

# BMJ Open Altered serum calcium homeostasis independently predicts mortality in patients with acute coronary syndrome: a retrospective observational cohort study

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## ABSTRACT

**Objectives** Serum calcium levels (sCa) were reported to be associated with risk of cardiovascular diseases. The aim of this study was to analyse the association between sCa and long-term mortality in patients with acute coronary syndrome (ACS).

**Design** A retrospective observational cohort study.

**Setting** Single-centre study with participants recruited from the local area.

**Participants** A total of consecutive 13 772 patients with ACS were included in this analysis. Patients were divided based on their sCa profile ( $\leq 2.1$  mmol/L, 2.1–2.2 mmol/L, 2.2–2.3 mmol/L, 2.3–2.4 mmol/L, 2.4–2.5 mmol/L,  $> 2.5$  mmol/L) and followed up for a median of 2.96 years (IQR 1.01–4.07).

**Primary outcome** Long-term all-cause mortality.

**Results** During a median follow-up period of 2.96 years, patients with sCa  $\leq 2.1$  mmol/L had the highest cumulative incidences of all-cause mortality (16.7%), whereas those with sCa 2.4–2.5 mmol/L had the lowest cumulative incidences of all-cause mortality (3.5%). After adjusting for potentially confounding variables, the Cox analysis revealed that compared with the reference group (sCa 2.4–2.5 mmol/L), all the other groups had higher mortality except for the sCa 2.3–2.4 mmol/L group (HR, 1.32, 95% CI 0.93 to 1.87). Restricted cubic splines showed that the relationship between sCa and all-cause mortality seemed to be U shaped. The optimal sCa cut-off point, 2.35 mmol/L, was determined based on the shape of restricted cubic splines.

**Conclusions** Altered serum calcium homeostasis at admission independently predicts all-cause mortality in patients with ACS. In addition, a U-shaped relationship between sCa and all-cause mortality exists, and maintaining sCa at approximately 2.35 mmol/L may minimise the risk of mortality.

## INTRODUCTION

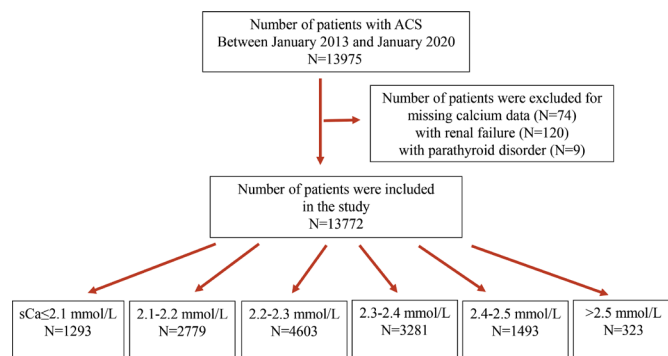
Serum calcium ions play a pivotal role in various metabolic and regulatory processes, including excitation, contraction and relaxation of the myocardium, platelet adhesion, blood coagulation and neurotransmitter

## Strengths and limitations of this study

- We provided new evidence regarding the association between serum calcium levels (sCa) and long-term outcomes in a large ‘real-world’ cohort of acute coronary syndrome patients.
- This cohort study had a longer follow-up time and larger sample size than other published studies.
- This was a retrospective observational study from one single centre.
- Follow-up data were partially collected by telephone interviews, which might cause information bias.
- Due to our retrospectively collected data, it is not possible to report the serial change of sCa.

release.<sup>1–3</sup> Thus, alterations in serum calcium ions may interfere with platelet aggregation, electrical stability and cause myocardial dysfunction, which may adversely affect prognosis of patients with acute coronary syndrome (ACS).

Abnormal serum calcium levels (sCa) have been previously reported to be an independent predictor of the incidence of cardiovascular diseases and associated with cardiovascular risk factors such as hypertension, dyslipidaemia and diabetes.<sup>4–12</sup> Since sCa can be easily measured through established assays, identifying the association between sCa and outcomes can be useful in clinical practice. A few published studies have shown that altered serum calcium homeostasis was an independent risk factor for short-term mortality in patients with cardiovascular diseases.<sup>13–16</sup> However, studies evaluating the association between sCa and long-term outcomes in the setting of ACS are still limited and, when exist, are possibly too small to extensively uncover the true associations.<sup>17</sup> There is still no consensus on



**Figure 1** Study population and selection. ACS, acute coronary syndrome.

the cut-off points to define the levels of serum calcium needed to reduce the risk of death in most studies.

The current study aimed to investigate the association between sCa and long-term outcome in a large ‘real-world’ cohort of patients with ACS.

## METHODS

### Study design

The present investigation was a retrospective observational cohort study with a long-term follow-up. As shown in [figure 1](#), a total of 13 975 patients with ACS including ST elevation myocardial infarction (STEMI), Non-STEMI (NSTEMI) and unstable angina pectoris (UAP) who were admitted to Beijing Friendship Hospital from January 2013 to January 2020 were considered for enrollment into the study. Two hundred and three patients were excluded because of missing calcium data, with known renal failure or parathyroid disorder. Medical records were collected from the Cardiovascular Center Beijing Friendship Hospital Database Bank.

### Clinical assessments and follow-up

Clinical characteristics including demographic data and laboratory test results were collected during hospitalisation. Peripheral venous blood was drawn within 24 hours of presentation and tested for calcium, creatinine, glycosylated haemoglobin (HbA1c) and low-density lipoprotein cholesterol (LDL-C), by a certified laboratory at our institution. Total sCa were tested and corrected for albumin levels in order to evaluate values of ionised calcium in our study. sCa were corrected according to the following formula: observed serum calcium (mmol/L)+0.02×(40 g/L–albumin g/L).<sup>18</sup> Patients were divided based on their sCa profile: ≤2.1 mmol/L, 2.1–2.2 mmol/L, 2.2–2.3 mmol/L, 2.3–2.4 mmol/L, 2.4–2.5 mmol/L, >2.5 mmol/L. The peak values of cardiac troponin I (cTnI) and N-terminal pro-brain natriuretic peptide (NTproBNP) after serial measurements were used as indicators of myocardial injury. The estimated glomerular filtration rate (eGFR) was calculated by the Cockcroft–Gault formula. Echocardiography was performed on the second day of hospitalisation. The biplane left ventricular ejection fraction (LVEF) was calculated by the disc summation method.

Patients were treated according to prevailing guidelines and individual need, which was determined by the attending physician. Follow-up data were collected by telephone interviews and reviewing outpatient medical records. The median follow-up was 2.96 years (IQR 1.01–4.07). The primary endpoint of this study was all-cause mortality.

### Statistics analyses

Due to skewed distribution, continuous variables in our study were reported as medians with IQRs and categorical variables as frequencies with percentages. Baseline characteristics of the study population across sCa groups were compared using the Kruskal-Wallis rank sum test for continuous variables and the Pearson  $\chi^2$  test for categorical variables. To visualise the relationship between sCa groups and long-term prognosis, Kaplan-Meier plots were generated. Unadjusted and adjusted associations of sCa groups with follow-up mortality were assessed using the Cox proportional hazards models. HRs with 95% CIs were calculated for each sCa category compared with reference group. The 2.4–2.5 mmol/L group was chosen as the reference group after showing the mortality results. A multiple restricted cubic spline Cox regression model was used to explore the non-linear association between sCa and all-cause mortality. The following covariates were adjusted for the multivariable model: age, sex, classification of ACS, history of myocardial infarction, history of percutaneous coronary intervention (PCI), history of coronary artery bypass grafting, history of hypertension, history of diabetes, current smoker, systolic blood pressure at admission, HbA1c, LDL-C, eGFR, albumin, LVEF, PCI therapy and medical therapy. All data analyses were performed with the use of SPSS V.22.0 (IBM, Armonk, New York, USA) and R (V.3.6.3).  $p < 0.05$  was considered statistically significant.

### Patient and public involvement

No patient was involved.

## RESULTS

### Baseline characteristics

As [table 1](#) shows, patients in various sCa categories were different in most baseline characteristics. Patients with low sCa were older, more likely to be men and current smokers, have more prevalent diagnosis of STEMI and NSTEMI, more likely to have lower levels of LDL-C and HbA1c, higher levels of cTnI and NTproBNP, and more likely to have LVEF <50%. Those with high sCa were mostly women, have higher rates of prior hypertension and diabetes, more prevalent diagnosis of UAP, have lower levels of eGFR and cTnI and were less likely to receive PCI.

### Study outcomes

Over the median follow-up period of 2.96 years, 1043 patients died (7.6%). The cumulative incidences of

**Table 1** Baseline characteristics according to serum calcium levels

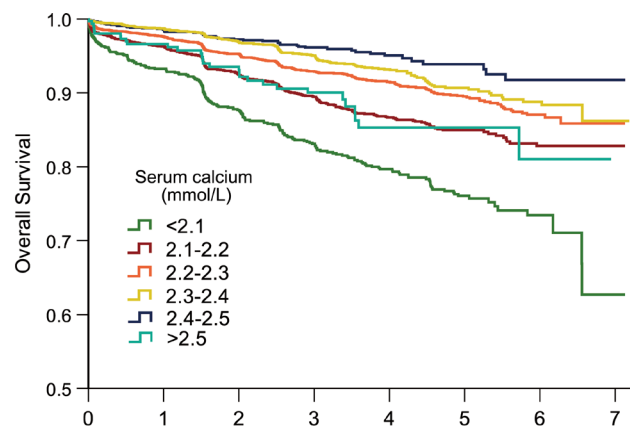
	≤2.1 (n=1293)	2.1–2.2 (n=2779)	2.2–2.3 (n=4603)	2.3–2.4 (n=3281)	2.4–2.5 (n=1493)	>2.5 (n=323)	P value
Ca <sup>2+</sup> , mmol/L	2.06 (2.01–2.09)	2.16 (2.14–2.19)	2.26 (2.23–2.28)	2.34 (2.32–2.37)	2.43 (2.41–2.46)	2.55 (2.52–2.60)	<0.001
Age, years	68 (60–78)	66 (59–75)	64 (58–73)	64 (57–72)	63 (57–72)	65 (58–74)	<0.001
Male, n (%)	902 (69.8)	1870 (67.3)	3059 (66.5)	2009 (61.2)	842 (56.4)	152 (47.1)	<0.001
Medical history, n (%)							
Myocardial infarction	141 (10.9)	297 (10.7)	432 (9.4)	294 (9.0)	122 (8.2)	35 (10.8)	0.032
Prior PCI	195 (15.1)	430 (15.5)	692 (15.0)	483 (14.7)	220 (14.7)	41 (12.7)	0.832
Prior CABG	27 (2.1)	76 (2.7)	118 (2.6)	62 (1.9)	30 (2.0)	8 (2.5)	0.226
Hypertension	861 (66.6)	1890 (68.0)	3226 (70.1)	2346 (71.5)	1114 (74.6)	250 (77.4)	<0.001
Diabetes	442 (34.2)	882 (31.7)	1528 (33.2)	1229 (37.5)	662 (44.3)	151 (46.7)	<0.001
BMI, kg/m <sup>2</sup>	25.0 (22.9–27.3)	25.4 (23.1–27.7)	25.5 (23.4–27.9)	25.8 (23.7–28.0)	25.7 (23.6–28.0)	25.2 (23.3–27.8)	<0.001
Current smoker, n (%)	473 (36.6)	989 (35.6)	1615 (35.1)	1090 (33.2)	455 (30.5)	86 (26.6)	<0.001
Diagnosis							<0.001
STEMI, n (%)	340 (26.3)	538 (19.4)	646 (14.0)	377 (11.5)	124 (8.3)	33 (10.2)	
NSTEMI, n (%)	406 (31.4)	496 (17.8)	642 (13.9)	391 (11.9)	158 (10.6)	33 (10.2)	
UAP, n (%)	547 (42.3)	1745 (62.8)	3315 (72.0)	2513 (76.6)	1211 (81.1)	257 (79.6)	
Systolic BP, mm Hg	126 (114–140)	130 (118–140)	130 (120–141)	130 (120–141)	130 (120–143)	131 (120–145)	<0.001
Heart rate, bpm	72 (64–82)	70 (62–78)	70 (63–78)	70 (63–78)	71 (64–79)	73 (64–82)	<0.001
Multivessel disease, n (%)	634 (70.3)	1451 (67.3)	2418 (64.9)	1714 (64.2)	802 (66.2)	165 (64.7)	0.013
Left main lesion, n (%)	129 (14.3)	233 (10.8)	400 (10.7)	281 (10.5)	125 (10.3)	36 (14.1)	0.015
PCI therapy, n (%)	647 (50.0)	1458 (52.5)	2386 (51.8)	1672 (51.0)	734 (49.2)	142 (44.0)	0.028
Medical treatment							
Antiplatelet, n (%)	1142 (88.3)	2521 (90.7)	4274 (92.9)	3053 (93.1)	1404 (94.0)	289 (89.5)	<0.001
Beta-blockers, n (%)	853 (66.0)	1828 (65.8)	3125 (67.9)	2221 (67.7)	1057 (70.8)	222 (68.7)	0.022
ACE inhibitors, n (%)	712 (55.1)	1474 (53.0)	2465 (53.6)	1793 (54.6)	817 (54.7)	193 (59.8)	0.215
Statins, n (%)	1075 (83.1)	2410 (86.7)	4088 (88.8)	2904 (88.5)	1313 (87.9)	274 (84.8)	<0.001
Creatinine, μmol/L	78 (66–100)	74 (64–89)	74 (64–86)	72 (63–85)	73 (64–86)	77 (64–95)	<0.001
eGFR, mL/min·1.73 m <sup>2</sup>	79 (60–94)	83 (67–97)	85 (71–98)	85 (71–97)	84 (70–95)	77 (63–92)	<0.001
Albumin, g/L	39.0 (36.7–41.7)	38.9 (36.5–41.4)	38.5 (36.2–41.0)	38.5 (35.7–41.0)	38.3 (35.7–41.0)	38.1 (35.6–40.4)	<0.001
LDL-C, mmol/L	2.2 (1.8–2.7)	2.3 (1.8–2.8)	2.3 (1.9–2.9)	2.4 (1.9–2.9)	2.4 (1.9–3.0)	2.4 (1.9–2.9)	<0.001
HbA1c, %	5.9 (5.6–6.8)	6.0 (5.6–6.9)	6.0 (5.6–6.9)	6.1 (5.6–7.1)	6.3 (5.7–7.4)	6.2 (5.6–7.5)	<0.001
cTnI, ng/mL	3.19 (0.34–12.2)	3.43 (0.43–13.3)	2.63 (0.21–14.5)	2.17 (0.18–11.5)	2.09 (0.09–10.8)	1.59 (0.07–13.0)	0.016

Continued

Table 1 Continued

	≤2.1 (n=1293)	2.1–2.2 (n=2779)	2.2–2.3 (n=4603)	2.3–2.4 (n=3281)	2.4–2.5 (n=1493)	>2.5 (n=323)	P value
NTproBNP, pg/mL	1573 (319–6824)	457 (131–2224)	254 (88–1052)	189 (71–682)	166 (66–619)	199 (75–888)	<0.001
LVEF <50%, n (%)	242 (18.7)	336 (12.1)	422 (9.2)	215 (6.6)	94 (6.3)	31 (9.6)	<0.001

BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; cTnI, cardiac troponin I; eGFR, estimated glomerular filtration rate; HbA1C, glycosylated haemoglobin; LDL-C, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NSTEMI, Non-ST elevation myocardial infarction; NTproBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; UAP, unstable angina pectoris.



NO. at Risk	Years							
	0	1	2	3	4	5	6	7
<2.1	1293	972	772	612	486	318	93	11
2.1-2.2	2779	2142	1691	1331	1025	652	244	33
2.2-2.3	4603	3503	2817	2211	1609	919	404	52
2.3-2.4	3281	2559	2054	1576	1060	518	255	23
2.4-2.5	1493	1181	939	674	398	201	100	7
>2.5	323	246	206	143	73	31	15	0

**Figure 2** Kaplan-Meier curves indicating the all-cause mortality in different serum calcium categories among patients with acute coronary syndrome.

all-cause mortality differed significantly, as shown in figure 2. Patients with sCa ≤2.1 mmol/L had the highest cumulative incidences of all-cause mortality (16.7%), whereas those with sCa 2.4–2.5 mmol/L had the lowest cumulative incidences of all-cause mortality (3.5%).

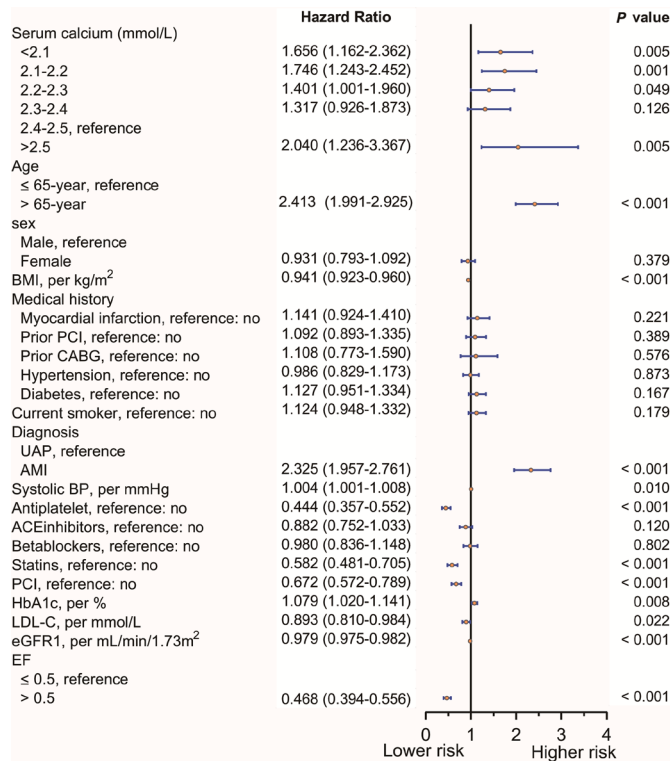
On multivariable analysis (figure 3), compared with the reference group (sCa 2.4–2.5 mmol/L), all the other groups had higher mortality (≤2.1 mmol/L, HR 1.66, 95% CI 1.16 to 2.36; 2.1–2.2 mmol/L, HR 1.75; 95% CI 1.24 to 2.45; 2.2–2.3 mmol/L, HR 1.40, 95% CI 1.00 to 1.96; >2.5 mmol/L, HR 2.04, 95% CI 1.24 to 3.37, respectively), except for the sCa 2.3–2.4 mmol/L group, which had similar mortality with the reference group (HR, 1.32, 95% CI 0.93 to 1.87). Restricted cubic splines showed that the relationship between sCa and all-cause mortality seemed to be U shaped. The optimal sCa cut-off point, 2.35 mmol/L, was determined based on the shape of restricted cubic splines (figure 4).

## DISCUSSION

Our study revealed that sCa were an independent predictor of the all-cause mortality risk in patients with ACS. Furthermore, the study showed a U-shaped relationship between sCa and all-cause mortality, and maintaining sCa at approximately 2.35 mmol/L at admission could minimise the risk of mortality.

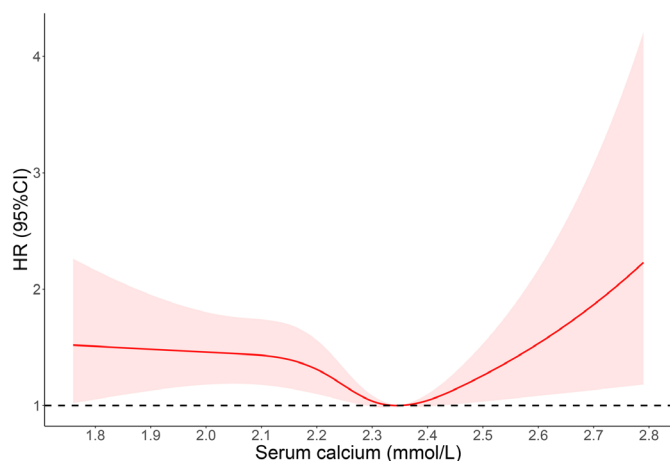
Evidence is inconsistent in the studies regarding the relationship between sCa and outcomes in patients with cardiac diseases. A few previous studies have assessed the impact of sCa on short-term mortality in patients with ACS. Lu *et al* reported that lower sCa were associated with higher in-hospital mortality in patients with STEMI.<sup>15</sup>





**Figure 3** Multivariate Cox proportional hazards models for prediction of all-cause mortality among patients with acute coronary syndrome. AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass grafting; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated haemoglobin; LDL-C, low density lipoprotein cholesterol; PCI, percutaneous coronary intervention; UAP, unstable angina pectoris.

Similarly, Yan *et al* evaluated the effectiveness of sCa in increasing the predictive value of GRACE risk score in patients with ACS and also showed that decreased baseline sCa were an independent predictor of in-hospital mortality.<sup>14</sup> Although higher sCa had not been shown to impact outcomes in the above two studies, it had been reported to be a significant predictor of in-hospital mortality in another research done by Shiyovich *et al*.<sup>13</sup>



**Figure 4** Association between serum calcium levels and all-cause mortality using restricted cubic splines.

Studies evaluating the relationship between sCa and long-term outcomes are scarce. Chen *et al* reported that lower baseline sCa were correlated with increased risk of long-term all-cause and cardiovascular mortality among patients with coronary heart disease, while higher sCa were not.<sup>19</sup> One recent study showed an upward trend of long-term mortality in patients with ACS with higher sCa; however, there was no statistical difference reached.<sup>17</sup> The discrepancies among these studies could be attributed to differences in the populations, the study sample size and the length of follow-up. In this study, we analysed a total of 13 975 patients with median follow-up period of 2.96 years and suggested that both lower and higher sCa were associated with increased mortality, and the lowest risk of mortality was associated with sCa, approximately 2.35 mmol/L. Our findings were consistent with the research done by Shiyovich *et al*, showing a U-shaped association between sCa and in-hospital mortality in patients with acute myocardial infarction.<sup>13</sup> However, our findings extended the conclusion to patients with ACS, and we evaluated the long-term outcomes.

About 50% calcium circulates in the blood as ionised calcium, which is the biologically active form, with the remainder circulating bound to plasma proteins or complexed with anions. Since the total sCa are affected by variations in the serum concentrations of albumin which are frequently changed in the acutely ill patient population, we used the values of ionised calcium that were corrected for albumin levels for statistical analysis as previous studies described.<sup>4 13 17</sup> Several conditions may disturb the calcium homeostasis and cause either hypocalcemia or hypercalcemia, including abnormal parathyroid hormone secretion and renal dysfunction. The patients with known renal failure or parathyroid disorder have been excluded in our study. There are potential explanations for the mechanisms accounting for the association between abnormalities of sCa and increased mortality in patients with ACS. First, abnormalities of sCa may cause calcium disturbance in the cytoplasm of cardiomyocytes and interfere with myocardial contraction function.<sup>20</sup> Second, altered calcium homeostasis may lead to change of platform depolarisation and cardiac action potential, causing increased arrhythmic risk.<sup>21</sup> Third, calcium metabolism disorders may accelerate the formation of atherosclerotic plaques and progression of coronary artery calcification.<sup>22</sup> In addition, the association of sCa with all-cause mortality risk in our study does not demonstrate causation. There is a possibility that abnormal sCa are just a response to the more serious myocardial damage, which should be responsible for the increased mortality. The last but not the least, a relation of sCa with mortality caused by non-cardiovascular diseases cannot be excluded in the present study. Abnormalities of sCa have been reported to be associated with stroke, cancer and infection, which would also contribute to increased mortality.<sup>8 23 24</sup>

From the multivariable analysis, compared with the reference group (sCa 2.4–2.5 mmol/L), all the other

groups had poor prognosis except for the 2.3–2.4 mmol/L group. During the acute coronary event, impaired serum calcium homeostasis in ACS patients was prevalent, with more than half of the patients presenting with sCa <2.3 or >2.5 mmol/L. There have been conflicting results about the correlation between dietary calcium intake and cardiovascular risk among general patients.<sup>25 26</sup> However, the potential impacts of pharmacologic modulation of calcium homeostasis in patients with ACS remain to be further investigated.

**Clinical implications:** our study has confirmed that altered serum calcium homeostasis at admission can predict mortality in patients with ACS. A U-shaped relationship between sCa and all-cause mortality exists. Thus, sCa should be routinely monitored in patients with ACS and maintaining calcium homeostasis at admission might improve the outcomes of patients with ACS.

Several limitations in our study should be taken into account: (1) this was a retrospective observational study from one single centre, (2) follow-up data were partially collected by telephone interviews, which might cause information bias, (3) we assessed sCa at only one point in time. It is possible that the serial change of sCa may provide other important information regarding long-term prognosis following ACS, (4) the association of sCa with all-cause mortality risk does not demonstrate causation, (5) based on this retrospective observational study, we could not determine the exact optimal interval or cut-off point of sCa. The interval and cut-off point of sCa might change along with the change of sample size and other unknown confounders. The exact optimal interval and cut-off point of sCa need to be determined by additional prospective studies.

## CONCLUSIONS

Altered serum calcium homeostasis at admission independently predicts all-cause mortality in patients with ACS. In addition, a U-shaped relationship between sCa and all-cause mortality exists, and maintaining sCa at approximately 2.35 mmol/L may minimise the risk of mortality.

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**Contributors** WS designed study and wrote manuscript. J-GZ contributed to the analysis and interpretation of data for the work. X-QZ critically revised the manuscript. HC and W-PL participated in study data collection. H-WL contributed to the conception of the work and reviewed manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy. All authors read and approved the final manuscript. WS is the guarantor of this paper.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** The study protocol was developed following the ethical guidelines of the 1975 Declaration of Helsinki. This study involves human participants and was approved by Institutional Review Board of the Research Institute for Beijing Friendship Hospital, Capital Medical University (approval number 2019-P2-068-01).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information.

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