The relevance of serum albumin among elderly patients with acute decompensated heart failure

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Abstract

Objective To assess the prognostic utility of serum albumin among elderly patients admitted for acute decompensated heart failure (ADHF) in terms of all-cause mortality and also to identify the predictors of hypoalbuminemia. Methods Retrospective cohort study of 119 elderly patients admitted for ADHF. Elderly patients were defined as patients over the age of 65 years. The patients were followed up for approximately 11 years. Patients with advanced renal failure, liver disease not due to HF, cancer and other causes of low life expectancy were excluded. Hypoalbuminemia was defined as serum albumin ≤ 2.9 g/dL. Results The study was made up of 65 females and 54 males with age ranging from 65 to 96 years. Of the 119 elderly patients with ADHF, there were 26 deaths. A significantly higher proportion of patients in the mortality group had an admission serum albumin level of ≤ 2.9 g/dL than those surviving (P = 0.011). After Cox’s logistic regression, low albumin (P = 0.016), elevated direct bilirubin (P = 0.03), age greater than 85 (P = 0.008), lack of use of beta blockers (P = 0.0001) and left ventricular ejection fraction less than 35% (P = 0.005) increased the risk of death. Elevated serum creatinine (P = 0.0357) was the only predictor of hypoalbuminemia following multiple linear regression. Conclusions Hypoalbuminemia may be an unrecognized marker of death in elderly patients with ADHF.

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1 Introduction

Heart failure (HF) affects more than 5 million people in the United States.[1,2] This number is expected to rise due to increased life expectancy.[1–3] Several prognostic markers have been identified among patients with HF but risk stratification is still a dilemma.[9] Elderly patients with HF have worse outcomes when compared to younger patients. Sadly, elderly patients are underrepresented in many clinical trials resulting in sparsity of evidence-based therapies for this unique population.[5,6]

Hypoalbuminemia is one of the common adverse features among patients with HF especially in the elderly with a prevalence of about 25%.[7–9] Since reduction in serum albumin occurs over a period of time, it may serve as a marker of HF severity.[4,7]

Severe HF is reported to be associated with cachexia and malnutrition.[8] Angiotensin converting enzyme inhibitors (ACEIs) have also been noted to prevent malnutrition and sarcopenia as an addition to its role in improving survival among patients with HF.[8,10]

Therefore, the aim of this study is to assess the prognostic utility of serum albumin among elderly patients admitted for acute decompensated HF in terms of all-cause mortality and also to identify the predictors of hypoalbuminemia. It would also be worthwhile to assess the role of ACEIs and other medications for HF in reducing the odds of developing hypoalbuminemia.

There is paucity of data on the adverse outcomes that may occur in elderly patients who have reduced serum albumin and acute decompensated HF (ADHF). Therefore, the findings from this study may bring to light new areas of focused study that may improve outcomes among elderly patients with HF.

2 Methods

This is a retrospective cohort study of elderly patients
admitted for ADHF. Approval from relevant institutional review boards were obtained before starting the study.

A total of 119 elderly patients admitted for ADHF were included in this study from a total of 936 electronic medical records reviewed over a period of 11 years (from January 1 2006 to October 31, 2016).

Inclusion criteria: (1) patients 65 years and above admitted for ADHF who had previous history of chronic HF evidenced by prior documentation in the electronic medical record or cardiology clinic follow up records; and (2) elderly patients admitted for ADHF who had all the investigations in this study protocol.

Exclusion criteria: (1) patients who died within 48 h of admission who couldn’t have full assessment and investigations; (2) patients with acute HF without prior history of chronic heart failure; (3) patients with advanced renal failure defined as those with end stage renal disease, dialysis dependent or post renal transplant patients; (4) patients with documented liver disease with a cause other than HF; (5) patients with cancer or conditions associated with low life expectancy of less than one year; (6) patients with stroke or problems with swallowing or other risk of poor nutrition were excluded; and (7) patients whose status could not be determined (apparent loss to follow up evidenced by three consecutive clinic follow up visits).

Elderly patients were defined as patients older than 65 years. A sub-group analysis was carried out for patients termed the extremely elderly group and compared with the non-extremely elderly group. The extremely elderly group was defined as patients older than 85 years of age while the non-extremely elderly group was defined as patients between 65 and 84 years. All the study participants had echocardiographic and other clinical assessment on the day of admission.

HF was defined based on standard criteria. The ADHF was defined as deterioration of chronic stable HF. Chronic HF was defined as symptoms of HF spanning a period of greater than three months.

Hypoalbuminemia in this study was defined as serum albumin value of less than 2.9 g/dL after a receiver operating characteristic (ROC) cutoff point was obtained.

All admitted patients had diets referred to as heart healthy diet which had normal protein, medium carbohydrates about 1800 kcal to 2000 kcal and low salt. None of the patients were on diets that were protein deficient.

Baseline clinical and demographic data were recorded. Echocardiographic data, etiology of HF, guideline directed medications for HF were also recorded.

The patients were followed up upon discharge for a minimum of 1 year and a maximum of 11 years. The length of time from date of discharge to mortality was recorded.

The data analysis was carried out using IBM SPSS software version 24.0 (Armonk, NY: IBM Corp.). The continuous variables were expressed as mean ± SD while categorical data would be expressed as percentages. Differences between variables were determined with the independent Student t-test and the Chi-squared ($X^2$) test for continuous and categorical data respectively. The relevant coefficient tests were used for correlation among various variables. Multiple linear regression was used to assess predictors of hypoalbuminemia. Cox regression analysis was carried out to test for predictors of mortality and relevant survival curves were plotted. The level of significance in this study was set at $P \leq 0.05$ and confidence interval of 95%.

### 3 Results

The study was made up of 65 females and 54 males with age ranging from 65 to 96 years. The median age of the study population is 75 years. Of the 119 elderly patients with ADHF, there were 26 deaths. The number of patients with preserved ejection fraction (EF) (EF > 40%) was 78, while those with reduced EF (EF < 40%) was 41. About 31% of the study population had type 2 diabetes mellitus while about 36% of the study population had micro-albuminemia.

A large proportion of the study population as expected had high blood pressure (83%), while 55% of the patients had echocardiographic evidence of left ventricular hypertrophy.

About 24% of all the study participants had serum albumin of ≤ 2.9 g/dL. About 48 (40.3%) of the patients in this study had HF secondary to coronary artery disease. Spironolactone was the least used guideline directed medical therapy (GDMT) among patients in this study (16%).

A significantly higher proportion of patients in the mortality group had an admission serum albumin level of ≤ 2.9 g/dL than those alive (42.3% vs. 18.3%; $P = 0.011$). The patients in the mortality group also had significantly higher direct bilirubin level ($0.45 \pm 0.5$ vs. $0.24 \pm 0.18$ mg/dL; $P = 0.047$) than survivors. A significantly smaller proportion of the patients in the mortality group were on beta blockers (53.8% vs. 83.9%; $P = 0.001$) when compared to the survivors. A significantly higher proportion of patients in the mortality group had left ventricular ejection fraction (LVEF) less than 35% (89.5% vs. 66.7%; $P = 0.005$) when compared to survivors.

There was no significant difference in the age of patients who died when compared to survivors ($P = 0.061$). How-
ever, when the comparison was made between patients older than 85 years vs. patients between 65 and 84 years, the former group had a higher proportion of patients with mortality (23.1% vs. 7.5%; \( P = 0.025 \)) when compared to the latter group. The baseline variables for mortality vs. survivors among the study population in this study is depicted in Table 1.

None of the study participants had cardiac resynchronization therapy. Five patients met criteria for implantable cardioverter defibrillator (ICD) but refused. Twenty one patients had ICD implantation.

As shown in Table 2, after Cox’s logistic regression, serum albumin \( \leq 2.9 \) g/dL (\( P = 0.016 \)), elevated direct bilirubin (\( P = 0.03 \)), age greater than 85 years (\( P = 0.008 \)), lack of use of beta blockers (\( P = 0.0001 \)) and LVEF less than 35% (\( P = 0.005 \)) increased the risk of death among elderly patients with acute decompensated HF.

There were three early deaths which occurred at 9, 11 and 19 days respectively after discharge. These three patients were 96 years, 87 and 82 years respectively. Two of them had LVEF of < 25% while serum albumin was very low in two of the patients with values as low as 1.8 g/dL in one of them.

There was negative correlation between serum albumin and the following; serum creatinine (\( r = -0.212; P = 0.021 \)) and age (\( r = -0.191; P = 0.037 \)). There was also a positive correlation between serum albumin and the left ventricular internal diameter in diastole on echocardiography (\( r = 0.202; P = 0.028 \)).

As shown in Table 3 elevated creatinine (\( P = 0.0357 \)) was the only predictor of hypoalbuminemia following multiple linear regression.

### Table 1. Baseline variables for mortality vs. survivors among patient with heart failure.

| Parameters                  | Mortality n = 26 | Survivors n = 93 | \( P \)-value |
|-----------------------------|------------------|------------------|---------------|
| Age, yrs                    | 78.19 ± 8.99     | 75.10 ± 6.88     | 0.061         |
| BMI, kg/m\(^2\)             | 28.86 ± 10.42    | 31.37 ± 12.01    | 0.343         |
| SBP, mmHg                   | 144.77 ± 30.17   | 145.6 ± 22.92    | 0.897         |
| Hemoglobin, g/dL            | 11.50 ± 2.48     | 11.82 ± 2.05     | 0.493         |
| Sodium, mmol/L              | 139.46 ± 4.19    | 152.56 ± 12.81   | 0.604         |
| BUN, mg/dL                  | 30.96 ± 13.39    | 25.29 ± 13.90    | 0.066         |
| Creatinine, mg/dL           | 1.74 ± 1.59      | 1.49 ± 0.93      | 0.308         |
| PASP, mmHg                  | 43.58 ± 10.73    | 41.64 ± 17.66    | 0.502         |
| Length of stay, days        | 5.85 ± 4.81      | 5.59 ± 4.25      | 0.794         |
| LVIDD, cm                   | 5.53 ± 1.16      | 5.29 ± 0.803     | 0.226         |
| LVIDD index, cm/m\(^2\)     | 3.45 ± 0.99      | 3.17 ± 0.76      | 0.189         |
| LAD, cm                     | 4.35 ± 0.76      | 4.34 ± 0.77      | 0.959         |
| LAD index, cm/m\(^2\)       | 2.69 ± 0.62      | 2.58 ± 0.61      | 0.459         |
| AST, units/L                | 37.35 ± 24.29    | 41.89 ± 39.08    | 0.575         |
| ALT, units/L                | 36.08 ± 28.38    | 41.48 ± 32.85    | 0.447         |
| Total bilirubin, mg/dL      | 0.98 ± 0.77      | 0.72 ± 0.51      | 0.117         |
| Direct bilirubin, mg/dL     | 0.45 ± 0.50      | 0.24 ± 0.18      | 0.047**       |
| Age > 85 years              | 6 (23.1%)        | 7 (7.5%)         | 0.025**       |
| Albumin ≥ 2.9 g/dL          | 11 (42.3%)       | 17 (18.3%)       | 0.011**       |
| Beta blocker (yes)          | 14 (53.8%)       | 78 (83.9%)       | 0.001**       |
| EF < 35%                    | 17 (89.5%)       | 32 (66.7%)       | 0.005**       |
| Gender (male)               | 16 (61.5%)       | 38 (40.9%)       | 0.061         |
| Race (black)                | 6 (23.1%)        | 21 (22.6%)       | 0.957         |
| ACE/ARB (yes)               | 15 (57.7%)       | 60 (64.5%)       | 0.524         |
| Calcium blocker (yes)       | 7 (26.9%)        | 28 (30.1%)       | 0.753         |
| Spiromolactone (yes)        | 5 (19.2%)        | 14 (15.1%)       | 0.607         |
| Dignoxin (yes)              | 9 (34.6%)        | 20 (21.5%)       | 0.169         |
| Atrial fibrillation (yes)   | 8 (30.8%)        | 29 (31.2%)       | 0.968         |
| CAD (yes)                   | 9 (34.6%)        | 39 (41.9%)       | 0.501         |
| ICD (yes)                   | 2 (7.69%)        | 19 (20.4%)       | 0.158         |
| Pacemaker (yes)             | 4 (15.4%)        | 6 (6.45%)        | 0.222         |

Data are presented as n (%) or mean ± SD; **P ≤ 0.05. ACE/ARB: angiotensin converting enzyme/angiotensin receptor blocker; ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; BUN: blood urea nitrogen; CAD: coronary artery disease; EF: ejection fraction; ICD: implantable cardioverter defibrillator; LAD: left atrial diameter; LVIDD: left ventricular internal diameter in diastole; PASP: pulmonary artery systolic pressure; SBP: systolic blood pressure.

### Discussion

In this study, patients with serum albumin level less than 2.9 g/dL at the time of admission for ADHF had a higher risk of death when compared to those who had higher albumin levels at admission. The survival plot for this relationship is displayed in Figure 1. Reduction in serum albumin occurs over a period of time and may be a reflector of the chronicity and severity of HF.[4,7] Hypoalbuminemia may also be a marker of the degree of ongoing inflammation, malnutrition as well as burden of comorbidities.[4,7] The co-existence of hypoalbuminemia and HF has been reported to be related to early satiety, increased loss of nutrients through the gastrointestinal tract because of gut edema and malabsorption, increased metabolic rate due to cytokine dysfunction involving tumor necrosis factor alpha (TNF-\( \alpha \)), cortisol, epinephrine, renin as well as aldosterone.[8] More pathophysiologic mechanisms of hypoalbuminemia in patients with HF are: decreased synthesis from the liver synthesis, increased vascular permeability and losses through the kidney.[12] It is interesting to note that some of the cytokines mentioned above have been implicated as poor prognostic factor among patients with HF and hypoalbuminemia may be a surrogate marker of HF severity.[13]

Apart from being a surrogate marker, hypoalbuminemia may have a direct effect on adverse outcomes among pa-

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Table 2. Regression analysis for mortality among patients with heart failure.

| Parameters                          | B    | Hazard ratio | Exp(β) | P-value | 95% confidence interval for Exp(β) |
|-------------------------------------|------|--------------|--------|---------|-----------------------------------|
| Age < 85 vs. Age > 85 yrs           | -1.281 | 0.278        |        | 0.008** | 0.107–0.719                       |
| Albumin > 2.9 vs. ≤ 2.9 g/dL       | -0.988 | 0.372        |        | 0.016** | 0.166–0.834                       |
| Beta blocker (no vs. yes)           | 1.535  | 4.642        |        | 0.0001** | 1.991–10.825                     |
| EF < 35% (no vs. yes)               | -1.239 | 0.290        |        | 0.005** | 0.121–0.692                       |
| Direct bilirubin                   | 1.124  | 3.077        |        | 0.03**  | 1.459–6.491                       |

**P ≤ 0.05. EF: ejection fraction.

Table 3. Multiple linear regressions for predictors of hypoalbuminemia among patients with heart failure.

| Parameters | B    | β    | P-value |
|------------|------|------|---------|
| LVIDD      | 0.068 | 0.121 | 0.204   |
| Age        | -0.010 | -0.149 | 0.113   |
| Creatinine | -0.087 | -0.192 | 0.0357  |

**P ≤ 0.05. LVIDD: Left ventricular diameter in diastole.

Figure 1. Cox regression survival plot for elderly patients with acute decompensated heart failure based on serum albumin level.

Patients with HF. Some authors have reported that hypoalbuminemia may hasten the progression of HF by promoting pulmonary congestion even at low left atrial pressures. Other reports suggest that hypoalbuminemia also results in increased oxidative stress and inflammation which subsequently worsens myocardial dysfunction and sets up vicious cycle of worsening inflammation, HF and hypoalbuminemia.

The role of administering albumin in patients with HF and hypoalbuminemia is still controversial. The role of nutritional supplementation among malnourished patients with HF was assessed in the PICNIC STUDY (Nutritional Intervention Program in Hospitalized Patients with Heart Failure who are Undernourished). The PICNIC study revealed no difference among undernourished acute HF patients who had nutritional intervention irrespective of the presence of normal serum albumin or hypoalbuminemia.

The findings from the PICNIC study, also revealed that nutritional intervention reduced the risk of death from any cause and the risk of readmission for worsening of HF in undernourished patients acute HF. By implication they opined that albumin alone is not a good marker of nutritional status and other parameters should be looked at to determine patients who may need nutritional supplementation. Since the efficacy of nutritional supplementation among patients with HF and hypoalbuminemia has not been fully corroborated, attempts have been made to assess the role of therapy directed at important targets in the pathophysiology of hypoalbuminemia in HF. One of these targets is the renin-angiotensin-aldosterone system (RAAS) which is implicated in the potentiation of inflammatory cytokines involved in the occurrence of hypoalbuminemia in patients with HF.

ACEIs and angiotensin receptor blockers (ARBs) have been noted to prevent malnutrition and sarcopenia as an addition to their role in improving survival among patients with HF. ACEIs and ARBs are thought to mediate this effect by reducing C-reactive protein levels which is modulated by the RAAS. However, ACEIs and ARBs were not frequently among elderly patients with HF in the mortality group possibly because of intolerable side effects such as renal dysfunction.

Other authors have reported diuretics may reduce transcapillary loss of albumin and also loss through the gut by decreasing splanchnic congestion. The efficacy of diuretics in improving mortality has not been established. In a recent study, an assessment was done to identify the effect of diuretics on short and long term mortality among patients with HF. Parén, et al after review of a cohort of 26,218 patients from a nationwide HF register in Sweden found no difference in risk for 90-day all-cause mortality.
between patients with and without diuretic treatment at hospital discharge. They also reported there was an association of diuretic treatment at hospital discharge with increased long-term mortality.\[19\]

Interestingly, spironolactone is already known to improve mortality among patients with HF as it also modulates the RAAS system in addition to diuresis.\[20\] Sadly, these medications were not frequently used among patients in this study.

Lack of beta blocker use on the other hand, seemed to be a major risk of death because it increased the risk of death as much as 5 times in this study. It is unknown why beta blocker use was significantly lower in the mortality group than those that survived. This may be due to intolerable side effects of beta blockers such as fatigue, bradycardia, hypotension, nausea, weakness, and dizziness. Beta blockers are established medications in reducing mortality among patients with HF.\[21\] The efficacy and tolerability of bisoprolol, carvedilol and metoprolol CR/XL are similar in patients with systolic HF, irrespective of NYHA class or ejection fraction.\[21\] However, nebivolol is less effective and not better tolerated even though it was found to be somewhat effective especially in elderly patients with HF.\[21\]

It suffices to state that more work needs to be done in increasing the adherence with beta blocker therapy among patients with HF as well as formulating more tolerable beta blockers among elderly patients with HF.

In this study, low EF and hypoalbuminemia were predictors of mortality among elderly patients with HF which is in consonance with other studies.\[14\] Not many studies have looked into this relationship among elderly patients.\[22\] In fact, some authors have stated that hypoalbuminemia is also predictive of a poor outcome in patients with preserved EF indicating it may be an independent predictor of a poor outcome irrespective of the EF.\[21\]

In this study, elevated direct bilirubin was a very potent predictor of mortality in elderly patients with HF as it increases the risk of death by more than three times. Hepatic dysfunction in HF is thought to be due to transmission of increased pressure in the right atrium to the hepatic veins with resultant dilatation of the hepatic sinusoids.\[24\] The resultant compression of the hepatocytes in combination with hypoxia may lead to atrophy, necrosis and fibrosis.\[24\] Also, acute decompensated or advanced HF may be associated with sympathetic nervous system induced portal vasoconstriction, splanchnic congestion and worsening of liver ischemia.\[24\]

Liver ischemia may progress to centrilobular necrosis which is a common finding in hepatic lesions secondary to HF.\[24\] Hepatic congestion typically manifests as painful hepatomegaly, increased direct bilirubin and alkaline phosphatase.\[25\] Interestingly, few other authors have noted elevated direct bilirubin as a maker of poor prognosis especially in patients with chronic HF.\[25\]

By implication, hepatic dysfunction exemplified by low albumin and elevated direct bilirubin may therefore be crucial predictors of death among elderly patients with HF as they may be markers of hepatic congestion and severe HF.

Serum albumin levels less than 3 g/dL has been associated with declining renal function during therapy for patients with acute HF which is in keeping with the very strong association between elevated creatinine and hypoalbuminemia in this study.\[9,14\] Not many studies have assessed the direct relationship between hypoalbuminemia and elevated serum creatinine. Most studies rather describe these two parameters as independent risk factors for poor outcome among patients with HF.\[14,26\] The exact pathophysiology of the relationship is poorly understood and may need further exploration. It is still an important point to take into consideration as from this study we imply that increasing serum creatinine pre-dates hypoalbuminemia and may therefore be a marker predicting worsening hypoalbuminemia among patients with HF.

There was no difference in terms of outcomes among elderly patients who had device therapy in addition to GDMT in this study. It is a well-known fact that device therapy reduces mortality among patients with HF.\[27\] However, their role among elderly patients have not been fully explored.\[27\] The findings by Cortès, et al.\[27\] was in consonance with our findings. They compared patients aged 75 years and above who had device therapy with GDMT versus patients 75 years and above with GDMT alone. Further review of the literature indicates that device therapy among elderly patients did not offer benefit in terms of reduction in arrhythmia burden or even mortality.\[28\] Sadly, some other reports even indicate increased mortality among elderly patients with HF with device therapy.\[29,30\] These findings may be attributable to the fact that elderly patients already have high risk of poor outcomes based on their age, increased number of co-morbidities, frailty, cognitive decline which makes them possibly less responsive when compared to younger individuals.\[27-30\] It is possibly expedient for the physician and patient to weigh the risk benefit ratio and make informed choices with regards to device therapy especially among elderly patients with HF.

In conclusion, hypoalbuminemia and elevated direct bilirubin may be unrecognized markers of death among elderly patients with acute decompensated HF.
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