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Serum uric acid and acute coronary syndrome: Case-Control study

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Abstract:

Background: Acute Coronary Syndrome represents a challenge to the global public health, because of the high morbidity and mortality. Identifying the risk factors and biomarkers is important for early detection, risk stratification, and effective management. Recent studies suggest a potential association between elevated serum uric acid levels and Acute Coronary Syndrome, yet the relationship remains poorly understood and need further investigation.

Objective: This study aims to assess the relationship between serum uric acid levels and the incidence of ACS in a defined population. thereby assessing its potential as a biomarker for detection and prognosis.

Methods: Employing a case-control design, this study will involve participants diagnosed with ACS at IBN SINA Hospital and a matched control group of apparently healthy individuals. Exclusion criteria include chronic kidney disease, malignancies, active inflammatory conditions, and the use of drugs affecting serum uric acid levels. Data collection will focus on demographic information, medical history, clinical characteristics, and serum uric acid levels, determined through blood sample analysis.

Results: Our study involved 64 ACS cases with a mean age of 59.39±11.886 years and 60 healthy controls with a mean age of 56.35±8.631 years. We observed that the median serum uric acid level was significantly higher in ACS cases (341.0) compared to controls (333.0) with a p-value of 0.046, indicating a statistically significant difference.

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Gender-based analysis revealed a significant difference in serum uric acid levels among females between cases and controls (p=0.035), but not among males (p=0.602). Age group analysis showed a significant difference only in the 70-79 age group (p=0.045). The ROC analysis suggested that serum uric acid level has a modest discriminatory ability for ACS with an area under the curve of 0.604 (p=0.046).

Conclusion: Elevated serum uric acid levels are associated with an increased risk of ACS, particularly among females and in older age groups. Serum uric acid could serve as a potential biomarker for ACS detection and prognosis, though its utility may vary across different demographic groups. Our findings highlight the importance of considering serum uric acid levels in the risk stratification and management of ACS patients

Keywords: acute coronary syndrome, ACS, serum uric acid, IBN SINA Hospital

Introduction:

Acute coronary syndrome (ACS) is a the most serious cardiovascular condition that is caused by the blockage of blood flow to the heart. It is a leading cause of death all over the world and is associated with significant morbidity and mortality [(1)] ACS often occurs due to the breaking of an atherosclerotic plaque within a coronary artery, which results in the creation of a blood clot that blocks the flow of blood to the heart. This can be resulting in myocardial ischemia, ACS can be classified into three subtypes based on the severity and duration of symptoms: unstable angina, non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI). [(2)] The burden of coronary heart diseases worldwide is substantial and has been increasing over the years According to the Global Burden of Disease (GBD) Study in 2019, the prevalent cases of total cardiovascular diseases nearly doubled from 271 million in 1990 to 523 million in 2019, and the number of cardiovascular diseases deaths steadily rising from 12.1 million in 1990 to 18.6 million in 2019. highlighting the significant and growing impact of these conditions on global health. [(3)]

Recently, there has been an increasing interest in the relationship between serum uric acid levels and cardiovascular disease especially ACS, certain studies show positive correlation between serum uric acid levels and the severity of coronary artery stenosis in

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patients with ACS, indicating that higher uric acid levels might be associated with more severe coronary artery disease. [4,5,6] High serum uric acid level is significantly associated with endothelial dysfunction in patients with acute coronary syndrome. This association suggests that hyperuricemia could lead to poor outcomes in ACS [7]. Uric acid is a metabolic end product of purine metabolism, formed mainly in liver, the main source of uric acid is endogenous and there is a little role to food consumption, 90% percent of filtrated uric acid is reabsorbed actively in the renal tubule. Two-thirds of uric acid is eliminated through the kidneys, while the remaining one-third is expelled via the intestinal tract [8,9].

Elevated levels of serum uric acid in the blood have been associated with a variety of medical conditions, including gout, kidney disease, hypertension, and metabolic syndrome [10]. A recent study shows, Hyperuricemia contributes to the production of reactive oxygen species (ROS) alongside the formation of uric acid by xanthine oxidases. These ROS, along with intracellular uric acid, regulate several intracellular signaling pathways. Alterations in these pathways can lead to the development of atherosclerotic lesions. This has led to discussions on the efficacy of treatments for hyperuricemia in protecting against atherosclerosis development [11]

Recent studies have also explored the mechanistic aspects of how high levels of uric acid promote atherosclerosis, for instance, research has shown that high uric acid levels can promote atherosclerosis development in animal models with mechanism involves the impairment of cellular antioxidant defenses and the promotion of lipid peroxidation within atherosclerotic lesions. [12]

MATERIALS AND METHODS

This case-control study was conducted at the Ibn Sina Teaching Hospital in the CCU ward, aiming to investigate the relationship between serum uric acid levels and acute coronary syndrome (ACS). A thorough case-control design was employed to compare the serum uric acid levels in individuals diagnosed with ACS to those in a carefully matched control group.

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Participant Selection:

The study included patients admitted to the CCU ward at Ibn Sina Teaching Hospital between 2nd of January 2023 and 15th of June 2023 . Cases comprised individuals diagnosed with ACS based on a combination of clinical symptoms, electrocardiographic findings, and elevated cardiac biomarkers. Controls without a history of ACS.

Inclusion and Exclusion Criteria:

ACS cases were included if they met the standard diagnostic criteria for ACS, including symptoms of chest pain or discomfort, characteristic changes on electrocardiogram (ECG), and elevated cardiac biomarkers. Exclusion criteria for both cases and controls included a history of chronic kidney disease, inflammatory disorders, the use of certain medications, such as diuretics and drugs used in chemotherapy, can increase uric acid levels.

Data Collection:

Comprehensive clinical data were collected through detailed interviews, medical record reviews, and physical examinations. Fasting blood samples were obtained from both ACS cases and controls for the measurement of serum uric acid levels. Additional information, comorbidities, and medication use, was recorded to account for potential confounders.

laboratory Analysis:

Serum uric acid levels were determined at the Ibn Sina hospital's certified laboratory. Quality control measures were implemented to ensure the precision and accuracy of the results. Laboratory personnel were blinded to the case or control status of the samples.

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Statistical analysis:

The data collected during the study were summarized in sheets of Microsoft Excel 2007. The statistical analysis performed by using IBM-SPSS 26. The normality of these data tested by Shapiro-Wilk test, and the non-parametric tests were decided to be chosen. Median, 25^{th} with 75^{th} quartiles, ranges, minimum and maximum values were estimated. The Mann-Whitney U has been used to find the difference between two nonparametric numerical variables while the Kruskal-Wills test has been used for the difference among more than two non-parametric numerical variables. ROC test was calculated and area under the curve was estimated. P-value ≤ 0.05 considered as significant.

2.8 Ethical Considerations:

The study received ethical approval from Medical Research Ethical Committee (MREC) of University of Mosul college of Medicine, ref no. UOM/COM/MERC/23-24/MAR1, date 26/3/2024.

Results and Discussion

The study sample consisted of two groups; ACS group included 64 patients with mean age 59.39±11.886 years and 60 healthy individuals as controls with mean age of 56.35±8.631years. The most frequent age group was (50-59) which represented 35.9% and 40.0% of cases and controls respectively. Those with age below than 40 were 3.1% and 1.7% among the ACS group and controls in that order. Patient with age more than 80 years was 6.2% while among the controls this age group was 1.7%.

The distribution of the studied groups according to the gender was demonstrated in figure (3.1) which illustrated that the male gender represented 82.8% of the cases while the females found in 17.2% while among the controls the males and females had an equal representation.

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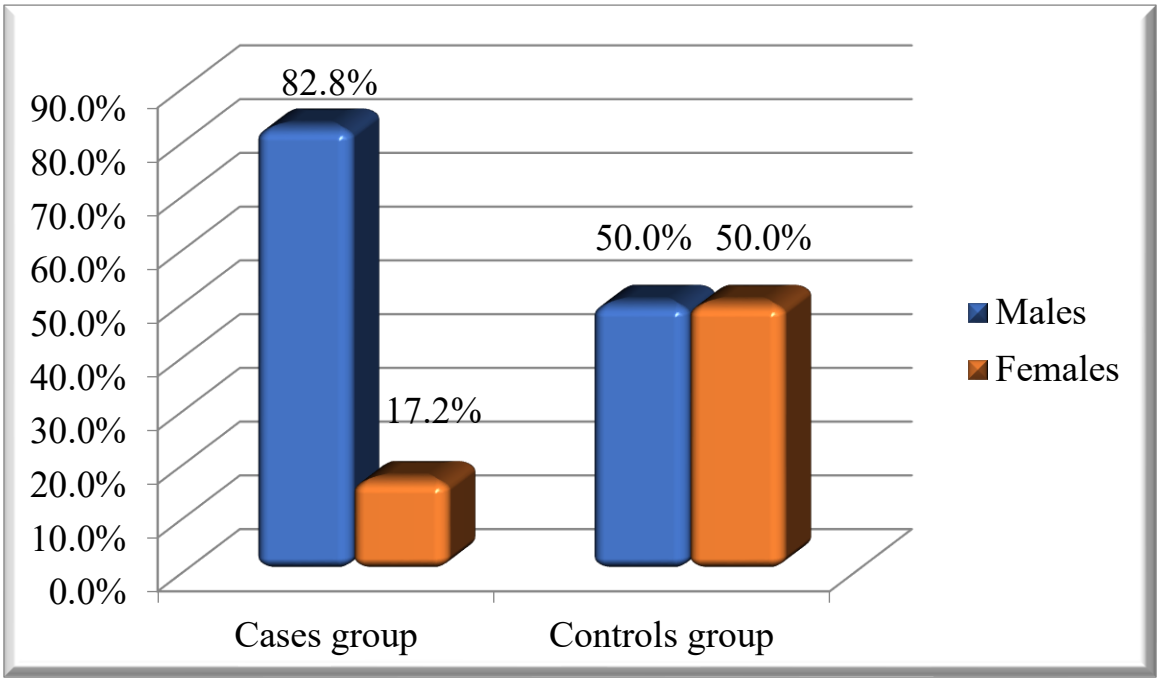

Figure (3.1): The distribution of the studied groups according to the gender.

A comparison of Uric acid level between cases and controls was demonstrated in table (3.2) and revealed that the median level of the uric acid among the cases was higher than that among the controls in a statistically significant way (0.046).

Table (3.2): Comparison of Uric acid level between cases and controls.

Level of Uric acid	ACS group	Controls	p-value*
Median	341.0	333.0	**0.046**
25th , 75th Quartiles	288.5, 461.5	271.5, 389.7	
Minimum, Maximum	201.0, 797.0	180.0, 535.0	
Range	596.0	355.0	

***Mann-Whitney U has been used**

Comparison of uric acid level between ACS group and controls in relation to age groups was demonstrated in table (3.4) and depicted no statistically significant differences in the uric acid levels between the ACS group and controls for all the age groups apart from

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the age group (70-79) in which the uric acid level was significantly (p=0.045) higher among the cases (416.0) in comparison to controls (305.5). the differences of uric acid level among the age groups for each study groups were statistically not significant.

Table (3.4): Comparison of uric acid level between cases and controls in relation to age groups.

Age groups	Level of Uric acid		p-value*
	ACS group Median (25^{th},75^{th} Q) Range (Min. , Max.)	Controls Median (25^{th},75^{th} Q) Range (Min. , Max.)	
<40	368.5(344.0, 386.0) 49.0(344.0, 393.0)	180.0	0.221
40-49	396.0(305.5, 451.5) 221.0(281.0, 502.0)	321.0(252.0, 399.0) 303.0(190.0, 493.0)	0.133
50-59	307.0(262.0, 460.0) 446.0(201.0, 647.0)	350.5(290.5, 396.7) 214.0(232.0, 446.0)	0.551
60-69	328.0 (277.5, 512.0) 557.0(240.0, 797.0)	340.0(283.5, 437.0) 348.0(187.0, 535.0)	0.617
70-79	416.0(362.5, 555.0) 448.0(201.0, 649.0)	(262.0, 340.0) 101.0(249.0, 350.0)	0.045
≥80	421.5(347.2, 569.2) 291.0(325.0, 616.0)	202.0	0.157
p-value**	0.347	0.201	

***Mann-Whitney U has been used; **Kruskal-Wills test**

By performing the ROC test and estimating the area under the curve, table (3.5) and figure (3.2) revealed that the area under the curve for the uric acid level among the study sample was 0.604 with a statistically significant association (p=0.046).

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Table (3.5): Area under the curve for uric acid level.

Area	Std. Error [a]	p-value [b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.604	0.051	0.046	0.504	0.704

The test result variable(s): VAR00002 has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under nonparametric assumption

b. Null hypothesis: true area = 0.5

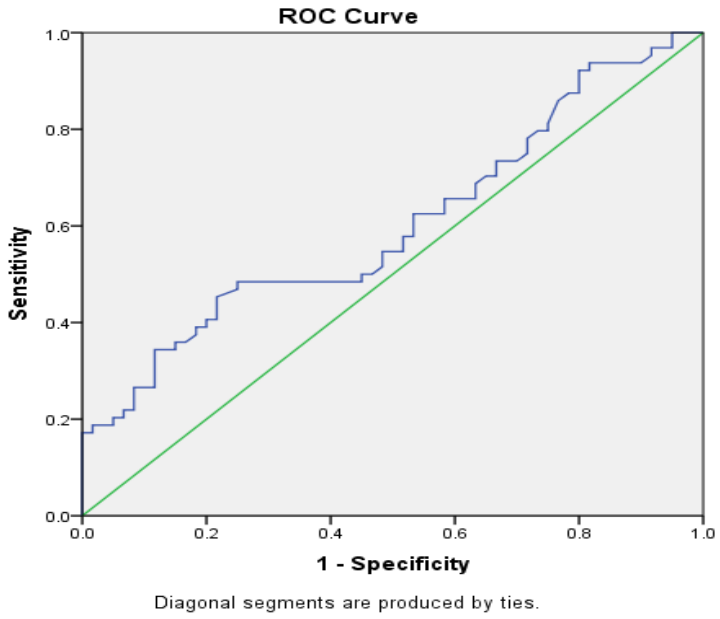

Figure (3.2): ROC test for uric acid level.

Sensitivity, specificity, positive predictive value, and negative predictive value for different cut-off points of uric acid and the best cut-off point was 333.5 as demonstrated in table (3.6).

In Our study, the findings show a statistically significant difference in median serum uric acid levels between ACS patients (341.0 µmol/L) and healthy controls (333.0 µmol/L), with a p-value of 0.046, suggesting higher uric acid levels in the ACS group. This observation aligns with the hypothesis that elevated serum uric acid may be linked to an increased risk of ACS, potentially serving as a biomarker for its detection and prognosis.

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Our findings go with the study of Pagidipati NJ which concludes that there is a correlation between higher serum uric acid levels and an increased likelihood of cardiovascular incidents. It's crucial to explore further the underlying mechanisms of this link and assess if serum uric acid levels could be a viable target for lowering the risk of cardiovascular diseases. [13] and also, there is a study of Padda, which concludes that Hyperuricemia independently increases the risk for coronary artery disease (CAD), and treatments that lower urate levels enhance cardiovascular health and decrease death rates in CAD patients. [14] .

On the contrary, the study by Moriarity, said that there was little evidence of an association of uric acid with coronary heart diseases in either sex, indicating that serum uric acid may not serve as an independent risk factor for coronary heart diseases [15]. Gaubert et al They pointed out that more emphasis needs to be placed on understanding the prevalence of hyperuricemia and its association with coronary heart disease, suggesting that the relationship might not be as straightforward as thought [16]. These discrepancies highlight the complexity of the relationship between uric acid and cardiovascular diseases, suggesting that further research is needed to clarify these associations. [ppp]

In our study, the distribution of serum uric acid levels across genders revealed interesting patterns. There is a significant difference between cases and control was observed among females (p=0.035). While the difference in levels between male cases and controls was not statistically significant (p=0.602, indicating that the association between uric acid levels and ACS might be influenced by gender. Higher median uric acid level in female cases (416.0 µmol/L) compared to males (338.0 µmol/L) and suggests that female patients with ACS may have distinctly elevated uric acid levels, warranting further investigation into gender-specific mechanisms. This finding goes with results of a meta-analysis conducted by Li, M., et al, which shows that higher serum uric acid levels may increase the risk for coronary heart disease (CHD), with a notable impact on CHD mortality among women [17].

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Age-related analysis showed no significant differences in uric acid levels across most age groups, except for the 70-79 age group, where ACS patients had significantly higher levels (p=0.045) compared to controls In his study, Yahya found that there is no significant difference between men and women, or among different age groups, regarding uric acid levels in patients with coronary artery disease. [18]

This finding could indicate that the impact of uric acid on ACS risk may become more pronounced in older age groups, possibly due to cumulative exposure to elevated uric acid levels or other age-related physiological changes. [19]) discussed how oxidative stress is a consequence of the imbalance between the generation of reactive oxygen species (ROS) and the body's antioxidant system's ability to detoxify them. This imbalance contributes to aging and age-related diseases through mitochondrial dysfunction, impaired protein homeostasis, and increased production of advanced glycation end products (AGEs), which are implicated in various age-related chronic pathologies including neurodegenerative diseases, atherosclerosis, and diabetes mellitus. [19]

The area under the curve (AUC) of 0.604 from the ROC analysis, with a p-value of 0.046, suggests a moderate ability of serum uric acid levels to discriminate between ACS cases and controls. The best cut-off point identified was **333.5** µmol/L, providing a basis for further studies to validate serum uric acid as a diagnostic marker for ACS. study by [29], the cutoff value of serum uric acid (UA) for predicting adverse events in elderly acute coronary syndrome (ACS) patients with diabetes mellitus was indeed identified as **353.6 µmol/L**[20]

Conclusion

Our findings suggest that high serum uric acid associated with increased risk of acute coronary syndrome, particularly among female and older age groups. And how uric acid effects on acute coronary syndrome is area of future, of more future investigation to find more ways for protection and treatment, protection and prevention and treatment of acute coronary syndrome.

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Recommendations

Encourage use of serum uric acid as a part of routine screening for individuals of high risk of acute coronary syndrome with focusing on female and older age group.

Also, for the need for larger study on this topic.

Encourage gender and age specific analysis to ensure better protection and care.

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