Biomarkers in Medicine

ISSN: 1752-0363 (Print) 1752-0371 (Online) Journal homepage: www.tandfonline.com/journals/ibmm20

Comparison of the effect of Uric Acid/Albumin Ratio on Coronary Slow Flow with Other Inflammation-Based Markers

Kenan Toprak, Kaya Özen, Tolga Memioğlu, Mehmet İnanır, Mustafa Kaplangöray, Selahattin Akyol, Mustafa B Tascanov, Asuman Biçer & Recep Demirbağ

To cite this article: Kenan Toprak, Kaya Özen, Tolga Memioğlu, Mehmet İnanır, Mustafa Kaplangöray, Selahattin Akyol, Mustafa B Tascanov, Asuman Biçer & Recep Demirbağ (2024) Comparison of the effect of Uric Acid/Albumin Ratio on Coronary Slow Flow with Other Inflammation-Based Markers, Biomarkers in Medicine, 18:1, 25-37, DOI: 10.2217/bmm-2023-0386

To link to this article: https://doi.org/10.2217/bmm-2023-0386

Published online: 07 Feb 2024.

Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Biomarkers in Medicine

Comparison of the effect of uric acid/albumin ratio on coronary slow flow with other inflammation-based markers

Kenan Toprak*[,1], Kaya Özen[2], Tolga Memioğlu[3], Mehmet İnanır[3], Mustafa Kaplangöray[4], Selahattin Akyol[5], Mustafa B Tascanov[1], Asuman Biçer[1] & Recep Demirbağ[1]

[1]Harran University, Faculty of Medicine, Department of Cardiology, Sanliurfa, 63050, Turkey
[2]Gazi Yaşargil Training & Research Hospital, Department of Cardiology, Diyarbakır, 21010, Turkey
[3]Abant Izzet Baysal University, Medical Faculty, Department of Cardiology, Bolu, 14300, Turkey
[4]Şeyh Edebali University, Medical Faculty, Department of Cardiology, Bilecik, 11230, Turkey
[5]Kartal Kosuyolu High Specialization Training & Research Hospital, Department of Cardiology, İstanbul, 34865, Turkey
*Author for correspondence: Tel.: +90 414 318 3000; kentoprak@hotmail.com

Background: Many inflammation-based markers (IBMs) have been shown to be closely related to coronary slow flow (CSF), but the effect of the uric acid/albumin ratio (UAR) on CSF and its relationship with other IBMs are not clearly known. In this study, we aimed to compare the effects of UAR and other IBMs on CSF. **Methods:** After the exclusion criteria, 126 patients with CSF detected on coronary angiography and 126 subjects with normal coronary flow as the control group were included in the study. **Results:** UAR was determined as an independent predictor for CSF. In addition, the UAR was superior to other IBMs in detecting CSF ($p < 0.05$ for all). **Conclusion:** This study is the first to investigate the effect of UAR on CSF in comparison with other IBMs.

First draft submitted: 20 June 2023; Accepted for publication: 4 January 2024; Published online: 7 February 2024

Keywords: coronary slow flow • inflammation-based markers • uric acid/albumin ratio

Coronary slow flow (CSF) is a type of microvascular disease characterized by the late delivery of radiopaque material to the distal vascular structures without any mechanical obstruction in the epicardial coronary arteries during coronary angiography [1]. Although the essential pathophysiology of CSF has not been fully elucidated, there is increasing evidence that systemic inflammation, subclinical atherosclerosis, microvascular and endothelial dysfunction and increased thrombogenicity play a pivotal role [2]. Many studies have revealed that the inflammatory process predisposes to CSF in association with endothelial and microvascular dysfunction [3–5]. In many studies, it has been shown that inflammation-based markers (IBMs) obtained by combining blood parameters in various fractions can predict CSF strongly and independently. IBMs such as systemic immune-inflammation index (SII) [6], C-reactive protein (CRP)-to-albumin ratio (CAR) [7], platelet-to-lymphocyte ratio (PLR) [8], neutrophil-to-lymphocyte ratio (NLR) [9] and monocyte-to-high-density lipoprotein cholesterol (HDL-C) ratio (MHR) [10] have been found to be independent predictors for CSF in previous studies.

Uric acid is the end product of purine metabolism, which can be exogenously or endogenously produced, with pro-oxidant, proinflammatory and proatherogenic properties [11,12]. Hyperuricemia plays a role in the etiopathogenesis of coronary artery disease by increasing endothelial dysfunction, inflammation and oxidative stress, and is associated with increased cardiovascular mortality, morbidity and poor clinical outcomes in coronary artery disease patients [11–14]. It has been shown in various studies that uric acid may play a role in the etiopathogenesis of CSF by causing possible microvascular and endothelial dysfunction due to these properties [15–17]. Albumin, on the other hand, shows antioxidant, anti-inflammatory and antithrombogenic effects in contrast to uric acid, and low serum albumin levels have been shown to be closely associated with adverse cardiovascular events [18]. The uric acid/albumin ratio (UAR) is a relatively new IBM obtained by the ratio of uric acid and albumin in a single fraction, and recent studies have shown that the UAR can be a strong predictor for some cardiovascular adverse events [19–21].

Taylor & Francis
Taylor & Francis Group

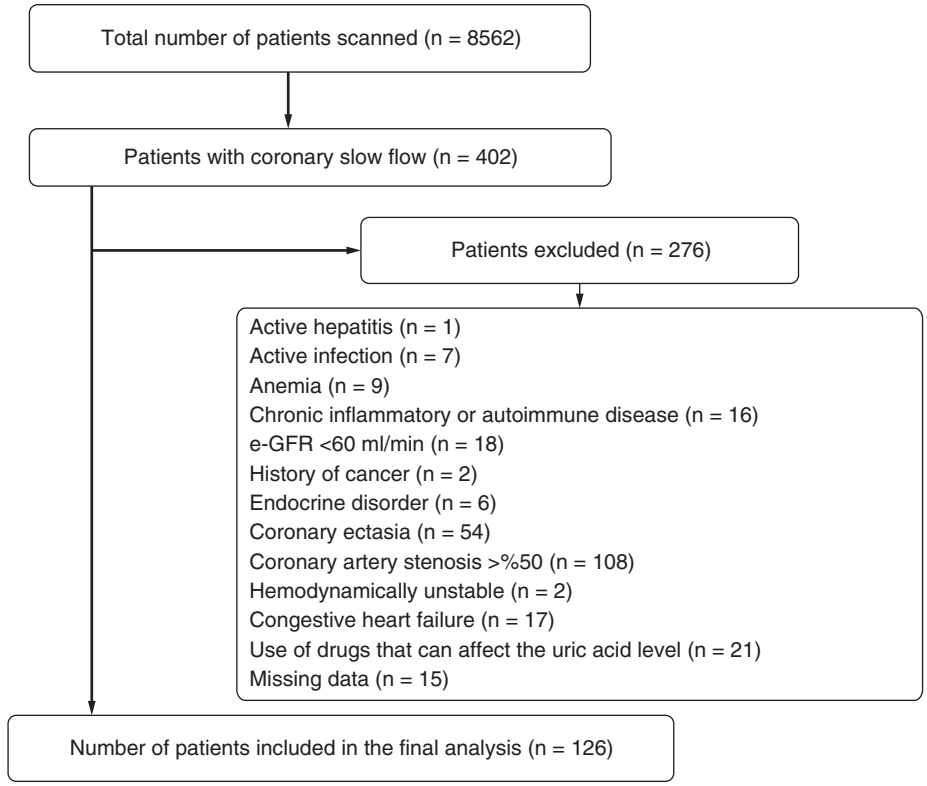


Figure 1. Flowchart illustrating the study population selection. The diagram is a visual representation of the step-by-step process through which individuals were chosen to participate in the research.

Recent reports increasingly support the potential role of systemic inflammatory status and subclinical diffuse atherosclerosis in CSF etiopathogenesis [1–3]. The presence of CSF is associated with an increased incidence of cardiovascular events and poor clinical outcomes [22,23], so predicting and modifying the determinants of CSF may contribute to increased surveillance of these patients with intensive preventive treatments. In this context, it is of great importance to determine the effectiveness of easily available and cost-effective markers in clinical practice to detect and predict CSF. IBMs, which are easily available and inexpensive markers obtained from blood parameters, seem to be ideal candidates in this respect. Therefore, revealing the comparative effects of IBMs on CSF may contribute greatly to clinical practice. Given that UAR reflects systemic inflammatory status and proatherogenic effect superiorly to uric acid and albumin alone, we aimed to investigate whether UAR can predict CSF better than its constituent parameters. In addition, by comparing the power of UAR and other traditional IBMs to detect and predict CSF, we tried to reveal the effect of UAR and other IBMs on CSF. To our knowledge, this is the first study to compare the predictive power of UAR and traditional IBMs for CSF.

Patients & methods

Study population & design

Between January 2019 and February 2023, a total of 8562 patients who were suspected of having coronary artery disease by noninvasive cardiac stress tests (treadmill stress test, stress echocardiography, myocardial perfusion scintigraphy) and underwent coronary angiography were retrospectively screened. In total, CSF was detected in the epicardial coronary arteries in 402 patients. The remaining 126 patients after exclusion criteria were included in the study. As the control group, 126 consecutive patients with normal coronary flow (NCF) in the epicardial coronary arteries were included in the study. Those with active hepatitis, kidney failure, acute infection, obstructive coronary artery disease, hematological and endocrine disorders, chronic inflammatory disease or autoimmune disease, malignancy, coronary ectasia or congestive heart failure; subjects with a history of using drugs that alter the uric acid level such as allopurinol and thiazide diuretics; those who were hemodynamically unstable; and those whose data were missing were excluded from the study (Figure 1). Basic demographic, clinical and laboratory

characteristics of the subjects were obtained from the hospital's patient medical record database. The study was approved by the local ethics committee of Bolu Abant İzzet Baysal University Faculty of Medicine (decision no: 2023/194, 20 February 2023) and was conducted in accordance with the principles of the Declaration of Helsinki.

Laboratory examination

After the patients were admitted to the hospital for coronary angiography, all blood samples were taken from peripheral venous blood. Lipid panel and fasting plasma glucose were recorded from the results obtained after at least 12 h of fasting. Complete blood count was evaluated with an automated blood cell counter (Coulter LH 780 Hematology Analyzer, Beckman Coulter Corp., FL, USA) and biochemical parameters evaluated with Roche Cobas 6000 c501 (Roche, Mannheim, Germany). The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation formula [24]. UAR was obtained by dividing the serum uric acid level by the serum albumin level. The CAR was obtained by dividing the CRP by the serum albumin value; NLR was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count; PLR was obtained by dividing the absolute platelet count by the absolute lymphocyte count; MHR was obtained by dividing the absolute number of monocytes by serum HDL-C; and the SII was obtained with the formula absolute platelet count × absolute neutrophil count/absolute lymphocyte count. The inter-test coefficients of variation (CVs) for uric acid, which indicates the variability between different laboratories, was calculated to be 3.5% through repeated measurements of samples across different days. Within a single laboratory session, the within-test CV for uric acid measurements was determined to be 1.8% based on replicate measurements. The inter-test CV for albumin, reflecting the variation between different laboratories, was computed as 2.7% by conducting measurements on the same samples across multiple days. To evaluate the precision of albumin measurements within a single laboratory session, the within-test CV was determined to be 1.3% through replicated measurements.

Clinical definitions & measurements

Hypertension was defined as at least two office blood pressure measurements >140/90 mmHg or the presence of antihypertensive medication. Dyslipidemia was defined as the presence of one of four parameters of the lipid profile measured after at least 8 h of fasting or a history of lipid-lowering drug use: total cholesterol >200 mg/dl; low-density lipoprotein cholesterol >130 mg/dl; HDL-C <40 mg/dl in men and <50 mg/dl in women; and triglycerides >150 mg/dl. Diabetes mellitus was defined as fasting serum glucose ≥126 mg/dl, hemoglobin A1c ≥6.5%, or the use of antidiabetic drugs. Current smokers were defined as those who smoked for a certain period of time within the past year. Body mass index was calculated by dividing weight (kg) by the square of height (m^2). Estimated glomerular filtration rate <60 ml/min was accepted as renal failure. Left ventricular ejection fraction was measured by two experienced cardiologists with the modified Simpson method by echocardiography (EPIQ 7 device, Philips, MA, USA) during hospitalization.

Coronary angiography & thrombolysis in myocardial infarction frame count assessment

All coronary angiographic interventions were performed by experienced invasive cardiologists using the standard Judkins technique, either femoral or radial (Allura Xper FD10 cardiovascular x-ray system; Philips). Iopromide was used as a radiocontrast agent in coronary angiography (Omnipaque™; GE Healthcare, Cork, Ireland). Coronary angiographic images were acquired at a rate of 15 frames/s from at least four projections for the left coronary system and at least two projections for the right coronary system, in the right and left oblique planes, as well as cranial and caudal angles. All angiographic images were digitized for quantitative analysis (DICOM Viewer, MedCom GmbH, Darmstadt, Germany) and the final decision was made by evaluating angiographic thrombolysis in myocardial infarction ('TIMI') frame counts (TFCs) to determine CSF by at least two experienced invasive cardiologists unaware of patient demographics and clinical characteristics. The TFC method proposed by Gibson *et al.* was used for the quantitative measurement of coronary blood flow [25]. The frame in which the contrast agent was first visualized in the coronary ostium and the coronary artery was defined as the first frame, and the frame in which the contrast agent was first seen in the distal coronary bed was defined as the last frame. Ending markers were defined as the distal bifurcation of the left anterior descending artery (LAD), the distal bifurcation of the longest branch of the circumflex artery (CX) and the level at which the first lateral branch exits the posterolateral artery for the right coronary artery (RCA). Because the LAD has a longer course than the RCA and CX arteries, the TFC value is on average 1.7-times higher than for the RCA and CX arteries, which causes errors in the evaluation of the flow frame count of the LAD [25]. Therefore, the corrected TFC standardized for LAD is obtained by dividing the

TFC obtained for LAD by a coefficient of 1.7. The mean reference values for TFC were accepted as 36.2 ± 2.6 for LAD, 22.2 ± 4.1 for CX and 20.4 ± 3.0 for RCA [25]. The obtained TFC values were considered to indicate CSF if they were greater than two standard deviations from the reported normal mean for at least one epicardial coronary artery. The mean TFC of the study population was calculated by dividing the sum of the TFCs of LAD, CX and RCA by three. Intraobserver and interobserver reliability were determined on 40 subjects randomly selected from the study population. For the assessment of TFC values, Cohen's κ-coefficient for intraobserver reliability was 0.98 and the interobserver reliability was 0.96.

Statistical analysis

Statistical analyses were performed using SPSS v. 26.0 software (IBM Corp, NY, USA). The Kolmogorov–Smirnov test was used to evaluate whether the distribution of continuous variables was normal. Continuous variables were expressed as mean ± standard deviation or median (interquartile range) and compared with Student's *t*-test or Mann–Whitney *U* test, where appropriate. Categorical variables were expressed as percentages and numbers and compared with the χ^2 test. In order to determine the relationship between UAR and other IBM levels and TFC, Spearman or Pearson correlation analysis was performed according to whether the parameters showed normal distribution or not. Receiver operating characteristic curve analysis was used to calculate the best cutoff value of UAR to detect and predict CSF. The ideal cutoff value was calculated from the point of maximum sensitivity and specificity with the Youden's J index. Determination of the diagnostic accuracy and discriminatory power of UAR and other traditional IBMs (CAR, SII, NLR, PLR, MHR) on CSF was attempted by pairwise comparison using the DeLong test via MedCalc 16 statistical software (MedCalc Software Ltd, Ostend, Belgium). In addition, univariate and multivariate regression analyses were performed to identify independent determinants of CSF. The parameters that were found to be statistically significant between the CSF group and the NCF group were included in the univariate regression analysis. Baseline variables with statistical significance ($p < 0.05$) by univariate analysis were included in the multivariate logistic regression analysis. The Hosmer–Lemeshow test showed sufficient fit for the regression model. Variance inflation factor (>3) and tolerance (<0.1) values were calculated to detect multicollinearity. The sample size of the study group was calculated using G*Power software (v. 3.1.9.2) (http://www.gpower.hhu.de/) via effect size (Cohen's d) and power value ($1 - \beta$). The power value is 95%, and the effect size is 0.77. A two-tailed $p < 0.05$ was considered statistically significant.

Results

A total of 126 subjects with CSF and 126 subjects with NCF as the control group were included in the study. The main demographic, clinical and laboratory characteristics of the study population are summarized in Table 1. The mean age of the CSF group was 57.9 ± 13.0 years and the mean age of the NCF group was 57.5 ± 12.9 years, and there was no significant difference between them (p = 0.778). The incidence of male gender was significantly higher in the CSF group than in the NCF group (72.2 vs 59.5%; p = 0.034). The incidence of dyslipidemia and smoking was significantly higher in the CSF group than in the NCF group (55.6 vs 40.5%, p = 0.016; and 29.4 vs 16.7%, p = 0.017, respectively). There was no significant difference between the groups in terms of body mass index, diabetes mellitus or hypertension (p = 0.188; p = 0.069; p = 0.614, respectively). There was no significant difference between the groups in terms of left ventricular ejection fraction, blood pressure, heart rate, or preprocedural medications ($p > 0.05$ for all). While fasting plasma glucose, uric acid, total cholesterol, CRP and monocyte count were significantly higher in the CSF group than in the NCF group, albumin and HDL-C were significantly lower ($p < 0.05$ for all). The levels of the IBMs CAR (0.26 [0.08–1.10] vs 0.11 [0.03–0.43]; $p < 0.001$), MHR (17.7 [12.7–24.7] vs 15.5 [11.3–21.3]; p = 0.013), NLR (3.29 [2.23–6.50] vs 2.94 [1.82–5.70]; p = 0.019), PLR (143 [109–194] vs 130 [91–181]; p = 0.033) and SII (899 [604–1505] vs 681 [419–1089]; $p < 0.001$) were significantly higher in the CSF group than in the NCF group, consistent with the literature (Table 1 & Figure 2). In addition, UAR levels were significantly higher in the CSF group than in the NCF group (2.07 ± 0.65 vs 1.57 ± 0.48; $p < 0.001$) (Table 1 & Figure 2). Corrected LAD-TFC, CX-TFC, RCA-TFC and mean TFC values were significantly higher in the CSF group than in the NCF group ($p < 0.001$ for all) (Table 2). While TFC showed a positive correlation with UAR (r = 0.2265; p = 0.0003), CAR (r = 0.1356; p = 0.0314), NLR (r = 0.1510; p = 0.0165) and SII (r = 0.1558; p = 0.0133) levels, no significant correlation was found with MHR (r = 0.09363; p = 0.1383) or PLR (r = 0.1026; p = 0.1040), and UAR showed a stronger correlation with TFC than other IBMs (Figure 3). In the multivariable regression analysis, male gender and the presence of dyslipidemia were determined as independent predictors for CSF (odds ratio [OR]: 2.781, 95% CI: 1.391–5.562, p = 0.004; and OR:

Table 1. Basic demographic and clinical characteristics and laboratory findings of the study population.

Variables	NCF (n = 126)	CSF (n = 126)	p-value
Demographics and medical history			
Age, years	57.5 ± 12.9	57.9 ± 13.0	0.778
Gender, male, n (%)	75 (59.5)	91 (72.2)	0.034
BMI, kg/m^2	26.7 ± 4.2	27.4 ± 4.3	0.188
Diabetes mellitus, n (%)	34 (27.0)	22 (17.5)	0.069
Hypertension, n (%)	65 (51.6)	61 (48.4)	0.614
Dyslipidemia, n (%)	51 (40.5)	70 (55.6)	0.016
Smoking, n (%)	21 (16.7)	37 (29.4)	0.017
Hemodynamic properties			
Systolic blood pressure, mmHg	146 ± 19	144 ± 18	0.493
Diastolic blood pressure, mmHg	79 ± 15	80 ± 14	0.583
Heart rate, bpm	81 ± 7	82 ± 8	0.157
LVEF (%)	57 ± 6	56 ± 6	0.482
Preprocedural medications (%)			
Antiplatelet	19 (15.1)	16 (12.7)	0.585
β-blocker	26 (20.6)	17 (13.5)	0.132
Statins	22 (17.5)	13 (10.3)	0.101
CCB	14 (11.1)	15 (11.9)	0.844
ACEI/ARB	34 (27.0)	36 (28.6)	0.778
Laboratory results			
FPG (mg/dl)	115 ± 32	125 ± 38	0.027
Creatinine (mg/dl)	0.79 ± 0.14	0.78 ± 0.19	0.602
Uric acid (mg/dl)	4.4 ± 0.7	5.6 ± 0.5	0.008
Albumin (mg/dl)	4.2 ± 0.9	2.9 ± 0.9	0.005
Triglyceride (mg/dl)	166 (122–220)	173 (136–222)	0.093
TC (mg/dl)	156 ± 53	170 ± 47	0.031
HDL-C (mg/dl)	35 (30–41)	33 (30–37)	0.031
LDL-C (mg/dl)	109 (73–133)	114 (94–138)	0.105
CRP (mg/dl)	0.40 (0.10–0.74)	0.50 (0.21–1.23)	0.018
eGFR (ml/min)	91 ± 20	93 ± 19	0.404
WBC (×1000/mm^3)	8.7 (7.0–11.2)	9.6 (7.0–12.0)	0.106
Lymphocytes (×1000/mm^3)	2.1 (1.5–2.6)	1.9 (1.4–2.4)	0.068
Monocytes (×1000/mm^3)	0.60 (0.50–0.87)	0.72 (0.50–0.98)	0.043
Neutrophils (×1000/mm^3)	6.0 (4.9–7.7)	6.7 (4.8–9.1)	0.089
RDW, fl	12.6 ± 1.5	13.0 ± 1.6	0.084
MPV, fl	8.1 ± 1.7	8.5 ± 1.2	0.104
Hemoglobin (mg/dl)	14.1 ± 1.9	13.8 ± 1.8	0.154
Hematocrit (%)	42.8 ± 5.0	41.7 ± 5.7	0.105
Platelet count (×1000/mm^3)	262 (224–303)	278 (221–329)	0.144
Inflammation-based markers			
CAR	0.11 (0.03–0.43)	0.26 (0.08–1.10)	<0.001
MHR† ×10^3	15.5 (11.3–21.3)	17.7 (12.7–24.7)	0.013
NLR	2.94 (1.82–5.70)	3.29 (2.23–6.50)	0.019
PLR	130 (91–181)	143 (109–194)	0.033
SII	681 (419–1089)	899 (604–1505)	<0.001
UAR	1.57 ± 0.48	2.07 ± 0.65	<0.001

†The MHR value is multiplied by 10^3.
Values are mean ± standard deviation, n (%), or median (interquartile range) unless otherwise stated.
ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; CAR: C-reactive protein/albumin ratio; CCB: Calcium channel blocker; CRP: C- reactive protein; eGFR: Estimated glomerular filtration rate; FPG: Fasting plasma glucose; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction; MHR: Monocyte/high-density lipoprotein cholesterol ratio; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; RDW: Red cell distribution width; SII: Systemic immune-inflammation index; TC: Total cholesterol; UAR: Uric acid/albumin ratio; WBC: White blood cell.

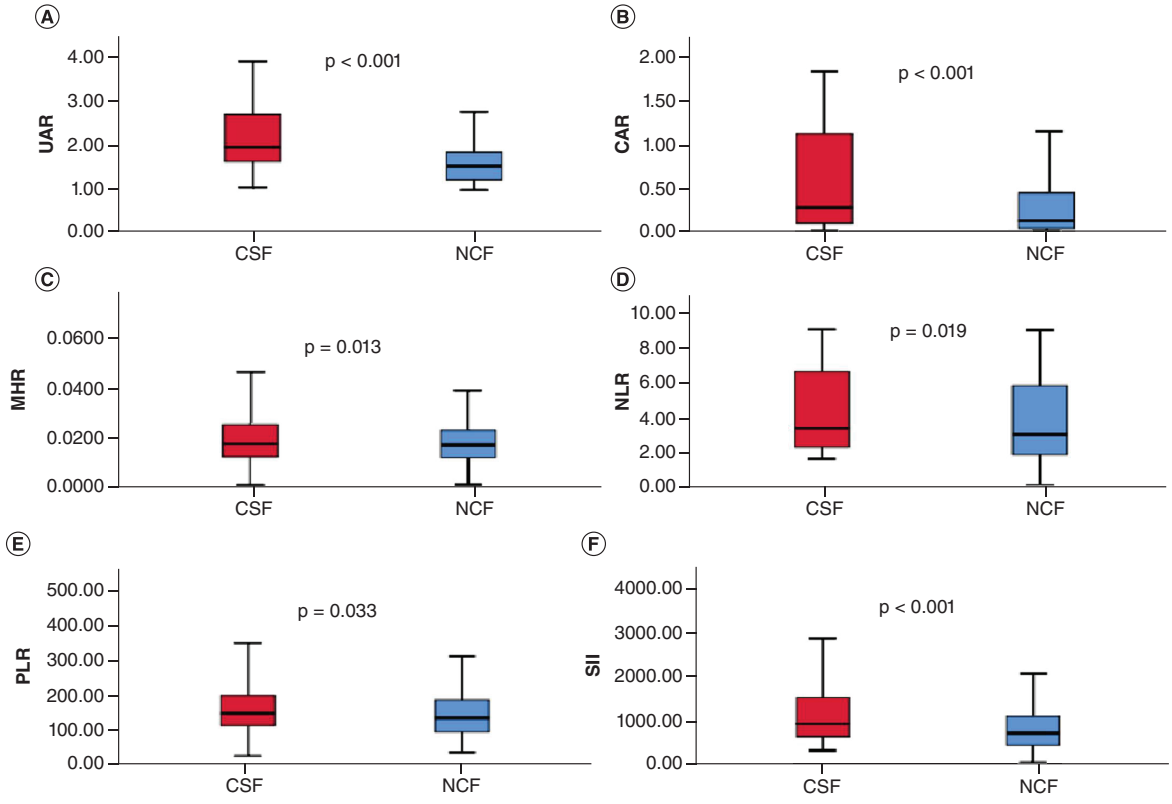


Figure 2. Box plot representation of the comparison of study populations in terms of uric acid/albumin ratio and traditional inflammation-based markers.
CAR: C-reactive protein/albumin ratio; CSF: Coronary slow flow; MHR: Monocyte/high-density lipoprotein cholesterol ratio; NCF: Normal coronary flow; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; UAR: Uric acid/albumin ratio.

Table 2. Angiographic data of study population.

Characteristic	NCF (n = 126)	CSF (n = 126)	p-value
Artery involvement			
LAD (%)		72.4	0.135
CX (%)		61.2	
RCA (%)		68.6	
Vessel involvement			
One vessel (%)		36.5	0.224
Two vessel (%)		33.3	
Three vessel (%)		30.2	
TFC			
Corrected LAD	20.1 ± 4.1	35.8 ± 6.6	<0.001
CX	20.3 ± 4.0	33.8 ± 4.6	<0.001
RCA	19.6 ± 3.3	32.6 ± 6.2	<0.001
Mean TFC	20.1 ± 3.9	34.5 ± 6.2	<0.001

CSF: Coronary slow flow; CX: Circumflex coronary artery; LAD: Left anterior descending coronary artery; NCF: Normal coronary flow; RCA: Right coronary artery; TFC: Thrombolysis in myocardial infarction frame count.

1.991, 95% CI: 1.048–3.785, p = 0.035, respectively). In addition, in the multivariable regression analysis, the IBMs MHR (OR: 0.962, 95% CI: 0.829–0.995; p = 0.025), SII (OR: 0.916, 95% CI: 0.813–0.980; p = 0.018) and UAR (OR: 0.105, 95% CI: 0.051–0.217; p < 0.001) were determined as independent potential predictors for CSF (Table 3). CAR, NLR and PLR were not detected as independent predictors in multivariable regression

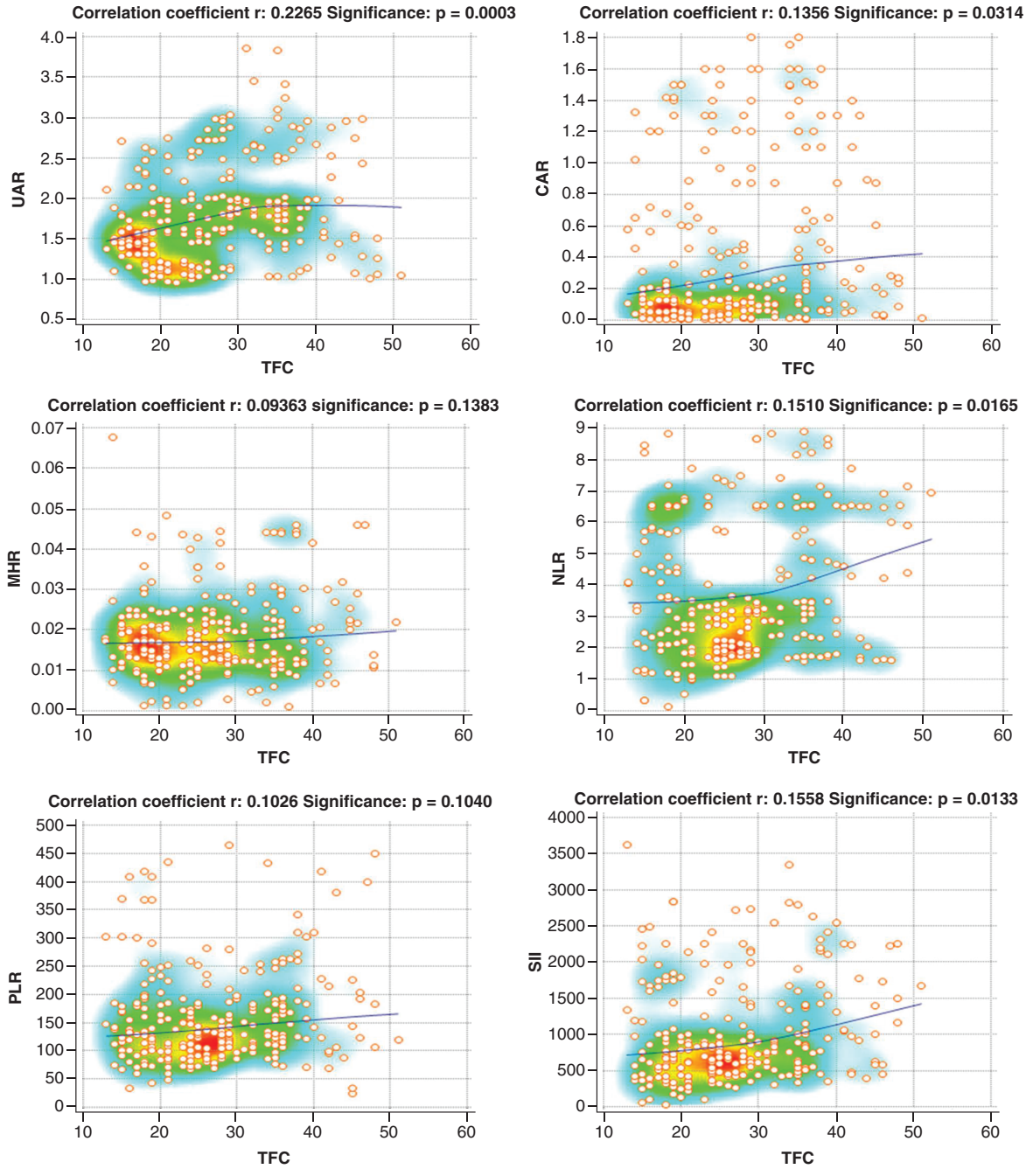


Figure 3. Representation of correlation between uric acid/albumin ratio and traditional inflammation-based markers with thrombolysis in myocardial infarction frame count in scatter diagram with heat map.
CAR: C-reactive protein/albumin ratio; MHR: Monocyte/high-density lipoprotein cholesterol ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; TFC: Thrombolysis in myocardial infarction frame count; UAR: Uric acid/albumin ratio.

analysis ($p > 0.05$ for all). To avoid multicollinearity, the parameters forming the IBMs were excluded from the regression analysis. When the receiver operating characteristic curves of UAR, serum uric acid and albumin were compared in relation to detecting and predicting CSF, UAR was found to be superior to uric acid and albumin ($p = 0.0015$ and $p < 0.0001$, respectively) and also UAR predicted CSF at the best cutoff value of 1.72, with 71% sensitivity and 71% specificity (Figure 4). When UAR and other inflammation-based biomarkers (CAR, NLR, PLR, SII, MHR) were subjected to pairwise comparison, the ability of UAR to detect CSF was superior to all (UAR

Table 3. Univariable and multivariable logistic regression analysis for identifying independent predictors of coronary slow flow.

Variables	Univariable analyses		Multivariable analysis	
			Nagelkerke R^2 in final step = 0.452	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Gender, male	1.768 (1.043–2.997)	0.034	2.781 (1.391–5.562)	0.004
Dyslipidemia	1.838 (1.115–3.031)	0.017	1.991 (1.048–3.785)	0.035
Smoking	2.079 (1.135–3.808)	0.018	1.699 (0.783–3.685)	0.180
FPG	0.992 (0.985–0.999)	0.029	0.998 (0.985–1.008)	0.088
TC	0.995 (0.990–1.000)	0.033	0.997 (0.988–1.018)	0.079
CAR	0.431 (0.258–0.718)	0.001	0.516 (0.346–1.016)	0.072
MHR	0.962 (0.936–0.990)	0.007	0.962 (0.829–0.995)	0.025
NLR	0.880 (0.783–0.987)	0.030	0.853 (0.703–1.033)	0.081
PLR	0.998 (0.995–1.001)	0.135	–	–
SII	0.947 (0.913–0.984)	0.005	0.916 (0.813–0.980)	0.018
UAR	0.173 (0.098–0.304)	<0.001	0.105 (0.051–0.217)	<0.001

CAR: C-reactive protein/albumin ratio; CRP: C- reactive protein; FPG: Fasting plasma glucose; HDL-C: High-density lipoprotein cholesterol; MHR: Monocyte/high-density lipoprotein cholesterol ratio; NLR: Neutrophil-to-lymphocyte ratio; OR: Odds ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; TC: Total cholesterol; UAR: Uric acid/albumin ratio.

vs CAR, p = 0.0375; UAR vs NLR, p = 0.0050; UAR vs PLR, p = 0.0014; UAR vs SII, p = 0.0398; UAR vs MHR, p = 0.0026) (Figure 5). These results suggest that UAR plays a more dominant role in CSF pathophysiology than other IBMs, given the etiopathogenesis of CSF.

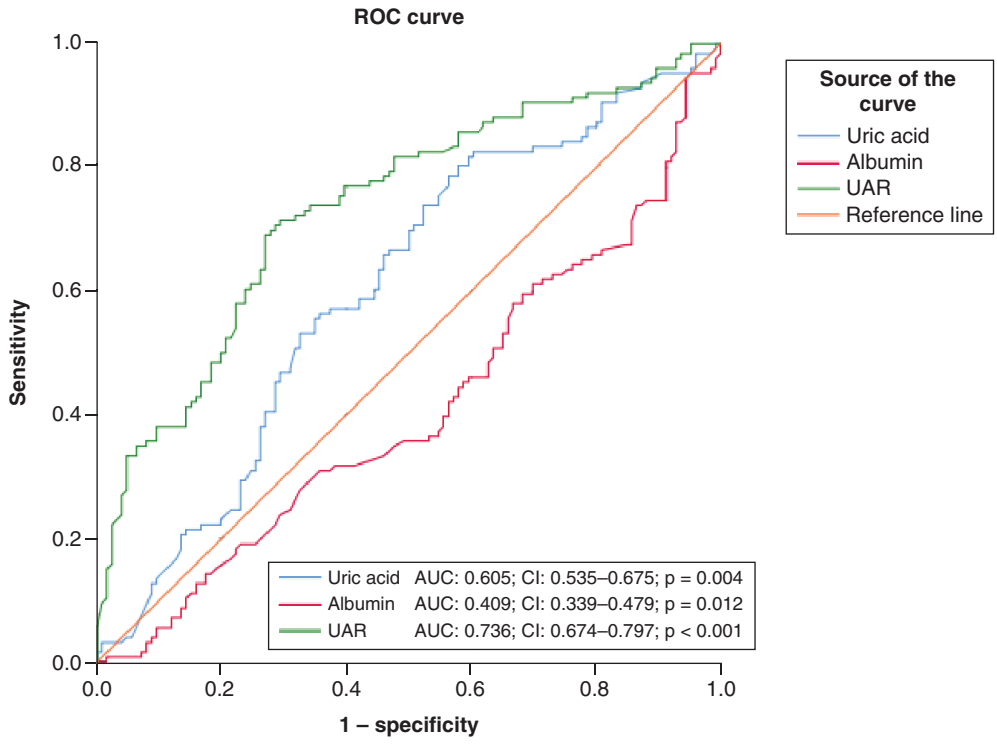
Discussion

To the best of our knowledge, this is the first study to compare the ability of traditional IBMs with UAR to predict CSF head-to-head. The most important result of our study is that the UAR was shown to be a strong and independent predictor for CSF. Furthermore, the ability of UAR to detect and predict CSF was superior to that of conventional IBMs and self-contained fractions of uric acid and albumin.

Tambe *et al.* long ago defined delayed opacification of distal vasculature structures of epicardial coronary arteries without mechanical occlusion as a CSF phenomenon in subjects undergoing selective coronary angiography for chest pain [26]. Although the etiopathogenesis of CSF has not been fully elucidated, increasing evidence holds that systemic inflammation and extensive subclinical atherosclerosis leading to endothelial and microvascular dysfunction are responsible for its pathophysiology [1–10]. Coronary flow reserve, which is an important indicator of coronary microvascular function, was found to be impaired in patients with CSF, and TFC values were negatively correlated with coronary flow reserve [27]. Sezgin *et al.* showed that endothelial-dependent vasodilation, which is an important indicator of endothelial function, is impaired in patients with CSF [28].

Chronic systemic inflammation plays a pivotal role in the development of atherosclerosis and is an effective causal process at all stages of the atherosclerotic process from its onset to its progression [29]. Chronic systemic inflammation and subclinical diffuse atherosclerosis caused by this process are thought to play a critical role in the pathogenesis of CSF by causing endothelial and microvascular dysfunction [30]. Indeed, many studies have shown that inflammatory cytokines and mediators are significantly increased in individuals with CSF compared with individuals with NCF [31]. Turhan *et al.* showed that serum plasma soluble adhesion molecules such as ICAM-1, VCAM-1 and E-selectin were significantly increased in subjects with CSF compared with individuals with NCF [32]. Li *et al.* showed that serum levels of inflammatory mediators such as IL-6 and CRP in patients with CSF were significantly higher than in individuals with NCF [33]. Kaplangoray *et al.* showed a close relationship between CSF and the triglycerides-glucose index [34]. Roshanravan *et al.* showed that the expression of inflammatory pathway mediators such as IL-1β and NF-κB expression was significantly increased in patients with CSF [5].

In recent years, it has been shown that inflammation-based formulae obtained by combining the parameters related to inflammatory processes from whole blood parameters in various fractions show better diagnostic and prognostic performance than the parameters that compose them. It has been well documented in many clinical studies that these IBMs reflect well the chronic inflammatory status *in vivo* and play an active role in the etiopathogenesis of many cardiovascular pathologies [35]. Many of these IBMs have been shown to be closely associated with



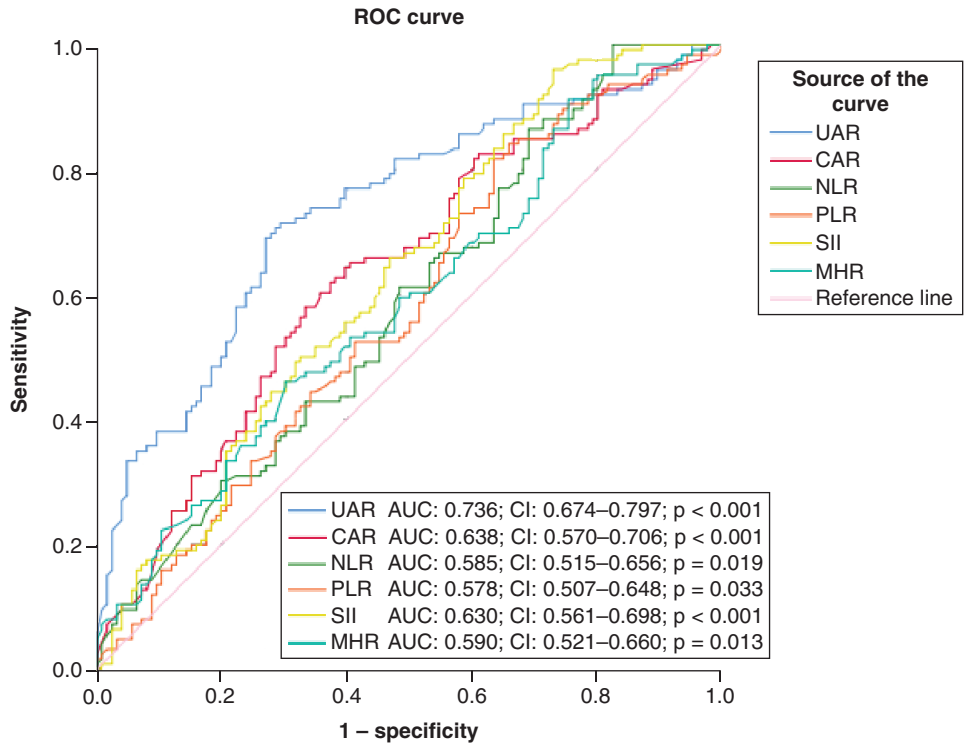
Pairwise comparison of ROC curves for detecting CSF

Compared variables	ΔAUC	95% CI	p-value
UAR and uric acid	0.130	0.049–0.211	0.0015
UAR and albumin	0.144	0.091–0.197	<0.0001
Uric acid and albumin	0.014	-0.070–0.098	0.7472

Figure 4. Comparison of receiver operating characteristic curves of uric acid/albumin ratio, serum uric acid and serum albumin for detecting coronary slow flow. At the best cutoff value of 1.72, UAR predicted CSF with 71% sensitivity and 71% specificity, and the power of UAR to predict CSF was superior to uric acid and albumin alone (p = 0.0015, p = <0001, respectively).
AUC: Area under the curve; ΔAUC: Difference between areas under the curves; CSF: Coronary slow flow; UAR: Uric acid/albumin ratio.

CSF in many recent studies. Dai *et al.* showed a close relationship between CSF and SII [6], Yesin *et al.* between CSF and CAR [7], Qiu *et al.* between CSF and PLR [8], Doğan *et al.* between CSF and NLR [9] and Canpolat *et al.* between CSF and MHR [10]. Yayla *et al.* showed that lymphocyte-to-monocyte ratio is an independent predictor for CSF [36].

UAR is an IBM that has emerged recently and has a stronger prognostic and predictive value than its uric acid and albumin fractions individually for some cardiovascular diseases [19–21]. Uric acid is the end product of purine metabolism; it can be produced endogenously or taken exogenously and shows pro-oxidant, proinflammatory and proatherogenic properties *in vivo* [11,12]. Due to these features, it has been shown to be closely related to a number of cardiovascular diseases, especially endothelial dysfunction, microvascular insufficiency and atherosclerosis [11–14]. Moreover, high serum uric acid levels have been shown to be closely related to CSF, in which chronic systemic inflammation, diffuse subclinical atherosclerosis and endothelial and microvascular dysfunction play a pivotal role in pathogenesis [15–17]. Unlike uric acid, albumin has anti-inflammatory, antioxidant, anticoagulant and anti-platelet-aggregation properties, which are protective mechanisms from atherosclerosis and low albumin levels have been associated with poor cardiovascular clinical outcomes in many studies [18,37,38]. In our study, UAR was identified as an independent potential risk factor for CSF and strongly and independently predicted CSF. Due to the opposing effects of uric acid and albumin on chronic inflammatory and atherosclerotic status, which play a fundamental role in the pathophysiology of CSF, it can be said that combining both parameters in a single fraction has a synergistic



Pairwise comparison of ROC curves of inflammation-based markers to detect CSF

Compared variables	ΔAUC	95% CI	p-value
UAR and CAR	0.097	0.005–0.190	0.0375
UAR and NLR	0.150	0.045–0.255	0.0050
UAR and PLR	0.158	0.060–0.255	0.0014
UAR and SII	0.106	0.004–0.207	0.0398
UAR and MHR	0.145	0.050–0.240	0.0026

Figure 5. Pairwise comparisons of receiver operating characteristic curves of C-reactive protein/albumin ratio, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, monocyte/high-density lipoprotein cholesterol ratio and uric acid/albumin ratio for detecting coronary slow flow.
When UAR and other inflammation-based biomarkers (CAR, NLR, PLR, SII, MHR) pairwise compared, the ability of UAR to detect CSF was superior to all ($p < 0.05$, for all).
AUC: Area under the curve; ΔAUC: Difference between areas under the curves; CAR: C-reactive protein/albumin ratio; CSF: Coronary slow flow; MHR: Monocyte/high-density lipoprotein cholesterol ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; UAR: Uric acid/albumin ratio.

effect in predicting and detecting CSF. Furthermore, the superior diagnostic accuracy and performance of UAR over other IBMs in predicting CSF may possibly be due to the stronger and broader involvement of UAR in the chronic inflammatory status and proatherogenic process compared with other IBMs.

Study limitations

Our study had some limitations. First of all, this study was a retrospective, observational study and was conducted with a relatively small sample size. Secondly, although multivariate regression analysis was performed to adjust for known confounders to identify independent predictors for CSF, it is not possible to completely control for unknown confounders in such studies. Third, we only used a single UAR value for our analysis, rather than a dynamic trend. Fourth, data on dynamic endothelial functions such as coronary flow reserve and methods that more clearly show intracoronary topography, such as intravascular ultrasound results, were not available due to the retrospective design. Fifth, the cause-and-effect relationship between UAR and CSF cannot be clearly established

due to the observational nature of the study. Finally, the study did not have short- and long-term clinical follow-up results.

Conclusion

Our study showed that high UAR values were significantly and independently associated with the presence of CSF. Furthermore, the diagnostic performance of UAR in predicting CSF was superior to that of the traditional IBMs SII, PLR, NLR, MHR and CAR. Also, UAR showed a stronger correlation with CSF than other IBMs. These results suggest that higher UAR values may represent a stronger proinflammatory and pro-oxidant effect than other IBMs, which may affect blood flow in the coronary bed. However, in order to clearly reveal the causal role of UAR on coronary flow, the results of our study should be confirmed by prospective studies with larger samples.

Summary points

- The uric acid/albumin ratio (UAR) was found to be an independent predictor for the presence of coronary slow flow (CSF) in the study population.
- UAR exhibited superior diagnostic accuracy and performance compared with traditional inflammation-based markers (IBMs) such as C-reactive protein/albumin ratio, systemic immune-inflammation index, platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio and monocyte/high-density lipoprotein cholesterol ratio in detecting and predicting CSF.
- The study revealed a significant positive correlation between UAR levels and the thrombolysis in myocardial infarction frame count, which is used to quantify coronary blood flow. This suggests that higher UAR values may indicate compromised coronary flow.
- In multivariate regression analysis, UAR was identified as an independent potential risk factor for CSF, along with male gender and the presence of dyslipidemia.
- The study suggests that the combined effects of uric acid (proinflammatory) and albumin (anti-inflammatory) within UAR may provide a stronger and broader reflection of chronic inflammatory status and proatherogenic processes related to CSF compared with other IBMs.
- UAR was shown to have a stronger correlation with CSF than other IBMs, emphasizing its potential as a valuable marker for assessing CSF risk.
- The study concludes that UAR, due to its ability to reflect systemic inflammatory status and proatherogenic effects, may play a crucial role in the pathophysiology of CSF, making it a promising tool for identifying individuals at risk for this condition. Further prospective studies with larger samples are recommended to confirm these findings.

Author contributions

K Toprak contributed to acquisition, analysis and interpretation of data; revising it critically for important intellectual content; and final approval of the version to be published. K Özen contributed to acquisition, analysis and interpretation of data; drafting the article; revising it critically for important intellectual content; and final approval of the version to be published. T Memioğlu and M İnanır contributed to the acquisition, analysis and interpretation of data; drafting the article; and final approval of the version to be published. S Akyol, M Begenc Tascanov and A Biçer made substantial contributions to conception and design; drafting the article; and final approval of the version to be published. M Kaplangöray contributed to acquisition of data; drafting the article; and final approval of the version to be published. R Demirbağ made substantial contributions to conception and design; revising the article critically for important intellectual content; and final approval of the version to be published.

Financial disclosure

The authors have no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

Papers of special note have been highlighted as: • of interest

1. Fineschi M, Bravi A, Gori T. The 'slow coronary flow' phenomenon: evidence of preserved coronary flow reserve despite increased resting microvascular resistances. *Int. J. Cardiol.* 127(3), 358–361 (2008).
2. Chalikias G, Tziakas D. Slow coronary flow: pathophysiology, clinical implications, and therapeutic management. *Angiology* 72(9), 808–818 (2021).

• **Emphasises the pathophysiological mechanism of the coronary slow flow phenomenon.**

3. Ghaffari S, Tajlil A, Aslanabadi N *et al.* Clinical and laboratory predictors of coronary slow flow in coronary angiography. *Perfusion* 32(1), 13–19 (2017).
4. Zhang E, Gao M, Gao J *et al.* Inflammatory and hematological indices as simple, practical severity predictors of microdysfunction following coronary intervention: a systematic review and meta-analysis. *Angiology* 71(4), 349–359 (2020).
5. Roshanravan N, Shabestari AN, Alamdari NM *et al.* A novel inflammatory signaling pathway in patients with slow coronary flow: NF-κB/IL-1β/nitric oxide. *Cytokine* 143, 155511 (2021).
6. Dai XT, Kong TZ, Zhang XJ *et al.* Relationship between increased systemic immune-inflammation index and coronary slow flow phenomenon. *BMC Cardiovasc. Disord.* 22(1), 362 (2022).

• **This study well demonstrates the relationship between inflammation-based markers and the coronary slow flow phenomenon.**

7. Yesin M, Çağdaş M, Karabağ Y *et al.* Assessment of the relationship between C-reactive protein-to-albumin ratio and slow coronary flow in patients with stable angina pectoris. *Coron. Artery Dis.* 30(7), 505–510 (2019).
8. Qiu Z, Jiang Y, Jiang X *et al.* Relationship between platelet to lymphocyte ratio and stable coronary artery disease: meta-analysis of observational studies. *Angiology* 71(10), 909–915 (2020).
9. Doğan M, Akyel A, Çimen T *et al.* Relationship between neutrophil to lymphocyte ratio and slow coronary flow. *Clin. Appl. Thromb. Hemost.* 21(3), 251–254 (2015).
10. Canpolat U, Çetin EH, Cetin S *et al.* Association of monocyte-to-HDL cholesterol ratio with slow coronary flow is linked to systemic inflammation. *Clin. Appl. Thromb. Hemost.* 22(5), 476–482 (2016).
11. Coutinho Tde A, Turner ST, Peyser PA *et al.* Associations of serum uric acid with markers of inflammation, metabolic syndrome, and subclinical coronary atherosclerosis. *Am. J. Hypertens.* 20(1), 83–89 (2007).
12. Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. *Semin. Nephrol.* 25(1), 39–42 (2005).
13. Saito Y, Tanaka A, Node K *et al.* Uric acid and cardiovascular disease: a clinical review. *J. Cardiol.* 78(1), 51–57 (2021).

• **The relationship between uric acid and cardiovascular diseases is discussed in detail.**

14. Kleber ME, Delgado G, Grammer TB *et al.* Uric acid and cardiovascular events: a mendelian randomization study. *J. Am. Soc. Nephrol.* 26(11), 2831–2838 (2015).
15. Yildiz A, Yilmaz R, Demirbag R *et al.* Association of serum uric acid level and coronary blood flow. *Coron. Artery Dis.* 18(8), 607–613 (2007).

• **Study examining the relationship between coronary slow flow and uric acid.**

16. Elbasan Z, Sahin DY, Gür M *et al.* Serum uric acid and slow coronary flow in cardiac syndrome X. *Herz* 38(5), 544–548 (2013).
17. Prasad M, Matteson EL, Herrmann J *et al.* Uric acid is associated with inflammation, coronary microvascular dysfunction, and adverse outcomes in postmenopausal women. *Hypertension* 69(2), 236–242 (2017).
18. Chien SC, Chen CY, Leu HB *et al.* Association of low serum albumin concentration and adverse cardiovascular events in stable coronary heart disease. *Int. J. Cardiol.* 241, 1–5 (2017).
19. Şaylık F, Çınar T, Selçuk M *et al.* The relationship between uric acid/albumin ratio and carotid intima-media thickness in patients with hypertension. *Arq. Bras. Cardiol.* 120(5), e20220819 (2023).
20. Yalcinkaya D, Karacali K, Ilhan BC *et al.* Relation between serum uric acid to albumin ratio and severity of chronic coronary artery disease. *Angiology* doi: 10.1177/00033197231161902 (2023) (Epub ahead of print).
21. Çınar T, Şaylık F, Hayıroğlu Mİ *et al.* The association of serum uric acid/albumin ratio with no-reflow in patients with ST elevation myocardial infarction. *Angiology* 74(4), 381–386 (2023).
22. Sadr-Ameli MA, Saedi S, Saedi T *et al.* Coronary slow flow: benign or ominous? *Anatol. J. Cardiol.* 15(7), 531–535 (2015).

23. Zhu X, Shen H, Gao F *et al.* Clinical profile and outcome in patients with coronary slow flow phenomenon. *Cardiol. Res. Pract.* 2019, 9168153 (2019).
24. Soares AA, Eyff TF, Campani RB, Ritter L, Camargo JL, Silveiro SP. Glomerular filtration rate measurement and prediction equations. *Clin. Chem. Lab. Med.* 47(9), 1023–1032 (2009).
25. Gibson CM, Cannon CP, Daley WL *et al.* TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation* 93(5), 879–888 (1996).
26. Tambe AA, Demany MA, Zimmerman HA *et al.* Angina pectoris and slow flow velocity of dye in coronary arteries – a new angiographic finding. *Am. Heart J.* 84(1), 66–71 (1972).
27. Erdogan D, Caliskan M, Gullu H *et al.* Coronary flow reserve is impaired in patients with slow coronary flow. *Atherosclerosis* 191(1), 168–174 (2007).
28. Sezgin AT, Barutcu I, Sezgin N, Gullu H *et al.* Contribution of plasma lipid disturbances to vascular endothelial function in patients with slow coronary flow. *Angiology* 57(6), 694–701 (2007).
29. Zhu Y, Xian X, Wang Z *et al.* Research progress on the relationship between atherosclerosis and inflammation. *Biomolecules* 8(3), 80 (2018).
30. Zhu Q, Wang S, Huang X *et al.* Understanding the pathogenesis of coronary slow flow: recent advances. *Trends Cardiovasc. Med.* S1050-1738(22), 00142–6 (2022).
31. Li JJ, Xu B, Li ZC *et al.* Is slow coronary flow associated with inflammation? *Med. Hypotheses* 66(3), 504–508 (2006).
32. Turhan H, Saydam GS, Erbay AR *et al.* Increased plasma soluble adhesion molecules; ICAM-1, VCAM-1, and E-selectin levels in patients with slow coronary flow. *Int. J. Cardiol.* 108(2), 224–230 (2006).
33. Li JJ, Qin XW, Li ZC *et al.* Increased plasma C-reactive protein and interleukin-6 concentrations in patients with slow coronary flow. *Clin. Chim. Acta* 385(1–2), 43–47 (2007).
34. Kaplangoray M, Toprak K, Başanalan F *et al.* Investigation of the relationship between triglycerides-glucose index and coronary slow flow: a retrospective case–control study. *Arq. Bras. Cardiol.* 120(6), e20220679 (2023).
35. Van Lente F. Markers of inflammation as predictors in cardiovascular disease. *Clin. Chim. Acta* 293(1–2), 31–52 (2000).
36. Yayla Ç, Akboğa MK, Gayretli Yayla K *et al.* A novel marker of inflammation in patients with slow coronary flow: lymphocyte-to-monocyte ratio. *Biomark. Med.* 10(5), 485–493 (2016).
37. Belinskaia DA, Voronina PA, Shmurak VI *et al.* Serum albumin in health and disease: esterase, antioxidant, transporting and signaling properties. *Int. J. Mol. Sci.* 22(19), 10318 (2021).
38. Arques S. Human serum albumin in cardiovascular diseases. *Eur. J. Intern. Med.* 52, 8–12 (2018).