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Original Article

Elevated serum uric acid levels are associated with increased risk score and MACE development in patients with STEMI

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Abstract

Aim: Although the relationship between changes in serum uric acid (UA) levels and adverse events in ST segment elevation myocardial infarction (STEMI) patients is well known, the effect of an increase in UA levels on risk scores or major adverse cardiovascular event (MACE) development are not well established. In this study, we investigated the effects of ordinal changes in serum UA levels on adverse events and risk scores in STEMI patients.

Material and Methods: The patients presenting with a diagnosis of STEMI and undergoing coronary angiography were included in the study. The patients were divided into seven groups evenly according to baseline UA levels and the effects of changes in UA levels on risk score and MACE were investigated.

Results: A total 1200 STEMI patients was included in the study. The mean age of the patients was 62 years and 72% of them were males. While both Syntax score-II (SS-2) and Cadillac scores (CS) were lower among Group-1 and Group-4; SS-2, CS and development of MACE were markedly increased with an increase in UA levels.

Conclusions: The UA levels in STEMI patients can be guiding for the clinician regarding the development of adverse event and patient-based intensive approaches should be considered in the patients with higher UA levels.

Keywords: Uric Acid; Myocardial Infarction; Risk Score.

INTRODUCTION

Uric acid (UA) is the degradation product occurring as a result of catabolism of nucleic acids and it has been shown in previous studies that it could be associated with cardiovascular diseases. While increased UA level was associated with coronary complexity in patients with stable coronary disease, it has been associated with increased mortality in STEMI patients (1-3).

STEMI defines the process of myocardial ischemia and infarction development as a result of rupture of vulnerable plaque in the coronary artery and then total occlusion of the lumen with platelet activation. Many inflammatory mediators or hormones play a role in this process. Percutaneous coronary intervention is the standard method in the therapy. STEMI mortality and morbidity decreased markedly with this method (4,5). Various risk scores are used for both determinations of patients who will benefit from the treatment and for the prediction of an adverse event in STEMI patients. It has been reported in previous studies that clinical predictive value of these risk factors are good (6-8). Syntax score II (SS-2) is a scoring system including both coronary artery lesion characteristics and demographic and clinical characteristics of the patients obtained from Syntax study data (9). It has been shown that its correlation in both coronary artery patients and with surrogate markers is good and its predictive values for the prediction of an adverse event is better than TIMI and SS (10).

Cadillac score (CS) is a score developed by Halkin et al. for the prediction of an adverse event in STEMI patients. It has been shown that also this score has higher predictability in coronary artery disease and it can provide beneficial information (11). In STEMI patients, both relationships and correlation of changes in UA levels with risk scores

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and their effects on the development of major adverse cardiovascular events (MACE) during one year follow-up were not clearly defined. In this study, we investigated the relationships of UA levels with risk scores and MACE in STEMI patients.

MATERIAL and METHODS

This study was performed in patients presenting to our hospital with a diagnosis of STEMI between February 2014 and December 2018 and undergoing percutaneous coronary intervention. Baseline demographic and clinical characteristics, medical histories of the patients were recorded. Patients undergoing percutaneous coronary intervention (PCI) (n=65) or coronary artery bypass graft surgery (CABG) (n=23) previously, patients without archive records (n=45), patients with diseases causing an increase in UA level (n=11) or patients using drugs like furosemide (n=54) were excluded from the study. The study was performed after receiving approval of the ethics committee.

Descriptions:
STEMI was defined to be the presence of followings in two contiguous leads beginning from the J point in leads V2-V3;

≥2.5 mm in men younger than 40 years of age,

≥2 mm in men over 40 years of age,

≥1.5 mm in women,

≥1 mm ST segment elevation in all other leads.

A definition of STEMI in ECGs with the morphology of left bundle branch block was assessed according to Scarbossa criteria (12). Hypertension was defined to have a blood pressure value of ≥ 140/90 mmHg in consecutive measurements or previous chronic use of antihypertensive medication. Diabetes mellitus was defined as the measurement of a fasting blood glucose level of > 126 mg/dL or measurement of a postprandial blood glucose level of > 200 mg/dL or an HbA1c level of > 6.5 or chronic use of antidiabetic medication. Peripheral artery disease was defined according to current ESC guideline (13) and COPD was defined according to current GOLD guideline (14).

Uric acid measurement and groupings
A blood sample was obtained via a peripheral venous catheter from all of the patients during the presentation. After the blood samples were centrifuged, they were analyzed in the serum analyzer with the turbidimetric method. Serum UA levels were categorized as ordinal variables. The patients with UA levels of ≤ 4 mg/dL, ≤ 5 mg/dL, ≤ 6 mg/dL, ≤ 7 mg/dL, ≤ 8 mg/dL, ≤ 9 mg/dL, and > 9 mg/dL were expressed as Group 1, Group 2, Group 3, Group 4, Group 5, Group 6 and Group 7; respectively.

Coronary angiography
Coronary angiography was performed in all of the patients either via femoral approach or radial approach. Angiography was performed by using standard Judkins method. During angiography, bare or DES (biorilimus or zotarilimus) implantation was performed in all of the patients depending on clinician preference. Intracoronary g2b3a antagonist was performed in some patients according to the lesion and patient characteristics. The patients were discharged at the 3rd Day after the intervention. All of the patients received dual anti-aggregant therapy for 1 year.

SS-2 and Cadillac scores
Halkin et al. obtained CS from their study entitled "The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC)" performed in 2005.11 This score was comprised of ejection fraction, renal failure, anemia, final TIMI flow, three vessel disease, Killip classification and age parameters and it has been reported that it has an area under curve (AUC) value of 82% for the prediction of one year mortality.

SS-2 score was obtained with the addition of clinical and demographic characteristics in addition to characteristics obtained from a study9 entitled "The Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX Study)". Cadillac and SS-2 score calculations of each patient were performed by two experienced cardiologists who were unaware of each other. Same measurements were repeated after one week and intra-observer and inter-observer variabilities were calculated.

Clinical outcome
The patients were followed up for one year after the development of STEMI and stent thrombosis (ST), myocardial infarction(MI) and development of cardiac death were defined as MACE.

Statistics
Variables with a normal distribution, variables without normal distribution and categorical variables were evaluated by using the Student t test, Mann– Whitney U test, Chi Square test; respectively. Serum UA levels were divided into seven groups as ordinal variables. Both relationships and correlation of changes in UA levels with risk scores and their effects on the development of MACE during one year follow-up were investigated. Pearson's or Spearman's correlation analysis was used when applicable, the correlation coefficient and significance value were expressed with r and p; respectively. A p value of <0.05 was considered to be significant. All calculations were performed by using the software IBM SPSS version 23.

RESULTS

One thousand and two hundred patients were included in the study. The mean age of the patients was 62 years and 72% of them were males. Baseline demographic and clinical characteristics of the patient population were shown in Table 1.

Table 1. Baseline demographic and angiographic characteristics of the study groups

Variables	Group-1 N=102	Group-2 N=185	Group-3 N=193	Group-4 N=195	Group-5 N=206	Group-6 N=201	Group-7 N=118
Age(years)	59.5±5	64±3.7	62±5.1	66±6.2	65±5.1	62.2±4	62±5
Sex(male,%)	72	75	75	69	77	78	80
DM(%)	21	19	22	25	28	32	33
HT (%)	33	34	37	31	39	40	41
PAD (%)	8	9	10	12	14	18	20
COPD (%)	12	11	9	14	16	15	16
SS-2	21±2	22±2.5	23±3.1	23±3	27±4.2	30±5	33±5.7
CS	2 (1-3)	3 (1-4)	3 (2-5)	3 (3-6)	5 (5-10)	7 (7-13)	8 (10-14)
MACE (%)	4	7.2	6	8	16	21	26
GFR (ml/sec/1.73 m2)	82±5.8	78±5.3	85±3.2	75±6.4	70±5.1	68±7.5	82±5.6
Na (mmol/l)	138±3.3	139±3.7	138±2.4	139±3.2	137±2.5	138±2.7	139±2.2
K (mmol/l)	4.1±0.9	4.2±1	3.9±0.7	4.3±1.2	4.6±1.1	4.2±1.2	4.5±1
Glucose(mg/dl)	103±6.1	100±8.2	107±5.2	104±8.5	110±9.6	114±7.1	118±8.3
AST (UI/L)	23 (15-42)	22 (18-31)	32 (25-44)	27 (20-42)	37 (31-45)	42 (36-48)	41 (34-49)
ALT (UI/L)	27(17-36)	28 (23-37)	32 (26-40)	36 (30-42)	41 (35-45)	37 (31-45)	44 (38-50)
Uric acid (mg/dl)	3.1±1.1	4.4 ±0.8	5.7±1	6.5±2.1	7.6±1.3	8.5±1.7	10.1±3.1
LDL (mg/dl)	128±10.1	132±12.3	134±14.5	136±15.7	151±13.1	147±12.9	162±15.2
HDL (mg/dl)	49±6.1	42±5.2	39±6.8	36±5.4	34±5	31±7.1	30±8.3
Triglyceride (mg/dl)	132±10.5	128±14.2	129±17.5	145±20.1	167±21.2	162±18.3	165±16.2
WBC (10*3 /µL)	8.2±1.1	6.5±0.9	5.7±1.2	8.6±1.7	9.7±2.2	9.4±2.6	10.1±3.4
HGB(g/dl)	14.1±3	14.3±2.5	14.7±2.4	13.9±2.6	13.8±2.3	13.9±3.2	13.5±3.5
PLT (10*3 /µL)	234 (195-2620)	253 (210-290)	244 (216-289)	243 (224-292)	289 (245-321)	286 (267-341)	278 (258-316)
Trop (ng/mL)	1.5±0.1	1.7±0.1	1.8±0.3	2.1±0.4	2.3±0.6	2.2±0.5	2.7±0.7

Abbreviations: DM; diabetes mellitus, HT; hypertension, PAD; peripheral arterial disease, COPD; chronic obstructive pulmonary disease, SS-2; syntax score II, CS; Cadillac score, MACE; major adverse cardiovascular events, LDL; low density lipoprotein, HDL; High density lipoprotein, WBC; white blood count, HGB; hemoglobulin, PLT; platelet count

The patients were divided into seven different groups according to changes in serum UA levels and the correlation of these groups with SS-2 score (Figure 1A), Cadillac risk score (Figure 1B) and their effects on the development of MACE during one year follow-up were investigated.

While SS-2 score was mean 21 in Group 1, it was 33 with a linear increase in Group 7 (Table 1). There was an intermediate correlation(r=0.55) between SS-2 and serum UA level (Figure 2A)

Similarly, while CS was 2 in Group 1, it was at the highest level in Group 7 and measured to be 8 (Table 1). There was an intermediate correlation(r=0.62) between CS and serum UA levels (Figure 2B).

From group-1 to group-7, an increase in both SS-2 and CS was observed. However, while increases until Group-4 were not significant in pair comparisons, there was a statistical significance between the SS-2 score and CS in all groups beginning from Group-5 (Table 2).

During one year follow-up, when the incidence of development of MACE was investigated, while this rate was at the lowest level in Group 1, it was at the highest level in Group 7 and statistical significance began after Group 5 (Table 2 and Figure 3).

While intra-observer and inter-observer variability for SS score were 0.89 and 0.86, respectively; intra-observer and inter-observer variability for CS was calculated to be 0.92 and 0.88; respectively.

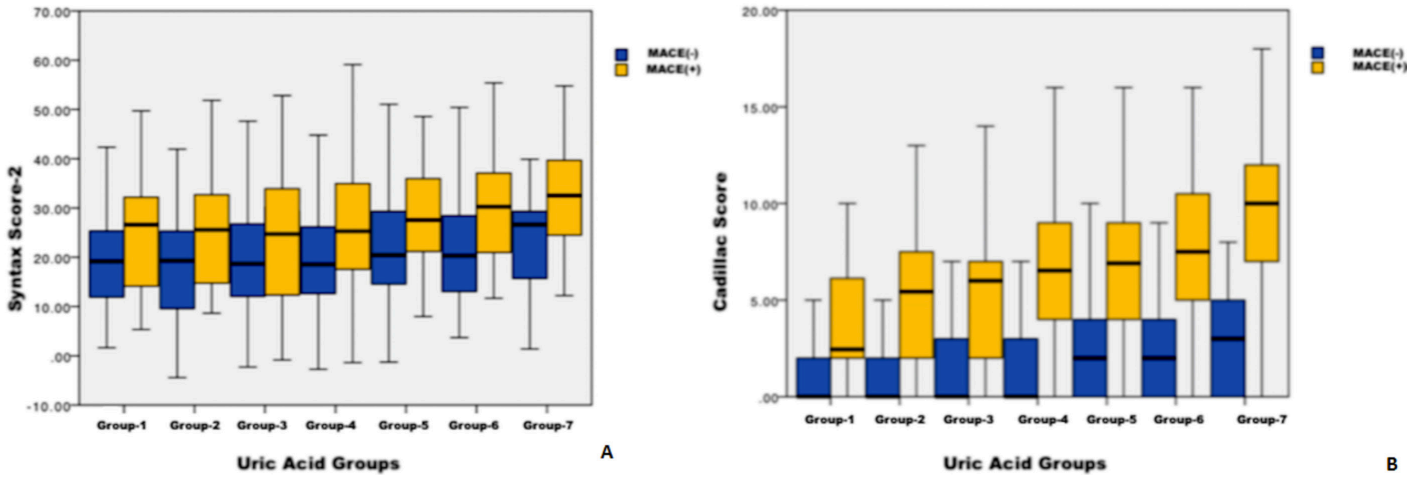

Figure 1. Distribution of development of MACE according to Syntax score-2 (A) and Cadillac score (B)

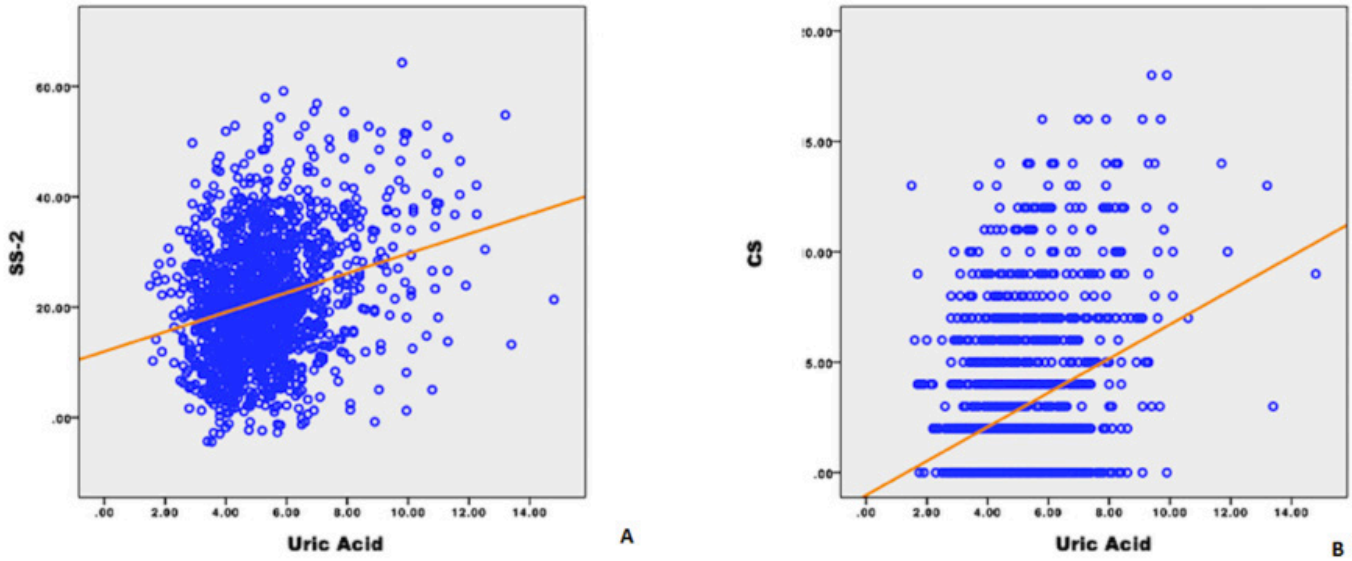

Figure 2. Correlation plots between Syntax score-2 (A) and Cadillac score (B) and uric acid levels

Table 2. Pair comparison of study groups regarding the relationship between risk scores and adverse events

Groups	P value		
	SS-2	Cadillac Score	Overall MACE
Group-1- Group-2	0.55	0.98	0.99
Group-1- Group-3	0.95	0.99	0.95
Group-1- Group-4	0.98	0.95	0.96
Group-1- Group-5	0.05	0.019	0.035
Group-1- Group-6	0.012	<0.001	<0.001
Group-1- Group-7	<0.001	<0.001	<0.001
Group-2- Group-3	0.15	0.39	0.61
Group-2- Group-4	0.35	0.09	0.35
Group-2- Group-5	<0.001	<0.001	0.004
Group-2- Group-6	<0.001	<0.001	<0.001
Group-2- Group-7	<0.001	<0.001	<0.001
Group-3- Group-4	0.73	0.98	0.99
Group-3- Group-5	0.003	0.011	0.038
Group-3- Group-6	0.001	<0.001	<0.001
Group-3- Group-7	<0.001	<0.001	<0.001
Group-4- Group-5	0.045	0.041	0.044
Group-4- Group-6	0.026	0.001	<0.001
Group-4- Group-7	<0.001	<0.001	<0.001
Group-5- Group-6	0.05	0.001	0.048
Group-5- Group-7	0.039	<0.001	<0.001
Group-6- Group-7	0.042	<0.001	0.021

Abbreviations: MACE; major adverse cardiovascular events

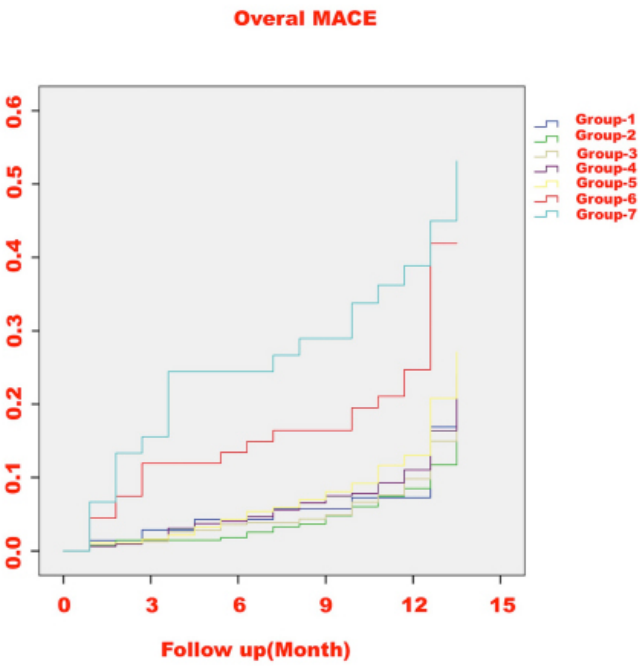

Figure 3. Demonstration of distribution of development of MACE with Kaplan Maier analysis during one year follow-up

DISCUSSION

Study findings can be summarized as follows 1). There is a strong relationship between UA level and coronary artery disease 2). Increase in UA levels are positively correlated with both SS-2 and CS. 3) Higher UA levels are associated with the increased adverse event beginning from Group-5 and this relationship is more marked as the UA levels increase.

STEMI is the clinical condition developing due to rupture of the plaque occurred in the coronary artery and causing transmural myocardial ischemia. Its mortality is high in the acute period and adverse events like the development of heart failure and arrhythmia are commonly seen in the long term. Percutaneous coronary intervention is the basic method in its therapy (5). Several risk scores are frequently used for adverse events prediction such as cardiac death or RS development in the long term follow up. The leading one among these scores is SS-2 score with an increasing frequency (9,10,15). In this system developed with reference to Syntax study data, anatomical coronary lesions, and clinical and demographic data were combined and better results were obtained compared to traditional risk scores. It has been shown that it has a better cut-off value in patients with acute coronary syndrome compared to TIMI risk score or SS-1 score (10). CS was obtained with a combination of 6 clinical parameters and it has been shown that it was useful for the prediction of one month and one year in-hospital adverse event (11). In a retrospective study including 1506 STEMI patients, TIMI, PAMI, CADILLAC, and GRACE risk scores were compared and it has been reported that CS had the best predictive value for 30-day and 1-year mortality, but the difference between them was not statistically significant (16). Contrary to this study, in the study performed by Kozieradzka et al., the relationship between risk scores and 1-year and 5-year mortality was investigated and the predictive value of CS was found to be less than the predictive values of TIMI and Zwolle scores (17).

Serum UA level has a strong association with the severity of coronary artery disease and an increase in UA levels is a marker of poor prognosis (3). Again, it has been demonstrated in an extensive study that UA levels could also be associated with the development of contrast-induced nephropathy after PCI (18). However, although the relationship between serum UA levels and cardiovascular risk are well established, the effect of increases in UA levels on MACE development or risk score are not clearly demonstrated. While a cut-off value of 5.95 was a predictor for chronic total occlusion in the study performed by Kurtul et al., it was reported in the study performed by Uysal et al. that coronary collateral circulation was poorer in patients with a UA level ≥ 5.65 (19-20). In this context, patients were divided into seven groups according to UA levels in order to investigate the effects of ordinal increases in UA levels on risk scores and mace development and from group-1 to group-7, an increase in both SS-2 and CS and 1-year MACE development was observed. However, while increases until Group-4 were not significant in pair comparisons, there was a statistical significance between the development of MACE and SS-2 score and CS in all groups beginning from Group-5. Within this context, our study data is similar to data of the study performed by Duran et al. and associating serum UA level and severity of coronary artery disease in nondiabetic and non-hypertensive patient group with ACS in which UA levels showed a correlation with multi-vessel disease (21). In another study, UA levels were found to be correlated with poor coronary collateral vessels in patients with acute coronary syndrome and this condition was associated with adverse event (22). Also, this finding was similar to our study and an increase in adverse events was observed in parallel to an increase in UA levels during one year follow-up. Although there are similar points between our study and aforementioned studies, our study differ from the others since it shows the relationship between UA level and adverse event linearly and the effects of ordinal changes in UA level on risk scores MACE. In the light of these findings, we can say that increase in UA levels also leads to increased cardiovascular risk and patients with increased UA levels are under increased cardiovascular risk and we think that aiming at least UA level of Group-4 in STEMI patients will be useful.

CONCLUSION

Higher UA levels are correlated with higher SS-2, CS and MACE development in STEMI patients. The UA levels in these patients can be guiding for the clinician regarding the development of adverse event and patient-based intensive approaches should be considered in the patients with higher UA levels.

Limitations

Our study has some limitations. First, its retrospective

design can be considered as the main limitation. Again, the exclusion of patients undergoing CABG surgery or PCI previously can also be considered as a limitation. However, a large number of patients in our study population increase the power of the study and it can guide for future studies.

Competing interests: The authors declare that they have no competing interest.
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