Uric Acid-to-Albumin Ratio as a Non-Invasive predictor for the Severity of Coronary Atherosclerosis

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Abstract

Background: Hyperuricemia is associated with coronary artery disease (CAD). Hypoalbuminemia is a prognostic marker of many cardiovascular diseases, including CAD.

Objectives: This study investigates the value of the uric acid-to-serum albumin ratio (UAR) as a non-invasive predictor of significant CAD.

Patients and methods: This cross-sectional study included 100 non-diabetic, normotensive patients tested for CAD by coronary angiography. Serum uric acid and albumin were measured, and UAR was calculated. On coronary angiography, coronary stenosis > 50% in at least one of the major coronary arteries was considered significant.

Results: Significant coronary stenosis was found in 57 patients. Significant stenosis was more frequent among males and smokers. Albumin was significantly lower in patients with significant stenosis, while uric acid, UAR, LDL, and triglycerides were significantly higher in patients with significant stenosis ($p< 0.001$, for all). Hypoalbuminemia was significantly associated with coronary stenosis ($p = 0.002$), while hyperuricemia was not ($p=0.181$). The sensitivity and specificity of hypoalbuminemia to predict coronary stenosis was 77.2% and 72.1%. UAR ≥ 1.56 predicts coronary stenosis with sensitivity and specificity of 71.9% and 74.4%. Albumin, uric acid, and UAR do not expect the severity of coronary affection.

Conclusion: Hypoalbuminemia is a valuable marker for the likelihood of severe coronary stenosis. Hyperuricemia is not associated with coronary stenosis, and the uric acid-to-albumin ratio does not improve the predictive value of hypoalbuminemia in diagnosing significant coronary stenosis.

Keywords: Uric acid-to-serum albumin ratio; Atherosclerosis; Hyperuricemia & Hypoalbuminemia.

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Introduction

Hyperuricemia is strongly associated with hypertension **(Sun et al., 2015)**, type 2 diabetes mellitus **(van der Schaft et al., 2017)**, and metabolic syndrome **(Choi et al., 2007)**, which are well-known risk factors of atherosclerosis. Many epidemiological studies investigated the association between hyperuricemia and coronary artery disease (CAD). Numerous studies reported a positive correlation between hyperuricemia and cardiovascular diseases **(Keenan, 2020; Çakmak et al., 2021)**, whereas others did not find this association **(Weintraub et al., 2011; Chien et al., 2017)**. A meta-analysis of 14 studies, including 341,389 participants reported increased mortality risk from coronary heart disease (CHD) in association with hyperuricemia, especially in women. The risk of CHD mortality increased by 9% for every 1 mg/dL increase in serum uric acid (**Zuo et al., 2016)**. Another meta-analysis of 29 studies showed an increased risk of CHD morbidity and mortality in patients with hyperuricemia (**Li et al., 2016)**.

Serum albumin (SA), the most abundant human serum protein, has many important physiological functions, including anti-inflammatory, antioxidant, anticoagulant, and antiplatelet aggregation activity (**Arques, 2020)**. Many studies identified hypoalbuminemia as a powerful prognostic marker in many diseases (**Oster et al., 2022)**. In the context of cardiovascular disease, hypoalbuminemia is an independent predictor of various conditions such as CAD, atrial fibrillation, stroke, and heart failure **(Arques, 2018).**

The complex interaction between synthesis, catabolism, and renal and gastrointestinal clearance of albumin generates albumin homeostasis (**Levitt et al., 2016)**. Also, many dietary and genetic factors affect the development of hyperuricemia **(Keenan, 2020)**. Therefore, **Çakmak et al.(2021)** used the Uric Acid-to-Albumin Ratio (UAR) to investigate its relationship with the extent of CAD. They found that UAR is a better predictor of clinical outcomes than the C-reactive protein-to-albumin ratio in patients with non-ST-elevated myocardial infarction (**Çakmak et al., 2021)**.

This study aimed to investigate the value of the uric acid-to-serum albumin ratio as a non-invasive predictor of significant coronary artery disease in patients examined for ischemic heart disease by coronary angiography.

Patients and Methods

This cross-sectional study included 100 patients recruited between January 2021 and December 2021 from those investigated for ischemic heart disease (IHD) by coronary angiography at the coronary catheterization unit of Sohag University Hospital. The ethics committee approved the study (Approval no.: Soh-Med-22-04-35), and informed consent was obtained from each participant.

The exclusion criteria include hypertension, diabetes mellitus, chronic kidney disease, other cardiac illness, a history of gout, and patients on medication that may affect uric acid or serum albumin.

All patients were subjected to detailed history taking and clinical examination. Laboratory investigations included serum uric acid, serum albumin, lipid profile, blood glucose, and renal function tests. The UAR was calculated as the ratio of serum uric acid (mg/dL) to serum albumin (g/dL). Electrocardiogram (ECG) and Echocardiography were done for all patients. The normal albumin levels were defined as 3.5 to 5.5 g/dL, and the normal urine acid values were defined as 3.5 to 7.0 mg/dL.

Selective coronary angiography was performed in all patients under local anesthesia via the femoral artery using the Judkins technique. The severity of each lesion was assessed by quantitative coronary angiography. The results of the

coronary angiography were classified into significant coronary stenosis (> 50%) in at least one of the major coronary arteries or Non-significant coronary stenosis (≤ 50%) **(Weintraub et al, 2011).** The results of the coronary angiography were then compared with the results of UAR.

Statistical Analysis

Statistical analysis was done using IBM© SPSS© Statistics version 25 (IBM© Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage. The Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, two groups were compared using an independent sample t-test. Comparison between 3 groups was made using the ANOVA test. The Receiver Operating Characteristic (ROC) curve was used to estimate cut-off values, Sensitivity, and specificity. A p-value < 0.05 was considered significant.

Results

The study included 100 patients with a mean age of 61.1±9.0 years. The baseline clinical characteristics of the patient are shown in (**Table 1**).

Table 1. Baseline demographic, clinical, and laboratory characteristics of the studied group

Variables	Value
Age (years)	60.1±9.0
Sex (male/female)	70/30
Smoking (Smoker/Non-smoker/Ex-smoker)	55/35/10
BMI (kg/m^2)	26.4±1.2
Degree of coronary stenosis (> 50%/≤ 50%)	57/43
Number of Vessels with significant stenosis	
1	25 (43.9%)
2	20 (35.1%)
3	12 (21.1%)
Ejection fraction (%)	58.9±5.8
Segmental wall motion abnormality	34 (34.0%)
Diastolic Dysfunction	50 (50.0%)
Albumin (g/dL)	3.7±0.2
Uric acid (mg/dL)	6.0±1.0
Uric acid-albumin ratio	1.64±0.31
Low-density lipoprotein cholesterol (mg/dL)	120.4±27.8
Triglycerides (mg/dL)	214.9±60.8

Data are presented as mean ±SD or number (%)

According to the angiographic examination, 57 patients had significant coronary stenosis. Significant stenosis was more frequent among males and smokers. Albumin was significantly lower in patients with significant stenosis, while uric acid, UAR, LDL, and triglycerides were significantly higher in patients with significant stenosis than those with non-significant stenosis (**Table 2**).

Table 2.Baseline characteristics of patients with significant compared to non-significant coronary stenosis

Variables	Coronary Stenosis		p-value
	> 50%	≤ 50%	
Age (years)	61.0±10.5	58.8±6.6	0.214*
Sex (male/female)	47/10	23/20	0.002§
Smoking (Smoker/Non-smoker/Ex-smoker)	39/12/6	16/23/4	0.003§
BMI (kg/m^2)	26.4±1.0	26.5±1.4	0.864*
Ejection fraction (%)	56.7±6.1	61.9±3.7	< 0.001*
Segmental wall motion abnormality			
Yes	31 (91.2%)	3 (8.8%)	< 0.001§
No	26 (39.4%)	40 (60.6%)	
Diastolic Dysfunction			
Yes	29 (58.0%)	21 (42.0%)	0.840§
No	28 (56.0%)	22 (44.0%)	
Albumin (g/dL)	3.6±0.2	3.8±0. 2	< 0.001*
Uric acid (mg/dL)	6.4±0.9	5.5±0.8	< 0.001*
Uric acid-albumin ratio	1.79±0.29	1.45±0.23	< 0.001*
LDL cholesterol (mg/dL)	131.7±28.2	105.4±18.7	< 0.001*
Triglycerides (mg/dL)	234.3±60.8	189.0±50.8	< 0.001*

*Data are presented as mean ±SD or number (%); Low-density lipoprotein cholesterol. * Independent sample t-test; § Chi-square test.*

The serum uric acid and UAR have moderate sensitivity and specificity and comparable diagnostic accuracy in predicting significant coronary stenosis (**Table 3**).

Table 3. Diagnostic accuracy of serum albumin, uric acid, and uric acid-albumin ratio for prediction of significant coronary stenosis

Variables	Cut-off level	Sensitivity	Specificity
Serum Albumin (g/dL)	≤ 3.75	77.2%	72.1%
Uric acid (mg/mL)	≥ 5.95	71.9%	74.4%
Uric acid-albumin ratio	≥ 1.56	71.9%	74.4%

However, low serum albumin below 3.5 gm/dL was encountered in 15 patients; 14 of them had significant coronary stenosis (p = 0.002). In contrast, hyperuricemia (uric acid > 7.0 mg/dL) was not associated with significant coronary stenosis (p=0.181), (**Table 4**).

Table 4. Association between hypoalbuminemia and hyperuricemia with significant coronary stenosis

Variables	Coronary Stenosis		p-value§
	> 50%	≤ 50%	
Albumin			
Hypoalbuminemia (< 3.5 g/dL)	14 (93.3%)	1 (6.7%)	
Normal (3.5-5.5 g/dL)	43 (50.6%)	42 (49.4%)	0.002
Uric acid (mg/dL)			
Hyperuricemia (>7.0 mg/dL)	8 (80.0%)	2 (20.0%)	0.181
Normal (3.5-7.0 mg/dL)	49 (54.4%)	41 (45.6%)	

Data are presented as numbers (%); § Fisher's Exact Test

Table 5. Levels of albumin, uric acid, and uric acid-albumin ratio concerning the number of vessels with significant stenosis

Variables	Number of vessels with significant stenosis			p-value*
	1	2	3	
Albumin (g/dL)	3.6±0.3	3.6±0.2	3.6±0.2	0.981
Uric acid (mg/dL)	6.2±0.8	6.5±1.0	6.6±1.0	0.305
Uric acid-albumin ratio	1.74±0.29	1.83±0.29	1.83±0.28	0.501

** One-way ANOVA test*

Regarding the number of vessels with significant stenosis, there were no visible variations in the levels of albumin, uric acid, or UAR between patients with one, two, or three considerably stenosed coronary arteries (**Table 5**).

Discussion

There is a growing body of evidence linking hypoalbuminemia to the development of many cardiovascular diseases (CVD), including ischemic heart diseases and stroke. Moreover, hypoalbuminemia appears to be a strong prognostic marker of CVDs, even after adjusting for conventional markers. In the current study, hypoalbuminemia (serum albumin < 3.5 gm/dL) was significantly associated with coronary stenosis (p = 0.002). On the contrary, hyperuricemia (uric acid > 7.0 mg/dL) was not associated with coronary stenosis (p=0.181). A threshold for UAR of 1.56 was a useful marker of coronary stenosis. Nevertheless, it did not add to the diagnostic accuracy of hypoalbuminemia alone. The sensitivity and specificity of hypoalbuminemia were 77.2% and 72.1%, and those of UAR was 71.9% and 74.4%. Thus, we consider hypoalbuminemia alone could be a useful marker for the risk of significant coronary stenosis.

Previous studies have reported a prevalence of hypoalbuminemia of about 13% in stable coronary disease **(Chien et al., 2017)** and 20-30% in acute coronary syndromes and MI (**González-Pacheco et al., 2017; Plakht, et al., 2016**). Recent data from 4947 persons participating in the Atherosclerosis Risk in Communities (ARIC) Study revealed an association between hypoalbuminemia with adverse CV outcomes **(Shannon et al., 2021**). A significant inverse relationship between serum albumin level and MI risk was reported in the multiple risk factor intervention trial and the Framingham offspring study **(Djoussé et al., 2002).** The risk of incident MI was limited to current smokers in the atherosclerosis risk in communities study **(Nelson et al., 2000**). A prospective study on the elderly revealed a high risk for CAD in women but not men with hypoalbuminemia **(Corti et al., 1996).** Therefore, the risk categorization of incident CAD using serum albumin levels is inconsistent. Probably, hypoalbuminemia may have a direct causal effect on CAD but could be an indication of an underlying condition **(Djoussé et al., 2002).**

The role of hypoalbuminemia in the physiopathology of CVD is possibly caused by the antioxidant, anti-inflammatory, anticoagulant, and anti-aggregating capabilities of serum albumin. Serum albumin is the most important antioxidant in the whole blood **(Taverna et al., 2013).** It contained over 80% of the total plasma thiols, the scavengers of reactive oxygen and nitrogen species **(Zoanni et al., 2021).** The binding of free transition metals (copper and iron) to albumin can limit their availability to produce aggressive ROS through interaction with hydrogen peroxide **(Young et al., 2001**). Besides, serum albumin has anticoagulant and antiplatelet aggregation activity **(Paar et al., 2017).**

Patients with hypoalbuminemia have impaired cyclooxygenase-1 (COX-1) inhibition and a higher incidence of long-term cardiovascular events, especially coronary diseases **(Sciacqua et al., 2021)**. Low serum albumin exerts its adverse action independent of other confounders like inflammation, malnutrition, or liver dysfunction **(Manolis et al., 2022).**

Epidemiologic studies indicated that low serum albumin is a biomarker of vascular endothelial dysfunction **(Arques, 2018; Rohrmann et al., 2016)**. Kadono et al. demonstrated an association between hypoalbuminemia and increased risk of inflammation, which is the main mechanism of endothelial dysfunction **(Kadono et al., 2010).** Moreover, Kinoshita et al. showed that serum albumin correlated inversely with oxidative stress and positively with endothelial function in pregnant women. They suggested that serum albumin may be a significant determinant of vascular oxidative stress and that hypoalbuminemia can play a role in developing CVD **(Kinoshita et al., 2017)**. Endothelial dysfunction is strongly involved in the pathogenesis of cardiovascular disorders **(Boulanger et al., 2016).** It leads to interrupted vascular tone, redox imbalance, and increased inflammation inside the vessel wall **(Ooi et al., 2018).** Impaired endothelium-dependent vasodilatation is responsible for atherosclerosis, among other cardiovascular disorders **(Park K-H et al., 2015).** Besides, low albumin level after a percutaneous coronary intervention is an independent prognostic indicator of worse long-term outcomes **(Shiyovich et al., 2020).**

In the current study, we did not find a significant association between hyperuricemia (uric acid > 7.0 mg/dL) and coronary stenosis (p=0.181). Previous studies have suggested that hyperuricemia may increase the risk of CVDs through endothelial dysfunction **(Papežíková et al., 2013)**, oxidative stress **(Sautin et al., 2008),** and inflammation **(White et al., 2016).** However, other studies did not support a causal role between serum urate levels and CAD **(Palmer et al., 2013; Keenan et al., 2016). Palmer et al., 2013** found a causal effect between BMI, uric acid levels, and hyperuricemia. This effect proposes a role of increased BMI in the development of uric acid-related conditions. This may explain the inconsistent findings of these studies and the current one, which includes mostly normal-weight individuals.

Importantly, hypoalbuminemia is a potentially modifiable risk factor for CAD. Therefore, screening for serum albumin levels in all patients with a possible diagnosis of CAD is recommended. Patients with low albumin should be subjected to the necessary investigations to identify the reason for hypoalbuminemia. Besides, they should receive aggressive therapy to reduce coronary risks, including nutritional support for those with malnourishment. Previous studies showed improved outcomes in patients with congestive heart failure with the correction of serum albumin levels **(Bonilla-Palomas et al., 2018).** Customized treatments, including nutritional intervention and albumin administration, in high-risk individuals with hypoalbuminemia should be investigated in randomized placebo-controlled trials to explore the clinical efficacy and safety **(Lim et al., 2012).**

We can conclude that hypoalbuminemia can predict significant coronary stenosis with a moderate sensitivity and specificity of 77.2% and 72.1%, respectively. However, hyperuricemia alone is not associated with coronary stenosis. Using the uric acid-to-albumin ratio does not improve the predictive value of hypoalbuminemia in the diagnosis of significant coronary stenosis. A uric acid-to-albumin ratio ≥

1.56 has a sensitivity and specificity of 71.9% and 74.4%, respectively, in predicting coronary stenosis.
Hypoalbuminemia appears to be a valuable marker for the likelihood of severe coronary stenosis. Screening for serum albumin levels in patients suspected to have CAD is recommended.

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