

**SERUM URIC ACID LEVEL IN ACUTE MYOCARDIAL INFARCTION- A POSSIBLE
IMPACT ON PROGNOSIS****¹Dr. Suresh Raghavan* and ²Dr. Rashmi K. P.**¹Professor of Medicine, Government TD Medical College, Alappuzha.²Assistant Professor, Department of Medicine, Government TD Medical College, Alappuzha.***Corresponding Author: Dr. Suresh Raghavan**

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ABSTRACT

Uric acid is the final break down product of the metabolism of the purine. Mean serum uric acid levels of adult males and females are 6.8 and 6.0 mg/dL respectively. Hyperuricemia is defined as serum uric acid levels more than 6.8mg/dL. The role of serum uric acid as an independent risk factor for coronary artery disease remains controversial. Cardiac tissue ischemia and hypoxia deplete adenosine tri phosphate (ATP) and results in the formation of uric acid. This uric acid undergoes rapid efflux into the vascular lumen due to the low intracellular pH. Xanthine oxidase activity and uric acid synthesis are increased in vivo under ischemic conditions. Therefore elevated uric acid may act as a marker of underlying tissue ischemia. Hyperuricemia is associated with deleterious effect on endothelial dysfunction, oxidative metabolism, platelet adhesion hemorrheology and aggregation. Despite these findings, little attention has been paid to the possible relationship between hyperuricemia and Coronary Artery Disease in our population. This study on 100 patients with Acute Myocardial Infarction was undertaken to clarify the apparent association between raised serum uric acid levels and coronary artery disease and the correlation with the Killip class and to find the relationship between uric acid level and mortality. The study concluded that serum uric acid may be a marker of cardiac ischemia and correlated well with the Killip class. Combination of Killip class and serum uric acid after Acute Myocardial Infarction was a good predictor of mortality and helped in predicting the prognosis. However the role of hyperuricemia as an independent risk factor in the development of Coronary Artery Disease could not be established.

KEY WORDS: Hyperuricemia, Uric Acid, Coronary Artery Disease, Acute Myocardial infarction.**MATERIALS AND METHODS**

The study was conducted on 100 patients admitted to the Government TD Medical College, Alappuzha, with the diagnosis of acute myocardial infarction during the year 2015-16 with the following objectives:

1. To study the association of serum uric acid level in patients with acute myocardial infarction.
2. To correlate the serum uric acid level with the Killip class.
3. To determine whether serum uric acid is a predictor of mortality following myocardial infarction.

It was an observational study carried out in the Departments of Medicine and Cardiology. 100 patients above 20 years of age of either sex who were diagnosed as myocardial infarction (ST segment elevation or Non – ST segment elevation), who presented within 24 hours of onset of symptoms were included. Fifty age and sex matched controls were recruited for baseline serum uric acid levels.

Individuals below 20 years of age, those who presented after 24 hours of symptom onset, those with a known condition producing hyperuricemia (chronic kidney disease, malignancies, hypothyroidism, alcoholics), those who were on drugs which increases the serum uric acid levels(salicylates, diuretics, pyrazinamide) were excluded from the study.

All participants went through baseline evaluation, including a detailed history, a review of old medical records, physical examination including the Body Mass Index. Cardiovascular system examination with special reference to Killip class was carried out. A Body Mass Index of > 25 was considered as overweight and a Blood Pressure > 140/ 90 mm Hg was considered hypertension.

Blood samples were taken for assessment of hemogram, random blood sugar, blood urea, serum creatinine, lipid profile, liver function test, serum electrolytes and cardiac biomarkers. Diabetes was defined as fasting blood sugar more than 126 mg/dL and/or patients already on oral

hypoglycemic agents or insulin. Dyslipidemia was defined as plasma triglyceride > 150 mg/L or patients already on lipid lowering drugs.

A standard 12 lead Electrocardiogram was recorded in all subjects for diagnosing acute myocardial infarction. Patients were divided into ST segment elevation myocardial infarction and Non ST segment elevation myocardial infarction according to the ECG and the cardiac biomarkers.

ST elevation myocardial infarction was defined based on ECG finding of 0.1mV elevation of ST segment in at least two contiguous leads or a new onset Left Bundle Branch Block. Non ST segment elevation myocardial infarction is defined as absence of ST segment elevation in ECG and elevation of cardiac enzymes.

Killip classification was done based on history and physical examination findings, on the day of admission, as well as on day 3 and 7.

Serum uric acid levels were estimated on days 0,3 and 7 of admission in mg/dL. Serum uric acid levels were measured in the 50 control population as well.

Patients were treated according to the existing guidelines. Mortality was defined as death within 7 days of hospitalization due to complications of myocardial infarction.

Data were analyzed using SPSS software. Appropriate statistical tests were applied for associations and comparisons. A two- tailed probability value of <0.05 was considered significant.

RESULTS

Of the 100 cases, 62 were males and 38 were females. 30 of the controls were males and 20 were females. Since the comparisons between the cases and controls were statistically insignificant [Chi square test ($p > 0.05$)], both the groups were matched.

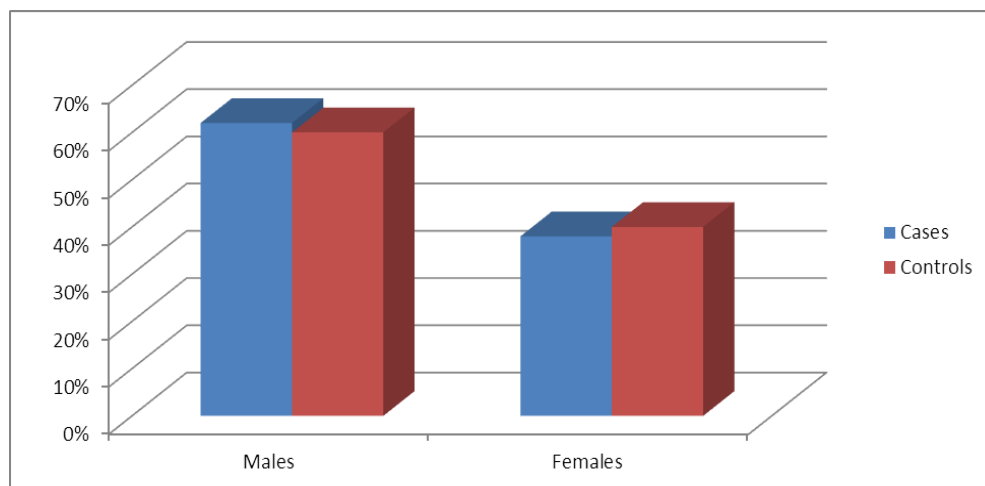


Figure 1: Distribution of gender among cases and controls

There was a comparable age distribution between the cases and controls. Maximum distribution was in the age group 60- 69 years [Chi square test (p value > 0.05)].

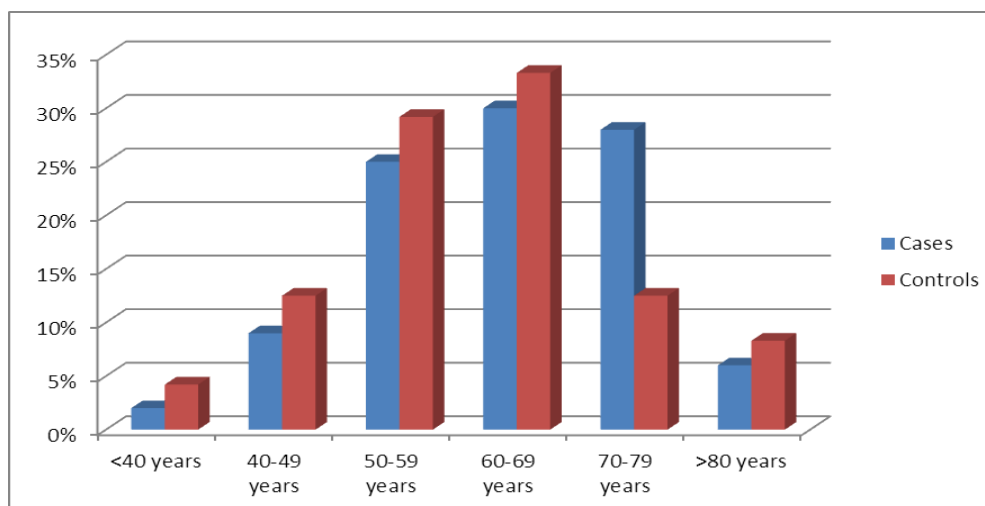


Figure 2: Distribution of age among cases and controls:

Among the cases, 67% were ST segment elevation myocardial infarction and 33% were Non ST segment elevation myocardial infarction.

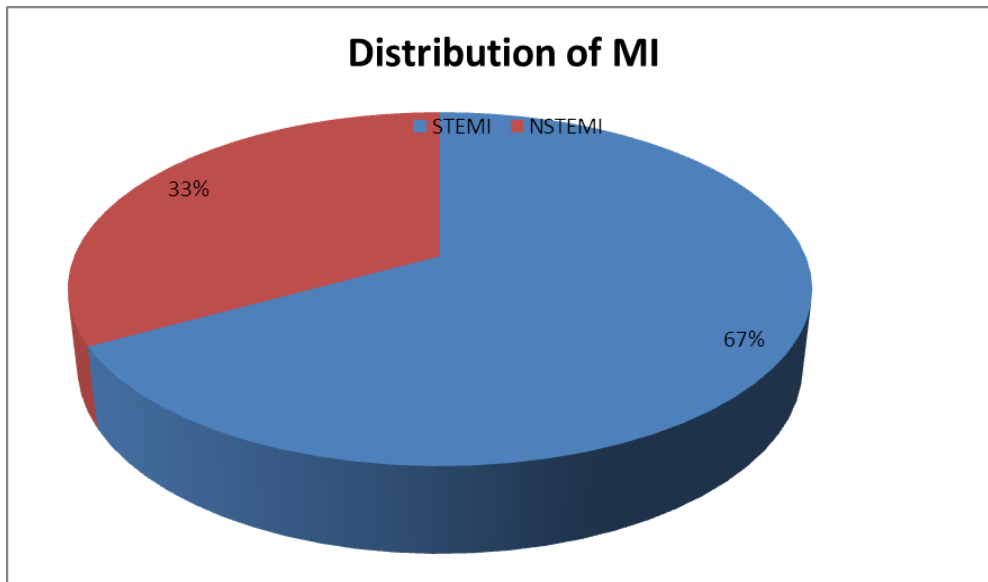


Figure 3: Distribution of Myocardial infarction among cases.

Cases were distributed in the higher serum uric acid level group than the controls on the day of admission. In 76% of cases serum uric acid level was > 4 mg/dL against 44 % of the controls and the difference was statistically significant [Chi square test p value < 0.001].

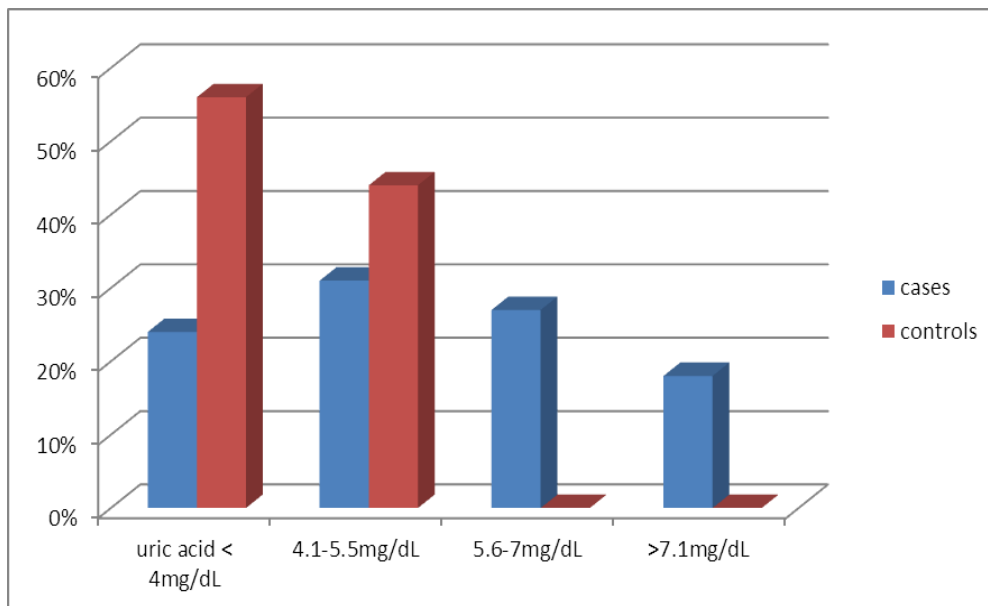


Figure 4: Distribution of cases and controls based on serum uric acid on day 0

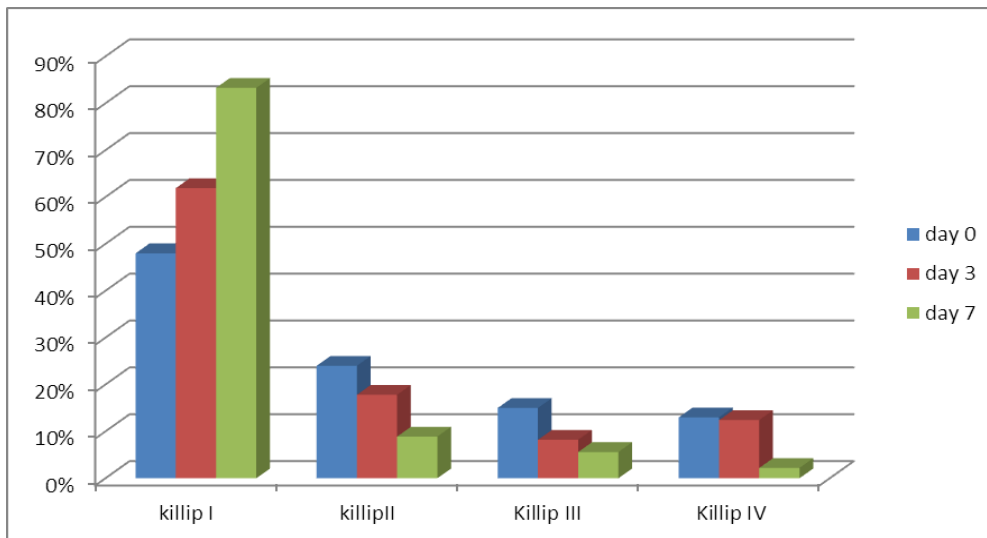


Figure 5: Distribution of Killip classification among cases of Myocardial infarction on Day 0, day3 and day7 of admission.

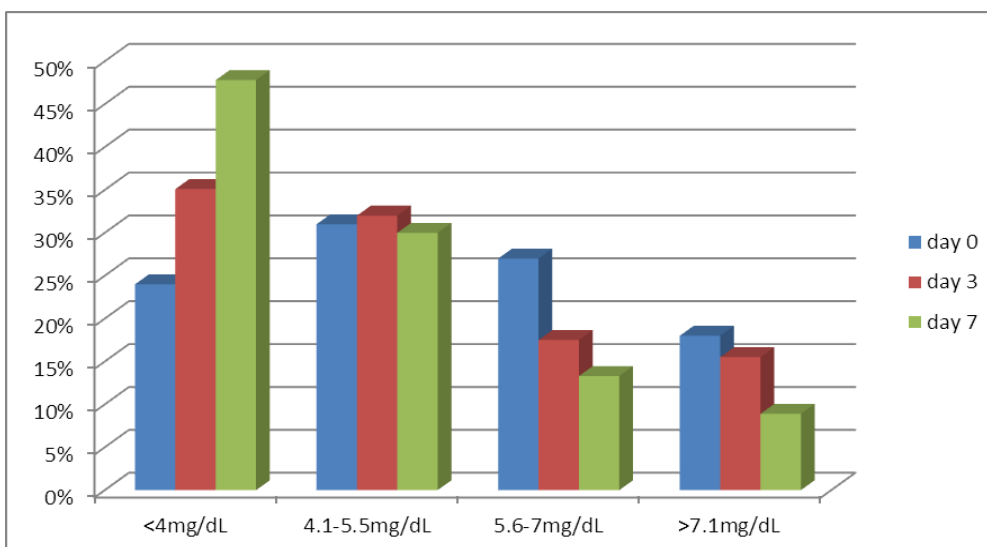


Figure 6: Distribution of serum uric acid among cases on Day0, Day 3 and Day 7 of admission

Out of 100 patients 90 % had survived and 10% died during the 7 day hospital stay.

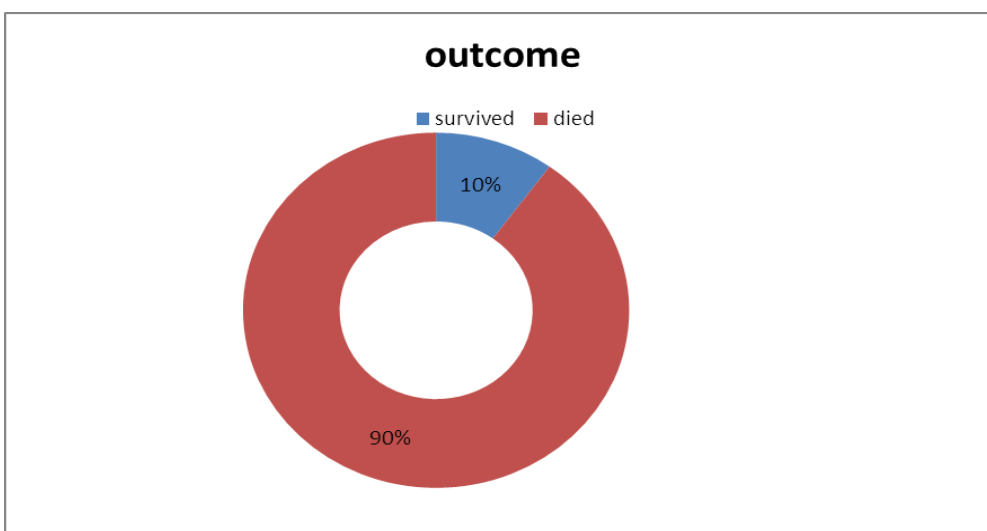


Figure 7: Outcome of the study population

Table 1: Association between Serum uric acid level and Diabetes Mellitus

Diabetes mellitus	Serum uric acid on Day 0 in mg/dL			
	<4	4.1-5.5	5.6-7	>7
Yes	12.5%	32.3%	59.3%	50.0%
No	87.5%	67.7%	40.7%	50%

Statistically significant relationship between serum uric acid level and diabetes was found in the study. [Chi square: 13.337, $p < 0.01$]

Table 2: Association between serum uric acid and Hypertension

Hypertension	Serum uric acid on Day 0 in mg/dL			
	<4	4.1-5.5	5.6-7	>7.1
Yes	33.3%	41.9%	70.4%	77.8%
No	66.7%	58.1%	29.6%	22.2%

There was significant relation between serum uric acid level and hypertension. [Chi square: 12.953, p value < 0.01 .]

Table 3: Association between serum uric acid and Dyslipidemia

Dyslipidemia	Serum uric acid on Day 0 in mg/dL			
	<4	4.1-5.5	5.6-7	>7.1
Yes	20.80%	45.20%	48.10%	66.70%
No	79.20%	54.80%	51.90%	33.30%

There was significant association between serum uric acid level and dyslipidemia. [Chi square: 9.186, p value < 0.05 .]

Table 4: Association between serum uric acid and Body Mass Index > 25(BMI)

BMI >25	Serum uric acid on Day 0 in mg/dL			
	<4	4.1-5.5	5.6-7	>7.1
Yes	4.2%	38.7%	14.8%	50%
No	95.8%	61.3%	85.2%	50%

There was statistically significant association between BMI of > 25 and serum uric acid level. [Chi square: 15.693, p value < 0.01 .]

Table 5: Association between type of myocardial infarction with serum uric acid

Type of MI	Serum uric acid on Day 0 in mg/dL			
	<4	4.1-5.5	5.6-7	>7.1
STEMI	37.5%	35.5%	33.3%	22.2%
NSTEMI	62.55	64.5%	66.7%	77.8%

There was no significant difference between the uric acid level among the types of myocardial infarction. [Chi square 1.253, p value > 0.05 .]

There was no statistically significant association between serum uric acid level and age or gender.

Table 6: Serum uric acid level and Killip class on Day 0

Killip class on Day 0	Serum uric acid on Day 0 in mg/dL			
	<4	4.1-5.5	5.6-7	>7.1
Class I	66.7%	67.7%	29.6%	16.7%
Class II	29.2%	22.6%	29.6%	11.1%
Class III	4.2%	6.5%	25.9%	27.85
Class IV	0%	3.2%	14.8%	44.4%

There was statistically significant association between higher serum uric acid level and higher Killip class on day 0. [Chi square: 38.388, p value < 0.001 .]

Table 7: Serum uric acid level and Killip class on Day 3

Killip class on Day 3	Serum uric acid on Day 3 in mg/dL			
	<4	4.1-5.5	5.6-7	>7.1
Class I	88.2%	77.4%	29.4%	6.7%
Class II	8.8%	16.1%	35.3%	20%
Class III	2.9%	3.2%	17.6%	20%
Class IV	0%	3.2%	17.6%	53.3%

There was statistically significant association between higher serum uric acid level and higher Killip class on day 3. [Chi square: 53.407, p value < 0.001.]

Table 8: Serum uric acid level and Killip class on Day 7

Killip class on Day 7	Serum uric acid on Day 7 in mg/dL			
	<4	4.1-5.5	5.6-7	>7.1
Class I	93%	92.6%	66.7%	25%
Class II	7%	7.4%	16.7%	12.5%
Class III	0	0	16.7%	37.5%
Class IV	0	0	0	25%

There was significant correlation between higher serum uric acid level and higher Killip class on 7th day of admission. [Chi square: 47.357, p value < 0.001.]

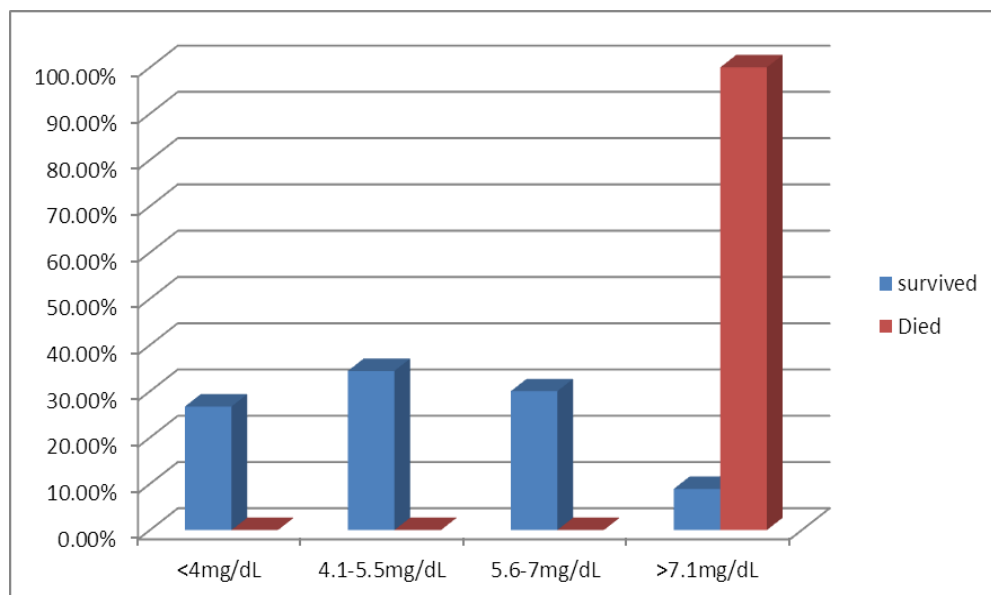


Figure 8: Association between Serum uric acid on Day 0 and outcome

All the ten patients who died had serum uric acid more than 7mg/dL on the day of admission and it was statistically significant. [Chi square : 50.617, p value < 0.001]

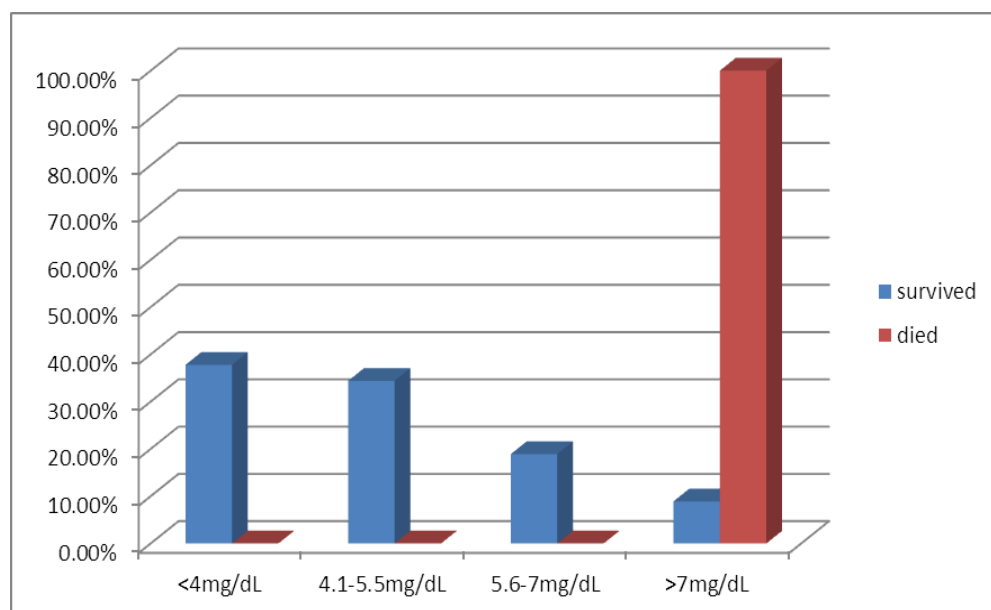


Figure 9: Association between Serum uric acid level on Day 3 and outcome

Chi square : 41.243, p value < 0.001.

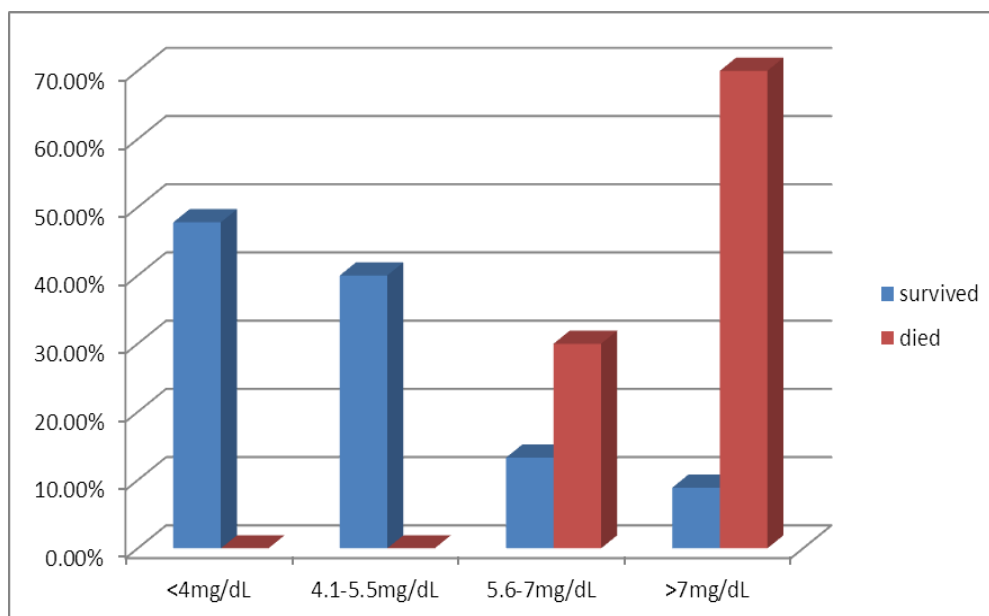


Figure 10: Association between serum uric acid level on Day 7 and outcome

Chi square: 31.852, p value <0.001.

The outcome showed a significant association with high uric acid levels. 70% of the population who died had a serum uric acid level >7mg/dL and 30% of the population who died had serum uric acid level >5.5mg/dL.

Table 9: Analysis of variance (one way ANOVA) of Killip class and Serum Uric acid levels comparing different days of observation.

Parameter	Day	Mean	SD	F value	p value
Killip class	0	1.93	1.08	11.613	<0.001
	3	1.71	1.06		
	7	0.67	0.67		
S. uric Acid level	0	5.59	1.42	10.160	<0.001
	3	5.1	1.42		
	7	4.7	1.21		

DISCUSSION

Ever since Gertler *et al* reported an association of elevated serum uric acid level with myocardial infarction in 1951, numerous large epidemiological studies have confirmed a positive association between raised serum uric acid level and coronary artery disease.^[1-7]

In a study done in Japan, it was shown that the serum uric acid levels correlate with Killip classification and combination of Killip class and serum uric acid level after acute myocardial infarction was a good predictor of mortality in patients who had myocardial infarction.^[6] An Indian study also concluded the same.^[7] This was the reference study that we used.

In this study 100 patients of acute myocardial infarction admitted to the Department of Medicine and Cardiology, Government TD Medical College, Alappuzha during the period from June 2015-June 2016 were included.

Fifty age and sex matched healthy controls were also evaluated for the comparison of the base line uric acid levels.

Out of 100 patients, 67 had ST elevation myocardial infarction and 33 had Non ST elevation myocardial infarction. Out of the ST elevation myocardial infarction, sixty two patients were thrombolysed while five were not due to the delayed presentation. Uric acid was treated as a continuous variable and as a categorical variable and variables were divided into quartiles according to serum uric acid level in mg/dL as <4, 4.1-5.5, 5.6-7, >7 same as in the referral study.

Our patients were age and sex matched which was statistically proved as comparable. 89% of the patients were in the age group more than 50 years of age with the mean age of 63.96. this observation was consistent with the established data of cardiovascular disease regarding age as the risk factor.

On analysis, it was found that patients admitted with myocardial infarction had a statistically significant higher level of serum uric acid on the day of admission when compared to the controls. Cases were distributed in higher serum uric acid level group than controls. In 76% of the cases serum uric acid level was >4mg/dL as

against 44% of the controls. This demonstrates an association between increased levels of serum uric acid and acute myocardial infarction. Similar findings were seen in the reference study and also in many other epidemiological studies.^[5,6]

Our study was in partial agreement with the findings of the well known study by Alderman et al, who found an association between serum uric acid level and subsequent cardiovascular events in a large multiracial population of subjects.^[8] In that study, cardiovascular risk was better predicted by in treatment serum uric acid levels rather than pre treatment serum uric acid levels and such association persisted after adjustment for diuretic therapy, serum creatinine and race, in addition to the traditional risk factors.

The NHANES I (National Health and Nutrition Examination Survey Epidemiologic follow up study, a multivariate analysis of follow up data through 1992 on 5926 subjects who had serum uric acid levels at baseline showed that raised serum uric acid in both men and women was associated with significantly higher risk of all cause cardiovascular disease and ischemic heart disease mortality.^[9]

However the role of serum uric acid as an independent risk factor for the cardiovascular events remain controversial. Conflicting epidemiological data on the independent prognostic role of serum uric acid might be accounted for by the complex interrelations between serum uric acid and a variety of risk markers for cardiovascular diseases, including male gender, hypertension, diabetes, dyslipidemia, obesity and previous cardiovascular events.^[10-13]

Hyperuricemia in myocardial infarction may be the result of various mechanisms, including the accelerated breakdown of ATP in ischemic conditions leading to the increased synthesis.^[14-16]

As in most of the epidemiological studies, our study also have shown a significant correlation between serum uric acid level and hypertension, diabetes,^[16,17] dyslipidemia, and over weight which are powerful risk factors of cardiovascular disease contributing increased cardiovascular mortality.

These entities are part of metabolic syndrome in which hyperuricemia is known to occur and it might represent additional cardiovascular disease risk factor in these patients.^[18,19] However, in this study no adjustment was made for important risk factors such as diabetes duration, glycemic control and albuminuria.

In this study, we could not find any significant difference in the levels of serum uric acid in between patients with ST segment elevation and Non ST segment elevation myocardial infarction. This may be because of the same

mechanism involved in the generation of uric acid in both these conditions.

In our study there was a correlation between serum uric acid level and the Killip class on admission. This was comparable to an earlier study.^[7] On days 3 and 7 following admission also patients with Killip class III or IV had higher uric acid levels than class I or II.

Out of the 100 patients in our study, 10 patients expired during the hospital stay. Three patients before the third day of admission and seven between the third and seventh day.

Of these 10 patients, two were Killip class I, two in Killip class II, two in Class III and four were in class IV on the day of admission. Thus 60% of patients who died were in the Killip class III or IV at the time of admission.

The outcome showed significant association with high serum uric acid levels and death (p value <0.001). All the patients who expired had serum uric acid levels more than 7mg/dL on the day of admission. At the end of 7 day follow up period, 70% of those who dies had serum uric acid level in the fourth quartile.

All the patients who expired were in higher Killip class and associated with higher uric acid levels. Hence the mortality following acute myocardial infarction is related to the serum uric acid level in correlation with the Killip class. These findings were consistent with the previous studies.^[20,21]

So from the present study we presume that an association of higher serum uric acid level in acute myocardial infarction exists even though we could not predict its role as an independent risk factor in cardiovascular disease. The study suggests that serum uric acid may provide valuable clue to the prediction of prognosis.

These findings not only reveal a potentially new diagnostic test as a marker but also provide further evidence of the possible importance of serum uric acid in the prognosis of cardiac ischemia and also support the possibility that interventions to reduce the uric acid levels may affect cardiovascular outcomes.

CONCLUSIONS

1. Serum uric acid levels were higher in patients of acute myocardial infarction as compared to normal healthy persons establishing an association of higher serum uric acid level in acute coronary syndromes.
2. Serum uric acid level may act as a marker for underlying cardiac ischemia.
3. Age and gender differences did not significantly influence the serum uric acid level in patients with myocardial infarction in this study.
4. Hyperuricemia was linked to the powerful cardiovascular risk factors like hypertension, diabetes, dyslipidemia and over weight.

5. The findings lend little support for the role of hyperuricemia as an independent risk factor for the development of coronary artery disease.
6. There was comparable serum uric acid levels in patients with ST segment elevation and Non ST segment elevation myocardial infarction.
7. Serum uric acid levels correlated well with the Killip class.
8. Combination of Killip class and serum uric acid level may be a good predictor of mortality after myocardial infarction.
9. If results of future studies support the conclusion that increased levels of serum uric acid may play a direct role in the pathophysiology of cardiovascular disease, reduction of hyperuricemia will be another target for the treatment of coronary artery disease.

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