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ORIGINAL ARTICLE

Association Between Neutrophil Percentage-to-Albumin Ratio and Clinical Outcomes in Myocardial Infarction with Non-obstructive Coronary Arteries Patients

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Abstract

Introduction: This study sought to analyze the predictive importance of neutrophil percentage/albumin ratio (NPAR) levels at hospitalization for one-year major adverse cardiovascular and cerebrovascular events (MACCE) in patients with non-obstructive myocardial infarction (MINOCA).

Methods: This retrospective cohort study included 495 patients. Patients were categorized into two groups: those with MACCE and those without. The neutrophil percentage-to-albumin ratio (NPAR), C-reactive protein (CRP)/albumin ratio (CAR), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation (SII) index, and advanced lung cancer inflammation index (ALI) were calculated for all patients, and the correlations of these inflammation-based biomarkers with 1-year MACCE were assessed.

Results: CRP, neutrophil count, neutrophil percentage, NLR, SII, CAR, and NPAR were significantly higher in MACCE (+) patients ($p<0.001$). In contrast, body mass index (BMI), lymphocyte count, albumin, and ALI values were markedly lower in the MACCE (+) group ($p<0.001$). In receiver operating characteristic (ROC) curve analysis, NPAR had a greater area under the curve (AUC: 0.970) value than either ALI (AUC: 0.932), SII (AUC: 0.927), or CAR (AUC: 0.928).

Discussion and Conclusion: Inflammatory biomarkers NPAR, CAR, SII, and ALI can predict one-year major adverse cardiovascular and cerebrovascular events for patients with MINOCA. NPAR shows better predictive value compared to other biomarkers.

Keywords: Adverse outcome, inflammatory biomarkers, MINOCA, neutrophil percentage-to-albumin ratio.

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a clinical condition defined by angiographic findings of myocardial infarction (MI) in the absence of significant obstructive coronary artery disease, comprising roughly 5–10% of all acute MI instances [1,2]. The diagnosis and prognosis of MINOCA are challenging due to its heterogeneous underlying mechanisms, including coronary microvascular dysfunction, plaque disruption, vasospasm, and myocarditis [3].

Inflammatory processes play a pivotal role in the initiation and progression of myocardial damage, influencing both obstructive coronary syndromes and MINOCA [4,5]. In recent years, numerous inflammatory biomarkers have been examined as potential prognostic indicators in acute coronary syndromes [6,7]. The neutrophil percentage-to-albumin ratio (NPAR) emerged as a novel inflammatory marker indicative of elevated neutrophilic response and diminished serum albumin levels. These features are often

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associated with systemic inflammatory activity, oxidative stress, and poor nutritional condition [8–10].

Previous studies indicate that increased NPAR levels correlate with heightened morbidity and mortality in critically ill patients, as well as those suffering from sepsis, heart failure, and ischemic stroke [11–13]. Moreover, NPAR was identified as an independent predictor of in-hospital mortality in patients with acute ST-segment elevation myocardial infarction (STEMI) [14]. A further study identified NPAR as an independent predictor of all-cause mortality at 180 days and 365 days in critically ill patients with acute MI [15]. The predictive advantage of NPAR in patients with MINOCA remains largely unexplored. This study evaluated the correlation between NPAR levels upon admission and the occurrence of major adverse cardiovascular and cerebrovascular events (MACCE) within 1 year in patients diagnosed with MINOCA. In addition to NPAR, we evaluated and compared several other widely utilized inflammatory markers in this cohort, namely the C-reactive protein-to-albumin ratio (CAR), the systemic immune-inflammation index (SII), and the advanced lung cancer inflammation index (ALI).

Materials and Methods

Study Population and Design

This retrospective analysis encompassed 7,680 consecutive patients admitted to our tertiary cardiovascular center with acute myocardial infarction from 2015 to 2020. Patients were eligible if they were over 18 years old at the time of presentation, had an acute MI, and satisfied the MINOCA criteria. Patients who did not undergo coronary angiography, had experienced another type of acute myocardial infarction, or had a confirmed diagnosis of myocarditis or Takotsubo syndrome were excluded. In addition, patients with conditions that could potentially influence albuminuria—such as viral hepatitis (defined as positive serologic markers for hepatitis B or C virus and a physician-confirmed diagnosis), excessive alcohol consumption (defined as >1 alcoholic drink per day for women or >2 drinks per day for men), liver cancer, severe hepatic injury (characterized by aspartate aminotransferase [AST], alanine aminotransferase [ALT], and γ-glutamyl transpeptidase [GGT] levels >500 IU/L), or evident malnutrition—were also excluded from the study. Our dataset comprised demographic information, transthoracic echocardiography (TTE) and electrocardiogram (ECG) parameters, laboratory results, prescribed medications, procedural details, and complications, all retrieved from hospital records and national health databases.

Definitions and Study Endpoints

The Fourth Universal Definition of Myocardial Infarction (2018) was applied to define MINOCA and other forms of acute MI. In patients admitted between 2015 and 2018 and included in the study, MINOCA was defined according to the most recent criteria established in 2018. Laboratory diagnosis of MI required elevated cardiac biomarkers above the 99th percentile with a rising or falling pattern, in addition to at least one of the following: ischemic symptoms, ECG changes consistent with ischemia, new regional wall motion abnormalities on TTE, or angiographic evidence of coronary thrombus. Coronary stenosis not resulting in significant obstruction was defined as <50% luminal narrowing. Coronary ectasia was defined as ≥50% dilatation compared with an adjacent normal segment, and coronary slow flow was defined as delayed opacification in the absence of significant epicardial coronary artery stenosis. Progression of index lesions in patients who underwent repeat angiography during follow-up was defined as a visually estimated increase of ≥10% in the degree of stenosis. Repeat angiography was performed due to the diagnosis of acute coronary syndrome or suspicion of coronary artery disease based on clinical, ECG, laboratory, exercise treadmill testing, and non-invasive imaging results. Dyslipidemia was defined as total cholesterol >200 mg/dL, triglycerides >150 mg/dL, LDL cholesterol >100 mg/dL, and/or HDL cholesterol <40 mg/dL [1,16–18].

Inflammatory indices were calculated as follows:

- NPAR: neutrophil percentage×100/serum albumin (g/dL),
- NLR: neutrophil count / lymphocyte count,
- CAR: C-reactive protein (CRP) (mg/dL) / albumin (g/dL),
- SII: platelet count×neutrophil count/lymphocyte count,
- ALI: body mass index × serum albumin / neutrophil-to-lymphocyte ratio (NLR).

The primary endpoint was the occurrence of MACCE within 12 months, defined according to the Academic Research Consortium-2 (ARC-2) consensus, and included cardiovascular death (MI, malignant arrhythmia, heart failure, or stroke), non-fatal MI, non-fatal cerebrovascular accident (ischemic stroke or transient ischemic attack), or cardiovascular rehospitalization due to MI, arrhythmia, heart failure, or stroke [19]. MACCE was evaluated based on hospital medical records, and a total of 495 patients meeting the inclusion criteria with accessible MACCE data were analyzed.

Laboratory Analyses

Laboratory parameters included complete blood counts, liver function tests, renal function tests, electrolytes, lipid

profiles, and cardiac biomarkers measured at admission. High-sensitivity troponin levels were classified into three categories: <10-fold increase, 10–100-fold increase, and >100-fold increase above the upper reference limit.

Coronary Angiography

Coronary angiography was performed using the standard Judkins technique and analyzed by two experienced interventional cardiologists on an Axiom (Siemens Medical Solutions) workstation. Written informed consent was obtained from all patients prior to the procedure.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 30 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean±standard deviation or median with interquartile range, while categorical data are presented as counts and percentages. The Shapiro–Wilk test was applied to evaluate normality, and homogeneity of variance was assessed with Levene's test. For comparisons between two groups, the independent-samples t test was used when normal distribution was confirmed, whereas the Mann–Whitney U test was applied otherwise. Categorical variables were compared with Pearson's chi-square, Yates's chi-square, or Fisher's exact test, as appropriate. When a chi-square result was significant, subgroup comparisons were performed with Bonferroni-adjusted two-proportion Z tests. Correlations between continuous variables were assessed using Spearman's rank correlation coefficient. The predictive ability of biomarkers for MACCE was examined with Receiver Operating Characteristic (ROC) curve analysis. A two-sided p value of <0.05 was considered statistically significant.

Ethics Approval and Compliance Statement

The research followed the ethical guidelines specified in the Declaration of Helsinki. There was no utilization of AI-powered tools such as Large Language Models (LLMs), chatbots, or image generators in developing this article. The study received approval from the ethics committee on March 06, 2025, with reference number E-10840098-202.3.02-1849, under the supervision of the Scientific Research Applications Review Commission.

Results

A total of 495 patients were included in the study, of whom 356 were in the MACCE(–) group and 139 in the MACCE(+) group. The overall incidence of MACCE was higher in male patients compared to females (33.0% vs. 20.3%, p<0.05). Patients in the MACCE(+) group were significantly older than those in the MACCE(–) group. No significant differences were observed between the groups with respect to diabetes mellitus, hypertension, hyperlipidemia, or anemia. However, MACCE incidence was significantly higher in patients with chronic kidney disease (64.0% vs. 25.7%, p<0.001).

The presence of atrial fibrillation was not associated with MACCE. In contrast, a history of MI was strongly associated with MACCE (41.6% vs. 23.5%, p<0.05). Similarly, patients with prior revascularization and those with post-discharge adverse events developed MACCE at markedly higher rates compared to their counterparts (p<0.001 for both). Patients who developed MACCE had a significantly shorter follow-up duration. Troponin stratification did not show a significant association with MACCE.

Regarding laboratory parameters, glucose and creatinine levels were significantly higher in MACCE(+) patients. Conversely, low-density lipoprotein (LDL)-cholesterol and thyroid-stimulating hormone (TSH) levels were significantly lower in the MACCE(+) group.

Ejection fraction (EF) was strongly associated with outcomes: the incidence of MACCE was 72.2% in patients with EF <30%, 50.8% in those with EF 30–50%, and 22.3% in those with EF >50% (p<0.001). Patients with nonobstructive coronary artery stenosis (defined as <50% stenosis) had a significantly higher MACCE incidence compared with those without lesions (32.9% vs. 23.9%, p<0.05). The presence of coronary ectasia, STEMI, or Non-ST-elevation Myocardial Infarction (NSTEMI) presentation did not differ significantly between groups. Coronary slow flow was inversely associated with MACCE, with a lower incidence in patients with slow flow (16.0% vs. 29.7%, p<0.05).

Repeat angiography was significantly associated with MACCE (44.4% vs. 24.3%, p<0.01), as was the progression of native stenoses (53.8% vs. 24.5%, p<0.001).

Inflammatory indicators, including CRP, neutrophil count, neutrophil percentage, NLR, SII, CAR, and NPAR, were considerably higher in MACCE(+) patients compared to MACCE(–) patients (p<0.001). Conversely, BMI, lymphocyte count, albumin, and ALI values were markedly diminished in the MACCE(+) group compared to the MACCE(–) group (p<0.001).

In the comparisons presented in Table 1, parameters that showed significant differences between the MACCE(+) and MACCE(–) groups were further analyzed. The predictive performances of the ALI, SII, CAR, and NPAR for MACCE were evaluated in Table 2 using ROC curve analysis,

Table 1. Comparison of demographic, clinical characteristics, laboratory and angiographic parameters and medications of patients according to MACCE groups

Variable	MACCE (-) n=356		MACCE (+) n=139		Test statistic	p
	n	%	n	%		
Demographics						
Male	191	67.0	94	33.0	9.658	0.002
Female	165	79.7	42	20.3	–	–
Age, (years)	49.9±16.2		55.6±18.1		3.180	0.002
Diabetes	42	65.6	22	34.4	1.303	0.254
Hypertension	66	64.7	36	35.3	3.300	0.069
Dyslipidemia	216	70.4	91	29.6	1.632	0.201
Anemia	26	74.3	9	25.7	0.005	0.945
Chronic renal failure	9	36.0	16	64.0	15.545	<0.001
Atrial fibrillation	30	61.2	19	38.8	2.783	0.095
Prior MI	66	58.4	47	41.6	14.274	<0.001
Revascularization	0	0.0	30	100.0	79.821	<0.001
Death after discharge	0	0.0	102	100.0	336.831	<0.001
Smoking	25	71.4	10	28.6	0.000	1.000
Cerebrovascular disease	3	75.0	1	25.0	–	1.000
Laboratory parameters						
Troponin increase						
<10 fold	182	73.3	65	26.3	0.439	0.803
10–100 fold	90	70.9	37	29.1		
>100 fold	84	71.2	34	28.8		
Glucose (mg/dL)	106 (37.0)		113 (51.8)		2.346	0.019
Hemoglobin (g/dL)	13.58±1.68		13.53±1.75		0.344	0.731
PLT ($\times 10^3$/µL)	230.5 (76.3)		231.5 (81.5)		0.168	0.867
Creatinine (mg/dL)	0.80 (0.20)		0.90 (0.30)		4.339	<0.001
LDL (mg/dL)	106.0 (42.5)		98.5 (56.8)		2.027	0.043
TSH (mU/L)	1.51 (1.77)		1.28 (1.13)		3.321	0.001
Ejection fraction						
<30	5	27.8	13	72.2	40.215	<0.001
30–50	30	49.2	31	50.8		
>50	321	77.7	92	22.3		
Angiographic parameters						
Number of stenosed vessels						
Null	218	76.2	68	23.8	7.314	0.063
One	62	72.1	24	27.9		
Two	31	60.8	20	39.2		
Three	45	65.2	24	34.8		
Coronary lesion (<50%)	217	76.1	68	23.9	4.846	0.028
Ectasia	336	72.4	128	27.6	0.000	1.000
Coronary slow flow	293	70.3	124	29.7	5.330	0.021
NSTEMI	164	76.3	51	23.7	2.936	0.087
STEMI	351	72.8	131	27.2	–	0.149
Recurrent angiography	311	75.7	100	24.3	12.699	<0.001
Native stenosis change	332	75.5	108	24.5	18.523	<0.001
Medications						
Acetylsalicylic acid	265	71.6	105	28.4	0.404	0.525
Clopidogrel	206	74.4	71	25.6	1.281	0.258
Prasugrel	349	72.9	130	27.1	–	0.204

Table 1. Cont.

Variable	MACCE (-) n=356		MACCE (+) n=139		Test statistic	p
	n	%	n	%		
Ticagrelor	343	72.7	129	27.3	0.246	0.620
Beta-blockers	250	73.3	91	26.7	0.508	0.476
ACE inhibitors	241	73.5	87	26.5	0.615	0.433
Statins	232	72.3	89	27.7	0.003	0.955
BMI (kg/m^2)	28.80 (2.30)		28.00 (3.40)		5.173	<0.001
CRP	0.50 (1.50)		3.05 (3.24)		11.312	<0.001
Neutrophil (×10^3/μL)	5.30 (2.60)		7.75 (3.65)		8.803	<0.001
Neutrophil (%)	53.0 (8.0)		67.0 (12.0)		12.798	<0.001
Lymphocyte (×10^3/μL)	2.20 (1.20)		1.80 (1.10)		3.425	<0.001
NLR	2.41 (1.93)		3.67 (3.48)		7.690	<0.001
Albumin (mg/dL)	4.00 (0.20)		3.70 (0.98)		9.032	<0.001
ALI	48.27 (39.08)		26.97 (16.84)		10.137	<0.001
SII	567.7 (468.7)		860.8 (774.4)		7.328	<0.001
CAR	0.13 (0.37)		0.85 (0.86)		11.920	<0.001
NPAR	1329.2 (255.1)		1900.0 (415.3)		14.826	<0.001

MACCE: Major adverse cardiovascular and cerebrovascular events; PLT: Platelet count; LDL: Low-density lipoprotein; TSH: Thyroid-stimulating hormone; NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-Elevation myocardial infarction; ACEIs: Angiotensin-converting-enzyme inhibitors; BMI: Body mass index; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; ALI: Advanced lung cancer inflammation index; SII: Systemic immune-inflammation; CAR: C-reactive protein-to-albumin ratio; NPAR: Neutrophil percentage-to-albumin ratio.

Table 2. Evaluation of Biomarker Performance in Predicting MACCE by receiver operating characteristic (ROC) Curve Analysis

	AUC (95.0% CI)	p	Cutoff	Sensitivity (95.0% CI)	Specificity (95.0% CI)	PPV (95.0% CI)	NPV (95.0% CI)
ALI*	0.932 (0.906–0.953)	<0.001	>39.26	96.3 (91.6–98.8)	78.7 (74.0–82.8)	63.1 (58.3–67.7)	98.2 (95.9–99.3)
SII*	0.927 (0.901–0.949)	<0.001	>526.2	92.6 (86.8–96.4)	79.5 (74.9–83.6)	63.1 (58.1–67.9)	96.6 (94.0–98.1)
CAR*	0.928 (0.902–0.949)	<0.001	>0.67	90.4 (84.1–94.8)	79.8 (75.2–83.8)	62.9 (57.8–67.7)	95.6 (92.9–97.3)
NPAR*	0.970 (0.951–0.983)	<0.001	>1487.8	94.1 (88.7–97.4)	91.6 (88.2–94.2)	80.9 (75.0–85.7)	97.6 (95.4–98.8)

*: The analysis was adjusted for age, sex, glucose, creatinine, LDL, TSH, BMI, CRP, NLR, albumin, chronic renal disease (CRD), ejection fraction (EF), coronary lesion, coronary slow flow, recurrent angiography, and changes in native stenosis. MACCE: Major adversecardiovascular and cerebrovascular events; AUC: Area under the curve; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; ALI: Advanced lung cancer inflammation index; SII: Systemic immune-inflammation; CAR: C-reactive protein-to-albumin ratio; NPAR: Neutrophil percentage-to-albumin ratio.

after adjustment for potential confounding variables (excluding prior MI, revascularization, post-discharge events, and time to death).

According to Table 2 and Figure 1, the area under the curve (AUC) values were 0.932 for ALI, 0.927 for SII, 0.928 for CAR, and 0.970 for NPAR, indicating discriminatory capacity for all indices. Among these, ALI demonstrated the highest sensitivity (96.3%), whereas NPAR exhibited the highest specificity (91.6%). Furthermore, NPAR had the highest positive predictive value (PPV, 80.9%), while ALI achieved the highest negative predictive value (NPV, 98.2%).

According to Table 3, correlation analyses were performed to further evaluate the relationships between NPAR and other inflammatory indices.

In the overall cohort, NPAR demonstrated a statistically significant moderate negative correlation with ALI, a weak positive correlation with SII, and a moderate positive correlation with CAR. In the MACCE(+) group, NPAR

Table 3. Spearman correlation coefficients showing the relationships between biomarkers in the entire patient group and MACCE groups

	All groups			MACCE (+)			MACCE (-)		
	SII	CAR	NPAR	SII	CAR	NPAR	SII	CAR	NPAR
ALİ	-0.876**	-0.432**	-0.524**	-0.893**	-0.280**	-0.361**	-0.824**	0.060ns	-0.303**
SII	–	0.343**	0.386**	–	0.262**	0.285**	–	-0.119ns	0.086ns
CAR	–	–	0.414**	–	–	0.108*	–	–	0.004ns

*: p<0.05, **: p<0.001. MACCE: Major adverse cardiovascular and cerebrovascular events; ALI: Advanced lung cancer inflammation index; SII: Systemic immune-inflammation; CAR: C-reactive protein-to-albumin ratio; NPAR: Neutrophil percentage-to-albumin ratio; ns: Not significant.

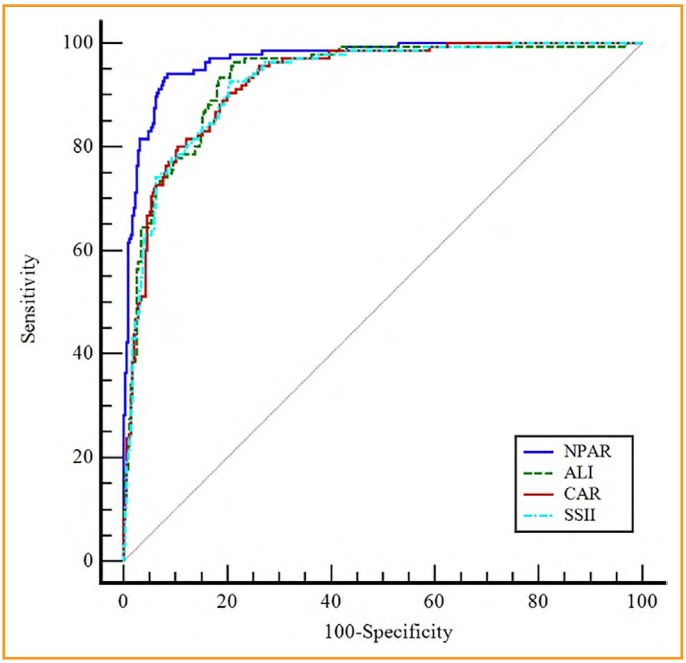

Figure 1. The receiver operating characteristic (ROC) curve analysis of ALI, SII, CAR and NPAR for predicting MACCE.

ALI: Advanced lung cancer inflammation index; SII: Systemic immune-inflammation index; CAR: C-reactive protein-to-albumin ratio; NPAR: Neutrophil percentage-to-albumin ratio; MACCE: Major adverse cardiovascular and cerebrovascular events.

showed a statistically significant weak negative correlation with ALI, a weak positive correlation with SII, and a very weak positive correlation with CAR. In the MACCE(–) group, NPAR exhibited a statistically significant weak negative correlation with ALI, whereas no significant correlations were observed between NPAR and either SII or CAR.

Discussion

This study identified higher NPAR, CAR, and SII, and lower ALI values as independent predictors of one-year MACCE occurrence in MINOCA patients. Among these biomarkers, NPAR was particularly prominent and demonstrated a stronger predictive capacity for 1-year MACCE development compared to other biomarkers. These findings highlight NPAR as a simple, cost-effective, and readily accessible biomarker that could potentially aid in clinical risk stratification and management of MINOCA patients, a group characterized by considerable heterogeneity and diagnostic uncertainty.

The pathophysiological mechanisms of MINOCA are multifaceted and frequently entail inflammatory processes, despite the lack of substantial coronary artery occlusion [20]. Inflammation significantly contributes to MINOCA and serves as a robust prognostic factor. Numerous studies emphasize the importance of inflammatory biomarkers in outcome prediction. Plasma biomarkers, including C-reactive protein (CRP) and interleukin-6 (IL-6), indicate the extent of local vascular inflammation resulting from several non-atherosclerotic etiologies of MINOCA, such as coronary vasospasm and coronary microvascular dysfunction [21,22]. Increased neutrophil levels indicate an acute-phase systemic inflammatory response, linked to plaque destabilization, microvascular dysfunction, and myocardial damage. Neutrophils play a pivotal role in these processes through the release of proteolytic enzymes, reactive oxygen species, and neutrophil extracellular traps (NETs), contributing to endothelial dysfunction and a prothrombotic state [23,24]. On the other hand, hypoalbuminemia may signify chronic inflammation, inadequate nutritional status, or hepatic dysfunction, all of which are recognized predictors of unfavorable outcomes in cardiovascular disease [25,26]. All four biomarkers in our study showed strong associations with one-year MACCE, underscoring the clinical significance of systemic inflammation in MINOCA prognosis. However, our findings suggest that NPAR outperforms these markers, likely due to its ability to capture both increased innate immune activation (via neutrophil percentage) and decreased endogenous antioxidant/anti-inflammatory defenses (via serum albumin levels).

Recent studies demonstrate that NPAR serves as an inflammation-based prognostic predictor for several

cardiovascular disorders, including STEMI and NSTEMI, which are elements of acute coronary syndrome, as well as chronic heart failure and atrial fibrillation (AF) [12,14,27,28]. In a comparable manner, a study by Huang et al. [29] similarly identified CAR as a predictor of MACCE in patients with STEMI and hypertension. Zhang et al. [30] conducted a study demonstrating that SII elevated the risk of MACCE in patients with STEMI undergoing coronary angiography. A study conducted by Trimarchi et al. [31] identified ALI as an independent predictive indicator for all-cause mortality in patients with STEMI. The study by Zhou et al. [22] established a correlation between various biomarkers and the incidence of MACE in patients with MINOCA. One such biomarker is SII. Zhao et al. [32] revealed that low ALI values independently predicted MACCE in patients with MINOCA. Despite these findings, the relationship between NPAR, CAR, and adverse outcomes in MINOCA had not been previously established. Our study fills this gap and suggests that NPAR, due to its accessibility and strong predictive power, may serve as a valuable tool for early risk assessment and personalized management strategies in MINOCA patients.

Limitations

This study possesses multiple limitations that warrant consideration. The principal restriction is its retrospective, single-center design. Secondly, biomarker levels were evaluated solely at baseline and may not represent temporal fluctuations. Third, although there is a considerable population from a particular patient category, the overall number may be inadequate to extrapolate our findings to all MINOCA patients. Fourth, even adjusting for many confounders, the potential for enduring confounding remains uneliminated. Additionally, the presence of albuminuria in patients with chronic kidney disease constituted an important limitation of the study, as it may have influenced serum albumin levels and, consequently, the interpretation of their prognostic value. Consequently, further rigorously planned, prospective, multicenter trials are required to validate and enhance our findings.

Conclusion

In MINOCA patients, this study identified higher NPAR, CAR, SII, and lower ALI values as independent predictors of 1-year MACCE development. In comparison to other biomarkers, NPAR reveals superior predictive value. Due to its simplicity, accessibility, and predictive capability, NPAR may function as an essential instrument for early risk categorization and tailored management measures in MINOCA.

Ethics Committee Approval: The study was approved by Medipol University Ethics Committee (No: E-10840098-202.3.02-1849, Date: 06.03.2025).

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Conflict of Interest: The authors declare that there is no conflict of interest.

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