

# Prognostic value of prealbumin, N-terminal pro-B-type natriuretic peptide, heart type fatty acid binding protein, and cardiac troponin I in elderly patients for heart failure and poor outcomes

Shengzhuo Wang<sup>1</sup> , Ketong Liu<sup>2</sup>,  
Shoukun Guan<sup>2</sup> and Ge Cui<sup>3</sup> 

## Abstract

**Objectives:** This study aimed to investigate the prognostic value of serum prealbumin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), heart type fatty acid binding protein (hFABP), and cardiac troponin I (cTnI) for heart failure and cardiac death in elderly patients.

**Methods:** We studied 426 consecutive patients with New York Heart Association classes I to IV who were recruited between February 2014 and 2018. Cardiac mortality was the primary end point. Receiver operator characteristic curves were created to analyze predictive values.

**Results:** When prealbumin, NT-proBNP, hFABP, and cTnI were combined, the areas under the receiver operator characteristic curve reached 0.930 and 0.903 for heart failure and cardiac death, respectively. Prealbumin, NT-proBNP, hFABP, and cTnI levels changed differently during therapy in patients in different prognosis groups. These parameters improved in patients who did not develop major adverse cardiovascular events (MACEs), but were unchanged or deteriorated in patients with MACEs. Multivariate Cox regression analysis showed that these parameters were significant independent risk factors for MACEs and cardiac death.

<sup>1</sup>Department of Cardiology, Jinchang Hospital of Integrated Traditional Chinese and Western Medicine, Jinchang, China

<sup>2</sup>Department of Cardiovascular Medicine, the Second Affiliated Hospital of Qiqihar Medical College, Qiqihar, China

<sup>3</sup>Department of Pathology, the Second Affiliated Hospital of Huzhou University, Huzhou, China

## Corresponding author:

Ge Cui, Department of Pathology, the Second Affiliated Hospital of Huzhou University, 727 Tianmu Road, Huzhou 31300, China.

Email: cui3382@126.com



**Conclusions:** Our study shows that serum prealbumin, NT-proBNP, hFABP, and cTnI levels are significant prognostic factors for elderly patients with poor cardiac function. These parameters are more accurate for prognosis when used together.

### Keywords

Heart failure, prealbumin, N-terminal pro-B-type natriuretic peptide, heart type fatty acid binding protein, cardiac troponin I, prognosis

Date received: 29 January 2021; accepted: 8 February 2021

### Introduction

Severe heart failure (HF) is a terminal illness of patients with heart disease and is the main cause of cardiac death in up to 40% of patients.<sup>1</sup> This rate is even higher in elderly patients with New York Heart Association (NYHA) functional classes III and IV where the cardiac death rate could be >70%.<sup>2,3</sup> Timely diagnosis and treatment for HF are important for reducing the mortality rate and improving prognosis. One approach is to use biomarkers to predict the prognosis of HF.<sup>4</sup> However, the diagnosis and evaluation of disease severity for HF are still clinically challenging. In recent years, a number of biomarkers have been proposed to assist in diagnosis of HF.<sup>5,6</sup> An example of one of these biomarkers is N-terminal pro-B-type natriuretic peptide (NT-proBNP), which is a useful indicator for estimating the prognosis of HF.<sup>5</sup> NT-proBNP levels are also elevated when myocardial ischemia occurs in patients with HF.<sup>7</sup>

The progress of cardiac disease is associated with many factors, such as reduced nutritional intake, increased degenerative metabolism, reduced liver function, and chronic inflammation.<sup>8</sup> Therefore, a multiple biomarker approach is likely to provide better diagnosis and prognosis for HF. Prealbumin is mostly synthesized in the

liver and is a tetrameric protein with a molecular weight of 54 kDa<sup>9</sup> and a half-life of approximately 2 days. Prealbumin has been proposed as a biomarker for impaired nutritional status that has a risk for surgical site infection.<sup>10</sup> This protein is also a sensitive and early indicator of nutritional conditions compared with other widely used indicators, such as serum albumin, total cholesterol, and the lymphocyte count.<sup>11</sup> NT-proBNP is a cardiac natriuretic hormone that regulates heart function. When HF occurs, there is profound activation of ventricular synthesis of NT-proBNP.<sup>12</sup> Fatty acid binding protein (FABP) is a 15-kDa protein consisting of 132 amino acids.<sup>13</sup> Heart type fatty acid binding protein (hFABP) belongs to the FABP superfamily and is located primarily in the heart, and it constitutes 5% to 15% of the cytosolic protein pool<sup>14</sup> where it transports fatty acids to mitochondria for  $\beta$ -oxidation and energy expenditure.<sup>15</sup> Cardiac troponin I (cTnI) is the molecular switch of the sarcomere and is related to relaxation performance in cardiac myocytes.<sup>16,17</sup>

In this study, we evaluated the combined prognostic value of prealbumin, NT-proBNP, hFABP, and cTnI for HF in elderly patients who are hospitalized because of chronic HF. Our findings could help evaluate and stratify the severity and

risk of death in patients with HF and provide monitoring tools for treatment of this disease.

## Materials and methods

### Patients

Elderly patients with HF who were treated in our hospital owing to worsening of chronic HF between February 2014 and 2018 were studied. Patients were included if they were diagnosed with HF in accordance with the national guidelines<sup>18</sup> and aged between 65 to 91 years. Patients were excluded if they had a tumor, severe respiratory diseases, surgery involving the heart or brain, and mental disorders. Included patients were assessed for the NYHA functional class<sup>19</sup> at admission and further grouped on the basis of primary outcome into the non-major adverse cardiovascular event (MACE) or MACE group. Patients were treated according to the national guidelines.<sup>18</sup> Drugs including diuretics (e.g., bumetanide, metolazone, and tolvaptan), renin and angiotensin system inhibitors (e.g., the angiotensin-converting enzyme inhibitor drugs benazepril and captopril and the angiotensin II receptor blocker drugs azilsartan, eprosartan, and losartan), and  $\beta$  receptor blockers (e.g., acebutolol and bisoprolol) were used for treatment. The MACE group included patients with readmission, cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke. The primary end point was cardiovascular mortality.

Demographic and clinical data, including age, sex, underlying diseases, and laboratory findings were collected. The study complied with the Declaration of Helsinki and was approved by the institutional ethics committee of the First Affiliated Hospital of Huzhou University, Huzhou, China (approval number: HUE2013-84). Written

informed consent was received from all patients.

### Biochemical measurements

Fasting venous blood was drawn from patients within 24 hours after admission and during the hospitalization and treatment periods. Prealbumin, NT-proBNP, hFABP, and cTnI levels were determined using enzyme-linked immunosorbent assays with commercial kits purchased from Ruilai Bioeng (Beijing, China). The assays were carried out in triplicate according to the manufacturer's instructions on an ARCHITECT c16000 Clinical Chemistry Analyzer (Abbott, Abbott Park, IL, USA). The detection limit, coefficients of variation, and normal limits for NT-proBNP, hFABP, and cTnI levels were as follows: 3 pg/mL, 5%, and 4000 pg/mL; 1.25 ng/mL, 4%, and 1000 ng/mL; and 25 fg/mL, 4%, and 100 fg/mL; respectively.

### Follow-up and determination of MACEs

All patients were followed up for 180 days starting from admission. Follow-up was performed through a telephone interview and hospital visit during initial hospitalization and readmission. MACEs were recorded during the visit. MACEs were defined as cardiovascular mortality, recurrent myocardial ischemia, acute myocardial infarction, deterioration of HF, non-fatal myocardial infarction and non-fatal stroke, and readmission due to severe arrhythmia.

### Statistical analysis

The data were analyzed by SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). The normality of distribution of continuous variables was tested by the one-sample Kolmogorov–Smirnov test. Continuous variables with a normal distribution are presented as mean  $\pm$  standard

deviation and non-normal variables are reported as median (interquartile range). Means of two continuous normally distributed variables were compared by the independent samples Student's *t* test. Receiver operator characteristic (ROC) curves were created to analyze the prognostic values of biomarkers for HF. Survival curves were calculated using the Kaplan–Meier method and compared by the log-rank test according to univariate analysis. Multivariate Cox regression analysis was used to analyze the factors affecting MACEs, death, and readmission for patients with HF. A *P* value <0.05 was considered statistically significant.

## Results

### Baseline characteristics

A total of 426 patients were included in this study, with 190 men and 236 women with a mean ( $\pm$  standard deviation) age of  $73.6 \pm 18.2$  years. Among them, 146 and 280 patients were assessed as having NYHA classes I to II and classes III to IV, respectively. There were no differences in age, sex, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, estimated glomerular filtration rate, and left ventricular ejection fraction between the two groups (Table 1). The percentages of patients with myocardial infarction, hypertension, and diabetes mellitus were also similar between the two groups. However, in NYHA classes III to IV, there were significantly higher rates of patients with newly diagnosed HF, HF with preserved ejection fraction, atrial fibrillation, and stroke compared with those in patients with NYHA classes I to II (all *P* < 0.05, Table 1).

### Associations of prealbumin, NT-proBNP, hFABP, and cTnI levels with NYHA class

Patients with NYHA classes III to IV had significantly lower prealbumin levels and

significantly higher NT-proBNP, hFABP, and cTnI levels compared with patients with NYHA classes I to II (all *P* < 0.001, Table 1). Furthermore, the rate of MACEs was significantly higher in the NYHA III to IV group than in the NYHA I to II group (*P* < 0.001, Table 1). MACEs were negatively correlated with prealbumin levels ( $r = -0.89$ , *P* < 0.05) and positively correlated with NT-proBNP, hFABP, and cTnI level ( $r = 0.89$ , 0.91, and 0.62, respectively, all *P* < 0.05).

### ROC curve analysis and risk stratification

ROC curve analysis showed that the area under the curves (AUCs) of prealbumin, NT-proBNP, hFABP, and cTnI for predicting readmission for HF were 0.822 (*P* = 0.015), 0.901 (*P* = 0.011), 0.818 (*P* = 0.022), and 0.650 (*P* = 0.031), respectively (Figure 1a). The sensitivity and specificity of prediction were highest with NT-proBNP and hFABP alone. Use of all markers (prealbumin, NT-proBNP, hFABP, and cTnI) increased the sensitivity and specificity to 95.0% and 95.6%, respectively, with an AUC of 0.930 (*P* = 0.009, Table 2). For cardiac death, the AUCs were 0.662, 0.672, 0.721, and 0.613 for these biomarkers (Figure 1b). The sensitivity was high with NT-proBNP and sensitivity and specificity were high with hFABP in single biomarker assessment (Table 2). When these biomarkers were combined, the specificity and specificity increased to 93.9% and 91.4%, respectively (Table 2), and the AUC was significantly higher than that for single parameters (all *P* < 0.05, Table 2). When the cutoffs were used to stratify mortality, the survival rate was significantly higher when prealbumin levels were  $\geq 2.24 \mu\text{mol/L}$ , NT-proBNP levels were  $< 6335.1 \text{ ng/L}$ , hFABP levels were  $< 6335.1 \text{ ng/L}$ , and cTnI levels were  $< 3.08 \text{ ng/mL}$  (Figure 2a–d). Patients with HF and high cTnI levels had a significantly

**Table 1.** Baseline characteristics of the patients (n = 426).

	NYHA functional classification I–II	NYHA functional classification III–IV	P value
Demographic characteristics			
Age, years (IQR)	75.2 (22.3)	72.8 (21.3)	0.521
Men, n (%)	66 (45.2)	80 (54.8)	0.431
Women, n (%)	136 (48.6)	144 (51.4)	0.341
Measurements at baseline			
Body mass index, kg/m <sup>2</sup>	26.1 ± 2.2	26.4 ± 2.4	0.232
Systolic blood pressure, mm Hg	124.2 ± 8.4	125.2 ± 7.4	0.213
Diastolic blood pressure, mm Hg	75.2 ± 2.3	75.8 ± 2.4	0.552
Heart rate, beats/minute	95.3 ± 5.2	96.1 ± 4.4	0.318
eGFR, mL/minute/1.73 m <sup>2</sup>	45.8 ± 6.6	45.2 ± 6.5	0.518
Left ventricular ejection fraction, %	30.3 ± 4.3	31.2 ± 4.8	0.418
Medical history			
Newly diagnosed heart failure, n (%)	12 (2.2)	66 (4.6)	0.012
Heart failure with preserved ejection fraction, n (%)	14 (9.6)	55 (19.6)	0.016
Ischemic heart failure, n (%)	22 (15.1)	55 (19.6)	0.034
Myocardial infarction, n (%)	21 (14.4)	56 (20.0)	0.114
Hypertension, n (%)	55 (37.7)	90 (32.1)	0.324
Atrial fibrillation, n (%)	23 (15.8)	76 (27.1)	0.031
Diabetes mellitus, n (%)	44 (30.1)	101 (36.1)	0.122
Stroke, n (%)	16 (11.0)	54 (19.3)	0.025
Biomarkers			
Prealbumin, mg/L	30.5 ± 3.3	13.3 ± 1.2	<0.001
NT-proBNP, ng/L	855.3 ± 34.8	9320.2 ± 78.2	<0.001
hFABP, ng/L	3.2 ± 0.1	28.6 ± 3.9	<0.001
cTnI, ng/mL	2.33 ± 0.1	34.1 ± 3.1	<0.001
MACEs, n (%)	23 (17.5)	95 (33.9)	<0.001

Values are mean ± standard deviation, median (IQR), or n (%).

NYHA, New York Heart Association; IQR, interquartile range; eGFR, estimated glomerular filtration rate; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; hFABP, heart type fatty acid binding protein; cTnI, cardiac troponin I; MACEs, major adverse cardiovascular events.

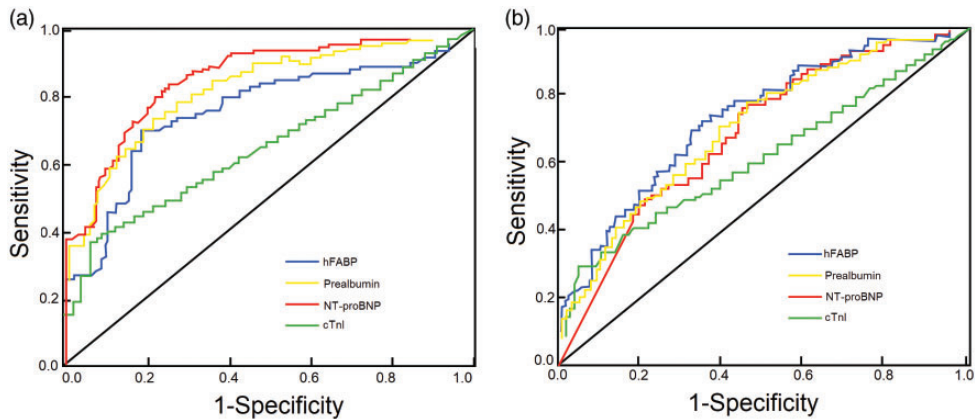
higher mortality rate than those with low cTnI levels (33.8% vs 12.7%,  $P < 0.05$ ).

### *Changes in prealbumin, NT-proBNP, hFABP, and cTnI levels during treatment*

Before treatment, prealbumin levels were significantly lower, and NT-proBNP, H-FABP, and cTnI levels were significantly higher in the MACE group (including the readmission group and cardiac death group shown in Table 3) than in the non-MACE group (all  $P < 0.05$ ). Additionally,

prealbumin levels were significantly lower, and NT-proBNP, H-FABP, and cTnI levels were significantly higher in the cardiac death group than in the readmission group (all  $P < 0.05$ ) (Table 3).

For patients in the non-MACE group, NT-proBNP, hFABP, and cTnI levels significantly decreased (all  $P < 0.05$ ), while prealbumin levels remained unchanged during the first 2 weeks of treatment. Prealbumin levels were significantly increased after treatment for 30 days, while NT-proBNP, hFABP and cTnI



**Figure 1.** Receiver operator characteristic curves for prealbumin, NT-proBNP, hFABP, and cTnI-based prediction in elderly patients for prognosis of heart failure (a) and cardiac death (b).

NT-proBNP, N-terminal pro-B-type natriuretic peptide; hFABP, heart type fatty acid binding protein; cTnI, cardiac troponin I.

**Table 2.** Comparison of prognostic value of serum prealbumin, NT-proBNP, hFABP, and cTnI levels for cardiac death and HF.

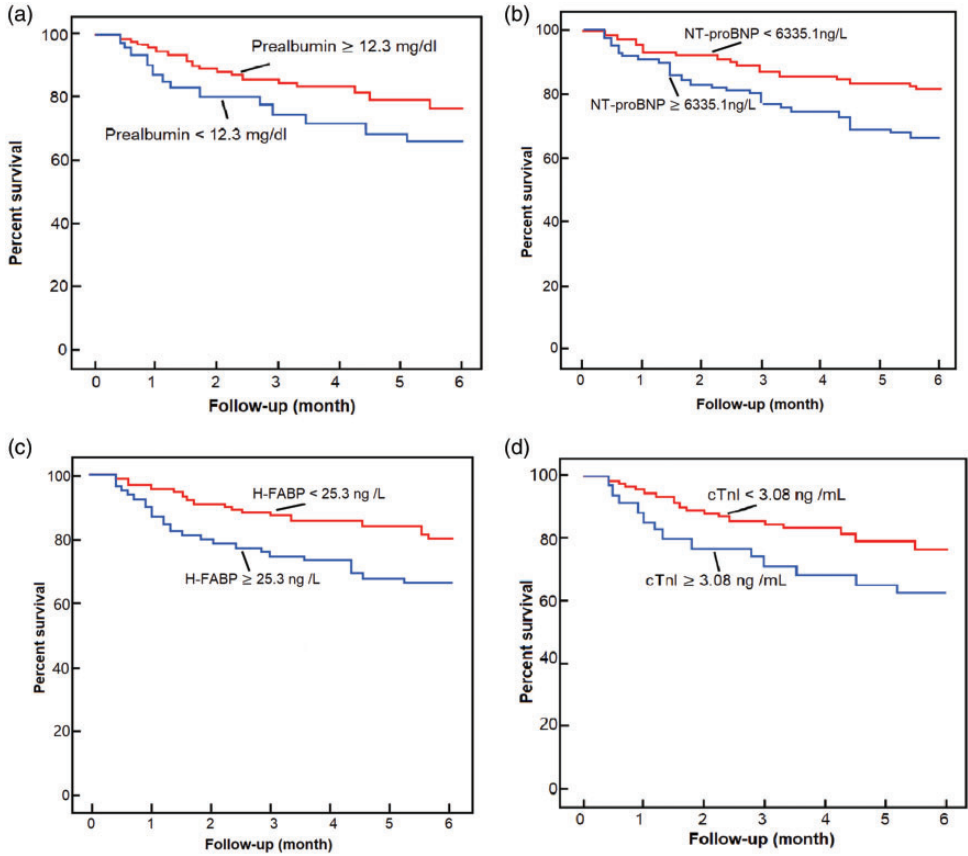
Parameter	AUC		Cutoff		Sensitivity (%)		Specificity (%)	
	HF	Mortality	HF	Mortality	HF	Mortality	HF	Mortality
Prealbumin	0.822 <sup>a</sup>	0.662	4.05 $\mu\text{mol/L}$	2.24 $\mu\text{mol/L}$	71.7	69.7	72.6	54.2
NT-proBNP	0.901 <sup>a</sup>	0.672	4335.1 ng/L	6335.1 ng/L	80.1	75.7	81.6	58.2
hFABP	0.818 <sup>a</sup>	0.721	18.3 ng/L	25.3 ng/L	76.4	71.7	90.3	74.9
cTnI	0.650	0.613	2.91 ng/mL	3.08 ng/mL	37.6	36.2	77.4	71.4
Combined	0.930 <sup>a</sup>	0.903 <sup>a</sup>			95.0	93.9	95.6	91.4

Data followed by the same letter in the same column are not significantly different at  $P < 0.05$ .

AUC, area under the curve; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hFABP, heart type fatty acid binding protein; cTnI, cardiac troponin I.

levels continued to decrease (all  $P < 0.05$ , Table 3). For patients in the readmission group, prealbumin and hFABP levels remained relatively stable during 60 days of treatment, but NT-proBNP and cTnI levels tended to decrease, although this reduction appeared to occur mostly with 15 days of treatment and did not increase thereafter. In the cardiac death group, prealbumin levels were relatively stable during the treatment period, but the remaining three parameters tended to increase, particularly after treatment for 30 days (Table 3).

**Multivariate Cox regression analysis.** The factors affecting MACES, death, and readmission for patients with HF were analyzed using multivariate Cox regression analysis with all four biomarkers and the left ventricular ejection fraction as independent variables. We found that prealbumin, NT-proBNP, hFABP, and cTnI were significant risk factors for MACES and death (all  $P < 0.05$ ), but not readmission. The left ventricular ejection fraction was not associated with these outcomes (Table 4).



**Figure 2.** Kaplan–Meier survival curves for patients with heart failure stratified with the cutoff values of prealbumin (a), NT-proBNP (b), hFABP (c), and cTnI (d). NT-proBNP, N-terminal pro-B-type natriuretic peptide; hFABP, heart type fatty acid binding protein; cTnI, cardiac troponin I.

## Discussion

HF is a complex clinical syndrome, which is rarely characterized using single biochemical markers for its clinical and pathophysiological characteristics.<sup>20</sup> Except for NT-proBNP/B-type natriuretic peptide, which is widely used in diagnosing acute HF,<sup>21,22</sup> no other biomarkers have been widely accepted as significant indicators for diagnosis and treatment of HF. A recent study showed that in chronic HF, myocardial injury may occur because of inflammation or deprivation of nutrition, particularly in elderly patients.<sup>23</sup> Therefore,

prealbumin, as well as NT-proBNP, hFABP, and cTnI levels, were assessed for their value in prognosis of patients with HF in this study.

Our study showed that prealbumin levels were lower, and NT-proBNP, hFABP, and cTnI levels were higher in patients with a high NYHA functional class, which indicated that these parameters were important for the prognosis of HF. Prealbumin is a negative acute-phase reactant, and its synthesis is inhibited in an inflammatory environment. Because of the shorter half-time of prealbumin than albumin, it can be used

**Table 3.** Changes in prealbumin, NT-proBNP, hFABP, and cTnl levels during the treatment period.

Group	No. of patients	Prealbumin, $\mu\text{mol/L}$	NT-proBNP, ng/L	hFABP, ng/L	cTnl, ng/mL
<b>Non-MACEs</b>					
Before therapy	308	$5.3 \pm 0.1$	$6648.9 \pm 127.6$	$10.6 \pm 3.4$	$0.97 \pm 0.19$
Therapy, day					
7	308	$5.4 \pm 0.1$	$3356.7 \pm 275.1^a$	$7.6 \pm 1.4^a$	$0.93 \pm 0.15$
15	308	$5.5 \pm 0.1$	$1921.6 \pm 151.2^a$	$4.7 \pm 1.1^a$	$0.88 \pm 0.11^a$
30	306	$5.9 \pm 0.1^a$	$1428.7 \pm 119.6^b$	$3.1 \pm 0.3^b$	$0.28 \pm 0.01^b$
60	306	$5.9 \pm 0.1^a$	$1178.7 \pm 93.5^c$	$2.2 \pm 0.2^c$	$0.18 \pm 0.01^c$
<b>Readmission</b>					
Before therapy	106	$3.7 \pm 0.2$	$9205.5 \pm 404.9$	$18.0 \pm 2.7$	$2.2 \pm 0.11$
Therapy, day					
7	106	$3.8 \pm 0.2$	$8286.2 \pm 431.8^a$	$17.8 \pm 1.2$	$2.1 \pm 0.11$
15	106	$3.9 \pm 0.2$	$7643.1 \pm 428.7^a$	$17.5 \pm 1.1$	$1.1 \pm 0.08^a$
30	101	$3.7 \pm 0.1$	$7755.7 \pm 711.2^a$	$18.4 \pm 1.9$	$0.8 \pm 0.08^a$
60	99	$4.1 \pm 0.1^a$	$8469.8 \pm 393.2^a$	$17.7 \pm 1.7$	$0.8 \pm 0.08^a$
<b>Death</b>					
Before therapy	84	$2.6 \pm 0.1$	$9746.84 \pm 427.8$	$39.9 \pm 1.9$	$5.0 \pm 0.84$
Therapy, day					
7	84	$2.2 \pm 0.1$	$10226.7 \pm 404.7^a$	$38.5 \pm 1.0$	$4.7 \pm 0.44$
15	81	$2.4 \pm 0.1$	$9868.5 \pm 437.3$	$37.8 \pm 1.8$	$5.1 \pm 0.34$
30	80	$2.6 \pm 0.1$	$10915.7 \pm 410.8$	$49.5 \pm 2.6^a$	$5.2 \pm 0.24$
60	73	$2.4 \pm 0.1$	$11165.2 \pm 404.7^a$	$\pm 2.3^a$	$5.9 \pm 0.24^a$

Data followed by different letters in the same column are significantly different ( $P < 0.05$ ) versus before therapy.

NT-proBNP, N-terminal pro-B-type natriuretic peptide; hFABP, heart type fatty acid binding protein; cTnl, cardiac troponin I; non-MACEs, non-major adverse cardiovascular events.

to estimate nutrition and the inflammatory state of patients more accurately than serum albumin (ranges from  $<35$  g/L in patients with hypoalbuminemia to  $>45$  g/L in healthy individuals). Low prealbumin levels are associated with poorer overall survival and disease-free survival in patients with advanced gastric cancer.<sup>24,25</sup> Furthermore, patients with HF and low prealbumin levels at discharge are associated with high short-term mortality<sup>26</sup> and decreased admission serum albumin levels are associated with high long-term mortality in hospital survivors of acute myocardial infarction.<sup>27</sup> These results are consistent with our observations, indicating that prealbumin is a reliable indicator for the prognosis of HF.

NT-proBNP was originally isolated from porcine brain extracts and is a cardiac

natriuretic hormone. Together with the highly homologous atrial natriuretic peptide, NT-proBNP forms a dual natriuretic peptide system of the heart. In HF, secretion of B-type natriuretic peptide is stimulated owing to increased wall stretch, neurohormonal activation, and hypoxia. In the normal condition, the atrium is the main cardiac production site, but as HF develops, there is profound activation of ventricular NT-proBNP synthesis.<sup>12</sup> Therefore, serum NT-proBNP levels can sensitively reflect changes in ventricular pressure and load capacity, and they increase with increasing severity of HF.<sup>28</sup>

In healthy humans, the normal range of hFABP levels in serum or plasma is  $<5$  ng/mL.<sup>29,30</sup> The diagnostic value of hFABP has been assessed comprehensively in



**Table 4.** Multivariate Cox regression analysis of the factors associated with MACEs, readmission, and cardiac death in patients with heart failure

Independent variable	MACEs					Readmission					Cardiac death				
	b	SE	OR (95% CI)	P	Wald $\chi^2$	b	SE	OR (95% CI)	P	Wald $\chi^2$	b	SE	OR (95% CI)	P	Wald $\chi^2$
Prealbumin	0.481	0.443	3.22 (1.66, 7.32)	0.022	1.243	0.281	0.142	1.143	0.255	2.143	0.221	0.242	0.015	2.143	3.23 (1.66, 7.42)
NT-proBNP	0.181	0.243	4.22 (2.66, 7.52)	0.012	0.243	0.112	0.042	0.153	0.212	0.043	0.128	0.102	0.009	0.043	4.23 (1.46, 6.22)
hFABP	1.481	0.493	2.22 (1.16, 5.32)	0.017	3.243	1.281	0.532	2.173	0.215	2.143	1.221	0.542	0.011	2.143	2.53 (1.06, 3.41)
cTnI	0.281	0.245	5.22 (3.66, 9.32)	0.015	0.248	2.283	1.146	6.443	0.311	4.133	2.331	1.264	0.017	4.133	5.23 (2.76, 8.62)
LVEF	0.431	0.113	1.02 (0.66, 1.32)	0.232	9.243	0.541	0.242	2.143	0.655	1.143	0.661	0.132	0.345	1.143	1.05 (0.66, 1.42)

MACEs, non-major adverse cardiovascular events; SE, standard error; OR, odds ratio; CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hFABP, heart type fatty acid binding protein; cTnI, cardiac troponin I; LVEF, left ventricular ejection fraction.

patients suffering from acute myocardial infarction with varying diagnostic areas under ROC curves.<sup>31,32</sup> However, hFABP sometimes generates conflicting results when combined with cTnI for early diagnosis of acute myocardial infarction.<sup>33,34</sup> cTnI has reliable accuracy for early diagnosis of acute myocardial infarction with an AUC of 0.95.<sup>35,36</sup> Levels of cTnI are frequently elevated in patients with HF and can be an indicator for high mortality in emergency departments.<sup>37</sup> Additionally, circulating cTn levels are highly specific for measuring myocardial damage<sup>38</sup> and are associated with acute and advanced chronic HF.<sup>39,40</sup> High hFABP and cTnI levels in patients with a high NYHA functional class and HF in our study suggested that there might be more myocardial cell injury or progressive necrosis, which is consistent with a previous report.<sup>41</sup>

ROC curve analysis showed that the AUCs based on the four parameters for mortality were > 0.5, which indicated that they might have prognostic value for HF. For prognosis of HF, NT-proBNP had the highest prognostic value (AUC = 0.901) followed by prealbumin, hFABP, and cTnI. For prognosis of mortality, hFABP had the highest AUC of 0.721, followed by NT-proBNP, prealbumin, and cTnI. These results are consistent with previous reports.<sup>42,43</sup> However, when these four parameters were used together, the diagnostic accuracy significantly improved compared with single biomarkers. Additionally, the AUC reached 0.903 for mortality of HF and the specificity and specificity increased to 95.0% and 95.6% for HF and to 93.9% and 91.4% for mortality, respectively. These findings indicated that the multimarker approach increases prognostic reliability for elderly patients with HF. A combination of uric acid and NT-ProBNP was shown to be a better prognostic marker for short-term clinical outcomes in patients with acute HF.<sup>42</sup> Multimarker strategy is essential for

accurate prediction of cardiac death in patients with acutely decompensated chronic HF.<sup>44</sup>

In the current study, when these cutoffs were used to stratify risk, Kaplan–Meier survival curve analysis showed that the survival probability was high when prealbumin levels were above and other parameter levels were below the cutoff values. This finding suggests that these measurements can be used as objective indicators of risk stratification in patients with HF. Furthermore, multivariate Cox regression analysis showed that the four parameters were significant risk factors for MACEs and death. Levels of cTnI can be detected in the blood of patients with HF. Even when cTnI levels are within the normal range, their detection is an indication of a poor prognosis of patients, particularly if serum cardiac troponin T levels are persistently high, despite conventional treatment.<sup>45</sup> This finding is probably due to ongoing subclinical degeneration of myocytes associated with deterioration of the patients' clinical status. In our study, patients with HF and high cTnI levels had a significantly higher mortality rate than those with low cTnI levels (33.8% vs 12.7%,  $P < 0.05$ ). This finding is consistent with a previous study.<sup>46</sup>

In this study, we measured prealbumin, NT-ProBNP, hFABP, and cTnI levels before and after treatment. We found that changes in these levels were different among patients with a different prognosis. In the non-MACE group, levels of these four parameters improved as the treatment time increased. However, in patients in the readmission and cardiac death groups, these levels deteriorated or remained unchanged over the treatment period. These findings were particularly remarkable for NT-proBNP and cTnI levels. Therefore, these parameters can be used to predict the progress of therapy. This finding is also in line with previous studies that showed that

persistently increased serum cardiac troponin levels in patients with acute HF are predictive of adverse outcomes.<sup>47</sup> Therefore, patients should be monitored continuously during the therapy period for better management of HF.

## Conclusion

Our study shows that serum prealbumin, NT-proBNP, hFABP, and cTnI levels are significant predictors for prognosis of elderly patients with HF and poor cardiac function, and are more accurate when used in combination. These parameters can be used to judge the severity of HF and monitor therapeutic progress for better management of HF.

## Availability of data and material

The datasets used during the current study are available from the corresponding author on reasonable request.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.


## Funding


This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## Author contributions

KL and GC designed the study. KL and SG collected the data and performed analysis. SW analyzed the data and revised the manuscript. KL and GC drafted the manuscript. All authors read and approved the final manuscript.

## ORCID iDs

Shengzhuo Wang  <https://orcid.org/0000-0002-9443-8681>

Ge Cui  <https://orcid.org/0000-0001-7626-6583>

## References

1. Uretsky BF and Sheahan RG. Primary prevention of sudden cardiac death in heart failure: will the solution be shocking? *J Am Coll Cardiol* 1997; 30: 1589–1597. DOI: 10.1016/s0735-1097(97)00361-6.
2. Group CTS. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; 316: 1429–1435. DOI: 10.1056/NEJM198706043162301.
3. Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). *Am Heart J* 1997; 134: 44–54. DOI: 10.1016/s0002-8703(97)70105-4.
4. Braunwald E. Biomarkers in heart failure. *N Engl J Med* 2008; 358: 2148–2159. DOI: 10.1056/NEJMra0800239.
5. Mega JL, Morrow DA, De Lemos JA, et al. B-type natriuretic peptide at presentation and prognosis in patients with ST-segment elevation myocardial infarction: an ENTIRE-TIMI-23 substudy. *J Am Coll Cardiol* 2004; 44: 335–339. DOI: 10.1016/j.jacc.2004.04.033.
6. Omland T, De Lemos JA, Sabatine MS, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med* 2009; 361: 2538–2547. DOI: 10.1056/NEJMoa0805299.
7. De Greef J, Funk M, Vermaak WJ, et al. NT-proBNP and the diagnosis of exercise-induced myocardial ischaemia. *Cardiovasc J Afr* 2008; 19: 264–267.
8. Premer C, Kanelidis AJ, Hare JM, et al. Rethinking Endothelial Dysfunction as a Crucial Target in Fighting Heart Failure. *Mayo Clin Proc Innov Qual Outcomes* 2019; 3: 1–13. DOI: 10.1016/j.mayocpiqo.2018.12.006.
9. Sann L, Bienvenu F, Bienvenu J, et al. Evolution of serum prealbumin, C-reactive protein, and orosomucoid in neonates with bacterial infection. *J Pediatr* 1984; 105: 977–981. DOI: 10.1016/s0022-3476(84)80094-3.
10. Tempel Z, Grandhi R, Maserati M, et al. Prealbumin as a serum biomarker of impaired perioperative nutritional status and risk for surgical site infection after spine surgery. *J Neurol Surg A Cent Eur Neurosurg* 2015; 76: 139–143. DOI: 10.1055/s-0034-1394188.
11. Cardenas D, Blonde-Cynober F, Ziegler F, et al. Should a single centre for the assay of biochemical markers of nutritional status be mandatory in multicentric trials? *Clin Nutr* 2001; 20: 553–558. DOI: 10.1054/clnu.2001.0498.
12. Hall C. NT-ProBNP: the mechanism behind the marker. *J Card Fail* 2005; 11: S81–S83. DOI: 10.1016/j.cardfail.2005.04.019.
13. Offner GD, Brecher P, Sawlivich WB, et al. Characterization and amino acid sequence of a fatty acid-binding protein from human heart. *Biochem J* 1988; 252: 191–198. DOI: 10.1042/bj2520191.
14. Wang TY, Liu M, Portincasa P, et al. New insights into the molecular mechanism of intestinal fatty acid absorption. *Eur J Clin Invest* 2013; 43: 1203–1223. DOI: 10.1111/eci.12161.
15. Fournier NC and Richard MA. Role of fatty acid-binding protein in cardiac fatty acid oxidation. *Mol Cell Biochem* 1990; 98: 149–159. DOI: 10.1007/BF00231379.
16. Thompson BR, Houang EM, Sham YY, et al. Molecular determinants of cardiac myocyte performance as conferred by isoform-specific TnI residues. *Biophys J* 2014; 106: 2105–2114. DOI: 10.1016/j.bpj.2014.04.017.
17. Vetter AD, Houang EM, Sell JJ, et al. TnI Structural Interface with the N-Terminal Lobe of TnC as a Determinant of Cardiac Contractility. *Biophys J* 2018; 114: 1646–1656. DOI: 10.1016/j.bpj.2018.02.015.
18. Cardiology CSO. Guidelines for diagnosis and treatment of chronic heart failure. *Chinese Journal of Cardiology* 2007; 35: 1076–1095.
19. Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical

- nomenclature. *Circulation* 1979; 59: 607–609. DOI: 10.1161/01.cir.59.3.607.
20. Taniguchi R, Sato Y, Nishio Y, et al. Measurements of baseline and follow-up concentrations of cardiac troponin-T and brain natriuretic peptide in patients with heart failure from various etiologies. *Heart Vessels* 2006; 21: 344–349. DOI: 10.1007/s00380-006-0909-1.
  21. De Vecchis R, Esposito C, Di Biase G, et al. B-type natriuretic peptide-guided versus symptom-guided therapy in outpatients with chronic heart failure: a systematic review with meta-analysis. *J Cardiovasc Med (Hagerstown)* 2014; 15: 122–134. DOI: 10.2459/JCM.0b013e328364bde1.
  22. Chen AA, Wood MJ, Krauser DG, et al. NT-proBNP levels, echocardiographic findings, and outcomes in breathless patients: results from the ProBNP Investigation of Dyspnoea in the Emergency Department (PRIDE) echocardiographic substudy. *Eur Heart J* 2006; 27: 839–845. DOI: 10.1093/eurheartj/ehi811.
  23. Gotsman I, Shauer A, Zwas DR, et al. Low serum albumin: A significant predictor of reduced survival in patients with chronic heart failure. *Clin Cardiol* 2019; 42: 365–372. DOI: 10.1002/clc.23153.
  24. Shen Q, Liu W, Quan H, et al. Prealbumin and lymphocyte-based prognostic score, a new tool for predicting long-term survival after curative resection of stage II/III gastric cancer. *Br J Nutr* 2018; 120: 1359–1369. DOI: 10.1017/S0007114518002854.
  25. Brink AJ, Richards GA, Lautenbach EE, et al. Albumin concentration significantly impacts on free teicoplanin plasma concentrations in non-critically ill patients with chronic bone sepsis. *Int J Antimicrob Agents* 2015; 45: 647–651. DOI: 10.1016/j.ijantimicag.2015.01.015.
  26. Peng W, Zhang C, Wang Z, et al. Prediction of all-cause mortality with hypoalbuminemia in patients with heart failure: a meta-analysis. *Biomarkers* 2019; 24: 631–637. DOI: 10.1080/1354750X.2019.1652686.
  27. Plakht Y, Gilutz H and Shiyovich A. Decreased admission serum albumin level is an independent predictor of long-term mortality in hospital survivors of acute myocardial infarction. Soroka Acute Myocardial Infarction II (SAMI-II) project. *Int J Cardiol* 2016; 219: 20–24. DOI: 10.1016/j.ijcard.2016.05.067.
  28. Palomo-Pinon S, Mora-Villalpando CJ, Del Carmen Prado-Urbe M, et al. Inflammation and myocardial damage markers influence loss of residual renal function in peritoneal dialysis patients. *Arch Med Res* 2014; 45: 484–488. DOI: 10.1016/j.arcmed.2014.07.003.
  29. Azzazy HM, Pelsers MM and Christenson RH. Unbound free fatty acids and heart-type fatty acid-binding protein: diagnostic assays and clinical applications. *Clin Chem* 2006; 52: 19–29. DOI: 10.1373/clinchem.2005.056143.
  30. Colli A, Josa M, Pomar JL, et al. Heart fatty acid binding protein in the diagnosis of myocardial infarction: where do we stand today? *Cardiology* 2007; 108: 4–10. DOI: 10.1159/000095594.
  31. Hartmann F, Kampmann M, Frey N, et al. Biochemical markers in the diagnosis of coronary artery disease. *Eur Heart J* 1998; 19: N2–N7.
  32. Dekker MS, Mosterd A, Van 't Hof AW, et al. Novel biochemical markers in suspected acute coronary syndrome: systematic review and critical appraisal. *Heart* 2010; 96: 1001–1010. DOI: 10.1136/hrt.2009.189886.
  33. Lippi G, Mattiuzzi C and Cervellin G. Critical review and meta-analysis on the combination of heart-type fatty acid binding protein (H-FABP) and troponin for early diagnosis of acute myocardial infarction. *Clin Biochem* 2013; 46: 26–30. DOI: 10.1016/j.clinbiochem.2012.10.016.
  34. McMahon CG, Lamont JV, Curtin E, et al. Diagnostic accuracy of heart-type fatty acid-binding protein for the early diagnosis of acute myocardial infarction. *Am J Emerg Med* 2012; 30: 267–274. DOI: 10.1016/j.ajem.2010.11.022.
  35. Boeddinghaus J, Nestelberger T, Koechlin L, et al. Early Diagnosis of Myocardial Infarction With Point-of-Care High-Sensitivity Cardiac Troponin I. *J Am Coll Cardiol* 2020; 75: 1111–1124. DOI: 10.1016/j.jacc.2019.12.065.
  36. Boeddinghaus J, Nestelberger T, Twerenbold R, et al. High-Sensitivity Cardiac Troponin I

- Assay for Early Diagnosis of Acute Myocardial Infarction. *Clin Chem* 2019; 65: 893–904. DOI: 10.1373/clinchem.2018.300061.
37. Jacob J, Roset A, Miro O, et al. EAHFE - TROPICA2 study. Prognostic value of troponin in patients with acute heart failure treated in Spanish hospital emergency departments. *Biomarkers* 2017; 22: 337–344. DOI: 10.1080/1354750X.2016.1265006.
  38. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation* 2018; 138: e618–e651. DOI: 10.1161/CIR.0000000000000617.
  39. Peacock WF 4th, De Marco T, Fonarow GC, et al. Cardiac troponin and outcome in acute heart failure. *N Engl J Med* 2008; 358: 2117–2126. DOI: 10.1056/NEJMoa0706824.
  40. Kociol RD, Pang PS, Gheorghiane M, et al. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. *J Am Coll Cardiol* 2010; 56: 1071–1078. DOI: 10.1016/j.jacc.2010.06.016.
  41. Sato Y, Kita T, Takatsu Y, et al. Biochemical markers of myocyte injury in heart failure. *Heart* 2004; 90: 1110–1113. DOI: 10.1136/hrt.2003.023895.
  42. Park HS, Kim H, Sohn JH, et al. Combination of uric acid and NT-ProBNP: a more useful prognostic marker for short-term clinical outcomes in patients with acute heart failure. *Korean J Intern Med* 2010; 25: 253–259. DOI: 10.3904/kjim.2010.25.3.253.
  43. He Y, Li F, Du Z, et al. The clinical significance on the combined detection of the serum BNP, hs-CRP, cTnI and UA in heart failure. *Laboratory Medicine* 2012; 27: 647–651.
  44. Zairis MN, Tsiaousis GZ, Georgilas AT, et al. Multimarker strategy for the prediction of 31 days cardiac death in patients with acutely decompensated chronic heart failure. *Int J Cardiol* 2010; 141: 284–290. DOI: 10.1016/j.ijcard.2008.12.017.
  45. Sato Y, Yamada T, Taniguchi R, et al. Persistently increased serum concentrations of cardiac troponin t in patients with idiopathic dilated cardiomyopathy are predictive of adverse outcomes. *Circulation* 2001; 103: 369–374. DOI: 10.1161/01.cir.103.3.369.
  46. Chen X and Yao G. The relationship between recent-onset of heart failure in acute myocardial infarction and the changes in serum troponin-I. *China Journal of Modern Medicine* 12: 51–55.
  47. Kuwabara Y, Sato Y, Miyamoto T, et al. Persistently increased serum concentrations of cardiac troponin in patients with acutely decompensated heart failure are predictive of adverse outcomes. *Circ J* 2007; 71: 1047–1051. DOI: 10.1253/circj.71.1047.