

[ORIGINAL ARTICLE]

Relationship between Hypoalbuminemia on Admission and Long-term Mortality in Patients with Acute Decompensated Heart Failure

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Abstract:

Objective Although several studies have reported the relationship between hypoalbuminemia and the clinical outcome, it remains disputable in patients with acute decompensated heart failure (ADHF). We therefore investigated the relationship between hypoalbuminemia on admission and long-term mortality in hospitalized patients following ADHF.

Methods We examined a cohort of 751 consecutive patients who were admitted to the cardiac intensive-care unit between 2007 and 2011 with a diagnosis of ADHF. These patients were divided into 2 groups according to the presence or absence of hypoalbuminemia on admission, which was defined as a serum albumin ≤ 3.4 g/dL. A propensity score (PS) was calculated to evaluate the effects of variables related to the presence or absence of hypoalbuminemia. The association between hypoalbuminemia and mortality was assessed using two Cox regression models—namely, conventional adjustment and matching patients with and without hypoalbuminemia using the PS.

Results Among the pre-match patients (n=551), 311 (56%) were classified as exhibiting hypoalbuminemia on admission. There were 152 deaths (27.5%), and the median follow-up was 1.9 years. The presence of hypoalbuminemia on admission tended to be associated with increased mortality in the unadjusted model [hazard ratio (HR) 1.32, 95% confidence interval (95% CI) 0.95-1.84; p=0.098] but not in the conventional adjusted model (HR 0.98, 95% CI 0.64-1.52; p=0.938). Even in post-match patients, no association between hypoalbuminemia and mortality was observed (HR 1.09, 95% CI 0.68-1.76; p=0.722).

Conclusion Hypoalbuminemia on admission was not associated with long-term mortality in patients with ADHF, even if PS matching was used.

Key words: hypoalbuminemia, serum albumin, acute decompensated heart failure, long-term mortality, propensity score matching

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Introduction

Although many treatments for heart failure (HF) have been developed, HF is still recognized as a major health issue associated with poor clinical outcomes (1). Many reports

have shown that, in addition to an altered cardiovascular physiology, such as hypotension, an impaired renal function, an impaired cardiac function, and abnormal biomarkers, all of which are frequently observed in patients with ADHF, malnutrition may also be associated with poor clinical outcomes in these patients (2-8).

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Serum albumin levels are an indicator of a patient's nutritional state. Low serum albumin levels (i.e., hypoalbuminemia) have been frequently observed and shown to be significantly associated with poor clinical outcomes in patients with chronic illnesses, such as neoplasm and kidney disease (9-12). It has also been reported that hypoalbuminemia is associated with poor clinical outcomes in chronic HF patients (13-15). However, in patients with ADHF, conflicting results have been reported regarding the relationship between serum albumin levels and clinical outcomes. For example, while some reports have shown that hypoalbuminemia in patients with ADHF is an independent predictor of in-hospital mortality and general long-term mortality (16-19), it was also conversely reported that baseline serum albumin levels were not associated with 60-day composite outcomes in patients with ADHF (20).

Therefore, we evaluated the impact of hypoalbuminemia at admission on long-term mortality in hospitalized patients with ADHF.

Materials and Methods

Subjects

Patients who were admitted to the cardiac intensive-care unit at Juntendo University Hospital, Tokyo, Japan, from January 2,007 to December 2,011 with a diagnosis of ADHF were included in this study. ADHF was defined based on the modified Framingham criteria (21). Patients >18 years of age who had acute coronary syndrome and/or had undergone cardiac surgery during the previous 4 weeks or during initial hospitalization as well as those who had a life-threatening malignancy were excluded from the study. Patients whose serum albumin levels were not measured on admission were also excluded. All eligible patients were divided into two groups according to their serum albumin level on admission.

The Institutional Review Board of the Juntendo University Hospital approved the study protocol, and the study complied with the Declaration of Helsinki. Informed consent was obtained from all patients.

Data collection

Baseline data were prospectively collected at the time of initial hospital admission. Serum albumin and other baseline biochemical parameters were obtained in the first 24 hours after admission. The medical history was obtained from a review of the patients' clinical chart. Because a median albumin level of 3.4 mg/dL is generally used as the cut-off value (16, 18, 19), hypoalbuminemia was defined as a serum albumin level ≤ 3.4 mg/dL on admission. The albumin level at hospital discharge and the change in the albumin level from admission to discharge were recorded. Diabetes mellitus was defined as either a hemoglobin A1c $\geq 6.5\%$ or current medication including insulin or oral hypoglycemic drugs. The estimated glomerular filtration rate (eGFR) was

calculated using the Modification of Diet in Renal Disease equation with a Japanese coefficient from baseline serum creatinine levels (22). Complete two-dimensional echocardiography was performed in each patient. The left ventricular ejection fraction (LVEF) was calculated according to the modified Simpson method.

All patients were followed from the date of index admission until July 2013; outcome data were obtained by reviewing the medical records of our hospital for all deaths recorded following discharge. The endpoint of interest was all-cause mortality and cardiovascular mortality.

Propensity score (PS) matching

To reduce bias caused by imbalances in baseline characteristics dependent on the presence or absence of hypoalbuminemia, we used propensity scores to assemble a matched and balanced cohort. We calculated hypoalbuminemia PSs for each participant using a non-parsimonious multivariable logistic regression model. A propensity analysis aims to identify patients with similar probabilities of having hypoalbuminemia based on observed clinical characteristics. In our PS model, hypoalbuminemia was the dependent variable, and 23 baseline characteristics were used as covariates [age, sex, body mass index (BMI), atrial fibrillation, diabetes, smoking status, ischemic etiology, history of heart failure (HF), New York Heart Association (NYHA) class, systolic and diastolic blood pressure, heart rate, LVEF, hemoglobin level, eGFR, serum sodium and potassium level, log-transformed CRP and BNP levels, use of beta blockers, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, aldosterone blocker, and diuretics]. To evaluate the discriminatory power of the logistic regression model for the PS, the area under the receiver operating characteristic curve (c-statistic) was calculated. We computed the logit of the estimated PS for each patient in order to match patients with and without hypoalbuminemia. We then used a greedy matching algorithm to match patients using calipers set to have a maximum width of 0.2 standard deviations (SD) of the estimated PS. Absolute standardized differences for all covariates were used to compare the balance of baseline covariates between the two groups before and after matching. An absolute standardized difference of <10% suggested inconsequential bias.

Statistical analyses

Continuous variables are expressed as the mean \pm SD or median and interquartile range. Categorical data were tabulated as frequencies and ratios (%). To compare the baseline characteristics between the two groups, χ^2 test or Fisher's exact test was used for categorical variables, and a *t*-test or Mann-Whitney U test was used for continuous variables. The event-free survival curves were established using the Kaplan-Meier method and compared between groups with and without hypoalbuminemia in both the entire (pre-match) and post-match datasets by the log-rank test. In pre-match datasets, unadjusted and adjusted Cox proportional hazards

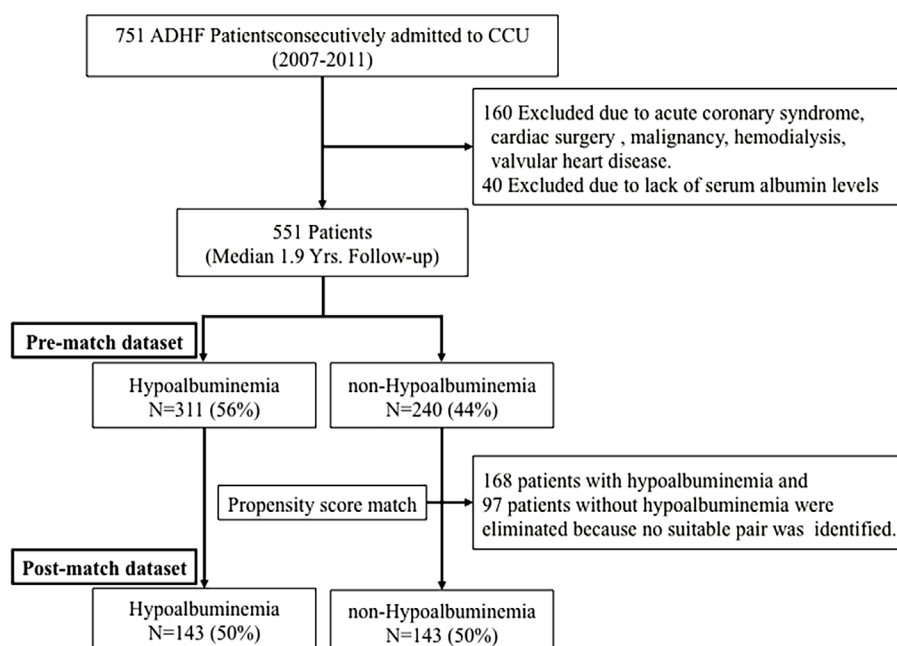


Figure 1. Flow chart of this study. There were 751 patients admitted to the cardiac intensive-care unit due to ADHF. Among these, 160 patients who had acute coronary syndrome and/or had undergone cardiac surgery, had malignancy, were on hemodialysis, or had severe valvular heart disease were initially excluded, as were 40 patients who did not have serum albumin levels measured on admission. The 551 ultimately eligible patients with ADHF were then divided into 2 groups. In addition, propensity score matching resulted in the creation of 143 matched pairs of patients with and without hypoalbuminemia. ADHF: acute decompensated heart failure

models were used to determine the relationship between hypoalbuminemia and long-term mortality. Among variables used in the logistic regression model for the PS, variables regarded as significant ($p < 0.10$) in univariable analyses were included in adjusted analysis in addition to hypoalbuminemia. In post-match datasets, Cox proportional hazards regression was used to estimate the relationship between hypoalbuminemia and long-term mortality. To determine whether the results differed from the cut-off points, we performed secondary analyses in which the serum albumin level was treated as a continuous variable in both pre-match and post-match datasets. In addition, the relationships between the discharge albumin level and post-discharge mortality as well as the change in the albumin level from admission to discharge and post-discharge mortality were analyzed in patients without in-hospital death in the pre-match data set because one recent report suggested that an increase in the albumin level during hospitalization was a significant predictor of a better clinical outcome (23). The assumption of proportional hazards was assessed using a log-minus-log survival graph.

A p value of < 0.05 was considered statistically significant. All analyses were performed using a statistical software package (SPSS ver. 23.0, IBM, Armonk, USA; and JMP ver. 11.0, SAS, Cary, USA).

Results

Baseline characteristics in the entire study group

Overall, 751 patients were admitted to our institution with ADHF between 2007 and 2013. Of those, 160 patients with concomitant acute coronary syndrome and/or who had undergone cardiac surgery during the previous 4 weeks or during initial hospitalization as well as those who had a life-threatening malignancy were initially excluded, as were 40 patients without a serum albumin value on admission. Ultimately, 551 patients were classified into 2 groups according to the presence or absence of hypoalbuminemia, as shown in Fig. 1. Of these, 331 patients (56.4%) were classified into the hypoalbuminemia group. The baseline characteristics of the patients are shown in Table 1. In patients with hypoalbuminemia, both admission and discharge serum albumin levels were significantly lower (3.86 ± 0.29 mg/dL and 2.90 ± 0.41 mg/dL, $p < 0.001$, and 3.52 ± 0.58 mg/dL and 3.00 ± 0.61 mg/dL, $p < 0.001$, respectively), and the change in serum albumin level from admission to discharge was significantly higher (-0.33 ± 0.63 mg/dL and 0.11 ± 0.60 mg/dL, $p < 0.001$) than in those without hypoalbuminemia. There were no significant differences in other baseline characteristics between the two groups.

Table 1. Baseline Characteristics of All Subjects (Pre-match) and Matched Pairs (Post-match).

	Pre-match			Post-match	
	ALB >3.4 n=240	ALB ≤3.4 n=311	p	ALB >3.4 n=143	ALB ≤3.4 n=143
Age, years	70.7±13.6	69.6±14.0	0.361	69.2±13.0	69.8±14.0
Male gender, n (%)	157 (65.4)	200 (64.7)	0.787	94 (65.7)	95 (66.4)
BMI, kg/m ²	23.1±4.6	22.8±5.0	0.498	23.3±4.6	23.1±5.4
AF, n (%)	91 (37.9)	107 (34.4)	0.394	54 (37.8)	54 (37.8)
Diabetes, n (%)	90 (37.5)	126 (40.5)	0.472	58 (40.6)	57 (39.9)
Current smokers, n (%)	104 (43.3)	153 (49.2)	0.171	67 (46.9)	66 (46.2)
Ischemic etiology, n (%)	99 (41.3)	125 (40.2)	0.802	57 (39.9)	62 (43.4)
History of HF, n (%)	118 (49.1%)	176 (56.5%)	0.083	65 (51.2)	72 (56.7)
NYHA class- II, n (%)	29 (12.0%)	53 (17.0%)	0.246	21 (14.7%)	22 (15.4%)
III, n (%)	91 (37.9%)	107 (34.4%)		52 (36.4%)	49 (34.3%)
IV, n (%)	120 (50.0%)	151 (48.5%)		70 (49.0%)	72 (50.4%)
Systolic BP, mmHg	136.8±33.2	136.4±32.2	0.898	137.6±32.0	138.6±28.0
Diastolic BP, mmHg	74.9±19.9	76.5±19.5	0.379	77.1±20.7	77.7±20.1
HR, /min	91.5±27.0	95.7±30.1	0.111	91.9±28.4	93.5±28.9
LVEF, %	43.3±17.4	42.7±17.6	0.696	42.6±17.0	41.9±17.2
Hemoglobin, g/dL	12.3±2.4	12.0±2.6	0.204	12.3±2.5	12.4±2.7
eGFR, mL/min/1.73 m ²	51.4±25.5	50.9±29.7	0.821	51.6±26.7	52.5±25.8
Sodium, mmol/L	138.4±4.5	138.3±4.4	0.721	138.6±4.5	138.8±3.8
Potassium, mmol/L	4.3±0.7	4.2±0.7	0.339	4.3±0.7	4.3±0.8
CRP, mg/dL	0.9 [3.9]	1.0 [3.3]	0.495	0.70 [3.8]	0.70 [2.7]
BNP, pg/mL	642.3 [860.7]	677.1 [1044.2]	0.233	641.6 [861.6]	671.1 [854.4]
Beta blockers, n (%)	83 (34.5)	91 (29.2)	0.183	44 (30.8)	45 (31.5)
ACE-Is/ARBs, n (%)	92 (38.3)	121(38.9)	0.891	55 (38.5)	54 (37.8)
Aldosterone blocker, n (%)	36 (15.0)	42 (13.5)	0.618	15 (10.5)	18 (12.6)
Diuretics, n (%)	92 (38.3)	131 (42.1)	0.368	47 (36.7)	47 (36.7)
Serum albumin, mg/dL (on admission)	3.86±0.29	2.90±0.41	<0.001	3.84±0.28	2.87±0.41

Variables are expressed as the mean±standard deviation, median [interquartile range] or n (%).

AF: atrial fibrillation, ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, BMI: body mass index, BNP: B-type natriuretic peptide, BP: blood pressure, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, HF: heart failure, HR: heart rate, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association

PS and matching based on the PS

Based on the area under the receiver operating characteristics curve (0.64), the discriminatory power of the logistic regression model used to derive the PS was confirmed. PS matching resulted in the creation of 143 matched pairs of patients with and without hypoalbuminemia (Fig. 1). For 168 patients in the hypoalbuminemia group, no suitable control was identified. This resulted in the elimination of 168 patients with hypoalbuminemia and 97 patients without hypoalbuminemia from the matched analysis. PS matching reduced the standardized difference for all variables to an absolute value <10% (Fig. 2).

Outcomes

A total of 152 patients died (27.5%), and cardiovascular deaths were observed in 96 (17.4%) patients; the median follow-up was 1.9 years. Ninety-six (30.9%) patients with hypoalbuminemia died, and 56 (23.3%) patients without hypoalbuminemia died. The cumulative event-free survival curves of these two groups are shown in Fig. 3. Patients with hypoalbuminemia tended to have a lower event-free

survival rate than those without hypoalbuminemia (p=0.097). In an unadjusted model of pre-match datasets, patients with hypoalbuminemia showed a tendency toward increased mortality compared with patients without hypoalbuminemia [hazard ratio (HR), 1.32; 95% confidence interval (CI), 0.95-1.84; p=0.098] (Table 2). In the secondary analysis in which the serum albumin level was treated as a continuous variable, the serum albumin level was not associated with increased mortality (Table 2). An adjusted model showed that neither hypoalbuminemia nor serum albumin level was a significant predictor of mortality (Table 2). In addition, the albumin level at discharge and the change in the albumin level were not associated with mortality (HR 0.95, 95% CI 0.74-1.24, p=0.721 and HR 0.96, 95%CI 0.73-1.26 p=0.749, respectively).

In post-match datasets (n=286), the presence of hypoalbuminemia was not associated with an increase in mortality (Log-rank test: p=0.722) (Fig. 4). Mortality risk of the hypoalbuminemia group was similar to that of the non-hypoalbuminemia group (HR 1.09, 95% CI 0.68-1.76; p=0.722) (Table 2). Although we also treated serum albumin level as a continuous variable, serum albumin level was not

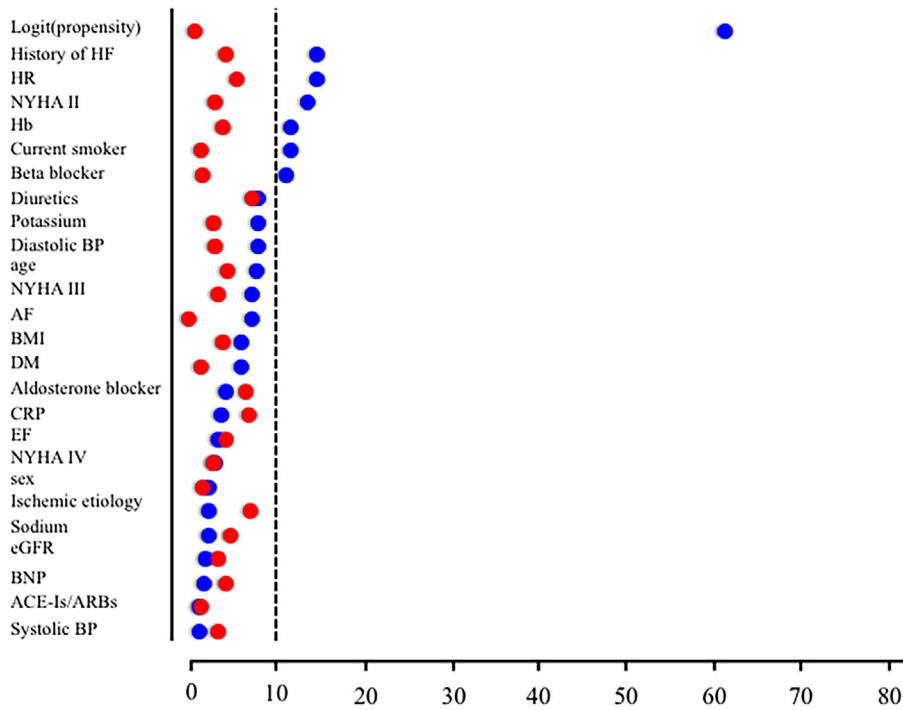


Figure 2. Absolute standardized differences before and after PS matching. AF: atrial fibrillation, ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, BMI: body mass index, BNP: B-type natriuretic peptide, BP: blood pressure, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, HF: heart failure, HR: heart rate, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, PS: propensity score

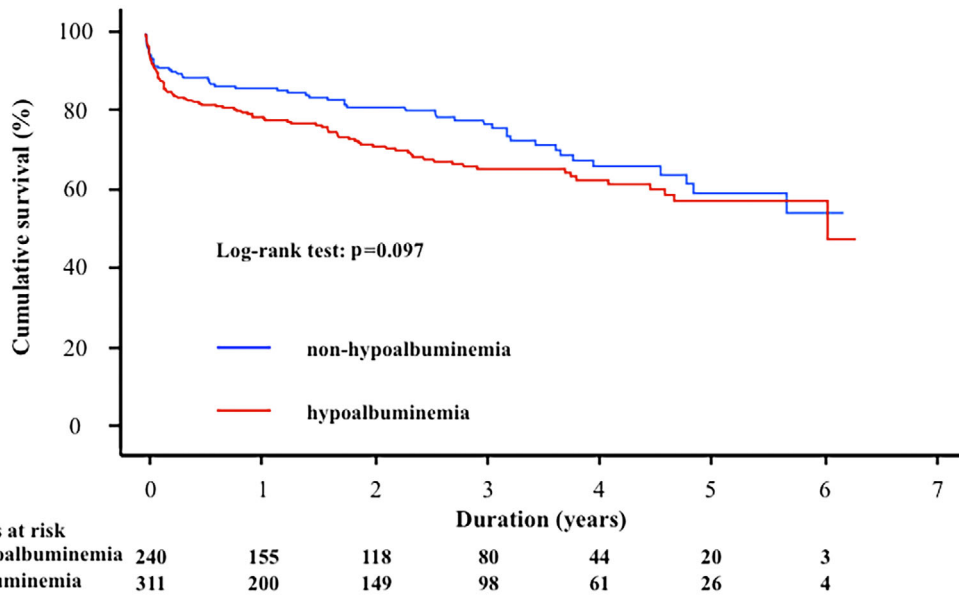


Figure 3. Cumulative event-free survival curves in patients with acute decompensated heart failure and hypoalbuminemia in pre-match patients. The cumulative event-free survival curves tended to be higher in patients with hypoalbuminemia than in non-hypoalbuminemia patients (Log-rank test: $p=0.097$).

associated with mortality risk (HR 1.01, 95% CI 0.68-1.50; $p=0.974$) (Table 2).

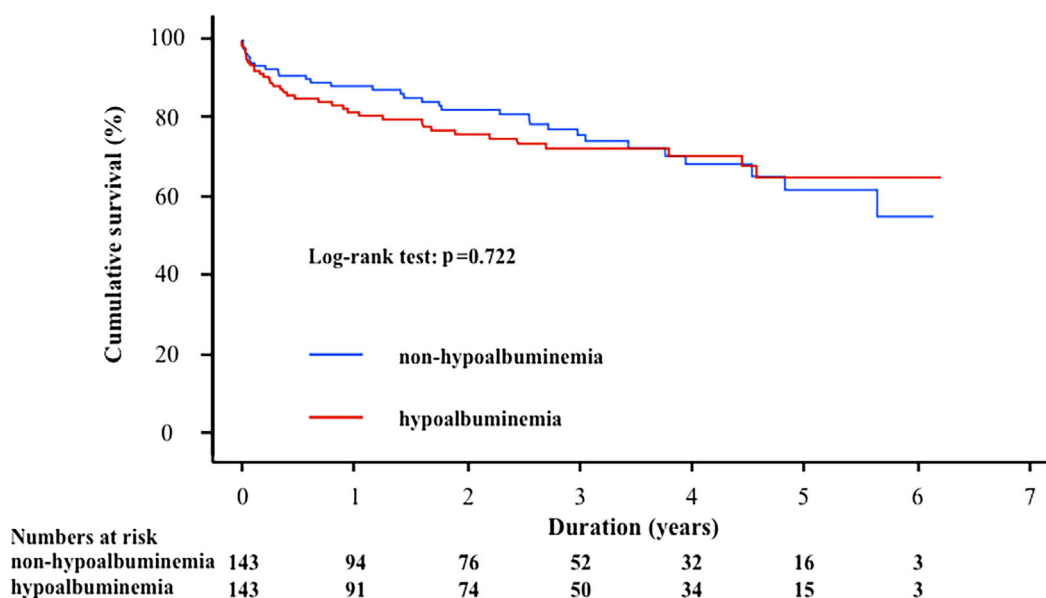
Cardiovascular deaths were observed in 61 (19.6%) patients with hypoalbuminemia and in 35 (14.6%) patients

without hypoalbuminemia in the pre-match datasets. Patients with hypoalbuminemia did not have an increased risk of cardiovascular death compared to those without hypoalbuminemia (HR 1.34, 95% CI 0.89-2.05, $p=0.158$), and the serum

Table 2. Hazard Ratio of Hypoalbuminemia and the Serum Albumin Level on Multiple Assessments of Mortality.

Variables	Pre-match				Post-match	
	Unadjusted		Adjusted		HR (95% CI)	p
	HR (95% CI)	p	HR (95% CI)	p		
Hypoalbuminemia (≤ 3.4 mg/dL)	1.32 (0.95-1.84)	0.098	0.98 (0.64-1.52)	0.938	1.09 (0.68-1.76)	0.722
Serum albumin level (1-mg/dL increase)	0.89 (0.68-1.15)	0.368	1.06 (0.73-1.55)	0.761	1.01 (0.68-1.50)	0.974

HR: hazard ratio, CI: confidence interval

**Figure 4. Cumulative event-free survival curves in patients with acute decompensated heart failure and hypoalbuminemia after propensity score matching. The cumulative event-free survival curves were not increased in patients with hypoalbuminemia compared to non-hypoalbuminemia patients (Log-rank test: $p=0.722$).**

albumin level was not associated with increased cardiovascular deaths (HR 0.87, 95% CI 0.63-1.21, $p=0.408$), even when we treated the serum albumin level as a continuous variable. In addition, neither the albumin level at discharge nor the change in the albumin level was associated with cardiovascular mortality (HR 1.07, 95% CI 0.76-1.51, $p=0.713$ and HR 1.13, 95% CI 0.80-1.61 $p=0.497$, respectively).

Discussion

In this study, we evaluated the existence and prognostic value of hypoalbuminemia in patients with ADHF and came to several novel conclusions based on our results. First, although hypoalbuminemia on admission tended to be associated with mortality in the pre-match unadjusted model, no significant association between hypoalbuminemia and long-term mortality was found in the pre-match conventional adjusted analysis. Second, even in the secondary analysis, no association between the serum albumin level as a continuous variable and long-term mortality was found. Finally, in the patients matched using PS, hypoalbuminemia on admission was not associated with long-term mortality. To our knowl-

edge, no other studies have shown a lack of association between hypoalbuminemia on admission and long-term mortality using PS matching. Thus, this is the first report where a lack of such an association was shown even when PS matching was used. In addition, this study had the longest follow-up time duration among those assessing the association between hypoalbuminemia and mortality in patients with ADHF.

In previous studies, hypoalbuminemia was considered a significant predictor of mortality in patients with chronic illness and chronic HF (9-12). However, inconsistent results have been found in ADHF patients. Although some studies have shown a significant association between hypoalbuminemia on admission and poor clinical outcome in ADHF patients (16-19), one study found no significant association between hypoalbuminemia on admission and short-term (60 days) composite events of mortality, rehospitalization, or unscheduled emergency room visits (20). However, two studies clearly showed an independent association between hypoalbuminemia and in-hospital mortality in patients with ADHF (17, 19). In addition, Uthamalingam et al. reported that hypoalbuminemia on admission was common and was

independently associated with an increased 1-year cardiac mortality rate among patients with ADHF (16). Furthermore, Bonilla-Palomas et al. showed that hypoalbuminemia on admission in ADHF patients was a significant predictor of long-term (30 months) mortality and was associated with malnutrition and inflammation (18). In the present study, although the mortality in patients with hypoalbuminemia seemed to increase until two years after hospitalization, this relationship was not significant when patients were followed for a longer time. These results suggest that previous studies may not have observed significant increases in mortality if they had followed patients for a longer time. Therefore, it remains disputable whether hypoalbuminemia on admission is indeed associated with a worse prognosis in the ADHF patient population. A recent report showed that there were fluctuations in the serum albumin levels throughout the course of hospitalization [serum albumin level decreased from admission to the next day (day 2) and then increased toward the admission level at 7 days after hospital admission] and that an increase in the serum albumin level (from day 2 to day 7) was a significant predictor of a better clinical outcome (23). These findings suggest that the change in the serum albumin level during hospitalization may have a greater prognostic impact on the clinical outcome than a single assessment (i.e., serum albumin level on admission). We therefore also analyzed whether or not increased albumin levels from admission to discharge were associated with mortality in our participants. Ultimately, increased albumin levels during hospitalization were not associated with an increase in mortality in our study.

Several studies have suggested that serum albumin levels are affected by the function of other organs, such as the liver and kidneys, nutritional status, and systemic inflammation (9, 24). Indeed, hypoalbuminemia in ADHF patients was also shown to be associated with malnutrition and inflammatory factors (18). This is one possible explanation for our detecting no significant association between hypoalbuminemia and long-term mortality in the present study, as our results showed no significant differences in the baseline characteristics, including the renal function and CRP, between the two groups, and the results did not change even when we used PS matching.

This study has several limitations. First, this study was a single-center, retrospective observational study and included a limited number of patients. Second, we cannot exclude the possibility that unmeasured factors may have influenced some of our findings, even after taking confounding factors into account. Third, although a positive change in the serum albumin level in patients with ADHF was a predictor of the long-term prognosis according to a recent study (23), a positive change from admission to discharge was not associated with increased mortality in our study population. Thus, a further study in which multiple measurements of the serum albumin level are performed is needed to confirm the impact of the albumin level in ADHF.

Conclusion

Based on our findings in this ADHF patient population, the presence of hypoalbuminemia on admission may not be useful for predicting a negative long-term clinical outcome. This result did not change even when we used PS matching. In addition, no relationship between the serum albumin level as a continuous variable and long-term mortality was found.

Author's disclosure of potential Conflicts of Interest (COI).

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