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Original Research Article

Evaluate the Role of Serum Uric Acid in Acute Myocardial Infarction as a Prognostic Marker

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ABSTRACT

Background and Objectives: To assess serum uric acid (SUA) levels determined on admission as a potential predictor of short-term mortality (7 days) in acute myocardial infarction (AMI) patients. To evaluate whether uric acid is significantly elevated in AMI as compared to normal subjects. To validate hyperuricemia is a poor prognostic marker in AMI. To see for correlation of hyperuricemia with Killip's class and mortality. **Settings and Design:** Study design was case control prospective study from OCT 2011 to DEC 2012, we studied 100 cases which were diagnosed as acute myocardial infarction and 100 controls who were healthy volunteers with mixed diet. **Materials & Methods:** All cases and controls were taken from KIMS Karad, by applying inclusion and exclusion criteria with random sampling method. On admission serum Uric acid with ECG with routine investigations like CBC, Urea, Creatinine, CPKMB, Troponin I, and Chest X-ray were done. Uric acid was checked on Day 0, Day 3, and Day 7 to monitor the changes in uric acid levels. Basal serum uric acid levels were compared with cases. Uric acid levels of <6.5mg%, 6.51-8.5mg %, >8.5mg% were classified as low risk, moderate risk and high risk respectively. Patients were monitored till 7th day of admission. Blood sample was taken immediately after admission in hospital. The biochemical analysis of serum UA is done by Erba chem. 7, Erba chem.-plus, Erba chem. Pro machines and using uricase – PAP method which are a semi automated machine matching the international standards Statistical analysis was done calculating Mean± SD, Chi square test, Z –test **Results:**1. Serum uric acid was significantly higher in case group (patients with AMI) as compared to control group and it was associated with high mortality irrespective of day of estimation of uric acid.2. Higher serum uric acid level (>8.5mg%) on day 0 was associated with highest mortality (18/23 deaths) in our study; therefore patients with high UA on day 0 should be closely monitored for complication pertaining to AMI.3. High serum uric acid (8.5mg%) along with higher Killip's class (III,IV) was associated with higher mortality (23/23 deaths).**Conclusion:** Serum uric acid was significantly higher in case group as compared to control group and it was associated with higher Killip's class classification (III, IV) and higher mortality. Hence serum uric acid can be used as a short term prognostic marker in patients with acute myocardial infarction.

KEY WORDS: Serum uric acid, myocardial infarction, mortality, Killip's class

INTRODUCTION

In myocardial infarction (MI) some proteins and enzymes labelled as cardiac markers (CPK, MB/ Troponin T & I and myoglobin) which are released in the blood in large quantity from necrotic heart muscle. These markers had specific temporal profile in relation to MI, however, they do not correlate with myocardial function. Epidemiological studies have recently shown that serum uric acid may be a risk factor for cardiovascular diseases and a negative prognostic marker for mortality in subjects with pre-existing heart failure. Elevated serum uric acid is highly predictive of mortality in patients with heart failure or coronary artery disease and of cardiovascular events in patients. [1]

Therefore we conducted a study to assess serum uric acid (SUA) levels determined on admission as a potential predictor of short-term mortality (7 days) in acute myocardial infarction (AMI) patients. We also evaluated whether uric acid is significantly elevated in AMI as compared to normal subjects or not. We also validated hyperuricemia as a poor prognostic marker in AMI and correlation of hyperuricemia with Killip's class and mortality.

WHY URIC ACID: Adenosine synthesized locally by vascular smooth muscle in cardiac tissue is rapidly degraded by the endothelium to uric acid, which undergoes rapid efflux to the vascular lumen due to low intracellular pH and negative membrane potential [2] Xanthine oxidase activity [3] and uric acid synthesis [4] are increased in vivo under ischemic conditions, and therefore elevated serum uric acid may act as a marker of underlying tissue ischemia. Hyperuricaemia is associated with deleterious effects on endothelial dysfunction, oxidative metabolism, platelet adhesiveness, haemorheology, and aggregation.

There is evidence that high uric acid is a negative prognostic factor in patients with mild to severe heart failure although the development of hyperuricaemia is almost always associated with worsening of renal failure in these patients.[5]

Therefore, it is difficult to dissect the roles played by reduced renal function and high uric acid in affecting prognosis of these patients. Some evidences suggest that uric acid may exert a negative effect on cardiovascular disease by stimulating inflammation, which is clearly involved in the pathogenesis of cardiovascular disease. [6,7]

A recent study done in Japan (Japanese Acute Coronary Syndrome Study) [8] showed that there was a close correlation between serum uric acid concentration and Killip's classification in patients of acute myocardial infarction. Patients who developed short-term adverse events had high uric acid concentrations. Serum uric acid levels, Killip's class, age, and peak creatinine phosphokinase level would be significant predictors of long-term mortality. Patients with angiographically confirmed coronary artery disease with serum uric acid levels in the upper quartile are five times more likely to die than those in the lowest quartile. 1 mg/dl increase in serum acid levels was associated with a 26% increase in mortality. [9]

MATERIALS AND METHODS

We included 100 patients with acute myocardial infarction (STEMI AND NSTEMI) as cases and 100 age and sex matched controls.

We studied patients of more than 18 years of age who are diagnosed as ST segment elevation acute myocardial infarction (STEMI) or non-ST segment elevation acute myocardial infarction (NSTEMI) on the basis of clinical history, examination, ECG changes, biochemical

markers and admitted in Krishna hospital, Karad. Any patient with a condition known to elevate uric acid level e.g. chronic kidney disease, gout, hematological malignancy, hypothyroidism etc. were excluded. Also patients on drugs which increase serum uric acid e.g. salicylates (>2 gm/d), diuretics, ethambutol, pyrazinamide, anticancer drugs, etc. and also chronic alcoholics were excluded.

One hundred patients of acute myocardial infarction who fulfilled inclusion/exclusion criteria were enrolled for the study. A detailed history and physical examination with special reference to Killip's class was carried out. Patients were treated as decided by attending physician. Patients were followed up till hospital stay i.e. 7 days. Serum uric acid level was measured on day 0, 3 & 7 of MI. [10]100 age and sex matched controls were also be evaluated for baseline serum uric acid level who were among the staff and students of Krishna hospital, Karad and few healthy volunteers. All the subjects in control group were having mixed dietary habit. Basal serum uric acid levels of controls were compared with cases. Uric acid levels of <6.5mg%, 6.51-8.5mg %, >8.5mg% were classified as low risk, moderate risk and high risk respectively.[8]

Methodology

This study was approved by the Ethics Committee of the institute, consent of both the groups was taken for participation in study.

The biochemical analysis of serum uric acid is done in Krishna hospital and research center by Erba chem. 7, Erba chem.-plus, Erba chem. Pro machines and using uricase – PAP method which are a semiautomated machine matching the international standards.

RESULTS

We studied 100 patients with acute MI and 100 age and sex matched healthy controls. The comparison of two groups and the profile of patients' comparative uric acid levels are given in Table 1. There was a statistically very significant higher level of serum uric acid concentration in patients of MI on day of admission as compared to controls ($P < 0.01$).Table no.2 .Serum uric acid levels were comparable on Day 0, 3 and 7 in MI group, 7.03 ±1.54, 7.36± 1.9., 6.32± 1.6 respectively ($P < 0.01$). Tables 3 ,4,5 show the levels of uric acid in relation to Killip class and sex that uric acid in cases are higher than control group with on Day 0, 3 and 7 of admission. On all the days serum uric acid levels were higher in patients who were in higher Killip class ($P < 0.05$). All the 23 patients who died had uric acid above 6.5 and all of them were Killip class III and IV (table 6). 60% cases were in killips class 1, 12 % had class II, 10 % had class III and 18% class IV respectively. 55% had anterior wall MI, 12 had posterior 42% inferior wall and 11 % had RV wall infarction. We studied the Association between mortality and serum uric acid levels in STEMI and NSTEMI group on day 0, 3,7 respectively we found that morality was highest in patients with UA more than 8.5 in all the three days of UA estimations. This association was found significant by applying Z test $p<0.01$(Table 7,8,9) .Relation between uric acid level and Killip's class and death was studied was found that combination of UA with killips class was good indicator of mortality in AMI. It was seen that all patients who died were in killips class III and IV with UA >6.5 mg%. (table 10).

Table no. 1 Age and sex wise distribution

Age in years	Cases group (n=100)		Control group (n=100)	
	Males	Females	Males	Females
	No. (%)	No. (%)	No. (%)	No. (%)
< 40	7	3	18	6
40-50	6	0	10	8
50-60	12	17	10	12
60-70	16	17	10	6
70-80	9	8	6	4
>80	4	1	8	2
Total	54(54%)	46(46%)	62(62%)	38(38%)
Mean ± SD	60.59±12.04		58.90±14.15	

Value of $\times^2 = 21.14$, d.f.=15, $p<0.05$, significant

By applying Chi-square test there is a significant association between age and sex (i.e. $p<0.05$) in case and control group

Table No.2: Comparison of Uric acid in cases and control group:

Uric acid	Cases group	Control group	Z test value	p value and result
	Mean ± SD	Mean ± SD		
Day 0	7.03±1.54	5.77±1.15	10.96	p<0.01, highly significant
Day 3	7.36±1.9		10.66	p<0.01, highly significant
Day 7	6.32±1.6		39.50	p<0.01, highly significant

Mean uric acid in cases on day 0 is 7.03±1.54 and in control group was 5.77±1.15 Mean uric acid in cases on day 3 was 7.36±6.9 Mean uric acid in cases on day 7 was 6.32±1.6

By applying Z test of difference between two sample means there is a highly significant difference between mean values of Uric acid in experimental and control group at day1, day 3 and day7 ($p<0.01$)

Table no.3-Comparison of uric acid levels in cases and control group in relation to age, sex and Killip's class on day 0

Uric Acid (Mean)										
	Control		Cases							
	Male	Female	Male				Female			
Age Group			Killips Class I	Killips Class II	Killips Class III	Killips Class IV	Killips Class I	Killips Class II	Killips Class III	Killips Class IV
<40	5.40	5.04	6.36	-	-	-	5.7	-	-	-
40-50	5.56	5.57	6.25	6.30	8.6	9.8	5.85	-	-	-
51-60	6.04	6.29	6.04	7.35	-	10.1	5.34	7.85	8.5	8.5
61-70	6.52	5.30	5.78	7.2	8.37	9.9	6.5	7.1	-	9.76
71-80	5.98	6.7	7.33	7.0	8.35	8.85	6.46	6.4	7.2	9.0
>80	7.3	5.84	7.2	-	8.7	8.7	5.1	-	-	-

Note: (-) is considered as no cases fell in these groups.

Table no. 4- Comparison of uric acid levels in cases and control group in relation to age, sex and Killip's class on day 3

Uric Acid (Mean)										
	Control		Cases							
	Male	Female	Male				Female			
Age Group			Killips Class I	Killips Class II	Killips Class III	Killips Class IV	Killips Class I	Killips Class II	Killips Class III	Killips Class IV
<40	5.40	5.04	6.2	-	-	-	5.2	-	-	-
40-50	5.56	5.57	5.97	5.9	-	-	5.9	-	-	-
51-60	6.04	6.29	5.8	7.2	-	-	5.4	7.6	9.05	9.5
61-70	6.52	5.30	5.64	7.9	8.4	8.9	6.4	6.85	-	9.3
71-80	5.98	6.7	7.53	7.85	7.30	11	5.9	5.8	8.6	-
>80	7.3	5.84	7.0	-	8.9	9.3	5.1	-	-	-

Note: (-) is considered as no cases fell in these groups

Table no. 5- Comparison of uric acid levels in cases and control group in relation to age, sex and Killip's class on day 7

Uric Acid (Mean)										
	Control		Cases							
	Male	Female	Male				Female			
Age Group			Killips Class I	Killips Class II	Killips Class III	Killips Class IV	Killips Class I	Killips Class II	Killips Class III	Killips Class IV
<40	5.40	5.04	6.34	-	-	-	5.7	-	-	-
40-50	5.56	5.57	6.07	5.6	-	-	5.46	-	-	-
51-60	6.04	6.29	5.64	7.5	-	-	5.64	7.25	-	8.2
61-70	6.52	5.30	5.68	7.2	-	8.15	6.27	6.4	-	-
71-80	5.98	6.7	7.06	7.25	7.7	-	5.36	5.4	8.6	-
>80	7.3	5.84	6.5	-	9.7	9.9	5.4	-	-	-

Note: (-) is considered as no cases fell in these groups.

Table No 6: Association with Killip's class and mortality in STEMI / NSTEMI

Killip's class	STEMI	NSTEMI	Total
	Mortality	Mortality	Mortality
I	0	0	0
II	0	0	0
III	6(28.57%)	2(100%)	8(34.78%)
IV	15(71.43%)	0	15(65.22%)
Total	21 / 23 (91.30%)	2 /23 (8.70%)	23/23 (100%)

By applying Chi-square test there is a significant association between Killip's class and higher mortality in STEMI and NSTEMI (i. e. $p<0.05$).

Table no7 -Association between mortality and serum uric acid levels in STEMI and NSTEMI group on day 0

Uric acid day 0	Total number of deaths (23)							
	STEMI				NSTEMI			
	Before day 3	On or after Day 3 before day 7	On day 7	Total	Before day 3	On or after Day 3 before day 7	On day7	Total
<6.5	0	0	0	0	0	0	0	0
6.5-8.5	4	1	0	5	0	0	0	0
>8.5	10	4	2	16	0	1	1	2
Total	14	5	2		0	1	1	

By applying Z test difference between two proportions it is seen that there is a highly significant increase in mortality as uric acid level increases at day1, day3 and day7 in STEMI and NSTEMI groups. ($p<0.01$)

Table no 8-Association between mortality and serum uric acid levels in STEMI and NSTEMI group on day 3

Uric acid day 3	Total deaths					
	STEMI			NSTEMI		
	On or after Day 3 before day 7	On day 7	Total	On or after Day 3 before day 7	On day 7	Total
<6.5	0	0		0	0	0
6.5-8.5	1	0	1	0	0	0
>8.5	4	2	6	1	1	2
Total	5	2		1	1	

By applying Z test of difference between two proportions there is a significant difference between proportions of deaths at Before day 3, on or before day 3 before day7 and On day 7in STEMI group compared with NSTEMI group when uric acid level at day 3 is 6.5-8.5 and > 8.5 ($p<0.05$).

Table no 9-Association between mortality and serum uric acid levels in STEMI and NSTEMI group on day 7

Uric acid day 7	Total deaths			
	STEMI		NSTEMI	
	On-day7	Total	On day 7	Total
<6.5	0	0	0	0
6.5-8.5	0	0	0	0
>8.5	2	2	1	1
Total	2		1	

By applying Z test of difference between two proportions there is a significant difference between proportions of deaths at Before day 3, on or before day 3 before day7 and On day 7in STEMI group compared with NSTEMI group when uric acid level at day 7 is 6.5-8.5 and > 8.5 ($p<0.05$)

Table no 10: Relation between uric acid level and Killip's class and death:

Killip's class	Uric acid day 0			Uric acid day 3			Uric acid day 7		
	<6.5	6.5-8.5	>8.5	<6.5	6.5-8.5	>8.5	<6.5	6.5-8.5	>8.5
	NO. OF DEATHS			NO. OF DEATHS			NO. OF DEATHS		
I	0	0	0	0	0	0	0	0	0
II	0	0	0	0	0	0	0	0	0
III	0	1	7	0	2	3	0	0	1
IV	0	3	12	0	0	5	0	0	2
TOTAL	0	4	19	0	2	8	0	0	3

DISCUSSION

In our study mean age in case group and mean age in control group was 60±12 and 58±14 respectively and hence the two groups were considered age matched. There were significant No. of patients in the age Group of 50-70 Years and hence we conclude that age itself is a independent risk factor for AMI.

In our study patients in cases and control group were sex matched.

In our study percentage of patients with STEMI was significantly higher than that of NSTEMI i.e. 80% vs 20% respectively.

In our study incidence of MI was highest in the anterior myocardial wall.

According to a study by *Myung Hwan Bae, MD et al* [11] also the incidence of anterior wall is 52%. Our findings correlate with this study.

In our study majority of patients with AMI were in Killip's class I.

According to study by *MY Nadkar et al* [10] also majority of cases of AMI are in Killip's class I (45%). Hence our findings correlate with their study.

In our study mean uric acid levels in the cases on day 0 was 7.03±1.54 and in the controls was 5.77±1.15. Average uric acid levels were higher in the case group as compared to the control group. This difference seen was also statistically very significant ($p<0.01$)

According to *MY Nadkar et al* [10] study the mean uric acid levels in case and control group is 5.23±1.95 and 3.78±0.74 respectively .Our findings correlate with this study.

In our study 86% patients of STEMI were actively thrombolysed and the remaining 14% could not be thrombolysed and hence were managed with heparin alone. Overall, following the course of treatment, 73% patients of AMI were discharged and 23 % patients expired.

In our study there is a significant association seen between Killip's class and mortality in STEMI and NSTEMI (i. e. $p<0.05$). Higher the Killip's class of AMI greater is the mortality.

According to the study by Sunao Kojima, MD et al [8] there is a close relation between serum UA concentration and Killip's classification in patients who died. All of them have high UA concentrations and high Killip's class. Our findings correlate with their study

We observed here that there was rising trend of UA levels as the Killip's class increased in AMI as compared to controls in males, females and all the age groups.

According to study by M Y Nadkar et al, [10] there is direct correlation between Killip's class and uric acid that is as Killip's class increase the level of uric acid increase. Our study was in conjunction with their study.

In our study the association of deaths in AMI with UA levels and day of death of the patients was studied. This difference seen was statistically very significant.

Hence we conclude that there is a higher mortality and early mortality as uric acid levels increases at day0, day3 and day7 in STEMI as well as NSTEMI groups($p<0.01$).

We also found that, admission UA levels above 6.5 are associated with highest mortality before day 3.

UA on day 3 was also significantly associated with higher mortality ($p<0.05$)

UA was estimated on day 7 hence UA on day 7 was significantly associated with mortality. ($p<0.05$)

Comparing stats of UA on day 0, 3 and 7 we noticed that UA levels on day 0 were more significantly associated with mortality as compared to those seen on day 3 and 7.

Hence UA level on day 0 alone can be used to predict the prognosis of AMI rather than repeating the test on day 3 and day 7 for economic benefit.

According to study by MY NADKAR et al t[10] here is a statistically significant higher level of serum uric acid concentration in patients of MI on day of admission as compared to controls.

According to the study by Myung Hwan Bae, MD et al [11] Serum UA is an independent and incremental short term prognostic marker in patients of AMI along with anti pro BNP.

According to a study by Siniša Car1 et al [12]- Higher serum uric acid determined on admission is associated with higher in-hospital mortality and poorer long-term survival after AMI.

In our study correlation between levels of uric acid on day0, day 3 and 7 along with Killip's class and the mortality of AMI was studied. Uric acid levels were grouped in 3 groups of <6.5, 6.5-8.5, >8.5. So we conclude that serum uric acid levels were higher in patients with AMI with higher Killip's class.

Higher mortality was also observed in patients with high UA and higher Killip's class. Therefore combination of Killip's class and UA level after AMI is a predictor of mortality.

According to study by *MY NADKAR et al* [10] here is a statistically significant higher level of serum uric acid concentration in patients of MI on day of admission as compared to controls. On all the days serum uric acid levels are higher in patients who are in higher Killip's class. All the five patients who died after 3 days of hospital stay have serum uric acid level more than 7.0 mg/dl and all of them are in Killip's class IV. Our study correlates with them

According to the study by *Sunao Kojima, MD et al* [8] -There is a close relation between serum UA concentration and Killip's classification. Patients who developed short-term adverse events had high UA concentrations. Serum UA levels, Killip's class, age, and peak creatine phosphokinase level is significant predictors of long-term mortality. Serum UA level is a suitable marker for predicting AMI related future adverse events, and the combination of Killip's class and serum UA level after AMI is a good predictor of mortality in patients who have AMI. Results shows that serum UA concentrations are significantly correlated with male gender, body mass index, Killip's class, serum creatinine, previous myocardial infarction, and hypertension $r = 0.3659$, $p <0.0001$. Our study correlates with them

According to the study by Myung Hwan Bae, MD et al.[11] The study included 850 patients with AMI who were enrolled in the Korea AMI Registry from a single center. A major adverse cardiovascular event (MACE) is defined as a composite of death, recurrent myocardial infarction, and

revascularization. During 6-month follow-up, MACE developed in 109 (12.8%). UA is higher in patients with MACE than in those without MACE (6.5±2.4 mg/dl vs. 5.4±1.8 mg/dl, P<0.001). Serum UA is an independent and incremental short term prognostic marker in patients AMI along with anti pro BNP. Our study correlates with them

According to a study by Siniša Car1 and et al [12] A total of 621 patients (age 27-90 years, 64.7% men, 77.5% AMI with ST elevation, SUA 63-993 μmol/L) are included. Higher SUA on admission is independently associated with higher in-hospital mortality (RR, 1.016; 95% confidence interval [CI], 1.001-1.031, *P* = 0.043) and higher thirty-day mortality (RR, 1.016; 95% CI, 1.003-1.029, *P* = 0.018). Higher serum uric acid determined on admission is associated with higher in-hospital mortality and poorer long-term survival after AMI. Our study correlates with them.

In our study Uric acid on day 3 and day 7 showed maximum range of 5-5.9 mg% in 31 % of cases each.

According to study by MY Nadkar et al[10] serum uric acid levels are comparable on Day 0, 3 and 7 in MI group, 5.23±1.95, 5.20±2.15 and 5.28±2.52 respectively. Our study correlates with them.

CONCLUSIONS

- Serum uric acid is significantly elevated in patients with acute myocardial infarction.
- Serum uric Acid (>6.5mg %) was associated with high mortality irrespective of day of estimation of UA.
- Serum uric acid is significantly elevated in patients with Killip's class III and IV.
- Higher uric acid level (>8.5mg%) on day 0 was associated with highest mortality (18/23 deaths) in our study.
- High uric acid (>6.5mg%) along with higher Killip's class(III,IV) was associated with higher mortality(23/23 deaths).
- Hence uric acid can be used as a short term prognostic marker for cases of acute myocardial infarction.

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