Predicting In-Hospital Mortality in Patients With Acute Coronary Syndrome in China

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Currently available risk scores (RSs) were derived from populations with very few participants from China. We aimed to develop an RS based on data from patients with acute coronary syndrome in China and to compare its performance with the commonly promoted Global Registry of Acute Coronary Events (GRACE) RS. Clinical Pathways for Acute Coronary Syndromes—Phase 2 was a trial of a quality improvement intervention in China. Patients recruited from 75 hospitals from October 2007 to August 2010 were divided into training and validation sets based on immediate or delayed implementation. A Clinical Pathways for Acute Coronary Syndromes (CPACS) RS for in-hospital mortality was developed separately by gender, using the training set (6,790 patients). Discrimination and calibration of the CPACS RS and GRACE RS were compared on the validation set (3,801 patients). Although discrimination of the GRACE RS was acceptable, this was improved with the CPACS RS (c-statistic 0.82 vs 0.87, p = 0.012 for men; c-statistic 0.78 vs 0.85, p = 0.006 for women). The absolute bias was significantly lower with CPACS RS for both genders (7.6% vs 97.5% in men and 21.5% vs 77.2% in women), compared with the GRACE RS, which systematically overestimated risk. The CPACS RS underestimated risk in women, but only in those already above threshold levels currently used to define a clinical high-risk population. In conclusion, the GRACE RS substantially overestimates the risk of in-hospital death in patients presenting to the hospital with a suspected acute coronary syndrome in China. We have developed and independently validated a new RS utilizing data from Chinese patients. **(Am J Cardiol 2017;120:1077–1083)**

The use of formal assessment of the risks of an adverse clinical outcome is increasingly promoted in clinical guidelines for the management of acute coronary syndrome (ACS) globally.[1,2] A number of risk tools that predict in-hospital and longer-term risk of death after discharge from the hospital have been developed.[3–5] Currently, the most commonly used risk scores (RSs) for patients with ACS are the Global Registry of Acute Coronary Events (GRACE) and Thrombolysis in Myocardial Infarction (TIMI) RSs. The GRACE RS was developed from a multinational ACS registry but included few participants from Asia, including China.[5,6] The TIMI RS was derived from a trial population in North America.[4,7] Whether currently available clinical risk tools are appropriate in the context of cardiac care delivery in China is unknown. In the current study, we evaluated the GRACE RS in a large population of patients with suspected ACS consecutively admitted to 75 hospitals across China. We also develop and validate a risk model specific for Chinese patients with ACS, and compare its performance with the GRACE RS.

Methods

The Clinical Pathways for Acute Coronary Syndromes (CPACS) program, a quality improvement initiative focused on the management of hospitalized patients with suspected ACS and conducted under the auspices of the Chinese Cardiac Society. Clinical Pathways for Acute Coronary Syndromes—Phase 1 from September 2004 to May 2005, described the characteristics of and the practice patterns for 2,973 patients with suspected ACS admitted to 51 hospitals.[8] This program was followed by Clinical Pathways for Acute Coronary Syndromes—Phase 2 (CPACS-2), a quality improvement initiative from October 2007 to August 2010 that evaluated the effectiveness of interventions based on clinical pathways

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A list of all CPACS Investigators is given in Appendix I in the online-only data supplement.

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See page 1082 for disclosure information.

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implementation for ACS management in 75 hospitals.[9,10] After piloting the intervention in 5 centers, the remaining 70 hospitals participating in CPACS-2 were randomized to early intervention (Group A hospitals) or late intervention (Group B hospitals). Group B hospitals commenced data collection and deployment of the intervention 12 months after Group A hospitals. Eligible hospitals were those admitting ≥100 patients with a suspected ACS annually, and at each hospital, data on consecutive adult (≥18 years) patients with a final diagnosis for ACS were included. For each patient, these data included demographic characteristics, medical history, results of laboratory tests, and in-hospital treatment including reperfusion therapy (thrombolysis or primary percutaneous coronary intervention) or revascularization (percutaneous coronary intervention or coronary artery bypass grafting) and prescribed medications during the final diagnosis (ST-segment elevation myocardial infarction [STEMI], non–ST segment elevation myocardial infarction [NSTEMI], or unstable angina pectoris [UAP]) and in-hospital events, including death. Data from patients in all 75 hospitals were used for the evaluation of the GRACE RS. Data collected from the Group A and pilot hospitals were used to develop the CPACS RS; performance of the score was validated and compared with GRACE RS using data from the Group B hospitals.

The research study was approved by the Human Research Ethics Committees at Cardiovascular Institute and Fuwai Hospital, the Chinese Academy of Medical Sciences, and Peking Union Medical College, Beijing, China, and by the University of Sydney, Australia. All research subjects gave written informed consent.

Details of the performance of GRACE RS and the development of CPACS RS are described in The Expanded Methods in Appendix II in the online-only data supplement. Briefly, each patient from the CPACS-2 trial was assigned a predicted risk of in-hospital death using the GRACE risk model.[5] Discrimination of GRACE RS in the CPACS-2 population was evaluated using the c-statistic from ROC curves with recorded death in hospital as the outcome and the GRACE RS probability of death in hospital as the predictor. We assessed calibration by comparing the predicted and observed mortality rates in each decile of risk and tested the difference using the Hosmer-Lemeshow goodness-of-fit test.[11] To overcome the tendency of large data sets to show a statistically significant lack of calibration with small differences, we also reported overall and absolute measurements of bias in Appendix V in the online-only data supplement.

Data from CPACS-2 patients treated at the pilot and Group A hospitals were used to generate the CPACS RS (training set). The initial model utilized the same variables used in the GRACE RS, but also initially included the following baseline variables based on known or suspected associations with clinical outcomes: medication history (prehospital use of antiplatelets, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and statins), smoking status (current vs not), previous diagnoses (diabetes, stroke, or heart disease), and initial diagnosis (STEMI, NSTEMI or UAP). Patients with missing data for any of these variables were excluded from model development (27.8% with at least 1 missing variable). We estimated 3 RSs using different methods that are fully described in Appendixes IV and V in the online-only data supplement, and ultimately selected that which minimized absolute bias. We estimated a separate RS for both men and women.

Using the methods described previously, the CPACS RS and GRACE RS were compared by evaluating discrimination and calibration using data from CPACS-2 patients enrolled at Group B hospitals (validation set) without any missing data (33.7% with at least 1 variable missing). To determine the practice implications of using the CPACS RS instead of the GRACE RS, we used in-hospital mortality rates of >3% and >5%, respectively, to define high-risk groups for non–ST elevation acute coronary syndrome (NSTE-ACS, represented by a diagnosis of UAP or NSTEMI in CPACS-2) and ST elevation acute coronary syndrome (STE-ACS). These levels are consistent with those used for the GRACE RS.[12] For each risk score we also derived an optimal cut-point based on Youden's index and calculated the sensitivity and the specificity at this cut-point.[13] As a sensitivity analysis, we further evaluated the CPACS RS separately for patients with STE-ACS and for those with NSTE-ACS because of the unexpectedly high proportion of patients with a final diagnosis of UAP. All analyses were performed in SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

A total of 15,141 patients were enrolled in the CPACS-2 study. After excluding the patients with missing data, we divided patients into training (Group A + pilot hospitals, n = 6,790) and validation (Group B hospitals, n = 3,801) sets. The in-hospital mortality rates were 2.5% (95% confidence interval 2.2% to 2.9%) in Group A plus pilot and 3.6% (95% confidence interval 3.0% to 4.2%) in Group B, respectively. The admission characteristics of the CPACS-2 population are described in Table 1, stratified by hospital group. The patient characteristics between the 2 hospital groups were similar. The characteristics and the mortality rates of patients before and after exclusion of those with at least 1 missing variable for the RSs were also similar (Appendix III in the online data supplement).

The GRACE RS discriminated the risk of in-hospital death well in Group B of the CPACS-2 population, with a c-statistic of 0.82 for men and 0.78 for women (Table 2). However, the GRACE RS systematically overestimated the risk across all deciles in the CPACS-2 population (Figure 1). The CPACS RSs for men and women are presented in Table 3. Notably, the variables as well as the coefficients in the final models differed by gender.

Compared with the GRACE RS, discrimination with the CPACS RS was greater overall ($\chi^2 = 4.17$, $p < 0.001$) and by gender ($\chi^2 = 2.51$, $p = 0.012$ for men; $\chi^2 = 2.75$, $p = 0.006$ for women), and was associated with a substantially less absolute bias (Table 2). Conversely, compared with the GRACE RS (Figure 1), the CPACS RS underestimated risk, but only among those within the highest 2 or 3 deciles of predicted risk, especially in women. The results for the subgroup analyses of STE-ACS and non-STE-ACS showed a similar pattern; however, the improvements in calibration with CPACS RS were greater in STE-ACS than in NSTE-ACS (Table 2). Nonetheless, the CPACS RS underestimated risk among the highest-risk female patients for both STE-ACS and NSTE-ACS