Original Article

Impact of Admission Serum Calcium Level Added on Grace Risk Score for Predicting In-Hospital Adverse Outcome in Patients with Acute Coronary Syndrome

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Abstract

Introduction: Abnormal calcium metabolism predicts worse outcomes after acute coronary syndrome (ACS). However, this parameter is not included in risk prediction scores, including the Global Registry of Acute Coronary Events (GRACE) risk score. The objective of this study was to assess whether including admission serum calcium value in the GRACE risk score model improves the prediction of in-hospital adverse outcomes in ACS patients.

Methods: This prospective observational study was conducted in the Department of Cardiology, Dhaka Medical College Hospital (DMCH), Dhaka, from May 2019 to April 2020. Patients with ACS were approached for this study according to the inclusion and exclusion criteria. 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 left ventricular failure (LVF), cardiogenic shock, ventricular tachyarrhythmia, atrio-ventricular (AV) block, and deaths were recorded. The predictive values of in-hospital adverse outcomes were compared between the two groups.

Results: The 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 a high GRACE risk score group. Receiver operator characteristic (ROC) curve analysis was performed to compare the predictive efficacy of the GRACE risk score alone and the combination of admission hypocalcemia with the GRACE risk score. The sensitivity and specificity of the GRACE risk score for predicting in-hospital adverse outcomes were 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 the 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 outcomes in ACS patients (OR= 1.932, 95% CI: 1.089-3.429, p= 0.024). A high GRACE score plus low serum calcium was the most powerful predictor of in-hospital adverse outcomes (OR= 5.345, 95% CI: 1.546-18.480, p= 0.008).

Conclusion: A high GRACE risk score plus on-admission hypocalcemia was a strong predictor of in-hospital adverse outcomes in patients with ACS. Therefore, the 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 Coronary Syndrome.

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Introduction

Several models of risk scores have been developed for predicting short and long-term outcomes in patients with acute coronary syndrome (ACS) like the Global Registry of Acute Coronary Events (GRACE), Thrombolysis in Myocardial Infarction (TIMI), Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), Fragmin and Fast Revascularization During Instability in Coronary Artery Disease (FRISC), and

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history, electrocardiography, age, risk factors, troponin (HEART) scores [1,2]. Among all these scores, the GRACE score appears to be the most suitable for assessing the prognosis of short and long-termoutcomes of the patient with acute coronary syndrome [3,4]. Risk assessment should be performed at the time of hospital admission as it gives an idea about the probability of in-hospital adverse outcomes and also guides the appropriate treatment plan for patients with acute coronary syndrome [5]. 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 [6].

Extra-skeletal calcium, which is widely distributed throughout the organs and tissues, plays a critical role in a range of biological processes related to cardiovascular disease, including platelet adhesion, blood coagulation, cardiac contraction, cardiomyocyte apoptosis, and electrophysiology of the heart [7]. Recently, hypocalcemia has been reported to be a predictor of increased in-hospital adverse outcomes in patients with acute myocardial infarction (AMI) [8]. 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 outcomes in patients with AMI [9].

Recently, a study was done in Chinaon patients admitted with acute coronary syndrome and the result revealed that the inclusion of serum calcium value in the GRACE risk score model may lead to a more accurate prediction of occurrence of in-hospital mortality [10].The present study evaluated whether the inclusion of admission serum calcium values in a model with GRACE risk score will improve risk stratification of in-hospital adverse outcomes in patients with ACS.

Methods

This prospective observational study was conducted in the Department of Cardiology, Dhaka Medical College Hospital (DMCH), Dhaka, during the period from May 2019 to April 2020. The study protocol was approved by the Ethical Review Committee (ERC) of DMCH. Patients with ACS were approached for this study according to the inclusion and exclusion criteria. Study subjects with prior myocardial infarction (MI), percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG), moderate to severe degree of valvular heart disease, congenital heart disease, primary myocardial disease (HCM), chronic renal failure, advanced liver disease, advanced chronic lung disease, thyrotoxicosis, adrenal insufficiency, malignancy, and being treated with long term steroid and thiazide diureticswere excluded from the study. Informed written consent was taken from each participant. 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 left ventricular failure (LVF), cardiogenic shock, ventricular tachyarrhythmia, atrio-ventricular (AV) block, and deaths were recorded. The predictive values of in-hospital adverse outcomes were compared between the two groups. Data analyses were done using the Statistical Package for Social Science (SPSS) Program version 20.0 for Windows.

Results

The majority of the patients (42.14%) belonged to the 50-59 years age group. The least number of patients (3.04%) belonged to the < 40-year age group (Figure 1). Among the patients, 142 (72%) were male and 55 (28%) were female. The male and female ratio was 2.6:1 (Figure 2). The mean GRACE risk score was 151.54±10.56 and 145.97±11.93 in Group A and Group B respectively. The mean serum calcium value was 2.01±0.06 mmol/L and 2.34±0.11 mmol/L in Group A and Group B respectively (Table 1). Table 2 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 2). Table 3 shows that the maximum number of heart failure patients belonged to Killip Class-II (11.17%). Killip Class II, III & IV showed significant statistical differences between the two groups (P-value <0.05). Table 4 showed that in-hospital complications like acute LVF, cardiogenic shock, ventricular tachyarrhythmia, and in-hospital mortality were significantly higher in Group A than in Group B. The differences were statistically significant between the two groups (P-value <0.05). Table 5 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 the two groups (P-value <0.05). Table 6 shows that there were significant differences between the two groups of patients regarding the duration of hospital stay. The receiver operator characteristic (ROC) curve analysis shows that the sensitivity, specificity, and area under the curve (AUC) increased after the addition of admission total serum calcium value to the GRACE risk score (Figure 3, Table 7). Multivariate logistic regression analysis was done to see the overall combined effects of determinants of in-hospital adverse outcomes among ACS patients. Table VIII shows that a high GRACE risk score (>154) with low serum calcium (<2.1mmol/L) was the most powerful predictor of the in-hospital adverse outcomes as it had the 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) (Table 8).

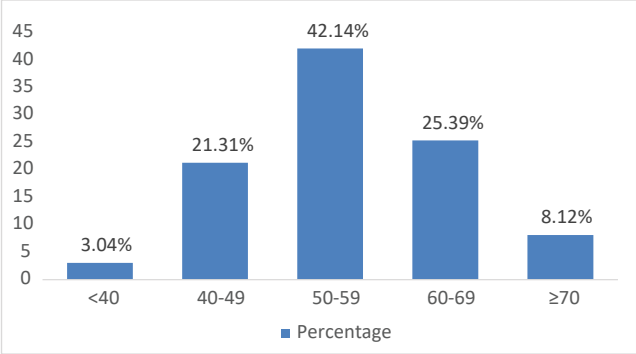


Figure 1: Age distribution of the study subjects (n=197)

Table 1: 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

Table 2: 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; * 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)

Table 3: 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; * Chi-square test (χ^2) was performed to compare between groups; ns= not significant (p>0.05), s= significant (p< 0.05)

Table 4: Distribution of in-hospital adverse outcomes 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; * Chi-square test (χ^2) was performed to compare between groups; ns= not significant (p>0.05), s= significant (p< 0.05)

Table 5: Distribution of in-hospital adverse outcomes 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%)	5(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; * Fisher's exact test was performed to compare between groups; ns= not significant (p>0.05), s= significant (p< 0.05)

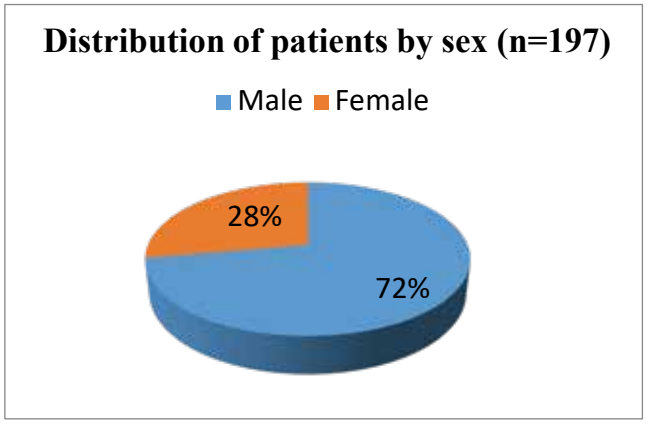


Figure 2: Pie chart showing the distribution of patients by sex (n=197)

Table 6: 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 *Unpaired t-test was performed to compare between groups. ns= not significant (P>0.05), s= significant (P< 0.05)

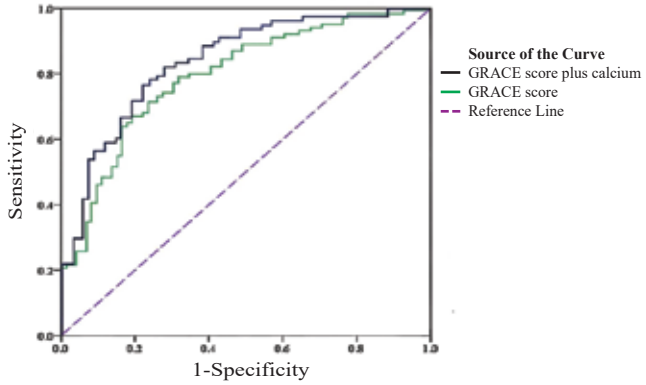


Figure 3: Receiver operator characteristic (ROC) curves of GRACE risk score and GRACE risk score + admission total serum calcium value for prediction of in-hospital adverse outcome among patients. (n=197)

Table- VII: Result of ROC curve

Parameters	Sensitivity	Specificity	LR(+)	LR(-)	Area under the ROC curve	95% CI Lower	95% CI Upper	p-value
GRACE score (>154)	76.2	74.5	2.98	0.31	0.798	0.761	0.835	< 0.001[s]
GRACE score (>154) + admission serum calcium (<2.1mmol/L)	79.6	76.7	3.41	0.26	0.862	0.824	0.901	0.016[s]

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

Table 8: Multivariate logistic regression analysis to detect predictors of in-hospital adverse outcome

Predictor	Regression Coefficient (β)	Odds Ratio (OR)	95% CI Lower	95% CI Upper	p-value
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	00.008[s]

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

Discussion

In our study, among the 197 ACS patients, the mean age of the total patients was 56.32±10.22 years. Male subjects were predominant (72%) with a male and female ratio of 2.6:1. A recent study done by Alam et al. [11] at Bangladesh Medical University, Dhaka, Bangladesh, showed that the mean age of his study population was 53.38±9.40 years, most of the patients were male (84%). A similar study was done by Islam et al. [12] at the Department of Cardiology, DMCH, Dhaka, Bangladesh. The mean age of his study population was 55.2±11.6 years, most of the patients were male, and the male-female ratio was 2.8:1. Yan et al. [10] did a similar study in China and showed that the mean age of his study population was 64.55±10.66 years with a 78.9% male predominance.

In our study, the mean systolic blood pressure (BP) and diastolic BP of all patients with ACS were 122.61±17.01 and 75.48±12.22 mm Hg respectively, with lower mean systolic BP (120.34±15.82) and diastolic BP (74.41±11.48) were being recorded in Group A consisting of patients with lower baseline serum calcium values. In this study, Group A patients also had a higher mean heart rate (79.86±11.90) in comparison to another group. Yan et al. [10] and Lu et al. [8] also showed in their study that patients with lower baseline serum calcium levels had lower blood pressure and higher heart rate.

In our study mean serum creatinine value was higher in Group A (1.22±0.16) than in Group B (1.21±0.15) but there was no statistically significant difference between the two groups. Serum troponin-I level was raised in 92.39% of patients in our study. In the rest of the patients, it was not found to be raised probably because of taking the samples too early.

An increasing level of intracellular calcium in platelets is one of the most important links in atherosclerotic plaque formation or thrombogenesis process in coronary artery disease [13], thus calcium is consumed, which induces hypocalcemia in these patients [14]. Acute myocardial infarction also affects the balance of calcium ions in the body through neurohormonal activation, impaired gastrointestinal function, and renal insufficiency, causing the occurrence of hypocalcemia. 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'. Calcium influx would cause chondriosome swelling and then lead to a series of cellular toxin damage [15]. The dysfunction of vascular endothelial cells leads to more lipid deposition and thrombus formation [16], thus increasing ionized calcium consumption. Therefore, a hypocalcemia vicious cycle is formed.Possible mechanisms of the association between serum calcium level and in-hospital adverse outcomes 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 [17] and diminished myocardial contractility, as demonstrated by decreased left ventricular work index [18].In our study, the mean GRACE risk score of all patients was 148.76±11.25 and the 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 scores (Group A). Yan et al. [10] also revealed the similar findings.

In this study, acute heart failure and its severity (>Killip class-I) were significantly more in Group A compared to another group. 14.54% of patients in Group A developed cardiogenic shock which is significantly higher than Group B (4.93%). This finding is also congruent with the study done by Yan et al. [10] and Lu et al. [8]. Calcium ions play a vital role in excitation-contraction coupling of the cardiac muscle fibers. Contraction of cardiac muscle requires the availability of calcium from extracellular fluid, as well as release from the sarcoplasmic reticulum. So, cardiac contractility can be seriously impaired by prolonged hypocalcemia. There are several reports of congestive heart failure caused by severe hypocalcemia and cardiomyopathy in long-standing hypocalcemia [19,20].

In this study, ventricular tachycardia, and ventricular fibrillation were significantly higher in the 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. It is 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”[21,22].

In our study, total in-hospital mortality was 8.12% and significantly higher in hypocalcemic patients. Studies done by Jiang et al. [9], Yan et al. [10], and Lu et al. [8] conducted on patients with ACS had shown low serum calcium levels as a possible indicator of increased risk of in-hospital mortality. Among the other adverse outcomes, conductive defects showed no significant difference between the two groups (P=0.196). As our sample size was not large enough, it might not reflect all the adverse outcomes proportionately in different groups. In this study, 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 the hospital for longer periods than patients of Group B because Group A patients experienced significantly more complications.

Receiver operator characteristic (ROC) analysis showed that the sensitivity and specificity of the GRACE score for predicting in-hospital adverse outcomes 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 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 the 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 a similar type of study, Yan et al. [10] 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 ACS.

Multivariate logistic regression analysis showed that GRACE risk score (>154) with admission serum calcium (<2.1 mmol/L) was an independent predictor of in-hospital adverse outcomes. High GRACE score plus low serum calcium was the most powerful predictor of in-hospital adverse outcomes as it had the 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. [10] also showed that serum calcium added incremental predictive value when combined with the GRACE risk score.

Thus, the results from theabove-cited studies are consistent with those of our study where hypocalcemia patients own worse vascular conditions than those with normal calcium levels and may have more severe coronary damage and worse prognosis.

Limitations

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

Conclusion

This study demonstrated that low serum calcium level on admission was an independent predictor of in-hospital adverse outcomes in ACS patients. Admission with low

serum calcium level plus a high GRACE risk score was a stronger predictor of in-hospital adverse outcomes than GRACE risk score alone in patients with ACS. Therefore, the inclusion of admission serum calcium value into the GRACE risk score could predict in-hospital adverse outcomes more accurately. However, further larger studies with appropriate design will be able to shed more light on this matter.

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