Original article

The Relationship between the C-reactive Protein to Albumin Ratio and Three-Month Mortality in Hospitalized Patients with Heart Failure

Željka Dragila [1, 2], Lea Maršić [2,3], Anamaria Mikolčić [1], Romana Marušić [2, 4], Lana Maričić [2,5]

1 Department of Emergency Medicine, University Hospital Centre Osijek, Osijek, Croatia
2 Faculty of Medicine, Josip Juraj Strossmayer University, Osijek, Croatia
3 Department of Emergency Medicine, General Hospital Našice, Našice, Croatia
4 Department of Internal Medicine, National Memory Hospital Vukovar, Vukovar, Croatia
5 Department of Cardiology, Department of Internal Medicine, University Hospital Centre Osijek, Osijek, Croatia

*Corresponding author: Željka Dragila, zeljka.dragila5@gmail.com

Abstract

Aim of the study: This study aimed to investigate the association between the C-reactive protein (CRP) to albumin ratio and three-month mortality status (survived vs. died) after hospitalization for heart failure.

Methods: Patients hospitalized for heart failure at the Department of Cardiology, University Hospital Centre Osijek, over a 10-month period were included.

Results: A total of 145 patients were included, with 67 (46.2%) male and 78 (53.8%) female. The median age was 74 years (interquartile range 65–82 years). The most common comorbidities were hypertension (83.4%) and atrial fibrillation (58.6%). Patients treated with a mineralocorticoid receptor antagonist (P = 0.02) and furosemide (P = 0.04) had a significantly higher CRP/albumin ratio. The CRP/albumin ratio showed a significant positive correlation with neutrophil percentage, red cell distribution width, N-terminal pro-B-type natriuretic peptide, and urate concentration, and a significant negative correlation with diastolic arterial pressure, lymphocyte percentage, hemoglobin, prothrombin time, and sodium concentration. An elevated CRP/albumin ratio was associated with higher mortality during the three-month follow-up (P = 0.04). Higher mortality was also observed in patients with chronic obstructive pulmonary disease, those receiving a mineralocorticoid receptor antagonist and furosemide, lower systolic and diastolic blood pressure, and higher urea, creatinine, and urate concentrations.

Conclusion: The CRP/albumin ratio shows a stronger association with three-month mortality status (survived vs. died) in hospitalized heart failure patients than CRP or albumin individually.

(Dragila Ž, Maršić L, Mikolčić A, Marušić R, Maričić L. The Relationship between the C-reactive Protein to Albumin Ratio and Three-Month Mortality in Hospitalized Patients with Heart Failure. SEEMEDJ 2026; 10(1); 1-14)

Received: Sep 24, 2025; revised version accepted: Feb 10, 2026; published: Mar 23, 2026

KEYWORDS: albumin; C-reactive protein; heart failure; survival

Introduction

Heart failure is a complex clinical syndrome that places a significant burden on healthcare systems due to its high prevalence, risk of rehospitalization, and mortality. In developed countries, the prevalence of heart failure is 1 to 2% of the adult population (1). There are three types based on the ejection fraction (EF) of the left ventricle: heart failure with reduced EF (< 40%, HFrEF), heart failure with mildly reduced EF (40–49%, HFmrEF), and heart failure with preserved EF (≥ 50%, HFpEF) (2).

C-reactive protein (CRP), a positive acute-phase inflammatory protein, and albumin, a negative acute-phase protein, have been studied as possible prognostic factors in various diseases, including cardiovascular diseases. The combination of these two biomarkers can serve as a stronger predictor of mortality in patients with sepsis, malignancy, and cardiovascular disease. Studies have shown that CRP interferes with fibrinolysis, activates the complement system, and increases monocyte collagen degradation. It may also be associated with macrophage low-density lipoprotein uptake and their subsequent transformation into foam cells. Conversely, hypoalbuminemia is associated with endothelial dysfunction and increased blood viscosity (3–6).

Inflammatory processes play an important role in the pathophysiology of heart failure, and the characteristics of these processes differ in HFpEF and HFrEF. HFpEF results from chronic systemic inflammation – such as that caused by hypertension, diabetes mellitus, and obesity – which leads to endothelial dysfunction and increased oxidative stress. In contrast, HFrEF is caused by direct myocardial injury from ischemia or myocarditis, which ultimately triggers an inflammatory response, resulting in ventricular dilatation and focal fibrosis (eccentric hypertrophy) (7).

The combination of systemic inflammation markers, such as the CRP/albumin ratio, may serve as a better prognostic factor in heart failure patients than these indicators individually. This study aimed to examine the association between the CRP/albumin ratio and three-month mortality status (survived vs. died) in patients hospitalized for heart failure.

Patients and methods

Study design

This research is a retrospective cohort study with follow-up of patients treated at the Department of Cardiology, University Hospital Centre Osijek, Croatia. The study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The research was approved by the Ethics Committee of the Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek (KLASA: 602-04/20-08/07; URBROJ: 2158-61-07-20-183).

Patients

The study included patients treated for heart failure at the Department of Cardiology, University Hospital Centre Osijek over a period of 10 months. Patients with acute myocardial infarction and active malignant disease were excluded.

Methods

Demographic and clinical data were collected from patients' medical histories using the hospital information system. Data collected included age, gender, comorbidities (hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and atrial fibrillation), heart rate at admission, number of prior hospitalizations, and therapy the patient was taking upon admission (beta blocker, angiotensin-converting enzyme [ACE] inhibitor, sacubitril/valsartan, mineralocorticoid receptor antagonist [MRA], diuretic, calcium channel blocker, antiplatelet, and anticoagulant therapy), as well as three-month mortality status (survived vs. died) after hospitalization for heart failure. Laboratory findings included levels of leukocytes, neutrophils, lymphocytes,

erythrocytes, red blood cell distribution width (RDW), hemoglobin, creatinine, urate, CRP, albumin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), sodium, and potassium. The CRP/albumin ratio was calculated by dividing serum CRP concentration (mg/L) by serum albumin concentration (g/L), using laboratory values obtained at hospital admission. Echocardiographic findings used for this study included left ventricular ejection fraction (EF), left atrium diameter, left ventricular diameter in diastole and systole, and presence of aortic stenosis, mitral regurgitation, and tricuspid regurgitation. Patients were divided into groups based on three-month mortality status (survived vs. died) after hospitalization for heart failure and into groups according to left ventricular EF: patients with HFrEF (EF < 40%), patients with HFmrEF (EF 40–50%), and patients with HFpEF (EF ≥ 50%).

Statistical analysis

Categorical data were presented as absolute and relative frequencies. Differences in categorical variables were tested with the χ^2 test. The normality of the distribution of numerical variables was tested with the Shapiro-Wilk test. Numerical data are described by median and interquartile range. Differences in continuous variables between two groups were analyzed using the Mann–Whitney U test. In accordance with biomedical reporting guidelines, the P value is accompanied by the absolute difference between groups, estimated using the Hodges–Lehmann method, together with the corresponding 95% confidence interval. The association of variables was assessed by the Spearman correlation coefficient ρ (rho). Missing data were handled using complete-case analysis. No imputation methods were applied. All P values are two-sided. The significance level was set at alpha = 0.05. The statistical program MedCalc Statistical Software version 19.1.7 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) was used for statistical analysis.

Results

The CRP/albumin ratio

The study included 145 patients, of whom 67 (46.2%) were male and 78 (53.8%) were female. The median age was 74 years (interquartile range 65–82 years).

Table 1. The relationship between the C-reactive protein to albumin ratio with the patient's gender and comorbidities

		C-reactive protein/albumin Median (Interquartile range)	P*	Total N (%)
Gender	Male	2.98 (1.49 – 6.88)	0.64	67 (46.2)
	Female	3.33 (1.3 – 6.27)		78 (53.8)
Comorbidities				
Hypertension	Yes	3.32 (1.38 – 6.84)	0.79	121 (83.4)
	No	3.36 (1.46 – 6.02)		24 (16.6)
Diabetes mellitus	Yes	4.33 (1.99 – 8)	0.09	45 (31)
	No	2.87 (1.28 – 6.36)		100 (69)
Coronary artery disease	Yes	3.51 (1.75 – 6.56)	0.31	49 (33.8)
	No	2.97 (1.2 – 6.98)		96 (66.2)
Atrial fibrillation	Yes	3.32 (1.3 – 6.56)	0.72	85 (58.6)
	No	3.23 (1.42 – 6.86)		60 (41.4)
COPD	Yes	3.88 (1.43 – 9.4)	0.54	20 (13.8)
	No	3.21 (1.39 – 6.45)		125 (86.2)
Aortic stenosis	Yes	4.72 (2.27 – 9.7)	0.15	34 (23.4)
	No	2.87 (1.28 – 6.4)		111 (76.6)
Total				145 (100)

COPD = Chronic obstructive pulmonary disease
* Mann Whitney U test

The most common comorbidities were hypertension (83.4%) and atrial fibrillation (58.6%). There was no significant difference in the CRP/albumin ratio between male and female patients. Furthermore, the CRP/albumin ratio did not differ among patients with different comorbidities (Table 1).

The most frequently used therapies were beta blockers (69%), ACE inhibitors (60%), and furosemide (58.6%). The CRP/albumin ratio was significantly higher in patients receiving MRA (Mann-Whitney U test, P = 0.02) and in those treated with furosemide (Mann-Whitney U test, P = 0.04) (Table 2).

Table 2. The relationship between the C-reactive protein to albumin ratio with the therapy that the patients were taking before the admission for heart failure

		C-reactive protein/albumin Median (Interquartile range)	HL difference	95% CI (lower; upper)	P*†	Total N (%)
Beta blocker	Yes	3.49 (1.48 – 7.75)	0.47	-38.59; 31.75	0.36	100 (69)
	No	2.79 (1.38 – 5.11)				45 (31)
ACE inhibitor	Yes	2.98 (1.37 – 6.73)	-0.01	-36.30; 33.19	0.99	87 (60)
	No	3.4 (1.44 – 6.56)				58 (40)
MRA	Yes	4.63 (2.16 – 8.8)	1.37	-33.23; 34.57	**0.02**	46 (31.7)
	No	2.79 (1.2 – 5.95)				99 (68.3)
Sacubitril/valsartan	Yes	3.24 (1.65 – 5.22)	0.01	-36.51; 19.45	0.99	16 (11)
	No	3.34 (1.36 – 6.91)				129 (89)
Loop diuretic (furosemide)	Yes	3.62 (1.71 – 8.5)	1.03	-44.77; 32.24	**0.04**	85 (58.6)
	No	2.39 (1.18 – 4.85)				60 (41.4)
Other diuretics‡	Yes	2.79 (1.25 – 4.78)	-0.57	-34.22; 45.97	0.33	27 (18.6)
	No	3.5 (1.44 – 7.6)				118 (81.4)
Calcium channel blocker§	Yes	1.99 (1.2 – 4.76)	-0.86	-32.77; 44.89	0.12	29 (20)
	No	3.53 (1.45 – 7.75)				116 (80)
Antiaggregation therapy	Yes	4.88 (1.6 – 9.21)	0.81	-34.06; 32.58	0.18	40 (27.6)
	No	3.16 (1.3 – 5.97)				105 (72.4)
Anticoagulation therapy¶	Yes	3.47 (1.71 – 5.97)	0.08	-40.09; 14.16	0.91	49 (33.8)
	No	2.85 (1.35 – 8.28)				96 (66.2)
TOTAL						145 (100)

HL= Hodges–Lehmann; ACE inhibitor = Angiotensin-converting enzyme inhibitors; MRA = Mineralocorticoid receptor antagonist

* Bold denotes statistical significance

† Mann Whitney U test; ‡ Indapamide, Hydrochlorothiazide; § Except verapamil; ¶ Low molecular weight heparin, Novel oral anticoagulants. Warfarin

The median systolic pressure was 128 mmHg (interquartile range 110–150 mmHg) and the median diastolic pressure was 80 mmHg (interquartile range 70–88 mmHg). The median NT-proBNP was 6530 pg/L (interquartile range 2681–12407 pg/L). A significant positive

correlation was observed between the CRP/albumin ratio and neutrophil percentage, RDW, NT-proBNP, urates, and furosemide dose. A significant negative correlation was observed with diastolic arterial pressure, lymphocyte percentage, hemoglobin levels, prothrombin time, and sodium levels (Table 3).

Mitral (97.9%) and tricuspid (93.8%) regurgitation were present in most patients on transthoracic echocardiography, while aortic stenosis was present in fewer patients (23.4%). The median left ventricular EF was 35% (interquartile range 30–45%), ranging from 15% to 79%. No significant association was found between the CRP/albumin ratio and left ventricular EF. There was no significant correlation between the CRP/albumin ratio and left atrial diameter, left ventricular diameter, or TAPSE.

Table 3. Spearman's correlation coefficient (Rho) of the C-reactive protein to albumin ratio with other laboratory values

	Spearman's correlation coefficient (Rho) of the C-reactive protein to albumin ratio			
	Rho	95% confidence interval		P*
		From	To	
Age (years)	0.008	-0.155	0.171	0.93
Heart rate (/min)	-0.035	0.197	0.128	0.67
Systolic blood pressure (mmHg)	-0.158	-0.313	0.005	0.06
Diastolic blood pressure (mmHg)	-0.227	-0.376	-0.066	**0.006**
Leukocytes (x10^9/L)	0.079	-0.085	0.239	0.34
Neutrophils (%)	0.182	0.013	0.341	**0.04**
Lymphocytes (%)	-0.240	-0.394	-0.074	**0.005**
Erythrocytes (x10^12/L)	-0.158	-0.313	0.005	0.06
RDW (%)	0.361	0.211	0.495	**<0.001**
Haemoglobin (g/L)	-0.172	-0.326	-0.009	**0.04**
Thrombocytes (x10^9/L)	0.154	-0.009	0.309	0.06
Prothrombin time (s)	-0.178	-0.332	-0.016	**0.03**
Glucose (mmol/L)	-0.101	-0.260	0.063	0.23
NT-proBNP (pg/L)	0.238	0.079	0.386	**0.004**
Blood urea nitrogen(mmol/L)	0.107	-0.057	0.265	0.20
Creatinine (µmol/L)	0.122	-0.042	0.280	0.14
Urate (µmol/L)	0.282	0.109	0.437	**0.002**
Sodium (mmol/L)	-0.190	-0.343	-0.028	**0.02**
Potassium (mmol/L)	0.132	-0.032	0.289	0.11
Furosemide dose (mg/day)	0.171	0.009	0.325	**0.04**

RDW = Red blood cell distribution width; NT-proBNP = N-terminal pro b-type natriuretic peptide
* Bold denotes statistical significance

More than half of the patients were rehospitalized (52.4%). No significant difference in the CRP/albumin ratio was found between patients for whom it was their first hospitalization for heart failure (median 2.59; interquartile range 1.08–6.84) and those who were rehospitalized (median 3.53; interquartile range 1.76–6.64). Of 141 patients, 35 (24.8%) died in the three months after hospitalization for heart failure. These patients had a significantly higher CRP/albumin ratio (median 4.3; interquartile range 2.2–8.61) compared to those who survived (median 2.69; interquartile range 1.21–5.94) (Mann-Whitney U test, P = 0.04). The distribution of the CRP/albumin ratio according to three-month mortality status is shown in Figure 1.

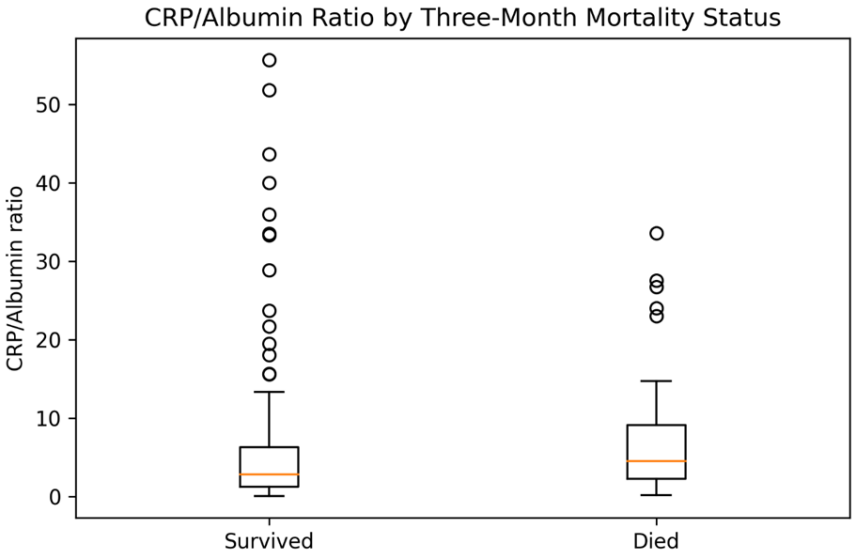

Figure 1. Distribution of the C-reactive protein (CRP)/albumin ratio according to three-month mortality status after hospitalization for heart failure

The box represents the interquartile range, the horizontal line indicates the median and whiskers represent the range of values. Circles represent individual outlier values.

Table 4. The relationship of the three-month mortality status (survived vs. died) after hospitalization with gender, patient comorbidities, number of hospitalizations and ejection fraction

		Three-month mortality status after hospitalization N (%)		*P**ǂ	Total N (%)
		YES	NO		
Gender	Male	46 (70.8)	19 (29.2)	0.26	65 (46.1)
	Female	60 (78.9)	16 (21.1)		76 (53.9)
Comorbidities					
Hypertension	Yes	87 (74.4)	30 (25.6)	0.62	117 (83)
	No	19 (79.2)	5 (20.8)		24 (17)
Diabetes mellitus	Yes	36 (83.7)	7 (16.3)	0.12	43 (30.5)
	No	70 (71.4)	28 (28.6)		98 (69.5)
Coronary artery disease	Yes	39 (79.6)	10 (20.4)	0.38	49 (34.8)
	No	67 (72.8)	25 (27.2)		92 (65.2)
Atrial fibrillation	Yes	58 (70.7)	24 (29.3)	0.15	82 (58.2)
	No	48 (81.4)	11 (18.6)		59 (41.8)
COPD	Yes	11 (55)	9 (45)	**0.02**	20 (14.2)
	No	95 (78.5)	26 (21.5)		121 (85.8)
Aortic stenosis	Yes	23 (69.7)	10 (30.3)	0.41	33 (23.4)
	No	83 (76.9)	25 (23.1)		108 (76.6)
First hospitalization	Yes	55 (82.1)	12 (17.9)	0.07	67 (47.5)
	No	51 (68.9)	23 (31.1)		74 (52.5)
Ejection fraction	HFrEF	67 (75.3)	22 (24.7)	0.72	89 (63.1)
	HFmrEF	22 (71)	9 (29)		31 (22)
	HFpEF	17 (81)	4 (19)		21 (14.9)
Total		106 (75.2)	35 (24.8)		141 (100)

COPD = Chronic obstructive pulmonary disease; HFrEF = heart failure with reduced ejection fraction (<40%); HFmrEF = heart failure with mildly reduced ejection fraction (40-49%), HFpEF = heart failure with preserved ejection fraction (≥50%)

* Bold denotes statistical significance

ǂ $\chi 2$ test

Three-month mortality status (survived vs. died) after hospitalization for heart failure

Three-month mortality status (survived vs. died) data were available for 141 patients, of whom 35 (24.8%) died during this period. The groups of patients who died and those who survived during the three months did not differ significantly regarding gender, number of prior hospitalizations, or left ventricular EF. Patients who died during the three months had a significantly higher prevalence of chronic obstructive pulmonary disease (COPD), 25.7% (χ 2 test, P = 0.02), compared to 10.4% (Table 4).

No significant correlation was found between the use of ACE inhibitors or beta blockers and three-month mortality status (survived vs. died). MRA (χ 2 test, P = 0.001) and furosemide (χ 2 test, P = 0.04) therapy before admission were present in significantly more patients who died than in those who survived. Calcium channel blockers, except verapamil, were used significantly more often in the therapy of patients who survived (96.3%) than in those who did not (χ 2 test, P = 0.005) (Table 5).

Table 5. The relationship of the three-month mortality status (survived vs. died) after hospitalization with the therapy that the patients were taking before the admission for heart failure

		Three-month mortality status after hospitalization N (%)		*P**†	Total N (%)
		YES	NO		
Beta blocker	Yes	70 (71.4)	28 (28.6)	0.12	98 (69.5)
	No	36 (83.7)	7 (16.3)		43 (30.5)
ACE inhibitor	Yes	61 (73.5)	22 (26.5)	0.58	83 (58.9)
	No	45 (77.6)	13 (22.4)		58 (41.1)
MRA	Yes	26 (57.8)	19 (42.2)	**0.001**	45 (31.9)
	No	80 (83.3)	16 (16.7)		96 (68.1)
Sacubitril/valsartan	Yes	12 (75)	4 (25)	0.99	16 (11.3)
	No	94 (75.2)	31 (24.8)		125 (88.7)
Loop diuretic (furosemide)	Yes	58 (69)	26 (31)	**0.04**	84 (59.6)
	No	48 (84.2)	9 (15.8)		57 (40.4)
Other diuretics‡	Yes	21 (80.8)	5 (19.2)	0.47	26 (18.4)
	No	85 (73.9)	30 (26.1)		115 (81.6)
Calcium channel blocker§	Yes	26 (96.3)	1 (3.7)	**0.005**	27 (19.1)
	No	80 (70.2)	34 (29.8)		114 (80.9)
Antiaggregation therapy	Yes	29 (72.5)	11 (27.5)	0.64	40 (28.4)
	No	77 (76.2)	24 (23.8)		101 (71.6)
Anticoagulation therapy¶	Yes	34 (70.8)	14 (29.2)	0.39	48 (34)
	No	72 (77.4)	21 (22.6)		93 (66)
Total		106 (75.2)	35 (24.8)		141 (100)

ACE inhibitor = Angiotensin-converting enzyme inhibitors; MRA = Mineralocorticoid receptor antagonist
* Bold denotes statistical significance
† χ 2 test
‡ Indapamide, Hydrochlorothiazide; § Except verapamil; ¶ Low molecular weight heparin, Novel oral anticoagulants. warfarin

The median age of patients with a fatal outcome was 75 years (interquartile range 66–84 years). Patients who survived had significantly higher systolic (Mann-Whitney U test, P = 0.03) and

diastolic blood pressure (Mann-Whitney U test, P = 0.008). Urea (Mann-Whitney U test, P = 0.04) and creatinine levels (Mann-Whitney U test, P = 0.003) were significantly lower in patients who survived. No significant difference was observed in sodium and potassium concentrations regarding patient outcome (Table 6). No significant association was observed between echocardiographic features and three-month mortality status (survived vs. died) after hospitalization.

Table 6. The relationship of the three-month mortality status (survived vs. died) after hospitalization with laboratory values

	Three-month mortality status after hospitalization Median (Interquartile range)		HL difference	95% CI (lower; upper)	*P**†
	yes	no			
Age (years)	73.5 (64 – 81)	75 (66.3 – 84)	-2	-34; 28	0.28
Heart rate (/min)	100 (78 – 120)	100 (76.5 – 112.5)	4	-83; 91.28	0.52
Systolic blood pressure (mmHg)	130 (112 – 157)	120 (102.3 – 140)	10	-55;86	**0.03**
Diastolic blood pressure (mmHg)	80 (70 – 90)	72 (60 – 80)	9	-35; 48	**0.008**
Leukocytes (x10^9/L)	8.7 (7.2 – 12)	8.7 (7.1 – 10.5)	0.2	-7.13; 11.8	0.63
Neutrophils (%)	73 (66 – 80)	70 (66 – 80)	1	-46; 27	0.67
Lymphocytes (%)	16.5 (11 – 22)	17 (10 – 24)	0	-21; 47	0.11
Erythrocytes (x10^12/L)	4.4 (4.1 – 4.8)	4.3 (3.8 – 4.9)	0.11	-2.29; 1.98	0.49
RDW (%)	14.6 (13.6 – 16)	14.9 (13.9 – 16.2)	-0.2	-5.3; 8.6	0.52
Haemoglobin (g/L)	127 (114 – 141)	127 (115.5 – 139)	0	-56; 60	0.92
Thrombocytes (x10^9/L)	202 (169 – 273)	223 (188 – 246.8)	-6	-169; 233.55	0.71
Prothrombin time (s)	0.7 (0.4 – 0.9)	0.6 (0.4 – 0.8)	0.08	-0.71; 0.88	0.21
Glucose (mmol/L)	8 (6.3 – 10.7)	6.9 (5.9 – 8.9)	0.7	-12.4; 13.2	0.14
NT-proBNP (pg/L)	6098.5 (2436 – 12291)	7591 (3817.8 – 17258)	-1547	-62359; 35733	0.18
Blood urea nitrogen (mmol/L)	9.1 (6.9 – 12.7)	12.3 (7.8 – 17.8)	-2	-31.7; 18.8	**0.04**
Creatinine (µmol/L)	100.5 (78 – 127)	130 (98 – 154)	-19	-70.9; -2	**0.003**
C-reactive protein (mg/L)	8.9 (4.7 – 21.2)	14.1 (7.4 – 29.1)	-15.4	-61; -5.4	0.06
Urate (µmol/L)	474 (387.5 – 621)	586.5 (433 – 751)	-0.9	-51; 12	**0.02**
Albumin (g/L)	36 (32.6 – 38.9)	35.1 (32.8 – 37.4)	1	-1; 2	0.24
Sodium (mmol/L)	139 (137 – 141)	139 (135.3 – 140)	1	-1; 2	0.11
Potassium (mmol/L)	4.1 (3.8 – 4.5)	4.4 (3.8 – 4.8)	-0.1	-0.4; 0	0.28
Furosemide dose (mg/day)	20 (0 – 40)	40 (5 – 80)	0	-80; 40	**0.03**

HL= Hodges–Lehmann; RDW = Red blood cell distribution width; NT-proBNP = N-terminal pro b-type natriuretic peptide
* Bold denotes statistical significance
† Mann Whitney U test

Discussion

This study investigated the association between the CRP/albumin ratio and three-month mortality status (survived vs. died) following hospitalization for heart failure. The primary aim was to identify biomarkers that could aid in prognostication and facilitate timely therapeutic interventions. Patients who died within three

months of hospitalization for heart failure had significantly elevated CRP/albumin ratios.

Heart failure is frequently accompanied by multiple comorbidities, many of which contribute to a poor prognosis. Among these, the most pronounced difference in the CRP/albumin ratio was observed between diabetic and non-diabetic patients, although this difference did not reach statistical significance. While no significant differences in short-term survival were found with respect to most comorbid conditions, COPD was notably associated with worse outcomes. In the DIAMOND study, which analyzed 5,491 patients hospitalized for heart failure, diabetes was shown to increase the risk of mortality: one-year mortality among diabetic patients was 31%, and 50% had died within three years. In comparison, the three-month mortality rate for diabetic patients in our study was 16% (8). The prevalence of COPD among patients with heart failure in large-scale studies ranges from 10% to 20%, aligning with our findings. Similarly, in a study by Staszewsky et al. involving 5,010 patients with heart failure, all-cause mortality was significantly higher among those with COPD – a result consistent with our observations (9).

In our study, more than half of the patients were receiving furosemide therapy. These patients had a significantly higher CRP/albumin ratio compared to those not receiving furosemide, and a significantly greater proportion of them died within three months. Furthermore, a significant positive correlation was observed between the furosemide dose and the CRP/albumin ratio. Furosemide is primarily used for symptom relief in patients with volume overload, and its use prior to hospitalization likely reflects more advanced disease and greater hemodynamic compromise (10). The observed association between furosemide therapy and higher mortality should be interpreted with caution, as it most likely reflects confounding by indication and greater disease severity rather than a negative effect of furosemide itself.

Similarly, patients who were receiving MRAs at the time of admission had significantly higher CRP/albumin ratios and significantly worse outcomes. The indication for MRA therapy is a left ventricular EF of less than 35% that does not respond adequately to dual therapy with ACE inhibitors and beta-blockers (2). This suggests that these patients had more advanced and prolonged disease, which, along with other contributing factors, negatively impacted their prognosis. Of the 46 patients receiving MRAs, 41 (89.1%) were rehospitalized. In a study by Ford et al., the risk of poor outcomes increased by 7% to 9% for every two additional years lived with heart failure (11). The association between MRA use and increased mortality should not be interpreted as evidence of harm, but rather as a marker of advanced heart failure.

An important goal in heart failure management is the control of hypertension. Persistent elevation of systolic and diastolic blood pressure is a known negative prognostic factor in cardiovascular disease and a major risk factor for the development of heart failure (12). In this study, a significant negative correlation was observed between diastolic pressure and the CRP/albumin ratio, along with significantly worse survival in patients who presented with lower median systolic and diastolic pressures at admission. Higher systolic pressure upon admission may reflect better myocardial contractile function and tissue perfusion, indicative of a more robust physiological response to hemodynamic stress. Conversely, low diastolic pressure may impair coronary artery perfusion during diastole (13). Sherwood et al. examined the relationship between cardiovascular reactivity to psychological stress and five-year outcomes in patients with heart failure. They found that patients with higher blood pressure reactivity had 50% fewer adverse events, including rehospitalization and death (14). Their findings suggest that the ability to mount an adequate pressor response to stress is indicative of greater left ventricular functional reserve, potentially explaining the observed lower mortality in such patients. Conversely, lower blood pressure at admission is associated with increased mortality, consistent with the results of this study.

The prevalence of anemia in patients with heart failure varies but generally ranges from 14% to 61% among hospitalized individuals (15). In this study, hemoglobin concentrations were significantly negatively correlated with the CRP/albumin ratio; however, no significant differences in hemoglobin levels were observed between survivors and non-survivors. Red cell distribution width, a marker of anisocytosis, is a biomarker whose prognostic relevance has been extensively studied in recent years across a range of diseases (16). Many of the underlying mechanisms associated with elevated RDW also contribute to the pathophysiology of heart failure. Accordingly, the significant positive correlation between RDW and the CRP/albumin ratio observed in this study supports these shared mechanisms.

Estimates suggest that 40% to 50% of patients with heart failure also have chronic kidney disease as part of the cardiorenal syndrome (17). In our study, patients who experienced a fatal outcome within the three-month follow-up period had significantly higher levels of both urea and creatinine. These findings are consistent with those of Singh et al., who analyzed 7,394 patients hospitalized for heart failure and demonstrated that elevated urea and creatinine levels at admission were predictive of increased mortality during the first year post-discharge. Notably, urea levels above 11.1 mmol/L were associated with a 4.6-fold increase in mortality risk (18). In comparison, the median urea concentration among patients with a fatal outcome in our study was 12.3 mmol/L.

A linear relationship was observed between mortality and uric acid concentrations exceeding the threshold value of 416 µmol/L. Elevated uric acid levels in patients with heart failure result from both decreased renal clearance and increased production (19). In this study, a significant positive correlation was found between uric acid concentration and the CRP/albumin ratio, likely reflecting an underlying state of systemic inflammation. Furthermore, patients who experienced a fatal outcome within the three-month follow-up period had significantly higher uric acid levels, with a median value of 586.5 µmol/L.

The prognostic utility of CRP and albumin as biomarkers of inflammation and clinical outcome in heart failure is the subject of ongoing investigation. Pellicori et al. examined the association between CRP concentrations and mortality in 3,756 patients with heart failure, regardless of ejection fraction (20). Over a median follow-up period of 53 months, 48% of patients died – substantially higher than the 25% mortality rate observed in our study, which is expected given the shorter three-month follow-up period. In that study, elevated CRP levels were independently and significantly associated with increased all-cause and cardiovascular mortality. By contrast, our study did not find a significant difference in CRP concentrations between survivors and non-survivors at three months. The impact of serum albumin on mortality in heart failure was assessed by Gotsam et al. in a cohort of 5,779 patients, also irrespective of ejection fraction (21). They reported that low serum albumin levels were independently associated with reduced survival. In our study, however, no significant difference in albumin levels was observed between survivors and those who died within three months. When considered individually, CRP and albumin levels were not associated with three-month mortality in our cohort. However, the combined CRP/albumin ratio showed a significant association with patient outcomes: those who died had markedly higher ratios than those who survived. These findings suggest that the CRP/albumin ratio may provide additional diagnostic information in patients hospitalized for heart failure compared to CRP or albumin levels alone. However, these findings should be interpreted as associative rather than causal and do not imply independent prognostic value of the CRP/albumin ratio.

Limitations

This study has several limitations. First, its retrospective cohort design with follow-up limits the ability to infer causality between the CRP/albumin ratio and mortality. Second, the follow-up period was limited to three months, restricting conclusions about long-term outcomes. However, the study was designed to

assess early post-hospitalization mortality, which reflects acute disease severity and inflammatory status at admission. Several clinically important variables, such as body mass index, smoking status, dyslipidemia, and post-discharge management, were not available in the medical records and could not be included in the analysis. These variables may influence systemic inflammation and mortality risk, representing potential sources of residual confounding. Finally, due to the limited number of outcome events, multivariable analysis was not performed. Therefore, the CRP/albumin ratio cannot be considered an independent predictor of mortality, and the observed associations should be interpreted as exploratory.

Conclusion

This research was designed as a retrospective cohort study with follow-up to investigate the relationship between the CRP to albumin ratio and three-month mortality status (survived vs. died) in patients after hospitalization for heart failure. Since CRP is a positive acute-phase reactant and albumin is a negative acute-phase reactant, it was expected that the ratio would be elevated in patients who died, reflecting a greater state of inflammation associated with higher mortality, which was supported by our findings.

Acknowledgement. No acknowledgment.

Disclosure

Funding. No specific funding was received for this study.
Competing interests. None to declare.

References

1. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. Eur J Heart Fail. 2020; 22:1342-56. Available from: https://doi.org/10.1002/ejhf.1858

2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016; 37:2129–200. Available from: https://doi.org/10.1093/eurheartj/ehw128

3. Çağdaş M, Rencüzoğullari I, Karakoyun S, Karabağ Y, Yesin M, Artaç I, Iliş D, Çağdaş OS, Tezcan AH, Tanboğa HI. Assessment of relationship between C-reactive protein to albumin ratio and coronary artery disease severity in patients with acute coronary syndrome. Angiology. 2019; 70:361–8. Available from: https://doi.org/10.1177/0003319717743325

4. Yucel O, Günes H, Kerkütlüoglu M, Yılmaz MB. C-reactive protein/albumin ratio designates advanced heart failure among outpatients with heart failure. Int J Cardiovasc Acad. 2020; 6:51. Available from: https://doi.org/10.4103/IJCA.IJCA_49_19

5. Karabağ Y, Çağdaş M, Rencuzogullari I, Karakoyun S, Artaç İ, İliş D, Atalay E, Yesin M, Gursoy MO, Tanboğa HI. Relationship between C-reactive protein/albumin ratio and coronary artery disease severity in patients with stable angina pectoris. J Clin Lab Anal. 2018; 32:e22457. Available from: https://doi.org/10.1002/jcla.22457

6. Ranzani OT, Zampieri FG, Forte DN, Azevedo LCP, Park M. C-reactive protein/albumin ratio predicts 90-day mortality of septic patients. PLoS One. 2013; 8:e59321. Available from: https://doi.org/10.1371/journal.pone.0059321

7. Castillo EC, Vázquez-Garza E, Yee-Trejo D, García-Rivas G, Torre-Amione G. What is the role of the inflammation in the pathogenesis of heart failure? Curr Cardiol Rep. 2020; 22:139. Available from: https://doi.org/10.1007/s11886-020-01382-2

8. Lehrke M, Marx N. Diabetes mellitus and heart failure. Am J Cardiol. 2017; 120:37–47. Available from: https://doi.org/10.1016/j.amjcard.2017.05.014

9. Staszewsky L, Wong M, Masson S, Barlera S, Carretta E, Maggioni AP, Anand IS, Cohn JN, Tognoni G, Latini R. Prognostic role of chronic obstructive pulmonary disease in patients with heart failure: data from the Val-HeFT trial. J Card Fail. 2007; 13:797–804. Available from: https://doi.org/10.1016/j.cardfail.2007.07.012

10. Katta N, Balla S, Alpert MA. Does long-term furosemide therapy cause thiamine deficiency in patients with heart failure? Am J Med. 2016; 129:753.e7–753.e11. Available from: https://doi.org/10.1016/j.amjmed.2016.01.037

11. Ford I, Robertson M, Komajda M, Böhm M, Borer JS, Tavazzi L, Swedberg K. Top ten risk factors in chronic systolic heart failure: the SHIFT risk model. Int J Cardiol. 2015; 184:163–9. Available from: https://doi.org/10.1016/j.ijcard.2015.02.001

12. Kannan A, Janardhanan R. Hypertension as a risk factor for heart failure. Curr Hypertens Rep. 2014 ;16:447. Available from: https://doi.org/10.1007/s11906-014-0447-7

13. Torrente Iranzo S, Garcés Horna V, Josa Laorden C, Rubio Gracia J, Ruiz Laiglesia FJ, Sánchez Marteles M, Perez Calvo JI. Influence of blood pressure at the beginning of decompensations on prognosis of heart failure patients. Med Clin (Barc). 2017; 149:147–52. Available from: https://doi.org/10.1016/j.medcle.2017.07.017

14. Sherwood A, Hill LK, Blumenthal JA, Adams KF, Paine NJ, Koch GG, O'Connor CM, Johnson KS, Hinderliter AL. Blood pressure reactivity to stress is associated with outcomes in heart failure. Am Heart J. 2017; 191:82–90. Available from: https://doi.org/10.1016/j.ahj.2017.07.003

15. Shah R, Agarwal AK. Anemia in chronic heart failure: current concepts. Clin Interv Aging. 2013; 8:111–22. Available from: https://doi.org/10.2147/CIA.S27105

16. Ni Q, Wang X, Wang J, Chen P. The RDW-albumin ratio: a promising predictor of mortality in heart failure. Clin Chim Acta. 2022; 527:38–46. Available from: https://doi.org/10.1016/j.cca.2021.12.027

17. Schefold JC, Filippatos G, Hasenfuss G, Anker SD, von Haehling S. Heart failure and kidney dysfunction: mechanisms and management. Nat Rev Nephrol. 2016; 12:610–23. Available from: https://doi.org/10.1038/nrneph.2016.113

18. Singh G, Peterson EL, Wells K, Williams LK, Lanfear DE. Comparison of renal predictors for mortality after heart failure hospitalization. J Cardiovasc Med. 2012; 13:246–53. Available from: https://doi.org/10.2459/JCM.0b013e3283516767

19. Kumrić M, Borovac JA, Kurir TT, Božić J. Clinical implications of uric acid in heart failure: a review. Life (Basel). 2021; 11:53. Available from: https://doi.org/10.3390/life11010053

20. Pellicori P, Zhang J, Cuthbert J, Urbinati A, Shah P, Kazmi S, Clark AL, Cleland JGF. High-sensitivity CRP in chronic heart failure: characteristics and mortality. Cardiovasc Res. 2020; 116:91–100. Available from: https://doi.org/10.1093/cvr/cvz198

21. Gotsman I, Shauer A, Zwas DR, Tahiroglu I, Lotan C, Keren A. Low serum albumin predicts reduced survival in chronic heart failure. Clin Cardiol. 2019; 42:365–72. Available from: https://doi.org/10.1002/clc.23153.

Author contribution.

Acquisition of data: ŽD, LeM, AM, RM
Administrative, technical, or logistic support: LaM
Analysis and interpretation of data: ŽD, LaM
Conception and design: ŽD, LeM
Critical revision of the article for important intellectual content: LaM
Drafting of the article: ŽD, LeM, AM, RM
Final approval of the article: ŽD, LM
Guarantor of the study: ŽD, LaM
Statistical expertise: ŽD

Povezanost omjera C-reaktivnog proteina (CRP) i albumina s tromjesečnim preživljenjem nakon hospitalizacije zbog srčanog zatajivanja

Sažetak

Cilj: Ispitati povezanost omjera C-reaktivnog proteina (CRP) i albumina s tromjesečnim preživljenjem nakon hospitalizacije zbog srčanog zatajivanja.

Metode: U studiju su uključeni bolesnici hospitalizirani zbog srčanog zatajivanja na Zavodu za bolesti srca i krvnih žila Kliničkog bolničkog centra Osijek u razdoblju od 10 mjeseci.

Rezultati: U studiju je uključeno 145 bolesnika od kojih je bilo 67 (46,2 %) muškaraca i 78 (53,8 %) žena. Medijan dobi iznosio je 74 godine (interkvartilni raspon 65–82 godine). Najčešći komorbiditeti bili su arterijska hipertenzija (83,4 %) i fibrilacija atrija (58,6 %). Bolesnici liječeni antagonistom mineralokortikoidnog receptora (P = 0,02) i furosemidom (P = 0,04) imali su značajno viši omjer CRP-a i albumina. Uočena je značajna pozitivna korelacija omjera CRP-a i albumina s postotkom neutrofila, širinom distribucije volumena eritrocita, N-terminalnim pro-brain natriuretičkim peptidom, koncentracijom urata, dok je značajna negativna korelacija uočena s dijastoličkim arterijskim tlakom, postotkom limfocita, hemoglobinom, protrombinskim vremenom i koncentracijom natrija. Povišen omjer CRP-a i albumina bio je povezan s većom smrtnošću tijekom tromjesečnog praćenja (P = 0,04). Također, viša smrtnost uočena je kod bolesnika s kroničnom opstruktivnom plućnom bolesti, onih na terapiji antagonistom mineralokortikoidnog receptora i furosemidom, s nižim sistoličkim i dijastoličkim krvnim tlakom te višim koncentracijama uree, kreatinina i urata.

Zaključak: Omjer CRP-a i albumina pokazuje veću povezanost s tromjesečnim preživljenjem hospitaliziranih bolesnika zbog srčanog zatajivanje u odnosu na CRP i albumin pojedinačno.

Ključne riječi: albumin; C-reaktivni protein; preživljenje; srčano zatajivanje