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Original Article

Admission Serum Uric Acid Levels and In-Hospital Outcomes in Patients with Acute Coronary Syndrome

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Abstract

***Background**: Uric acid is an independent risk factor for cardiovascular disease. Hospital admission for ischemic heart disease (IHD) is increasing rapidly in our country. Although studies were conducted abroad regarding association of serum uric acid with in-hospital outcomes in patients with acute coronary syndrome (ACS), no data is yet available to show the association in our country. **Objective**: The objective of this study was to assess the association of serum uric acid level on admission with in-hospital outcomes of the patients with ACS. **Materials and Methods**: This cross sectional comparative study was done in the Department of Cardiology, Dhaka Medical College Hospital (DMCH) from January to December 2012. After proper ethical consideration total 93 ACS patients were enrolled in the study by nonrandom sampling. Serum uric acid of all subjects was measured within 24 hours of admission. Then in-hospital outcomes were observed in all subjects. **Results**: The frequency of hyperuricemia among ACS patients was 24.7% (22.54% in male and 31.82% in female). Hyperuricemic patients significantly developed heart failure (30.4% vs 11.4%, p=0.032) and conduction defect (13.0% vs 1.4%, p=0.017) than normouricemic subjects. The mean ejection fraction was significantly lower in hyperuricemic patients than patients with normal uric acid level (50.87 ± 10.27% vs 55.94 ± 6.66%). The mean ± SD duration of hospital stay of hyperuricemic group was significantly longer in patients with ACS (8.26 ± 1.18 vs 7.51±1.18 days, p=0.010). **Conclusion**: The measurement of serum uric acid level, an easily available and inexpensive biochemical tool, might turn out as a valuable risk marker for prediction of in-hospital outcomes in patients with ACS.*

***Key words**: Serum uric acid; Ischemic heart disease; Acute coronary syndrome; Heart failure*

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Introduction

Coronary artery disease (CAD) is the most prevalent manifestation of cardiovascular disease and is associated with high mortality and morbidity.[1] Among the CADs, acute coronary syndrome (encompassing ST-segment elevation myocardial infarction, non-ST segment elevation myocardial infarction and unstable angina) is the leading cause of death in developed countries and second leading cause of death in developing countries and by the year 2020, CAD will hold the first place in the WHO's list of leading cause

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of disability.[2,3] About 7.1 million deaths occurred globally in 1999 due to CAD and it will rise to 11.1 million by 2020. In the United Kingdom (UK), 1.3 million people develop CAD every year while in USA, 0.8 million people suffer from new heart attacks each year.[4] Various studies have pointed out that South Asians have a higher prevalence of CAD as compared with other ethnicities with a higher rate at younger ages.[5,6] In India, 4% rural and 11% urban populations suffer from CAD.[4] Being a South Asian country Bangladesh is not immune to this higher prevalence of CAD. Atherosclerosis is the main pathology behind CAD and non-invasive methods for the prediction of the severity of atherosclerotic lesions have become an important objective for early treatment as well as primary preventive measures.

Acute coronary syndrome (ACS) is a common disease in Bangladesh. It causes a great cost in care and has significant morbidity and mortality.[7] The progressively increasing trend of the disease in our country shows that the prevalence of CAD in our country was 3.3/1000 in 1976 and 17.2/1000 in 1986 indicating a 5 fold increase in 10 years.[4]

Ischemic heart disease (IHD) is becoming a significant burden on health care services in Bangladesh. The average prevalence of IHD from 3 small scale population-based studies in Bangladesh was 6.56/1000.[8-10] Hospital admission for IHD is increasing rapidly in our country and the number of young patients having ACS has been increasing dramatically.[11] Socioeconomic improvement and changes in lifestyle, increase in tobacco consumption and saturated fat intake, decrease in physical activity, increasing body weight and consequently increasing rate of diabetes mellitus (DM), hypertension (HTN) and dyslipidemia might have contributed to this increase in our population.[4]

Uric acid is the final breakdown product of purine degradation in humans.[12] Elevated serum uric acid has proved to be risk factor for ischemic heart disease and other cardiovascular diseases in several epidemiologic studies.[13,14] It is also associated with increased death from cardiac causes.[15] Experimental studies have shown a uric acid link to endothelial dysfunction[16,17], impaired oxidative metabolism[18], platelet adhesiveness[19] and platelet aggregation[20].

Uric acid is an independent risk factor for cardiovascular disease. It can exert its effect by several mechanisms. Studies in both in vitro and in animal models have raised some possibilities. Soluble concentrations of uric acid, when applied to vascular endothelial cells, inhibit the synthesis of nitric oxide in a dose-dependent manner.[21] Uric acid also induces vascular smooth muscle proliferation in a dose-dependent manner. The combination of loss of the vasodilatory actions of nitric oxide, together with the proliferation of vascular smooth muscle, would appear to be a potent combination for constriction of the vascular bed.[21]

Since the underlying pathophysiology of disease in patients with acute coronary syndrome (ACS) varies widely, accurate risk stratification to determine appropriate management and improve outcomes is essential.[22] Increased serum uric acid levels are linked to obesity, dyslipidemia and hypertension (insulin resistance or syndrome X), all of which are also associated with increased risk for cardiovascular disease.[23] However, the specific role of serum uric acid in this constellation remains uncertain.[24] Several studies have investigated whether serum uric acid (SUA) is an independent marker of cardiovascular disease (CVD) risk.[25-31] Most prospective studies found a positive association between SUA and CVD mortality as well as all-cause mortality.[13,28,31]

Although studies were conducted abroad regarding association of SUA with in-hospital outcome in patients with ACS, no data is yet available to show the association in our country. So this study has been done on newly diagnosed ACS patients admitted in coronary care unit (CCU), Dhaka Medical College Hospital (DMCH), Dhaka to find out the association between on-admission serum uric acid level and in-hospital outcomes of these patients.

Materials and Methods

This cross sectional comparative study was conducted in the department of Cardiology, DMCH, Dhaka during the period of January to December 2012. A total of 93 patients from admitted ACS patients in the coronary care unit (CCU), DMCH within the study period were enrolled in the study by purposive sampling. The

patients who had history of previous myocardial infarction (MI), percutaneous transluminal coronary angiogram (PTCA), coronary artery bypass grafting (CABG), known cases of valvular heart disease or cardiomyopathy, patients taking drugs (pyrazinamide, ethambutol, diuretics, aspirin, alcohol), patients with serious co-morbid conditions (i.e. severe renal or liver dysfunction), history of gout, malignancies, psoriasis etc. were excluded from the study.

After admission various clinical presentations, severity and extent of ACS were documented. Traditional risk factors of ACS like smoking, hypertension, diabetes mellitus, dyslipidemia and family history of premature CAD were also documented.

Serum uric acid level was measured within 24 hours of admission. Patients with serum uric acid level >7 mg/dL in male and >6 mg/dL in female were placed in Group I and patients with serum uric acid ⩽7 mg/dL in male and ⩽6 mg/dL in female were placed in Group II.

The in-hospital outcomes (heart failure, arrhythmia, heart block, cardiogenic shock, cardiac arrest and mortality) and duration of hospital stay were compared between the two groups.

Statistical analysis

Data were analyzed by using SPSS for windows version 16.0. Categorical data were expressed as frequency and percentage and association between two variables were tested by using Pearson chi-square test. Continuous data were expressed as mean ± SD and difference of mean of two groups was determined by unpaired Student t test. Level of significance was set at 0.05.

Results

Among the total study subjects (N=93), 71 were male and 22 were female. The mean age of the study subjects was 57.43 ± 15.26 years. Out of them 23 (16 male and 7 female) were hyperuricemic. Table I shows the mean ± SD of serum uric acid levels of Group I (hyperuricemic group) and Group II (normouricemic group). It was significantly higher in Group I than in Group II (8.64 ± 2.24 mg/dL vs 5.22 ± 1.05 mg/dL, p<0.001).

Table I: Comparison of serum uric acid levels between two groups (N=93)

Groups	Serum uric acid level (mg/dL)	p
Group I (n=23)	8.64 ± 2.24	<0.001^{S}
Group II (n=70)	5.22 ± 1.05	

Group I (hyperuricemic group), Patients with serum uric acid concentrations >7 mg/dL in men and >6 mg/dL in women; Group II (normal uric acid level group), Patients with serum uric acid concentrations ⩽7 mg/dL in men and ⩽6 mg/dL in women; p value derived from Student t test; S=Significant

The mean ± SD of ejection fraction of the patients of Group I and Group II were 50.87 ± 10.27% and 55.94 ± 6.66% respectively and the difference between them was statistically significant (p<0.05) (Table II). We found no significant difference in pulse rates, blood pressure and Hb levels between two groups.

Table II: Comparison of hemodynamic status between two groups (N=93)

Hemodynamic status	Groups		P
	Group I (n=23)	Group II (n=70)	
	Mean ± SD	Mean ± SD	
Pulse (beats/min)	75.48 ± 14.65	72.49 ± 9.15	0.249 ^{NS}
SBP (mm Hg)	123.48 ± 21.02	126.57 ± 16.23	0.464^{NS}
DBP (mm Hg)	75.43 ± 13.13	78.36 ± 9.35	0.245^{NS}
Hb (gm/dL)	12.29 ± 2.01	12.94 ± 5.69	0.590 ^{NS}
Ejection fraction (%)	50.87 ± 10.27	55.94 ± 6.66	0.007^{S}

Group I (hyperuricemic group), Patients with serum uric acid concentrations >7 mg/dL in men and >6 mg/dL in women; Group II (normal uric acid level group), Patients with serum uric acid concentrations ⩽7 mg/dL in men and ⩽6 mg/dL in women. p value derived from Student t test; S=Significant; NS=Nonsignificant

The mean ± SD of fasting blood glucose was 7.62 ± 3.47 mmol/L in Group I and 6.64 ± 3.16 mmol/L in Group II with no statistical difference (p=0.208). The mean ± SD of serum creatinine was 1.93 ± 0.73 mg/dL in Group I and 1.32 ± 0.36 mg/dL in Group II. The serum creatinine level was significantly higher in hyperuricemic group (p<0.001). The mean ± SD of SGPT was 45.00 ± 8.75 IU/L in Group I and 40.81 ± 6.90 IU/L in Group II with no statistical difference (p=0.121). The mean ± SD of troponin I was 12.32 ± 13.74 ng/mL in Group I and 7.62 ± 11.68 ng/mL in Group II without any significant difference between two groups (p=0.112) (Table III).

Table III: Comparison of biochemical parameters between two groups (N=93)

Biochemical parameters	Groups		p
	Group I (n=23)	Group II (n=70)	
	Mean ± SD	Mean ± SD	
Fasting blood glucose level (mmol/L)	7.62 ± 3.47	6.64 ± 3.16	0.208^{NS}
Serum creatinine (mg/dL)	1.93 ± 0.73	1.32 ± 0.36	<0.001^{S}
SGPT (IU/L)	45.00 ± 8.75	40.81 ± 6.90	0.021^{NS}
Troponin I (ng/mL)	12.32 ± 13.74	7.62 ± 11.68	0.072^{NS}

Group I (hyperuricemic group), Patients with serum uric acid concentrations >7 mg/dL in men and >6 mg/dL in women; Group II (normal uric acid level group), Patients with serum uric acid concentrations ⩽7 mg/dL in men and ⩽6 mg/dL in women; p value derived from Student t test (for Troponin I Mann-Whitney U test). NS=Nonsignificant; S=Significant

The mean ± SD of total cholesterol (165.39 ± 41.07 vs 179.14 ± 46.55 mg/ dL, p=0.210), LDL cholesterol (121.61 ± 39.21 vs 124.83 ± 40.84 mg/dL, p=0.741), HDL cholesterol (37.96 ± 8.06 vs 36.19 ± 6.19 mg/dL, p=0.274) and triglyceride (169.43 ± 88.20 vs 166.11 ± 92.17 mg/dL) level between two groups were similar (Table IV).

Table IV: Comparison of lipid profiles between two groups (N=93)

Parameters	Groups		p
	Group I (n=23)	Group II (n=70)	
	Mean ± SD	Mean ± SD	
Total cholesterol (mg/dL)	165.39 ± 41.07	179.14 ± 46.55	0.210^{NS}
LDL cholesterol (mg/dL)	121.61 ± 39.21	124.83 ± 40.84	0.741^{NS}
HDL cholesterol (mg/dL)	37.96 ± 8.06	36.19 ± 6.19	0.274^{NS}
Triglyceride (mg/dL)	169.43 ± 88.20	166.11 ± 92.17	0.880^{NS}

Group I (hyperuricemic group), Patients with serum uric acid concentrations >7 mg/dL in men and >6 mg/dL in women; Group II (normal uric acid level group), Patients with serum uric acid concentrations ⩽7 mg/dL in men and ⩽6 mg/dL in women; p value derived from Student t test; NS=Nonsignificant

Table V shows comparison of in-hospital outcomes between two groups. In patients of Group I development of heart failure and conduction defect was significantly higher compared to Group II patients (30.4% vs 11.4%, p=0.032 and 13.0% vs 1.4%, p=0.017 respectively). There was no significant difference in arrhythmia, cardiogenic shock, cardiac arrest and mortality between two groups.

Table V: Comparison of in-hospital outcomes between two groups (N=93)

Individual in-hospital outcomes	Groups			p
	Group I (n=23)	Group II (n=70)	Total (n=93)	
	Number (%)	Number (%)	Number (%)	
Heart failure	7 (30.4%)	8 (11.4%)	15 (16.1%)	0.032^{S}
Conduction defect	3 (13.0%)	1 (1.4%)	4 (4.3%)	0.017^{S}
Arrhythmias (AF/VT/VF)	1 (4.3%)	5 (7.1%)	6 (6.5%)	0.636^{NS}
Cardiogenic shock	1 (4.3%)	3 (4.3%)	4 (4.3%)	0.990^{NS}
Cardiac arrest	1 (4.3%)	2 (2.9%)	3 (3.2%)	0.726^{NS}
Death	2 (8.7%)	3 (4.3%)	5 (5.4%)	0.416^{NS}

Group I (hyperuricemic group), Patients with serum uric acid concentrations >7 mg/dL in men and >6 mg/dL in women; Group II (normal uric acid level group), Patients with serum uric acid concentrations ⩽7 mg/dL in men and ⩽6 mg/dL in women; p value derived from Pearson Chi-square test; NS=Nonsignificant**;** S=Significant

The mean ± SD of duration of hospital stay of Group I patients was 8.65 ± 0.98 days and that of Group II was 7.56 ± 1.76 days. Group I patients with ACS stayed at hospital for significantly more days than Group II patients (p=0.006) (Table VI).

Table VI: Comparison of duration of hospital stays between two groups of patients with ACS (N=93)

Groups	Mean hospital stay (days)	p
Group I (n=23)	8.65 ± 0.98	0.006^{S}
Group II (n=70)	7.56 ± 1.76	

Group I (hyperuricemic group), Patients with serum uric acid concentrations >7 mg/dL in men and >6 mg/dL in women; Group II (normal uric acid level group), Patients with serum uric acid concentrations ⩽7 mg/dL in men and ⩽6 mg/dL in women; p value derived from Student t test; S=Significant

Discussion

High SUA has been indicated as a risk factor for CAD and as an independent prognostic factor of poorer outcomes in patients with verified CAD.[32-34] In our study, Group I (hyperuricemic) and Group II (normouricemic) had similar prevalence of traditional risk factors like smoking (p=0.846), hypertension (p=0.497), diabetes mellitus (p=0.142), dyslipidemia (p=0.245) and CAD (p=0.435).

The frequency of hyperuricemia among ACS patients in our study is 24.7% (22.54% in male and 31.82% in female). The frequency of hyperuricemia in our study is lower than the prevalence observed by Jularattanaporn et al[35] which was 42.9%. The difference between two studies may be due to difference in sample size and food habit of the participants. Jularattanaporn et al enrolled only 49 Thai patients with acute coronary syndrome (ACS).

Baruah et al, Cheng et al and Nadkar & Jain found statistically significant higher uric acid level in patients with acute MI than age and sex matched healthy controls.[36-38]

In this study we found that higher number of patients with hyperuricemia developed heart failure than patients with normal serum uric acid level (30.4% vs 11.4%, p=0.032). Similarly conduction defect was significantly more frequent in hyperuricemic group than normal uric acid level group (13.0% vs 1.4%, p=0.017). However, there were no significant differences in development of arrhythmia (4.3% vs 7.1%, p=0.636), cardiogenic shock (4.3% vs 4.3%, p=0.990), mortality (8.7% vs 4.3%, p=0.416) and cardiac arrest (4.3% vs 2.9%, p=0.723) between two groups.

The findings of our study are consistent with a number of studies abroad.[39-44] In a recent study conducted in China Chen et al[40] have shown that hyperuricemia patients had more in-hospital major adverse cardiac events (MACE) including heart failure, cardiogenic shock, acute renal failure and mortality compared with non-hyperuricemia patients (p<0.05). But there were no differences in rates of arrhythmia and atrioventricular block between the two groups (p>0.05).[40] Kojima and co-workers evaluated 1,124 consecutive Japanese patients who were hospitalized within 48 hours of onset of symptoms of AMI and revealed that patients who developed short-term adverse events had high SUA concentrations. The study also suggested that hyperuricemia after AMI is associated with the development of heart failure.[41] Kaya et al observed significantly higher hospital mortality, heart failure, and MACE in patients with high UA levels.[42] Wu et al conducted a study with 3648 in-patients with high cardiovascular (CV) risk at baseline in Shanghai and Beijing and observed that patients in the lower and higher uric acid groups had increased cardiac and overall mortality risks compared with patients in the normal uric acid groups.[43] Bae et al studied 660 consecutive patients with CAD, and they were followed-up for a mean of 27 months. They found that the highest uric acid level was a predictor of AMI, CHF and MACE.[44] Krishnan et al collected data on 4,352 participants and revealed that patients in the highest quartile of uric acid had higher all-cause mortality, CHD mortality, and coronary incidence. They concluded that serum UA may be an independent prognostic marker for poor all-cause and CHD mortality in patients with recent acute MI.[39]

Dharma et al enrolled 75 patients with acute STEMI in a cohort study. They found that STEMI patients with higher uric acid levels (>7.3 mg/dL) had increased rate of cardiovascular events compared with lower uric acid levels (<4.8 mg/dL).[45] Framingham Heart Study found no significant association between SUA levels with CVD in either men or women after adjustment for other risk factors and diuretic use.[27] Poullis suggested that the association of serum uric acid level with myocardial infarction, left ventricular dysfunction, and elevated inflammatory markers must be interpreted as an association, not a causal relation.[46]

In our study 2 (8.7%) hyperuricemic patients and 3 (4.3%) normouricemic patients died during hospital stay. Though the short term mortality rate was higher in hyperuricemic patients than normouricemic group, the difference did not reach the level of significance (p=0.416). Our finding is similar with the finding of the study conducted by Jularattanaporn et al and Culleton et al.[27,35] Jularattanaporn et al studied 49 patients with ACS and showed no significant difference in in-hospital adverse outcomes between hyperuricemic and normouricemic patients.[35] Culleton et al reported that an elevated serum uric acid at baseline was not independently associated with increased risk of cardiovascular mortality.[27] However, our findings were not supported by some published studies conducted by

Car & Trkulja[47], Fang & Alderman.[13] Those studies included either a large number of patients or were conducted during a period of long time and allowed a long follow-up period. For these reasons their findings were not similar to our findings.

Car & Trkulja observed that higher SUA on admission was independently associated with higher in-hospital mortality and higher thirty-day mortality. They assessed 621 patients with AMI with ST elevation during a period of almost 5 years.[47]

Fang & Alderman found that mortality from ischemic heart disease was significantly higher in age- and race-adjusted patients with highest quartile of uric acid level compared with the patients with lowest quartile of uric acid level for both men and women during 16.4 years of follow-up. They observed 77% increased death rate from ischemic heart disease in men and 3-fold increase in women with highest quartile serum uric acid level.[13]

In our study, the patients of hyperuricemic group had to stay in hospital for significantly longer period than patients of normal uric acid level group (8.26 ± 1.18 days vs 7.51 ± 1.18 days, p=0.010). Chen et al[40] did not support this. They showed the average stay in hospital was similar in both groups.

The present study provides evidence for positive association between elevated serum uric acid level on admission and poor in-hospital outcomes like heart failure, conduction defect and reduced ejection fraction in patients with ACS. The mean ± SD of hospital stay of hyperuricemic group was significantly longer than patients with normal uric acid level. The measurement of serum uric acid level, an easily available and inexpensive biochemical tool, might turn out as a valuable risk marker for prediction of in-hospital outcomes in patients with acute coronary syndrome.

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