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# Prognostic Value of Serum Cystatin C in patients with Acute Coronary syndrome

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**Original Research Article**

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**Abstract:** Elevated serum cystatin-C in the first few hours of hospitalization for acute coronary syndrome (ACS) is an independent predictor of major adverse cardiovascular event (MACE), especially of heart failure, either in-hospital or during follow-up. We conducted this prospective study to analyze the prognostic value of Serum Cystatin C in patients with ACS. A total of sixty-six patients with ACS were enrolled in the study. Serum cystatin C were measured immediately after hospitalization, before discharge and at 6 months of follow up. Patients were divided into two groups according to serum cystatin C concentration at hospitalization as follows: group a - serum cystatin C ≤ 1.5; and group B- serum cystatin C > 1.5 mg/dl. Coronary angiogram was performed for the entire study population. Study end point was the MACE which included angina, re-infarction, stent thrombosis, stent re-stenosis; urgent revascularization and mortality at index and at six months follow up. Serum cystatin C concentration doesn`t differ in different forms of ACS presentation. Higher basal serum cystatin C level is associated with higher killip class at presentation. Lower basal serum cystatin C level is associated with single vessel coronary artery disease (SVD in group A with serum cystatin C ≤ 1.5 mg/dl, p < 0.05). Higher serum cystatin C concentration at presentation of ACS is directly proportional in predicting the MACE outcome and is independent of renal function. Therefore we can conclude that serum cystatin C concentration is a novel marker in the early risk stratification of ACS patients.
**Keywords**: serum cystatin-C, acute coronary syndrome, major adverse cardiovascular event.

## INTRODUCTION

Atherosclerotic cardiovascular disease (CVD) is a chronic disorder developing insidiously throughout life and usually progressing to an advanced stage by the time symptoms occur. Although mortality rates have improved considerably in recent years, partly due to advances in treatment strategies and even more importantly to increased awareness and improved treatment of risk factors for coronary artery disease(CAD) , the occurrence of cardiovascular disease and the recurrence rate remain high[1-9].

CV disease is strongly connected to lifestyle, especially the use of tobacco, unhealthy diet habits, physical inactivity and psychosocial stress [1,3, 6 – 11]. Among the co-morbidities, reduced kidney function is a major risk factor with both increased risk for recurrent cardiovascular morbidity and mortality [1,12-16]. Furthermore kidney disease is of great importance, not only as a marker of risk but also, as an important piece of information in choosing treatment strategies as well as dosing adjuvant drugs [17,18]. Elevated serum cystatin-C in the first few hours of hospitalization for acute coronary syndrome (ACS) is an independent predictor of MACE. High total cholesterol or LDL cholesterol and low HDL cholesterol are risk factors of ischemic heart disease (IHD), but cystatin-C could be a useful marker for diagnosing coronary arteriosclerosis. Cystatin-C has been associated with the risk of future CAD, independent of serum creatinine or glomerular filteration rate (GFR). The aim of the study is to evaluate the prognostic value of serum cystatin C in patients with ACS.

## MATERIALS AND METHODS

### Study population

Overall sixty-six (66) subjects were included for the study at the department of cardiology, Rajendra Institute of Medical Sciences, Ranchi, in between March 2017 to February 2018. Patients who presented with ACS (STEMI, NSTEMI and USA) were eligible for the study.

Patients with chronic renal failure were excluded from the study. Detailed history, clinical examination, and investigations were done in each case. Blood sugar, lipid profile, renal function test and echocardiography were done routinely.

The study was approved by the hospital ethics committee and conforms to the principles outlined in the Declaration of Helsinki.

**Collection of samples and measurement**

Venous blood was drawn in plain tubes. Plasma was separated centrifugated, aliquoted and stored at – 70 uC until analysis. Analysis of blood sugar, lipid profile, renal function test and serum cystatin C level were done at initial hospitalization, before discharge and at six months follow up. Serum cystatin C concentration was accessed with AU2700 plus, Beckman Coulter machine.

**Interventions**

All patients underwent coronary angiography and subsequent revascularization if required.

**Outcomes and follow up**

End points of the study were the major adverse cardiovascular events (MACE) which included angina, re-infarction, stent thrombosis, stent re-stenosis; urgent revascularization and mortality at index hospitalization and at six months follow up.

**Statistical Analysis**

Mean of the variables was analyzed with two sample t-test whereas significance (p-value) of the study among the groups during follow up was analyzed by Pearson chi square and Z-test using SPSS software (version 21).

**RESULTS**

Base line characteristics are shown in table 1. A total of 66 patients were recruited for the study. Group A comprised of ACS patients with serum cystatin C level ≤ 1.5 mg/dl and consisted of 47 (71.21 %) patients whereas group B included patients with serum cystatin C level > 1.5 mg/dl and consisted of 19 (28.78 %) patients.

**Table-1: Baseline characteristics of patients**

| | Total (N=66) | Group A, N=47 (71.21 %) | Group B, N=19 (28.78 %) | p-value |
|---|---|---|---|---|
| Age | 57 years | 57 years | 60 years | 0.294 |
| Male | 54 (81.83 %) | 39 (82.97 %) | 15 (78.9 %) | 0.602 |
| Female | 12 (18.18 %) | 8 (17.02 %) | 4 (21.1 %) | 0.596 |
| Systemic Hypertension | 25 (37.87 %) | 18 (38.29 %) | 7 (36.8 %) | 0.975 |
| Diabetes Mellitus | 22 (33.33 %) | 15 (31.91 %) | 7 (36.8 %) | 0.665 |
| ACS | | | | |
| STEMI | 38 (57.57 %) | 26 (55.31 %) | 12 (63.2 %) | NS |
| NSTEMI | 12 (18.18 %) | 06 (12.76 %) | 06 (31.6 %) | NS |
| USA | 16 (24.24 %) | 15 (31.91 %) | 1 (5.3 %) | <0.05 |
| Killip class | | | | |
| I – II | 60 (90.90 %) | 47 (100 %) | 13 (68.42 %) | NS |
| III – IV | 6 (1.96 %) | 0 | 06 (31.57 %) | < 0.05 |
| LVfunction (LVEF) | | | | |
| Mild | 36 (54.54 %) | 27 (57.44 %) | 9 (47.4 %) | NS |
| Moderate | 13 (19.69 %) | 4 (8.5 %) | 9 (47.4 %) | NS |
| Severe | 1 (1.51 %) | 0 | 1 (5.3 %) | NS |
| Normal | 16 (24.24 %) | 16 (34.04 %) | 0 | <0.05 |

NS=nonsignificant; P<0.05 was considered significant

Majority (90.9 %) of patients were in killip class II at presentation with significant difference between the groups (p < 0.05).

Significant coronary artery disease was defined as more than fifty percent (> 50 %) luminal diameter stenosis for the individual arteries. Patients were then classified into single, double or triple vessel disease on basis of number of coronary artery involvement.

**Table-2: Angiographic profile of patients**

| | | | | |
|---|---|---|---|---|
| SVD | 24 (36.36 %) | 22 (46.8 %) | 2 (10.5 %) | < 0.05 |
| DVD | 17 (25.75 %) | 11 (23.4 %) | 6 (31.6 %) | NS |
| TVD | 22 (33.33 %) | 14 (29.78 %) | 8 (42.1 %) | NS |
| LM | 3 (4.54 %) | 0 | 3 (15.8 %) | NS |

NS=nonsignificant; P<0.05 was considered significant; SVD= single vessel disease; DVD=double vessel disease; TVD= triple vessel disease

Overall single vessel disease (SVD) and triple vessel disease (TVD) involvement were common finding in angiography. Group A had more incidence of SVD whereas group B had more TVD involvement. Left main (LM) was involved in group B only. There was significant difference ($p < 0.05$) for SVD involvement between the groups.

**Table-3: Shows mean cystatin C level between groups**

| Serum Cystatin C level (mg/dl) | | | |
|---|---|---|---|
| Group | At admission | Discharge | 6 months |
| Group A | 0.716 | 1.250 | 1.083 |
| Group B | 1.916 | 2.668 | 2.316 |

At index hospitalization, serum cystatin C level reflects the lowest and the basal level, which initially increased and later on is relatively static.

There was no significant difference in mean serum cystatin C level in different forms of acute coronary syndrome presentation at different time interval (p = NS).

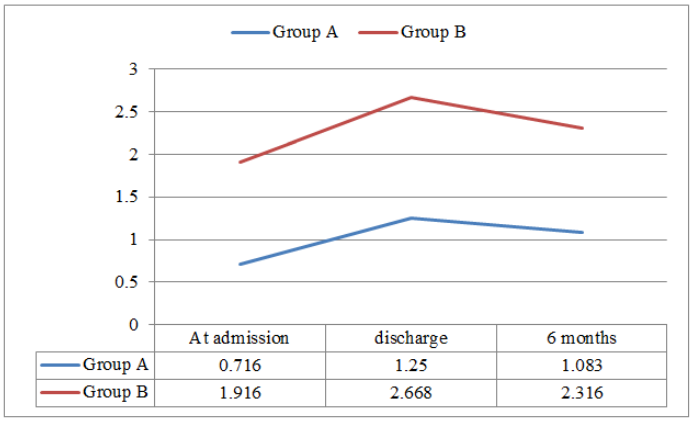


**Fig-1: Line diagram showing mean cystatin C concentration in group A and B at different time**

**Table-4: Shows mean cystatin C level in all forms of ACS presentation**

| Serum Cystatin C level (mg/dl) | | | |
|---|---|---|---|
| | STEMI | NSTE – ACS (NSTEMI / USA) | P value |
| At admission | 1.145 | 1.16 (1.616 / 0.818) | NS |
| Discharge | 1.665 | 1.78 (2.38 / 1.343) | NS |
| 6 month | 1.505 | 1.599 (2.09 / 1.23) | NS |

NS=nonsignificant; P<0.05 was considered significant

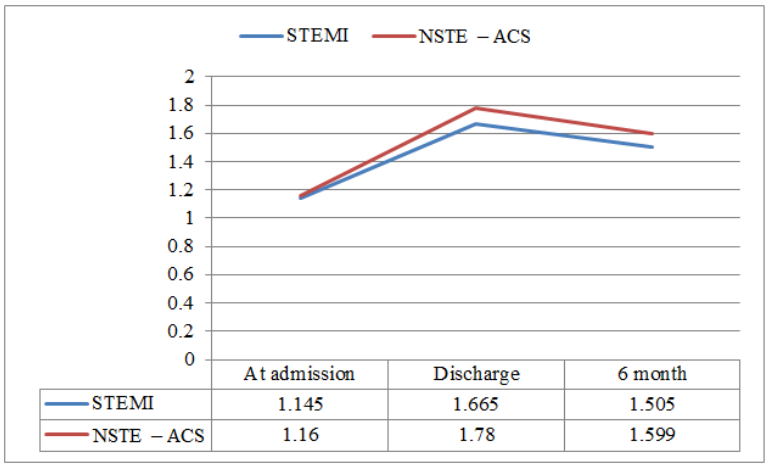


**Fig-2: Line diagram showing mean cystatin C concentration in ACS presentations at different time**

**Table-5: Shows comparison of MACE between groups**

| MACE | In-hospital | | | 6 months | | |
|---|---|---|---|---|---|---|
| | Group A | Group B | P value | Group A | Group B | P value |
| Angina | 3 (5.9%) | 5 (26.3%) | NS | 6(12.8%) | 6(31.6%) | NS |
| Reinfarction | 0 | 0 | NS | 1(2.1 %) | 1(5.3 %) | NS |
| Stent thrombosis / restenosis | 0 | 0 | NS | 1(2.1 %) | 1(5.3 %) | NS |
| Urgent revascularization | 0 | 0 | NS | 1(2.1 %) | 1(5.3 %) | NS |
| Heart Failure | 0 | 6 (31.6%) | < 0.05 | 2(4.3 %) | 8(42.1%) | < 0.05 |
| Mortality | 1(2%) | 0 | NS | 1(2.1 %) | 2(10.5%) | NS |

NS=nonsignificant; P<0.05 was considered significant

There was significant difference in heart failure ($p < 0.05$) at admission and at 6 months of follow up between the group A and B. Group B had 6 (31.6 %) patients with heart failure at admission whereas none in group A in initial hospitalization. Similarly at 6 months, group B had 8 (42.1 %) patients with heart failure whereas in group A had only 2 (4.3 %) patients.

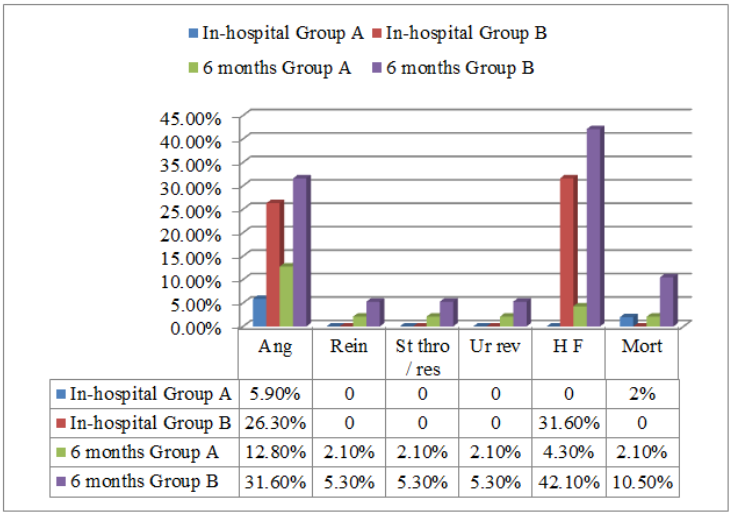


**Fig-3: Bar diagram showing comparison of MACE in between group A and B**

**Table-6: Shows MACE in group A and B**

| | Group A (MACE) | | | Group B (MACE) | | |
|---|---|---|---|---|---|---|
| | Inhospital | 6 months | p-value | Inhospital | 6 months | p-value |
| Angina | 3 (5.9 %) | 6 (12.8 %) | 0.238 | 5 (26.3 %) | 6 (31.6 %) | 0.720 |
| Reinfarction | 0 | 1 (2.1 %) | 0.295 | 0 | 1 (5.3 %) | 0.310 |
| Stent Thrombosis/restenosis | 0 | 1 (2.1 %) | 0.295 | 0 | 1 (5.3 %) | 0.310 |
| Urgent revascularization | 0 | 1 (2.1 %) | 0.295 | 0 | 1 (5.3 %) | 0.310 |
| Heart Failure | 0 | 2 (4.3 %) | 0.136 | 6 (31.6 %) | 8 (42.1 %) | 0.501 |
| Mortality | 1 (2 %) | 1 (2.1 %) | 0.953 | 0 | 2 (10.5 %) | 0.146 |

In both groups, there was increased incidence of MACE as the outcome in follow up with no significant difference (p = NS).

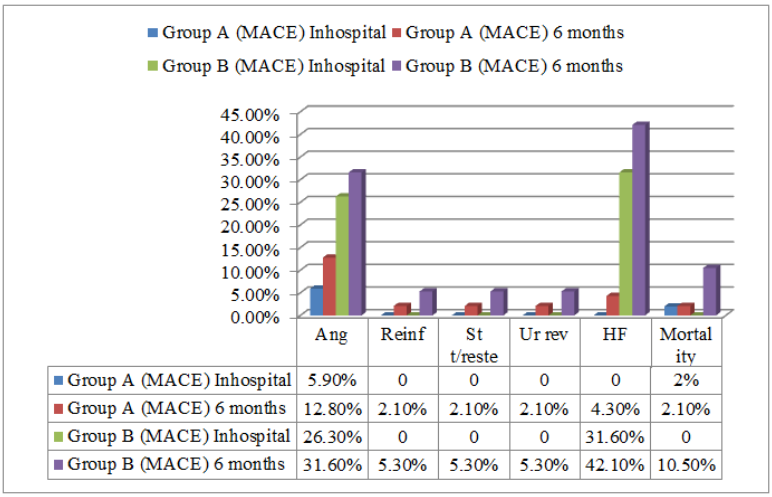


**Fig-4: Bar diagram showing comparison of MACE in group A and B at inhospital and at six months**

**Table-7: Shows MACE according to number of coronary artery involvement at recruitment**

| MACE (At admission) | SVD | DVD | TVD | LM | p-value |
|---|---|---|---|---|---|
| Angina | 0 | 1 (1.4 %) | 5 (7.1 %) | 2 (2.9 %) | 0.002 |
| Reinfarction | 0 | 0 | 0 | 0 | |
| Stent thrombosis/restenosis | 0 | 0 | 0 | 0 | |
| Urgent revascularization | 0 | 0 | 0 | 0 | |
| Heart Failure | 0 | 0 | 5 (7.1 %) | 1 (1.4 %) | 0.012 |
| Mortality | 0 | 0 | 1 (1.4 %) | 0 | 0.584 |

MACE as the end point was significantly different ($p < 0.05$) for angina and heart failure in patients with CAD according to the number of significant obstructive coronary artery involvement.

**Table-8: Shows MACE according to number of coronary artery involvement at 6 month**

| MACE ( at 6 month) | SVD | DVD | TVD | LM | p-value |
|---|---|---|---|---|---|
| Angina | 1 (1.5 %) | 1 (1.5 %) | 8 (12.1 %) | 2 (3 %) | 0.002 |
| Reinfarction | 0 | 1 (1.5 %) | 1 (1.5 %) | 0 | 0.685 |
| Stent thrombosis/restenosis | 0 | 1 (1.5 %) | 1 (1.5 %) | 0 | 0.685 |
| Urgent revascularization | 0 | 1 (1.5 %) | 1 (1.5 %) | 0 | 0.685 |
| Heart Failure | 1 (1.5 %) | 2 (3 %) | 6 (9.1 %) | 1 (1.5 %) | 0.128 |
| Mortality | 0 | 1 (1.5 %) | 2 (3 %) | 0 | 0.493 |

MACE as the end point was significantly different ($p < 0.05$) for angina in patients with CAD according to the number of significant obstructive coronary artery involvement.

## DISCUSSION

We enrolled a total of sixty-six (66) consecutive ACS patients for the study. Group A comprised of ACS patients with serum cystatin C level ≤ 1.5 mg/dl and consisted of 47 (71.21 %) patients whereas group B with serum cystatin C level > 1.5 mg/dl consisted of 19 (28.78 %) patients.

### Conventional risk factors (Table 1)

The mean age in our study was 57 years. Approximately one third of the patients had systemic hypertension (37.87 %) and diabetes mellitus (33.33 %) which was similar to previous study[19] with no difference between groups (p = NS).

### Clinical profile of patients (Table 1)

In our study, STEMI (57.57 %) was the commonest presentation followed by unstable angina (24.24 %) and NSTEMI (18.18 %) with no difference between groups (p = NS). In accordance to previous study [19]. Majority (90.90 %) of the patients were in Killip class I or II. All group A patients (N = 47) were in killip class I – II at presentation whereas all killip class III patients (N = 6) were in group B which was significantly different between groups ($p < 0.05$).

### LV function profile (Table 1)

The overall prevalence of LV dysfunction in our patients was 50 (75.75 %). 16 (24.24 %) patients had normal LV function while 36 (54.54 %) had mild, 13 (19.69 %) and 1 (1.51 %) had moderate and severe ventricular dysfunction respectively, with no difference between groups (p = NS).

**Angiographic profile (Table 2)**

Coronary angiography was performed in all enrolled cases. Overall the SVD was the most common (36.36 %), involvement followed by TVD (33.33 %), and DVD 17 (25.75 %) respectively. LM involvement was present in only 3 (4.54 %) of the patients. SVD was most prevalent in group A whereas TVD was more common in group B and was significantly different between groups ($p < 0.05$). Lower serum cystatin C level is associated with SVD which is similar to previous study [19].

**Serum cystatin C concentration (Table 3 and 4)**

The mean serum cystatin C concentration at initial hospitalization, before discharge and at six month following myocardial infarction in group A and group B were 0.71, 1.25 and 1.08 mg/dl; 1.91, 2.60 and 2.31 mg/dl respectively. The mean serum cystatin C concentration in different forms of ACS presentation at initial hospitalization, before discharge and at six month were 1.14, 1.66 and 1.50 in STEMI patients; 1.16, 1.78 and 1.59 mg/dl in NSTE – ACS patients respectively with no significant difference between ACS presentations (p = NS).

Serum cystatin C concentration was the lowest and the basal level at the presentation of the coronary events which initially increased and later were relatively static in due course with no significant difference in its serum concentration in different forms of acute coronary syndrome presentation at different frame time and these findings are in accordance to the previous study[20].

**Comparison of MACE between group A and B (Table 5)**

Prevalence of heart failure was significantly higher ($p < 0.05$) in group B with higher serum cystatin C concentration ( > 1.5 mg/dl) compared to group A patients (serum cystatin C ≤ 1.5 mgdl). Group B had 6 (31.6 %) patients with heart failure at admission. Similarly at 6 months, group B had 8 (42.1 %) patients with heart failure whereas in group A had only 2 (4.3 %) patients.

**Comparison of MACE in group (Table 6)**

In-group A, incidence of angina increased from 5.9% to 12.8%; reinfection, stent thrombosis/restenosis, urgent revascularization were each 2.1 %; heart failure was 4.3 % and mortality was 2.1% at 6 months with no difference (p = NS), because of the small number of individual MACE components. Similarly in group B analysis, incidence of angina increased from 26.3 % to 31.6 %, new appearance of 5.3 % of reinfection, stent thrombosis/restenosis, and urgent revascularization whereas heart failure increased from 31.6 % to 42.1 % with no difference ($p < 0.05$).

**Comparison of MACE on basis of number of coronary artery involvement (Table 7 and 8)**

MACE as the outcome at inhospital / discharge was significantly different ($p < 0.05$) for coronary angiography profile. The incidence of angina was 1.4 %, 7.1 % and 2.9 % in DVD, TVD, LMCA respectively (p-0.002); heart failure was 7.1 % and 1.4 % in TVD and LMCA respectively (p-0.012). Similarly MACE as the outcome during follow up also showed significant difference for angina which was 1.5 %, 1.5 %, 12.1 %, 3 % in SVD, DVD, TVD, LMCA disease respectively (p-0.002) and no difference for reinfection, stent thrombosis / restenosis, urgent revascularization, heart failure and mortality.

**Principal Finding**

**Observations of the present study are**

- Serum cystatin C concentration is lowest and at the basal level at the presentation of the acute coronary event which initially rises in due course and remains static.
- Serum cystatin C concentration doesn`t differ in different forms of ACS (STEMI VS NSTE – ACS at initial hospitalization, before discharge and at six months follow up is 1.14, 1.66 and 1.5 mg/dl VS 1.16, 1.78, and 1.59 mg/dl, p = NS) which is in accordance to the previous study.[21]
- Higher basal serum cystatin C level is associated with higher killip class at presentation is in accordance to the previous study [19].
- Lower basal serum cystatin C level is associated with single vessel coronary artery disease (SVD in group A with serum cystatin C ≤ 1.5 mg/dl, $p < 0.05$) which is in accordance to the previous study[21]
- Higher serum cystatin C concentration at presentation of acute coronary syndrome is directly proportional in predicting the MACE outcome ( heart failure in group B with higher serum cystatin C > 1.5 mg/dl, $p < 0.05$) and is independent of renal function, which is in accordance to the previous studies[19, 21].
- Serum cystatin C basal concentration may be used as an incremental value in the early risk stratification of acute coronary syndrome patients independent of renal function status

**Limitation**

In our study, the patients were from same ethnic group. Clinical history, blood urea and serum creatine level is considered as renal function status not the eGFR. Though the blood sample is collected immediately on the day of hospitalization, it is of variable duration from the cardiac event. Further randomized controlled trials with larger number of patients and longer duration of follow up required.

## CONCLUSION

Basal serum cystatin C concentration at the moment of acute coronary event contribute to predicting MACE outcome and is independent of creatinine level, glomerular filtration rate, different spectrums of ACS presentation and management strategy. Its concentration at the initial hours of the acute coronary event reflects the lowest and the basal level, did not differ between the different forms of ACS and directly related to adverse outcome (MACE) with higher basal concentration. Serum cystatin C may be used as a marker in the risk stratification in the early risk stratification of the ACS patients.

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