Original Article

A risk score to predict in-hospital mortality in patients with acute coronary syndrome at early medical contact: results from the Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome (CCC-ACS) Project

Peng Ran[1#], Jun-Qing Yang[1#], Jie Li[1#], Guang Li[1], Yan Wang[2], Jia Qiu[1], Qi Zhong[1], Yu Wang[1], Xue-Biao Wei[1], Jie-Leng Huang[1], Chung-Wah Siu[3], Ying-Ling Zhou[1], Dong Zhao[4], Dan-Qing Yu[1], Ji-Yan Chen[1]; on behalf of the CCC-ACS Investigators

[1]Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China; [2]School of Public Health, Fudan University, Key Laboratory of Public Health Safety, Ministry of Education, Shanghai, China; [3]Cardiology Division, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China; [4]Department of Epidemiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China

Contributions: (I) Conception and design: JY Chen, DQ Yu; (II) Administrative support: JY Chen, DQ Yu, JQ Yang; (III) Provision of study materials or patients: D Zhao; (IV) Collection and assembly of data: P Ran, J Li, J Qiu, Q Zhong, Y Wang, XB Wei, JL Huang; (V) Data analysis and interpretation: P Ran, JQ Yang, J Li, G Li, Y Wang, CW Siu, YL Zhou; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this study.

Correspondence to: Ji-Yan Chen, MD; Dan-Qing Yu, MD. Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, China. Email: gdphospital@163.com; yudanqing2017@126.com.

Background: A number of models have been built to evaluate risk in patients with acute coronary syndrome (ACS). However, accurate prediction of mortality at early medical contact is difficult. This study sought to develop and validate a risk score to predict in-hospital mortality among patients with ACS using variables available at early medical contact.

Methods: A total of 62,546 unselected ACS patients from 150 tertiary hospitals who were admitted between 2014 and 2017 and enrolled in the Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome (CCC-ACS) project, were randomly assigned (at a ratio of 7:3) to a training dataset (n=43,774) and a validation dataset (n=18,772). Based on the identified predictors which were available prior to any blood test, a new point-based risk score for in-hospital death, CCC-ACS score, was derived and validated. The CCC-ACS score was then compared with Global Registry of Acute Coronary Events (GRACE) risk score.

Results: The in-hospital mortality rate was 1.9% in both the training and validation datasets. The CCC-ACS score, a new point-based risk score, was developed to predict in-hospital mortality using 7 variables that were available before any blood test including age, systolic blood pressure, cardiac arrest, insulin-treated diabetes mellitus, history of heart failure, severe clinical conditions (acute heart failure or cardiogenic shock), and electrocardiographic ST-segment deviation. This new risk score had an area under the curve (AUC) of 0.84 (P=0.10 for Hosmer-Lemeshow goodness-of-fit test) in the training dataset and 0.85 (P=0.13 for Hosmer-Lemeshow goodness-of-fit test) in the validation dataset. The CCC-ACS score was comparable to the Global Registry of Acute Coronary Events (GRACE) score in the prediction of in-hospital death in the validation dataset.

Conclusions: The newly developed CCC-ACS score, which utilizes factors that are acquirable at early medical contact, may be able to stratify the risk of in-hospital death in patients with ACS.

Clinical trial registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT02306616.

Keywords: Acute coronary syndrome (ACS); in-hospital death; risk score; early medical contact

Submitted Dec 24, 2020. Accepted for publication Jan 21, 2021.
doi: 10.21037/atm-21-31
View this article at: http://dx.doi.org/10.21037/atm-21-31

Introduction

Ischemic heart disease (IHD) is the leading cause of death globally (1,2). In 2018, the annual mortality ratio among Chinese patients with IHD exceeded 110/100,000, and it is steadily increasing (3). Acute coronary syndrome (ACS) is a severe manifestation of IHD with a prognosis that varies significantly among patients. Therefore, risk stratification is critical for decision-making and management implementation, such as timely invasive strategies for patients at high risk.

Several risk scores for ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation ACS (NSTE-ACS), and unselected ACS have been developed (4-8), among which some have been recommended by clinical guidelines (9-12). However, the existing risk score systems have some limitations (13). Firstly, most of them were developed prior to or during the early phase of the drug-eluting stent era, and minority of patients underwent percutaneous intervention, thus the discrimination power was relatively poor in those patients. Secondly, acquiring the variables for these risk scores is time consuming, which limits their utility at the point of early medical contact. Further, some risk scores at early medical contact were available, however some ACS patients at high risk were excluded in the registries developing risk score.

The present study aimed to develop and validate a simple and accurate risk score to predict in-hospital death in unselected patients with ACS at early medical contact by using data from the CCC-ACS registry, which represents the real-world practice in the drug-eluting stent era. We present the following article in accordance with the TRIPOD reporting checklist (available at http://dx.doi.org/10.21037/atm-21-31).

Methods

Study protocol

The CCC-ACS project design has been reported previously (14). Briefly, the American Heart Association (AHA) and Chinese Society of Cardiology (CSC) launched the CCC-ACS project in 2014 as a nationwide hospital-based quality improvement registry program to improve the quality of care of patients with ACS. The present study was approval by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University. As the study used data from a retrospective registry, the requirement for informed consent was waived. All patient information was anonymized and de-identified before analysis. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Study population and data collection

From November 1, 2014 to June 30, 2017, CCC-ACS phases I and II enrolled 63,641 patients with ACS from 150 tertiary hospitals, which represented the highest level of medical care in the 7 geographical regions of China (Northern, Northeast, Eastern, Central, Southern, Southwest, and Northwest China).

Data were collected by trained data abstractors (medical doctors, nurses, medical postgraduates, and clinical research coordinators) at the participating hospitals through a web-based data collection platform (Oracle Clinical Remote Data Capture, Oracle). At each hospital, the first 20–30 ACS patients each month were consecutively enrolled. To ensure that consecutive cases were enrolled, quality audits were performed by third-party clinical research associates. The accuracy and completeness of the clinical data were verified using documents from approximately 5% of enrolled cases, who were randomly selected.

Definitions

Briefly, STEMI and non–ST-segment elevation myocardial infarction (NSTEMI) were defined according to the 2010 CSC STEMI guidelines (15) and the 2012 CSC NSTE-ACS guidelines (16), respectively. Unstable angina (UA) was defined as reported previously (14). Acute heart failure (AHF) and cardiogenic shock (CS) were defined according

to the Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2014 (17), based on the patient's clinical condition recorded in the medical documentation on hospital admission. The endpoint was in-hospital death. Troponin I (TnI), troponin T (TnT), and creatine kinase MB isoenzyme (CK-MB) elevation was considered when the levels of these markers exceeded the upper level of normal (ULN) of the corresponding local laboratory. Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease equation.

Statistical analysis

Statistical analyses were performed in SAS (version 9.4, SAS Institute, Cary, North Carolina). Data were presented as the mean ± standard deviation (SD) for normally distributed data, or medians and interquartile ranges (IQR) for non-normally distributed data. Normally and non-normally distributed variables were compared using Student's t-test and the Mann-Whitney U test, respectively. Categorical data were expressed as numbers (%). Pearson's χ^2 test or Fisher's exact test were used for categorical data, as appropriate. Using Proc Surveyselect (SAS, SAS Institute, Cary, North Carolina), the simple random sampling method was employed to randomly assign patients to a training dataset or a validation dataset at a ratio of 7:3. The CCC-ACS risk score was constructed by fitting demographic, medical history, clinical, and electrocardiographic variables, which were selected based their clinical significance and the findings of previous studies, as well as on their availability during early medical contact. Variables obtained by laboratory tests were not considered for entry into the model. Potential risk factors were screened through univariate logistic regression analysis with the level of significance set at P<0.05. Independent predictors were identified by performing multivariate logistic regression analysis. Only variables with a P value of <0.05 in the multivariate analysis were entered into the final model. The integer score was generated by multiplying the β coefficient of each selected variable by a constant and rounding the product to the nearest integer. Discrimination and calibration were assessed using the area under the receiver operating characteristic (ROC) curve (AUC) and the Hosmer-Lemeshow (H-L) goodness-of-fit test, respectively. Differences in the discriminatory power between the CCC-ACS score and the Global Registry of Acute Coronary Events (GRACE) score were evaluated using the χ^2 test. All P values were 2-tailed, and a P value of <0.05 was considered to represent statistical significance.

Results

There were 63,641 unselected ACS patients analyzed in this study, 44,549 patients initially assigned to the training dataset and 19,092 to the validation dataset. During the modeling process, 775 (1.7%) and 320 (1.7%) patients were excluded from the training and validation cohorts, respectively, due to having missing values for the finally incorporated variables (age, systolic blood pressure, cardiac arrest, and severe clinical conditions). The remaining 43,774 and 18,772 patients were enrolled in the final analyses (*Figure 1*).

In total, 1,181 in-hospital deaths occurred among the study patients, including 824 (1.9%) in the training dataset and 357 (1.9%) in the validation dataset. As shown in *Table 1*, except for prior dialysis (0.2% *vs*. 0.4%, P=0.002), there were no significant differences in demographic, clinical, laboratory, electrocardiographic, or therapeutic characteristics, or in-hospital outcomes between the training and validation cohorts.

In the training dataset, the in-hospital death group had higher proportions of patients with STEMI, a history of heart failure, hypertension, diabetes mellitus, insulin-treated diabetes mellitus (ITDM), previous dialysis, ST-segment deviation, elevated CK-MB, and 5-fold elevated TNT or TNI. Furthermore, these patients were less likely to smoke or have a history of percutaneous coronary intervention (PCI). Patients in the in-hospital death group in the training dataset were also older, had higher heart rates and serum creatinine levels, and lower systolic blood pressure (SBP), diastolic blood pressure (DBP), and eGFR. Moreover, patients who died in hospital were more likely to present with cardiac arrest, AHF, and CS at admission (*Table 2*).

Development and Validation of the CCC-ACS score

The results of univariate and multivariate logistic regression analyses are displayed in Table S1. After univariable and multivariable selection, 7 variables emerged as predictors of mortality, including age, SBP, cardiac arrest, ITDM, history of heart failure, severe clinical conditions at admission (AHF and/or CS), and ST-segment deviation. The scores assigned to each variable based on their estimated β coefficients in the training dataset are shown in *Table 3*. The AUC for the original model was 0.84, and the χ^2 statistic for calibration was 11.48 (P=0.18).

The scores for each predictor based on their estimated β coefficients are presented in *Figure 2*. The sum of the score which could theoretically range from 0 to 36, could be used to estimate the risk of in-hospital death for individual patients. In

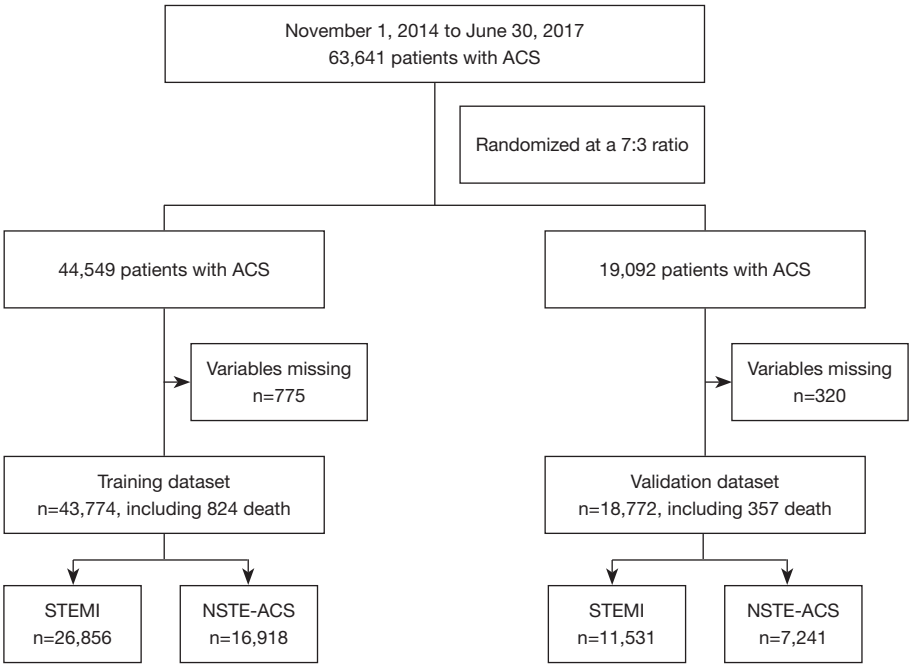

Figure 1 Study flow chart. The enrolled study population was divided into a training dataset and a validation dataset. ACS, acute coronary syndrome. STEMI, ST-segment elevation myocardial infarction. NSTE-ACS, non–ST-segment elevation acute coronary syndromes.

Table 1 Patient clinical characteristics

Characteristics	Total (n=62,546)	Training (n=43,774)	Validation (n=18,772)	P value
Age, years	63±12	63±13	63±12	0.598
Female, n (%)	15,678 (25.1)	10,967 (25.1)	4,711 (25.1)	0.911
Type of ACS, n (%)				0.860
STEMI	38,387 (61.4)	26,856 (61.4)	11,531 (61.4)	
NSTE-ACS	24,159 (38.6)	16,918 (38.6)	7,241 (38.6)	
Medical history, n (%)				
Smoking	27,052 (43.3)	18,912 (43.2)	8,140 (43.4)	0.713
History of MI	4,823 (7.7)	3,385 (7.7)	1,478 (7.7)	0.755
History of CABG	316 (0.5)	210 (0.5)	106 (0.6)	0.170
History of PCI	4,777 (7.6)	3,378 (7.7)	1,399 (7.5)	0.254
History of heart failure	1,246 (2.0)	8,47 (1.9)	399 (2.1)	0.118
Hypertension	33,094 (52.9)	23,170 (52.9)	9,924 (52.9)	0.858
Diabetes mellitus	13,859 (22.2)	9,716 (22.2)	4,143 (22.1)	0.729
ITDM	3,655 (5.8)	2,562 (5.9)	1,093 (5.8)	0.882
Prior dialysis	181 (0.3)	108 (0.2)	73 (0.4)	0.002
Clinical conditions at admission				
GRACE score*	144±37	144±37	144±37	0.719

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total (n=62,546)	Training (n=43,774)	Validation (n=18,772)	P value
Cardiogenic shock, n (%)	1,893 (3.0)	1,357 (3.1)	536 (2.9)	0.102
AHF without cardiogenic shock, n (%)	5,584 (8.9)	3,861 (8.8)	1,723 (9.2)	0.150
Cardiac arrest, n (%)	1,198 (1.9)	817 (1.9)	381 (2.0)	0.172
HR*, beats/min	77±16	77±16	77±16	0.816
SBP, mmHg	130±23	130±24	130±23	0.259
DBP, mmHg	78±14	78±14	78±14	0.504
Killip class*, n (%)				0.377
I	41,007 (70.2)	28,649 (70.0)	12,358 (70.4)	
II–III	15,058 (25.8)	10,601 (25.9)	4,457 (25.4)	
IV	2,377 (4.1)	1,649 (4.0)	728 (4.1)	
ST-segment deviation, n (%)	42,795 (68.4)	29,964 (68.5)	12,831 (68.4)	0.647
Laboratory variables				
Scr† μmol/L	76 (64, 93)	76 (64, 93)	76 (64, 93)	0.168
eGFR†, mL/min/1.73 m^2	90.89±30.18	91.00±31.85	90.63±31.68	0.181
Elevated TnT or TnI‡, n (%)	46,944 (84.1)	32,792 (84.0)	14,152 (84.4)	0.280
5×elevated TnT or TnI‡, n (%)	40,540 (72.6)	28,298 (72.5)	12,242 (73.0)	0.233
Elevated CK-MB‡, n (%)	37,026 (65.3)	25,892 (65.2)	11,134 (65.5)	0.596
LVEF§ %	55.13±10.24	55.19±10.20	55.01±10.34	0.077
In-hospital treatment, n (%)				
Aspirin	59,201 (94.7)	41,393 (94.6)	17,808 (94.9)	0.121
P2Y12 antagonist	59,620 (95.3)	41,720 (95.3)	17,900 (95.4)	0.798
Statins	58,642 (93.8)	41,042 (93.8)	17,600 (93.8)	0.992
ACEIs or ARBs	29,863 (47.7)	20,899 (47.7)	8,964 (47.8)	0.983
β-blocker	34,587 (55.3)	24,254 (55.4)	10,333 (55.0)	0.403
PCI	45,198 (72.3)	31,697 (72.4)	13,501 (71.9)	0.210
CABG	661 (1.1)	479 (1.1)	182 (1.0)	0.162
In-hospital adverse outcomes, n (%)				
Death	1,181 (1.9)	824 (1.9)	357 (1.9)	0.870

*, GRACE score and Killip class were not available for 11.8% (7,351/62,546) and 6.6% (4,104/62,546) of patients with ACS in the study population, respectively. HR was not available for 19 patients with ACS in the study population; †, 2.9% (1,836/62,546) of patients did not have Scr and 2.9% (1,836/62,546) of patients did not have eGFR in the study population; ‡, TnT or TnI were not available for 10.8% (6,739/62,546) of patients with ACS, and elevated CK-MB were not available for 9.4% (5,856/62,546) of patients with ACS in the study population, respectively; §, LVEF was not available for 22.8% (14,255/62,546) of patients with ACS in the study population. ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AHF, acute heart failure; ARBs, angiotensin receptor blockers; CABG, coronary artery bypass grafting; CK-MB, creatine kinase-MB; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GRACE score, Global Registry of Acute Coronary Events risk score; HR, heart rate; ITDM, insulin-treated diabetes mellitus; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTE-ACS, non–ST-segment elevation acute coronary syndromes; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; Scr, serum creatinine; STEMI, ST-segment elevation myocardial infarction.

Table 2 Patient clinical characteristics in the training dataset

Characteristics	Survived (n=42,950)	Died (n=824)	P value
Age, years	63±12	72±11	<0.001
Female, n (%)	10,664 (24.8)	303 (36.8)	<0.001
Type of ACS, n (%)			<0.001
NSTE-ACS	16,684 (38.8)	234 (28.4)	
STEMI	26,266 (61.2)	590 (71.6)	
Medical history, n (%)			
Smoking	18,684 (43.5)	228 (27.7)	<0.001
History of MI	3,313 (7.7)	72 (8.7)	0.276
History of CABG	204 (0.5)	6 (0.7)	0.297
History of PCI	3,332 (7.8)	42 (6.0)	0.020
History of heart failure	788 (1.8)	59 (7.2)	<0.001
Hypertension	2,267 (52.8)	483 (58.6)	<0.001
Diabetes mellitus	9,458 (22.0)	258 (31.3)	<0.001
ITDM	2,470 (5.8)	92 (11.2)	<0.001
Prior dialysis	100 (0.2)	8 (1.0)	<0.001
Clinical conditions at admission			
GRACE score*	143±36	194±41	<0.001
Cardiogenic shock, n (%)	1,107 (2.6)	250 (30.3)	<0.001
AHF without cardiogenic shock, n (%)	3,532 (8.2)	329 (40.0)	<0.001
Cardiac arrest, n (%)	636 (1.5)	181 (22.0)	<0.001
HR*, beats/min	77±16	89±23	<0.001
SBP, mmHg	130±23	118±30	<0.001
DBP, mmHg	78±14	71±17	<0.001
Killip class*, n (%)			<0.001
I	28,362 (70.7)	287 (37.0)	
II–III	10,342 (25.8)	259 (33.4)	
IV	1,419 (3.5)	230 (29.6)	
ST-segment deviation, n (%)	29,278 (68.2)	686 (83.3)	<0.001
Laboratory variables			
Scr†, μmol/L	76 (64, 92)	100 (76, 143)	<0.001
eGFR†, mL/min/1.73m^2	91.47±31.61	65.08±34.25	<0.001
Elevated TnT or TnI‡, n (%)	32,114 (83.8)	678 (96.4)	<0.001
5× Elevated TnT or TnI‡, n (%)	27,676 (72.2)	622 (88.5)	<0.001
Elevated CK-MB‡, n (%)	25,274 (64.9)	618 (85.2)	<0.001
LVEF§ %	55±10	44±12	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Survived (n=42,950)	Died (n=824)	P value
In-hospital therapy, n (%)			
Aspirin	40,701 (94.8)	692 (84.0)	<0.001
P2Y12 antagonist	41,007 (95.5)	713 (86.5)	<0.001
Statins	40,407 (94.1)	635 (77.1)	<0.001
ACEIs or ARBs	20,671 (48.1)	228 (27.7)	<0.001
β-blocker	23,977 (55.8)	277 (33.6)	<0.001
PCI	31,384 (73.1)	313(38.0)	<0.001
CABG	406 (0.9)	73 (8.9)	<0.001

*, GRACE score and Killip class were not available for 11.7% (5,123/43,774) and 6.6% (2,875/43,774) of patients with ACS in the training dataset, respectively. HR was not available for 15 patients with ACS in the training dataset; †, 2.9% (1,257/43,774) of patients did not have Scr and 2.9% (1,257/43,774) of patients did not have eGFR in the training dataset; ‡, TnT or TnI were not available for 10.8% (4,740/43,774) of patients with ACS, and elevated CK-MB were not available 9.3% (4,089/43,774) of patients with ACS in the training dataset; §, LVEF was not available for 23.1% (10,102/43,774) of patients with ACS in the training dataset. ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AHF, acute heart failure; ARBs, angiotensin receptor blockers; CABG, coronary artery bypass grafting; CK-MB, creatine kinase-MB; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GRACE score, Global Registry of Acute Coronary Events risk score; HR, heart rate; ITDM, insulin-treated diabetes mellitus; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; Scr, serum creatinine; STEMI, ST-segment elevation myocardial infarction.

the training dataset, the actual obtained scores ranged from 0 to 31. The CCC-ACS score displayed good discrimination ability (AUC: 0.84) and calibration (χ^2=13.43, P=0.10) (*Figure 3A*). In the validation dataset, the actual obtained scores ranged from 0 to 29, and the CCC-ACS score also displayed good discrimination ability (AUC: 0.85) and calibration (χ^2=12.63, P=0.13, Brier score =0.02) (*Figure 3B*).

Based on the obtained risk scores for in-hospital death, the training dataset was further categorized into the following 3 groups: low risk (score ≤12, n=40,452), moderate risk (score: 13–20, n=2,919), and high risk (score≥21, n=403). The event rate was 0.96%,10.11%, and 34.49%, respectively (*Figure 4*). The validation dataset was also categorized into 3 groups: low risk (score ≤12, n=17,323), moderate risk (score: 13–20, n=1,269), and high risk (score ≥21, n=180). The event rate was 0.96%,10.01%, and 35.56%, respectively (*Figure 4*).

Performance in subgroups

The CCC-ACS score also exhibited good discrimination ability after the patients were divided into subgroups according to sex, ACS type, and previous PCI or not (Table S2). After the exclusion of 2,228 patients who had missing values for GRACE variables, the remaining 16,544 patients in the validation dataset were used to compare the performances of the CCC-ACS score and the GRACE score. The 2 scores performed comparably in the prediction of in-hospital death (AUC: CCC-ACS 0.84, 95% CI: 0.81–0.86 *vs.* GRACE 0.83, 95% CI: 0.81–0.86, P=0.69). The χ^2 statistics for the CCC-ACS and GRACE scores were 5.12 (P=0.74) and 8.44 (P=0.39) respectively, showing the good calibration for in-hospital mortality.

Discussion

In the present study, a new in-hospital mortality risk score (CCC-ACS score) was developed and validated. The CCC-ACS risk score comprises 7 variables [age, cardiac arrest, ITDM, history of heart failure, severe clinical conditions at admission (AHF and/or CS), SBP, and ST-segment deviation], and demonstrated good discrimination ability and calibration in predicting the risk of in-hospital death for unselected ACS patients at early medical contact.

Several risk scores have been developed for risk stratification in patients with ACS. Among them, the Thrombolysis in Myocardial Infarction (TIMI) and GRACE scores are recommended by clinical guidelines and are widely applied in clinical practice. Both of these risk scoring systems can provide important information for predicting prognosis and determining the timing of interventions;

Table 3 CCC-ACS risk sore final model

Predictors	β coefficient	χ^2	OR	95% CI	P value
Cardiac arrest	1.8500	244.94	6.36	5.05–8.02	<0.0001
History of heart failure	0.4766	9.04	1.61	1.18–2.20	0.0026
ITDM	0.6845	31.79	1.98	1.56–2.52	<0.0001
ST-segment deviation	0.6148	39.37	1.85	1.53–2.24	<0.0001
Clinical conditions at admission					
No AHF or CS (reference)	–	–	–	–	–
AHF without CS	1.0462	103.74	2.85	2.33–3.48	<0.0001
CS	1.9255	275.19	6.86	5.46–8.61	<0.0001
SBP					
≥140 (reference)	–	–	–	–	–
100–139	0.3216	12.18	1.38	1.15–1.65	0.0005
80–99	0.7974	39.53	2.22	1.73–2.85	<0.0001
<80	1.1011	30.27	3.01	2.03–4.45	<0.0001
Age (years)					
<60 (reference)	–	–	–	–	–
60–69	0.6075	23.69	1.84	1.44–2.35	<0.0001
70–79	1.3572	134.96	3.89	3.09–4.89	<0.0001
80–89	1.8523	216.36	6.37	4.98–8.16	<0.0001
≥90	2.5142	108.12	12.36	7.69–19.85	<0.0001

AHF, acute heart failure; CCC-ACS Risk Score: Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome Risk Score; CS, cardiogenic shock; ITDM, insulin-treated diabetes mellitus; SBP, systolic blood pressure.

however, they have some limitations (13). The TIMI risk score was derived from clinical trials and thus has inherent bias due to the exclusion of high-risk patients. The GRACE score was developed from a large-scale unbiased multi-center registry and was validated in external datasets; thus, it has an excellent performance when applied to the general population. Nevertheless, it has been found to lack accuracy for patients undergoing PCI (6), which may because less than 30% of patients in the GRACE (18) and Global Use of Strategies to Open Occluded Coronary Arteries IIB (GUSTO IIB) studies underwent PCI (19,20). Furthermore, in the contemporary era, PCI has been used more widely, and its use has been accompanied by advances in medical treatments, such as P2Y12 antagonist, statin, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), and β-blockers. In the real-world registry used in the present study, which was compiled in the drug-eluting stent era, 72.3% of ACS patients underwent PCI. Therefore, an updated risk score that is fitting of current clinical practice is needed to supplement the use of previous scoring systems.

The CCC-ACS risk score shares 5 variables (age, cardiac arrest, SBP, severe clinical conditions at admission, and ST-segment deviation) with previous risk scores (4,21), and includes 2 (ITDM and history of heart failure) newly introduced variables. ITDM has been proven as a risk factor for adverse clinical outcomes in patients with NSTE-ACS or those undergoing PCI (22,23). Patients with ITDM may have suffered a longer course of diabetes mellitus and may therefore represent a more severe disease condition (24). History of heart failure, another newly incorporated variable, has also been proved to be associated with in-hospital, 6-month, and 1-year mortality in ACS patients (25-28). A majority of previous studies have focused on AHF in patients with ACS, but a history of heart failure is also important and of independent value. ACS

1. Find the score for each predictor

Age, yrS	Points	SBP, mmHg	Points	Severe condition at admission	Points
<60	0	≥140	0	No AHF or CS	0
60~70	2	100~140	1	AHF without CS	4
70~80	5	80~100	3	CS	8
80~90	7	<80	4		
≥90	10				

Other Risk Factors	Points
Cardiac arrest	7
History of heart failure	2
Insulin treated diabetic mellitus	3
ST-segment deviation	2

2. Sum the score for all predictors

3. Look up risk corresponding to total score

Total Points	≤4	8	12	16	20	24	>24
Probability of in-hospital mortality	0.30%	1.25%	3.51%	10.23%	20.55%	34.51%	50.88%

Figure 2 Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome risk score (CCC-ACS score). SBP, systolic blood pressure. AHF, acute heart failure. CS, cardiogenic shock.

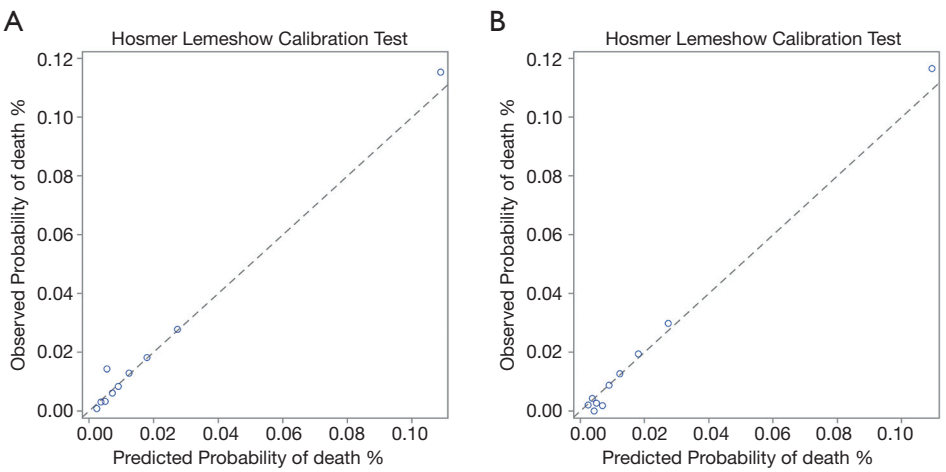

Figure 3 Calibration of Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome risk score (CCC-ACS score). (A) Calibration of CCC-ACS score in the training dataset. (B) Calibration of CCC-ACS score in the validation dataset. The diagonal line indicates perfect calibration.

patients with a history of heart failure may have lower cardiac reserve at baseline, and receive evidence-based therapies, such as β-blockers, ACEIs, and PCI, less frequently (25). Although some studies have associated a history of myocardial infarction with adverse outcomes (29,30), it was not found to be an independent predictor after regression in the current analysis. This may be because, at least in part, a history of heart failure is correlated with and more powerful predictor than a history of myocardial infarction. Cardiac markers (TnI, TnT, and CK-MB) and serum creatinine have been demonstrated to be

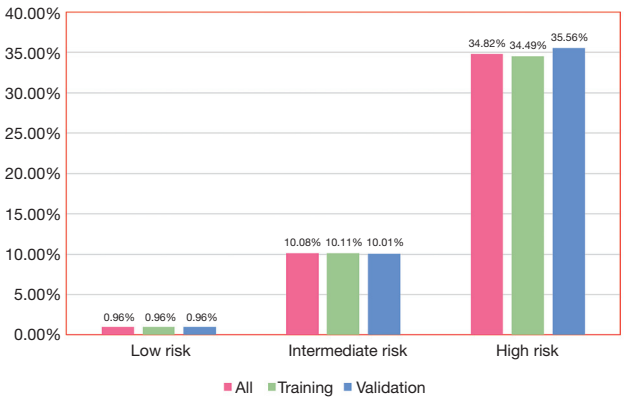

Figure 4 Observed incidence of in-hospital death. Observed incidence of in-hospital death according to categories of the Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome risk score (CCC-ACS score) in the training and validation datasets. low risk (score ≤12), moderate risk (score: 13–20), and high risk (score ≥21).

independently associated with adverse outcomes (4,21,31,32), and can improve the discrimination ability of risk scores. However, these markers demand additional time and effort for blood tests to be performed; thus, they are usually not available during early medical contact. In fact, the data of cardiac markers and serum creatinine were lacking for a number of patients in the real-world registry used in the present study.

The main aim of this study was not to replace existing risk scores, but to establish a risk score with variables that are rapidly available at early medical contact. In the emergency unit, where it is busy and risk evaluation needs to be conducted promptly, a risk score based on readily available variables is practically more meaningful. This is also true for ambulance services, community health services, and other facilities with limited medical resources. Although it consists of rapidly obtainable variables, the CCC-ACS risk score displayed similar predictive ability for in-hospital death compared to the GRACE score. In addition, the CCC-ACS risk score exhibited good discrimination ability for those underwent PCI (AUC: 0.84), which is fitting of current clinical practice. Therefore, the CCC-ACS score may serve as a complement to previous risk scores.

There are potential applications of the CCC-ACS risk score. Firstly, stratifying patients at early medical contact without the need for blood tests may facilitate the quick identification of those with the highest risk and, subsequently, their quick and appropriate treatment. Secondly, some identified predictors in this model may provide useful information for updating other ACS risk scores.

Limitations

The present study has several limitations. Firstly, the rate of in-hospital mortality was relatively low among the patients in this study. One explanation was that phase I and phase II of the CCC-ACS project involved only tertiary hospitals, which exhibit a higher standard of patient care than other levels of hospitals. Furthermore, patients who died before or during transfer to the involved hospitals were not included in this study. Secondly, even though the CCC-ACS score was derived from a large-scale dataset, external validation is always required before its general application. Thirdly, the CCC-ACS project is a nationwide hospital-based quality improvement registry program without follow-up data. Therefore, whether the CCC-ACS risk score holds value for long-term prognosis is unknown. This question needs to be solved in further studies with follow-up. Finally, since the data in the CCC-ACS project were obtained from Chinese patients, further investigation is needed to determine whether the risk score performs as well in other populations.

Conclusions

The CCC-ACS CS score, which was developed from a large-scale dataset of unselected ACS patients, can quantify the risk of in-hospital death for patients with ACS at early medical contact and may facilitate clinical decision-making. However, further external validation of this risk score is required.

Acknowledgments

We thank all participating hospitals for their contributions to the CCC-ACS project (Table S3).

Funding: The Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome (CCC-ACS) project is a collaborative program of the American Heart Association (AHA) and Chinese Society of Cardiology (CSC). The AHA was funded by Pfizer for the quality improvement initiative through an independent grant for learning and change. This work was also supported by Science and Technology Program of Guangzhou (No. 201704020124) and Sailing Foundation (Grant No. LHJJ201611011, LHJJ201612127), Beijing, China.

Footnote

Reporting Checklist: The authors have completed the

TRIPOD reporting checklist. Available at http://dx.doi.org/10.21037/atm-21-31

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-21-31

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-21-31). Dr. DQY and Dr. PR report grants from Guangzhou Science and Technology Innovation Commission, during the conduct of the study; Dr. GL and Dr. JQY reports grants from Sailing Foundation, during the conduct of the study. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The present study was approval by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). As the study used data from a retrospective registry, the requirement for informed consent was waived.

References

1. Roth GA, Forouzanfar MH, Moran AE, et al. Demographic and epidemiologic drivers of global cardiovascular mortality. N Engl J Med 2015;372:1333-41.
2. Zhou M, Wang H, Zeng X, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2019;394:1145-58.
3. Hu S, Gao R, Liu L, et al. Summary of the 2018 Report on Cardiovascular Diseases in China. Chinese Circulation Journal 2019;34:209-20.
4. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003;163:2345-53.
5. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 2000;284:835-42.
6. Palmerini T, Genereux P, Caixeta A, et al. A new score for risk stratification of patients with acute coronary syndromes undergoing percutaneous coronary intervention: the ACUITY-PCI (Acute Catheterization and Urgent Intervention Triage Strategy-Percutaneous Coronary Intervention) risk score. JACC Cardiovasc Interv 2012;5:1108-16.
7. Morrow DA, Antman EM, Giugliano RP, et al. A simple risk index for rapid initial triage of patients with ST-elevation myocardial infarction: an InTIME II substudy. LANCET 2001;358:1571-5.
8. Huynh T, Kouz S, Yan AT, et al. Canada Acute Coronary Syndrome Risk Score: a new risk score for early prognostication in acute coronary syndromes. Am Heart J 2013;166:58-63.
9. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77.
10. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267-315.
11. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:485-510.
12. 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. J Am Coll Cardiol 2014;64:e139-e228.

13. Bawamia B, Mehran R, Qiu W, et al. Risk scores in acute coronary syndrome and percutaneous coronary intervention: a review. Am Heart J 2013;165:441-50.
14. Hao Y, Liu J, Liu J, et al. Rationale and design of the Improving Care for Cardiovascular Disease in China (CCC) project: A national effort to prompt quality enhancement for acute coronary syndrome. Am Heart J 2016;179:107-15.
15. Guideline for diagnosis and treatment of patients with ST-elevation myocardial infarction. Zhonghua Xin Xue Guan Bing Za Zhi 2010;38:675-90.
16. Guidelines for the diagnosis and treatment of non–ST-segment elevation acute coronary syndromes. Chin J Cardiol 2012;40:353-67.
17. Chinese guidelines for the diagnosis and treatment of heart failure 2014. Zhonghua Xin Xue Guan Bing Za Zhi 2014;42:98-122.
18. Steg PG, Goldberg RJ, Gore JM, et al. Baseline characteristics, management practices, and in-hospital outcomes of patients hospitalized with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE). Am J Cardiol 2002;90:358-63.
19. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. N Engl J Med 1996;335:775-82.
20. Tamis-Holland JE, Palazzo A, Stebbins AL, et al. Benefits of direct angioplasty for women and men with acute myocardial infarction: results of the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes Angioplasty (GUSTO II-B) Angioplasty Substudy. Am Heart J 2004;147:133-9.
21. Chin CT, Chen AY, Wang TY, et al. Risk adjustment for in-hospital mortality of contemporary patients with acute myocardial infarction: the acute coronary treatment and intervention outcomes network (ACTION) registry-get with the guidelines (GWTG) acute myocardial infarction mortality model and risk score. Am Heart J 2011;161:113-22.e2.
22. Palmerini T, Dangas G, Mehran R, et al. Predictors and implications of stent thrombosis in non-ST-segment elevation acute coronary syndromes: the ACUITY Trial. Circ Cardiovasc Interv 2011;4:577-84.
23. Ritsinger V, Saleh N, Lagerqvist B, et al. High event rate after a first percutaneous coronary intervention in patients with diabetes mellitus: results from the Swedish coronary angiography and angioplasty registry. Circ Cardiovasc Interv 2015;8:e002328.
24. Cosmi F, Shen L, Magnoli M, et al. Treatment with insulin is associated with worse outcome in patients with chronic heart failure and diabetes. Eur J Heart Fail 2018;20:888-95.
25. Zhang H, Goodman SG, Yan RT, et al. In-hospital management and outcomes of acute coronary syndromes in relation to prior history of heart failure. Eur Heart J Acute Cardiovasc Care 2016;5:214-22.
26. Ranasinghe I, Naoum C, Aliprandi-Costa B, et al. Management and outcomes following an acute coronary event in patients with chronic heart failure 1999-2007. Eur J Heart Fail 2012;14:464-72.
27. Sanchis J, Nunez J, Bodi V, et al. Influence of comorbid conditions on one-year outcomes in non-ST-segment elevation acute coronary syndrome. Mayo Clin Proc 2011;86:291-6.
28. Iakobishvili Z, Feinberg MS, Danicek V, et al. Prior heart failure among patients with acute coronary syndromes is associated with a higher incidence of in-hospital heart failure. Acute Card Care 2006;8:143-7.
29. Heggunje PS, Wade MJ, O'Rourke RA, et al. Early invasive versus ischaemia-guided strategies in the management of non-Q wave myocardial infarction patients with and without prior myocardial infarction; results of Veterans Affairs Non-Q Wave Infarction Strategies in Hospital (VANQWISH) trial. Eur Heart J 2000;21:2014-25.
30. Sutton AG, Finn P, Hall JA, et al. Predictors of outcome after percutaneous treatment for cardiogenic shock. Heart 2005;91:339-44.
31. Bagai A, Schulte PJ, Granger CB, et al. Prognostic implications of creatine kinase-MB measurements in ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. Am Heart J 2014;168:503-11.e2.
32. Galla JM, Mahaffey KW, Sapp SK, et al. Elevated creatine kinase-MB with normal creatine kinase predicts worse outcomes in patients with acute coronary syndromes: results from 4 large clinical trials. Am Heart J 2006;151:16-24.

Cite this article as: Ran P, Yang JQ, Li J, Li G, Wang Y, Qiu J, Zhong Q, Wang Y, Wei XB, Huang JL, Siu CW, Zhou YL, Zhao D, Yu DQ, Chen JY; on behalf of the CCC-ACS Investigators. A risk score to predict in-hospital mortality in patients with acute coronary syndrome at early medical contact: results from the Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome (CCC-ACS) Project. Ann Transl Med 2021;9(2):167. doi: 10.21037/atm-21-31

Supplementary

Table S1 Logistic regression analysis for in-hospital mortality

Predictors	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Cardiac arrest	19.03	15.91–22.76	<0.0001	6.36	5.05–8.02	<0.0001
History of heart failure	4.14	3.16–5.42	<0.0001	1.61	1.18–2.20	0.003
ITDM	2.06	1.66–2.56	<0.0001	1.98	1.56–2.52	<0.0001
ST-segment deviation	2.34	1.95–2.80	<0.0001	1.85	1.53–2.24	<0.0001
Clinical conditions at admission						
No AHF or CS (reference)	–	–	–	–	–	–
AHF without CS	5.06	4.21–6.08	<0.0001	2.85	2.33–3.48	<0.0001
CS	21.5	18.22–25.38	<0.0001	6.86	5.46–8.61	<0.0001
Systolic blood pressure						
≥140 (reference)	–	–	–	–	–	–
100–139	1.31	1.10–1.56	0.002	1.38	1.15–1.65	<0.001
80–99	4.05	3.26–5.03	<0.0001	2.22	1.73–2.85	<0.0001
<80	15.89	11.62–21.73	<0.0001	3.01	2.03–4.45	<0.0001
Age (years)						
<60 (reference)	–	–	–	–	–	–
60–69	1.93	1.53–2.43	<0.0001	1.84	1.44–2.35	<0.0001
70–79	4.25	3.43–5.26	<0.0001	3.89	3.09–4.89	<0.0001
80–89	7.13	5.68–8.94	<0.0001	6.37	4.98–8.16	<0.0001
≥90	14.43	9.33–22.30	<0.0001	12.36	7.69–19.85	<0.0001

AHF, acute heart failure; CS, cardiogenic shock; ITDM, insulin-treated diabetes

http://dx.doi.org/10.21037/atm-21-31

Table S2 Model performance in subgroups

Subgroup	Sample size	AUC
Sex		
Female	15,678 (25.1%)	0.81
Male	46,868 (74.9%)	0.85
Age		
≥75 years	12,983 (20.8%)	0.77
<75 years	49,563 (79.2%)	0.82
Smoking		
Yes	27,052 (43.3%)	0.82
No	35,494 (56.7%)	0.84
Hypertension		
Yes	33,094 (52.9%)	0.84
No	29,452 (47.1%)	0.84
eGFR, mL/min/1.73 m^2		
≥60	51,517 (84.9%)	0.81
<60	9,193 (15.1%)	0.79
ACS type		
STEMI	38,387 (61.4%)	0.84
NSTE-ACS	24,159 (38.6%)	0.84
Cardiac arrest		
Yes	1,198 (1.9%)	0.72
No	61,348 (98.1%)	0.81
PCI		
Yes	45,198 (72.3%)	0.84
No	17,348 (27.7%)	0.81

ACS, acute coronary syndrome; AHF, acute heart failure; AUC, area under the curve; CS, cardiogenic shock; eGFR, estimated glomerular filtration rate; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; STEMI, ST-segment elevation myocardial infarction.

http://dx.doi.org/10.21037/atm-21-31

Table S3 Investigators of CCC-ACS project

Hospitals	Territory	Province	City	Investigator
Hospitals for Phase I				
Shanxi Cardiovascular Hospital	Northern China	Shanxi	Taiyuan	Bao Li
Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School	Eastern China	Jiangsu	Nanjing	Biao Xu, Guangshu Han
Hainan General Hospital	Southern China	Hainan	Haikou	Bin Li
The Second Hospital of Jilin University	Northeast China	Jilin	Changchun	Bin Liu
The 2nd Affiliated Hospital of Harbin Medical University	Northeast China	Heilongjiang	Harbin	Bo Yu
The Ninth Hospital Affiliated to Shanghai Jiaotong University School of Medicine	Eastern China	Shanghai	Shanghai	Changqian Wang
Henan Provincial People's Hospital	Central China	Henan	Zhengzhou	Chuanyu Gao
Shanxi Provincial People's Hospital	Northern China	Shanxi	Taiyuan	Chunlin Lai
Xinqiao Hospital, Third Military Medical University	Southwest China	Chongqing	Chongqing	Cui Bin, Lan Huang
China Meitan General Hospital	Northern China	Beijing	Beijing	Di Wu
The 309th Hospital of Chinese People's Liberation Army	Northern China	Beijing	Beijing	Fakuan Tang, Jun Xiao
Zhongda Hospital, Southeast University	Eastern China	Jiangsu	Nanjing	Genshan Ma
The First Affiliated Hospital of Liaoning Medical University	Northeast China	Liaoning	Jinzhou	Guizhou Tao
Xinjiang Uygur Autonomous Region People's Hospital	Northwest China	Xinjiang	Urumchi	Guoqing Li
Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University	Eastern China	Zhejiang	Hangzhou	Guosheng Fu
Beijing Friendship Hospital, Capital Medical University	Northern China	Beijing	Beijing	Hongwei Li
The First Affiliated Hospital of Bengbu Medical College	Eastern China	Anhui	Bengbu	Honhju Wang
General Hospital of TISCO	Northern China	Shanxi	Taiyuan	Huifeng Wang
Dongguan People's Hospital	Southern China	Guangdong	Dongguan	Jianfeng Ye
Panyu Hospital of Chinese Medicine	Southern China	Guangdong	Guangzhou	Jianhao Li
Peking University First Hospital	Northern China	Beijing	Beijing	Jie Jiang
Sun Yat-sen Memorial Hospital, Sun Yat-sen University	Southern China	Guangdong	Guangzhou	Jingfeng Wang
Guangdong General Hospital	Southern China	Guangdong	Guangzhou	Jiyan Chen
Hospital of Xinjiang Production & Construction Corps	Northwest China	Xinjiang	Urumchi	Junming Liu
The Military General Hospital of Beijing PLA	Northern China	Beijing	Beijing	Junxia Li
The First Affiliated Hospital of Guangxi Medical University	Southern China	Guangxi	Nanning	Lang Li
Tongren Hospital Affiliated to Shanghai Jiaotong University School of Medicine	Eastern China	Shanghai	Shanghai	Li Jiang
Binzou City Center Hospital	Eastern China	Shandong	Binzhou	Lijun Meng
The First Affiliated Hospital of Zhengzhou University	Central China	Henan	Zhengzhou	Ling Li
Xijing Hospital	Northwest China	Shaanxi	Xi'an	Ling Tao
The Affiliated Hospital of Guizhou Medical University	Southwest China	Guizhou	Guiyang	Lirong Wu

Table S3 (*continued*)

http://dx.doi.org/10.21037/atm-21-31

Table S3 (*continued*)

Hospitals	Territory	Province	City	Investigator
First Affiliated Hospital of the People's Liberation Army General Hospital	Northern China	Beijing	Beijing	Miao Tian
The Second People's Hospital of Yunnan Province	Southwest China	Yunnan	Kunming	Minghua Han
Haikou People's Hospital	Southern China	Hainan	Haikou	Moshui Chen
Gansu Provincial Hospital	Northwest China	Gansu	Lanzhou	Ping Xie
The First Affiliated Hospital of Henan University of Science and Technology	Central China	Henan	Luoyang	Pingshuan Dong
Chenzhou First People's Hospital	Central China	Hunan	Chenzhou	Qiaoqing Zhong
People's Hospital of Qinghai Province	Northwest China	Qinghai	Xining	Rong Chang
Affiliated Hospital of Ningxia Medical University	Northwest China	Ningxia	Yinchuan	Shaobin Jia
Beijing Anzhen Hospital, Capital Medical University	Northern China	Beijing	Beijing	Shaoping Nie, Xiaohui Liu
North Jiangsu People's Hospital	Eastern China	Jiangsu	Yangzhou	Shenghu He
Shanghai Sixth People's Hospital	Eastern China	Shanghai	Shanghai	Shixin Ma
The First Hospital of Handan	Northern China	Hebei	Handan	Shuanli Xin
Huai'an First People's Hospital	Eastern China	Jiangsu	Huai'an	Shuren Ma
The First Affiliated Hospital of Chongqing Medical University	Southwest China	Chongqing	Chongqing	Suxin Luo
Navy General Hospital	Northern China	Beijing	Beijing	Tianchang Li
Zhejiang Provincial Hospital of TCM	Eastern China	Zhejiang	Hangzhou	Wei Mao
The Third Xiangya Hospital of Central South University	Central China	Hunan	Changsha	Weihong Jiang
Affiliated Hospital of Qinghai University	Northwest China	Qinghai	Xining	Weijun Liu
Teda International Cardiovascular Hospital	Northern China	Tianjin	Tianjin	Wenhua Lin
The Second Hospital of Hebei Medical University	Northern China	Hebei	Shijiazhuang	Xianghua Fu
Changhai Hospital of Shanghai	Eastern China	Shanghai	Shanghai	Xianxian Zhao
The Second Affiliated Hospital to Nanchang University	Eastern China	Jiangxi	Nanchang	Xiaoshu Cheng
Hebei General Hospital	Northern China	Hebei	Shijiazhuang	Xiaoyong Qi
Inner Mongolia People's Hospital	Northern China	Inner Mongolia	Hohhot	Xingsheng Zhao
The General Hospital of Shenyang Military Region	Northeast China	Liaoning	Shenyang	Yaling Han
The First Hospital of Jilin University	Northeast China	Jilin	Changchun	Yang Zheng
Tianjin Chest Hospital	Northern China	Tianjin	Tianjin	Yin Liu
Hunan Provincial People's Hospital	Central China	Hunan	Changsha	Ying Guo
People's Hospital of Yuxi City	Southwest China	Yunnan	Yuxi	Yinglu Hao
The People's Hospital of Guangxi Zhuang Autonomous Region	Southern China	Guangxi	Nanning	Yingzhong Lin
The First Teaching Hospital of Xinjiang Medical University	Northwest China	Xinjiang	Urumchi	Yitong Ma
Baogang Hospital	Northern China	Inner Mongolia	Baotou	Yongdong Li
Tianjin Medical University General Hospital	Northern China	Tianjin	Tianjin	Yuemin Sun

Table S3 (*continued*)

http://dx.doi.org/10.21037/atm-21-31

Table S3 (*continued*)

Hospitals	Territory	Province	City	Investigator
The Second Affiliated Hospital of Zhengzhou University	Central China	Henan	Zhengzhou	Yulan Zhao
Nanfang Hospital of Southern Medical University	Southern China	Guangdong	Guangzhou	Yuqing Hou
The First Affiliated Hospital to Nanchang University	Eastern China	Jiangxi	Nanchang	Zeqi Zheng
The First Affiliated Hospital of Lanzhou University	Northwest China	Gansu	Lanzhou	Zheng Zhang
The Third Hospital of Shijiazhuang	Northern China	Hebei	Shijiazhuang	Zhenguo Ji
Wuxi People's Hospital	Eastern China	Jiangsu	Wuxi	Zhenyu Yang
Jiangsu Province Hospital	Eastern China	Jiangsu	Nanjing	Zhijian Yang
The Second Hospital of Shanxi Medical University	Northern China	Shanxi	Taiyuan	Zhiming Yang
The Affiliated Hospital of Xuzhou Medical College	Eastern China	Jiangsu	Xuzhou	Zhirong Wang
Southwest Hospital, Third Military Medical University	Southwest China	Chongqing	Chongqing	Zhiyuan Song
The First Affiliated Hospital of Xi'an Jiaotong University	Northwest China	Shaanxi	Xi'an	Zuyi Yuan
Hospitals for Phase II				
Yangzhou First People's Hospital	Eastern China	Jiangsu	Yangzhou	Aihua Li
Hospital 463 of Chinese People's Liberation Army	Northeast China	Liaoning	Shenyang	Bosong Yang
The Central Hospital of Mianyang	Northwest China	Sichuan	Mianyang	Caidong Luo
Liaocheng People's Hospital	Eastern China	Shandong	Liaocheng	Chunyan Zhang
Yancheng Third People's Hospital	Eastern China	Jiangsu	Yancheng	Chunyang Wu
The Second Xiangya Hospital of Central South University	Central China	Hunan	Changsha	Daoquan Peng
The Central Hospital of Panzhihua	Northwest China	Sichuan	Panzhihua	Dawen Xu
The First Hospital of Qiqihaer City	Northeast China	Heilongjiang	Qiqihaer	Gang Xu
The Third the People's Hospital of Bengbu	Eastern China	Anhui	Bengbu	Gengsheng Sang
The First Hospital of Jiamusi	Northeast China	Heilongjiang	Jiamusi	Guixia Zhang
Zhoushan People's Hospital	Eastern China	Zhejiang	Zhoushan	Guoxiong Chen
Dalian Municipal Central Hospital	Northeast China	Liaoning	Dalian	Hailong Lin
Renmin Hospital of Wuhan University	Central China	Hubei	Wuhan	Hong Jiang
Ningxia People's Hospital	Northwest China	Ningxia	Yinchuan	Hong Luan
The First People's Hospital of Yunnan Province (Kunhua Hospital)	Northwest China	Yunnan	Kunming	Hong Zhang
The Central Hospital of Zhoukou	Central China	Henan	Zhoukou	Hualing Liu
Anyang District Hospital	Central China	Henan	Anyang	Hui Liu
Sichuan Provincial People's Hospital	Northwest China	Sichuan	Chengdu	Jianhong Tao
Mudanjiang Cardiovascular Disease Hospital	Northeast China	Heilongjiang	Mudanjiang	Jianwen Liu
Yichang Central Hospital	Central China	Hubei	Yichang	Jiawang Ding
Qilu Hospital of Shandong University	Eastern China	Shandong	Jinan	Jifu Li
Affiliated Hospital of Jiangsu University	Eastern China	Jiangsu	Zhenjiang	Jinchuan Yan

Table S3 (*continued*)

http://dx.doi.org/10.21037/atm-21-31

Table S3 (*continued*)

Hospitals	Territory	Province	City	Investigator
The First People's Hospital of Nanning City	Southern China	Guangxi	Nanning	Jinru Wei
The First Affiliated Hospital of Fujian Medical University	Eastern China	Fujian	Fuzhou	Jinzi Su
Chengdu Third People's Hospital	Northwest China	Sichuan	Chengdu	Jiong Tang
Yantaishan Hospital	Eastern China	Shandong	Yantai	Juexin Fan
Qingdao Municipal Hospital	Eastern China	Shandong	Qingdao	Jun Guan
Zhongshan Hospital Affiliated to Fudan University	Eastern China	Shanghai	Shanghai	Junbo Ge
Longyan First Hospital	Eastern China	Fujian	Longyan	Kaihong Chen
Affiliated Hospital of Guangdong Medical College	Southern China	Guangdong	Guangzhou	Keng Wu
Jiangxi Provincial People's Hospital	Eastern China	Jiangxi	Nanchang	Lang Ji
Anhui Provincial Hospital	Eastern China	Anhui	Hefei	Likun Ma
Xiangtan City Central Hospital	Central China	Hunan	Xiangtan	Lilong Tang
The First Hospital of Haerbin City	Northeast China	Heilongjiang	Harbin	Lin Wei
Central Hospital Affiliated to Shenyang Medical College	Northeast China	Liaoning	Shenyang	Man Zhang, Kaiming Chen
The Central Hospital of Wuhan	Central China	Hubei	Wuhan	Manhua Chen
Hangzhou First People's Hospital	Eastern China	Zhejiang	Hangzhou	Ningfu Wang
The Central Hospital of Xuzhou	Eastern China	Jiangsu	Xuzhou	Peiying Zhang
The Second Hospital of Dalian Medical University	Northeast China	Liaoning	Dalian	Peng Qu
The First Affiliated Hospital of Liaoning University of Traditional Chinese Medicine	Northeast China	Liaoning	Shenyang	Ping Hou
Beijing Tsinghua Changgung Hospital	Northern China	Beijing	Beijing	Ping Zhang
Guizhou Provincial People's Hospital	Northwest China	Guizhou	Guiyang	Qiang Wu
The First Affiliated Hospital of Xiamen University	Eastern China	Fujian	Xiamen	Qiang Xie
Quanzhou First Hospital	Eastern China	Fujian	Quanzhou	Rong Lin
Wuzhou People's Hospital	Southern China	Guangxi	Wuzhou	Shaowu Ye
The Central Hospital of Jilin	Northeast China	Jilin	Changchun	Shuangbin Li
Xiangya Hospital Central South University	Central China	Hunan	Changsha	Tianlun Yang
Guangzhou Red Cross Hospital	Southern China	Guangdong	Guangzhou	Tongguo Wu
The First Affiliated Hospital of Guangzhou Medical College	Southern China	Guangdong	Guangzhou	Wei Wang
The First Affiliated Hospital of Wenzhou Medical University	Eastern China	Zhejiang	Wenzhou	Weijian Huang
The Second Affiliated Hospital of Soochow University	Eastern China	Jiangsu	Suzhou	Weiting Xu
Wuhan Asia Heart Hospital	Central China	Hubei	Wuhan	Xi Su
The First Affiliated Hospital of Soochow University	Eastern China	Jiangsu	Suzhou	Xiangjun Yang
Affiliated Hospital of Yan'an University	Northwest China	Shaanxi	Yan'an	Xiaochuan Ma
The First People's Hospital of Jining	Eastern China	Shandong	Jining	Xiaofei Sun

Table S3 (*continued*)

http://dx.doi.org/10.21037/atm-21-31

Table S3 (*continued*)

Hospitals	Territory	Province	City	Investigator
The Central Hospital of Taiyuan	Northern China	Shanxi	Taiyuan	Xiaoping Chen
West China Hospital of Sichuan University	Northwest China	Sichuan	Chengdu	Xiaoping Chen
The Third Affiliated Hospital of Guangzhou Medical College	Southern China	Guangdong	Guangzhou	Ximing Chen
The First Affiliated Hospital of Wannan Medical College	Eastern China	Anhui	Wuhu	Xingsheng Tang
Tangdu Hospital of The Fourth Military Medical University	Northwest China	Shaanxi	Xi'an	Xue Li
Shanghai East Hospital Affiliated to Tongji University	Eastern China	Shanghai	Shanghai	Xuebo Liu
Xiamen Cardiovascular Disease Hospital	Eastern China	Fujian	Xiamen	Yan Wang
Zhongnan Hospital of Wuhan University	Central China	Hubei	Wuhan	Yanggan Wang
Fujian Provincial Hospital	Eastern China	Fujian	Fuzhou	Yansong Guo
The First Affiliated hospital of Dalian Medical University	Northeast China	Liaoning	Dalian	Yanzong Yang
The First People's Hospital of Changde	Central China	Hunan	Changde	Yi Huang
The First Affiliated Hospital of China Medical University	Northeast China	Liaoning	Shenyang	Yingxian Sun
The Fourth Affiliated Hospital of China Medical University	Northeast China	Liaoning	Shenyang	Yuanzhe Jin
Cangzhou Central Hospital	Northern China	Hebei	Cangzhou	Zesheng Xu
The Central Hospital of Shaoyang	Central China	Hunan	Shaoyang	Zewei Ouyang
The People's Hospital of Liaoning Province	Northeast China	Liaoning	Shenyang	Zhanquan Li
The First Affiliated Hospital of Jiamusi University	Northeast China	Heilongjiang	Jiamusi	Zhaofa He
Tangshan Gongren Hospital	Northern China	Hebei	Tangshan	Zheng Ji
Huaibei Miners' General Hospital	Eastern China	Anhui	Huaibei	Zhenqi Su
Linyi People's Hospital	Eastern China	Shandong	Linyi	Zhihong Ou

http://dx.doi.org/10.21037/atm-21-31