ORIGINAL ARTICLE

Markers of malnutrition, inflammation, and tissue remodeling are associated with 1-year outcomes in patients with advanced heart failure

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KEY WORDS

advanced heart failure, advanced lung cancer inflammation index, biomarkers, neutrophil percentage-to-albumin ratio, prognosis

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ABSTRACT

INTRODUCTION A number of predictive models and biomarkers are used to assess outcomes in patients with advanced heart failure (HF).

OBJECTIVES We sought to evaluate whether markers of malnutrition, inflammation, and tissue remodeling are associated with 1-year mortality in patients with advanced HF.

PATIENTS AND METHODS We analyzed 200 consecutive patients with advanced HF. We assessed markers of inflammation and malnutrition, such as the neutrophil percentage-to-albumin ratio (NPAR), the advanced lung cancer inflammation index (ALI), and the level of high-sensitivity C-reactive protein (hsCRP). We also evaluated the level of tenascin-C (TNC), as well as known markers of HF, such as N-terminal pro–B-type natriuretic peptide (NT-proBNP), creatinine, and bilirubin. Receiver operating characteristic (ROC) and Kaplan–Meier survival analyses were performed to evaluate the association of each parameter with 1-year mortality.

RESULTS The median (interquartile range) age of the patients was 58 (51–64) years. The independent predictors of death were ALI (odds ratio [OR], 0.966; 95% CI, 0.941–0.992; $P = 0.01$) and NPAR (OR, 1.373; 95% CI, 1.126–1.674; $P = 0.002$), as well as serum levels of TNC (OR, 1.04; 95% CI, 1.020–1.050; $P < 0.001$), hsCRP (OR, 1.187; 95% CI, 1.037–1.360; $P = 0.01$), NT-proBNP (OR, 1.110; 95% CI, 1.100–1.200; $P = 0.02$), creatinine (OR, 1.034; 95% CI, 1.013–1.055; $P = 0.001$), and bilirubin (OR, 1.079; 95% CI, 1.014–1.149; $P = 0.02$). The ROC analysis indicated a good discriminatory power of TNC (area under the curve [AUC] = 0.807), NT-proBNP (AUC = 0.760), hsCRP (AUC = 0.706), ALI (AUC = 0.749), and NPAR (AUC = 0.785) in predicting mortality during the 1-year follow-up.

CONCLUSIONS Our study demonstrated that a decreased ALI value, increased NPAR value, as well as elevated serum concentrations of TNC, NT-proBNP, hsCRP, creatinine, and bilirubin are associated with 1-year mortality in patients with advanced HF.

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INTRODUCTION A number of predictive models and biomarkers have been used to assess outcomes in patients with advanced heart failure (HF).[1-7] Noninterventional, cost-effective, and easy-to-perform tests for markers reflecting various pathophysiologic processes underlying HF play a vital role in risk stratification and improvement of HF management. Most of the evidence suggests that key pathophysiologic processes involved in the development and progression of HF are inflammation, malnutrition, and cardiac remodeling.[3,4] Thus, we sought to analyze the prognostic value of the simple and available markers of these processes, including the advanced lung cancer inflammation index (ALI), the neutrophil percentage-to-albumin ratio (NPAR), as well as serum levels of tenascin-C (TNC), high-sensitivity C-reactive protein

WHAT'S NEW?

In this single-center study, we found that the serum level of tenascin-C is associated with 1-year mortality in patients with advanced heart failure. This extracellular matrix glycoprotein could reflect the extent of myocardial remodeling, as it upregulates the activity of matrix metalloproteinases and their tissue inhibitors, is involved in the degradation of connective tissue, stimulates the inflammatory response, and influences the development of myocardial fibrosis. Furthermore, our analysis demonstrated that the values of the advanced lung cancer inflammation index and neutrophil percentage--to-albumin ratio, which reflect inflammation and malnutrition, respectively, allow for risk stratification in the analyzed group of patients.

(hs-CRP), and N-terminal pro–B-type natriuretic peptide (NT-proBNP).[4-7]

There are several possible explanations for the association between malnutrition, inflammation, remodeling, left ventricular (LV) dysfunction, and signs of HF. Cardiac remodeling, a series of structural and functional changes that involve cardiomyocyte injury, cell death, fibrosis, and electrophysiologic changes, is associated with heart adaptation to pathologic stimuli, and leads to an increase in LV dimensions, volume, or mass, and worsening of the LV systolic and diastolic functions. LV dysfunction causes the release of natriuretic peptides, which stimulate dysregulation of the leptin–adiponectin axis.[8,9] Adiponectin plays an anti-inflammatory role, while leptin is a proinflammatory adipokine. The effects of adiponectin and leptin on cardiac remodeling are associated with the induction of autophagy, which is a mechanism of cell death in response to pathologic stimuli.[8,9] Elevated levels of leptin and reduced levels of adiponectin stimulate lipolysis and promote fatty acid and glucose utilization.[4,8] The abovementioned mechanisms and chronic inflammation are connected with muscle catabolism, albumin consumption, appetite suppression, and weight loss.[9] In addition, an important link mediating the association between malnutrition and poor outcomes in patients with HF is frailty.[10]

There are various laboratory markers of systemic inflammation, including plasma CRP concentration, hypoalbuminemia, and absolute numbers of white cells and their components (neutrophils, lymphocytes). When the neutrophil count is evaluated in combination with other inflammatory markers, it may provide better prognostic information than when it is analyzed alone.[11] There is evidence that changes in the levels of acute-phase proteins, such as serum albumin, do not only reflect poor nutritional status but also indicate the severity of inflammation.[12] Thus, NPAR, which is calculated as the neutrophil percentage divided by the serum albumin concentration, may be a precise and rapid parameter of systemic inflammation. This index is used as a predictor of outcomes in patients with cancer and acute kidney injury.[13]

ALI, which is calculated based on the body mass index (BMI), serum albumin concentration, and neutrophil-to-lymphocyte ratio (NLR), may theoretically represent both malabsorption and chronic inflammation in HF.[4] Originally, ALI was developed to assess prognosis in patients with metastatic non–small cell lung cancer. This novel marker of inflammation and nutritional status in chronic diseases has been shown to be an independent prognostic factor in neoplastic diseases.[5]

TNC, an extracellular matrix glycoprotein, is specifically expressed at high levels during embryonic development but it is not normally detected in the adult heart. Fetal TNC regulates cell adhesion, influences the activity of matrix metalloproteinases and their tissue inhibitors, and stimulates the inflammatory response and the early stages of fibrosis. TNC reappears at sites of tissue and vascular remodeling under various pathologic conditions that are associated with inflammation and tissue injury.[14]

Given the close relationship between inflammation, malnutrition, and cardiac remodeling, we speculated that biomarkers of these processes might be associated with HF progression and patient outcomes. Therefore, the purpose of this study was to elucidate whether ALI, NPAR, and serum TNC levels are useful in predicting all-cause mortality in patients with advanced HF during 1-year follow-up.

PATIENTS AND METHODS

Study population and data collection

We prospectively analyzed consecutive ambulatory patients with advanced HF (New York Heart Association [NYHA] classes III–IV; Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS] profiles 4–6) hospitalized in our institution for heart transplantation (HT) evaluation between July 2018 and July 2019. The exclusion criteria comprised acute HF, neoplastic diseases, autoimmune diseases, endocrine disorders, peripheral artery disease, signs of infection, previous LV assist device (LVAD) implantation, any previous heart surgery, severe chronic obstructive pulmonary disease, history of pulmonary embolism, irreversible renal dysfunction (estimated glomerular filtration rate <30 ml/min/1.73 m^2), and inotropic or mechanical circulatory support (intra-aortic balloon pump or LVAD) during index hospitalization. Furthermore, the patients who underwent HT or LVAD implantation during the 1-year follow-up were excluded from the study. All participants received optimal therapy and had been taking β-blockers, mineralocorticoid receptor antagonists, and angiotensin-converting enzyme inhibitors / angiotensin II receptor blockers at the maximum tolerated doses for at least 3 months prior to the study inclusion.[15] To eliminate the effect of infection on the levels of inflammatory markers, we evaluated the white blood cell count. In all cases the count was lower than the limit indicating infection, confirming that none of the participants had an infection. Furthermore, according

to the center protocol, pulmonary, laryngological, dental, and urogenital infections were excluded (using clinical examination and imaging methods) in all the included individuals.

The collected data included medical history, comorbidities, demographic information, physical examination results, assessment of the nutritional status using the Nutritional Risk Screening 2002 (NRS-2002),[3] biochemical blood test results, echocardiographic examination, right heart catheterization, and current pharmacological treatment.

The study end point was defined as all-cause mortality during the 1-year follow-up. Death within 1 year was confirmed based on the information obtained from the national health care provider. The study was approved by the Bioethical Committee of the Medical University of Silesia (KNW/0022/KB1/53/1/18; date of approval, June 19, 2018). The study conformed to the principles outlined in the Declaration of Helsinki on the ethical principles for medical research involving human subjects. Written informed consent was obtained from all the included patients.

Biochemical measurements Fasting venous blood samples obtained at the time of enrolment to the study were frozen and stored at –80 °C until further analysis. The complete blood count and hematologic parameters were determined using automated blood cell counters (Sysmex XS1000i and XE2100, Sysmex Corporation, Kobe, Japan). The inter-and intra-assay coefficients of variation of the blood samples were 4.5% and 5%, respectively. Liver and kidney function parameters as well as plasma levels of cholesterol and albumin were measured with a COBAS Integra 800 analyzer (Roche Instrument Center AG, Rotkreuz, Switzerland). A high-sensitivity latex-based immunoassay was used on a Cobas Integra 70 analyzer (Roche Diagnostics Ltd., Mannheim, Germany) to detect plasma hs-CRP levels. The plasma concentration of fibrinogen was measured using a Sysmex CA-6000 automated coagulation analyzer. The mean value in our laboratory was 300 mg/dl, with a reference range of 200 to 400 mg/dl. The plasma concentration of NT-proBNP was measured using a commercially available kit from Roche Diagnostics on an Elecsys 2010 analyzer, with an analytical sensitivity of less than 5 pg/ml.

The serum TNC level was measured by a sandwich enzyme-linked immunosorbent assay (ELISA) with a commercially available kit (Human Tenascin ELISA Kit, SunRedBio Technology Co Ltd., Shanghai, China). The concentration of TNC was expressed as ng/l.

Nutritional screening The NRS-2002 score was calculated in each patient.[3] In the first part of this questionnaire impaired nutrition status is assessed. The patient may score between 0 and 3 points (0 points indicate no health deterioration, and 3 points indicate severe health deterioration). In the second part of the questionnaire, severity of disease and nutritional requirements are assessed. The patient may score between 0 and 3 points (0 points indicate normal nutritional requirements, and 3 points indicate high disease severity). Patients older than 70 years receive 1 additional point. Overall, patients can score from 0 to 7 points. In the participants with the NRS-2002 score greater than or equal to 3, malnutrition was diagnosed and nutritional therapy was recommended.[3]

Scales of inflammation and malnutrition NPAR was calculated as the neutrophil percentage multiplied by 100 and divided by the serum albumin concentration (g/dl).[6]

ALI was calculated using the following formula: ALI = BMI (kg/m^2) × serum albumin level (g/dl) / NLR.[5]

NLR was calculated as the neutrophil count divided by the lymphocyte count.[4]

BMI was calculated as weight (kg) divided by the square of height (m^2).

Statistical analysis All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina, United States). Categorical variables are presented as frequencies and percentages, and were compared using the χ^2 test. Normally distributed continuous variables are reported as the mean (SD), and were compared using the *t* test. Other continuous data are expressed as the median and interquartile range (IQR) and were compared using the Mann–Whitney test.

A multivariable logistic regression model was built to identify the predictors of 1-year mortality. The covariates were determined based on the results of the univariable analysis, the criteria were a *P* value below 0.3 in the univariable model and clinical relevance. The correlation between the explanatory variables was checked using the Spearman correlation coefficient (R), and multicollinearity was evaluated by means of the tolerance and variance inflation factor. Due to a strong correlation between several covariates associated with inflammation and malnutrition (eg, R = 0.49 for NT-proBNP and NPAR, and R = 0.74 for NPAR and ALI), we built 2 multivariable models. The results are presented as odds ratios (ORs) with 95% CIs.

Receiver operating characteristics (ROC) curves were plotted and the Youden index was used to determine the cutoff value for the parameters of inflammation, malnutrition, and remodeling that were significant in the multivariable analysis. The prognostic strength of the factors was evaluated based on the area under the ROC curve (AUC), sensitivity, specificity, negative predictive value, positive predictive value, and accuracy. The Kaplan–Meier curves with the log-rank test were used to compare mortality rates in patients dichotomized according to the cutoff values of TNC, NT-proBNP, hs-CRP, ALI, and NPAR

determined in the ROC analysis. A *P* value below 0.05 was considered significant.

RESULTS The final study population consisted of 200 patients with advanced HF who were placed on the HT waiting list, including 179 patients in NYHA class III and 21 patients in NYHA class IV. The median (IQR) age of the participants was 58 (51.5–64) years, and 179 patients (89.5%) were men. During the follow-up, 60 patients died (mortality rate, 30%). Baseline characteristics of the entire study population as well as the survival and nonsurvival subgroups are presented in TABLE 1.

The ROC curve analysis indicated a good discriminatory power of TNC, NT-proBNP, and hs-CRP as well as of the ALI and NPAR values in predicting mortality during the 1-year follow-up (TABLE 2). According to the Kaplan–Meier analysis, lower ALI values, higher NPAR values, higher TNC, and higher hs-CRP serum levels were associated with a significantly worse 1-year survival. The ROC curves and the Kaplan–Meier survival curves for all the analyzed parameters are shown in FIGURE 1A–1J.

The multivariable logistic regression analysis confirmed that ALI and NPAR values, as well as serum levels of TNC, NT-proBNP, hs-CRP, creatinine, and bilirubin were independent predictors of death at 1 year. The results of univariable and multivariable analyses are shown in TABLE 3.

DISCUSSION The present study demonstrated that nutrition and inflammation statuses reflected by ALI and NPAR as well as serum hs-CRP levels in the patients with advanced HF were associated with 1-year all-cause mortality. Furthermore, serum level of TNC, which is a marker of inflammation and tissue remodeling, and the level of NT-proBNP, which is a marker of myocardial wall tension, predicted 1-year mortality in the analyzed group of patients.

There is evidence that undernutrition is associated with increased mortality in patients with advanced HF. The pathophysiology of malnutrition in advanced HF may involve diminished perfusion of the gut and disturbed microcirculation of the intestine, resulting in local edema, abnormal mucosal permeability to endotoxins, and subsequent inflammation.[16] Furthermore, malnutrition and cardiac cachexia result from inflammatory cytokine–induced hypercatabolic syndrome, loss of bone mass, and insulin resistance.[17] Many factors can influence the nutritional status in HF patients, including decreased caloric intake due to malabsorption, tiredness, and dyspnea, as well as increased catabolism due to inflammatory cytokines and neurohormonal activation.

ALI, which was one of the factors associated with 1-year mortality in the analyzed group of patients, reflects systemic inflammation and malnutrition, which are the 2 main pathophysiologic processes in HF. It is a simple marker calculated based on NLR, BMI, and serum albumin level.

NLR is a biomarker of systemic inflammation that can be calculated based on the results of blood tests as a ratio of circulating neutrophils and lymphocytes. During inflammation, a large number of stimulated neutrophils cause thrombosis and increase the level of oxidative stress.[18] Neutrophils produce cytokines, which inhibit the lymphocyte-mediated immune activity comprising natural killer T cells or activated T cells.[5] An increased NLR due to elevated neutrophil count or decreased lymphocyte count indicates an imbalance between the innate and adaptive immune systems, resulting in a systemic increase in the levels of proinflammatory cytokines. A low lymphocyte count may reflect a poorly regulated immune response.[19]

BMI and serum albumin levels have been shown to be useful parameters for evaluating the nutritional status.[20,21] In patients with HF, low BMI is associated with poor prognosis (the obesity paradox).[22] However, it must be emphasized that using BMI to assess the nutritional status in HF patients has limitations. Based on BMI, it is not possible to distinguish between body fat and the presence of fluid retention or lean body mass. Albumins have anti-inflammatory and antioxidative properties. They inhibit the secretion of proinflammatory cytokines and complement factor C5a by modulating the interactions between neutrophils and endothelial cells.[23] Furthermore, serum albumins show anticoagulant and antiplatelet aggregation activity as well as a colloid osmotic effect.[24] In patients with advanced HF, a reduction in serum albumin levels is associated with increased metabolic activity, proteinuria, malnutrition, and decreased synthesis by the liver due to low perfusion and congestion.[25,26] There is evidence that hypoalbuminemia in patients with HF is associated with adverse outcomes, especially because it promotes fluid retention and edema by reducing plasma osmotic pressure.[27] Originally, ALI was proposed as a prognostic marker in patients with several types of cancer, because cachexia and sarcopenia are the results of the chronic inflammatory response and indicate a poor outcome in this population.[28,29] However, there are no previous reports investigating the association between the ALI value and prognosis in patients with advanced HF. The only study about the prognostic value of ALI in patients with HF was conducted by Maeda et al[4] in a population of patients with acute decompensated HF. The authors concluded that ALI was a marker of inflammation and malnutrition as well as a prognostic predictor in the study group.

Another finding of the present study is the association between NPAR and 1-year mortality in the analyzed group of patients.[6] This index reflects the main pathophysiologic processes that contribute to the progression of HF. NPAR, which combines the neutrophil percentage and albumin level, performed better than either of these markers alone in evaluating inflammatory-related diseases. Clinical studies have evaluated the prognostic

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

Parameter	All patients (n = 200)	Survivors (n = 140)	Nonsurvivors (n = 60)	*P* value
Baseline data				
Age, y	58 (51.5–64)	57 (50–63)	60 (54.5–65)	0.09
Male sex, n (%)	179 (89.5)	123 (87.9)	56 (93.3)	0.25
Ischemic etiology of HF, n (%)	118 (59)	74 (52.9)	44 (73.3)	0.007
BMI, kg/m^2	26.9 (24.1–30.4)	27.3 (24.6–31.1)	25.9 (22.9–29.5)	0.024
NYHA III, n (%)	179 (89.5)	129 (92.1)	50 (83.3)	0.06
NYHA IV, n (%)	21 (10.5)	11 (7.9)	10 (16.7)	0.06
Comorbidities, n (%)				
Hypertension	114 (57)	74 (52.9)	40 (66.7)	0.07
Type 2 diabetes	81 (40.5)	55 (39.3)	26 (43.3)	0.59
Dyslipidemia	128 (64)	90 (64.3)	38 (63.3)	0.9
Persistent AF	99 (49.5)	72 (51.4)	27 (45)	0.4
Laboratory findings				
WBC, $\times 10^9$/l	7.4 (6.1–8.9)	6.9 (6.1–8.5)	8.1 (6.6–9.2)	0.04
Lymphocytes, $\times 10^9$/l	1.5 (1.2–1.9)	1.5 (1.3–2)	1.4 (1.2–1.9)	0.14
Platelets, $\times 10^9$/l	201 (165–245.5)	184 (159–223.5)	231 (207.5–271.5)	<0.001
TNC, ng/l	374.7 (225.7–632.6)	278.8 (205.2–520.6)	570.8 (436.5–785.5)	<0.001
Hemoglobin, mmol/l	8.8 (0.9)	8.8 (0.9)	8.84 (1.1)	0.8
Creatinine, µmol/l	107 (95–125.5)	104 (91.5–110)	127 (104–144.5)	<0.001
Total bilirubin, µmol/l	16.7 (11.9–21.1)	15.5 (11.9–19.6)	20.1 (12.2–25.9)	0.002
Albumin, g/l	43 (41–46)	44 (41.5–46)	41.5 (38.5–44)	<0.001
Uric acid, µmol/l	425.5 (360.5–517.5)	425.5 (362–520.5)	435.5 (356–515)	0.74
Urea, µmol/l	8.2 (6–12.4)	7.9 (5.9–10.3)	9.2 (6.6–17.7)	0.01
Fibrinogen, mg/dl	381.5 (315–447)	372 (313–433)	398.5 (326.5–464)	0.09
AST, U/l	26 (20–32)	26 (20–32)	26 (19–31)	0.85
ALT, U/l	22 (15–33)	22 (16–33)	21.5 (14–36.5)	0.68
ALP, U/l	76.5 (62–100)	74 (61.5–96.5)	89.5 (64.5–107)	0.05
GGTP, U/l	74 (34–130.5)	64.5 (31.5–127)	81 (47–145.5)	0.08
Total cholesterol, mmol/l	4 (1)	4.05 (0.9)	3.98 (1.2)	0.67
hs-CRP, mg/l	4.2 (2–6.9)	3.7 (1.7–5.5)	6.8 (3.3–9)	<0.001
Sodium, mmol/l	139 (137–141)	140 (138–141)	137 (135–139)	<0.001
NT-proBNP, pg/ml	3293.5 (1683–6543)	2004 (1542.5–4658)	6339.5 (3565.5–9586.5)	<0.001
Hemodynamic data				
mPAP, mm Hg	25 (19–32)	25 (19–31)	24.5 (19–35.5)	0.58
CI, l/min/m^2	1.9 (1.8–2)	1.9 (1.8–2)	1.9 (1.8–2)	0.99
TPG, mm Hg	9 (7–13)	9 (7–13)	9 (7–12)	0.81
PVR, Wood units	1.9 (1.5–2.3)	1.8 (1.5–2.3)	1.9 (1.5–2.3)	0.32
Echocardiographic parameters				
LA, mm	52 (47–58)	50 (46–58)	54 (48.5–57)	0.16
RVEDD, mm	39 (35–40)	38 (34–40)	39.5 (37–43)	0.002
LVEDD, mm	71 (65–80)	71 (65–79.5)	71 (64.5–81)	0.45
LVEF, %	17 (15–20)	18 (15–20)	15 (12.5–18)	<0.001
Cardiac medication on admission, n (%)				
β-Blockers	198 (99)	138 (98.6)	60 (100)	0.35
ACEI/ARB	198 (99)	138 (98.6)	60 (100)	0.35
Loop diuretics	200 (100)	140 (100)	60 (100)	0.35
MRA	200 (100)	140 (100)	60 (100)	0.35
Digoxin	61 (30.5)	39 (27.9)	22 (36.7)	0.22
Ivabradine	38 (19)	28 (20)	10 (16.7)	0.58
Statin	149 (74.5)	105 (75)	44 (73.3)	0.8
Acetylsalicylic acid	73 (36.5)	49 (35)	24 (40)	0.5
ICD/CRT-D	200 (100)	140 (100)	60 (100)	0.59

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

Parameter	All patients (n = 200)	Survivors (n = 140)	Nonsurvivors (n = 60)	*P* value
Other				
VO_2max, ml/kg/min	11.25 (10.3–12.2)	11.3 (10.4–12.25)	11.05 (9.70–12.05)	0.15
ALI	39.8 (27–54.3)	44.4 (31.4–60.2)	30 (16.9–42.8)	<0.001
NPAR	14.9 (13.4–16.7)	14.2 (12.8–15.9)	16.8 (15.3–18.3)	<0.001
Malnutrition (NRS-2002 >3 points)	13 (6.5)	7 (5)	6 (10)	0.19

Data are presented as median (interquartile range) or mean (SD) unless otherwise indicated.

SI conversion factors: to convert hemoglobin to g/l, multiply by 0.6206; fibrinogen to g/l, by 0.01; ALP, ALT, AST, and GGTP to µkat/l, by 0.0167; hs-CRP to nmol/l, by 9.524; NT-proBNP to ng/l, by 1.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ALI, advanced lung cancer inflammation index; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CI, cardiac index; CRT-D, cardiac resynchronization therapy–defibrillator; GGTP, γ-glutamyl transpeptidase; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter–defibrillator; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; MRA, mineralocorticoid receptor antagonist; NPAR, neutrophil percentage-to-albumin ratio; NRS-2002, Nutritional Risk Score; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; PVR, pulmonary vascular resistance; RVEDD, right ventricular end-diastolic dimension; TNC, tenascin-C; TPG, transpulmonary gradient; VO_2max, maximal oxygen uptake; WBC, white blood cell count

TABLE 2 Results of receiver operating characteristic analysis

Parameter	AUC (95% CI)	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy
TNC	0.807 (0.748–0.865)	≥411	0.87 (0.75–0.94)	0.72 (0.64–0.79)	0.57 (0.46–0.67)	0.93 (0.86–0.97)	0.77 (0.70–0.82)
NPAR	0.785 (0.718–0.853)	≥15.1	0.8 (0.68–0.89)	0.65 (0.56–0.73)	0.49 (0.39–0.6)	0.88 (0.81–0.94)	0.7 (0.63–0.76)
ALI	0.749 (0.678–0.821)	≤54.3	0.99 (0.94–1)	0.35 (0.27–0.44)	0.4 (0.32–0.48)	1 (0.93–1)	0.55 (0.47–0.62)
NT-proBNP	0.756 (0.685–0.826)	≥3761	0.75 (0.62–0.85)	0.69 (0.61–0.77)	0.51 0.4–0.62)	0.87 (0.79–0.92)	0.71 (0.64–0.77)
hs-CRP	0.706 (0.626–0.786)	≥5.46	0.62 (0.48–0.74)	0.74 (0.66–0.81)	0.51 (0.39–0.63)	0.81 (0.74–0.88)	0.71 (0.64–0.77)

Abbreviations: AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; others, see **TABLE 1**

value of NPAR in clinical states such as sepsis, cardiogenic shock, acute kidney injury, or acute myocardial infarction.[13,30,31] However, only 1 previous study explored the prognostic value of NPAR in patients with HF. In that study, Hu et al[32] concluded that the NPAR value upon admission to the hospital was related to the risk of death or hospitalization in the analyzed cohort. The advantage of NPAR is its simplicity, low cost, and availability, as it can be easily and quickly calculated based on routine laboratory test results in each HF patient on admission.

We also demonstrated a strong and independent association between 1-year mortality and serum TNC levels. It is known that fetal variants of TNC are not only expressed during embryogenesis but also appear in pathophysiologic conditions during myocardial and vascular remodeling in adults.[33] TNC molecules are deposited in the myocardium, but soluble forms of this glycoprotein are released into the bloodstream. They are synthesized in interstitial fibroblasts in response to elevated levels of proinflammatory cytokines, mechanical stress, hypoxia, or acidosis.[33] TNC upregulates the activity of matrix metalloproteinases, which promote the degradation of connective tissue.[7,33] Furthermore, TNC promotes the progression of fibrosis and contributes to LV systolic and diastolic dysfunction. Therefore, increased serum TNC levels in patients with advanced HF may reflect the presence of active pathophysiologic processes that contribute to the development and progression of the disease. Our results support this possibility, as we showed that serum TNC concentrations are associated with 1-year mortality in the analyzed group of patients with advanced HF. Our findings were consistent with the results of some studies that analyzed patients at different stages of HF.[34-36] Several studies have shown that increased serum TNC levels in patients with dilated cardiomyopathy and HF are associated with adverse outcomes, inflammation, cardiac remodeling, and the stage of LV dysfunction.[34-36] Additionally, Yao et al[37] found that the levels of TNC were associated with long-term outcomes and the stage of LV dysfunction in patients with ischemic HF.

Our study also confirmed the importance of conventional HF risk factors, such as higher serum concentrations of NT-proBNP, hsCRP, creatinine, and bilirubin, in predicting outcomes in our study population.

We showed an independent association between serum NT-proBNP levels and 1-year mortality in the patients with HF. This marker of myocardial remodeling is secreted from cardiomyocytes as a consequence of interactions between mechanical, immunological, and neurohormonal factors. The main regulatory mechanism that causes the secretion of natriuretic peptides is increased cardiac wall tension and intravascular volume. Additionally, elevated serum concentration

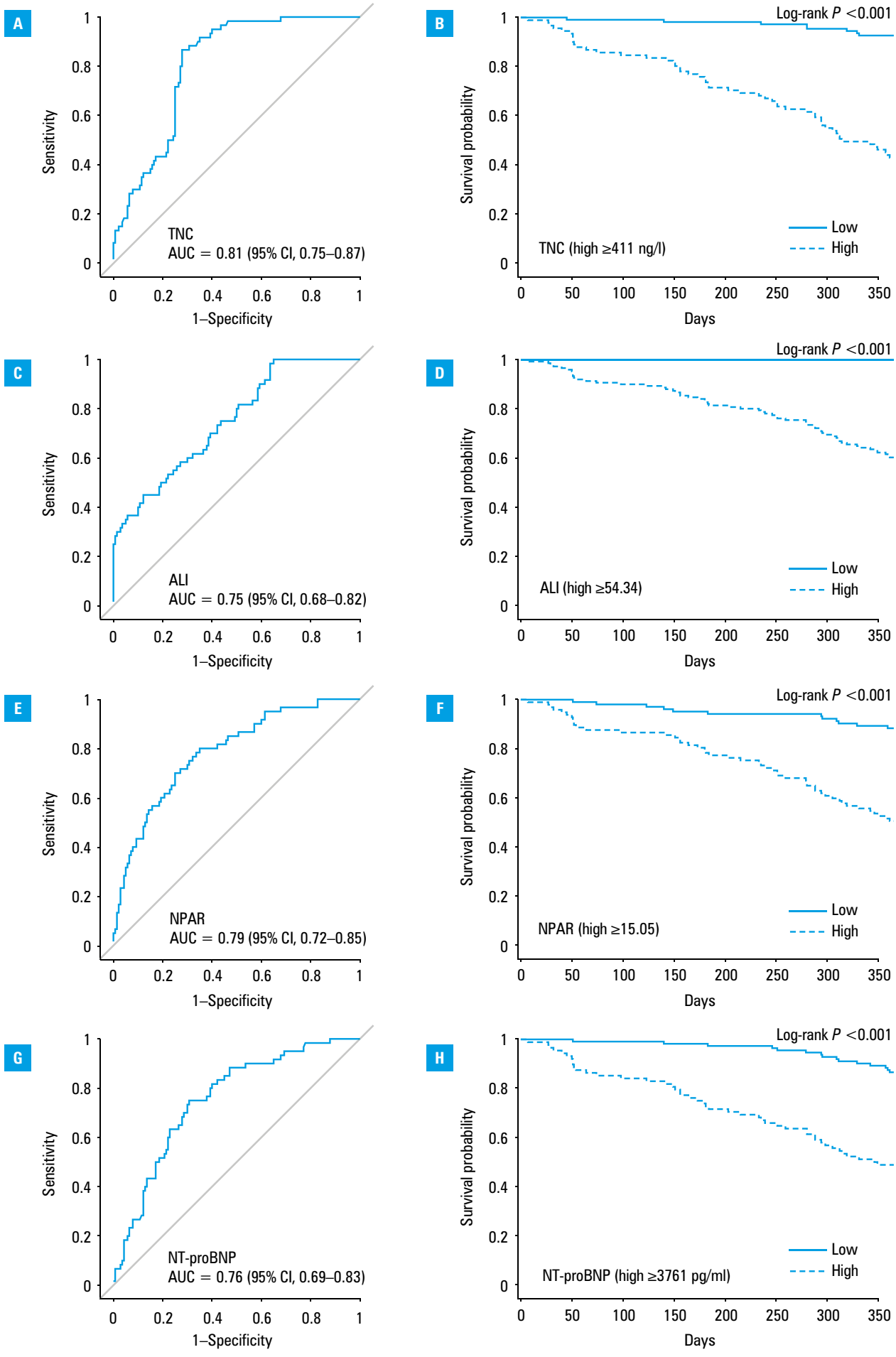

FIGURE 1 Receiver operating characteristic curves and Kaplan–Meier curves, respectively, for TNC (**A**, **B**), ALI (**C**, **D**), NPAR (**E**, **F**), and NT-proBNP (**G**, **H**)
Abbreviations: see **TABLE 1**

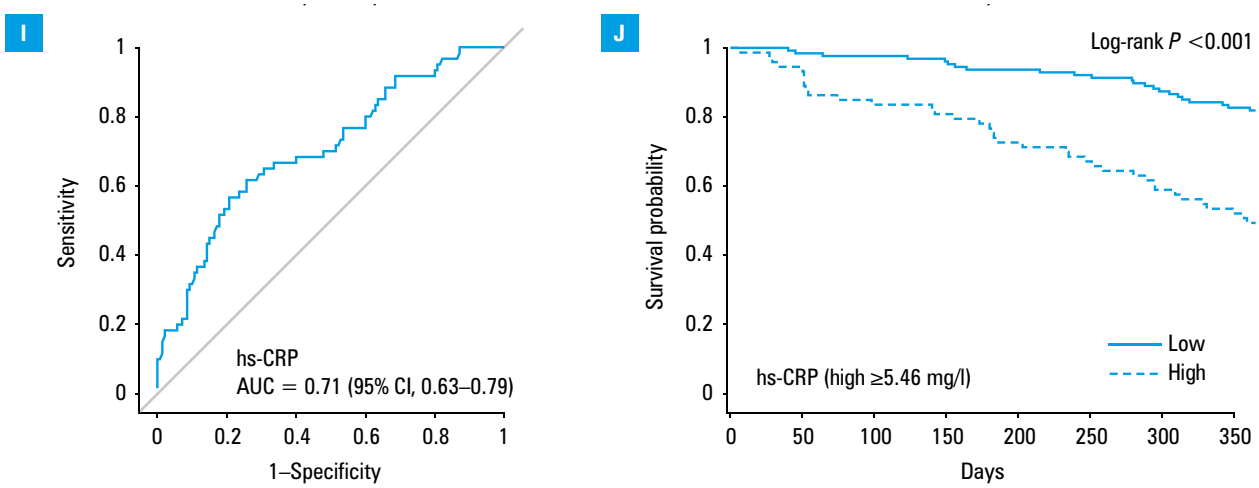

FIGURE 1 Receiver operating characteristic curves and Kaplan–Meier curves, respectively, for hs-CRP (I, J)
Abbreviations: see TABLE 1

TABLE 3 Results of univariable and multivariable analyses

Univariable analysis				
Parameter	OR (95% CI)		*P* value	
TNC[a]	1.04 (1.02–1.05)		<0.001	
Bilirubin	1.074 (1.008–1.144)		0.03	
Creatinine	1.031 (1.009–1.053)		0.005	
BMI	0.935 (0.878–0.995)		0.04	
ALI	0.979 (0.946–0.998)		0.22	
NPAR	1.168 (1.031–1.496)		0.22	
Albumin	0.849 (0.737–0.979)		0.02	
Urea	1.05 (0.954–1.156)		0.32	
hs-CRP	1.198 (1.044–1.375)		0.01	
NT-proBNP[b]	1.09 (1.01–1.19)		0.06	
Multivariable analysis				
Parameter	Model 1		Model 2	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
TNC	1.04 (1.02–1.05)	<0.001	1.03 (1.02–1.05)	<0.001
Bilirubin	1.079 (1.014–1.149)	0.02	1.08 (1.015–1.149)	0.02
Creatinine	1.034 (1.013–1.055)	0.001	1.032 (1.011–1.053)	0.003
CRP	1.187 (1.037–1.360)	0.01	1.22 (1.067–1.393)	0.004
ALI	0.966 (0.941–0.992)	0.01	–	–
NT-proBNP	1.11 (1.01–1.2)	0.02	–	–
NPAR	–	–	1.373 (1.126–1.674)	0.002

a Per 10-unit increase

b Per 100-unit increase

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

of NT-proBNP is related to renal and hepatic failure associated with HF and pulmonary hypertension secondary to LV dysfunction. Furthermore, NT-proBNP synthesis in cardiomyocytes is induced by angiotensin II, endothelin, and proinflammatory cytokines (interleukin-6 [IL-6]).[38,39] Assessment of the NT-proBNP level is commonly used in clinical practice to diagnose HF and predict mortality and morbidity in various populations of patients with HF.[40-43]

Another prognostic factor in our study group was serum hs-CRP level. This acute-phase protein is synthesized by hepatocytes in response to IL-6 production, and is part of the immune response. In line with our findings, several previous studies have shown that elevated hs-CRP levels on admission may be associated with worse clinical outcomes in patients with advanced HF.[44,45] Furthermore, it has already been established that hs-CRP is a nonspecific marker of inflammatory diseases, infections, and neoplastic disorders, and a mediator of endothelial dysfunction.[46]

The present study also confirmed the relevance of serum bilirubin and creatinine levels in predicting outcomes in the analyzed population. It is known that 2 hemodynamic abnormalities, namely, hypoperfusion and venous congestion, explain the processes underlying renal and hepatic dysfunction in advanced HF.[47] Hepatic congestion associated with right ventricular dysfunction may result in cholestatic changes, with elevated serum bilirubin level.[47] Although early stages are reversible, long-term hepatopathy leads to irreversible damage of the liver.[47] Renal dysfunction has been attributed to decreased cardiac output, a subsequent decrease in glomerular filtration rate, and an increase in tubular sodium retention.[48] Furthermore, chronic inflammatory state, cytokine production, and oxidative stress play an important role in the development of renal dysfunction in HF.[48]

Several limitations of the study should be noted. First, it was a single-center analysis; therefore, it was subject to selection bias. The second limitation is a relatively small number of patients, which warrants for the results to be interpreted with caution. Considering these limitations, multicenter studies with a larger sample size are required to further validate the clinical value of the analyzed parameters and indices.

Conclusions This study shows that the assessment of easily-obtainable nutritional and inflammatory markers plays an important role in

the risk stratification of patients with HF. The results of our analysis support the hypothesis that markers of inflammation and malnutrition—ALI, NPAR, and serum hs-CRP—allow for mortality risk assessment in patients with advanced HF. Furthermore, in our study population, higher serum levels of TNC, NT-proBNP, creatinine, and bilirubin were associated with 1-year mortality.

ARTICLE INFORMATION

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

CONFLICT OF INTEREST None declared.

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REFERENCES

1 Pytka MJ, Pałasz-Borkowska A, Tarchalski JL, et al. The serum concentration of brain-derived neurotrophic factor is lower in ambulatory and clinically stable patients with more advanced systolic heart failure. Pol Arch Intern Med. 2022; 132: 16303.

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

3 Czapla M, Juárez-Vela R, Łokiec K, Karniej P. The association between nutritional status and in-hospital mortality among patients with heart failure—a result of the retrospective Nutritional Status Heart Study 2 (NSHS2). Nutrients 2021; 13: 1669-1687.

4 Maeda D, Kanzaki Y, Sakane K, et al. Prognostic impact of a novel index of nutrition and inflammation for patients with acute decompensated heart failure. Heart Vessels. 2020; 9: 1201-1208.

5 He X, Zhou T, Yang Y, et al. Advanced lung cancer inflammation index, a new prognostic score, predicts outcome in patients with small-cell lung cancer. Clin Lung Cancer. 2015; 16: e165-e171.

6 Cui H, Ding X, Li W, et al. The neutrophil percentage to albumin ratio as a new predictor of in-hospital mortality in patients with ST-segment elevation myocardial infarction. Med Sci Monit. 2019; 25: 7845-7852.

7 Imanaka-Yoshida K, Hiroe M, Yoshida T. Interaction between cell and extracellular matrix in heart disease: multiple roles of tenascin-C in tissue remodeling. Histol Histopathol. 2004; 19: 517-525.

8 Yamauchi T, Kamon J, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med. 2002; 8: 1288-1295.

9 Kamareddine L, Ghantous CM, Allouch S, et al. Between inflammation and autophagy: the role of leptin-adiponectin axis in cardiac remodeling. J Inflamm Res. 2021; 14: 5349-5365.

10 Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol SciMed Sci. 2001; 56: M146-M156.

11 Hartaigh B, Bosch JA, Thomas GN, et al. Which leukocyte subsets predict cardiovascular mortality? From the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Atherosclerosis. 2012; 1: 161-169.

12 Eckart A, Struja T, Kutz A, et al. Relationship of nutritional status, inflammation, and serum albumin levels during acute illness: a prospective study. Am J Med. 2020; 6: 713-722.e7.

13 Wang B, Li D, Cheng B, et al. The neutrophil percentage-to-albumin ratio is associated with all-cause mortality in critically ill patients with acute kidney injury. Biomed Res Int. 2020; 2020: 5687672.

14 Midwood KS, Hussenet T, Langlois B, Orend G. Advances in tenascin-C biology. Cell Mol Life Sci. 2011; 68: 3175-3199.

15 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.

16 Sandek A, Swidsinski A, Schroedl W, et al. Intestinal blood flow in patients with chronic heart failure: a link with bacterial growth, gastrointestinal symptoms, and cachexia. J Am Coll Cardiol. 2014; 64: 1092-1102.

17 Lin H, Zhang H, Lin Z, et al. Review of nutritional screening and assessment tools and clinical outcomes in heart failure. Heart Fail Rev. 2016; 5: 549-565.

18 Döring Y, Libby P, Soehnlein O. Neutrophil extracellular traps participate in cardiovascular diseases: recent experimental and clinical insights. Circ Res. 2020; 9: 1228-1241.

19 Wada H, Dohi T, Miyauchi K, et al. Prognostic impact of nutritional status assessed by the controlling nutritional status score in patients with stable coronary artery disease undergoing percutaneous coronary intervention. Clin Res Cardiol. 2017; 11: 875-883.

20 Nakagawa T, Toyazaki T, Chiba N, et al. Prognostic value of body mass index and change in body weight in postoperative outcomes of lung cancer surgery. Interact Cardiovasc Surg. 2016; 23: 560-566.

21 Jin Y, Zhao L, Peng F. Prognostic impact of serum albumin levels on the reccurence of stage I non-small cel lung cancer. Clinics (Sao Paulo). 2014; 68: 686-893.

22 Sharma A, Lavie CJ, Borer JS, et al. Metaanalysis of the relation of body mass index to all-cause and cardiovascular mortality and hospitalization in patients with chronic heart failure. Am J Cardiol. 2015; 10: 1428-1434.

23 Levitt DG, Levitt MD. Human serum albumin homeostasis: a new look at the roles of synthesis, catabolism, renal and gastrointestinal excretion, and the clinical value of serum albumin measurements. Int J Gen Med. 2016; 9: 229-255.

24 Arques S. Human serum albumin in cardiovascular diseases. Eur J Intern Med. 2018; 52: 8-12.

25 Uthamalingam S, Kandala J, Daley M, et al. Serum albumin and mortality in acutely decompensated heart failure. Am Heart J. 2010; 6: 1149-1155.

26 Bonilla-Palomas JL, Gamez-Lopez AL, Moreno-Conde M, et al. Hypoalbuminemia in acute heart failure patients: causes and its impact on hospital and long-term mortality. J Card Fail. 2014; 5: 350-358.

27 Horwich TB, Kalantar-Zadeh K, MacLellan RW, Fonarow GC. Albumin levels predict survival in patients with systolic heart filure. Am Heart J. 2008; 5: 883-889.

28 Zhang Y, Chen B. Prognostic value of the advanced lung cancer inflammation index in patients with lung cancer: a meta-analysis. Dis Markers. 2019; 2019: 2513026.

29 Cole CL, Kleckner IR, Jatoi A, et al. The role of systemic inflammation in cancer-associated muscle wasting and rationale for exercise as a therapeutic intervention. JCSM Clin Rep. 2018; 2: e00065.

30 Peng Y, Xue Y, Wang J, et al. Association between neutrophil-to--albumin ratio and mortality in patients with cardiogenic shock: a retrospective cohort study. BMJ Open. 2020; 10: e039860.

31 Gong Y, Li D, Cheng B, Ying B, Wang B. Increased neutrophil percentage-to-albumin ratio is associated with all-cause mortality in patients with severe sepsis or septic shock. Epidemiol Infect. 2020; 148: e87.

32 Hu Z, Wang J, Xue Y, et al. The neutrophil-to-albumin ratio as a new predictor of all-cause mortality in patients with heart failure. J Inflamm Res. 2022; 15: 701-713.

33 Imanaka-Yoshida K, Hiroe M, Nishikawa T, et al. Tenascin-C modulates adhesion of cardiomyocytes to extracellular matrix during tissue remodeling after myocardial infarction. Lab Invest. 2001; 81: 1015-1024.

34 Fujimoto N, Onishi K, Sato A, et al. Incremental prognostic values of serum tenascin-C levels with blood B-type natriuretic peptide testing at discharge in patients with dilated cardiomyopathy and decompensated heart failure. J Card Fail. 2009; 10: 898-905.

35 Yokokawa T, Sugano Y, Nakayama T, et al. Significance of myocardial tenascin-C expression in left ventricular remodelling and long-term outcome in patients with dilated cardiomyopathy. Eur J Heart Fail. 2016; 4: 375-385.

36 Terasaki F, Okamoto H, Onishi K, et al. Higher serum tenascin-C levels reflect the severity of heart failure, left ventricular dysfunction and remodeling in patients with dilated cardiomyopathy. Circ J. 2007; 3: 327-330.

37 Yao HC, Han QF, Zhao AP, et al. Prognostic values of serum tenascin-C in patients with ischaemic heart disease and heart failure. Heart Lung Circ. 2013; 3: 184-187.

38 Horia T, Kohno M, Takeda T. Effects of arginine vasopressin, angiotensin II and endothelin-1 on release of brain natriuretic peptide in vivo and in vitro. Clin Exp Pharmacol Physiol. 1992; 19: 575-582.

39 Ma KK, Ogawa T, de Bold AJ. Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by proinflammatory cytokines and by conditioned medium derived from mixed lymphocyte reactions via p38-MAP kinase. J Moll Cell Cardiol. 2004; 36: 505-513.

40 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.

41 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: 1787-1847.

42 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.

43 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.

44 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.

45 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.

46 Clapp BR, Hirschfield GM, Storry C, et al. Inflammation and endothelial function: direct vascular effects of human C-reactive protein on nitric oxide bioavailability. Circulation 2005; 111: 1530e6.

47 Giallourakis CC, Rosenberg PM, Friedman LS. The liver in heart failure. Clin Liver Dis. 2002; 6: 947e67.

48 Giamouzis G, Butler J, Triposkiadis F. Renal function in advanced heart failure. Congest Heart Fail. 2011; 17: 180-188.