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ORIGINAL ARTICLE

MELD score predicts outcomes in patients with advanced heart failure: A longitudinal evaluation

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Abstract

Aims Advanced heart failure (AHF) is characterized by recurrent episodes of haemodynamic instability and frequent hospitalizations, leading to a progressive decline in quality of life and high mortality rates. The objectives of this study were to evaluate the effect of the model for end-stage liver disease (MELD) score and its variations in predicting adverse outcomes [death, urgent heart transplant, and left ventricular assist device (LVAD) implant] among patients with AHF to assess the clinical associations of the MELD score in this population and to compare the efficacy of this tool with other prognostic scores in AHF.

Methods and results In this longitudinal prospective study, 162 patients with advanced heart failure (AHF) were enrolled; all patients included in the study were receiving the maximum tolerated medical therapy according to guidelines. The MELD score was measured at baseline and every 6 months during follow-up. All patients underwent echocardiographic assessment and cardiopulmonary testing, which included the evaluation of maximal oxygen uptake (VO2max) and the minute ventilation/carbon dioxide production (VE/VCO2) slope. The mean age of the study group was 57.7 ± 11.6 years. There were 26 deaths, 5 urgent transplants, and 1 LVAD implantation during a follow-up period of 31.4 ± 15.6 months. The mean New York Heart Association (NYHA) class was 2.8 ± 0.5, ejection fraction (EF) was 26.3 ± 6.5%, the mean VO2max was 11.7 ± 3.5 mL/kg/min. Multiple regression analysis revealed a positive correlation between the MELD score and NT-proBNP ($\beta = 0.215$; $P = 0.041$) and furosemide dosage ($\beta = 0.187$; $P = 0.040$). Conversely, a negative correlation was observed between the MELD score and TAPSE ($\beta = -0.204$; $P = 0.047$). Multivariate Cox regression on combined outcome shows a HR of 1.094 (95% CI 1.003–1.196) for unit increase in MELD considered as a continuous variable. The predictive role is independent by the effect of covariates considered in the analysis such as age, sex, NYHA class, EF, TAPSE, PASP, VO2max, NT-proBNP, MELD score worsening, and NT-proBNP increase. Changes in MELD score percentage, considered as a dichotomous variable ($\leq$100% and $>$100%), were found to be predictors of mortality, urgent heart transplant and LVAD implant. Receiver operating characteristic (ROC) curves showed an area under the curve (AUC) of 0.887 for MELD score and composite outcome of death, urgent transplant, and need for LVAD. The predictive performance of MELD was even superior compared with MELD-Na, MELD-XI, MAGGIC risk score, and MECKI.

Conclusions The MELD score and its longitudinal changes are effective predictors of adverse outcomes in AHF.

Keywords Advanced heart failure; Heart transplant listing; MELD score; Mortality

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Introduction

Advanced heart failure (AHF) describes a clinical syndrome characterized by persistent or progressive symptoms worsening despite conventional treatments (i.e., guideline-directed drugs, devices, and conventional surgery) in which advanced therapies (e.g., cardiac transplantation and mechanical support) or palliative therapies (e.g., inotropic infusions, ultrafil-

tration, peritoneal dialysis, or end-of-life comfort care) are needed.[1] AHF is characterized by recurrent episodes of haemodynamic instability, frequent and prolonged hospitalizations, and a progressive decline in quality of life. With each subsequent hospitalization due to heart failure instability, patients typically experience further impairment of heart function and an increased likelihood of subsequent re-hospitalizations or death.[2]

Recent studies have highlighted the potential predictive role of the Model for End-Stage Liver Disease (MELD) score in outcomes such as hospitalization and mortality among patients with acute heart failure.[3,4] Originally developed at the Mayo Clinic in Rochester, Minnesota, USA, to forecast the survival of patients undergoing trans-jugular intrahepatic portosystemic shunts,[5] the MELD score has since found widespread use in assessing prognosis in liver cirrhosis and in the evaluation of patients for liver transplantation.[6] The MELD score is derived from the measurement of total bilirubin, international normalized ratio (INR), and creatinine levels. These parameters are routinely obtained from blood tests performed on patients with AHF. A higher MELD score indicates a more severe clinical condition in the patient. Liver congestion, a systemic effect of heart failure, leads to abnormalities in liver function. The MELD score incorporates three non-cardiac biomarkers that assess the severity of liver dysfunction, reflecting aspects of synthesis (INR), metabolism (total bilirubin), and renal function (creatinine).

The aims of our study were to evaluate the predictive role of the MELD score in patients with AHF concerning mortality and urgent transplantation, to investigate the clinical and biological factors correlated with the MELD score, and to assess whether longitudinal changes in the MELD score provide additional prognostic value for predicting mortality and the need for urgent transplantation in AHF. Additionally, we compared the prognostic capabilities of the MELD score with its derived indices, such as MELD-Na (which incorporates serum sodium levels) and MELD-XI (which excludes INR),[7–9] and with other validated prognostic tools in heart failure, including the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score and Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score.[10,11]

Methods

Study population

One hundred sixty-two patients with AHF were consecutively evaluated from November 2016 to May 2020 and prospectively followed at the Heart Transplant Center of the Monaldi Hospital and the Department of Cardiovascular Emergencies, Cardiorespiratory Clinical Medicine, and Geriatrics at the University Hospital 'Federico II' in Naples. Thirty-eight patients were excluded due to the presence of severe chronic obstructive pulmonary disease, chronic liver disease, renal replacement therapy, and anticoagulation with vitamin K antagonists (VKAs). Eighteen patients were unable to perform the cardiopulmonary exercise test (CPET), resulting in a final sample size of 106 patients.

At the time of enrolment, 42 patients were on the waiting list for heart transplantation, 14 were under evaluation for inclusion in the list, and 50 were excluded from the list due to incident comorbidities and age limits. All patients underwent evaluation for the optimization of medical therapy in accordance with the guidelines at that time.[12] The assessment of the MELD and other scores (MELD-Na, MELD-XI, MAGGIC risk score, and MECKI score) was performed at study entry and every 6 months during follow-up.

During follow-up, patients underwent blood chemistry exams, including creatinine, INR, and bilirubin measurements, necessary for calculating the MELD score, as well as N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Each patient received a clinical evaluation, which included a cardiological assessment with echocardiography and implantable cardioverter-defibrillator (ICD) interrogation, and a functional assessment with CPET. The MELD score was calculated at the time of enrolment using three non-cardiac biomarkers that reflect the severity of liver dysfunction in terms of synthesis (INR), metabolism (total bilirubin), and renal function (creatinine).[5]

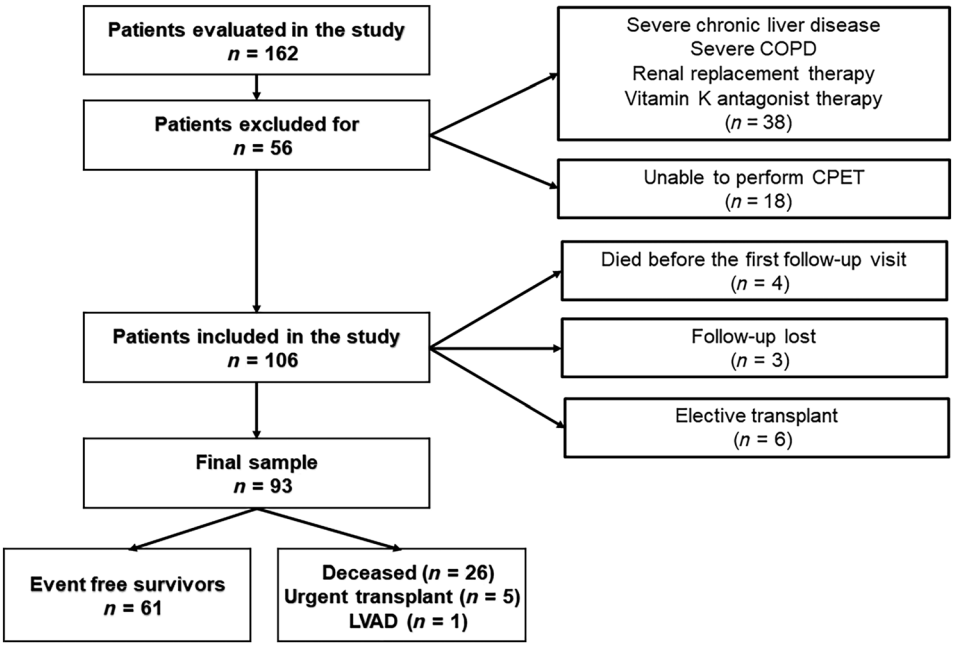
Throughout the follow-up period, 4 patients died before the first follow-up visit, 3 were lost to follow-up, and 11 underwent heart transplantation (6 as elective transplants and 5 as emergencies). One patient was implanted with a left ventricular assist device (LVAD), resulting in a final sample size of 93 patients for analysis (*Figure 1*).

Ethics approval was obtained from the local institutional review committee, and all participants provided informed consent. The study adhered to the ethical guidelines outlined in the Declaration of Helsinki.

Statistical analysis

The baseline characteristics of the sample were expressed as mean ± standard deviation for continuous variables. The categorical variables were expressed as a percentage. Differences in sex, age, NYHA class, systolic blood pressure, diastolic blood pressure, heart rate, left ventricular ejection fraction (EF), tricuspid annular plane systolic excursion (TAPSE), inferior vena cava diameter (IVCd), pulmonary artery systolic pressure (PASP), TAPSE/PASP ratio, maximal oxygen uptake (VO2max), minute ventilation/carbon dioxide production (VE/VCO2), NT-proBNP, creatinine, total bilirubin, INR, MELD score, MELD-Na, MELD-XI, MAGGIC risk score and MECKI score, coronary artery disease (CAD), atrial fibrillation (AF), diabetes, pharmacological treatments, MitraClip implan-

Figure 1 Flow chart of the study.



tation, ICD, and cardiac resynchronization therapy (CRT) were evaluated among event-free survivors and deceased or urgently transplanted LVAD patients.

Variables associated with the MELD score were evaluated using linear regression analysis, and those variables statistically significant were used in a multiple linear regression model to evaluate the independent effect. Collinearity was assessed using the variance inflation factor (VIF) with a threshold of 3. Variables with a VIF >3 were not included in multivariate analysis. TAPSE/PASP ratio was not included in multivariate analysis because the variable is derived from TAPSE and PASP already included in the model. The percentage variation of the MELD score ($\leq$100% or $>$100%) between baseline and the follow-up visit at 6 months was evaluated, and for Cox regression, it was dichotomized to the value of 1, thus distinguishing the patients into two groups: the one that remained stable or improved ($\leq$100%) and those that worsened ($>$100%), similarly NT-proBNP increase was evaluated at 6 months of follow up. Unpaired Student's t-test was used to evaluate the difference in MELD variation and age, NYHA class, EF, TAPSE, IVCd, PASP, TAPSE/PASP ratio, VO2max, VE/VCO2, NT-pro-BNP, and NT-proBNP increase. Cox regression analysis was performed using mortality and emergency LVAD/heart transplant as dependent variable and age, sex, NYHA class, EF, TAPSE, PASP, VO2max, NT-proBNP (log trasformed), NT-proBNP increase, MELD and MELD increase during follow-up as independent variables. ROC curves were utilized to compare MELD, MELD-Na and MELD-XI on mortality and urgent heart transplant/LVAD implant and to compare MELD score against MAGGIC risk score and MECKI score. We considered a P value <0.05 to be statistically significant. Data were collected and then analysed using SPSS software (version 27.0, SPSS Inc., Chicago, IL).

Results

The analysed sample comprised 93 patients with a mean age of 57.7 ± 11.6 years, of whom 77 were males (82.8%). Over a median follow-up period of 31.4 ± 15.6 months, 26 patients (27.9%) died, 5 patients underwent emergency heart transplantation, and 1 patient received a LVAD. *Table 1* presents the clinical characteristics and therapies of the sample, stratified according to the combined outcome of death, urgent heart transplantation, or urgent LVAD implantation.

In the total sample, the mean NYHA class was 2.8 ± 0.5, EF was 26.3 ± 6.5%, TAPSE was 17.0 ± 4.0 mm, PASP was 43.8 ± 15.3 mmHg, and NT-proBNP levels were 2858.0 ± 2507.0 ng/L. The mean VO2max was 11.7 ± 3.5 mL/kg/min, while the mean VE/VCO2 slope was 37.0 ± 10.4; 79.6% of patients received treatment with sacubitril/valsartan, while 90.3% were on beta-blockers. Furosemide was administered to 87.1% of patients at an average dose of 99.7 ± 67.9 mg/day, and mineralocorticoid receptor antagonists were used in 74.7% of cases. Additionally, 36.6% of patients received amiodarone therapy. 83.9% of patients were with ICD and 32.3% also with CRT. Finally, 7.5% of patients had undergone mitral valve clipping.

Upon analysing the data stratified by event-free survivors and deceased/transplated patients, notable differences were

Table 1 Clinical variables differences between event-free survivors and adverse outcomes group

Variables	All (# 93)	Event-free survivors (# 61)	Adverse event group[a] (#32)	*P*
Age (years, mean ± SD)	57.7 ± 11.6	55.8 ± 11.9	61.0 ± 9.7	>0.047
Male (%)	82.8	82.0	84.4	>0.770
Heart Rate (b.p.m., mean ± SD)	70.9 ± 14.4	72.1 ± 11.9	66.4 ± 8.4	>0.088
SBP (mmHg, mean ± SD)	111.7 ± 18.9	117.5 ± 27.3	101.1 ± 15.5	>0.001
DBP (mmHg, mean ± SD)	76.2 ± 13.7	72.3 ± 11.9	71.2 ± 9.8	>0.088
NYHA class (mean ± SD)	2.8 ± 0.5	2.7 ± 0.6	3.2 ± 0.4	><0.001
EF (%, mean ± SD)	26.3 ± 6.5	27.7 ± 6.2	23.0 ± 6.0	><0.001
TAPSE (mm, mean ± SD)	17.0 ± 4.0	18.3 ± 3.9	14.8 ± 3.6	><0.001
PASP (mmHg, mean ± SD)	43.8 ± 15.3	38.6 ± 11.7	54.8 ± 12.4	><0.001
TAPSE/PASP ratio	0.48 ± 0.30	0.56 ± 0.25	0.29 ± 0.17	><0.001
IVCd (mm, mean ± SD)	19.3 ± 4.0	18.2 ± 4.0	20.8 ± 3.6	>0.012
VO2max (mL/kg/min, mean ± SD)	11.7 ± 3.5	12.8 ± 3.5	9.6 ± 2.2	><0.001
VE/VCO2 (slope, mean ± SD)	37.0 ± 10.4	35.3 ± 9.5	40.5 ± 11.4	>0.029
NT-proBNP (ng/L, mean ± SD)	2858.0 ± 2507.0	1884.0 ± 1669.5	4626.2 ± 2849.1	><0.001
Creatinine (mg/dL, mean ± SD)	1.4 ± 0.6	1.3 ± 0.6	1.5 ± 0.4	>0.006
AST (U/L, mean ± SD)	20.6 ± 5.8	18.9 ± 4.3	27.4 ± 7.0	>0.082
ALT (U/L, mean ± SD)	25.6 ± 14.8	22.5 ± 10.4	30.8 ± 19.2	>0.218
Total bilirubin (mg/dL mean ± SD)	1.1 ± 0.5	0.8 ± 0.4	1.2 ± 0.6	>0.001
INR (mean ± SD)	1.4 ± 0.6	1.2 ± 0.7	1.8 ± 0.8	>0.005
Sodium (mEq/L) (mean ± SD)	138.4 ± 3.8	139.9 ± 3.4	136.2 ± 3.6	><0.001
MELD score (mean ± SD)	14.5 ± 6.0	11.9 ± 5.1	19.4 ± 4.1	><0.001
MELD-Na (mean ± SD)	15.1 ± 6.1	12.9 ± 5.1	20.1 ± 5.4	><0.001
MELD-XI (mean ± SD)	13.6 ± 4.6	12.5 ± 4.4	16.3 ± 4.0	><0.001
MECKI (mean ± SD)	17.2 ± 13.6	13.1 ± 11.6	28.8 ± 13.4	><0.001
MAGGIC (mean ± SD)	23.8 ± 8.4	20.8 ± 7.7	30.9 ± 5.3	><0.001
CAD (%)	59.1	59.0	59.4	>0.973
Diabetes (%)	39.6	36.1	46.7	>0.331
Atrial fibrillation (%)	36.6	36.1	37.5	>0.891
MitraClip (%)	7.5	8.2	6.3	>0.735
ICD (%)	83.9	75.4	100	>0.002
CRT (%)	32.3	34.4	28.1	>0.577
Sacubitril/valsartan (%)	79.6	82.0	75.0	>0.429
Furosemide (%)	87.1	80.3	100	>0.007
Amiodarone (%)	36.6	19.7	68.8	>0.001
Metolazone (%)	5.4	3.3	9.4	>0.216
Ivabradine (%)	6.5	3.3	12.5	>0.085
SGLT2 inhibitors (%)	47.3	52.0	37.5	>0.170
MRAs (%)	74.7	75.4	73.7	>0.830
Digoxin (%)	10.8	8.2	15.6	>0.431
Beta-blockers (%)	90.3	93.4	84.4	>0.160

[a]Composite outcome of death, urgent heart transplant, and left ventricular assisting device implantation.
ALT, alanine transaminase; AST, aspartate transaminase; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; EF, left ventricular ejection fraction; ICD, implantable cardioverter defibrillator; INR, international normalized ratio; IVCd, inferior vena cava diameter; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MECKI, Metabolic Exercise test data combined with Cardiac and Kidney Indexes; MELD, model for end-stage liver disease; MELD-Na, MELD-sodium; MELD-XI, MELD excluding INR; MRAs, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal fragment of pro brain natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; SBP, systolic blood pressure; SGLUT2, sodium-glucose transport protein 2; TAPSE, tricuspid annular plane systolic excursion; VE/VCO2, minute ventilation/carbon dioxide production; VO2max, maximal oxygen consumption.

observed. Patients who experienced the outcome were found to be older (61.0 ± 9.7 vs. 55.8 ± 11.9 years; $P = 0.047$) and exhibited a poorer functional profile, as evidenced by a higher NYHA class (3.2 ± 0.4 vs. 2.7 ± 0.6; $P \leq 0.001$), lower values of VO2max (9.6 ± 2.2 vs. 12.8 ± 3.5 mL/kg/min; $P \leq 0.001$. Furthermore, these patients displayed significantly elevated levels of NT-proBNP (4626.2 ± 2849.1 vs. 1884.0 ± 1669.5 ng/L; $P \leq 0.001$) and MELD score (19.4 ± 4.1 vs. 11.9 ± 5.1; $P \leq 0.001$), as outlined in *Table 1*. All prognostic scores considered (MELD-Na, MELD-XI, MAGGIC, and MECKI) were worse in patients who experienced outcomes.

The MELD score exhibited significant univariate correlations with clinical and echographic parameters, including age, NYHA class, EF, TAPSE, PASP, TAPSE/PASP ratio, IVCd, VO2max, NT-proBNP, and furosemide use and dosage. Multiple linear regression analysis revealed a positive association between the MELD score and NT-proBNP ($\beta = 0.215$; $P = 0.041$), indicating that as the MELD score increases, levels of NT-pro-BNP tend to rise. Additionally, furosemide dosage was positively correlated with MELD score ($\beta = 0.187$; $P = 0.040$). Conversely, a negative correlation was observed between the MELD score and TAPSE ($\beta = -0.204$; $P = 0.047$), suggesting that higher MELD scores are associated

with decreased TAPSE values. Notably, no significant correlations were found between the MELD score and the remaining clinical variables, as summarized in *Table 2*. Multicollinearity was not detected among the independent variables.

Table 3 shows the differences between the groups of patients whose MELD scores improved during follow-up, assessed by percentage change, and those whose scores worsened. The increase in MELD values was found to be associated with higher baseline levels of NT-proBNP (3457.3 ± 2789.0 vs. 2244.0 ± 2117.1 ng/L; P = 0.024), IVCd (20.3 ± 4.0 vs. 18.6 ± 3.8 mm; P = 0.036), and PASP (48.0 ± 15.2 vs. 41.1 ± 14.6 mmHg; P = 0.033) and lower TAPSE/PASP ratio (0.40 ± 0.24 vs. 0.53 ± 0.26; P = 0.026). No statistically significant differences were detected in the other variables examined.

Multivariate Cox regression on combined outcome shows a HR of 1.094 (95% CI 1.003–1.196) for unit increase in MELD considered as a continuous variable. The predictive role is independent by the effect of covariates considered in the analysis such as age, sex, NYHA class, EF, TAPSE, PASP, VO2max, NT-proBNP (log transformed), MELD score worsening, and NT-proBNP increase. The independent predictive role of NT-proBNP on mortality and urgent transplant/LVAD implantation is noteworthy (HR = 2.032; 95% CI 1.176–3.513). Of interest is the predictive role of MELD score worsening on outcomes, while no predictive effect is observed for NT-proBNP increase (*Table 4* and *Figure 4*). Moreover, a similar HR for mortality and urgent transplant/LVAD implantation was found for both MELD-Na (1.159; 95% CI 1.092–1.229) and MELD-XI (1.131; 95% CI 1.052–1.216).

The ROC curves illustrate an area under the curve (AUC) of 0.887 for the MELD score in predicting outcomes. The optimal cutoff value for MELD, determined by the highest sensitivity and specificity, is identified as 14.5 (sensitivity 0.92 and specificity 0.77) (*Figure 2*). The ROC curves for MELD-Na and MELD-XI were calculated to assess the differences among scores. The AUC for MELD-Na was 0.847, while the AUC for MELD-XI was 0.790.

The differences in AUC were also evaluated among the MELD, MAGGIC risk, and MECKI scores. The AUCs were 0.877, 0.845, and 0.802, respectively (*Figure 3*).

Furthermore, patients experiencing worsening MELD scores during follow-up exhibited a significantly higher rate of events compared with those with either stable or improved MELD scores (61.0% vs. 13.5%; $P < 0.001$) (*Figure 4*).

Table 2 Variables associated with MELD score

Variables	Linear regression		Multiple linear regression		
	Beta	*P*	Beta	*P*	VIF
Age	0.235	0.023	0.064	0.499	1.244
NYHA class	0.339	0.001	−0.047	0.704	1.717
EF	−0.320	0.002	−0.088	0.380	1.442
TAPSE	−0.446	0.001	−0.204	0.047	1.502
PASP	0.444	0.001	0.098	0.394	1.876
TAPSE/PASP ratio	−0.472	0.001	—	—	—
IVCd	0.338	0.001	0.092	0.347	1.368
VO2max	−0.471	0.001	−0.113	0.308	2.044
VE/VCO2	0.180	0.090	—	—	—
NT-proBNP	0.474	0.001	0.215	0.041	1.530
Furosemide	0.279	0.007	—	—	—
Furosemide dose	0.342	0.001	0.187	0.040	1.144

EF, left ventricular ejection fraction; IVCd, inferior vena cava diameter; NT-proBNP, N-terminal fragment of pro brain natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; TAPSE, tricuspid annular plane excursion; VE/VCO2, minute ventilation/carbon dioxide production; VIF, variance inflation factor; VO2max, maximal oxygen consumption.

Table 3 Variables associated with MELD percent change

Variables	MELD percent variation		*P*
	≤100 (# 52)	>100 (# 41)	
Age	55.9 ± 12.1	60.1 ± 11.0	0.084
NYHA class	2.8 ± 0.6	3.0 ± 0.5	0.127
EF	26.8 ± 6.1	25.8 ± 7.0	0.465
TAPSE (mm)	17.6 ± 3.6	16.0 ± 4.6	0.080
IVCd (mm)	18.6 ± 3.8	20.3 ± 4.0	0.036
PASP	41.1 ± 14.6	48.0 ± 15.2	0.033
TAPSE/PASP	0.53 ± 0.26	0.40 ± 0.24	0.026
VO2max (mL/kg/min)	12.3 ± 3.4	11.0 ± 3.4	0.077
VE/VCO2	35.4 ± 9.3	39.2 ± 11.5	0.083
NT-proBNP (ng/L)	2404.4 ± 2328.6	3432.8 ± 2688.9	0.049
↑ NT-proBNP (%)	26.9	58.5	0.002

↑NT-proBNP, percent of patients in which the NT-proBNP increases during the follow-up period; EF, left ventricular ejection fraction; IVCd, inferior vena cava diameter; NT-proBNP, N-terminal fragment of pro brain natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; TAPSE, tricuspid annular plane excursion; VE/VCO2, minute ventilation/carbon dioxide production; VO2max, maximal oxygen consumption.

Discussion

The study demonstrated that the MELD score is an independent predictor of poor outcomes in patients with AHF. Univariate analysis showed a positive correlation between the MELD score and age, NYHA class, PASP, NT-proBNP,

Table 4 Cox regression on mortality and urgent transplant/LVAD implant

Variables	HR	95% CI	*P*
Age	0.981	0.926–1.018	0.221
Sex (male)	1.704	0.553–5.254	0.354
NYHA class	2.555	0.808–8.078	0.110
EF	0.952	0.888–1.022	0.173
TAPSE	1.023	0.895–1.170	0.895
PASP	1.001	0.965–1.037	0.969
VO2max	1.068	0.862–1.323	0.549
NT-proBNP (ln)	2.032	1.176–3.513	0.011
↑NT-proBNP	1.261	0.405–3.930	0.689
MELD	1.094	1.003–1.196	0.045
↑MELD	3.743	1.343–10.428	0.012

↑NT-proBNP, NT-proBNP increase during the follow-up period; EF, left ventricular ejection fraction; NT-proBNP, N-terminal fragment of pro brain natriuretic; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; TAPSE, tricuspid annular plane excursion; VO2max, maximal oxygen consumption.

Figure 2 ROC curve for MELD, MELD-Na, MELD-XI, and combined outcome (mortality and urgent transplant/LVAD implant).

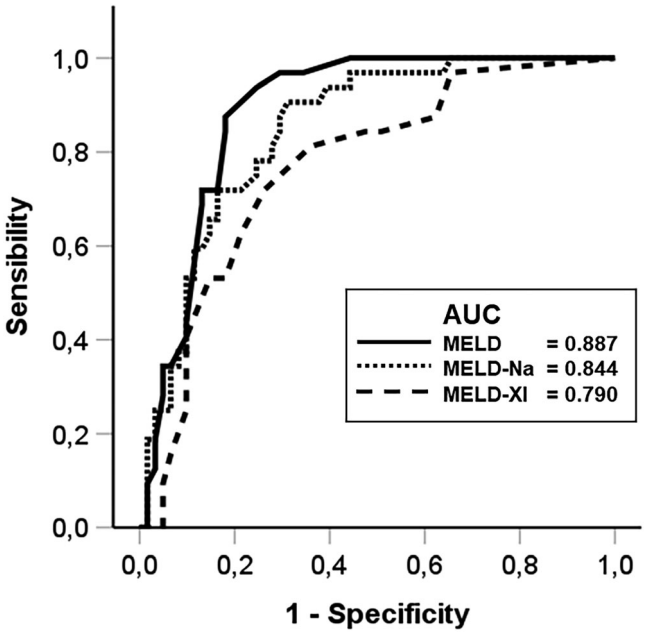
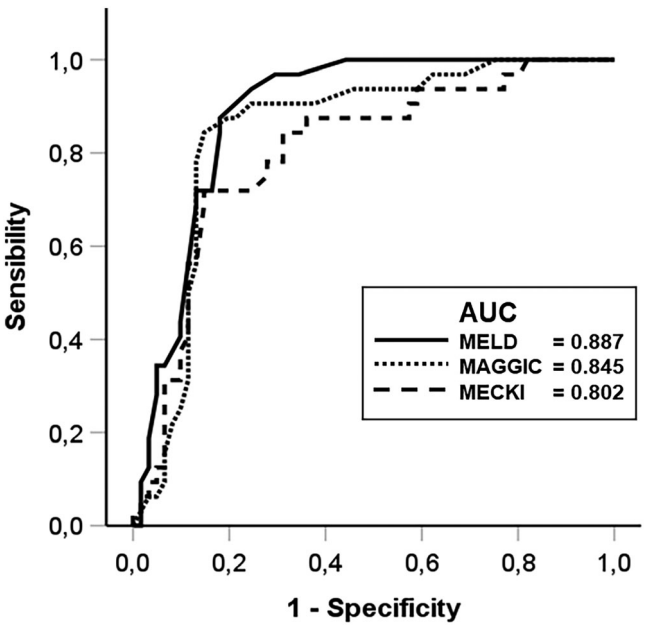


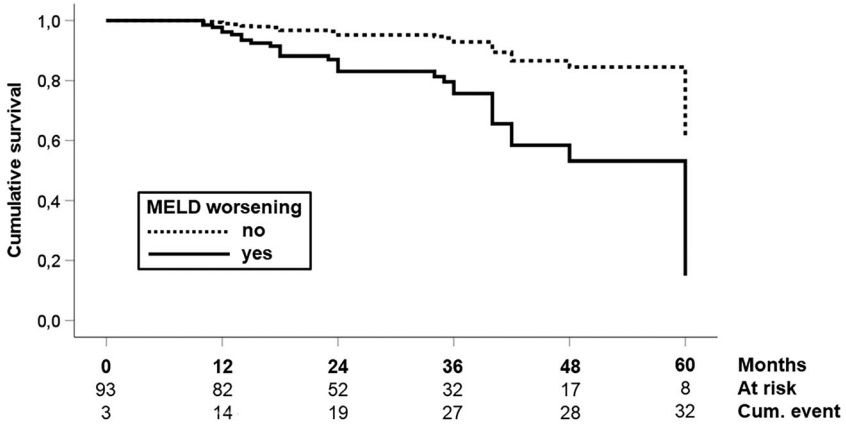
Figure 3 ROC curve for MELD, MAGGIC, and MECKI and combined outcome (mortality and urgent transplant/LVAD implant).



and diuretic dose, while a negative correlation was observed for VO2max, EF, TAPSE, and TAPSE/PASP. In multivariate regression analysis, TAPSE, NT-proBNP, and furosemide dose remained statistically significant in relation to the MELD score.

The MELD score effectively describes the severity of heart failure by incorporating parameters that reflect hepatic congestion and renal hypoperfusion, both of which are critical components of heart failure pathophysiology. Multiple regression analysis confirmed a significant correla-

Figure 4 Cox regression analysis based on longitudinal variations in MELD scores and combined outcomes.



tion between the MELD score and NT-proBNP, a principal biological marker of HF.[13] Additionally, the MELD score correlated with TAPSE, highlighting the crucial role of right ventricular function in the progression of heart failure.[14] Furthermore, the required dose of diuretics, serving as an index of the degree of decompensation, also correlated with the MELD score.

These findings underscore the importance of the MELD score as a comprehensive prognostic tool that integrates multiple facets of heart failure severity. The coexistence of hepatorenal dysfunction was commonly observed in patients with more advanced heart failure. An increase in the MELD score reflects liver and kidney dysfunction due to mechanisms such as low cardiac output, reduced organ perfusion, sympathetic activation, tricuspid valve insufficiency, right ventricular failure, and increased central venous and intraperitoneal pressure. The increase of NT-proBNP indicates cardiac dysfunction due to reduced function or increased volume overload. The association between the MELD score and both NT-proBNP and TAPSE reduction is clinically relevant as it reflects the biventricular involvement in heart failure.

Even after adjusting for multiple variables, the association of the MELD score with poor outcomes remained statistically significant. Importantly, there were no obvious clinical signs to identify patients with hepatorenal dysfunction upon admission. This subset of patients may be predisposed to organ injury or may experience more profound haemodynamic, metabolic, or neurohormonal disturbances leading to multiorgan dysfunction that cannot be detected through simple clinical examination.

Notably, the study also presents, for the first time in the literature, that a reduction in the MELD score during follow-up is associated with lower mortality, suggesting that monitoring MELD scores in these patients may provide additional prognostic information, particularly concerning their response to medical treatment. These findings align with previous studies highlighting the prognostic significance of hepatic and renal function indices on mortality in patients with acute heart failure,[3,4] thereby contributing valuable insights to the existing literature on this subject.

The MELD score and its modifications, widely employed as prognostic indicators in patients with liver disease, have been demonstrated to be associated with poorer clinical outcomes in patients with HF. Kim et al. retrospectively studied 343 AHF outpatients undergoing evaluation for heart transplant.[15] In their analysis, the authors utilized the MELD score and its modified versions: the MELDNa and the MELD-XI. The scores were used separately and in combination with the Heart Failure Survival Score (HFSS) and Seattle Heart Failure Model (SHFM). Elevated MELD, MELD-XI, and MELDNa scores were associated with an increased risk for the composite endpoint of death, heart transplant, and the need for a LVAD in outpatients with HF (HR = 1.10, 95% CI 1.06–1.14 for MELD; HR = 1.13, 95% CI 1.07–1.19 for MELD-XI; HR = 1.10, 95% CI 1.06–1.14 for MELDNa). When the MELD scores were combined with the HFSS and SHFM, it was observed that low MELD scores (<12) predicted favourable outcomes and clinical stability in the low-risk group, while high scores (>12) in the medium-risk group identified patients at the highest risk for the outcomes. The MELD scores were found to be independent of VO2max and several other parameters in HFSS and SHFM. MELD-XI was able to identify patients with shorter survival among those receiving anticoagulation with warfarin, although the survival difference was more pronounced for non-anticoagulated patients. However, the MELD and MELDNa scores did not offer helpful prognostic information for anticoagulated patients. In this study, over 40% of the patients were receiving anticoagulant therapy with coumarin derivatives. We believe that the significance of MELD-XI may be diminished by the increasingly common use of direct oral anticoagulants.

Biegus et al. demonstrated that MELD and MELD-XI scores calculated during hospitalization for acute heart failure were

significant predictors of poor outcomes (HR = 1.11, 95% CI 1.06–1.17; HR = 1.14, 95% CI 1.09–1.20 per point, respectively, both $P < 0.001$).[3] Similar findings were observed in a comparable setting in the RELAX-AHF trial, where the MELD-XI score was significantly associated with death from all causes (HR = 1.11, 95% CI 1.04–1.17).[4] Our study confirms these results, highlighting substantial equivalence of the MELD-derived score in prognostication HF. The differences in the hazard ratios between our findings and previous ones may stem from several factors, including the relatively larger sample size and type of population, different duration of follow-up, differences in outcomes, and adjustment factors.

Furthermore, preoperative liver dysfunction estimated by the MELD score has been shown to be associated with higher mortality in patients undergoing LVAD implantation,[16] cardiac surgery,[17,18] and transcatheter tricuspid valve repair.[19]

The utilization of the MELD score in HF is grounded in robust pathophysiology, due to the common occurrence of hepatic and renal dysfunction in these patients. Congestion, which occurs when blood accumulates upstream of the right ventricle, represents a crucial pathophysiological mechanism leading to impaired organ function in HF. Hypoperfusion exacerbates organ dysfunction by failing to meet the metabolic demands of tissues, resulting in hypoxia, insufficient aerobic metabolism, and ultimately, cellular injury and organ failure.

In our study sample, the MELD score was found to be comparable to, and even superior to, other validated prognostic indices, such as the MAGGIC risk score and the MECKI score, in the stratification of patients with HF. The MELD score can be calculated more easily compared with other prognostic tools, even in general medical practice, because it relies on three laboratory parameters that are commonly measured in clinical practice, even outside of a cardiology setting. Specifically, unlike the MECKI score, the MELD score does not require specialized assessments such as CPET, which cannot be performed in a significant proportion of patients with advanced HF. Therefore, we believe that the MELD score is more practical and effective for prognostication in these patients.

Although we observed a correlation between MELD and NT-proBNP values, which supports the utility of MELD as a prognostic stratification tool capable of detecting worsening heart failure, we believe that using MELD as a prognostic index, compared with NT-proBNP, is preferable despite it being less immediate and derived from a formula. This is because MELD is more cost-effective and, interestingly, its longitudinal variations are predictive of mortality. In our sample, increases in NT-proBNP values were not predictive of worse outcomes, unlike MELD, likely due to a ceiling effect beyond which further increases in NT-proBNP lose significance. MELD variations, derived from three different indices reflecting worsening congestion and hypoperfusion, are better suited to detect changes in clinical status and can be useful for general practitioners in referring patients to a cardiology specialist.

Limitation of the study

This is a single-centre study. Although evidence suggests that the MELD score can also be used to assess multi-organ failure in other conditions, it is primarily validated as a transplant score in end-stage liver disease. The number of patients included in our study is relatively small given the prevalence of HF in the general population. Furthermore, our study population consists of patients with AHF who were able to perform CPET, limiting the generalizability of our findings to patients with preserved or mildly reduced left ventricular ejection fraction or those with comorbidities such as severe COPD, chronic hepatopathy, or valvular disease treated with VKAs. Consequently, our study population does not closely represent the broader HF population.

Therefore, this study should be considered a preliminary approach to the dynamic evaluation of HF prognosis using the MELD score.

Conclusion

The study confirms the value of the MELD score in the prognostic assessment of patients with AHF and underscore the rationale and usefulness of re-evaluating the score during follow-up. This allows the identification of more severe patients at increased risk of mortality. These findings could aid physicians in improving tailored follow-up strategies, risk stratification, and resource allocation for HF patients.

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Conflict of interest

The authors declare no financial or personal conflicts of interest.

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