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A Study Of Association Between Serum Uric Acid And Killip Class In Acute Myocardial Infarction

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Abstract

Acute myocardial infarction (AMI) has quickly become the biggest contributor to rising morbidity and mortality. In published literature, the elevation of uric acid has been introduced as major prognostic marker predicting mortality. The present study was undertaken to study the association between serum uric acid (SUA) levels and Killip class in patients of AMI.

Method: A total 116 patients of age above 12 years with ECG showing ST Elevation Myocardial Infarction (STEMI) were included in the study. The demographic data, complete history, clinical and physical examination was done. Killip class were applied at the time of admission. Baseline SUA level was done by withdrawing 4ml of blood after 1 hour of admission.

Results: The mean uric acid level was significantly higher in male patients (6.12) than female (4.98). Diabetes and hypertension remain the major risk factors for AMI. Maximum cases belonged to Killip class I (57) followed by class II (26), class III (18) and class IV (15). The uric acid level was significantly higher among patients in class IV (16.04) and class III (11.49) than patients in class II (8.38) and class I (4.98), (p=0.001). There was 15.51% (18 cases) mortality of them 15 patients in Killip class IV while only 3 patients in Killip class III. The mean SUA for discharged patients was 6.91±2.54mg/dl and for died patients it was 15.63±1.33mg/dl.

Conclusion: The elevated SUA level showed positive correlation with Killip classification in AMI. The SUA concentration and Killip's classification independently and significantly predicted poor prognosis after AMI. However, combination of Killip's class and SUA is a good predictor of mortality after AMI.

Keywords: Acute myocardial infarction; Uric acid; Killip class; STEMI; Mortality

Introduction

Acute myocardial infarction (AMI) is a form of ischaemic heart disease (IHD), despite spectacular progress in their prevention, detection, and treatment over the last three decades [1] which continues to be the leading cause of death in the industrialized and developing countries like India. Many risk factors for MI are well known, like age, male sex, smoking, diabetes, hypertension, metabolic syndrome explain only a part of the cases [2]. However, AMI is associated with high death rate within 24 hours and most of the deaths occur within one hour of onset of symptoms. So, risk stratification has an important role in the management of AMI. Blood pressure, localisation of infarct, killip class, TIMI score are some methods useful in risk stratification and estimation of mortality in intensive coronary unit [3].

In 1967, Killip and Kimball [4] proposed a prognostic classification scheme on the basis of the presence and severity of rales detected in patients

presenting with STEMI. It has 4 classes in which class III and IV has a higher mortality than the class I and II. The mortality rate of killip class IV is 81%. Despite overall improvement in mortality rate in each class, compared with data observed during the original development of the classification scheme, the classification scheme remains useful today, as evidenced by data from large myocardial infarction (MI) trials involving STEMI patients [5].

Although, multiple molecules in AMI have been studied and used as prognostic predictors. There has been growing interest in the link between uric acid levels, xanthine oxidoreductase and cardiovascular disease. 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 [6, 7]. A failing heart due to AMI may cause tissue hypo perfusion and hypoxia, which trigger xanthine oxidase activation and oxidative stress [8, 9]. Xanthine oxidase and oxidative stress, as reflected by uric acid levels, may form a vicious cycle that promotes severe heart failure [7, 8]. Therefore, SUA may not be only a bystander marker but also a causative marker of mortality in patients who have AMI. In this regard, improvement of coronary reperfusion alone may be less effective in ameliorating heart failure and decreasing mortality rate in patients who have AMI and high UA level and are in a high KILLIP class. Considering all this background the present research was undertaken to study the association between serum uric acid levels and Killip class in patients of AMI.

Methods and Materials

After obtaining Institutional Ethical Committee approval and written informed consent from all the patients, this, cross-sectional observational study was carried out in the Department of General Medicine, at Tertiary care hospital in central India over a period of 1 year from 1st February 2019 to 31st Oct 2020. A total of 116 patients age above 12 years with ECG showing ST Elevation Myocardial Infarction (STEMI) admitted in our ICCU were included in the study. Patients with a condition known to elevate SUA level (eg, chronic kidney disease, gout, hematological malignancy, hypothyroidism, hyperparathyroidism), patients taking drugs that increase SUA salicylates (>2 g/day), ethambutol, amiloride, bumetanide, chlorthalidone, cisplatin, cyclophosphamide, cyclosporine, ethacrynic acid, thiazide diuretics, furosemide, indapamide, isotretinoin, ketoconazole, levodopa, metolazone, pentamidine, phencyclidine, pyrazinamide, theophylline, vincristine or vitamin C and who were thrombolysed outside were excluded from the study.

Patient with typical chest pain persisting more than 30 minutes with ECG changes for STEMI include New ST ELEVATION at J point in two or more contiguous leads with >1mm (.1Mv) in all leads except V2-V3 and in leads V2-V3 - >2mm (.2mv) in men > 40 years of age (>2.5mm (.25mv) in men <40 years of Age; >1.5mm (.15mv) in women). The data of each patient were collected in a special proforma which includes patient's name, age, sex, demographic status, complete history, and physical examination. Blood pressure, random sugar, urea, creatinine was taken immediately after admission, Killip class were applied at the time of admission. Baseline serum uric acid level was done by withdrawing 4ml of blood after 1 hour of admission. Uric acid level in serum was measured by uricase (enzymatic) method in cobra integra or cobas c system. Reference level for uric acid in our labarotory= 2-7 mg/dl.

Statistical Analysis

The collected data were analysed using SPSS 25.0 and EPI Info version 7.3. To find the significance of categorical variable the descriptive statistics i.e., frequency and percentage analysis were used. The mean was used for continuous variable. The significance of two variables were calculated by using unpaired t test and the correlation between two variables was calculated by using Kruskal Wallis test. P value less than 0.05 was considered significant.

Observations and Results

Among the total 116 patients participated in the study, 72 patients were males and 44 patients were females. The maximum number of patients i.e., 75.86% cases of AMI were found in the age group of 51-70 years with mean age of patients was 59.83±8.29 years, ranged from 29-80 years. There were 58 patients with BMI <24.9 and 58 patients with BMI ≥25. The mean BMI was 25.93±3.84 kg/m2, ranging from 19-40 kg/m2, (Table 1).

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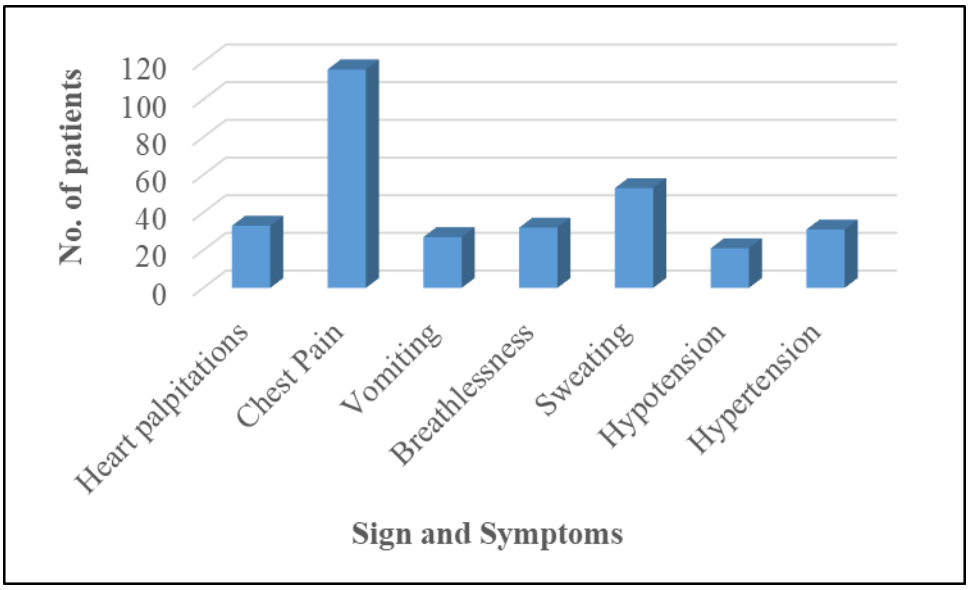
Table 1: Distribution of patients according to demographic data

Demographic data		No. of cases	Percentage
Age group (In years)	<30	01	0.86
	31-40	00	0.0
	41-50	17	14.66
	51-60	44	37.93
	61-70	44	37.93
	71-80	10	8.62
Gender	Male	72	62.06
	Female	44	37.93
BMI (kg/m2)	Normal (<25)	58	50
	Overweight (25-29.9)	49	42.24
	Obesity class I (30-34.9)	08	6.89
	Obesity class II (35-39.9)	01	0.86

The chest pain was the chief complaint observed in all the patients (100%). However, patients were presented with different symptoms as depicted in figure 1. Out of total 116 patient, 51 patients had history of alcohol consumption, 38 patients had smoking habits, 51 patients were hypertensive, 35 had diabetes mellitus and 28 patients had history of IHD.

Figure 1: Signs and symptoms among study population



Most of the patients (47; 40.51%) had ASWMI, 29 (25%) patients were IWMI, 19 (16.37%) patients each had IPLWMI and IPWMI and only 2 (1.72%) patients had AWMI. The majority of cases belonged to Killip class I (57; 47.41%) followed by class II (26; 22.41%). However, the majority of cases had higher serum uric acid levels i.e., >7 mg/dl (53.44%) and 46.55% cases had serum uric acid levels between 2.1-7 mg/dl. The mean uric acid levels were more among males (6.12) and less among females (4.98) and this difference was statistically

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significant by unpaired t test, (p=0.0034). The association between serum uric acid levels and Killip classification was statistically significant as shown in table 2.

Table 2: Association between serum uric acid (SUA) levels and Killip classification

Killip Class	Serum uric acid levels				P value
	<2 mg/dl	2.1-7 mg/dl	>7 mg/dl	Total	
Class I	00	45	12	57	0.034
Class II	00	11	15	26	
Class III	00	00	18	18	
Class IV	00	00	15	15	
Total	00	56	60	116	

From the figure 2, it was observed that the mean uric acid level was significantly higher among patients in class IV and III than patients in class I and II which was statistically significant with p value of 0.034.

Figure 2: Association between mean serum acid and Killip class

There was no relation between the uric acid level and type of AMI and the difference was not statistically significant with p value of 0.624 as shown in table 3

Table 3: Relation between serum uric acid and type of AMI

Type of AMI	Serum uric acid levels				P value
	<2 mg/dl	2.1-7 mg/dl	>7 mg/dl	Total	
AWMI	00	00	02	02	0.624
ASWMI	00	24	23	47	
IPLWMI	00	11	08	19	
IPWMI	00	09	10	19	

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IWMI	00	10	19	29	

Table 4 show that those patients having higher uric acid level (>7 mg/dl) had more complications than patients having uric acid level between 2.1-7 mg/dl. However, the most common complication observed in >7 mg/dl group was cardiogenic shock and ventricular tachycardia.

Table 4: Relation between complications and serum uric acid

Complications	**Serum uric acid levels**				**P value**
	<2 mg/dl	2.1-7 mg/dl	>7 mg/dl	Total	
Cardiogenic Shock	00	00	23	23	0.0432
Re Infarction	00	00	02	02	
Ventricular tachycardia	00	00	21	21	
1st Degree Heart Block	00	00	07	07	
3 rd Degree Heart Block	00	00	05	05	
No complications	00	54	03	57	

There was 15.51% (18 Cases) mortality among the cases of AMI during the hospital stay and the higher serum uric acid level was associated with higher mortality which was statistically highly significant (p=0.001). The most common cause of death was cardiogenic shock with ventricular tachycardia as shown in table 5.

Table 5: Relation between serum uric acid and mortality

Mortality and causes		Serum uric acid levels (mg/dl)				P value
		<2	2.1-7	>7	Mean	
Mortality	Alive	00	91	07	-	0.001
	Dead	00	00	18	-	
Mortality Causes	Cardiogenic Shock	00	00	06	16.65	0.021
	VT	00	00	02	20.3	
	Cardiogenic Shock + VT	00	00	10	15.33	

Of the 18 patients who died, most of the patients in Killip class IV (15 out of 18) (100%) while only 3 patients (17%) in Killip class III expired. Thus, patients who died were more in higher class i.e., class IV (100% mortality), (Figure 3). The mean SUA for discharged patients was 6.91±2.54 mg/dl and it was 15.63±1.33 mg/dl for the patients who died in the hospital.

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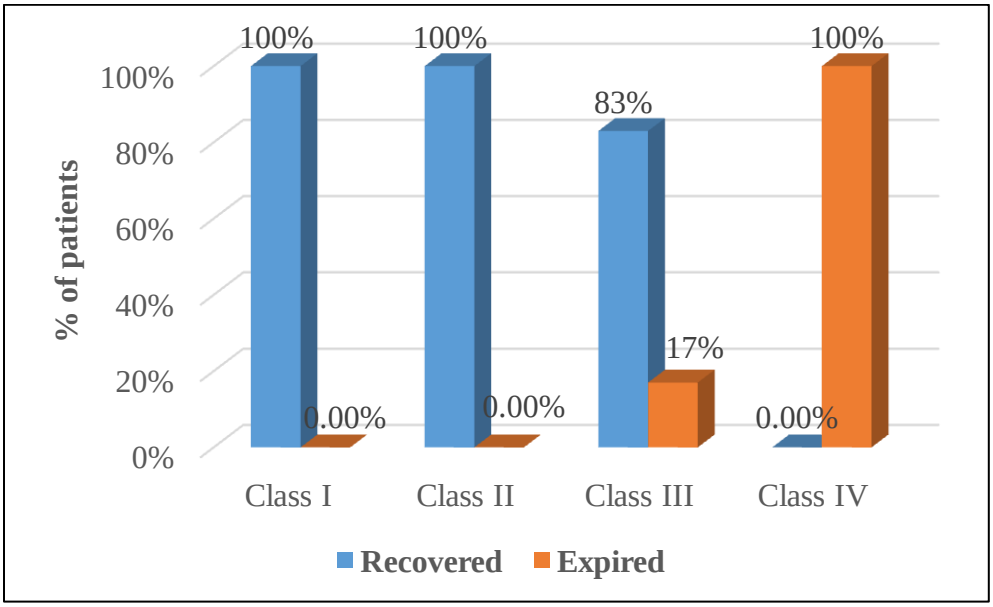
Figure 3: Relationship between Killip class and mortality



Discussion

Acute myocardial infarction manifests as either STEMI or Non-STEMI. Risk stratification of AMI is done by various clinical assessment and score. KILLIP Classification is used assess the severity and prognosis in AMI. Serum uric acid is a metabolite of purine often used as a biomarker of inflammation. It can be used as an important yet independent prognostic predictor for worse outcomes, it would be helpful for earlier and accurate assessment of AMI going in for deterioration and for implementation of more effective and timely therapeutic strategies.

As like the other studies [10-12], in present study predominance of males in AMI was observed. Uric acid of male patients was significantly higher (6.12) than the female patient (4.98), which is similar to previous studies [12, 13]. This discrepancy in serum uric acid in females is apparently related to the protective effect of estrogen level. Estrogen is known to possess the effect of promoting excretion of uric acid. Here, the sex difference in the risk of hyperuricemia may lie in the fact that estrogen is a uricosuric agent. A previous study by Anton et al showed that higher renal clearance of urate in women was due to their higher plasma estrogen levels and lower tubular urate post secretory reabsorption [14]. The mean age of patients was 59.83±8.29 years which is comparable with the study done by Nadkar and Jain where the mean age of cases was 58.29±11.31 years [12]. Out of 116 patients with AMI, 51 patients were hypertensive, 35 patients have diabetes, 51 patients had alcohol consumption and 38 patients had smoking habits. The alcohol consumption and smoking were common in males in current study. Hence it is evident that hypertension, diabetes, smoking, and alcoholism were the most prevalent risk factors for MI. These findings are correlated with the previous studies [10, 12, 15-17].

In the present study the serum uric acid level was significantly higher in Killip class III and IV as compared to patients of class I and II, this is comparable with the other studies [4,11,12, 15-18]. Similarly, Shah et al showed that the patients who were graded higher in Killip's class had higher uric acid levels [19].

There was 15.51% mortality among the cases of AMI during the hospital stay. The most common cause of death was cardiogenic shock with ventricular tachycardia observed in 55.55% cases followed by only cardiogenic shock in 33.33% and only ventricular tachycardia in 11.11% cases. The relationship between Killip class and mortality showed that out of the 18 patients who died, none was in Killip class I and II. Most of the patients in Killip class IV (15 out of 18) while only 3 patients in Killip class III. Thus, patients who died were more in higher class i.e., class IV. The mean SUA levels were significantly higher in the patients who succumbed as compared to those who were discharged from the

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hospital (p=0.000). These findings are consistent with the previous studies [10, 12, 20].

An important question that remains to be answered is the role of SUA in pathogenesis of AMI. In present study, as discussed above, SUA was found to be associated with nearly all the major risk factors for acute MI viz. hypertension, diabetes mellitus and smoking. Apart from its association with the risk factors of MI, the various other plausible mechanisms which can explain the role of SUA in AMI are as follows: Nitric oxide, which is known to be a potent vasodilatator, is important for maintaining vascular tone. Synthesis of nitric oxide is disrupted, and its degradation is accelerated by excessive free radical activity. This condition disrupts functions of endothelium dependent vasodilatation; a condition known as endothelial dysfunction. Endothelial dysfunction is the first step for the beginning of atherosclerosis [21]. Thus, increased oxidative stress appears to play an important role in the development and progression of atherosclerosis [22]. One may speculate that SUA may be an indicator of the degree of myocardial energy status. Accordingly, the SUA levels reported here might reflect the extent of myocardial energy depletion that may occur after MI with marked cellular damage. Moreover, SUA has been recognised as a DAMP (danger-associated molecular pattern molecule) that can set off and maintain pro-inflammatory responses, and which may be linked to Cardiovascular morbidity [14, 23]. Novel mechanistic insights on allopurinol have prompted clinical evaluation as a putative HF therapeutic. Furthermore, serum uric acid reduction has been considered a potential and novel approach to lower coronary artery disease burden [24]. Recent studies have also pointed that concomitantly employing allopurinol (a uric acid lowering agent) with antihypertensive and lipid-lowering drugs might act synergistically with these therapies to reduce cardiovascular risk [24]. Hence, 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 AMI.

Farquharson et al indicated that allopurinol given at 300 mg/day improved endothelial function (forearm blood flow response to acetylcholine) in 11 patients with New York. Heart Association class II and III chronic heart failure. Plasma malondialdehyde, a marker of oxidative stress was also reduced [25]. In another study done by Doehner et al, infused allopurinol with acetylcholine, lowering UA by 2.0 mg/dL and improved endothelial function in patients with CHF. Allopurinol administered at 300 mg/d for 1-week improved peak arm and leg blood flow. Thus, in patients with CHF, reduction in serum UA levels may prove to be an effective adjunctive therapy [26]. Because of the above discrepancies between various studies and possibilities of newer treatment modalities and paucity of data in the Indian population, we aimed to further study the relationship between serum uric acid and its use as a prognostic marker in patients with acute myocardial infarction.

Conclusion

The elevated serum uric acid level showed positive correlation with Killip classification in AMI. The serum uric acid concentration and Killip's classification independently and significantly predicted poor prognosis after AMI. Combination of Killip's class and serum uric acid is a good predictor of mortality after AMI. This simple, easily available, inexpensive laboratory parameter (estimation of serum uric acid) may help in settings where facilities are lacking. Therapeutic trials on ameliorating the adverse effects of serum uric acid on a cardiovascular mortality are needed. Thus, ameliorating the negative effects of uric acid could be a newer paradigm in preventing cardiovascular morbidities.

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