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ADULT CARDIOLOGY

# Uric Acid/ HDL Ratio as a Marker of Disease in Coronary Artery Ectasia Versus Normal Coronaries

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## ABSTRACT

***Objective***: To determine the strength of association of raised uric acid/ High-Density Lipoprotein ratio in patients with Coronary Artery Ectasia versus normal coronaries.

***Study Design***: Analytical Cross-sectional study.

***Place and Duration of Study***: Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi, Dec 2022 to May 2023

***Methodology***: Total n=146 patients aged between 20-90 years of both gender, with chest pain who had CAE or unobstructed coronaries on coronary angiography, and normal heart structure and valvular function were included. Patients were divided into two groups: those with Coronary Artery Ectasia (Group-I) and those without Coronary Artery Ectasia (Group-II). Serum uric acid and High-Density Lipoprotein level were measured for each patient and their ratio was calculated. Qualitative variables were compared across groups using the Chi-square test/Fischer Exact test, while quantitative variables were compared using the independent samples t-test. Univariate and multivariate logistic regression analysis was used to predict the odds ratio to show association between predictors and outcome (Coronary Artery Ectasia) and $p<0.05$ was considered as statistically significant

***Results***: Study sample n=146 had mean age of 52.83 ± 9.67 years, comprised of 113(77.4%) males and 33(22.6%) females. Uric acid to HDL ratio above 0.12 had an adjusted odds ratio (aOR) of 9.3 (CI 95% 3.3–26.0) for having Coronary artery ectasia ($p<0.001$). Males and age of 60 years or greater were also associated with an increased odds, with (aORs) of 4.0(CI 95% 1.2–13.1) and 2.8(CI 95% 1.0–8.3) ($p<0.001$), respectively.

***Conclusion***: Uric acid/HDL ratio is a useful variable in predicting odds of coronary artery ectasia in patients with chest pain.

**Keywords**: Coronary artery ectasia, Unobstructed coronaries, Uric Acid/HDL Ratio

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## INTRODUCTION

Coronary Artery Ectasia (CAE) is an abnormal, diffused dilatation of the coronary artery ≥1.5 times to its normal caliber.[1] Its incidence is estimated to be about 1.0% in the general population, but may vary from region to region.[2] The exact etiopathogenesis of the disorder is unclear, however, patients tend to have a history of connective tissue/inflammatory diseases, vasculitis, atherosclerosis and/or coronary interventions, while some cases may be congenital.[3] Arterial wall dilatation results in slowing and turbulence in blood flow velocity and an increased risk of coagulation.[4] Complications include the potential for development of occlusive thrombosis, distal embolization, vasospasm, dissection, shunt formation, rupture, acute myocardial infarction, heart failure and sudden cardiac death which are associated with significant morbidity and mortality.[5,6] Identifying reliable markers of disease in CAE patients, is crucial for improving risk stratification and developing effective management strategies.

Several factors including derangements in the renin-angiotensin system, different lipoprotein levels, inflammatory markers, insulin, nitric oxide and even homocysteine levels are thought to be associated with CAE.[7] In recent years, uric acid/HDL ratio (UHR) has emerged as a potential marker of cardiovascular disease risk. High levels of uric acid can lead to the formation of crystals in the joints, causing gout; however, uric acid has also been linked to a range of other health conditions, including cardiovascular disease.[8,9] HDL, or high-density lipoprotein helps to remove cholesterol from the blood vessels and transport it to the liver for processing and elimination.[8] Both increased serum uric acid level and low HDL are associated with an increased risk of mortality in patients with Ischaemic Heart Disease (IHD), and their ratio may be of use in patients with other cardiovascular diseases.[8-10]

However, the relationship between UHR and CAE has not been well studied. In this article, we

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explored the potential role of UHR as a marker of disease in CAE patients compared to those with normal coronaries. The existing literature on the topic provides insights into the potential clinical applications of this marker. Our findings may have important implications for the management of CAE patients. UHR is a simple, non-invasive marker that can be easily measured in clinical practice. Identifying patients with a high UHR may allow clinicians to implement more aggressive treatment strategies, such as lifestyle modifications and pharmacological interventions, to reduce the risk of adverse cardiovascular events. Our study aimed to determine the strength of association of raised uric acid/HDL ratio in patients with CAE versus normal coronaries.

## METHODOLOGY

This Analytical Cross-Sectional study was conducted from Dec 2022 to May 2023 in Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi Pakistan, after taking approval from Institutional Ethical Review Board (IERB) (Ltr# 9/2/R&D/2022/228), on n=146 patients who reported for evaluation of CAE after obtaining written, informed consent from them for participation in the study.

The WHO sample size calculator was used to calculate the sample size keeping a margin of error 5%, confidence level 95% and 5% prevalence of CAE[5] which gave a sample size of n=73 per group. We collected data from 146 patients ($n_1$=73 cases; $n_2$=73 controls)

**Inclusion Criteria**: All patients with age ranging from 20 to 90 years, of both gender, with chest pain who had CAE or unobstructed coronaries on coronary angiography, and normal heart structure and valvular function, were included.

**Exclusion Criteria**: Patients with complex coronary artery disease or coronary artery spasm, autoimmune disease, chronic liver, kidney or lung disease, valvular disease, congenital heart disease, left ventricular or ventricular septal hypertrophy, were excluded.

All the study participants were selected via non-probability consecutive sampling. All patients presenting to the emergency room/out-patient department with chest pain were evaluated with a detailed history, examination, electrocardiogram, baseline investigations and 2D echocardiography. The patient underwent coronary angiography, as per requirement. All patients with CAE were enrolled as cases (Group-I) while those with non-ectatic and unobstructed coronary arteries were included as controls (Group-II). All patients then underwent a phlebotomy after an overnight fast and a total of 5 mL of venous blood was withdrawn which was used to measure uric acid and HDL, and the UHR was calculated. A serum uric acid level of >7.2 mg/dL, an HDL level of <40 mg/dL, UHR >0.12 and low-density lipoprotein (LDL) levels >160 mg/dL were considered abnormal.[11]

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 26:00. Mean/ standard deviation were calculated for quantitative variables specifically age, ejection fraction, uric acid level, HDL level, LDL level, UHR value. Qualitative variables like gender, presence of comorbidities, smoking, and which coronary arteries were ecstatic were recorded in terms of frequency and percentages. Qualitative variables were compared across groups using the Chi square test/Fischer exact test, while quantitative variables were compared using the independent samples t-test/non-parametric tests, where appropriate. *p*-value of <0.05 was considered significant. Odds ratio was also calculated to determine the odds of various variables including UHR with the presence of CAE, followed by logistic regression to calculate adjusted odds ratios.

## RESULTS

Total n=146 patients with a mean age of 52.83±9.67 years were enrolled. The majority of the participants were males 113(77.4%) and 29(19.7%) patients were smokers. The mean ejection fraction was 56.74±6.84%; 78(53.4%) patients were hypertensive, while 14 (9.6%) suffered from diabetes mellitus. Our patients had a mean uric acid level of 5.59±1.67 mg/dL, mean HDL level was 38.40±7.18 mg/dL, while the UHR was 0.15±0.07. The mean LDL level was 91.48±29.73 mg/dL. Findings were significant with respect to age, gender, hypertension status, ejection fraction, mean levels of Uric acid, HDL, LDL and UHR ($p$<0.05) across study groups: CAE group and a control group.

Table-II displays the frequencies of ectasia in different coronary arteries in our study participants. Right coronary artery 49(33.6%) was found to be the most commonly affected by ectasia, followed by the left anterior descending artery 38(26.0%).

Table-III showed the adjusted odds ratios for various factors in the developments of CAEs. Our model showed that patients with UHR above 0.12 had

**Table-I: Group Wise Distribution of Patient Characteristics (n=146)**

| Variables | | Group-I CAE (n=73) Frequency(%) | Group-II Controls (n=73) Frequency (%) | *p*-value |
|---|---|---|---|---|
| Age (years) (Mean±SD) | | 56.12±9.10 | 49.53±9.15 | <0.001 |
| Gender | Male | 66(90.4) | 47(64.4) | <0.001 |
| | Female | 7(9.6) | 26(35.6) | |
| Comorbidities | Hypertension | 47(64.4) | 31(42.5) | 0.008 |
| | Diabetes Mellitus | 10(13.7) | 4(5.5) | 0.15 |
| | Smokers | 19(26.0) | 10(13.7) | 0.06 |
| Ejection Fraction (%) (Mean±SD) | | 53.49±8.53 | 60.00±0.00 | <0.001 |
| Chemical Analysis (Mean±SD) | Uric Acid Levels (mg/dL) | 6.57±1.39 | 4.61±1.32 | <0.001 |
| | HDL Levels (mg/dL) | 37.10±7.25 | 39.70±6.91 | 0.028 |
| | LDL Levels (mg/dL) | 101.27±32.17 | 81.68±23.47 | <0.001 |
| | Uric Acid/HDL Ratio | 0.18±0.06 | 0.12±0.06 | <0.001 |

HDL=high-density lipoprotein; LDL=low-density lipoprotein

**Table-II: Frequency of Coronary Artery Ectasia (n=146)**

| Coronary Artery Ectasia | Frequency (%) |
|---|---|
| Right Coronary Artery | 49(33.6) |
| Left Anterior Descending Artery | 38(26.0) |
| Left Circumflex Artery | 31(21.2) |
| Left Main Stem | 8(5.5) |

**Table-III: Predictors of Coronary Artery Ectasia (n=146)**

| Factors | Coronary Artery Ectasia | | Univariate logistic regression | | | Multivariate logistic regression | | |
|---|---|---|---|---|---|---|---|---|
| | Yes Frequency (%) | No Frequency (%) | *p*-value | Un-adjusted OR | 95% CI for uOR | *p*-value | Adjusted OR | 95% CI for aOR |
| Age >59 years | 30(76.9) | 9(23.1) | <0.001 | 5.0 | 2.1–11.5 | 0.057 | 2.8 | 1.0–8.3 |
| Male | 66(58.4) | 47(41.6) | <0.001 | 5.2 | 2.1–13.0 | 0.020 | 4.0 | 1.2-13.1 |
| Comorbids | | | | | | | | |
| Smoking | 19(65.5) | 10(34.5) | 0.06 | 2.2 | 2.1–5.2 | - | - | - |
| Hypertension | 47(60.3) | 31(39.7) | 0.008 | 2.5 | 1.3–4.8 | 0.38 | 1.5 | 0.6–3.8 |
| Diabetes Mellitus | 10(71.4) | 4(28.6) | 0.09 | 2.7 | 0.8 – 9.2 | - | - | - |
| Chemical Analysis | | | | | | | | |
| Uric Acid >7.2 mg/dL | 21(84.0) | 4(16.0) | <0.001 | 7.0 | 2.3–21.5 | 0.25 | 2.1 | 0.6-7.7 |
| HDL <40 mg/dL | 54(55.1) | 44(44.9) | 0.07 | 1.9 | 0.9–3.8 | - | - | - |
| Uric Acid to HDL ratio >0.12 | 61(76.3) | 19(23.7) | <0.001 | 14.4 | 6.4–32.5 | <0.001 | 9.3 | 3.3-26.0 |

*HDL=High Density Lipid Protein*

an adjusted odds ratio (aOR) of 9.3(CI 95% 3.3–26.0) for having CAE. Males and age of 60 years or greater were also associated with an increased risks, with aORs of 4.0 (CI 95% 1.2–13.1) and 2.8 (CI 95% 1.0–8.3), respectively. Raised Uric acid levels and UHR were found to be the major predictors.

## DISCUSSION

The present study aimed to investigate the potential use of UHR as a predictor of odds/marker of disease in patients with CAE compared to those with normal coronary arteries. The results of this study suggested that UHR could be a useful indicator in this role and high levels predict CAE.

The mean age of our patients with CAE was 56.12±9.10 years. Willner *et al.*, in their study noted that the average age at detection of CAE in their study was 59.6±11.2 years while Djohan *et al.*, reported a mean age of 57.1±11.7 years, both of which were similar to our study.12,13 The aOR for age 60 or greater in predicting odds of CAE was 2.8(CI 95% 1.0– 8.3, $p$<0.001) in our study. However, Ipek *et al.*, and Qin *et al.*, both noted that age did not appear to have a significant association with the development of CAEs, ($p$=0.91 and $p$=0.058, respectively).[14,1] We believed in the difference in results was due to the latter studies looking at a patient population that was different from

ours such as patients with acute myocardial infarctions, or patients with low prevalence of comorbidities.

Approximately four-fifth of our study sample comprised of males, who had an aOR of 4.0(CI 95% 1.2–13.1, $p$<0.001), for the development of CAEs. Qin *et al*., also reported that males had a higher association with the development of CAEs in their study, ($p$=0.028),15 while Subhan *et al*., also reported an aOR of 1.2(CI 95% 1.0–1.7, $p$=0.04) for male gender in developing CAEs[16]. Both Wilner *et al*., and Djohan *et al*., reported a male preponderance of 90.7% and 91.7%, respectively, in their studies.[12,13]

Approximately, one-fifth of the population in the current study were smokers, with the OR 2.2 (CI 95% 2.1-5.2, $p$=0.062) indicating a mild increase in CAEs in smokers that was not statistically significant. Qin *et al*., reported that smokers did not appear to have a significant association with the increased formation of CAEs, ($p$=0.64). Conversely, Subhan *et al*.,reported an aOR of 3.0(95% CI 1.0–9.5 $p$=0.005),[16] this finding that was concurred with by Gahlan *et al*., who reported an OR of 3.0.[17] This difference in magnitude was likely due to the lower percentage of smokers in our study as compared to the latter studies; however, further research focused on this aspect is required before drawing firm conclusions.

Current study showed that hypertension was also associated with a mild, but statistically significant increase in odds for the development of CAEs; aOR: 1.5 (CI 95% 0.6-3.8, $p$=0.008). Bahremand *et al*, in their meta-analysis, noted that hypertension had minimal effect on increasing the odds of CAEs, with an aOR of 1.4 (95 % CI 1.2–1.7).[18] Patients suffering from diabetes mellitus had an OR of 2.7(CI 95% 0.8–9.2, $p$=0.092), for the development of CAEs in the current study, similar to the result that was reported by Subhan et al., [OR: 1.03 (95% CI): 1.01-1.06)], while Rojas-Milán *et al*, documented : aOR 1.382 (CI 95%; 1.1–1.6).[19]

Our study showed that an increase in serum uric acid levels was associated with a marked increase in odds of development of CAEs, with an aOR of 2.1 (CI 95%; 0.6–7.7) ($p$<0.001). Barman et al., also reported a similar but slightly lower OR of 1.6 for uric acid, noting that it was significantly raised in patients with CAEs.[20] However, another study noted that there was no significant difference between serum uric acid levels in patients with CAEs versus those who did not, ($p$=0.06). This difference in results is likely due to the inclusion of patients with coronary artery disease where serum uric acid levels were also observed as risk factors, producing a degree of confounding within the results. Jafari *et al*., noted an OR of 0.858(CI 95% 0.75–0.98, $p$=0.029) in their study.[21]

An aOR of 9.3 (CI 95% 3.3–26.0) ($p$<0.001). for UHR in our study depicted that it was a useful marker in predicting odds of CAEs in patients with chest pain. Mansiroglu *et al* also noted that patients with CAEs had high UHRs when compared to patients without CAEs, ($p$<0.001).[11]

Lastly, the most common artery affected in our study, by CAEs, was the right coronary artery (33.6%), followed by the left anterior descending artery (26.0%), which was similar to studies by Wilner *et al*., and Djohan *et al*.[12,13]

## LIMITATIONS OF STUDY

High protein and fat meals prior to testing serum uric acid and HDL levels may alter serum levels and while we tested our patients after an over-night fast, it was unclear how effective this would be in mitigating confounding. Additionally, this was a single-center study based on a population of middle-class families, and it was unclear whether our results will be generalizable to the large population, which requires further multicenter and more diverse research.

## CONCLUSION

The serum UHR appears to be a clinically useful laboratory measure for assessment of odds of presence of CAEs. Requirements for measurement of both the component parameters are readily available in most laboratories, in a cheap manner, thus it can be readily per-formed in low-resource settings. Future research may focus on the diagnostic accuracy of UHR in predicting the presence of CAEs in patients with chest pain as well as its ability to differentiate CAEs from patients with coronary artery disease.

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**Conflict of Interest**: None.

**Authors' Contribution**

Following authors have made substantial contributions to the manuscript:

MA & AN: Concept, study design, drafting the manuscript, approval of the final version to be published

MBS & FKT: Concept, data acquisition, critical review, approval of the final version to be published

AZK & SPM: Data acquisition, data analysis, data interpretation, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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