

## Serum uric acid as a marker of left ventricular failure in acute myocardial infarction

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**Abstract:** Coronary Heart Disease is a worldwide health epidemic. Of particular concern from a global perspective is the burden of myocardial infarction in developing countries. Limitations in available resources to treat ST elevation myocardial infarction in developing countries mandate major efforts on an international level to strengthen primary prevention programs. Elevated serum uric acid is highly predictive of mortality in patients with heart failure or coronary artery disease. We undertook this study to know the usefulness of serum uric acid in acute myocardial infarction and to study the use of serum uric acid as a marker of short-term mortality in acute myocardial infarction. A prospective study was conducted at Kasturba Medical College Hospital, Mangalore between August 2009 & August 2011. A total of 100 cases of Acute Myocardial Infarction were studied where 77% were males and 23% were females. 58% were hypertensives and 71% were diabetics. We found a close relation between serum uric acid concentrations and Killip class. Serum uric acid levels were elevated in cases of acute myocardial infarction with systemic hypertension & diabetes mellitus. Hyperuricemia after acute myocardial infarction is an indicator of poor prognosis in acute myocardial infarction. High uric acid concentrations on admission were strongly associated with adverse clinical outcome like mortality. Serum uric acid can be used as a marker of short-term mortality in acute myocardial infarction.

**Key Words:** Serum Uric Acid, Acute Myocardial Infarction, prognostic marker.

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### I. Introduction:

Worldwide, 30% of all deaths can be attributed to cardiovascular disease, of which more than half are caused by Coronary heart disease (CHD), and the forecasts for the future estimate a growing number as a consequence of lifestyle changes in developing countries. Globally, of those dying from cardiovascular diseases, 80% are in developing countries. Of particular concern from a global perspective is the burden of myocardial infarction in developing countries. Limitations in available resources to treat ST elevation myocardial infarction (STEMI) in developing countries mandate major efforts on an international level to strengthen primary prevention programs.<sup>1</sup>

There has been growing interest in the link between uric acid levels, xanthine oxidoreductase and cardiovascular disease. A failing heart due to AMI may cause tissue hypoperfusion and hypoxia, which trigger xanthine oxidase activation and oxidative stress production.<sup>2,3</sup> Xanthine oxidoreductase exists in two forms, xanthine oxidase and xanthine dehydrogenase. Both of these enzymes are responsible for metabolizing uric acid from hypoxanthine and xanthine. Xanthine oxidase and oxidative stress as reflected by uric acid may form a vicious cycle that promotes severe heart failure.<sup>4,2</sup>

Previous studies have reported that a high concentration of uric acid is a strong marker of an unfavourable prognosis of moderate to severe heart failure and cardiovascular disease.<sup>4,5</sup> Evidence 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.<sup>6,7</sup> Elevated serum uric acid is highly predictive of mortality in patients with heart failure or coronary artery disease and of cardiovascular events in patients.<sup>8</sup> High SUA has been indicated as a risk factor for CAD<sup>9</sup> and as an independent prognostic factor of poorer outcomes (occurrence of AMI, fatal AMI, sudden death, all-cause mortality) in patients with verified CAD.<sup>10</sup>

According to the Japanese Acute Coronary Syndrome Study<sup>11</sup>, there was a close correlation between serum uric acid concentration and Killip classification in patients of acute myocardial infarction. Elevated SUA is also associated with hypertension and renal disease. It is present in more than 75% of patients with malignant hypertension.<sup>12</sup> This elevation in these settings may be the result of decreased renal blood flow and resultant increased urate reabsorption, although this relationship is not completely understood.<sup>12</sup> Hypertension and prehypertension, renal disease (including reduced glomerular filtration rate and microalbuminuria), metabolic syndrome (including abdominal obesity, hypertriglyceridemia, low level of high-density lipoprotein cholesterol, insulin resistance, impaired glucose tolerance, elevated leptin level), obstructive sleep apnea, vascular disease

(carotid, peripheral, coronary artery), stroke and vascular dementia, preeclampsia, inflammation markers (C-reactive protein, plasminogen activator inhibitor type1, soluble intercellular adhesion molecule type 1), endothelial dysfunction, oxidative stress, sex and race (postmenopausal women, blacks), and demographic (movement from rural to urban communities, westernization, immigration to western cultures) are certain risk factors associated with Elevated Uric Acid.<sup>13</sup> The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study and Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study<sup>15</sup> demonstrated that lowering serum uric acid concentrations was associated with a beneficial effect on cardiovascular outcome.<sup>14</sup> Therefore, any drug interventions, such as therapy to decrease serum uric acid level in addition to coronary reperfusion, may have a favourable effect on mortality in patients who have Acute Myocardial Infarction.

We undertook this study to study the prognostic usefulness of serum uric acid in acute myocardial infarction and to study the use of serum uric acid as a marker of short-term mortality in acute myocardial infarction.

### Objectives :

1. To study the serum uric acid levels in Acute Myocardial Infarction,
2. To study the relation between serum uric acid levels with Killip classification suggestive of Left Heart Failure, cardiac troponin T and CK-MB in acute myocardial infarction,
3. To study the relation between serum uric acid and systemic hypertension & diabetes mellitus in acute myocardial infarction,
4. To study the role of serum uric acid as a marker of short-term mortality in Acute Myocardial Infarction.

### II. Methodology:

A prospective study was conducted at Kasturba Medical College Hospital, Mangalore between August 2010 and August 2011. All patients aged more than 18 years with ST segment elevation myocardial infarction (STEMI) or non-ST segment elevation myocardial infarction (NSTEMI) on the basis of history, clinical examination, ECG changes and biochemical markers and willing to participate were included into the study.

Patients with a condition known to elevate serum uric acid level (e.g. Chronic Kidney Disease, Gout, Hematological malignancy, Hypothyroidism, Hyperparathyroidism); Patients on drugs which increase serum uric acid (e.g. Salicylates (>2 gm/day), Ethambutol, Amiloride, Bumetanide, Chlorthalidone, Cisplatin, Cyclophosphamide, Cyclosporine, Ethacrynic Acid, Ethambutol, Thiazide diuretics, Furosemide, Indapamide, Isotretinoin, Ketoconazole, Levodopa, Metolazone, Pentamidine, Phencyclidine, Pyrazinamide, Theophylline, Vincristine, Vitamin C) and chronic alcoholics were excluded. Ethics committee approval was obtained from the Institutional Ethics Committee.

Demographic details and detailed clinical history of these cases were taken using a semi-structured questionnaire after getting their informed written consent. Baseline investigations like Electrocardiogram, Echocardiography, blood investigations such as Serum Uric Acid, Troponin T and CPK-MB were done on admission. During follow up of one week, Serum Uric Acid was repeated on day 3 and day 5 of admission.

Analysis was done using SPSS. To study the prognostic usefulness of serum uric acid in acute myocardial infarction, to correlate relation between serum uric acid and Killip classification/ hypertension/ diabetic status and to study the use of serum uric acid as a marker of short-term mortality in acute myocardial infarction tests like t-Test, Pearson correlation and ANOVA were used.

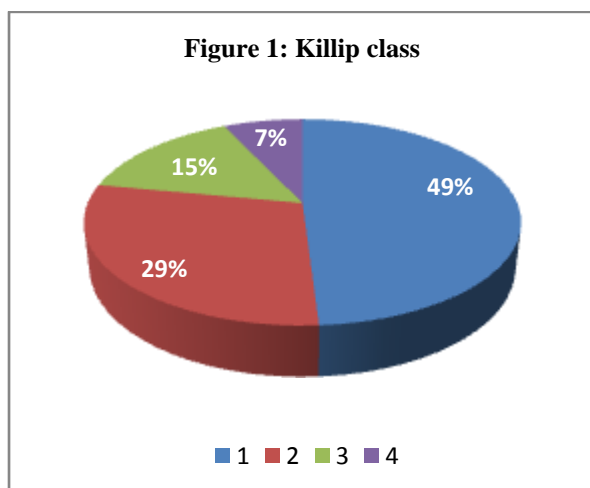
### III. Results:

A total of 100 cases of Acute Myocardial Infarction were studied where 77% were males and 23% were females. Among the 100 study subjects, 58% were hypertensives and 71% were diabetics. The baseline profile on the day of admission with regards to their age, mean serum uric acid level, CPK-MB, Troponin T and Ejection Fraction are given in Table 1.

**Table 1 Baseline Profile on the Day of Admission of AMI Cases (N=100)**

Parameter	Mean ± SD	Minimum	Maximum
Age	57.99 ± 9.698	27	90
Mean Serum Uric Acid	7.84 ± 2.91	4	16
Mean CK-MB	44.36 ± 17.01	28	94
Mean Troponin T	0.5 ± 0.51	0	3
Ejection Fraction	49.53 ± 13.93	20	70

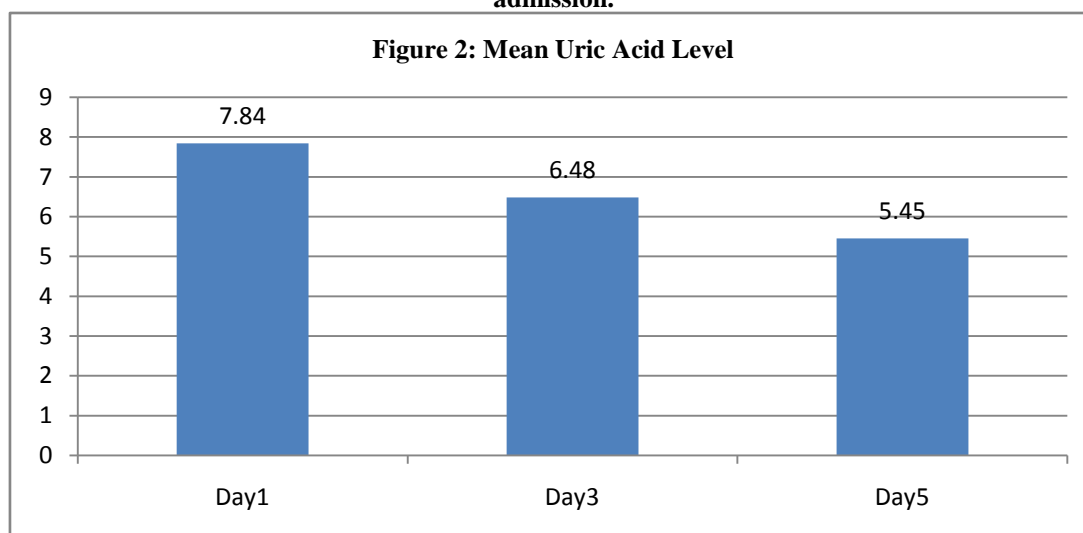
Figure 1 shows the distribution of 100 acute MI cases according to Killip classification. Majority (49%) of the cases belonged to Killip class1, followed by class2. Only 7% belonged to class 4. The distribution of study population based on the underlying pathology has been depicted in table 2.



**Table 2: Underlying pathology**

Type of MI	Proportion (%)
AS STEMI	19
AW STEMI	44
ExAWSTEMI	7
IW STEMI	22
IW NSTEMI	8
TOTAL	100

Figure 2 shows the serum uric acid levels of the Acute MI patients on Day 1, Day 3 and Day 5 of admission.



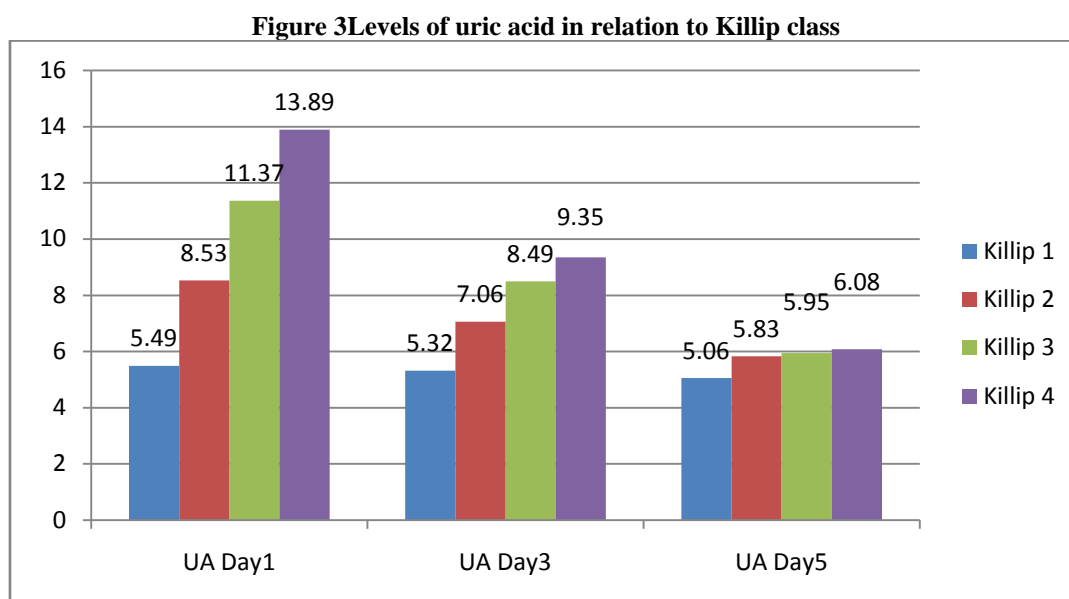
The mean Serum uric acid levels on Day 1( $7.84 \pm 2.91$ ), day 3 ( $6.48 \pm 1.75$ ) and day 5 ( $5.45 \pm 1.16$ ) were found to decrease significantly ( $<0.001$ ) as days passed by (Figure 2).

Table 3 shows the relation of serial serum uric acid on Day 1, Day 3 and Day 5 with gender. It was seen that the mean serum uric acid levels of male and female MI cases were not significantly different on the day of admission (day 1) and Day 3. The mean serum uric acid levels on day 5 following admission were found to be higher in male cases when compared to female cases. This difference between males and females was found to be significant (0.001).

**Table 3 Relation of serial serum uric acid levels and Day 5 with gender**

Uric Acid Level	Sex	Mean	SD	t value	p value
Uric Acid Day 1	Female	8	2.61	0.29	0.773
	Male	7.79	3.00		
Uric Acid Day 3	Female	5.84	1.13	1.868	0.065
	Male	6.65	1.85		
Uric Acid Day 5	Female	4.71	0.751	3.42	0.001
	Male	5.66	1.18		

Figure 3 shows the levels of uric acid in relation to Killip class on Day 1, Day 3 and Day 5 of admission. The serum uric acid level was significantly higher among those cases who belonged to higher Killip class on the day of admission (day 1), day 3 and day 5 following admission.



The serum uric acid levels on the day of admission were significantly higher among those patients in higher Killip class (215.865,  $p < 0.001$ ). Excluding the four deaths by day 3 and the additional 2 deaths by day 5, the serum uric acid levels were found to be significantly higher in those belonging to higher Killip class on both day 3 (40.201,  $p < 0.001$ ) and Day 5 (4.522,  $p < 0.005$ ).

Figure 4 shows the mean serum uric acid levels on Day 1, Day 3 and Day 5 among Acute MI cases with hypertension and without hypertension.

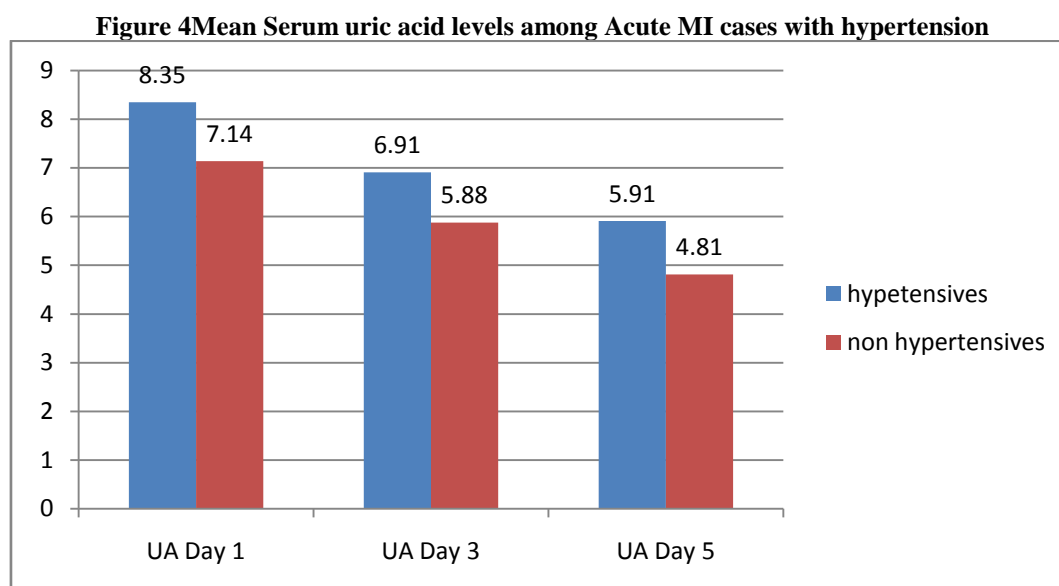
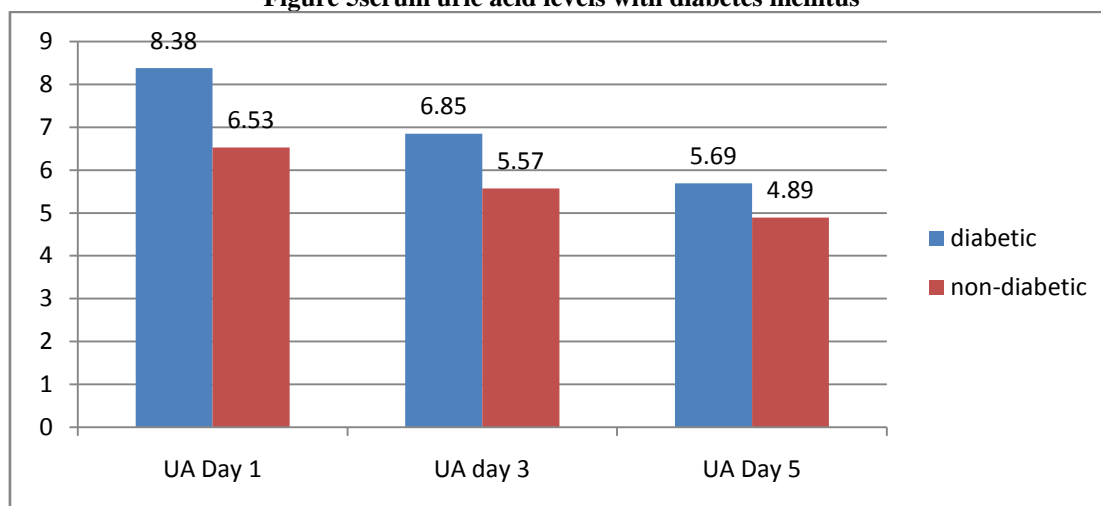


Figure 4 shows the mean serum uric acid level among the hypertensives were  $8.35 \pm 2.56$  on day1;  $6.91 \pm 1.52$  on day 3 and  $5.91 \pm 1.04$  on day 5. The mean serum uric acid level was found to be higher among hypertensive acute MI cases when compared with the non-hypertensives on day 1 (2.078;  $p < 0.04$ ), day 3 (2.95;  $p < 0.004$ ) and day 5 (5.098;  $p < 0.001$ ) following admission.

Figure 5 shows the serum uric acid levels on Day 1, Day 3 and Day 5 among cases with diabetes mellitus and without diabetes mellitus.

**Figure 5** serum uric acid levels with diabetes mellitus



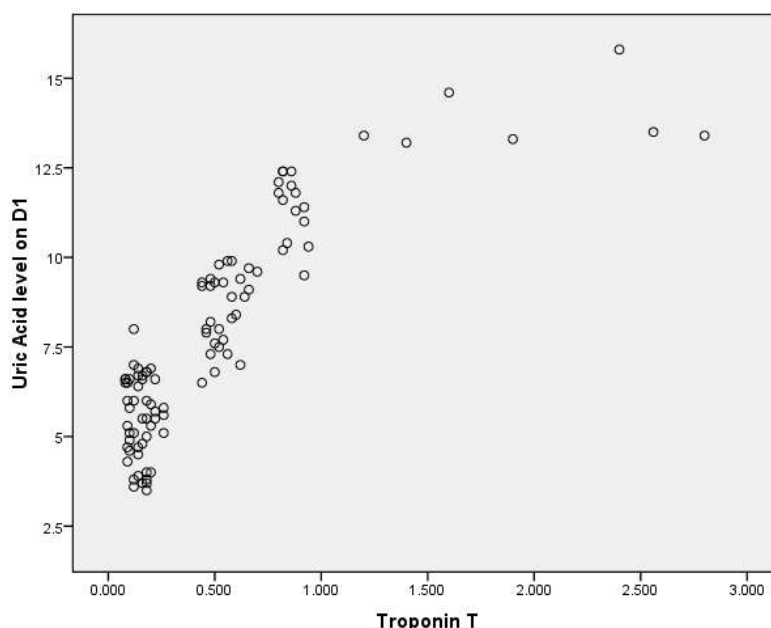
The mean serum uric acid level was found to be higher among those cases with diabetes, on day 1 ( $8.38 \pm 2.92$ ), day 3 ( $6.85 \pm 1.74$ ) and day 5 ( $5.69 \pm 1.17$ ) following admission when compared with the non-diabetics. The mean serum uric acid level among the MI cases who were diabetic was found to be significantly higher on all three days of follow up (t 2.995, p 0.003 on day 1; t 3.434, p 0.001 on day 3 and t 3.23, p 0.002 on day 5).

There was 6% mortality among the study group during the seven day follow up. There were four deaths by day 3 and another two more deaths by day 5. Table 4 shows the between Killip class and mortality. Of the six patients who died, none was in Killip class 1, one was in Killip class 2, two were in Killip class 3 and three were in Killip class 4 at the time of admission. Thus, 83.3% of patients who died were in higher class i.e. class 3 and 4 at time of admission (p= 0.002).

The mean serum uric acid level on day of admission (Day 1) among those who died during the study was  $12.52 (+ 2.086)$  much higher than those who survived ( $7.54 \pm 2.69$ ). There is a significant association between serum uric acid level on admission and mortality as all the patients who died had high serum uric acid level (t 4.431; p<0.001). Thus serum uric acid level on the day of admission can be used as a prognostic marker.

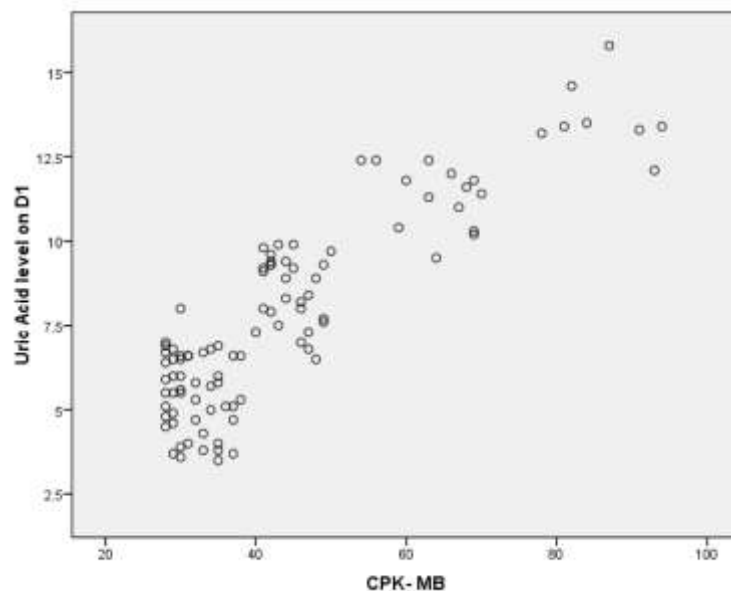
The following scatter plots are depicting relation between serum uric acid levels on day 1 and Troponin T (Figure 6), CPK-MB (Figure 7) and Ejection Fraction (Figure 8).

**Figure 6:** Scatter plot depicting relation between uric acid level and Troponin T



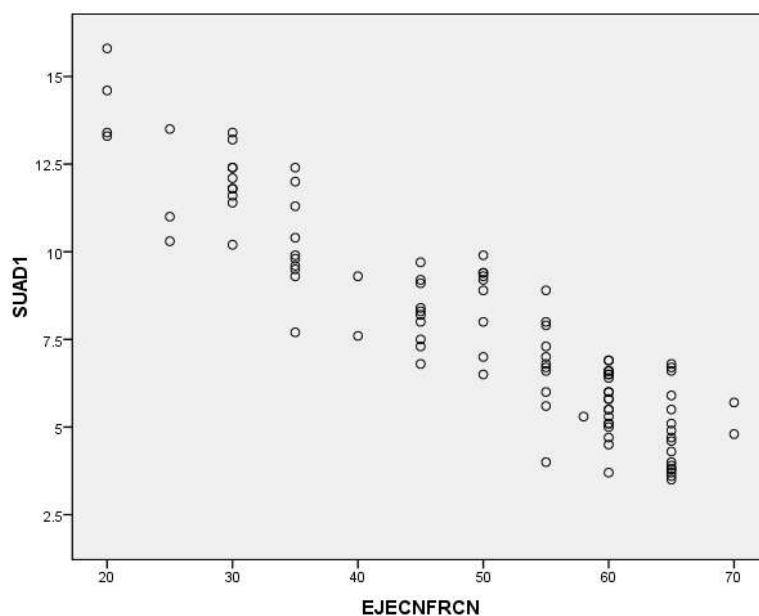
This scatter plot shows when serum uric acid level on the day of admission was correlated with Troponin T value, a strong positive correlation was obtained (Pearson correlation 0.840, p value <0.001), that is, as the value of one increases the other also increases.

**Figure 7: Scatter plot depicting relation between uric acid level and CK-MB**



This scatter plot shows that when the serum uric acid level on the day of admission was correlated with CPK-MB values, a strong positive correlation was obtained (Pearson correlation 0.876, p value <0.001), that is, as the value of one increases the other also increases as shown in this scatter plot.

**Figure 8: Scatter plot depicting relation between uric acid level and ejection fraction**



This scatter plot shows that when the serum uric acid level on the day of admission was correlated with Ejection Fraction, a strong negative correlation was obtained (Pearson correlation - 0.916, p value 0.001), that is, as the value of one increases the other decreases as shown in this scatter plot.

#### **IV. Discussion:**

We studied a total of 100 patients with acute myocardial infarction, of which 77 were males and 23 were females. In our study, majority (49%) of the cases belonged to Killip class 1, 29% in Killip class 2, 15% in Killip class 3 and 7% in Killip class 4.

Our study showed that hypertensive patients had more hyperuricemia and there was significant relation between serum uric acid level (p 0.040 on day 1, p 0.004 on day 3 and p<0.001 on day 5) in patients who were

known or found to be hypertensive on admission. In Kojima S<sup>11</sup> et al study it was noted that serum uric acid concentration was significantly correlated with hypertension ( $r=0.301$ ,  $p$  value = 0.005).

71% subjects were diabetic in our study and the serum uric acid level was significantly associated with diabetes mellitus ( $p=0.003$  on day 1;  $p=0.001$  on day 3 and  $p=0.002$  on day 5).

In our study patients of Killip class 3 and 4 had higher levels of uric acid as compared to patients of class 1 and 2. ( $p$  value  $<0.001$ ). Similar findings were noted by Kojima Set al<sup>11</sup> their study. MY Nadkar, VI Jain<sup>16</sup> showed that serum uric acid levels are higher in patients of acute myocardial infarction correlated with Killip class. However, VitoonJularattanapornet al<sup>17</sup> noted that there was no observed association between hyperuricemia and Killip class at first presentation.

We also found that there is statistically significant positive correlation (Pearson correlation 0.840,  $p=0.000$ ) between CPK-MB on day of admission and serum uric acid level on the day of admission, similarly there is a positive correlation (Pearson correlation 0.876,  $p=0.000$ ) between Troponin T levels and serum uric acid level on the day of admission.

We noted in the present study, there was significant relation between uric acid level and mortality. High serum uric acid levels on admission were strongly associated with adverse clinical outcome in patients who had acute myocardial infarction. Our study showed the value of serum uric acid as a marker of short-term mortality in acute myocardial infarction. Kojima S<sup>11</sup> et al in their study conducted in Japan noted that hyperuricemia after AMI is associated with the development of heart failure. However, VitoonJularattanapornet al<sup>17</sup> noted that there was no observed association between hyperuricemia and in-hospital adverse outcomes. Bickel C et al reported that one mg/dl increase in serum uric acid levels was associated with a 26% increase in mortality.<sup>18</sup> Siniša Caret al in their study found that higher serum uric acid determined on admission is associated with higher in-hospital mortality and thirty-day mortality and poorer long-term survival after AMI.<sup>19</sup>

## V. Conclusion:

In the present study, we found a close relation between serum uric acid concentrations and Killip classification suggestive of left ventricular failure in acute myocardial infarction. Serum uric acid levels are elevated in systemic hypertension, diabetes mellitus and in acute myocardial infarction. High uric acid concentrations on admission were strongly associated with adverse clinical outcome (mortality) in patients who had acute myocardial infarction. Hyperuricemia after acute myocardial infarction is an indicator of poor prognosis in acute myocardial infarction. Serum uric acid can be used as a marker of short-term mortality in acute myocardial infarction.

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