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# Decreased albumin is associated with elevated N-terminal pro-brain natriuretic peptide and poor long-term prognosis in patients with chronic heart failure

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**Abstract**

At present, the association between albumin, N-terminal pro-brain natriuretic peptide (NT-proBNP) and long-term prognosis in patients with chronic heart failure (CHF) is unclear. Therefore, the purpose of this study is to explore the relationship between albumin, NT-proBNP and all-cause mortality in CHF patients.

Three hundred fifty two CHF patients were recruited in our study, and patients were divided into 2 groups according to the mean (37.16 g/L) of albumin concentration [low group (albumin < 37.16 g/L) and high group (albumin≥37.16 g/L)]. Differences between groups was compared by odds ratio (OR) and 95% confidence interval (CI).

NT-proBNP in the high group was significantly lower than that in the low group at baseline [1811.50 (698.75–4037.00) vs 3479.50 (1538.50–7824.25), $P < .001$]. Spearman correlation analysis showed that there was a negative correlation between albumin and NT-pro BNP log10 transform ($\rho = -0.217$, $P < .001$). Furthermore, curve fitting further confirmed that albumin was negatively correlated with NT-proBNP. After a median follow-up of 1726 days, 90 patients in the high group occur all-cause mortality, and 98 patients in the low group occur all-cause mortality (46.88% vs 61.25%, OR = 0.29, 95% CI: 0.08–0.50). After adjusting for the selected confounding covariates by multivariate regression analysis, decreased albumin was still associated with increased all-cause mortality (high group vs low group: OR = 0.62, 95% CI: 0.39–0.97).

Decreased albumin is associated with elevated NT-ProBNP and poor long-term prognosis in CHF patients. Clinicians need to pay enough attention to the nutritional status of CHF patients.

**Abbreviations:** CHF = chronic heart failure, CI = confidence interval, CHD = coronary heart disease, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, NT-proBNP = N-terminal pro-brain natriuretic peptide, OR = Odds ratio.

**Keywords:** albumin, chronic heart failure, NT-ProBNP, prognosis

## 1. Introduction

Chronic heart failure (CHF)[1–4] is an abnormality of cardiac structure or function caused by a series of diseases, which is characterized by cardiac systolic or diastolic dysfunction, resulting in insufficient cardiac pumping and body fluid retention. With the gradual increase of the elderly population, the number of people suffering from cardiovascular disease is on the rise worldwide,[5–7] and those population will inevitably develop to different degrees of heart failure. In developed countries, the prevalence rate of CHF among adults is about 1% to 2%, while for people over 70 years old, the prevalence rate of CHF is more than 10%.[8,9]

Although the current medical technology is becoming more and more improve and perfect, the clinical prognosis of CHF patients is still not optimistic.[10,11] Previous data show that 17% to 45% of CHF patients die 1 year after discharge, while most CHF patients die within 5 years globally.[12] On the other hand, data from the Chinese heart failure registry also show that the probability of in-hospital mortality among CHF patients is as high as 4.1%.[13] CHF has become a public health problem that needs to be paid more attention to in the whole world, which has brought a huge economic burden to the society and individuals, and is also one of the major challenges in the cardiovascular field.

Serum albumin plays a role in maintaining plasma colloid osmotic pressure and transporting various substances in human body.[14,15] Thus, it is usually used as one of the important indicators of nutritional status,[16] liver function[17] and disease prognosis.[18,19] Previous results have shown that decreased albumin is an independent risk factor for many diseases.[20–22] A retrospective cohort of 984 patients found that albumin was

*Editor: Robert Chen.*

*Data can be downloaded from public databases.*

*The authors declare that they have no competing interests.*

*The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.*

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*How to cite this article: Yi S, Chen M. Decreased albumin is associated with elevated N-terminal pro-brain natriuretic peptide and poor long-term prognosis in patients with chronic heart failure. Medicine 2020;99:51(e23872).*

*Received: 5 March 2020 / Received in final form: 11 November 2020 / Accepted: 23 November 2020*

*http://dx.doi.org/10.1097/MD.0000000000023872*

associated with the risk of acute renal injury after cardiac surgery.[23] Similarly, a cohort study of 2986 participants found a significant association between decreased albumin and increased risk of stroke, thromboembolic stroke, and cryptogenic stroke, and the authors further speculated that there might be some potential common pathophysiological relationship between albumin and thromboembolic and cryptogenic infarction.[24] However, few studies have reported the relationship between albumin and N-terminal pro-brain natriuretic peptide (NT-proBNP) and long-term prognosis in CHF patients, and lack of evidence to refine the risk stratification of CHF patients. Therefore, the purpose of this study is to explore the relationship between albumin, NT-proBNP and all-cause mortality in CHF patients.

## 2. Methods

### 2.1. Study population

This study is a single center, retrospective cohort study. Three hundred fifty two consecutive patients diagnosed as CHF in our hospital from July 2012 to July 2013 were recruited as the research object. Inclusion criteria: patient meets current CHF diagnostic criteria;[1,3] all patients were hospitalized due to the deterioration of cardiac function caused by heart diseases; cardiac function (New York Heart Association)[25] ≥class III. Exclusion criteria: Patients with acute myocardial infarction, acute stroke, aortic dissection, acute pulmonary embolism, impaired liver and kidney function, chronic obstructive pulmonary disease, cirrhosis, systemic infection, autoimmune disease, and hematological malignancy. This study has been approved by the ethics committee of The Second Affiliated Hospital of Guangxi Medical University.

### 2.2. Clinical information collection

We collected the baseline characteristics of participants through the electronic medical records of the Second Affiliated Hospital of Guangxi Medical University. The collected information includes age, gender, height, weight, albumin, creatine kinase, creatine kinase-MB, troponin I, NT-ProBNP, medication history, and disease history. The baseline characteristics of participants were collected face to face by nurses in cardiovascular medicine within 2 hours after admission. All the auxiliary examinations were carried out by the laboratory of the Second Affiliated Hospital of Guangxi Medical University within 2 hours after admission. The cardiac function grade was judged by 2 or more senior cardiovascular physicians.

### 2.3. Follow-up

The follow-up was started after admission, and the follow-up deadline of this study is July 2017. The primary outcome of this study was all-cause mortality, which mainly includes cardiovascular and non-cardiovascular death events. We mainly contact patients through telephone interview, wechat (make by Tencent, China), or QQ (make by Tencent, China). After positive screening for any potential heart event, a personal assessment was performed to determine if the outcome event had actually occurred. In addition, every 3 months, we screen the admission and discharge of patients in the Department of Cardiology in the Second Affiliated Hospital of Guangxi Medical University to find out the hospitalization and results that may not be recorded by telephone interview. When the patient has an outcome event, 2 cardiovascular physicians recheck it according to the patient's hospitalization record or death certificate.

### 2.4. Statistical analysis

Patients were divided into 2 groups according to the mean (37.16 g/L) of albumin concentration [low group (albumin<37.16 g/L) and high group (albumin≥37.16 g/L)]. Continuous variables satisfying normal distribution are represented by mean and standard deviation, and the differences between groups were compared by independent sample *t* test; Continuous variables that do not satisfy normal distribution are represented by median and quartile, and the differences between groups were compared by Kruskal–Wallis test. Classification variables are represented by number and percentage, and the differences between groups were compared by Chi-Squared test. Differences between groups was compared by odds ratio (OR) and 95% confidence interval (CI).

Considering the partial distribution of NT-proBNP, we used Spearman correlation analysis to explore the correlation between albumin and NT-proBNP. In addition, we used curve fitting to further explore the true relationship between albumin and NT-proBNP. On the other hand, we used univariate analysis to explore the covariates associated with all-cause mortality. Covariates with differences in univariate analysis ($P < .05$) will be further adjusted in multivariate regression analysis to explore the independent effect of albumin on all-cause mortality. In this study, SPSS and R software were used for statistical analysis, and $P < .05$ indicating significant difference between groups.

## 3. Results

### 3.1. Comparison of baseline characteristics between 2 groups

Table 1 shows the comparison of baseline characteristics between 2 groups. In 352 CHF patients, the mean albumin level was 37.16 ± 5.06 g/L (mean age 60.59 ± 13.70 years; 40.62% female). NT-proBNP in the high group was significantly lower than that in the low group [1811.50 (698.75–4037.00) vs 3479.50 (1538.50–7824.25), $P < .001$] at baseline (Table 1). Similarly, after a median follow-up of 1726 days, 90 patients in the high group occur all-cause mortality, and 98 patients in the low group occur all-cause mortality, which suggesting that the all-cause mortality in the high group is lower than that in the low group (46.88% vs 61.25%, OR = 0.29, 95% CI: 0.08–0.50) (Table 1). There were differences in gender, weight and troponin I between the 2 groups, but no significant differences in other variables at baseline (Table 1).

### 3.2. Correlation analysis of albumin and NT-pro BNP log10 transform

Considering the partial distribution of NT-proBNP, we used Spearman correlation analysis to explore the correlation between albumin and NT-pro BNP log10 transform. Spearman correlation analysis showed that there was a negative correlation between albumin and NT-pro BNP log10 transform ($\rho = -0.217$, $P < .001$) (Fig. 1). Furthermore, we further used curve fitting to explore the true relationship between albumin and NT proBNP, and curve fitting clarify that albumin was negatively correlated

**Table 1**

**Comparison of baseline characteristics between 2 groups.**

| Variables | Low group (albumin<37.16 g/L) | High group (albumin≥37.16 g/L) | Difference between groups | *P* value |
|---|---|---|---|---|
| N | 160 | 192 | | |
| Age, year | 59.01 ± 14.93 | 61.91 ± 12.47 | 0.21 (0.00, 0.42) | .078 |
| Height, cm | 161.43 ± 7.98 | 161.42 ± 8.68 | 0.00 (-0.21, 0.21) | .994 |
| Weight, kg | 57.98 ± 12.35 | 61.78 ± 13.84 | 0.29 (0.07, 0.51) | .018 |
| Creatine kinase, U/L | 81.50 (54.00–133.25) | 86.50 (56.00–140.00) | 0.09 (-0.13, 0.30) | .605 |
| Creatine kinase-MB, U/L | 16.00 (12.00–22.25) | 14.00 (11.00–20.00) | 0.05 (-0.17, 0.26) | .118 |
| Troponin I, μg/l | 0.05 (0.02–0.24) | 0.02 (0.01–0.16) | 0.01 (-0.22, 0.24) | .017 |
| LVEF (%) | 45.65 ± 6.12 | 44.87 ± 5.98 | 0.78 (-0.49, 2.05) | .23 |
| Albumin (g/L) | 32.96 ± 4.01 | 40.66 ± 2.55 | 2.29 (2.02, 2.56) | <.001 |
| NT-ProBNP, pg/ml | 3479.50 (1538.50–7824.25) | 1811.50 (698.75–4037.00) | 0.28 (0.07, 0.49) | <.001 |
| Follow-up duration (day) | 1290.70 ± 785.15 | 1343.99 ± 724.22 | 0.07 (-0.14, 0.28) | .509 |
| Sex, female | 55 (34.38%) | 88 (45.83%) | 0.24 (0.02, 0.45) | .029 |
| Cardiac function, class IV | 71 (44.38%) | 70 (36.46%) | 0.16 (-0.05, 0.37) | .131 |
| Coronary heart disease, yes | 64 (40.00%) | 75 (39.06%) | 0.02 (-0.19, 0.23) | .858 |
| Primary cardiomyopathy, yes | 31 (19.38%) | 44 (22.92%) | 0.09 (-0.12, 0.30) | .419 |
| Valvular heart disease, yes | 38 (23.75%) | 52 (27.08%) | 0.08 (-0.13, 0.29) | .475 |
| Hypertension, yes | 16 (10.00%) | 15 (7.81%) | 0.08 (-0.13, 0.29) | .471 |
| Beta-blockers, yes | 100 (62.50%) | 125 (65.10%) | 0.05 (-0.16, 0.26) | .612 |
| ACEI/ARB, yes | 83 (51.88%) | 116 (60.42%) | 0.17 (-0.04, 0.38) | .107 |
| Diuretic, yes | 95 (59.75%) | 119 (61.98%) | 0.05 (-0.16, 0.26) | .670 |
| All-cause mortality, yes | 98 (61.25%) | 90 (46.88%) | 0.29 (0.08, 0.50) | .007 |

Continuous variables satisfying normal distribution are represented by mean and standard deviation and continuous variables that do not satisfy normal distribution are represented by median and quartile. Classification variables are represented by number and percentage.

ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin II receptor blockers, LVEF = left ventricular ejection fraction, NT-proBNP = amino-terminal pro-brain natriuretic peptide.

with NT-proBNP, which is consistent with the results of Spearman correlation analysis (Fig. 2).

### 3.3. Univariate analysis of covariates and all-cause mortality

Univariate analysis was used to explore the covariates related to all-cause mortality. Univariate analysis showed that gender (female vs male: OR = 0.61, 95% CI: 0.40–0.94), cardiac function (Class IV vs Class III: OR = 3.80, 95% CI: 2.40–6.02), NT-ProBNP (OR = 1.00, 95% CI: 1.00–1.00), beta-blockers (yes vs no: OR = 0.49, 95% CI: 0.31–0.77) and albumin level (albumin level≥37.16 g/L vs albumin level <37.16 g/L: OR = 0.56, 95% CI: 0.36–0.85) were related to all-cause mortality (Table 2).

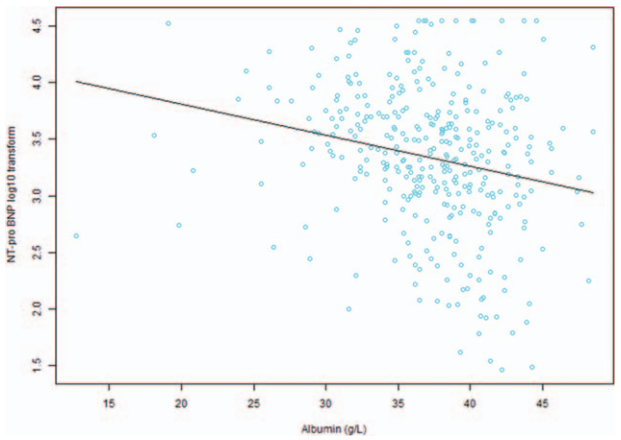


**Figure 1.** Spearman correlation analysis of albumin and NT-ProBNP.

### 3.4. Multiple regression analysis of albumin and all-cause mortality

We used multivariate regression analysis to explore the independent effect of albumin on all-cause mortality, and variables with differences ($P < .05$) in univariate analysis will be adjusted in multiple regression analysis. Considering that heart function grading and NT-proBNP are both indicators to measure the severity of heart function, there is a high correlation between the 2 indicators. Therefore, we only adjusted cardiac function grade as a covariate in the multivariate analysis. In model 1, none covariate was adjusted and the results are consistent with univariate analysis. In model 2, sex and cardiac function (NYHA) were adjusted and the results showed that decreased albumin was associated with increased all-cause mortality (albumin level ≥37.16 g/L vs albumin level <37.16 g/L: OR = 0.61, 95% CI: 0.39–0.95). In model 3, sex, cardiac function (NYHA) and beta-blockers were adjusted, and the results displayed that decreased albumin was still associated with increased all-cause mortality (albumin level≥37.16 g/L vs albumin level <37.16 g/L: OR = 0.62, 95% CI: 0.39–0.97) (Table 3).

## 4. Discussion

This study has the following findings. First, there is a negative correlation between albumin and NT-ProBNP levels in CHF patients [1811.50 (698.75–4037.00) vs 3479.50 (1538.50–7824.25), $P < .001$], which means that higher albumin level is associated with lower NT-ProBNP level. Second, correlation analysis and curve fitting further confirmed that there was a negative correlation between albumin and NT-pro BNP log10 transform ($\rho = -0.217$, $P < .001$). Third, decreased albumin levels are associated with increased all-cause mortality, and this trend persists despite adjustments for potential confounding factors (high group vs low group: OR = 0.62, 95% CI: 0.39–0.97).

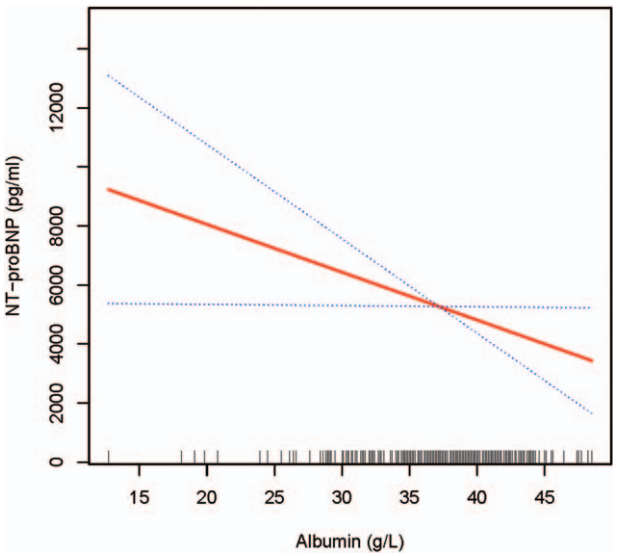


**Figure 2.** Curve fitting of albumin and NT-proBNP.

The death events of patients with cardiovascular diseases are caused by a variety of heart diseases.[26–28] The common clinical diseases are myocardial infarction, acute heart failure, acute exacerbation of chronic heart failure, malignant arrhythmia or cardiac arrest. There is clear evidence that the albumin level is negatively correlated with adverse cardiovascular events in patients with cardiovascular and cerebrovascular diseases.[29–32] A study involving 560 patients with ischemic stroke aim to explore the relationship between serum albumin levels and ST and prognosis. The results showed that low albumin level was significantly associated with poor prognosis, and the adjusted odds ratio was 1.972. In addition, patients with lower albumin levels also had a higher recurrence rate of stroke and mortality than patients with elevated albumin levels.[29] A prospective cohort study aimed to explore the relationship between albumin and long-term cardiovascular events in patients with stable coronary heart disease (CHD). The final result displayed that decreased albumin concentration was significantly associated with all-cause mortality and cardiovascular events. Despite adjusting potential covariables, this trend still exists (HR = 6.81 and HR = 3.68, respectively).[31] Similarly, another cohort study demonstrated that decreased serum albumin, although in the "normal" range, was still associated with poor long-term outcomes in patients newly visiting the Cardiovascular Institute.[32] In this study, we also discovered that the decrease of albumin level is related to the severity of heart function and all-cause mortality in CHF patients, which supports the previous conclusions.

Exploring serological biomarkers with high diagnostic sensitivity and specificity and prognostic value has always been an important research content in the field of heart failure. At present, the biomarker widely used in clinic is NT-proBNP.[33] A large number of studies have shown that NT-proBNP level has an important value in the diagnosis, condition judgment and prognosis prediction of heart failure patients.[34–36] However, the application of NT-proBNP also has some limitations, especially in the elderly, women and heart failure patients with renal insufficiency. Furthermore, the current guidelines recommend combined detection of a variety of biomarkers in the diagnosis, efficacy, and prognosis of heart failure patients.[37] Previous studies have shown that albumin combined with NT-proBNP plays an important role in the diagnosis and prognosis of

**Table 2**

**Univariate analysis of covariates and all-cause mortality.**

| | All-cause mortality |
|---|---|
| Age, year | 1.01 (0.99, 1.02) 0.316 |
| Sex | |
| Male | Reference |
| Female | 0.61 (0.40, 0.94) 0.024 |
| Cardiac function, NYHA | |
| Class III | Reference |
| Class IV | 3.80 (2.40, 6.02) <0.001 |
| Coronary heart disease | |
| No | Reference |
| Yes | 0.86 (0.56, 1.31) 0.479 |
| Primary cardiomyopathy | |
| No | Reference |
| Yes | 1.14 (0.68, 1.91) 0.612 |
| Valvular heart disease | |
| No | Reference |
| Yes | 1.00 (0.62, 1.61) 0.986 |
| Hypertension | |
| No | Reference |
| Yes | 0.80 (0.38, 1.68) 0.557 |
| Height, cm | 1.00 (0.98, 1.03) 0.969 |
| Weight, kg | 0.98 (0.96, 1.01) 0.051 |
| Creatine kinase, U/L | 1.00 (1.00, 1.00) 0.152 |
| Creatine kinase-MB, U/L | 1.01 (1.00, 1.03) 0.062 |
| Troponin I, μg/l | 0.99 (0.96, 1.02) 0.468 |
| NT-ProBNP, pg/ml | 1.00 (1.00, 1.00) 0.003 |
| Beta-blockers | |
| No | Reference |
| Yes | 0.49 (0.31, 0.77) 0.001 |
| ACEI/ARB | |
| No | Reference |
| Yes | 0.75 (0.49, 1.14) 0.176 |
| Diuretic | |
| No | Reference |
| Yes | 0.91 (0.59, 1.40) 0.659 |
| Albumin level | |
| Albumin level <37.16 g/L | Reference |
| Albumin level≥37.16 g/L | 0.56 (0.36, 0.85) 0.007 |

Data are represented as OR (95% CI) P value.
ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin II receptor blockers, NT-proBNP = amino-terminal pro-brain natriuretic peptide.

**Table 3**

**Multiple regression analysis of albumin and all-cause mortality.**

| Exposure | All-cause mortality |
|---|---|
| Model 1 | |
| Albumin level <37.16 g/L | Reference |
| Albumin level≥37.16 g/L | 0.56 (0.36, 0.85) 0.007 |
| Model 2 | |
| Albumin level <37.16 g/L | Reference |
| Albumin level ≥37.16 g/L | 0.61 (0.39, 0.95) 0.029 |
| Model 3 | |
| Albumin level <37.16 g/L | Reference |
| Albumin level ≥37.16 g/L | 0.62 (0.39, 0.97) 0.037 |

Data are represented as OR (95% CI) *P* value.
In model 1, none covariate was adjusted.
In model 2, sex and cardiac function (NYHA) were adjusted.
In model 3, sex, cardiac function (NYHA) and beta-blockers were adjusted.

CHF,[38–40] even the Glasgow Prognostic Score based on albumin level could effectively predict the prognosis of patients with intensive cardiovascular care unit.[41] In this study, we also found that there was a significant negative correlation between albumin and NT-proBNP in CHF patients, which suggested that albumin could be used as an important marker to refine the risk stratification of CHF patients.

At present, the biological mechanism of decreased albumin concentration and increased risk of cardiovascular disease is unclear. It is widely accepted that the pathological mechanism of the decrease of albumin level in CHF patients is caused by numerous factors. After the occurrence of CHF, due to the long-term increase of venous pressure, hepatic venous reflux is blocked, and then often complicated with congestive liver cirrhosis.[42,43] In addition, the decrease of cardiac output results in secondary liver damage, which leads to changes in the structure and function of liver and the decrease of the function of synthetic protein.[44] On the other hand, chronic heart failure leads to intestinal hypoperfusion and intestinal wall edema, intestinal absorption dysfunction, malnutrition, and lack of raw materials for serum protein synthesis, which further aggravates the occurrence of hypoproteinemia.[45] Additionally, fluid retention during heart failure may lead to hemodilution, leading to hypoproteinemia.[46,47] Correspondingly, the decrease of albumin concentration leads to the retention of a large amount of fluid in the tissue space, which seriously affects the microcirculation of CHF patients, and leads to the decrease of many kinds of enzyme activity,[48] which leads to the decline of body immunity and is easy to cause various infections.

This study also has the following limitations. First of all, albumin is a protein that measures nutritional status and inflammation, and there is no comprehensive analysis of the relationship between those variables in this study. Second, energy consumption and nutritional intake are closely related to albumin levels, but due to the limitations of measuring instruments, these covariates are not included in this study. Third, this study is based on a single-center study of Chinese population, and more trials are needed to confirm whether this conclusion are applicable to other populations. In addition, as a retrospective cohort study, this study may have potential follow-up bias. Fourth, this study belongs to a clinical study, and cannot explore the pathophysiological mechanism of albumin and cardiovascular events. Fifth, there may be some implementation bias in the data of deficient body composition, such as visceral fat content, subcutaneous fat content or lean body mass. Sixth, as a retrospective cohort study, this study may inevitably have some mixed bias and recall bias.

In conclusion, our results support this evidence that decreased albumin is associated with elevated NT-ProBNP and poor long-term prognosis in CHF patients. Clinicians need to pay enough attention to the nutritional status of CHF patients. In view of the strong correlation between low albumin level and adverse cardiovascular events, it is reasonable to speculate that hypoalbuminemia and cardiovascular events may share the same pathophysiological mechanism

## Author contributions

All the authors participated in the whole process of this study and approved the final manuscript.
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**Formal analysis:** Sheng Yi, menghua chen.
**Funding acquisition:** Sheng Yi, menghua chen.
**Investigation:** Sheng Yi, menghua chen.
**Methodology:** Sheng Yi, menghua chen.
**Project administration:** Sheng Yi, menghua chen.
**Resources:** Sheng Yi, menghua chen.
**Software:** Sheng Yi, menghua chen.
**Supervision:** Sheng Yi.
**Validation:** Sheng Yi, menghua chen.
**Visualization:** Sheng Yi, menghua chen.
**Writing – original draft:** Sheng Yi, menghua chen.
**Writing – review & editing:** Sheng Yi, menghua chen.

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