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

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 HFSS scores, as well as high alkaline phosphatase serum concentrations were independently associated with increased PVR in patients with advanced HF referred for transplantation.
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.\textsuperscript{1-5} 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.\textsuperscript{3,5,6,7} Early identification of elevated PVR in HF is of critical importance because it determines the correct approach to management.\textsuperscript{8} Introduction of appropriate therapy at the reversible stage of PVR significantly improves the outcomes and the possibility of HT.\textsuperscript{3,5} A right-sided heart catheterization is the gold standard for hemodynamic evaluation of patients with PH including PVR estimation.\textsuperscript{3} It should be emphasized that the pathophysiology of PH in left HF is complex and highly heterogeneous.\textsuperscript{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.\textsuperscript{5,8,5}

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 m²), 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 transcatheterly 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/m²) 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.\textsuperscript{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 x 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:

- HFSS = ([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 (VO₂)] + [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])
- MELD-XI = 5.11 × ln total bilirubin [mg/dl] + 11.76 × ln creatinine [mg/dl] + 9.44

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 χ² 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 Shapirowilk 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 covariables 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
## Factors of elevated pulmonary vascular resistance in heart failure

### 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/m²      | 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 m² | 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  |
| HBA₁c, %            | 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)          | 2222 (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/m² | 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 (58.2)                  | 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**

| Scales          | General population (n = 282) | PVR <3 (n = 197) | PVR >3 (n = 85) | P value |
|-----------------|-----------------------------|-----------------|----------------|---------|
| VO₂max, 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; HBA1C, hemoglobin A1C; HF, heart failure; HFSS, Heart Failure Survival Score; HR, heart rhythm; hs-CRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter-defibrillator; IVC, intraventricular conduction defect; LA, left atrium; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MELD, Model for End-Stage Liver Disease excluding INR; mPAP, mean pulmonary artery pressure; mPWP, 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; Vnatriuretic peptide; WEDD, right ventricular end-diastolic dimension; 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; HBA1C, hemoglobin A1C; HF, heart failure; HFSS, Heart Failure Survival Score; HR, heart rhythm; hs-CRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter-defibrillator; IVC, intraventricular conduction defect; LA, left atrium; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MELD-XI, Model for End-Stage Liver Disease excluding INR; mPAP, mean pulmonary artery pressure; mPWP, 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; VO₂max, maximal oxygen uptake

an increase in PVR. The HFSS-validated risk stratification model involves a calculation using 7 parameters. The first component of the HFSS is the serum sodium concentration, a commonly known prognostic marker in HF. 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. In addition, the degree of hyponatremia reflects the severity of HF. Another component of the HFSS, maximal oxygen uptake (VO₂max), is in combination with PVR provides an accurate risk stratification tool, underlying the important and complementary prognostic information obtained from cardiopulmonary exercise testing and resting invasive hemodynamic data. 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.

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 cardioenral and cardiohepatic interactions in HF. 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. Recent studies confirmed that a higher MELD-XI score was an indicator of HF progression and worse outcomes. 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. 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. 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. Another important pathophysiological 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. The second component of MELD-XI is the serum bilirubin level that reflects liver dysfunction, which is also linked to the combination of passive congestion from the elevated hepatic venous pressure coupled with a low CO. Impaired liver perfusion causes an increase in liver enzyme and serum bilirubin levels, as well as an impaired hepatic protein and lipid synthesis. 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 (1.002–1.010) | 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 | – | – |
| RVd       | 1.046 (1–1.094) | 0.05 | – | – |
| LVEF      | 0.926 (0.863–0.993) | 0.03 | – | – |
| LA        | 1.046 (1.014–1.078) | 0.005 | – | – |
| Albumin   | 0.902 (0.845–0.963) | 0.002 | – | – |

Abbreviations: OR, odds ratio; others, see Table 1

bile as well as lower levels of albumin, which indicates the impairment of both the metabolic and synthetic function.29 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.13,24-26 In our study, out of all liver markers, only higher serum ALP concentrations were independently associated with increased PVR.13,24-26 A more recent study by Poelzl et al28 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 al29 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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CONFLICT OF INTEREST None declared.

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REFERENCES

1. Guglin M, Khan H. Pulmonary hypertension in heart failure. J Card Fail. 2010; 16: 461-474.
2. Rao SD, Adusumalli S, Mazurek JA. Pulmonary hypertension in heart failure patients. Card Fail Rev. 2020; 6: e05.
3. Mehra MR, Canter CE, Hanman MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant. 2016; 35: 1-23.
4. Rosenkranz S, Gibbs JS, Wachter R, et al. Left ventricular heart failure and pulmonary hypertension. Eur Heart J. 2016; 37: 942-954.
5. Vachiery JL, Adir Y, Barberà JA, et al. Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol. 2013; 62: 100-108.
6. Syczurz W, Gąsior M, Skrzypek M, et al. Modified Model for End-Stage Liver Disease is an indicator of the ineffectiveness of sildenafil treatment in patients with advanced heart failure and increased pulmonary vascular resistance. Transplant Proc. 2020; 50:411-135: 31720-31728.
7. Fang JC, De Marco T, Givertz MM, et al. World Health Organization Pulmonary Hypertension group 2: pulmonary hypertension due to left heart disease in the adult - a summary statement from the Pulmonary Hypertension Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2012; 31: 913-933.
8. Kalogeropoulos AP, Georgiopoulou V, Borleug BA, et al. Left ventricular dysfunction with pulmonary hypertension: part 2: prognosis, noninvasive evaluation, treatment, and future research. Circ Heart Fail. 2013; 6: 584-593.
9. Barnett C, Selby V. Overview of WHO group 2 pulmonary hypertension due to left heart disease. Adv Pulm Hypertens. 2015; 14: 70-78.
10. Aaronson KD, Schwartz JS, Chen TM, et al. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation. 1997; 95: 2660-2667.

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11 Heuman DM, Mitas AA, Habib A, et al. MELD-XI: a rational approach to "sickest first" liver transplantation in cirrhotic patients requiring anticoagulant therapy. Liver Transpl. 2007; 13: 30-37.
12 Alba AC, Agaritsas T, Jankowski M, et al. Risk prediction models for mortality in ambulatory patients with heart failure: a systematic review. Circ Heart Fail. 2013; 6: 881-889.
13 Szczurek W, Sygula-Jurkiewicz B, Zakliczynski MW, et al. Prognostic value of selected risk scales in patients with end-stage heart failure. Kardiol Pol. 2018; 76: 1320-1326.
14 Szczurek W, Gąsior M, Romuk E, et al. Usefulness of combining prognostic scores to predict survival in patients with advanced heart failure. J Heart Lung Transplant. 2019; 38:1224-1227.
15 Abebe TB, Gebreyohannes EA, Tefera YG, et al. The prognosis of heart failure patients: Does sodium level play a significant role? PLoS One. 2018; 13: e0207242.
16 Rabinovitz A, Raiszadeh F, Zolty R. Association of hyponatremia and outcomes in pulmonary hypertension. J Card Fail. 2013; 19: 550-556.
17 Wensel R, Francis DP, Meyer FJ, et al. Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in pulmonary arterial hypertension. Int J Cardiol. 2013; 167: 1193-1198.
18 Kwon HJ, Park JH, Park JJ, et al. Improvement of left ventricular ejection fraction and pulmonary hypertension are significant prognostic factors in heart failure with reduced ejection fraction patients. J Cardiovasc Imaging. 2019; 27: 257-265.
19 Kim MS, Kato TS, Farr M, et al. Hepatic dysfunction in ambulatory patients with heart failure: application of the MELD scoring system for outcome prediction. J Am Coll Cardiol. 2013; 61: 2253-2261.
20 Yang JA, Kato TS, Shulman BP, et al. Liver dysfunction as a predictor of outcomes in patients with advanced heart failure requiring ventricular assist device support: use of the Model of End-stage Liver Disease (MELD) and MELD excluding INR (MELD-XI) scoring system. J Heart Lung Transplant. 2012; 31: 601-610.
21 Deo SV, Al-Kindi SG, Altarabsheh SE, et al. Model for end-stage liver disease excluding international normalized ratio (MELD-XI) score predicts heart transplant outcomes: Evidence from the registry of the United Network for Organ Sharing. J Heart Lung Transplant. 2016; 35: 222-227.
22 Nickel NP, D’Leary JM, Britain EL, et al. Kidney dysfunction in patients with pulmonary artery hypertension. Pulm Circ. 2017; 7: 38-54.
23 Kazory A, Ross EA. Pulmonary arterial hypertension and the kidney: getting to the heart of the matter. Am J Nephrol. 2018; 47: 130-133.
24 Alvarez AM, Mukherjee D. Liver abnormalities in cardiac diseases and heart failure. Int J Angiol. 2011; 20: 135-142.
25 Sygula-Jurkiewicz B, Nadziakiewicz P, Zakliczynski M, et al. Predictive value of hepatic and renal dysfunction based on the Models for End-Stage Liver Disease in patients with heart failure evaluated for heart transplant. Transplant Proc. 2016; 48: 1756-1760.
26 Samsky MD, Patel CB, DeWald TA, et al. Cardiohepatic interactions in heart failure: an overview and clinical implications. J Am Coll Cardiol. 2013; 61: 2397-2405.
27 Ortiz G, Rodriguez I, Hinostroza J, et al. Serum alkaline phosphatase levels and left ventricular diastolic dysfunction in patients with advanced chronic kidney disease. Nephron Extra. 2011; 1: 283-291.
28 Shamban L, Patel B, Williams M. Significantly elevated liver alkaline phosphatase in congestive heart failure. Gastroenterology Res. 2014; 7: 64-68.
29 Green RM, Flamm S. AGA technical review on the evaluation of liver chemistry tests. Gastroenterology. 2002; 123: 1367-1384.
30 Poelel G, Ess M, Mussner-Seebor C, et al. Liver dysfunction in chronic heart failure: prevalence, characteristics and prognostic significance. Eur J Clin Investig. 2012; 42: 153-163.
31 Lau GT, Tan HC, Kritikides D. Type of liver dysfunction in heart failure and its relation to the severity of tricuspid regurgitation. Am J Cardiol. 2002; 90: 1405-1409.