF.

Patients and Methods: A total of 470 end-stage HF patients who undergoing evaluation for heart transplantation (HT) were divided into two groups: ischemic cardiomyopathy (ICMP, n= 249) and nonischemic cardiomyopathy (NICMP, n= 221). RV dysfunction was defined as tricuspid annular plane systolic excursion (TAPSE) ≤ 1.5 cm (TAPSE-defined RV dysfunction) and right ventricular stroke work index (RVSWI) < 5 g/m/beat/m^2 (RVSWI-defined RV dysfunction). The primary outcome was defined as left ventricular assist device implantation, urgent HT, or death.

Results: Patients with ICMP had higher pulmonary vascular resistance, systolic and mean pulmonary artery pressures (PAPs and PAPm) than those with NICMP [3.0 (1.1-6.0) vs. 2.0 (1.0-5.0), p= 0.013; 53.5 (42.0-68.0) vs. 46.0 (32.5-64.5), p< 0.001 and 35.512.9 vs. 31.812.3, p= 0.002]. RVSWI levels were lower in NICMP patients than in ICMP patients [5.4 (3.7-7.6) vs. 6.5 (4.6-9.6), p< 0.001]. While TAPSE-defined RV dysfunction was comparable between NICMP and ICMP, RVSWI-defined RV dysfunction was higher in NICMP (44.3% vs. 55.0%, p= 0.069 and 45.2% vs. 31.3%, p= 0.012). NICMP was an independent predictor for RVSWI-defined RV dysfunction, but not for TAPSE-defined RV dysfunction, according to multivariate analyses (OR: 1.79, 95% CI: 1.13-2.82, p= 0.012 and OR: 0.63, 95% CI: 0.28-1.39, p= 0.254). Over a median follow-up of 503.5 days, it was demonstrated that HF etiology was not a predictor of primary outcome according to unadjusted and adjusted models (OR: 0.99, 95% CI: 0.80-1.23, p= 0.936 and OR: 0.89, 95% CI: 0.60-1.31, p= 0.542).

Conclusion: We that demonstrated patients with end-stage HF, ICMP had greater RV afterload and RVSWI value than NICMP and HF etiology was not predictor of primary outcome. However, we couldn't say for sure whether HF etiology has an effect on RV function because of the conflicting results in TAPSE-defined RV dysfunction and RVSWI-defined RV dysfunction.

Key Words: Clinical outcome; end-stage heart failure; heart failure etiology; ischemic cardiomyopathy; non-ischemic cardiomyopathy; right ventricular function.

Son Dönem Kalp Yetmezliğinde İskemik ve İskemik Olmayan Kardiyomiyopatinin Klinik Özellikleri, Hemodinamik Bulguları ve Klinik Sonlanımları Arasındaki Farklılıklar

ÖZ

Giriş: Bu çalışmanın amacı, son dönem kalp yetersizliği (KY) hastalarında KY etiyolojisinin klinik, ekokardiyografik, hemodinamik bulgular, sağ ventrikül (SV) fonksiyonu ve klinik sonlanım üzerindeki etkilerini araştırmaktır.

Hastalar ve Yöntem: Kalp nakli için değerlendirilen toplam 470 son dönem KY hastası iskemik kardiyomiyopati (İKMP, n= 249) ve iskemik olmayan kardiyomiyopati (NİKMP, n= 221) olmak üzere iki gruba ayrıldı. SV disfonksiyonu, triküspit anüler plan sistolik ekskürsiyonun (TAPSE) ≤ 1.5 cm olması (TAPSE-tanımlı SV disfonksiyonu) ve SV strok work indeksinin (RVSWI) < 5 g/m/beat/m^2 olması (RVSWI-tanımlı SV disfonksiyonu) olarak tanımlandı. Sol ventriküler destek cihazı (LVAD) implantasyonu, acil kalp nakli veya ölüm primer sonlanım olarak tanımlandı.

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Bulgular: İKMP'li hastalar, NİKMP'li hastalara göre daha yüksek pulmoner vasküler direnç, sistolik ve ortalama pulmoner arter basınçlarına sahipti [3.0 (1.1-6.0) vs. 2.0 (1.0-5.0), p= 0.013; 53.5 (42.0-68.0) vs. 46.0 (32.5-64.5), p< 0.001 ve 35.512.9 vs. 31.812.3, p= 0.002]. RVSWI seviyeleri NİKMP hastalarında İKMP hastalarına göre daha düşüktü [5.4 (3.7-7.6) vs. 6.5 (4.6-9.6), p< 0.001]. TAPSE tanımlı SV disfonksiyonu NİKMP ve İKMP arasında benzer iken, RVSWI tanımlı SV disfonksiyonu NİKMP'de daha yüksekti (%44.3 vs. %55.0, p= 0.069 ve %45.2 vs. %31.3, p= 0.012). Çok değişkenli analizlere göre, NİKMP, RVSWI-tanımlı SV disfonksiyonu için bağımsız bir prediktörü iken TAPSE-tanımlı SV disfonksiyonu için değildi (OR: 1.79, %95 CI: 1.13-2.82, p= 0.012 ve OR: 0.63, %95 CI: 0.28-1.39, p= 0.254). 503.5 günlük medyan takip süresinde, ayarlanmamış ve düzeltilmiş modellere göre KY etiyolojisinin primer sonlanım için bir prediktör olmadığı gösterildi (OR: 0.99, %95 CI: 0.80-1.23, p= 0.936 ve OR: 0.89, %95 CI: 0.60-1.31, p= 0.542).

Sonuç: Bu çalışmada, son evre KY olan hastalarda, İKMP'nin NİKMP'den daha yüksek SV artyüke ve RVSWI değerine sahip olduğu ve KY etiyolojisinin primer sonlanım prediktörü olmadığı gösterilmiştir. Ancak TAPSE-tanımlı SV disfonksiyonu ve RVSWI-tanımlı SV disfonksiyonundaki çelişkili sonuçlar nedeniyle KY etiyolojisinin SV fonksiyonu üzerinde bir etkisinin olup olmadığı kesin olarak söylenememiştir.

Anahtar Kelimeler: İskemik kardiyomiyopati; iskemik olmayan kardiyomiyopati; kalp yetersizliği etiyolojisi; klinik sonlanım; sağ ventrikül fonksiyonu; son dönem kalp yetersizliği.

INTRODUCTION

Ischemic cardiomyopathy (ICMP) and nonischemic cardiomyopathy (NICMP) are the two most common types of left ventricular (LV) systolic dysfunction[1,2]. They are among to leading causes of heart failure (HF) in the world[3]. Whereas ICMP is the most common cause, NICMP affects approximately 30%-40% of patients with reduced ejection fraction[4]. The ICMP was defined as a patient's history of myocardial infarction or more than 70% stenosis in the proximal, or midsection of at least one major epicardial coronary artery. The NICMP was defined as a patient's history of no coronary disease, coronary disease with 70% stenosis, or coronary disease with 70% stenosis restricted to a branch vessel[5]. Previous studies have shown that ICMP and NICMP have some variations in clinical, echocardiographic, and hemodynamic findings, as well as prognosis[6-15]. The findings of various studies examining the relationship between HF etiology and right ventricular (RV) function are contradictory. While some studies have reported that RV function is worse in NICMP patients, other studies have suggested that the degree of RV dysfunction is not dependent on the etiology of cardiomyopathy, and there is also one study that suggests RV function is worse in ICMP patients[5,16-20].

Currently, differences in clinical, echocardiographic, and hemodynamic findings, RV function, and prognosis between ICMP and NICMP in patients with end-stage HF are not well described. As a result, our primary goal was to investigate the relationship between HF etiology and clinical, echocardiographic, and hemodynamic findings, as well as RV function in patients with end-stage HF who were refered for HT evaluation. Our secondary goal was to investigate whether the etiology of HF is related to poor clinical outcomes such as left ventricular assist device implantation (LVAD), urgent heart transplantation (HT) or death in patients with end-stage HF.

PATIENTS and METHODS

Patient Population

This retrospective observational study enrolled 470 patients with end-stage HF who were referred for HT evaluation between June 2017 and June 2020. The ICMP was defined as a patient's history of myocardial infarction or more than 70% stenosis in the proximal or midsections of at least one major epicardial coronary artery. The NICMP was defined as patient's history of no coronary disease, coronary disease with < 70% stenosis, or coronary disease with a ≥ 70% stenosis limited to branch vessel[5]. The inclusion criteria were age ≥ 18 years, LVEF ≤ 25%, and New York Heart Association (NYHA) functional class II-IV. Mean while, the exclusion criteria were age ≥ 70, inotropic dependency, necessity of the intraaortic balloon pump, multiorgan deficiency, infiltrative, constrictive, or hypertrophic cardiomyopathy, congenital heart disease, history of moderate and severe chronic obstructive pulmonary disease, or primary lung disease, serum creatinin level ≥ 2.5 mg/dL, and comorbidities causing contraindication to heart transplantation or LVAD other than high pulmonary vascular resistance (PVR) determined by the International Society for Heart and Lung Transplantation. The study was approved by the local Ethical Committee at 2017 (2017.3/9-32).

Baseline Characteristics

Baseline characteristics of patients including age, gender, body mass index (BMI), and comorbidities such as hypertension, diabetes, dyslipidemia, smoking, atrial fibrillation, history of cerebrovascular disease, severe pulmonary disease, HF duration, NYHA functional class, hemoglobin, creatinine, sodium, albumin, bilirubin, alanine aminotransferase, and aspartate aminotransferase and medications of the patients were recorded.

Echocardiographic Measurements

The size of left atrium (LA) and LV, LV ejection fraction (LVEF), the parameters associated with LV filling pressure

such as ratio of early transmittal flow velocity (E) to early diastolic mitral annular velocity (e') and deceleration time (DT) of mitral E-wave, presence of grade 3 diastolic dysfunction (defined as mitral E wave DT ≤ 145 msec and e' ≤ 8 cm/sec or E/e' ≥ 15), presence of severe functional mitral regurgitation (FMR) (fined as effective regurgitation orifice area ≥ 20 mm^2 and regurgitation volume ≥ 30 mL while mitral valve was morphologically normal), the size of RV, presence of RV dilatation, tricuspid annular plane systolic excursion (TAPSE), and systolic tricuspid velocity (ST), systolic pulmonary arterial pressure (PAPs), PVR, presence of severe tricuspit regurgitation (defined as vena contracta ≥ 7 mm) were recorded.

Invasive Hemodynamic Measurements

Acute decompensated patients medically treated before catheterization were included to the study. The right heart catheterization (RHC) has been performed by Swan-Ganz catheter and LV and aortic pressures have been assessed by the pigtail catheter with hemodynamic and fluoroscopic guidance. The PAPs, pulmonary artery mean pressure (PAPm) and pulmonary artery diastolic pressure (PAPd), pulmonary artery wedge pressure (PAWP), right atrial mean pressure (RAPm), transpulmonary gradient (TPG), systolic blood pressure (SBP), diastolic blood pressure (DBP), left ventricle end-diastolic pressure (LVEDP), and transsystemic gradient (TSG), the cardiac output (CO) by measured by Fick method, cardiac index, stroke volume (SV), stroke volume index (SVI), PVR in wood units (WU), and systemic vascular resistance (SVR), right ventricular stroke work index [RVSWI= (PAPm-RAPm) x SVI x 0.0136] and pulmonary artery pulsatility index [PAPi= (PAPs-PAPd)/RA] were recorded. Pulmonary hypertension (PH) was defined as PAPm ≥ 20 mmHg assessed by RHC[21].

Right Ventricular Dysfunction

Both echocardiographic and RHC parameters were used to assess RV function. According to the ACC/AHA guidelines for echocardiographic assessment of the right heart in adults, a TAPSE ≤ 1.5 cm indicates RV dysfunction[22]. The RVSWI cut off value in patients with advanced HF has not been reported, whereas the normal range of RVSWI in healthy people is considered to be 5-10 gxm/m^2/beat. Previous research has shown that an RVSWI of less than 5 gxm/m^2/beat indicates RV dysfunction[23,24]. In this study, RV dysfunction was defined as a TAPSE ≤ 1.5 cm (TASE-defined RV dysfunction) and a RVSWI < 5 gxm/m^2/beat (RVSWI-defined RV dysfunction).

Primary Outcome Definition

The outcomes were LVAD implantation, urgent HT, and death. The HT or LVAD implantation was carried out in accordance with the ISHLT guidelines by a joint decision of our hospital's HT/LVAD committee[25,26]. Urgent HT was defined as transplantation in a patient who required inotropic drug support, an IABP, or temporary mechanical circulatory support. HT from the routine waiting list was not considered to be the end point.

Statistical Analysis

Means were used to express values for normally distributed continuous variables, and medians were used to express values for non-normally distributed variables (interquartile range). Group comparisons for continuous variables were analyzed by using an independent t-test if data distribution was normal. Mann-Whitney U test was used for group comparisons of continuous variables if data distribution was not normal. Comparisons of categorical variables were evaluated by the chi-square test. The B value and odds ratio (OR) with the 95% confidence interval (CI) were calculated in univariate and multivariate analyses with logistic risk analysis. NICMP, severe FMR, severe tricuspid regurgitation, atrial fibrillation, LVEF, and PAPm were all included in the model as potential predictors of RV dysfunction. Covariates in multivariate analysis were performed based on clinical and biological plausibility, as well as their association with RV dysfunction, as demonstrated in previous studies. The outcome was assessed using the Cox proportional hazards model in both univariate and multivariate analyses. The model was built based on previous research and our focused variable, which was expected to have an impact on the outcome[27,28]. Age, gender, HF type (ischemic vs. non-ischemic), diabetes, atrial fibrillation, LVEF, severe FMR, severe tricuspid regurgitation, LV diastolic dysfunction grade 3, TAPSE, hemoglobin, sodium, N-Terminal pro-brain natriuretic peptide, and RVSWI were all included in the model. Significance level was considered as $p< 0.05$ in all statistical analyses. All statistical analyses were performed using SPSS version 21.0 (SPSS Inc. Chicago, Illinois).

RESULTS

Demographic and Clinical Characteristics

Table 1 summarizes the patients' baseline demographic and clinical measurements. ICMP was found in 249 (52.9%) of the 470 subjects, while NICMP was found in 221 (47.0%). The majority of the ICMP patients were older men. The two groups had comparable rates of atrial fibrillation, mild to moderate chronic obstructive pulmonary disease, HF length, and NYHA functional class. The ICMP had higher rates of hypertension, diabetes, hyperlipidemia, cerebrovascular disease, and smoking ($p< 0.001$ at all). Patients with ICMP had a higher BMI than those with NICMP. The serum creatinine, sodium, albumin, and bilirubin levels of the two groups did not differ significantly. Serum haemoglobin and transaminases (AST and ALT) were lower in the ICMP group (all $p< 0.05$). The medications used by the two groups were similar.

Table 1. Demographic and clinical characteristics of the patients with ischemic and non-ischemic cardiomyopathy

Variable	ICMP (n= 249)	NICMP (n= 221)	p
Age (yrs)	52.5 (46.0-57.0)	46.0 (37.0-54.0)	< 0.001
Males (n, %)	231	181	< 0.001
BMI (kg/m^2)	27.0 ± 4.6	26.0 ± 4.8	0.019
Comorbidities (n, %)			
Hypertension	87 (34.9)	31 (14.0)	< 0.001
Diabetes	71 (28.1)	26 (11.7)	< 0.001
Hyperlipidemia	99 (39.7)	26 (11.7)	< 0.001
CVD	20 (8.0)	4 (1.8)	< 0.001
COPD (mild-moderate)	6 (2.4)	4 (1.8)	0.653
Smoking	134 (53.8)	61 (27.6)	< 0.001
Atrial fibrillation	46 (18.4)	31 (14.0)	0.233
HF duration (years, median)	3.1 (2.1-6.3)	3.0 (2.0-6.0)	0.621
NYHA	3.1 ± 0.6	3.3 ± 0.4	0.225
NYHA (n, %)			
II	34 (13.6)	33 (14.9)	
III	159 (63.8)	139 (62.8)	> 0.05 in all
IV	56 (22.4)	49 (22.1)	
Haemoglobin (g/dL)	13.0 (11.0-14.3)	14.0 (12.0-15.0)	0.045
Creatinin (mg/dL)	1.1 ± 0.7	1.0 ± 0.6	0.156
Sodium (mEq/L)	136.5 (134.0-139.0)	137.0 (134.0-140.0)	0.050
Albumin (mg/dL)	4.0 (3.9-4.1)	4.0 (3.9-3.2)	0.494
Bilirubin (mg/dL)	1.0 (0.88-2.0)	1.0 (0.9-2.1)	0.694
NT Pro-BNP (pg/mL)	2157.0 (883.0-4748.0)	1836.0 (695.0-4265.0)	0.283
AST (mEq/L)	23.5 (19.0-32.0)	27.0 (21.0-38.0)	0.001
ALT (mEq/L)	22.0 (15.0-30.0)	24.0 (16.0-38.0)	0.016
HF medications (n, %)			
Beta blocker	220 (88.3)	198 (89.5)	0.734
ACEI or ARB	161 (64.6)	143 (64.7)	0.584
Spirinolactone	171 (68.6)	164 (74.2)	0.383
Diuretic	225 (90.3)	201 (90.9)	0.311
Ivabradin	76 (30.5)	53 (23.9)	0.128
Sacubitril/Valsartan	36 (14.4)	34 (15.5)	0.453

Values are presented as mean ± SD, % of cohort, median (25th-75th percentile).
ACEI: Angiotensin converting enzyme inhibitor, ALT: Alanine aminotransferase, ARB: Angiotensin receptor blocker, AST: Aspartate aminotransferase, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular disease, HF: Heart failure, ICMP: Ischemic cardiomyopathy, NICMP: Nonischemic cardiomyopathy, NT Pro-BNP: N-terminal pro-brain natriuretic peptide, NYHA: New York Heart Association.

Echocardiographic Characteristics

Table 2 summarizes the echocardiographic characteristics of the patients. The LA dimension, the LV end-diastolic dimension, the LV end-systolic dimension, the rate of diastolic dysfunction grade 3, the rate of severe FMR and tricuspid regurgitation, TAPSE, ST, PVR, and the rate of RV dilatation were comparable between the two groups. The PAPs could be measured in 225 (90.3%) of ICMP patients and 195 (88.2%) of NICMP patients. PAPs values measured by echocardiography were higher in patients with ICMP than in patients with NICMP (49.5 ± 15.8 vs. 45.8 ± 14.2, p= 0.019). Patients' PVRs were comparable in both groups (4.4 ± 1.9 vs. 4.1 ± 2.1, p= 0.405).

Invasive Hemodynamic Characteristic

The invasive hemodynamic measures are summarized in Table 3. The patients with ICMP had higher PAPs and PAPm compared to those with NICMP [53.5 (42.0-68.0) vs. 46.0

Table 2. Echocardiographic findings of the patients with ischemic and non-ischemic cardiomyopathy

Variable	ICMP (n= 249)	NICMP (n= 221)	p
Echocardiography			
LAD (cm)	4.76 ± 1.01	4.8 ± 2.8	0.533
LVEDD (cm)	6.79 ± 0.88	6.93 ± 1.12	0.137
LVESD (cm)	6.22 ± 3.47	6.14 ± 1.16	0.761
LVEF (%)	21.3 ± 4.4	20.6 ± 6.7	0.375
LV diastolic dysfunction grade 3 (n, %)	87 (34.9)	81 (36.6)	0.630
Severe FMR (n, %)	75 (30.1)	58 (26.2)	0.352
Severe tricuspid regurgitation (n, %)	63 (25.3)	54 (24.4)	0.828
PAPs (mmHg)	49.5 ± 15.8	45.8 ± 14.2	0.019
PVR (Wood units)	4.4 ± 1.9	4.1 ± 2.1	0.405
TAPSE (mm)	1.46 ± 0.54	1.54 ± 0.5	0.112
ST (cm/sec)	9.1 ± 2.6	9.4 ± 2.6	0.241
RV dilatation (n, %)	88 (35.3)	101 (45.7)	0.007

Values are presented as mean ± SD, % of cohort, median (25^{th}-75^{th} percentile).
FMR: Functional mitral regurgitation, ICMP: Ischemic cardiomyopathy, LAD: Left atrial dimension, LADI: Left atrial dimension index, LVEDD: Left ventricular end diastolic dimension, LVEF: Left ventricular ejection fraction, LVESD: Left ventricular end systolic dimension, LV: Left ventricle, NICMP: Nonischemic cardiomyopathy, PAPs: Systolic pulmonary arterial pressure, PVR: Pulmonary vascular resistance, RV: Right ventricle, ST: Systolic tricuspid velocity, TAPSE: Tricuspid annular plane systolic excursion.

Table 3. Right and left heart catheterization findings of patients with ischemic cardiomyopathy and non-ischemic cardiomyopathy

Variable	ICMP (n= 249)	NICMP (n= 221)	p
Invasive haemodynamics			
PAPs (mmHg)	53.5 (42.0-68.0)	46.0 (32.5-64.5)	< 0.001
PAPm (mmHg)	35.5 ± 12.9	31.8 ± 12.3	0.002
PAPd (mmHg)	23.4 ± 9.4	21.8 ± 10.1	0.082
PAWP (mmHg)	22.6 ± 8.3	21.7 ± 6.7	0.689
RAP (mmHg)	10.9 ± 6.4	10.5 ± 5.9	0.528
TPG (mmHg)	12.6 ± 8.8	10.1 ± 7.9	0.003
PVR (WU)	3.0 (1.1-6.0)	2.0 (1.0-5.0)	0.013
SBP (mmHg)	111.8 ± 24.3	111.2 ± 22.5	0.791
DBP (mmHg)	67.7 ± 13.3	68.9 ± 14.9	0.335
CO (L/min)	3.4 ± 0.9	3.4 ± 1.6	0.788
Cardiac index (L/min/m^2)	1.9 ± 1.1	1.8 ± 0.8	0.621
SV (mL/beat)	44.0 ± 7.6	41.1 ± 17.3	0.836
SVI (mL/beat/m^2)	22.6 ± 8.1	22.0 ± 8.4	0.514
RVSWI (g/m/beat/m^2)	6.5 (4.6-9.6)	5.4 (3.7-7.6)	< 0.001

Values are presented as mean ± SD, % of cohort, median (25th-75th percentile).
CO: Cardiac output, DBP: Diastolic blood pressure, ICMP: Ischemic cardiomyopathy, NICMP: Nonischemic cardiomyopathy, PAPd: Diastolic pulmonary arterial pressure, PAPm: Mean pulmonary arterial pressure, PAPs: Systolic pulmonary arterial pressure, PAWP: Pulmonary arterial wedge pressure, PVR: Pulmonary vascular resistance, RAP: Right atrial pressure, RVSWI: Right ventricle stroke work index, SBP: Systolic blood pressure, SV: Stroke volume, SVI: Stroke volume index, TPG: Transpulmonary gradient.

(32.5-64.0), p< 0.001 and 35.5 ± 12.9 vs. 31.8 ± 12.3, p= 0.002]. PVR and TPG were also significantly higher in the ICMP group compared to the NICMP group [3.0 (1.1-6.0) vs. 2.0 (1.0-5.0), p= 0.013 and 12.6 ± 8.8 vs. 10.1 ± 7.9, p= 0.003, respectively). The PAPd, PAWP, RAPm, SBP, DBP, CO, cardiac index, SV, SVI, LVEDP, TSG, SVR, and LVSWI were all similar in both groups. Patients with NICMP had lower RVSWI levels than non-NICMP patients [5.4 (3.7-7.6) vs. 6.5 (4.6-9.6), p< 0.001].

Right Ventricular Dysfunction

RV dysfunction was defined as a TAPSE ≤ 1.5 cm and an RVSWI < 5 gxm/m²/beat. While TAPSE-defined RV dysfunction was comparable between NICMP an ICMP (44.3% vs. 55.0, p= 0.069), RVSWI-defined RV dysfunction was higher in NICMP than in ICMP (45.2% vs. 31.3%, p= 0.012), Figure 1. Univariate analysis and multivariate analysis revealed that only severe tricuspid regurgitation was independent risk for TAPSE-defined RV dysfunction [Odds ratio (OR): 3.07, 95% confidence interval (CI): 1.19-7.97, p= 0.020 and OR: 2.9, %95 CI: 1.10-7.64, p= 0.031]. HF etiology (ICMP or NICMP), severe FMR, atrial fibrillation and LVEF, and PAPm were not at risk for TAPSE-defined RV dysfunction (Table 4). Univariate analysis revealed that severe tricuspid regurgitation and NICMP were associated with RVSWI-defined RV dysfunction (OR: 2.35, 95% CI: 1.31-2.26, p= 0.032 and OR: 1.79, 95% CI: 1.13-2.82, p= 0.012). Severe FMR, atrial fibrillation, LVEF and PAPm were not associated with RVSWI-defined RV dysfunction. Multivariate analysis demonstrated that NICMP and severe tricuspid regurgitation were independent risks of RVSWI-defined RV dysfunction (OR: 2.04, 95% CI: 1.21-3.42, p= 0.007 and OR: 2.01, 95% CI: 1.23-2.23, p= 0.035) (Table 5).

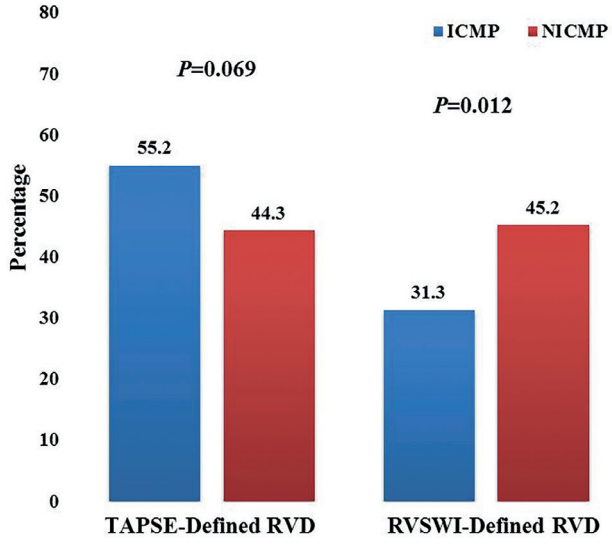

Figure 1. SDemonstrates that prevalence of RV dysfunction defined by TAPSE and RVSWI (ICMP: Ischemic cardiomyopathy, NICMP: Nonischemic cardiomyopathy, RVD: Right ventricular dysfunction, RVSWI: Right ventricular stroke work index, TAPSE: Tricuspid annular plane systolic excursion.

Table 4. Univariate and multivariate analyses for TAPSE

	Right ventricular dysfuction			
Variables	**Univariate OR, 95% CI**	**p**	**Multivariate OR, 95% CI**	**p**
NICMP	0.72 (0.42-1.25)	0.253	0.63 (0.28-1.39)	0.254
Severe MR	1.07 (0.60-1.90)	0.808	1.09 (0.48-2.45)	0.829
Severe TR	3.07 (1.19-7.97)	0.020	2.90 (1.10-7.64)	0.031
AF	1.80 (0.77-4.18)	0.170	1.53 (0.51-4.58)	0.447
LVEF	0.98 (0.92-1.03)	0.412	0.98 (0.92-1.04)	0.401
PAPm	0.97 (0.95-1.10)	0.053	0.99 (0.95-1.02)	0.675

AF: Atrial fibrillation, CI: Confidence interval, LVDD: Left ventricular diastolic dysfunction, LVEF: Left ventricle ejection fraction, MR: Mitral regurgitation, NICMP: Nonischemic cardiomyopathy, OR: Odds ratio, PAPm: Pulmonary artery mean pressure, TAPSE: Tricuspid annular plane systolic excursion, TR: Tricuspid regurgitation.

Table 5. Univariate and multivariate analyses for RVSWI

	Right ventricular dysfuction			
Variables	**Univariate OR, 95% CI**	**p**	**Multivariate OR, 95% CI**	**p**
NICMP	1.79 (1.13-2.82)	0.012	2.04 (1.21-3.42)	0.007
Severe FMR	1.35 (0.81-2.26)	0.246	1.51 (0.858-2.629)	0.154
Severe TR	2.35 (1.31-2.26)	0.032	2.01 (1.23-2.23)	0.035
AF	1.48 (0.8-2.75)	0.214	1.71 (0.887-3.31)	0.109
LVEF	0.998 (0.942-1.056)	0.933	1.01 (0.955-1.086)	0.582
PAPm	0.992 (0.983-1.00)	0.123	0.993 (0.20-1.01)	0.051

AF: Atrial fibrillation, CI: Confidence interval, LVEF: Left ventricle ejection fraction, FMR: Functional mitral regurgitation, NICMP: Nonischemic cardiomyopathy, OR: Odds ratio, PAPm: Pulmonary artery mean pressure, RVSWI: Right ventricle stroke work index, TR: Tricuspid regurgitation.

Table 6. Unadjusted and adjusted Cox proportional hazards model of primary outcome

Variables	Unadjusted HR (95% CI)	p	Adjusted HR (95% CI)	p
Age (from 42 to 56)	1.02 (0.88-1.18)	0.780	0.97 (0.77-1.23)	0.800
Gender (reference: female)	0.88 (0.62-1.24)	0.460	1.41 (0.80-2.51)	0.238
HF type (reference: non-ischemic)	0.99 (0.80-1.23)	0.936	0.89 (0.60-1.31)	0.542
DM	0.81 (0.61-1.07)	0.131	0.74 (0.45-1.23)	0.250
Hypertension	0.92 (0.69-1.12)	0.545	0.84 (0.52-1.35)	0.474
AF	1.27 (0.90-1.80)	0.161	0.31 (0.923-1.92)	0.057
LVEF (from 20 to 25)	0.68 (0.58-0.81)	0.002	0.68 (0.57-0.82)	< 0.001
Severe FMR	1.41 (1.06-1.88)	0.001	1.37 (1.03-1.82)	0.029
Severe TR	1.69 (1.27-2.26)	0.001	1.08 (0.77-1.51)	0.791
Grade 3 LVDD	0.95 (0.72-1.26)	0.372	0.88 (0.64-1.21)	0.394
TAPSE (from 1.1 to 1.8)	0.96 (0.68-1.05)	0.171	1.00 (0.92-1.08)	0.844
Hb (from 11.7 to 14.7)	0.62 (0.51-0.75)	< 0.001	0.63 (0.51-0.77)	< 0.001
Na (from 134 to 139)	0.96 (0.88-1.05)	0.33	0.71 (0.57-0.89)	0.003
NT Pro-BNP (from 813 to 4685)	1.05 (0.92-1.20)	0.431	0.87 (0.74-1.03)	0.989
Cardiac index (from 1.56 to 2.0)	0.90 (0.79-0.94)	0.001	0.90 (0.79-1.04)	0.154
PAPm (from 28 to 48)	1.17 (1.01-1.35)	0.034	1.30 (1.39-1.93)	0.022
RVSWI (from 3.62 to 9.75)	1.14 (0.95-2.36)	0.351	0.96 (0.73-1.27)	0.237

Model was adjusted for all univariate variables. Outcome was defined as LVAD implantation, urgent HT, or cardiac mortality.
AF: Atrial fibrillation, CI: Confidence interval, DM: Diabetes mellitus, Hb: Hemoglobin, HF: Heart failure, HR: Hazard ratio, HT: Heart transplantation, LVAD: Left ventricular assist device, LVDD: Left ventricle diastolic dysfunction, LVEF: Left ventricle ejection fraction, FMR: Functional mitral regurgitation, Na: Sodium, NT Pro-BNP: N-terminal pro-brain natriuretic peptide, PAPm: Pulmonary artery mean pressure, RVSWI: Right ventricular stroke work index, TAPSE: Tricuspid annular plane systolic excursion, TR: Tricuspid regurgitation.

Association of ICMP and NICMP with Outcome

Over a median follow-up of 503.50 days, 246 of 470 (52.3%) cases had a primary outcome (IQR= 115.25-1003.25) days. Table 6 displays univariate and multivariate clinical, echocardiographic, and hemodynamic predictors of outcomes based on previously described clinical variables. Age, gender, HF type (reference is NICMP), diabetes, hypertension, atrial fibrillation, LVEF, severe FMR, severe tricuspid regurgitation, LV diastolic dysfunction grade 3, TAPSE, hemoglobin, sodium, pro-BNP, cardiac index, PAPm and RVSWI were all potential confounding factors for ACE in the dataset. Univariate analysis revealed that LVEF from 20 to 25 [Hazard ratio (HR): 0.68, 95% CI: 0.58-0.81, p= 0.002), sodium from 134 to 139 (HR: 0.61, 95% CI: 0.48-0.88, p= 0.032), hemoglobin from 11.7 to 14.7 (HR: 0.62, 95% CI: 0.51-0.75, p< 0.001) and cardiac index from 1.56 to 2.0 (HR: 0.90, 95% CI: 0.79-0.44, p= 0.001) were associated with better outcome, while severe FMR (HR: 1.41, 95% CI: 1.06-1.88, p= 0.001), severe tricuspid regurgitation (HR: 1.69, 95% CI: 1.27-2.26, p= 0.001), and PAPm from 28 to 48 (HR: 1.17, 95% CI: 1.01-1.35, p= 0.034) were associated with worse outcome. In an adjusted analysis, patients with higher LVEF (HR: 0.68, 95% CI: 0.57-0.82, p< 0.001), higher hemoglobin (HR: 0.63, 95% CI: 0.51-0.77, p< 0.001), and higher sodium (HR: 0.71, 95% CI: 0.57-0.89, p= 0.003) had a better outcome. Patients with severe FMR (HR: 1.37, 95% CI: 1.03-1.82, p= 0.029) and higher PAPm (HR: 1.30, 95% CI: 1.39-1.93, p= 0.022) had a worse outcome.

DISCUSSION

In this study, we demonstrated a number of significant findings:

1. Unsurprisingly, patients with ICMP had a higher rate of atherosclerotic risk factor than patients with NICMP;

2. While NICMP had more RV dilatation, TAPSE and ST were similar in both groups;

3. ICMP patients had higher PAPs, PAPm, and PVR values;

4. ICMP patients had higher RVSWI;

5. TAPSE-defined RV dysfunction was similar between NICMP an ICMP, however RVSWI-defined RV dysfunction was higher in NICMP;

6. While NICMP was predictor for RVSWI-defined RV dysfunction, this was not the case for TAPSE-defined RV dysfunction;

7. HF etiology was not predictor for primary outcome including LVAD implantation, HT transplantation or death in patients with end-stage HF.

Patients with ICMP had higher PAPs, PAPm, PVR, and TPG than those with NICMP in the current study. Despite the fact that RHC is the gold standard for assessing RV afterload, very few studies comparing ischemic and nonischemic HF have invasive measurements. Patients with ICMP had higher PAPs than patients with NICMP, according to Felker et al, who researched the underlying causes and long-term survival of patients with cardiomyopathy. The PAPm and PVR, on the other hand, were not calculated in this analysis[9]. By La Vecchia et al., PAPs, PAPm, and PVR were found to be similar in ICMP and NICMP[16]. The LVEF, NYHA functional class, cardiac index, and SVI of this study's patients, on the other hand, were all higher than those of our study patients. Because the patients in the previous study had better clinical conditions than the patients in our study, RV afterload in these patients may not have increased. This circumstance may have prevented the previous study from demonstrating the difference in RV afterload between two groups accurately. The PAPm and RV dimensions assessed before the LVAD implantation were similar between the ischemic and nonischemic groups in a study investigating the effects of HF on LVAD outcomes. However, the sample size in this study was limited[19].

The RVSWI is a well-known invasive measure that demonstrates RV function, and it was found to be higher in ICMP than in NICMP in the current study. There have been few studies that have investigated the effect of HF etiology on RV function, and the results have been inconsistent; additionally, RVSWI have not been included in any of the existing studies.

While some studies have reported that RV is worse in patients with NICMP, other studies suggest that the degree of RV dysfunction is not dependent on the etiology of cardiomyopathy[5,16-19]. In contrast to these studies, there is one that suggests that RV function is even worse in ICMP[20]. The use of RVSWI in the evaluation of RV function in patients with end-stage HF has grown in popularity as the number of LVADs implantation in these patients has increased. There is not a study that has investigated the effect of HF etiology on RVSWI. We found that RVSWI was lower in NICMP than in ICMP in the current study.

In patients with left HF, RV dysfunction is linked to an increased risk of death. TAPSE and RVSWI were utilized to define RV dysfunction. TAPSE is a simple, non-invasive test that is widely used to evaluate RV function. RV dysfunction was defined as TAPSE ≤ 1.5 cm. RVSWI is primarily used to assess the necessity for right-sided assist devices in LVAD patients. Low RVSWI was discovered to be a risk factor for RV assist device (RVAD) after LVAD[29-31]. RV failure was defined as RVSWI < 5 gxm/m^2/beat, as described in the study by Imamura et al.[24]. TAPSE-defined RV dysfunction was comparable in NICMP and ICMP, but RVSWI-defined RV dysfunction was greater in NICMP. We couldn't say for sure whether NICMP is a risk factor for RV dysfunction because of the contradictory findings and the lack of a gold standard technique for testing RV function. Furthermore, no research has been done to compare TAPSE and RVSWI in terms of demonstrating RV function.

According to previous studies, patients with ICMP had a worse prognosis than those with NICMP[10,14,32]. However, in the current study, we found that HF etiology was not a predictor of primary outcomes including LVAD implantation, urgent HT, or mortality. This contrasting result could be due to a variety of factors. First, our primary outcome differed from that of the previous study. Second, our study's patient population differed significantly from those in the other studies. Unlike previous studies, we only included patients who were being evaluated for HT, and some cardiomyopathies such as infiltrative cardiomyopathy, hypertrophic cardiomyopathy, severe renal disease, and other comorbidities that were contraindicated for HT were excluded. Because of this circumstance, the clinical outcome may have differed from that of other studies. Finally, the LV functions of our study's patients were worse than those of previous studies' patients, and in the advanced stages of HF, the etiology may have no effect on clinical outcome.

LIMITATIONS

There were some limitations to this study. First, this study has the limitations of being retrospective and single-center. Second, the findings of our study are only applicable to patients with end-stage HF who are candidates for HT or LVAD implantation, and generalizations to patients with severe comorbidities or better LV function are not possible. Third, the lack of invasive or non-invasive gold standard methods to evaluate RV function, the difficulty of detecting biventricular failure by physical examination in this group of patients, and the inability to evaluate with MRI due to the majority of patients having an intracardiac device made identifying RV dysfunction difficult. TAPSE and RVSWI were used to identify RV dysfunction, but it is unknown which is more accurate at determining RV function.

CONCLUSION

As a result, we found that RV afterload was higher in ICMP than in NICMP due to higher PAPs, PAPm, and PVR values in ICMP. Because of the conflict between TAPSE-defined RV

dysfunction and RVSWI-defined RV dysfunction, we couldn't say for sure whether HF etiology has an effect on RV function. Finally, we demonstrated that HF etiology was not predictor of primary outcomes including LVAD implantation, HT transplantation or death in patients with end-stage HF.

Ethics Committee Approval: This study was approved by the Local Ethical Commitee (approval number: 2017.3/9-32 date: 08.05.2017).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

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