

# Association of admission vs. nadir serum albumin concentration with short-term treatment outcomes in patients with acute heart failure

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## Abstract

**Objectives:** Hypoalbuminemia occurs in 25% to 76% of patients hospitalized for acute heart failure (HF) and is associated with increased mortality. Hypoalbuminemia may predispose patients to intravascular volume depletion, hypotension, and acute worsening of renal function; however, its association with treatment outcomes during hospitalization is unknown.

**Methods:** This retrospective cohort study involved 414 adult patients hospitalized for HF requiring intravenous diuretics. Temporal changes in serum albumin and the association of hypoalbuminemia with urine output, renal function changes, blood pressure, use of intravenous vasoactive drugs, and short-term outcomes were assessed.

**Results:** Serum albumin decreased in most patients (72%) during hospitalization. Hypoalbuminemia was present in 29% and 50% of patients based on the mean admission and nadir serum albumin level, respectively. Hypoalbuminemia as assessed by the nadir albumin level was associated with an increased risk of acute worsening of renal function. A nadir albumin level of <3.0 g/dL remained significantly associated in the multivariate analyses.

**Conclusions:** Serum albumin commonly decreases during hospitalization for acute HF. Hypoalbuminemia assessed using the nadir level during hospitalization, not the admission level, was associated with an increased risk of acute worsening of renal function. The timing of serum albumin measurement may influence its utility as a biomarker.

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**Keywords**

Albumin, heart failure, worsening renal function, biomarker, hospitalization, temporal

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**Introduction**

Numerous novel laboratory biomarkers have demonstrated value in the prognostication and diagnosis of heart failure (HF). However, application of these biomarkers to daily clinical practice remains challenging because data are lacking on how these biomarkers could influence treatment decisions. In addition, many biomarkers require assays that are not readily available. The utility of biomarkers obtained in routine laboratory testing also needs further exploration.

Serum albumin is a potentially important biomarker in HF. Patients with HF exhibit multiple pathophysiologic alterations that may influence the serum albumin concentration, including hemodilution, cardiac cachexia and chronic malnutrition, impaired synthesis, and inflammation.<sup>1,2</sup> Hypoalbuminemia is common in patients with HF and has a reported incidence ranging from 25% to 76%.<sup>3–5</sup> Hypoalbuminemia is a risk factor for the development of HF<sup>6</sup> and is predictive of mortality in patients with chronic HF<sup>7,8</sup> and acute HF.<sup>1,4,9–16</sup>

However, interpretation of the serum albumin concentration and how it may influence clinical treatment decisions in patients hospitalized with HF is poorly understood. Additionally, whether the timing of serum albumin measurement influences the association of the albumin level with clinical outcomes remains unknown. One study suggested that this association may be related to the severity of hypoalbuminemia,<sup>12</sup> but this effect has

not been well studied. Most studies have reported albumin levels from admission,<sup>4,10–12</sup> however, one study measured albumin at the time of clinical stabilization.<sup>9</sup> Only a few studies have examined temporal changes in serum albumin in hospitalized patients with HF, and these studies mainly compared admission levels to discharge and outpatient levels.<sup>13,16,17</sup> Limited data suggest that repeat albumin measurements may be useful; in a subanalysis from the ESCAPE trial, increases in albumin, total protein, and hematocrit were associated with an increase in survival.<sup>18</sup>

In addition, because albumin is the primary determinant of the plasma oncotic pressure, the presence of hypoalbuminemia may affect intravascular volume homeostasis and the response to diuretic treatment.<sup>2</sup> Patients with hypoalbuminemia may have relative intravascular depletion, potentially predisposing them to hypotension and reduced renal perfusion and contributing to reduced diuresis and an increased risk of acute worsening of renal function. A single-center study showed that hypoalbuminemia was the only factor associated with worsening renal function in patients with acute HF.<sup>19</sup> However, this finding was not replicated in a post-hoc analysis of the DOSE-AHF and ROSE-AHF trials.<sup>20</sup>

This study was performed to evaluate the potential clinical utility of serum albumin as a biomarker in the management of acute HF by assessing the association of the serum albumin concentration, evaluated temporally during hospitalization, with

hemodynamic and renal outcomes in patients hospitalized for acute HF.

## Methods

### Study design

This retrospective study included consecutive patients with acute HF who were hospitalized and admitted to the Intensive Cardiac Care Unit of the Los Angeles County-University of Southern California Medical Center from 1 January 2010 to 31 December 2010. Data were extracted from a computerized charting system and verified using paper charts as necessary. Patients at least 18 years of age admitted for acute HF who were treated with intravenous loop diuretics for a minimum of 48 hours and who had at least one serum albumin level measurement were included. In the initial diuretic regimen, 65% of patients were treated with a bolus of furosemide, 34% were treated with a continuous infusion of furosemide, and 1% were treated with a continuous infusion of bumetanide. Additionally, 8.2% of patients were switched from a bolus to a continuous infusion of furosemide, while 4.8% also received metolazone. The exclusion criteria were end-stage renal disease under treatment with scheduled hemodialysis, receipt of intravenous inotropic or vasopressor therapy at admission, or administration of intravenous albumin at any time during hospitalization. Hypoalbuminemia was defined as a serum albumin level of  $\leq 3.4$  g/dL. Acute worsening of renal function was defined as an increase in serum creatinine (SCr) of 0.3 mg/dL or 25% above baseline.

The study protocol was approved by the Institutional Review Board of the University of Southern California. Waiver of informed consent was granted by the Institutional Review Board because this study was retrospective and utilized existing data.

### Objectives

The primary objective of this study was to determine the incidence of hypoalbuminemia based on the initial and lowest (nadir) recorded albumin levels during hospitalization. The secondary objectives were assessment of the temporal changes in albumin levels and the association of hypoalbuminemia with acute in-hospital clinical outcomes [daily urine output, in-hospital mortality, length of stay, incidence of sustained hypotension (systolic blood pressure of  $<90$  mmHg for two consecutive readings 1 hour apart), diuretic dose, acute worsening of renal function, and need for diuretic regimen escalation]. To evaluate changes in albumin in relation to other laboratory markers that could indicate the intravascular volume status and hemoconcentration, the association of changes in albumin with changes in total protein, bicarbonate, hematocrit, and the ratio of blood urea nitrogen to SCr (BUN/SCr) was also examined.

### Statistical analysis

Descriptive statistics were used to evaluate the incidence of hypoalbuminemia and describe temporal changes in the serum albumin concentration. Hypoalbuminemia was stratified into two levels of severity: mild (3.0–3.4 g/dL) and moderate/severe ( $<3.0$  g/dL). For all comparative analyses across the admission and nadir serum albumin categories, one-way analysis of variance and the chi-square test (or Fisher's exact test) were performed for continuous variables and categorical variables, respectively. If either the normality or equal-variance assumptions underlying the traditional analysis of variance were violated, the Kruskal–Wallis test was used because it does not depend on normality or equal-variance assumptions.

Because an association between the nadir serum albumin concentration and incidence of acute worsening renal function was apparent upon the univariate analysis, a multivariable regression analyses was performed to assess the strength of the association. A stepwise model selection method was employed to identify the significant factors. Statistical significance was assessed using an  $\alpha$  level of 0.05. Statistical analysis was performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

## Results

### *Patient population*

In total, 441 patients met the inclusion criteria during the study period; of these, 27 met the exclusion criteria. Therefore, 414 patients hospitalized for acute HF were included in the study. Their mean age was  $57 \pm 13$  years, and 35% were female. Most patients were Hispanic (60%); the remaining were Caucasian (17%), Asian (13%), African-American (9%), or undefined (1%). The etiology of HF was ischemic in 40% of patients. The mean left ventricular ejection fraction was  $40\% \pm 17\%$ , and 33% of patients had a preserved ejection fraction of  $\geq 50\%$ . The in-hospital mortality rate was 1%, and the mean length of stay was  $6.9 \pm 5.8$  days.

### *Serum albumin and incidence of hypoalbuminemia*

The median number of albumin level measurements for each patient was 2 (range, 1–27; interquartile range, 1–4). Among the 310 patients who underwent multiple measurements during their hospitalization, the mean change in the albumin level between the first and last recorded value was  $-0.25 \pm 0.41$  g/dL. The albumin level decreased in 72% of patients, remained unchanged in 8%, and increased in 20%. With respect

to other laboratory markers with the potential to indicate hemoconcentration, albumin was moderately and strongly correlated with hematocrit and total protein, respectively, as expected. However, the serum albumin changes were not correlated with serum sodium, BUN/SCr, or serum bicarbonate. Categorical changes in the albumin level were not associated with clinical outcomes (data not shown).

The initial albumin level was measured within 24 hours of admission in 89% of patients. The mean initial albumin level was  $3.7 \pm 0.6$  g/dL, and 29% of patients had an initial level of  $\leq 3.4$  g/dL. The distribution of patients presenting with hypoalbuminemia was as follows: 1% of patients had an albumin level of  $< 2.0$  g/dL, 6% had a level of 2.0 to 2.4 g/dL, 27% had a level of 2.5 to 2.9 g/dL, and 66% had a level of 3.0 to 3.4 g/dL. Because of the small number of patients, the lowest three tiers of severity were pooled and subsequent analyses were conducted by comparing the cohorts of patients with an albumin level of  $< 3.0$  g/dL (moderate/severe), 3.0 to 3.4 g/dL (mild), and  $> 3.4$  g/dL (normal).

The mean nadir serum albumin level was  $3.4 \pm 0.4$  g/dL. Based on the nadir level, hypoalbuminemia was present in 50% of patients, with 29% in the mild range and 21% within the moderate/severe range. The median time between measurement of the initial and nadir albumin level was 1 day (interquartile range, 0–3 days). The patients' demographics and baseline characteristics stratified by the nadir albumin level are shown in Table 1.

### *Hypoalbuminemia and outcomes*

When patients were stratified by the initial serum albumin level, moderate/severe hypoalbuminemia was associated with a significantly higher in-hospital mortality rate (moderate/severe, 10.0%; mild, 0.0%; normal, 0.3%;  $p < 0.001$ ), but not length of

**Table 1.** Patient characteristics according to nadir serum albumin level

	<3.0 mg/dL (n = 87)	3.0–3.4 mg/dL (n = 122)	>3.4 mg/dL (n = 205)
Age, years	58 ± 14	59 ± 13	56 ± 13
Male sex	62 (71)	80 (66)	129 (63)
Weight, kg	80.2 ± 24.9	86.9 ± 28.9	83.2 ± 23.7
Heart rate, bpm	88 ± 17	89 ± 19	88 ± 17
Systolic BP	128 ± 19	130 ± 24	126 ± 23
Diastolic BP	74 ± 21	79 ± 21	75 ± 17
SCr, mg/dL	1.50 ± 1.04	1.40 ± 1.49	1.12 ± 0.71
Hematocrit, %	32 ± 8	33 ± 7	37 ± 6
NT-proBNP, pg/mL	11912 ± 11544**	9121 ± 13468**	5084 ± 6368**
LVEF, %	40 ± 15	40 ± 17	39 ± 17
Ischemic HF	35 (40)	44 (36)	68 (33)
LVEF ≥50%	28 (33)	41 (35)	67 (34)
Hypertension	61 (70)	77 (63)	140 (68)
Diabetes	44 (51)*	62 (51)*	76 (37)*
Arrhythmia	20 (23)	37 (30)	64 (31)
Dyslipidemia	24 (28)	30 (25)	72 (31)

Data are presented as n (%) or mean ± standard deviation.

LVEF, left ventricular ejection fraction; HF, heart failure; BP, blood pressure; SCr, serum creatinine; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

\* $p = 0.02$ , \*\* $p < 0.001$ .

stay. In patients with hypoalbuminemia, the baseline SCr concentration was significantly higher (moderate to severe hypoalbuminemia vs. normoalbuminemia,  $p = 0.018$ ; mild hypoalbuminemia vs. normoalbuminemia,  $p = 0.014$ ) and the glomerular filtration rate was significantly lower (moderate to severe hypoalbuminemia vs. normoalbuminemia,  $p = 0.022$ ; mild hypoalbuminemia vs. normoalbuminemia,  $p = 0.049$ ), but the incidence of acute worsening of renal function was not significantly different among the groups. Other clinical endpoints, such as the mean hourly urine output, incidence of sustained hypotension, and use of intravenous vasoactive therapy (vasodilators, inotropes, and/or vasopressors), were not different in the univariate analyses. The clinical outcomes stratified by the initial serum albumin categories are shown in Table 2.

In contrast, when patients were stratified by the nadir serum albumin, moderate/

severe hypoalbuminemia was significantly associated with in-hospital mortality (moderate/severe, 6%; mild, 0%; normal, 0%;  $p < 0.001$ ) and length of stay (moderate/severe,  $9.8 \pm 8.3$  days; mild,  $7.5 \pm 5.9$  days; normal,  $5.3 \pm 3.5$  days;  $p < 0.001$ ). In patients with hypoalbuminemia, the baseline SCr concentration was significantly higher (moderate to severe hypoalbuminemia vs. normoalbuminemia,  $p = 0.011$ ; mild hypoalbuminemia vs. normoalbuminemia,  $p = 0.016$ ) and the glomerular filtration rate was significantly lower (moderate to severe hypoalbuminemia vs. normoalbuminemia,  $p = 0.012$ ; mild hypoalbuminemia vs. normoalbuminemia,  $p = 0.036$ ). The incidence of acute worsening of renal function occurred significantly more often in patients with moderate/severe hypoalbuminemia (moderate/severe, 53%; mild, 34%; normal, 33%;  $p = 0.004$ ). The use of intravenous vasodilators, inotropes, and

**Table 2.** Treatments and outcomes according to initial serum albumin level

	<3 mg/dL (n = 39)	3.0–3.4 mg/dL (n = 83)	>3.4 mg/dL (n = 292)	p-value
Mortality	4 (10)	0 (0)	1 (0)	<0.001
Length of stay, days	8.2 ± 5.9	7.3 ± 5.5	6.6 ± 5.8	0.212
Acute worsening of renal function	18 (46)	30 (36)	108 (37)	0.513
Mean hourly urine output, mL	71 ± 33	90 ± 54	81 ± 37	0.051
IV inotrope use	5 (13)	8 (10)	36 (12)	0.783
IV vasopressor use	2 (5)	0 (0)	9 (3)	0.184
IV vasodilator use	15 (39)	46 (55)	126 (43)	0.095
Renal replacement use	2 (5)	1 (1)	2 (1)	0.058

Data are presented as n (%) or mean ± standard deviation.  
IV, intravenous.

**Table 3.** Treatments and outcomes according to nadir serum albumin level

	<3 mg/dL (n = 87)	3.0–3.4 mg/dL (n = 122)	>3.4 mg/dL (n = 205)	p-value
Mortality	5 (6)	0 (0)	0 (0)	<0.001
Length of stay, days	9.8 ± 8.3	7.5 ± 5.9	5.3 ± 3.5	<0.001
Acute worsening of renal function	46 (53)	42 (34)	68 (33)	0.004
Mean hourly urine output, mL	76 ± 35	89 ± 48	80 ± 38	0.047
IV inotrope use	16 (18)	20 (16)	13 (6)	0.003
IV vasopressor use	6 (7)	3 (3)	2 (1)	0.016
IV vasodilator use	39 (45)	69 (57)	79 (39)	0.007
Renal replacement use	3 (3)	2 (2)	0 (0)	0.042

Data are presented as n (%) or mean ± standard deviation.  
IV, intravenous.

vasopressors was significantly higher in patients with hypoalbuminemia ( $p = 0.007$ ,  $0.003$ , and  $0.016$ , respectively). The patients' clinical outcomes stratified by the nadir serum albumin categories are shown in Table 3.

The association of the nadir serum albumin category with acute worsening of renal function was further assessed in a multivariate regression (Table 4). The presence of moderate/severe hypoalbuminemia relative to a normal albumin level was found to be significantly associated with an approximately two-fold increased risk for developing acute worsening of renal function ( $p = 0.0483$ ). Other variables found to be significantly associated with acute

worsening of renal function were baseline SCr ( $p < 0.0001$ ), hematocrit ( $p = 0.0039$ ), length of stay ( $p < 0.0001$ ), and antiplatelet use ( $p = 0.0054$ ). The association of the nadir serum albumin with in-hospital mortality was not explored in the multivariate analysis because of the low event rate.

## Discussion

Hypoalbuminemia is a common finding in patients with HF and an established marker of a poorer prognosis. However, data regarding the importance of serum albumin in hospitalized patients have been largely limited to interpretation of a single level, usually obtained upon admission. Our

**Table 4.** Independent predictors of acute worsening of renal function

	OR (95% CI)	p-value*
ICU length of stay, days	1.183 (1.115–1.255)	<0.0001
Baseline serum creatinine	0.298 (0.179–0.497)	<0.0001
Hematocrit	0.940 (0.901–0.980)	0.0039
Antiplatelet use	2.672 (1.337–5.341)	0.0054
Nadir albumin		
<3.0 vs. >3.4 mg/dL	1.987 (1.005–3.929)	0.0483
3.0–3.4 vs. >3.4 mg/dL	0.732 (0.409–1.308)	0.2920
Diabetes**	1.565 (0.948–2.583)	0.0799

OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

\*Significant at  $\alpha$  level of 0.05.

\*\*Diabetes mellitus was a controlled confounder in the model.

analysis of patients hospitalized for acute HF receiving intravenous diuretics confirms that the incidence of hypoalbuminemia is high. However, the most important finding of the current analysis is that serum albumin levels changed during hospitalization and that the timing of the laboratory evaluation may influence the utility of albumin as a biomarker.

### Temporal changes in serum albumin

Overall, the serum albumin levels tended to decrease in patients who had undergone sequential serum albumin level measurement during hospitalization. Therefore, the incidence of hypoalbuminemia was greater when considering the nadir serum albumin level (50%) than when considering the serum albumin level at the time of admission (29%). With respect to the prognostic utility of serum albumin, this difference may have implications for proper patient risk stratification. Temporal changes in serum albumin have not been studied extensively. Our results are consistent with those of a retrospective analysis of patients enrolled in clinical trials of serelexin, which revealed a similar mean decrease ( $-1.4$  mg/dL on day 2).<sup>21</sup> Conversely, post-hoc analyses of the EVEREST and ESCAPE study populations

found no substantial decrease in the mean albumin levels.<sup>16,17</sup> However, these studies only evaluated levels at admission and discharge or day 7; therefore, we cannot draw conclusions regarding the acute changes seen in our study and the serelexin studies.

### Mechanisms for the observed temporal decrease in albumin

Although there is evidence for the contribution of a fluid overload-induced increase in the intravascular volume to the development of hypoalbuminemia in patients with HF,<sup>1</sup> the net decline in albumin during hospitalization suggests that other mechanisms may also contribute to hypoalbuminemia by decreasing albumin synthesis; such mechanisms include cardiac cachexia, chronic malnutrition, and/or hepatic congestion.<sup>22</sup> In addition, changes in the serum level of albumin (a negative acute-phase reactant) may be related to systemic inflammatory responses during acute HF,<sup>1</sup> which could initially increase the albumin level followed by a decline once the patient is initially stabilized. Increased transcapillary escape of albumin from the intravascular to extravascular space may also be associated with hypoalbuminemia.<sup>2</sup> Consistent with the above hypotheses, the serum albumin level was not correlated with

other laboratory biomarkers commonly used to assess intravascular volume depletion or hemoconcentration in the present study. In all studies evaluating temporal changes in serum albumin, the lack of a clear increase in levels and improvement in the incidence of hypoalbuminemia highlight the need for continued study of the mechanisms influencing liver function tests in patients with acute HF.

### *Practical utility of albumin as a biomarker*

Moderate to severe hypoalbuminemia as defined by the nadir but not the admission serum albumin concentration was significantly associated with important acute treatment and clinical endpoints. A nadir serum albumin level of  $<3$  g/dL was associated with an increased risk of acute worsening of renal function, lower mean hourly urine output, and increased use of intravenous vasoactive therapies and renal replacement therapy. Considering the importance of acute worsening of renal function to HF, we conducted a multivariate analysis that confirmed the independent prognostic value of a nadir serum albumin level of  $<3$  g/dL. Using the admission serum albumin levels to categorize patients only provided signals related to these endpoints. Limited literature exists regarding the association of hypoalbuminemia with acute treatment outcomes. Our results differ from those of a previous observational study that found no association with worsening renal function or response to diuretic therapy in patients with a serum albumin level of  $\leq 3$  g/dL.<sup>19,23</sup> However, the definition of worsening renal function differed (only SCr changes of  $>0.3$  mg/dL) and the timing of the baseline serum albumin measurement was not explicitly stated. The mean diuretic doses were much higher than in our study population, and all their patients received continuous infusions. Post-hoc analysis of the DOSE and

ROSE-AHF studies also showed no association of serum albumin with worsening renal function using a dichotomous cut-off of 3.5 g/dL; however, only baseline serum albumin was assessed.<sup>20</sup> Notably, the authors did find a trend toward greater diuresis in patients with normal albumin levels. These discordant findings across heterogeneous studies support the need for further examination of the potential influence of the timing of serum albumin measurement in the context of acute prognostication.

### *Limitations*

As with all observational studies, the current results should be viewed as hypothesis-generating. The primary limitation is the non-standardized sampling of albumin levels. The initial albumin levels reported are likely representative of the admission values because the vast majority were obtained within 24 hours of admission. Conversely, the nadir values that were significantly associated with worse renal outcomes were not obtained at standard times, making it more difficult to use this information to assess risk in other patients. However, most nadir levels were reached the day after admission; therefore, measurement of the albumin level in the early part of admission may still allow for determination of this risk. Although hypoalbuminemia was associated with acutely worsening renal function in the multivariate analysis, whether it predicts or causes the acute worsening of renal function or whether renal insufficiency contributes to the development of hypoalbuminemia remains unclear. Most of the nadir albumin levels were obtained within 1 day of hospitalization, suggesting that hypoalbuminemia preceded the development of acute worsening of renal function rather than being the result of the renal event in many patients. However, whether hypoalbuminemia is



simply a marker or a causative factor in different patients requires further study. In addition, studies involving albumin levels in patients with decompensated HF have also included different thresholds for hypoalbuminemia. Thus, whether the observed associations are reflective of a certain threshold as opposed to a linear relationship to serum albumin remains uncertain. We were unable to include patients' New York Heart Association functional class because it is not well documented at our institution. Therefore, we could not determine whether more patients with severe hypoalbuminemia had functional class IV heart failure and thus we cannot rule out the possibility of functional class contributing to the mortality difference.

## Conclusion

Overall, our results suggest that the timing of serum albumin level assessment may influence the utility of albumin as a biomarker of short-term clinical outcomes in patients with acute HF. In patients with acute HF receiving intravenous diuretics, moderate/severe hypoalbuminemia as determined by the nadir but not admission serum albumin level is associated with a greater risk of acute worsening of renal function and the need for intravenous vasoactive therapies. The mechanisms underlying these associations require further study before determination of how the serum albumin level may influence clinical practice decisions.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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