Print ISSN: 2321-6379
Online ISSN: 2321-595X
DOI: 10.17354/ijss/2016/480

Original Article

Serum Uric Acid Level as an Independent Mortality Marker in Patients with Acute Myocardial Infarction

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Abstract

Background: Hyperuricemia has been defined in patients who have congestive heart failure. Serum uric acid levels were noted in patients with acute MI and correlation with Killip's classification was studied and at the same time it was decided whether it affects mortality in such patients.

Objective: To study the relationship between serum uric acid level and mortality following acute myocardial infarction.

Materials and Methods: A total of 50 patients who were admitted and fulfilled the inclusion/exclusion criteria were evaluated by history, physical examination, electrocardiogram echocardiography, and serum uric acid levels.

Result: Out of 50 patients, 23 were females and 27 were males. 70% patients had ST-elevated myocardial infarction (STEMI), while 30% patients were of non-STEMI. In control group, 22 were females and 28 were males. The mean age of patients was 60.06 years with age ranging from 45 to 80 years. The mean age of the control group was 58.62 years with age ranging from 47 to 80 years. Standard deviation of test group was 7.70 while of control was 7.66, so test and controls were matching for age.

Conclusion: Serum uric acid levels are higher in patients of acute myocardial infarction as compared to normal healthy persons. Patients of higher Killip's class have higher uric acid levels. Patients who had myocardial infarction in past have higher serum uric acid and are in higher Killip's class.

Key words: Acute coronary syndromes, Cardiac failure, Killip's classification, Myocardial infarction, Serum uric acid

INTRODUCTION

Acute coronary syndrome is composed of patients with,

1. Acute myocardial infarction with ST-segment elevation on their presenting electrocardiogram (ECG)
2. NSTEMI
3. Unstable angina.

ST segment elevation myocardial infarctions have been diagnosed on the basic of triad of:

1. Chest pain
2. Electrocardiographic changes
3. Elevated plasma enzyme activity.

Although acute myocardial infarction can occur without chest pain (20-25%) chest pain remains.

The most common symptom:

1. Chest pain

   Pain is the most common presenting complaint in patients with ST-segment elevation myocardial infarction. Pain is deep and visceral, adjectives commonly used to describe it are heavy, squeezing and crushing although occasionally described as stabbing and burning.
2. Electrocardiographic changes

   ECG is sensitive for detecting myocardial ischemia and infarction ECG criteria for diagnosis of ST

Access this article online

www.ijss-sn.com

Month of Submission : 07-2016
Month of Peer Review : 08-2016
Month of Acceptance : 09-2016
Month of Publishing : 09-2016

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segment myocardial infarction outlined in MILIS study are presence of any one of the following section.

i. New or presumably new Q waves (at least 30 m wide and 0.20 my deep) in at least
   a. II, III or Avf
   b. Leads vl through v6 or
   c. Leads I and Avl

ii. New or presumably new ST-T segment elevation or depression (>0.01 mv measured 0.02s after J point in two contagious leads of previously motioned lead combination or

iii. Complete left bundle branch block in appropriate clinical setting.

iv. The ECG diagnosis of right ventricular (RV) infarction offers special challenges, RV infarction occurs in the presence of inferior left ventricular infarction, and the resulting ST elevation is usually overwhelmed in the conventional precordial leads overlying the right ventricle (v2,v3) by the ST elevation in the opposing LV myocardium on the inferior surface. ST elevation must be sought in the right chest leads v1 and v3R through v6R, when found it provides reasonably strong evidence for the presence of RV infarction.
   d. Posterior wall MI is indicated by ST-segment elevation in posterior leads v7-9.

3. Serum cardiac biomarkers:

Certain proteins called serum cardiac markers (CPK-MB/ Troponin-T and I) are released into the blood in large quantities from necrotic heart muscle agree myocardial infarction.[1]

Creatinine phosphokinase (CPK) rises within 4 to 8 h and returns to normal by 48-72 h. An important drawback of CPK measurement is a lack of specificity for ST-elevated myocardial infarction (STEMI) as it may be elevated in skeletal muscle trauma. It's MB enzyme is more specific. A ratio of creatine kinase-MB mass CK activity >2.5 suggests but is not diagnostic of myocardial rather than a skeletal muscle source for the CKMB elevation.

Cardiac-specific Troponin T and I have amino acid sequence different from those of skeletal muscle forms of their proteins. Myoglobin is one of the first serum cardiac markers that rise above normal range after MI, it lacks cardiac specificity and is rapidly excreted in urine. Unstable Angina is defined as angina pectoris or equivalent Ischemic discomfort with at least one of three features:

1. It occurs at rest (or with minimal exertion) usually lasting >10 min
2. It is severe and of new onset (i.e., within prior 4 to 6 weeks), and/or
3. It occurs with a crescendo pattern.

NSTEMI; diagnosis of NSTEM is established if a patient with clinical features of unstable angina develops evidence of myocardial necrosis as reflected in elevated cardiac biomarkers as described above.

The Killip's classification; Killip classified[2] patients with acute MI into 4 classes depending on the clinical manifestations of cardiac failure.

It is as follows:

Class 1: No signs of pulmonary or venous congestion

Class 2: Moderate heart failure as evidenced by rales at lung bases, s3 gallap, tachypnea or signs of failure of right side of heart including venous and hepatic congestion

Class 3: Severe heart failure, pulmonary edema

Class 4: Shock with systolic pressure <90 mmHg and evidence of peripheral venous constriction, peripheral cyanosis, mental confusion, and oliguria.

Serum Uric Acid

It reflects circulating xanthine oxidase activity and oxidative stress production. Hyperuricemia has been defined in patients who have congestive heart failure. Serum uric acid levels were noted in patients with acute MI and correlation with Killip's classification was studied, and at the same time, it was decided whether it affects mortality in such patients.[3-15]

Aims and Objectives

1. To note the Killip's classification of patients with acute myocardial infarction
2. To note the level of serum uric acid in patients of acute myocardial infarction
3. To correlate serum uric acid level with age, sex, body, mass index, diabetes mellitus, hypertension, past history of Ischemic heart disease, serum triglycerides
4. To correlate serum uric acid level with the Killip's classification
5. To note any relationship between serum uric acid level and mortality following acute myocardial infarction
6. To compare serum uric acid levels of patients with age and sex-matched healthy controls.

MATERIALS AND METHODS

About 50 patients of acute MI who fulfill inclusion/ exclusion criteria presented in 24 h onset of symptoms were studied. A detailed history and examination were carried out. All patients underwent routine investigations including hemoglobin, complete blood count, renal and liver function test, ECG, serum uric acid, serum triglycerides.

Patients were started on the treatment as per the attending physician. Patients were followed up till hospital stay.

About 50 age/sex matched normal healthy adults were also evaluated. People who had come for health check-up in OPD were studied for the same purpose.

Inclusion Criteria

Any adult (>18 years) patients who were diagnosed as a case of acute MI (NSTEMI, STEMI) on the basis of clinical history, examination, biochemical markers, and admitted to emergency medical services/intensive care unit/medical wards of a tertiary care teaching hospital.

Exclusion Criteria

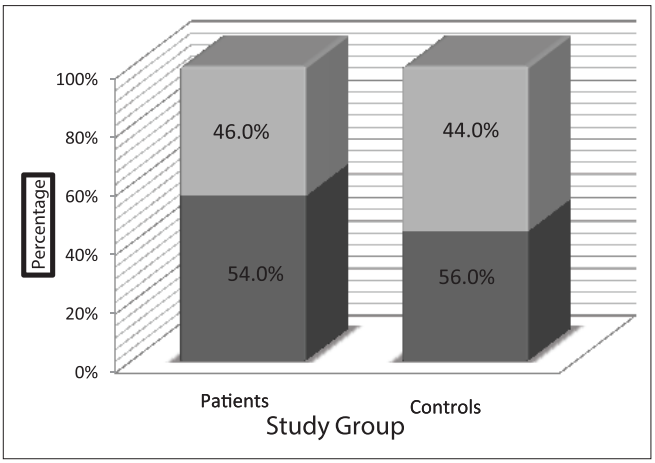
a. Age <18 years
b. Any patients who are a known case of:
   i. Chronic renal failure/end stage renal disease
   ii. Hyperuricemia/gout
   iii. Hematological malignancy
   iv. Hypothyroidism
   v. Hyperparathyroidism
   vi. Down's syndrome
   vii. Barters syndrome
   viii. Polycystic kidney disease
   ix. Toxemia of pregnancy
   x. Lead intoxication
   xi. Sarcoidosis
   xii. Berylliosis
   xiii. Pagets disease
   xiv. Patients in diabetic ketoacidosis
   xv. H/O recent muscle injury/trauma
c. Patients on drugs which increase serum uric acid
   i. Salicylates (>2 g/day)
   ii. Nicotinic acid
   iii. Diuretics
   iv. Ethambutol
   v. Alcohol
   vi. Pyrazinamide
   vii. Levodopa
   viii. Cyclosporine

From Table 1, it can be said that there is no significant difference as far as the sex ratio between the two groups is concerned.

Graph 1 shows that there was no significant difference in the sex ratio between the two study groups.

From Table 2, it can be said that there is no significant difference as far as the smoking status between the two groups.

From Table 3, it can be said that there is no significant difference in the diabetes status between the two groups.



Graph 1: Distribution of study group as per sex

Table 1: Association among study group between sex

St Group	Sex		Total
	Male	Female	
Patients			
Count (%)	27 (54.0)	23 (46.0)	50 (100.0)
Controls			
Count (%)	28 (56.0)	22 (44.0)	50 (100.0)
Total			
Count (%)	55 (55.0)	45 (45.0)	100 (100.0)

Chi-square test	Value	DF	*P*	Association is
Pearson Chi-square	0.040	1	0.841	Not significant
Fisher's exact test			1.000	Not significant

Table 2: Association among study group between, St. Group*smoking

St Group	Smoking		Total
	Yes	No	
Patients			
Count (%)	27 (54.0)	23 (46.0)	50 (100.0)
Controls			
Count (%)	23 (46.0)	27 (54.0)	50 (100.0)
Total			
Count (%)	55 (50.0)	45 (50.0)	100 (100.0)

Chi-square test	Value	DF	*P*	Association is
Pearson Chi-square	0.640	1	0.424	Not significant
Fisher's exact test			0.549	Not significant

Graph 2 shows the ratio of diabetics and non-diabetics in both the study groups.

From Table 4, it can be said that there is no significant difference in hypertension between the two groups.

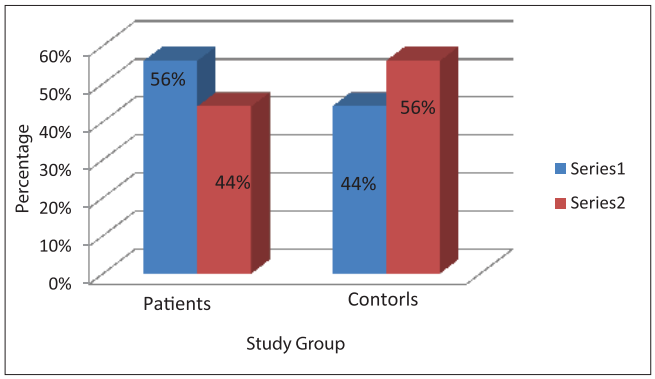
Graph 3 shows the ratio of hypertensive and non-hypertensive in both the study groups.

In Table 5 as $P = 0.214$, it can be said that there is no significant difference in both the groups far as age is concerned.

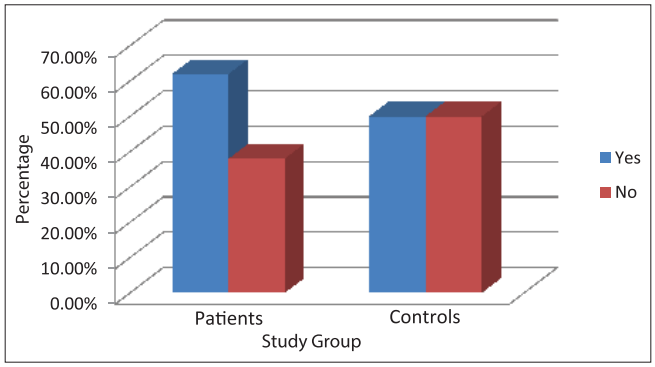
Hence, according to Table 6 and Mann-Whitney test, it can be said that there is a significant difference in uric acid levels between patients group. Thus, the patients with acute myocardial infarction have higher uric acid levels when compared with controls.

From the above Graph 4, it can be said that the serum uric acid levels in patients were higher (4.9) when compared to that of the controls (3.7).

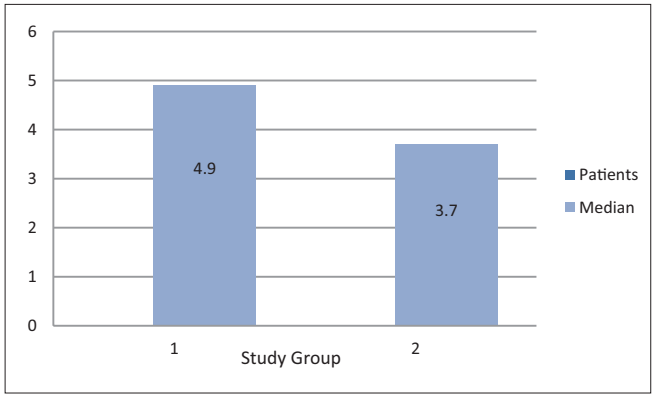
From Table 7, it can be said that there is no significant difference in uric acid levels in patients when compared on the basis of sex.



Graph 2: Comparison of DM among study groups



Graph 3: Comparison of DM among study



Graph 4: Comparison of Uric acid among study groups

From Table 8, it can be said that there is no significant difference in uric acid levels in patients when compared on the basis of sex.

Graph 5 shows serum uric acid level in both the study groups for both the sexes. It can be seen that there is no

Table 3: Association among study group between, St. Group*DM

St Group	DM		Total
	Yes	No	
Patients			
Count (%)	28 (56.0)	22 (44.0)	50 (100.0)
Controls			
Count (%)	22 (44.0)	28 (56.0)	50 (100.0)
Total			
Count (%)	50 (50.0)	50 (50.0)	100 (100.0)

Chi-square test	Value	DF	*P*	Association is
Pearson Chi-square	1.440	1	0.230	Not significant
Fisher's exact test			0.317	Not significant

Table 4: Association among study group between, St. Group*HTN

St Group	HTN		Total
	Yes	No	
Patients			
Count (%)	31 (62.0)	19 (38.0)	50 (100.0)
Controls			
Count (%)	25 (50.0)	25 (50.0)	50 (100.0)
Total			
Count (%)	56 (56.0)	44 (44.0)	100 (100.0)

Chi-square test	Value	DF	*P*	Association is
Pearson Chi-square	1.461	1	0.227	Not significant
Fisher's exact test			0.314	Not significant

Table 5: Comparison among study group for age

Age	*n*	Mean±SD	Median	IQR	Mann-Whitney Test	*P*
Patients	50	60.06±7.70	59.00	9.00	1.243	0.214
Controls	50	58.62±7.66	58.00	10.00	Difference is not significant	

Table 6: Comparison among study group for, uric acid

Uric acid	*n*	Mean±SD	Median	IQR	Mann-Whitney Test	*P*
Patients	50	5.25±1.17	4.90	0.90	7.846	4.31E-15
Controls	50	3.72±0.60	3.70	0.80	Difference is not significant	

Table 7: Comparison of uric acid level among patient group

Uric acid	*n*	Mean±SD	Median	IQR	Mann-Whitney test	*P*
Male	27	5.3±1.5	5.0	0.8	0.108	0.914
Female	23	5.2±0.6	4.9	0.9	Difference is not significant	

significant difference in both the groups as far as sex is concerned although the average is higher in the patient group.

Thus, Table 9 shows that there is no significant correlation between serum uric acid levels and age group, total cholesterol, total triglycerides, and body mass index in the patient group.

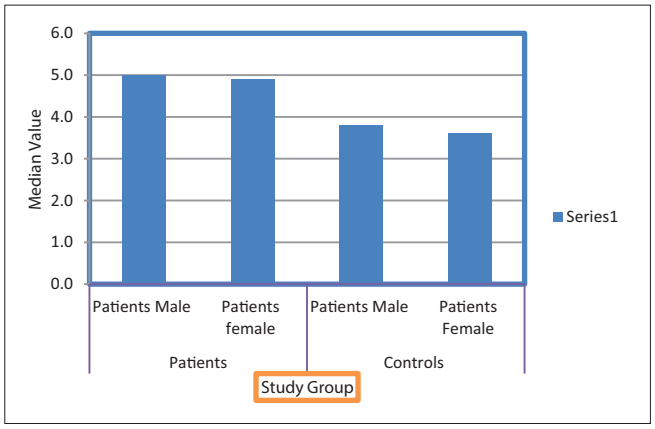
Thus, Table 10 shows that there is no significant correlation between serum uric acid levels and age group, total cholesterol, total triglycerides, and body mass index in the patient group.

Thus, Table 11 shows that there is no significant correlation between serum uric acid levels and the status of diabetes mellitus status.

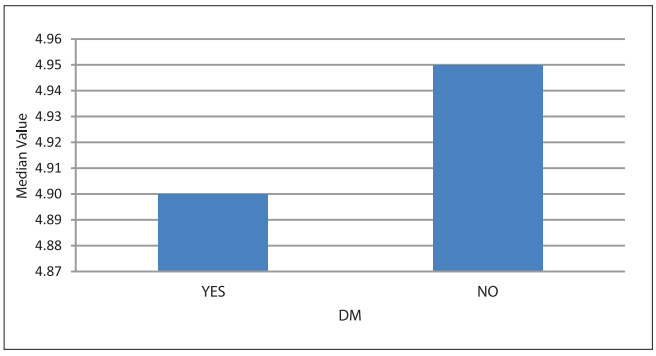
Graph 6 compares the serum uric acid levels among diabetics and non-diabetics,

Thus, Table 12 shows that there is no significant correlation between serum uric acid levels and the status of hypertension in the patient group.

Graph 7 compares the serum uric acid levels among hypertensive and hypertensives,



Graph 5: Comparison of uric acid among study groups



Graph 6: Comparison of uric acid among diabetic groups

Thus, Table 13 shows that there is a significant correlation between serum uric acid levels and past history of ischemic heart disease in the patients.

From the Graph 8, it can be seen that the serum uric acid levels in patients with past history of ischemic heart disease were significantly higher when compared to those with no history of ischemic heart disease.

Thus, Table 14 shows that as the Killip's class goes on increasing it has a significant correlation with the serum uric acid levels of the patients.

Graph 9 shows that as the Killip's class goes on increasing so does the serum uric acid levels, there being a significant correlation between the two.

Table 8: Comparison of uric acid level among control group

Uric acid	*n*	Mean±SD	Median	IQR	Mann-Whitney Test	*P*
Male	28	3.8±0.6	3.8	0.7	0.676	0.499
Female	22	3.7±0.6	3.6	0.8	Difference is not significant	

Table 9: Correlation between uric acid level and various study parameters among patient group

Variable	*n*	Mean±SD	Pearson correlation	*P*	Correlation is
Uric acid	50	5.252±1.1664			
Age	50	60.06±7.699	−0.067	0.664	Not significant
CHOL	50	225.78±35.438	−0.012	0.935	Not significant
TG	50	153.94±32.639	0.041	0.780	Not significant
BMI	50	26.688±1.9637	−0.017	0.906	Not significant

BMI: Body, mass index

Table 10: Correlation between uric acid level and various study parameters among patient control group

Variable	*n*	Mean±SD	Pearson correlation	*P*	Correlation is
Uric acid	50	3.722±0.6028	−0.051	0.724	Not significant
Age	50	58.62±7.664	−0.152	0.292	Not significant
CHOL	50	235.40±28.338	−0.231	0.106	Not significant
TG	50	138.38±34.467	−0.110	0.447	Not significant
BMI	50	25.126±3.0139			

Table 11: Comparison of uric acid level among patients with St Group=Patients

DM	*n*	Mean±SD	Median	IQR	Mann-Whitney test	*P*
Yes	28	5.35±1.46	4.90	0.90	307	0.992
No	22	5.13±0.64	4.95	0.80	Difference is not significant	

Thus, Table 15 shows that is a significant correlation between serum uric acid levels in patients who survived and those who died.

From Graph 10, it can be seen that the serum uric acid levels were higher in patients when compared to those who survived.

DISCUSSION

The previous study has shown that serum uric acid increases in cardiac failure. Killip's classification denotes severity of cardiac failure in myocardial infarction. In a study done in Japan in 2005 by Kojima *et al.*,[16] it was shown that serum uric acid levels correlate with Killip's classification. Combination of Killip's class and serum uric acid levels after acute myocardial infarction is a good predictor of mortality in patients who have acute myocardial infarction. Using this study as referral study, we tried to study the correlation between serum uric acid and Killip's class and their prognostic value in our patients.

This study was conducted in 50 patients of myocardial infarction, who presented to the hospital within 24 h of the onset symptoms; 50 normal healthy controls of age and sex matching were also evaluated.

Table 12: Comparison of uric acid level among patients with, HTN

HTN	*n*	Mean±SD	Median	IQR	Mann-Whitney test	*P*
Yes	31	5.30±1.40	4.90	0.80	269	0.616
No	19	5.17±0.64	4.90	0.90	Difference is not significant	

Table 13: Comparison of uric acid level among patients with, IHD

IHD	*n*	Mean±SD	Median	IQR	Mann-Whitney test	*P*
Yes	12	6.15±1.93	5.75	1.05	92.5	0.002
No	38	4.97±0.39	4.90	0.50	Difference is significant	

Table 14: Kruskal Walls one way analysis

K-class	*n*	Mean±SD	Median	IQR	Kruskal-Walls one way analysis	
1.00	20	4.78±0.52	4.80	0.60	Chi-square	*P*
2.00	15	5.01±0.32	4.90	0.50	17.28	<0.001
3.00	9	5.73±0.73	5.70	0.60	Difference is	
4.00	6	6.72±2.66	5.85	1.00	significant	

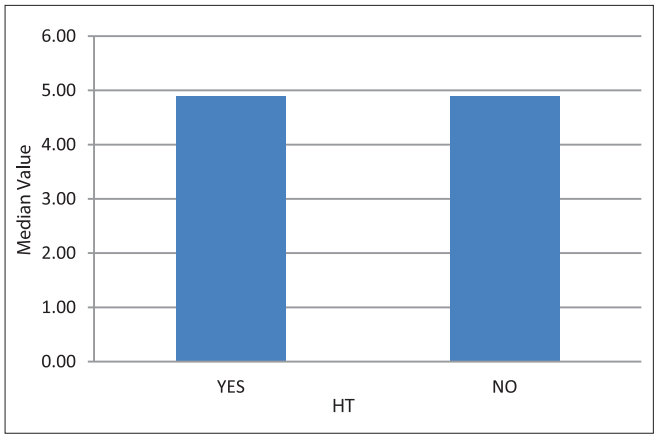
Table 15: Outcome

Outcome	*n*	Mean±SD	Median	IQR	Mann-Whitney test	*P*
Death	3	8.17±3.33	6.50	6.00	3.5	0.006
Survive	47	5.07±0.61	4.90	0.80	Difference is significant	

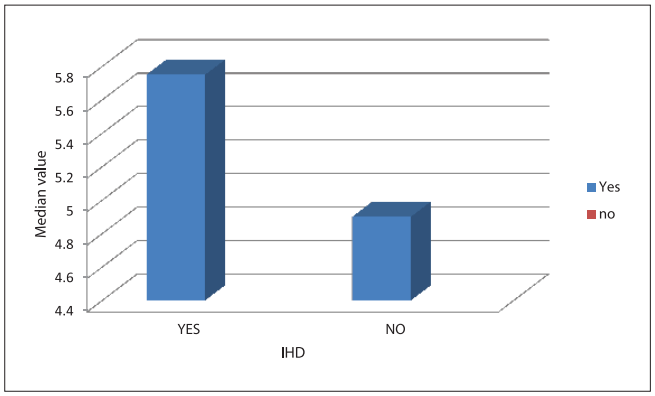
About 70% patients had STEMI, while 30% patients were of NSTEMI.

Blood samples for measurements of serum uric acid and other biochemical assessments were obtained immediately after admission. In controls, all the biochemical tests were done as a part of the health check-up plan.[17-23]

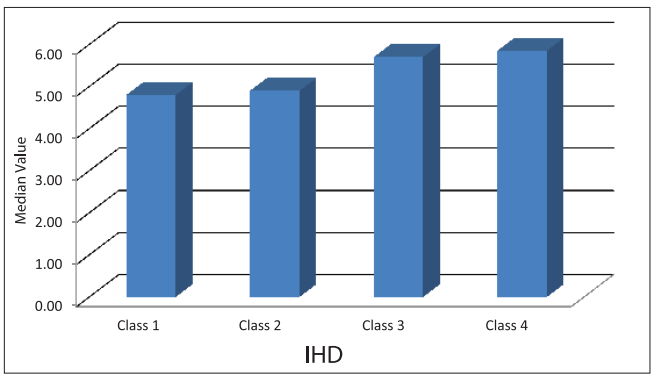
Uric acid concentration was expressed as mg per deciliter; uric acid was treated as a continuous variable and as a categorical variable and variables were divided into quartiles according to serum uric acid concentrations. The mean age



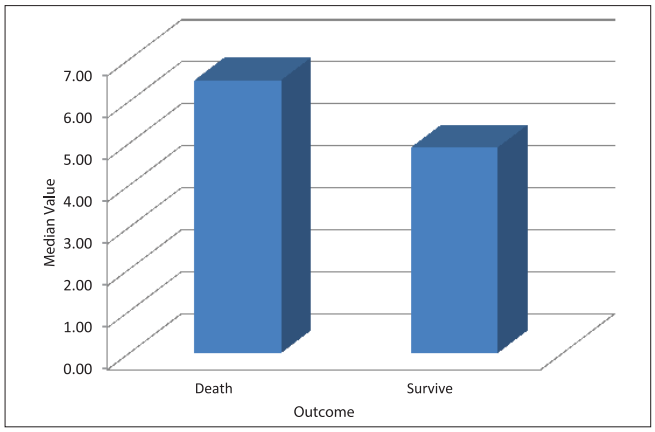
Graph 7: Comparison of uric among HT groups



Graph 8: Comparison of uric acid among IHD groups



Graph 9: Comparison of uric acid among K class



Graph 10: Comparison of uric acid among patients who died and those survived

of control group was 58.62 years with age ranging from 47 to 80 years.

Standard deviation of test group was 7.70 while of control was 7.66, so test and controls were matching for age.

Out of 50 patients, 23 were females and 27 were males. In control group, 22 were females and 28 were males.

A categorical variable and continuous variable.

Mean age of patients was 60.06 years with age ranging from 45-80 years.

Quantitative data is presented with the help of Mean, SD, Median and IQR. Comparison among study groups is done with the help of Mann-Whitney test and Kruskal-Wallis one-way analysis as per result of normality test.

Quantitative data are presented with the help of frequency and percentage table, the association among study groups is assessed with the help of Chi-square test.

$P < 0.05$ is taken as significant level.

Thus, the patients had higher serum uric acid levels probably because of acute myocardial infarction.

In referral study,[16] there were no controls. 1124 patients who presented with acute myocardial infarction within 48 hrs of onset of symptoms were evaluated and serum uric acid level at the time of admission was measured and correlated with Killip's class and other laboratory parameters.

$P = 0.644$ for correlation between serum uric acid and age. Hence, serum uric acid levels were not significantly associated with age of patients. In control group also there is no correlation between serum uric acid level and age. In study population, there may not be a correlation between serum uric acid level and age for which further study needs to be done. This finding is different from study done by Conen *et al.* in 2004, Switzerland which showed serum uric acid levels were significantly associated but to a lesser degree with age.

There is no significant correlation between serum uric acid level n days of admission with sex of patients. Similarly, in control group also serum uric acid levels are not correlated with sex. While in referral study males had higher uric acid levels as compared to females.[24,25]

There was no significant correlation ($P = 0.616$) between serum uric acid level and hypertension in patients. This is different from other studies[16,23] which show that hypertensive patients had hyperuricemia.

A total of 28 patients were known diabetics in the present study. $P = 0.992$ for correlation between serum uric acid levels and diabetes (not significant). Hence, diabetic status was not significantly associated with serum uric acid levels. This finding is consistent with the study by Jakko *et al.* in which there was no significant association between serum uric acid levels and diabetic status. This finding is in contrast with other by Safi *et al.* which showed that Hyperuricemia is significantly associated with type 2 DM.

About 12 patients were known cases of ischemic heart disease p value was <0.005 for correlation between serum uric acid levels and past history of ischemic heart disease. Hence, there is a significant correlation between serum uric acid level on the day of admission and history of ischemic heart disease. This finding is in confirmation with referral study.[27]

There is no significant correlation ($P = 0.447$) between serum uric acid level on day of admission and body mass index. This finding is different from the previous studies[27] which showed that serum uric acid levels were significantly associated with components of metabolic syndrome, particularly obesity.

Total 3 patients expired. These patients are evaluated separately due to statistical reasons.

There is a correlation between serum uric acid level and Killip's class on day of admission. This finding is consistent with referral study.[27] Killip's classification is an indicator of severity of heart failure. The previous studies have shown that serum uric acid level increases in hear failure. So in this study serum, uric acid levels are indirectly correlated with severity of cardiac failure.

Thus there was a statistically significant correlation found between serum uric acid level and Killip's class. Patients

of Killip's class 3 and 4 had higher levels of uric acid as compared to patients of Class 1 and 2. This finding is consistent with referral study.[27]

Referral study had shown that there is a graded relation between serum uric acid concentration and creatinine concentrations in patients of acute myocardial infarction. In this study, there was no significant correlation between serum uric acid levels and creatinine concentration.

There is no significant correlation (R^2 linear=0.001) between serum triglyceride level and serum uric acid concentration after acute myocardial infarction. This finding is inconsistent with Y Li *et al*. and one other study which showed serum uric acid levels were strongly associated with serum triglyceride levels.

Out of 50 patients 3 expired. They were in Killip's class 4 at the time of admission. Hence, higher Killip's class predicts poor prognosis. This result is similar to referral study. these patients had serum uric acid levels on the higher side. Therefore, it shows that serum uric acid is significantly correlated with Killip's class. However because of small number of patients statistical analysis could not be performed.

Thus overall from this study, it is concluded that combination of Killip's class and serum uric acid concentration is a good predictor of mortality in patients of acute myocardial infarction.

CONCLUSION

1. Serum uric acid levels are higher in patients of acute myocardial infarction as compared to normal healthy persons.
2. Serum uric acid levels are correlated with Killip's classification. Patients of higher Killip's class have higher uric acid levels.
3. Serum uric acid levels and Killip's class are influenced significantly by previous myocardial infarction. Patients who had myocardial infarction in past have higher serum uric acid and are in higher Killip's class.
4. Serum uric acid and Killip's class independently and significantly predicted poor prognosis after acute myocardial infarction.
5. Combination of Killip's class and serum uric acid levels after myocardial infarction is a good predictor of mortality.
6. There is no correlation between serum uric acid level after acute myocardial infarction and age, sex, diabetic status, hypertension, body mass index, and serum triglyceride level.

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How to cite this article: Shetty V, Jain HR, Singh GS, Shetty S. Serum Uric Acid Level as an Independent Mortality Marker in Patients with Acute Myocardial Infarction. Int J Sci Stud 2016;4(6):27-35.

Source of Support: Nil, **Conflict of Interest:** None declared.