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ORIGINAL RESEARCH

The predictive capacity and additional prognostic power of N-terminal pro-B-type natriuretic peptide in Chinese elderly with chronic heart failure

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Objective: This study was conducted to research the prognostic utility of N-terminal pro-B-type natriuretic peptide (NT-proBNP), compare the utility of the Seattle Heart Failure Score (SHFS) with NT-proBNP, develop a risk-evaluation model based on NT-proBNP, assess the associations of NT-proBNP with patient characteristics, and screen for decisive factors of NT-proBNP in Chinese elderly with chronic heart failure (CHF).

Patients and methods: There were 306 patients (≥60 years) with CHF chosen as study subjects. Each one received an assessment of NT-proBNP on serum. The end point was all-cause mortality during a mean follow-up period of 471 days.

Results: Subjects had a median age of 85 (60–100) years, a median NT-proBNP of 1,743.4 pg/mL, and a median SHFS of 1.87. During the follow-up period, 104 deaths occurred. NT-proBNP was significantly related to mortality (odds ratio 1.603, 95% confidence interval 1.407–1.826; $P<0.001$) and the significance persisted after full adjustment (odds ratio 1.282, 95% confidence interval 1.103–1.489; $P=0.001$). Age, New York Heart Association class IV CHF, plasma albumin, and neutrophils/lymphocytes were also independent predictors for mortality ($P<0.05$ for all). NT-proBNP and the SHFS showed similar predictive capacities (0.736 versus 0.796, $P=0.105$). The addition of NT-proBNP to the SHFS (0.818 versus 0.796, $P=0.168$) generated marginal growth in the *c*-statistic. The model based on NT-proBNP consisting of all selected predictors in this study, including age, New York Heart Association class IV CHF, plasma albumin, neutrophils/lymphocytes, and NT-proBNP, had a moderately higher *c*-statistic compared with the SHFS (0.846 versus 0.796, $P=0.066$). NT-proBNP was bound with the SHFS ($r=0.500$, $P<0.001$). Characteristics regarding general condition, inflammation, and cardiac and renal function were the decisive factors of NT-proBNP ($P<0.05$ for all).

Conclusion: As a comprehensive representation of the patient characteristics described earlier, NT-proBNP values provided significant prognostic power similar to the SHFS in Chinese elderly with CHF. A novel model based on NT-proBNP could offer help for risk stratification.

Keywords: NT-proBNP, prognosis, chronic heart failure, elderly

Introduction

The elderly represent a growing proportion of patients with chronic heart failure (CHF), and CHF is a leading source of morbidity and mortality in the elderly.[1,2] Accurate prognostic evaluation of elderly with CHF is an increasingly important clinical goal for physicians. Current understanding of the risk factors for survival of the elderly with CHF has been derived largely from former studies, which mainly focused on traditional risk factors and did not aim directly at contemporary elderly. Moreover,

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ethnicity plays a significant role in prognostic evaluation of elderly with CHF, and the same risk factors might have different influences on mortality, due to ethnicity disparities. Specific and newer risk factors for contemporary elderly have been less thoroughly investigated, especially in the People's Republic of China.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is recognized as a prognostically meaningful biomarker in patients with CHF.[3,4] However, few investigators have attempted to make use of NT-proBNP values to assess the risk of elderly with CHF.[5] The Seattle Heart Failure Score (SHFS) has been developed to determine the risk of dying, and has been validated as a useful tool in estimating CHF mortality in several data sets.[6] Whether NT-proBNP values have similar or superior predictive capacities compared to the SHFS is uncertain.[7] In addition, the novel risk-evaluation model combining NT-proBNP values and other significant risk factors is more likely to provide better prognostic evaluation of patients with CHF. Meanwhile, for the convenience of a better understanding of the prognostic information of NT-proBNP values, their correlations with traditional risk factors have received attention.

To address these issues, the purposes of the current analysis were the following: 1) to research the prognostic utility of NT-proBNP values, compare the utility of the SHFS with NT-proBNP values, and tentatively develop the risk-evaluation model based on NT-proBNP values in older Chinese patients with CHF; and 2) to assess the associations between NT-proBNP values and characteristics of older Chinese patients with CHF and screen for decisive factors of NT-proBNP values.

Patients and methods

Study population

There were 306 older patients (≥60 years) chosen as study subjects. They had long-standing symptoms (dyspnea and/or fatigue), signs (edema and/or pulmonary rales), and abnormalities of cardiac structure or function, and was diagnosed with CHF by chief physicians or associate chief physicians according to European Society of Cardiology (ESC) 2008 guidelines.[8] Each patient received an assessment of serum NT-proBNP. Excluded from the current analysis were patients with severe aortic stenosis, anticipated cardiac transplantation, and left ventricular assist devices. The Chinese People's Liberation Army General Hospital was their designated hospital and held their integrated long-term medical and death records, which made it easier for us to follow them up effectively and judge end points accurately.

Physical measurements

Baseline characteristics were collected from all patients after admission to the Chinese People's Liberation Army General Hospital, and the measurements were completed by physicians who were well trained by the research team. Body mass index (BMI) was defined as weight in kilograms divided by the square of height in meters. Mean systolic blood pressure (MSBP) and mean diastolic blood pressure (MDBP) were the averages of five separate measurements. Standardized echocardiography was performed. Left ventricular ejection fraction was measured by Simpson's method. Left ventricular mass was calculated as $0.80\times1.04\times([IVST + LVPWTd + LVDd]^3 - LVDd^3) + 0.60$, and was indexed to body surface area ($[m^2 = 0.0061\times \text{height [cm]} + 0.0128\times \text{weight [kg]} - 0.153$) to compute the left ventricular mass index.

Biochemical analyses

Blood assays were carried out at the central laboratory in the Department of Biochemistry, Chinese People's Liberation Army General Hospital. The technicians who performed the tests were blinded to the clinical data of the subjects. Serum NT-proBNP values were measured by the NT-proBNP Flex Reagent Cartridge (PBNP/LPBN), produced by Siemens Healthcare Diagnostics, on the Dimension RXL Max (AMR 10–30,000 pg/mL). Estimated glomerular filtration rate (eGFR) was calculated by a modified Modification of Diet in Renal Disease (MDRD) equation based on data from Chinese patients: $175\times \text{serum creatinine (mg/dL)}^{-1.234} \times \text{age (years)}^{-0.179} \times 0.79$ (if female).[9]

Definitions

Acute myocardial infarction and atrial fibrillation (AF) were defined on the grounds of the universal definition of myocardial infarction and the American College of Cardiology/American Heart Association/ESC 2006 guidelines for AF.[10,11] Subjects with MSBP ≥140 mmHg, MDBP ≥90 mmHg, or receiving medication for treatment of hypertension were defined as having hypertension, and with fasting glucose concentration ≥7 mmol/L or treatment with an oral hypoglycemic agent/insulin as having diabetes mellitus. Metabolic syndrome was determined as the presence of at least three of the following criteria of the Chinese Diabetes Society: 1) BMI ≥25 kg/m^2; 2) triglycerides ≥1.7 mmol/L; 3) high-density lipoprotein cholesterol <0.9 mmol/L in men and <1.0 mmol/L in women; 4) MSBP ≥140 mmHg or MDBP ≥90 mmHg; and 5) fasting glucose concentration ≥6.1 mmol/L. Smoking status was categorized as current, former, and never. Subjects were considered to be

current smokers if they had smoked one or more cigarettes per day for the last year. Former smoking was defined as a history of cigarette consumption on a regular basis (one or more cigarettes per day), but no current smoking.

End point

Given the obviously high incidence of multiple organ failure in the elderly, as well as the priority of all-cause mortality in outcome studies, the end point assessed in the current analysis was all-cause death. The study population had a mean follow-up period of 471 days (median 342 days). Follow-up data were obtained from a review of medical records and telephone contact. No patients were lost to follow-up. Death was ascertained from the death record, a legal document including time, site, and other information.

Calculation of the score

The SHFS was derived in the PRAISE1 database, and provided an estimate of survival of patients with CHF.[6] The hazard ratios for certain CHF medications in the SHFS could not be effectively estimated in PRAISE1, because of either widespread or rare use, and were results directly from prior clinical trials. They might not be generalizable to a wider population with CHF, and were abandoned in the current analysis.[6]

Statistical methods

Continuous variables were described using mean and standard deviation for variables with normal distribution and by median and interquartile range for nonnormally distributed variables. Categorical data were expressed as number and percentage of total. NT-proBNP values were logarithmically transformed to meet the multinormality assumption. In order to test prognostic abilities of NT-proBNP values and other risk factors for mortality, covariates with $P<0.10$ were picked up by Cox regression univariate analysis and taken into a Cox regression multivariate model with death as the dependent variable. Survival curves were generated by means of Kaplan–Meier estimates. The added predictive abilities of NT-proBNP values to the SHFS regarding mortality were investigated by comparison of areas under the curve (*c*-statistics) between the score and score + NT-proBNP values. Correlations between NT-proBNP values and other variables were determined by Pearson's or Spearman's correlation coefficients, and covariates with $P<0.10$ were taken into a multiple linear regression analysis to decide independent determinants of NT-proBNP values. A two-tailed *P*-value of less than 0.05 was considered to be statistically significant. All information on the characteristics of patients was entered into the database by trained abstractors and checked by other independent abstractors. SPSS 17 (SPSS, Chicago, USA) and MedCalc 9.6 for Windows (MedCalc Software, Mariakerke, Belgium) were used as the statistical systems.

Results

The whole cohort had a median age of 85 (60–100) years, a median NT-proBNP value of 1,743.4 pg/mL, and a median SHFS of 1.87. Patient characteristics for all patients are given in Table 1. During the follow-up period, 104 deaths occurred (34% of the whole cohort). NT-proBNP values were significantly related to all-cause death (hazard ratio 1.603, 95% confidence interval 1.407–1.826; $P<0.001$) and the significance persisted (hazard ratio 1.282, 95% confidence interval 1.103–1.489; $P=0.001$) after adjusting for all the factors in Table 1. In addition to NT-proBNP values, other factors, including age, New York Heart Association class IV CHF, plasma albumin, and neutrophils/lymphocytes, were also independent predictors for mortality ($P<0.05$ for all). The unadjusted influences of NT-proBNP values and other variables on mortality are displayed in Table 1. The independent prognostic abilities of NT-proBNP values and other predictors for mortality are provided in Table 2. Meanwhile, Kaplan–Meier estimates of survival for all subjects according to the quartile of NT-proBNP values are shown in Figure 1.

Table 3 demonstrates that NT-proBNP values and the SHFS showed similar predictive capacities (0.736 versus 0.796, $P=0.105$). The addition of NT-proBNP values to the SHFS (0.818 versus 0.796, $P=0.168$) generated a marginal growth in the *c*-statistic (Figure 2). The model based on NT-proBNP values consisting of all selected predictors in the current analysis, including age, New York Heart Association class IV CHF, plasma albumin, neutrophils/lymphocytes, and NT-proBNP values, had a moderately higher *c*-statistic compared with the SHFS (0.846 versus 0.796, $P=0.066$).

NT-proBNP values were bound with the SHFS ($r=0.500$, $P<0.001$). The univariate correlations of NT-proBNP values with patient characteristics are shown in Table 1. The multivariate regression model indicated that NT-proBNP values were positively linked to acute myocardial infarction, New York Heart Association class IV CHF, AF, C-reactive protein, left ventricular mass index, and right atrial diameter ($P<0.05$ for all). In turn, there was negative relevance of NT-proBNP values with BMI, MDRD-eGFR, plasma albumin, and ejection fraction ($P<0.05$ for all). The independent factors associated with NT-proBNP values are listed in Table 4.

Table 1 Patient characteristics and their correlations with NT-proBNP values, along with their unadjusted influences on mortality

Variables	Descriptions	r[a]	P[b]	HR[c]	P[d]
Demographics					
Age (years)[e]	85.0 (80.0–89.0)	0.023	0.685	1.051	0.001
Males (%)	248 (81.0)	0.028	0.625	0.867	0.600
History of smoking					
Never (%)	191 (62.4)				
Former (%)	98 (32.0)	0.010	0.856	0.852	0.433
Current (%)	17 (5.6)	0.090	0.116	0.932	0.868
BMI (kg/m^2)[e]	23.1 (20.6–25.7)	–0.178	0.002	0.954	0.077
Diseases					
AMI (%)	29 (9.5)	0.220	<0.001	2.762	<0.001
NYHA class IV CHF (%)	78 (25.5)	0.334	<0.001	3.537	<0.001
Hypertension (%)	246 (80.4)	–0.063	0.271	0.759	0.251
DM (%)	136 (44.4)	–0.013	0.826	1.216	0.320
Atrial fibrillation (%)	96 (31.4)	0.208	<0.001	1.106	0.631
Metabolic syndrome (%)	126 (41.2)	0.024	0.675	1.417	0.077
Clinical presentation					
HR (bpm)[e]	73.0 (64.8–82.3)	0.144	0.011	1.022	<0.001
MSBP (mmHg)[e]	131.0 (121.6–140.1)	–0.111	0.053	0.987	0.084
MDBP (mmHg)[e]	67.4 (62.4–73.6)	–0.054	0.346	0.977	0.038
Investigative variables					
EF (%)[e]	57.0 (49.5–61.0)	–0.240	<0.001	0.988	0.255
IVS (mm)[e]	11.0 (10.0–12.0)	0.133	0.020	1.114	0.031
LVPW (mm)[e]	10.0 (10.0–11.0)	0.147	0.010	1.088	0.283
LVESD (mm)[e]	34.0 (32.0–38.3)	0.227	<0.001	1.010	0.497
LVEDD (mm)[e]	50.0 (46.3–54.0)	0.205	<0.001	1.010	0.491
LVMI (g/m)[e]	112.4 (97.0–132.2)	0.350	<0.001	1.007	0.010
LAD (mm)[e]	39.0 (35.0–43.0)	0.204	<0.001	1.005	0.752
RAD (mm)[e]	38.0 (35.0–41.8)	0.187	0.001	1.013	0.412
RVD (mm)[e]	36.0 (34.0–38.0)	0.122	0.034	1.008	0.724
AD (mm)[e]	35 (32.0–37.0)	–0.071	0.224	0.987	0.554
PD (mm)[e]	25.0 (23.0–26.9)	0.092	0.123	1.042	0.166
Laboratory results					
NT-proBNP (pg/mL)[e]	1743.4 (513.5–4796.3)			1.603	<0.001
Hemoglobin (g/L)[f]	115.2 (22.1)	–0.314	<0.001	0.974	<0.001
Plasma albumin (g/L)[f]	36.6 (4.5)	–0.325	<0.001	0.850	<0.001
Glucose (mmol/L)[e]	5.6 (4.9–6.6)	0.054	0.342	1.100	0.007
Cholesterol (mmol/L)[e]	3.8 (3.2–4.3)	–0.096	0.097	0.976	0.814
Triglyceride (mmol/L)[e]	1.2 (0.9–1.9)	–0.047	0.413	1.129	0.138
HDL-C (mmol/L)[e]	1.0 (0.8–1.2)	–0.124	0.031	0.284	<0.001
LDL-C (mmol/L)[e]	2.1 (1.6–2.6)	–0.138	0.017	0.920	0.515
MDRD-eGFR (mL/min/1.73 m^2)[f]	59.7 (23.2)	–0.340	<0.001	0.986	0.001
Uric acid (mmol/L)[e]	389.6 (297.0–458.7)	0.231	<0.001	1.002	0.004
Sodium (mmol/L)[e]	140.0 (136.2–142.4)	–0.057	0.317	0.981	0.287
ALT (U/L)[e]	14.2 (10.1–19.8)	–0.108	0.060	1.002	0.311
N/L (100%)[e]	2.9 (2.0–5.0)	0.337	<0.001	1.066	<0.001
CRP (mg/dL)[e]	1.2 (0.3–3.9)	0.210	<0.001	1.047	0.003
Fibrinogen (g/L)[e]	3.7 (3.0–4.6)	0.162	0.005	1.333	<0.001

Notes: [a]Correlation coefficients; [b]for correlations; [c,d]for Cox regression univariate analysis; [e]median (interquartile range); [f]mean (standard deviation).

Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; HR, hazard ratio; BMI, body mass index; AMI, acute myocardial infarction; NYHA, New York Heart Association; CHF, chronic heart failure; DM, diabetes mellitus; HR, heart rate; MSBP, mean systolic blood pressure; MDBP, mean diastolic blood pressure; EF, ejection fraction; IVS, interventricular septum; LVPW, left ventricular posterior wall; LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; LVMI, left ventricular mass index; LAD, left atrial diameter; RAD, right atrial diameter; RVD, right ventricular diameter; AD, aortic dimension; PD, pulmonic dimension; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDRD-eGFR, estimated glomerular filtration rate calculated by modified Modification of Diet in Renal Disease equation; ALT, alanine transaminase; N/L, neutrophils/lymphocytes; CRP, C-reactive protein.

Table 2 Independent risk factors of mortality

Risk factors[a]	Adjusted HR	95% CI	*P*
Age (years)	1.039	1.007–1.072	0.016
NYHA class IV CHF	1.890	1.250–2.858	0.003
Plasma albumin (g/L)	0.926	0.881–0.973	0.002
N/L (100%)	1.039	1.007–1.073	0.016
NT-proBNP (pg/mL)	1.282	1.103–1.489	0.001

Notes: [a]Cox regression multivariate model with adjustment of all the factors.
Abbreviations: HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association; CHF, chronic heart failure; N/L, neutrophils/lymphocytes; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 3 Prognostic abilities of NT-proBNP values and model based on NT-proBNP values compared with the SHFS

	c-Statistic (95% CI)	*Z*	*P*
NT-proBNP	0.736 (0.683–0.785)		
SHFS	0.796 (0.746–0.840)	1.620	0.105[a]
SHFS + NT-proBNP	0.818 (0.770–0.860)	1.377	0.168[b]
Model based on NT-proBNP	0.846 (0.801–0.885)	1.836	0.066[c]

Notes: [a]Drawn from comparison between SHFS and NT-proBNP values; [b]drawn from comparison between SHFS + NT-proBNP values and the SHFS; [c]drawn from comparison of the model based on NT-proBNP values consisting of all selected predictors in the current analysis including age, New York Heart Association class IV chronic heart failure, plasma albumin, neutrophils/lymphocytes, and NT-proBNP values with the SHFS.
Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; SHFS, Seattle Heart Failure Score; CI, confidence interval.

Discussion

The current analysis demonstrated that NT-proBNP values were independent predictors of outcome and predictive capacity was comparable between NT-proBNP values and the SHFS in Chinese elderly with CHF. Moreover, this analysis formulated a risk-evaluation model based on NT-proBNP values consisting of all selected predictors in the current analysis, including age, New York Heart Association class IV CHF, plasma albumin, neutrophils/lymphocytes, and NT-proBNP values. Finally, the relationships between NT-proBNP values and several clinical features of Chinese elderly with CHF were thoroughly evaluated.

NT-proBNP values have previously shown their predictive ability in general patients with CHF.[3,4] One study tried to determine the effect of age on the short-term prognostic abilities of NT-proBNP values in elderly with CHF.[12] However, its study population was restricted to Caucasians with a mean age of 73.1 years, and thus its results might not be suitable for very older patients of other ethnicities. The current analysis verified that NT-proBNP values carried independent prognostic information in Chinese elderly and very elderly with CHF. As a comprehensive representation of the decisive factors described earlier, the predictive power of NT-proBNP values was obvious in Chinese elderly with CHF.

The SHFS is a multimarker and validated model, developed to predict mortality in patients with CHF.[6] NT-proBNP values have been observed to have similar or superior predictive capacities compared to the SHFS.[7] However, there was no analogous study with Chinese elderly as the study population. In the current analysis, NT-proBNP values showed similar prognostic value with respect to the complex SHFS. The addition of NT-proBNP values to the SHFS resulted in a marginal improvement in risk assessment. Moreover,

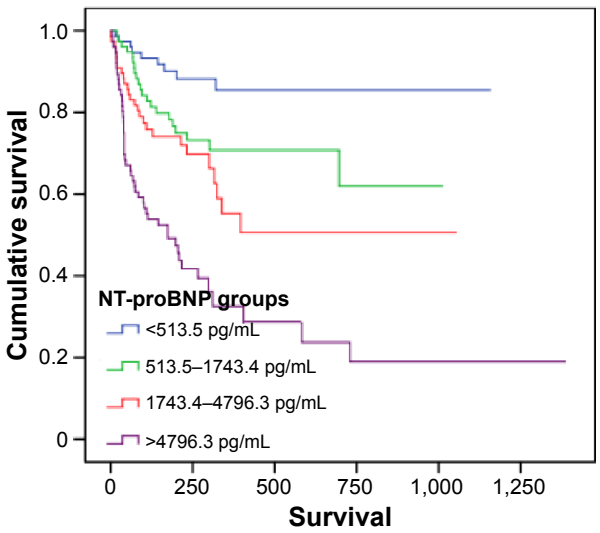

Figure 1 Kaplan–Meier estimate of survival for all subjects according to the quartile of NT-proBNP values.
Abbreviation: NT-proBNP, N-terminal pro-B-type natriuretic peptide.

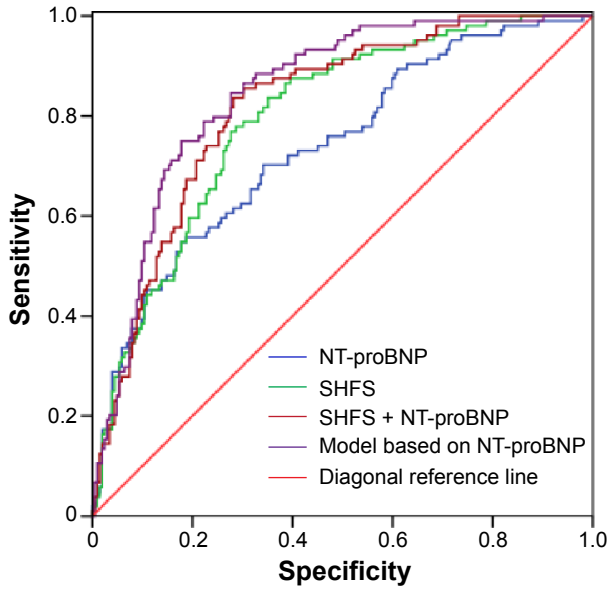

Figure 2 Comparison of *c*-statistic between NT-proBNP values, SHFS, and our model based on NT-proBNP values.
Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; SHFS, Seattle Heart Failure Score.

Table 4 Independent determinants of NT-proBNP values

Variables[a]	β	95% CI	P
AMI	0.665	0.199–1.131	0.005
NYHA class IV CHF	0.497	0.180–0.815	0.002
Atrial fibrillation	0.807	0.513–1.101	<0.001
BMI (kg/m^2)	–0.048	–0.083 to –0.012	0.009
MDRD-eGFR (mL/min/1.73 m^2)	–0.022	–0.028 to –0.017	<0.001
Plasma albumin (g/L)	–0.076	–0.107 to –0.045	<0.001
CRP (mg/dL)	0.053	0.022–0.085	0.001
Ejection fraction (%)	–0.024	–0.039 to –0.010	0.001
LVMI (g/m)	0.011	0.007–0.016	<0.001
RAD (mm)	0.026	0.002–0.049	0.030

Notes: [a]Multiple linear regression model with adjustment of all the factors.
Abbreviations: NT-proBNP, N-terminal pro B-type natriuretic peptide; CI, confidence interval; AMI, acute myocardial infarction; NYHA, New York Heart Association; CHF, chronic heart failure; BMI, body mass index; MDRD-eGFR, estimated glomerular filtration rate calculated by modified Modification of Diet in Renal Disease equation; CRP, C-reactive protein; LVMI, left ventricular mass index; RAD, right atrial diameter.

the model based on NT-proBNP values provided modestly superior predictive ability than the SHFS.

The current analysis demonstrated that in Chinese elderly with CHF, elevated NT-proBNP values reflected the abnormality of cardiac structure and function, as well as lesions of cardiac tissue. Additionally, the elevation of NT-proBNP values had an independent relationship with reduced renal clearance, which was in agreement with other studies.[13] The degree to which increased NT-proBNP values tied to AF itself versus its comorbidities, such as left ventricular hypertrophy, was debated, and the current analysis suggests that AF itself had a direct association with NT-proBNP values.[14] Moreover, we validated the results of other studies wherein BMI exerted an independently inverse relation with NT-proBNP values.[5] The conclusion of the current analysis was in line with prior studies that hypoalbuminemia was independently related to NT-proBNP values. The current analysis showed that C-reactive protein was independently associated with elevated NT-proBNP values, and supported the relevance between NT-proBNP values and inflammation.[15]

Conclusion

The current analysis showed that as a comprehensive representation of general condition, inflammation, and cardiac and renal function, NT-proBNP values provided significant prognostic power similar to the SHFS in Chinese elderly with CHF. Moreover, a novel model based on NT-proBNP values could offer some help for risk stratification.

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Disclosure

The authors report no conflicts of interest in this work.

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