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URIC ACID AS A PROGNOSTIC INDICATOR TO ESTIMATE THE RISK OF IN-HOSPITAL MORTALITY AND MAJOR ADVERSE CARDIAC EVENTS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Background: Uric acid (UA) is a risk factor associated with an increased incidence of cardiovascular disease, and an indicator of oxidative stress that plays a fundamental role in the pathogenesis of acute myocardial infarction (AMI) and it's subsequent consequences .**Objective:** to assess the prognostic value of UA as an indicator of in-hospital complications and mortality in patients with AMI. **Materials and methods**: Study sample included patients with AMI admitted to the cardiac care unit at Tishreen University Hospital-Lattakia –Syria from September 2019 to September 2020. Serum UA tests were performed for all patients, in addition to all required investigative and therapeutic procedures. Study sample was divided into two groups according to the admission value of uric acid (high uric acid, and normal uric acid). **Results**: 98 patients were included, 74 were male (76%). Means of age, Hemoglobin, Urea, and glucose of high uric acid group were higher and the prevalence of diabetes and hypertension was higher. UA values were positively correlated with GRACE scores ($r=0.6, P<0.001$). According to multivariate analysis, high UA was associated with an increased risk of mortality (OR 3.3,P=0.04), cardiogenic shock(CS) (OR 5.6,P=0.04), acute heart failure(AHF) (OR 3.8,P=0.01) and systolic dysfunction (OR 4,97,P=0.01). There was an inverse correlation between changes in UA level (between day1 and day3) and left ventricular ejection fraction($r=-0.42$, $P<0.001$). **Conclusions**: high UA on admission and increased UA level between day 1 and day 3 were predictive indicators for mortality and complications (CS and AHF) in patients with AMI.

KEYWORDS: Acute myocardial infarction, uric acid, mortality, cardiogenic shock, acute heart failure.

INTRODUCTION

Worldwide, ischaemic heart disease is the single most common cause of death and its frequency is increasing. Several recent studies have highlighted a fall in acute and long-term mortality following ST segment elevation myocardial infarction (STEMI) (and NSTEMI) in parallel with greater use of reperfusion therapy, primary percutaneous coronary intervention (PCI), modern antithrombotic therapy, and secondary prevention; Nevertheless, mortality remains substantial; the in-hospital mortality of unselected patients with STEMI in the national registries of the ESC countries varies between 4 and 12%.[1]

In humans, uric acid (UA) is an end-product of catabolism of purine nucleotides arising from endogenous (nucleic acids and internal pool of purine nucleotides, mostly adenosine triphosphate (ATP), or their derivatives, by xanthine oxidoreductase (XOR) enzyme which converts hyoxantine to xanthine and xanthine to UA), and exogenous (dietary purines) sources.

UA is correlated closely with almost all known cardiovascular risk factors, insulin resistance, metabolic syndrome, obesity, non-alcoholic fatty liver disease and chronic kidney disease.

In general, pro-oxidant activity, depletion of nitric oxide (NO) and endothelial dysfunction, promotion of inflammation and potentiation of vasoconstrictor and proliferative vascular stimuli are the most accepted mechanisms of UA involvement in the pathophysiology of CVD.[2]

Vascular injury occurs in response to reactive oxygen species (ROS) that are a byproduct of xanthine oxidase (XO) enzymatic activity during production of uric acid. Thus, hyperuricemia may simply represent a surrogate marker for high levels of damaging oxidative stress associated with increased XO activity, rather than being directly responsible for vascular injury and the subsequent increase in risk.[3]

Human patients with decompensated heart failure have elevated serum uric acid concentrations, suggestive of increased xanthine oxidase activity.[4] And It is well recognised that there is an increase in ROS production and oxidative stress post-MI, both experimentally and clinically.[5-7] And XOR is one of the most important ROS producers.[2]

MATERIALS AND METHODS

The present analysis was a prospective observational study conducted at Tishreen University Hospital)Lattakia, Syria (between September 2019 and September 2020.

Patients with acute myocardial infarction (AMI) (both STEMI and NSTEMI) admitted to the cardiac care unit, Tishreen University Hospital, Lattakia, were studied. Patients with chronic kidney disease, gout, malignancy, were excluded. Patients taking drugs that lower (eg, allopurinol) or increase (eg, diuretics) UA were also excluded.

Blood samples were taken for measurement of complete blood count, urea, creatinine, cardiac markers, uric acid, and glucose at the critical care unit after presentation. Baseline characteristics and clinical data of participants were collected by patients' interviewing and recorded at study checklists.

All subjects underwent two-dimensional echocardiography to determine left ventricular ejection fraction (LVEF) before discharge (unless needed earlier). All required investigative and therapeutic procedures were done as available.

According to admission uric acid levels, patients were divided into two groups: high uric acid (> 7 mg\dl for men, > 6 mg\dl for women) and normal uric acid.

We also measured uric acid on day 3, and divided patients into two groups: increased uric acid level and decreased uric acid level, according to the difference between uric acid values on day 1 and day 3.

We defined major adverse cardiac events (MACE) as cardogenic shock, acute heart failure (with reduced ejection fraction), stroke and re-infarction.

Statistical analysis

The analysis was performed using the Statistical Package for Social Sciences (SPSS) (version 20) (IBM Corporation, Armonk, New York, USA) and Excel 2010 program. A predictive value less than 0.05 was considered statistically significant. Basic Descriptive statistics included means, standard deviations(SD), Frequency and percentages. Statistical analyses were performed using the chi- square test, Student’s t-test, Spearman and Pearson correlation and Fischer’s exact test. Multivariate logistic regression was used to assess the association of explanatory variables (including high uric acid) with mortality in the presence of other potential confounders/risk factors.

RESULTS

Our study included 98 patients with acute myocardial infarction, males were 74 patients (76%) and females were 24 patients (24%).The mean age of patients was 58 ± 10.4 years in a range of 35-84 years. The distribution of additional baseline characteristics is presented in (Table 1).

As shown below, 7.14% of the patients died, 13.3% had cardiogenic shock, and 29.6% had acute heart failure. Table 1 also shows the distribution according to killip scores and GRACE risk scores.

Table 1: Demographic, clinical, and biochemical characteristics of patients.

All patients	98
Age (years ± SD)	57.9 ± 10.4
Male	74 (76 %)
Diabetes Mellitus	45 (45.9 %)
hypertension	44 (44.9%)
CAD or PAD	21 (21.4%)
Smoking	76 (77.5%)
Family history	38 (38.7%)
Hemoglobin	12.6 ± 1.7
Urea	38 ± 17.4
Glucose	208.7 ± 98.5
Killip's class	
I	61 (62.2%)
II	21 (21.4%)

III	12 (12.2%)
IV	4 (4%)
Grace risk score	
Low	29 (29.6%)
Intermediate	39 (39.8%)
High	30(30.6%)
Hospital stay	4 ± 1.4
Mortality	7 (7.14%)
Cardiogenic shock	13 (13.3%)
Acute heart failure	29 (29.6%)
Stroke	3 (3.1%)
Re-infarction	3 (3.1%)

Table 2 shows comparison of the demographic, clinical and biochemical characteristics between patients with high uric acid (> 7 mg\dl for men, > 6 mg\dl for women) and patients with normal uric acid.

Patients with high uric acid were older (60.56 ± 11.5 vs. 56.4 ± 9.5 years, p=0.02) and were significantly more likely to present with hypertension (64.8% vs. 32.4%, P < 0.009), diabetes (59.4 % vs 37.7 %, P=0.03) decreased mean hemoglobin (11.7 ± 1.9 grams/dL vs. 13 ± 1.2 13 ± 1.2 grams/dL , P < 0.001), increased urea (43.9 ± 21.1 mg\dl vs 33.6 ± 12.4 mg\dl, P=0.002), increased blood glucose (250 ± 98 mg\dl vs 177.8 ± 87 mg\dl, P=0.0001), higher killip class (0.02) and higher GRACE risk scores (0.0003) compared with those with normal uric acid.

Analysis of MACE showed that in high uric acid group, a significantly greater proportion of patients experienced Mortality (16.2% vs 1.6%, P= 0.006), Cardiogenic shock (27% vs 4.9%, P= 0.001) and Acute heart failure (51% vs 16%, P< 0.001) compared with patients with normal uric acid.

Table 2: Comparison of the demographic, clinical and biochemical characteristics between patients with high uric acid and patients with normal uric acid.

	High Uric Acid	**Normal Uric Acid**	**P-value**
All patients	37	61	
Age (years ± SD)	60.56 ± 11.5	56.4 ± 9.5	0.02
Male	27 (73%)	47 (77%)	0.6
Diabetes	22 (59.4 %)	23 (37.7 %)	0.03
hypertension	24 (64.8%)	20 (32.4%)	0.009
CAD or PAD	11 (29.7%)	10 (16.4%)	0.1
Smoking	29 (78.3%)	47 (77%)	0.8
Family history	15 (40.5%)	23 (37.5%)	0.7
Hemoglobin grams/dL	11.7 ± 1.9	13 ± 1.2	<0.001
Urea	43.9 ± 21.1	33.6 ± 12.4	0.002
Glucose	250 ± 98	177.8 ± 87	0.0001
Killip class			
I	16 (43%)	45 (73.7%)	0.02
II	11 (30%)	10 (16.3%)	
III	7 (19%)	5 (8.2%)	
IV	3 (8%)	1 (1.6%%)	
Grace risk score			
Low	6(16.2%)	23(27.7%)	0.0003
Intermediate	11(29.7%)	28(45.9%)	
High	20(54%)	10(16.4%)	
Hospital stay	4.35 ± 1.7	3.8 ±1.17	0.5
Mortality	6 (16.2%)	1 (1.6%)	0.006
Cardiogenic shock	10 (27%)	3 (4.9%)	0.001
Acute heart failure	19 (51%)	10 (16%)	<0.001
Stroke	2 (5.4%)	1 (1.6%)	0.3
Re-infarction	1 (2.7%)	2 (3.2%)	0.8

We studied the correlation between uric acid and GRACE risk scores (figure1), There is a significant positive correlation between uric acid and GRACE risk scores, (r= -0.6, P<0.001).

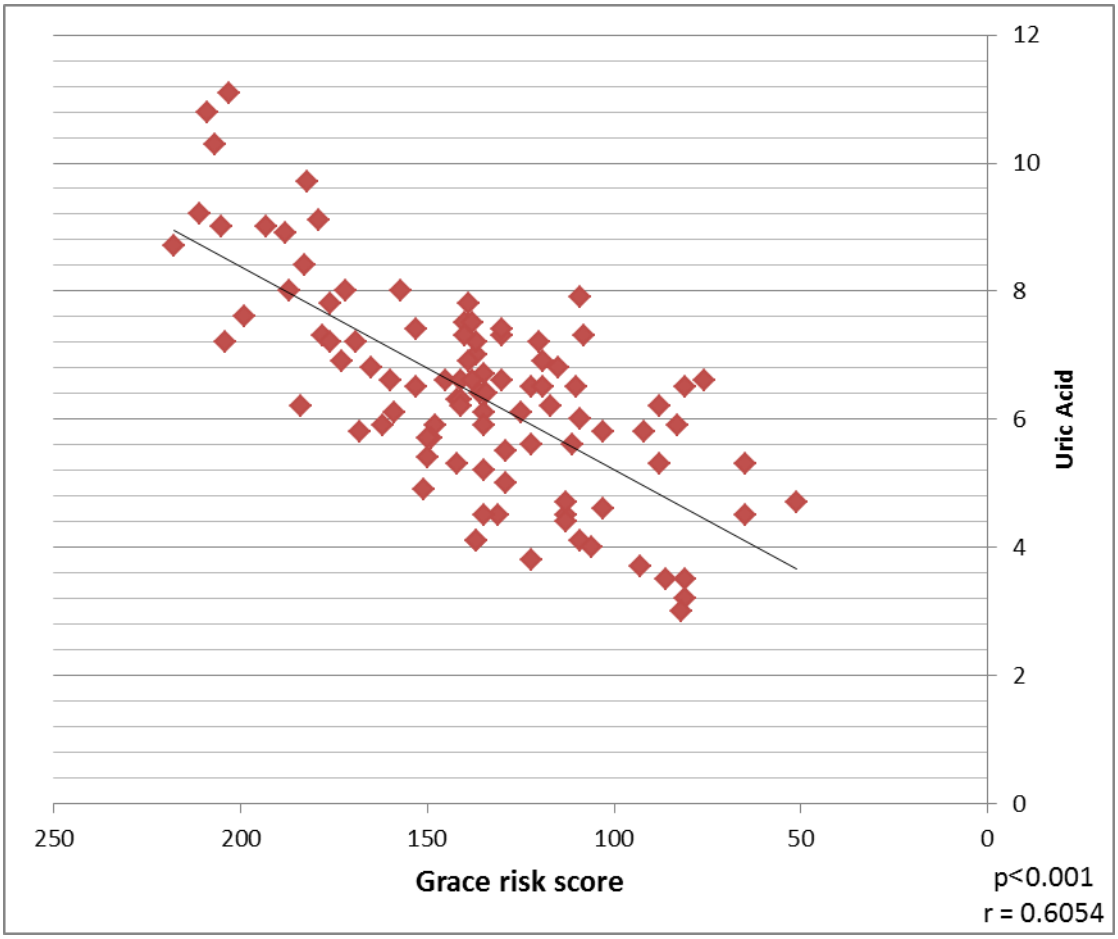

Figure 1: Correlation between uric acid and GRACE risk score in our study.

Comparison of clinical outcomes between patients with high uric acid and patients with normal uric acid in subgroups (STEMI AND NSTEMI) are shown in table 3.

Table 3: Comparison of clinical outcomes between patients with high uric acid and patients with normal uric acid in subgroups (STEMI AND NSTEMI).

		High Uric Acid	Normal Uric Acid	P-value
STEMI	All patients	27	36	
	Mortality	5 (18.5%)	1 (2.7%)	0.03
	Cardiogenic shock	6 (22.5%)	2(5.5%)	0.04
	Acute heart failure	13 (48%)	6(16.6%)	0.007
NSTEMI	All patients	10	25	
	Mortality	1(%10)	0	0.2
	Cardiogenic shock	4(30%)	1(4%)	0.01
	Acute heart failure	6(60%)	4(16%)	0.009

We measured changes in uric acid levels between day 1 and day 3 (in 58 patients) and divided them into two groups (patients with increased uric acid level and patients with decreased uric acid level) according to that. Comparsion of the clinical outcomes between the two groups are shown in table 4.

Table 4: Comparison of the clinical outcomes between patients with increased uric acid level and patients with decreased uric acid level (between day 1 and day 3).

	Increased Uric Acid level	Decreased Uric Acid level	P-value
All patients	20	38	
Mortality	3(15%)	0	0.03
Cardiogenic shock	7(35%)	2(5.3%)	0.002
Acute heart failure	13(65%)	6(15.8%)	0.0001

We studied the correlation between changes in uric acid level and LVEF (before discharge) (figure 2), There is a significant reverse correlation between changes in uric acid level and LVEF, (r= - 0.42, P<0.001).

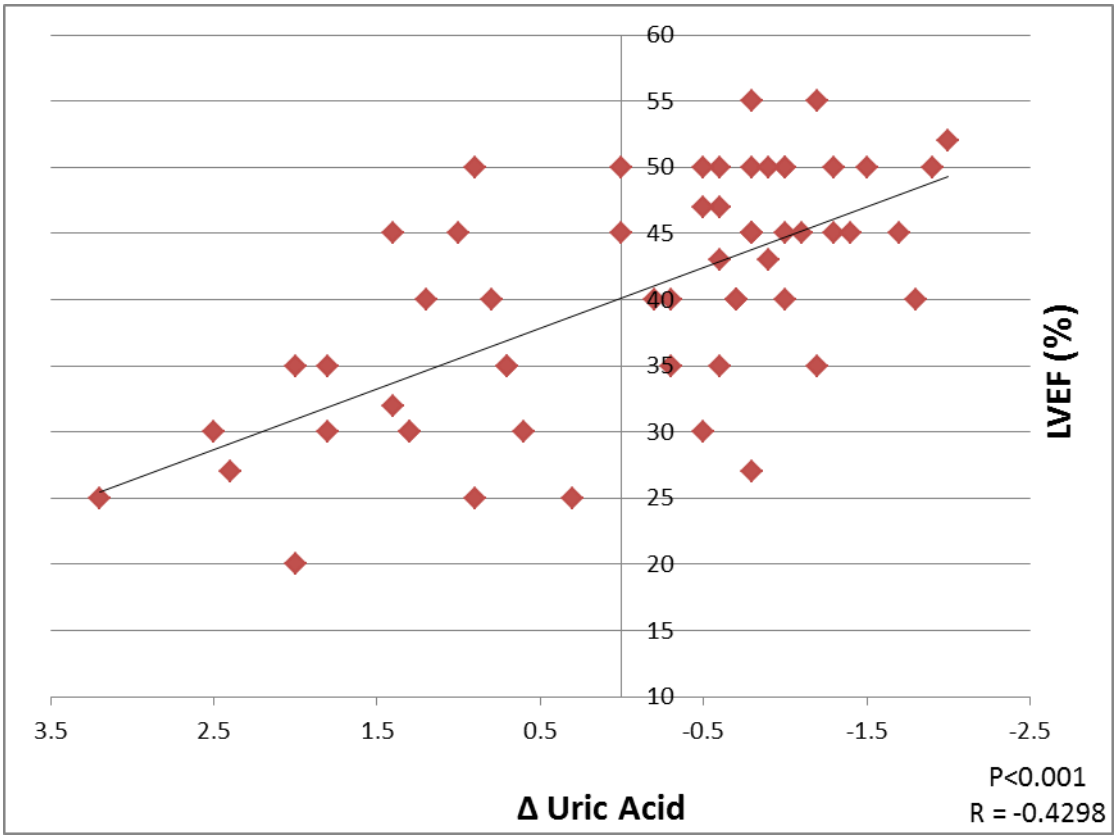

Figure 2: Correlation between changes in uric acid level and LVEF.

A multivariate analysis for all factors associated with LVEF<35% by logistic regression analysis is shown in table 5.

High uric acid [oods ratio (OR) 4.97 (95% Confidence interval "CI" 1.47, 16.76); P = 0.01], glucose >200 mg\dl [OR 3.82 (95% CI 3. 1.14 , 12.83); P - 0.03] and Hemoglobin > 11 g\dl [OR 3.65 (95% CI 1.03 , 12.85); P = 0.04] conferred a significant risk of LVEF <35%.

Table 5: Multivariate logistic regression analysis of clinical and laboratory parameters associated with LVEF< 35%.

	OR	95% Confidence Interval	P-value
Age > 65	1.14	(0.31 , 4.1)	0.8
Hypertension	0.75	(0.19 , 2.9)	0.69
Diabetes Mellitus	1.61	(0.4 , 6.35)	0.49
High uric acid	4.97	(1.47 , 16.76)	0.01
Glucose >200 mg\dl	3.82	(1.14 , 12.83)	0.03
Urea > 30 mg\dl	2.52	(0.61 , 10.26)	0.19
Hemoglobin > 11 g\dl	3.65	(1.03 , 12.85)	0.04

A multivariate analysis for all factors shows that high uric acid conferred a significant risk of mortality (OR 3.3, P = 0.04), CS (OR 5.6, P = 0.04) and AHF (OR 3.8, P = 0.01). Also uric acid was significantly correlated with mortality (Spearman's r = 0.39, P<0.001), CS (Spearman's r = 0.53, P<0.001) and AHF (Spearman's r = 0.51, P<0.001).

Table 6: Correlation and multivariate logistic regression analysis of clinical and laboratory parameters associated with mortality, Cardiogenic shock, Acute heart failure. (uric acid results are shown).

	OR	P-value	r	P-value
Mortality	3.3	0.04	0.39	<0.001
Cardiogenic shock	5.6	0.04	0.53	<0.001
Acute heart failure	3.8	0.01	0.51	<0.001

DISCUSSION

Our study was carried out with the primary aim of evaluation serum uric acid as a prognostic indicator for AMI. A total of 98 patients were included, 37.8% of them had high uric acid. Patients with high uric acid were older (p=0.02) and more likely to have hypertention (p=0.009) and diabetes (p=0.03). Our data are consistent with previous studies, Grayson PC et al showed that hyperuricemia is associated with an increased risk of incident hypertension, independent of conventional risk factors.[8] And other studies showed that hyperuricemia is correlated closely with insulin resistance.[9,10]

Our study found that patients with high uric acid level had higher Killip's class, which is an indicator of severity of heart failure. Padma V found that there was statistically significant correlation between serum uric acid level and Killip class (p=0.001) on day 3 and patients of Killip class lll and lV had higher levels of uric acid as compared to patients of class l and ll.[11] Similar findings were also noted by Kojima S1 et al.[12] A possible explanation for such an association may be the fact that the failing heart in AMI leads to tissue hypoperfusion and hypoxia, which triggers xanthine oxidase activation and oxidative stress thereby increasing uric acid levels and triggering a vicious cycle,[13,14] and that may also explain our finding that changes in uric acid levels were inversely correlated with LVEF, as shown in figure 2. We also found a significant positive correlation between uric acid and GRACE risk scores, (r= 0.6, P<0.001), which is an indicator of poor prognosis.

Patients with high uric acid were more likely to experience death (P= 0.006), Cardiogenic shock (P= 0.001) and Acute heart failure (P< 0.001) compared with patients with normal uric acid. And multivariate analysis for all factors shows that high uric acid conferred a significant risk of mortality (P = 0.04), CS (P = 0.04), AHF (P= 0.01) and with left ventricular dysfunction (EF<35%) (0.01). These findings are consistent with previous studies, Ranjith N et al retrospectively found that patients with hyperuricemia experienced cardiac failure (24% vs. 14%, P < 0.001), death (14% vs. 7%, P < 0.001), cardiogenic shock (8% vs. 4%, P < 0.001) more compared with patients with normal uric acid levels, and hyperuricemia was associated with a significantly higher risk of mortality (OR 1.7, P = 0.042) based on multivariable analysis.[15]

Gazi E et al also concluded that hyperuricemia was a Independent predictor of advanced heart failure and/or in-hospital mortality in STEMI patients.[16]

Gazi E et al also determined UA levels of 7 mg/dl for men and 6 mg/dl for women to be effective cut-off points in female and male patients with ST elevation for in-hospital mortality with a sensitivity of 70% and a specificity of 90% for women and with a sensitivity of 68% and a specificity of 68% for men. The same cut-off point was determined in our study, and almost similar cut-off points were determined in other studies.[11,15]

This prospective study, similar to other publications, recognized high uric acid as a possible good indicator of death, CS, AHF and left ventricular dysfunction (EF<35%) in patients with AMI. That can be explained by the fact that increased levels of ROS observed following MI (by XOR pathway and other sources) are directly involved in the structural and functional changes that occur during the development and progression of cardiac remodeling.[17] And it has been shown that excess amount of ROS can result in both reentry and focal activity by modifying many of the ionic currents in cardiomyocytes, cardiomyocyte coupling, and important elements of the extracellular matrix, so ROS play an important role in the genesis of arrhythmias.[18]

CONCLUSION

Uric acid can be considered as an independent, cheap and effective prognostic indicator in patients with AMI during the in-hospital period, so it can be used in risk stratification in parallel with other biomarkers and scores. And patients with AMI with high uric acid should be monitored closely for cardiovascular events during the in-hospital period.

List of abbreviations

AMI: Acute myocardial infarction.
UA: Uric acid.
XOR: xanthine oxidoreductase.
LVEF: left ventricular ejection fraction.
ROS: reactive oxygen species.
AHF: acute heart failure.
CS: cardiogenic shock.

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