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Prognostic role of C-reactive protein/albumin ratio on cardiovascular mortality in outpatients with heart failure

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Abstract

In light of recent advancements in the field of heart failure management and treatment, it remains crucial to acknowledge that individuals diagnosed with heart failure and presenting with low ejection fraction face a significant risk of adverse outcomes. This high risk is primarily due to impaired pumping function of the heart and concomitant comorbidities. The objective of this study was to assess the prognostic significance of the C-reactive protein/albumin ratio in predicting overall mortality among individuals receiving outpatient care for heart failure. This retrospective, single-center cohort study comprised a total of 218 patients diagnosed with heart failure with low ejection fraction. These patients were diligently monitored as outpatients in a specialized heart failure outpatient clinic. During a median follow-up period of 26 months, the CRP/albumin ratios at the time of the initial hospitalization were assessed in patients who experienced mortality and those who survived. The mean age of the study participants was 56±10 years, 82% were male and 18% were female. The mean C-reactive protein/albumin ratio was 0.12 (0.02-2.1) and the mean left ventricular ejection fraction was 26% (10-40%). It was observed that the predictive accuracy of mortality could be determined by the C-reactive protein/albumin ratio with an optimal threshold value > 0.12. The sensitivity and specificity of this method were 95% and 63%, respectively (AUC: 0.824, 95% CI: 0.740-0.890). In conclusion, the C-reactive protein/albumin ratio can be defined as a prognostic indicator for mortality in outpatients with heart failure.

Keywords: CRP/albumin ratio, heart failure, mortality

Introduction

The role of the chronic inflammatory process in the prognosis of heart failure is of significant importance. Hence, it is frequently observed that individuals with heart failure (HF) exhibit increased levels of plasma C-reactive protein (CRP), which serves as a reliable indicator of inflammation. In certain patients with HF, inflammation has been identified as a potential primary etiological factor, while in others, it is believed to play a contributory role in the progression of HF. However, of paramount significance is the recognition that inflammation can be regarded as a viable target for therapeutic intervention [1,2].

In patients with HF, the presence of low levels of albumin is primarily characterized by a reduction in the synthesis of albumin and the loss of protein. This can be attributed to various factors including chronic inflammatory processes, hemodilution, hepatic congestion, malnutrition, and proteinuria. Albumin has been found to be intricately involved in various biological processes that have been linked to unfavorable outcomes in HF [3]. Decreased levels of albumin in individuals with HF can lead to an increased inclination towards congestion. This is primarily attributed to a reduction in intravascular colloidal osmotic pressure, along with heightened oxidative stress, inflammation, and vulnerability to infection [4-6].

The correlation between the presence of a chronic inflammatory process and mortality in individuals with heart failure has been demonstrated in numerous studies [7-9]. The objective of this study was to examine the correlation between the CRP/albumin ratio (CAR), a convenient and easily accessible indicator of

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chronic inflammatory processes and mortality rates among outpatients diagnosed with HF.

Material and Methods

The study comprised a cohort of 280 consecutive patients diagnosed with ischemic HF. Patients diagnosed with cancer, sepsis, infections necessitating hospitalization, individuals experiencing decompensation upon admission, patients unable to adhere to medication regimen during follow-up, individuals with systemic inflammatory conditions, pregnant individuals, those with autoimmune disease, individuals undergoing glucocorticoid therapy, individuals with acute myocardial ischemia and individuals with cardiogenic shock were excluded from the study. Consequently, a retrospective evaluation was conducted on a cohort of 218 patients who received outpatient treatment for HF. The laboratory results, clinical characteristics, cardiovascular risk factors, comorbidities, and medical treatments utilized by the patients during their outpatient visits were acquired from the data documented in the hospital system. Following the initial consultation, mortality data and medical records pertaining to the patients were meticulously documented through the utilization of the national health record system or through direct communication with the patients or their respective family members via telephone. The study encompassed a cohort of patients who were diligently monitored for a mean duration of 26 (3-61) months. The study population was stratified into two distinct cohorts: the living group (n=176) and the mortality group (n=42). These cohorts were subsequently assessed with regards to their CAR. Hypertension was defined as a blood pressure ≥140/90 mmHg more than two times during the outpatient clinic visit, antihypertensive treatment was initiated during the outpatient clinic visit or the patient was receiving antihypertensive treatment. Diabetes mellitus (DM) was defined as a fasting blood glucose level of ≥126 mg/dL, a diagnosis of diabetes mellitus by the endocrinology clinic, or the patient receiving antidiabetic treatment. The presence of coronary artery disease (CAD) was defined as abnormal stress test results with evidence of ischemia, >50% coronary stenosis documented on coronary angiogram or clinical history of CAD. The study was conducted in accordance with the Helsinki Declaration on Human Research and approved by the Kahramanmaras Sutcuimam University Ethics Committee (Approval number: 2023-11).

Biomarker tests

Venous blood samples were obtained during the patient's initial presentation. Blood samples were obtained through the peripheral vein to conduct a comprehensive analysis of serum biochemistry, encompassing a complete blood count, serum albumin, and CRP levels. These tests are routinely prescribed for all patients diagnosed with heart failure within our clinic. CRP measurement was performed using the CRP-Latex (II) immunoturbidimetric assay (Denka Seiken Co., Ltd., Tokyo, Japan).

Echocardiography

Echocardiographic examinations are conducted within the heart failure outpatient clinic of our esteemed medical facility, under the expertise of cardiologists who possess specialized knowledge in this particular domain. During the standard evaluation process, the utilization of a Vivid E90 (General Electric, Horten, Norveç) echocardiography device is employed to capture images of patients positioned in the left lateral decubitus posture. Doppler tracings and two-dimensional images are acquired from various perspectives, including the parasternal long and short axes, as well as the apical and subcostal windows. The dimensions of the left ventricles, septum, and posterior wall thickness are assessed using two-dimensional M-mode in the left ventricular minor axis. The utilization of Simpson's method is employed for the purpose of quantifying the left ventricular ejection fraction (LVEF) [10].

Statistical analysis

Continuous variables were reported as mean±standard deviation or median (min - max) in cases where the distribution was abnormal. Categorical variables, on the other hand, were presented as percentages. Comparisons among patient groups were conducted utilizing the Chi-square test for categorical variables, the independent sample t-test for normally distributed continuous variables, and the Mann-Whitney U-test for variables with skewed distribution. Correlations were assessed utilizing either the Pearson or Spearman correlation tests. In this study, the association between mortality and various factors was assessed using univariate regression analysis. A forward step method was employed to conduct multiple Cox regression analysis, aiming to identify prognostic factors associated with cardiovascular mortality. Factors considered in the analysis included CAR>0.12, age, creatinine, sodium, B-type natriuretic peptide (BNP), triglycerides, high density lipoprotein (HDL) cholesterol, aspartate aminotransferase and alanine aminotransferase levels, diabetes mellitus and beta-blocker use. Statistical analyses were performed using SPSS software (version 24.0, SPSS Inc., Chicago, IL, USA). Statistically significant p-value was set at <0.05.

Results

The mean age of the patients was 56±10 years, 82% were male and 18% were female. The mean CRP/albumin ratio was 0.12 (0.02-2.1). Furthermore, the mean LVEF was 26% (10-40). The mean follow-up period was 26 (3-61) months and mortality occurred in 42 (19%) patients. Of the 42 patients who died, 28 had heart failure, 8 had sudden death and 6 were diagnosed with acute coronary syndrome. A significant proportion of the patients who died were prescribed antiplatelet drugs (57%), beta-blockers (86%), diuretics (57%), angiotensin converting enzyme inhibitors (50%), aldosterone inhibitors (48%), angiotensin receptor-neprilysin inhibitors (16%), sodium-glucose cotransporter-2 (SGLT2) Inhibitors (7%) and digital (38%).

The patients were classified into two distinct groups: those who were surviving and mortality. No notable disparity in the demographic attributes of the two groups was observed (Table 1).

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Table 1. Baseline characteristics of study patients

Variable	All (n=218)	Survivors (n=176)	Nonsurvivors (n=42)	p value
Baseline characteristics				
Mean age (years)	56±10	55±9	59±11	0.249
Male/female	180/38	148/28	32/10	0.521
Hypertension	78 (36%)	66 (38%)	12 (29%)	0.608
Diabetes mellitus	38 (17%)	30 (17%)	8 (19%)	0.759
Coronary artery disease	178 (82%)	144 (82%)	34 (81%)	1.000
Heart rate (beats/minute)	76±12	75±18	80±16	0.131
Systolic blood pressure (mm Hg)	112±20	108±17	119±19	0.304
Diastolic blood pressure (mmHg)	79±18	82±14	70±12	0.105
Atrial fibrillation	22 (10%)	20 (11%)	2 (5%)	0.687
LVEF (%)	26 (10-40)	28 (10-40)	22 (10-40)	0.989
Laboratory findings				
C-reactive protein	0.8 (0.1-7.6)	0.45 (0.1-7.6)	3.1 (0.2-7.1)	<0.001
Albumin	4.4±0.4	4.4±0.4	4.1±0.6	0.044
C-reactive protein/albumin ratio	0.12 (0.02-2.1)	0.1 (0.02-1.7)	0.7 (0.07-2.1)	<0.001
C-reactive protein/albumin ratio>0.12	106 (49%)	66 (38%)	40 (95%)	<0.001
Fasting glucose (mg/dl)	94 (56-236)	94.5 (56-236)	93 (65-189)	0.629
Creatinine (mg/dl)	1.0±0.3	0.9±0.3	1.1±0.4	0.014
Sodium (mEq/L)	139±3	141±3	137±4	0.005
Potassium (mEq/L)	4.5±0.5	4.7±0.4	4.2±0.5	0.894
Hemoglobin (gr/dl)	13.9±1.9	14±2	13.3±2	0.138
BNP (pg/ml)	311 (35-3716)	185 (35-2734)	959 (40-3716)	<0.001
BNP>500 pg/ml	102 (53%)	78 (45%)	34 (90%)	0.001
Total cholesterol (mg/dl)	177 (78-362)	178 (78-362)	171 (78-315)	0.495
High-density lipoprotein cholesterol (mg/dl)	40±11	40±11	38±15	0.661
Low-density lipoprotein cholesterol (mg/dl)	108 (37-280)	108 (37-247)	104 (52-280)	0.466
Triglyceride (mg/dl)	126 (41-455)	131 (41-455)	111 (49-379)	0.129
Alanine aminotransferase (IU/L)	25 (6-608)	27 (7-293)	22 (6-608)	0.344
Aspartat aminotransferase (IU/L)	25 (12-283)	25 (13-219)	26 (12-283)	0.596
Medication				
Antiplatelet agents	108 (45%)	74 (42%)	24 (57%)	0.315
Beta-blockers	200 (92%)	164 (93%)	36 (86%)	0.371
ACE inhibitor/ARB	120 (55%)	99 (56%)	21 (50%)	0.990
Digoxine	92 (42%)	76 (43%)	16 (38%)	0.859
Diuretics	120 (55%)	96 (55%)	24 (57%)	1.000
ARNI	30 (13%)	23 (13%)	7 (16%)	0.541
SGLT-2 inhibitors	22 (10%)	19 (10%)	3 (7%)	0.745
Aldosterone antagonist	128 (59%)	108 (61%)	20 (48%)	0.367

Values are shown as mean±SD (n), Me (Q1–Q3) or % (n/N). LVEF: left ventricular ejection fraction, BNP: B-type natriuretic peptide, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, ARNI: angiotensin receptor-neprilysin inhibitors, SGLT-2: sodium-glucose cotransporter-2

The deceased individuals exhibited a comparatively lower age bracket in comparison to the cohort of survivors. The deceased patients exhibited decreased levels of sodium and elevated levels of creatinine and BNP. The study findings indicate that patients who succumbed to their condition exhibited a notably elevated CAR in comparison to those who survived [0.1 (0.02-1.7) vs. 0.7 (0.07-2.1), p<0.001]. The diagnostic performance of the CAR was assessed in conjunction with independent predictors of mortality through the utilization of Receiver Operating Characteristic (ROC) Curve analysis. The predictive value of the CAR for mortality was found to be greater than 0.12, with a sensitivity of 95% and a specificity of 63% (AUC: 0.824, 95% CI: 0.740-0.890) (Figure 1). A higher percentage of patients who experienced mortality exhibited a CRP/albumin ratio greater than 0.12 at the beginning of the study, in contrast to those who survived [66 patients (38%) vs. 40 patients (95%), p<0.001].

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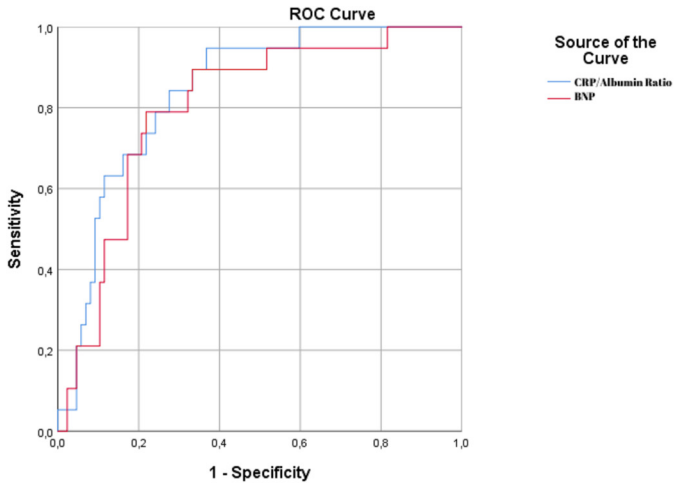

Figure 1. ROC Curve for BNP and C-reactive protein to Albumin Ratio to predict mortality. The optimal cut-off value predicting mortality for C-reactive protein/Albumin Ratio was >0.12 with a sensitivity of 95% and a specificity of 63% (AUC: 0.824, 95% CI: 0.740-0.890)

In individuals diagnosed with HF, it was observed that the CAR exhibited a negative correlation with the utilization of beta-blockers, sodium levels, hemoglobin levels, as well as the levels of alanine aminotransferase and aspartate aminotransferase. Conversely, a positive correlation was found between the CRP/albumin ratio and age, the presence of diabetes, and the levels of BNP (Table 2).

Table 3 displays the outcomes of both univariate and multivariate Cox regression analyses pertaining to mortality. In the univariate analysis, it was observed that the CAR, creatinine, sodium, and BNP levels exhibited significant predictive value for mortality. The CRP/albumin ratio (HR=2.125, p=0.045, 95% CI=1.017-4.443) and BNP level (HR=7.224, p=0.002, 95% CI=2.051-25.441) demonstrated a significant association with an elevated risk of mortality. These findings were obtained through multiple Cox regression analyses, which included variables that exhibited statistical significance in the univariate analysis and were found to be correlated with the CAR. The Kaplan-Meier analysis revealed disparate survival outcomes between the two groups based on the CRP/albumin ratio, with a threshold value of 0.12 (p<0.001) (Figure 2).

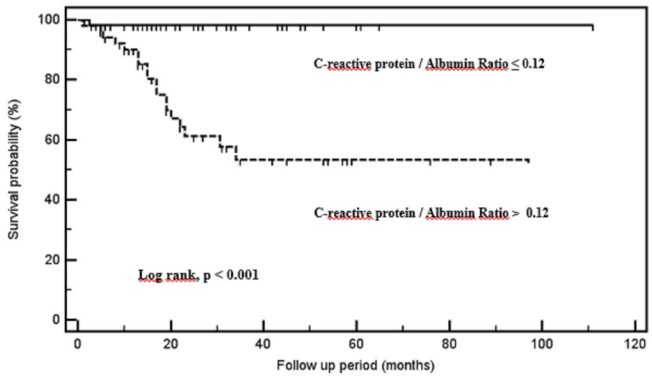

Figure 2: Kaplan Meier Curve for mortality

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

	R	P value
C-reactive protein	0.893	<0.001
Albumin	-0.201	0.036
Age (years)	0.310	0.001
Sodium (mEq/L)	-0.303	0.001
Hemoglobin (gr/dl)	-0.253	0.008
Presence of diabetes mellitus	0.235	0.014
Alanine aminotransferase (IU/L)	-0.262	0.006
Aspartat aminotransferase (IU/L)	-0.283	0.003
B-type natriuretic peptide (pg/ml)	0.236	0.015
B-type natriuretic peptide >500 pg/ml	0.344	<0.001
Beta-blockers usage	-0.271	0.002

Table 3. Univariate and multivariate analyses of mortality

	Univariate			Multivariate		
Variable	**p**	**HR**	**(95% CI)**	**p**	**HR**	**(95% CI)**
Statistically significant variables						
C-reactive protein/albumin ratio	0.002	2.800	1.437-5.457	0.045	2.125	1.017-4.443
Brain natriuretic peptide >500 pg/ml	0.003	9.356	2.718-32.202	0.002	7.224	2.051-25.441
Creatinine (mg/dL)	0.004	6.439	1.822-22.758			
Sodium (mEq/L)	0.001	0.840	0.754-0.935			
High-density lipoprotein cholesterol (mg/dl)	0.081	0.964	0.925-1.005			
Hemoglobin (gr/dl)	0.146	0.831	0.646-1.067			
Triglyceride (mg/dl)	0.190	0.995	0.988-1.002			
Aspartat aminotransferase (IU/L)	0.151	1.006	0.998-1.013			
Alanine aminotransferase (IU/L)	0.206	1.002	0.999-1.006			
Age (years)	0.250	1.020	0.986-1.054			
Variables which correlated with C-reactive protein/albumin Ratio >1.2						
Presence of diabetes mellitus	0.841	1.120	0.371-3.377			
Beta-blockers usage	0.491	1.572	0.435-5.683			

All the variables from Table 1 were examined and only those significant at a p<0.250 level and those with a correlated C-reactive protein/albumin ratio level are shown in univariate analysis. The multivariate cox regression model with backward stepwise method included all univariate predictors and those with correlated C-reactive protein/albumin ratio level. CI: confidence interval; HR: hazard ratio

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Discussion

Systemic inflammation is widely acknowledged as a prominent characteristic within the pathophysiology of chronic heart failure [11]. While CRP serves as an indicator of the presence of inflammation, hypoalbuminemia is a reflection of the overall burden of comorbidities, cachexia, and inflammatory status in patients with HF [12,13]. In our comprehensive study, a noteworthy finding emerged, indicating a significant correlation between an elevated CAR and the occurrence of cardiovascular mortality among outpatients diagnosed with HF. Moreover, our analysis demonstrated an independent association between levels of BNP and mortality. These findings shed light on the potential prognostic value of these biomarkers in predicting adverse cardiovascular outcomes in HF patients. The CRP/albumin ratio represents a promising avenue for exploration as a potential biomarker in the prediction of mortality among outpatients diagnosed with HF. This ratio holds the advantage of being readily accessible, straightforward to measure, and cost-effective. By assessing this ratio, clinicians may gain valuable insights into the prognosis of HF patients and their likelihood of experiencing mortality.

Hypoalbuminemia, a condition characterized by low levels of albumin in the blood, has been linked to harmful physiological processes that are frequently involved in the progression of heart failure [14]. Moreover, the existence of inflammation in patients with HF results in a reduction in levels of serum albumin, an acute phase reactant. This decline in serum albumin levels may have an adverse impact on the patient's prognosis. Prior research has demonstrated a noteworthy association between serum albumin concentrations below 3.5 g/dl and increased hospitalization rates among individuals with chronic HF due to cardiovascular complications. Moreover, it has been established that albumin plays a vital role in the survival of patients with acute HF. Consequently, measuring albumin levels can serve as a pivotal prognostic indicator in assessing the potential outcomes for these patients [14-16]. In a study conducted on patients diagnosed with chronic heart failure, the presence of hypoalbuminemia was demonstrated to be a significant prognostic factor for survival [17].

The investigation of the correlation between indicators of inflammation and HF holds significant importance for numerous compelling reasons. Several studies have been conducted to elucidate the biological significance of inflammatory markers in the advancement of HF. The pathogenesis of HF syndrome has been elucidated, with evidence supporting the role of proinflammatory cytokines in mediating its physiological effects across diverse circumstances [18]. The aforementioned conditions encompass pulmonary edema, left ventricular remodeling, myocyte hypertrophy, apoptosis-induced myocyte loss, and endothelial dysfunction. Moreover, a clear association has been established between the expression of cytokines and a decline in the New York Heart Association functional classification [19]. This bears resemblance to the effects observed in neurohormones like angiotensin II and norepinephrine, which are thought to exert a substantial influence on the advancement of heart failure. Simultaneously, a growing body of research is highlighting the existence of significant interactions between inflammatory components and neurohormonal systems [17,18]. There is also a suggestion that conventional therapies utilized in the treatment of heart failure may potentially exert their effects through the regulation of proinflammatory cytokines [20]. At present, it is evident that CRP stands out as the most suitable inflammatory marker for the evaluation of inflammation [21]. Elevated CRP levels have been observed to be correlated with an unfavorable prognosis in individuals who have received a diagnosis of HF [22]. Furthermore, it has been postulated that increased levels of CRP may serve as prognostic indicators for the initiation of HF in individuals exhibiting heightened risk factors for HF [23]. The superior prognostic value of the CAR, as compared to CRP or albumin alone, has been demonstrated in multiple cases [24]. In our comprehensive study, it was determined that the CRP/albumin ratio exhibited superior predictive accuracy when compared to the individual measurements of CRP and albumin levels. A significant correlation has been observed between the CAR and the risk of mortality in outpatients diagnosed with HF. Moreover, it has been determined that the CAR serves as a crucial independent predictor of mortality in individuals suffering from HF. The identification of heightened levels of inflammatory mediators in the progression of heart failure amidst a backdrop of chronic inflammation is expected to continue piquing interest. The question of whether these mediators hold potential as clinical biomarkers, capable of furnishing diagnostic, prognostic, and/or therapeutic insights for patients with heart failure, remains a subject of significance.

BNP secreted into the circulation in response to increased cardiac wall stress is a reliable biomarker used in the diagnosis and follow-up of HF patients. The relationship between BNP, which has prognostic importance in HF patients, and mortality has been demonstrated in previous studies [25]. In our study, it was observed that BNP has a prognostic value for mortality in patients with HF and a significant association with CAR.

Conclusion

The findings of our study have revealed that the CAR could potentially serve as a prognostic marker for mortality among individuals diagnosed with HF who receive outpatient care. Importantly, this association remains significant even after accounting for various other clinical and laboratory factors. The utilization of the CAR, a readily available and cost-effective measure in outpatient clinics specializing in HF, holds promise for its application in patient monitoring and the evaluation of optimal treatment approaches.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The study was commenced after receiving local ethics committee approval, numbered 2023.10.11.

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