

Relationship between right atrial pressure and the Model for End-Stage Liver Disease (MELD) score in patients with advanced heart failure

İleri evre kalp yetmezliği hastalarında sağ atriyum basıncı ile Son Dönem Karaciğer Hastalığı Modeli (MELD) skoru arasındaki ilişkinin değerlendirilmesi

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ABSTRACT

Background: This study aims to investigate the association between right atrial pressure and the Model for End-Stage Liver Disease score and to evaluate the ability of this scoring system to accurately predict the value of right atrial pressure.

Methods: Between April 2016 and November 2018, a total of 137 patients (118 males, 19 females; median age: 49 years; range, 40 to 54 years) with advanced heart failure who were candidates for left ventricular assist device implantation or heart transplantation were retrospectively analyzed. We developed a formula calculated by using the biochemical and cardiac catheterization parameters of the patients.

Results: There was a strong correlation between the right atrial pressure and the scores ($r=0.510$, $p<0.001$). The estimated right atrial pressure was calculated as “ $2 + (0.92 \times \text{Model for End-Stage Liver Disease Score})$ ” (unstandardized coefficient 0.920, t value 7.674, $p<0.001$). The Model for End-Stage Liver Disease score was found to be an independent predictor of high right atrial pressure (odds ratio=1.491, 95% confidence interval: 1.244-1.786, $p<0.001$). The calculated area under the curve was 0.789 (95% confidence interval: 0.710-0.867, $p<0.001$) and the cut-off value of the Model for End-Stage Liver Disease score in the prediction of high right atrial pressure was 10.5 with 75% sensitivity and 73% specificity.

Conclusion: We define a method to calculate right atrial pressure obtained by using the Model for End-Stage Liver Disease score without the need for cardiac catheterization during the hospitalization and follow-up period of patients with advanced heart failure.

Keywords: Advanced heart failure, Model for End-Stage Liver Disease Score, right atrial pressure.

ÖZ

Amaç: Bu çalışmada sağ atriyal basınç ve Son Dönem Karaciğer Hastalığı Modeli skoru arasındaki ilişki incelendi ve skorlamanın sağ atriyal basınç değerini doğru bir şekilde öngörebilme özelliği değerlendirildi.

Çalışma planı: Nisan 2016 - Kasım 2018 tarihleri arasında sol ventrikül destek cihazı implantasyonu veya kalp nakli adayları olan toplam 137 ileri kalp yetmezlikli hasta (118 erkek, 19 kadın; medyan yaş: 49 yıl; dağılım, 40-54 yıl) retrospektif olarak incelendi. Hastaların biyokimya ve kardiyak kateterizasyon parametreleri kullanılarak hesaplanan bir formül geliştirildi.

Bulgular: Sağ atriyal basınç ve skorlar arasında güçlü bir ilişki izlendi ($r=0.510$, $p<0.001$). Tahmini sağ atriyal basınç şu şekilde hesaplandı: “ $2 + (0.92 \times \text{Son Dönem Karaciğer Hastalığı Modeli Skoru})$ ” (standardize edilmemiş katsayı 0.920, t değeri 7.674, $p<0.001$). Son Dönem Karaciğer Hastalığı Modeli skoru, sağ atriyal basıncın bağımsız bir öngördürücüsü idi (olasılık oranı=1.491, %95 güven aralığı: 1.244-1.786, $p<0.001$). Hesaplanan eğri altında kalan alan 0.789 (%95 güven aralığı: 0.710-0.867, $p<0.001$) ve Son Dönem Karaciğer Hastalığı Modeli skorunun yüksek sağ atriyal basıncı öngörmedeki kestirim değeri, %75 duyarlılık ve %73 özgüllük ile 10.5 idi.

Sonuç: İleri kalp yetmezlikli hastaların hastanede yatış ve takip döneminde kardiyak kateterizasyona gerek olmaksızın Son Dönem Karaciğer Hastalığı Modeli skoru kullanılarak sağ atriyal basıncın hesaplanabildiği bir model tanımlanmıştır.

Anahtar sözcükler: İleri kalp yetmezliği, Son Dönem Karaciğer Hastalığı Modeli Skoru, sağ atriyal basınç.

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Cardiohepatic syndrome, particularly encountered in advanced stages in patients with heart failure (HF) is a clinical condition characterized by the development of congestive hepatic dysfunction, and the Model for End-Stage Liver Disease (MELD) can be used to predict prognosis. Indeed, the MELD is an established scoring system used to calculate liver dysfunction and determine a patient's functional health status using baseline serum creatinine, serum bilirubin, and international normalized ratio (INR) levels, and a high score is associated with poor prognosis regardless of the cause of the liver disease.^[1,2]

The MELD scoring system, which was subsequently introduced in HF patients and has been shown to correlate with high-risk tricuspid valve surgery even in patients without primary liver disease was originally developed and validated to assess the short-term prognosis of patients undergoing the transjugular intrahepatic portosystemic shunt procedure.^[3,4] Recently, it has been shown that a high MELD score is a prognostic factor in predicting death in heart transplant candidates, and a high pre-transplant MELD score (>20) is associated with an increased risk of morbidity and mortality in patients undergoing orthotopic heart transplantation.^[5,6]

Increased central venous pressure, reflecting right atrial pressure (RAP), is associated with impaired renal function and all-cause mortality in a wide range of patients with cardiovascular disease, including HF.^[7] Since a high RAP leads to hepatic and venous congestion, we aimed to demonstrate the association between RAP and the MELD score, as well as the ability of the MELD score to accurately predict the value of RAP obtained by cardiac catheterization in patients with advanced HF.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Kartal Koşuyolu High Specialization Training and Research Hospital, Department of Cardiology between April 2016 and November 2018. A total of 137 patients (118 males, 19 females; median age: 49 years; range, 40 to 54 years) with advanced HF who were candidates for left ventricular assist device (LVAD) implantation or heart transplantation were included in this study. The patients were evaluated to confirm candidacy for heart transplantation or LVAD implantation. Baseline creatinine is known to have considerable fluctuations in patients awaiting heart transplantation due to their right ventricular function and fluid status. Therefore, only patients who underwent biochemical parameter screening

and echocardiography no later than 24 h before the procedure were included. Patients with end-stage HF, being evaluated for cardiac transplantation or LVAD implantation, usually undergo preoperative anticoagulant therapy; however, this allows for inaccuracies in the MELD score. Thus, we excluded patients using oral anticoagulant therapy, including warfarin or direct oral anticoagulants. Patients with long-term pre-existing renal disease and high creatinine levels (>2 mg/dL) were also excluded from the study. A written informed consent was obtained from each patient. The study protocol was approved by the Kartal Koşuyolu High Specialization Training and Research Hospital Ethics Committee (Date: 21.09.2021, No: 2021/12/532). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The standard MELD score was calculated using the following formula: $MELD = 3.78 \times \ln [\text{serum bilirubin (mg/dL)}] + 11.2 \times \ln [INR] + 9.57 \times \ln [\text{serum creatinine (mg/dL)}] + 6.43$.

Cardiac catheterization

The patients underwent cardiac catheterization during the period of evaluation to decide their candidacy for LVAD implantation or heart transplantation at the Heart Failure Department of our hospital. In the catheter laboratory, continuous pressure monitoring was used, and the catheter was inserted via the femoral vein and positioned in the right heart and the pulmonary arteries. The transducer was calibrated in the middle of the chest. The observers were blinded to all echocardiographic data. The RAP (mmHg), mean pulmonary artery pressure, aortic blood pressure, and left ventricular end-diastolic pressure were recorded at the end of a normal expiration. The cardiac output (CO, L/min) was calculated using the Fick method. For all patients, RAP measurements were performed during 5 to 10 cardiac cycles, and the mean value was calculated.

Echocardiography

Transthoracic echocardiography was performed with the IE 33 device (Philips Medical System, Bothell, WA, USA) after the patient was placed in the left lateral position, by using a 3 MHz transducer. Linear internal measurements of the left ventricle were made in the parasternal long-axis view. Values were obtained carefully perpendicular to the left ventricular long axis and measured at or just below the mitral valve tips. Left ventricular ejection fraction was calculated using the biplane disc method (modified Simpson's rule). Tricuspid annular plane systolic excursion was

measured by M-mode echocardiography with an optimally aligned cursor along the direction of the tricuspid lateral ring in apical four-chamber view. All measurements were made by two trained cardiologists blinded to invasive hemodynamics.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Normally distributed data were presented in mean \pm standard deviation (SD), while non-normally

distributed variables were presented in median (min-max). Categorical variables were presented in number and frequency. Univariate comparisons between the groups were performed using the chi-square test for categorical variables and Student t-test or Mann-Whitney rank-sum test for continuous variables, as appropriate. The correlation between the variables was analyzed using the Pearson or Spearman correlation coefficient. To estimate the independent predictors of high RAP, a multiple logistic regression model was performed for the variables with a p value of <0.05 in the univariate analyses. Receiver operating characteristic curves were plotted to determine the optimal cut-off values for individual parameters to predict high RAP and to establish the optimal cut-off points for use in clinical decision-making. A p value of <0.05 was considered statistically significant.

Table 1. Baseline and demographic characteristics of patients

	%	Mean \pm SD	Median	Min-Max
Age (year)			49	40-54
Sex				
Male	87			
Presence of ischemia	37			
LVDD (cm)			7	6.4-7.5
LVSD (cm)			6.1	5.6-6.6
EF (%)			20	17-21
TAPSE (cm)			1.3	1.0-1.6
MR, severe	40			
TR, severe	28			
AR, severe	2			
CO (L/min)			3.1	2.5-3.5
CI			1.6	1.49-1.90
SV (mL)		36 \pm 10		
SVI		19 \pm 5.8		
RAP (mmHg)			12	8-16
RVWI (g/m/beat/m ²)		9.2 \pm 3.8		
Mean PAP (mmHg)			35	26-44
PVR (WU)			3.5	1.9-6.1
Mean BP (mmHg)			78	69-86
LVEDP (mmHg)		22 \pm 7.1		
Urea (mg/dL)			46	34-62
Creatinine (mg/dL)			0.9	0.76-1.11
GFR (mL/min)		95 \pm 31		
Albumin (g/dL)			3.9	3.4-4.2
T bilirubin (mg/dL)			1.3	0.8-2.0
PT (sec)			15	14-16
INR			1.25	1.08-1.32
AST (IU/L)			27	20-33
ALT (IU/L)			22	14-32
MELD score			10	8-12

SD: Standard deviation; LVDD; Left ventricular diastolic diameter; LVSD; Left ventricular systolic diameter; EF: Ejection fraction; TAPSE: Tricuspid annular plane systolic excursion; MR: Mitral regurgitation; TR: Tricuspid regurgitation; AR: Aortic regurgitation; CO: Cardiac output; CI: Cardiac index; SV: Stroke volume; SVI: Stroke volume index; RAP: Right atrial pressure; RVWI: Right ventricular work index; PAP: Pulmonary artery pressure; PVR: Pulmonary vascular resistance; WU: Wood unit; BP: Blood pressure; LVEDP: Left ventricular end diastolic pressure; GFR: Glomerular filtration rate according to the MDRD formula; PT: Prothrombin time; INR: International normalized ratio; AST: Aspartate transaminase; ALT: Alanine aminotransferase; MELD: Model for End-Stage Liver Disease

RESULTS

All patients had ischemic (37%) and non-ischemic (63%) cardiomyopathies. Baseline and demographic characteristics of the patients are shown in Table 1.

The median value of the RAP was 12 (range, 8 to 16) mmHg and the median MELD score was 10 (range, 8 to 12). There was a good correlation between the RAP and the MELD score ($r=0.510$, $p<0.001$). In the linear regression analysis, the estimated RAP was calculated as follows: “2 + (0.92 \times MELD Score)” (Unstandardized coefficient 0.920, t value 7.674 and $p<0.001$) (Figure 1).

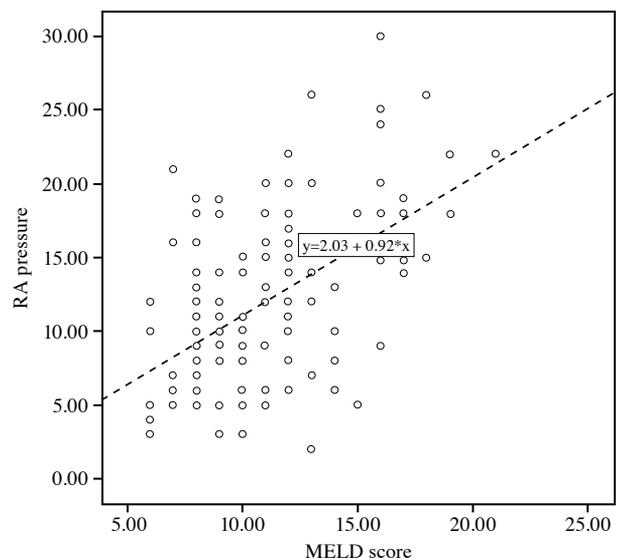


Figure 1. The estimated RA pressure was calculated as “2 + (0.92 \times MELD Score)” (unstandardized coefficient 0.920, t value 7.674 and $p<0.001$) according to the linear regression analyses.

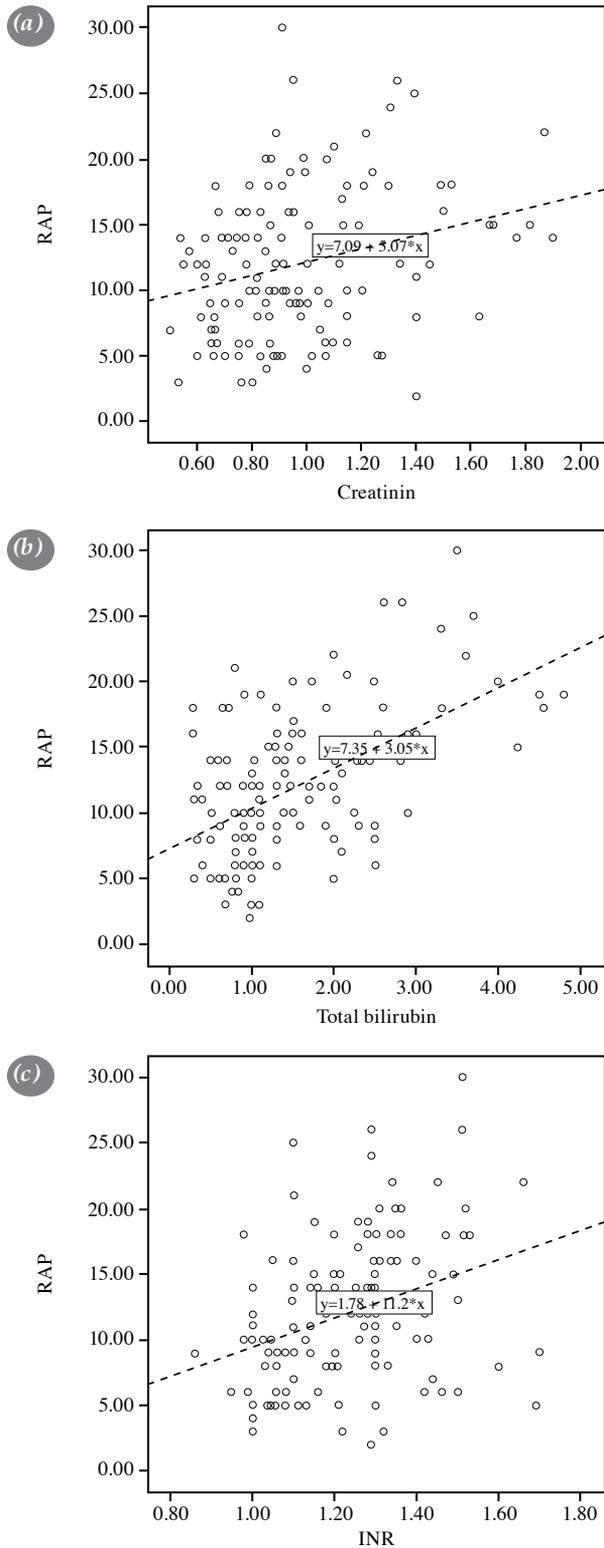


Figure 2. (a-c) The correlation coefficients between RAP and the parameters that are used in the calculation of the MELD Score such as total bilirubin, INR and creatinine were 0.521 ($p < 0.001$), 0.358 ($p < 0.001$) and 0.251 ($p = 0.003$) respectively.
RAP: Right atrial pressure; INR: International normalized ratio

In addition, the correlation between the MELD score and RAP was higher in patients with ischemic cardiomyopathy than in non-ischemic individuals ($r = 0.569$, $p < 0.001$ vs. $r = 0.443$, $p < 0.001$). The correlation coefficients between RAP and the parameters used in the calculation of the MELD score, such as total bilirubin, INR, and creatine, were 0.521 ($p < 0.001$), 0.358 ($p < 0.001$), and 0.251 ($p = 0.003$), respectively (Figure 2a-c).

The patients were divided into two groups based on a RAP of 12 mmHg (Table 2). In patients with higher RAP, the ejection fraction was lower, tricuspid regurgitation was severe, and cardiac output and index were lower. In addition, left ventricular end-diastolic pressure, mean pulmonary artery pressure, and pulmonary vascular resistance were higher. The MELD score was also higher in patients with a higher RAP. In the logistic regression analyses, only the MELD score was found to be an independent predictor of high RAP (odds ratio [OR]=1.491, 95% confidence interval [CI]: 1.244-1.786, $p < 0.001$) (Table 3). In the receiver operating characteristic curve analysis, the MELD score was used to estimate high RAP (> 12 mmHg). The calculated area under the curve (AUC) was 0.789 (95% CI: 0.710-0.867, $p < 0.001$), and the cut-off value for the MELD score in the prediction of high RAP

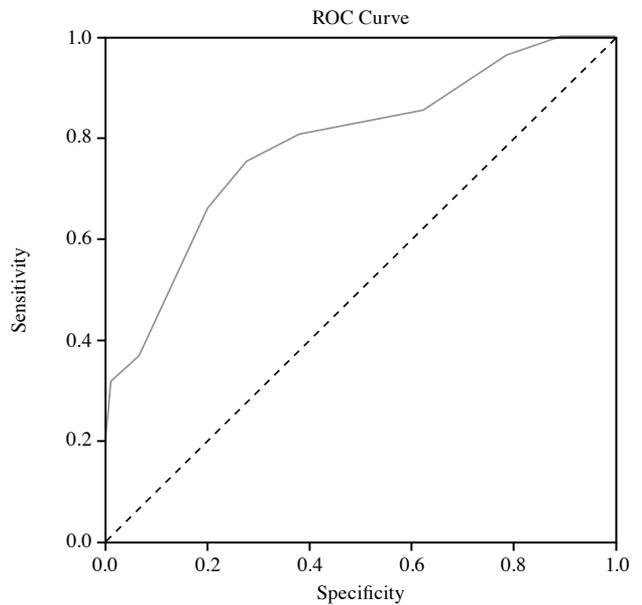


Figure 3. The calculated AUC was 0.789 (95% CI: 0.710-0.867, $p < 0.001$) and cut-off value of MELD score in prediction of high RAP was 10.5 (sensitivity and specificity was 75% and 73%, respectively).
ROC: Receiver operating characteristic; AUC: Under the curve; CI: Confidence interval; RAP: Right atrial pressure.

Table 2. The differences of baseline and demographic characteristics of patients between the groups with high and low right atrial pressure

	Low RAP (<12 mmHg) (n=79)				High RAP (>12 mmHg) (n=58)				p
	%	Mean±SD	Median	Min-Max	%	Mean±SD	Median	Min-Max	
Age (year)			49	41-54			48	38-53	0.777
Sex									
Male	84				91				0.066
Presence of ischemia	35				39				0.129
LVDD (cm)			7	6.4-7.6			7	6.4-7.3	0.206
LVSD (cm)			6.1	5.6-7			6.1	5.5- 6.5	0.117
EF (%)			20	18- 22			18	15-20	0.021*
TAPSE (cm)			1.4	1.04-1.6			1.2	1-1.5	0.068
MR (severe)	44				32				0.854
TR (severe)	16				43				0.000*
CO (L/min)			3.25	2.76-3.85			2.99	2.35-3.30	0.005*
CI			1.8	1.5-2			1.52	1.3-1.7	0.000*
SV (mL)		37±10				35±10			0.182
SVI		19±5.6				18±6			0.135
RVWI (g/m/beat/m ²)		8.5±4				10±3.4			0.050
Mean PAP (mmHg)			29	25-39			39	34-45	0.000*
PVR (WU)			3	1.7-4.6			4.1	2.5-6.4	0.013*
Mean BP (mmHg)			79	68-86			78	70-86	0.666
LVEDP (mmHg)		20±6.9				25±6.1			0.000*
Urea (mg/dL)			42	33- 55			52	34-72	0.030*
Creatinine (mg/dL)			0.88	0.75-1			0.95	0.78-1.27	0.017*
GFR (mL/min)		100±31				88±31			0.066
Albumin (g/dL)			3.9	3.5-4.2			3.7	3.2-4.1	0.141
T bilirubin (mg/dL)			1	0.6-1.4			1.95	1.3-2.84	0.000*
PT (sec)			14.4	13.8-15.1			15.6	14.6-17	0.000*
INR			1.14	1.04-1.3			1.29	1.20-1.38	0.000*
AST (IU/L)			26	19-35			27	22- 32	0.561
ALT (IU/L)			22	15-36			20	13-29	0.198
MELD score			9	8-11			12	10-16	0.000*

RAP: Right atrial pressure; LVDD: Left ventricular diastolic diameter; LVSD: Left ventricular systolic diameter; EF: Ejection fraction; TAPSE: Tricuspid annular plane systolic excursion; MR: Mitral regurgitation; TR: Tricuspid regurgitation; AR: Aortic regurgitation; CO: Cardiac output; CI: Cardiac index; SV: Stroke volume; SVI: Stroke volume index; RVWI: Right ventricular work index; PAP: Mean pulmonary artery pressure; PVR: Pulmonary vascular resistance; WU: Wood unit; BP: Mean blood pressure; LVEDP: Left ventricular end diastolic pressure; GFR: Glomerular filtration rate according to the MDRD formula; PT: Prothrombine time; INR: International normalized ratio; AST: Aspartate transaminase; ALT: Alanine aminotransferase; MELD: Model for End-Stage Liver Disease

Table 3. Logistic regression analysis results

Variables	Multivariate		p
	OR	95% CI	
CO (L/min)	0.525	0.197-1.396	0.197
LVEDP (mmHg)	1.065	0.886-1.282	0.502
LVEF (%)	1.028	0.883-1.197	0.721
TR, severe	1.869	0.625-5.587	0.263
PVR (WU)	0.750	0.449-1.256	0.274
Mean PAP (mmHg)	1.085	0.909-1.294	0.367
MELD score	1.491	1.244-1.786	<0.001

OR: Odds ratio; CI: Confidence interval; CO: Cardiac output; LVEDP: Left ventricular end diastolic pressure; LVEF: Left ventricular ejection fraction; TR: Tricuspid regurgitation; PVR: Pulmonary vascular resistance; PAP: Pulmonary artery pressure.

was 10.5 (sensitivity and specificity was 75% and 73%, respectively) (Figure 3). The AUC values for total bilirubin, INR, and creatine, which are included in the MELD score, were 0.765 (0.681-0.849), 0.696 (0.608-0.784), and 0.621 (0.524-0.717), respectively.

DISCUSSION

In this study, we demonstrated that the MELD score, which can be calculated by non-invasive methods, correlates with a high RAP, measured using cardiac catheterization in patients with advanced HF. Furthermore, the MELD score is also an independent predictor of high RAP. In addition, a strong correlation

between the MELD score and RAP was found in patients with ischemic cardiomyopathy.

The MELD, MELD-Na, and MELD-XI scores assess renal and hepatic dysfunction, which can be associated with death, cardiac transplantation, and ventricular assist device implantation in patients with advanced HF.^[8,9] Abe et al.^[10] showed an association between a high MELD-XI score in a modified form since the INR value and echocardiographic parameters of right ventricular dilatation and overload such as increased inferior vena cava diameter were not included. Patients with a high MELD-XI score had a higher risk for cholestasis right heart volume overload, and pulmonary arterial pressure. They argued that a high MELD-XI score was an independent predictor of cardiac death and all-cause death in patients with HF. In addition, Moraes^[11] suggested that the use of MELD could contribute to the evaluation of the severity of HF in patients who are candidates for transplantation. This could help in setting up a system, similar to liver transplantation, of priority-based transplants for patients requiring a transplant at the earliest.^[11]

Hepatic dysfunction in HF can be identified through a cholestatic profile, such as increased bilirubin, rather than a hepatitis (increased alanine aminotransferase and aspartate aminotransferase) profile; therefore, it has been suggested that the main targets are hepatocytes and biliary epithelium.^[12] Backward obstruction of the central region of the hepatic lobule causes deposition of sinusoidal collagen and fibrosis of the septa. The sensitivity of the hepatocytes and biliary epithelium to an increased pressure due to lobular obstruction causes cholestatic bilirubin changes.^[13]

It has been reported that the strongest hemodynamic determinant of an increase in creatinine levels and worsening renal failure is the presence of venous congestion as measured by elevated central venous pressure,^[14] which also indicates an elevated RAP. Therefore, we attempted to determine the association between RAP obtained by right heart catheterization and the MELD score.

Adequate assessment of RAP is important for the management of patients with HF. Several methods have been proposed for the noninvasive estimation of RAP. It is usually estimated using two-dimensional echocardiographic parameters, such as the presence of inferior vena cava dilation and the degree of inspiratory inferior vena cava collapse.^[15-20] In patients with acute decompensated HF, Patel et al.^[21] suggested that the use of three-dimensional echocardiographic right atrial volume along with traditional two-dimensional

echocardiographic parameters had an increased accuracy in detecting high RAP. However, according to the American Society of Echocardiography (ASE) criteria,^[22] RAP can be classified as low (0-5 mmHg), normal (6-10 mmHg), or elevated (11-20 mmHg). In addition, Taniguchi et al.^[23] suggested that liver stiffness, due to liver obstruction caused by RAP elevation, assessed using transient elastography, might provide a non-invasive diagnostic method to evaluate RAP in patients with HF.

In the present study, when we divided the participants with advanced HF into two groups according to the median value of RAP, the patients with higher RAP (>12 mmHg) had a lower cardiac output and cardiac index, as well as a higher left ventricular end-diastolic pressure and mean pulmonary artery pressure. Additionally, as expected, the MELD score was higher in patients with a high RAP. Although the degree of tricuspid regurgitation was higher in this group, it was not found to be a predictor of high RAP, indicating that RAP increases independently, irrespective of the degree of regurgitation. Patients with advanced HF may worsen, even with mild tricuspid regurgitation; this is an unexpected, yet interesting finding. We have also attempts to discover a rapid, non-invasive, and convenient bedside formula to predict high RAP.

Nonetheless, there are some limitations to this study. This is a single-center, retrospective study. In addition, blood sampling and non-invasive measurements were performed simultaneously. Cardiac catheterization was performed within 24 h of blood sampling and echocardiography. The MELD-XI score was not assessed. Also, brain natriuretic peptide values, main rhythm of the patient (atrial fibrillation or not) and hemoglobin values were not included in the study. Further studies including patients receiving warfarin treatment may be needed, particularly those with LVADs. However, this new formula should be validated in studies with a large number of patients with advanced HF, as well as in the general population to give a better representation of RAP.

In conclusion, adequate evaluation of right atrial pressure is important for the management of heart failure patients. Various methods have been proposed for the non-invasive estimation of right atrial pressure, usually using two-dimensional echocardiographic parameters. The Model for End-Stage Liver Disease score, which can be calculated by non-invasive methods, correlates with higher right atrial pressure measured using cardiac catheterization in patients with advanced heart failure. We describe a method to calculate the right atrial pressure obtained using the Model for End-Stage

Liver Disease score in patients with advanced heart failure without the need for cardiac catheterization during hospitalization and follow-up.

Declaration of conflicting interests

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