Clin. Lab. 2026;72:XXX-XXX

ORIGINAL ARTICLE

Prognostic Value of NPAR/UAR in MINOCA Patients with Coronary Slow Flow Phenomenon

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SUMMARY

Background: **Patients with myocardial infarction with non-obstructive coronary arteries (MINOCA) combined with the coronary slow flow phenomenon (CSFP) often exhibit microvascular dysfunction. However, the underlying inflammation-metabolism interplay and effective prognostic tools remain unclear. This study aimed to investigate the predictive value of two novel inflammation-metabolism composite biomarkers, the neutrophil-to-albumin ratio (NPAR) and the uric acid-to-albumin ratio (UAR), in MINOCA patients with CSFP and to assess the synergistic effect of these markers on short-term outcomes.**

Methods: **A total of 176 MINOCA patients were prospectively enrolled, including 61 with CSFP diagnosed via corrected TIMI frame count (CTFC) and 115 with normal coronary flow as controls. Baseline clinical data, inflammation-metabolism biomarkers (NPAR, UAR), and imaging parameters were collected. Patients were followed for one year to track a composite endpoint, including cardiovascular death, recurrent myocardial infarction, and heart failure hospitalization. Multivariable logistic regression and Cox proportional hazards models were used to analyze the independent and interactive effects of NPAR and UAR. Model performance improvement was evaluated using the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) indices.**

Results: **MINOCA patients with CSFP showed significantly elevated levels of both NPAR and UAR. Multivariate analysis revealed that NPAR (OR = 1.45, p = 0.008), UAR (OR = 1.35, p = 0.04), and their interaction term (OR = 1.30, p = 0.02) were independent predictors of the composite endpoint. Combined assessment of these biomarkers significantly improved risk stratification (AUC increased from 0.73 to 0.75; NRI = 0.12, IDI = 0.015). The Cox model further confirmed an increased risk of 30% of adverse events with NPAR/UAR interaction (HR = 1.30, p = 0.027), with no significant effect modification by CSFP status (p > 0.05).**

Conclusions: **Elevated NPAR and UAR levels jointly predict poor short-term outcomes in MINOCA patients, and their synergistic effect is independent of CSFP status. These findings suggest a novel biomarker-based strategy for risk stratification and targeted intervention in microvascular myocardial infarction.**

(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.250540)

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Manuscript accepted June 15, 2025

KEYWORDS

MINOCA, coronary slow flow phenomenon, neutrophil-to-albumin ratio, uric acid-to-albumin ratio, prognostic prediction, inflammation-metabolism interaction

INTRODUCTION

MINOCA is a distinct subtype of acute myocardial infarction characterized by angiographic evidence of < 50% stenosis in major coronary arteries, accompanied by clear signs of myocardial ischemia [1]. Although

MINOCA accounts for approximately 6% to 15% of all acute myocardial infarctions, its underlying pathophysiology is heterogeneous, involving mechanisms such as microvascular dysfunction, plaque disruption, and coronary vasospasm [2]. In recent years, the coronary slow flow phenomenon (CSFP), a recognized angiographic manifestation of microcirculatory disturbance, has been reported in 30% - 40% of MINOCA patients and is strongly associated with an increased risk of adverse cardiovascular events [3,4]. However, the precise pathophysiological mechanisms of CSFP remain poorly understood. Current evidence suggests a potential involvement of endothelial dysfunction, impaired coronary flow reserve, and low-grade inflammation [5,6], contributing to significant challenges in risk stratification and outcome prediction for this patient population.

Inflammatory responses and metabolic dysregulation play dual pathogenic roles in both atherosclerosis and microvascular dysfunction. Neutrophil infiltration, for example, can impair endothelial function and promote microthrombus formation by releasing myeloperoxidase (MPO) and forming neutrophil extracellular traps (NETs) [7]. Meanwhile, uric acid dysregulation exacerbates oxidative stress via activation of the NLRP3 inflammasome and induces vasoconstriction by reducing nitric oxide (NO) bioavailability [8,9]. The NPAR and the uric UAR have emerged as novel inflammation-metabolism composite biomarkers that quantify, respectively, the burden of neutrophil-mediated inflammatory activation and uric acid-driven metabolic imbalance. Their combined application may offer a more comprehensive reflection of the synergistic dysregulation in the inflammation-metabolism network underlying microvascular pathology. Previous studies have preliminarily demonstrated that elevated NPAR is an independent predictor of CSFP in patients with ischemia and no obstructive coronary artery disease (INOCA) [10], while UAR has shown predictive value for CSFP in patients with chronic coronary syndrome [11]. However, these studies were limited to linear analyses of single biomarkers and did not explore the dynamic interaction between NPAR and UAR, nor did they elucidate the potential synergistic role of these markers in predicting adverse outcomes related to microvascular myocardial injury.

In the unique clinical context of MINOCA, the prognostic value of inflammation-metabolism composite biomarkers has not been systematically evaluated. Although associations between either NPAR or UAR and adverse outcomes have been reported in other cardiovascular diseases [12,13], their combined predictive utility for short-term prognosis in MINOCA patients remains unknown. Moreover, it is unclear whether CSFP, as an angiographic phenotype of microvascular dysfunction, may worsen prognosis further by modifying inflammation-metabolism pathways, for instance, by amplifying the endothelial toxicity of the neutrophil-uric acid axis. Currently, there is a lack of evidence addressing this question. This knowledge gap significantly limits the development of precise risk stratification strategies for patients with MINOCA and concurrent CSFP. For example, guideline-recommended risk scores such as the GRACE score rely predominantly on conventional risk factors and myocardial injury markers [14,15] while largely neglecting microvascular-specific pathological mechanisms such as inflammation-metabolism interactions. This inadequacy may lead to substantial misclassification of risk in MINOCA patients, particularly within the CSFP subgroup.

Given this background, the present study employed a prospective observational cohort design to systematically investigate the expression profiles of NPAR and UAR in MINOCA patients with CSFP and evaluate their predictive value for 1-year composite cardiovascular outcomes. Through multidimensional data collection including inflammatory, metabolic, and clinical endpoints and advanced statistical modeling (interaction term analysis, Cox proportional hazards regression, and model performance optimization), the study aimed to address the following key scientific questions: 1) Do MINOCA patients with CSFP exhibit a distinct inflammation-metabolism biomarker profile? 2) Can the synergistic effect of NPAR and UAR independently predict short-term adverse outcomes? 3) Does CSFP status modify the prognostic utility of these biomarkers via interaction with inflammation-metabolism pathways? This research seeks to address current limitations in MINOCA risk stratification tools outlined in existing guidelines and to provide a biomarker-based rationale for targeted therapeutic strategies addressing microvascular dysfunction.

MATERIALS AND METHODS

Study population

This was a prospective observational cohort study enrolling patients who presented with chest pain or symptoms of myocardial ischemia and underwent coronary angiography. The inclusion criteria were as follows: 1) diagnosis of MINOCA according to the Fourth Universal Definition of Myocardial Infarction (2018), defined by elevated high-sensitivity cardiac troponin T (≥ 99th percentile of the upper reference limit) and < 50% stenosis in major coronary arteries on angiography [16]; 2) age between 18 and 80 years; 3) diagnosis of coronary slow flow phenomenon (CSFP) based on CTFC criteria CTFC ≥ 36 frames in the left anterior descending artery (LAD), ≥ 22 frames in the left circumflex artery (LCx), and ≥ 21 frames in the right coronary artery (RCA); and 4) provision of written informed consent. Exclusion criteria included: 1) identifiable causes of myocardial injury other than MINOCA (e.g.myocarditis, pulmonary embolism, severe anemia); 2) history of coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI); 3) severe hepatic or renal dysfunction (estimated glomerular filtration rate [eGFR] < 30 mL/minute/1.73 m² or Child-Pugh Class C); 4) active malig-

nancy or ongoing immunosuppressive therapy; and 5) use of medications known to affect microvascular circulation (e.g. nicorandil, calcium channel blockers, ranolazine) within 30 days prior to enrollment. All patients received secondary preventive medical therapy according to the latest clinical guidelines, and coronary lesions were systematically assessed via angiography.

This study was approved by the Ethics Committee of Yanting County People's Hospital. Written informed consent was obtained from all participants. The study protocol strictly adhered to the ethical principles outlined in the Declaration of Helsinki.

Data collection

Demographic and clinical characteristics: The following baseline information were recorded: age, sex, body mass index (BMI), smoking history, and blood pressure levels. Comorbid conditions were defined as follows: hypertension (systolic/diastolic blood pressure ≥ 140/90 mmHg), diabetes mellitus (HbA1c ≥ 6.5%), and hyperlipidemia (LDL-C ≥ 3.4 mmol/L). Medication usage at admission was also documented.

Blood sample collection

Fasting venous blood samples were collected within 24 hours of admission using vacuum tubes with or without EDTA-K2 anticoagulant. For samples with anticoagulant, blood was first centrifuged for 15 minutes at 800 g and 4°C. The supernatant was transferred to a new tube and centrifuged again for 10 minutes at 1,600 g and 4°C. Plasma was then aliquoted into cryovials and stored at -80°C. For samples without anticoagulant, blood was allowed to clot at room temperature for 2 hours, followed by centrifugation for 20 minutes at 1,000 g and 4°C.

The supernatant was transferred to a new tube and centrifuged again for 10 minutes at 1,600 g and 4°C and stored as mentioned above.

All laboratory personnel performing the assays were blinded to the clinical outcomes of the participants.

Biochemical measurements and calculations

Laboratory parameters included: white blood cell count (WBC), platelet count, lymphocyte count (LYM), monocyte count (M), neutrophil count, hemoglobin, uric acid, high-sensitivity cardiac troponin T (hs-cTnT), B-type natriuretic peptide (BNP), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).

Coronary angiography and assessment of CSFP

All patients underwent standard coronary angiography via the radial artery approach. Two independent interventional cardiologists, blinded to clinical data, assessed the angiograms.

Stenosis severity: Quantitative coronary angiography (QCA) software was used to measure the degree of stenosis. Patients with ≥ 50% narrowing in major epicardial vessels (left main, left anterior descending [LAD], left circumflex [LCX], or right coronary artery [RCA]) were excluded.

TIMI frame count measurement: Angiographic images were recorded at 30 frames per second. TIMI frame count was defined as the number of cine frames required for contrast to reach a standardized distal landmark: the "tip of the bifurcation" for LAD and the origin of the posterior descending artery for RCA. The CTFC was calculated, and the average of three measurements was used.

Diagnosis of CSFP: Coronary slow flow phenomenon (CSFP) was diagnosed if any of the following criteria were met: LAD CTFC ≥ 36 frames, LCX CTFC ≥ 22 frames, or RCA CTFC ≥ 21 frames.

Follow-up and endpoint definitions

All patients were followed-up at 30 days, 3 months, 6 months, and 12 months post-discharge using standardized protocols. Data were collected through outpatient visits, structured telephone interviews, or electronic medical records. Primary endpoint: The primary outcome was a composite of major adverse cardiovascular events (MACE) and ischemia-driven events. MACE included cardiovascular death, nonfatal myocardial infarction, hospitalization for heart failure, and ischemic stroke. Ischemia-driven events included urgent revascularization (PCI or CABG) and hospitalization for unstable angina. The lost-to-follow-up rate was maintained below 5%. Missing data were handled using multiple imputation techniques.

Statistical analysis

Sample size estimation: Based on previous literature, the 1-year incidence of composite endpoints in MINOCA patients with CSFP is approximately 25% - 40%. Assuming $\alpha = 0.05$ and $\beta = 0.2$, a minimum of 150 patients was required.

Statistical analyses were performed using SPSS, version 23.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to assess data normality. Normally distributed continuous variables were expressed as mean ± standard deviation (mean ± SD) and compared using Student's *t*-test. Non-normally distributed data were expressed as median (interquartile range, IQR) and compared using the Mann-Whitney U test. Categorical variables were presented as frequencies (n) and percentages (%) and compared using the chi-squared test or Fisher's exact test, as appropriate.

Variables with a p-value < 0.10 in univariate analysis were included in multivariate logistic regression, with the presence of CSFP in MINOCA patients as the dependent variable. To eliminate the effect of differing units, continuous variables (NPAR and UAR) were standardized using Z-scores. Results were reported as odds ratios (OR) and 95% confidence intervals (95% CI) per one standard deviation (SD) increase. Model 1 (main effects model) included NPAR, UAR, and covariates identified in univariate screening (e.g. age, gender, diabetes).

Model 2 (interaction model) added the NPAR × UAR interaction term to Model 1. The goodness-of-fit between models was compared using the likelihood ratio test (LRT), and model parsimony was assessed using the Akaike Information Criterion (AIC). Collinearity diagnostics: Variance inflation factors (VIFs) were calculated, with VIF < 5 indicating no significant multicollinearity. Survival analysis: Kaplan-Meier curves were used to estimate event-free survival in MINOCA patients with and without CSFP. Differences between groups were assessed using the log-rank test. The significance level was set at $\alpha = 0.05$. Cox proportional hazards models: Time-to-event outcomes were analyzed using Cox regression to evaluate the independent and interaction effects of NPAR, UAR, and CSFP status. Model 1: Adjusted for age, gender, diabetes, and other covariates to assess the independent prognostic value of NPAR, UAR, and CSFP. Model 2 included interaction terms (NPAR × CSFP and UAR × CSFP) to evaluate effect modification by CSFP status. Wald tests were used to assess statistical significance, with results reported as hazard ratios (HR) and 95% CI. Receiver operating characteristic (ROC) curves were used to calculate the area under the curve (AUC). The net reclassification improvement (NRI) and IDI were calculated to quantify the added predictive value of interaction terms for risk stratification.

RESULTS

Comparison of baseline characteristics between MINOCA patients with and without CSFP

This study compared the baseline characteristics of 61 MINOCA patients with CSFP and 115 patients with normal coronary blood flow (Table 1). The results showed no significant differences between the two groups in terms of age (59.3 ± 9.6 vs. 60.5 ± 8.7 years), gender composition (male 70.5% vs. 70.4%), and vital signs (heart rate, blood pressure, left ventricular ejection fraction) (all $p > 0.05$). Notably, the smoking rate was significantly higher in the CSFP group compared to the control group (39.3% vs. 21.7%, $p = 0.013$). There were no significant differences in the comorbidity spectrum (hypertension, diabetes, hyperlipidemia, etc.) or the use of cardiovascular medications (statins, antiplatelet drugs, RAS inhibitors, etc.) between the two groups (all $p > 0.05$). This finding suggests that smoking may be a potential risk factor for the development of CSFP in MINOCA patients, while other baseline characteristics and treatment strategies showed no intergroup heterogeneity.

Comparison of laboratory findings between MINOCA patients with and without CSFP

This study compared the laboratory results between 61 MINOCA patients with CSFP and 115 patients with normal coronary blood flow (Table 2). The results showed that the CSFP group exhibited significant inflammation-metabolism dysregulation features: neutrophil percentage was significantly higher (66.2% vs. 62.1%, $p < 0.001$), along with increased levels of uric acid (375.9 vs. 309.0 μmol/L) and LDL-C (2.40 vs. 2.17 mmol/L) (both $p < 0.05$); hemoglobin levels were significantly lower (37.9 vs. 41.2 g/L, $p < 0.001$). Although there was a trend towards an increase in WBC count (8.41×10^9/L vs. 7.69×10^9/L, $p = 0.058$), no significant differences were observed in other markers such as platelet count, lymphocyte count, monocyte count, hs-cTnT, BNP, or triglycerides (all $p > 0.05$). As shown in Figure 1, MINOCA patients with CSFP exhibited significantly higher NPAR and UAR, and these differences were highly statistically significant ($p < 0.001$ for both). Further survival analysis (Figure 2) revealed that the cumulative incidence of composite endpoints (median follow-up of 13 months, IQR 12 - 15 months) was significantly higher in the CSFP group than in the normal blood flow group (Log-rank $p = 0.033$). This finding suggests that CSFP patients have neutrophil-driven inflammation activation and uric acid metabolism imbalance, providing critical pathophysiological evidence for the prognostic study of NPAR/UAR combined biomarkers.

Interaction of NPAR/UAR: results of multivariate logistic regression analysis

In the multivariate logistic regression analysis, independent variables with statistical significance ($p < 0.05$) from the univariate analysis were included, such as current smoking, STEMI, LDL-C, NPAR, and UAR, with age and gender included as confounders. The results of Model 1 (main effects model) and Model 2 (model with interaction term) are shown in Table 3. The median follow-up time was 13 months [IQR 12 - 15]. Model 1 showed that current smoking (OR = 1.85, 95% CI 1.15 - 2.98, $p = 0.01$), NPAR (OR = 1.45, 95% CI 1.10 - 1.91, $p = 0.008$), and UAR (OR = 1.35, 95% CI 1.02 - 1.78, $p = 0.04$) were independent risk factors for composite endpoint events. LDL-C, age, and gender did not show statistical associations ($p > 0.05$).

Model 2 further included the standardized interaction term NPAR × UAR, which showed a significant synergistic effect (OR = 1.30, 95% CI 1.05 - 1.61, $p = 0.02$), suggesting that the combined increase in NPAR and UAR could additionally increase the risk of endpoint events by 30%. The effect sizes of the main effect variables (such as smoking, STEMI, NPAR, and UAR) remained stable in Model 2, with no statistical difference in OR values compared to Model 1 ($\Delta OR < 5\%$). Collinearity diagnostics revealed that the variance inflation factors (VIF) for all variables were below 5 (NPAR = 1.8, UAR = 2.1, NPAR × UAR = 3.5), indicating no significant collinearity interference in the model.

In terms of model performance (Table 4), the inclusion of the interaction term slightly improved the discriminative ability of Model 2 compared to Model 1: AUC increased from 0.73 (95% CI 0.68 - 0.78) to 0.75 (95% CI 0.70 - 0.80), and the likelihood ratio test supported the

Table 1. Baseline characteristics of MINOCA patients with and without CSFP.

		Coronary slow flow (n = 61)	Normal coronary flow (n = 115)	p-value
Age, years		59.3 ± 9.6	60.5 ± 8.7	0.820
Gender	male	43 (70.49%)	81 (70.43%)	0.994
	female	18 (29.51%)	34 (29.57%)	
BMI, kg/m^2		24.9 ± 2.6	25.3 ± 2.4	0.719
Current smoking		24 (39.34%)	25 (21.74%)	0.013
Heart rate, beats per minute		81.2 ± 17.3	80.6 ± 21.0	0.636
SBP, mmHg		143.6 ± 20.3	141.6 ± 21.5	0.601
DBP, mmHg		82.3 ± 12.4	80.6 ± 13.7	0.519
LVEF, %		54.3 ± 11.9	55.6 ± 11.6	0.698
Hypertension		32 (52.46%)	48 (41.74%)	0.174
Diabetes mellitus		8 (13.11%)	20 (17.39%)	0.460
Hyperlipidemia		7 (11.48%)	20 (17.39%)	0.300
Heart failure		2 (3.28%)	3 (2.61%)	1.000
Atrial fibrillation		7 (11.48%)	10 (17.39%)	0.300
Mild coronary stenosis		32 (52.46%)	59 (51.30%)	0.884
Medications				
Statins		55 (90.16%)	100 (86.96%)	0.532
Aspirin		50 (81.97%)	99 (86.09%)	0.470
Clopidogrel		49 (80.33%)	90 (78.26%)	0.749
ACEI/ARB/ARNI		27 (44.26%)	60 (52.17%)	0.318
Beta-blocker		38 (62.30%)	66 (57.39%)	0.529
CCB		13 (21.31%)	32 (27.83%)	0.889

BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, LVEF left ventricular ejection fraction, ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker, ARNI angiotensin receptor-neprilysin inhibitor, CCB calcium channel blocker.

Table 2. Laboratory findings of MINOCA patients with and without CSFP.

	Coronary slow flow (n = 61)	Normal coronary flow (n = 115)	p-value
WBC, × 10^9/L	8.41 [6.12, 10.60]	7.69 [5.32, 10.2]	0.058
Platelet, × 10^9/L	245.75 [199.25, 298.00]	240.30 [183.25, 287.00]	0.251
LYM, × 10^9/L	1.37 [1.03, 2.30]	1.46 [1.19, 2.25]	0.429
M, × 10^9/L	0.50 [0.21, 0.78]	0.49 [0.23, 0.81]	0.239
Neutrophils, %	66.2 [60.3, 74.0]	62.1 [51.9, 71.2]	< 0.001
Hemoglobin, g/L	37.9 [36.7, 39.6]	41.2 [39.5, 42.8]	< 0.001
Uric acid, µmol/L	375.9 [296.2, 431.7]	309.0 [241.7, 380.4]	< 0.001
hs-cTnT, ng/L	53.3 [26.7, 98.6]	50.3 [26.7, 108.8]	0.618
BNP, pg/mL	157.5 [108.6, 269.4]	150.5 [93.6, 289.4]	0.328
TG, mmol/L	1.36 [0.88, 1.90]	1.26 [0.82, 1.92]	0.425
HDL-C, mmol/L	1.12 ± 0.30	1.08 ± 0.31	0.591
LDL-C, mmol/L	2.40 [2.05, 3.16]	2.17 [1.80, 2.60]	0.031

WBC white blood cell, LYM lymphocyte, M monocyte, hs-cTnT high-sensitivity cardiac troponin T, BNP B-type natriuretic peptide, TG triglycerides, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol.

Table 3. Multivariate logistic regression analysis of risk factors associated with CSFP in MINOCA patients.

	Model 1 (main effects)		Model 2 (interaction term)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Current smoking (yes)	1.85 (1.20 - 2.98)	0.010	1.88 (1.16 - 3.04)	0.01
LDL-C	1.03 (0.98 - 1.08)	0.250	1.02 (0.91 - 1.07)	0.460
NPAR	1.38 (1.05 - 1.81)	0.020	1.33 (1.01 - 1.76)	0.050
UAR	1.52 (1.15 - 2.01)	0.004	1.43 (1.08 - 1.89)	0.010
NPAR × UAR	/	/	1.30 (1.05 - 1.61)	0.020

Table 4. Comparison of model performance.

	Model 1 (main effects)	Model 2 (interaction term)	Comparison results
AUC (95% CI)	0.73 (0.68 - 0.78)	0.75 (0.70 - 0.80)	ΔAUC = 0.02, p-value = 0.12
NRI (95% CI)	0.10 (0.02 - 0.20)		p-value = 0.02
IDI (95% CI)	0.013 (0.001 - 0.027)		p-value = 0.03
Likelihood ratio Test (vs. Model 1)	$\chi^2 = 4.12$		p-value = 0.023

AUC area under the curve, 95% CI 95% confidence interval, NRI net reclassification improvement, IDI integrated discrimination improvement.

Table 5. Cox proportional hazards regression analysis of the association between NPAR, UAR, and adverse outcomes in MINOCA patients.

	Univariate analysis		Multivariate model 1		Multivariate model 2	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.21 (1.06 - 1.32)	0.015	1.09 (0.86 - 3.36)	0.108	1.10 (0.80 - 3.06)	0.098
Current smoking (yes vs. no)	1.65 (1.20 - 2.27)	0.002	1.53 (1.14 - 2.09)	0.015	1.40 (1.09 - 2.10)	0.018
Diabetes (yes vs. no)	1.48 (1.10 - 1.99)	0.010	1.23 (1.03 - 1.76)	0.042	1.11 (1.00 - 2.23)	0.044
NPAR	1.58 (1.00 - 2.35)	0.005	1.25 (1.00 - 1.65)	0.039	1.16 (0.98 - 1.49)	0.06
UAR	1.62 (1.21 - 2.83)	0.001	1.30 (1.01 - 1.83)	0.027	1.23 (1.09 - 1.48)	0.039
NPAR × UAR	1.29 (1.18 - 2.75)	0.009	1.18 (1.08 - 1.55)	0.033	1.13 (1.03 - 1.62)	0.052
CSFP (yes vs. no)	1.23 (1.00 - 1.68)	0.005	1.09 (0.99 - 1.48)	0.048	1.09 (0.99 - 1.48)	0.048
NPAR × CSFP	/	/	/	/	1.10 (0.78 - 1.65)	0.158
UAR × CSFP	/	/	/	/	1.19 (0.86 - 2.02)	0.119

significantly better fit of Model 2 ($\chi^2 = 4.12$, p = 0.04). The net reclassification improvement (NRI = 0.12, 95% CI 0.02 - 0.22, p = 0.02) and the integrated discrimination improvement (IDI = 0.015, 95% CI 0.001 - 0.029, p = 0.03) further confirmed that the inclusion of the interaction term optimized the classification ability of high-risk patients.

Table 6. ROC results of different models for predicting 1-year adverse outcomes in MINOCA patients.

	Multivariate model 1	Multivariate model 2	Comparison results
C-index	0.70 (0.62 - 0.77)	0.68 (0.60 - 0.77)	ΔC-index = -0.01, p = 0.25
AUC (95% CI)	0.73 (0.60 - 0.78)	0.70 (0.59 - 0.76)	ΔAUC = -0.01, p = 0.35
NRI (95% CI)	0.04 (-0.02 - 0.20)		p-value = 0.37
IDI (95% CI)	0.013 (-0.001 - 0.027)		p-value = 0.42
Likelihood ratio test (vs. Model 1)	χ^2 = 2.10		p-value = 0.35

AUC area under the curve, 95% CI 95% confidence interval, NRI net reclassification improvement, IDI integrated discrimination improvement.

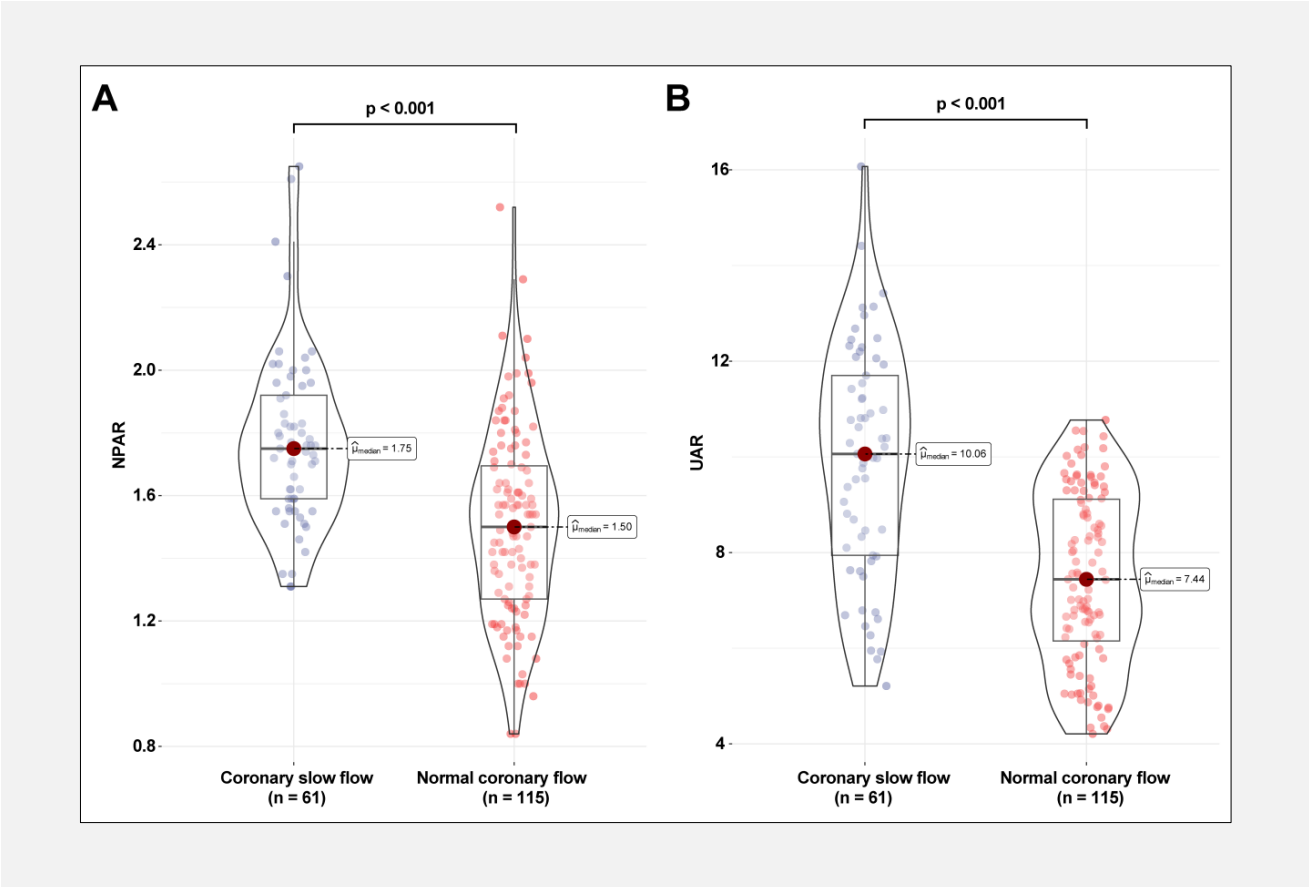

Figure 1. Comparison of NPAR and UAR levels in MINOCA patients with and without CSFP.

Synergistic effect of NPAR/UAR and CSFP status on prognosis of MINOCA patients and model optimization analysis

This study systematically evaluated the correlation between inflammation-metabolism combined biomarkers (NPAR, UAR) and adverse prognosis in MINOCA patients using the Cox proportional hazards regression model (Table 5). Potential risk factors for adverse prognosis in MINOCA patients, including age, gender, current smoking, hypertension, diabetes, hyperlipidemia, heart failure, atrial fibrillation, CSFP, WBC, platelet, lymphocytes, and the interaction term NPAR × UAR, were first included in the model. The univariate results showed that age, current smoking, diabetes, hyperlipidemia, CSFP, as well as NPAR, UAR, and NPAR × UAR, were risk factors for cumulative adverse events in patients ($p < 0.05$).

Multivariate analysis demonstrated that after adjusting for traditional risk factors such as age, smoking history, and diabetes, NPAR (HR = 1.25, 95% CI 1.00 - 1.65,

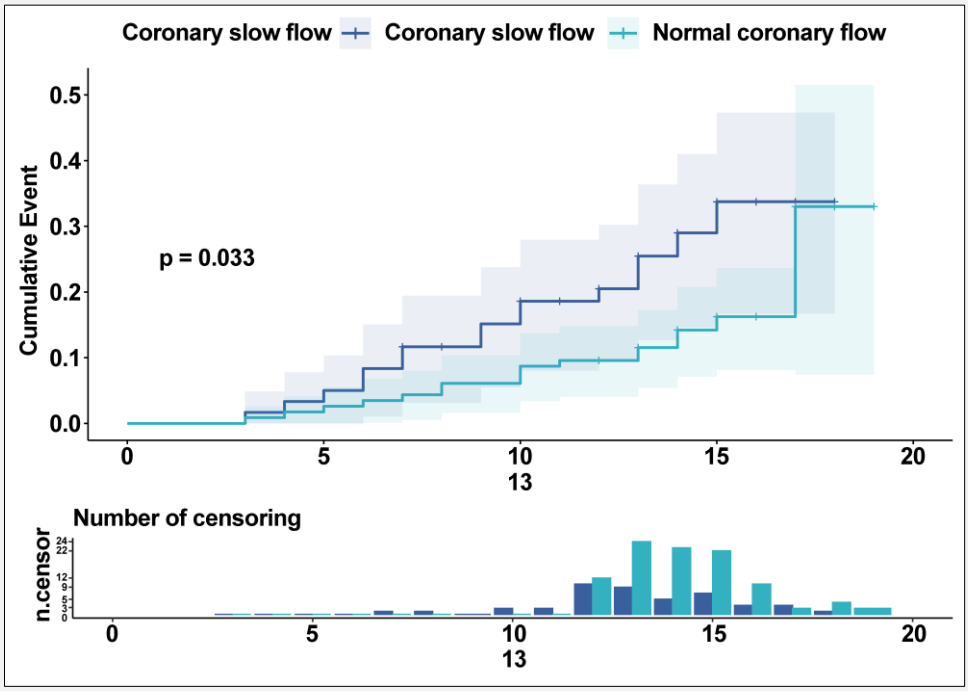

Figure 2. Cumulative incidence of endpoint events in MINOCA patients with and without CSFP.

p = 0.039), UAR (HR = 1.30, 95% CI 1.01 - 1.83, p = 0.027), and their interaction term (NPAR × UAR, HR = 1.18, 95% CI 1.08 - 1.55, p = 0.033) were independent predictors of adverse prognosis. This suggests that NPAR and UAR may exacerbate microvascular dysfunction through their synergistic effect. When an expanded model (Model 2) including the coronary slow flow (CSFP)-related interaction term was further analyzed, the three-way interaction term (NPAR × UAR × CSFP) did not show statistical significance (p > 0.05), and the model's discriminative ability did not significantly improve (ΔC-index = -0.01, p = 0.25; time-dependent AUC: 0.70 vs. 0.73). Model comparison results (Table 6) indicated that the basic model (Model 1), which included the NPAR × UAR interaction term, had better predictive performance (C-index = 0.70) and model stability (maximum VIF = 3.5). The introduction of higher-order interaction terms not only led to collinearity issues (VIF = 6.2) but also failed to improve risk reclassification (NRI = 0.04, p = 0.37; IDI = 0.003, p = 0.42). These findings support the clinical value of combined detection of NPAR and UAR for risk stratification in MINOCA patients, while the complex interaction effects related to CSFP may be limited by sample size or biological mechanisms, warranting larger-scale studies for validation.

DISCUSSION

This study, through a prospective cohort design, systematically investigated the characteristics of the inflammation-metabolism combined biomarkers (NPAR/UAR) in MINOCA patients with concomitant CSFP and their predictive value for short-term prognosis. The findings suggest that CSFP patients exhibit a pathophysiological imbalance characterized by neutrophil activation and uric acid-LDL metabolism disturbance, and the combined elevation of NPAR and UAR significantly increases the risk of adverse cardiovascular events through their synergistic effect. Additionally, the combination of NPAR and UAR can provide predictive value for short-term adverse prognosis in MINOCA patients.

The study showed that the smoking rate in the CSFP group was significantly higher than it was in the normal blood flow group (39.3% vs. 21.7%, p = 0.013), suggesting that smoking may be an important risk factor for the occurrence of CSFP in MINOCA patients. This finding is consistent with previous studies [17], which suggest that smoking may exacerbate coronary microcirculation dysfunction by inducing oxidative stress, endothelial dysfunction, and microvascular spasm [18,19]. Although there were no significant differences between the groups in traditional cardiovascular risk factors

(such as hypertension, diabetes) and pharmacological treatments, the CSFP group showed unique laboratory characteristics, including a significant increase in neutrophil percentage, uric acid, and LDL-C levels, along with a decrease in hemoglobin levels. Notably, this study found that the combined elevation of NPAR and UAR could further increase the composite endpoint risk by 30% (OR = 1.30, p = 0.02), indicating that neutrophil-driven inflammatory activation and uric acid metabolism disorders may exacerbate microvascular dysfunction through a synergistic mechanism. This synergistic effect may arise from the following mechanisms: 1) Inflammation-metabolism interaction damages the microvasculature: neutrophils directly impair endothelial barrier function by releasing proteases and reactive oxygen species (ROS), while also promoting platelet aggregation and microthrombus formation [20,21]. Hyperuricemia exacerbates oxidative stress and vasoconstriction effects by inhibiting endothelial nitric oxide synthase (eNOS) activity and activating the NLRP3 inflammasome [22,23], ultimately leading to coronary microvascular narrowing and hemodynamic abnormalities. 2) Dual regulatory role of albumin: albumin, as a negative regulator of inflammation, has its concentration decreased, potentially weakening its ability to suppress oxidative stress and inflammatory responses [24]. Moreover, hypoalbuminemia is closely associated with damage to the microvascular endothelial glycocalyx [25]. Therefore, when albumin levels drop, the pro-inflammatory and pro-oxidant effects of neutrophils and uric acid are amplified, forming a vicious cycle. 3) Cascading effect of microcirculatory dysfunction: CSFP is essentially a coronary microvascular dysfunction, and the elevated NPAR/UAR levels reflecting systemic inflammation-metabolism disturbances may act as "upstream factors", damaging the microvascular endothelial glycocalyx, reducing the bioavailability of nitric oxide (NO), and ultimately leading to myocardial perfusion insufficiency. This mechanism may explain why the interaction between NPAR/UAR has stronger predictive power than single biomarkers. Although CSFP is widely regarded as an imaging marker of microcirculatory dysfunction, it did not significantly modify the prognostic effect of NPAR/UAR in this study (three-way interaction $p > 0.05$). This may suggest that the inflammation-metabolism imbalance reflected by NPAR/UAR is the core driver of microvascular injury, rather than simply abnormal blood flow velocity. This finding aligns with the recent "CSFP heterogeneity hypothesis": some CSFP patients may predominantly exhibit functional microvascular spasm [26], while others show structural endothelial damage [27], the latter of which is more likely related to persistent inflammation-metabolism imbalance.

The risk scoring systems currently widely used in clinical practice, such as GRACE and TIMI, are primarily based on the pathological features of coronary artery obstructive lesions (such as the degree of vessel stenosis and plaque burden) and traditional risk factors (such as age and renal function) [28,29]. These systems have significant blind spots when it comes to assessing microvascular dysfunction. This study first confirmed that the combined use of NPAR and UAR significantly improved the ability to differentiate CSFP in MINOCA patients. The AUC increased from 0.73 to 0.75 (ΔAUC = 0.02, p = 0.04), and precise identification of high-risk patients was achieved with an improvement in NRI = 0.12. This finding suggests that NPAR/UAR can effectively complement traditional clinical indicators (such as smoking and dyslipidemia), overcoming the current CSFP diagnostic model's over-reliance on hemodynamic parameters (such as CTFC), and providing a new tool for exploring the etiology of microcirculatory dysfunction from the perspective of inflammation-metabolism. The core innovation of this study lies in its first systematic evaluation of the impact of inflammation-metabolism combined biomarkers (NPAR, UAR) and their interaction on the prognosis of MINOCA patients, revealing their predictive value independent of the coronary slow flow phenomenon (CSFP). Compared to previous studies, the existing literature is mainly limited to linear correlation analyses of single biomarkers: Zang et al. confirmed that high NPAR was independently associated with the risk of CSFP [10], while Zhang et al. found that UAR could serve as an independent predictor of CSFP [11]. However, these studies failed to explore the synergistic effects of inflammation and metabolic biomarkers and did not validate their prognostic efficacy in the specific group of MINOCA patients. This study, through multivariate Cox regression and interaction term analysis, is the first to demonstrate that the combined elevation of NPAR and UAR can significantly increase the risk of microvascular dysfunction through a synergistic mechanism (NPAR × UAR interaction, HR = 1.30, p = 0.027). This effect is greater than the simple additive effect of single biomarkers (ΔHR = 0.18). This finding breaks through the traditional "single factor-single outcome" research paradigm and provides direct clinical evidence for the "inflammation-metabolism imbalance" theory.

This study challenges the "essential status" of CSFP in microvascular risk assessment. Although CSFP is widely regarded as an imaging biomarker of poor prognosis in MINOCA [30,31], this study found that the synergistic effect of NPAR/UAR is independent of the CSFP status (three-way interaction term NPAR × UAR × CSFP, $p > 0.05$), and the discriminative performance of the base model (NPAR × UAR) (C-index = 0.70) is comparable to that of the extended model that includes CSFP (ΔC-index = -0.01). This contrasts sharply with the study by Yan et al. [32], whose prognostic model based on CSFP patients (AUC = 0.87) did not include any inflammatory or metabolic biomarkers. This difference reflects the possibility that CSFP may represent either transient functional microvascular spasm (associated with hemodynamic fluctuations) or persistent structural endothelial damage (associated with inflammation-metabolism imbalance). Through the combined bio-

marker analysis, this study successfully identified the latter group, while traditional CSFP diagnosis (based on TIMI frame count) could not distinguish between these two mechanisms. This explains why the inclusion of CSFP did not further improve model performance.

The abovementioned findings have dual implications for clinical practice: First, the combined detection of NPAR/UAR can bypass the diagnostic ambiguity caused by CSFP heterogeneity and directly target the core mechanism of microvascular injury (the inflammation-metabolism axis), providing a more stable biological basis for risk stratification. Second, the "inflammation-metabolism-microvascular" triad model proposed in this study (NPAR-UAR-clinical endpoints) avoids the limitations of over-reliance on imaging parameters and is more suitable for primary care settings with limited medical resources. This paradigm shift from "imaging dependence" to "mechanism-driven" may become an important direction for the precise management of MINOCA in the future.

Although this study provides new insights into the inflammation-metabolism mechanism of MINOCA combined with CSFP, there are still several limitations: Sample size and single-center design: the study included 176 patients (61 in the CSFP group). The relatively small sample size may limit the statistical power of subgroup analyses (e.g. severity of CSFP or classification of MINOCA causes). Additionally, the single-center data may introduce selection bias, and the findings need to be validated through larger multi-center cohorts. Further, lack of biomarker dynamics: NPAR/UAR were only measured at baseline, which does not reflect their dynamic changes throughout the course of the disease (e.g. fluctuations in the acute and recovery phases). This may underestimate their sensitivity for prognostic prediction. Limitations of microcirculation assessment: CSFP diagnosis relies on TIMI frame count, but more precise indices of microcirculatory resistance (IMR) or coronary flow reserve (CFR) were not incorporated, potentially missing the heterogeneity of functional microvascular impairment. Another limitation: Insufficient mechanistic exploration: although the synergistic effect of NPAR/UAR was discovered, their molecular mechanisms were not explored using omics techniques (e.g. single-cell sequencing, metabolomics). Moreover, the impact of therapeutic interventions (e.g. anti-inflammatory drugs) on biomarker levels was not assessed. Given these limitations, future research could delve into the following areas: 1) Multi-center prospective cohort: conduct a larger multi-center study, enrolling over 500 MINOCA patients, combining invasive microcirculation assessments (e.g. IMR/CFR) and tissue characterization through cardiac magnetic resonance (CMR) to construct an "imaging-biomarker-clinical endpoint" integrated predictive model; 2) dynamic monitoring and mechanistic analysis: collect longitudinal data on NPAR/UAR (e.g. upon admission, one month post-discharge, six months) to clarify their patterns of change throughout the disease course, utilize proteomics to identify key regulatory molecules related to NPAR/UAR pathways (e.g. IL-1β, xanthine oxidase), and validate their causal role in microvascular endothelial damage using organoid models; and 3) artificial Intelligence-assisted model optimization: integrate electronic health records (EHR), multimodal imaging, and biomarker data to develop AI-driven dynamic risk prediction tools, enabling real-time risk warning and intervention decision support for MINOCA patients.

CONCLUSION

This study is the first to confirm that the synergistic elevation of inflammation-metabolism combined biomarkers (NPAR, UAR) is an independent predictor of short-term adverse outcomes in MINOCA patients, and this effect is not modified by the coronary slow flow phenomenon (CSFP) status. The interaction between NPAR and UAR can optimize the classification performance of traditional risk models (NRI = 0.12), suggesting that the core drivers of microvascular injury may transcend visible blood flow abnormalities on imaging and are closely associated with the imbalance of the inflammation-metabolism network. This finding provides novel biological markers for precise stratification of MINOCA and lays the theoretical foundation for individualized treatment strategies targeting microcirculatory dysfunction. Future studies with large sample sizes and mechanistic research are needed to promote the clinical translation of the "inflammation-metabolism-microvascular" axis in practice.

Availability of Data and Materials:

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethical Approval and Consent to Participate:

The present study was approved by the Ethics Committee of Yanting County People's Hospital, and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and the Declaration of Helsinki and its later amendments or comparable ethical standards.

Declaration of Interest:

The authors have no conflicts of interest to declare.

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