Prognostic Value of Rising Serum Albumin During Hospitalization in Patients With Acute Heart Failure

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Hypoalbuminemia is an important predictor of a poor long-term prognosis in acute heart failure (AHF). However, changes in serum albumin levels in AHF have not been described to date. Therefore, we investigated the changes in serum albumin levels in patients hospitalized for AHF. This observational study included 115 consecutive patients admitted with AHF. Serum albumin was measured on days 1, 2, 4, and 7 of their hospitalization, and the changes in its levels were assessed. Cox multivariate analysis was used to compare the long-term mortality and readmission rate between 2 groups defined according to whether their serum albumin changes showed a rising pattern (serum albumin level increased from day 2 to day 7) or not. The mean serum albumin levels were 3.51 mg/dl on day 1, 3.21 mg/dl on day 2, 3.23 mg/dl on day 4, and 3.35 mg/dl on day 7 ($p < 0.001$ by multivariate analysis of variance). The rising pattern group including 66 patients (60.6%) was independently associated with a lower mortality and readmission rate (hazard ratios 0.450 and 0.522; $p = 0.01$ and 0.02, respectively). Furthermore, based on multiple linear regression analysis, the changes in hemoglobin and C-reactive protein levels during days 1 to 7 were independently correlated with the changes in serum albumin levels over the same period. In conclusion, a rising pattern of serum albumin change in a patient with AHF was correlated with a good long-term prognosis. Furthermore, the change in serum albumin levels was also associated with changes in cachectic factors. **© 2016 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2016;117:1305−1309)**

The correlation between serum albumin and heart failure (HF) has recently been emphasized. Hypoalbuminemia is associated with a poor prognosis in patients with chronic HF.[1−8] The half-life of serum albumin is shortened to about 9 days during the acute phase of a severe illness.[9,10] Serum albumin is a biomarker of nutritional state; therefore, hypoalbuminemia is associated with prolonged malnutrition.[11] The correlation between hypoalbuminemia and malnutrition in patients with acute HF (AHF) is, however, controversial. This is because serum albumin can be affected by several factors apart from the nutritional state, such as inflammation, accelerated metabolism, impaired synthesis, enteric or renal losses, and hemodilution.[12] A recent study[1] found that malnutrition and inflammatory activations were important etiologic factors associated with hypoalbuminemia in AHF. These previous studies demonstrated a significant correlation between a single measurement of serum albumin and prognosis in patients with AHF. However, it is also necessary to assess the changes in serum albumin during hospitalization when considering therapeutic interventions such as nutritional support. Furthermore, hypoalbuminemia is one of cachectic abnormalities including increased levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 and anemia.[13] Chronic HF is a common cause of cachexia, and patients with cachexia have a poor prognosis.[14] However, the value of these biochemical markers in AHF is unknown.

Methods

This was a single-center, observational study. The study was approved by the ethics committee of our institution. From April 2009 to December 2011, we enrolled 115 consecutive patients aged >18 years who presented to our hospital with AHF and were diagnosed by a cardiologist, based on physical examination, chest x-ray, laboratory tests, and echocardiography, according to the American Heart Association guidelines. The patients received standard HF therapy, including noninvasive positive-pressure ventilation, vasodilators, diuretics, and catecholamines. Presenting with acute myocardial infarction, hypotension requiring fluid replacement or continuous infusions of norepinephrine, overt infection, a history of dialysis, or the need for a ventricular assist device or mechanical ventilation were grounds for exclusion from this study. To preserve the integrity of the data and expedite the handling and storage of samples collected, we excluded patients admitted from 5:00 P.M. to 9:00 A.M., on the weekends or holidays, as described previously.[15]

The patients underwent a review of their medical history and drug therapy at admission. Body height and weight,

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See page 1309 for disclosure information.

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Table 1
Baseline characteristics (n = 115)

Age (years)	74.2 ±2.0
Women	57(51%)
Coronary heart disease	39(34%)
Diabetes mellitus	44(38%)
Atrial fibrillation	59(51%)
Drug therapy at admission	
Renin-angiotensin-aldosterone axis antagonist	59(51%)
Beta-adrenergic blocker	52(43%)
Diuretic	76(66%)
Body mass index on day 10 (kg/m^2)	24.3±0.9
Body weight on day 1 (kg)	59.5±2.8
Day 1	
Systolic blood pressure (mmHg)	138.8±4.9
Diastolic blood pressure (mmHg)	79.5±3.4
Heart rate (beats per minute)	82.0±4.0
Left-ventricular ejection fraction (%)	50.0±3.4
Patients with ejection fraction>45%	66(58%)
Hemoglobin (g/dL)	11.3±0.4
Sodium (mEq/L)	139.5±0.8
Albumin (mg/dL)	3.53±0.09
Blood urea nitrogen (mg/dL)	26.9±2.6
Creatinine (mg/dL)	1.36±0.16
Estimated glomerular filtration rate (mL/min per 1.73 m^2)	47.3±4.2
Total bilirubin (mg/dL)	1.03±0.18
NT-pro b-type natriuretic peptide (pg/ml)	9859±3079
C-reactive protein (mg/dL)	0.74±0.31
Aspartate aminotransferase (IU/L)	46.5±19.5

Values are means ± SD or numbers (%) of observations.

systemic blood pressure, and heart rate were recorded throughout the course of treatment. Left-ventricular ejection fraction was measured using ventriculography or echocardiography and calculated using the modified 2-dimensional Simpson method or the Teichholz formula.

Blood samples were collected ≤6 hours after the patient's admission to the hospital. The day-2 samples were collected on the day after the admission day, the day-4 samples were collected from day 3 to day 5, and the day-7 samples were collected from day 6 to day 8 of hospitalization, depending on the day of the week on which the patient was admitted, to guarantee proper storage of the samples, as mentioned earlier. Because the equation used to estimate the glomerular filtration rate in Western countries might not be applicable to Asian patients, we used recently published equations for Japanese men (194 × serum creatinine − 1.094 × age − 0.287) and women (194 × serum creatinine − 1.094 × age − 0.287 × 0.739). NT-pro b-type natriuretic peptide (NT-proBNP) was measured using an Elecsys 2010 system (Roche Diagnostics, Tokyo, Japan). All study procedures were in compliance with the principles outlined in the Declaration of Helsinki and the institutional guidelines of Hyogo Prefectural Amagasaki Hospital. The investigators had full access to and take responsibility for the integrity of the data. Continuous variables are presented as mean ± SD and categorical variables as percentages. The fit to the normal distribution of quantitative variables was assessed using the Shapiro−Wilk test. The differences in the mean serum albumin levels on days 1, 2, 4, and 7 were examined using the paired *t* test and multivariate analysis of variance.

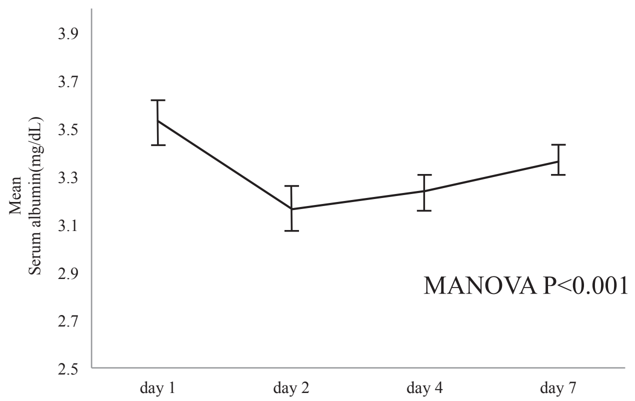

Figure 1. Serum albumin means in patients with AHF during hospitalization was decreasing from day 1 to day 2 and increasing from day 4 to day 7. This change was statistically significant by MANOVA (p <0.0001). MANOVA = multivariate analysis of variance.

All-cause mortalities of early (in-hospital) and long term were assessed. We checked long-term mortality in October 2015, 4 years after the last patient was discharged, by phone whether the patients who we were unable to come for follow-up visits were alive or not. We were unable to reach one patient by phone. We also assessed readmissions caused by HF. The 18 patients who either underwent a surgical operation (n = 5) or could not be followed up (n = 13) were excluded. We divided the patients into 2 groups according to whether their serum albumin changes had shown a rising pattern (serum albumin level increased from days 2 to 7) or not (serum albumin level decreased or did not change from days 2 to 7). This grouping was only focus on the values of serum albumin on days 2 and 7; therefore, the values of serum albumin on days 1 and 4 had no contribution to these groups. For comparisons between groups, the chi-square test was used for qualitative variables, whereas the Student *t* test and Wilcoxon rank-sum were used for parametric and nonparametric quantitative variables, respectively. Kaplan−Meier survival curves were derived for the groups and were then compared using the log-rank test. To assess whether a change in serum albumin was an independent predictor of mortality and readmission, multivariate analysis was performed using the Cox regression model. Factors that showed significant prognostic influence on bivariate analyses (p <0.05) were included, together with age and female gender. The results are given as hazard ratios and 95% CIs.

We evaluated the correlation between the changes in albumin level and baseline characteristics, changes in body weight, systolic blood pressure, hemoglobin, bilirubin, aspartate transaminase, blood urea nitrogen, creatinine, estimated glomerular filtration rate, CRP, and NT-proBNP by simple linear regression analyses. As the changes in creatinine and NT-proBNP were nonparametric quantitative variables, these variables were log transformed for analysis. Factors with a probability value of ≤0.05 on bivariate regression analyses were included in the multivariate linear regression analysis, together with age and female gender. The results are expressed as correlation coefficients.

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