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Serum uric acid levels on admission and prognosis of acute coronary syndrome: a bi-institutional report

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Abstract: **Objective:** This study aimed to determine the association between the baseline serum uric acid (SUA) level and the short-term outcomes of patients with acute coronary syndrome (ACS).

Methods: In this retrospective, bi-institutional study, patients with a diagnosis of ACS were recruited and followed-up for 30 days regarding the development of major adverse cardiovascular and cerebrovascular events (MACCEs). The associations between the SUA level upon admission and cardiovascular morbidities and patient prognosis were examined using univariate and multivariate analyses.

Results: A total of 145 patients with ACS, with a mean age of 67.5±12.2 years, were recruited in this study. The rates of cardiovascular risk factors were higher in patients with elevated SUA levels. A cumulative MACCE was reported in 42 (29%) patients (19.5% in normal individuals and 39.7% in patients with elevated SUA levels, respectively; P=0.007). Based on the receiver operating characteristic (ROC) curve analysis, an on-admission SUA level above 6.9 mg/dL could discriminate patients with MACCE from those without MACCE during 30 days of follow-up (AUC=0.637; 95% CI: 0.553–0.715), with 64.3% sensitivity and 66% specificity. Based on multivariate logistic regression analysis, an elevated SUA level was associated with an increased risk of MACCE (odds ratio, 15.353; 95% CI: 2.026–116.328).

Conclusion: In patients with ACS, an elevated baseline SUA level was associated with a higher prevalence of cardiovascular risk factors and morbidities, as well as an increased risk of MACCE in a short-term follow-up.

Keywords: Acute Coronary Syndrome; Mortality; Myocardial Infarction; Prognosis; Uric Acid

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1. Introduction

Serum uric acid (SUA) is the end product of purine metabolism. Hyperuricemia indicates the increased activity of xanthine oxidase pathway, leading to the production of oxygen free radicals (1). Cardiovascular risk factors seem to be associated with the gut, and the SUA level is postulated to result in hypertension (2). According to numerous studies, the SUA level is related to hypertension, diabetes mellitus, metabolic syndrome, coronary artery disease (CAD), and heart failure (3-7). Recently, several studies have indicated that the SUA level is associated with the increased risk of all-cause mortality and major cardiovascular events in patients with CAD (8-11). On the other hand, the Framingham Heart Study reported that the SUA level had no significant association with the development of CAD and cardiovascular or all-cause mortality (12). Also, in the Atherosclerosis Risk in Communities (ARIC) study (13), no significant association was reported between the SUA level and CAD in men and women.

A recent meta-analysis of prospective cohort studies, including 958,410 participants, revealed that hyperuricemia was associated with an increased risk of morbidity and mortality in patients with CAD (14). In another meta-analysis of a mixed cohort of healthy individuals and patients with cardiovascular disease, a positive dose-response association was found between the SUA level and cardiovascular mortality risk (15). However, there is no research in the literature evaluating the association between the SUA level and the full spectrum of acute coronary syndrome (ACS) in the Iranian population. The results of such studies can help us determine the role of SUA level in the risk stratification of ACS patients.

This bi-institutional prospective study aimed to investigate the association between conventional cardiovascular risk factors and SUA concentration upon admission among patients diagnosed with ACS in the emergency departments and severe CAD, based on an invasive coronary angiography. Moreover, this study aimed to determine the effect of SUA level upon admission on the short-term outcomes of patients with ACS.

2. Method

2.1. Study design and population

In this retrospective study, patients with a diagnosis of ACS, who underwent invasive coronary angiography in two institutions of Tehran, Iran, were evaluated between January 2018 and December 2019. The evaluated institutions included

Firoozgar General Hospital and Hazrat Rasool General Hospital, which are two teaching centers affiliated to Iran University of Medical Sciences, Tehran, Iran. The study population was selected among eligible patients, using convenience sampling. Patients undergoing invasive coronary angiography, with a narrowing of the coronary artery lumen >70%, were recruited in this study.

The exclusion criteria were as follows: a diagnosis of gout; receiving SUA-lowering agents; a history of chronic kidney disease; and receiving a renal replacement therapy. The study protocol was approved by the local ethics committee of our institution. Since this study was retrospective, the requirement to obtain consent from the patients was waived for this cohort. The local ethics committee approved this study (ID: IR.IUMS.FMD.REC.1397.184).

2.2. Data collection and follow-up

The baseline characteristics, laboratory test results, and electrocardiogram (ECG) changes were determined and collected. The left ventricular ejection fraction (LVEF) was evaluated by two-dimensional transthoracic echocardiography in the initial presentation. The diagnosis of ACS spectrum was based on the latest recommendations (16). CAD was diagnosed based on invasive coronary angiography, which was performed through femoral or radial arteries. The patients' medical history was also collected from their medical charts. Hypertension was defined as blood pressure higher than 130/80 mmHg and/or using any antihypertensive agents (17).

Moreover, the diagnosis of diabetes mellitus was based on the following criteria: 1) classic symptoms of diabetes, along with a serum glucose level >200 mg/dL; 2) a fasting blood glucose level ≥126 mg/dL; 3) a two-hour post-load glucose level ≥200 mg/dL in an oral glucose tolerance test; and 4) use of antidiabetic agents (18). Besides, the familial history of ischemic heart disease was defined as having a first-degree male relative with CAD younger than 55 years or a female relative with CAD younger than 65 years. Also, an elevated SUA level was defined based on sex-specific threshold values for males (≥7 mg/dL) and females (≥6 mg/dL) (19). All patients were followed-up for 30 days after admission to the hospital. The clinical outcomes, defined as major adverse cardiovascular and cerebrovascular events (MACCEs), were collected via chart reviews and telephone interviews with the patients or their family members. In the 30-day follow-up, the MACCEs included reduced LVEF (i.e., new-onset heart failure defined as LVEF<55%, measured by transthoracic echocardiography), arrhythmias requiring invasive therapy at the hospital or in the outpatient setting, re-hospitalization due to a cardiac ischemic event, revascularization of the involved coronary arteries in a percutaneous coronary intervention or surgery, cerebrovascular events, and all-cause mortality. The identification of MACCEs during the follow-up was based on the hospital discharge summary or the patients or their family members' remarks.

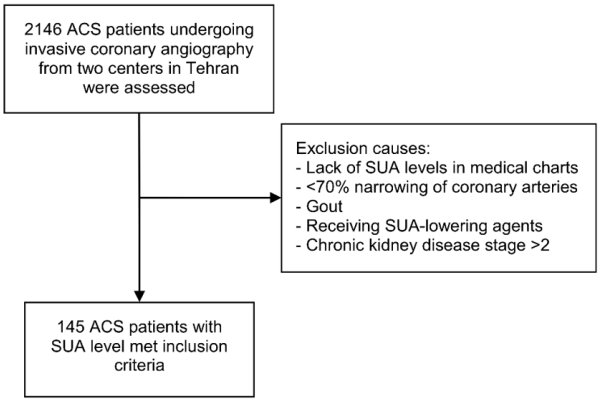

Figure 1 Study flow (ACS, acute coronary syndrome; SUA, serum uric acid)

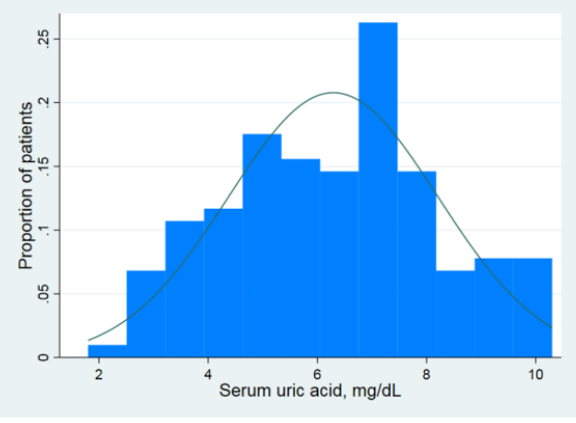

Figure 2 The distribution of baseline serum uric acid levels in study population

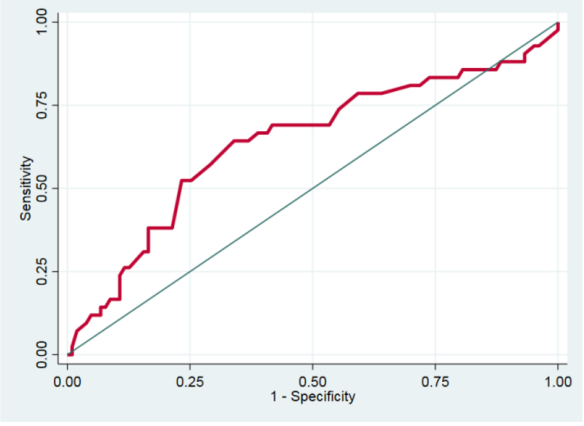

Figure 3 ROC curve depicting the discrimination of patients with or without MACCE using serum uric acid levels

2.3. Statistical analysis

The SUA levels, as categorical data, are reported as number and percentage, and Chi-square or Fisher's exact test was used for analysis as appropriate. Continuous variables are reported as mean±standard deviation (SD) or median (interquartile range) and analyzed using t-test or Mann-

Table 1 Baseline characteristics of population in groups by serum uric acid levels

Variable	Normal SUA (n = 77)	Elevated SUA (n = 68)	P
	mean ± SD / number (%)		
Age, year	65.8 ± 11.9	69.5 ± 12.3	0.070
Male sex	48 (62.3)	27 (39.7)	0.006
BMI, kg/m^2	26.6 ± 7.2	28.2 ± 5.3	0.345
Hypertension	39 (50.6)	51 (75.0)	0.003
Dyslipidemia	32 (41.6)	31 (45.6)	0.625
Diabetes mellitus	23 (29.9)	30 (44.1)	0.075
Smoking	25 (32.5)	20 (29.4)	0.691
Familial history of CAD	11 (14.3)	9 (13.2)	0.855
CAD involvement			0.024
1VD	36 (46.8)	17 (25.0)	
2VD	24 (31.2)	28 (41.2)	
3VD	17 (22.1)	23 (33.8)	
Type of ACS			0.022
ST-segment elevation MI	20 (26.0)	30 (44.1)	
Non-ST ACS	57 (74.0)	38 (55.9)	
Reduced baseline LVEF <55%	25 (32.5)	42 (61.8)	<0.001
Admission laboratories			
SUA levels, mg/dl	4.8 ± 1.1	7.9 ± 1.1	<0.001
Triglyceride, mg/dl [a]	110 (80, 139)	143 (90, 184)	0.148
LDL, mg/dl	104.7 ± 32.3	100 ± 39.7	0.648
HDL, mg/dl	43.6 ± 13.3	41.3 ± 10	0.495

ACS, acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; HDL, high density lipoprotein; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SUA, serum uric acid; VD, vessel disease

[a] Due to non-normal distribution, this value is presented as median (interquartile range)

Table 2 Events during follow-up period in groups by SUA levels

Variable	Normal SUA (n = 77)	Elevated SUA (n = 68)	P
	number (%)		
Re-hospitalization	8 (10.4)	21 (30.9)	0.002
Revascularization	0 (0.0)	2 (2.9)	0.130
Cerebrovascular accidents	1 (1.3)	7 (10.3)	0.018
New-onset HF	1 (1.3)	8 (11.8)	0.009
Arrhythmias	6 (7.8)	11 (16.2)	0.117
Mortality	4 (5.2)	4 (5.9)	0.856
MACCE	15 (19.5)	27 (39.7)	0.007

HF, heart failure; MACCE, major adverse cardiovascular and cerebrovascular events; SUA, serum uric acid

Whitney U test as appropriate. The receiver operating characteristic (ROC) curve analysis was used for determining the accuracy of SUA to distinguish patients with and without MACCEs in short-term follow-ups. Moreover, the area under the curve (AUCs) and 95% confidence intervals (CIs) for sensitivity and specificity were measured. The optimal cut-off point was also defined based on the highest sum of sensitivity and specificity values. Besides, a multivariable logistic regression analysis was performed using a backward stepwise method. All variables with P-values <0.2 in the univariate analysis were entered into the regression model. All statistical analyses were performed using STATA 16.0 (StataCorp LLC, TX, USA).

3. Results

The process of patient selection from two hospitals in Tehran, Iran, is presented in Figure 1. After excluding 22 patients (10

Table 3 ROC curve analyses for SUA discriminating events from no events at follow-up period

Events at follow-up period	Cut-off	AUC	Sensitivity	Specificity (95% CI)	PPV	NPV	P
MACCE	6.9	0.637 (0.553 – 0.715)	64.3% (48 – 78.4)	66% (56 – 75.1)	43.5% (35.2 – 52.3)	81.9% (74.7 – 87.4)	0.011
Mortality	7.2	0.545 (0.460 – 0.628)	50.0% (15.7 – 84.3)	69.3% (60.9 – 76.9)	8.7% (4.4 – 16.6)	96.0% (92.2 – 98)	0.695
CVA	7.3	0.744 (0.665 – 0.812)	75% (34.9 – 96.8)	73.7% (65.5 – 80.9)	14.3% (9.3 – 21.4)	98.1% (93.8 – 99.4)	<0.001
Arrhythmia	6.9	0.597 (0.512 – 0.677)	64.7% (38.3 - 85.8)	60.2% (51.1 - 68.7)	17.7% (12.5 - 24.5)	92.8% (86.9 - 96.1)	0.226
Revascularization	7	0.689 (0.607 – 0.763)	100% (15.8 – 100)	63.6% (55.2 - 71.5)	3.7% (3.0 - 4.6)	100% (100 – 100)	<0.001
Re-hospitalization	6.9	0.681 (0.599 – 0.756)	72.4% (52.8 - 87.3)	64.7% (55.2 - 73.3)	33.9% (26.8 - 41.7)	90.4% (83.7 - 94.5)	0.001
New-onset reduced LVEF	9	0.768 (0.690 – 0.834)	55.6% (21.2 - 86.3)	94.1% (88.7 - 97.4)	38.5% (20.4 - 60.4)	97.0% (93.9 - 98.5)	0.009

AUC, area under the curve; CI, confidence interval; CVA, cerebrovascular events; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiovascular and cerebrovascular events; SENS, sensitivity; SPCF, specificity; SUA, serum uric acid

Table 4 Multivariate logistic regression analysis showing predictors of outcome

Variable	Univariate	Multivariate
OR (95% CI)		
Male sex	0.793 (0.387 – 1.628)	2.377 (0.431 – 13.105)
Age	1.015 (0.984 – 1.046)	1.026 (0.959 – 1.099)
Diabetes mellitus	1.928 (0.926 – 4.015)	1.624 (0.257 – 10.260)
Hypertension	1.792 (0.825 – 3.891)	5.134 (0.713 – 36.973)
CAD involvement		
2VD	1.134 (0.472 – 2.722)	0.357 (0.046 – 2.779)
3VD	1.846 (0.754 – 4.519)	0.614 (0.035 – 10.809)
ST-segment elevation MI vs. Non-ST ACS	1.249 (0.592 – 2.633)	0.443 (0.050 – 3.920)
Elevated SUA	2.722 (1.293 – 5.730)	15.353 (2.026 – 116.328)
Reduced baseline LVEF <55%	2.320 (1.104 – 4.873)	6.443 (0.841 – 49.345)
Triglyceride	1.014 (1.003 – 1.025)	1.016 (1.002 – 1.030)

ACS, acute coronary syndrome; CAD, coronary artery disease; CI, confidence interval; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OR; odds ratio; SUA, serum uric acid; VD, vessel disease

patients with a chronic kidney disease stage >2, seven patients with a diagnosis of gout, and five patients receiving allopurinol), a total of 145 patients (51.7% male), with a mean age of 67.5±12.2 years, were recruited in the study. The distribution of SUA level in the study groups is shown in Figure 2. After categorization of patients according to the SUA level, it was found that 77 patients had a normal SUA level, while 68 patients had elevated SUA levels. Patients with elevated SUA levels were found to have a higher rate of hypertension (P=0.003), a higher rate of multi-vessel CAD (P=0.024), a higher rate of ST-segment elevation myocardial infarction (STEMI) (P=0.022), and a higher rate of reduced LVEF<55% at baseline (P<0.001). Other baseline characteristics are summarized in Table 1.

A cumulative MACCE was reported in 42 (29%) patients (15 [19.5%] cases in the normal SUA group and 27 [39.7%] cases in the elevated SUA group; P=0.007). Single events were mostly identified among patients with elevated SUA levels as compared to those with a normal SUA level (Table 2). Based on the ROC curve analysis, a SUA cut-off point >6.9 mg/dL could discriminate patients with and without MACCE, with an AUC of 0.637 (95% CI: 0.553–0.715), sensitivity of 64.3% (95% CI: 48–78.4), and specificity of 66% (95% CI: 56–75.1) (Figure 3). By separately analyzing the events, the highest AUC was attributed to the new-onset reduced LVEF <55% in the follow-up (AUC=0.768; 95% CI: 0.690–0.834). Other results of the ROC curve analysis are summarized in Table 3.

Moreover, the results of a multivariate logistic regression analysis (including age, sex, diabetes mellitus history, hypertension history, reduced LVEF at baseline, degree of coronary artery involvement, triglyceride level, type of ACS, and normal SUA vs. elevated SUA groups) revealed that an elevated SUA level was associated with an increased risk of MACCE in the follow-up (odds ratio: 15.353 [95% CI: 2.026–116.328]). Other results of the multivariate regression analysis are summarized in Table 4.

4. Discussion

This retrospective study evaluated the relationship between the SUA level at admission and the clinical outcomes of ACS patients in a short-term follow-up. It was found that patients

with an elevated SUA level had more conventional cardiovascular risk factors and more MACCEs during the follow-up. The on-admission SUA level showed relatively high sensitivity and specificity to distinguish patients with and without MACCEs in the follow-up. Moreover, an elevated SUA level was associated with an increased risk of MACCE during the short-term follow-up.

The importance of SUA level in the development of cardiovascular diseases and the prognosis of patients is a matter of controversy in the literature. According to the Framingham Heart Study, the on-admission SUA level did not play a causal role in the development of CAD and its mortality. They argued that the association between the SUA level and these outcomes might be mediated by other risk factors (12). In another prospective cohort study among middle-aged Finnish men, the SUA level significantly predicted cardiovascular mortality, independent of factors associated with gout or metabolic syndrome (20). Moreover, in the Japanese population (21), the presence of baseline hyperuricemia (>7 mg/dL) in the healthy population was associated with all-cause and cardiovascular mortalities in the Cox proportional-hazards model, adjusted for confounding factors (adjusted hazard ratio: 1.36 [95% CI: 1.25–1.4] and 1.69 [95% CI: 1.41–2.01], respectively).

In a recent community-based study (21), the all-cause and cardiovascular mortalities were significantly associated with hyperuricemia during a nine-year follow-up, particularly in males, smokers, and those with renal insufficiency. Moreover, in a systematic and dose-response meta-analysis of prospective studies, hyperuricemia was associated with an increased risk of CAD and morbidity (adjusted risk ratio: 1.13 [95% CI: 1.05–1.21]) and mortality (adjusted risk ratio: 1.27 [95% CI: 1.16–1.39]) (14). Moreover, some small-scale trials reported that SUA-lowering agents conferred cardio-renal benefits (22, 23). However, the normal population was not evaluated in the present study, and further research is needed to elucidate the role of SUA in the development of cardiovascular diseases.

So far, the prognostic value of SUA level has been evaluated among patients with cardiovascular disease in several studies. In this regard, Hajizadeh et al. (24) evaluated the effect of SUA level on the mid-term outcomes of patients with STEMI. They found that an elevated SUA level in patients with STEMI was not associated with increased mortality, while it was associated with a lower LVEF, elevated cardiac enzyme levels, renal failure, and a higher incidence of atrial fibrillation. In another study on STEMI patients, an increased SUA level independently predicted the one-year mortality, and a higher SUA level could help identify patients at a higher risk of renal failure and bleeding (8).

Moreover, Tscharre et al. (1) assessed 1215 patients with ACS and conducted a follow-up for a mean period of 5.5 years. They found an independent association between the elevated SUA levels and the development of long-term cardiovascular events in ACS patients undergoing a percutaneous coronary intervention. In another cohort of 1548 ACS patients, a SUA level >6 mg/dL was associated with in-hospital mortality (9). Also, Timóteo et al. (11) evaluated 683 patients with ACS in a one-year follow-up. They found that the best cut-off point of SUA to predict one-year mortality was 6.25 mg/dL (sensitivity, 59%; specificity, 72%). The one-year all-cause mortality rate was higher in patients with increased SUA levels (15.5% vs. 4.2%; log-rank test $P < 0.001$).

Additionally, some studies have assessed the relationship between the SUA level and cardiovascular diseases other than CAD. In a retrospective study, Virdis et al. (25) evaluated 22,714 individuals in a hypertension clinic. After 20 years of follow-up, they found that the SUA thresholds, associated with the risk of all-cause and cardiovascular mortalities, were significantly lower than those applied for the detection of hyperuricemia in clinical practice. Another study assessed the sex-specific association of baseline SUA level and hyperuricemia status with the risk of type 2 diabetes mellitus in a Chinese population (4). In a median follow-up of >3 years, 6% of recruited adults developed type 2 diabetes mellitus. The higher quartiles of SUA were associated with an increased risk of type 2 diabetes mellitus in women (hazard ratio: 1.78 for Q3 and 1.93 for Q4), but not in men. In our cohort of patients with ACS, patients with elevated SUA levels had a higher rate of morbidities (i.e., hypertension, low LVEF, STEMI, and multivessel CAD). Moreover, in patients with increased SUA levels, a higher prevalence of MACCE was reported during the follow-up (19.5% vs. 39.7%).

The optimal cut-off point for the SUA level to discriminate patients with and without MACCE was >6.9 mg/dL (sensitivity, 64.3%; specificity, 66%). An elevated SUA level was associated with an increased risk of MACCE in the follow-up (odds ratio: 2.722). Based on our findings and previous reports, the SUA level could predict cardiovascular morbidity and mortality in different ethnicities and populations; however, further large-scale studies and trials using SUA-lowering agents are needed to find the proper cut-off point of SUA for predicting the prognosis of patients and to examine the causal relationship between an elevated SUA level and the prognosis of ACS patients. Also, further large-scale clinical trials can elucidate the effects of SUA-lowering agents on the outcomes of patients with cardiovascular diseases.

5. Limitations

This study had some limitations. First, a relatively small group of ACS patients with severe CAD, diagnosed by invasive coronary angiography, was included in this study. It should be noted that the ACS spectrum also includes patients with less severe involvements and has various prognoses compared to more severe types. Second, the patients were followed-up for a short period, while a longer follow-up can improve the prognostic value of SUA level in patients with ACS. Although our findings were in line with the majority of previous studies, it is suggested to examine a large group of patients with ACS in a long-term follow-up in fu-

ture studies. Finally, the small group of patients with severe CAD examined in this study cannot be a proper representative of ACS patients or the Iranian population. If the significant association between the SUA level and prognosis of ACS patients is confirmed, therapeutic modalities can be implemented to modify the SUA level and evaluate the probability of improvement in the outcomes.

6. Conclusion

The present findings indicated an association between an elevated baseline SUA level and an increased risk of MACCE among patients with ACS in a short-term follow-up. However, the role of SUA-lowering agents in improving the patient outcomes needs to be investigated in future studies.

7. Declarations

7.1. Acknowledgment

None.

7.2. Authors' contribution

All the authors met the standards of authorship based on the recommendations of the International Committee of Medical Journal Editors.

7.3. Conflict of interest

Authors have nothing to declare.

7.4. Funding

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