ORIGINAL ARTICLE

One-year survival of ambulatory patients with end-stage heart failure: the analysis of prognostic factors

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KEY WORDS

heart failure, liver dysfunction, modified Model for End-Stage Liver Disease, risk factors

ABSTRACT

INTRODUCTION An increasing number of ambulatory patients are placed on orthotopic heart transplantation (OHT) waiting lists, which results in an extended waiting time and a higher mortality rate.

OBJECTIVES The aim of this study was to identify the factors associated with reduced survival during a 1-year follow-up in patients with end-stage heart failure listed for an OHT.

PATIENTS AND METHODS We retrospectively analyzed the data of 221 adult patients, who were accepted for OHT in our institution over a 2-year period between 2013 and 2014.

RESULTS The mean (SD) age of the patients was 54.7 (9.6) years, and 90.1% of them were male. The mortality rate during the follow-up period was 43.3%. The modified Model for End-Stage Liver Disease (modMELD) score (odds ratio [OR], 1.70; P <0.001), as well as the plasma levels of high-sensitivity C-reactive protein (hs-CRP; OR, 1.10; P <0.01), sodium (OR, 0.74; P <0.001), and uric acid (UA; OR, 1.003; P <0.05) were independent factors affecting death. The receiver-operating characteristic (ROC) analysis indicated that a modMELD cut-off of 10 (area under the ROC curve [AUC], 0.868; P <0.001), hs-CRP cut-off of 5.6 mg/l (AUC, 0.674; P <0.001), plasma sodium level cut-off of 135 mmol/l (AUC, 0.778; P <0.001), and a plasma UA cut-off of 488 µmol/l (AUC, 0.634; P <0.001) were the most accurate factors affecting death.

CONCLUSIONS In conclusion, although limited to a single center, our study demonstrated that an elevated modMELD score, incorporating a combination of renal and hepatic laboratory parameters, as well as plasma sodium, UA, and hs-CRP levels at the time of listing are associated with reduced survival in ambulatory patients with end-stage heart failure, accepted for OHT.

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INTRODUCTION Orthotopic heart transplantation (OHT) is an effective treatment for patients with end-stage heart failure (HF).[1] An increasing number of ambulatory patients are placed on OHT waiting lists, while the supply of donor organs remains limited and is increasingly allotted to urgent transplantations. This has resulted in an extended waiting time and a higher mortality rate on the waiting list. Therefore, it places enormous responsibility on transplant teams evaluating HF patients, so that an OHT is offered only when it is expected to substantially improve the chances of survival or the quality of life, as compared with the medical therapy. Peak oxygen consumption (VO_2) derived from cardiopulmonary exercise testing has been used for the selection of heart transplant candidates who are on optimal medical therapy. A peak VO_2 of less than 12 to 14 ml/kg/min has been reported to be an independent predictor of 1-year mortality and

TABLE 1 Baseline characteristics by survival and death

Parameter	Survival n = 125 (57%)	Death n = 96 (43%)	*P* value
Age, y	58 (50–61)	56 (52–60)	0.8
BMI, kg/m^2	28.1 (4.6)	25.9 (4.4)	<0.001
Mean PAP, mmHg	23 (16–32)	28 (22.5–36)	<0.001
Mean RAP, mmHg	5 (3–9)	5 (3–9)	0.9
TPG, mmHg	8 (7–10)	10 (6–14)	0.04
CI, l/min/m^2	2.26 (1.9–2.5)	2.1 (1.8–2.4)	0.02
PVR, Wood units	1.9 (1.5–2.4)	2.4 (1.8–3.4)	<0.001
LVEF, %	20.0 (18.0–25.0)	20.0 (16.5–24.0)	0.4
LA, mm	48.0 (43.0–55.0)	50.0 (45.5–57.0)	0.07
RVEDd, mm	30 (28–34)	33 (30–37.5)	<0.001
Peak VO_2, ml//kg/min	12.8 (10.9–15.4)	10.2 (9–12.2)	<0.001
modMELD score	7.9 (6.4–9.9)	12.8 (10.4–15.3)	<0.001
Creatinine, µmol/l	90.0 (77.0–103.0)	110.0 (83.0–138.5)	<0.001
Bilirubin, µmol/l	14.5 (10.1–22.4)	25.3 (16.0–37.3)	<0.001
AST, U/l	24.0 (20.0–31.0)	25.0 (21.0–30,5)	0.7
ALT, U/l	22.0 (18.0–32.0)	20.0 (14.0–29.0)	0.01
Alkaline phosphatase, U/l	82.0 (63.0–110.0)	84.0 (63.0–125.0)	0.4
GGTP, U/l	72.0 (34.0–146.0)	86.0 (51.5–164.0)	0.1
Cholesterol, mmol/l	3.91 (3.28–4.96)	3.93 (3.25–4.93)	0.8
Triglycerides, mmol/l	1.29 (0.90–1.96)	1.07 (0.79–1.48)	0.006
Sodium, mmol/l	136 (135–138)	133 (131–135)	<0.001
Fibrinogen, mg/dl	367 (308–416)	422.5 (351.5–544.5)	<0.001
UA, µmol/l	443 (359–528)	506.5 (432–609.5)	<0.001
hs-CRP, mg/l	3.0 (1.3–5.8)	6 (2.7–12.4)	<0.001
NT-proBNP, pg/ml	2624 (1180–4770)	4322 (2501.5–8326)	<0.001
Hematocrit, %	0.41 (0.04)	0.40 (0.05)	0.2
Hemoglobin, mmol/l	8.7 (1.0)	8.46 (1.1)	0.09

Values are expressed as mean (SD) or median (25th–75th percentile).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, cardiac index; hs-CRP, high-sensitivity C-reactive protein; modMELD, modified Model of End-Stage Liver Disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VO_2, oxygen consumption; PAP, pulmonary artery pressure, PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVEDd, right ventricular end-diastolic diameter (M-mode); TPG, transpulmonary pressure gradient; UA, uric acid

is widely used as a cut-off for heart transplant listing. However, peak VO_2 may be influenced by multiple factors such as age, sex, motivation, anemia, lung function, body weight, skeletal muscle strength, and peripheral circulation.[2]

There are 2 other risk stratification tools that are often used to predict the prognosis of patients with end-stage HF: the Heart Failure Survival Score and the Seattle Heart Failure Score.[3,4] These prediction tools fail to adequately address the impact of other organ dysfunctions. Patients with end-stage HF can develop varying degrees of hepatic dysfunction due to congestive hepatopathy and reduced hepatic blood flow. Renal dysfunction occurs in these patients as a consequence of reduced cardiac output and decreased renal perfusion, accompanied by sodium and water retention. The use of diuretics and angiotensin-converting enzyme inhibitors can also contribute to worsening renal failure.

The Model for End-Stage Liver Disease (MELD) scoring system is used to evaluate both cardiorenal and cardiohepatic interactions simultaneously. A number of studies have investigated the utility of the MELD score and its modifications as a predictor of outcome in patients with HF.[5-8] The prognostic value of the standard MELD score calculated using baseline plasma creatinine and bilirubin levels as well as the international normalized ratio (INR) may be limited in patients receiving warfarin.

In the present study, we used a modified MELD (modMELD) score, which is identical to the standard MELD score, except for the substitution of the INR with albumin, a protein produced by the liver.[8] The modMELD score eliminates the confounding effect of anticoagulation in the analyzed group of patients. The aim of this study was to determine the association between the individual modMELD score and 1-year survival in ambulatory patients with end-stage HF listed for OHT. Moreover, we aimed to identify additional risk factors of death during the 1-year follow-up in this group of patients.

PATIENTS AND METHODS

The study was a retrospective review of the clinical records of 328 adult patients, who were put on the OHT waiting list in our institution between January 1, 2013, and December 31, 2014.

The study included ambulatory patients who died after inclusion on the transplant waiting list or survived 1 year on the waiting list. All included patients were treated in accordance with the guidelines of the European Society of Cardiology at the time of inclusion on the waiting list.[9] They were on optimal medical therapy as well as defibrillation therapy with or without resynchronization therapy. Only initial listing episodes were included. Repeated episodes of listing for any reason were excluded from the analysis.

Patients who underwent OHT (n = 58) during the follow-up and patients awaiting heart transplantation with the "urgent status" because of inotropic support (n = 16) or mechanical circulatory support at the time of listing were excluded from the study, resulting in a study sample of 221 participants.

As an indicator of multiorgan dysfunction, we calculated the modMELD score. In place of the INR, a conditional value was used calculated as the difference between the plasma albumin and normal albumin (4.1 g/dl) level. Therefore, if the plasma albumin level was higher than 4.1 g/dl, then the modMELD score was calculated as follows: 1.12 × (ln 1) + 0.378 × (ln total bilirubin, in mg/dl) + 0.957 × (ln creatinine) + 0.643. If the plasma albumin level was less than 4.1 g/dl, then the modMELD score was calculated as 1.12 × (ln [1 + 4.1 – albumin)]) + 0.378 × (ln total bilirubin) + 0.957 × (ln creatinine) + 0.643.

A lower limit was 1.0 for all variables and the upper limit for creatinine was capped at 4.0 mg/dl. There was no upper limit for bilirubin and albumin.

TABLE 2 Baseline medical therapy and electrotherapy by survival and death

Parameter	Survival n = 125 (57%)	Death n = 96 (43%)	*P* value
β-blockers	109 (87.2)	90 (93.6)	0.11
ACEIs	117 (93.6)	95 (99)	0.05
ARBs	8 (6.4)	1 (1.04)	0.05
Aldosterone antagonists	117 (93.6)	93 (96.9)	0.27
Digoxin	44 (35.2)	41 (42.5)	0.26
Diuretics	119 (95.2)	91 (94.8)	0.89
Statins	82 (65.6)	38 (39.6)	0.51
Warfarin/acenocoumarol	55 (44)	38 (39.6)	0.50
Aspirin	55 (44)	51 (53.1)	0.18
ICD	84 (67.2)	53 (55.2)	0.07
CRT-D	38 (30.4)	37 (38.5)	0.21

Data are presented as number (percentage) of patients.

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-II receptor blockers; CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter–defibrillator

TABLE 3 Prognostic factors for death in a multivariate stepwise logistic regression analysis

Factor	OR	95% CI	*P* value
modMELD	1.70	1.45–1.99	<0.001
hs-CRP, mg/l	1.10	1.03–1.16	<0.01
Sodium, mmol/l	0.74	0.65–0.84	<0.001
Uric acid, μmol/l	1.03	1.00–1.06	<0.05

Goodness of fit: C-statistic, 0.91; Deviance, $P = 0.99$; Pearson χ^2, $P = 0.89$; Hosmer–Lemeshow, $P = 0.98$

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

As with the standard MELD score, these raw scores were multiplied by 10 and rounded to the nearest integer.[8]

Laboratory data for the calculation of the modMELD score, as well as other data, were obtained at the time of inclusion on the transplant waiting list. Liver function parameters and plasma uric acid (UA), sodium, and C-reactive protein (CRP) levels were determined using the COBAS Integra 800 analyzer (Roche Instrument Center AG, Rotkreuz, Switzerland), in accordance with the manufacturer's instructions. A highly sensitive latex-based immunoassay was used to detect the plasma CRP concentration. High-sensitivity CRP (hs-CRP) concentrations were determined with a standard detection limit of 0.0175 mg/dl. The follow-up survey by a chart review and telephone contact was performed in all patients at the end of the 1-year follow-up.

Statistical analysis The statistical analysis was performed using the SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina, United States). Continuous variables were expressed as the mean (SD) if normally distributed, or as the median (25th–75th percentile) if skewed; categorical variables were expressed as percentages.

Continuous variables were compared using an independent-sample *t* test, and categorical variables were compared using the χ^2 test. A univariate logistic regression analysis was used to select the potential independent predictive factors of death for inclusion in the multivariate analysis. The examined covariables included laboratory parameters (modMELD score and plasma sodium, UA, fibrinogen, hs-CRP, and N-terminal pro-B-type natriuretic peptide [NT-proBNP] concentrations), right ventricular end-diastolic dimension, body mass index, transpulmonary gradient, and cardiac index. Univariate predictors of death with a *P* value of less than 0.2 were entered into a multivariate logistic regression model with stepwise backward elimination. The correlation between explanatory variables was checked, and multicollinearity was evaluated by means of tolerance and variance inflation factor. The C-statistic, Deviance, and Pearson goodness-of-fit statistics, as well as Hosmer–Lemeshow test for the final model were calculated. Differences were considered statistically significant at a *P* value of less than 0.05. The results were presented as odds ratios (ORs) with 95% CIs. Receiver operator characteristic (ROC) curves were plotted and the Youden index was used to determine the cut-off for parameters that were significant in the multivariate analysis. The results were presented as an area under the ROC curves (AUC), sensitivity, and specificity with 95% CIs and significance levels.

RESULTS Our analysis encompassed 221 ambulatory patients with HF in New York Heart Association (NYHA) classes III (20.8%) and IV (79.2%), and with an Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) score of 4–6, who were accepted on the waiting list between January 1, 2013, and December 31, 2014.

Baseline demographic, clinical, and laboratory characteristics by survival and death are summarized in TABLE 1, while baseline medical therapy and electrotherapy by survival and death—in TABLE 2. During 1-year follow-up, 96 patients (43%) died. The multivariate stepwise logistic regression analysis confirmed that the modMELD score and plasma hs-CRP, sodium, and UA concentrations were significant independent factors affecting death (TABLE 3). The AUC indicated a good discriminatory power of the modMELD score as well as plasma hs-CRP, sodium, and UA concentrations in the prediction of death (TABLE 4, FIGURES 1–4).

DISCUSSION Based on a single-center study, we found that the elevation in the modMELD score—an objective numerical score obtained by inserting the values of plasma total bilirubin, albumin, and creatinine into a logarithmic formula—could reliably identify patients with end-stage HF at a higher risk for reduced survival during the 1-year follow-up. The main advantage of this

TABLE 4 Receiver operating characteristic curves analysis

Parameter	*P* value	AUC	95% CI	Cut-off	Sensitivity	95% CI	Specificity	95% CI
modMELD	<0.001	0.868	0.821–0.915	10	0.82	0.73–0.89	0.77	0.68–0.84
hs-CRP, mg/l	<0.001	0.674	0.603–0.746	5.6	0.56	0.46–0.66	0.73	0.64–0.80
Sodium, mmol/l	<0.001	0.778	0.717–0.839	135	0.84	0.75–0.91	0.64	0.55–0.72
UA, µmol/l	<0.001	0.634	0.561–0.708	488	0.59	0.49–0.69	0.66	0.57–0.74

Abbreviations: AUC, area under the receiver characteristic operating curves; others, see **TABLE 1**

scoring system is its low cost and the common availability of the analyzed parameters.

It is a well-known fact that end-stage HF adversely affects other organs, especially the kidneys and the liver. Hypervolemia and the transmission of venous congestion to the renal veins impair the glomerular filtration rate by reducing the glomerular net filtration pressure.[10] Hepatopathy secondary to chronic HF may result in hypoalbuminemia and cholestatic changes, with an often increased plasma bilirubin level.[11,12] The above parameters are elements of the modMELD score system. Hypoalbuminemia is associated with a significantly increased 1-year mortality and increased risk of an urgent OHT in patients with symptoms of NYHA classes III and IV.[11]

Single-center studies have described higher rates of death and hospitalization due to HF exacerbation in patients with an increased bilirubin level.[12] We identified only 2 publications discussing the prognostic value of the modMELD score in the group of patients with advanced HF. In a retrospective study, Kato et al[13] assessed the data of 151 ambulatory patients on optimal medical therapy and defibrillation therapy with or without resynchronization therapy. The population analyzed in this study differed from ours, because it included patients who underwent heart transplant evaluation. In addition, the modMELD cut-off value was higher than in our study and was part of a risk stratification model, which had been created in this analysis and consisted of peak VO_2, modMELD, right ventricular stroke work index, and pulmonary capillary wedge pressure. Based on their study, the authors demonstrated that this model could discriminate between patients with a high risk of death at 1 year, ventricular assist device implantation, or OHT. Interpretation of these results should allow for the fact that the United States differ from Poland with respect to the care of ambulatory patients with end-stage HF.

In a single-center retrospective study, Chokshi et al[8] found that the modMELD score of more than 20 predicts a significantly higher mortality rate after OHT compared with the modMELD score below this value. The results of our study, together with the analysis by Chokshi et al,[8] suggest that patients on the transplant waiting list with a modMELD score fluctuating between 10 and 20 are at an increased risk of death during the subsequent 12 months, and they should undergo an OHT as soon as possible. However, in the group of patients with a higher modMELD score (>20), it is necessary to conduct a careful selection, because these patients show a high risk of death while waiting for and after the heart transplant.

Our study showed that decreased plasma sodium concentrations were an independent risk factor for death in ambulatory patients awaiting an OHT. In our previous study, we found that a plasma sodium concentration measured in patients with end-stage HF directly before the OHT may be used to estimate the postoperative risk in heart transplant recipients during 1-year follow-up.[14] Importantly, hyponatremia is one of the most powerful predictors of mortality in different populations of patients with HF.[14-16] Moreover, it was shown to be an independent variable in numerous prognostic models for outpatients with HF.[4,17-19]

An increased plasma UA concentration was another independent factor that increased the risk of death in our patients. In patients with advanced HF, elevated UA levels are associated with high morbidity and mortality rates.[16,20] Whether UA is only a marker of poor prognosis or is an active participant in the pathogenesis of HF is currently unknown. The mechanism of hyperuricemia is complex and consists in an increased production due to the upregulation of xanthine oxidase and a decreased excretion due to renal insufficiency, which can be a consequence of cardiorenal syndrome and renal congestion.[21] Recently, it was reported that the association between UA levels and poor outcome in patients with HF was significant only when hyperuricemia was a marker of increased xanthine oxidase activity and not a consequence of decreased renal excretion in chronic kidney disease.[22] The sources of UA are the liver and endothelium. Therefore, UA produced in hypoxic states originates from endothelial cells, and hyperuricemia in HF patients may reflect the metabolic effect of hypoxia on the microvasculature. Impaired oxidative metabolism due to enhanced reactive oxygen species release is the reason for the development of myocardial fibrosis, hypertrophy, left ventricular remodeling, and contractility impairment responsible for decreased cardiac function. Moreover, UA has antioxidant properties and could protect against oxidative stress and oxidative injury.[22]

In this study, we found that an elevated plasma hs-CRP concentration is another independent predictor of death. This acute-phase reactant

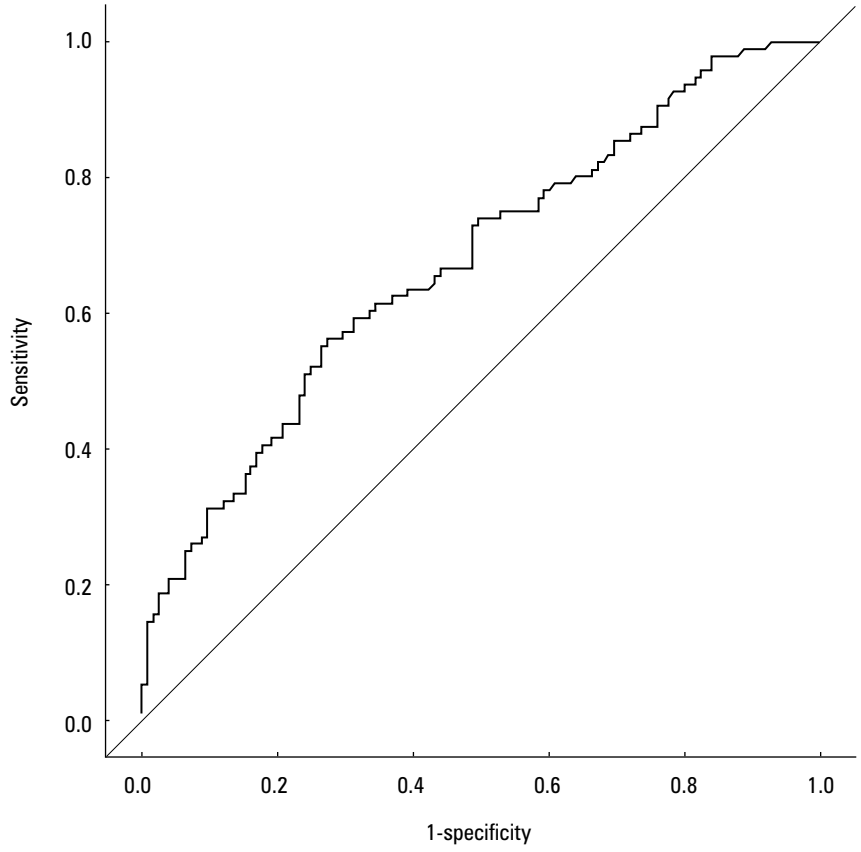

FIGURE 1 Receiver operating characteristic curve for high-sensitivity C-reactive protein

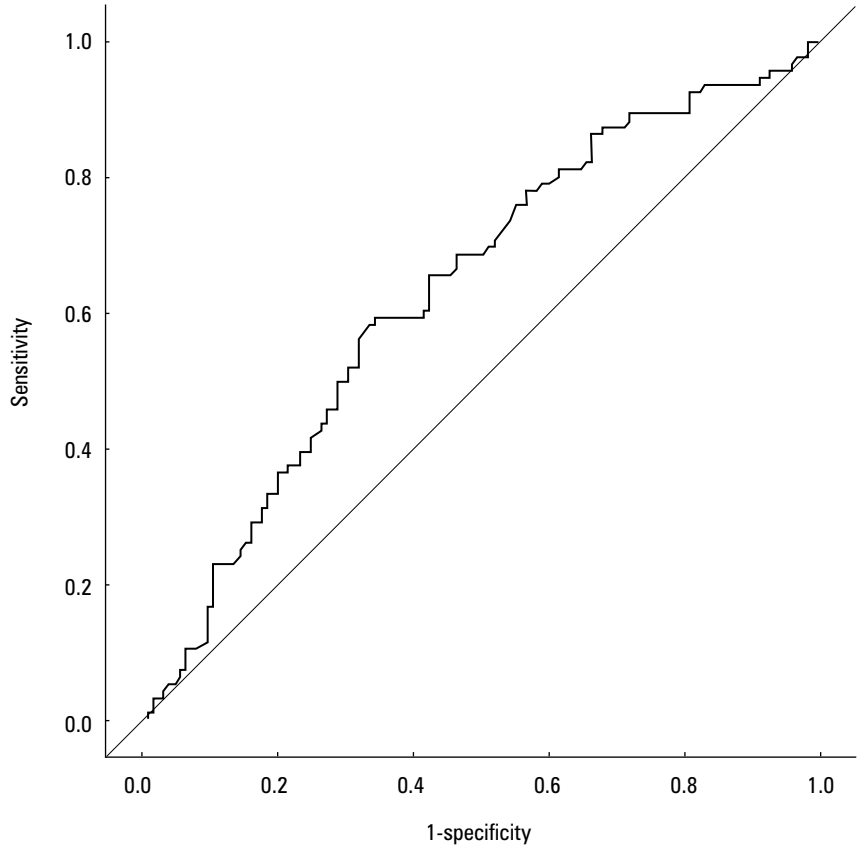

FIGURE 2 Receiver operating characteristic curve for uric acid

protein is a nonspecific biochemical marker for inflammation, which is a key process in the development and progression of chronic HF. Elevated levels of hs-CRP have been observed in patients with HF, and the activation of the immune response may be involved in HF through modification in the sympathetic and renin–angiotensin–aldosterone systems. Moreover, hs-CRP is directly involved in HF because it can cause cell apoptosis, ventricular dysfunction, and impaired function

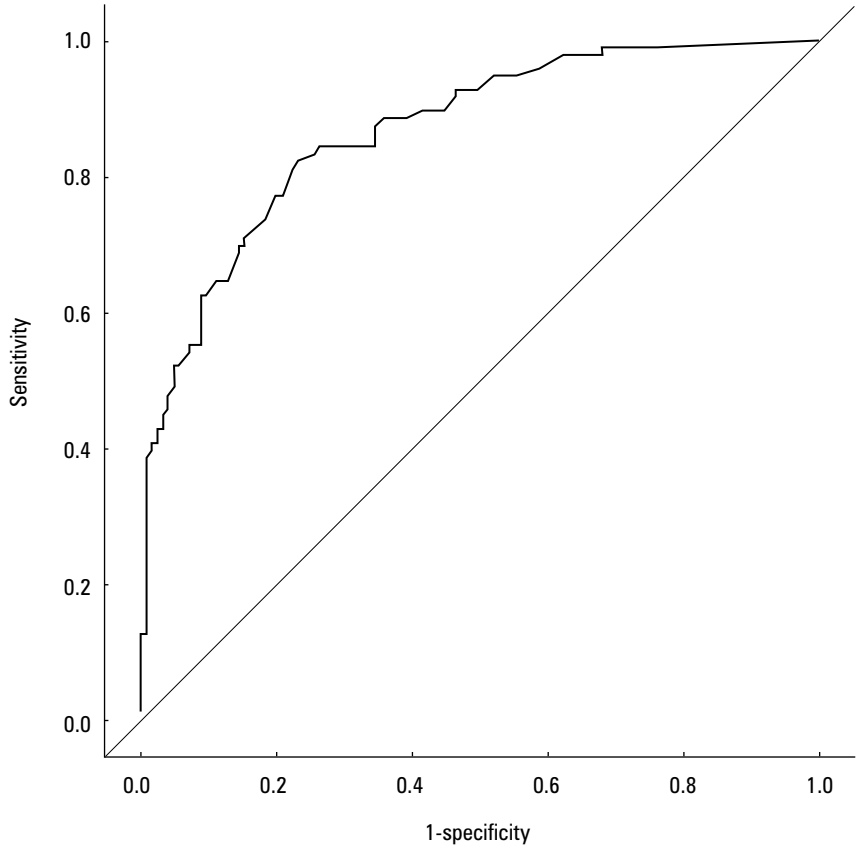

FIGURE 3 Receiver operating characteristic curve for the modified Model of End-Stage Liver Disease score

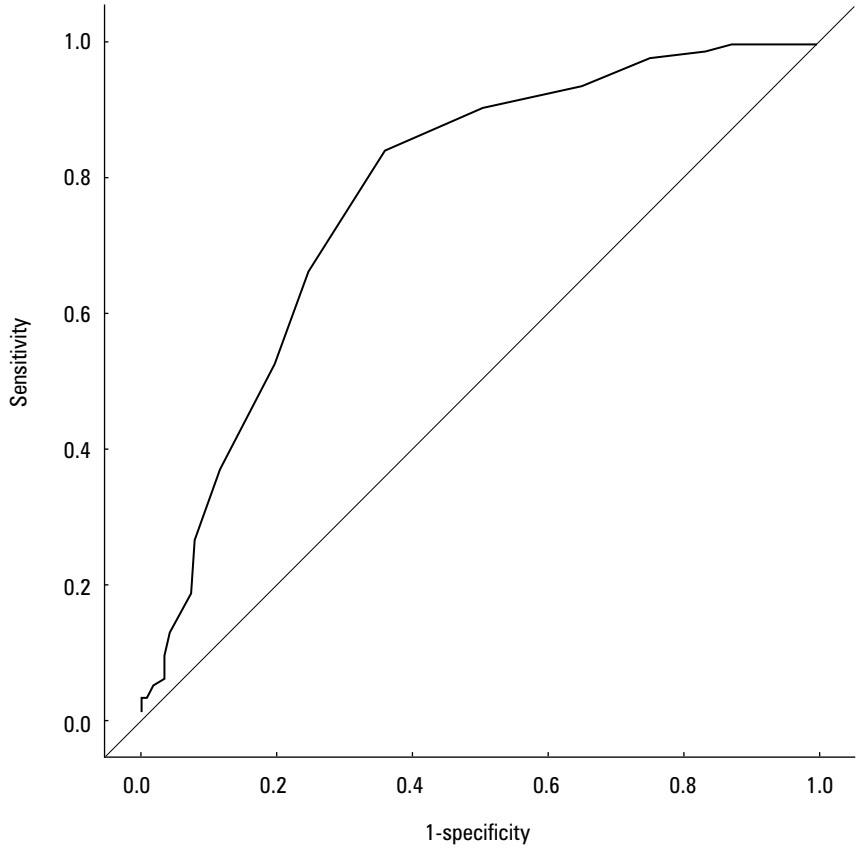

FIGURE 4 Receiver operating characteristic curve for serum sodium level

of organs other than the heart.[23] The prognostic role of hs-CRP in the current study is in agreement with our previous analysis conducted in patients with HF evaluated for a heart transplant.[24] In our previous study, the follow-up was longer and lasted 4 years, while the plasma hs-CRP cut-off value was lower than in the present study. We found that the plasma hs-CRP level was an independent factor for death during the follow-up. Li et al[25] analyzed patients in NYHA classes

III and IV with left ventricular dysfunction and demonstrated that mortality rates were higher in patients with hs-CRP levels exceeding 3.90 mg/l compared with patients with hs-CRP levels below this value.

Study limitations The present study has a number of limitations, which mostly arose from its single-center and retrospective design and the limited sample size. Owing to a small number of enrolled patients, the number of variables included in the univariate analysis had to be limited. Moreover, our patients underwent symptom-limited cardiopulmonary exercise testing, with the goal of achieving respiratory gas-exchange ratio exceeding 1. Some patients could not reach this value, but we used their data as their best effort.

It is necessary to comment on the lack of an independent prognostic value of the well-established predictor of outcomes in patients with HF, namely, NT-proBNP, in our study group. We found a strong positive correlation between the NT-proBNP level and modMELD score. This correlation made it impossible to include both those parameters in the multivariate logistic regression model.

Although we collected comprehensive information on candidates at the time of listing, as well as information regarding the mortality rate, limited data were gathered when the patient was removed from the waiting list. Specifically, information regarding the proportions of patients removed from the waiting list because of improvement, deterioration, or withdrawal of consent were not analyzed. We were able to analyze only survival data after removal from the waiting list. Because no clinical data on such patients were available, we were unable to comment on the follow-up therapy and morbidities after removal from the waiting list. Moreover, we were not able to analyze clinical data of patients whose status had changed to the "urgent status".

Conclusions Although limited to a single center, our study demonstrated that an elevated modMELD score, incorporating a combination of renal and hepatic laboratory parameters, as well as plasma sodium, UA, and hs-CRP concentrations are associated with reduced survival in ambulatory patients with end-stage HF accepted for OHT.

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

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