İSTANBUL UNIVERSITY PRESS

ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE
Journal of Advanced Research in Health Sciences / Sağlık Bilimlerinde İleri Araştırmalar Dergisi 2023
DOI: 10.26650/JARHS2023-1199242

COMPARISON OF URIC ASID HIGH DENSITY LIPOPROTEIN CHOLESTEROL RATIO AND SERUM URIC ASID LEVELS ON CORONARY COLLETERAL CIRCULATION IN PATIENTS WITH CHRONIC TOTAL OCCLUSION

KRONİK TOTAL OKLÜZYONU OLAN HASTALARDA ÜRİK ASİT YÜKSEK YOĞUNLUKLU LİPOPROTEİN KOLESTEROL ORANI VE SERUM ÜRİK ASİT DÜZEYLERİNİN KORONER KOLLATERAL DOLAŞIM ÜZERİNDE KARŞILAŞTIRILMASI

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Citation/Atıf: Baykiz D, Demirtakan ZG, Ayduk Govdeli E, Emet S, Elitok A. Comparison of uric acid to high-density lipoprotein cholesterol ratio and uric acid on coronary collateral circulation in patients with chronic total occlusion. Journal of Advanced Research in Health Sciences 2023;6(1):1-9. https://doi.org/10.26650/JARHS2022-1041198. https://doi.org/10.26650/JARHS2023-1199242

ABSTRACT

Objective: Coronary collateral circulation (CCC) plays a significant role in cardiovascular prognosis, and well-developed CCC improves survival. The aim of this study was to investigate whether the serum uric acid to high-density lipoprotein cholesterol ratio (UA/HDL-C) is associated with coronary collateral development.

Materials and Methods: This retrospective study enrolled 111 patients with stable coronary artery disease and at least one chronic total occlusion (CTO) at invasive coronary angiography. Blood samples were obtained from all patients before the angiography procedure. The collateral degree was determined according to the Rentrop scoring system. Patients were classified into a poor CCC group (Rentrop grades 0-1, n=47) or a good CCC group (Rentrop grades 2-3, n=64). The UA/HDL-C ratios were compared between the two groups.

Results: The UA/HDL-C ratios were significantly higher in patients with poor CCC compared with the patients with good CCC (0.18 [0.06-0.49] *vs* 0.14 [0.05-0.31], respectively; p<0.001). In correlation analysis, the CCC was significantly negatively correlated with UA/HDL-C and UA levels (r=-0.333, p<0.001; r=-0.502, p<0.001, respectively). According to the ROC analysis, a cut-off value of > 0.17 for the UA/HDL-C ratio predicted poor collateral development with 54.3% sensitivity and 79.3% specificity (AUC=0.711, 95% CI 0.617–0.794, p<0.001). In multivariate regression analysis, serum UA was found to be an independent predictor of poor collateral development (OR=2.818, p=0.022).

Conclusion: The present study showed that although the UA/HDL-C ratio may be associated with poor collateral development, serum UA levels seem to be a better predictor of poor CCC than UA/HDL-C ratios in patients with CTO.

Keywords: Chronic total occlusion, coronary collateral circulation, uric acid, high-density lipoprotein cholesterol

ÖZ

Amaç: Koroner kollateral dolaşım (KKD) kardiyovasküler prognoz üzerinde önemli bir rol oynar ve iyi gelişmiş KKD surviyi iyileştirir. Bu çalışmanın amacı, serum ürik asit ve yüksek yoğunluklu lipoprotein kolesterol oranının (ÜA/HDL-K) koroner kollateral gelişimi ile ilişkili olup olmadığını araştırmaktır.

Gereç ve Yöntem: Bu retrospektif çalışmaya stabil koroner arter hastalığı ve invaziv koroner anjiyografide en az bir kronik total oklüzyonu (KTO) olan 111 hasta dahil edildi. Anjiyografi işlemi öncesi tüm hastalardan kan örnekleri alındı. Kollateral derecesi Rentrop sınıflamasına göre belirlendi. Hastalar kötü KKD grubu (Rentrop derece 0-1, n=47) veya iyi KKD grubu (Rentrop derece 2-3, n=64) olarak sınıflandırıldı. ÜA/HDL-K oranları iki grup arasında karşılaştırıldı.

Bulgular: ÜA/HDL-K oranları, kötü KKD'si olan hastalarda, iyi KKD'si olan hastalarla karşılaştırıldığında anlamlı olarak daha yüksekti (0,18 [0,06-0,49] *vs* 0,14 [0,05-0,31], sırasıyla; p<0,001). Korelasyon analizinde, KKD, ÜA/HDL-K ve ÜA seviyeleri ile anlamlı bir negatif korelasyon gösterdi (r=-0,333, p<0,001; r=-0,502, p<0,001, sırasıyla). ROC analizinde, ÜA/HDL-K oranı için > 0,17'lik bir kesme değeri, %54,3 duyarlılık ve %79,3 özgüllük ile zayıf kollateral gelişimini öngördü (AUC=0,711, 95% CI 0,617–0,794, p<0,001). Çok değişkenli regresyon analizinde, serum ÜA kötü kollateral gelişiminin bağımsız bir prediktörü olarak bulundu (OR=2,818, p=0,022).

Sonuç: Bu çalışma göstermiştir ki, ÜA/HDL-K oranı zayıf kollateral gelişimi ile ilişkili olabilse de, serum ÜA seviyeleri, KTO'lu hastalarda ÜA/HDL-K oranlarından kötü KKD'nin daha iyi bir öngördürücüsü olarak görünmektedir.

Anahtar Kelimeler: Kronik total oklüzyon, koroner kollateral dolaşım, ürik asit, yüksek yoğunluklu lipoprotein kolesterol

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Submitted/Başvuru: 04.11.2022 • **Revision Requested/Revizyon Talebi:** 04.11.2022 • **Last Revision Received/Son Revizyon:** 25.11.2022 • **Accepted/Kabul:** 28.11.2022 • **Published Online/Online Yayın:** 09.02.2023

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INTRODUCTION

Cardiovascular disease (CVD) constitutes an important cause of cardiac mortality in developed countries. Atherosclerosis in the large arteries contributes to the increased burden of CVD (1). Inflammation and lipid accumulation are major prominent factors in the progression of atherosclerosis.

Coronary collateral circulation (CCC) has been considered an adaptive mechanism for myocardial ischemia to provide adequate tissue perfusion (1,2). However, the grade of collateral development can show differences between patients having a coronary artery disease (CAD). Well-developed CCC may improve major adverse cardiovascular events and consequently cardiac mortality, and it plays a preventive role against myocardial infarction, ventricular failure and fatal arrhythmias (2). Various clinical parameters, including cardiac ischemia and endothelial dysfunction, and endogenous mediators, such as growth factors, oxidative stress, and inflammation are responsible for collateral development (2-3). Therefore, the identification of the potential risk factors related to the development of CCC has been an important research topic in the cardiovascular field. Although many related factors can influence the coronary collateral growth, the main causative mechanism is not yet clear.

Chronic inflammation causes vascular endothelial dysfunction in different ways. As an important mechanism, an increased generation of reactive oxygen species are induced by inflammation and oxidative stress reaction consequently triggers a course of endothelial dysfunction; however, a normal endothelial function with a normal vascular endothelium provides well-developed coronary collaterals (4). Consequently, an intact endothelium with a sufficient endothelial function is an indispensable factor of adequate collateral circulation, and vascular endothelial dysfunction has been identified as being an important part of the CCC formation (5).

Many studies have revealed that inflammatory processes prevent the development of collateral formation, affecting the endothelial function (1). Inflammatory cytokines, such as TNF-alpha and interleukin-6 (IL-6), have been revealed to be associated with poorly developed coronary collaterals. Moreover, C-reactive protein (CRP) levels are shown to be related with insufficient CCC development (2). Inflammatory white blood cells, such as monocytes, neutrophils, and lymphocytes significantly affect the development of the CCC (6).

Serum uric acid (UA) is a metabolic marker of the purine nucleotide metabolism. UA is endogenously synthesized in the liver, intestines, muscles, and vascular endothelium (7). Experimental studies have shown that elevated UA levels can induce inflammation in vascular endothelial cells as well as induce intracellular oxidative stress, consequently causing endothelial dysfunction (8). In clinical studies, serum UA levels have potentially been considered to be a useful indicative biomarker in predicting CVD, including heart failure, stable CAD, and acute coronary syndromes (8-9).

Dyslipidemia is another important risk factor of vascular endothelial dysfunction (10). Some studies have reported that the incidence of endothelial dysfunction is inversely correlated with high-density lipoprotein cholesterol (HDL-C) levels (11).

As indicated by previous studies, the relationship between coronary collateral development and its possible mechanisms needs to be clarified. Thus, the determination of the related mechanisms could improve prognosis, patients' treatment strategies, and clinical management.

In the present study, we aimed to evaluate the relationship between hyperuricemia, the UA/HDL-C ratio, and coronary collateral development in patients with chronic total occlusion (CTO). We hypothesized that the UA/HDL-C ratio may be associated with the development of CCC.

MATERIALS AND METHODS

Study population and design

This retrospective study was conducted at the Istanbul University School of Medicine. The research protocol was approved by Medical Research Ethics Committee of Istanbul University, Faculty of Medicine (Date:27.10.2022, Approval no: 1350712). All study procedures were applied according to the Declaration of Helsinki. Patients with stable CAD with documented CTO in one of the major coronary arteries who underwent an invasive coronary angiography (ICA) due to objective signs of ischemia in non-invasive stress tests between January 2018 and January 2022 were recruited from our institution.

After adjusting the exclusion criteria, overall 111 patients were recruited in the study. Patients with severe chronic inflammatory disease or autoimmune disease, infectious disease, hematological diseases, malignancy, severe chronic renal disease (estimated glomerular filtration rate<30 mL/minute/1.73 m^2) or chronic liver disease, and thyroid disorders and patients with acute coronary syndrome within the last month or a history of revascularization of percutaneous coronary intervention/coronary artery bypass grafts before a diagnostic ICA were excluded from the study.

The clinical characteristics of the patients, such as age, gender, history of hypertension, diabetes mellitus, smoking status, dyslipidemia, and other risk factors for CAD were evaluated. Data consisting of comorbidities, physical examination findings, transthoracic echocardiography, hematologic indices with complete blood counts (CBC), laboratory parameters, lipid profile, serum CRP, and UA levels were carefully reviewed and recorded from the hospital's electronic medical records. A fasting glucose level ≥ 126 mg/dL or taking any antidiabetic drugs identified the diagnosis of diabetes mellitus (DM). Patients with hypertension (HT) were described when their blood pressure ≥ 140/90 mm Hg at any time of measurements or taking any antihypertensive medications. Hyperlipidemia was identified as a total cholesterol (TC) level over 200 mg/dL, low-density lipoprotein cholesterol (LDL-C) above 130 mg/dL, triglyceride (TG) above 150 mg/dL, and HDL-C ≤ 40 mg/dL, as described (12).

All blood samples with biochemical and hematologic indices were obtained within 24 hours of admission prior to the ICA procedure. All CBC analyses were conducted using the LH780 Hematology Analyzer (Beckman Coulter, Inc., CA, USA), and routine biochemical tests were carried out using an automatic biochemical analyzer (Cobas 8000, Roche Diagnostics, Mannheim, Germany).

The UA/HDL-C was calculated as the ratio of the serum UA level to HDL-C.

Coroner angiography analysis

The coronary angiography was carried out using the femoral standard Judkins' techniques. The coronary angiography films and the grade and presence of CCC were assessed by two independent experienced cardiologists who had no information about the patients' data and laboratory findings. Any disagreement in interpretation was resolved by another experienced cardiologist.

CTOs are defined as a complete occlusion in the coronary arteries resulting in an interruption of antegrade blood flow with a duration >3 months. When the presence of ≥ 50% of luminal stenosis with at least two major epicardial coronary arteries, the diagnosis of multivessel disease is made. The calculation of Gensini score consisting of the degree of luminal stenosis of coronary arteries and its stenosis score based on geographic structure was also performed for each patient by two independent experienced cardiologists (13).

The CCC grading was detected according to the Rentrop-Cohen scoring system: no filling of any coronary vessels indicated grade 0; filling of side branches via collateral vessels without a visualization of the epicardial coronary artery indicated grade 1; partial filling of the epicardial coronary artery by collateral vessels showed grade 2; and complete filling of the epicardial segment being perfused via the collateral vessels grade 3 (14).

Patients were classified into two groups according to the CCC grading. Patients who developed grade 0 or 1 collateral vessels indicated a poorly developed CCC group, while patients with grade 2 or 3 collateral vessels indicated a well-developed CCC group.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences 26.0 for Windows (SPSS Inc., Chicago, IL, USA). To analyze the normality of the variables, the Kolmogorov–Smirnov test was used. The continuous variables are expressed as mean ± standard deviation (SD), and the categorical data are expressed as percentages. The differences between the CCC groups were assessed by using the Chi-square test for the categorical variables. Comparisons between the two groups were made by using the Student's t-test or the Mann–Whitney U test according to the normality of distribution, as appropriate. The receiver operating characteristic (ROC) analysis was performed to detect the predictive value of the UA/HDL-C ratio on the development of poor CCC. The multivariate logistic regression analysis was performed to identify the independent predictors of a poor development of CCC. The Pearson's or the Spearman's correlation test was used for determining the correlation between the UA/HDL–C ratio and the CCC. The results of the model were expressed as an odds ratio (OR), 95% CI, and p-values. Significance was considered at a two-sided $p < 0.05$.

RESULTS

After applying the exclusion criteria, a total of 111 patients with stable CAD and CTO were enrolled in our study. The average age of the study population was 61.87±8.7 years (83% male, 17% female). The information about clinical and angiographic characteristics of the study population are presented in Table 1. The poor CCC group (Rentrop 0 or 1) consisted of 47 patients, and 64 patients had well-developed CCC (Rentrop 2 or 3). No statistically significant difference was found with respect to age, gender, or treatment between the two groups (p>0.05). The frequencies of dyslipidemia, HT, DM, and smoking were also similar. The poorly developed and well-developed CCC groups included subjects with similar left ventricular ejection fraction, the number of diseased vessels, or the Gensini scores (p>0.05) (Table 1).

The laboratory findings are shown in Table 2. The serum UA and CRP levels were significantly increased in patients having poor CCC compared with the patients having good CCC (p<0.001, p=0.02, respectively; Table 2). The serum UA/HDL-C levels were significantly higher in patients with poor CCC than those of well-developed CCC (0.18 [0.06-0.49] *vs* 0.14 [0.05-0.31], respectively; p<0.001) (Table 2, Figure 1). Other laboratory variables were similar between the two groups.

In the ROC curve analysis, a cut-off of 0.17 was identified as the predictive UA/HDL-C value for determining poorly developed CCC with a sensitivity of 54.3% and a specificity of 79.3 (AUC=0.711, 95% CI 0.617-0.794, p<0.001) (Table 3) (Figure 2A, 3). The ROC analysis also showed that a cut-off value of >6.3 for the UA levels predicted poor collateral development with a 61.7% sensitivity and 100% specificity (AUC=0.806, 95% CI 0.720–0.875, p<0.001) (Figure 2B, 3) (Table 3).

The determination of the possible risk factors for poor CCC was carried out by using a multivariate logistic regression analysis. Serum UA was an independent predictor of poor collateral growth (OR=2.818, 95% CI 1.164 to 6.819 p=0.022; Table 4); however, UA/HDL-C was found to be an independent predictor of poor CCC based on the univariate regression analysis (OR=1.117, 95% CI 0.703 to 3.369 p<0.001; Table 4).

The correlation analysis revealed a significant and moderate negative association between the CCC, UA/HDL-C ratio, UA, and CRP (r=-0.333, p<0.001; r=-0.502, p<0.001; r=-0.231, p=0.016, respectively) (Table 5).

DISCUSSION

In this study, we evaluated the relationship between coronary collateral development and the serum UA levels and UA/HDL-C

Table 1: Baseline clinical data, treatment and angiographic characteristics of the study population

Variable	Total patients (n=111)	Poor Collateral (n=47)	Good Collateral (n=64)	p-value
Clinical characteristics				
Age (years)	61.87±8.7	60.08±9.68	63.18±7.72	0.063
Gender Male n (%) Female n (%)	92 (82.9%) 19 (17.1%)	39 (83.0%) 8 (17.0%)	53 (82.8%) 11 (17.2%)	1.000
SBP (mmHg)	130 (100-174)	130 (110-160)	130 (100-174)	0.879
Comorbidities				
Hypertension n (%)	70 (65.4%)	28 (60.9%)	42 (68.9%)	0.545
Diabetes mellitus n (%)	42 (39.6%)	22 (47.8%)	20 (33.3%)	0.190
Smoking n (%)	68 (64.2%)	29 (63.0%)	39 (65.0%)	0.997
Dyslipidemia n (%)	66 (61.7%)	30 (65.2%)	36 (59.0%)	0.651
Carotid artery disease n (%)	12 (11.2%)	6 (13.0%)	6 (9.8%)	0.833
LVEF (%)	55 (35-77)	52 (35-77)	55 (35-75)	0.952
Treatment				
Antiplatelet n (%)	81 (78.6%)	34 (79.1%)	47 (78.3%)	1.000
Beta blockers n (%)	69 (67.0%)	30 (69.8%)	39 (65.0%)	0.674
CCB n (%)	24 (23.3%)	11 (25.6%)	13 (21.7%)	0.645
Statin n (%)	75 (72.8%)	33 (76.7%)	42 (70.0%)	0.593
ACEi/ARB n (%)	71 (68.9%)	32 (74.4%)	39 (65.0%)	0.422
Number of diseased vessels				
One vessel disease n (%)	25 (22.9%)	11 (23.9%)	14 (22.2%)	1.000
Two vessel disease n (%)	43 (39.4%)	15 (32.6%)	28 (44.4%)	0.294
Three vessel disease n (%)	41 (37.6%)	20 (43.5%)	21 (33.3%)	0.379
Gensini Score	55 (34 -138)	56 (34.5-138)	47.5 (34-120)	0.392

SBP: Systolic blood pressure, LVEF: Left ventricular ejection fraction, CCB: Calcium channel blocker, ACEi/ARB: Angiotensin converting enzyme inhibitör/ angiotensin receptor blocker

ratios in patients with stable CAD and CTO. We demonstrated that higher UA levels and UA/HDL-C ratios are associated with poor collateral development. The UA/HDL-C ratio was found to be significantly higher in the group with poor collateral development than in those with well-developed CCC. The UA/HDL-C ratio was significantly inversely associated with the degree of CCC. Moreover, values above 0.17 predicted poor CCC with a sensitivity of 54.3% and a specificity of 79.3%. Therefore, we suggest that the UA/HDL-C ratio could be a simple and reproducible parameter for routine use in clinical practice in the prediction of the grade of CCC.

UA is an end-product of the purine nucleotide metabolism, and it originates from endogenous and exogenous metabolism of the purine system. The majority of UA is eliminated through urination (8,15). UA is endogenously synthesized in the liver, intestines, muscles, and vascular endothelium (7). Experimental studies have shown that elevated UA levels can induce inflammation in vascular endothelial cells as well as induce intracellular oxidative stress, consequently causing endothelial dysfunction (8,15).

Epidemiological studies have revealed that UA levels are positively correlated with CVD, including HT, DM, atherosclerosis, CAD, and heart failure (9,16). Based on a meta-analysis, it was shown that every 1 mg/dL increase in serum UA levels increases the risk of CAD and all-cause mortality by 20 % and 9 %, respectively (8). Moreover, serum UA levels were previously shown to be associated with greater coronary lipid plaques, which indicates UA as a possible surrogate indicator of vulnerable plaque in acute coronary syndromes (17). Borghi et al found that higher UA levels are linked with a higher 10-year CV death risk score (18). UA levels have also been propounded as a biomarker of CCC; however, the underlying molecular mechanisms remain unclear (8-9).

Various previous studies have indicated that high UA levels are associated with a reduction in nitric oxide (NO), endothelial

Table 2: Laboratory findings of the study population

Variable	Total patients (n=111)	Poor Collateral (n=47)	Good Collateral (n=64)	*p*-value
Fasting Glucose (mg/dL)	112 (76-304)	114 (79-304)	104 (76-285)	0.379
Creatinine (mg/dL)	0.99 (0.6-1.9)	1.0 (0.6-1.5)	0.9 (0.6-1.9)	0.652
eGFR (mL/min/1.73 m²)	79.77±18.76	79.59±17.89	79.91±19.55	0.930
Uric acid (mg/dL)	5.6 (2.3-14.6)	7.0 (3.5-14.6)	5.2 (2.3-6.3)	<0.001*
CRP (mg/L)	4.4 (0.3-39.2)	5.94 (0.3-28)	4.0 (0.4-39.2)	0.02*
Hgb (gr/dL)	13.45±2.32	13.37 ± 2.48	13.51 ± 2.23	0.818
Hematocrit (%)	40.99±5.77	41.11 ± 5.54	40.90 ± 6.01	0.893
WBC ($10^3/\mu l$)	8.87±2.02	8.63±2.09	9.04±1.97	0.314
Neutrophile ($10^3/\mu l$)	5.55±1.66	5.40±1.71	5.66±1.63	0.441
Lymphocyte ($10^3/\mu l$)	2.35±0.80	2.33±0.70	2.37±0.87	0.832
Monocyte ($10^3/\mu l$)	0.7 (0.4-1.7)	0.69 (0.4-1.0)	0.8 (0.4-1.7)	0.014*
Platelet ($10^3/\mu l$)	237.7±61.38	232.52±51.01	241.38±68.32	0.586
RDW (%)	14.2 (12.7-23.4)	13.9 (12.9-18.8)	14.4 (12.7-23.4)	0.141
MPV (fL)	8.75 (6.7-13.1)	8.6 (6.7-13.1)	8.8 (7.1-12.5)	0.887
Total cholesterol (mg/dL)	192.25±42.17	190.95±43.28	193.20±41.65	0.785
Triglyceride (mg/dL)	148 (63-443.5)	145.85 (63-435)	149.9 (63-443.5)	0.510
HDL-C (mg/dL)	37 (20-69)	37.5 (22-61)	36.8 (20-69)	0.859
LDL-C (mg/dL)	117.18±36.16	116.73±35.99	117.50±36.58	0.913
UA/HDL-C	0.15 (0.05-0.49)	0.18 (0.06-0.49)	0.14 (0.05-0.31)	<0.001*
TG/HDL-C	3.92 (1.05-15)	3.46 (1.51-15)	4.03 (1.05-11.25)	0.697
Lymphocyte/HDL-C	0.06 (0.01-0.17)	0.06 (0.02-0.17)	0.06 (0.01-0.13)	0.943
Monocyte/ HDL-C	0.017 (0.01-0.05)	0.016 (0.01-0.04)	0.02 (0.01-0.05)	0.127

GFR: Glomerular filtration rate, CRP: C-reactive protein, Hgb: Hemoglobin, WBC: White blood cell, RDW: Red cell distribution width, MPV: Mean platelet volüme, HDL-C: High density lipoprotein-cholesterol, LDL-C: Low density lipoprotein-cholesterol, UA: Uric acid, TG: Triglyceride
* p significance <0.05

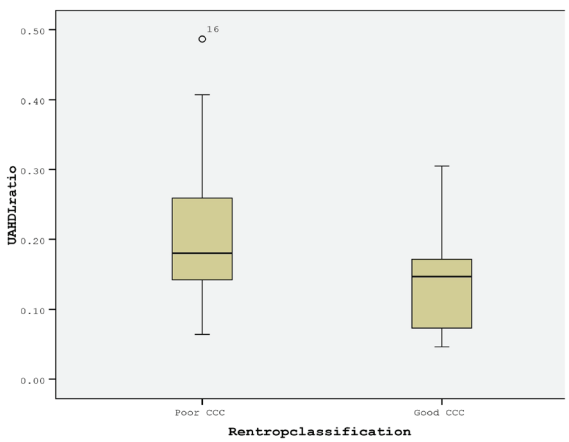

Figure 1: Comparison of UA/HDL-C ratio according to Rentrop collateral classification

dysfunction, arterial stiffness, insulin resistance, metabolic syndrome, and inflammation (19-20). Hyperuricemia reduces the amount of NO released from the vascular endothelial cells (15, 19, 20). UA also triggers the expression of proinflammatory cytokines, including CRP, which accelerate atherosclerosis (15,19).

Myocardial ischemia due to partial coronary artery stenosis or complete total occlusion causes coronary collateral vessel formation which is established by the reproduction of endothelial and smooth muscle cells (21). When the pressure gradient increases in the CCC due to a stenosis in the epicardial coronary arteries, these vessels become visible on an angiography (3). Well-developed CCC has been shown to protect ventricular function, prevent heart failure and fatal arrhythmias, and improve survival (22). Previous studies have shown that patients with a poor CCC have an increased risk of mortality (2). Acute coronary syndromes with well-developed CCC have also been reported to be related to better improvements in myocardial perfusion and a less likely adverse cardiovascular events in the long-term (2,22). However, many related factors are responsible for the development of CCC. In addition to the severity of coronary stenosis, HT, DM, smoking status, exercise, oxidative stress, vascular endothelial dysfunction, and inflammation can affect the development of CCC (22-23). In addition, endogenous

Table 3: ROC analysis for poor coronary collateral development

	AUC	95%CI	Sensivity (%)	Specificity (%)	p-value
UA/HDL-C > 0.17	0.711	0.617 - 0.794	54.35	79.37	<0.001*
TG/HDL-C ≤ 3.35	0.522	0.424 - 0.619	50.00	68.25	0.705
Lymphocyte/HDL-C > 0.05	0.504	0.405 - 0.603	61.36	45.90	0.944
Monocyte/HDL-C ≤ 0.01	0.619	0.481 - 0.745	33.33	93.94	0.119
Uric acid > 6.3 mg/dL	0.806	0.720 - 0.875	61.70	100.00	<0.001*
CRP > 5.46 mg/L	0.632	0.533 - 0.723	56.52	70.49	0.016*

CRP: C-reactive protein, UA: Uric acid, HDL-C: High density lipoprotein-cholesterol, TG: Triglyceride, ROC: Receiver operating characteristic, AUC: Area under the curve
* p significance <0.05

Figure 2A

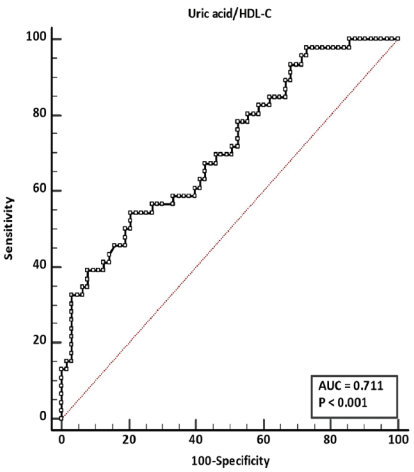

Figure 2B

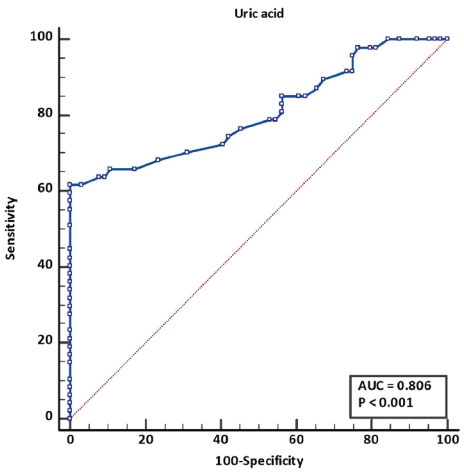

Figure 2: A) The receiver operating characteristics (ROC) curve analysis of UA/HDL-C ratio for prediction of poor coronary collateral, **B)** ROC curve analysis of uric acid for prediction of poor coronary collateral

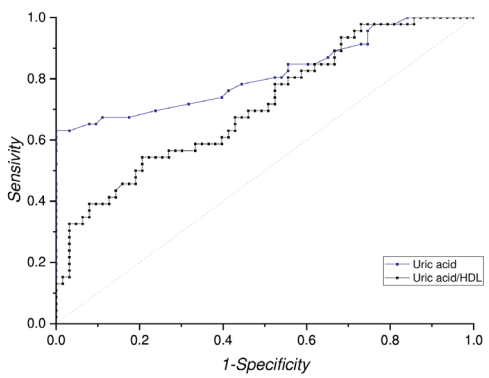

Figure 3: ROC curve analysis of UA/HDL-C ratio with uric acid for prediction of poor coronary collateral

mediators, such as the vascular endothelial growth factor, NO, and proinflammatory cytokines, are involved in the collateral development (3). Higher CRP concentrations have been reported to inhibit the synthesis of NO and angiogenesis, which can result in impaired collateral development (1,3,24).

The relationship between serum UA levels and collateral formation has been demonstrated by previous studies. Kasapkara et al found that serum UA levels are significantly higher in patients with poor CCC with acute coronary syndrome (25). Again, Uysal et al revealed high levels of UA to be an independent predictor of poor CCC in stable CAD patients (26).

Consistent with these results, higher serum UA levels were found to be an independent predictor of poor collateral development in our study, and a cut-off value above 6.3 mg/dL predicted poor CCC.

Dyslipidemia is another important risk factor for vascular endothelial dysfunction, inflammation, and atherosclerotic process (10, 27). Various studies have shown the relationship between elevated LDL–C and decreased HDL–C levels in many CVDs (28). In addition, some previous studies have reported

Table 4: Regression analysis of predictive factors for poor collateral development

Variables	Analysis Univariate			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
Age	0.959	0.447-2.708	0.066	1.000	0.917-1.092	0.993
Gender	0.988	0.274-1.335	0.982			
HT	0.956	0.703-3.369	0.824			
DM	1.833	0.993-1.011	0.132			
HL	1.302	1.685-3.626	0.514			
Smoking	0.919	0.991-1.103	0.835			
Uric acid	2.472	0.674-1.538	<0.001*	2.818	1.164-6.819	0.022*
CRP	1.046	0.990-1.008	0.100	1.031	0.937-1.134	0.536
Monocyte	0.037	0.955-1.025	0.023*	0.018	0.001-0.591	0.024*
Total cholesterol	0.999	0.266-3.798	0.783			
Triglyceride	1.001	0.417-1.248	0.820			
HDL-C	0.989	0.447-2.708	0.551			
LDL-C	0.999	0.274-1.335	0.912			
UA/HDL-C	1.117	0.703-3.369	<0.001*	0.981	0.834-1.154	0.818
TG/HDL-C	1.027	0.993-1.011	0.708			
Lymphocyte/HDL ratio	1.005	1.685-3.626	0.994			
Monocyte/HDL ratio	0.721	0.991-1.103	0.242			

HT: Hypertension, DM: Diabetes mellitus, HL: Hyperlipidemia, CRP: C reactive protein, HDL-C: High density lipoproteincholesterol, LDL-C: Low density lipoprotein-cholesterol, UA: Uric acid, TG: Triglyceride
* p significance <0.05

that HDL-C levels are inversely associated with the endothelial dysfunction (11).

High serum UA and low HDL-C concentrations are found to be linked with an increased risk of CVD as well as cardiac mortality in the general public (29). UA/HDL-C ratio, a novel index, was also investigated in type 2 DM patients (30). In this study, Kocak et al demonstrated that the UA/HDL-C ratio is a strong predictor of metabolic syndrome, and it has a higher sensitivity than serum UA and HDL-C levels alone (30). Therefore, lower serum HDL-C values and higher UA values may have a synergistic effect on the cardiovascular system.

In our study, the UA/HDL-C ratio was significantly higher in patients with poor CCC than those of well-developed CCC. Moreover, CCC was significantly inversely correlated with the UA/HDL-C ratio. Our study results are in line with study of Aydın et al (20). Similar to our findings, they showed a relationship between high UA/HDL-C ratios and a low collateral index. Based on the ROC analysis, Aydın et al found a cut-off value of 0.18, similar to our results, to predict poor CCC. However, the serum UA levels were found to be an independent predictor of low-grade CCC, whereas the UA/HDL-C ratio was not in the multivariate regression analysis. This finding may be explained by the small number of study population.

In addition, the TG/HDL-C ratio, a novel atherogenic dyslipidemia index, has been shown to be a better indicator of metabolic syndrome and CAD than other lipid profiles (27). The TG/HDL-C ratio was considered an inflammatory marker in regulating endothelial function and collateral circulation. In a recent study by Liu et al, the TG/HDL-C ratio was found to be significantly associated with poor CCC (10). Again, the TG/HDL-C ratio was reported to have an impact on the IL-6 levels in patients with metabolic syndrome (10). Contrary to their results, we showed no significant association between the TG/HDL-C ratio and the grade of CCC.

Table 5: Correlations between Rentrop classification and laboratory parameters

Variable	r	p
Uric acid (mg/dL)	-0.502	<0.001*
CRP (mg/L)	-0.231	0.016*
UA/HDL-C	-0.333	<0.001*
TG/HDL-C	0.06	0.489
Lymphocyte/HDL-C	-0.03	0.731
Monocyte/ HDL-C	0.207	0.123

CRP: C-reactive protein, UA: Uric acid, HDL-C: High density lipoprotein-cholesterol, TG: Triglyceride
* p significance <0.05

In addition, inflammatory white blood cells, such as monocytes, neutrophils, and lymphocytes, also play an important role in the development of CCC (6). As described, monocytes have a

key role in the development of atherosclerosis as a predictor of future coronary events (31). Moreover, circulating monocytes constitute inflammatory and prothrombotic states. Many studies have shown that high monocyte counts and low HDL-C levels may be associated with inflammation (31). The monocyte/HDL-C ratio was also reported to be a novel defined prognostic marker in several CVDs (32). For the first time, we assessed a possible relationship of the monocyte/HDL-C ratio with the grade of CCC in patients with CTO; however, we could not show significant associations between the monocyte/HDL-C ratio and collateral circulation. Therefore, we can speculate that the UA/HDL-C ratio could be a more sensitive marker than the others in predicting collateral development in patients with CTO.

It is well known that the severity of coronary stenosis constitutes a powerful independent determinant for the development of CCC (33). In our study however, the number of diseased vessels or the Gensini scores were similar between the two groups. Therefore, we suggest that a possible interference of the coronary stenosis on the formation of CCC could be ruled out based on our study. Furthermore, no differences were found among patients in potential confounding factors, such as HT, DM, and dyslipidemia. Therefore, we consider that the strength of our study results may have been increased by this way.

According to our study results, although UA/HDL-C ratio may be associated with collateral development, serum UA levels seem to be more sensitive than UA/HDL-C ratios in predicting poor development of CCC. It is hard to draw definite conclusions due to the small number of the study cohort and its retrospective nature; nevertheless, we can suggest that the UA/HDL-C ratio could be offered as a simple and easily measurable biomarker in predicting poorly developed CCC, and therefore the use of this novel index could provide improvements in patients' clinical management and in treatment strategies.

Study limitations

There are several limitations of this study. First, this was a retrospective, single-center, cross-sectional study, and it is limited by the relatively small sample size. Second, it is compelling to make a comment on the cause-effect relationship of the UA/HDL-C ratio and poorly developed CCC due to the cross-sectional plan of the present study. Third, because of the retrospective design of the study, we could not predict whether correcting serum UA and HDL-C levels via related treatment and consequently a decreased UA/HDL-C ratio could improve poorly developed CCC. Finally, it is known that diabetes or insulin resistance, and metabolic syndrome affect serum UA and HDL-C levels. Therefore, if the UA/HDL-C ratio was only studied in patients with diabetes or insulin resistance, the UA/HDL-C ratio might be a better biochemical indicator than serum UA alone. Prospective multicenter studies with a larger study population should be designed to provide more evidence.

CONCLUSION

The present study suggests that high serum UA and UA/HDL-C levels could be associated with a poor development of CCC. Although, the UA/HDL-C ratios are not better than uric acid values to predict poor CCC, the use of this simple biomarker could still be considered in clinical practice and could provide insights for clinicians to predict collateral development in patients with CTO. Nevertheless, further multicenter prospective studies with larger populations are needed to validate our findings.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 27.10.2022, No: 1350712).

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- D.B., S.E., A.E.; Data Acquisition- D.B., Z.G.D., S.E.; Data Analysis/Interpretation- D.B., E.A.G., S.E., A.E.; Drafting Manuscript- D.B., Z.G.D., E.A.G.; Critical Revision of Manuscript- D.B., S.E., A.E., Z.G.D.; Final Approval and Accountability- S.E., A.E., D.B.; Material and Technical Support- E.A.G, Z.G.D.; Supervision- S.E., A.E.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: Authors declared no financial support.

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