The Relationship Between CRP to Albumin Ratio and Non Ischemic Cardiomyopathy in Atrial Fibrillation Patients

Ayca ARSLAN
hivda.arslan@hotmail.com
Kafkas University School of Medicine
Dogan ILIS
Kafkas University School of Medicine
Inanç ARTAC
Kafkas University School of Medicine
Muammer KARAKAYALI
Kafkas University School of Medicine
Timor OMAR
Kafkas University School of Medicine
Ezgi GUZEL
Kafkas University School of Medicine
Ozcan YAGCIBULUT
Dr. Ersin Arslan Training and Research Hospital
Yavuz KARABAG
Kafkas University School of Medicine
Ibrahim RENCUZOGULLARI
Kafkas University School of Medicine

Research Article

Keywords: heart failure, CRP, albumin, CRP albumin ratio, atrial fibrillation

Posted Date: December 2nd, 2024

DOI: https://doi.org/10.21203/rs.3.rs-5456454/v1

Additional Declarations: No competing interests reported.

Abstract

Introduction and Objectives

Heart failure(HF) poses a significant threat to morbidity, mortality, and overall quality of life. Early diagnosis in patients with atrial fibrillation(AFib) is crucial in managing this condition. While previous studies have demonstrated the association between HF, elevated C-reactive protein (CRP), and decreased serum albumin (SA) levels, there is a lack of investigation into the predictive capacity of the CRP to SA ratio(CAR) for diagnosing HF in patients with AFib.This study aims to elucidate the prognostic value of CAR in the diagnosis of HF patients with AFib.

Methods

This retrospective study comprised 279 patients with permanent AFib attending our outpatient clinic.The study population was categorized into two groups based on left ventricular ejection fraction(LVEF):patients with LVEF < 40% and those with LVEF ≥ 40%.

Results

In the study cohort,75 patients(26.9%) were identified with heart failure with reduced ejection fraction (HFrEF).Patients with HFrEF exhibited elevated levels of neutrophils, CRP and CAR, along with increased left ventricular end-diastolic diameter (LVEDD) and left atrial volume index (LAVI).Multivariate analyses demonstrated that LVEDD, LAVI, and CAR(OR:0.5, 95% CI: 0.38–0.67; P < 0.001) were independent predictors of HFrEF in patients with AFib.

Conclusion

CAR may be an easily accessible marker for diagnosing HF in AFib patients.

INTRODUCTION

Heart failure (HF), a prevalent chronic condition worldwide, is linked to increased mortality and morbidity rates, frequent hospitalizations, diminished quality of life, and compromised functional status [1]. Various clinical conditions, including ischemic heart disease, hypertension, valvular pathologies, and arrhythmias, can significantly contribute to the development of HF [2–4].

Atrial fibrillation (AFib) stands out as the most prevalent rhythm disorder among the adult population [5]. Previous studies have established its association with an elevated risk of stroke [6], cognitive dysfunction [7], and HF [8]. Although the role of inflammation has been previously demonstrated in the

onset and perpetuation of AFib [9, 10, 11], the specific impact of inflammatory status and the role of inflammatory markers in the development of HF in patients with AFib remain unclear.

Recent studies have shown that increased C-reactive protein (CRP) and low serum albumin (SA) levels can be used as biomarkers of systemic inflammation and are associated with adverse cardiovascular events [12, 13]. Furthermore, many studies have demonstrated that the CRP/SA ratio (CAR) is more sensitive than these two parameters separately in predicting systemic inflammatory status and adverse outcomes [12, 14]. However, the role of these inflammatory parameters in the diagnosis of HF in AFib patients is not clear. Therefore, this study aims to elucidate the prognostic value of CAR in the diagnosis of HF patients with AFib.

METHODS

Study Population

This retrospective study design enrolled 279 consecutive patients over 18 years of age with AFib who presented to our outpatient clinic in between 2022 and 2023. Patients with a history of coronary artery bypass graft surgery or percutaneous coronary intervention, malignancy, and active infection were excluded from the study. The local ethics committee approved the study protocol in accordance with the Declaration of Helsinki.

Data Collection

Patients' baseline clinical and demographic characteristics, along with their medical histories, were extracted from hospital records. Upon admission to the hospital, all patients underwent complete blood counts and blood biochemical analyses. Laboratory variables, including hemoglobin, blood glucose, creatinine, SA, and CRP levels, were documented. CAR was calculated as the ratio of CRP to SA. Electrocardiograms were recorded upon admission, and AFib was defined according to the current guidelines [15]. All patients' echocardiographic parameters were recorded using a Philips Epic 7c echocardiography device, following the recommendations of the American Society of Echocardiography. Left ventricular ejection fraction (LVEF) was determined using Simpson's rule from left ventricular end-diastolic and end-systolic volumes in apical four- and two-chamber views. Left atrial (LA) volume was determined using the biplane method of disks (modified Simpson's rule) with apical four-chamber and apical two-chamber views at ventricular end-systole (maximum LA size). LA volume index was calculated by dividing LA volume by body surface area. All echocardiographic measurements described in this study were obtained by averaging five beats due to the presence of AFib [15, 16].

Statistical Analyses

Statistical analysis was conducted using SPSS version 22.0 (SPSS Inc., Chicago, IL). The normality of the data was assessed using the Kolmogorov–Smirnov test. Continuous variables with normal distribution were presented as mean ± standard deviation and compared using analysis of variance. Non-normally distributed data were expressed as median (0.25–0.75 percentile) values and compared using the Kruskal–Wallis H-test. Categorical variables were reported as numbers (percentages) and compared using Fisher's exact test or the $\chi 2$ test.

The risk factors for LVEF < 40% were analyzed using multivariate Cox proportional hazard analyses of variables that showed statistically significant associations with mortality in univariate analyses. Multicollinearity between CAR and CRP and SA levels was assessed using the eigenvalue and condition index. Linearity was tested by interacting with the logarithmic transformation of each parameter. The receiver operating characteristic (ROC) curve was utilized to determine the best cut-off values of CAR for predicting LVEF using Youden's J statistic. Subsequently, the method proposed by DeLong et al.[17] was employed to compare the ROC curves of CAR, CRP, and SA for predicting LVEF. A p-value < 0.05 indicated statistical significance.

RESULTS

The study enrolled 279 patients diagnosed with AFib with a mean age of 73 ± 10 years, of whom 51.3% were females. Patients were categorized into two groups based on their LVEF: patients with LVEF < 40% (n:75, 26.9%) and patients with LVEF ≥ 40% (n:204, 73.1%). Among patients with LVEF < 40%, elevated levels of neutrophils, CRP, CAR, left atrial volume index (LAVI), and left ventricular end-diastolic diameter (LVEDD) were observed. Additionally, patients with LVEF < 40% exhibited lower levels of SA and high-density lipoprotein (HDL) cholesterol. The distribution of patients' baseline characteristics, laboratory parameters, and echocardiographic findings is presented in Table 1.

Table 1
Demographic, clinical and laboratory characteristics of all patients with EF < 40 and EF ≥ 40 group, with p value

	EF < 40 (n:75)	**EF ≥ 40 (n:204)**	**Total patients (n:279)**	**P value**
Age (years)	74 ± 9	73 ± 10	73 ± 10	0.81
Female gender, n (%)	33(44.0)	110(53.9)	143(51.3)	0.14
Body mass index (kg/m^2)	1.95 ± 0.17	1.97 ± 0.20	1.96 ± 0.19	0.41
Hypertension, n (%)	60(80.0)	152(74.5)	212(76.0)	0.34
Diabetes mellitus, n (%)	26(34.7)	70(34.3)	96(34.4)	0.95
Hyperlipidemia, n (%)	22(29.3)	75(36.8)	97(34.8)	0.24
Smoking, n (%)	13(17.3)	37(18.1)	50(17.9)	0.87
ACEi/ARB (%)	63(84.0)	149(73.0)	212(76.0)	0.06
DHP-CCB (%)	17(22.7)	60(29.4)	77(27.6)	0.26
Betablocker (%)	58(77.3)	158(77.5)	216(77.4)	0.98
Diltiazem/Verapamil (%)	11(14.7)	15(7.4)	26(9.3)	0.06
Anticoagulant				0.90
Warfarin(%)	19(25.3)	51(25.0)	70(25.1)	
Rivoraxaban(%)	40(53.3)	107(52.5)	147(52.7)	
Apixaban (%)	6(8.0)	20(9.8)	26(9.3)	
Dabigatran (%)	2(2.7)	5(2.5)	7(2.5)	
Edoxaban (%)	8(10.7)	21(10.3)	29(10.4)	
Statin (%)	28(37.3)	76(37.0)	104(37.3)	0.99
SGLT-2 inh. (%)	10(13.3)	19(9.3)	29(10.4)	0.33
Digoxin (%)	20(26.7)	44(21.6)	64(22.9)	0.37
WBC (10^3/uL)	8.88 ± 3.26	8.23 ± 3.17	8.41 ± 3.20	0.06
Neutrophil (10^3/uL)	6.12 ± 2.71	5.40 ± 2.52	5.59 ± 2.59	0.02

ACEi: Angiotensin-converting-enzyme inhibitors; ARB: Angiotensin receptor blocker; DHP-CCB :dihydropyridine calcium channel blocker;SGLT 2 inh: sodum glucose co-transporter 2 inhibitor;CRP: C-reactive protein; LDL-C: low-density lipoprotein cholesterol ; HDL- C: high-density lipoprotein cholesterol; TSH:Thyroid Stimulating Hormone; WBC: white blood cell; LA-AP:left atrial anterior-posterior;LAVI:left atrial volüme index,LVEDD: Left ventricular end-diastolic diameter

	EF < 40 (n:75)	EF ≥ 40 (n:204)	Total patients (n:279)	P value
Hemoglobin (g/dL)	13.13 ± 2.34	13.36 ± 2.01	13.3 ± 2.1	0.49
Platelet (10^3/uL)	219 ± 82	236 ± 140	216(176–267)	0.18
Creatinine (mg/dL)	1.17 ± 0.43	1.09 ± 0.41	1.11 ± 0.42	0.11
Glucose (mg/dL)	131 ± 64	130 ± 53	130 ± 56	0.9
Sodium (mmol/L)	138 ± 3.6	139 ± 3.3	139 ± 3.4	0.01
Potassium (mmol/L)	4.05 ± 0.5	4.18 ± 0.51	4.15 ± 0.51	0,06
CRP (mg/L)	23.86(8.6–52.4)	6.44(3.09–15.07)	8.60(3.53-25.00)	< 0,001
Serum albumin (g/L)	35.04 ± 5.38	36.5 ± 4.44	36.1 ± 4.75	< 0.001
CRP/serum albumin ratio	0.68(0.24–1.87)	0.18(0.07–0.42)	0.24(0.09–0.71)	< 0,001
Total cholesterol (mg/dl)	151.87 ± 51.91	155.78 ± 44.18	154.73 ± 46.32	0.16
LDL-C (mg/dl)	93.29 ± 40.54	93.63 ± 35.44	93.54 ± 36.8	0.56
Triglycerides (mg/dl)	98 ± 42	105 ± 66	103 ± 60	0.88
HDL-C (mg/dl)	39.23 ± 10.64	42.44 ± 12.91	41.58 ± 12.40	0.02
TSH (mIU/L)	1.18(0.69–2.07)	1.42(0.86–2.15)	1.38(0.77–2.13)	0.18
T3 (pg/mL)	3.17 ± 1.25	3.29 ± 1.22	3.25 ± 1.23	0.08
Heart rate (bpm)	94 ± 13	91 ± 15	92 ± 15	0.13
LA-AP dimension (cm)	4.5 ± 0.8	4.4 ± 0.7	4.4 ± 0.7	0.09
LAVI (mL/m^2)	38.2 ± 14.2	33.7 ± 14.4	34.9 ± 14.5	0.01
LVEDD (cm)	4.98 ± 0.84	4.71 ± 0.76	4.79 ± 0.79	0.007

ACEi: Angiotensin-converting-enzyme inhibitors; ARB: Angiotensin receptor blocker; DHP-CCB :dihydropyridine calcium channel blocker;SGLT 2 inh: sodum glucose co-transporter 2 inhibitor;CRP: C-reactive protein; LDL-C: low-density lipoprotein cholesterol ; HDL- C: high-density lipoprotein cholesterol; TSH:Thyroid Stimulating Hormone; WBC: white blood cell; LA-AP:left atrial anterior-posterior;LAVI:left atrial volüme index,LVEDD: Left ventricular end-diastolic diameter

Variables related to CAR were analyzed by dividing the study group into two based on the median value of CAR (0.2735). Patients with CAR ≤ 0.2735 were assigned to the low CAR group (n = 139 patients) and those with CAR > 0.2735 were assigned to the high CAR group (n = 140 patients). The baseline characteristics of all the patients as well as those of the low and high CAR groups are shown in Table 2.

Patients with CAR > 0.2735 were older, had higher levels of white blood cells, neutrophil, creatinine, CRP, and heart rate and lower levels of hemoglobin, sodium, SA, triglycerides, HDL cholesterol, and T3.

Table 2
Demographic, clinical and laboratory characteristics of the study population according to C-reactive protein/serum albumin ratio.

	CRP/serum albumin ratio ≤ 0,2735 (n:139)	CRP/serum albumin ratio > 0,2735 (n:140)	P value
Age (years)	72 ± 10	75 ± 9	0,003
Female gender, n (%)	71(51.1)	72(51.4)	0,954
Body mass index (kg/m^2)	1.97 ± 0.20	1.96 ± 0.19	0,927
Hypertension, n (%)	104(74.8)	108(77.1)	0,650
Diabetes mellitus, n (%)	48(34.5)	48(34.3)	0,965
Hyperlipidemia, n (%)	51(36.7)	46(32.9)	0,502
Smoking, n (%)	25(18.0)	25(17.9)	0,978
ACEi/ARB (%)	99(71.2)	113(80.7)	0,064
DHP-CCB (%)	38(27.3)	39(27.9)	0,923
Betablocker (%)	109(78.4)	107(76.4)	0,692
Diltiazem/Verapamil (%)	8(5.8)	18(12.9)	0,042
Warfarin (%)	34(24.5)	36(25.7)	0,023
Rivoraxaban (%)	70(50.4)	77(55.0)	0,589
Apixaban (%)	14(10.1)	12(8.6)	0,829
Dabigatran (%)	4(2.9)	3(2.1)	0,010
Edoxaban (%)	17(12.2)	12(8.5)	0,001
Statin (%)	47(33.8)	57(40.7)	0,234
SGLT-2 inh. (%)	13(0.09)	16(11.4)	0,571
Digoxin (%)	26(18.7)	38(27.1)	0,094
WBC (10^3/uL)	7.82 ± 2.4	8.99 ± 3.75	0,008
Neutrophil (10^3/uL)	4.93 ± 2.0	6.25 ± 2.92	< 0,001

ACEi: Angiotensin-converting-enzyme inhibitors; ARB: Angiotensin receptor blocker; DHP-CCB: dihydropyridine calcium channel blocker;SGLT 2 inh: sodum glucose co-transporter 2 inhibitor ;CRP: C-reactive protein; LDL-C: low-density lipoprotein cholesterol ; HDL- C: high-density lipoprotein cholesterol; TSH:Thyroid Stimulating Hormone; WBC: white blood cell;LA-AP:left atrial anterior-posterior;LAVI:left atrial volüme index, LVEDD: Left ventricular end-diastolic diameter

	CRP/serum albumin ratio ≤ 0,2735 (n:139)	CRP/serum albumin ratio > 0,2735 (n:140)	P value
Hemoglobin (g/dL)	13.66 ± 2.0	12.94 ± 2.15	0,007
Platelet(10^3/uL)	217(177–268)	215(176–267)	0,706
Creatinine (mg/dL)	1.01 ± 0.27	1.21 ± 0.5	< 0,001
Glucose (mg/dL)	124.3 ± 46.9	135.8 ± 63.7	0,116
Sodium (mmol/L)	139.5 ± 2.8	138.2 ± 3.7	0,001
Potassium (mmol/L)	4.1 ± 0.5	4.1 ± 0.5	0,896
CRP (mg/L)	4.1(2.2–6.7)	29.3(14.9–61.1)	< 0,001
Serum albumin (g/L)	37.2 ± 3.8	35.3 ± 4.8	< 0,001
Total cholesterol (mg/dl)	157.4 ± 45.8	152.0 ± 46.7	0,171
LDL-C (mg/dl)	93.2 ± 35.7	93.8 ± 37.9	0,820
Triglycerides (mg/dl)	87 (69–132)	81(65–110)	0,045
HDL-C (mg/dl)	43.6 ± 12.3	39.5 ± 12.1	0,002
TSH (mIU/L)	1.4(0.9–1.9)	1.4(0.7–2.4)	0,953
T3 (pg/mL)	3.5 ± 1.5	2.9 ± 0.8	< 0,001
Heart rate (bpm)	88.6 ± 15.4	94.7 ± 13.1	0,002
LA-AP dimension (cm)	4.4 ± 0.8	4.4 ± 0.7	0,683
LAVI (mL/m^2)	34.2 ± 14.7	35.7 ± 14.3	0,397
LVEDD (cm)	4.7 ± 0.7	4.7 ± 0.9	0,359

ACEi: Angiotensin-converting-enzyme inhibitors; ARB: Angiotensin receptor blocker; DHP-CCB: dihydropyridine calcium channel blocker;SGLT 2 inh: sodum glucose co-transporter 2 inhibitor ;CRP: C-reactive protein; LDL-C: low-density lipoprotein cholesterol ; HDL- C: high-density lipoprotein cholesterol; TSH:Thyroid Stimulating Hormone; WBC: white blood cell;LA-AP:left atrial anterior-posterior;LAVI:left atrial volüme index, LVEDD: Left ventricular end-diastolic diameter

Logistic regression analyses were performed to determine independent predictors of heart failure with reduced ejection fraction (HFrEF) using variables that had a p-value < 0.1 in univariate analysis (neutrophil, Na, HDL cholesterol, LAVI, LVEDD, CAR). CRP and SA were not included in the multivariate regression analysis with CAR due to multicollinearity between CAR and its constituent parameters (CRP

and SA). In the multivariate analysis, independent predictors of HFrEF in patients with AFib were LAVI, LVEDD, and CAR (OR, 0.63; 95% CI, 0.44–0.91; P < 0.001), as shown in Table 3.

Table 3
Univariate and multivariate logistic regression analysis of biochemical and echocardiographic parameters for diagnosis of heart failure prediction

	Univariate analysis of HFrEF (EF < 40)			**Multivariate analysis of HFrEF (EF < 40)**		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Neutrophil	0.904	0.819–0.997	0.04	-	-	-
Na	1.098	1.015–1.187	0.02	-	-	-
HDL-C	1.117	0.999–1.045	0.05	-	-	-
LAVI	0.980	0.962–0.997	0.01	0.975	0.957–0.995	0.01
LVEDD	0.654	0.464–0.921	0.02	0.663	0.462–0.951	0.02
CAR	0.552	0.428–0.711	0.00	0.529	0.408–0.686	< 0.00

HFrEF: heart failure with reduced ejection fraction, HDL- C: high-density lipoprotein cholesterol, LAVI: left atrial volüme index, LVEDD: Left ventricular end-diastolic diameter, CAR: C-reactive protein serum albumin ratio

The optimal cut-off value of CAR for predicting HFrEF was > 0.208, with a sensitivity of 52.9% and a specificity of 89.3% (area under the curve (AUC): 0.755; 95% CI: 0.701–0.805). To assess whether CAR has additional prognostic value over CRP and SA levels, ROC curve comparison analyses revealed that CAR was a better predictor of HFrEF than CRP (AUC: 0.732, 95% CI: 0.676–0.783) and SA (AUC: 0.692, 95% CI: 0.634–0.745) **(Fig. 1).**

DISCUSSION

Our findings underscore the notable association between CAR levels and HF, affirming CAR as an independent predictor for HFrEF in patients with AFib. Furthermore, CAR emerges as a more robust predictor for diagnosing HFrEF in patients with AFib.

HF is associated with poor survival, increased hospitalizations, financial burden, and diminished quality of life (1). Its prevalence among adults ranges from 1–2%, with a notable increase with age, reaching over 10% in individuals aged 70 years or older [18, 19, 20]. Additionally, it carries a mortality rate of nearly 67% within five years post-diagnosis [21]. Given its widespread occurrence and adverse outcomes, the etiology of HF has been extensively studied. One of the most common etiological factors for HF is AFib [2, 3], which leads to progressive atrial abnormalities and adversely affects ventricular function [22, 23]. While stroke remains a significant complication of AFib, hospitalization rates due to HF are two to four times higher than those for stroke in patients with both AFib and HF undergoing oral anticoagulation

therapy [24]. Furthermore, the leading cause of mortality among anticoagulated patients with AFib is attributed to HF, accounting for deaths resulting from progressive HF (14%) or sudden cardiac death (21%), rather than thromboembolism-related deaths (8%) [25, 26].

In parallel to current knowledge [15], in our study, which was conducted on AFib patients, HF was observed at 26.8%. Many demographic, biochemical, hematological, electrocardiographic, and morphological parameters have been shown to be associated with the development of HFrEF in AFib patients [3, 4, 8]. Although in our study there was no difference in demography between the two groups, in alignment with previous studies, impaired left atrial and left ventricular indexes were associated with HFrEF [4, 27]. The impairment of left ventricular indexes, which is known as remodeling, mostly occurs by the loss of synchronized atrial contraction, impaired myocardial perfusion due to microvascular coronary dysfunction, and irregular/high ventricular rates [28, 29]. In addition to these remodeling mechanisms, AFib is also linked to systemic inflammation and compromised endothelial function [30, 31].

In HFrEF patients, it is expected to observe lower sodium levels because of volume overload and dilution [32]. Similarly in our study, patients with HFrEF had lower sodium levels. Likewise, in the present study, white blood cell and neutrophil levels were higher in patients with HFrEF. Previous studies have shown that in patients with HF, activated neutrophils may release significant quantities of pro-inflammatory cytokines and oxidative stress substances, potentially playing a role in the advancement of cardiovascular disease and the onset of HF [33].

CAR is a parameter obtained by combining CRP and SA and has been demonstrated to have both diagnostic and prognostic effectiveness in acute coronary syndrome, pulmonary embolism, and HF [12, 14, 34, 35]. In our study, patients had higher CAR had lower hemoglobin levels. This could be attributed to the pro-inflammatory cytokines that influence iron metabolism, iron turnover, and ferritin synthesis, leading to low serum iron levels without clear evidence of iron deficiency [36]. Further, in the present study, patients who had higher creatinine levels also had higher CAR levels, representing enhanced inflammation. Associations between damaged renal function and inflammation have been shown previously [37].

Earlier studies have established a direct correlation between elevated CRP levels and the progression of HF. It independently predicts adverse cardiovascular outcomes, regardless of the etiology of being ischemic or non-ischemic [38]. SA acts as a negative acute-phase reactant, and its serum concentrations are anticipated to decrease in pro-inflammatory conditions, such as HF. Individuals with advanced HF may develop hypoalbuminemia due to suppressed appetite and reduced bowel absorption due to severe congestion, apart from basal inflammation [39]. Not only in HF but also in AFib, inflammation plays a crucial role in both the initiation and the progression of AFib [31]. That is, it has not been newly documented that CRP and SA are associated with adverse events in AFib patients [40, 41]. As a merged parameter, CAR, however, has been shown as a superior parameter in predicting adverse outcomes both in HF [14] and AFib [40] compared to CRP and SA alone. Nonetheless, the role of CAR in predicting HF is

not clear in the course of AFib. The reason why the inflammation is associated with HF could be attributed mostly to the myopathic effect of inflammation, the alteration of atrial fibroblast-cardiomyocyte distribution, and the promotion of atrial remodeling [42]. Increased wall stress results in the accumulation of damaged mitochondria and apoptogenic proteins and then promotes cardiomyocyte death in the failing heart by activation in recruited macrophages and neutrophils [43]. In our study, we hypothesized that CAR may be associated with the presence of HF in AFib patients because of its role in both AFib and HF. Indeed, according to our results, CAR was found to be an independent predictor of HF. Moreover, in accordance with studies that compare the predictive power of several parameters [12, 14, 34, 35], in our study, CAR was stronger in predicting HF, compared to CRP and SA, in patients with AFib.

AFib, which is the most common arrhythmia in clinical practice, can cause HF and facilitate cardiovascular mortality. Therefore, early diagnosis of HF is vital. CAR is an inexpensive, useful, and accessible parameter at first contact that could be used effectively to diagnose HF in patients with AFib.

CONCLUSION

This study suggests that baseline inflammatory status appears to be a significant factor in diagnosing HFrEF in AFib patients. Based on evidence that CAR is a better predictor than CRP or SA, evaluation of CAR may be useful in diagnosing HFrEF in individual AFib patients. Additionally, LAVI and LVEDD have been found to be independent predictors of HFrEF.

Limitations

The present study has several limitations. First, although the data were acquired prospectively, the study had a retrospective design and was based on a registry analysis. Second, the study group included a relatively small number of patients. Third, there is the potential for undetected infectious diseases among the participants. While we excluded patients with severe concurrent infections as the primary cause of admission during the initial eligibility screening, there remains a possibility that some individuals had undiagnosed infections. This could have introduced confounding variables and affect the generalizability of our findings as these undetected infections might have influenced the outcomes being studied. Therefore, future research should consider implementing more comprehensive screening measures to minimize this potential limitation.

Declarations

The study protocol was approved by the local ethics committee (Ethics Committee of the Dean of the Faculty of Medicine of Kafkas University- 80576354-050-99/397 numbered ethics committee approval).

Authors' contributions: Ayca Arslan, Dogan Ilis, Ozcan Yagcibulut have given substantial contributions to the conception or the design of the manuscript. Ezgi Guzel, Timor Omar and Muammer Karakayali have

given substantial contribution to the collection of the data. Inanc Artac and Yavuz Karabag have participated mostly to statistical data analysis. Ayca Arslan and Ibrahim Rencuzogullari have participated to design, analysis and drafting of the manuscript. All authors have participated to data analysis and drafting the manuscript. All authors read and approved the final version of the manuscript. All authors contributed to the manuscript and read and approved the final version of the manuscript.

Data sharing: No additional data

Contributorship: All of the authors contributed planning, conduct, and reporting of the work. All contributors are responsible for the overall content as guarantors.

Funding: No funding.

Competing interests: All of the authors have no conflict of interest.

References

1. Lee, J. K., & Son, Y. J. (2018). Gender Differences in the Impact of Cognitive Function on Health Literacy among Older Adults with Heart Failure. International journal of environmental research and public health, 15(12), 2711. https://doi.org/10.3390/ijerph15122711
2. Ziaeian, B., & Fonarow, G. C. (2016). Epidemiology and aetiology of heart failure. Nature reviews. Cardiology, 13(6), 368–378. https://doi.org/10.1038/nrcardio.2016.25
3. Kotecha, D., Lam, C. S., Van Veldhuisen, D. J., Van Gelder, I. C., Voors, A. A., & Rienstra, M. (2016). Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation: Vicious Twins. Journal of the American College of Cardiology, 68(20), 2217–2228. https://doi.org/10.1016/j.jacc.2016.08.048
4. Wijesurendra, R. S., & Casadei, B. (2015). Atrial fibrillation: effects beyond the atrium?. Cardiovascular research, 105(3), 238–247. https://doi.org/10.1093/cvr/cvv001
5. Benjamin, E. J., Muntner, P., Alonso, A., Bittencourt, M. S., Callaway, C. W., Carson, A. P., Chamberlain, A. M., Chang, A. R., Cheng, S., Das, S. R., Delling, F. N., Djousse, L., Elkind, M. S. V., Ferguson, J. F., Fornage, M., Jordan, L. C., Khan, S. S., Kissela, B. M., Knutson, K. L., Kwan, T. W., … American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee (2019). Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation, 139(10), e56–e528. https://doi.org/10.1161/CIR.0000000000000659
6. Ceornodolea, A. D., Bal, R., & Severens, J. L. (2017). Epidemiology and Management of Atrial Fibrillation and Stroke: Review of Data from Four European Countries. Stroke research and treatment, 2017, 8593207. https://doi.org/10.1155/2017/8593207
7. Kalantarian, S., Stern, T. A., Mansour, M., & Ruskin, J. N. (2013). Cognitive impairment associated with atrial fibrillation: a meta-analysis. Annals of internal medicine, 158(5 Pt 1), 338–346. https://doi.org/10.7326/0003-4819-158-5-201303050-00007

8. Ziff, O. J., Carter, P. R., McGowan, J., Uppal, H., Chandran, S., Russell, S., Bainey, K. R., & Potluri, R. (2018). The interplay between atrial fibrillation and heart failure on long-term mortality and length of stay: Insights from the, United Kingdom ACALM registry. International journal of cardiology, 252, 117–121. https://doi.org/10.1016/j.ijcard.2017.06.033
9. Harada, M., & Nattel, S. (2021). Implications of Inflammation and Fibrosis in Atrial Fibrillation Pathophysiology. Cardiac electrophysiology clinics, 13(1), 25–35. https://doi.org/10.1016/j.ccep.2020.11.002
10. Hu, Y. F., Chen, Y. J., Lin, Y. J., & Chen, S. A. (2015). Inflammation and the pathogenesis of atrial fibrillation. Nature reviews. Cardiology, 12(4), 230–243. https://doi.org/10.1038/nrcardio.2015.2
11. Boos C. J. (2020). Infection and atrial fibrillation: inflammation begets AF. European heart journal, 41(10), 1120–1122. https://doi.org/10.1093/eurheartj/ehz953
12. Çağdaş, M., Rencüzoğullari, I., Karakoyun, S., Karabağ, Y., Yesin, M., Artaç, I., Iliş, D., Çağdaş, Ö. S., Tezcan, A. H., & Tanboğa, H. I. (2019). Assessment of Relationship Between C-Reactive Protein to Albumin Ratio and Coronary Artery Disease Severity in Patients With Acute Coronary Syndrome. Angiology, 70(4), 361–368. https://doi.org/10.1177/0003319717743325
13. Yamada, T., Haruki, S., Minami, Y., Numata, M., & Hagiwara, N. (2021). The C-reactive protein to prealbumin ratio on admission and its relationship with outcome in patients hospitalized for acute heart failure. Journal of cardiology, 78(4), 308–313. https://doi.org/10.1016/j.jjcc.2021.05.009
14. Çinier, G., Hayıroğlu, M. İ., Kolak, Z., Tezen, O., Yumurtaş, A. Ç., Pay, L., Eren, S., Çetin, T., Özcan, S., Türkkan, C., Özbilgin, N., Tekkeşin, A. İ., Alper, A. T., & Gürkan, K. (2021). The value of C-reactive protein-to-albumin ratio in predicting long-term mortality among HFrEF patients with implantable cardiac defibrillators. European journal of clinical investigation, 51(8), e13550. https://doi.org/10.1111/eci.13550
15. Hindricks, G., Potpara, T., Dagres, N., Arbelo, E., Bax, J. J., Blomström-Lundqvist,C., Boriani, G., Castella, M., Dan, G. A., Dilaveris, P. E., Fauchier, L., Filippatos,G., Kalman, J. M., La Meir, M., Lane, D. A., Lebeau, J. P., Lettino, M., Lip, G. Y.H., Pinto, F. J., Thomas, G. N., … ESC Scientific Document Group (2021). 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. European heart journal, 42(5), 373–498. https://doi.org/10.1093/eurheartj/ehaa612
16. Lang, R. M., Bierig, M., Devereux, R. B., Flachskampf, F. A., Foster, E., Pellikka, P. A., Picard, M. H., Roman, M. J., Seward, J., Shanewise, J. S., Solomon, S. D., Spencer, K. T., Sutton, M. S., Stewart, W. J., Chamber Quantification Writing Group, American Society of Echocardiography's Guidelines and Standards Committee, & European Association of Echocardiography (2005). Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology.

Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography, 18(12), 1440–1463. https://doi.org/10.1016/j.echo.2005.10.005

17. DeLong, E. R., DeLong, D. M., & Clarke-Pearson, D. L. (1988). Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics, 44(3), 837–845.
18. McDonagh, T. A., Metra, M., Adamo, M., Gardner, R. S., Baumbach, A., Böhm, M., Burri,H., Butler, J., Čelutkienė, J., Chioncel, O., Cleland, J. G. F., Coats, A. J. S.,Crespo-Leiro, M. G., Farmakis, D., Gilard, M., Heymans, S., Hoes, A. W., Jaarsma,T., Jankowska, E. A., … ESC Scientific Document Group (2022). 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. European journal of heart failure, 24(1), 4–131. https://doi.org/10.1002/ejhf.2333
19. Conrad, N., Judge, A., Tran, J., Mohseni, H., Hedgecott, D., Crespillo, A. P., Allison, M., Hemingway, H., Cleland, J. G., McMurray, J. J. V., & Rahimi, K. (2018). Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet (London, England), 391(10120), 572–580. https://doi.org/10.1016/S0140-6736(17)32520-5
20. van Riet, E. E., Hoes, A. W., Wagenaar, K. P., Limburg, A., Landman, M. A., & Rutten, F. H. (2016). Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. European journal of heart failure, 18(3), 242–252. https://doi.org/10.1002/ejhf.483
21. Tsao, C. W., Lyass, A., Enserro, D., Larson, M. G., Ho, J. E., Kizer, J. R., Gottdiener, J. S., Psaty, B. M., & Vasan, R. S. (2018). Temporal Trends in the Incidence of and Mortality Associated With Heart Failure With Preserved and Reduced Ejection Fraction. JACC. Heart failure, 6(8), 678–685. https://doi.org/10.1016/j.jchf.2018.03.006
22. Nattel, S., Burstein, B., & Dobrev, D. (2008). Atrial remodeling and atrial fibrillation: mechanisms and implications. Circulation. Arrhythmia and electrophysiology, 1(1), 62–73. https://doi.org/10.1161/CIRCEP.107.754564
23. Cha, Y. M., Redfield, M. M., Shen, W. K., & Gersh, B. J. (2004). Atrial fibrillation and ventricular dysfunction: a vicious electromechanical cycle. Circulation, 109(23), 2839–2843. https://doi.org/10.1161/01.CIR.0000132470.78896.A8
24. McMurray, J. J., Ezekowitz, J. A., Lewis, B. S., Gersh, B. J., van Diepen, S., Amerena, J., Bartunek, J., Commerford, P., Oh, B. H., Harjola, V. P., Al-Khatib, S. M., Hanna, M., Alexander, J. H., Lopes, R. D., Wojdyla, D. M., Wallentin, L., Granger, C. B., & ARISTOTLE Committees and Investigators (2013). Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial. Circulation. Heart failure, 6(3), 451–460. https://doi.org/10.1161/CIRCHEARTFAILURE.112.000143

25. Marijon, E., Le Heuzey, J. Y., Connolly, S., Yang, S., Pogue, J., Brueckmann, M., Eikelboom, J., Themeles, E., Ezekowitz, M., Wallentin, L., Yusuf, S., & RE-LY Investigators (2013). Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. Circulation, 128(20), 2192–2201. https://doi.org/10.1161/CIRCULATIONAHA.112.000491
26. Sharma, A., Hijazi, Z., Andersson, U., Al-Khatib, S. M., Lopes, R. D., Alexander, J. H., Held, C., Hylek, E. M., Leonardi, S., Hanna, M., Ezekowitz, J. A., Siegbahn, A., Granger, C. B., & Wallentin, L. (2018). Use of Biomarkers to Predict Specific Causes of Death in Patients With Atrial Fibrillation. Circulation, 138(16), 1666–1676. https://doi.org/10.1161/CIRCULATIONAHA.118.034125
27. Shah, M. A., Soofı, M. A., Jafary, Z., Alhomrani, A., Alsmadi, F., Wani, T. A., & Bajwa, I. A. (2020). Echocardiographic parameters associated with recovery in heart failure with reduced ejection fraction. Echocardiography (Mount Kisco, N.Y.), 37(10), 1574–1582. https://doi.org/10.1111/echo.14859
28. Ling, L. H., Taylor, A. J., Ellims, A. H., Iles, L. M., McLellan, A. J., Lee, G., Kumar, S., Lee, G., Teh, A., Medi, C., Kaye, D. M., Kalman, J. M., & Kistler, P. M. (2013). Sinus rhythm restores ventricular function in patients with cardiomyopathy and no late gadolinium enhancement on cardiac magnetic resonance imaging who undergo catheter ablation for atrial fibrillation. Heart rhythm, 10(9), 1334–1339. https://doi.org/10.1016/j.hrthm.2013.06.019
29. Hunter, R. J., Berriman, T. J., Diab, I., Kamdar, R., Richmond, L., Baker, V., Goromonzi, F., Sawhney, V., Duncan, E., Page, S. P., Ullah, W., Unsworth, B., Mayet, J., Dhinoja, M., Earley, M. J., Sporton, S., & Schilling, R. J. (2014). A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circulation. Arrhythmia and electrophysiology, 7(1), 31–38. https://doi.org/10.1161/CIRCEP.113.000806
30. Freestone, B., Chong, A. Y., Nuttall, S., & Lip, G. Y. (2008). Impaired flow mediated dilatation as evidence of endothelial dysfunction in chronic atrial fibrillation: relationship to plasma von Willebrand factor and soluble E-selectin levels. Thrombosis research, 122(1), 85–90. https://doi.org/10.1016/j.thromres.2007.09.008
31. Guo, Y., Lip, G. Y., & Apostolakis, S. (2012). Inflammation in atrial fibrillation. Journal of the American College of Cardiology, 60(22), 2263–2270. https://doi.org/10.1016/j.jacc.2012.04.063
32. Alem M. M. (2020). Predictors of Mortality in Patients with Chronic Heart Failure: Is Hyponatremia a Useful Clinical Biomarker?. International journal of general medicine, 13, 407–417. https://doi.org/10.2147/IJGM.S260256
33. Swirski, F. K., & Nahrendorf, M. (2013). Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure. Science (New York, N.Y.), 339(6116), 161–166. https://doi.org/10.1126/science.1230719
34. Rencuzogullari, I., Karabağ, Y., Çağdaş, M., Karakoyun, S., Seyis, S., Gürsoy, M. O., Yesin, M., Artaç, İ., İliş, D., & Tanboğa, İ. H. (2019). Assessment of the relationship between preprocedural C-reactive protein/albumin ratio and stent restenosis in patients with ST-segment elevation myocardial

infarction. Revista portuguesa de cardiologia, 38(4), 269–277. https://doi.org/10.1016/j.repc.2018.08.008

35. Artac, I., Omar, T., Karakayali, M., Ilis, D., Karabag, Y., & Rencuzogullari, I. (2023). Assessment of the relationship between C-reactive protein to albumin ratio and late-term mortality in patients with acute pulmonary embolism. Asian cardiovascular & thoracic annals, 31(4), 332–339. https://doi.org/10.1177/02184923231167310
36. Roy, C. N., & Andrews, N. C. (2005). Anemia of inflammation: the hepcidin link. Current opinion in hematology, 12(2), 107–111. https://doi.org/10.1097/00062752-200503000-00001
37. Baer, P. C., Koch, B., & Geiger, H. (2021). Kidney Inflammation, Injury and Regeneration 2020. International journal of molecular sciences, 22(11), 5589. https://doi.org/10.3390/ijms22115589
38. Anand, I. S., Latini, R., Florea, V. G., Kuskowski, M. A., Rector, T., Masson, S., Signorini, S., Mocarelli, P., Hester, A., Glazer, R., Cohn, J. N., & Val-HeFT Investigators (2005). C-reactive protein in heart failure: prognostic value and the effect of valsartan. Circulation, 112(10), 1428–1434. https://doi.org/10.1161/CIRCULATIONAHA.104.508465
39. Sundaram, V., & Fang, J. C. (2016). Gastrointestinal and Liver Issues in Heart Failure. Circulation, 133(17), 1696–1703. https://doi.org/10.1161/CIRCULATIONAHA.115.020894
40. ABUŞ S. C-reactive protein to albumin ratio in atrial fibrillation. Eur Res J. July 2023;9(4):674–679.
41. Aronson, D., Boulos, M., Suleiman, A., Bidoosi, S., Agmon, Y., Kapeliovich, M., Beyar, R., Markiewicz, W., Hammerman, H., & Suleiman, M. (2007). Relation of C-reactive protein and new-onset atrial fibrillation in patients with acute myocardial infarction. The American journal of cardiology, 100(5), 753–757. https://doi.org/10.1016/j.amjcard.2007.04.014
42. Wijesurendra, R. S., & Casadei, B. (2019). Mechanisms of atrial fibrillation. Heart (British Cardiac Society), 105(24), 1860–1867. https://doi.org/10.1136/heartjnl-2018-314267
43. Nishida, K., & Otsu, K. (2017). Sterile Inflammation and Degradation Systems in Heart Failure. Circulation journal: official journal of the Japanese Circulation Society, 81(5), 622–628. https://doi.org/10.1253/circj.CJ-17-0261