Albumin levels predict survival in patients with systolic heart failure

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Background Hypoalbuminemia is associated with poor prognosis in patients with certain chronic diseases, such as end-stage renal disease and cancer. Although low serum albumin is common in patients with heart failure (HF), the relationship between albumin and HF prognosis has not been well characterized. This study investigated the effect of serum albumin level on survival in patients with advanced HF.

Methods We analyzed 1726 systolic HF patients (age 52 ± 13 years, ejection fraction [EF] 23% ± 7%) followed at a university HF center. Albumin level was determined at initial referral. Patients were divided by into groups based on presence of hypoalbuminemia (≤3.4 g/dL). Mean albumin was 3.8 ± 0.6 g/dL, and 25% of patients had hypoalbuminemia.

Results Patients with and without low albumin levels were similar in age, HF etiology, and EF. Hypoalbuminemia was associated with higher New York Heart Association (NYHA) class, higher serum urea nitrogen, creatinine level, C-reactive protein, and B-type natriuretic peptide but lower levels of sodium, hemoglobin, and cholesterol. In patients with BMI <25 kg/m^2, 27% had albumin ≤3.4 g/dL, compared to 22% of those with BMI ≥25 kg/m^2 ($P < .01$). One-year survival was 66% in patients with and 83% in those without hypoalbuminemia ($P < .0001$). Risk-adjusted hazard ratios for 1- and 5-year mortality were 2.2 (1.4-3.3) and 2.2 (1.4-3.2), respectively.

Conclusions Hypoalbuminemia is common in HF and is independently associated with increased risk of death in HF. Further investigation of pathophysiologic mechanisms underlying hypoalbuminemia in HF is warranted. (Am Heart J 2008;155:883-9.)

Hypoalbuminemia is common in patients with systolic heart failure (HF), occurring in approximately one third of patients.[1] Hypoalbuminemia in patients with HF may result from hemodilution, malnutrition, chronic inflammation, infection, proteinuria, and other mechanisms. Hypoalbuminemia, with a resulting reduction in colloid osmotic pressure, can influence the degree of pulmonary congestion as well as HF symptoms.[2-5] In disease states, such as end-stage renal disease, infection, and cancer, and in the elderly, hypoalbuminemia is known to be associated with poor outcomes.[6-11] Hypoalbuminemia has been demonstrated to be the strongest predictor of death in dialysis patients.[12,13] However, the importance of serum albumin levels as a prognostic factor in systolic HF has not been well described.

Wasting disease in HF, also known as "cardiac cachexia," is associated with low body mass index (BMI) and/or weight loss over time and inflammation as reflected by increased levels of inflammatory cytokines. Cardiac cachexia is known to predict increased mortality in HF,[14-16] but whether low albumin is characteristic of cardiac cachexia or HF patients with low BMI is unknown. In studies of non-HF subjects including the general population, cardiothoracic surgery patients, and end-stage renal disease patients on dialysis, albumin had no or weak correlation with BMI.[17-19]

The primary goal of this study was to examine the hypothesis that serum albumin is an independent predictor of survival in patients with advanced, systolic HF. Our secondary objective was to examine the relationship between BMI and albumin levels in advanced HF, as well as the interaction between BMI and albumin levels in predicting survival.

Methods

Patient population

The study population consisted of 2796 patients referred to a single university center for HF management and/or transplant

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evaluation between 1983 and 2006, of whom 1867 had serum albumin levels drawn within 3 months of referral date. Patients without baseline serum albumin levels (n = 929) were similar to the study cohort for age, left ventricular ejection fraction (LVEF), serum sodium, and renal function. Patients were excluded if LVEF >40% (n = 137) or follow-up data was incomplete (n = 4). The final study population consisted of 1726 patients. All subjects were followed in a comprehensive HF management program. Medical record review was approved by the University of California Los Angeles (UCLA) medical institutional review board.

Baseline patient data

Serum albumin levels were analyzed by the UCLA clinical laboratory using a bromocresol purple dye-binding method. The reference range for this albumin assay is 3.5 to 4.7 g/dL at our institution, with total imprecision <2.5%. B-Type natriuretic peptide was measured through the use of an industry-standard analytical platform (Triage, Biosite, San Diego, CA). C-Reactive protein level was measured via nephelometry on the Dad Behring BNII instrument (Deerfield, IL). Body mass index (BMI) —weight in kilograms (kg) divided by height in square meters— was available in 1541 subjects. Height was recorded at first clinic visit or subsequent clinic visits. To eliminate edematous weight as a confounder of accurate body weight measurements, BMI calculations were made using the patients' weights recorded at the time of euvolemia after hemodynamically guided unloading therapy or as clinically determined by the physician. Additional laboratory testing, echocardiography, and cardiopulmonary exercise testing all occurred within 3 months of referral.

Definition of end points

The primary end point for the study was all-cause mortality, with censoring at time of heart transplant.[20] Secondary outcomes included (1) sudden death, (2) HF death, and (3) the combined end point of death plus urgent heart transplant.[21] 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. For the combined outcome of death plus urgent transplant, an urgent heart transplants (status Ia) was analyzed as a death, as it is assumed that the patient would have died within 1 week if heart transplant was not done. For this analysis, nonurgent heart transplants were censored.

Statistical analysis

Data are presented as mean ± SDs for normally distributed continuous variables, median and interquartile range for nonnormally distributed continuous variables, and as frequencies for categorical variables. 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. To further explore the relationship between albumin and BMI, 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.[22] Baseline characteristics between patients with and without hypoalbuminemia were compared using independent samples *t* test, χ^2, and Wilcoxon rank sum test as appropriate. To determine whether low BMI or other variables were associated with increased odds of hypoalbuminemia independent of other prognostic factors, multivariable logistic regression was performed with albumin (low vs high) as the outcome variable, and predictor variables including BMI, sex, age, LVEF, HF etiology, blood urea nitrogen, serum sodium, hemoglobin, total cholesterol, and medications. Kaplan-Meier survival curves were constructed to demonstrate 1- and 5-year survival in patients with low versus normal albumin levels as well as in the albumin Q. The log-rank test was used to determine if actuarial survival was significantly different. Kaplan-Meier survival analysis was performed by strata of clinically significant variables including age, sex, BMI, medications, and referral date. Multivariable survival analysis (Cox proportional hazards regression) was performed to estimate adjusted hazard ratios (HRs) and included formal testing for interaction between albumin and BMI categories. Multivariate analysis included variables found to be significantly different between albumin groups and with potential to influence survival outcomes such as BMI category, demographics, LVEF, NYHA class, diabetes, etiology of HF, medications (angiotensin-converting enzyme inhibitor and β-blocker), hemodynamics (right atrial pressure and pulmonary capillary wedge pressure), serum sodium, total cholesterol, hemoglobin, and creatinine. Data were analyzed using SPSS 15.0 for Windows (SPSS, Inc, Chicago, IL).

Results

Albumin and baseline patient characteristics

The study cohort had a mean age of 52 ± 13 years, mean LVEF (%) of 23 ± 7, with NYHA III and IV comprising 37% and 52% of the cohort, respectively. Mean albumin was 3.8 ± 0.6 g/dL (range 1.5-5.5 g/dL), and 25% of patients had hypoalbuminemia (serum albumin ≤3.4 g/dL). Albumin was normally distributed in the study population. Baseline characteristics of the study cohort are presented in Table I. 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 B-type natriuretic peptide, C-reactive protein, blood urea nitrogen, 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 I or angiotensin-receptor blocker and had small but significant increases in right atrial and pulmonary capillary wedge pressures (Table I).

Albumin and BMI

Body mass index was not significantly different among patients with and without hypoalbuminemia (Table I). Body mass index also did not differ between albumin Qs, with mean BMI in Q1 to Q4 of 26.0 ± 5.6, 26.0 ± 5.4, 26.4 ± 5.2, and 26.6 ± 5.0 kg/m^2, respectively (P = .30). Underweight and normal weight HF patients had slightly

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

	No. of observations	Total cohort (N = 1726)	Albumin ≤3.4 g/dL (n = 426)	Albumin >3.4 g/dL (n = 1300)	P
Age (y)	1726	52 ± 13	52 ± 12	53 ± 13	.55
Female (%)	1499	25	31	22	.0001
BMI (kg/m^2)	1520	26.5 ± 7.8	26.0 ± 5.6	26.4 ± 5.2	.38
NYHA III/IV (%)	1499	37/52	23/69	41/46	.0001
Ischemic etiology (%)	1725	44	46	43	.41
Diabetes (%)	1596	26	31	25	.02
Hypertension (%)	1601	40	41	40	.95
Smoking (current or prior) (%)	1616	58	54	60	.08
LVEF (%)	1726	23 ± 7	23 ± 7	23 ± 7	.36
LVEDDI (mm/m^2)	1501	37 ± 7	36 ± 7	37 ± 7	.29
Severe MR (%)	1500	26	29	25	.51
Severe TR (%)	1454	15	17	14	.07
Peak Vo_2 (mL/kg per minute)	1010	13.3 ± 4.6	12.6 ± 4.9	13.5 ± 4.5	.05
ICD (%)	1719	27	29	27	.52
Laboratory					
Albumin (g/dL)	1726	3.8 ± 0.6	3.0 ± 0.4	4.1 ± 0.4	.0001
Serum sodium (mmol/L)	1722	136 ± 5	135 ± 5	137 ± 4	.0001
Blood urea nitrogen (mg/dL)	1715	29 ± 19	33 ± 21	27 ± 18	.0001
Creatinine (mg/dL)	1710	1.5 ± 1.1	1.6 ± 1.3	1.4 ± 1.0	.006
Hemoglobin (g/dL)	1546	13.3 ± 2.0	12.4 ± 2.0	13.7 ± 1.8	.0001
Total cholesterol (mg/dL)	1506	171 ± 55	143 ± 48	180 ± 54	.0001
B-type natriuretic peptide (pg/mL)	434	577 (219-1300)	1270 (619-1745)	360 (138-819)	.0001
C-reactive protein (mg/L)	54	3.7 (1.3-9)	9 (2.3-9.2)	3.1 (1.2-7.4)	.0001
Hemodynamics					
Mean blood pressure (mm Hg)	1436	74 ± 13	73 ± 13	74 ± 13	.11
Right atrial pressure (mm Hg)	1344	8 ± 5	9 ± 5	7 ± 4	.0001
Pulmonary capillary wedge pressure (mm Hg)	1289	15 ± 6	16 ± 6	15 ± 6	.001
Medications					
ACEI or ARB (%)	1442	84.5	76.5	87.4	.0001
β-Blocker (%)	1430	40.0	40.3	42.7	.42
Aldosterone antagonist (%)	1436	25.6	27.3	24.9	.36
Statin (%)	1588	32.4	27.8	34.0	.02

LVEDDI, Left ventricular end-diastolic dimension index; *MR*, mitral regurgitation; *TR*, tricuspid regurgitation; *Vo_2*, oxygen consumption; *ICD*, implantable cardioverter defibrillator; *ACEI*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin-receptor blocker.

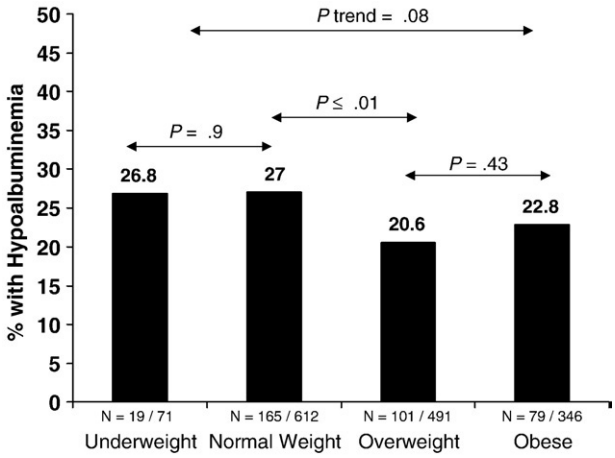
higher rates of hypoalbuminemia compared to overweight and obese patients (Figure 1). In patients with BMI <25 kg/m^2, 27% had hypoalbuminemia compared to 22% in those with BMI ≥25 kg/m^2 ($P \leq .01$). On multivariate logistic regression analysis, BMI was not significantly associated with hypoalbuminemia; variables that were independent predictors of low albumin included lower total cholesterol, hemoglobin, and sodium levels, and higher NYHA class (Table II).

Albumin and survival

There were 314 deaths in the first year of follow-up, including 147 progressive HF deaths (47%), 91 sudden deaths (29%), 6 from MI, and 59 deaths because of other or unknown causes. By 5-year follow-up, 591 subjects had died. There were 422 transplants during the first year (246 urgent, status I or IA and 176 nonurgent, status IB or II) and 634 transplants by year 5 (329 urgent and 305 nonurgent).

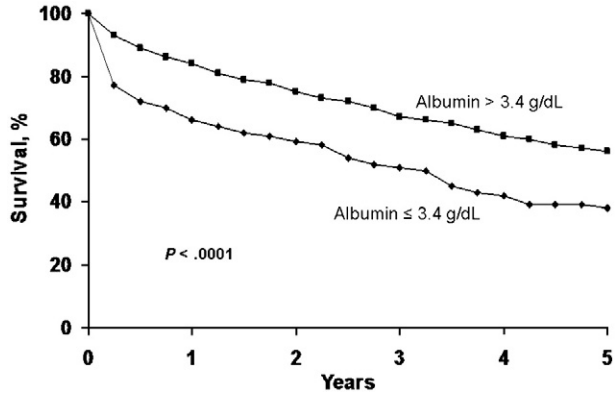
Significantly, worse 1-year survival was seen in patients with low albumin compared to those with normal albumin (66% vs 83%, $P < .0001$; HR 1.8 with 95% confidence interval [CI] 1.5-2.3). At 5-year follow-up, low albumin levels remained associated with significantly worse survival (38% vs 56%, $P < .0001$; HR 1.7, 95% CI 1.4-2.0) (Figure 2). Per each gram per deciliter increase in albumin, HR (95% CI) was 0.5 (0.4-0.6). Low 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 albumin and BMI (Table III). When the cohort was subdivided by albumin Q, 1-year survival improved as albumin Q increased, with 1-year survival rates of 66%, 79%, 82%, and 88%, for Q 1 to Q4, respectively ($P <$ .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. When the cohort was stratified by deciles, there was an incremental relationship between

Figure 1



Percentage of patients with hypoalbuminemia (albumin ≤3.4 g/dL) in the 4 BMI categories: underweight BMI ≤18.5, normal weight BMI 18.5-24.9, overweight BMI 25.0-29.9, and obese BMI ≥30.0.

Figure 2



Kaplan-Meier survival analysis. Patients with hypoalbuminemia (albumin ≤3.4 g/dL) have significantly worse survival than patients without hypoalbuminemia ($P < .0001$).

Table II. Logistic regression analysis: predictors of hypoalbuminemia

Characteristic	OR (95% CI)	P
Female sex (vs male)	1.42 (0.96-2.10)	.08
Serum sodium (per mmol/L increase)	0.89 (0.86-0.93)	.0001
Hemoglobin (per g/dL increase)	0.72 (0.65-0.79)	.0001
NYHA III-IV (vs I-II)	1.68 (0.91-3.11)	.10
ACEI or ARB therapy (vs no therapy)	0.68 (0.43-1.06)	.09
Total cholesterol (per mg/dL increase)	0.99 (0.98-0.99)	.0001

OR, Odds ratio; other abbreviations as per Table I.

Table III. All-cause mortality in patients with low albumin compared to those without low albumin

Albumin (g/dL)	Hypoalbuminemia (≤3.4)	No hypoalbuminemia (>3.4)	P
n	426	1300	
1 y			
Mortality (%)	34	17	<.0001
Age- and sex-adjusted HR (95% CI)	2.5 (2.0-3.2)	1.0 (reference)	<.0001
Multivariate* HR (95% CI)	2.4 (1.6-3.7)	1.0 (reference)	<.0001
5 y			
Mortality (%)	62	44	<.0001
Age- and sex-adjusted HR (95% CI)	2.0 (1.6-2.3)	1.0 (reference)	<.0001
Multivariate* HR (95% CI)	2.1 (1.3-3.6)	1.0 (reference)	.02

*Multivariate adjusted for BMI category, demographics, LVEF, NYHA class, diabetes, etiology of heart failure, medications (ACEI and β-blocker), hemodynamics (right atrial pressure and pulmonary capillary wedge pressure), serum sodium, total cholesterol, hemoglobin, and creatinine.

albumin and mortality, with decreased mortality observed across increasing albumin deciles (Figure 3).

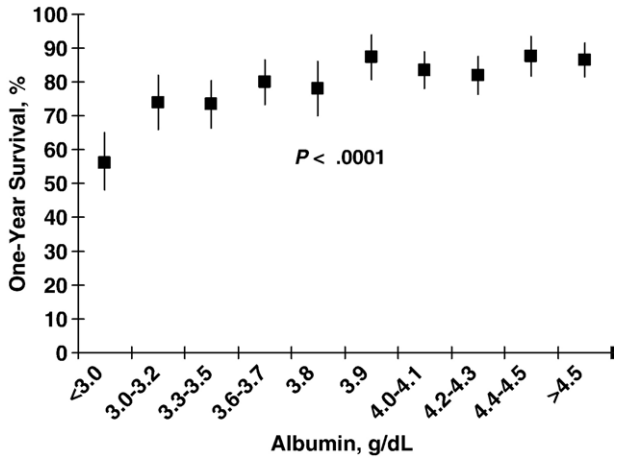
Low albumin was associated with increased mortality because of progressive HF as well as increased risk of the combined end point of death and urgent transplant ($P < .0001$) but was not associated with sudden death. After stratification of the study cohort into subgroups based on BMI (Figure 4), referral year, medical therapy, and sex (data not shown), hypoalbuminemia remained significantly associated with increased mortality.

Discussion

Our data demonstrates that hypoalbuminemia is not only common in patients with advanced systolic HF but is associated with significantly increased 1- and 5-year all-cause mortality, progressive HF death, as well as increased risk of death or urgent heart transplantation. Low albumin levels were associated with worse symptoms of HF and higher intracardiac filling pressures but were not associated with echocardiographic indices of cardiac dysfunction, as indexed by LVEF, left ventricular end-diastolic dimension index, or degree of mitral and tricuspid regurgitation. Interestingly, patients with low BMI were only slightly more likely to have hypoalbuminemia compared to patients with normal or high BMI.

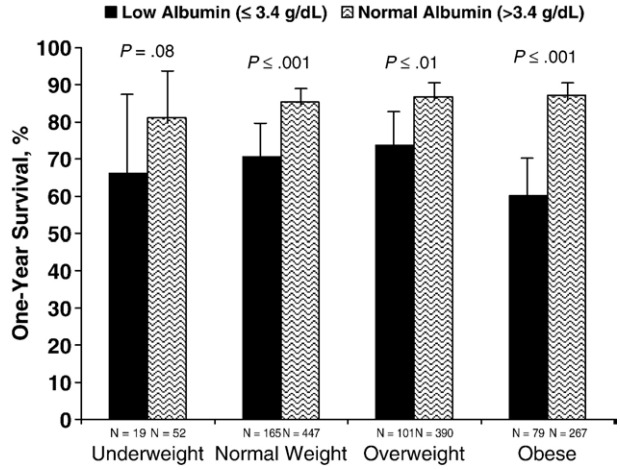
Albumin is a hepatic protein, and its plasma concentration is controlled by several factors, including rate of albumin synthesis, catabolic rate, albumin distribution,

Figure 3



One-year survival (and 95% CI) in deciles of albumin level ($P < .0001$).

Figure 4



Low albumin is associated with worse survival in subgroups of the cohort based on BMI. One-year survival (with upper 95% CI displayed) in groups of patients based on BMI: underweight BMI ≤18.5, normal weight BMI 18.5-24.9, overweight BMI 25.0-29.9, and obese BMI ≥30.0.

and exogenous albumin loss.[23-25] Synthesis of albumin is affected by nutritional intake, colloid oncotic pressure variations, and the presence of systemic inflammation.[23,26] Plasma albumin levels are known to be decreased in inflammatory conditions, including infection, trauma, and surgery.[27]

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.[10,28] The syndrome of HF is characterized by activation of inflammatory factors, including C-reactive protein and circulating cytokines and chemokines.[29-31] Our analysis demonstrates a significant correlation of high-sensitivity C-reactive protein to low albumin levels, suggesting that inflammation may be an underlying etiology of hypoalbuminemia in HF. Furthermore, patients with hypoalbuminemia in this cohort were more likely to have low cholesterol levels and anemia, additional conditions that may be associated with inflammation in HF.[32,33]

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[34]; however, the pulmonary capillary wedge pressures and right atrial pressures of patients with hypoalbuminemia were only slightly higher than those without hypoalbuminemia, arguing against hemodilution as the major underlying cause of hypoalbuminemia. 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.[23,35] There is also evidence to suggest that HF patients have increased resting and total energy expenditure and thus may have a negative balance of calories and proteins.[36]

"Wasting disease" in HF, also known as cardiac cachexia, has been identified as a strong predictor of adverse prognosis.[15] This undernutrition, 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.[3,15,16,37] However, the interrelationship between cardiac cachexia and albumin levels had not previously been studied. 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.[29,30] Low albumin may be because of decreased albumin synthesis from hepatic congestion and right heart failure.[3] Heart failure patients with low albumin may have a higher rate of comorbidities, 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.[38,39]

We acknowledge certain limitations to the current study. This study is observational and evaluates a cohort of patients with advanced disease, referred to a tertiary center for disease management and transplantation evaluation. Patients without serum albumin levels at time of referral were excluded, and this introduces the potential for selection bias in the final study cohort. Also, this study excludes patients with HF and preserved systolic function. Although BMI was only weakly associated with serum albumin, we do not have information on 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 assesses albumin and BMI at time of referral and does 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 but are presumed to be low in a heart transplant referral population. Residual measured and unmeasured confounding variables may explain the observed relationship.

Conclusions

Advanced, systolic HF patients 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 study identifies albumin levels as a simple biomarker for identifying patients with HF who are at increased risk for urgent heart transplantation and death. Further investigation into mechanisms underlying hypoalbuminemia is warranted and may result in identifying potential novel targets for HF therapy.

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