

URIC ACID/ALBUMIN RATIO AS A NOVEL BIOMARKER FOR PREDICTING POOR CORONARY COLLATERAL CIRCULATION IN CORONARY ARTERY DISEASE: META-ANALYSIS STUDY

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СЪОТНОШЕНИЕТО МЕЖДУ ПИКОЧНА КИСЕЛИНА И АЛБУМИН КАТО НОВ БИОМАРКЕР ЗА ПРОГНОЗИРАНЕ НА ЛОША КОРОНАРНА КОЛАТЕРАЛНА ЦИРКУЛАЦИЯ ПРИ ИСХЕМИЧНА БОЛЕСТ НА СЪРЦЕТО: МЕТААНАЛИЗ

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Abstract.

Background: Coronary collateral plays a role in maintaining myocardial function, limiting infarct size, and reduced morbidity and mortality. Uric acid to albumin ratio (UAR) has recently been discovered as a novel biomarker associated with cardiovascular disease. However, studies investigating the relationship between UAR and coronary collateral circulation (CCC) formation are limited and have low magnitude. Therefore, this study aims to determine the relationship between UAR and CCC formation in coronary artery disease patients. **Methods:** The literature was searched in PubMed, Medline, SpringerLink, ScienceDirect, and Scopus for articles published before August 2024. Studies that did not report UAR results as one of the parameters but included uric acid and albumin in their laboratory parameters, had UAR values calculated using the error propagation for ratio formula. Statistical analysis for meta-analysis using Review Manager 5.4 software to evaluate the relationship between UAR and CCC. **Results:** A systematic search retrieved nine studies that met the eligibility criteria. The total population in these studies was 5290 subjects, including 3744 subjects with good coronary collateral circulation and 1546 subjects with poor coronary circulation. Four of the nine studies assessed albumin parameters using glycated albumin and one study assessed albumin parameters using ischemic modified albumin. The uric acid/albumin ratio is correlated with CCC formation, with the lower the UAR, the more likely CCC formation will occur (SMD -0.31, 95% CI -0.56 to -0.05, p-value 0.02, I² 93%). In the subanalysis of the different parameters, uric acid is also correlated with CCC formation (SMD -0.41, 95% CI -0.74 to -0.08, p-value 0.01, I² 96%), while albumin has no strong correlation. **Conclusion:** Uric acid to albumin ratio could be a new parameter in predicting the formation of coronary collateral circulation in patients with stable coronary artery disease.

Key word:

albumin, CAD, coronary collateral circulation, uric acid

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Резюме.

Въведение: Колатералите на коронарните съдове играят роля за поддържането на миокардната функция, ограничаването на размера на инфаркта и намалената заболяемост и смъртност. Съотношението пикочна киселина/албумин (UAR) наскоро е открито като нов биомаркер, свързан със сърдечно-съдовите заболявания. Въпреки това проучванията, изследващи връзката между UAR и формирането на коронарна колатерална циркулация, са ограничени и с ниска значимост. Това проучване цели да се определи връзката между UAR и формирането на коронарна колатерална циркулация при пациенти с коронарна артериална болест. **Методи:** Проведено е литературно търсене в PubMed, Medline, SpringerLink, ScienceDirect и Scopus на статии, публикувани преди август 2024 г. За проучванията, които не докладват резултати за UAR като един от параметрите, но включват пикочна киселина и албумин в лабораторните си параметри, стойностите на UAR са изчислени с помощта на формула за разпространение

на грешките за формулата на съотношението. Статистическият анализ в този метаанализ е извършен чрез софтуер Review Manager 5.4, за да се оцени връзката между UAR и коронарната колатерална циркулация. **Резултати:** Чрез систематичното търсене се откриха 9 проучвания, отговарящи на критериите за допустимост. Общата популация в тези проучвания е 5290 лица, вкл. 3744 лица с добра коронарна колатерална циркулация и 1546 с лоша коронарна циркулация. В 4 от 9 проучвания албуминовите параметри се оценяват чрез гликирания албумин и в 1 проучване – чрез исхемично модифициран албумин. Съотношението пикочна киселина/албумин корелира с формирането на коронарна колатерална циркулация, като колкото по-ниско е UAR, толкова по-вероятно е образуването на коронарна колатерална циркулация (SMD -0,31, 95% CI -0,56 до -0,05, p-стойност 0,02, I² 93%). При поданализа на различните параметри пикочната киселина също корелира с формирането на коронарна колатерална циркулация (SMD -0,41, 95% CI -0,74 до -0,08, p-стойност 0,01, I² 96%), докато албуминът няма силна корелация. **Заклучение:** Съотношението пикочна киселина/албумин може да е нов параметър за прогнозиране на формирането на коронарна колатерална циркулация при пациенти със стабилна коронарна артериална болест.

Ключови думи: албумин, коронарна артериална болест (исхемична болест на сърцето), коронарна колатерална циркулация, пикочна киселина

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BACKGROUND

Coronary artery disease (CAD) is caused by narrowing of the coronary arteries, which leads to ischemia. The reduced oxygen supply causes the heart muscle to work at suboptimal levels [1, 2]. In ischemic conditions, coronary blood vessels generate additional blood flow to reduce ischemia, called collateral circulation. Coronary collateral arteries originate from other coronary arteries with better blood flow to help perfuse the ischemic region of the heart [3]. The process of coronary collateral formation begins with the mechanism of fluid shear stress at the endothelial level and the presence of ischemia-induced inflammatory factors. Coronary collateral plays a role in maintaining myocardial function, limiting infarct size, and reduced morbidity and mortality [4, 5].

Inflammation is a contributing factor to collateral formation. Uric acid is a parameter that has been found to be associated with inflammatory conditions. Serum uric acid is the end product of purine metabolism. Uric acid plays a role in the inflammatory process and may impair vascular endothelial function [6, 7]. Uric acid has been associated with cardiovascular disease and its prognosis. Hypertension, heart failure, CAD, and arrhythmias are some of the cardiovascular diseases associated with elevated uric acid [8]. Meanwhile, albumin is one of the parameters in the blood that has anti-inflammatory and protective effects against oxidative stress [9, 10] Hypoalbuminemia is associated with increased mortality and incidence of cardiovascular disease [11]. Therefore, uric acid and albumin have opposite effects on cardiovascular disease.

Uric acid to albumin ratio (UAR) has recently been discovered as a novel biomarker associated with cardiovascular disease. Higher UAR levels are associated

with increased severity in CAD patients [12, 13] However, studies investigating the relationship between UAR and CCC formation are limited and have low magnitude. Therefore, this study aims to determine the relationship between UAR and CCC formation in coronary artery disease patients.

METHODS

Study Design and Literature Search

This study was registered at the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42024575003. The literature was searched in PubMed, Medline, SpringerLink, ScienceDirect, and Scopus for articles published before August 2024. The search used the keywords “acute myocardial infarction”, “uric acid”, “albumin”, and “coronary collateral circulation”. The detailed key words used are listed in the Table 1.

Table 1. Search keywords in the database

Database	Key word
PubMed, Medline, ScienceDirect, Scopus	(“Coronary Artery Disease*” OR “CAD” OR “Atheroslero*” OR “Coronary Atherosclero*” OR “Chronic total occlu*”) AND (“Uric Acid” OR “Albumin” OR “Uric Acid to Albumin Ratio” OR “Uric Acid to Albumin” OR “Uric Acid/Albumin” OR “UAR”) AND (“Coronary Collateral Circulation*” OR “CCC” OR “Rentrop” OR “Coronary Collateralization” OR “Coronary Collateral*” OR “Collateral Index”)
SpringerLink	(“Uric Acid to Albumin Ratio” OR “Uric Acid to Albumin” OR “UAR”) AND (“Coronary Collateral Circulation” OR “CCC” OR “Rentrop” OR “Coronary Collateralization” OR “Collateral Index”)

Eligibility Criteria

Inclusion criteria for this study were studies with a population of patients with chronic stable coronary artery disease with or without chronic total occlusion who were measured for albumin and uric acid with the outcome of coronary collateral circulation. Glycated albumin and ischemia-modified albumin measurements were also included in this study. Coronary collateral circulation was assessed using the Rentrop classification, where grades 0-1 represent poor coronary collateral circulation and 2-3 represent good coronary collateral circulation. The study designs included in this study were cross-sectional, cohort, and case-control. Manuscripts that are not published in English and are not available as full papers will be excluded from this study.

Data Extraction

Eligible studies and those included in this study were screened by two independent reviewers, who initially screened the abstract and title. In case of disagreement between the two reviewers, the decision was taken by a third person with higher competence in the cardiovascular field.

Quality Assessment

Risk of bias was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies. This assessment was performed by two independent reviewers. The parameters assessed consisted of eight questions. The interpretation of the value is if it has a value of more than 70% is considered low risk category, 50% - 70% is considered moderate risk and less than 50% is considered high risk [14].

Outcome of Interest

The primary outcome of this study is to find the correlation between uric acid to albumin ratio to predict coronary collateral formation in patients with stable coronary artery disease. The secondary outcome of this study is the correlation between each uric acid and albumin on the development of coronary collateral circulation.

Statistical Analysis

Studies that did not report UAR results as one of the parameters but included uric acid and albumin in their laboratory parameters, had UAR values calculated. The UAR was calculated based on the mean \pm standard deviation data of uric acid and albumin using the error propagation for ratio formula. When the studies do not provide mean and standard deviation data, it will be estimated using median and percen-

tile (first and third quartile) [15, 16]. Statistical analysis for meta-analysis using Review Manager 5.4 software to evaluate the relationship between UAR and CCC formation using the effect measure standard mean difference. Random effect model is used because the units of measurement for uric acid and albumin examination are not the same between each study. Heterogeneity is assessed using the I² value, which indicates that if I² > 50% and p value < 0.1, the heterogeneity category is high. Publication bias was measured using funnel plots and Egger's test which was analyzed with IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0.2.0 Armonk, NY: IBM Corp.

RESULTS

A systematic search conducted in accordance with the research method yielded a total of 772 studies after the removal of duplicate studies. After reviewing the titles and abstracts, a total of 53 studies were obtained, which were then assessed by two reviewers to determine which studies would be included in this review. After reviewing the full papers, 9 studies were included in this review [17-25]. All studies included in this research were assessed for risk of bias using JBI, where eight of the nine studies had a low risk of bias and one study had a moderate risk of bias (Table 2).

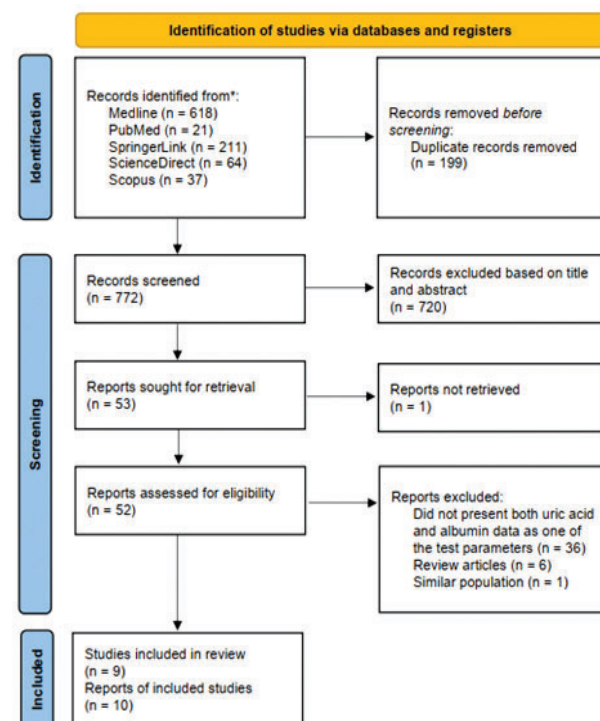


Fig. 1. Diagram of systematic search process based on PRISMA flow 2020

Table 2. Baseline characteristic of the study included in this review

Study ID	Study population	Study Method	Albumin parameter	Good coronary collateral circulation				Poor coronary collateral circulation			
				Sample size	Age	Sex (Male)	BMI	Sample size	Age	Sex (Male)	BMI
Dong et al. 2024	1093 patients CAD and CTO	Cross-sectional	Glycated albumin	775	59.1 ± 10.2	666 (85.9%)	26.23 ± 3.32	318	58.0 ± 10.1	270 (84.9%)	26.70 ± 3.21
Zhao et al. 2020	391 patients Stable CAD	Cross-sectional	Albumin	298	60.83 ± 11.77	230 (77.2)	-	93	63.06 ± 9.56	79 (84.9)	-
Shen et al. 2013	434 patients CAD and CTO	Cross-sectional	Glycated albumin	95 (non-diabetes) and 199 (diabetes)	62.4 ± 10.4 (non-diabetes) and 64.6 ± 11.1 (diabetes)	83 (87.4%) in non-diabetes and 172 (84.6%) in diabetes	24.8 ± 3.0 (non-diabetes) and 25.1 ± 3.4 (diabetes)	22 (non-diabetes) and 118 (diabetes)	68 ± 11.1 (non-diabetes) and 66.5 ± 10.1 (diabetes)	10 (45.5%) in non-diabetes and 77 (65.3%) in diabetes	25.3 ± 2.8 (non-diabetes) and 25.8 ± 3.4 (non-diabetes)
Toprak et al. 2023	415 patients CAD and CTO	Cross-sectional	Albumin	232	57 ± 13	156 (67.2)	26.6 ± 4.0	183	57 ± 12	111 (60.7)	27.3 ± 4.3
Chen et al. 2020	128 patients CAD and CTO	Cross-sectional	Ischemic modified albumin	59	60.92 ± 11.61	45 (76.3)	-	69	61.28 ± 11.61	45 (65.2)	-
Gao et al. 2022	792 patients CAD and CTO	Cross-sectional	Glycated albumin	570	59.15 ± 10.40	493 (86.5%)	26.30 ± 3.33	222	58.51 ± 9.93	184 (82.9%)	26.62 ± 3.09
Liu et al. 2021	1653 CAD inpatients with CTO	Cohort	Glycated albumin	1298	59.1 ± 10.3	1074 (82.7)	26.0 ± 3.1	355	57.7 ± 10.5	294 (82.8)	28.1 ± 3.7
Akbuga et al. 2022	172 CAD patients with CTO	Cross-sectional	Albumin	98	67.5 ± 10.2	80 (81.6)	-	74	67.7 ± 10.7	53 (71.7)	-
Şaylık et al. 2023	212 CAD patients with CTO	Cross-sectional	Albumin	120	59.5386 ± 14.2571	79 (65.8)	27.289 ± 3.3016	92	60.1761 ± 11.674	69 (75.0)	27.8 ± 2.862

Baseline Characteristics

The total population in these studies was 5290 subjects, including 3744 subjects with good coronary collateral circulation and 1546 subjects with poor coronary circulation. Four of the nine studies assessed albumin parameters using glycated albumin and one study assessed albumin parameters using ischemic modified albumin (Table 3).

Primary Outcome: Uric Acid to Albumin Ratio and Coronary Collateral Circulation Formation

The uric acid/albumin ratio is correlated with CCC formation, with the lower the UAR, the more likely CCC formation will occur (SMD -0.31, 95% CI -0.56 to -0.05, p-value 0.02, I² 93%). Subanalysis of UAR in the two groups of albumin and glycated albumin examination showed similar results, showing that lower UAR was

Table 3. Risk of bias assessed by the Joanna Briggs Institute (JBI) Critical Appraisal Tools for use in JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	% Yes	Risk
Shen et al. 2013	✓	✓	✓	✓	✓	✓	✓	✓	100%	Low
Zhao et al. 2020	✓	✓	✓	-	-	-	✓	✓	62.5%	Moderate
Chen et al. 2020	✓	✓	✓	✓	-	-	✓	✓	75%	Low
Liu et al. 2021	✓	✓	-	✓	✓	✓	-	✓	75%	Low
Akbuga et al. 2022	✓	✓	-	✓	-	✓	✓	✓	75%	Low
Gao et al. 2022	✓	✓	-	✓	-	✓	✓	✓	75%	Low
Toprak et al. 2023	✓	✓	✓	✓	-	-	✓	✓	75%	Low
Şaylık et al. 2023	✓	✓	✓	✓	-	-	✓	✓	75%	Low
Dong et al. 2024	✓	✓	✓	✓	✓	✓	✓	✓	100%	Low

Q1. Were the criteria for inclusion in the sample clearly defined? Q2. Were the study subjects and the setting described in detail? Q3. Was the exposure measured in a valid and reliable way? Q4. Were objective, standard criteria used for measurement of the condition? Q5. Were confounding factors identified? Q6. Were strategies to deal with confounding factors stated? Q7. Were the outcomes measured in a valid and reliable way? Q8. Was appropriate statistical analysis used? ✓: Yes; -: No.

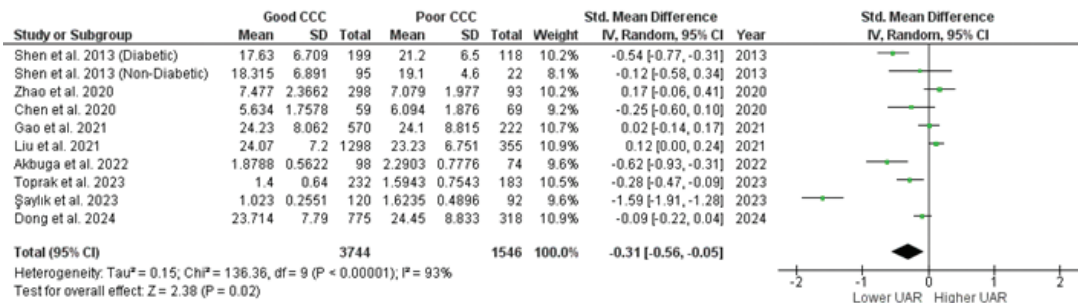


Fig. 2. Forest plot meta-analysis on the association between uric acid to albumin ratio and coronary collateral circulation formation

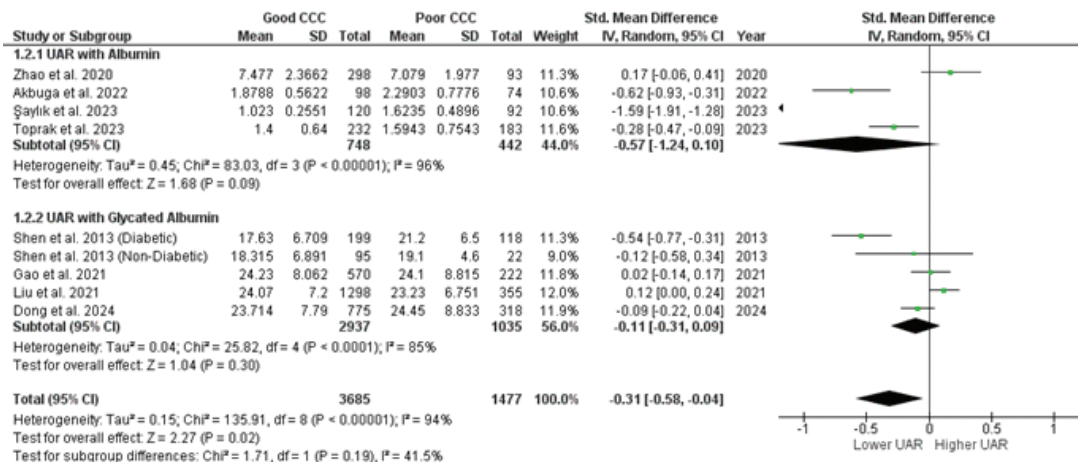


Fig. 3. Subanalysis of UAR based on albumin and glycated albumin examination parameters

more likely to result in CCC formation, but both groups were not statistically significant.

Secondary Outcome: Uric Acid and Albumin Levels to Coronary Collateral Circulation Formation

In the analysis of the different parameters, uric acid is also correlated with CCC formation (SMD -0.41, 95% CI -0.74 to -0.08, p-value 0.01, I² 96%), while albumin

has no strong correlation. However, when subanalysis is performed based on albumin and glycated albumin parameters, both are correlated with CCC formation, but with opposite results. There were four studies for each parameter. Higher albumin increased the likelihood of CCC (SMD 0.22, 95% CI 0.10 to 0.34, p-value 0.0004, I² 0%), while lower glycated albumin increased the likelihood of CCC (SMD -0.24, 95% CI -0.35 to -0.14, p-value <0.001, I² 48%).

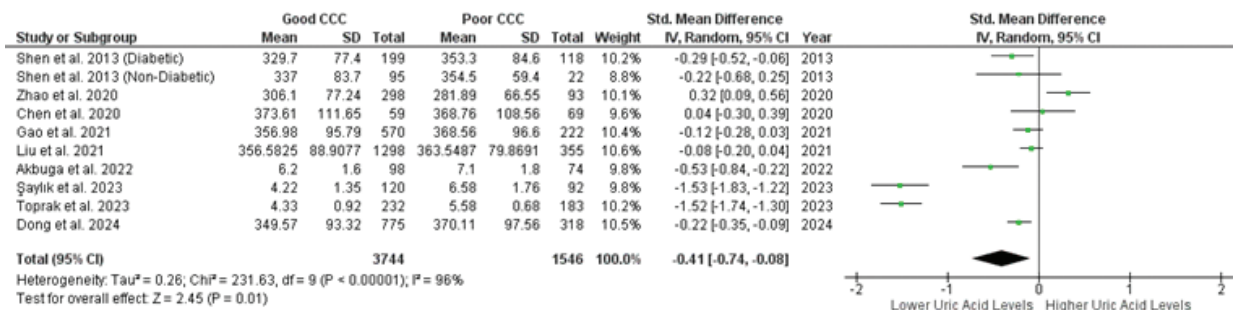


Fig. 4. Forest plot meta-analysis on the association between uric acid and coronary collateral circulation formation

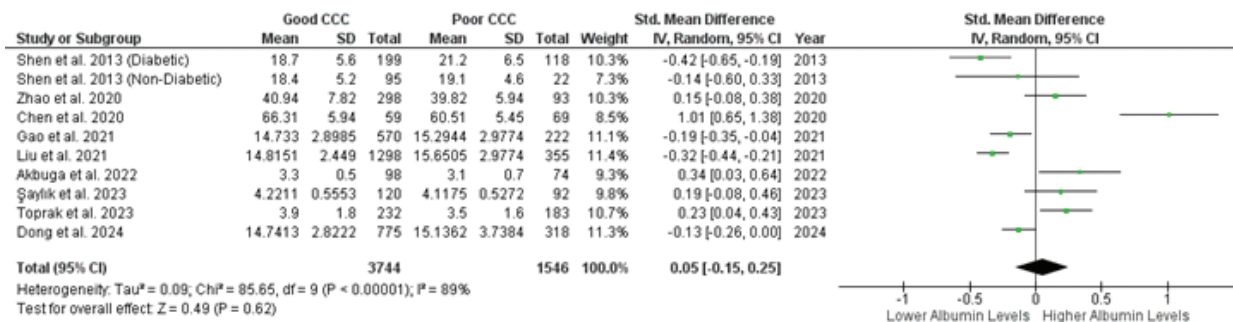


Fig. 5. Forest plot meta-analysis on the association between albumin and coronary collateral circulation formation

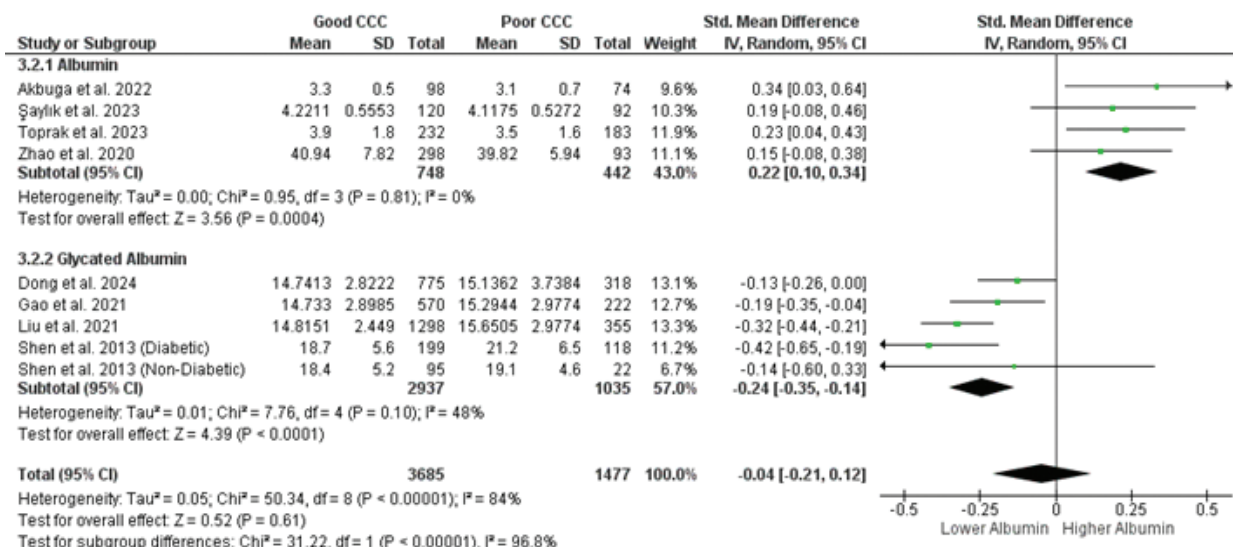


Fig. 6. Subanalysis based on albumin and glycated albumin examination parameters

Heterogeneity and Publication Bias

There was high heterogeneity in the primary and secondary outcome analysis, but the heterogeneity was not significant in the subanalysis based on albumin measurement type. The albumin parameters influenced the heterogeneity score of the study. The funnel plot analysis showed a symmetric picture, and the results of the Egger's test analysis showed a p-value of 0.69, indicating that there was no significant publication bias in this study.

Sensitivity Analysis

Sensitivity analysis was performed by eliminating studies based on the type of albumin assayed and also by eliminating each study to see how each study affected the results. The results of the sensitivity analysis of the exclusion studies based on the type of albumin examined showed results that remained consistent but were not statistically significant (Fig. 8, 9). This indicates that it is still less robust. However, the results of the sensitivity analysis by excluding each study showed consistent results (Table 4).

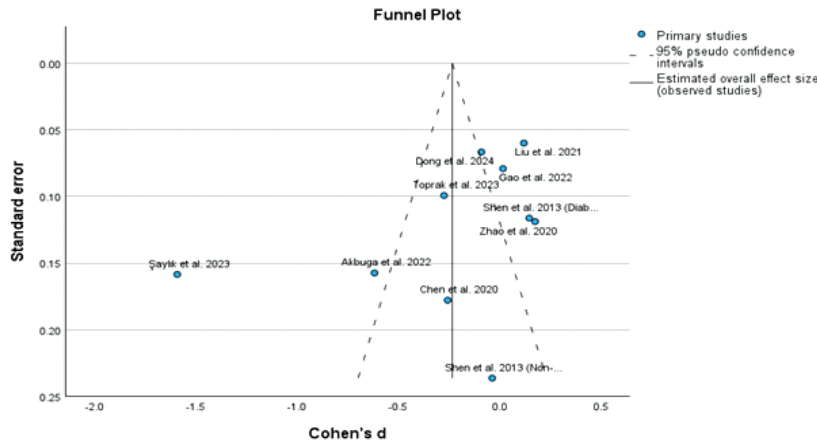


Fig. 7. Funnel plot for publication bias

Study or Subgroup	Good CCC			Poor CCC			Weight	Std. Mean Difference IV, Random, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
Chen et al. 2020	5.634	1.7578	59	6.094	1.876	69	19.5%	-0.25 [-0.60, 0.10]	2020
Zhao et al. 2020	7.477	2.3662	298	7.079	1.977	93	20.4%	0.17 [-0.06, 0.41]	2020
Akbuga et al. 2022	1.8788	0.5622	98	2.2903	0.7776	74	19.8%	-0.62 [-0.93, -0.31]	2022
Saylik et al. 2023	1.023	0.2551	120	1.6235	0.4896	92	19.8%	-1.59 [-1.91, -1.28]	2023
Toprak et al. 2023	1.4	0.64	232	1.5943	0.7543	183	20.6%	-0.28 [-0.47, -0.09]	2023
Total (95% CI)	807			511			100.0%	-0.51 [-1.06, 0.04]	

Heterogeneity: Tau² = 0.37; Chi² = 83.76, df = 4 (P < 0.00001); I² = 95%
Test for overall effect: Z = 1.92 (P = 0.07)

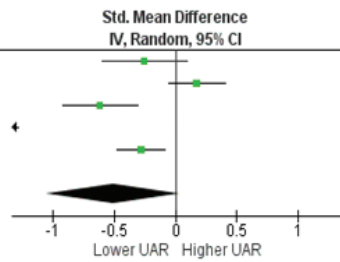


Fig. 8. Sensitivity analysis by exclusion of glycated albumin parameters

Study or Subgroup	Good CCC			Poor CCC			Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
Shen et al. 2013 (Diabetic)	17.63	6.709	199	21.2	6.5	118	9.1%	-0.54 [-0.77, -0.31]	2013
Shen et al. 2013 (Non-diabetic)	18.315	6.891	95	19.1	4.6	22	2.3%	-0.12 [-0.58, 0.34]	2013
Chen et al. 2020	5.634	1.7578	59	6.094	1.876	69	4.0%	-0.25 [-0.60, 0.10]	2020
Gao et al. 2021	24.23	8.062	570	24.1	8.815	222	20.4%	0.02 [-0.14, 0.17]	2021
Liu et al. 2021	24.07	7.2	1298	23.23	6.751	355	35.5%	0.12 [0.00, 0.24]	2021
Dong et al. 2024	23.714	7.79	775	24.45	8.833	318	28.7%	-0.09 [-0.22, 0.04]	2024
Total (95% CI)	2996			1104			100.0%	-0.04 [-0.11, 0.03]	

Heterogeneity: Chi² = 27.24, df = 5 (P < 0.0001); I² = 82%
Test for overall effect: Z = 1.20 (P = 0.23)

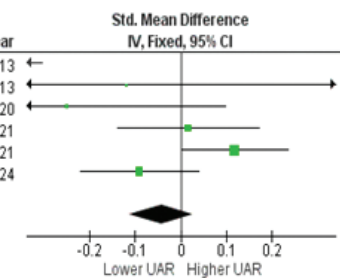


Fig. 9. Sensitivity analysis by exclusion of albumin parameters

Table 4. Sensitivity analysis

	SMD (95% CI)	I ²
Omitting Shen et al. 2013	-0.30 (-0.58 - -0.01)	94%
Omitting Zhao et al. 2020	-0.36 (-0.63 - -0.09)	94%
Omitting Chen et al. 2020	-0.31 (-0.58 - -0.04)	94%
Omitting Liu et al. 2021	-0.36 (-0.64 - -0.08)	93%
Omitting Gao et al. 2021	-0.35 (-0.64 - -0.06)	94%
Omitting Akbuga et al. 2022	-0.27 (-0.54 - -0.01)	94%
Omitting Saylik et al. 2023	-0.16 (-0.33 - 0.01)	84%
Omitting Toprak et al. 2023	-0.31 (-0.59 - -0.03)	94%
Omitting Dong et al. 2024	-0.34 (-0.64 - -0.03)	94%

DISCUSSION

Coronary artery disease (CAD) remains a major global health problem. The high morbidity and mortality rates of this disease require simple screening parameters to assess future prognosis. One of the new parameters that can assess the prognosis is UAR. Uric acid plays a role in the inflammatory process in the cardiovascular system, while albumin has the opposite role as an anti-inflammatory and antioxidant. Uric acid can increase inflammatory responses through the activation process of nucleotide-binding oligomerization domain-like receptors (NLRs) [26, 27]. A study by Rugerrio et al. showed an association between uric acid levels and increased markers of inflammation [28]. Inflammatory conditions are closely related to the incidence of cardiovascular disease and may represent one of the parameters that predict worse outcomes [29, 30]. Hyperuricemia may be considered a risk factor for heart failure and a parameter in the prognosis of higher cardiovascular mortality [31, 32].

Inflammation also plays a role in the pathophysiology of CAD [33]. Inflammatory conditions are closely related to the process of coronary collateral formation (CCC) in patients with CAD. Several studies have reported that CCC formation is correlated with several inflammatory parameters [34, 35, 36]. In CAD patients, good CCC has the function of reducing infarct area to preserve myocardial function [37, 38]. People with poorer coronary collaterals also have a higher tendency to develop acute coronary occlusion [39]. Therefore, CAD patients with good CCC formation have a better prognosis.

This meta-analysis study showed that patients with good CCC had lower UAR values. The study by Toprak et al. showed similar results to this study with an AUC value of 0.733, 95% CI 0.685 to 0.781, p -value < 0.01, and when compared with other inflammatory parameters such as C-reactive protein to albumin ratio (CAR), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), systemic immune-inflammation index (SSI), and monocyte to high-density lipoprotein cholesterol ratio (MHR), UAR was superior to all of them. UAR was also superior to both uric acid and albumin [24]. In the population of CAD patients with CTO, UAR can also be used as a parameter to detect CCC formation [22]. In the setting of non-ST elevation myocardial infarction (NSTEMI) cases, UAR also has the ability to predict CCC conditions and is superior when compared to uric acid or albumin separately and C-reactive protein (CRP) [40].

In addition to its association with CCC, UAR is also a parameter for determining the severity of CAD and NSTEMI [12, 41]. In patients who have undergone percutaneous coronary intervention (PCI), UAR may predict long-term mortality and in-stent restenosis [42, 43]. In the setting of ST elevation myocardial infarction (STEMI), UAR has a role in predicting the incidence of no-reflow and new-onset atrial fibrillation [44, 45]. The role of UAR as a novel parameter in coronary artery disease and myocardial infarction needs to be further explored with a larger sample size, considering its role as a novel inflammatory marker has been performed very well in several previous studies.

This meta-analysis study could not show the cut-off value of UAR in predicting coronary collateral events. This is because the included albumin parameters had different types of testing methods. However, the study by Saylik et al. showed a cut-off value of 1.32 to detect poor CCC with a sensitivity of 72% and a specificity of 83%. Another study by Toprak et al. also showed a not too different cut-off point of 1.62 with a sensitivity of 70% and a specificity of 71% [22, 24].

This study did not evaluate the relationship between poor collaterals and occurrence of ACS, so patients with good collaterals may still develop ACS, but patients with good collaterals tend to have a higher survival rate.

CONCLUSION

UAR could be a new parameter in predicting the formation of CCC in patients with stable coronary artery disease, with lower UAR values indicative of good CCC formation.

No conflict of interest was declared

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