Prognostic Significance of Serum Albumin Levels in Patients with Systolic Heart Failure

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ABSTRACT:

BACKGROUND:

Hypoalbuminemia is considered as poor prognostic factor in patients with certain chronic diseases, such as cancer and end-stage renal failure. Low serum albumin is common in patients with heart failure; nevertheless, the relationship between serum albumin and heart failure prognosis has not been well verified.

OBJECTIVE:

To elucidate the effect of serum albumin level on prognosis of patients with systolic heart failure.

METHODS:

This study included 250 patients with systolic heart failure who were admitted to Baghdad teaching hospital between February 2008 and April 2010. Patients were divided into groups based on presence of hypoalbuminemia (≤3.4 g/dL).

RESULTS:

The mean age of patients was 55 ± 14 years and the mean left ventricular ejection fraction [LVEF] was 28 ± 11 %). The mean serum albumin was 3.9 ± 0.7 g/dL; 27.2 % of patients had hypoalbuminemia. Patients with and without low serum albumin levels were similar in age, cause of heart failure, and ejection fraction. Patients with hypoalbuminemia had higher New York Heart Association (NYHA) class, higher serum urea, creatinine and C-reactive protein levels but lower levels of sodium, hemoglobin, and cholesterol. In patients with body mass index (BMI) < 25 kg/m^2, 26% had hypoalbuminemia compared to 20% in those with BMI ≥25 kg/m^2 (P ≤ 0.01). One-year survival was 64.71% in patients with and 85.72% in those without hypoalbuminemia (P < 0.001). Risk-adjusted hazard ratio for 1-year mortality was 1.9 (1.5-2.4).

CONCLUSION:

Hypoalbuminemia is common in patients with heart failure and is independently associated with increased mortality.

KEYWORDS: albumin, systolic heart failure, prognosis.

INTRODUCTION:

Hypoalbuminemia is a common laboratory finding in patients with systolic heart failure (HF), occurring in approximately one third of patients. [1] The possible mechanisms of hypoalbuminemia in patients with HF are malnutrition, chronic inflammation, infection, hemodilution, proteinuria, and other mechanisms. By reducing colloid osmotic pressure, hypoalbuminemia can affect the degree of pulmonary congestion and HF symptoms.[2,3,4] In disease states, such as end-stage chronic renal failure, cancer and infection, and in the elderly, hypoalbuminemia is associated with poor outcomes.[5,6,7,8,9] For example, hypoalbuminemia has been found to be the strongest predictor of death in dialysis patients.[10,11] The importance of serum albumin levels as a prognostic factor in systolic HF has not been well characterized.

Wasting disease in HF, which is known as "cardiac cachexia", is associated with low body mass index (BMI) and/or weight loss over time. It is also associated with inflammation as reflected by increased levels of inflammatory cytokines. Cardiac cachexia is known to predict increased mortality in HF. [12,13,14] but whether low albumin is characteristic of cardiac cachexia or HF patients with low BMI is unknown.

The primary aim of this study was to examine whether serum albumin is an independent predictor of survival in patients with systolic HF. Secondary objective was to examine the relationship between BMI and albumin levels in HF, as well as the interaction between BMI and albumin levels in predicting survival.

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PATIENTS AND METHODS:

The study included 250 patients with systolic heart failure who were admitted to Baghdad teaching hospital between February 2008 and April 2010. Systolic heart failure was defined as clinical features of heart failure with echocardiographically measured left ventricular ejection fraction of less than 50 %. Patients with asymptomatic left ventricular systolic dysfunction were not included. Ischemic etiology of heart failure was considered when patients gave definite history of ischemic heart disease, electrocardiography revealed Q-wave myocardial infarction and/or previous coronary angiography showed significant coronary artery stenosis (≥ 50 % stenosis in left main stem or ≥ 70% stenosis in other coronary arteries). Radioisotope cardiac perfusion scan was not available at the time of study.

Serum albumin levels were analyzed in patients using a bromocresol purple dye-binding method. The reference range for this albumin assay is 3.5 to 4.7 g/dL. Low albumin, or hypoalbuminemia, was defined as the lowest quartile of albumin, ≤3.4 g/dL. Patients were also divided into groups based on serum albumin (g/dL) quartiles (Qs): Q1 (≤3.4), Q2 (3.5-3.8), Q3 (3.9-4.2), Q4 (≥4.3). Body mass index (BMI), defined as weight in kilograms (kg) divided by height in square meters, was calculated in the studied patients. Patients were divided into categories of BMI (kg/m^2) according to the following: underweight (BMI ≤18.5), normal weight (BMI 18.5-24.9), overweight BMI (25.0-29.9), and obese (BMI ≥30.0) (15). Additional laboratory testing and echocardiography were obtained in all studied patients.

One-year follow-up was done for patients by recording mobile number of a first-degree relative for each patient and making regular calls with them every 3 months asking every time about health status of patients and the type of death (as defined below) if they were dead.

Definition of end points

The primary end point for the study was all-cause mortality. Secondary outcomes included sudden death and heart failure death. Death was considered sudden if it was unexpected based on the patient's clinical status and if it occurred outside the hospital within 15 minutes of the onset of unexpected symptoms or during sleep.

Death during hospitalization for worsening congestive symptoms or multisystem organ failure was considered an HF death.

Statistical analysis

Data are presented as mean ± SDs for normally distributed continuous variables, median and interquartile range for non-normally distributed continuous variables, and as frequencies for categorical variables. Baseline characteristics between patients with and without hypoalbuminemia were compared using independent samples t test, $\chi 2$, and Wilcoxon rank sum test as appropriate. Multivariable logistic regression was performed with albumin (low vs high) as the outcome variable, and predictor variables including BMI, sex, age, left ventricular ejection fraction (LVEF), heart failure etiology, blood urea, serum sodium, hemoglobin, total cholesterol, and medications. Kaplan-Meier survival analysis was performed by strata of clinically significant variables including age, sex, BMI, and medications. Data were analyzed using SPSS 15.0 for Windows.

RESULTS:

Albumin and baseline patient characteristics

A total of 250 patients with males to females ratio of 2.67:1 were included in this study. The mean age of patients was 55 ± 14 years, mean LVEF (%) was 28 ± 11, with NYHA III and IV comprising 51% and 34% of the cohort, respectively. Mean serum albumin was 3.9 ± 0.7 g/dL (range 1.7-5.6 g/dL), and 27.2 % of patients had hypoalbuminemia (serum albumin ≤3.4 g/dL). Baseline characteristics of the study cohort are presented in (Table 1). Hypoalbuminemia was more common in women and those with NYHA IV. Low albumin was also associated with lower levels of serum sodium, hemoglobin, and cholesterol but higher levels of C-reactive protein, blood urea, and creatinine. There was no difference in LVEF or left ventricular end-diastolic dimension index between those with and without hypoalbuminemia. Patients with low albumin were less likely to be on angiotensin converting enzyme inhibitor or angiotensin-receptor blocker (Table 1).

Albumin and BMI

Body mass index was not significantly different among patients with and without hypoalbuminemia (Table 1). Body mass index also did not differ between albumin Qs, with mean BMI in Q1 to Q4 of 25.8 ± 5.7, 26.1 ± 5.3, 26.6 ± 5.4, and 26.7 ± 5.2 kg/m^2, respectively (P = 0.30). Underweight and normal weight HF patients had slightly higher rates of hypoalbuminemia compared to overweight and obese patients. In patients with BMI <25 kg/m^2, 26% had hypoalbuminemia compared to 20% in

those with BMI ≥25 kg/m^2 (P ≤ 0.01).
On multivariate logistic regression analysis, BMI was not significantly associated with hypoalbuminemia; variables that were independent predictors of low albumin included lower total cholesterol, hemoglobin, and sodium levels, and higher NYHA class (Table 2).

Albumin and survival

There were fifty deaths in the first year of follow-up, including twenty-three progressive HF deaths (46%), fifteen sudden deaths (30%), one from myocardial infarction, and eleven deaths because of other or unknown causes (22%). Significantly, worse one-year survival was seen in patients with low serum albumin compared to those with normal albumin (64.71% vs 85.72%, P 0.001; Hazard ratio [HR] 1.9 with 95% confidence interval [CI] (1.5-2.4). Per each gram per deciliter increase in albumin, HR (95% CI) was 0.5 (0.4-0.6). Low serum albumin was an independent predictor of all-cause mortality, after adjustment for multiple risk factors in multivariable Cox regression analysis, with no interaction found between serum albumin and BMI (Table 3). When the cohort was subdivided by albumin Qs, one-year survival improved as albumin Q increased, with 1-year survival rates of 65%, 78%, 83%, and 89%, for Q 1 to Q4, respectively (P 0.0001). Risk-adjusted HR (95% CI) for Q1, Q2, and Q3 compared to Q4 were 2.9 (1.6-5.3), 2.1 (1.1-3.7), and 1.3 (0.7-2.3), respectively. After stratification of the study population into subgroups based on BMI, medical therapy, and sex (data not shown), hypoalbuminemia remained significantly associated with increased mortality.

Table 1: Baseline characteristics of the cohort based on presence or absence of hypoalbuminemia (albumin ≤3.4 g/dL)

	Total cohort (N = 250)	Albumin ≤3.4 g/dL (n = 68)	Albumin >3.4 g/dL (n = 182)	P value
Age (y)	55 ± 1 4	55 ± 13	56 ± 14	0.54
Female (%)	27.2	33.2	24	0.001
BMI (kg/m2)	27 ± 7.6	26.5 ± 5.4	26.9 ± 5.1	0.36
NYHA III/IV (%)	51.2/34	36.76/51.47	54.94/28.02	0.001
Ischemic etiology (%)	46	48.52	45.05	0.43
Diabetes (%)	28	32.35	26.92	0.02
Hypertension (%)	42	42.64	41.75]	0.93
Smoking (current or prior) (%)	57.2	52.94	58.79	0.07
LVEF (%)	28 ± 11	27± 11	28 ± 11	0.35
LVEDDI (mm/m2) *	38 ± 8	37 ± 8	38± 8	0.3
Laboratory				
Albumin (g/dL)	3.9 ± 0.7	3.0 ± 0.4	4.2 ± 0.5	0.01
Serum sodium (mmol/L)	137 ± 6	136 ± 5	138± 5	0.01
Blood urea (mg/dL)	58 ± 29	66 ± 31	54 ± 28	0.001
Creatinine (mg/dL)	1.5 ± 1.0	1.6 ± 1.3	1.4 ± 1.0	0.02
Hemoglobin (g/dL)	13.6 ± 2.0	12.6 ± 2.0	14 ± 1.9	0.01
Total cholesterol (mg/dL)	169 ± 52	141 ± 45	178 ± 51	0.001
C-reactive protein (mg/L)	3.7 ±3.6	6.5±3.4	3.1± 3	0.001
Hemodynamics				
Mean blood pressure (mm Hg)	71 ± 12	70 ± 12	71 ± 12	0.12
Medications				
ACEI or ARB (%)	72.4	64.3	75.4	0.001
β-Blocker (%)	32.0	32.3	34.7	0.42
Aldosterone antagonist (%)	19.7	21.2	18.8	0.35
Statin (%)	35.3	30.7	37.1	0.02

LVEDDI, Left ventricular end-diastolic dimension index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.

* LVEDDI (LVEDD/body surface area) was used to eliminate the effect of variation of body size on cardiac dimensions including LVEDD.

Table 2: Logistic regression analysis: predictors of hypoalbuminemia

Characteristic	OR (95% CI)	P value
Female sex (vs male)	1.44 (0.98-2.12)	0.07
Serum sodium (per mmol/L increase)	0.87 (0.85-0.91)	0.001
Hemoglobin (per g/dL increase)	0.75(0.68-0.82)	0.001
NYHA III-IV (vs I-II)	1.65 (0.88-3.08)	0.10
ACEI or ARB therapy (vs no therapy)	0.70(0.45-1.08)	0.08
Total cholesterol (per mg/dL increase)	0.97(0.96-0.98)	0.001

OR, Odds ratio; CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.

Table 3: All-cause mortality in patients with low albumin compared to those without low albumin

	Serum albumin level (g/dL)		P value
	Hypoalbuminemia (≤3.4)	No hypoalbuminemia (>3.4)	
Number (total=250)	68 (27.2 %)	182 (72.8 %)	
1 y Mortality (total = 50) (20%)	24 (35.29 %)	26 (14.28 %)	<0.001
Age- and sex-adjusted HR (95% CI)	2.6 (2.0-3.1)	1.0 (reference)	<0.001
Multivariate* HR (95% CI)	2.5 (1.6-3.5)	1.0 (reference)	<0.001

HR, hazard ratio; CI, confidence interval.
*Multivariate adjusted for BMI category, demographics, LVEF, NYHA class, diabetes, etiology of heart failure, medications (ACEI and β-blocker), serum sodium, total cholesterol, hemoglobin, and creatinine.

DISCUSSION:

The results of this study illustrate that hypoalbuminemia is common in patients with advanced systolic HF and is associated with significantly increased one- year all cause mortality, death to progressive HF, or sudden death. Similar results were found by Tamara B. Horwich et al though that study involved much larger number of patients and assessed one and five-year mortality.[16]

Low serum albumin levels were associated with worse symptoms of HF but were not associated with echocardiographic indices of cardiac dysfunction, as measured by LVEF, left ventricular end-diastolic dimension index, or degree of mitral and tricuspid regurgitation. Patients with low BMI were only slightly more likely to have hypoalbuminemia compared to patients with normal or high BMI. These findings are in agreement with those of Tamara B. Horwich et al. [16]

Synthesis of albumin is affected by nutritional intake, colloid oncotic pressure variations, and the presence of systemic inflammation [17,18]. Plasma albumin levels are decreased in inflammatory conditions, including infection, trauma, and surgery [19,20]. In chronic disease states such as end-stage renal disease or dialysis and advanced cancer, hypoalbuminemia is common and is associated with elevation of inflammatory mediators [8,21]. Heart failure is characterized by activation of inflammatory factors, including C-reactive protein and circulating cytokines and chemokines [22,23].

Furthermore, patients with hypoalbuminemia in this study were more likely to have low cholesterol levels and anemia, which may be associated with inflammation in HF [24,25]. In addition to inflammation, there are several other potential contributors to the hypoalbuminemia of HF. Hemodilution may be present in HF and contribute to hypoalbuminemia [26]. Patients with advanced HF may have loss of appetite and decreased energy intake leading to low serum albumin; however, in non-HF subjects, severe protein-energy malnutrition without the presence of advanced, chronic disease does not lead to hypoalbuminemia [17,27]. It is also suggested that HF patients have increased resting and total energy expenditure and thus may have a negative balance of calories and proteins [28].

Wasting disease in HF (cardiac cachexia) has been identified as a strong predictor of adverse prognosis [13]. This under-nutrition, which has been variably defined as weight loss over time, low BMI, low percent ideal body weight, or decreased fat mass, has invariably been linked to poor outcomes in HF [3,13,29]. This study demonstrates that hypoalbuminemia is present to a similar degree in lean, overweight, and obese HF patients, and thus suggests that hypoalbuminemia and cachexia in HF may have discrete pathophysiologic mechanisms and that hypoalbuminemia may not only be related to energy intake but also a reflection of inflammation.

There are several potential explanations for the relationship between albumin levels and survival in HF. Hypoalbuminemia is associated with decreased colloid oncotic pressure, which can lead to the development of pulmonary edema and acute HF exacerbations (2). Hypoalbuminemia is associated with activation of inflammatory

mediators, which are known to predict worse HF outcomes [22,23]. Low albumin may be due to decreased albumin synthesis from hepatic congestion and right heart failure (3). Heart failure patients with low albumin may have a higher rate of co-morbidities, such as cancer or pulmonary disease, which contribute to their increased mortality rates. Alternatively, normal levels of albumin may have direct protective effects such as antiapoptotic and antioxidant activity [30,31].

There are certain limitations to the current study. This study excluded patients with HF and preserved systolic function. Although BMI was only weakly associated with serum albumin, we do not take into consideration body composition; lean or fat mass may be more highly correlated with albumin levels. Information on weight loss was not collected. Other serum markers of inflammation such as cytokines or chemokines to further delineate the pathophysiologic relationship between albumin, inflammation, and mortality were not available. This study assessed albumin and BMI at one time and did not track changes in these parameters. Other disease states with potential to confound the relationship between hypoalbuminemia and survival in HF such as chronic obstructive pulmonary disease, cancer, and liver disease were not tracked.

CONCLUSION:

Patients with systolic heart failure with hypoalbuminemia have a greater than 2-fold increased risk of mortality compared to those without hypoalbuminemia, even after adjustment for multiple prognostic factors. This identifies serum albumin level as a simple biomarker that could be considered as a predictor of increased mortality in patients with advanced systolic heart failure.

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