ORIGINAL ARTICLE

Predictors of 1-year mortality in ambulatory patients with advanced heart failure awaiting heart transplant

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KEY WORDS

biomarkers, heart failure, procalcitonin, prognosis, risk stratification

ABSTRACT

INTRODUCTION Heart failure (HF) is a complex syndrome involving diverse pathways and pathological processes that can manifest themselves in circulation as abnormal levels of various biomarkers.

OBJECTIVE The aim of the study was to assess the factors associated with a worse prognosis in patients with advanced HF awaiting heart transplant during a 1-year follow-up.

PATIENTS AND METHODS We prospectively assessed the data of 203 adult patients with advanced HF, who were hospitalized at our institution between 2016 and 2018. The study end point was all-cause death during a 1-year follow-up.

RESULTS The median age of patients was 57 years (range, 52–60); 87.7% of patients were male. During follow-up, 62 patients (30.5%) died. Serum levels of procalcitonin (hazard ratio [HR], 1.027; 95% CI, 1.020–1.034; P <0.001; per 10-unit increase), high-sensitivity C-reactive protein (hs-CRP; HR, 1.099; 95% CI, 1.016–1.883; P = 0.02; per 1-unit increase), sodium (HR, 1.171; 95% CI, 1.076–1.272; P <0.001; per 1-unit increase), and N-terminal pro–B-type natriuretic peptide (NT-proBNP; HR, 1.068; 95% CI, 1.033–1.105; P <0.001; per 1000-unit increase) were independent risk factors for mortality. Procalcitonin generated the largest area under the curve (0.780; 95% CI, 0.712–0.848).

CONCLUSIONS Our study showed that higher serum hs-CRP, NT-proBNP, and procalcitonin levels and lower serum sodium levels were independent risk factors for death during a 1-year follow-up in patients with advanced HF. Procalcitonin showed the strongest predictive power, sensitivity, and specificity, allowing for an effective identification of 1-year survivors and nonsurvivors awaiting heart transplant.

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INTRODUCTION Despite advances in the prevention and treatment of cardiovascular diseases, heart failure (HF) remains a major challenge in developed countries, and its economic and social burden is still increasing. Therefore, the availability of reliable noninterventional, cost-effective, and easy-to-perform tools for early diagnosis and risk stratification may aid the effective management of HF patients.[1-3] Biomarkers reflecting the various pathophysiological processes underlying HF, such as inflammation, myocardial damage, fibrosis, and remodeling, play a vital role in improving HF management.[1-2] More specifcally, the use of different complementary biomarkers can provide important information on disease progression, response to therapeutic interventions, and prognosis. Therefore, significant efforts have been undertaken in the area of biomarker research. Novel cardiac biomarkers can complement traditional clinical and laboratory tests (such as natriuretic peptides with a well-established role in clinical practice) to better understand the complex disease process of HF and, possibly, to personalize the care of affected patients by improving individual phenotyping.[4-6] Inflammatory indicators are among

WHAT'S NEW?

In this single-center study, higher serum levels of procalcitonin, high-sensitivity C-reactive protein, and N-terminal pro–B-type natriuretic peptide and lower serum sodium levels were independently associated with death during 1-year follow-up in ambulatory patients with advanced heart failure (HF) referred for a heart transplant. Among the independent risk factors, procalcitonin had the strongest predictive power, sensitivity, and specificity, allowing for an effective identification of 1-year survivors and nonsurvivors on the heart transplant waiting list. Our results imply that the measurement of biomarkers associated with HF may provide prognostic information in addition to global risk assessment in patients with HF. This may refine the risk stratification in HF patients by identifying individuals who will benefit from treatment intensification and more advanced treatment options for HF.

the promising biomarkers that are closely related to the pathophysiology of HF. Inflammation was shown to be an important factor in the development and progression of HF, although the mechanisms underlying the inflammatory response in HF are not fully understood.[7,8] Therefore, the aim of this study was to investigate factors associated with a worse prognosis in patients with advanced HF awaiting heart transplant (HT) during a 1-year follow-up, with a particular focus on inflammatory biomarkers.

PATIENTS AND METHODS

Study population and data collection We prospectively assessed 248 consecutive ambulatory patients with end-stage HF, who were hospitalized at our institution and were referred for HT between 2016 and 2018. We included ambulatory patients who either died after the inclusion on the transplant waiting list or survived for 1 year on the waiting list. Patients with infections (n = 5), ischemic bowel disease (n = 4), and those who underwent HT or mechanical circulatory support implantation during a 1-year follow-up (n = 36) were excluded. To eliminate the effect of infection on the levels of inflammatory markers, we measured the white blood cell count. In all patients, it was below the threshold for infection. Moreover, according to the center's protocol, clinical examination and imaging studies were used to exclude lung, ear, nose, and throat, dental, and urogenital infections in all patients.

The collected data included medical history, comorbidities, demographic characteristics, physical examination, biochemical blood tests, echocardiographic and right heart catheterization findings, and current medical therapy. The study end point was defined as all-cause mortality during a 1-year follow-up. Information on death during follow-up was obtained from the national healthcare provider.

The study was approved by the Bioethical Committee of the Medical University of Silesia (no. KNW/0022/KB1/88/15; date of approval, July 7, 2015). It conformed to the principles outlined in the Declaration of Helsinki on the ethical principles for medical research involving human subjects. A written informed consent was obtained from all included patients.

Biochemical measurements Fasting venous samples were obtained at the time of enrollment to the study and were frozen at –80 °C for further analysis. The complete blood count and hematologic parameters were determined using automated blood cell counters (Sysmex XS1000i and XE2100, Sysmex Corporation, Kobe, Japan). Liver and kidney function parameters, as well as serum cholesterol and albumin levels, were measured with a COBAS Integra 800 analyzer (Roche Instrument Center AG, Rotkreuz, Switzerland). A highly sensitive latex-based immunoassay was used to measure serum levels of high-sensitivity C-reactive protein (hs-CRP) with a Cobas Integra 70 analyzer (Roche Diagnostics, Mannheim, Germany). Serum fibrinogen levels were measured using an STA Compact analyzer (Roche Instrument Center AG, Rotkreuz, Switzerland). The serum level of N-terminal pro–B-type natriuretic peptide (NT-proBNP) was assessed with a commercially available kit (Roche Diagnostics) on an Elecsys 2010 analyzer (Roche Instrument Center AG). Human procalcitonin levels were measured by a sandwich enzyme-linked immunosorbent assay (ELISA) with a commercially available kit (Human PCT ELISA, SunRedBio Technology Co, Ltd, Shanghai, China). Procalcitonin levels were expressed as pg/ml, the sensitivity for the procalcitonin assay was 5.125 pg/ml, and the assay range was 6 to 2000 pg/ml. No significant cross-reactivity or interference between procalcitonin and analogs was observed. The ELISA was performed using a BioTek Elx50 reader (BioTek Instruments Inc, Tecan Group, Mannedorf, Switzerland).

Renal insufficiency was defined as a glomerular filtration rate of less than 60 ml/min/1.73 m^2 of the body surface area, as calculated using the simplified Modification of Diet in Renal Disease formula.[9]

To calculate the prognostic scores, the following formulas were used:

1. Heart Failure Survival Score (HFSS): ([0.0216 × resting heart rhythm] + [–0.0255 × mean arterial blood pressure] + [–0.0464 × left ventricular ejection fraction] + [–0.0470 × serum sodium] + [–0.0546 × maximal oxygen uptake] + [0.6083 × presence (1) or absence (0) of interventricular conduction defect (QRS duration ≥0.12 due to any cause)] + [0.6931 × presence (1) or absence (0) of ischemic cardiomyopathy]).[10]

2. Model for End-stage Liver Disease Excluding INR (MELD-XI) = 5.11 × (ln of total bilirubin, in mg/dl) + 11.76 × (ln of creatinine, in mg/dl) + 9.44.[11]

3. Modified Model for End-stage Liver Disease (modMELD) = 1.12 × (ln 1) + 0.378 × (ln total bilirubin, in mg/dl) + 0.957 × (ln creatinine, in mg/dl) + 0.643; if the plasma level of albumin was higher than 4.1 g/dl.

4. modMELD = 1.12 × (ln [1 + 4.1 – albumin, in g/dl)]) + 0.378 × (ln total bilirubin, in mg/dl) + 0.957 × (ln creatinine, in mg/dl) + 0.643, if the plasma level of albumin was lower than 4.1 g/dl.[12]

As with the standard MELD score, these raw modMELD scores were multiplied by 10. The lower limit of all variables in the modMELD and MELD-XI scores was set at 1.0 mg/dl, and the upper limit for creatinine was set at 4 mg/dl.

Statistical analysis Demographic characteristics were presented as frequencies and percentages for categorical data, and the χ^2 test was used for comparisons. Categorical variables were expressed as percentages. Normally distributed continuous variables were reported as mean (SD) and were compared using the *t* test. Continuous data expressed as the median with upper and lower quartiles were compared using the Mann–Whitney test. The univariate Cox proportional analysis was used to identify potential predictors of worse 1-year survival for inclusion in the multivariate analysis. Correlations between variables were assessed by the Spearman rank correlation coefficient. Variables with a *P* value of less than 0.2 in the univariate analysis were investigated by a multivariate Cox regression model with stepwise backward elimination. The results were presented as hazard ratios (HRs) with 95% CIs. The receiver operating characteristic (ROC) curves were created to determine the utility of the factors obtained from the multivariate logistic regression to predict 1-year mortality in patients with advanced HF. The prognostic power of biomarkers was evaluated by the area under the curves from the ROC analysis, sensitivity, specificity, negative predictive value, positive predictive value, negative likelihood ratio, and positive likelihood ratio. The optimal cutoff value for the assessed biomarkers was determined using the Youden criterion. Sensitivity, specificity, negative predictive values, positive predictive values, negative likelihood ratios, and positive likelihood ratio were calculated based on appropriate cutoff points for the assessed biomarkers. The Kaplan–Meier survival curves were created to evaluate the effect of procalcitonin on all-cause mortality. A *P* value of less than 0.05 was considered significant. All statistical analyses were performed using the SAS software, version 9.4 (SAS Institute Inc, Cary, North Carolina, United States).

RESULTS The final study group included 203 patients with end-stage HF awaiting HT. The median age of the study population was 57 years (range, 52–60); 87.7% of patients were male. All patients were classified as New York Heart Association (NYHA) functional class III to IV and as profiles 4 to 6 according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) scale.

All participants were on optimal medical therapy, resynchronization therapy, and / or a defibrillator therapy, if appropriate, in accordance with the guidelines of the European Society of Cardiology (ESC).[13] The maximum tolerated doses of β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers, and mineralocorticoid receptor antagonists were used in all patients. Target doses and dose equivalents for ACEIs were derived from the ESC guidelines.[13] For example, the daily doses of ramipril of 10 mg, enalapril of 20 mg, or lisinopril of 20 mg were considered as a 100% dose equivalent, while the daily doses of ramipril of 5 mg, enalapril of 10 mg, or lisinopril of 10 mg were defined as a 50% dose equivalent. A total of 186 patients (91.6%) used ACEIs (ramipril, 155 patients; enalapril, 14 patients; and lisinopril, 17 patients). The doses of β-blockers were converted into carvedilol-equivalent doses according to the study by Choi et al.[14] β-Blockers were used by 202 participants (99.5%): carvedilol, by 33; metoprolol succinate, by 103; and bisoprolol, by 66 patients. Valsartan was used by 12 patients (5.9%), while 201 patients (99%) were treated with mineralocorticoid receptor antagonists, including 96 (47.3%) with spironolactone and 107 (52.7%) with eplerenone.

The clinical characteristics of the study population are presented in TABLE 1. During the 1-year follow-up, 62 patients (30.5%) died and 115 patients (56.7%) required rehospitalization due to worsening of HF. There were no differences in the incidence of rehospitalization between survivors and nonsurvivors (79 [56%] and 36 [58.1%], respectively; $P = 0.79$).

In the multivariable Cox proportional hazard analysis, higher procalcitonin, hs-CRP, and NT-proBNP levels and lower sodium levels were associated with a higher risk of mortality at 1 year. The univariate and multivariate predictors of death are presented in TABLE 2.

Among the 1-year mortality factors, procalcitonin showed the best prognostic power, sensitivity, and specificity to identify survivors and nonsurvivors on the waiting list during a 1-year follow-up (FIGURE 1). The results of the ROC analysis for biomarkers are shown in TABLE 3.

According to the Kaplan–Meier survival curves, higher procalcitonin levels (≥556 pg/ml) were associated with a worse prognosis compared with lower procalcitonin levels (<556 pg/ml) (1-year survival, 44.3% and 82.7%, respectively; log-rank $P < 0.001$). The survival curves are presented in FIGURE 1.

DISCUSSION In this prospective, single-center study, we found that 2 inflammatory biomarkers, hs-CRP and procalcitonin, were independently associated with death during a 1-year follow-up in ambulatory patients with advanced HF awaiting HT. Among the inflammatory biomarkers, procalcitonin had the highest discriminatory power, sensitivity, and specificity, allowing for effective risk stratification in this group of patients.

TABLE 1 Baseline characteristics of the study population (continued on the next page)

Parameter	Whole study population (n = 203)	Survivors (n = 141)	Nonsurvivors (n = 62)	*P* value
Baseline data				
Age, y	57 (52–60)	57 (52–60)	57 (54–60)	0.8
Male sex	178 (87.68)	121 (85.8)	57 (91.9)	0.22
Ischemic etiology of HF	113 (56.67)	80 (56.7)	33 (53.2)	0.47
HF due to dilated cardiomyopathy	82 (40.4)	57 (40.4)	25 (40.3)	
HF due to valvular disease	8 (3.9)	4 (2.8)	4 (6.5)	
BMI, kg/m^2	27.44 (24.20–30.76)	27.92 (24.91–31.23)	26.23 (22.47–29.64)	0.01
HR, bpm	72 (65–78)	71 (65–77)	74 (65–80)	0.94
SBP, mm Hg	100 (90–110)	100 (90–114)	100 (90–104)	0.03
DBP, mm Hg	60 (55–70)	60 (55–70)	60 (55–66)	0.54
NYHA class III	185 (91.13)	131 (92.9)	54 (87.1)	0.18
NYHA class IV	18 (8.87)	10 (7.1)	8 (12.9)	
Comorbidities				
Hypertension	112 (55.17)	70 (49.6)	42 (67.7)	0.02
Type 2 diabetes	83 (40.89)	57 (40.4)	26 (41.9)	0.27
Persistent AF	99 (48.77)	75 (53.2)	24 (38.7)	0.06
Reversible pulmonary hypertension	68 (33.5)	47 (33.3)	21 (33.9)	0.94
COPD	22 (10.8)	16 (11.3)	6 (9.7)	0.72
Chronic kidney disease	102 (50.2)	67 (47.5)	35 (56.5)	0.24
Previous ischemic stroke	23 (11.3)	17 (12.1)	6 (9.7)	0.7
Hypercholesterolemia	154 (75.86)	112 (79.4)	42 (67.7)	0.07
Laboratory parameters				
WBC, × 10^9/l	7.54 (6.26–8.92)	7.34 (6.26–8.68)	8.08 (6.33–9.14)	0.17
Hemoglobin, mmol/l	8.90 (8.20–9.40)	8.84 (0.98)	8.89 (1.06)	0.75
Creatinine, µmol/l	112 (91–137)	109 (91–133)	121 (92–148)	0.1
GFR, ml/min/1.73m^2	59.71 (46.84–73.40)	60.72 (48.80–73.10)	54.18 (44.39–75.73)	0.21
Platelets, × 10^9/l	187 (157–234)	185 (156–234)	192 (161–230)	0.83
Total bilirubin, µmol/l	16.7 (11.70–22.90)	15.90 (11.40–21.90)	18.70 (12.10–23.70)	0.09
Albumin, g/l	43 (41–46)	44 (42–46)	42.50 (39–44)	0.003
Uric acid, µmol/l	419 (351–520)	413 (350–520)	441 (352–520)	0.34
Urea, µmol/l	8.90 (6.40–13.30)	8.70 (6.30–10.80)	10.90 (6.90–18.50)	0.01
Sodium, mmol/l	139 (137–140)	139 (137–141)	138.5 (135–140)	0.004
Fibrinogen, mg/dl	392 (324–459)	387 (321–458)	396 (329–459)	0.47
AST, U/l	26 (20–34)	26 (20–34)	25 (19–31)	0.83
ALT, U/l	22 (15–33)	22 (16–33)	19 (14–33)	0.31
ALP, U/l	80 (64–101)	77 (64–100)	81.5 (64–104)	0.51
GGTP, U/l	76 (35–133)	76 (33–132)	77 (45–142)	0.37
Total cholesterol, mmol/l	4.02 (3.35–4.77)	4.04 (1.01)	4.02 (0.98)	0.89
LDL cholesterol, mmol/l	2.16 (1.63–2.78)	2.07 (1.61–2.82)	2.31 (1.78–2.70)	0.41
Hs-CRP, mg/l	4.33 (2.11–6.91)	4.03 (1.89–5.99)	6.78 (3.30–9.11)	<0.001
ESR, mm/h	16 (9–22)	13 (8–22)	18.50 (12–25)	<0.001
HbA_{1c}, %	5.80 (5.30–6.20)	5.90 (5.40–6.40)	5.60 (5.30–6.20)	0.14
NT-proBNP, pg/ml	3131 (1764–6537)	2429 (1706–5276)	5224 (2666–9540)	<0.001
Procalcitonin, pg/ml	483.45 (385.19–657.62)	455.30 (256.25–541.32)	674.85 (477.81–1253.53)	<0.001
MELD-XI score	13.03 (10.87–15.74)	12.74 (11.02–15.26)	13.69 (10.77–16.42)	0.07
modMELD score	9.82 (7.99–12.29)	9.35 (7.80–11.61)	11.58 (8.43–13.51)	0.002*
HFSS, mean (SD)	7.59 (0.63)	7.64 (0.61)	7.48 (0.64)	0.08
Hemodynamic parameters				
MPAP, mm Hg	25 (20–32)	25 (20–31)	26 (22–35)	0.46
Cardiac index, l/min/m^2	1.93 (1.77–1.99)	1.93 (1.76–1.99)	1.94 (1.82–2.01)	0.67
TPG, mm Hg	9 (7–13)	9 (7–13)	9 (7–12)	0.83

TABLE 1 Baseline characteristics of the study population (continued from the previous page)

Parameter	Whole study population (n = 203)	Survivors (n = 141)	Nonsurvivors (n = 62)	*P* value
PVR, Wood units	1.87 (1.50–2.35)	1.84 (1.48–2.40)	1.99 (1.52–2.35)	0.7
Echocardiographic parameters				
LA, mm	53.5 (47–59)	53 (47–58.5)	54 (47–59)	0.93
RVEDD, mm	39 (35–40)	38 (34–40)	39 (36–44)	0.01
LVEDD, mm	71 (65–78)	71 (65–78)	70.5 (63–81)	0.55
LVEF, %	17 (15–20)	18 (15–20)	16 (13–19)	0.007
Cardiac medications				
β-Blockers	202 (99.51)	140 (99.3)	62 (100)	0.51
β-Blocker dose, mg/d	37.5 (25.0–50.0)	37.50 (25–50)	37.50 (25–50)	0.97
ACEIs	186 (91.6)	129 (91.5)	57 (91.9)	0.92
ACEI dose, mg/d	5 (5–10)	5 (5–10)	5 (5–10)	0.69
ARBs	12 (5.9)	8 (5.7)	4 (6.5)	0.83
Valsartan dose, mg/d	160 (80–160)	80 (80–160)	160 (120–160)	0.45
Loop diuretics	203 (100)	141 (100)	62 (100)	1
MRAs	201 (99.01)	139 (98.6)	62 (100)	0.35
Spironolactone dose, mg/d	50 (25–50)	50 (25–50)	50 (25–50)	0.93
Eplerenone dose, mg/d	50 (25–50)	50 (25–50)	50 (25–50)	0.89
Digoxin	63 (31.03)	44 (31.2)	19 (30.6)	0.94
Ivabradine	44 (21.67)	33 (23.4)	11 (17.7)	0.37
Statin	154 (75.86)	112 (79.4)	42 (67.7)	0.07
Coumarin derivatives	122 (60.10)	86 (61)	36 (58.1)	0.69
Acetylsalicylic acid	75 (36.95)	52 (36.9)	23 (37.1)	0.98
Sildenafil	68 (33.5)	47 (33.3)	21 (33.9)	0.94
Inotropic therapy during follow-up	18 (8.9)	10 (7.1)	8 (12.9)	0.18
ICD/CRT-D	203 (100)	141 (100)	62 (100)	1
Other parameters				
VO_{2max}, ml/kg/min	11.20 (10.30–12.10)	11.20 (10.30–12.10)	11.30 (10.10–12.30)	0.78
VE/VCO_2 slope	43.10 (42.10–44.30)	43.10 (42.10–44.30)	43.20 (42.05–44.40)	0.99
High-energy therapy with ICD/CRT-D	22 (10.8)	15 (10.6)	7 (11.3)	0.89

Data are presented as median (interquartile range) or number (percentage) of patients unless otherwise indicated. *P* values of less than 0.05 were significant.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy-defibrillator; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; GGTP, γ-glutamyl transpeptidase; HbA_{1c}, glycated hemoglobin A_{1c}; HF, heart failure; HFSS, Heart Failure Survival Score; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter-defibrillator; LA, left atrium; LDL, low-density lipoprotein; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MELD-XI, Model for End-Stage Liver Disease Excluding INR; modMELD, modified Model for End-stage Liver Disease; MPAP, mean pulmonary artery pressure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PVR, pulmonary vascular resistance; RVEDD, right ventricular end-diastolic dimension; SBP, systolic blood pressure; TPG, transpulmonary pressure gradient; Vo_{2max}, maximal oxygen uptake; VE/VCO_2, ratio of minute ventilation to carbon dioxide production; WBC, white blood cell

Although the clinical utility of established inflammatory markers such as hs-CRP, erythrocyte sedimentation rate, interleukins (ILs), tumor necrosis factor, and leukocyte levels has been extensively studied in patients with chronic HF, it remains unclear whether the inflammation is a cause or a consequence of chronic HF.[15,16] However, it was determined that severe or worsening HF is associated with smoldering inflammation.[15-17] Procalcitonin was originally identified as a marker of sepsis and invasive bacterial infections.[15] Yet, minor elevations of procalcitonin levels were reported in noninfectious conditions such as trauma, cardiac arrest, cardiac surgery, burns, pancreatitis, severe renal or liver dysfunction, or myocardial infarction.[18] Even though some studies showed that procalcitonin might be considered also as a potential biomarker of HF, little is known about the clinical significance of changes in procalcitonin levels in patients with HF.[15,19,20] Cvetinovic et al[20] reported that procalcitonin levels were significantly elevated in HF patients compared with healthy controls.[20] In a small group of patients with HF in NYHA functional classes I and III, Canbay et al[19] demonstrated that serum procalcitonin levels allowed for the assessment of HF severity. In a univariate analysis, Banach et

TABLE 2 Univariable and multivariable Cox proportional hazard analysis of factors associated with worse prognosis

Parameter	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Procalcitonin[a]	1.027 (1.020–1.035)	<0.001	1.027 (1.020–1.034)	<0.001
BMI (–)	1.076 (1.018–1.139)	0.01	–	–
Albumin (–)	1.101 (1.038–1.170)	0.001	–	–
Hs-CRP (+)	1.191 (1.110–1.278)	<0.001	1.099 (1.016–1.883)	0.02
ESR (+)	1.059 (1.024–1.096)	0.001	–	–
NT-proBNP[b]	1.070 (1.041–1.100)	<0.001	1.068 (1.033–1.105)	<0.001
Sodium (–)	1.133 (1.049–1.221)	0.001	1.171 (1.076–1.272)	<0.001
Urea (+)	1.088 (1.042–1.135)	<0.001	–	–
RVEDD (+)	1.043 (1.004–1.084)	0.03	–	–
LVEF (–)	1.106 (1.031–1.186)	0.005	–	–

(+) Per 1-unit increase

(–) Per 1-unit decrease

a Per 10-unit increase

b Per 1000-unit increase

Abbreviations: HR, hazard ratio; others, see TABLE 1

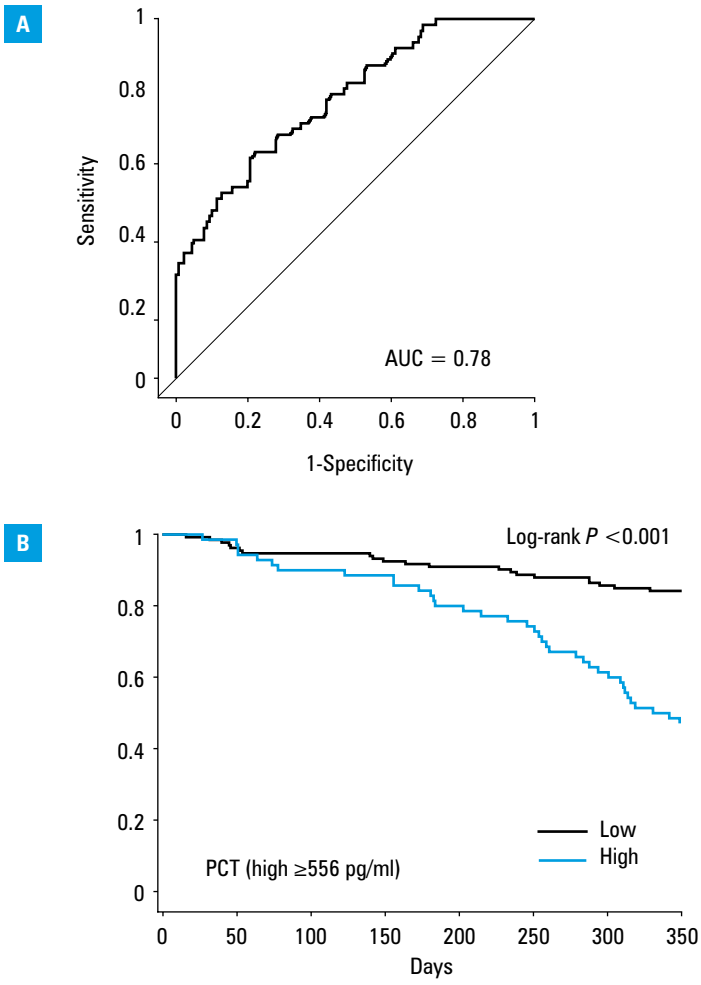

FIGURE 1 The receiver operating characteristic curve (A) and Kaplan–Meier survival curve (B) for procalcitonin levels
Abbreviations: AUC, area under the curve; PCT, procalcitonin

al[15] revealed that procalcitonin predicted a worse outcome in patients with chronic systolic HF during a 24-month follow-up.[15] However, this was not confirmed in a multivariate analysis. Other investigators reported that higher procalcitonin levels were associated with a worse prognosis in HF patients without evidence of infection.[20,21] Another study showed that patients with bacterial infection complicated by HF had significantly higher procalcitonin levels compared with those with isolated infection.[22] Moreover, the usefulness of procalcitonin for the diagnosis of infection was reduced significantly with increasing severity of HF.[22]

There are several mechanisms that may explain the elevated concentration of procalcitonin in HF. Anker et al[23] developed a hypothesis that inflammation in HF patients with systemic congestion leads to increased bowel permeability and bacterial endotoxin translocation from the gut into the circulation, with a subsequent activation of an immune response and the release of tumor necrosis factor-α and soluble CD14.[23] Increased stimulation of the inflammatory process as a result of altered intestine function in patients with HF is not a new concept explaining the pathophysiology of the disease.[15] Procalcitonin is released from the liver and peripheral blood mononuclear cells, and significantly correlates with inflammatory markers.[24] Another study also showed that markers of venous congestion are closely related to an increase in procalcitonin levels.[25] Given the significant role of inflammation and venous congestion in HF and their association with an increase in procalcitonin levels, these results provide an explanation for the observed higher procalcitonin levels in HF.

Another interesting finding of the current study was the strong and independent association between hs-CRP levels and a worse prognosis in patients with advanced HF. The prognostic value of hs-CRP in this study is in agreement with our previous reports on patients with advanced HF.[26,27] Other studies also confirmed increased hs-CRP levels in HF and their association with higher mortality and morbidity.[28-30] Hs-CRP is an acute-phase reactant and an indicator of chronic inflammation, which is closely related to the development and progression of chronic HF.[26-28] The exact mechanism of enhanced CRP production in patients with HF and without infection is not exactly known. Moreover, it is unclear whether CRP merely reflects a smoldering inflammatory process or directly modulates the course of the disease.[28] C-reactive protein is produced in the liver and secreted into the bloodstream in response to IL-6 signaling (and, to a lesser extent, IL-1β and other proinflammatory cytokines).[31] Numerous conditions observed in HF, such as left ventricular dysfunction, hypoperfusion, and venous congestion, are factors that induce an increased secretion of IL-6 or IL-1β and, secondarily, hs-CRP.[28,31] C-reactive protein is the key player involved in inflammatory

TABLE 3 Receiver operating characteristic curve analysis of the assessed biomarkers

Parameter	AUC	Cutoff	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Positive LR	Negative LR
NT-proBNP, pg/ml	0.688 (0.609–0.767)	≥4845	0.56 (0.43–0.69)	0.74 (0.66–0.81)	0.49 (0.37–0.61)	0.79 (0.71–0.86)	2.15 (1.39–2.92)	0.59 (0.41–0.77)
Procalcitonin, pg/ml	0.780 (0.712–0.848)	≥556	0.63 (0.50–0.75)	0.78 (0.70–0.85)	0.56 (0.43–0.68)	0.83 (0.75–0.89)	2.86 (1.81–3.91)	0.48 (0.31–0.64)
ESR, mm/h	0.653 (0.572–0.734)	≥10	0.89 (0.78–0.95)	0.38 (0.30–0.46)	0.38 (0.30–0.47)	0.88 (0.77–0.95)	1.42 (1.20–1.64)	0.30 (0.08–0.52)
Hs-CRP, mg/l	0.677 (0.593–0.760)	≥6.74	0.52 (0.39–0.65)	0.82 (0.74–0.88)	0.55 (0.42–0.68)	0.79 (0.72–0.86)	2.80 (1.61–3.99)	0.59 (0.43–0.75)
Sodium, mmol/l	0.628 (0.546–0.711	≤139	0.73 (0.60–0.83)	0.46 (0.38–0.55)	0.37 (0.29–0.46)	0.79 (0.69–0.87)	1.35 (1.05–1.64)	0.59 (0.33–0.86)

Data are presented as hazard ratios with 95% CIs.

Abbreviations: LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; others, see TABLE 1 and FIGURE 1

process: it promotes phagocytosis by neutrophils and macrophages, activates the complement system, neutrophils, and monocytes, and promotes the secretion of other cytokines.[31,32] These mechanisms are responsible for myocyte loss as well as right and left ventricular remodeling and dysfunction. Moreover, hs-CRP inhibits the production of nitric oxide and has a direct proinflammatory effect on endothelial cells.[33] In turn, endothelial dysfunction plays an important role in the development and progression of HF.[34] Therefore, it seems that the relationship of CRP with HF is multifaceted, but the exact underlying mechanisms have not been defined.

In our study, lower serum sodium levels were another independent predictor of death. However, the prognostic power of a single sodium measurement in stable hospitalized patients with advanced HF appeared to be limited. Our earlier study showed that a lower sodium concentration at the time of listing for HT is associated with reduced survival in ambulatory patients with endstage HF.[26] Previous studies also showed that hyponatremia is an independent predictor of morbidity and mortality as well as readmission to the hospital due to HF in different populations of HF patients.[34-36] Hyponatremia is one of the most common electrolyte abnormalities in patients with HF, with an incidence close to 25%.[37,38] The causes of hyponatremia in HF are complex and multifactorial.[39] A low cardiac output secondary to reduced left ventricular systolic function activates several neurohormonal systems to maintain blood volume and pressure.[39] In turn, neurohormonal activation, involving the activation of the renin–angiotensin–aldosterone system, arginine vasopressin release, and upregulation of sympathetic nervous activity, results in decreased water and sodium delivery to the kidneys, decreased water excretion, water retention by the kidneys, and, ultimately, hyponatremia.[40] There is a strong correlation between serum sodium and plasma neurohormone concentrations, such as norepinephrine, renin, and angiotensin II, which are powerful promoters of cardiac myocyte hypertrophy and necrosis, and are linked to a poor outcome in HF patients.[40-42] In this context, lower serum sodium levels may be a marker of neurohormonal activation, reflecting the severity of HF.[43] Hyponatremia may also develop as a complication of HF therapy. The drugs commonly used in HF, such as loop diuretics, may also activate the renin–angiotensin–aldosterone system, increasing the levels of angiotensin II. This, in turn, can stimulate the nonosmotic release of arginine vasopressin, thus promoting water retention and further predisposing to hyponatremia.[34,36,38]

This study also demonstrated the validity of another parameter associated with a worse prognosis in ambulatory patients with advanced HF, namely, a higher NT-proBNP concentration. Unfortunately, the prognostic power of a single NT-proBNP measurement in our patient population was not sufficient. The natriuretic peptides are among the most extensively studied and used biomarkers in HF. They are released by the heart in response to myocardial tension and an increased intravascular volume, and are commonly used to exclude HF, monitor its treatment, and distinguish cardiac from noncardiac causes of dyspnea.[44-46] Numerous studies confirmed the importance of natriuretic peptides such as NT-proBNP as predictors of mortality and morbidity in various populations of HF patients.[45,47,48] Our current results are in line with our previous studies that also showed a relatively limited prognostic power of NT-proBNP in ambulatory patients with advanced HF.[49,50] This may be due to the fact that clinically stable patients on optimal medical therapy present with optimal neurohormone suppression, which may limit the prognostic value of natriuretic peptides.[49] Another important explanation for the limited prognostic power of NT-proBNP in the population of HF patients with other comorbidities is the fact that this biomarker is not specific for HF. There are numerous other reasons for the elevation of natriuretic peptide levels besides HF. These include cardiac causes, such as acute coronary syndrome, myocarditis, cardioversion, and atrial fibrillation, and noncardiac causes, such as age, anemia, diabetes mellitus, pulmonary hypertension, obesity, and renal dysfunction.[44,49,50]

There are some important limitations of the present study. First, it was a single-center study, which entails a limited sample size. Second, we included a selected group of inpatients with advanced HF, and so the obtained results cannot be applied to the entire population of HF patients. Prospective and multicenter studies with a large number of participants are required to clarify the associations between procalcitonin levels and prognosis of patients with advanced HF. Third, we excluded patients who underwent HT or mechanical circulatory support implantation during the follow-up. Therefore, further studies without such exclusion criteria are needed to assess the prognostic utility of procalcitonin in these patients. Finally, our participants underwent symptom-limited cardiopulmonary exercise testing to achieve 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, this single-center, prospective study showed that higher serum hs-CRP, procalcitonin, and NT-proBNP levels and lower serum sodium levels are associated with an increased risk of death during 1-year follow-up in ambulatory patients with advanced HF awaiting HT. Among the independent risk factors, procalcitonin showed the strongest predictive power, sensitivity, and specificity, allowing for an effective identification of 1-year survivors and nonsurvivors on the HT waiting list. The present study may have clinical implications. The measurements of biomarkers associated with HF may provide important prognostic information in addition to global risk assessment in patients with HF. It seems that the multimarker approach can help refine therapeutic strategies and allow for tailored treatment based on the clinical and biochemical profile of individual patients with HF. In addition, these results may improve the risk stratification of HF patients by identifying patients who will benefit from treatment intensification and more advanced treatment options for HF.

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REFERENCES

1 Nadar SK, Shaikh MM. Biomarkers in routine heart failure clinical care. Card Fail Rev. 2019; 5: 50-56.

2 Spoletini I, Coats AJS, Senni M, Rosano GMC. Monitoring of biomarkers in heart failure. Eur Heart J Suppl. 2019; 21: M5-M8.

3 Szczurek W, Gąsior M, Skrzypek M, et al. Factors associated with elevated pulmonary vascular resistance in ambulatory patients with end-stage heart failure accepted for heart transplant. Pol Arch Intern Med. 2020; 130: 830-836.

4 Ibrahim NE, Januzzi JL Jr. Established and emerging roles of biomarkers in heart failure. Circ Res. 2018; 123: 614-629.

5 Szczurek-Wasilewicz W, Szyguła-Jurkiewicz B, Skrzypek M, et al. Fetuin-A and sodium concentrations are independently associated with allcause mortality in patients awaiting heart transplantation. Pol Arch Intern Med. 2021; 131: 16081.

6 Piek A, Du W, de Boer RA, Silljé HHW. Novel heart failure biomarkers: why do we fail to exploit their potential? Crit Rev Clin Lab Sci. 2018; 55: 246-263.

7 Chow SL, Maisel AS, Anand I, et al. Role of biomarkers for the prevention, assessment, and management of heart failure: a scientific statement from the American Heart Association. Circulation. Circulation. 2017; 136: e345.

8 Shirazi LF, Bissett J, Romeo F, Mehta JL. Role of inflammation in heart failure. Curr Atheroscler Rep. 2017; 19: 27.

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

10 Aaronson KD, Schwartz JS, Chen TM, et al. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation. 1997; 95: 2660-2667.

11 Heuman DM, Mihas AA, Habib A, et al. MELD-XI: a rational approach to "sickest first" liver transplantation in cirrhotic patients requiring anticoagulant therapy. Liver Transpl. 2007; 13: 30-37.

12 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.

13 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37: 2129-2200.

14 Choi DJ, Park CS, Park JJ, et al. Assessment of clinical effect and treatment quality of immediate-release carvedilol-IR versus SLOW release carvedilol-SR in Heart Failure patients (SLOW-HF): study protocol for a randomized controlled trial. Trials. 2018; 19: 103.

15 Banach J, Wołowiec Ł, Rogowicz D, et al. Procalcitonin (PCT) predicts worse outcome in patients with chronic heart failure with reduced ejection fraction (HFrEF). Dis Markers. 2018; 2018: 9542784.

16 Windram JD, Loh PH, Rigby AS, et al. Relationship of high-sensitivity C-reactive protein to prognosis and other prognostic markers in outpatients with heart failure. Am Heart J. 2007; 153: 1048-1055.

17 Möckel M, Searle J, Maisel A. The role of procalcitonin in acute heart failure patients. ESC Heart Fail. 2017; 4: 203-208.

18 Meisner M. Update on procalcitonin measurements. Ann Lab Med. 2014; 34: 263-273.

19 Canbay A, Celebi OO, Celebi S, et al. Procalcitonin: a marker of heart failure. Acta Cardiol. 2015; 70: 473-478.

20 Cvetinovic N, Isakovic AM, Lainscak M, et al. Procalcitonin in heart failure: hic et nunc. Biomark Med. 2017; 11: 893-903.

21 Mollar A, Villanueva MP, Carratala A, et al. Determinants of procalcitonin concentration in acute heart failure. Int J Cardiol. 2014; 177: 532-534

22 Wang W, Zhang X, Ge N, et al. Procalcitonin testing for diagnosis and short-term prognosis in bacterial infection complicated by congestive heart failure: a multicenter analysis of 4,698 cases. Crit Care. 2014; 18: R4.

23 Anker SD, Egerer KR, Volk HD, et al. Elevated soluble CD14 receptors and altered cytokines in chronic heart failure. Am J Cardiol. 1997; 79: 1426-1430.

24 Mollar A, Villanueva MP, Carratala A, et al. Determinants of procalcitonin concentration in acute heart failure. Int J Cardiol. 2014; 177: 532-534.

25 Sandek A, Rauchhaus M, Anker SD, von Haehling S. The emerging role of the gut in chronic heart failure. Curr Opin Clin Nutr Metab Care. 2008; 11: 632-639.

26 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.

27 Szyguła-Jurkiewicz B, Nadziakiewicz P, Zakliczynski M, et al. Predictive value of hepatic and renal dysfunction based on the models for endstage

liver disease in patients with heart failure evaluated for heart transplant. Transplant Proc. 2016; 48: 1756-1760.

28 Anand IS, Latini R, Florea VG, et al. C-reactive protein in heart failure: prognostic value and the effect of valsartan. Circulation. 2005; 112: 1428-1434.

29 Pellicori P, Zhang J, Cuthbert J, et al. High-sensitivity C-reactive protein in chronic heart failure: patient characteristics, phenotypes, and mode of death. Cardiovasc Res. 2020; 116: 91-100.

30 Alonso-Martínez JL, Llorente-Diez B, Echegaray-Agara M, et al. C-reactive protein as a predictor of improvement and readmission in heart failure. Eur J Heart Fail. 2002; 4: 331-336.

31 Del Giudice M, Gangestad SW. Rethinking IL-6 and CRP: why they are more than inflammatory biomarkers, and why it matters. Brain Behav Immun. 2018; 70: 61-75.

32 Black S, Kushner I, Samols D. C-reactive Protein. J Biol Chem. 2004; 279: 48487-48490.

33 Verma S, Wang CH, Li SH, et al. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. Circulation. 2002; 106: 913-919.

34 Kearney MT, Fox KA, Lee AJ, et al. Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure. J Am Coll Cardiol. 2002; 40: 1801-1808.

35 Ali K, Workicho A, Gudina EK. Hyponatremia in patients hospitalized with heart failure: a condition often overlooked in low-income settings. Int J Gen Med. 2016; 9: 267-273.

36 Rodriguez M, Hernandez M, Cheungpasitporn W, et al. Hyponatremia in heart failure: pathogenesis and management. Curr Cardiol Rev. 2019; 15: 252-261.

37 Mohan S, Gu S, Parikh A, Radhakrishnan J. Prevalence of hyponatremia and association with mortality: results from NHANES. Am J Med. 2013; 126: 1127-1137.

38 Gheorghiade M, Abraham WT, Albert NM, et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. Eur Heart J. 2007; 28: 980-988.

39 Bae MH, Chae SC. Hyponatremia in acute heart failure: a marker of poor condition or a mediator of poor outcome? Korean J Intern Med. 2015; 30: 450-452.

40 Guha K, Spiesshöfer J, Hartley A, et al. The prognostic significance of serum sodium in a population undergoing cardiac resynchronisation therapy. Indian Heart J. 2017; 69: 613-618.

41 Forfia PR, Mathai SC, Fisher MR, et al. Hyponatremia predicts right heart failure and poor survival in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2008; 177: 1364-1369.

42 Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. Circulation. 1986; 73: 257-267.

43 Klein L, O'Connor CM, Leimberger JD, et al. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME--CHF) study. Circulation. 2005; 111: 2454-2560.

44 Kim HN, Januzzi JL Jr. Natriuretic peptide testing in heart failure. Circulation. 2011; 123: 2015-2019.

45 Cheng V, Kazanagra R, Garcia A, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. J Am Coll Cardiol. 2001; 37: 386-391.

46 Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. BMJ. 2005; 330: 625.

47 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.

48 Oremus M, Don-Wauchope A, McKelvie R, et al. BNP and NT-proBNP as prognostic markers in persons with chronic stable heart failure. Heart Fail Rev. 2014; 19: 471-505.

49 Szczurek W, Gąsior M, Skrzypek M, Szyguła-Jurkiewicz B. Apelin improves prognostic value of HFSS (Heart Failure Survival Score) and MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) scales in ambulatory patients with end-stage heart failure. J Clin Med. 2020; 9: 2300.

50 Szczurek W, Szyguła-Jurkiewicz B, Zakliczyński M, et al. Prognostic utility of the N terminal prohormone of brain natriuretic peptide and the modified Model for End Stage Liver Disease in patients with end stage heart failure. Pol Arch Intern Med. 2018; 128: 235-243.