Original Article

C-Reactive Protein/Albumin Ratio Designates Advanced Heart Failure among Outpatients with Heart Failure

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Abstract

Background: Exercise intolerance has a relation with poor prognosis for patients with heart failure (HF). The high C-reactive protein (CRP) levels have prognostic effects on many cardiovascular diseases such as HF, coronary artery disease, and ischemic stroke. The low serum albumin levels are related with poor prognosis in patients with HF. We aimed to investigate whether the assessment of CRP/albumin ratio would enable clinicians to identify patients with advanced HF. **Materials and Methods:** This retrospective study included 102 HF patients with reduced ejection fraction (≤40%). The mean age of patients was 44 ± 13 years. Advanced HF (New York Heart Association [NYHA] Functional Class III–IV) was observed in 27 patients (26.5%). **Results:** CRP/albumin ratio was on average higher in patients with NYHA functional Classes III and IV than in patients with NYHA functional Classes I and II (0.4 [0.02–1.97] vs. 0.12 [0.02–1.63], $P < 0.001$). In multiple logistic regression model with forward stepwise method, CRP/albumin ratio (odds ratio [OR]: 3.084, *P*: 0.036, 95.0% confidence interval [CI]: 1.074–3.855) and brain natriuretic peptide >500 pg/ml (OR: 3.526, *P*: 0.014, 95.0% CI: 1.290–9.637) remained associated with advanced HF. **Conclusions:** For the first time in the literature, we showed that elevated CRP/albumin ratio was found to be independently associated with advanced HF. We have also shown that high CRP/albumin ratio was associated with poor hemodynamic parameters.

Keywords: Albumin, C-reactive protein, C-reactive protein/albumin ratio, heart failure with reduced ejection fraction, outpatients, poor functional capacity

Introduction

It is known that exercise intolerance has a relation with poor prognosis for patients with heart failure (HF).[1,2] The New York Heart Association (NHYA) classification is the most widely used method to show the effect of HF on daily activities. It has been shown that patients in high NYHA classification are more frequently hospitalized, have worse life qualities, and lose their lives earlier.[3,4] In a consensus report published by the European Society of Cardiology in 2018, NYHA Class 3–4 HF diagnosis of advanced functional capacity is said to be one of the most important parameters used.[5]

C-reactive protein (CRP) is an acute-phase reactant and an indicator of chronic inflammation.[6] It has been documented that the high CRP levels have prognostic and therapeutic effects on many cardiovascular diseases such as HF,[7] coronary artery disease (CAD),[8] and ischemic stroke.[9] Hypoalbuminemia is widely encountered in patients with HF and can give information about malnutrition and inflammatory situation.[10] It has been shown that the low serum albumin levels are related with poor prognosis in patients with HF.[11,12]

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The combination of these two parameters, namely the ratio of CRP to albumin, may have more value than either of them individually for predicting poor NYHA functional capacity in chronic HF. In this study, we aimed to investigate whether the assessment of CRP/albumin ratio would enable clinicians to identify patients with advanced HF.

Materials and Methods

Patients

In this retrospective study, 152 adult patients with left ventricular ejection fraction (LVEF) ≤40% were screened in the HF outpatient clinic. Patients with acute decompensated HF and new-onset HF; patients without albumin and CRP values at admission; and chronic renal failure patients with low albumin levels due to severe malnutrition, hematological disease, cancer, neoplastic metastases to bone marrow, sepsis, ongoing systemic inflammatory conditions, pregnancy, autoimmune disease, glucocorticoid therapy, acute myocardial ischemia, and cardiogenic shock were excluded from the study [Figure 1]. The study included 102 HF patients (mean age: 44 ± 13 years) with reduced ejection fraction (EF) applying to our HF center. Patients were classified into two groups based on NYHA functional class. NYHA functional classification was determined by the cardiologists who were blinded to the clinical data of the patients. The study was approved by the local ethics committee under protocol number 2010-01/13. Written informed consent was acquired from each participant. The research was conducted in accordance with the principles specified in the Declaration of Helsinki.

All venous blood samples were obtained upon patient presentation. Blood samples for a complete blood count and serum chemistry including serum albumin and CRP levels were collected through peripheral vein. The measurement of CRP was performed using CRP-Latex (II) immunoturbidimetric assay (Denka Seiken Co., Ltd., Tokyo, Japan).[13]

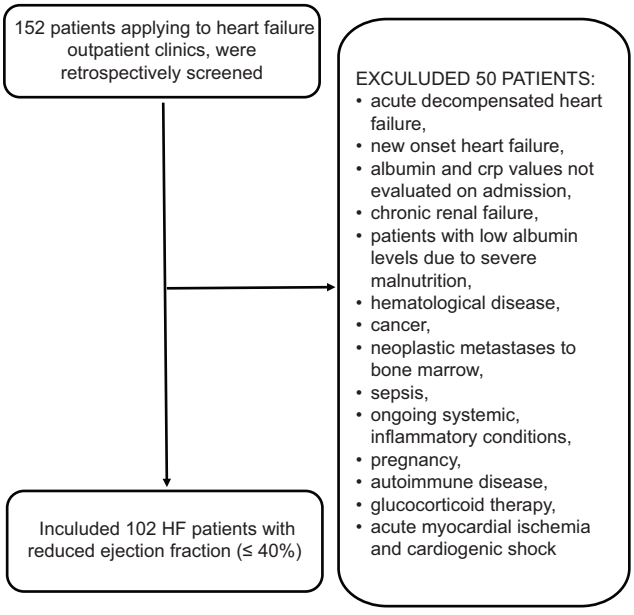

Figure 1: Flowchart shows the patient selection process

Echocardiography

Senior operators have carried out the echocardiography examinations. A system available in the mercantile (Vivid 7, General Electric Vingmed Ultrasound, Horten, Norway) was used to image the patients in the left lateral decubitus position. Making use of the parasternal long and short axes and apical and subcostal views, Doppler tracings, and two-dimensional images were attained. Left ventricles' internal dimensions and septum and posterior wall thicknesses were measured in two-dimensional guided M-mode at the LV minor axis. Simpson's biplane method was utilized for measuring LVEF.[14]

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (min − max) in the presence of abnormal distribution and categorical variables as percentages. Comparisons between groups of patients were made by the use of a Chi-square test for categorical variables, independent samples *t*-test for normally distributed continuous variables, and Mann–Whitney U-test when the distribution was skewed. Correlations were evaluated either through Pearson or Spearman correlation tests. We used univariate logistic regression analysis to quantify the association of advanced HF. Patients CRP, albumin, CRP/albumin ratio, sodium, brain natriuretic peptide (BNP) >500 pg/ml, hemoglobin, age, fasting glucose, alanine aminotransferase, aspartate aminotransferase, creatinine levels and diabetes mellitus, beta - blockers use, aldosterone antagonist use characteristics were evaluated with the multivariate logistic regression model with forward stepwise method to determine the independent prognostic factors of advanced HF. Receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cutoff point of CRP/albumin ratio (at which sensitivity and specificity would be maximal) for the prediction of poor functional capacity. Areas under the curve (AUC) were calculated as measures of the accuracy of the tests. We compared the AUC with the use of the *Z*-test. All statistical procedures were performed using SPSS software version 14.0 (SPSS Inc., Chicago, IL, USA). $P = 0.05$ was considered as statistically significant.

Results

Considering the whole cohort, the mean age of patients was 44 ± 13 years (85% – male and 15% – female). The mean LVEF was 23 ± 6%, and the median CRP/albumin ratio was 0.15 (0.02–1.97). Advanced HF (NYHA Functional Class III–IV) was observed in 27 patients (26.5%).

A comparison of two groups of patients with HF was summarized in Table 1. CRP/albumin ratio was on average higher in patients with NYHA functional Classes III and IV than in patients with NYHA functional Classes I and II (0.4 [0.02–1.97] vs. 0.12 [0.02–1.63], $P < 0.001$). Presence of CAD, CRP, albumin, CRP/albumin ratio, sodium, hemoglobin, and BNP levels differed significantly in relation to NYHA functional class groups [Table 1].

Table 1: Baseline characteristics of study patients

Variable	All (*n*=102)	NYHA I-II (*n*=75; 73.5%)	NYHA III-IV (*n*=27; 26.5%)	*P*
Baseline characteristics				
Mean age (years)	44±13	44±12	46±14	0.334
Male/female	87/15	63/12	24/3	0.754
Hypertension, *n* (%)	37 (36)	30 (40)	7 (26)	0.284
Diabetes mellitus, *n* (%)	18 (18)	13 (17)	5 (19)	1.000
CAD, *n* (%)	84 (82)	57 (76)	26 (96)	0.042
Heart rate (beats/min)	87±15	86±14	89±16	0.262
Systolic blood pressure (mmHg)	119±19	121±19	114±18	0.085
Diastolic blood pressure (mmHg)	77±15	78±13	75±18	0.292
Atrial fibrillation, *n* (%)	11 (11)	9 (12)	2 (7)	0.723
LVEF (%)	23±6	23±6	21.5±7	0.294
Laboratory findings				
CRP	0.6 (0.1-7.1)	0.5 (0.1-7)	1.7 (0.1-7.1)	0.004
Albumin	4.4±0.5	4.4±0.4	4.2±0.4	0.028
CRP/albumin ratio	0.15 (0.02-1.97)	0.12 (0.02-1.63)	0.4 (0.02-1.97)	0.002
Fasting glucose (mg/dl)	106±36	105±35	111±37	0.468
Creatinine (mg/dl)	1.0±0.3	1.0±0.3	1.1±0.3	0.258
Sodium (mEq/L)	139±3.5	140±3	138±4	0.011
Potassium (mEq/L)	4.6±0.5	4.6±0.5	4.5±0.5	0.333
Hemoglobin (gr/dl)	14±2	14.1±2	13.2±2	0.031
Brain natriuretic peptide (pg/ml)	399 (2-4333)	190 (2-2470)	1103 (3-4333)	<0.001
Brain natriuretic peptide >500 pg/ml, *n* (%)	43 (43)	24 (33)	19 (70)	0.002
Total cholesterol (mg/dl)	175±51	181±46	158±61	0.079
Alanine aminotransferase (IU/L)	37±52	34±25	46±93	0.515
Aspartate aminotransferase (IU/L)	31±25	30±13	35±44	0.551
Medication, *n* (%)				
Antiplatelet agents	47 (46)	34 (45)	13 (48)	0.979
Beta-blockers	94 (92)	69 (92)	25 (93)	1.000
ACE inhibitor/ARB	70 (69)	51 (68)	19 (70)	1.000
Digoxine	45 (44)	30 (40)	15 (56)	0.242
Diuretics	57 (56)	40 (53)	17 (63)	0.523
Aldosterone antagonist	60 (59)	43 (57)	17 (63)	0.778

ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, NYHA: New York Heart Association, CAD: Coronary artery disease, LVEF: Left ventricular ejection fraction, CRP: C-reactive protein

CRP/albumin ratio was correlated with CRP, albumin, BNP, sodium, alanine aminotransferase, aspartate aminotransferase, creatinine, hemoglobin, and fasting glucose levels, age, presence of diabetes mellitus, beta-blockers, and aldosterone antagonist usage [Table 2].

Univariate and multiple logistic regression analyses for identifying poor NYHA functional class were listed in Table 3. CRP, albumin, CRP/albumin ratio, sodium, hemoglobin, and BNP >500 pg/ml were found to designate poor NYHA functional class. In multiple logistic regression model with forward stepwise method, CRP/albumin ratio (odds ratio [OR]: 3.084, *P*: 0.036, 95.0% confidence interval [CI]: 1.074–3.855) and BNP >500 pg/ml (OR: 3.526, *P*: 0.014, 95.0% CI: 1.290–9.637) remained associated with advanced HF after adjustment for variables found to be statistically significant in univariate analysis and correlated with CRP/albumin ratio.

According to the ROC curve analysis, the optimal cutoff value of CRP/albumin ratio to predict advanced HF was found as >0.15, with 74% sensitivity and 61% specificity [AUC: 0.700, 95% CI: 0.601–0.787, Figure 2].

Discussion

Although new treatment methods have been developed, HF still has a poor prognosis.[15] Lots of factors have been shown to predict the poor prognosis, and the most important of those is the frequency of hospitalization.[16] The most significant indicator of hospitalization is, in turn, the worsening functional capacity.[16] By the way, the determination of the clinical and laboratory parameters which can make us predict will have a contribution to ameliorate the prognosis.

High levels of CRP in HF are caused by cardiac decompensation and damage to the other organs due to low cardiac output and venous congestion. Previous studies have also shown that inflammatory markers are elevated in patients with HF. CRP has been shown to increase in patients with HF and is associated with the severity of HF and increased cardiovascular mortality during follow-up.[17,18] It is known that the inflammation in HF

patients is related both with bad prognosis and bad functional capacity.[10-12] In our study, CRP levels were found to be correlated with functional capacity.

Hypoalbuminemia is one of the most important indicators of malnutrition. Moreover, serum albumin level, which is a negative acute-phase reactant, decreases secondary to inflammation in HF. In addition, it has been shown that the increasing CRP levels and decreasing albumin levels are also interrelated.[19] In our study, serum albumin levels were found to be related to functional capacity in patients with HF, similar to the literature.

In recent studies, it has been shown that the combination of those two parameters can be used as a strong prognostic marker for mortality in older adults admitted to the emergency department and in acute kidney failure, sepsis, and cancer.[20-23] In addition, the CRP/albumin ratio in patients with acute coronary syndrome has been shown to be related to the severity of CAD.[24] Inflammation is a fundamental characteristic of HF, and CRP/albumin ratio might better reflect the inflammatory status; thus, we investigated the possible relationship between the functional capacity in HF and CRP/albumin ratio. We found that CRP/albumin ratio was an independent predictor of functional capacity in HF, and the predictive accuracy of

Table 2: Correlation coefficients for C-reactive protein/albumin ratio

	R	*P*
CRP	0.992	<0.001
Brain natriuretic peptide (pg/ml)	0.356	<0.001
Brain natriuretic peptide >500 pg/ml	0.429	<0.001
Age (years)	0.334	0.001
Sodium (mEq/L)	−0.312	0.001
Beta-blocker usage	−0.289	0.003
Alanine aminotransferase (IU/L)	−0.280	0.004
Aspartate aminotransferase (IU/L)	−0.248	0.012
Presence of diabetes mellitus	0.242	0.014
Creatinine (mg/dl)	0.236	0.017
Albumin	−0.219	0.027
Aldosterone antagonist usage	−0.218	0.028
Hemoglobin (gr/dl)	−0.215	0.030
Fasting glucose (mg/dl)	0.214	0.031

CRP: C-reactive protein

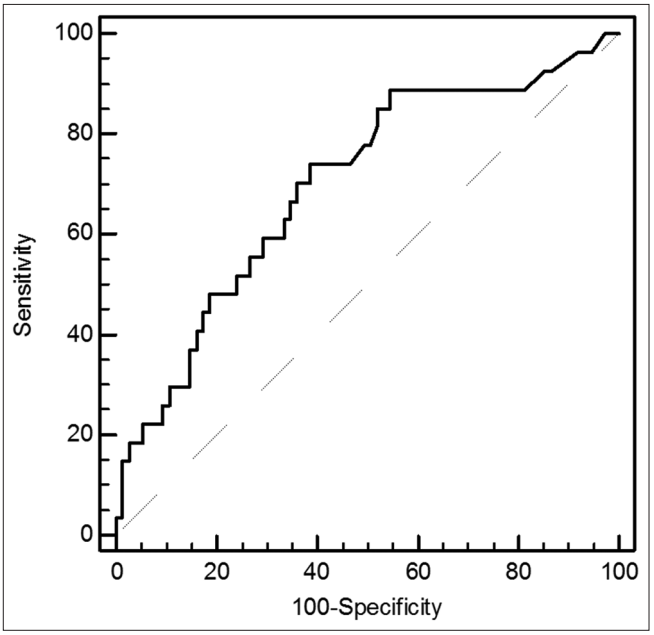

Figure 2: Receiver operator characteristic curve of C-reactive protein/albumin ratio to predict advanced heart failure

Table 3: Univariate and multivariate analyses of advanced heart failure

Variable	Univariate			Multivariate		
	P	OR	95% CI	*P*	OR	95% CI
Statistically significant variables						
CRP	0.008	1.370	1.085-1.729			
Albumin	0.035	0.360	0.139-0.933			
CRP/albumin ratio	0.004	4.296	1.589-11.612	0.036	3.084	1.074-3.855
Sodium (mEq/L)	0.015	0.846	0.740-0.968			
Brain natriuretic peptide >500 pg/ml	0.001	4.750	1.818-12.411	0.014	3.526	1.290-9.637
Hemoglobin (gr/dl)	0.035	0.764	0.595-0.981			
Variables which correlated with CRP/albumin ratio						
Age (years)	0.332	1.018	0.982-1.056			
Beta-blocker usage	0.922	1.087	0.206-5.742			
Alanine aminotransferase (IU/L)	0.334	1.004	0.996-1.012			
Aspartate aminotransferase (IU/L)	0.376	1.007	0.991-1.024			
Presence of diabetes mellitus	0.890	1.084	0.347-3.390			
Creatinine (mg/dl)	0.258	2.314	0.541-9.905			
Aldosterone antagonist usage	0.611	1.265	0.512-3.128			
Fasting glucose (mg/dl)	0.466	1.004	0.993-1.016			

All the variables from Table 1 were examined, and only those significant at a $P<0.05$ level and those with a correlated CRP/albumin ratio level are shown in univariate analysis. The multiple logistic regression model included all univariate predictors and those with correlated CRP/albumin ratio level.
CI: Confidence interval, OR: Odds ratio, CRP: C-reactive protein

CRP/albumin ratio was better than that of CRP and albumin level, as per the comparison of the ROC curves. Furthermore, in our present study, we have documented that the CRP/albumin ratio is strongly positively correlated with BNP level which is an indicator of left ventricular filling pressure. Furthermore, we have shown that the patients having high CRP/albumin ratio are hyponatremic and anemic and have bad kidney functionalities. Hence, we think that CRP/albumin ratio seems to reflect the increasing severity of HF.

Limitations

Our study has certain limitations. First, the other inflammatory markers which are not part of the routine evaluation were not analyzed. In addition, this study was carried out with a small number of Turkish patients. However, on the contrary, the objective evaluation of functional status on top of NYHA has potentially increased the value of the findings. The second limitation was that the NHYA classification inevitably included subjective judgments of symptoms and clinical data, and variability between the interobservers and intraobservers has been widely reported. Various psychological and environmental factors can influence the functional status, and adherence to the therapy is affected by cognitive factors and patient attitude. In addition, some genre of functional assessments such as cardiopulmonary exercise test or 6-min walk test was not performed. The final limitation was that our study included only patients with impaired EF (LVEF <0.40); hence, our results cannot be extrapolated to the population of patients with HF and preserved EF.

Conclusions

For the first time in the literature, we showed that, in the presence of the other clinical and laboratory parameters, elevated CRP/albumin ratio was found to be independently associated with advanced HF. We have also shown that high CRP/albumin ratio was associated with poor hemodynamic parameters. Our study showed that this simple and widely available test might help to identify HF patients who are at a higher risk of hospitalization and may help risk stratification of these patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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