Prognostic Role of Serum Uric Acid in Critically Ill Patients with Non-ST Elevation Acute Myocardial Infarction

Charan Reddy KV, MD, DNB and Jaishree Ghanekar, MD*

Abstract
Cardiovascular disease (CVD) is the leading cause of death worldwide. Several epidemiological studies have proved that serum uric acid (SUA) is associated with CVD. It is unclear whether increased levels of SUA in CVD promotes or protects against cardiovascular damage. In the present study, we sought to investigate whether the levels of SUA and cardiac biomarkers [Creatine kinase (CK)-MB and Troponin-I] determined on admission will serve as predictors of mortality in non-ST Elevation Myocardial Infarction (NSTEMI) patients during short term in-hospital stay. The results revealed that the mean levels of SUA in males were significantly higher (P<0.001) than the females. A negative correlation between age and SUA levels was observed. Higher SUA, CK-MB and Troponin-I (TPN-I) values correlated with increased amounts of triglycerides, LDL-c and in-hospital mortality. Cox multivariate analysis revealed that higher risk of cardiac failure was observed in patients who had higher levels of SUA, CK-MB and TPN-I on admission. These levels were increased consistently in them during 72 hrs in-hospital stay (HR: 4.83, 95% CI: 1.920-2.490, P<0.001). Seven patients who died during in-hospital stay were belonged to Killip class 2/3 and presented with SUA levels ≥ 7 mg/dl (males) and > 5 mg/dl (females) as compared to control subjects or those discharged. In conclusion, determination of circulating CK-MB and TPN-I levels on admission adds prognostic indicator value to SUA in early prediction of mortality in NSTEMI patients.

Keywords- Cardiovascular disease, Killip class, Mortality, Myocardial infarction, Serum uric acid, Survival.


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I. INTRODUCTION

Developing countries of the world face a double burden of infectious or communicable diseases [e.g: human immunodeficiency virus (HIV), tuberculosis etc] and non-communicable diseases (NCDs) [e.g: diabetes, cardiovascular disease (CVD), renal disease and cancer etc]1-2. More people die annually from CVD than from any other cause. (source:http://www.who.int/mediacentre/tre/factsheets/fs317/en/accessed on 17th October 2014). The average age for myocardial infarction (MI) attack in Indians has decreased by 20 years and about half of the reported cases are below the age of 50 years3. Of the 17.5 million deaths due to CVD globally, 20% deaths occurred in high income countries, 8% in upper-middle income countries, 37% in lower-middle income countries and 35% in low income countries including India3,4. The emerging data suggests that many of the CVD risk factors including smoking, tobacco use and alcohol drinking, low physical activity, high dietary fat intake, obesity, hypertension, diabetes, hypercholesterolemia and high blood pressure (BP) are more common among the low socioeconomic individuals5,6. Efforts to improve lifestyles, controlling lifestyle-related such risk factors, will certainly contribute to CVD prevention7.

Each year, a large number of patients are seen in the Emergency Department with presentations necessitating investigation for possible acute myocardial infarction (AMI). Patients can be stratified by symptoms, risk factors and ECG results but cardiac biomarkers have prime role both diagnostically and prognostically8. Measurement of multiple biomarkers may accelerate current diagnostic protocols for the assessment of patients having CVD. In this regard, serum uric acid (SUA), creatine kinase muscle-brain (CK-MB) fraction and troponin-I (TPN-I) have become the biomarkers of choice for patients with AMI9-11.

Uric acid (UA) is the final breakdown product of purines, the principal constituent of adenosine triphosphate, DNA, and RNA, and its synthesis is mediated by an enzyme xanthine oxidase. Our understanding of the role of SUA in human disease has been largely confined to gout, until recently when it was also shown to be related to hypertension, obesity, increased triglycerides and insulin resistance12-14. A number of clinical and epidemiological evidences revealed that SUA levels correlated with all major forms of death, including acute, sub-acute and chronic forms of CVD, heart failure (HF) and stroke15.
It is documented that prediction of death/survival after AMI is very important in planning interventions strategy. For this, till date, several studies have evaluated the predictive value of on-admission biomarkers (interleukin-6, B-type natriuretic peptide (BNP), Lactate dehydrogenase (LDH-1) Glycogen phosphorylase isoenzyme-BB (GPBB), C-reactive protein (CRP) and myoglobin etc) and their outcomes though none is currently available over the counter (OTC)16-18. Cardiac troponin-I, the current “gold standard biomarker for the diagnosis of AMI is sensitive and specific for cardiac damage. Serum levels of these markers increase within 3-12 hrs from the onset of chest pain, peak at 24-48 hrs and return to baseline over 5-14 days20. Prior to the introduction of cardiac troponins, the biomarker of choice for the diagnosis of AMI was the CK-MB iso-enzyme. CK-MB first appears 4-6 hrs after symptom onset, peaks at 24-48 hrs and returns to normal on or after 72 hrs10. Though SUA, CK-MB and TPN-I recognized for over 60 years as independent diagnostic markers of AMI, their prognostic role in patients presented with non-ST segment elevation myocardial infarction (NSTEMI) remains a controversial issue. The purpose of this study was to demonstrate the relationship between the levels of serum biomarkers (SUA, CK-MB and TPN-I) and patient mortality on admission followed by 3-day hospital stay in critically ill NSTEMI patients. The results demonstrated that these can form as the biomarkers of prognosis in patients with NSTEMI. SUA ≥ 7 mg/l identified patients at high risk of death or need an urgent attention. CK-MB and TPN-I added prognostic information to the predictive value of SUA.

II. MATERIAL AND METHODS
Approval of Ethics Committee
The study design and protocol was approved by the Institutional Ethical Review Committee (IERC) of Mahatma Gandhi Mission (MGM) Medical College and Hospital, Kamothe, Navi Mumbai, India. The study was conducted between the period from June 2011 to November 2013 in MGM Hospital. All the AMI cases and the control subjects were selected from MGM hospital by applying strict inclusion and exclusion criteria. Study subjects were informed of the possibility of using the data obtained for academic purpose. Confidentiality was assured to all participants and data used for this study were stripped of personally identifiable information. They were also informed about their right to withdraw their consent at any point, without any consequence to them. Patients were treated as decided by attending physician. Patients were monitored till the end of 72 hrs ICU stay.

Patient’s selection criteria
Twenty five AMI patients admitted to ICU, MGM Hospital were included on the basis of the following criteria: For comparison, twenty five age matched control subjects admitted in the ICU for reasons other than AMI or any other serious organic illness (e.g: renal disease) were selected. Care was taken to select these subjects, whose SUA levels were at per with the standard reference values recommended by WHO21.

AMI patients in the age group of 20-75 yrs and stayed at least for 72 hrs in ICU were included in this study. Excluded were the patients with prior history of gout, renal failure, liver disease, thyroid dysfunction, systemic or local infections, hematological malignancy, sepsis, neoplasms, coagulating disorders and stayed less than 72 hrs in ICU, discharged from the hospital and then readmitted to the ICU during the observation period. Patients who were on iron or vitamin supplements and on hyperuricemic drugs like thiazide diuretics, salicylates, ethambutol, pyrazinamide, allopurinol and patients whose serum creatinine levels are > 2 mg/dL were also excluded.

Evaluation of cardiac risk factors
On admission, physical examination, medical histories and a special questionnaire on lifestyle and risk factors like diabetes mellitus, hypertension and alcohol drinking and smoking history were obtained from the patient's clinical files and caregivers. Chest pain at rest, transient electrocardiogram (EKG) changes was recorded in each patient just after hospital admission and the NSTEMI. The diagnosis of NSTEMI was based on electrocardiographic (EKG) ST-segment depression or prominent T-wave inversion, evidence of hemodynamic instability and/or arrhythmias22 and/or raise in serum concentration of biomarker of necrosis (e.g:TPN-I, when used 99th percentile reference range23) as defined in American College of Cardiology/American Heart Association guidelines24. Baseline blood pressure of the patients in supine position was recorded. Survival time was defined as the period from the time of admission to the time of death during 72 hrs stay in ICU. Mortality if any between admission and during 72 hrs stay in ICU was also recorded.

Blood collection and determination of SUA concentration
Venous blood sampled on admission and during 24, 48 and 72 hrs post admission in 5 ml sterile vacutainer tubes. The plasma was separated by centrifugation at 1000 rpm for 10 min. Non-hemolyzed plasma was used for the determination of various biochemical parameters. Serum levels of UA were estimated on admission, 24, 48 and 72 hrs ICU stay by Uricase method described by Fossati et al25 - Briefly, oxidation of uric acid by uricase enzyme, which converts its substrate to allantoin.

\[
\text{Uricase} \\
\text{Uric acid + } 2\text{H}_2\text{O + O}_2 \rightarrow \text{Allantoin + H}_2\text{O}_2 + \text{CO}_2 \\
\text{(absorbs at 293 nm) (nonabsorbing at 293 nm)}
\]

The differential absorbance of these substances were measured at 293 nm and expressed as mg/dl. The methods for the determinations of lipids were made according to the Association for the Prevention of Atherosclerosis and its Complication (AMPAC) guidelines. The levels of triglycerides (TG’s)26, total cholesterol (TC), Low-density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c)27, CK-MB28, TPN-I29 and creatinine30 levels were determined as per the methods given in the parentenance. The LDL-c levels were calculated using the method described by Friedewald et al31. All methods were fully automated with
automatic calibration and accredited laboratory facilities.

**Killip Classification**

Killip’s clinical examination guidelines reported by Killip and Kimbal to stratify patients with HF. These guidelines were used in our study on admission and during 24, 48 & 72 hrs stay in ICU. A high SUA levels defined as a value in the 2.3 Killip’s scale or a value in the quartile 3/4 (> 6.50 mg/dl), which sits at the approximate limit of solubility forurate. Based on SUA concentration at baseline and during ICU stay, patients were divided into four groups using Killip scale with separate cut-off points for men and women.

**Statistical Analysis**

Data was analyzed using Graph Pad Prism software version 5.0 (Graph Pad software, CA, USA). Basic data on SUA, CK-MB, TPN-I, blood glucose, systolic blood pressure (SBP) & diastolic blood pressure (DBP), total cholesterol, low density lipid cholesterol (LDL-c), high density lipid cholesterol (HDL-c), triglycerides and creatinine were expressed as mean ± Standard Deviation (SD). The significance level of the statistical verification was set at P < 0.05. Levels of SUA, CK-MB, and TPN-I on admission and ICU stay after that were compared using paired “t” test. Cox proportional hazard regression models were used to perform univariate and multivariate analyses stratifying for gender and adjusting for age, cholesterol, HDL-c, LDL-c, triglycerides, creatinine, history of only diabetes, diabetes and AMI, only AMI etc. The contribution of SUA, CK-MB and TPN-I levels from the time of admission to 72 hrs stay and trends in SUA levels across quartiles were assessed in linear regression model by using the median values of each quartile to minimize the influence of outliers.

**III. RESULTS**

**Patient admission characteristics**

The study consists of 25 age matched control subjects to 25 NSTEMI patients admitted in the Emergency Department of Cardiac unit of MGM hospital, Navi Mumbai. The data on demographic information such as age, sex, SBP, DBP, status of diabetes, previous stroke, past and present history of smoking, alcohol drinking, fever, chest pain, dyspnea, edema, nausea and vomiting etc, on admission and during 72 hrs ICU stay were collected.

**Distribution of study participants based on age**

The average age of the control subjects (n=25) was 53.98 ± 11.14 was matched with AMI patients (n=25) i.e. 52.01 ± 12.06. The control subjects were in the age range of 20-39 yrs (4 males & 3 female), 40-59 yrs (10 males & 6 females) and over 60 yrs (1 male & 1 female). Whereas AMI patients fall in the age range of 20-39 yrs (4 males & 1 female), 40-59 yrs (10 males & 7 females) and over 60 yrs (2 males & 1 female).

**Demographic characteristics of study participants**

The baseline characteristics of the study subjects were shown in Figure-1. AMI patients comprising 24% hypertensive-H (n=6), 16 % diabetics-D (n=4), 24% smokers-S (n=6), 8% hypercholesterolemia-HC (n=2); 12% hypertensives + smokers-HS (n=3), 4% smokers + diabetics (n=1); 8% hypertension + diabetics + smokers-H +D + S (n=2), 4% hypertension + diabetics + smokers + hypercholesterolemia-H+D+S+HC (n=1). SUA levels were determined in all the study subjects. The results revealed that SUA levels were significantly (P<0.001) elevated in patients presented with hypertension and its combination with other CVD risk factors such as smoking, diabetes and hypercholesterolemia. SBP was significantly higher in AMI patients as compared to the control subjects after adjusting for age and sex (160 ± 5.31 Vs 121 ± 4.08 mm/Hg). In contrast, DBP was significantly lower in AMI patients than the control subjects (75.08 ± 4.87 Vs 80 ± 3.9 mm/Hg). A significant negative correlation was observed between age and SUA levels (r=-0.29, P<0.001) (Data not shown). Their past history showed none of the control subjects and AMI patients suffered with renal or liver diseases.

**Comparison of SUA levels in males Vs females on admission**

In order to know whether SUA levels varies between study participants, and significance of such changes in the development of AMI. Patients were divided according to quartile values of SUA. The mean SUA values of 1.75 mg/dl (range 1 - 2.5), 3.50 mg/dl (range 2.6 - 4.10), 2.86 mg/dl (range 4.11-5.61) and 6.45 mg/dl (range 5.62-7.20 and above) were used for men, and 3.1 mg/dl (range 0.50- 3.80), 4.3 mg/dl (range 3.9 - 4.7), 5.3 mg/dl (range 4.80 - 6.0) and 7.70 mg/dl (range 6.1 -15.4) for women. The results indicate a statistically significant difference in SUA level between men and women. On the day of admission, males (AMI cases & control subjects) showed 22.88% higher levels of SUA than females (5.42 ± 0.88 Vs 4.18±0.69 mg/dl). Similarly, AMI male patients (n=16) had 23.0% higher SUA levels than control male subjects (n=15). AMI female patients (n=9) had 20.78% higher SUA levels than
control female subjects (n=10) (4.67±0.79 Vs 3.70±0.59 mg/dl) (Fig-2a,b).

Grouping of study subjects using Killip classification based on SUA levels

The mean values of SUA in AMI male patients at the time of admission were higher than the control subjects. SUA levels were consistently raised by 4.30, 10.55 & 24.19 % by the end of ICU stay as compared to admission day. SUA levels were increased by 5.38, 10.44 & 30.18 % in male patients and 2.1, 10.70 & 18.20% in females by the end of 24, 48 and 72 hrs respectively as compared to the admission day (Fig-3).

Table 2a & 2b:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n=25)</th>
<th>AMI (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>5.85 ± 1.8</td>
<td>6.30 ± 1.60</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>146.09 ± 21.76</td>
<td>231.45 ± 15.29</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>200.89 ± 8.13</td>
<td>285.20 ± 17.65</td>
</tr>
<tr>
<td><strong>LDL-c (mg/dl)</strong></td>
<td>84.43 ± 11.76</td>
<td>159 ± 10.09</td>
</tr>
<tr>
<td><strong>HDL-c (mg/dl)</strong></td>
<td>46.02 ± 3.37</td>
<td>34.14 ± 2.21</td>
</tr>
<tr>
<td><strong>LDL-c/HDL-c ratio</strong></td>
<td>1.83</td>
<td>4.65</td>
</tr>
<tr>
<td><strong>Total Cholesterol / HDL-c ratio</strong></td>
<td>4.37</td>
<td>8.35</td>
</tr>
<tr>
<td><strong>SUA (mg/dl)</strong></td>
<td>4.21 ± 0.82</td>
<td>5.40 ± 1.02</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>0.65 ± 0.14</td>
<td>0.71 ± 0.21</td>
</tr>
</tbody>
</table>

Next, we determined the extent of elevation in SUA concentration between AMI patients and controls, and whether an elevation has any clinical significance in early prediction AMI patients mortality. Based on the SUA levels, patients were divided into 3 groups using Killip classification tool and in-hospital mortality outcomes were determined (Table 2a & 2b). At admission, SUA levels in AMI patients were higher than the control subjects (5.42 ± 1.02 Vs 4.20 ± 0.82 mg/dl). By the end of 72 hrs, the average SUA levels increased to 6.75 mg/dl, therefore, SUA may be considered as a powerful independent predictor of 72 hrs ICU mortality (HR: 4.83, 95% CI: 1.920-2.490, P = 0.001). The results indicated that on admission, the mean levels of SUA in AMI patients were on par with Killip class-1 range (~5 mg/dl). By the end of 72 hrs ICU stay, the levels in 5 AMI males (8.56, 7.27, 8.19, 8.22 & 8.34 mg/dl) and 2 females (5.72 & 5.45 mg/dl) were gradually raised as compared to admission day and the levels belonged Killip class-2/3 (>7 mg/dl), all these seven patients died.

Table 1:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Males (Control)</th>
<th>Male (AMI)</th>
<th>Females (Control)</th>
<th>Female (AMI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUA (mg/dl)</td>
<td>2.18 ± 0.09</td>
<td>4.56 ± 0.82</td>
<td>2.00 ± 0.14</td>
<td>4.20 ± 0.82</td>
</tr>
</tbody>
</table>

Fig-2a: Levels of SUA in control subjects and AMI cases on admission. (a) AMI males and females showed significantly higher SUA levels than the control males and females. Each value is the mean ± Standard Deviation (S.D). (**: P<0.05; **=P<0.01).

Fig-2b: Mean levels of SUA increased significantly in AMI patients than the control subjects. Each value is the mean ± Standardization Deviation (S.D). (**:P<0.01).

Fig-3: Levels of SUA in control and AMI patients on admission and during 72 hrs stay in ICU. Males have significantly higher SUA levels than females. SUA levels in some of the AMI patients were elevated during 72 hrs ICU stay. Each value is the mean ± Standard Deviation (S.D). (*: P<0.05; **: P<0.01; ***: P<0.001).
TABLE-2A

Association between Killip’s classification and SUA levels in AMI patients during 72 hrs stay in ICU. (M=Male; F=Female; *=AMI cases died during ICU stay).

<table>
<thead>
<tr>
<th>Sl.#</th>
<th>Killip class</th>
<th>Admission</th>
<th>During ICU stay</th>
<th>24</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

TABLE-2B

Distribution of AMI patients based on SUA levels using Killip Classification. (M=Male; F=Female; *=AMI cases died)

<table>
<thead>
<tr>
<th>Sl. #</th>
<th>Killip class</th>
<th>SUA (mg/dl)</th>
<th>&lt;5.0</th>
<th>5.1-7.4</th>
<th>&gt;7.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>-</td>
<td>10</td>
<td>10(2F*)</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>1(1M*)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Distribution pattern of study subjects in different quartiles based on SUA levels

In addition to Killip’s classification, we also performed quartiles distribution of study participants according to the protocol described earlier. SUA was treated as a categorical and as a continuous variable, divided into four quartiles. Considering SUA quartiles, SUA concentrations showed a positive correlation with gender. Patients with higher SUA exhibited increased levels of TPN-I (p< 0.021), belonged higher quartiles (Table-3). Incidentally, the same AMI patients who were in Killip class 2/3 were belonged to higher quartiles.

TABLE-3

Distribution of AMI patients in different Quartiles based on SUA levels. Seven patients (5 males & 2 females) who had high SUA levels are in Quartile- 4 were died.

<table>
<thead>
<tr>
<th>Quartile &amp; SUA range</th>
<th>Males (Control Subjects)</th>
<th>Males (AMI Patients)</th>
<th>Females (Control Subjects)</th>
<th>Females (AMI patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (1.00-2.50)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Q2 (2.51-4.00)</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Q3 (4.01-5.60)</td>
<td>14</td>
<td>2</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>(4.01-5.60)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 (5.61-7.12)</td>
<td>0</td>
<td>14 (5 died)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>16</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

Correlation between CK-MB & TPN-I levels and incidence of patients mortality

Studies were extended further to determine whether the activity levels of CVD biomarkers such as TPN-I and CK-MB and their relationship with SUA in the prediction of AMI patients mortality. CK-MB measures the blood levels of two variants, isoenzymes (CK)-B and (CK)-B) of the enzyme phosphocreatine kinase. Skeletal muscle releases CK-MB and AMI causes its elevation that peaks ~20 hrs after the onset of coronary occlusion. An elevated CK-MB is relatively specific for myocardial injury, particularly when skeletal muscle damage is not present. In clinical practice TPN-I is the cornerstone of the diagnosis, risk stratification and thus selection of the optimal treatment strategy in patients with AMI.

In the present study, the mean values of CK-MB (Figs-4) and TPN-I (Fig-5) were increased by 34.12% and 63.18% respectively at the end of 72 hrs ICU stay as compared to the admission day. The levels of CK-MB in AMI males and females were increased by 24.43% respectively and 46.34 % as compared to male and female control subjects. Whereas TPN-I levels in AMI males and females were increased by 41.69 % and 52.37% respectively as compared to control subjects. The
mean levels of CK-MB (2.60, 12.14, and 25.63 %) and TPN-I (3.76, 10.55 and 17.63 %) were increased during 24, 48 and 72 hrs respectively as compared to admission day. In AMI males, increase of CK-MB (9.37, 26.33 and 50.63 %) and TPN-I (3.76, 10.55 and 17.63 %) levels respectively by the end of 72 hrs stay in ICU as compared to admission day. The levels of CK-MB in 5 AMI male (11.12, 9.17, 11.01, 10.65 and 10.85 IU/L), and in 2 female patients (8.45 and 8.63 IU/L) and TPN-I in the same male (28.09, 28.22, 29.03, 28.76 and 29.00 ng/ml) and female patients (17.65 and 18.15 ng/ml) were raised by the end of 72 hrs stay in ICU. All the seven patients who had elevated levels of SUA also showed increased levels of CK-MB and TPN-I, and these patients were died between 0 to 72 hrs ICU stay, suggesting these markers have good correlation with the mortality AMI patients (Table-4).

TABLE-4

Levels of SUA (mg/dL), CK-MB (IU/L) and troponin-I (ng/ml) and their association with mortality in AMI patients during 72 hrs stay in ICU. (M: Male; F: Females).

<table>
<thead>
<tr>
<th>Subjects</th>
<th>SUA</th>
<th>CK-MB</th>
<th>Troponin-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-1 (M)</td>
<td>8.56</td>
<td>11.12</td>
<td>29.03</td>
</tr>
<tr>
<td>Patient-1(M)</td>
<td>7.27</td>
<td>9.17</td>
<td>28.22</td>
</tr>
<tr>
<td>Patient-1(M)</td>
<td>8.19</td>
<td>10.01</td>
<td>28.09</td>
</tr>
<tr>
<td>Patient-1(M)</td>
<td>8.22</td>
<td>10.65</td>
<td>29.00</td>
</tr>
<tr>
<td>Patient-1(M)</td>
<td>8.34</td>
<td>10.85</td>
<td>28.76</td>
</tr>
<tr>
<td>Patient-1(F)</td>
<td>5.72</td>
<td>8.45</td>
<td>17.65</td>
</tr>
<tr>
<td>Patient-1(F)</td>
<td>5.45</td>
<td>8.63</td>
<td>18.15</td>
</tr>
<tr>
<td>Controls (Males)</td>
<td>4.72±0.90</td>
<td>4.78</td>
<td>19.60</td>
</tr>
<tr>
<td>Controls (Females)</td>
<td>3.70±0.59</td>
<td>4.00</td>
<td>10.65</td>
</tr>
</tbody>
</table>

The importance of accurate prognostication during the care of patients with CVD is being increasingly recognised. Though, elevated levels of SUA is identified as an independent risk factor for AMI mortality, a significant controversy still exists, since elevated SUA levels are also associated with other AMI risk factors. In the present study, besides SUA, we also investigated the association of SUA, CK-MB and TPN-I levels with mortality on admission and during 3-day hospital stay after that in critically ill NSTEMI patients.

We observed a positive correlation between elevated SUA with gender and AMI risk factors like hypertension, smoking, diabetes, triglycerides, cholesterol, LDL-c, CK-MB and TPN-I. This finding is in consistent with the previously reported association of SUA with obesity, hypertension, metabolic syndrome, and glucose intolerance, all of which contribute to the pathogenesis of AMI. Furthermore, our results are also in agreement with the recent study reported in North-Eastern part of India by Baruah et al., which showed CAD patients who presented with AMI had higher SUA levels and remarkably low HDL-c levels. Bonora et al. studied 957 young men and reported a significant positive correlation of elevated SUA levels with triglycerides, cholesterol and LDL-c. Similar finding was reported by Chamorro et al. Using data from the Framingham study concerning the role of SUA as an independent risk factor in CVD, Cullen et al. reported an increased risk for adverse outcome after age adjustment only in women, which was not independently associated with death from CVD or from all causes after additional adjustment for CVD risk factors. Using stepwise Cox analysis, they concluded that SUA does not have a causal role in the development of coronary heart disease (CHD) and that any apparent association with these outcomes is probably due to the association of SUA levels with other risk factors.

Fig-5a. Mean levels of TPN-I (ng/ml) in male and female control subjects and AMI patients on admission. (a). TPN-I levels were significantly high in males than females. Each value is the mean ± S.D. (** P<0.01; ***: P<0.001).  

Fig-5b. Mean values of TPN-I in control subjects and AMI cases on admission. SUA levels were significantly elevated in AMI cases. Each value is the mean ± S.D. (**: P<0.001).
in Q1, 5 AMI cases (2 males & 3 females) were in Q1, 9 subjects (1 male & 8 females) were in quartile 2 and 16 subjects (14 male +2 females) were in Q3 and none were in Q4. On an average, the levels of SUA in control male subjects were 4.72 ± 0.90 mg/dl on admission, whereas in females the levels were 3.70±0.59 mg/dl. Of the total 25 AMI patients (16 males + 9 females), none of them were in Q1. 5 AMI cases (2 males & 3 females) were in Q2, 13 cases (9 males & 4 females) were in Q3 and 7 cases (5 males and 2 females) were in Q4. On an average the levels of SUA in male AMI cases was 6.13 ± 0.87 mg/dl and 4.67 ± 0.79 mg/dl in females. Males showed significantly higher levels of SUA than females (5.43 Vs 4.19 mg/dl) (*= Females; = Males).

At present, it is unclear whether high SUA levels promote or protect against the development of AMI, or simply act as a passive marker of increased risk in NSTEMI patients. It has been reported that UA is elevated in association with increased xanthine oxidase activity. During UA production, oxygen free radicals are generated and therefore, UA may be a simple and useful clinical indicator of excess oxidative stress. The generation of oxygen free radicals is one of probable mechanisms involved in the no-reflow phenomenon during reperfusion therapy. On the other hand, hyperuricemia is associated with decreased production of nitric oxide (NO) and endothelial dysfunction and myocardial microvascular disease and local inflammation. Hyperuricemia in NSTEMI patents may also be related to increasing production of SUA in the body or reduction of its elimination through the kidney or cellular injury to heart musclecaused by low cardiac output and tissue hypoxia.

In our study we did not find any such change in SUA levels among different age group of participants. However, SUA levels were found to be more in males than the females (5.42 ± 0.88 Vs 4.18±0.69 mg/dl). This could be due to the protective action of estrogen up to menopause stage or gender significance as majority of the women who presented with AMI was postmenopausal (8 out of 9 patients). Our results are in agreement with study done by Maxwell et al, who showed men had significantly higher SUA than women (5.5 ± 1.3 mg/dl Vs 4.2 ± 1.4 mg/ dl). A study done by Hyun et al demonstrated that SUA levels were better predictor of AMI in male patients than females. In contrast, others showed the relation between SUA and CVD is generally stronger in women than men.

Next, we classified AMI patients based on SUA levels using Killip classification. Based on the extent of SUA elevation in AMI males (>7.0mg/dl) and females (>5.0 mg/dl) they were grouped in Killip class-2/3 or Quartile-3/4 Patients whose SUA levels were in upper quartile were at higher risk of mortality as compared to those in the lowest quartile. These results were in agreement with the recent study done with 856 STEMI patients, wherein SUA levels reported in patients belonging to higher Killip class and that SUA was an independent risk factor to predict mortality. In contrast to our observation, a retrospective analysis of hospitalization data of 2,495 patients in Glasgow indicated that higher SUA on admission predicted poor outcome (dead or in care). In our study, out of 25 AMI patients, 14 were belonged to Killip Class-2 and one in Killip class-3 based on SUA levels. On admission day most of the patients had mean SUA levels as ~5.0 mg/dl, but consistently raised in few patients during 24, 48 and 72 hrs stay in ICU, attributing higher SUA level may be linked to patient’s mortality. These findings are in line with previous reports, wherein it showed good correlation between increased SUA and higher Killip class on admission. Car and Trkulja reported a univariate association between higher SUA levels at admission and higher 30 day mortality of AMI patients. Recently El-Manyar et al data with 6,689 acute coronary syndrome patients, grouped under Killip class 2/3 revealed higher cardiac risk factor. However, in this study the progression between the Killip classes during the hospital stay was not assessed. In our study, overall there were 7 deaths (5 males & 2 females) by the end of 72 hrs stay in ICU. Of the 5 AMI males, one male who belonged to Killip class-3 showed SUA levels as high as 8.56 mg/dl. Two female AMI cases that died in ICU had elevated levels of SUA (> 5 mg/dl). SUA levels in none of the patients were measured > 9 mg/dl during 72 hrs ICU stay, therefore none of the patient were in Killip class-4.

Blood testing for biomarkers of myocardial injury plays an increasingly important role for the evaluation and diagnosis of patients with chest pain, but the development is challenging. It has been reported that cardiac muscle injury is associated with CK-MB release. CK-MB levels increased within 3-12 hrs of onset of chest pain, reach peak values within 24 hrs, and return to baseline after 48-72 hrs. Troponins are proteins released from the cytosolic pool of the myocytes when irreversible myocardial damage occurs. Isoforms of the protein, T and I are specific to myocardium. However, the relationship between SUA, CK-MB and TPN-I with short-term outcomes in critically ill NSTEMI patients has not been fully evaluated. Therefore, next we examined the prognostic value of TPN-I and CK-MB in NSTEMI patients on admission and during 72 hrs ICU stay. We believe that, combined use of these biomarkers may lead to more appropriate therapy and improved outcomes in NSTEMI patients.
The results revealed that SUA, CK-MB and TPN-I levels were significant predictors of short-term mortality. The hazard ratio (HR) for patients in the highest quartile of SUA was significantly high (HR: 3.5; P< 0.001) compared with those in the lowest quartile for death after adjustment for independent AMI risk factors known to be associated with mortality. The strong association of SUA, CK-MB and TPN-I with mortality of NSTEMI males compared with women highlights the necessity of stratifying by gender in the investigations of CVD and exploration of these biomarkers in general population. In this context, the inclusion of SUA as variable for the stratification of CVD risk seems interesting, as it is an easy-to-perform and low-cost test that can be useful in clinical practice. In conclusion, our results suggest that hyperuricemia after AMI is associated with the development of HF. SUA, CK-MB and TPN-I levels are the suitable marker for predicting AMI-related future adverse events, and these biomarker levels appears to be a good predictor of mortality in AMI patients.

**Strengths and limitations of the study**

Some limitations apply to our study, and we need to be aware of such limitations in interpreting the results. Among the limitations is the fact that this is not a population-based study. It is a single-center case control study restricted to a local hospital, based on the data collected from a small number of ethnically homogeneous, unselected clinically assessed NSTEMI patients. Therefore, this may limit its generalizability to other racial groups, since the area was restricted to a local hospital. The other possible limitation is potential for the complicating effects of SUA with comorbidities are difficult to account for. Another possible limitation is the lack of information on use of drugs to treat hyperuricemia, such as allopurinol. Also we did not have information on serum insulin and fructose intake which could increase SUA levels and affect patients with AMI. When the study population was divided according to SUA values, patients in each quartile were quite small. Nonetheless, increased SUA concentration was effective in identifying AMI patients at high risk of death and worsening of AMI. Also we believe that greater risk of AMI events or morbidity/mortality attributable to hyperuricemia in our study, challenges the antioxidant properties shown by SUA. The results obtained in our study do not provide support for the view that the antioxidant capacity of UA that ameliorates the clinical prognosis of patients with NSTEMI. The practical application of this conclusion deserves some thought. Another limitation of the study is that we did not follow our discharged patients. Notwithstanding these limitations, we consider that our study makes an important contribution, since similar studies are few and their results are inconsistent.

**Conclusions and clinical implications of results**

The main findings of the present study are: 1) A significant negative correlation between age and SUA levels, 2) SUA levels were significantly higher in men than women, 3). Our study documents and validates that high SUA levels is a strong, independent predictor of mortality in males (>7.0 mg/dl) and females (>5 mg/dl), and 4). A significant positive association of SUA, cardiac biomarkers (CK-MB and TPN-I) with short term mortality in NSTEMI patients. We believe that incorporation of SUA, CK-MB and TPN-I will allow better risk stratification of patients with NSTEMI. Our findings have significant clinical implications, given the fact that AMI has been a growing public health burden across the world. SUA levels can be measured at a low cost in almost all hospitals in the world, especially in developing countries, which have no facilities to measure other more expensive prognostic markers such as high sensitive C-reactive protein, Brain-type Natriuretic Peptide, Interleukin-6 and many others. It is the need of the hour to set guidelines for the measurement of cost-effective biomarkers in general population. Besides this, controlling hyperuricemia might also be a promising strategy for the prevention of AMI.

Taking into account, all the previous literature on the prevalence of AMI, it is safe to conclude that higher SUA, CK-MB and TPN-I levels determined on admission and during short stay in ICU can be useful predictors of survival in critically ill NSTEMI patients. We strongly recommend that patients with higher levels of these markers on admission should be closely monitored for AMI associated complications. In support of our current findings, further studies are necessary to obtain prevalence data on these markers with a larger group of patients from many different areas.

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