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Impact of Admission Serum Calcium Level Added on Grace Risk Score for Predicting In-Hospital Adverse Outcome in Patients with Acute ST-segment Elevation Myocardial Infarction

Md. Saleh Faisal[1], Md. Khalequzzaman[2], Abdul Wadud Chowdhury[3], Umme Habiba Ferdaushi[4], Mohammad Aklas Uddin[5], Muhammad Masum Miah[6], Md. Ali Reza Faruque[7], Sumona Akhter[8]

[1]*Assistant Registrar, Department Of Cardiology, National Institute Of Cardiovascular Diseases & Hospital, Dhaka, Bangladesh*
[2]*Professor & Head, Department Of Cardiology, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh*
[3]*Professor & Head, Department Of Cardiology, Dhaka Medical College Hospital, Dhaka, Bangladesh*
[4]*Junior Consultant, Department Of Cardiology, National Institute Of Cardiovascular Diseases & Hospital, Dhaka, Bangladesh*
[5]*Junior Consultant (Cardiology), Upazila Health Complex,Hossainpur, Kishoreganj, Bangladesh*
[6]*Medical Officer, Department Of Cardiology, National Institute Of Cardiovascular Diseases & Hospital, Dhaka, Bangladesh*
[7]*Assistant Registrar, Department Of Cardiology, National Institute Of Cardiovascular Diseases & Hospital, Dhaka, Bangladesh*
[8]*Consultant (Radiologist), Medinet Medical Services, Mirpur, Dhaka, Bangladesh*
Corresponding Author: *Md. Saleh Faisal, Assistant Registrar, Department Of Cardiology, National Institute Of Cardiovascular Diseases & Hospital, Dhaka, Bangladesh*

Abstract
Background: *ST-segment elevation myocardial infarction (STEMI) comprises nearly one third or more of myocardial infarction in hospital presentations. In-hospital mortality of STEMI ranges approximately 5% to 6%. So, risk stratification is crucial for appropriate therapeutic decision making. Recently, hypocalcemia has been reported to be an independent predictor of in-hospital adverse outcome in patients with STEMI.*
Objectives: *To assess whether inclusion of admission serum calcium value in the GRACE risk score model improves prediction of in-hospital adverse outcome in STEMI patients.*
Methods: *This prospective observational study was conducted in the Department of Cardiology, Dhaka Medical College Hospital, Dhaka, during the period from May 2019 to April 2020. Patients with STEMI were approached for this study according to the inclusion and exclusion criteria. Total 197 individuals were selected and categorized into two groups: Group A- Those assessed by GRACE risk score with low total serum calcium level (<2.1 mmol/L), Group B- Those assessed by GRACE risk score alone. In-hospital complications like acute LVF, cardiogenic shock, ventricular tachyarrhythmia, AV block and deaths were recorded. The predictive values of in-hospital adverse outcome were compared between two groups. Data analysis were done using the Statistical Package for Social Science (SPSS) Program version 20.0 for windows.*
Results: *Mean age of the study population was 56.32 (±10.22) years with clear male predominance (72%). In-hospital complications like acute left ventricular failure, cardiogenic shock, ventricular tachyarrhythmia and in-hospital mortality were significantly more in patients with on-admission hypocalcemia plus high GRACE risk score group. Receiver operator characteristic (ROC) curve analysis was performed to compare the predictive efficacy of GRACE risk score alone and the combination of admission hypocalcemia with GRACE risk score. The sensitivity and specificity of GRACE risk score for predicting in-hospital adverse outcome were found to be 76.2% and 74.5% respectively. Whereas, after adding admission serum calcium value to the GRACE risk score both the sensitivity and specificity increased to 79.6% and 76.7% respectively. The likelihood ratio for a positive test (LR+) assessed by GRACE risk score (>154) and GRACE risk score (>154) plus on-admission hypocalcemia (<2.1mmol/L) were 2.98 and 3.41 respectively. The likelihood ratio for a negative test (LR-) assessed by GRACE risk score (>154) and GRACE risk score (>154) plus on-admission hypocalcemia (<2.1mmol/L) were 0.31 and 0.26 respectively. The area under curve (AUC) of in-hospital adverse outcome predicted based on GRACE risk score was 0.798 (P=<0.001, 95% CI: 0.761-0.835) and that based on GRACE risk score +admission hypocalcemia was 0.862 (P=0.016, 95% CI: 0.824-0.901). Multivariate logistic regression analysis determined that low serum calcium level at admission was an independent predictor of in-*

hospital adverse outcome in STEMI patients (OR= 1.932, 95% CI: 1.089-3.429, P= 0.024). Among all, high GRACE score plus low serum calcium was the most powerful predictor of in-hospital adverse outcome (OR= 5.345, 95% CI: 1.546-18.480, P= 0.008).

Conclusion: *High GRACE risk score plus on-admission hypocalcemia was a strong predictor of in-hospital adverse outcome in patients with STEMI. Therefore, inclusion of admission serum calcium value into the GRACE risk score could lead to a more accurate prediction of in-hospital adverse outcome.*

Keywords: *Serum Calcium Level, Grace Risk Score, Acute St segment Elevation Myocardial Infarction.*

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I. Introduction

Cardiovascular diseases remain the leading cause of deaths worldwide. In 2008, 17.3 million people died from Cardiovascular diseases, among them 7.3 million of deaths were due to ischaemic heart disease [1]. By the year 2020, Ischemic heart disease (IHD) will hold the first place in the WHO's list of leading cause of disability [2]. When compared to other ethnicities, South Asians have a higher prevalence of coronary artery disease and associated risk factors [3]. Data related to different aspects of coronary artery disease in Bangladesh are inadequate but it is highly prevalent in Bangladesh [4]. The prevalence rate of coronary artery disease in Bangladesh is 1.85% [5] to 3.4% in rural population [6] and 19.6% in urban population [7]. Acute myocardial infarction is usually the result of coronary atherosclerosis [8]. At present, ST-segment elevation myocardial infarction comprises approximately 25% to 40% of MI in hospital presentations and in-hospital mortality ranges approximately 5% to 6% [9]. So risk stratification is crucial for appropriate therapeutic decision making in patients with ST-segment elevation myocardial infarction. Using a risk-stratification tool can not only help clinicians with prognostication, but may also help them to decide which patients warrant higher-risk interventional strategies [10]. Several model of risk scores have been developed for predicting short and long term outcomes in patients with acute coronary syndrome like GRACE, TIMI, PURSUIT, FRISC, HEART score [11,12]. Among all these scores GRACE score appears to be the most suitable for assessing prognosis of short and long term outcome of the patient with acute coronary syndrome [13,14]. Risk assessment should be performed at the time of hospital admission as it gives an idea about the probability of in-hospital adverse outcome and also guides the appropriate treatment plan for patients with acute ST-segment elevation myocardial infarction [9]. The Grace risk score includes 8 independent risk factors: age, heart rate, systolic blood pressure, killip class of heart failure, cardiac arrest at admission, serum creatinine, elevated cardiac enzymes, ST segment deviation on ECG [15]. Hypercalcemia can result from hyperparathyroidism, hypervitaminosis D, Sarcoidosis, multiple myeloma, lymphoma, malignancies of lung, breast, kidney, thyroid etc. Hypocalcemia can result from hypoparathyroidism, chronic renal failure, vitamin D deficiency, steatorrhea etc [16]. Recently, hypocalcemia has been reported to be a predictor of increased in-hospital adverse outcome in patients with AMI [17]. After excluding the effects of age, serum lipids, and other factors, the risk of death in patients with hypocalcemia with AMI is 4.3 times higher than in patients with normal serum calcium levels. Therefore, hypocalcemia is a major independent predictor of in-hospital adverse outcome in patients with AMI [18]. An increasing level of intracellular calcium in platelet is one of the most important link in atherosclerotic plaque formation or thrombogenesis process in coronary artery disease [19], thus calcium is consumed, which induces hypocalcaemia in these patients [20]. Acute myocardial infarction also affects the balance of calcium ions in the body through neurohormonal activation, impaired gastrointestinal function, renal insufficiency, causing occurrence of hypocalcaemia. The decreased serum calcium concentration would increase the calcium channels on vascular smooth muscle cells and increase the level of intracellular calcium, which is known as 'the abnormal calcium influx [21]. Calcium influx would cause chondriosome swelling and then lead to a series of cellular toxin damage [22]. The dysfunction of vascular endothelial cells leads to more lipid deposition and thrombus formation [23], thus increases ionized calcium consumption. Therefore, a hypocalcaemia vicious cycle is formed. Possible mechanisms of the association between serum calcium level and in-hospital adverse outcome in patients with AMI have been suggested. First, low levels of serum calcium may prolong the plateau phase of the cardiac action potential following the delayed closure of calcium channel on the membrane of cardiomyocyte, and a prolonged plateau phase has been widely recognized as an independent high risk factor for increased mortality by causing QT prolongation and Torsades de Pointes. Second, hypocalcemia could reduce renal sodium excretion, thus contributing to fluid overload [24] and diminished myocardial contractility, as demonstrated by decreased left ventricular work index [25,26]. The present study evaluated whether inclusion of admission serum calcium values in a model with GRACE risk score will improve risk stratification of in-hospital adverse outcome in patients with ST-segment elevation myocardial infarction.

II. Materials & Methods

Study design: Prospective observational study.

Place of study: Department of Cardiology, Dhaka Medical College Hospital, Dhaka, Bangladesh.
Period of study: May 2019 to April 2020.
Sampling population: Patients with STEMI admitted in the Department of Cardiology, Dhaka Medical College Hospital, Dhaka, within the study period and who fulfilled the other inclusion and exclusion criteria.
Sampling technique: Purposive sampling technique.

Inclusion criteria:
- Patients diagnosed with first attack of acute ST-segment elevation myocardial infarction.

Exclusion criteria:
- Patients with prior MI, PCI or CABG.
- Patients with moderate to severe degree of valvular heart disease.
- Patients with congenital heart disease, primary myocardial disease (HCM).
- Patients with chronic renal failure, advanced liver disease, advanced chronic lung disease, thyrotoxicosis, adrenal insufficiency, malignancy.
- Patients treated with long term steroid and thiazide diuretics.
- Patients unwilling to give consent.

Sample Size (n):

As the study was conducted over a limited period of time and due to Corona epidemic, ultimately 197 subjects were taken as sample within the study period.

Study Procedure

The prospective observational study was carried out in the Department of Cardiology, Dhaka Medical College Hospital, Dhaka. All the patients of acute STEMI who matched the inclusion and exclusion criteria were taken as sampling population. Patients/attendants were briefed about the study and consent was taken. Details history including symptoms and risk factors was taken from each patient. Relevant physical examination was done. 12 lead ECG was done on admission, once daily and when necessary at a paper speed of 25 mm/s and 10 mm standardization by the machine "ADVANCED ELECTROCARDIOGRAPH, Model: ECG-12C ". Blood sample was taken and sent for total serum calcium measurement immediately after admission. Blood was collected by standard venipuncture technique into glass or plastic tubes. Complete clot formation in the test tube was ensured prior to centrifugation. Separated serum sample was placed in the automated analyzer machine "Dimension xpand plus". Arsenazo-III dye was reacted with calcium in an acid solution to form a blue-purple complex. The colour developed was measured at 660nm and was proportional to the calcium concentration in the sample. Troponin-I was done for each patient by reagent Advia XP-1(cut off value 0.100 ng/ml). Echocardiography was done for each patient on the next day after admission and later whenever necessary by the machine "PHILIPS CLEARVUE 550". Baseline investigations including Random Blood Sugar, Serum Creatinine, Serum Electrolytes, SGPT, Serum Lipid Profile were done for each patient. Daily follow up of the patients was done by checking their Pulse, BP, Lung base and other vital parameters. All the above information were recorded in a data collection sheet consisting of relevant questionnaire. GRACE score for each patient was calculated by using the online GRACE risk calculator by eight variables taken into account: patient's age, heart rate, systolic blood pressure, serum creatinine, Killip heart failure class, cardiac arrest at admission, any deviations of the ST segment and elevated cardiac enzyme levels. In-hospital complications like acute LVF, cardiogenic shock, ventricular tachyarrhythmia, AV blocks (2^{nd}/3^{rd} degree) were recorded till discharge or death of the patients. Sampling population was divided into two groups consisting of: Group A- Those assessed by GRACE risk score plus low total serum calcium level (<2.1mmol/L) i.e. hypocalcemia, Group B- Those assessed by GRACE risk score alone. Patients were then assessed by GRACE risk score alone (Group-B) and GRACE risk score + presence of hypocalcemia (Group-A). The adverse outcome prediction by GRACE risk score alone (Group-B) was compared with GRACE risk score + hypocalcemia group (Group-A).

Statistical Analysis:

After collection of all the required data, these were checked, verified for consistency and tabulated using the SPSS/PC software. Statistical significance was set as 95% confidence interval at 5% acceptable error level. Differences was considered significant at the $P< 0.05$ level for all these tests. The data were expressed as means ±SDs for continuous variables and as frequencies and percentages for categorical variables. Descriptive analyses were performed to investigate the participants' characteristics. Chi-square test, Fisher's exact test and Unpaired t-test test were used for inference. The receiver operator characteristic (ROC) analysis was performed to compare the predictive efficacy of GRACE risk score alone and the combination of admission serum calcium value with GRACE risk score. Multivariate logistic regression analysis was done to see the overall combined

effects of determinants of in-hospital adverse outcome among acute STEMI patients. Data was analyzed by the SPSS 20 Windows version (Chicago, Illinois, USA) and graph & chart were expressed by MS Excel 2016.

III. Observation & Results

Total 197 patients admitted with acute STEMI were included in this study. The general objective of the study was to assess whether inclusion of admission serum calcium value in the GRACE risk score model improves prediction of in-hospital adverse outcome in STEMI patients. In-hospital adverse outcome like acute LVF, cardiogenic shock, ventricular tachyarrhythmia, AV block ($2^{nd}/3^{rd}$ degree) were recorded for all study subjects. The study population were categorized into two groups: Group A- Those assessed by GRACE risk score + low total serum calcium level (<2.1 mmol/L), Group B- Those assessed by GRACE risk score alone. The predictive values of these two assessment methods for predicting in-hospital adverse outcome was analyzed. Appropriate statistical techniques were applied for data analysis. Results are presented with tables and graphs where required. The findings are documented below:

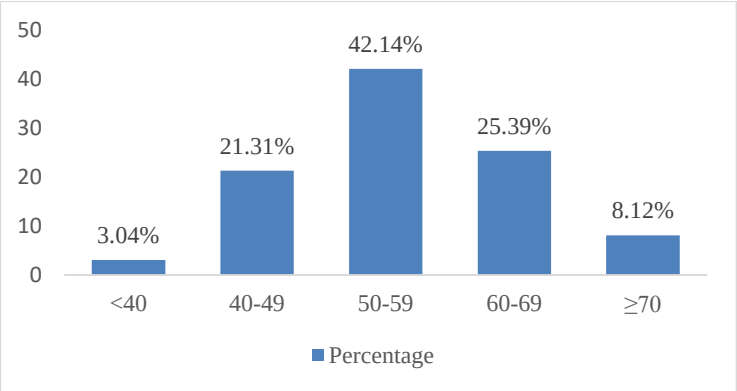


Figure 1. Age distribution of patients. (n=197)

Diagram shows, majority of the patients (42.14%) belonged to 50-59 years age group. The least number of patients (3.04%) belonged to <40-year age group.

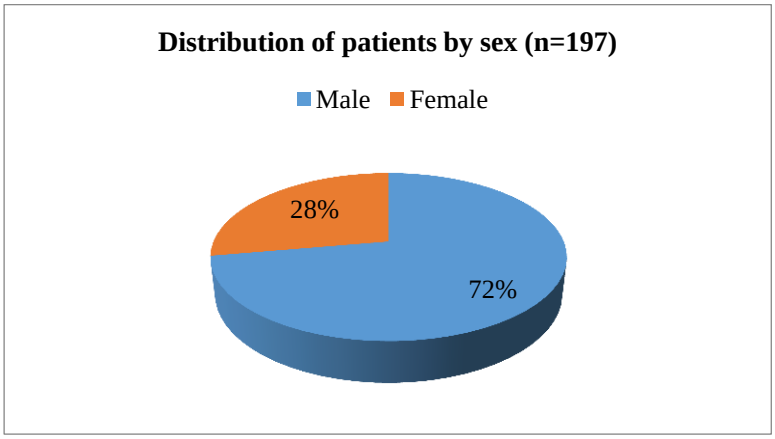


Figure 2. Pie chart showing the distribution of patients by sex (n=197)

Figure shows, among the patients, 142 (72%) were male and 55 (28%) were female. Male and female ratio was 2.6:1.

Table-I: Distribution of GRACE risk score and admission total serum calcium value (mmol/L) among all patients (n=197)

	Group A (n=55) Mean±SD	**Group B (n=142) Mean±SD**	**Total (n=197) Mean±SD**
GRACE score	151.54±10.56	145.97±11.93	148.76±11.25
serum calcium	2.01±0.06	2.34±0.11	2.18±0.08

Group A: Those assessed by GRACE risk score plus low total serum calcium level

Group B: Those assessed by GRACE risk score alone
Values are expressed as Mean±SD

Table shows that, mean GRACE risk score was 151.54±10.56 and 145.97±11.93 in Group A and Group B respectively. Mean serum calcium value was 2.01±0.06 and 2.34±0.11 in Group A and Group B respectively.

Table- II: Distribution of ECG pattern among all patients (n=197)

ECG (ST-Elevation)	Group A (n=55) No. (%)	Group B (n=142) No. (%)	Total (n=197) No. (%)	P-value
Antero-septal	9 (16.36%)	24(16.90%)	33 (16.75%)	0.585*^{ns}
Anterior	18 (32.72%)	35(24.64%)	53(26.90%)	
Extensive Anterior	6 (10.90%)	12 (8.45%)	18(9.14%)	
Inferior	22 (40.00%)	67(47.18%)	89 (45.18%)	
Lateral	0 (0.00%)	4 (2.81%)	4 (2.03%)	

Group A: Those assessed by GRACE risk score plus low total serum calcium level
Group B: Those assessed by GRACE risk score alone
Values are expressed within parenthesis percentage (%) over column in total.
* Fisher's exact test was performed to compare between groups.
ns= not significant (P>0.05), s= significant (P< 0.05)

The table shows that, majority of the patients presented with acute Anterior (Antero-septal, Anterior, Extensive Anterior) STEMI (52.79%). There were no significant differences between the two groups of patients regarding ECG pattern (P-value >0.05).

Table-III: Distribution of presentation characteristics among all patients (n=197)

Variables	Group A (n=55) Mean±SD	Group B (n=142) Mean±SD	Total (n=197) Mean±SD	P-value
Systolic BP (mmHg)	120.34±15.82	124.88±18.21	122.61±17.01	<0.001*^{s}
Diastolic BP (mmHg)	74.41±11.48	76.54±12.96	75.48±12.22	0.001*^{s}
HR (bpm)	79.86±11.90	76.97±13.80	78.42±12.85	<0.001*^{s}
S.Creatinine (mg/dL)	1.22±0.16	1.21±0.15	1.215±0.155	0.116*^{ns}
Elevated S.TroponinI No. (%)	52 (94.54%)	130 (91.54%)	182 (92.39%)	0.983**^{ns}
Cardiac arrest at admission No. (%)	2 (3.64%)	1 (0.70%)	3 (1.52%)	0.131**^{ns}

Group A: Those assessed by GRACE risk score plus low total serum calcium level
Group B: Those assessed by GRACE risk score alone
Values are expressed as Mean±SD and within parenthesis percentage (%) over column in total.
* Unpaired t-test was performed to compare between groups.
** Chi-square test (χ^2) was performed to compare between groups.
ns= not significant (P>0.05), s= significant (P< 0.05)

The table highlights that, there were statistically significant differences between the two groups of patients regarding systolic BP, diastolic BP and heart rate (P- value <0.05).

Table-IV: Distribution of Killip class of heart failure among all patients (n=197)

Killip Class	Group A (n=55) No. (%)	Group B (n=142) No. (%)	Total (n=197) No. (%)	P-value
I	3 (5.45%)	5 (3.52%)	08 (4.06%)	0.537*^{ns}
II	11 (20.0%)	11 (7.74%)	22 (11.17%)	0.014*^{s}
III	9 (16.36%)	10 (7.04%)	19 (9.64%)	0.046*^{s}
IV	9 (16.36%)	6 (4.22%)	15 (7.61%)	0.003*^{s}

Group A: Those assessed by GRACE risk score plus low total serum calcium level
Group B: Those assessed by GRACE risk score alone
Values are expressed within parenthesis percentage (%) over column in total.
* Chi-square test (χ^2) was performed to compare between groups.
ns= not significant (P>0.05), s= significant (P< 0.05)

Table shows that, maximum heart failure patients belonged to Killip Class-II (11.17%). Killip Class II, III & IV showed significant statistical differences between two groups (P-value <0.05).

Table-V: Distribution of in-hospital adverse outcome among all patients (n=197)

Adverse outcome	Group A (n=55) No. (%)	Group B (n=142) No. (%)	Total (n=197) No. (%)	P-value
ALVF	22 (40.00%)	27 (19.01%)	49 (24.87%)	0.002*^{s}
Cardiogenic shock	8 (14.54%)	7 (4.93%)	15 (7.61%)	0.022*^{s}
VT/VF	7 (12.73%)	3 (2.11%)	10 (5.07%)	0.002*^{s}
AV block	6 (10.91%)	8 (5.63%)	14 (7.10%)	0.196*^{ns}
In-hospital mortality	9 (16.36%)	7 (4.93%)	16 (8.12%)	0.008*^{s}

Group A: Those assessed by GRACE risk score plus low total serum calcium level
Group B: Those assessed by GRACE risk score alone
Values are expressed within parenthesis percentage (%) over column in total.
* Chi-square test (χ^2) was performed to compare between groups.
ns= not significant (P>0.05), s= significant (P< 0.05)

The table signifies that, in-hospital complications like acute LVF, cardiogenic shock, ventricular tachyarrhythmia and in-hospital mortality were significantly higher in Group A than Group B. The differences were statistically significant between two groups (P-value <0.05).

Table-VI: Distribution of in-hospital adverse outcome between high GRACE risk score plus low total serum calcium group vs high GRACE risk score group (n=85)

Adverse outcome	Group A (n=36) No. (%)	Group B (n=49) No. (%)	Total (n=85) No. (%)	P-value
ALVF	19 (52.77%)	15 (30.61%)	34 (40.00%)	0.046*^{s}
Cardiogenic shock	7 (19.44%)	2 (4.08%)	9 (10.58%)	0.032*^{s}
VT/VF	6 (16.67%)	1 (2.04%)	7 (8.24%)	0.038*^{ns}
AV block	4 (11.11%)	3 (6.12%)	7 (8.24%)	0.450*^{ns}
In-hospital mortality	8 (22.22%)	3 (6.12%)	11 (12.94%)	0.047*^{s}

Group A: Those assessed by High GRACE risk score (>154) with low total serum calcium level (<2.1mmol/L)
Group B: Those assessed by High GRACE risk score (>154) alone
Values are expressed within parenthesis percentage (%) over column in total.
* Fisher's exact test was performed to compare between groups.
ns= not significant (P>0.05), s= significant (P< 0.05)

The table highlights that, acute LVF, cardiogenic shock, ventricular tachyarrhythmia and in-hospital mortality were significantly more in Group A than Group B. The differences were statistically significant between two groups (P-value <0.05).

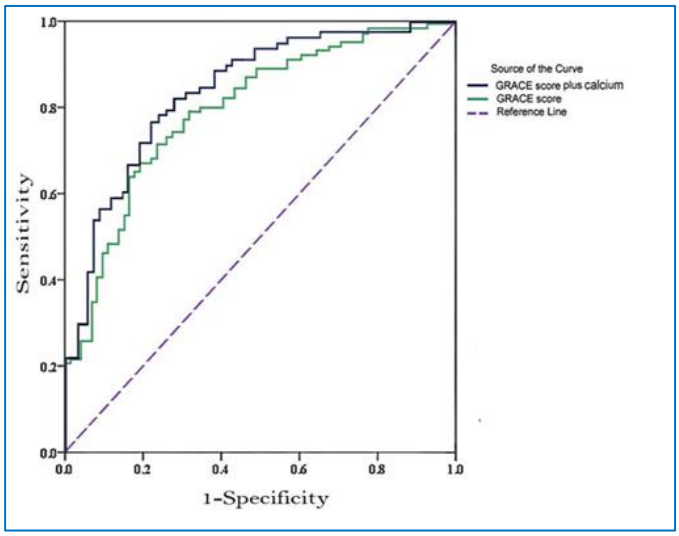
Table-VII: Duration of hospital stays between two groups of patients (n=197)

Parameter	Group A (n=55) Mean±SD	Group B (n=142) Mean±SD	Total (n=197) Mean±SD	P-value
Hospital stays (Days)	8.64±1.32	7.27±1.16	7.95±1.24	0.040*^{s}

Group A: Those assessed by GRACE risk score plus low total serum calcium level
Group B: Those assessed by GRACE risk score alone
Values are expressed as Mean±SD and within parenthesis percentage (%) over column in total.

* Unpaired t-test was performed to compare between groups.
ns= not significant (P>0.05), s= significant (P< 0.05)

The table shows that, there were significant differences between two groups of patients regarding duration of hospital stay.



ns= not significant (P>0.05), s= significant (P< 0.05)

Figure 3. Receiver operator characteristic (ROC) curves of GRACE risk score and GRACE risk score + admission total serum calcium value for prediction of in-hospital adverse outcome among patients. (n=197)

The receiver operator characteristic curve analysis shows that the sensitivity, specificity and area under the curve (AUC) increased after addition of admission total serum calcium value to the GRACE risk score.

Table-VIII: Multivariate logistic regression analysis to detect predictors of in-hospital adverse outcome

Predictor	Regression Coefficient (β)	Odds Ratio (OR)	95% CI		P-value
			Lower	Upper	
SBP (<90 mmHg)	0.003	0.997	0.975	1.791	0.059[ns]
DBP (<60 mmHg)	0.109	0.410	0.116	1.462	0.150[ns]
HR (>100 b/min)	-0.130	0.878	0.843	0.915	0.037[s]
Killip class (class II- IV)	-1.786	0.168	0.100	0.282	0.041[s]
High GRACE score (>154) only	1.383	3.986	1.144	13.892	0.030[s]
Low serum calcium (<2.1 mmol/L) only	0.659	1.932	1.089	3.429	0.024[s]
High GRACE score (>154) plus low serum calcium(<2.1 mmol/L)	1.676	5.345	1.546	18.480	0 .008[s]

ns= not significant (P>0.05), s= significant (P< 0.05)

Multivariate logistic regression analysis was done to see the overall combined effects of determinants of in-hospital adverse outcome among acute STEMI patients. Table shows that high GRACE risk score (>154) with low serum calcium (<2.1mmol/L) was the most powerful predictor of in-hospital adverse outcome as it had highest odds ratio (OR=5.345; P=0.008) compared to both high GRACE score only (OR=3.986; P=0.030) and low serum calcium only (OR=1.932; P=0.024).

IV. Discussion

This prospective observational study was carried out in the Department of Cardiology, Dhaka Medical College Hospital, Dhaka, over a period of one year from May 2019 to April 2020. The main objective was to assess whether inclusion of admission serum calcium value in the GRACE risk score model improves prediction of in-hospital adverse outcome in STEMI patients. For this purpose, total 197 patients admitted with acute ST-segment elevation myocardial infarction fulfilling inclusion & exclusion criteria were included in this study. The study population were categorized into two groups: Group A- Those assessed by GRACE risk score plus low total serum calcium level (<2.1 mmol/L), Group B- Those assessed by GRACE risk score alone. In our study, among the 197 patients with acute STEMI, mean age of the total patients was 56.32±10.22 years. Male were predominant (72%) with male and female ratio 2.6:1. A recent study done with acute STEMI patients by

Alam, et al. [27] in Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, had shown that mean age of his study population was 53.38±9.40 years, most of the patients were male (84%). A similar study done by Mesbahul Islam et al. [28] at Department of Cardiology, Dhaka Medical College Hospital, Dhaka, Bangladesh. The mean age of his study population was 55.2±11.6 years, most of the patients were male, male female ratio was 2.8:1. Yan, et al. [29] had done a similar study in China and showed that mean age of his study population was 64.55±10.66 years with a 78.9% male predominance. In our study, majority of the patient presented with anterior wall (anterior, antero-septal & extensive anterior) myocardial infarction (52.79%), followed by inferior wall infarction (45.18%) and lateral wall infarction (2.03%) which were insignificantly distributed between two groups. In our study, mean GRACE risk score of all patients was 148.76±11.25 and mean serum calcium value of all patients was 2.18±0.08 mmol/L. Patients with lower baseline serum calcium levels (Group A) had higher GRACE risk score (Group A). Yan, et al [29] also revealed the similar findings. In this study, acute heart failure and its severity (>Killip class-I) was significantly more in Group A compared to other group. 14.54% patients in Group A developed cardiogenic shock which is significantly higher than Group B (4.93%). There are several reports of congestive heart failure caused by severe hypocalcemia and cardiomyopathy in long-standing hypocalcemia [26,30,31]. In this study, ventricular tachycardia, ventricular fibrillation were significantly higher in hypocalcemic group (Group A-12.73%), in comparison to other group (Group B-2.11%). Low levels of serum calcium may prolong the plateau phase of the cardiac action potential following the delayed closure of calcium channel on the membrane of cardiomyocyte, and a prolonged plateau phase has been widely recognized as an independent high risk factor for increased mortality by causing QT prolongation and Torsades de Pointes [24]. Yarmohammadi, et al. [32] mentioned that "blood calcium levels lower than 8.95 mg/dl were associated with a 2.3 fold increase in odds of sudden cardiac arrest as compared with levels higher than 9.55 mg/dl". In our study, total in-hospital mortality was 8.12% and significantly higher in hypocalcemic patients. Hypocalcemia is prevalent in critically ill patients and has been shown to be associated with increased mortality in a considerable number of clinical studies [33,34,35]. Study done by Jiang, et al [18] Yan, et al [29] and Lu, et al. [17] conducted on patients with ACS had shown low serum calcium level as a possible indicator of increased risk of in-hospital mortality. Among the other adverse outcome, conductive defect showed no significant difference between two groups (P=0.196). As our sample size was not large enough, it might not reflect all the adverse outcome proportionately in different groups. In the subgroup of patients consisting of high GRACE risk score plus low total serum calcium level (Group-A) and high GRACE risk score only (Group-B) showed that, acute LVF (52.77% vs 30.61%), cardiogenic shock (19.44% vs 4.08%), ventricular tachyarrhythmia (16.67% vs 2.04%) and in-hospital mortality (22.22% vs 6.12%) were significantly more in Group A than Group B respectively. In our study, patients of Group-A had to stay in hospital for longer period than patients of Group-B because Group-A patients experienced significantly more complications. Receiver operator characteristic (ROC) analysis was performed to compare the predictive efficacy of GRACE risk score alone and the combination of admission hypocalcemia with GRACE risk score. Results showed that the sensitivity and specificity of GRACE score for predicting in-hospital adverse outcome were found to be 76.2% and 74.5% respectively. Whereas after adding admission serum calcium value to GRACE risk score both the sensitivity and specificity increased to 79.6% and 76.7% respectively in this new model. The likelihood ratio for a positive test (LR+) assessed by GRACE risk score (>154) and GRACE risk score (>154) plus on-admission hypocalcemia (<2.1mmol/L) were 2.98 and 3.41 respectively. The likelihood ratio for a negative test (LR-) assessed by GRACE risk score (>154) and GRACE risk score (>154) plus on-admission hypocalcemia (<2.1mmol/L) were 0.31 and 0.26 respectively. The AUC of in-hospital adverse outcome predicted based on GRACE risk score alone was 0.798 (P=<0.001, 95% CI: 0.761-0.835) and that based on GRACE risk score + admission hypocalcemia was 0.862 (P=0.016, 95% CI: 0.824-0.901). In similar type of study, Yan, et al [29] also showed that the AUC increased significantly after the addition of admission serum calcium value to the GRACE risk score (GRACE vs GRACE + serum calcium AUC: 0.646 vs 0.758) in patients with STEMI. Multivariate logistic regression analysis to determine the predictors of in-hospital adverse outcome showed that GRACE risk score (>154) and admission serum calcium (<2.1 mmol/L) was an independent predictor of in-hospital adverse outcome. High GRACE score plus low serum calcium was the most powerful predictor of in-hospital adverse outcome as it had highest odds ratio (OR=5.345; P=0.008) compared to both high GRACE score only (OR=3.986; P=0.030) and low serum calcium only (OR=1.932; P=0.024). In his study Yan, et al. [29] also showed that serum calcium added incremental predictive value when combined with the GRACE risk score. The mechanism which may account for the association between the admission serum calcium levels and in-hospital adverse outcome with acute STEMI was unknown. However, intracellular calcium overload may play a key role. Intracellular calcium acts as a second messenger Hovis, et al., [36] for the secretion of some hormones and neurotransmitters, as well as an intracellular permeation regulator and mediator of muscle contraction [37]. The decreased serum calcium concentration would increase the calcium channels on vascular smooth muscle cells (VSMCs), and increase the level of intracellular calcium, which is known as ''the abnormal calcium influx'' [21]. This change would play an important role in the

process of cell migration Pettit and Fay, [38] and atherosclerotic plaques formation [39]. Boya, et al. [22] reported that calcium influx would cause chondriosome swollen and then lead to a series of cellular toxin damage. The dysfunction of vascular endothelial cells leads to more lipid deposition and thrombus formation [22], thus increases ionized calcium consumption. Therefore, a hypocalcemia vicious cycle is formed. Cell toxin damage would aggravate inflammation in STEMI patients, which also plays an important role in coronary pathology and formation of plaque [40]. Low levels of serum calcium may prolong the plateau phase of the cardiac action potential and a prolonged plateau phase has been widely recognized as an independent high risk factor for increased mortality by causing QT prolongation and Torsades de Pointes [24]. Thus, the results from these above cited studies are consistent with those of our study where hypocalcemia patients own worse vascular condition than those with normal calcium level, and may have more severe coronary damage and worse prognosis.

V. Conclusion

This study demonstrated that low serum calcium level on admission was an independent predictor of in-hospital adverse outcome in STEMI patients. Admission low serum calcium level plus high GRACE risk score was a strong predictor of in-hospital adverse outcome than GRACE risk score alone in patients with STEMI. Therefore, inclusion of admission serum calcium value into the GRACE risk score could predict in-hospital adverse outcome more accurately. However, further larger study with appropriate design will be able to shed more light in this matter.

VI. Limitations

- This was a single-center study therefore all representative data may not come.
- Small sample size was one of the limitations, due to smaller sample size the result could not be generalized.
- Patients who were thrombolysed or underwent PCI or conservatively treated were not differentiated in this study.

VII. Recommendation

Further multicenter clinical study with larger sample size with appropriate design are recommended.

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