ORIGINAL ARTICLE

Prognostic utility of N-terminal pro-B-type natriuretic peptide and the modified Model for End-Stage Liver Disease in patients with end-stage heart failure

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KEY WORDS

end-stage heart failure, modified Model for End-Stage Liver Disease, N-terminal pro-B-type natriuretic peptide, prognosis

ABSTRACT

INTRODUCTION The N-terminal pro-B-type natriuretic peptide (NT-proBNP) is secreted by cardiomyocytes in response to increased wall stress resulting from pressure and volume overload. The modified Model for End-Stage Liver Disease (modMELD) score reflects the systemic effect of heart failure (HF), which includes end-organ congestion and subsequent hepatic and renal dysfunction.

OBJECTIVES The aim of this study was to assess the prognostic accuracy of NT-proBNP and the modMELD score, as well as to compare their usefulness in the risk stratification of patients with end-stage HF awaiting orthotopic heart transplantation (OHT).

PATIENTS AND METHODS We retrospectively analyzed the data of 641 consecutive adult patients awaiting OHT between 2012 and 2016. Exclusion criteria included "urgent status," OHT, and removal from the waiting list. Clinical and laboratory data were obtained on inclusion on the waiting list. The primary endpoint was all-cause mortality during a 1-year follow-up.

RESULTS In the overall population of 370 patients, the median age was 54.0 (46.0–60.0) years, and 87.6% of patients were male. During the follow-up, the mortality rate was 27.6%. The areas under the curve (AUCs) were 0.619 (95% CI, 0.557–0.681) for NT-proBNP and 0.870 (95% CI, 0.833–0.906) for the modMELD score. The difference between the AUCs for modMELD and NT-proBNP was 0.251 (95% CI, 0.179–0.322; $P < 0.0001$).

CONCLUSIONS The usefulness of NT-proBNP in evaluating the prognosis of patients with end-stage HF awaiting OHT is limited. The modMELD score is a better prognostic marker of waiting list mortality than the serum NT-proBNP concentration.

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Received: January 29, 2018.
Revision accepted: February 21, 2018.
Published online: February 21, 2018.
Conflict of interest: none declared.
Pol Arch Intern Med. 2018; 128 (4): 235-243
doi:10.20452/pamw.4210

INTRODUCTION The N-terminal pro-B-type natriuretic peptide (NT-proBNP) is released along with other natriuretic peptides by cardiac myocytes in response to increased wall stress resulting from myocardial dysfunction. This prohormone is processed into a biologically active natriuretic peptide, which can counteract the stress by inducing diuresis, natriuresis, and vasodilation.[1] The measurement of NT-proBNP is commonly used in clinical practice to evaluate left ventricular systolic dysfunction, diagnose heart failure (HF), and monitor the effectiveness of treatment in patients with HF.[2-4] Natriuretic peptides can also provide important prognostic information in patients with different stages of HF.[2,5] It is commonly known that a rise in the NT-proBNP level is linked with an increased risk of death or HF hospitalization, while its fall is associated with

a trend towards risk reduction.[2,3] It should be noted, however, that the prognostic value of NT-proBNP may change as a result of medical progress, as manifested by the updated management standards for patients with HF.[2,3]

Higher levels of natriuretic peptides have been shown to be associated with renal impairment, diabetes mellitus, cardiac arrhythmias, pulmonary hypertension, anemia, and hyperthyroidism.[1,4-8] Therefore, in the presence of comorbidities associated with HF, the prognostic value of NT-proBNP may be limited.[1] A number of studies have reported the utility of NT-proBNP in the diagnosis, treatment, and prognosis in patients with different stages of HF; however, we found no studies about the prognostic accuracy of NT-proBNP in patients with end-stage HF awaiting orthotopic heart transplantation (OHT).[7,9-12] It can be presumed that, in patients with end-stage HF, fluid-regulating hormones, such as NT-proBNP, may be of limited prognostic value because kidney function becomes the most important.[5] This raises the question whether NT-proBNP remains a sensitive biomarker for prognosis in patients with end-stage HF.

The modified Model for End-Stage Liver Disease (modMELD) is a scoring system that reflects the systemic effects of HF, which include end-organ congestion and subsequent hepatic and renal dysfunction. It is composed of 3 laboratory measures, which are routinely collected and easy to use. Two of them are noncardiac biomarkers which reflect the severity of the effect of hepatic dysfunction on metabolism (total bilirubin) and synthesis (albumin). The third component of the modMELD score system is the creatinine level.[11] A few studies have investigated the utility of the modMELD score as an indicator of multiorgan dysfunction (renal, cardiac, hepatic), which is the primary manifestation of end-stage HF, and as a predictor of outcomes in this population of patients.[11-14]

The aim of this study was to assess the prognostic accuracy of the serum NT-proBNP concentration and the modMELD score in ambulatory patients with advanced HF awaiting OHT during a 1-year follow-up. Furthermore, we compared the prognostic values of the NT-proBNP level and the modMELD score.

PATIENTS AND METHODS We retrospectively analyzed the clinical records of consecutive 641 adult patients who were placed on the waiting list for OHT in our institution from January 1, 2012, to September 1, 2016. Data on clinical characteristics, medical treatment, as well as laboratory, echocardiographic, and hemodynamic results were collected by reviewing the electronic records that had been used as the basis for including the patients on the waiting list. Patients awaiting OHT with the "urgent status" (n = 150) and those who underwent OHT (n = 40) during the 1-year follow-up were excluded from the study. Patients removed from the waiting list because of improvement, deterioration, or consent withdrawal during the 1-year follow-up (n = 81) were also excluded. The resulting study sample included 370 participants.

Pulmonary hypertension was defined as an increase in mean pulmonary arterial pressure of 25 mm Hg or higher at rest, as measured by right heart catheterization.[15]

Renal insufficiency was defined as a glomerular filtration rate of less than 60 ml/min/1.73 m^2 of body surface area, as calculated with the use of the simplified Modification of Diet in Renal Disease (MDRD) formula.[16]

Based on the obtained data, the modMELD score was calculated according to the following formulas: if the plasma level of albumin was higher than 4.1 g/dl: modMELD = 1.12 × (ln 1) + 0.378 × (ln total bilirubin, in mg/dl) + 0.957 × (ln creatinine, in mg/dl) + 0.643; and if the plasma level of albumin was lower than 4.1 g/dl: modMELD = 1.12 × (ln [1 + 4.1 – albumin, g/dl)]) + 0.378 × (ln total bilirubin, in mg/dl) + 0.957 × (ln creatinine, in mg/dl) + 0.643. As with the standard MELD score, these raw scores were multiplied by 10.[13,14]

The lower limit of all variables used to obtain the modMELD score was set at 1.0 to prevent negative scores, and the upper limit for creatinine was set at 4.0 mg/dl.

Laboratory data were obtained at the time of inclusion on the transplant waiting list. Liver and renal function parameters used to calculate the modMELD score were determined with a COBAS Integra 800 analyzer (Roche Instrument Center AG, Rotkreuz, Switzerland). NT-proBNP levels were measured with a commercially available test (Roche Diagnostics, Mannheim, Germany), using an Elecsys 2010 analyzer with an analytical sensitivity of less than 5 pg/ml (upper limits of normal: 100 pg/ml in men and 150 pg/ml in women, as proposed by the manufacturer).

The follow-up lasted 12 months (from the moment of inclusion on the waiting list). Follow-up data were obtained during control visits and from telephone interviews with patients or their families at the end of the 1-year follow-up. No patient was lost to follow-up. The primary endpoint was all-cause mortality during the follow-up. If there was no indication of death, the patient was recorded to be alive at the end of the follow-up. All the included patients were treated in accordance with the guidelines of the European Society of Cardiology at the time of their inclusion on the waiting list (as shown in TABLE 1).[2]

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 means (SD), if normally distributed, or medians (25th–75th percentile) if skewed. Categorical variables were expressed as percentages of the sample in a given category. Continuous variables were compared between the groups

TABLE 1 Baseline patient characteristics on inclusion on the waiting list

Parameter	All patients (n = 370)	Survivors (n = 268)	Nonsurvivors (n = 102)	*P* value
Age, y, median (IQR)	54.0 (46.0–60.0)	54.0 (45.0–59.0)	54.5 (49.0–60.0)	0.64[a]
Male, n (%)	324 (87.6)	234 (87.3)	90 (88.2)	0.81[b]
Ischemic etiology of HF, n (%)	164 (44.3)	124 (46.3)	40 (39.3)	0.03[b]
NYHA class III, n (%)	263 (71.1)	211 (78.7)	52 (51)	<0.001[b]
NYHA class IV, n (%)	107 (28.9)	57 (21.3)	50 (49)	<0.001[b]
BMI, kg/m^2, mean (SD)	26.0 (4.4)	25.9 (4.4)	26.5 (4.3)	0.17[c]
Hypertension, n (%)	151 (40.8)	116 (43.3)	35 (34.3)	0.23[b]
Type 2 diabetes, n (%)	134 (36.2)	87 (32.5)	47 (46.1)	0.04[b]
Pulmonary hypertension, n (%)	202 (54.6)	136 (50.7)	68 (66.7)	0.006[b]
Persistent atrial fibrillation, n (%)	162 (43.8)	117 (43.7)	45 (44.1)	0.94[b]
VO_{2max}, ml/kg/min, median (IQR)	12.3 (10.3–14.1)	13.1 (11.4–14.6)	12.3 (10.0–14.6)	0.12[a]
FEV_1, %, median (IQR)	74.0 (64.0–85.0)	76.0 (67.0–86.0)	67.0 (55.0–77.0)	<0.001[a]
FVC, %, median (IQR)	78.0 (67.0–89.0)	80.0 (71.0–90.0)	73.0 (62.5–82.0)	0.002[a]
RVEDd, mm, (IQR)	34.0 (30.0–41.0)	33.0 (30.0–40.0)	36.0 (31.0–44.0)	0.02[a]
LVEDd, mm, mean (SD)	73.0 (11.0)	72.9 (10.6)	73.17 (11.92)	0.85[c]
LVEF, %, median (IQR)	18.0 (15.0–20.0)	18.0 (15.0–20.0)	17.5 (15.0–20.0)	0.15[a]
MPAP, mm Hg, median (IQR)	27.0 (18.0–33.0)	25.0 (18.0–32.0)	29.0 (22.5–36.0)	0.003[a]
MPAWP, mm Hg, median (IQR)	17.0 (11.0–23.0)	16.0 (10.0–22.0)	20.0 (13.0–25.0)	0.003[a]

a Mann–Whitney test; **b** χ^2 test; **c** *t* test

Abbreviations: BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; HF, heart failure; IQR, interquartile range; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; MPAP, mean pulmonary artery pressure; MPAWP, mean pulmonary capillary wedge pressure; RVEDd, right ventricular end-diastolic diameter; VO_2, oxygen consumption

by using the *t* test or the Mann–Whitney test, whereas categorical variables were compared by using the χ^2 test.

The prognostic strength of the model was assessed by calculating each area under the curve (AUC) from the receiver operating characteristic (ROC) analysis for the 1-year endpoint events. The ROC curves were quantitatively compared with the DeLong test, and the optimal cutoff value for the model was determined by the Youden criterion. The results were presented as AUC, sensitivity, and specificity with 95% confidence intervals (CIs). Statistical significance between the AUC values was tested with the method of Hanley and McNeil. *P* values lower than 0.05 were considered significant. The Kaplan–Meier method and the log-rank test were used to assess and compare survival among groups.

RESULTS Our analysis comprised 370 ambulatory patients with HF in New York Heart Association (NYHA) classes III (71.1% of patients) and IV (28.9% of patients) and with an Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) scores of 4 to 5 (28.9% of patients) and 6 (71.1% of patients), who were accepted for the OHT waiting list between 2012 and 2016. The baseline demographic and biochemical characteristics of the study population are summarized in TABLES 1 and 2. All patients were receiving optimal medical therapy for HF (TABLE 3) as well as resynchronization or defibrillator therapy (41.1% and 58.9% of patients, respectively). The devices were implanted more often in primary than in secondary prevention of sudden cardiac death (84% vs 16% of patients, respectively). The primary endpoint of all-cause mortality was reached in 102 patients (27.6%). The results obtained from the ROC analysis of the modMELD score and NT-proBNP for 1-year endpoint events are summarized in TABLE 4. The AUC for modMELD and NT-proBNP was 0.870 and 0.619, respectively (FIGURES 1 and 2). The difference between between the AUCs was 0.251 (95% CI, 0.179–0.322; *P* <0.0001). The cutoff for the NT-proBNP level at 5513 pg/ml had a sensitivity of 51% (95% CI, 41%–61%) and a specificity of 71% (95% CI, 65%–77%). The cutoff for the modMELD score at 12.7 had a sensitivity of 88% (95% CI, 80%–94%) and a specificity of 78% (95% CI, 73%–83%). The respective Kaplan–Meier curves for the NT-proBNP level and the modMELD score are shown in FIGURES 3 and 4. Although the log-rank test showed a significant result (FIGURE 3), the AUC for NT-proBNP (0.619; 95% CI, 0.557–0.681), did not indicate the usefulness of this marker for the assessment of prognosis in the analyzed population (FIGURE 2).

DISCUSSION Based on a single-center study, we found that the modMELD score can predict 1-year waiting list mortality in the population of heart transplant candidates unsupported by left ventricular assist devices. To the best of our

TABLE 2 Baseline laboratory parameters at listing

	All patients (n = 370)	Survivors (n = 268)	Nonsurvivors (n = 102)	*P* value
Hemoglobin, mmol/l, median (IQR)	8.7 (8.0–9.5)	8.7 (8.0–9.4)	8.7 (8.0–9.6)	0.94[a]
Creatinine, μmol/l, median (IQR)	103.0 (85.0–130.0)	94.5 (81.5–118.0)	127.5 (103.0–143.0)	<0.001[a]
GFR, ml/min/1.73 m^2, median (IQR)	68.2 (52.7–85.8)	74.9 (58.9–90.1)	52.8 (45.4–68.6)	<0.001[a]
GFR <60 ml/min/1.73 m^2, n (%)	132 (35.7)	73 (27.2)	65 (63.7)	<0.001[b]
Total bilirubin, μmol/l, median (IQR)	18.4 (12.10–27.4)	15.9 (11.1–23.1)	27.2 (20.1–37.5)	<0.001[a]
Albumin, g/l, median (IQR)	41.0 (36.0–45.0)	42.0 (39.0–45.0)	35.5 (33.0–38.0)	<0.001[a]
Uric acid, μmol/l, mean (SD)	469.2 (151.2)	441.0 (141.6)	543.3 (151.2)	<0.001[c]
Sodium, mmol/l, median (IQR)	136.0 (133.0–140.0)	137.5 (134.0–141.0)	132.5 (130.0–136.0)	<0.001[a]
ModMELD score, median (IQR)	10.7 (7.5–15.1)	8.61 (6.86–11.99)	15.81 (13.90–18.18)	<0.001[a]
AST, U/l, median (IQR)	25.0 (20.0–32.0)	25.0 (20.0–31.0)	27.0 (22.0–35.0)	0.052[a]
ALT, U/l, median (IQR)	23.0 (18.0–34.0)	23.0 (17.5–32.5)	23.5 (19.0–38.0)	0.38[a]
ALP, U/l, median (IQR)	92.0 (69.0–127.0)	89.0 (66.0–127.0)	97.0 (78.0–131.0)	0.14[a]
GGTP, U/l, median (IQR)	102.0 (46.0–184.0)	87.0 (41.0–169.0)	143.0 (63.0–231.0)	0.02[a]
Cholesterol, mmol/l, median (IQR)	4.18 (3.47 – 5.10)	4.11 (3.50–4.96)	4.29 (3.37–5.52)	0.22[a]
Hs-CRP, mg/l, median (IQR)	4.37 (1.85–10.90)	3.86 (1.69–10.58)	5.88 (2.83–13.22)	0.07[a]
HbA_{1c}, %, median (IQR)	6.1 (5.7–6.6)	6.1 (5.7–6.5)	6.4 (5.9–6.8)	0.006[a]
NT-proBNP, pg/ml, median (IQR)	3760 (2100–6839)	3490 (1720–6134)	5556.5 (2781–8503)	<0.001[a]

a Mann–Whitney test; **b** χ^2 test; **c** *t* test

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GFR, glomerular filtration rate; GGTP, γ-glutamyl transpeptidase; HbA_{1c}, glycated hemoglobin A_{1c}; hs-CRP, high-sensitivity C-reactive protein; modMELD, modified Model for End-Stage Liver Disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; others, see **TABLE 1**

TABLE 3 Treatment in the study group

Treatment	All patients (n = 370)	Survivors (n = 268)	Nonsurvivors (n = 102)	*P* value[a]
β-Blockers	347 (93.8)	253 (94.4)	94 (92.2)	0.61
ACEIs/ARBs	343 (92.7)	252 (94.0)	91 (89.2)	0.11
Loop diuretics	370 (100)	268 (100)	102 (100)	
Thiazide diuretics	120 (32.4)	80 (29.9)	40 (39.2)	0.09
MRA	358 (96.8)	263 (98.1)	95 (93.1)	0.02
Digoxin	155 (41.9)	108 (40.3)	47 (46.1)	0.31
Statin	227 (61.4)	177 (66)	50 (49)	0.003
Coumarin derivatives	188 (50.8)	136 (50.7)	52 (51)	0.97
Acetylsalicylic acid	153 (41.1)	113 (42.2)	40 (39.2)	0.61
ICD/CRT-D	370 (100)	268 (100)	102 (100)	

Data are presented as number (percentage) of patients.

a χ^2 test

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist

knowledge, this is also the first study to demonstrate that the modMELD score is better than the serum concentration of NT-proBNP in evaluating the risk of death in this population of patients.

The relatively modest prognostic accuracy of NT-proBNP in the present study may result from the fact that our population included a selected optimally treated group of ambulatory patients with end-stage HF. Optimal neurohormone suppression with background therapy may have limited the prognostic performance of this marker. Another explanation of this finding may be that, in optimally treated patients with end-stage HF, the prognostic value of fluid-regulating hormones such as natriuretic peptides might be limited, because kidney function as the morphologic substrate of fluid regulation becomes the most important.[5,17] Furthermore, kidney dysfunction has been shown to affect the concentration of NT-proBNP, and the diagnostic value of its level in the presence of chronic kidney disease is

TABLE 4 Summary of the receiver operating characteristic curve analysis for 1-year death

	AUC	±95% CI	Cutoff	Sensitivity	±95% CI	Specificity	±95% CI
ModMELD score	0.870	0.833–0.906	>12.7	0.88	0.80–0.94	0.78	0.73–0.83
NT-proBNP	0.619	0.557–0.681	>5513	0.51	0.41–0.61	0.71	0.65–0.77

Abbreviations: AUC, area under the curve; others, see **TABLE 2**

FIGURE 1 Receiver operating characteristic curve for the modMELD score

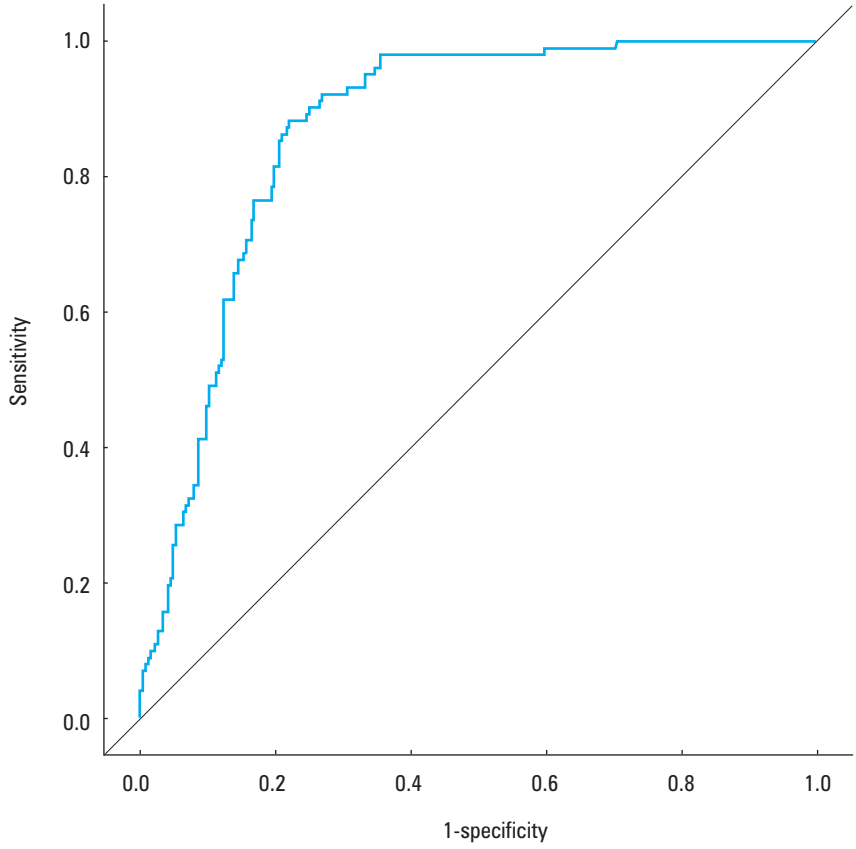
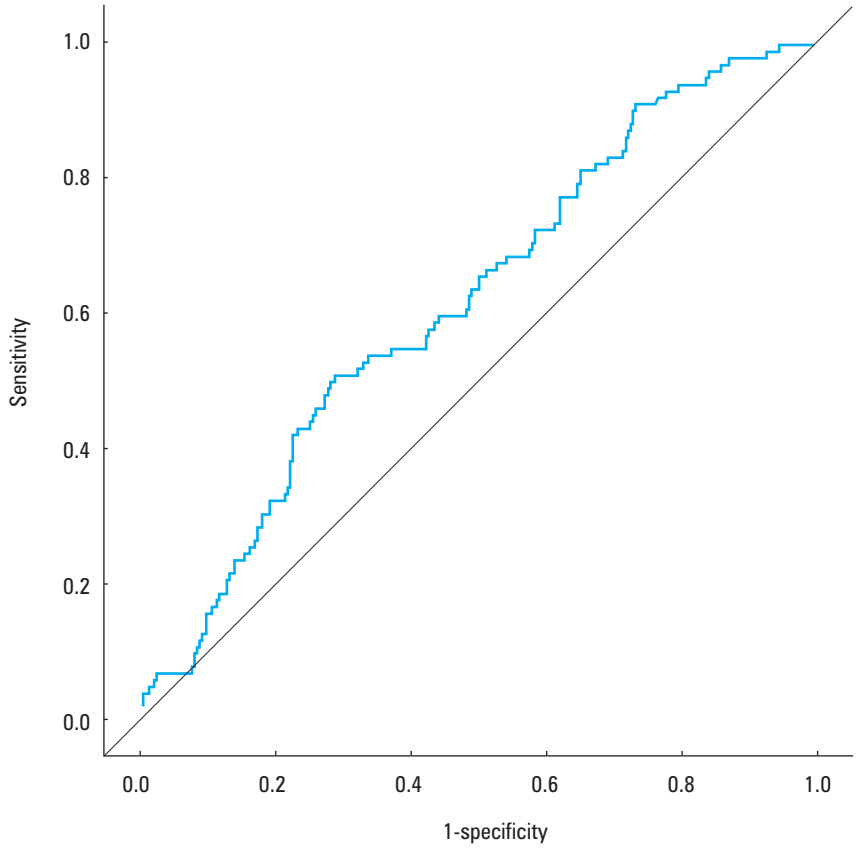


FIGURE 2 Receiver operating characteristic curve for NT-proBNP levels



questionable.[18,19] We observed kidney dysfunction (defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2) in 36% of the patients in our study. The serum NT-proBNP concentration is profoundly affected by renal dysfunction due to its impaired degradation and elimination, particularly in the presence of a more severe left ventricular dysfunction. The strong effect of renal dysfunction on NT-proBNP levels contributes to the decreased sensitivity and specificity

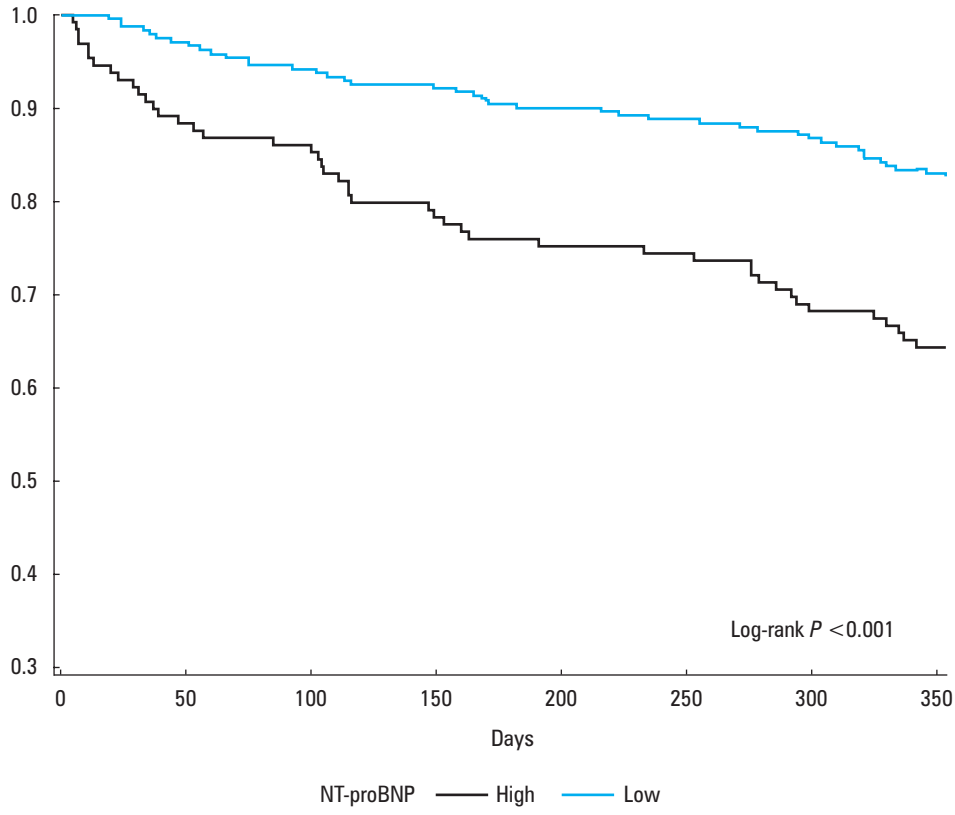


FIGURE 3 Kaplan–Meier survival curve according to NT-proBNP levels

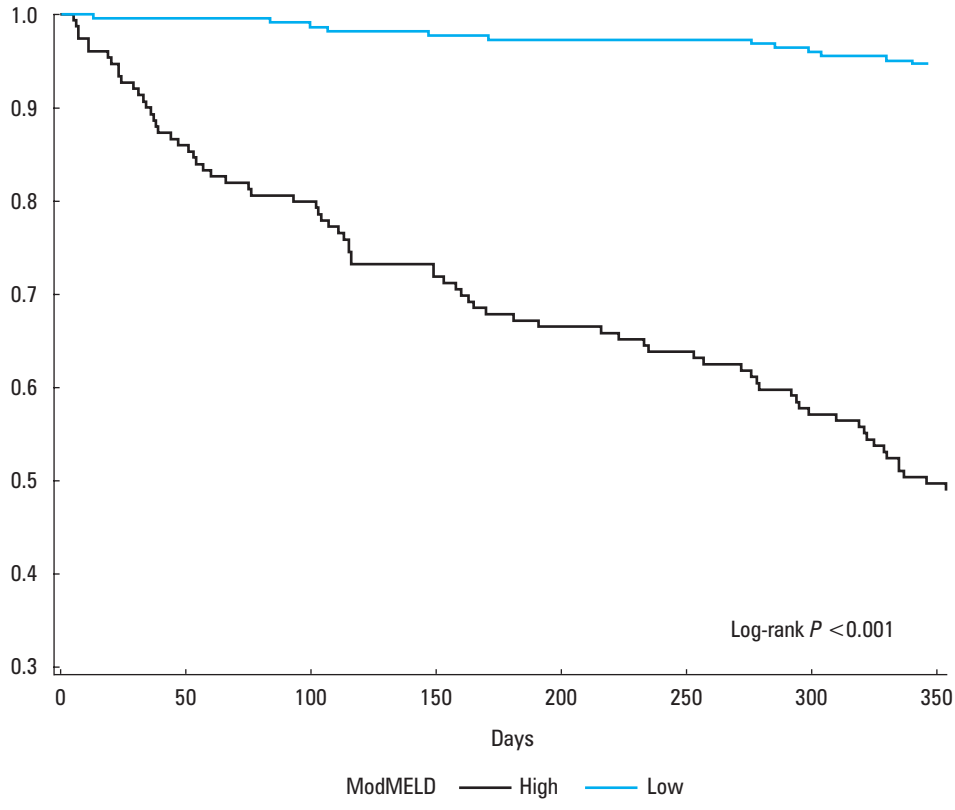


FIGURE 4 Kaplan–Meier survival curve according to the modMELD score

of NT-proBNP in patients with advanced systolic HF. Reduced utility of NT-proBNP in HF is observed in each stage of kidney disease, and reduced renal function is a strong independent clinical determinant of an elevated NT-proBNP level.[20,21] Furthermore, the presence of such comorbidities as diabetes mellitus, arrhythmias, pulmonary hypertension, and anemia may also have affected or modulated the NT-proBNP concentration in our study population.

The above findings suggest that the severity of HF and ventricular dysfunction is not the only determinant of the NT-proBNP level. Thus, the NT-proBNP level reflects the integrality of the risk factors resulting in the current cardiovascular status of the patient and cannot be seen as a pure

surrogate of left ventricular ejection fraction and the clinical severity of HF.

In the available literature, we found no current studies about the prognostic accuracy of NT-proBNP in the population of heart transplant candidates. The only such analysis was conducted in patients from the Polish Prospective National Registry POLCARD HF awaiting OHT between 2003 and 2007 when other guidelines for HF were applicable.[22,23] The registry differed from our analysis in terms of the applied pharmacological treatment and duration of follow-up.[22] Furthermore, the study group analyzed by Zieliński et al[22] included all waiting-list patients (ambulatory and urgent), and the authors used a different endpoint (death or urgent transplantation). In the above study, the ROC analysis revealed an AUC of 0.653 for NT-proBNP, which was clinically insignificant.[24,25]

Several other authors analyzed the utility of NT-proBNP in evaluating prognosis in patients with advanced HF.[5,9-11] Their studies, however, differed significantly from our analysis in terms of the advancement of the disease, the applied pharmacological treatment, or the duration of follow-up.

In contrast to our analysis, Adlbrecht et al[9] showed that NT-proBNP can be a potential marker for risk stratification in patients with advanced HF during long-term follow-up. It should be noted that the duration of follow-up in their study was 53.4 (20.6) months, which was significantly longer than in our study. In a subanalysis of patients with advanced HF, Adlbrecht et al[9] reported good discriminatory power of serum NT-proBNP concentrations in predicting all-cause mortality during a long-term follow-up. The ROC analysis revealed an AUC of 0.810 for log-transformed NT-proBNP. However, it should be emphasized that they classified patients into the advanced HF group based only on the subjective NYHA classification, while we applied the criteria that are used to select patients for OHT, that is, NYHA functional class, INTERMACS classification, and the peak oxygen consumption value of 2 ml/kg/min or higher in cardiopulmonary exercise test.[26] Furthermore, patients in the study by Adlbrecht et al[9] did not receive optimal therapy. Although there was an optimal percentage of patients who received β-blockers (92%) and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) (96%), the percentage of patients with implantable cardioverter-defibrillators (21%) or cardiac resynchronization therapy defibrillators (26%) in their group was relatively small.

A study by Gardner et al[11] showed that a single measurement of NT-proBNP can help identify patients at high risk of death in a population with advanced HF. The authors analyzed a cohort with advanced HF referred for consideration of OHT. Furthermore, relatively few patients in their study were prescribed β-blockers (69%) and mineralocorticoid receptor antagonists (59.8%), which could have affected the results. It is well known that the predictive value of the variable used for risk stratification is markedly influenced by optimal pharmacological treatment, especially β-blockers, as well as the administration of mineralocorticoid receptor antagonists and ACEIs.

In their analysis of patients representing the entire spectrum of HF severity, Neuhold et al[5] reported modest prognostic accuracy of NT-proBNP (AUC, 0.71) with respect to 2-year all-cause mortality. In their study, copeptin was superior to serum brain natriuretic peptide and NT-proBNP concentrations in predicting mortality during a 2-year follow-up. In an analysis of patients with chronic symptomatic HF from the GISSI-HF trial, Masson et al[10] found good prognostic accuracy of NT-proBNP (AUC, 0.73; specificity, 71%; sensitivity, 65%) in predicting mortality during a long-term follow-up (median, 3.9 years).[10] The percentages of patients with diabetes and kidney failure in their study were comparable to ours; however, most of their patients were in functional NYHA classes II and III, and the follow-up was longer.

Several different scales for the prediction of outcome in patients with end-stage HF have been developed over the years, but we believe that the MELD scale and its modifications may become particularly useful in clinical practice for several reasons.[27,28] Firstly, the scores are calculated on the basis of simple, low-cost, and commonly used laboratory parameters. Secondly, the scores reflect multiorgan dysfunction, especially kidney and liver damage, commonly observed in end-stage HF. Numerous clinical studies have considered kidney and liver dysfunction as one of the factors with the highest prognostic value in HF.[19,21,27] Therefore, markers or scales reflecting the varying degrees of kidney and liver dysfunction may provide valuable information about the prognosis in end-stage HF. The original MELD score provides objective prognostic information based on creatinine (an indicator of renal function), bilirubin (reflecting metabolic liver function), and international normalized ratio (reflecting the secretory function of the liver).[29] In the present study, we used the modMELD score, which excludes the effects of anticoagulation by substituting albumin for international normalized ratio. The serum level of albumin reflects the synthesizing function of the liver, and hypoalbuminemia is a remarkably strong prognostic indicator of poor prognosis in HF.[30,31]

Kato et al[32] demonstrated that a novel risk-stratification model containing modMELD can sufficiently predict 1-year prognosis of ambulatory patients with advanced HF. The population analyzed in their study differed from ours, because it included patients referred for consideration of OHT. In addition, Kato et al[32] used modMELD as part of a risk stratification model, while we analyzed only the modMELD score. Also, the percentage of patients using ACEIs or ARBs (71.3%) and mineralocorticoid receptor antagonists (61.8%)

in their group was relatively low. The AUC for modMELD in our analysis was higher than in the above study (AUC, 0.639). Our previous study also showed that an elevated modMELD score is a significant risk factor for 1-year death in ambulatory patients with end-stage HF accepted for OHT. The AUC for modMELD in our previous study indicated good discriminatory power in the prediction of death (AUC, 0.868).[14]

The major limitation of this study is its retrospective design; thus, the data on changes in variables over time are not available for analysis. Moreover, it was performed at a single center, and our findings may not be generalizable to all centers worldwide. Our study was not sufficiently powered to comment on the mode of death, and we limited our analysis to all-cause mortality. Furthermore, our patients underwent symptom-limited cardiopulmonary exercise testing, with the goal of achieving a respiratory exchange ratio higher than 1.05. Some patients could not reach this value, but we used their data as their best effort.

In conclusion, we showed that the utility of a single NT-proBNP measurement in evaluating the prognosis of patients with end-stage HF awaiting heart transplantation is limited. Our study is also the first to demonstrate that the modMELD score is a better prognostic marker of 1-year waiting list mortality than the serum NT-proBNP level.

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

REFERENCES

1 Iqbal N, Wentworth B, Choudhary R, et al. Cardiac biomarkers: new tools for heart failure management. Cardiovasc Diagn Ther. 2012; 2: 147-164.

2 McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012; 33:1787-847.

3 Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008; 29: 2388-2442.

4 Palazzuoli A, Gallotta M, Quatrini I, Nuti R. Natriuretic peptides (BNP and NT-proBNP): measurement and relevance in heart failure. Vasc Health Risk Manag. 2010; 6: 411-418.

5 Neuhold S, Huelsmann M, Strunk G, et al. Comparison of copeptin, B-type natriuretic peptide, and amino-terminal pro-B-type natriuretic peptide in patients with chronic heart failure: prediction of death at different stages of the disease. J Am Coll Cardiol. 2008; 52: 266-272.

6 Tsai SH, Lin YY, Chu SJ, et al. Interpretation and use of natriuretic peptides in non-congestive heart failure settings. Yonsei Med J. 2010; 51: 151-163.

7 Hartmann F, Packer M, Coats AJS, et al. Prognostic Impact of Plasma N-Terminal Pro-Brain Natriuretic Peptide in Severe Chronic Congestive Heart Failure A Substudy of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial. Circulation. 2004; 110: 1780-1786.

8 Szyguła-Jurkiewicz B, Siedlecki Ł, Pyka Ł, et al. Red blood cell distribution width, relative lymphocyte count, and type 2 diabetes mellitus predict all-cause mortality in patients with advanced heart failure. Pol Arch Intern Med. 2018; 128: 115-120.

9 Adlbrecht C, Hülsmann M, Neuhold S, et al. Prognostic utility of the Seattle Heart Failure Score and amino terminal pro B-type natriuretic peptide in varying stages of systolic heart failure. J Heart Lung Transplant. 2013; 32: 533-538.

10 Masson S, Latini R, Carbonieri E, et al. The predictive value of stable precursor fragments of vasoactive peptides in patients with chronic heart failure: data from the GISSI-heart failure (GISSI-HF) trial. Eur J Heart Fail. 2010; 12: 338-347.

11 Gardner RS, Ozalp F, Murday AJ, et al. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. Eur Heart J. 2003; 24: 1735-1743.

12 MacGowan GA, Neely D, Peaston R, et al. Evaluation of NT-proBNP to predict outcomes in advanced heart failure. Int J Clin Pract. 2010; 64: 892-899.

13 Chokshi A, Cheema FH, Schaefle KJ, et al. Hepatic dysfunction and survival after orthotopic heart transplantation: Application of the MELD scoring system for outcome prediction. J Heart Lung Transplant. 2012; 31: 591-600.

14 Szygula-Jurkiewicz B, Szczurek W, Skrzypek M, et al. One-year survival of ambulatory patients with end-stage heart failure: the analysis of prognostic factors. Pol Arch Intern Med. 2017; 127: 254-260.

15 Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Eur Respir J. 2015; 46: 903-975.

16 Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate GFR from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999; 130: 461-470.

17 Hillege HL, Nitsch D, Pfeffer MA, et al. Candesartan in heart failure. Assessment of Reduction in Mortality and Morbidity (CHARM) Investigators. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation. 2006; 113: 671-678.

18 Wiley CL, Switzer SP, Berg RL, et al. Association of B-type natriuretic peptide levels with estimated glomerular filtration rate and congestive heart failure. Clin Med Res. 2010; 8: 7-12.

19 Vanderheyden M, Bartunek J, Filippatos G, et al. Cardiovascular disease in patients with chronic renal impairment: role of natriuretic peptides. Congest Heart Fail. 2008; 14: 38-42.

20 Luchner A, Hengstenberg C, Löwel H, et al. Effect of compensated renal dysfunction on approved heart failure markers: direct comparison of brain natriuretic peptide (BNP) and N-terminal pro-BNP. Hypertension. 2005; 46: 118-123.

21 Ahmed A, Campbell RC. Epidemiology of chronic kidney disease in heart failure. Heart Fail Clin. 2008; 4: 387-399.

22 Zieliński T, Browarek A, Zembala M, et al. Risk stratification of patients with severe heart failure awaiting heart transplantation-prospective national registry POLKARD HF. Transplant Proc. 2009; 41: 3161-3165.

23 Nieminen MS, Böhm M, Cowie MR, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J. 2005; 26: 384-416.

24 Yang S, Berdine G. The receiver operating characteristic (Roc) curve. Southwest Respiratory and Critical Care Chronicles. 2017; 5: 34-36.

25 Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol. 2010; 5: 1315-1316.

26 Mehra MR, Canter CE, Hannan 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.

27 Szyguła-Jurkiewicz B, Zakliczyński M, Andrejczuk M, et al. The Model for End-Stage Liver Disease (MELD) can predict outcomes in ambulatory patients with advanced heart failure who have been referred for cardiac transplantation evaluation. Kardiochir Torakochirurgia Pol. 2014; 11: 178-181.

28 Nessler J, Rostoff P. Prognostic scores in advanced heart failure: where are we now and where are we going? Pol Arch Intern Med. 2017; 127: 235-237.

29 Inohara T, Kohsaka S, Shiraishi Y, et al. Prognostic impact of renal and hepatic dysfunction based on the MELD-XI score in patients with acute heart failure. Int J Cardiol. 2014; 176: 571-573.

30 Ancion A, Allepaerts S, Oury C, et al. Serum albumin level and hospital mortality in acute non-ischemic heart failure. ESC Heart Fail. 2017; 4: 138-145.

31 Horwich TB, Kalantar-Zadeh K, MacLellan RW, Fonarow GC. Albumin levels predict survival in patients with systolic heart failure. Am Heart J. 2008; 155: 883-889.

32 Kato TS, Stevens GR, Jiang J, et al. Risk stratification of ambulatory patients with advanced heart failure undergoing evaluation for heart transplantation. J Heart Lung Transplant. 2013; 32: 333-340.