ORIGINAL ARTICLE

Factors associated with elevated pulmonary vascular resistance in ambulatory patients with end-stage heart failure accepted for heart transplant

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KEY WORDS

factor, heart failure, pulmonary hypertension, pulmonary vascular resistance

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ABSTRACT

INTRODUCTION Pulmonary hypertension (PH) is a common complication of heart failure (HF) that results in worse prognosis and heart complications following heart transplantation. To better define and understand left-sided PH, it is necessary to integrate the clinical context, noninvasive assessment, and invasive hemodynamic variables.

OBJECTIVES The aim of the study was to search for noninvasive factors related to the presence of PH with elevated pulmonary vascular resistance (PVR) in patients with advanced HF.

PATIENTS AND METHODS The study is a retrospective analysis of 282 patients with end-stage HF accepted for transplantation in the cardiology department between 2016 and 2018. A panel of laboratory tests, echocardiography, ergospirometry, and right heart catheterization were performed in all included patients. The Model for End-Stage Liver Disease Excluding INR (MELD-XI) and the Heart Failure Survival Score (HFSS) were calculated according to the appropriate formulas.

RESULTS The median age was 57 (51–60) years and 87.6% of patients were men. Pulmonary hypertension with elevated PVR was found in 30.1% of patients. The multivariable logistic regression analysis confirmed that lower HFSS (OR, 0.59; 95% CI, 0.383–0.908; $P = 0.016$), and higher MELD-XI scores (OR, 1.13; 95% CI, 1.024–1.24; $P = 0.014$), as well as higher alkaline phosphatase levels (OR, 1.02; 95% CI, 1.007–1.024; $P < 0.001$) were independent factors associated with increased PVR.

CONCLUSIONS To the best of our knowledge, this is the first study to demonstrate that high MELD-XI and low HFFS scores, as well as high alkaline phosphatase serum concentrations were independently associated with increased PVR in patients with advanced HF referred for transplantation.

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INTRODUCTION Pulmonary hypertension (PH) with elevated pulmonary vascular resistance (PVR) in patients with end-stage heart failure (HF) presents a significant risk factor for mortality and heart complications following heart transplantation (HT), mainly secondary to right ventricular failure. Increased PVR often complicates standard treatment approaches and has significant prognostic implications.[1-3] Pulmonary hypertension secondary to HF develops in response to a passive backward transmission as a result of increased left ventricular filling pressures, which occur as a consequence of systolic or diastolic left ventricular dysfunction.[3,4] Initially, left-sided PH is described as "passive," because the elevation of pulmonary artery pressure is a consequence of left ventricular dysfunction, and there are no pathologic changes in

WHAT'S NEW?

In this study, we evaluated noninvasive and simple indicators associated with increased pulmonary circulation resistance in patients with advanced heart failure. We demonstrated that in patients with end-stage heart failure referred for transplantation simple and routinely used heart failure scales, the Model for End-Stage Liver Disease excluding INR (MELD-XI) and the Heart Failure Survival Score (HFSS), as well as alkaline phosphatase concentrations were independently associated with increased pulmonary vascular resistance.

the pulmonary arterial bed.[4-5] Over time, chronic elevation of left-sided filling pressures leads to the activation of neurohormonal and other mediators, endothelial dysfunction, and neurogenic effects that may cause excess vasoconstriction and structural remodeling of the pulmonary arterial bed, which in turn causes an increase in PVR. This stage of PH is known as "reactive" PH.[3,4,6,7] Early identification of elevated PVR in HF is of critical importance because it determines the correct approach to management.[8] Introduction of appropriate therapy at the reversible stage of PVR significantly improves the outcomes and the possibility of HT.[3,6] A right-sided heart catheterization is the gold standard for hemodynamic evaluation of patients with PH including PVR estimation.[3] It should be emphasized that the pathophysiology of PH in left HF is complex and highly heterogeneous.[4] Therefore, clinical characteristics accompanied by the history of comorbidities and laboratory variables considered together with hemodynamic parameters facilitate the final diagnosis of PH-HF. Notwithstanding recent advances in the understanding of pathophysiology of PH-HF as well as its clinical assessment, the interrelations between noninvasive variables and PH remain only partially understood. Providing a better definition and understanding of PH requires integration of the clinical context, noninvasive assessment, and invasive hemodynamic variables.[4,8,9]

Therefore, the aim of the study was to search for noninvasive factors related to PH with elevated PVR in patients with end-stage HF referred for heart transplantation.

PATIENTS AND METHODS The study is a retrospective analysis of 341 consecutive patients with end-stage HF hospitalized for HT evaluation in the cardiology department between 2016 and 2018. Exclusion criteria included: acute HF, HF due to valvular heart diseases, any previous valvular heart surgery, a device implanted in the previous 6 months (implantable cardioverter--defibrillator, cardiac resynchronization therapy--defibrillator, and left ventricular assist device), a history of severe chronic obstructive pulmonary disease or pulmonary embolism, PH with irreversible PVR, irreversible renal dysfunction (glomerular filtration rate <30 ml/min/1.73 m^2), inotropic support at presentation, as well as no right heart catheterization. The resulting study sample included 282 participants. A panel of laboratory tests, chest X-ray, echocardiography, ergospirometry, and right heart catheterization were performed in all included patients.

The Medical University of Silesia's local Institutional Review Board approved the study protocol and all patients provided informed consent.

Right heart catheterization was performed with a Swan-Ganz catheter (Edwards LifeSciences, Irvine, California, United States) inserted transcutaneously through the right internal jugular vein and advanced into the pulmonary artery. The following hemodynamic parameters were measured: mean pulmonary capillary wedge pressure; systolic, diastolic, and mean pulmonary artery pressures; and cardiac output (CO). Cardiac output was measured by thermodilution with the use of a rapid bolus injection of 10 ml cold saline (in the absence of severe tricuspid regurgitation) or by the estimation of oxygen uptake with the use of the Fick method (if tricuspid regurgitation was present). Cardiac index was calculated as the ratio of CO to the body surface area (l/min/m^2) using the Du Bois formula. The transpulmonary gradient (TPG) was calculated as the difference between mean pulmonary artery pressure and mean pulmonary capillary wedge pressure. Pulmonary vascular resistance was calculated by dividing TPG by CO and expressed in Wood units (WU).

After collecting baseline hemodynamic data, patients with systolic pulmonary artery pressure greater than 50 mm Hg and either TPG greater than 15 mm Hg or PVR greater than 3 WU were subjected to a reversibility test with sodium nitroprusside.[6] The infusion of sodium nitroprusside started with a dose of 10 ng/kg/min. After 5 minutes, hemodynamic parameters were measured again. The dose of nitroprusside was rapidly titrated until one of the following was reached: a normalization of PVR and TPG values, a reduction in systolic blood pressure below 85 mm Hg, or the patient was intolerant. Pulmonary vascular resistance was defined as reversible if it decreased below 2.5 WU and systolic blood pressure was above 85 mm Hg. In patients with reversible PVR, sildenafil treatment was included, starting at a dose of 3 × 25 mg, which was gradually increased to the maximum tolerated dose.

The complete blood count and hematologic parameters were analyzed using automated blood cell counters (Sysmex XS1000i and XE2100, Sysmex Corporation, Kobe, Japan). The intra-assay and inter-assay coefficients of variation of blood samples were 5% and 4.5%, respectively. Hepatic and renal function parameters, cholesterol, triglycerides, and albumin plasma concentrations were determined with a COBAS Integra 800 analyzer (Roche Instrument Center AG, Rotkreuz, Switzerland). Plasma concentration of fibrinogen was measured using the STA Compact analyzer (Roche). A highly sensitive latex-based immunoassay was used to detect plasma C-reactive protein with the Cobas Integra 70 analyzer (Roche Diagnostics, Ltd). The C-reactive protein

levels were determined with a typical detection limit of 0.0175 mg/dl. Plasma N-terminal brain natriuretic peptide (NT-proBNP) concentrations were measured with a commercially available kit from Roche Diagnostics (Mannheim, Germany) on an Elecsys 2010 analyzer (Roche Diagnostics, Bellport, New York, United States) with analytical sensitivity of less than 5 pg/ml. Glomerular filtration rate was estimated with the use of the Modification of Diet in Renal Disease study equation.

To calculate the Heart Failure Survival Score (HFSS) and the Model for End-Stage Liver Disease Excluding INR (MELD-XI), the following formulas were used:

- HFFS = ([0.0216 × resting heart rhythm] + [−0.0255 × mean arterial blood pressure] + [−0.0464 × (left ventricular ejection fraction (LVEF)] + [−0.0470 × serum sodium] + [−0.0546 × peak oxygen consumption (VO_2)] + [0.6083 × presence (1) or absence (0) of interventricular conduction defect (QRS duration ≥0.12 due to any cause)] + [0.6931 × presence (1) or absence (0) of ischemic etiology of HF])[10]
- MELD-XI = 5.11 × ln total bilirubin [mg/dl] + 11.76 × ln creatinine [mg/dl] + 9.44[11]

The lower limit of all variables used to calculate the MELD-XI score was set at 1.0 to prevent negative values, and the upper limit for creatinine was set at 4.0 mg/dl.

Statistical analysis Statistical analysis was performed using the SAS software, version 9.4 (SAS Institute Inc, Cary, North Carolina, United States). Categorical variables were expressed as count (percentage) and compared with the χ^2 test. Continuous variables were expressed as mean (SD) or median (interquartile range) and compared with the *t* test or the Mann–Whitney U test, according to their distribution. The Shapiro-Wilk test was used to determine whether a random sample came from a normal distribution. A univariable logistic regression analysis was employed to select the potential factors of PH for inclusion in the multivariable analysis. Factors for univariable analyses were selected based on clinical relevance and data from the existing literature. The examined covariables included: the MELD-XI scale, HFSS, fibrinogen, NT-proBNP, alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGTP), urea, creatinine, bilirubin, erythrocyte sedimentation rate, sodium, right ventricular end-diastolic dimension, LVEF, left atrium, albumin. The relationship between the variables was evaluated by the Spearman rank correlation coefficient. Because several covariates were highly correlated (eg, the correlation of regression coefficients was 0.38 for NT-proBNP with MELD-XI, 0.41 for fibrinogen with erythrocyte sedimentation rate, and 0.47 for bilirubin with MELD-XI), those that provided a better fit for the model were selected for further analysis. The univariable factors of PH with a *P* value of 0.05 or less, which did not correlate significantly, were entered into the multivariable logistic regression model with stepwise selection. The results are presented as odds ratios (ORs) with 95% CIs and their statistical significance. A *P* value of less than 0.05 was considered significant.

RESULTS The median age of the population was 57 (51–60) years, of whom 87.6% were men. The study population included patients with the New York Heart Association (NYHA) class III (89.4%) and IV (10.9%) and with profiles 4 to 6 according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) classification. The patients were all managed with standard medical therapy, following the guidelines of the European Society of Cardiology, consisting of β-blockers (99.3%), angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers (97.5%), aldosterone antagonists (99.3%), and diuretics (100%). All patients with reversible PVR were treated with sildenafil. Sildenafil was well tolerated and all patients continued medication without side effects. In all patients, implantable cardioverter-defibrillator (59.9%) or cardiac resynchronization therapy-defibrillator (40.1%) were implanted. The devices were implanted more often in primary than in secondary prevention of sudden cardiac death (81.9% vs 18.1%, respectively). Measurements of CO were taken using the Fick method and the data were available for 26.2% of included patients. The details of clinical characteristics of the analyzed population are provided in TABLE 1.

To identify factors for PH with elevated PVR, patients were categorized into 2 groups: PVR of less than 3 WU and PVR higher than 3 WU (TABLE 1). Pulmonary hypertension with elevated PVR was found in 30.1% of patients.

The results of the univariable and multivariable logistic regression analysis for the presence of PH with elevated PVR are summarized in TABLE 2. The multivariable logistic regression analysis confirmed that lower HFSS (OR, 0.59; 95 CI, 0.383–0.908; *P* = 0.016), and higher MELD-XI scores (OR, 1.127; 95% CI, 1.024–1.24; *P* = 0.014), as well as higher ALP level (OR, 1.016; 95% CI, 1.007–1.024; *P* <0.001) were independent factors associated with elevated PVR.

DISCUSSION Although various prognostic scales have been developed for patients with HF,[12] none was dedicated explicitly to the assessment of patients with PH and elevated PVR. To the best of our knowledge, this is the first study to demonstrate that a lower HFSS score is independently associated with increased PVR. The HFSS is commonly used for predicting survival in ambulatory patients with advanced HF awaiting HT.[10,12,13] This scale indirectly reflects the severity of HF by assessing simple and noninvasive parameters closely related to the development and progression of HF.[10,13,14] By contrast, PH reflects the progression of HF, the severity of adverse hemodynamics, and hormonal changes that result in the structural remodeling of the pulmonary circulation, leading to

TABLE 1 Baseline characteristics of the study population divided into groups with pulmonary vascular resistance <3 and >3 (continued on the next page)

Characteristics	General population (n = 282)	PVR <3 (n = 197)	PVR >3 (n = 85)	*P* value
Baseline data				
Age, y	57 (51–60)	57 (52–60)	57 (48–59)	0.31
Male sex, n (%)	247 (87.6)	174 (88.3)	73 (85.9)	0.57
NYHA III, n (%)	252 (89.4)	179 (90.9)	73 (85.9)	0.21
NYHA IV, n (%)	30 (10.9)	18 (9.1)	12 (14.1)	
Ischemic etiology of HF, n (%)	154 (54.6)	105 (53.3)	49 (57.6)	0.8
BMI, kg/m^2	27.28 (24.16–30.51)	27.11 (24.1–30.76)	27.28 (24.57–29.47)	0.35
Rest HR, bpm	72 (65–79)	71.5 (65–77.5)	72 (65–80)	0.53
Rest mean BP, mm Hg	74.68 (9.59)	75.18 (9.34)	73.51 (10.11)	0.18
Comorbidities				
Hypertension, n (%)	169 (59.9)	116 (58.9)	53 (62.4)	0.59
Type 2 diabetes, n (%)	106 (37.6)	70 (35.5)	36 (42.4)	0.28
Persistent AF, n (%)	136 (48.2)	89 (45.2)	47 (55.3)	0.19
Laboratory parameters				
Hemoglobin, mmol/l	8.84 (1)	8.85 (0.98)	8.81 (1.04)	0.79
Creatinine, μmol/l	109.5 (92–136)	104 (89–132)	121 (106–145)	0.002
eGFR, ml/min/1.73 m^2	60.90 (47.75–75.37)	64.41 (49.45–78.73)	54.71 (45.79–69.62)	0.003
Total bilirubin, μmol/l	16.45 (11.7–22.8)	15.4 (11.5–21.4)	18.9 (12.8–24.6)	0.01
Albumin, g/l	43 (41–46)	44 (41–46)	42 (39–44)	<0.001
Uric acid, μmol/l	410 (350–505)	403 (352–490)	433 (349–521)	0.44
Urea, mmol/l	8.4 (5.9–12.9)	7.8 (5.7–11.1)	9.7 (6.3–15.8)	0.01
Sodium, mmol/l	139 (137–141)	140 (137–141)	139 (136–140)	0.007
Fibrinogen, mg/dl	379 (313–443)	369 (306–425)	413 (354–485)	0.001
AST, U/l	26 (20–32)	26 (20–32)	25 (19–35)	0.99
ALT, U/l	21.5 (15–32)	22 (16–33)	20 (14–30)	0.3
ALP, U/l	77 (62–100)	75 (60–92)	93 (68–114)	<0.001
GGTP, U/l	70 (34–130)	54 (29–114)	104 (56–147)	<0.001
Cholesterol, mmol/l	4.02 (1.04)	4.06 (1.04)	3.93 (1.05)	0.32
LDL cholesterol, mmol/l	2.11 (1.61–2.72)	2.06 (1.62–2.7)	2.23 (1.6–2.85)	0.43
hs-CRP, mg/l	4.1 (2.05–6.81)	3.76 (1.81–6.84)	4.62 (3.02–6.32)	0.2
ESR, mm/h	14 (8–21)	12 (8–20)	17 (9–22)	0.0497
HBA_{1c}, %	5.8 (5.3–6.3)	5.7 (5.3–6.2)	6 (5.4–6.4)	0.16
NT-proBNP, pg/ml	2967.5 (1714–6041)	2223 (1598–5178)	4609 (2138–6710)	<0.001
Hemodynamic parameters				
mPCWP, mm Hg	14 (12–18)	13 (11–15)	20 (18–25)	<0.001
sPAP, mm Hg	34 (30–50)	31 (29–35)	53 (51–54)	<0.001
mPAP, mm Hg	21 (18–32)	19 (17–21)	37 (34–40)	<0.001
TPG, mm Hg	7 (6–12)	6 (5–8)	15 (13–18)	<0.001
Cardiac index, l/min/m^2	1.93 (1.77–2.01)	1.94 (1.87–2.01)	1.93 (1.68–1.99)	0.04
PVR, WU	1.95 (1.56–3.5)	1.68 (1.42–1.99)	4.52 (3.71–5.09)	<0.001
Echocardiographic parameters				
LA, mm	53 (47–58)	50 (46–57)	55 (49–59)	<0.001
RVEDd, mm	39 (35–41)	38 (34–40)	40 (35–44)	0.02
LVEDd, mm	70.5 (65–80)	70 (63–80)	72 (66–78)	0.37
LVEF, %	17 (15–20)	17 (15–20)	16 (14–20)	0.04
Cardiac medications				
β-Blockers, n (%)	280 (99.3)	195 (99)	85 (100)	0.35
ACEI/ARB, n (%)	275 (97.5)	193 (98)	82 (96.5)	0.46
Loop diuretics, n (%)	282 (100)	197 (100)	85 (100)	–
MRA, n (%)	280 (99.3)	196 (99.5)	84 (98.8)	0.54
Digoxin, n (%)	86 (30.5)	52 (26.4)	34 (40)	0.02

TABLE 1 Baseline characteristics of the study population divided into groups with pulmonary vascular resistance <3 and >3 (continued from the previous page)

Characteristics	General population (n = 282)	PVR <3 (n = 197)	PVR >3 (n = 85)	*P* value
Ivabradine, n (%)	57 (20.2)	42 (21.3)	15 (17.6)	0.48
Statin, n (%)	215 (76.2)	149 (75.6)	66 (77.6)	0.72
Coumarin derivatives, n (%)	167 (59.2)	106 (53.8)	61 (71.8)	0.005
Acetylsalicylic acid, n (%)	106 (37.6)	87 (44.2)	19 (22.4)	<0.001
ICD, n (%)	169 (59.9)	121 (61.4)	48 (56.5)	0.44
CRT-D, n (%)	113 (40.1)	76 (38.6)	37 (43.5)	0.44
Scales				
MELD-XI	12.79 (10.84–15.42)	12.14 (10.53–14.88)	14.16 (12.16–16.27)	<0.001
HFSS	7.63 (0.67)	7.72 (0.67)	7.43 (0.61)	<0.001
Other parameters				
Severe TR, n (%)	74 (26.2)	50 (25.4)	24 (28.2)	0.62
VO_{2max}, ml/kg/min	11.3 (10.3–12.3)	11.3 (10.4–12.2)	11.1 (9.7–12.3)	0.22
IVCD, n (%)	120 (42.6)	76 (38.6)	44 (51.8)	0.04

Data are presented as median (interquartile range) or mean (SD) unless otherwise indicated.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CRT-D; cardiac resynchronization therapy-defibrillator; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; GGTP, γ-glutamyl transpeptidase; HBA_{1C}, hemoglobin A_{1C}; HF, heart failure; HFSS, Heart Failure Survival Score; HR, heart rhythm; hs-CRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter-defibrillator; IVCD, intraventricular conduction defect; LA, left atrium; LDL, low-density lipoprotein; LVEDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MELD-XI, Model for End-Stage Liver Disease excluding INR; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; PVR, pulmonary vascular resistance; RVEDd, right ventricular end-diastolic dimension; sPAP, systolic pulmonary artery pressure; TPG, transpulmonary gradient; TR, tricuspid regurgitation; VO_{2max}, maximal oxygen uptake

an increase in PVR.[3,4,6] The HFSS-validated risk stratification model involves a calculation using 7 parameters.[10] The first component of the HFSS is the serum sodium concentration, a commonly known prognostic marker in HF.[15] Low sodium concentrations in HF result from a decreased CO and organ perfusion, as well as neurohormonal changes, and those mechanisms are closely related to PH.[16] In addition, the degree of hyponatremia reflects the severity of HF.[16] Another component of the HFSS, maximal oxygen uptake (VO_{2max}), in combination with PVR provides an accurate risk stratification tool, underlining the important and complementary prognostic information obtained from cardiopulmonary exercise testing and resting invasive hemodynamic data.[17] Furthermore, factors such as resting heart rhythm, mean arterial blood pressure, and interventricular conduction defect are also known predictors of HF and reflect the severity of HF. LVEF has a significant impact on the course and prognosis of patients with PH, and an improvement of LVEF is associated with favorable outcomes in this group of patients.[18]

In addition, we have demonstrated for the first time the validity of another parameter associated with PH with elevated PVR, namely, a higher MELD-XI score, which is a modification of the classic MELD scoring system. The MELD score is calculated on the basis of the international normalized ratio (INR), serum bilirubin, and serum creatinine levels, and reflects cardiorenal and cardiohepatic interactions in HF.[13,19,20] In order to exclude the impact of oral anticoagulation on INR in HF patients treated with vitamin K antagonists, we used a modified version of the MELD score, MELD-XI.[13] Recent studies confirmed that a higher MELD-XI score was an indicator of HF progression and worse outcomes.[13,20,21] In turn, the presence of elevated PVR observed in advanced stage PH reflects the progression of HF and is a consequence of vasoconstriction and remodeling of the pulmonary arterial bed leading to the right ventricular overload and failure.[4,7] Right ventricular dysfunction and systemic venous congestion secondary to PH affect the liver and kidneys and result in the derangement of their function. The first component of the MELD-XI score, the serum creatinine level, reflects kidney dysfunction.[11] The main reason for kidney dysfunction in left-sided PH is elevated right atrial pressure leading to renal venous congestion, and its downstream influence on intra- and extrarenal hemodynamics, as well as endothelial activation.[22,23] Another important pathophysiologic mechanism of kidney dysfunction in advanced HF is that of decreased CO, with a series of maladaptive hemodynamic and neurohormonal changes, which consistently lead to a decrease in the estimated glomerular filtration rate.[6,22,23] The second component of MELD-XI is the serum bilirubin level that reflects liver dysfunction,[11] which is also linked to the combination of passive congestion from the elevated hepatic venous pressure coupled with a low CO.[6,24-26] Impaired liver perfusion causes an increase in liver enzyme and serum bilirubin levels, as well as an impaired hepatic protein and lipid synthesis.[24] In our study, patients with end-stage HF and increased PVR had significantly higher concentrations of GGTP, ALP, and

TABLE 2 Univariable and multivariable analyses of elevated pulmonary vascular resistance indicators

Parameter	Univariable data		Multivariable data	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
MELD XI	1.175 (1.074–1.287)	<0.001	1.127 (1.024–1.24)	0.01
HFSS	0.509 (0.339–0.766)	0.001	0.59 (0.383–0.908)	0.02
Fibrinogen	1.005 (1.002–1.008)	0.001	–	–
ALP	1.017 (1.009–1.026)	<0.001	1.016 (1.007–1.024)	<0.001
GGTP	1.009 (1.005–1.014)	<0.001	–	–
ESR	1.033 (0.999–1.069)	0.06	–	–
Sodium	0.895 (0.826–0.970)	0.007	–	–
RVDd	1.046 (1–1.094)	0.05	–	–
LVEF	0.926 (0.863–0.993)	0.03	–	–
LA	1.046 (1.1.014–1.078)	0.005	–	–
Albumin	0.902 (0.845–0.963)	0.002	–	–

Abbreviations: OR, odds ratio; others, see **TABLE 1**

bilirubin as well as lower levels of albumin, which indicates the impairment of both the metabolic and synthetic function.[25] These abnormalities represent a typical liver profile for HF, which is predominantly of cholestatic nature, with normal transaminase levels but with increased bilirubin, GGTP, and ALP levels. This reflects the pathophysiology of liver function abnormalities in progressive HF, which is a combination of both congestion and reduced CO.[13,24-26] ALP and GGTP are localized in the bile epithelium and may be elevated in conditions that cause damage to the bile canaliculi.[27] By contrast, transaminases are released on cell damage or death, and due to the double blood supply to the liver (from the portal system and hepatic artery), hepatocytes are relatively resistant to necrosis.[13,28,29] In our study, out of all liver markers, only higher serum ALP concentrations were independently associated with increased PVR.[24,25,28,29] A more recent study by Poelzl et al[30] demonstrated a high prevalence of elevated levels of cholestatic liver enzymes (GGTP and ALP) in patients with HF and their direct association with the severity of HF. Lau et al[31] also confirmed that the most common liver function abnormalities in HF included increased cholestatic parameters and that the severity of PH was significantly associated with abnormal liver function tests. It seems that elevated ALP levels in patients with increased PVR reflect part of the cholestatic profile related to subclinical liver congestion secondary to the increased left ventricular filling and right ventricular dysfunction as well as to reducing CO. In addition, worsening liver function in patients with HF and elevated PVR reflects advanced HF.

Our study has several limitations. It was a single-center retrospective study involving a relatively small population. In addition, we did not perform a serial assessment of parameters and scales over time, and our analysis is limited to single measurements. Furthermore, our study lacks detailed data of the right ventricular function, and the analysis is limited only to the right ventricular dimension. Prospective and multicenter studies with a larger number of patients are required to confirm the usefulness of the HFSS and MELD-XI scores, as well as ALP in the assessment of patients with HF and elevated PVR. It is also necessary to develop simple prognostic models dedicated to patients with PH secondary to HF to facilitate the assessment and management of this population.

In conclusion, this study evaluated noninvasive and simple indicators associated with the presence of increased pulmonary circulation resistance in patients with advanced HF. To the best of our knowledge, this is the first study to demonstrate that simple and routinely used HF scales, MELD-XI and HFSS, as well as alkaline phosphatase levels were independently associated with increased PVR in patients with end-stage HF accepted for transplantation.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT WS and BS-J contributed to the study concept and design, data analysis and interpretation, drafting and revision of the manuscript. MS and ER were involved in data collection, analyzed the data, and performed statistical analysis. MG was responsible for the critical revision of the manuscript for intellectual content. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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