

SCIENTIFIC REPORTS



OPEN

The CAMI-score: A Novel Tool derived From CAMI Registry to Predict In-hospital Death among Acute Myocardial Infarction Patients

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Risk stratification of patients with acute myocardial infarction (AMI) is of clinical significance. Although there are many existing risk scores, periodic update is required to reflect contemporary patient profile and management. The present study aims to develop a risk model to predict in-hospital death among contemporary AMI patients as soon as possible after admission. We included 23417 AMI patients from China Acute Myocardial Infarction (CAMI) registry from January 2013 to September 2014 and extracted relevant data. Patients were divided chronologically into a derivation cohort ($n = 17563$) to establish the multivariable logistic regression model and a validation cohort ($n = 5854$) to validate the risk score. Sixteen variables were identified as independent predictors of in-hospital death and were used to establish CAMI risk model and score: age, gender, body mass index, systolic blood pressure, heart rate, creatinine level, white blood cell count, serum potassium, serum sodium, ST-segment elevation on ECG, anterior wall involvement, cardiac arrest, Killip classification, medical history of hypertension, medical history of hyperlipidemia and smoking status. Area under curve value of CAMI risk model was 0.83 within the derivation cohort and 0.84 within the validation cohort. We developed and validated a risk score to predict in-hospital death risk among contemporary AMI patients.

Ischemic heart disease has become the leading contributor of disease burden worldwide¹. Acute myocardial infarction (AMI) is the most severe manifestation of ischemic heart disease. In the United States, approximately 750000 individuals suffer from first or recurrent MI every year². In Europe, the 30-day case-fatality rate ranged from 4.5% in Sweden and 15.4% in Latvia³. In China, an increase in AMI mortality rate was observed and the rate was over 50 per 100000 population in 2014⁴.

Considerable variability exists among patients with AMI and many factors have an impact on an individual's prognosis. Careful risk stratification is of clinical significance, as it informs decisions regarding treatment strategies as well as triage among alternative levels of care and provides an opportunity to estimate patient's prognosis. Guidelines from both the American College of Cardiology/American Heart Association^{2,5} and the European Society of Cardiology⁶ recommended that the most appropriate pharmacological and interventional management should be determined after comprehensive risk assessment.

Many risk models of in-hospital mortality have been developed among patients with acute coronary syndrome^{7–11}. Among these scores, The Thrombolysis in Myocardial Infarction (TIMI) score and the Global Registry in Acute Coronary Events (GRACE) score are the most commonly used and are recommended in the guideline⁶. However, both scores were developed when patient characteristics and management differed significantly from now, and few participants were from Asia. Therefore, it is necessary to update the existing models and the purpose

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of our study is to develop a multivariable logistic regression model to predict in-hospital mortality risk among patients with AMI.

Methods

CAMI registry. Details of China AMI (CAMI) registry design and method were described previously¹². Briefly, CAMI registry was a prospective, multicenter observational registry conducted in China, which included patients with AMI and collected data on patients' demographics, clinical presentation, initial medical contact, medical history and risk factors, treatment and clinical outcomes. Data were collected at each participating site by trained clinical cardiologists using electronic clinical reporting form. A total of 108 hospitals with different levels covering a broad geographic region participated in the project, which assured a good representation of AMI patients from China. The CAMI registry was registered on www.Clinicaltrials.gov (registration number: NCT01874691).

Our study was approved by the institutional review board central committee at Fuwai Hospital, NCCD of China. Written informed consent was obtained from eligible patients before registration. We confirmed that all methods were performed in accordance with the relevant guidelines.

Study population. All patients enrolled in CAMI registry were included in our study. Eligible patients were diagnosed with AMI including ST-segment elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) in accordance with the third universal definition of myocardial infarction¹³. AMI classified as type 1, 2, 3, 4b and 4c were included in CAMI registry¹². Type 4a and type 5 were not eligible for the CAMI registry. We excluded those patients with missing or invalid data on age, BMI, admission diagnosis and in-hospital outcome.

Outcome measurement and clinical definition. The primary endpoint was all-cause in-hospital death defined as cardiac or non-cardiac death during hospitalization. Medical history and vital signs were determined at the time of first hospital presentation. Standard definition of the history and physical examination elements were well described in the ACC/AHA Task Force on clinical Data Standards and NCDR-ACTION-GWTG element dictionary. ECG and echocardiogram were interpreted locally.

Statistical analysis. Baseline continuous variables were presented as mean \pm SD or median (25th and 75th percentiles), and categorical variables were presented as counts and percentages. We used Student t tests to compare the continuous variables between in-hospital deaths and survivors, and chi-square tests to compare categorical variables. Univariate logistic regression was performed to examine the association between individual baseline variable and in-hospital mortality, which was described as odds ratio (OR) and 95% confidence interval (CI). All variables that achieved a significance level of $P \leq 0.25$ were selected to fit the multivariable logistic regression model. Stepwise selection process was used to identify independent predictors of in-hospital death.

After selection, those variables with $P < 0.05$ were retained in the final model. A simplified risk score was developed for clinical practice by attributing integer numbers to these variables. The variable with the smallest estimated coefficient (reference variable) was attributed 1 point. The scores of other variables were determined by dividing their estimated coefficients by the coefficient of the reference variable¹⁴. We used area under curve (AUC) value and Hosmer-Lemeshow (HL) goodness-of-fit test to assess discrimination and calibrationability of the model respectively.

Data availability statement. The data used in our study was from CAMI registry dataset and is not publicly available but is available from corresponding author on reasonable request.

Results

Baseline characteristics. From January 1st 2013 to September 30th 2014, a total of 26036 patients were enrolled in CAMI registry. We excluded 2619 patients with incomplete data on age, BMI, diagnosis on admission, in-hospital outcome and finally included 23417 patients in our study. There were 1504 (6.4%) patients died in the study sample (Fig. 1). Baseline characteristics are shown in Table 1. Compared with survivors, patients who died were older, more often female and had higher BMI. Proportion of cardiac arrest and higher Killip classification were higher among deaths vs. survivors. Patients who died also had more comorbidities.

We included 5795 patients with NSTEMI and 17622 patients with STEMI in our study. Among patients with NSTEMI, 541 (9.3%) patients received early invasive approach. Among patients with STEMI, 7587 (43.0%) patients were treated with primary PCI, and 1739 (9.9%) patients received thrombolytic therapy.

Independent predictors of in-hospital death. The association between baseline characteristics and in-hospital mortality are shown in Table 2. A total of 25 variables with $P \leq 0.25$ were selected to fit the multivariable logistic regression model: age, BMI, systolic blood pressure, heart rate, creatinine level, red blood cell, white blood cell, serum potassium level, serum sodium level, sex, ST-elevation, anterior wall involvement, fatal arrhythmia, cardiac arrest, Killip classification, hypertension, hyperlipidemia, diabetes, prior CAD, MI, PCI, HF, stroke, COPD and smoking status. After stepwise selection, a total of 16 variables achieved a significance level of $P \leq 0.05$ were identified as independent predictors of in-hospital death, including age, gender, BMI, SBP, heart rate, creatinine level, WBC count, serum potassium, serum sodium, ST-elevation on ECG, anterior wall involvement, cardiac arrest, Killip classification, medical history of hypertension, medical history of hyperlipidemia and smoking status (Table 3).

CAMI risk score. We developed a simplified risk score by attributing integer number to each variable according to their estimated coefficients (Table 4). Corresponding in-hospital mortality risk associated with each point

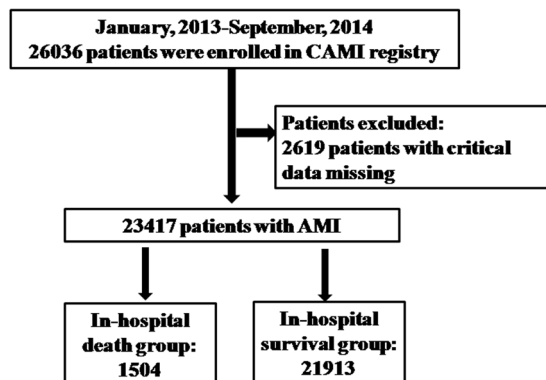


Figure 1. Study flow chart. From January 2013 to September 2014, a total of 26036 patients were enrolled in CAMI registry. After excluding 2619 patients due to critical data missing, we finally included 23417 AMI patients. A total of 1504 patients died during hospitalization.

is shown in supplementary Table 1. CAMI risk score ranges from 0 to 284, and corresponding in-hospital death risk ranges from 0.3% to 97.7%. Within derivation cohort, area under curve value for CAMI risk model was 0.83 (95% CI: 0.82–0.84). AUC value for the simplified CAMI risk score was only slightly worse than that of CAMI risk model (0.83 vs. 0.80, $p = 0.07$) (Fig. 2). Hosmer-Lemeshow P (HL-P) value for CAMI risk score was 0.10, which indicated good calibration. Within validation cohort, AUC value for CAMI risk model and score were 0.84 (95% CI: 0.82–0.86) and 0.80 (95% CI: 0.78–0.83), and no significant difference in AUC value was detected ($P = 0.07$) (Fig. 3).

We compared the diagnostic performance of CAMI risk score with GRACE risk score. The AUC value for CAMI score and GRACE risk score was 0.8043 and 0.8054 respectively ($p = 0.8$ for comparison). We also demonstrated that the diagnostic performance of CAMI risk score was superior to that of TIMI risk score (C-statistics: 0.8043 for CAMI and 0.7781 for TIMI risk score, $p < 0.0001$ for comparison).

Within derivation cohort, we divided all participants into three groups (Tertile I, II, III) based on tertiles. Each tertile contained approximately one third of the population (Table 5). Event rate increased significantly across tertiles: 1.12% in Tertile I (score range: 0–93), 3.47% in Tertile II (score range: 94–117), 14.70% in Tertile III (score range: ≥ 118). Within validation cohort, a similar pattern was observed and event rate also increased significantly across tertiles: 0.79% in Tertile I, 3.24% in Tertile II and 13.66% in Tertile III. Therefore, we defined Tertile I, II, III as low, intermediate and high risk group respectively.

Discussion

In a large-scale contemporary prospective registry of patients with AMI in China, we identified 16 independent predictors of in-hospital deaths, and by using these variables, we developed and validated a risk prediction tool of in-hospital death among AMI patients. CAMI risk score had high discrimination and calibration ability in both the derivation and validation cohort. A significant gradient of in-hospital mortality risk was identified with increased CAMI score.

Comparison with GRACE. Many risk prediction tools have been developed to assess short- or long-term mortality risk of ACS patients, among which GRACE and TIMI risk score were the most popular and validated tool. We demonstrated that CAMI risk score was non-inferior to GRACE and was superior to TIMI risk score in terms of c-statistics. In this part, we focused our comparison with GRACE risk score because CAMI score shared similar study design with GRACE score (GRACE score was designed from registry data while TIMI score was derived from clinical trial data).

Since the creation of GRACE risk score, patient profile of AMI has changed over time, with a slight increase in NSTEMI and a decrease in STEMI, and an overall decline in AMI¹⁵. Updated diagnostic criteria of AMI also have an impact on the detection and prevalence of AMI. For instance, the introduction of troponin, a relatively new biomarker, into AMI definition was reported to lead to increased annual incidence rate¹⁶. A proportion of unstable angina (UA) patients will be diagnosed as MI in the era of high-sensitive troponin, leading to an increase in MI and a reciprocal decrease in UA⁶. Due to improvement in medication and invasive treatment, in-hospital mortality of STEMI has declined significantly¹⁷. These changes require periodic updates of existing models, which justifies our work.

Although GRACE registry was a large-scale multinational registry enrolling patients from 14 countries in North America, South America, Europe, Australia, and New Zealand, few participants were from Asia¹⁸. However, including participants from Asia is of great clinical significance: The population of Asia is greater than 4.2 billion, which accounts for around 60% world population¹⁹. ACS is the leading cause of mortality in Asia and is estimated to account for half of the global burden²⁰. Our work bridged the evidence gap, developed and validated a novel risk model by using data from CAMI registry, the largest prospective multicenter registry of patients with AMI in Asia region.

Variables	In-hospital deaths N = 1504	In-hospital survivors N = 21913	P value
Age (years)	72.47 (64.21, 78.99)	62.41 (53.36, 71.57)	<0.001
Female (%)	42.2	24.4	<0.001
BMI (kg/m ²)	23.19 (21.37, 25.14)	24.03 (22.19, 25.95)	<0.001
Chest pain (%)	71.8	74.2	0.0704
ST-segment elevation (%)	72.6	68.6	0.0012
Anterior wall involvement (%)	56.3	47.7	<0.001
SBP (mmHg)	116.00 (99.00, 135.00)	129.00 (112.00, 145.00)	<0.001
HR (bpm)	86.00 (70.00, 102.00)	76.00 (66.00, 87.00)	<0.001
Fatal arrhythmia (%)	16.3	6.5	<0.001
Cardiac arrest (%)	5.4	0.9	<0.001
Killip classification (%)			<0.001
I	44.6	76.8	
II	22.2	16.1	
III	12.1	4.3	
IV	21.1	2.8	
Medical history (%)			
Hypertension	2.9	1.4	<0.001
Hyperlipidemia	4.1	6.8	<0.001
Diabetes	23.2	18.7	<0.001
Premature family CAD	1.5	3.5	<0.001
MI	9.6	7	<0.001
PCI	3.4	4.7	0.0136
CABG	0.6	0.4	0.4913
Heart failure	6.5	2.1	<0.001
PAD	0.7	0.6	0.6698
Stroke	14.7	8.9	<0.001
COPD	4.2	1.8	<0.001
Creatinine (μmol/L)	93.00 (70.70, 125.70)	74.00 (62.00, 90.00)	<0.001
Hemoglobin (g/L)	128.00 (113.00, 143.00)	138.00 (125.00, 150.00)	<0.001
WBC (10 ⁹ /L)	11.30 (8.72, 14.30)	9.54 (7.54, 11.98)	<0.001
K ⁺ (mmol/L)	4.00 (3.63, 4.46)	3.92 (3.64 ;4.21)	<0.001
Na ⁺ (mmol/L)	138.15 (135.50, 141.00)	139.20 (137.00, 141.70)	<0.001
Smoking status (%)			<0.001
Nonsmoker	62.4	43.9	
Ex-smoker	12.6	10.7	
Current smoker	24.9	45.4	

Table 1. Baseline characteristics between in-hospital deaths vs. survivors. BMI: body mass index; SBP: systolic blood pressure; HR: heart rate; CAD: coronary artery disease; MI: myocardial infarction PCI: percutaneous coronary intervention; PAD: peripheral artery disease; COPD: chronic obstructive pulmonary disease; WBC: white blood cell. Continuous variables are presented as median (interquartile range).

Variables in the model. Many variables in CAMI risk model were identical to those in GRACE risk score including: age, SBP, creatinine, ST-segment elevation, cardiac arrest, Killip classification, hypertension, anterior wall involvement. Novel variables in our score included: hyperlipidemia, gender, BMI and smoking. Unexpectedly, hyperlipidemia was a protective factor of in-hospital death. This may be explained by the fact that patients with hyperlipidemia are more likely to take lipid-lowering medications including statins, and there is a significant increase trend in statins use over decades²¹, which maybe associated with improved prognosis. Our study found that female gender was an independent risk factor of in-hospital death, while in GRACE risk score, gender was not associated with mortality risk in multivariable analysis. This discrepancy maybe caused by difference in study population. Approximately one third participants in GRACE registry were diagnosed with UA²², while we did not include UA patients. Compared with MI, patients with UA were more often females, and had lower death risk since they do not have myocardial necrosis. These factors can have an impact on the association between gender and mortality⁶.

Our study demonstrated the phenomenon of smoker's and obesity paradox. Although smoking and obesity are well established risk factors of coronary artery disease, current smokers (compared with nonsmokers) and patients with high BMI (compared with patients with low BMI) paradoxically had lower in-hospital mortality.

Variable	OR (95%CI)	P value
Age, per one year increase	1.066 (1.060, 1.072)	<0.0001
BMI, per 1 kg/m ² increase	0.911 (0.892, 0.930)	<0.0001
SBP, per 1 mmHg increase	0.979 (0.977, 0.982)	<0.0001
Heart rate, per 1 beat/min increase	1.022 (1.019, 1.025)	<0.0001
Creatinine level, per 1 μmol/L increase	1.006 (1.005, 1.006)	<0.0001
RBC, per 1 × 10 ¹² /L increase	0.984 (0.982, 0.986)	<0.0001
WBC, per 1 × 10 ⁹ /L increase	1.107 (1.093, 1.122)	<0.0001
K ⁺ , per 1 mmol/L increase	1.557 (1.397, 1.736)	<0.0001
Na ⁺ , per 1 mmol/L increase	0.984 (0.978, 0.989)	<0.0001
Male	0.449 (0.397, 0.507)	<0.0001
ST-segment elevation	1.269 (1.109, 1.452)	<0.0001
Anterior wall involvement	1.510 (1.338, 1.703)	<0.0001
Fatal arrhythmia	2.704 (2.283, 3.203)	<0.0001
Cardiac arrest	6.412 (4.765, 8.628)	<0.0001
Killip classification		<0.0001
II vs. I	2.431 (2.086, 2.834)	
III vs. I	4.505 (3.670, 5.529)	
IV vs. I	12.41 (10.36, 14.86)	
Medical history		
Hypertension	1.244 (1.103, 1.404)	<0.0001
Hyperlipidemia	0.544 (0.406, 0.729)	<0.0001
Diabetes	1.255 (1.087, 1.448)	0.002
Coronary artery disease	0.419 (0.261, 0.673)	<0.0001
Myocardial infarction	1.226 (0.990, 1.519)	0.062
PCI	0.683 (0.493, 0.948)	0.023
Heart failure	3.002 (2.310, 3.903)	<0.0001
Stroke	1.733 (1.457, 2.063)	<0.0001
COPD	2.224 (1.621, 3.050)	<0.0001
Current smoker vs. non smoker	0.384 (0.334, 0.442)	<0.0001

Table 2. Univariate analysis of the association between baseline characteristics and in-hospital mortality. BMI: body mass index; RBC: red blood cell; WBC: white blood cell; PCI: percutaneous coronary intervention; COPD: chronic obstructive pulmonary disease.

Variable	OR (95% CI)	P value
Age, per one year increase	1.053 (1.046, 1.060)	<0.0001
Cardiac arrest	3.218 (2.250, 4.601)	<0.0001
Killip classification		
II vs. I	1.440 (1.221, 1.699)	<0.0001
III vs. I	1.953 (1.554, 2.456)	<0.0001
IV vs. I	4.108 (3.327, 5.072)	<0.0001
Anterior wall involvement	1.404 (1.224, 1.611)	<0.0001
ST-segment elevation	1.397 (1.199, 1.628)	<0.0001
Hypertension	1.266 (1.103, 1.453)	<0.0001
Heart rate, per beat/min increase	1.013 (1.010, 1.016)	<0.0001
K ⁺ , per 1 mmol/L increase	1.264 (1.130, 1.414)	<0.0001
WBC, per 1 × 10 ⁹ /L increase	1.075 (1.059, 1.091)	<0.0001
Cr, per μmol/L increase	1.003 (1.002, 1.004)	<0.0001
Na ⁺ , per 1 mmol/L increase	0.990 (0.982, 0.997)	0.006
SBP, per 1 mmHg increase	0.983 (0.980, 0.985)	<0.0001
BMI, per 1 kg/m ² increase	0.968 (0.946, 0.990)	0.004
Hyperlipidemia	0.726 (0.529, 0.995)	0.047
Current smoker vs. non smoker	0.702 (0.591, 0.835)	<0.0001
Male vs. Female	0.685 (0.585, 0.801)	<0.0001

Table 3. Independent predictors of in-hospital death among AMI patients. BMI: Body mass index, SBP: Systolic blood pressure, Cr: Creatinine, WBC: white blood cell.

Variable	Level	Point	Variable	Level	Point
1. Age (years)	<55	0	9. Gender	Female	11
	[55–65)	18		Male	0
	[65–75)	33	10. ST-segment elevation		
	≥75	47	No	0	
2. BMI (Kg/m ²)	<18.5	11	Yes	10	
	[18.5–24)	7	11. Anterior wall involvement		
	[24–28)	4	No	0	
	≥28	0	Yes	10	
3. SBP (mmHg)	<111	31	12. Cardiac arrest		
	[111–128)	21	No	0	
	[128–144)	13	Yes	35	
	≥144	0	13. Killip Classification		
4. HR (bpm)	<66	0	I	0	
	[66–76)	4	II	11	
	[76–88)	8	III	22	
	≥88	15	IV	33	
5. Cr (μmol/L)	<63	0	14. Hyperlipidemia		
	[63–75)	1	No	10	
	[75–90)	2	Yes	0	
6. WBC (10 ⁹ /L)	<7.67	0	15. Smoking status		
	[7.67–9.61)	5	Nonsmoker		
	[9.61–12.08)	9	Ex-smoker		
	≥12.08	17	(quit smoking ≤ 1 year)		
7. K ⁺ (mmol/L)	<3.66	0	Ex-smoker		
	[3.66–3.92)	3	(quit smoking ≥ 1 year)		
	[3.92–4.22)	4	Current smoker		
	≥4.22	7	16. Na ⁺ (mmol/L)		
8. Hypertension	No	0	<136.9	3	
	Yes	7	[136.9–139.1)	2	
			[139.1–141.3)	1	
		≥141.3	0		

Table 4. Scores attributed to each variable. BMI: body mass index; SBP: systolic blood pressure; HR: heart rate.

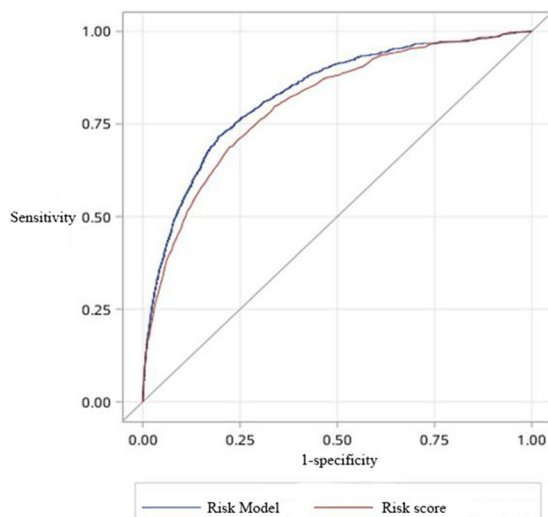


Figure 2. ROC curves of CAMI risk model and CAMI risk score within derivation cohort. Area under curve value was 0.83 (95% confidence interval (CI): 0.82 to 0.84) for CAMI risk model and 0.80 (95% CI: 0.77–0.82) for CAMI risk score.

Possible explanations for smoker's paradox were difference in fibrinolytic therapy effectiveness among smokers vs. nonsmokers. Smokers had increased level of circulating fibrinogen and more fibrin-rich thrombus compared with nonsmokers. Therefore, smokers may have improved myocardial perfusion and prognosis after fibrinolysis

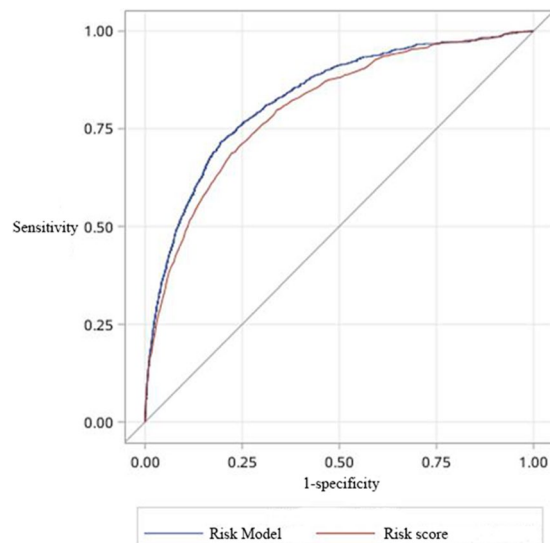


Figure 3. ROC curves of CAMI risk model and CAMI risk score within validation cohort. Area under curve value was 0.84 (95% confidence interval (CI): 0.82 to 0.86) for CAMI risk model and 0.80 (95% CI: 0.78–0.83) for CAMI risk score.

	Low Risk Group (Tertile I)	Intermediate Risk Group (Tertile II)	High Risk Group (Tertile III)	P value
Score range	0–93	94–117	≥118	
In-hospital mortality rate				
Derivation Cohort	1.12% (64/5649)	3.47% (203/5843)	14.70% (883/6007)	<0.001
Validation Cohort	0.79% (15/1888)	3.24% (63/1945)	13.66% (276/2021)	<0.001

Table 5. Event rate Across Different Risk Group.

treatment²³. The phenomenon of obesity paradox had been found in cases of several heart conditions including acute myocardial infarction, hypertension, heart failure, atrial fibrillation²⁴. Several mechanisms have been proposed to explain obesity paradox: Obese individuals may have higher energy reserve in response to acute stress²⁵, and more likely to receive optimal medication therapy and invasive treatment²⁶. Of note, we included smoking status and BMI in CAMI risk score to improve the diagnostic performance of the risk model, and should not interpreted as the encouragement of smoking or obesity.

Limitations. First, CAMI risk score should be further validated in separate large-scale cohort. Second, all participants were from China, whether CAMI score can be applied to other ethnicities need further validation. CAMI score was designed for rapid risk assessment after presentation, so we didn't include some laboratory test variables such as troponin level and left ventricular ejection fraction.

Conclusions

Using data from a large-scale contemporary cohort, we developed and validated a risk score to accurately predict risk of in-hospital death risk among patients with AMI. CAMI risk score had high discrimination and calibration ability and is likely to be useful for clinicians to assess in-hospital death risk accurately and to select optimal management.

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Acknowledgements

This work was supported by the CAMS Innovation Fund for Medical Sciences (CIFMS) (2016-I2M-1-009), Twelfth Five-Year Planning Project of the Scientific and Technological Department of China (2011BAI11B02) and 2014 Special fund for scientific research in the public interest by National Health and Family Planning Commission of the People’s Republic of China (No. 201402001). We are grateful for all participants in CAMI study group for their hard work and active participation. We are very grateful to the TIMI Study Group and the Duke Clinical Research Institute for their contributions in the design, conduct, and data analyses of CAMI registry.

Author Contributions

Kefei Dou and Yuejin Yang contributed equally to conception and design of the study. Both of them are corresponding authors. Chenxi Song and Rui Fu contributed equally in writing the manuscript. Jingang Yang, Haiyan Xu, Xiaojin Gao, Guofeng Gao, Zhiyong Zhao revised it critically for important intellectual content. Wei Li and Jia Liu contributed to analysis and interpretation of data.

Additional Information

Supplementary information accompanies this paper at <https://doi.org/10.1038/s41598-018-26861-z>.

Competing Interests: The authors declare no competing interests.

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