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Prognostic Factors for Patients with Sinus Rhythm and Patients with Atrial Fibrillation in Heart Failure with Reduced Ejection Fraction; The Importance of Albumin for Prognosis

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Abstract

Atrial fibrillation (AF) and heart failure have become cardiovascular epidemic in recent years. AF is the most common arrythmia in patients with heart failure and its prevalence is increased in parallel to the severity of heart failure, ranging from 10 to 50%. There are prognostic parameters like reduced left ventricular systolic function and right ventricular function that are among independent predictors of poor outcomes in patients with advanced systolic heart failure. Prognostic parameters could be different in patients with AF and in patients with sinus rhythm in heart failure. The aim of this study was to examine and compared to prognostic risk factors in patients with sinus rhythm and in patients with AF in heart failure with reduced ejection fraction (HFrEF) (left ventricular ejection fraction [LVEF] ≤40%)

Methods: 603 consecutive patients (399 men and 204women) with HFrEF of both ischemic and non-ischemic etiology were followed up for a mean period of 77 months. The mean age was 65 ± 12 years, the mean LVEF was 25.8±8.5% and the mean right ventricular fractional area change was 47.5±11.9 %, the mean brain natriuretic peptide level was 1955.3±3423.7 pg/mL. There were 424 patients with sinus rhythm and 179 patients with AF in this heart failure cohort. The primary endpoint was cardiovascular mortality.

Results: During the follow-up period, 251 (42%) patients died due to cardiovascular causes. 188 (44%) of patients with sinus rhythm and 63 (35 %) patients with AF died during follow up period p=0.037. Age, LVEF, right ventricular fractional area change, respiratory rate, albumin level, walking distance were among statistically significant parameters in univariate analysis in both groups.

After adjusting for multiple confounders in multivariate Cox regression analysis showed that the Age (HR-1.042, 95% CI 1.023-1.061, p<0.001), hospitalization (HR- 0.798, 95% CI 0.697-0.913, p=0.001), the walking distance (HR-0.582, 95% CI 0.414- 0.817, p=0.002) , E/e' (HR- 1.035, 95% CI 1.010-1.055, p=0.005), urea level (HR- 1.004, 95% CI 1.001-1.007, p=0.012) and serum albumin level (HR- 0.685, 95% CI 0.515-0.909, p=0.009) were the independent parameters that predict prognosis in patients with sinus rhythm in HFrEF, however, the age (HR-1.091, 95% CI 1.060-1.124, p<0.001) and albumin level (HR-0.545, 95% CI 0.336- 0.885, p=0.014) were independent parameters that predict prognosis in patients with AF in HFrEF in this cohort.

Conclusion: Age, hospitalization, walking distance in one minute, E/e', urea level and serum albumin level were independent parameters that predict prognosis in patients with sinus rhythm in HFrEF however, age and serum albumin level were independent predictors for prognosis in patients with AF

in HFrEF.

Keywords: Sinus rhythm, atrial fibrillation, heart failure with reduced ejection fraction, albumin, prognosis

Atrial fibrillation (AF) and heart failure (HF) have become a cardiovascular epidemic in recent years[1,2]. AF is the most common arrhythmia in patients with HF, and its prevalence is increased in parallel to the severity of heart failure, ranging from 10 to 50%[1,3-7]. It is widely acknowledged that HF promotes AF and that AF worsens HF prognosis[7-14] AF occurs in more than half of individuals with HF, and HF occurs in more than one third of individuals with AF. AF precedes and follows HF with both preserved and reduced ejection fraction[15]. Individuals with AF or HF who subsequently develop the other condition have a poor prognosis[12]. AF can precipitate acute HF and may facilitate the progression of HF in several ways. Due to rapid heart rates an irregular ventricular rhythm loss of atrioventricular synchrony, and an increase mitral and tricuspid regurgitation, the presence or onset of AF may further decrease cardiac output and aggravate HF[7,16,17]. Patients with heart failure with reduced ejection fraction (HFrEF) and AF are generally older, have a greater symptom burden, lower quality of life, and more comorbidity than those without AF[18-21]. Patients with AF may also be at higher risk of adverse outcomes, including HF hospitalization and death[20].

Aims of this study were to examine and compared to prognostic risk factors in patients with sinus rhythm and in patients with atrial fibrillation (AF) in HFrEF (left ventricular ejection fraction [LVEF] ≤40%).

Method

Patients who were hospitalized with acute decompensated HFrEF between March 2004 and May 2014 in cardiology department of Kocaeli University Hospital which is a high-volume specialized HF clinic. After the index hospitalizations patients were followed in a dedicated HF clinic. The study group consisted of 603 patients who were discharged alive from the hospital. HFrEF was defined as a left ventricular ejection fraction (LVEF) ≤ 40%, as determined by transthoracic echocardiography in patients with clinical signs and symptoms of HF. Baseline demographic characteristics; risk factors; clinical findings; biochemical laboratory results B-type natriuretic peptide (BNP), C-reactive protein, and tri-iodothyronine levels; and echocardiography reports were recorded. AF was diagnosed on a standard 12-lead electrocardiogram (ECG) during the hospitalization. Exclusion criteria were acute coronary syndromes in last six months, an indication for cardiac surgical procedure, primary chronic liver disease, malignant diseases and end-stages with diseases where life expectancy was less than one year and patients with pacemaker rhythm were excluded from the analysis.

Outcome data were obtained from patients or caregiver reports (communicated by outpatient clinical visits of phone contact) or hospital databases. Data collection for each patient was censored at the time point of their most recent contact with the study team or date of death.

Data collection

The cardiology clinic of Kocaeli University Hospital has a detailed clinical database of HF patients. The collected data included demographic information and medical history such as age, gender, prior cerebrovascular events, peripheral arterial disease, chronic obstructive pulmonary disease (COPD), chronic renal dysfunction, hypertension, and diabetes mellitus. Clinical findings and symptoms at admission were evaluated for the study. Demographic information, medical history and clinical signs and symptoms were used as clinical variables. Patient's rhythm and QRS duration were obtained from 12-lead electrocardiography (ECG). The method of ejection fraction assessment used was modified Simpson method and chamber's diameters had been measured according to recent echocardiography guidelines in all patients. Baseline biochemical analysis including blood urea nitrogen, creatinine, hepatic enzymes, serum sodium and potassium, cholesterols, serum albumin, thyroid stimulating hormone, free T3, free T4, BNP, hemoglobin and hematocrit levels were recorded in all patients. Medical therapy including beta-blockers, ACE-inhibitors, ARBs, aspirin, nitrates, digoxin and diuretics were computed as positive if the patients had these medications at discharge. All these data were obtained from the hospital database. Survival status of the patients in the study was obtained from the hospital records or from telephone contact with the patient or family members.

The study protocol was approved by local institutional ethic committees.

Statistical analysis

The statistical analysis of the study was performed using SPSS 21.0 software (SPSS Inc., Chicago, IL). Continuous variables are presented as mean ± standard deviation and categorical variables as numbers, percentages, or proportions. The normality of continuous variable's distribution was determined using the Kolmogorov-Smirnov test. Between-group comparisons were performed using the chi-square test for categorical variables, independent-samples t test for continuous variables with normal distributions and the Mann-Whitney U test for continuous variables with abnormal distributions. Cox proportional hazard analysis was used to arrive at the independent predictors of survival. The Kaplan-Meier method was used to analyze the timing of events during follow-up. All analyses were two-sided and considered significant at a value p value of 0.05.

Results

Six hundred and three patients were enrolled into the study, the mean age was 65±12 years old, 399 (66%) was male and 204 (34%) was female. While 424 (70%) patients were on sinus rhythm, 179 (30%) patients had atrial fibrillation during the index hospitalization (Table 1).

Table 1: General Characteristics of the study cohort.

	n=603
Age (years)	65.0±12.0
Gender (Male/female)	399/204 (66%/34%)
Sinus rhythm/atrial fibrillation	424/179 (70%/30%)
NYHA	3.1±0.2
SBP (mmHg)	123.5±18.0
DBP (mmHg)	75.0±11.5
Hemoglobin (g/dL)	12.5±1.9
BNP (pg/mL)	1955.3±3423.7
Creatinine (mg/dL)	1.4±0.8
Urea (mg/dL)	69.5±41.7
LVEF (%)	25.8±8.5
RVFAC (%)	47.5±11.9
E/e'	15.0±6.2
Coronary artery disease	377 (63%)
Diabetes mellitus	243 (40%)
Hypertension	441 (73%)
Aspirin Use	500 (83%)
ACE-I Use	436 (72%)
ARB Use	127 (21%)
Betablocker Use	434 (72%)
Thiazides	342 (57%)
Loop diuretics	501 (83%)
Spironolactone Use	292(48%)
Digoxin	129 (21%)
Statin	335 (56%)

SBP: Systolic blood pressure, DBP: Diastolic blood pressure. BNP: Brain natriuretic peptide, LVEF: Left ventricular ejection fraction. RVFAC: Right ventricular fractional area change, ACE-I: Angiotensin-converting enzyme inhibitor, Angiotensin II Receptor Blockers

The patients with AF were older than the patients with sinus rhythm, p=0.045. Heart rate was higher and left atrial dimension was larger in the AF group (p<0.001 and <0.001). There were more patients with coronary artery disease in patients with sinus rhythm p<0.001, (Table 2).

Table 2: Clinical differences between patients who were in sinus rhythm and patients with atrial fibrillation in the study group.

	Patients with sinus rhythm (n=424)	Patients with atrial fibrillation (n=179)	p
Age (years)	64.3±11.9	66.4±11.0	0.045
Gender (Men/women)	287/137(68 %/32%)	112/67 (63%/ 37%)	0.225
Hospitalization	2.6±1.3	2.6±1.3	0.907
Death	188 (44%)	63 (35 %)	0.037
NYHA functional class	3.1±0.3	3.1±0.2	0.503
SBP (mmHg)	122.9.1±18. 1	124.78.1±17.6	0.236
DBP (mmHg)	74.5±11.4	75.8.1±11.8	0.202
Heart rate (in a minute)	79.8±13.5	90.9±23.0	<0.001
Hemoglobin (g/dL)	12.5±1.9	12.5±1.9	0.907
BNP (pg/mL)	1867.4±266 5.7	1992.4±3699.6	0.682
Creatinine (mg/dL)	1.5±0.9	1.3±0.6	0.01
Urea (mg/dL)	70.2±43.8	67.9±36.3	0.492
eGFR (mL/min/1.73 m2)	57.3±24.4	59.6±26.9	0.304
CRP (mg/L)	2.6 ±4.3	2.5±3.8	0.628
AST (U/L)	83.1±270.8	51.9±108.3	0.044
ALT (U/L)	78.9±246.0	53.9±131.8	0.107
FT3/FT4	1.9±0.8	1.8±0.6	0.260
LA dimension (mm)	46.1±5.9	50.5±6.8	<0.001
LVEF (%)	25.5±8.3	26.5±9.1	0.193
RVFAC (%)	47.8±11.7	46.9±12.3	0.379
E/e'	14.8±6.5	15.5±6.0	0.228
Coronary artery disease	290 (68%)	87(49%)	<0.001
Diabetes mellitus	186 (44%)	57(32%)	0.006
Hypertension	305 (72%)	136 (76%)	0.306
Aspirin Use	365 (86%)	135(75%)	0.001
ACE-I Use	323 (76%)	113(63%)	0.001
ARB Use	85 (20%)	42(23%)	0.330
Betablocker Use	308(73%)	126(70%)	0.574
Thiazides	245(58%)	97(54%)	0.416
Loop diuretics	349 (82%)	152(85%)	0.436
Spironolactone Use	201(47%)	91(51%)	0.441
Digoxin	64(15%)	65(36%)	<0.001
Statin	262(62%)	73(41%)	<0.001

NYHA: New York heart association, SBP: Systolic blood pressure,

DBP: Diastolic blood pressure, BNP: Brain natriuretic peptide, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, FT3: Free triiodothyronine, FT4: Free thyroxine, LA: Left atrium, LVEF: Left ventricular ejection fraction, RVFAC: Right ventricular fractional area change, E: Early diastolic velocity, e': E prime, ACE-I: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker. p<0.05 was considered statistically significant.

More patients with sinus rhythm died compared to patients with AF during follow up period 44% vs 35 %, p=0.037 (Table 2).

Patients who did not survive during the follow up period in sinus rhythm were older, hospitalized more, had shorter walking distance, higher respiratory rate, worse renal function, and liver function. Non survivors in sinus rhythm also had worse left and right heart systolic functions (Table 3).

Table 3: Statistically different parameters between patients who were survival and patients who were non survival in sinus rhythm.

	Patients with sinus rhythm in heart failure with reduced ejection fraction		
	Survivals (n=236)	**Non survival (n=188)**	**p**
Age (years)	60.9±11.7	68.6±10.7	<0.001
Hospitalization	2.4±1.2	2.9±1.3	0.024
NYHA	3.0±0.1	3.1±0.4	<0.001
Walking distance in one minute >300 feet	181 (77%)	92(49%)	<0.001
Respiratory rate	24.2±3.9	27.3±4.7	<0.001
Hematocrit (%)	38.0±5.8	36.7±5.7	0.026
Creatinine (mg/dL)	1.3±0.7	1.7±1.1	<0.001
Urea (mg/dL)	59.4±34.4	83.8±50.1	<0.001
eGFR (mL/min/1.73m2)	62.0±24.0	51.5±23.7	<0.001
Homocysteine	16.3±7.7	18.0±8.7	0.056
Albumin (g/dL)	3.7±0.5	3.3±0.6	<0.001
AST (U/L)	33.9±53.4	144.9±394.2	<0.001
ALT (U/L)	31.0±40.3	139.0±358.2	<0.001
Estimated PASP (mmHg)	39.7±13.9	43.3±15.3	0.011
LVEF (%)	27.5±7.6	23.0±8.4	<0.001
RVFAC (%)	51.1±8.9	43.6±13.4	<0.001
E/e'	13.2±5.4	16.9±7.1	<0.001

NYHA: New York heart association, eGFR: Estimated glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, PASP: Pulmonary artery systolic pressure, LVEF: Left ventricular ejection fraction, RVFAC: Right ventricular fractional area change, E: Early diastolic velocity, e': E prime. p<0.05 was considered statistically significant.

Patients who did not survive during the follow up period in atrial fibrillation were older, hospitalized more, had shorter walking distance, higher respiratory rate, worse renal functions, and liver functions. Non survivors in atrial fibrillation also had worse left and right heart systolic functions (Table 4).

Table 4: Statistically different parameters between patients who were survival and patients who were non survival in atrial fibrillation.

	Patients with atrial fibrillation in heart failure with reduced ejection fraction		
	Survivals (n=116)	**Non survival (n=63)**	**p**
Age (years)	64.1±10.4	70.6±10.9	<0.001
Hospitalization	2.3±1.0	3.3±1.5	<0.001
NYHA	3.0±0.2	3.1±0.3	0.142
Walking distance in one minute >300 feet	76 (66%)	28 (44%)	0.006
Respiratory rate	24.9±4.3	26.6±4.6	0.015
Hematocrit (%)	38.3±5.5	36.6±5.8	0.050
Creatinine (mg/dL)	1.2±0.5	1.5±0.7	0.005
Urea (mg/dL)	63.2±31.3	76.4±42.1	0.034
eGFR (mL/min/1.73m2)	64.0±30.1	51.6±16.9	0.001
Homocysteine	13.8±8.3	16.6±6.5	0.022
Albumin (g/dL)	3.7±0.5	3.3±0.6	<0.001
AST (U/L)	30.1±23.3	92.0±173.7	0.006
ALT (U/L)	29.4±29.7	99.0±212.3	0.012
Estimated PASP (mmHg)	43.8±15.1	51.3±13.4	0.001
LVEF (%)	28.2±9.0	23.5±8.4	0.001
RVFAC (%)	48.9±11.0	43.1±13.7	0.004
E/e'	14.4±5.0	17.4±6.1	0.001

NYHA: New York heart association, eGFR: Estimated glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, PASP: Pulmonary artery systolic pressure, LVEF: Left ventricular ejection fraction, RVFAC: Right ventricular fractional area change, E: Early diastolic velocity, e': E prime. p<0.05 was considered statistically significant.

In Cox regression analysis age, hospitalization numbers, walking distance in one minute, e/e', albumin level and urea level were independent predictors for cardiovascular death in patients with sinus rhythm. Age and albumin level were independent predictors in patients with AF.

Table 5. Cox Regression Analysis for cardiovascular death in patients with sinus rhythm and in patients with atrial fibrillation in heart failure with reduced ejection fraction.

Variable	Hazard Ratio	95% CI	P value
Patients with sinus rhythm			
Age	1.042	1.023-1.061	<0.001
Hospitalization	0.798	0.697-0.913	0.001
Walking distance in one minute	0.582	0.414-0.817	0.002
e/e'	1.035	1.010-1.055	0.005
Albumin	0.685	0.515-0.909	0.009
Urea	1.004	1.001-1.007	0.012
Patients with atrial fibrillation			
Age	1.091	1.060-1.124	<0.001
Albumin	0.545	0.336-0.885	0.014

CI: Confidence interval, NYHA: New York Heart association, LVEF: Left ventricular ejection fraction, p<0.05 was considered statistically significant.

To define the predictor level in the study population, we used ROC curve analysis to detect the predictive cutoff values of albumin level for the occurrence of cardiovascular death in sinus rhythm (area under the curve [AUC]=0.294; 95% confidence interval [CI], 0.244–0.344; *P* < 0.001). The ROC curves showed that the best cutoff value for predicting cardiovascular death in sinus rhythm group was an albumin level of 2.95 mg/dL (76% sensitivity and 94% specificity) (Figure 1).

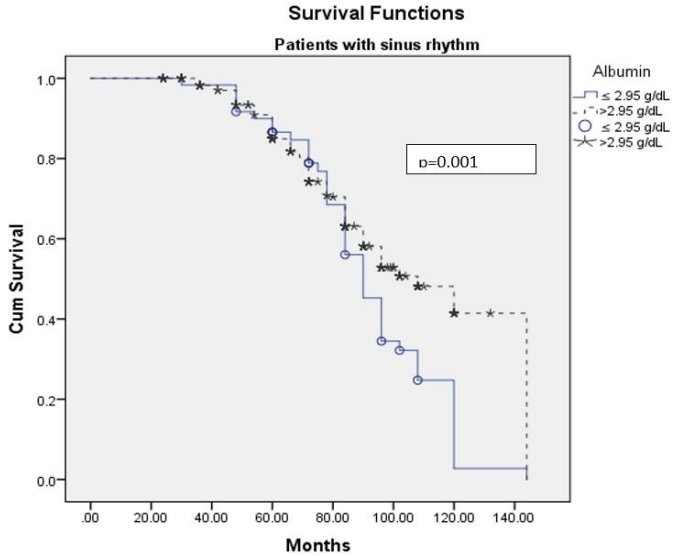

Figure 1: Survival differences between albumin level ≤2.95 g/dL and > 2.95 g/dL in patients with sinus rhythm.

The predictive cutoff values of albumin level for the occurrence of cardiovascular death in AF (area under the curve [AUC]=0.290; 95% confidence interval [CI], 0.208–0.372; *P* < 0.001). The ROC curves showed that the best cutoff value for predicting cardiovascular death in AF group was an albumin level of 2.95 mg/dL (73% sensitivity and 97% specificity) (Figure 2).

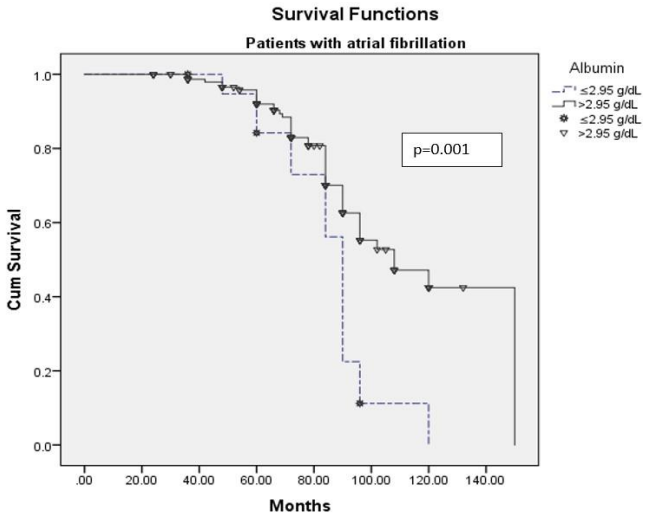

Figure 2. 1: Survival differences between albumin level ≤2.95 g/dL and > 2.95 g/dL in patients with atrial fibrillation.

Discussion

In both groups patients who died during the follow-up period were older and their left heart and right heart systolic functions were worse than in survivors. During the follow-up period, the kidney functions and liver functions of the patients who did not survive were worse than the patients who survived. In both groups, the walking distances of the non-survival patients were shorter and their respiratory rates were higher. Albumin levels in both groups were independent predictors for prognosis.

The normal reference range for serum albumin in adults is 3.5 and 5 g/dl. Serum albumin concentration is physiologically slightly lower in women than in men and decreases slightly with age. Serum albumin carries many endogenous and exogenous substances, such as inorganic ions, fatty acids, bilirubin, vitamins, hormones and steroids, and drugs[22].

Albumin represents a very abundant and important circulating antioxidant. Serum albumin may be the most important antioxidant in the whole blood[22-24]. The antioxidant properties of human serum albumin are largely dependent on Cys34 and its contribution to the maintenance of intravascular homeostasis, including protecting the vascular endothelium under disease conditions related to oxidative stress[24].

Serum albumin contributes to maintaining capillary membrane stability and fluid balance across the capillary wall through its colloid osmotic effect and interaction with the endothelial glycocalyx. According to Starling's law hydrostatic capillary pressure is the main force responsible for the fluid transfer from the intravascular to the interstitial space. The plasma colloid osmotic pressure, of which approximately 80% of the effect results from serum albumin, is the main force opposing fluid extravasation

outside the intravascular compartment. The imbalance of Starling's forces because of hypoalbuminemia induces a net extravasation of fluid to the interstitial space, leading to formation of interstitial edema, hypovolemia, and fluid retention. Pulmonary fluid homeostasis has specific characteristics that protect against an isolated decrease in serum colloid osmotic pressure, and increase in pulmonary capillary hydrostatic pressure, even moderate, is necessary for the development of pulmonary edema[22,25].

Prevalence of hypoalbuminemia varies from 20 to 25% in chronic heart failure to 90% in frail elderly patients with acute heart Failure. Hypoalbuminemia is due to decreased liver synthesis, increased catabolism, increased vascular permeability and renal and enteral loss[22,25]. Hypoalbuminemia is the result of the combined effects of inflammation and inadequate protein and caloric intake in patients with chronic diseases such as chronic renal failure. Inflammation and malnutrition both reduce albumin concentration by decreasing its rate of synthesis[26]. The occurrence of new onset heart failure was significantly related to low serum albumin concentration[27].

In a study, 8870 individuals without cardiovascular disease were followed for a mean of 7.5 years. The albumin levels were inversely associated with the risk of AF among women but not among men. Additional adjustment for cases of coronary heart disease, congestive heart failure, and stroke that occurred during follow-up did not attenuate these associations[28]. Zhao et all demonstrated that in Chinese population low albumin level was independently associated with AF in a retrospective study[29]. 12.833 individuals participated in the study. During a median follow-up of 25.1 years, 2259 (17.6%) participants developed incident AF. The serum albumin level was independently inverse associated with incident AF in a linear pattern. However, Mendelian randomization analyses did not support a causal role of serum albumin in the etiology of AF in this study[30]. In a prospective study low levels of serum albumin were associated with the occurrence of new onset AF during the first 48 h of intensive care unit admission. The incidence of new onset AF during the first 48 h of intensive care unit admission was 18%. Serum albumin levels were also significantly associated with the number of episodes of new onset AF in multivariate analysis[31].

In an observational study that included 385 patients with systolic heart failure followed for 25 months, serum albumin was a significant prognosis indicator for heart failure, and it added important information to NT-proBNP[32]. Hypoalbuminemia was also a strong predictor of death and delisting for adverse outcome in patients with heart failure listed for heart transplantation[33]. Low baseline serum albumin levels were independently associated with reduced 4-year survival in patients with HF and severe secondary mitral regurgitation enrolled in the COAPT trial[34].

A total of 48 studies examining 44.048 patients with HF were analyzed. The results suggested that hypoalbuminemia was associated with significantly higher in-hospital mortality as well as long-term mortality with a predictive accuracy comparable to that reported for serum BNP. These findings suggested that serum albumin may be useful in determining high-risk patients[35].

In this study, low serum albumin levels were independent predictors in both patients with sinus rhythm and patients with AF for prognosis. It seems that serum albumin may represent the total systemic effects of heart failure. Serum albumin levels can be used as a guide for the effective management of HFrEF.
Serum albumin level may also be a guide for advanced heart failure therapies.

Limitations

The limitation of this study is that it is a single-center and retrospective analysis study.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Conclusion

In advanced HFrEF, decreased albumin level predicts poor prognosis in patients in sinus rhythm and patients with atrial fibrillation. Albumin can be used as a marker representing the systemic response to HF. Monitoring of albumin levels after HF diagnosis and starting treatments may be used as a guide to follow the results of HF treatments.

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