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Original Article

Correlation between blood albumin and hospital death and long-term death in ICU patients with heart failure: data from the medical information mart for intensive care III database

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Abstract: Background: Elevated circulating levels of albumin (ALB) are often associated with improved prognosis in patients with heart failure (HF). However, investigations of its association with hospital death and long-term death in HF patients in the intensive care unit (ICU) are limited. Aim: We examined whether increased blood ALB levels (first value at admission and maximum and minimum values in the ICU) were related to a greater risk of hospital death and long-term death in ICU patients with HF. Methods: For the first time, we analyzed 4084 ICU patients with HF admitted to the ICU in The Medical Information Mart for Intensive Care III (MIMIC-III) database. Results: Among 4084 HF patients, 774 (18.95%), 1056 (25.86%) and 1720 (42.12%) died in the hospital, within 30 days and 1 year, respectively. We conducted a logistic regression analysis and found significant inverse associations between blood ALB concentration and risk of hospital death, 30-day death and 1-year death when the covariates including age, sex, myocardial infarction (MI), hypertension, diabetes, valvular diseases, atrial fibrillation, stroke and chronic kidney disease (CKD) were adjusted. We additionally used a smooth curve for univariate analysis to establish an association between blood ALB concentration and death risk. Surprisingly, we observed U-shaped correlations between blood ALB concentration and hospital mortality, 30-day mortality and 1-year mortality. We found that the "inflection point" for the blood ALB concentration at the lowest risk of death was 3.5 g/dL. We further observed that a higher blood ALB concentration (albumin-max) did not contribute to a reduced risk of death (hospital death, 30-day death and 1-year death) in HF patients with an albumin concentration >3.5 g/dL. Conclusions: A lower blood ALB concentration contributed to a greater risk of hospital death and long-term death in HF patients admitted to the ICU, further suggesting that nutritional support in the ICU is highly important for improving the short-term and long-term mortality of HF patients. However, in HF patients without hypoproteinaemia (>3.5 g/dL), the impact of increased serum ALB on patient prognosis still needs to be demonstrated.

Keywords: Albumin, cardiovascular, hospital death, long-term death, heart failure

Introduction

Acute heart failure (HF) or worsening chronic HF is a heavy medical burden associated with short-term and long-term risk of death [1]. In the United States (US), approximately 10-51% of HF patients are hospitalized in the intensive care unit (ICU), with a high death rate of 10.6% [2, 3]. The treatment and management of these HF patients is particularly important due to the high mortality risk in hospitals. Accurate risk stratification enables clinicians to perform appropriate medical decision-making [4].

Albumin (ALB) is a protective factor for HF patients. As a 69 kDa protein, blood ALB can maintain stable plasma colloid osmotic pressure and exhibit anti-inflammatory, antioxidant, anticoagulant, antiplatelet aggregation and colloidal permeation effects, contributing to key physiological functions [5, 6]. Hypoalbuminemia (HAE, albumin level <3.5 g/dL), however, is highly prevalent in HF patients [7] and is caused by malnutrition, chronic inflammation, hemodilution, infection and other factors [8, 9]. Existing evidence has shown that HAE is a predictor of all-cause mortality risk among HF patients. For

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example, Liu et al. reported that HAE is common in HF and preserved ejection fraction (HFPEF) patients and is associated with an increased risk of death [7]. Gotsman I et al. performed a cohort study involving a total of 5779 HF patients with a mean follow-up of 576 days, demonstrating that decreasing serum ALB was significantly associated with mortality after adjustment for significant confounding factors [10]. Uthamalingam S et al. conducted a cohort study including 438 consecutive patients with acute decompensation HF (ADHF) admitted to a large community hospital and reported that HAE is independently associated with increased one-year mortality in patients admitted with ADHF [11]. However, a series of prediction methods for in-hospital or long-term mortality are not currently available because these predictable models do not have good accuracy [12, 13]. Among patients without HAE (albumin level >3.5 g/dL), there is relatively little discussion on the impact of serum ALB on hospital mortality and long-term mortality in ordinary ward or ICU-treated HF patients.

Considering the current research background, we obtained HF data from the Medical Information Mart for Intensive Care III (MIMIC-III) database to develop a predictive model for the associations between serum ALB levels (first value at admission and maximum and minimum values in the ICU) and hospital death and long-term death among HF patients in the ICU. We further confirmed that increased blood ALB levels independently contributed to reduced risks of hospital death and long-term death among patients without HAE.

Methods

Study population

We obtained data from an open ICU clinical database named MIMIC-III [14]. The MIMIC-III is a large, freely available database comprising deidentified health-related data associated with more than 40,000 patients who stayed in critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012 and is available on PhysioNet (physionet.org/content/mimiciii/1.4/) [15, 16]. Before free access to certain resources on PhysioNet, we needed to complete training in human research and data privacy and then pass the test of human protection research participants. The project was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center (Boston, MA) and the Massachusetts Institute of Technology (Cambridge, MA), and informed consent from each patient was exempted because all patient privacy information was deidentified before the data were obtained. All analyses in our study were consistent with relevant guidelines and regulations [17]. The author "Xin Wan" (ID 12340542) is responsible for collecting and analyzing data.

The MIMIC-III database contains information such as demographic information, vital sign measurements taken at the bedside, laboratory test results, medication use and mortality (including posthospital discharge). For the purpose of this study, we retrospectively analyzed all patients with HF in the database. According to the International Classification of Diseases, Ninth Revision (ICD-9) codes, we first extracted the data from all patients with HF (n=8648) admitted to the ICU for the first time. Among these individuals, only the first ICU admission data were included in the analysis when they underwent several ICU admissions. Then, we obtained clinical characteristic data, including demographic characteristics, comorbidities, laboratory indicators, medications and mortality data. Additionally, patients aged <18 years or with incomplete laboratory data were excluded. The present study aimed to investigate whether increased blood ALB levels independently contributed to reduced risks of hospital death and long-term death among patients with or without HAE. On the basis of the initial admission data, multiple biochemical test results were recorded; thus, we included the first (1st), maximum (max) and minimum (min) blood albumin levels for analysis. Subsequently, 4084 HF patients were enrolled in our analysis.

Exposure and death information

The main independent variables were blood ALB-1st, the serum ALB concentration (max) and the serum ALB concentration (min); these variables were measured in 4084 HF patients beginning at the first ICU admission. Hospital death, 30-day death and 1-year death were selected as the primary endpoints. Hospital death was defined only by the first admission

to the ICU. Out-of-hospital death dates were obtained using the Social Security Administration death master file.

Covariates

The data were obtained from the database via the PostgreSQL Structured query language. Patient demographic data [age, sex (female and male)], blood-related biochemical data (creatinine, urea nitrogen and albumin), comorbidity information [myocardial infarction (MI), hypertension, diabetes, valvular disease, atrial fibrillation, stroke, chronic kidney disease (CKD) and malignant tumor] and medication information [albumin, beta-blockers (βRB), statins] were collected at the first admission to the ICU.

Statistical analysis

Continuous clinical variables are expressed as the mean (standard deviation) or median (quartile distance). The description of the frequency distribution is presented as N (%). The HF patients were divided into two subgroups according to the median blood ALB concentration (albumin <3 g/dL and albumin ≥ median 3 g/dL). The Kruskar-Wallis (K-W) test was used to determine the differences in continuous variables between the two subgroups, and the chi-square test was used to examine the differences in frequency distribution. Logistic regression analysis was used to evaluate the associations between blood ALB concentrations (albumin-1st, albumin-max and albumin-min) and the risk of hospital death, 30-day death and 1-year death, respectively, with a 95% confidence interval (CI). Logistic regression Model 1 to Model 2 were structured as follows: Model 1 was adjusted for age and sex; Model 2 was adjusted for age, sex, MI, hypertension, diabetes, valvular disease, atrial fibrillation, stroke and CKD. Malignant tumors have been confirmed to contribute to all-cause death risk [18]. Hence, we used sensitivity analysis to further evaluate the associations between blood ALB concentrations and death risk (hospital death, 30-day death and 1-year death) by using "malignant tumor" as a covariate in the above models. A smooth curve analysis was performed for univariate analysis to examine the nonlinear association between blood ALB concentrations (albumin-1st, albumin-max and albumin-min) and death risk (hospital death, 30-day death and 1-year death). Finally, according to the exact inflection point of the nonlinear relationship explored by the smoothed curve, further hierarchical analysis was performed to confirm the independence of the association. In this study, EmpowerStats 3.0 was used for all the statistical analyses, and a *P* value <0.05 was considered to indicate statistical significance.

Results

Admission characteristics in patients with HF

We selected a total of 4084 patients with HF admitted to the ICU after strictly screening the first ICU admission in the database. Among these patients (shown in **Table 1**), the medians for the albumin-1st, albumin-max and albumin-min levels were 3.00 g/dL, 3.10 dL and 2.80 g/dL, respectively, and the numbers of hospital deaths, 30-day deaths and 1-year deaths were 774 (18.95%), 1056 (25.86%) and 1720 (42.12%), respectively. Based on the median blood ALB-1 level, these HF patients were classified into two subgroups (albumin <3 g/dL and albumin ≥3 g/dL). The HF patients with an albumin concentration <3 g/dL had a significantly greater rate of hospital death, 30-day death and 1-year death (all P<0.05) than did the HF patients with an albumin concentration ≥3 g/dL. However, the HF patients with an albumin concentration <3 g/dL tended to be female and had a significantly lower incidence of concomitant diseases, including MI, hypertension, valvular disease, CKD and malignant tumors, and a greater percentage of patients who used medications (albumin).

Increased blood ALB concentrations contributed to reduced hospital death, 30-day death and 1-year death in HF patients

As previously reported, HF patients with lower serum ALB concentrations tend to have a significantly greater rate of death. Thus, we conducted a logistic regression analysis. After adjusting for the covariates of age and sex in Model 1 (**Table 2**), we observed that a high blood ALB concentration (for albumin-1st, OR=0.48, 95% CI=0.42, 0.55, P<0.001; for albumin-max, OR=0.52, 95% CI=0.45, 0.60, P<0.001; for albumin-min, OR=0.34, 95% CI=0.29, 0.39, P<0.001) was significantly asso-

Table 1. Admission characteristics in ICU patients with HF

Variables	Albumin-1st < median (3.00 g/dL) (N=1843)	Albumin-1st ≥ median (3.00 g/dL) (N=2241)	*P* value
Age (year)	73.46 (62.82-81.00)	72.98 (61.92-80.65)	0.255
Gender (male), n (%)	982 (53.28%)	1284 (57.30%)	0.010
Hospital mortality, n (%)	442 (23.98%)	332 (14.81%)	<0.001
30-day mortality, n (%)	600 (32.56%)	456 (20.35%)	<0.001
1-year mortality, n (%)	943 (51.17%)	777 (34.67%)	<0.001
Comorbidities			
Hypertension, n (%)	592 (32.12%)	900 (40.16%)	<0.001
Diabetes, n (%)	63 (3.42%)	84 (3.75%)	0.573
MI, n (%)	119 (6.46%)	214 (9.55%)	<0.001
Stroke, n (%)	64 (3.47%)	96 (4.28%)	0.184
Atrial fibrillation, n (%)	796 (43.19%)	1001 (44.67%)	0.344
Valvular diseaser, n (%)	358 (19.42%)	572 (25.52%)	<0.001
Malignant tumor, n (%)	165 (8.95%)	116 (5.18%)	<0.001
CKD, n (%)	221 (11.99%)	389 (17.36%)	<0.001
Blood parameters			
Albumin-1st (g/dL)	2.60 (2.30-2.70)	3.40 (3.20-3.70)	<0.001
Albumin-max (g/dL)	2.70 (2.40-2.90)	3.40 (3.20-3.70)	<0.001
Albumin-min (g/dL)	2.40 (2.10-2.70)	3.20 (3.00-3.50)	<0.001
Creatinine (mg/dL)	1.20 (0.80-2.00)	1.20 (0.90-1.90)	0.312
Urea nitrogen (mg/dL)	29.00 (18.00-45.00)	27.00 (18.00-44.00)	0.109
Medication			
Albumin, n (%)	289 (15.68%)	210 (9.37%)	<0.001
βRB, n (%)	1076 (58.38%)	1379 (61.54%)	0.041
Statins, n (%)	362 (19.64%)	565 (25.21%)	<0.001

-1st: the first laboratory value in ICU; -max: the maximum laboratory value in ICU; -min: the minimum laboratory value in ICU. ICU: intensive care unit; HF: heart failure; MI: myocardial infarction; CKD: chronic kidney disease; βRB: β receptor blocker.

ciated with a decreased risk of hospital death. When the covariates MI, hypertension, diabetes, valvular disease, atrial fibrillation, stroke and CKD were included in Model 2, the associations of blood albumin (for albumin-1st, OR=0.50, 95% CI=0.44, 0.58, P<0.001; for albumin-max, OR=0.54, 95% CI=0.47, 0.63, P<0.001; for albumin-min, OR=0.35, 95% CI=0.30, 0.40, P<0.001) with the risk of hospital death changed little. Similarly, a high blood ALB concentration (for albumin-1st, OR=0.50, 95% CI=0.44, 0.58, P<0.001; for albumin-max, OR=0.54, 95% CI=0.47, 0.63, P<0.001; for albumin-min, OR=0.35, 95% CI=0.30, 0.40, P<0.001) was associated with a reduced risk of death at 30 days and 1 year (**Table 2**). Cancers have been recognized as a major factor in the death of elderly patients [18]. Therefore, we performed sensitivity analysis to further evaluate the association between blood ALB concentrations and death risk (hospital death, 30-day death and 1-year death) by using "malignant tumor" as a covariate in the above models. We still found that increased blood ALB levels were independently associated with hospital death, 30-day death and 1-year death, as shown in **Table 3**. Importantly, substantial evidence has confirmed that albumin therapy can reduce the incidence of complications and risk of death in patients with HEA in the ICU. However, our results showed that there were no significant differences in hospital death, 30-day death or 1-year death between patients who did and did not receive albumin therapy (all *P* values for interactions >0.05) (**Table 4**).

Curvilinear relation analysis of blood ALB concentration with risk of hospital death, 30-day death and 1-year death in HF patients

Additionally, we used a smooth curve for univariate analysis to establish an association

Table 2. Logistic regression analysis of relationship between blood albumin level and mortality risk in ICU patients with HF

Variables	Hospital death		30-day death		1-year death	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Model 1						
Albumin-1st	0.48 (0.42, 0.55)	<0.001	0.49 (0.43, 0.55)	<0.001	0.47 (0.42, 0.52)	<0.001
Albumin-max	0.52 (0.45, 0.60)	<0.001	0.54 (0.47, 0.62)	<0.001	0.51 (0.45, 0.57)	<0.001
Albumin-min	0.34 (0.29, 0.39)	<0.001	0.36 (0.32, 0.41)	<0.001	0.39 (0.35, 0.44)	<0.001
Model 2						
Albumin-1st	0.50 (0.44, 0.58)	<0.001	0.51 (0.45, 0.58)	<0.001	0.49 (0.44, 0.55)	<0.001
Albumin-max	0.54 (0.47, 0.63)	<0.001	0.57 (0.50, 0.65)	<0.001	0.54 (0.48, 0.61)	<0.001
Albumin-min	0.35 (0.30, 0.40)	<0.001	0.38 (0.34, 0.43)	<0.001	0.41 (0.37, 0.46)	<0.001

Model 1: Adjusted for age and gender. Model 2: Adjusted for age, gender, MI, hypertension, diabetes, valvular diseaser, atrial fibrillation, stroke and CKD. -1st: the first laboratory value in ICU; -max: the maximum laboratory value in ICU; -min: the minimum laboratory value in ICU. ICU: intensive care unit; HF: heart failure; MI: myocardial infarction; CKD: chronic kidney disease.

Table 3. Sensitivity analysis for relationship between blood albumin level and mortality risk in ICU patients with HF

Variables	Hospital death		30-day death		1-year death	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Model 1						
Albumin-1st	0.48 (0.42, 0.55)	<0.001	0.49 (0.43, 0.56)	<0.001	0.47 (0.42, 0.53)	<0.001
Albumin-max	0.52 (0.45, 0.60)	<0.001	0.55 (0.48, 0.62)	<0.001	0.52 (0.46, 0.58)	<0.001
Albumin-min	0.34 (0.30, 0.39)	<0.001	0.37 (0.32, 0.42)	<0.001	0.39 (0.35, 0.44)	<0.001
Model 2						
Albumin-1st	0.50 (0.44, 0.58)	<0.001	0.52 (0.46, 0.59)	<0.001	0.50 (0.45, 0.56)	<0.001
Albumin-max	0.54 (0.47, 0.63)	<0.001	0.58 (0.51, 0.66)	<0.001	0.55 (0.49, 0.62)	<0.001
Albumin-min	0.35 (0.30, 0.40)	<0.001	0.38 (0.34, 0.44)	<0.001	0.41 (0.37, 0.46)	<0.001

Model 1: Adjusted for age, gender and malignant tumor. Model 2: Adjusted for age, gender, MI, hypertension, diabetes, valvular diseaser, atrial fibrillation, stroke, CKD and malignant tumor. -1st: the first laboratory value in ICU; -max: the maximum laboratory value in ICU; -min: the minimum laboratory value in ICU. ICU: intensive care unit; HF: heart failure; MI: myocardial infarction; CKD: chronic kidney disease.

between blood ALB concentration and death risk. Surprisingly, we observed a curvilinear (U-shaped) correlation between blood ALB concentration and hospital death, 30-day death and 1-year death, as shown in **Figure 1**. We found that the "inflection point" at which patients had the lowest risk of death was 3.5 g/dL. According to the "inflection point" (albumin level =3.5 g/dL), HF patients were further divided into two subgroups (albumin level <3.5 g/dL and with albumin ≥3.5 g/dL), as shown in **Table 5**. We observed that an elevated serum ALB concentration did not contribute to a reduced risk of hospital death (OR=1.441, 95% CI=0.713, 2.913; P=0.309), 30-day death (OR=1.161, 95% CI=0.608, 2.218; P=0.652) or 1-year death (OR=0.695, 95% CI=0.397, 1.217; P=0.203), after all covariates, sex, hypertension, diabetes, valvular disease, atrial fibrillation, stroke and CKD, were controlled for in HF patients with an albumin concentration ≥3.5 g/dL (**Table 5**). Consistently, we still observed that higher albumin-min and albumin-max levels contributed to a reduced risk of (hospital death, 30-day death and 1-year death) in HF patients with an albumin level <3.5 g/dL.

Discussion

There were several important findings in this study: 1) There was a U-shaped correlation between blood ALB-max and hospital death, 30-day death and 1-year death risk in ICU-treated HF patients. In patients without HAE (albumin level >3.5 g/dL), an increased albumin level could increase hospital mortality and

Table 4. Medication-related subgroup analysis for association between blood albumin level with mortality risk in ICU patients with HF

Variables		Hospital death			30-day death			1-year death		
		OR (95% CI)	*P* Value	*P**	OR (95% CI)	*P* Value	*P**	OR (95% CI)	*P* Value	*P**
Albumin-1st	Albumin	0.673 (0.487, 0.929)	0.016	0.191	0.581 (0.425, 0.794)	0.001	0.747	0.433 (0.316, 0.594)	<0.001	0.191
	NO Albumin	0.496 (0.425, 0.579)	<0.001		0.524 (0.455, 0.603)	<0.001		0.519 (0.457, 0.588)	<0.001	
Albumin-max	Albumin	0.696 (0.500, 0.969)	0.031	0.117	0.723 (0.536, 0.976)	0.034	0.083	0.615 (0.453, 0.835)	0.002	0.273
	NO Albumin	0.501 (0.425, 0.591)	<0.001		0.526 (0.454, 0.611)	<0.001		0.522 (0.457, 0.597)	<0.001	
Albumin-min	Albumin	0.447 (0.315, 0.633)	<0.001	0.426	0.414 (0.296, 0.578)	<0.001	0.855	0.339 (0.243, 0.473)	<0.001	0.101
	NO Albumin	0.352 (0.302, 0.411)	<0.001		0.395 (0.344, 0.453)	<0.001		0.430 (0.380, 0.485)	<0.001	

Adjusted for age, gender, MI, hypertension, diabetes, valvular diseaser, atrial fibrillation, stroke and CKD. P*: *P* value for interaction. -1st: the first laboratory value in ICU; -max: the maximum laboratory value in ICU; -min: the minimum laboratory value in ICU. ICU: intensive care unit; HF: heart failure; MI: myocardial infarction; CKD: chronic kidney disease.

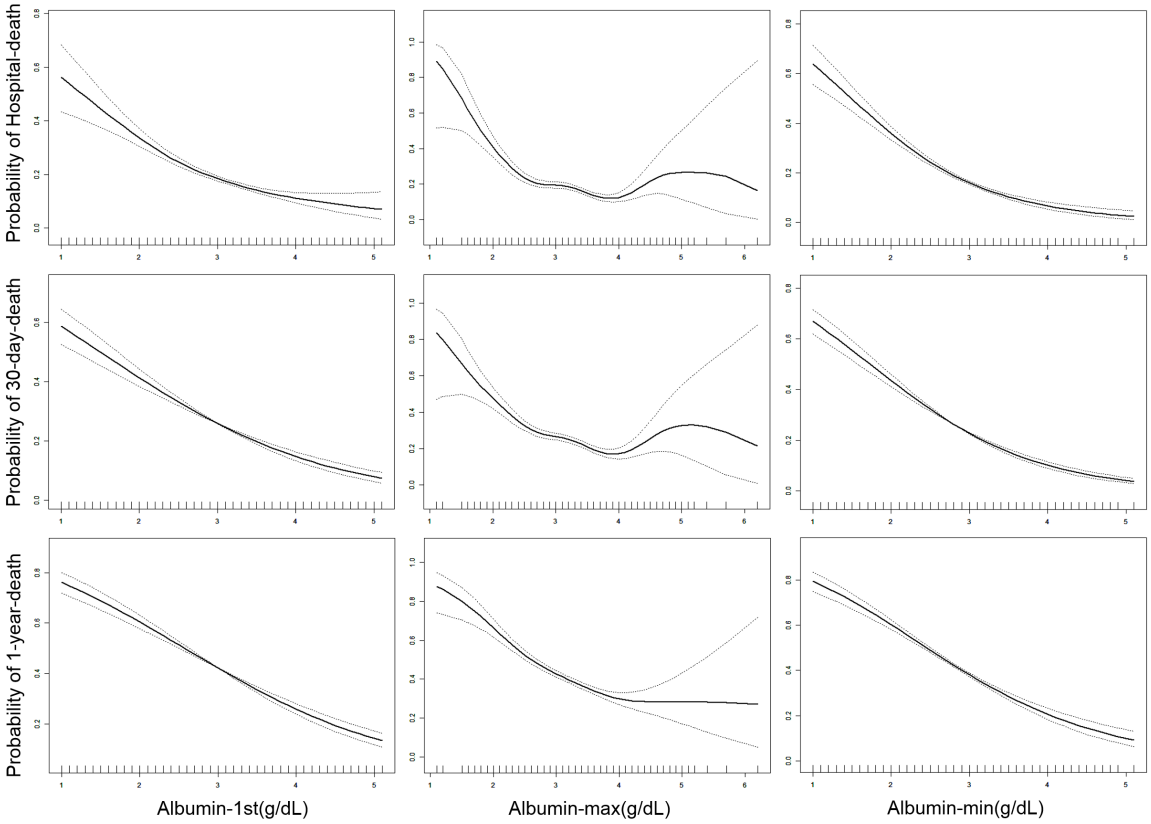

Figure 1. Smooth curve on association between blood albumin levels (first value on admission, maximum and minimum value during ICU) and hospital death and long-term death among HF patients from the ICU.

Table 5. Subgroup analysis for relationship between blood albumin level and mortality risk in ICU patients with HF by "Albumin-1st =3.5 g/dL" as the classification variable

Variables	Hospital death			30-day death			1-year death		
	OR (95% CI)	*P* Value	*P**	OR (95% CI)	*P* Value	*P**	OR (95% CI)	*P* Value	*P**
Albumin-max									
<3.5 (g/dL)	0.541 (0.444, 0.658)	<0.001	0.012	0.618 (0.516, 0.740)	<0.001	0.079	0.567 (0.479, 0.671)	<0.001	0.521
≥3.5 (g/dL)	1.441 (0.713, 2.913)	0.309		1.161 (0.608, 2.218)	0.652		0.695 (0.397, 1.217)	0.203	
Albumin-min									
<3.5 (g/dL)	0.309 (0.258, 0.370)	<0.001	0.868	0.343 (0.291, 0.405)	<0.001	0.916	0.355 (0.303, 0.415)	<0.001	0.284
≥3.5 (g/dL)	0.296 (0.205, 0.429)	<0.001		0.351 (0.249, 0.494)	<0.001		0.433 (0.319, 0.589)	<0.001	

Adjusted for age, gender, MI, hypertension, diabetes, valvular diseaser, atrial fibrillation, stroke and CKD. P*: *P* value for interaction. -1st: the first laboratory value in ICU; -max: the maximum laboratory value in ICU; -min: the minimum laboratory value in ICU. ICU: intensive care unit; HF: heart failure; MI: myocardial infarction; CKD: chronic kidney disease.

out-of-hospital death (hospital death, 30-day death and 1-year death). In particular, when the blood ALB concentration was above 3.5 g/dl, the risk of hospital death, 30-day death and 1-year death was significantly greater. 2) There were still negative associations between the serum ALB concentration and mortality risk in patients with HAE (albumin level <3.5 g/dL), which is consistent with the findings of previous studies.

There is already a large amount of evidence supporting HAE as a potentially modifiable risk factor for CVD and other chronic diseases. Clinical studies have indicated that reduced blood ALB levels are closely associated with HF, CHD, stroke and AF [9-13]. For example, the Health ABC Study demonstrated that lower serum ALB concentrations significantly contributed to new-onset HF [11]. The ARIC study indicated a significant association between re-

duced blood ALB and a high incidence of CHD [19]. The Framingham Offspring study included 4506 individuals with a follow-up of 22 years and suggested that the serum ALB concentration is a valuable risk factor for detecting the first MI [20]. The Northern Manhattan Study reported that reduced serum ALB levels can predict stroke events in 2986 patients [21]. The Copenhagen City Heart Study showed that a lower serum ALB concentration was associated with the development of AF in women after controlling for other known confounders [22]. Interestingly, we also found U-shaped correlations between blood ALB-max and in-hospital death, 30-day death and 1-year death risk in ICU-treated HF patients.

Especially for protein foods, the serum or plasma ALB concentration has been considered an important nutritional marker for several decades, and a circulating level <3.5 g/dL is defined as HAE. The levels of plasma and urine ALB can also reflect protein synthesis in the liver and the functional state of the vascular endothelium. Indeed, some previous clinical and basic studies have noted that the serum ALB concentration has a significant impact on circulating blood parameters and the incidence of many diseases, such as CVD [19-22], cancer [23] and infections [24]. Research has also suggested that the serum ALB concentration has an important influence on survival time [25]. In a previous meta-analysis, Peng et al. reported that HAE was related to increased mortality in HF patients [26]. Mahmoud et al. showed that a higher risk of in-hospital mortality in HF patients was related to lower serum ALB concentrations [27]. Jabbour et al. observed that reduced serum ALB at baseline contributed to an increased mortality risk after a follow-up of more than 2 years in 212 HF patients [28]. However, although multiple prognostic scores or risk grading models for HF patients have been proposed and validated, the accuracy and applicability of these models are not reliable. In-depth risk stratification may help clinicians make more appropriate clinical decisions. Recently, low albumin levels have been increasingly regarded as a predictor of morbidity and mortality risk, independent of age, sex, comorbidities and other confounding factors [29-31]. Consistent with these findings, our findings showed that a lower serum ALB concentration contributed to higher hospital mortality and out-of-hospital death in patients with HAE (albumin level <3.5 g/dL). Surprisingly, we additionally observed U-shaped correlations between blood ALB-max levels during the ICU and hospital death, 30-day death and 1-year death risk in ICU-treated HF patients. In patients without HAE (albumin level >3.5 g/dL), an increased serum ALB concentration (blood albumin maximum in the ICU) could inversely increase hospital mortality and out-of-hospital death, especially when the blood albumin concentration was above 4.0 g/dL. The U-shaped correlation may partially explain why some previous prediction models were not accurate. Furthermore, in a previous study, our team members also found that in 925 CKD patients with an albumin level >3.4 g/dL, increased albumin (blood albumin-max levels arriving in the ICU) contributed to an increased risk of CVD complications and 1-year mortality [32]. However, one study from the same database (MIMIC database) showed an almost linear negative correlation between blood ALB concentration and all-cause mortality by restricted cubic spline curve analysis [33]. The differences in the results might originate from the use of the average serum ALB concentration to represent the correlation between the serum ALB concentration and short-term mortality. Moreover, there were also significant differences in the population included and in the variables extracted in our study, which may be an important reason for the different results [33].

The advantages of this retrospective study were that we first selected ICU patients with HF from the MIMIC-III database with a large sample size (n=4084) and evaluated the relationships between blood ALB concentrations (albumin-1st, albumin-max and albumin-min) and the risk of hospital death, 30-day death and 1-year death. We were surprised to observe an important point of interest in our research: among ICU patients with HF, HAE patients had significantly increased hospital mortality and long-term mortality in the later stage. However, in patients without HAE, continuing to supplement patients with albumin may actually increase their mortality risk, which is also the first phenomenon we have reported. Certainly, the reliability of this research conclusion also needs to be confirmed by additional meta-analyses or clinical trials. Several shortcomings also need to be noted. First, even if multivari-

able adjustment was made, the major limitation of this study was that it was still a retrospective and observational study, making it impossible to confirm the causal association between blood ALB concentration and hospital mortality and out-of-hospital death. Additionally, known or unknown confounding factors were still not fully controlled. For example, blood ALB levels can be affected by malnutrition, chronic inflammatory states, hepatic congestion and other factors. The severity of HF and its accompanying conditions, such as acute decompensated HF, acute pulmonary edema and cardiogenic shock, were not included in the study. Second, the HF stage and exact cause of death could not be assessed due to the inherent limitations of the MIMIC database. Third, the influence of drugs on blood ALB concentrations in the ICU was not taken into account. Fourth, there were multiple measurements of blood ALB, so we included only the first, maximum and minimum blood ALB concentrations after admission to the ICU. Finally, it is currently unclear whether there are racial differences in the associations between blood ALB concentrations and hospital mortality and out-of-hospital death.

Conclusion

Our findings suggested that increased albumin levels were independently associated with reduced in-hospital death and out-of-hospital death risk in HF patients without HAE (blood albumin <3.5 g/dL). However, we additionally found that increasing albumin levels were inversely associated with increased in-hospital death and out-of-hospital death risk in HF patients without HAE.

Disclosure of conflict of interest

None.

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References

[1] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH and van der Meer P; Authors/Task Force Members; Document Reviewers. 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 J Heart Fail 2016; 18: 891-975.

[2] Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M and Horton DP; ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005; 149: 209-216.

[3] Safavi KC, Dharmarajan K, Kim N, Strait KM, Li SX, Chen SI, Lagu T and Krumholz HM. Variation exists in rates of admission to intensive care units for heart failure patients across hospitals in the United States. Circulation 2013; 127: 923-929.

[4] Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW and Boscardin WJ; ADHERE Scientific Advisory Committee, Study Group, and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA 2005; 293: 572-580.

[5] Roche M, Rondeau P, Singh NR, Tarnus E and Bourdon E. The antioxidant properties of serum albumin. FEBS Lett 2008; 582: 1783-7.

[6] Blunt MC, Nicholson JP and Park GR. Serum albumin and colloid osmotic pressure in survivors and nonsurvivors of prolonged critical illness. Anaesthesia 1998; 53: 755-61.

[7] Liu M, Chan CP, Yan BP, Zhang Q, Lam YY, Li RJ, Sanderson JE, Coats AJ, Sun JP, Yip GW and Yu CM. Albumin levels predict survival in patients with heart failure and preserved ejection fraction. Eur J Heart Fail 2012; 14: 39-44.

[8] Vincent JL, Russell JA, Jacob M, Martin G, Guidet B, Wernerman J, Ferrer R, McCluskey SA and Gattinoni L. Albumin administration in the acutely ill: what is new and where next? Crit Care 2014; 18: 231.

[9] Loffredo L, Campana A, Olivini N, Cotugno N, Palma P, Oliva A, Salvatori G, Zicari AM and Violi F. Hypoalbuminemia and clinical adverse events in children with COVID-19. J Med Virol 2021; 93: 2611-2613.

[10] Gotsman I, Shauer A, Zwas DR, Tahiroglu I, Lotan C and Keren A. Low serum albumin: a sig-

nificant predictor of reduced survival in patients with chronic heart failure. Clin Cardiol 2019; 42: 365-372.
[11] Uthamalingam S, Kandala J, Daley M, Patvardhan E, Capodilupo R, Moore SA and Januzzi JL Jr. Serum albumin and mortality in acutely decompensated heart failure. Am Heart J 2010; 160: 1149-1155.
[12] Peterson PN, Rumsfeld JS, Liang L, Albert NM, Hernandez AF, Peterson ED, Fonarow GC and Masoudi FA; American Heart Association Get With the Guidelines-Heart Failure Program. A validated risk score for in-hospital mortality in patients with heart failure from the American Heart Association get with the guidelines program. Circ Cardiovasc Qual Outcomes 2010; 3: 25-32.
[13] Tomcikova D, Felsoci M, Spinar J, Miklik R, Mikusova T, Vitovec J, Spinarova L, Widimsky P, Linhart A, Belohlavek J, Fedorco M, Cihalik C, Malek F, Bambuch M, Vaclavik J, Kettner J, Jarkovsky J, Dusek L and Parenica J. Risk of in-hospital mortality identified according to the typology of patients with acute heart failure: classification tree analysis on data from the Acute Heart Failure Database-Main registry. J Crit Care 2013; 28: 250-258.
[14] Johnson A, Pollard T and Mark R. MIMIC-III Clinical Database (version 1.4). PhysioNet. 2016. https://doi.org/10.13026/C2XW26.
[15] Johnson AE, Pollard TJ, Shen L, Lehman LW, Feng M, Ghassemi M, Moody B, Szolovits P, Celi LA and Mark RG. MIMIC-III, a freely accessible critical care database. Sci Data 2016; 3: 160035.
[16] Goldberger AL, Amaral LA, Glass L, Hausdorff JM, Ivanov PC, Mark RG, Mietus JE, Moody GB, Peng CK and Stanley HE. PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. Circulation 2000; 101: E215-E220.
[17] STROBE Group. STROBE statement: home. 2016. http://www.strobe-statement.org/index.php?id=strobe-home.
[18] Mukherji D, Murillo RH, Van Hemelrijck M, Vanderpuye V, Shamieh O, Torode J, Pramesh CS, Yusuf A, Booth CM, Aggarwal A and Sullivan R; COVID-19 and Cancer Task Force. Global cancer research in the post-pandemic world. Lancet Oncol 2021; 22: 1652-1654.
[19] Nelson JJ, Liao D, Sharrett AR, Folsom AR, Chambless LE, Shahar E, Szklo M, Eckfeldt J and Heiss G. Serum albumin level as a predictor of incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol 2000; 151: 468-477.
[20] Djoussé L, Rothman KJ, Cupples LA, Levy D and Ellison RC. Serum albumin and risk of myocardial infarction and all-cause mortality in the Framingham Offspring Study. Circulation 2002; 106: 2919-2924.
[21] Xu WH, Dong C, Rundek T, Elkind MS and Sacco RL. Serum albumin levels are associated with cardioembolic and cryptogenic ischemic strokes: Northern Manhattan Study. Stroke 2014; 45: 973-978.
[22] Mukamal KJ, Tolstrup JS, Friberg J, Grønbaek M and Jensen G. Fibrinogen and albumin levels and risk of atrial fibrillation in men and women (the Copenhagen City Heart Study). Am J Cardiol 2006; 98: 75-81.
[23] Merriel SW, Carroll R, Hamilton F and Hamilton W. Association between unexplained hypoalbuminaemia and new cancer diagnoses in UK primary care patients. Fam Pract 2016; 33: 449-452.
[24] Yang C, Liu Z, Tian M, Xu P, Li B, Yang Q and Yang Y. Relationship between serum albumin levels and infections in newborn late preterm infants. Med Sci Monit 2016; 22: 92-98.
[25] Bonilla-Palomas JL, Gámez-López AL, Moreno-Conde M, López-Ibáñez MC, Anguita-Sánchez M, Gallego de la Sacristana A, García-Catalán F and Villar-Ráez A. Hypoalbuminemia in acute heart failure patients: causes and its impact on hospital and long-term mortality. J Card Fail 2014; 20: 350-358.
[26] Peng W, Zhang C, Wang Z and Yang W. Prediction of all-cause mortality with hypoalbuminemia in patients with heart failure: a meta-analysis. Biomarkers 2019; 24: 631-637.
[27] El Iskandarani M, El Kurdi B, Murtaza G, Paul TK and Refaat MM. Prognostic role of albumin level in heart failure: a systematic review and meta-analysis. Medicine (Baltimore) 2021; 100: e24785.
[28] Jabbour R, Ling HZ, Norrington K, Amaral N, Zaman N, Aggarwal S, Aung N, Barron A, Manisty C, Baruah R, Cole GD, Missouris CG, Mayet J, Francis DP, Cheng AS, Thomas M, Woldman S and Okonko DO. Serum albumin changes and multivariate dynamic risk modelling in chronic heart failure. Int J Cardiol 2014; 176: 437-443.
[29] Deelen J, Kettunen J, Fischer K, van der Spek A, Trompet S, Kastenmüller G, Boyd A, Zierer J, van den Akker EB, Ala-Korpela M, Amin N, Demirkan A, Ghanbari M, van Heemst D, Ikram MA, van Klinken JB, Mooijaart SP, Peters A, Salomaa V, Sattar N, Spector TD, Tiemeier H, Verhoeven A, Waldenberger M, Würtz P, Davey Smith G, Metspalu A, Perola M, Menni C, Geleijnse JM, Drenos F, Beekman M, Jukema JW, van Duijn CM and Slagboom PE. A metabolic profile of all-cause mortality risk identified in an observational study of 44,168 individuals. Nat Commun 2019; 10: 3346.

[30] Gatta A, Verardo A and Bolognesi M. Hypoalbuminemia. Intern Emerg Med 2012; 7 Suppl 3: S193-199.

[31] Fischer K, Kettunen J, Würtz P, Haller T, Havulinna AS, Kangas AJ, Soininen P, Esko T, Tammesoo ML, Mägi R, Smit S, Palotie A, Ripatti S, Salomaa V, Ala-Korpela M, Perola M and Metspalu A. Biomarker profiling by nuclear magnetic resonance spectroscopy for the prediction of all-cause mortality: an observational study of 17,345 persons. PLoS Med 2014; 11: e1001606.

[32] Huang F, Fan J, Wan X, Liu H, Shi Y, Shu H, Liu Y, Lu T, Gong Z and Gu L. The association between blood albumin level and cardiovascular complications and mortality risk in ICU patients with CKD. BMC Cardiovasc Disord 2022; 22: 322.

[33] Chao P, Cui X, Wang S, Zhang L, Ma Q and Zhang X. Serum albumin and the short-term mortality in individuals with congestive heart failure in intensive care unit: an analysis of MIMIC. Sci Rep 2022; 12: 16251.