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Prognostic Value of Inflammatory Indices in Patients with Infective Endocarditis: Peak C-Reactive Protein/Albumin Ratio as a Better Biomarker

İnfektif Endokarditli Hastalarda İnflamatuar İndekslerin Prognostik Değeri: Pik C-Reaktif Protein/Albümin Oranı Daha İyi Bir Biyobelirteç

ABSTRACT

Objective: Infective endocarditis (IE) is a severe and potentially fatal infection associated with significant morbidity and mortality. Early identification of patients at high risk of adverse outcomes is essential for improving clinical management and prognosis. This study aimed to evaluate the prognostic value of various inflammatory indices, with a particular focus on the peak C-reactive protein/albumin ratio (CAR), in predicting in-hospital mortality among IE patients.

Method: This retrospective, single-center study included IE patients admitted between June 2020 and June 2023. The primary outcome was in-hospital mortality. For all patients, inflammatory indices, including peak serum CAR levels, were calculated, and their association with mortality was assessed.

Results: Of 165 patients, 62 (37.6%) experienced in-hospital mortality. Non-survivors had significantly higher peak CAR levels (8.1 vs. 5.0, P < 0.001) and elevated levels of other inflammatory indices compared to survivors. Peak CAR demonstrated the highest discriminatory ability for predicting in-hospital mortality, with an area under the curve (AUC) of 0.764, outperforming other indices. Multivariate analysis confirmed that peak CAR was an independent predictor of mortality (adjusted hazard ratio = 1.16, 95% confidence interval: 1.10–1.23, P < 0.001). Net reclassification improvement and integrated discrimination improvement analyses further supported the superior reclassification and discrimination capabilities of peak CAR.

Conclusion: Peak CAR is a significant prognostic marker for in-hospital mortality in IE patients compared to traditional inflammatory indices. Incorporating peak CAR into clinical practice may improve risk stratification and guide treatment decisions.

Keywords: C-reactive protein to albumin ratio, in-hospital mortality, infective endocarditis, inflammatory indices

ÖZET

Amaç: İnfektif endokardit (İE), yüksek morbidite ve mortaliteye ile seyreden, yaşamı tehdit eden bir enfeksiyondur. Advers sonuçlar açısından yüksek risk taşıyan hastaların erken tanımlanması, tedavi yönetimini optimize etmek ve prognozu iyileştirmek açısından kritik öneme sahiptir. Bu çalışmada, infektif endokarditli hastalarda, çeşitli inflamatuar indekslerin prognostik değerininin araştırılması ve özellikle hastane içi mortaliteyi öngörmede pik C-reaktif protein/albümin oranının (CAR) belirleyici rolünü değerlendirilmesi amaçlandı.

Yöntem: Bu retrospektif, tek merkezli çalışmaya Haziran 2020 ile Haziran 2023 tarihleri arasında kesin İE tanısı alan hastalar dahil edildi. Birincil sonlanım noktası hastane içi mortaliteydi. Tüm hastalarda inflamatuar indeksler, özellikle pik CAR düzeyleri kaydedildi ve mortalite ile ilişkileri analiz edildi.

Bulgular: Toplam 165 hastanın 62'sinde (%37,6) hastane içi mortalite tespit edildi. Mortalite grubunda, sağ kalanlara kıyasla anlamlı derecede pik CAR düzeyleri saptandı (8,1 vs. 5,0, P < 0,001). Pik CAR, hastane içi mortaliteyi öngörmede diğer inflamatuar indekslerle kıyaslandığında, yüksek ayırt edici güce sahipti (AUC: 0,764). Çok değişkenli Cox regresyon analizinde pik CAR, bağımsız bir mortalite belirleyicisi olarak saptandı (düzeltilmiş hazard oranı: 1,16; %95 GA: 1,10–1,23; P < 0,001). Net yeniden sınıflandırma iyileştirmesi (NRI) ve entegre diskriminasyon iyileştirmesi (IDI) analizleri de pik CAR'ın üstün öngörü performansını destekledi.

Sonuç: Pik CAR düzeyi, infektif endokarditli hastalarda hastane içi mortalitenin güçlü ve bağımsız bir belirleyicisidir. Klinik uygulamalara entegrasyonu, risk sınıflandırmasını güçlendirebilir ve tedavi kararlarını yönlendirebilir.

Anahtar Kelimeler: C-reaktif protein/albümin oranı, hastane içi mortalite, infektif endokardit, inflamatuar indeksler

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KLİNİK ÇALIŞMA

Duygu İnan[1]
Alev Kılıçgedik[1]
Ayşe İrem Demirtola Mammadli[2]
Arslan Erdoğan[1]
Duygu Genç Albayrak[1]
Funda Özlem Pamuk[1]
Sevil Tuğrul Yavuz[1]
Fatmatuz Zehra Eroğlu[1]
Cemal Ozanalp[1]
Ahmet İlker Tekkeşin[1]
Ömer Genç[1]

[1]Department of Cardiology, Başakşehir Çam and Sakura City Hospital, Istanbul, Türkiye
[2]Department of Cardiology, Ankara Bilkent City Hospital, Ankara, Türkiye

Corresponding author:
Duygu İnan
✉ dr.duyguinan@gmail.com

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Infective endocarditis (IE) is a serious, potentially life-threatening infection characterized by involvement of the endocardial surface of the heart. It is associated with relatively high short- and long-term mortality and morbidity rates.[1] Global data from the past 30 years reported 1,090,530 cases and 66,320 deaths in 2019, with an estimated annual increase in IE incidence of 1.2% and a mortality rate of 0.7%.[2] Despite advances in diagnostic techniques and treatment strategies, the challenges managing IE and its associated high costs continue to impose a heavy burden on both the society and the economy.[1] Early identification of patients at high risk of adverse outcomes is crucial for improving clinical management and prognosis.

The clinical course and complication rates of infective endocarditis are influenced by multiple factors, including the timing of diagnosis, baseline clinical status, the causative microorganism, and both the approach to and adequacy of treatment. Several variables have been consistently associated with increased mortality in IE patients, such as heart failure at presentation or New York Heart Association (NYHA) class III/IV symptoms, prosthetic valve involvement, larger vegetation size, Staphylococcus aureus infection, older age, renal dysfunction, and elevated inflammatory or cardiac biomarkers.[1–12]

The clinical features, laboratory findings, and associated complications of IE offer insights into the underlying biological processes and disease severity.[3] Systemic inflammation plays a key role in the pathophysiology of IE.[4] In the development of IE, there is an imbalance between pro-inflammatory and anti-inflammatory responses.[4,5,9] In recent studies, the use of combinations of multiple biochemical markers to diagnose various diseases and to compare the diagnostic and prognostic values has become increasingly popular.[6] In patients with IE, the diagnostic and prognostic value of different inflammatory markers has also been investigated.[1,4,5] White blood cell (WBC) count, procalcitonin, brain-type natriuretic peptide (BNP) levels, D-dimer, C-reactive protein (CRP), serum albumin level, and various indices derived from these parameters are known to have prognostic value in IE.[6-10] Among these, CRP and albumin levels have been used separately to assess the inflammatory and nutritional status of patients.[10–12] The prognostic significance of follow-up CRP levels in IE patients has been particularly emphasized.[13] The CRP/albumin ratio (CAR), which combines these two parameters, has emerged as a novel inflammatory index that may provide better prognostic value than CRP or albumin alone.[14]

Recent studies have suggested that CAR is a significant prognostic marker in various infectious and cardiovascular diseases, including IE.[14–17] However, data on the predictive value of peak CAR, which incorporates the maximum CRP and minimum albumin ratio, are limited. Moreover, while the prognostic values of different inflammatory indices in IE patients have been established individually, no study has clearly evaluated their comparative predictive performance.

In this study, we aimed to evaluate the predictive value of inflammatory indices for in-hospital mortality in IE patients, with a particular focus on peak CAR. We hypothesized that peak CAR would serve as a superior biomarker compared to traditional inflammatory markers, thereby providing clinicians with a valuable tool for risk stratification and management of this challenging patient population.

ABBREVIATIONS

AUC	Area under the curve
BNP	Brain-type natriuretic peptide
BUN	Blood urea nitrogen
CAR	CRP/albumin ratio
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
IDI	Integrated discrimination improvement
IE	Infective endocarditis
IQR	Interquartile range
NLR	Neutrophil-to-lymphocyte ratio
NRI	Net reclassification improvement
NYHA	New York Heart Association
PIV	Pan-immune-inflammation value
ROC	Receiver operating characteristic
SII	Systemic immune-inflammation index
SIRI	Systemic inflammatory response index
WBC	White blood cell count

Materials and Methods

Study Population and Design

This retrospective cohort study was conducted at a tertiary care hospital and involved patients diagnosed with definite IE between June 2020 and 2023. Our center is a tertiary referral facility with a dedicated IE team, receiving IE patients from surrounding cities. The study was approved by the Başakşehir Çam and Sakura Hospital Clinical Research Ethics Committee (Approval Number: 87, Date: 14.02.2024) and was conducted in accordance with the 'Good Clinical Practices' guidelines of the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study. The inclusion criteria were adult patients (≥ 18 years) with a definite diagnosis of IE according to the modified Duke criteria.[18] For patients who experienced more than one episode of IE, only the first episode was included in the study. Patients with autoimmune inflammatory diseases, leukemia or other blood system disorders, active corticosteroid or immunosuppressive therapy, chronic liver disease, or insufficient medical records were excluded.

Data Collection

Clinical and demographic data, including age, sex, comorbidities (e.g., diabetes mellitus, hypertension, and coronary artery disease), smoking status, intravenous drug use, body mass index, and NYHA classification, were collected from medical records. Laboratory parameters, including WBC count, peak CRP, procalcitonin, albumin, creatinine, blood urea nitrogen (BUN), troponin, and peak N-terminal pro-B-type natriuretic peptide (NT-proBNP), were recorded. From these data, the peak value of CRP and the lowest value of albumin within the first 48–72 hours, as well as the average values of other parameters at admission, were analyzed. Blood culture samples were obtained from all patients within 24 hours of hospital admission and before the initiation of antibiotic therapy, in accordance with the latest guidelines. Cultures were repeated in cases where clinically indicated.

All patients underwent detailed transthoracic echocardiography using the EPIQ CVx (X5-1 transducer, Philips, USA) within the first 24 hours of admission. Additionally, transesophageal echocardiography was performed for all patients at least once during hospitalization (X8-2t transducer, Philips, USA). Vegetation size was evaluated in multiple imaging planes, and the maximum dimension was recorded. Moreover, new-onset severe valve regurgitation, prosthetic valve dysfunction, abscess, pseudoaneurysm, and perforation were assessed as complications. Computed tomography (CT) or positron emission tomography-CT was used in cases where the diagnosis was uncertain or when it was necessary to evaluate for complications. The main indications for surgery were determined by the IE team in accordance with current guidelines.[18] All patients received appropriate medical treatment, including antibiotic therapy tailored to the clinical presentation and any developing complications.

Inflammatory Indices

Peak CAR was calculated using the maximum CRP value and the minimum albumin value recorded within the first 72 hours. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count.[19] The systemic immune-inflammation index (SII) was calculated by multiplying the platelet count by the neutrophil count and dividing by the lymphocyte count.[19] The systemic inflammatory response index (SIRI) was calculated by multiplying the neutrophil count by the monocyte count and then dividing by the lymphocyte count.[19] The pan-immune-inflammation value (PIV) was calculated by multiplying the neutrophil count by the platelet count, multiplying that result by the monocyte count, and then dividing by the lymphocyte count.[20]

Outcomes

The primary outcome was in-hospital mortality. The predictive power of the inflammatory indices was compared between survivors and non-survivors.

Statistical Analysis

Statistical analyses were conducted using R statistical software (version 4.3.2, Vienna, Austria). The normality of variables was assessed using the Kolmogorov-Smirnov test, supported by visual inspection of histograms and probability plots. Continuous variables were presented as mean ± standard deviation for normally distributed data and as median (interquartile range [IQR25-75]) for non-normally distributed data. Categorical variables were expressed as numbers and percentages. Group-wise comparisons of categorical variables were performed using Fisher's exact test or the χ^2 test, while continuous variables were compared using the independent Student's t-test or the Mann-Whitney U test.

The least absolute shrinkage and selection operator (LASSO) penalized selection method was used to identify and refine significant variables for adjustment in the multivariable Cox proportional hazards regression analyses, by applying an optimal lambda value to prevent overfitting (Appendix 1). The following variables were selected for inclusion in the subsequent analyses for adjustment: age, body mass index, aspartate transaminase level, troponin level, white blood cell count, thyroxine (T4) level, urea level, NYHA class, peak N-terminal pro-B-type natriuretic peptide level, vegetation size, treatment type, and infective endocarditis type (Appendix 1).

The optimal cut-off value for peak CAR in predicting all-cause mortality was identified using X-tile software (Version 3.6.1, Yale University School of Medicine), based on the lowest p-value and highest chi-square value (Appendix 2). Correlations between inflammatory indices were analyzed using Kendall's tau-b coefficient.

Kaplan-Meier plots, the log-rank test, and multivariable Cox proportional hazards models were used for the time-to-event analysis of all-cause mortality. The proportional hazards assumption was tested using Schoenfeld residuals and visual inspections of log-log plots. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for all regression analyses. The importance of individual variables within the multivariable Cox model, including peak CAR, was assessed using a permutation-based variable importance method, ranking variables based on the root mean squared error metric.

The accuracy of mortality prediction was evaluated using the receiver operating characteristic (ROC) curve, area under the curve (AUC), continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI) analyses. A decision curve analysis was also conducted to determine whether the biomarkers provided a net benefit compared to all-treatment and no-treatment strategies. All statistical analyses were two-sided, with a significance level (alpha) of 0.05.

Results

A total of 186 patients with a definite diagnosis of IE were enrolled in the study. After excluding 21 patients who met the exclusion criteria, 165 patients were included in the final analysis. Patients were divided into two groups based on in-hospital mortality: survivors and non-survivors. The mean age of the study population was 58.0 ± 15.0 years, and 66 patients (40%) were female. Of the total study population, 62 patients (37.6%) died during hospitalization. Non-survivors were signi§ficantly older than survivors (62.0 ± 14.1 years vs. 55.0 ± 15.7 years, P = 0.005). Comorbidities were comparable between the two groups. NYHA class III or IV clinical presentations were significantly more common in non-survivors than in survivors (P < 0.001). Embolic complications occurred at similar frequencies in both groups; however, acute heart failure at presentation was significantly more prevalent among non-survivors (P = 0.057 and P < 0.001, respectively). Notably, the majority of these patients had vegetation sizes ≥ 10 mm (83.9% vs. 68.0%, P = 0.038). More than half of the patients had native valve endocarditis, with prosthetic valve endocarditis being the second most common type. The rate of surgical treatment was significantly higher among survivors (52.4% vs. 43.5%, P = 0.032). Compared to survivors, non-survivors had similar peak CRP levels (103.8 vs. 77.9 mg/dL, P = 0.056) but statistically significantly lower albumin levels (31.3 ± 8.0 vs. 34.6 ± 5.7 mg/dL, P = 0.002). The peak CAR was significantly higher in non-survivors (8.1 vs. 5.0, P < 0.001). In addition, non-survivors had higher levels of systemic inflammatory indices compared to survivors, including PIV (1991.8 vs. 900.6, P < 0.001), SII (2026.2 vs. 1068.9, P = 0.005), SIRI (11.1 vs. 3.7, P < 0.001), and NLR (9.3 vs. 5.0, P = 0.001) (Central illustration). Table 1 presents additional characteristics of the study population.

Table 1. Baseline characteristics, clinical features, and laboratory findings of the study population

Variables	Survivors (n = 103)	Non-survivors (n = 62)	P*
Age, years	55.0 ± 15.7	62.0 ± 14.1	0.005
Female sex, n (%)	39 (37.9)	27 (43.5)	0.577
DM, n (%)	39 (37.9)	30 (48.4)	0.139
HT, n (%)	61 (59.2)	40 (64.5)	0.609
CAD, n (%)	39 (37.9)	31 (50.0)	0.172
CKD, n (%)	42 (36)	25 (40.3)	> 0.950
COPD, n (%)	11 (10.7)	3 (4.8)	0.310
CVA, n (%)	25 (24.3)	20 (32.2)	0.350
Smoking, n (%)	27 (26.2)	16 (25.8)	> 0.950
IV drug user, n (%)	2 (1.9)	3 (4.8)	0.560
BMI, kg/m^2	26.1 ± 4.8	24.7 ± 5.8	0.099
NYHA class, n (%)			<0.001
I	65 (63.1)	3 (4.8)	
II	23 (22.3)	15 (24.2)	
III	10 (9.7)	26 (41.9)	
IV	5 (4.9)	18 (29.0)	
LVEF, %	53.9 ± 11.4	54.0 ± 10.1	0.914
Embolic events, n (%)	17 (16.5)	18 (29.0)	0.057
Acute HF, n (%)	15 (14.6)	44 (71.0)	< 0.001
Vegetation size, n (%)			0.038
< 10 mm	33 (32)	10 (16.1)	
≥ 10 mm	70 (68)	52 (83.9)	
Infective endocarditis type, n (%)			0.081
Native valve IE	46 (44.7)	40 (64.5)	
Prosthetic valve IE	25 (24.3)	12 (19.4)	
Device-lead IE	15 (14.6)	3 (4.8)	
Transvenous catheter IE	15 (14.6)	5 (8.1)	
Other	2 (1.9)	2 (3.2)	
Treatment type, n(%)			0.032
Surgery	54 (52.4)	27 (43.5)	
Medical treatment only	42 (40.8)	35 (56.5)	
Lead extravasation	7 (6.8)	0 (0)	
WBC, 10^3 µ/L	9.4 (7.1-12.9)	13.8 (9.6-16.6)	< 0.001
Hemoglobin, g/dL	10.1 ± 2.4	10.0 ± 2.3	0.670
Platelet count, 10^3 µ/L	222.7 ± 102.1	215.3 ± 109.7	0.665
Lymphocyte count, 10^3 µ/L	1.2 (0.8-1.9)	1.1 (0.7-1.7)	0.167
Monocyte count, 10^3 µ/L	0.8 (0.5-1.1)	0.9 (0.7-1.6)	0.005
Neutrophil count, 10^3 µ/L	7.1 (4.9-11.5)	11.4 (6.9-14.3)	< 0.001
Peak CRP, mg/dL	77.9 (37.8-148.1)	103.8 (52.7-180.5)	0.056
Procalcitonin, µg/L	0.5 (0.1-2.9)	0.8 (0.2-6.9)	0.111
Albumin, mg/dL	34.6 ± 5.7	31.3 ± 8.0	0.002
AST, IU/L	22 (16-38.5)	29.5 (17.2-67.8)	0.099
Creatinine, mg/dL	1.1 (0.8-3.2)	1.4 (0.9-4.4)	0.167
BUN, mg/dL	43.2 (27.5-62.5)	72.0 (45.1-96.2)	< 0.001
Troponin, ng/L	36.9 (15.6-109.5)	103.5 (49.8-314.0)	< 0.001
Peak NT-proBNP, pg/mL	945.0 (323.5-4352.5)	9277 (5417-15664.5)	< 0.001
TSH, µIU/mL	1.4 (0.9-2.2)	1.7 (0.8-2.6)	0.439
Thyroxine, µg/dL	1.3 (1.1-1.6)	1.3 (1.1-1.6)	0.539
Glucose, mg/dL	131.2 ± 55.5	168.5 ± 85.6	0.001
Sodium, mEq/L	135.0 ± 4.4	134.1± 6.7	0353
Potassium, mEq/L	4.4 ± 0.7	4.4 ± 0.7	0.790
Peak CAR	5.0 (2.5-7.4)	8.1 (6.5-10.9)	< 0.001
PIV	900.6 (320.6-2112.1)	1991.8 (694.2-4094.2)	< 0.001
SII	1068.9 (597.6-2337.6)	2026.2 (968.6-3289.2)	0.005
SIRI	3.7 (1.7-11.4)	11.1 (4.4-28.3)	< 0.001
NLR	5.0 (3.2-12.0)	9.3 (4.8-19.0)	0.001

Values are presented as numbers (n) and percentages (%), mean ± standard deviation, or median (interquartile range, 25th-75th percentiles). *A p-value of <0.05 was considered statistically significant. Abbreviations: AST, Aspartate Aminotransferase; BMI, Body Mass Index; BUN, Blood Urea Nitrogen; CAD, Coronary Artery Disease; CAR, C-Reactive Protein-to-Albumin Ratio; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; CRP, C-Reactive Protein; CVA, Cerebrovascular Accident; DM, Diabetes Mellitus; HT, Hypertension; IE, Infective Endocarditis; IV, Intravenous; LVEF, Left Ventricular Ejection Fraction; NLR, Neutrophil-to-Lymphocyte Ratio; NT-proBNP, N-Terminal Pro-B-Type Natriuretic Peptide; NYHA, New York Heart Association; PIV, Pan-Immune Inflammation Value; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammatory Response Index; TSH, Thyroid Stimulating Hormone.

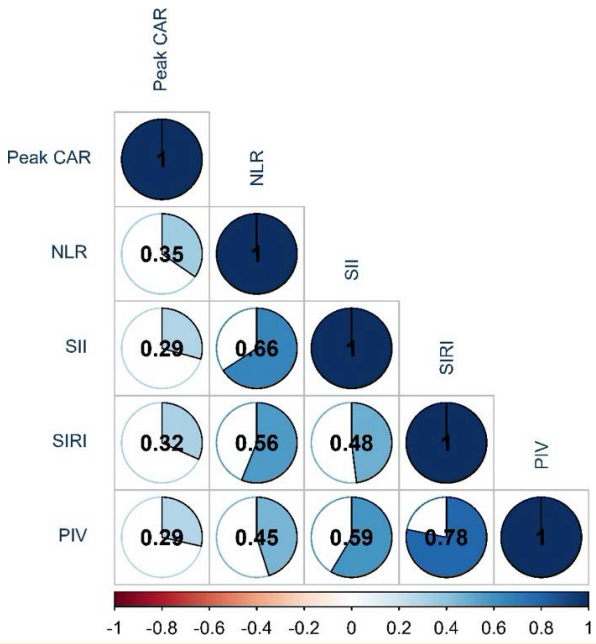

Figure 1. Visualization of the correlation matrix of inflammatory indices. The color legend illustrates the strength of correlation: the intensity of the color reflects the correlation coefficient, with darker shades indicating higher correlation coefficients. Corresponding correlation coefficients are represented using pie charts.

CAR, C-Reactive Protein-to-Albumin Ratio; NLR, Neutrophil-to-Lymphocyte Ratio; PIV, Pan-Immune Inflammation Value; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammatory Response Index.

Multivariate Cox proportional hazards regression analysis, adjusted following univariable analysis of variables selected using the LASSO method, demonstrated that in patients with infective endocarditis, PIV (adjusted HR [aHR] = 1.04, 95% CI: 1.00-1.08, P = 0.039), SII (aHR = 1.13, 95% CI: 1.04-1.23, P = 0.005), NLR (aHR = 1.59, 95% CI: 1.18-2.15, P < 0.001), and peak CAR (aHR = 1.16, 95% CI: 1.10-1.23, P < 0.001) were independently associated with in-hospital mortality (Table 2). Furthermore, multivariable Cox regression analysis including peak CAR revealed that the NYHA class made the largest contribution to the model, followed by peak NT-proBNP and peak CAR (Appendix 1). When examining correlations among hematologic inflammatory biomarkers, peak CAR showed a significant but weak positive correlation with the other indices ($r \leq 0.35$ and $P < 0.05$) (Figure 1).

Results of the ROC analysis indicated that peak CAR had stronger discriminatory power for predicting in-hospital mortality compared to NLR (NRI = 70.1%, IDI = 15.5%), PIV (NRI = 68.8%, IDI = 17.3%), SII (NRI = 71.4%, IDI = 17.8%), and SIRI (NRI = 54.6%, IDI = 14.8%) (Figure 2, Table 3). Kaplan-Meier curve analysis, based on peak CAR dichotomized by X-tile analysis (< 12.7 = low vs. ≥ 12.7 = high), demonstrated that individuals with high peak CAR had increased in-hospital mortality (34.0% vs. 73.3%, plog-rank < 0.001) (Figure 3). Additionally, decision curve analysis showed that models incorporating peak CAR, along with LASSO-derived parameters, provided a net clinical benefit across nearly all thresholds when compared to both the treat-none/treat-all strategies and models without CAR (Figure 4).

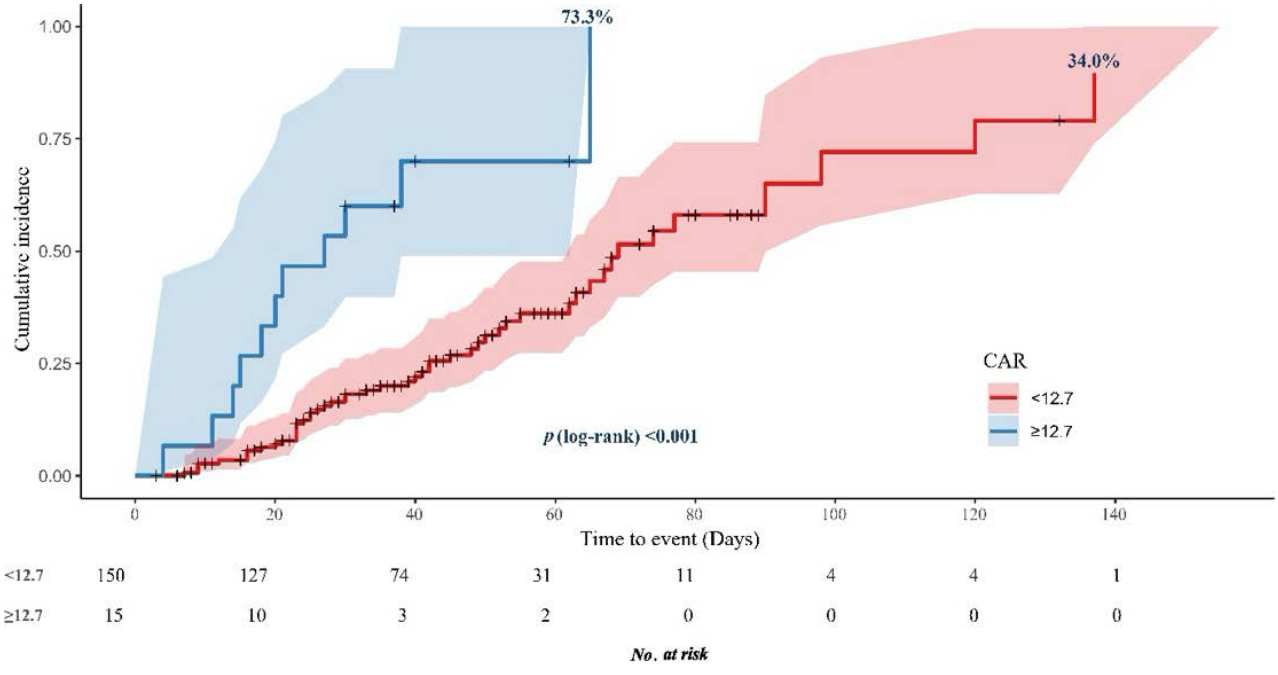

Figure 2. Receiver operating characteristic curve analysis of selected inflammatory biomarkers as predictors of in-hospital mortality among patients with infective endocarditis.

CAR, C-Reactive Protein-to-Albumin Ratio; NLR, Neutrophil-to-Lymphocyte Ratio; PIV, Pan-Immune Inflammation Value; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammatory Response Index.

Table 2. Multivariable proportional hazards regression models for in-hospital mortality

Indices	aHR (95% CI)	P*
PIV, per 1000 units	1.04 (1.00–1.08)	0.039
SII, per 1000 units	1.13 (1.04–1.23)	0.005
SIRI, per 100 units	0.58 (0.22–1.57)	0.300
NLR, per 10 units	1.59 (1.18–2.15)	< 0.001
Peak CAR	1.16 (1.10–1.23)	< 0.001

All models were adjusted for the following covariates; age, body mass index, aspartate transaminase, troponin, white blood cell count, thyroxine (T4) level, urea, NYHA class, peak N-terminal pro-B-type natriuretic peptide level, vegetation size, treatment type, and infective endocarditis type. *A p-value of <0.05 was considered statistically significant. Abbreviations: aHR, Adjusted Hazard Ratio; CAR, C-Reactive Protein-to-Albumin Ratio; CI, Confidence Interval; NLR, Neutrophil-to-Lymphocyte Ratio; PIV, Pan-Immune Inflammation Value; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammatory Response Index.

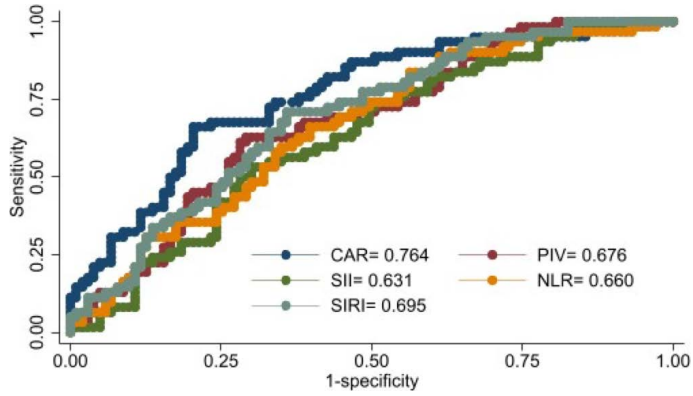

Figure 3. Kaplan-Meier curves illustrating in-hospital mortality stratified by peak C-reactive protein-to-albumin ratio (CAR) levels.

CAR, C-Reactive Protein-to-Albumin Ratio.

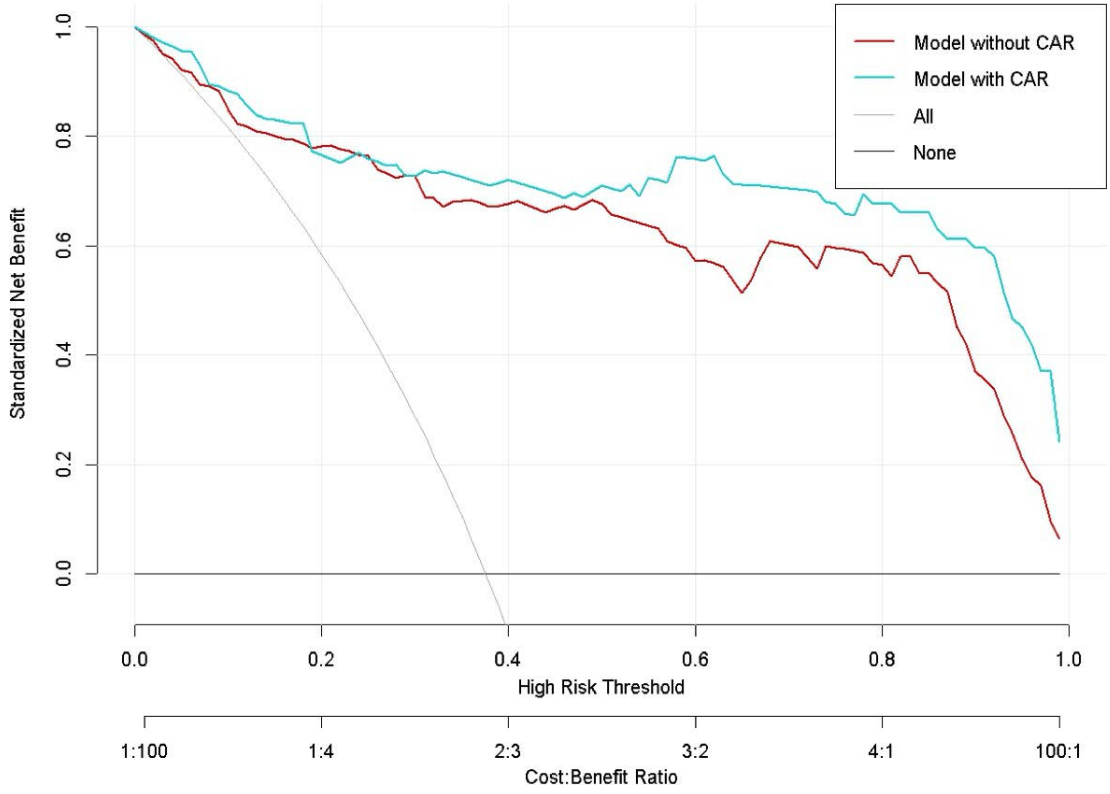

Figure 4. Decision curve analysis illustrating the standardized net benefit of inflammatory indices for predicting in-hospital mortality. The y-axis represents net benefit, while the x-axis indicates the threshold probability of mortality associated with C-reactive protein-to-albumin ratio (CAR).

CAR; C-Reactive Protein-to-Albumin Ratio.

Discussion

In this study, we investigated the predictive value of inflammatory indices for in-hospital mortality in IE patients, with a particular focus on peak CAR, alongside other established risk factors. Our findings highlight the significance of peak CAR as a superior prognostic biomarker in this patient population compared to traditional inflammatory indices.

Despite advances in medical and surgical treatments, high in-hospital mortality rates continue to be reported in patients with IE.[2,3,18] Murdoch et al.[21] reported an in-hospital mortality rate of approximately 18% in a large, international cohort of IE patients, while a multicenter cohort from Türkiye found an in-hospital mortality rate of approximately 33%.[22] In our study, the in-hospital mortality rate was 37.6%, which is relatively higher than those reported in other studies. Several factors may

Table 3. Comparative analyses of the discriminatory and reclassification abilities of certain inflammatory indices in predicting in-hospital all-cause mortality

	Discrimination and reclassification								
	Goodness of fit			Net reclassification improvement			Integrated Discrimination Index		
	C-Index	95% CI	P	NRI	Index (95% CI)	P	IDI	Index (95% CI)	P
CAR	0.764	0.691-0.826	**< 0.001**	ref	ref	-	ref	ref	-
NLR	0.660	0.583-0.732	**0.001**	-0.701	-(0.997-0.405)	**< 0.001**	-0.155	-(0.219-0.091)	**< 0.001**
SII	0.631	0.553-0.705	**0.005**	-0.714	-(1.008-0.420)	**< 0.001**	-0.178	-(0.242-0.114)	**< 0.001**
SIRI	0.695	0.619-0.764	**< 0.001**	-0.546	-(0.850-0.242)	**< 0.001**	-0.148	-(0.215-0.081)	**< 0.001**
PIV	0.676	0.599-0.747	**< 0.001**	-0.688	-(0.985-0.392)	**< 0.001**	-0.173	-(0.237-0.108)	**< 0.001**

*A P-value of <0.05 was considered statistically significant. CAR, C-Reactive Protein-to-Albumin Ratio; CI, Confidence Interval; IDI, Integrated Discrimination Improvement; NLR, Neutrophil-to-Lymphocyte Ratio; NRI, Net Reclassification Improvement; PIV, Pan-Immune Inflammation Value; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammatory Response Index.

explain the elevated mortality rate observed in our study. First, our study population included a higher proportion of patients with critical clinical conditions such as chronic renal failure, stroke, advanced age, and NYHA class III or IV heart failure. Second, as a tertiary referral center, our institution receives patients with more complex and severe clinical presentations, which may contribute to the increased mortality. Third, we observed higher rates of prosthetic valve endocarditis in our cohort, while the rates of surgical intervention, known to be associated with improved outcomes, were relatively low. The challenges of redo surgeries and the high surgical risk associated with comorbidities led both physicians and patients to prefer medical treatment, which was reflected in the mortality rates. In addition to these factors, differences in healthcare systems, diagnostic criteria, and treatment protocols across studies may also contribute to the observed variability in mortality rates.

Owing to the high mortality rate, basic risk classification among IE patients remains a key topic of discussion. Identifying high-risk patients using established predictors aims to improve early referral, surgical management, and treatment-related decision-making. At this point, systemic inflammation, which plays a central role in the pathophysiology of IE, is considered fundamental.[5,7] Numerous studies have focused on the prognostic value of inflammatory markers, and impactful findings continue to emerge for clinical application.[7,10,21] It has been demonstrated that CRP, a well-known marker of inflammation, also holds prognostic value in patients with IE.[7,10,12] The influence of initial CRP levels and/or repeated measurements on outcomes such as mortality and peripheral embolism has been shown in various studies.[12,13] Similarly, serum albumin, another serum parameter, is known to reflect a patient's nutritional and inflammatory status.[23] A low albumin level is a significant determinant of mortality in many cardiovascular diseases, including IE, due to increased inflammation, oxidative stress, and the formation of a pro-thrombotic environment.[11,24-26] Furthermore, combining these two markers into CAR has been shown to enhance prognostic assessment in cardiovascular diseases and more comprehensively reflect the patient's overall condition.[14-17] In a study involving approximately 6,414 sepsis patients, Zhou et al.[27] reported that those with high CAR levels had significantly higher in-hospital mortality compared to those with low CAR. Similarly, Baykız et al.[17] demonstrated that high CAR levels were associated with a composite outcome of mortality and the need for intensive care unit treatment in approximately 196 patients with IE. In the present study, high CAR levels were also associated with in-hospital mortality. Unlike the aforementioned studies, we used peak CAR levels rather than admission CAR, as repeated CRP measurements are known to offer greater sensitivity.[13] Moreover, to increase the sensitivity and accuracy of our analysis, we applied the LASSO regression model to identify predictors of mortality and used X-tile analysis to determine the optimal CAR cutoff value (< 12.7) for clinical risk stratification.

White blood cell subsets and platelets, which are important components of inflammation, are other critical parameters examined to identify risk groups in IE patients.[28] Indices derived from these cell groups, such as SII, NLR, and the platelet-lymphocyte ratio, have been shown to predict outcomes in IE patients in various studies.[17,28,29] In our study, the superiority of peak CAR over other inflammatory indices such as NLR, SII, SIRI, and PIV was notable. As demonstrated in the correlation matrix, peak CAR showed a strong correlation with mortality but only limited correlation with the other indices derived from WBC subsets. While these indices also reflect the systemic inflammatory response, peak CAR exhibited the highest discriminatory ability for predicting in-hospital mortality, as evidenced by ROC curve analysis, as well as NRI and IDI analyses. This suggests that peak CAR captures critical aspects of the inflammatory response not fully accounted for by other indices.

A high CAR level provides prognostic value that complements and enhances the predictive power of traditional markers in infective endocarditis.[7,17] Traditional risk factors such as age, renal insufficiency, cardiac biomarkers, microorganism type, and the presence of heart failure are well-established predictors of adverse outcomes.[3,10] These markers typically reflect individual aspects of the disease process, such as patient demographics, organ dysfunction, or microbial virulence.[3,7] For example, while cardiac biomarkers such as troponins and BNP primarily reflect myocardial stress or injury, CAR provides insight into the systemic burden of inflammation and its impact on the patient's metabolic reserves.[8] Similarly, although renal insufficiency or specific microorganisms like *Staphylococcus aureus* indicate severe disease, these factors do not directly quantify the ongoing inflammatory process.[3] By combining CRP and albumin, CAR offers a dynamic, real-time indicator of the systemic response to infection and the host's capacity to

recover.[15,17] In this study, we observed that patients with higher CAR values had significantly higher in-hospital mortality, even after adjusting for classical prognostic factors. This suggests that CAR captures additional dimensions of patient status that are not fully addressed by traditional markers. Furthermore, the simplicity and accessibility of CAR make it a practical addition to routine clinical assessments.[14,17] Unlike some classical markers that require specialized testing or may have limited availability in resource-constrained settings, CRP and albumin are widely available and cost-effective. This positions CAR as a viable tool for risk stratification, particularly in settings where advanced diagnostic methods are not readily available.

Our study has several limitations. First, the retrospective design may introduce bias and limit the ability to establish a causal relationship between peak CAR and in-hospital mortality. Further prospective studies are needed to validate these findings. Second, this study was conducted at a tertiary care center, and the patient population may not reflect the broader spectrum of IE cases seen in different healthcare settings or geographic regions. This could affect the generalizability of the results. Third, despite rigorous data collection, there may have been missing or incomplete data that could impact the accuracy of inflammatory indices and the overall findings. Fourth, it is important to acknowledge the need for meticulous and cautious interpretation of the results given the limited sample size. To ensure the generalizability of the results, comprehensive studies involving larger and more diverse patient cohorts are required. Lastly, laboratory measurements for CRP and albumin may vary due to differences in assay methods and the timing of sample collection, which could influence the calculation of peak CAR. Additionally, we lacked data on patients' dietary habits, which may have affected albumin levels.

Conclusion

Peak CAR is a valuable prognostic marker for in-hospital mortality in IE patients, outperforming traditional inflammatory markers and other composite indices. Incorporating peak CAR into clinical practice could enhance risk stratification and guide therapeutic decision-making, potentially improving outcomes in this challenging patient population. Future research should aim to validate these findings in larger, multicenter cohorts and explore the potential benefits of targeted interventions based on CAR levels.

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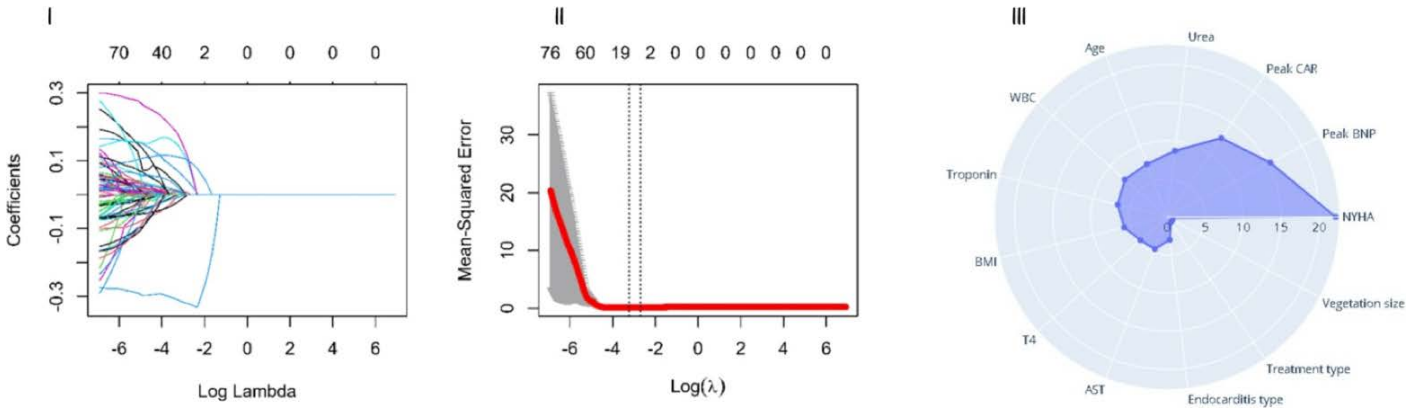
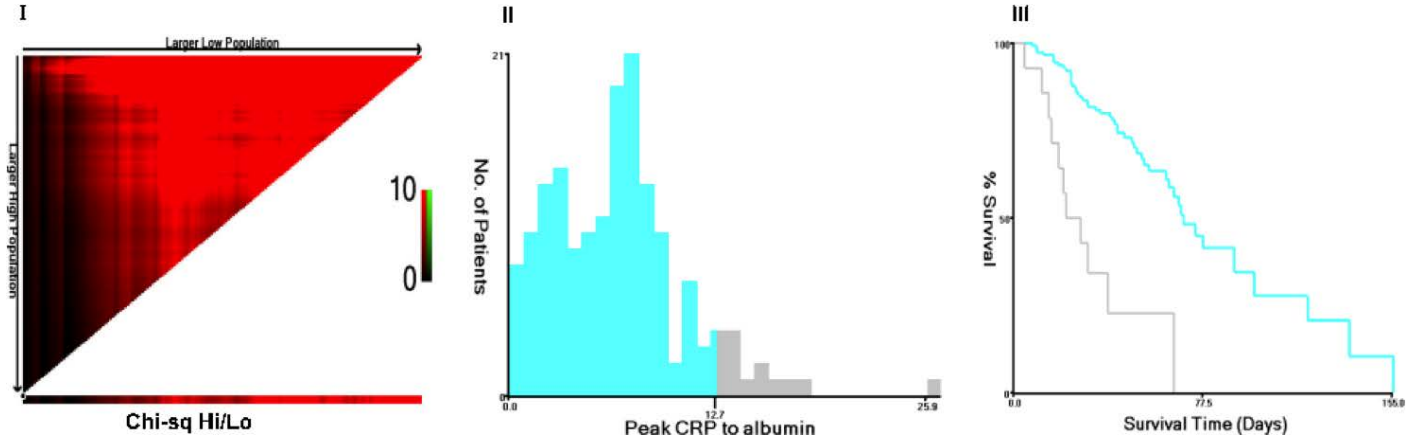


Appendix 1. The least absolute shrinkage and selection operator (LASSO) penalized feature selection to be adjusted for subsequent multivariable Cox regression analyses. I) Coefficient profile plots illustrate how the magnitude of coefficients for covariates decreases as the λ penalty increases. Factors and their corresponding regression coefficients are selected for the model based on the optimal λ value identified by the LASSO model. II) The plot displays the distribution of minimum mean squared errors along with their respective penalization lambda values in the LASSO-penalized model. III) Variable importance plot of the parameters selected with LASSO regression in the model.



Appendix 2. X-tile analysis used to determine the optimal cut-off value for peak C-reactive protein-to-albumin ratio (CAR).

CAR, C-Reactive Protein-to-Albumin Ratio.