Clinical Investigations

Admission Serum Calcium Levels Improve the GRACE Risk Score Prediction of Hospital Mortality in Patients With Acute Coronary Syndrome

Address for correspondence:
Mao Chen, MD
Department of Cardiology
West China Hospital,
Sichuan University
37 Guoxue Street
Chengdu, 610041,
PR China
hmaochen@vip.sina.com

Shao-di Yan, MD; Xiao-jing Liu, PhD; Yong Peng, MD; Tian-li Xia, MD; Wei Liu, MD; Jiay-yu Tsauo, MD; Yuan-ning Xu, MD; Hua Chai, MD; Fang-yang Huang, MD; Mao Chen, PhD, MD; De-jia Huang, MD

Laboratory of Cardiovascular Diseases (Yan, Liu, Chai) and Department of Cardiology (Peng, Xia, Liu, Tsauo, Xu, Huang, Chen, Huang), West China Hospital, Sichuan University, Chengdu, China

ABSTRACT

Background: The Global Registry of Acute Coronary Events (GRACE) risk score has been extensively validated to predict risk during hospitalization in patients with acute coronary syndrome (ACS). Recently, serum calcium has been suggested as an independent predictor for in-hospital mortality in patients with ST-segment elevation myocardial infarction; however, the relationship between the 2 has not been evaluated.

Hypothesis: The combination of GRACE risk score and serum calcium could provide better performance in risk prediction.

Methods: The study enrolled 2229 consecutive patients with ACS. Independent predictors were identified by a multivariate logistic regression model. The incremental prognostic value added by serum calcium to the GRACE score was evaluated by receiver operating characteristic, net reclassification improvement (NRI), and integrated discrimination improvement (IDI).

Results: Patients in the upper quartiles of serum calcium presented with lower in-hospital mortality (odds ratios for 3 upper quartiles vs lowest quartile, respectively: 0.443, 95% confidence interval [CI]: 0.206-0.953; 0.243, 95% CI: 0.090-0.654; and 0.210, 95% CI: 0.082-0.538). Area under the curve increased significantly after adding serum calcium to the GRACE score (0.685 vs 0.746; $Z = 2.617$, $P = 0.009$). Furthermore, inclusion of serum calcium in the GRACE score enhanced NRI (0.524; $P = 0.009$) and IDI (0.011; $P = 0.003$).

Conclusions: Lower serum calcium level on admission is a possible indicator of increased risk of in-hospital mortality in ACS patients. Inclusion of serum calcium in the GRACE score may lead to a more accurate prediction of this risk. Large prospective studies are needed to confirm this finding.

Introduction

Acute coronary syndromes (ACS), ranging from unstable angina (UA) to myocardial infarction, represent a life-threatening manifestation of atherosclerotic progression in the coronary district. Risk stratification is crucial for appropriate therapeutic decision-making in these patients. As a widely used risk-evaluating score from a large, multinational, prospective registry, the Global Registry of Acute Coronary Events (GRACE) risk score has been extensively validated and proven to have an excellent ability to predict in-hospital mortality across the spectrum of patients with ACS.[1–3] Some clinical parameters not incorporated in the GRACE risk score, such as C-reactive protein, platelet volume, and glycated hemoglobin, have been reported to further improve the prognostic performance of the GRACE score in ACS patients.[4–6]

Extraskeletal 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. Serum calcium is one of the main components of extraskeletal calcium and is also a widely applied biochemical index in clinical practice.[7,8] Recently, hypocalcemia has been reported to be a predictor of increased in-hospital mortality in patients with severe coronary artery disease (CAD).[9] However, the association

Shao-di Yan and Xiao-jing Liu are equally contributing authors. This work was funded by the National High-Tech Research and Development Program of China (grant number: 2012AA02A510, Beijing, China), the National Natural Science Foundation of China (grant numbers: 81370219 and 81400267, Beijing, China), and the General Financial Grant from the China Postdoctoral Science Foundation (grant number: 2015 M582559, Beijing, China).
The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Clin. Cardiol. 39, 9, 516–523 (2016)
Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22557
Received: February 23, 2016
Accepted with revision: April 27, 2016

between serum calcium and the GRACE score remains unclear to date.

In the present study, we sought to investigate the relationship between serum calcium at admission and the GRACE score and to identify the incremental prognostic value added by serum calcium when included in the GRACE score in patients with ACS.

Methods

Study Population

The data source for this study was the West China Hospital Coronary Artery Disease Database, which includes all CAD patients undergoing angiography in the West China Hospital of Sichuan University. We retrospectively recruited 2229 consecutive patients with angiography-confirmed ACS by cardiologists in our group from July 2008 to September 2012. Patients with ACS were eligible for inclusion if they met all 3 of the following criteria: (1) >50% stenosis in ≥1 epicardial coronary artery, confirmed by coronary angiography; (2) symptoms of ischemia that increased or occurred at rest; and (3) elevated cardiac troponin T levels (0.03 mg/L) or new electrocardiographic deviation in ≥2 contiguous leads (either pathologic Q waves [≥0.04 s in duration], ST-segment dynamic horizontal/downsloping depression ≥0.05 mV, or persistent ST-segment elevation ≥0.1 mV in ≥2 contiguous precordial leads or ≥2 adjacent limb leads, or new left bundle branch block). Patients were excluded for the following reasons: hemodynamic instability, malignancies, active bleeding, pregnancy, severe liver or hematological disorders, and missing laboratory value or measuring time of serum calcium on admission. Patients received care according to the current practice guidelines; treatment and management of the patients was not affected by participation in this study. The study protocol was approved by the local institutional review boards in accordance with the Declaration of Helsinki. All subjects provided written informed consent before enrollment.

Demographic and Clinical Data

All data entered into the computerized database were collected from the patient charts and by bedside inquiry and physical examination. Hypertension was defined as blood pressure >140/90 mm Hg on ≥2 independent readings, or the current use of antihypertensive medication. Diabetes mellitus was diagnosed in patients who had previously undergone dietary treatment, had received additional oral antidiabetic or insulin medication, or had a current fasting blood glucose level of >7.0 mmol/L in 2 blood samples.

Determination of Serum Calcium and GRACE Risk Score

Admission serum calcium level was defined as the first peripheral venous serum calcium level obtained during hospitalization and was measured by the laboratory medicine department as per usual practice.

Variables included in the GRACE risk score model were readily available at hospital admission (age, heart rate, systolic blood pressure, serum creatinine (SCr) concentration, Killip class, ST-segment deviation, elevated cardiac enzymes, and cardiac arrest). The GRACE risk score were calculated by software affiliated to the database as previously described[2] and in accordance with GRACE risk calculator (http://www.outcomes-umassmed.org/grace).

Statistical Analysis

Continuous variables are expressed as mean ± SD or as median (interquartile range), and categorical variables are reported as counts and percentages. Independent samples *t* test and Kruskal-Wallis test were applied, respectively, to assess normally distributed and non–normally distributed continuous and categorical variables. To assess categorical variables, χ^2 tests were applied. Pearson rank correlation was used to assess the relationship between serum calcium and the GRACE risk score. Univariate logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for in-hospital mortality. All significant variables ($P < 0.1$) were tested in a multivariate logistic regression model to identify independent predictors.

Serum calcium was performed as a continuous variable when it was included into the GRACE risk score. Two logistic regression models were constructed: one with GRACE risk score alone and the other with the combination of serum calcium. Receiver operating characteristic analysis was used to calculate the C statistic, and the increase in the area under curve (AUC) was evaluated and tested for significance using the test proposed by Hanley and McNeil.[10] Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were performed to analyze the degree to which the addition of serum calcium to the GRACE risk score model improved predictive ability, as previously described.[11] Two-sided *P* values <0.05 indicated statistical significance. All analyses were performed with SPSS software version 22.0 (IBM Corp., Armonk, NY), MedCalc software version 15.10 (MedCalc Software, Ostend, Belgium), and STATA software version 13.0 (StataCorp LP, College Station, TX).

Results

Population Characteristics

The baseline characteristics of the patients are listed in Table 1. A total of 2229 patients with angiography confirmed ACS were enrolled in this study in accordance with the inclusion criteria, and in-hospital mortality occurred in 56 patients. The mean age was 64.55 ± 10.66 years, 78.9% were men, 21.1% presented with ST-segment elevation myocardial infarction (STEMI), and 78.1% underwent percutaneous coronary intervention. The admission serum calcium levels were normally distributed (Figure 1), with a mean admission calcium level of 2.20 ± 0.15 mmol/L.

There were no significant differences in past medical history of hypertension or diabetes mellitus, arterial lesion characteristics, percutaneous coronary intervention, and primary drug treatment between the 4 groups of patients stratified by serum calcium level. Patients with lower baseline serum calcium levels were older, more likely to present with STEMI, and had higher GRACE risk score, higher heart rate, lower blood pressure, higher SCr levels, higher white blood cell counts, lower hemoglobin levels, and a higher frequency of smoking history.

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22557

Table 1. Baseline Characteristics of Overall Patients and Grouped Patients Stratified by Serum Calcium at Admission

Characteristics	Overall	Serum Calcium, mmol/L				*P* Value
		Q1, <2.12	Q2, 2.12– < 2.21	Q3, 2.21– < 2.28	Q4, ≥2.28	
No. of patients, n	2229	534	601	491	603	
In-hospital death	56 (2.5)	31 (5.8)	12 (2.0)	6 (1.2)	7 (1.2)	<0.001
Mean age, y	64.55 ± 10.66	66.34 ± 10.11	65.16 ± 10.32	63.87 ± 10.78	62.92 ± 11.11	<0.001
Male sex	1759 (78.9)	438 (82.0)	487 (81.0)	377 (76.8)	457 (75.8)	0.022
Serum calcium, mmol/L	2.20 ± 0.15	2.02 ± 0.13	2.16 ± 0.025	2.23 ± 0.02	2.36 ± 0.15	<0.001
Calcium measuring time from admission, h	2 (0.5–15)	1.5 (0.5–13.5)	2 (0.5–15)	3 (0.5–15)	2 (0.5–15)	0.025
Calcium measuring time of day						
6 AM to 11 AM	1129 (50.6)	267 (50.0)	320 (53.2)	251 (51.1)	290 (48.1)	0.344
12 PM to 5 PM	388 (17.4)	99 (18.5)	90 (15.0)	79 (16.1)	120 (19.9)	0.105
6 PM to 11 PM	484 (21.7)	108 (20.2)	128 (21.3)	115 (23.4)	133 (22.1)	0.650
00 AM to 5 AM	229 (10.3)	60 (11.2)	63 (10.5)	46 (9.4)	60 (10.0)	0.784
GRACE risk score	92.80 ± 26.27	98.23 ± 26.07	92.78 ± 25.97	89.49 ± 26.08	90.65 ± 26.20	<0.001
Previous or current smoker	1307 (58.6)	325 (60.9)	365 (60.7)	293 (59.7)	324 (53.7)	<0.001
HTN	1217 (54.6)	281 (52.6)	308 (51.2)	278 (56.6)	350 (58.0)	0.064
DM	554 (24.9)	133 (24.9)	135 (22.5)	119 (24.2)	167 (27.7)	0.208
Previous PCI or CABG						
PCI	162 (7.3)	40 (7.5)	47 (7.8)	41 (8.4)	34 (5.6)	0.316
CABG	22 (1.0)	5 (0.9)	5 (0.8)	4 (0.8)	8 (1.3)	0.796
Previous drug treatment						
Aspirin	724 (32.5)	139 (26.0)	203 (33.8)	175 (35.6)	207 (34.3)	0.003
Statin	460 (20.6)	87 (16.3)	124 (20.6)	124 (25.3)	125 (20.7)	0.006
ACEI/ARB	420 (18.8)	83 (15.5)	119 (19.8)	91 (18.5)	127 (21.1)	0.105
β-Blocker	531 (23.8)	92 (17.2)	149 (24.8)	132 (26.9)	158 (26.2)	0.001
BMI, kg/m^2	24.21 ± 2.94	24.06 ± 2.89	24.02 ± 2.75	24.27 ± 2.90	24.48 ± 3.17	0.028
BP at admission, mm Hg						
SBP	130.27 ± 22.08	125.69 ± 23.82	129.46 ± 20.50	132.97 ± 21.64	132.93 ± 21.68	<0.001
DBP	76.45 ± 12.84	73.90 ± 13.52	75.61 ± 11.98	77.55 ± 12.82	78.64 ± 12.64	<0.001
Heart rate at admission, bpm	74.54 ± 14.38	76.21 ± 16.74	73.59 ± 13.39	73.44 ± 12.52	74.92 ± 14.39	0.005
SCr, mmol/L	90.79 ± 28.68	92.74 ± 33.71	89.00 ± 24.96	90.08 ± 26.76	91.43 ± 28.80	0.146
Albumin, g/dL	40.45 ± 4.25	37.75 ± 4.17	40.32 ± 3.51	41.48 ± 3.66	42.09 ± 4.25	<0.001
Lipids, mmol/L						
TC	4.14 ± 1.08	3.82 ± 0.96	4.08 ± 1.11	4.23 ± 0.99	4.39 ± 1.15	<0.001
LDL-C	2.45 ± 0.94	2.28 ± 0.81	2.37 ± 0.95	2.49 ± 0.87	2.62 ± 1.04	<0.001
HDL-C	1.15 ± 0.37	1.12 ± 0.46	1.13 ± 0.37	1.17 ± 0.34	1.16 ± 0.30	0.077
TG	1.79 ± 1.17	1.50 ± 0.81	1.75 ± 1.25	1.78 ± 1.16	2.07 ± 1.28	<0.001
WBC count, $\times 10^9$/L	7.87 ± 3.42	8.49 ± 3.88	7.70 ± 3.47	7.48 ± 3.13	7.83 ± 3.10	<0.001

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22557

Table 1. Continued

Characteristics	Overall	Serum Calcium, mmol/L				*P* Value
		Q1, <2.12	Q2, 2.12– < 2.21	Q3, 2.21– < 2.28	Q4, ≥2.28	
Hgb, g/L	133.87 ± 18.09	126.70 ± 19.21	133.56 ± 17.36	136.43 ± 16.20	138.48 ± 17.24	<0.001
Platelet count, $\times 10^9$/L	162.88 ± 61.52	162.00 ± 63.39	158.19 ± 61.83	165.74 ± 65.09	166.01 ± 56.16	0.101
Serum potassium, mmol/L	3.94 ± 0.47	3.94 ± 0.53	3.93 ± 0.43	3.98 ± 0.44	3.99 ± 0.45	<0.001
Serum sodium, mmol/L	140.81 ± 3.73	139.91 ± 4.70	140.94 ± 3.34	141.17 ± 3.67	141.18 ± 2.98	<0.001
Serum chloride, mmol/L	104.73 ± 5.74	105.07 ± 7.32	105.30 ± 3.31	104.71 ± 4.84	103.87 ± 6.59	<0.001
Lesion characteristic						
LM disease	221 (9.9)	54 (10.1)	63 (10.5)	46 (9.4)	58 (9.6)	0.927
3-vessel disease	529 (23.7)	119 (22.3)	136 (22.6)	132 (26.9)	142 (23.5)	0.292
PCI	1741 (78.1)	420 (78.7)	472 (78.5)	380 (77.4)	469 (77.8)	0.952
Clinical diagnosis						
STEMI	471 (21.1)	137 (25.7)	116 (19.3)	92 (18.7)	127 (21.0)	0.023
NSTEMI	230 (10.3)	61 (11.4)	62 (10.3)	40 (8.1)	67 (11.1)	0.304
UA	1528 (68.6)	336 (62.9)	434 (72.1)	370 (75.2)	411 (67.9)	<0.001
Drug treatment in hospital						
ASA	2151 (96.5)	510 (95.5)	585 (97.3)	472 (96.1)	584 (96.8)	0.358
Clopidogrel	2137 (95.9)	507 (94.9)	576 (95.8)	472 (96.1)	582 (96.5)	0.597
Statin	2089 (93.7)	502 (94.2)	559 (93.0)	463 (94.3)	565 (93.7)	0.805
ACEI/ARB	1318 (59.1)	297 (55.6)	351 (58.5)	292 (59.5)	378 (62.7)	0.111
β-Blocker	1523 (68.3)	325 (60.9)	398 (66.3)	345 (70.3)	455 (75.5)	<0.001
Nitrated derivative	1025 (46.0)	212 (39.7)	290 (48.3)	237 (48.3)	286 (47.4)	0.10

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ASA, aspirin; BP, blood pressure; CABG, coronary artery bypass grafting; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; Hgb, hemoglobin; HTN, hypertension; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LM, left main; PCI, percutaneous coronary intervention; Q, quartile; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglycerides; UA, unstable angina; WBC, white blood cell.
Data are expressed as n (%), mean ± SD, or median (IQR), as appropriate.

Baseline Serum Calcium as an Independent Predictor

Admission serum calcium was stratified into quartiles (Q1: <2.12 mmol/L; Q2: 2.12– < 2.21 mmol/L; Q3: 2.21– < 2.28 mmol/L; and Q4: >2.28 mmol/L) to analyze its predictive value. Table 2 summarizes the results of the univariate and multivariate logistic regression analyses of the factors associated with in-hospital mortality. After adjustment for all potentially confounding variables ($P < 0.1$), including albumin, a low level of serum calcium (OR: 0.443, 95% CI: 0.206-0.953; OR: 0.243, 95% CI: 0.090-0.654; and OR: 0.210, 95% CI: 0.082-0.538) for the second, third, and fourth quartiles, respectively, compared with the lowest quartile) was still an independent predictor of in-hospital mortality in the multivariate logistic regression analysis.

Association and Combination of the GRACE Risk Score With Admission Serum Calcium

The correlation between serum calcium and the GRACE risk score was assessed by Pearson correlation. The result

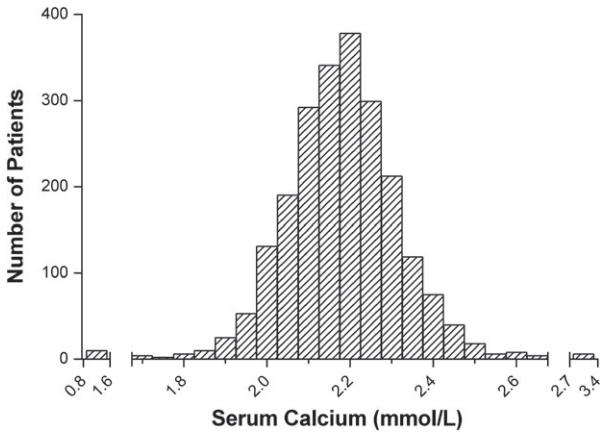


Figure 1. The distribution of admission serum calcium in overall participants.

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22557

Table 2. Univariate and Multivariate Logistic Regression Analysis for Predictors of In-hospital Mortality

Variables	Unadjusted OR	*P* Value	Adjusted OR	*P* Value
Serum calcium				
Q1	Ref	—	Ref	—
Q2	0.330	0.001	0.443	0.037
Q3	0.200	<0.001	0.243	0.005
Q4	0.190	<0.001	0.210	0.001
Calcium measuring time from admission	0.943	0.010	0.953	0.059
Calcium measuring time of day				
6 AM to 11 PM	Ref	—		
12 PM to 5 PM	1.092	0.823		
6 PM to 11 PM	1.370	0.355		
00 AM to 5 AM	1.882	0.112		
GRACE risk score	1.025	<0.001	1.017	0.017
Age	1.043	<0.001	1.010	0.701
Male sex	1.804	0.043	2.236	0.037
Smoking history	0.699	0.186		
HTN	1.112	0.699		
DM	2.155	0.005	1.585	0.158
Previous PCI	0.466	0.292		
Previous CABG	<0.001	0.998		
Previous ASA	0.560	0.078	1.423	0.421
Previous statin	0.454	0.070	0.609	0.367
Previous ACEI/ARB	0.712	0.379		
Previous β-Blocker	0.377	0.025	0.459	0.138
BMI	0.955	0.332		
SBP	0.982	0.006	0.996	0.688
DBP	0.977	0.031	0.996	0.806
Heart rate	1.044	<0.001	1.020	0.023
SCr	1.017	<0.001	1.010	0.013
Albumin	0.925	0.007	1.071	0.063
TC	1.009	0.947		
LDL-C	0.844	0.276		
HDL-C	0.749	0.526		
TG	0.844	0.276		
WBC	1.203	<0.001	1.139	<0.001
Hgb	0.982	0.007	0.998	0.816
Platelet counts	0.999	0.805		
Serum potassium	1.485	0.140		
Serum sodium	0.954	0.107		
Serum chloride	0.971	0.010	0.979	0.162
LM disease	2.285	0.016	3.124	0.011
3-vessel disease	2.296	0.003	2.870	0.002
PCI	1.297	0.461		
STEMI	2.297	0.003	1.480	0.447
NSTEMI	1.249	0.588		
UA	0.449	0.003	1.640	0.335
ASA	0.001	0.997		
Clopidogrel	0.001	0.997		
Statin	0.001	0.996		
ACEI/ARB	0.590	0.052	0.837	0.582
β-Blocker	1.273	0.430		
Nitrated derivative	1.180	0.542		

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, aspirin; BMI, body mass index; CABG, coronary artery bypass grafting; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; Hgb, hemoglobin; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; LM, left main; NSTEMI, non–ST-segment elevation myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; Q, quartile; Ref, reference; SBP, systolic blood pressure; SCr, serum creatinine; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglycerides; WBC, white blood cells.

showed that there was a very weak negative, though significant, correlation between serum calcium and the GRACE risk score ($r = -0.089$, $P = 0.001$; Figure 2).

The receiver operating characteristic analysis was performed to assess whether a combination of serum calcium and the GRACE score could improve predictive ability compared with the GRACE score alone. The results showed that the AUC increased significantly after the addition of serum calcium to the GRACE risk score (0.685 vs 0.746; $Z = 2.617$, $P = 0.009$; Figure 3A). Moreover, the inclusion of serum calcium into the GRACE risk score model was associated with a NRI of 52.4% ($P < 0.001$), suggesting an effective reclassification. The IDI again showed that the diagnostic performance of the model was significantly improved by adding serum calcium to the GRACE risk score (IDI: 0.011, $P = 0.003$; Figure 3A).

In the subgroup of patients with STEMI, serum calcium also significantly increased the AUC and led to a similar improvement in reclassification and discrimination when added to the GRACE risk score (AUC: 0.646 vs 0.758, $Z = 2.255$, $P = 0.024$; NRI: 0.386, $P = 0.042$; and IDI: 0.008,

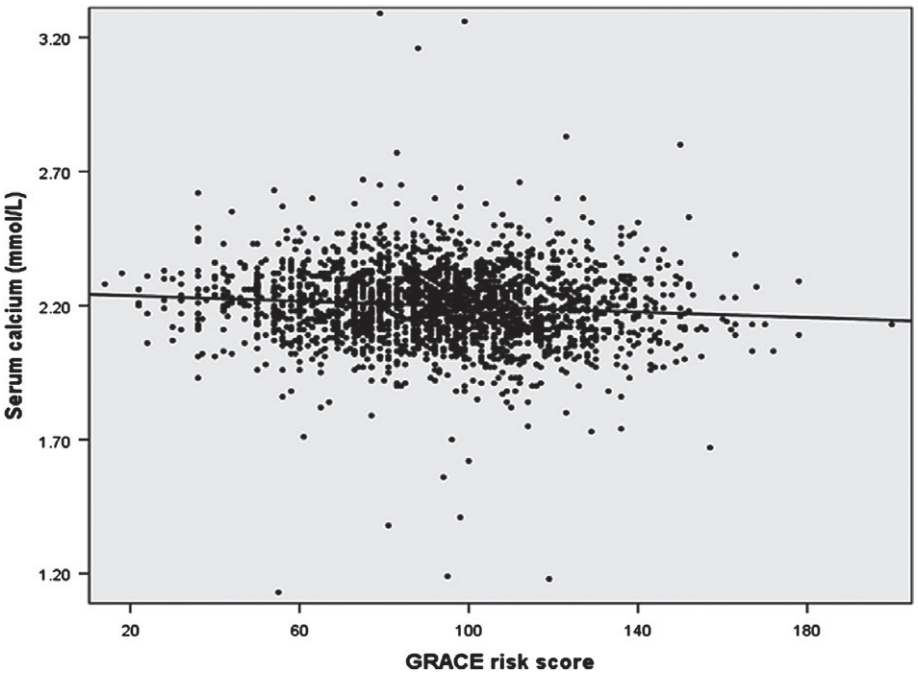


Figure 2. Correlation between serum calcium concentration and the GRACE risk score. Abbreviations: GRACE, Global Registry of Acute Coronary Events.

$P = 0.053$; Figure 3B). Serum calcium showed a tendency to increase the AUC, but this relationship did not reach significance (AUC: 0.691 vs 0.724, $Z = 1.417$, $P = 0.151$; Figure 3C) in patients with UA or non–ST-elevation myocardial infarction (UA/NSTEMI).

Discussion

The results of this study showed that a decreased baseline serum calcium level measured at admission in patients with ACS was an independent predictor of the in-hospital mortality after adjusting for the potential confounding predictors. Moreover, serum calcium was weakly correlated with the GRACE risk score and added incremental predictive value when combined with the GRACE score. The effectiveness of serum calcium in increasing the predictive value of the GRACE risk score was attenuated in the UA/NSTEMI group, which may be due to the relatively lower ratio of events, and suggests that serum calcium may be more influential in STEMI. Thus, a larger multicenter study is warranted to better evaluate the effects of baseline serum calcium in ACS patients.

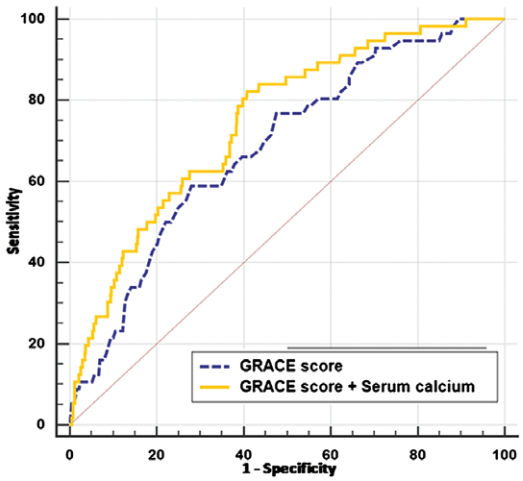
The use of various albumin adjustment formulas has been suggested to assess serum calcium, but no clear consensus has been reached[12–14]; in this study, albumin was included in the multivariable regression model but was not used directly to correct serum calcium. Hypocalcemia is prevalent in critically ill patients and has been shown to be associated with increased mortality in a considerable number of clinical studies.[15–18] Our results were consistent with those of a recent study by Xin Lu et al[9] conducted on patients with STEMI. Although a lower level of serum calcium was independently associated with in-hospital mortality, the mechanism that may account for this association was not clear. Possible mechanisms of the association between serum calcium and in-hospital mortality in patients with severe CAD 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 mortality. Second, hypocalcemia could reduce renal sodium excretion, thus contributing to fluid overload[19] and diminished myocardial contractility, as demonstrated by decreased left ventricular work index.[20,21]

To our knowledge, this is the first study to evaluate the association between serum calcium and the GRACE risk score. The current GRACE risk score only includes 2 laboratory-based biomarkers: SCr and troponin. Therefore, it is conceivable that variables that reflect other pathophysiological aspects of ACS could provide additional information. In this study, both serum calcium and the GRACE risk score were significantly different in 2 groups of patients with or without in-hospital mortality, but there was only a very weak correlation between them. Furthermore, the addition of serum calcium to the GRACE risk score could effectively improve the predictive power of the scoring system for the risk of hospitalization. All these results suggest that serum calcium offers independent information in addition to that provided by the GRACE risk score.

Although previous studies concerning calcium supplements have been conflicting,[22,23] some recent evidence suggests that the beneficial effects of calcium supplementation could be population-dependent, such as in patients with calcium deficiency.[24,25] A more recent study showed that calcium supplementation improves short-term outcomes in intensive care unit patients with hypocalcemia.[26] Thus, further investigations are needed to determine whether

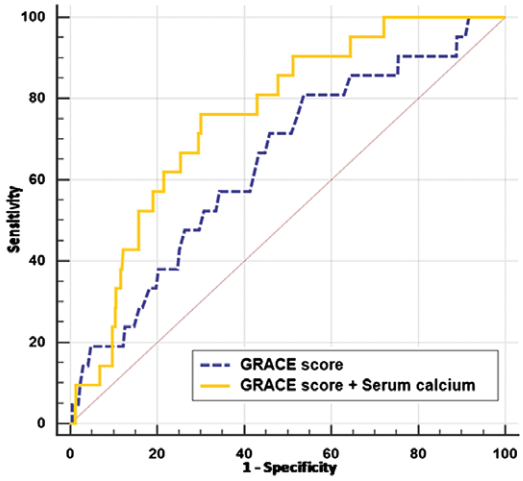
Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22557

(A)



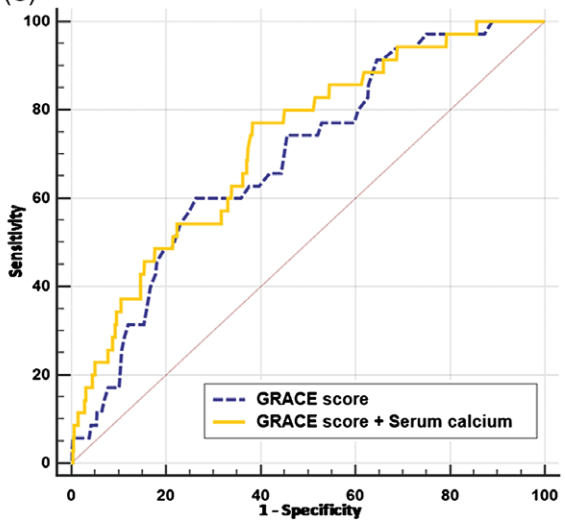
	GRACE vs GRACE + Serum calcium
The area under ROC (AUC)	0. 685vs. 0.746 (Z= 2.617, p= 0.009)
Net reclassification index (NRI)	0.524 (p< 0.001)
Incremental discrimination index (IDI)	0.011 (p= 0.003)

(B)



	GRACE vs GRACE + Serum calcium
The area under ROC (AUC)	0. 646vs. 0.758 (Z= 2.255, p= 0.024)
Net reclassification index (NRI)	0.386 (p= 0.042)
Incremental discrimination index (IDI)	0.008 (p= 0.053)

(C)



	GRACE vs GRACE + Serum calcium
The area under ROC (AUC)	0. 691vs. 0.724(Z= 1.417, p= 0.151)
Net reclassification index (NRI)	0.482 (p= 0.002)
Incremental discrimination index (IDI)	0.011 (p= 0.008)

Figure 3. The ROC curves of the GRACE risk score and its combination with admission serum calcium in (A) overall participants and subgroups of patients with (B) STEMI or (C) UA/NSTEMI. Abbreviations: AUC, area under the curve; GRACE, Global Registry of Acute Coronary Events; IDI, integrated discrimination improvement; NRI, net reclassification improvement; NSTEMI, non–ST-segment elevation myocardial infarction; ROC, receiver operating characteristic; UA, unstable angina.

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22557

calcium-supplementation therapy in ACS patients with low serum calcium could improve their prognosis.

Study Limitations

Despite consecutive patient recruitment and relatively comprehensive clinical data collection, there are still some limitations in our present study. First, this investigation was a single-center retrospective study and recruited exclusively from a Chinese population; therefore, our findings should be further validated in prospective studies recruiting other ethnic groups. Second, this investigation was a single-center observational study, and the lack of validation cohorts was another weakness.

Conclusion

Serum calcium level at admission was an independent predictor of in-hospital mortality in ACS patients. The inclusion of serum calcium into the GRACE risk score could lead to a more accurate prediction. We suggest considering low serum calcium level at admission as a possible indicator of increased risk of in-hospital mortality while awaiting more data to confirm this finding.

References

1. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;61:e78–e140.
2. Granger CB, Goldberg RJ, Dabbous O, et al; GRACE Investigators. Predictors of hospital mortality in the Global Registry of Acute Coronary Events. *Arch Intern Med.* 2003;163:2345–2353.
3. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non–ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in *J Am Coll Cardiol.* 2014;64:2713–2714]. *J Am Coll Cardiol.* 2014;64:e139–e228.
4. Correia LC, Souza AC, Sabino M, et al. Hemoglobin level adds prognostic value to the Global Registry of Acute Coronary Events score in non–ST-elevation acute coronary syndromes. *Cardiology.* 2012;121:213–219.
5. Schiele F, Meneveau N, Seronde MF, et al. C-reactive protein improves risk prediction in patients with acute coronary syndromes. *Eur Heart J.* 2010;31:290–297.
6. Niu X, Yang C, Zhang Y, et al. Mean platelet volume on admission improves risk prediction in patients with acute coronary syndromes. *Angiology.* 2015;66:456–463.
7. Kraft MD. Phosphorus and calcium: a review for the adult nutrition support clinician. *Nutr Clin Pract.* 2015;30:21–33.
8. Berridge MJ. Calcium signalling remodelling and disease. *Biochem Soc Trans.* 2012;40:297–309.
9. Lu X, Wang Y, Meng H, et al. Association of admission serum calcium levels and in-hospital mortality in patients with acute ST-elevation myocardial infarction: an eight-year, single-center study in China. *PLoS One.* 2014;9:e99895.
10. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology.* 1983;148:839–843.
11. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med.* 2011;30:11–21.
12. Slomp J, van der Voort PH, Gerritsen RT, et al. Albumin-adjusted calcium is not suitable for diagnosis of hyper- and hypocalcemia in the critically ill. *Crit Care Med.* 2003;31:1389–1393.
13. Björkman MP, Sorva AJ, Tilvis RS. Calculated serum calcium is an insufficient surrogate for measured ionized calcium. *Arch Gerontol Geriatr.* 2009;49:348–350.
14. Steele T, Kolamunnage-Dona R, Downey C, et al. Albumin-adjusted calcium concentration should not be used to identify hypocalcaemia in critical illness. *Crit Care.* 2013;17(suppl 2):446–450.
15. Miura S, Yoshihisa A, Takiguchi M, et al. Association of hypocalcemia with mortality in hospitalized patients with heart failure and chronic kidney disease. *J Card Fail.* 2015;21:621–627.
16. Müller B, Becker KL, Kranzlin M, et al. Disordered calcium homeostasis of sepsis: association with calcitonin precursors. *Eur J Clin Invest.* 2000;30:823–831.
17. Sauter TC, Lindner G, Ahmad SS, et al. Calcium disorders in the emergency department: independent risk factors for mortality. *PLoS One.* 2015;10:e0132788.
18. Zhang Z, Xu X, Ni H, et al. Predictive value of ionized calcium in critically ill patients: an analysis of a large clinical database MIMIC II. *PLoS One.* 2014;9:e95204.
19. Levine SN, Rheams CN. Hypocalcemic heart failure. *Am J Med.* 1985;78(6 part 1):1033–1035.
20. Hurley K, Baggs D. Hypocalcemic cardiac failure in the emergency department. *J Emerg Med.* 2005;28:155–159.
21. Suzuki T, Ikeda U, Fujikawa H, et al. Hypocalcemic heart failure: a reversible form of heart muscle disease. *Clin Cardiol.* 1998;21:227–228.
22. Bostick RM, Kushi LH, Wu Y, et al. Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. *Am J Epidemiol.* 1999;149:151–161.
23. Bolland MJ, Grey A, Avenell A, et al. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ.* 2011;342:d2040.
24. Larsson SC, Orsini N, Wolk A. Dietary calcium intake and risk of stroke: a dose–response meta-analysis. *Am J Clin Nutr.* 2013;97:951–957.
25. Michaëlsson K, Melhus H, Warensjö Lemming E, et al. Long-term calcium intake and rates of all cause and cardiovascular mortality: community-based prospective longitudinal cohort study. *BMJ.* 2013;346:f228.
26. Zhang Z, Chen K, Ni H. Calcium supplementation improves clinical outcome in intensive care unit patients: a propensity score matched analysis of a large clinical database MIMIC-II. *Springerplus.* 2015;4:594–601.

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22557