Comparison of Prognostic Value of Different Risk Score Methods on Outcome of Acute Coronary Syndrome

Bin Zhong, MD; Zengzhang Liu, MD; Li Su, PhD; Xianbin Lan, MD; Yunqing Chen, PhD; Zhiyu Ling, MD; Huaan Du, MD; Yuehui Yin, MD

Department of Cardiology, the Second Affiliated Hospital, Chongqing Medical University, Chongqing, China

ABSTRACT

Background: Thrombolysis in myocardial infarction (TIMI) flow grade (TFG) was a gold standard for comparison of the various methods of evaluating the efficacy of reperfusion, and risk score was a pragmatic method of risk stratification and evaluation of prognosis for acute coronary syndrome (ACS). However, it is uncertain whether or not the prognostic value of combining risk score and TFG on outcome of acute coronary syndrome could be improved.

Materials and Methods: A total of 279 consecutive patients with ACS (mean age 67.57 ± 9.88 years, 69.2% male) admitted to our hospital were enrolled. Clinical risk score, TFG, and combined risk score were calculated. The primary endpoint of this study included cardiac death and noncardiac death; the secondary endpoint included nonfatal stroke, reinfarction, heart failure, and recurrent angina.

Results: During the follow-up of 11.41 ± 5.33 months, 11 patients reached the primary endpoint, and 23 patients reached the secondary endpoint. The prognostic values evaluated by composite endpoint, primary endpoint, and secondary endpoint were 0.722, 0.685, and 0.721, respectively, for clinical risk score they were 0.774, 0.798, and 0.737, respectively, for TFG they were 0.805, 0.808, and 0.776, respectively, for combined risk score. In pair-wise comparisons of prognostic values, there were no significant differences among these methods, except that the combined risk score can more accurately predict the composite endpoint than the others.

Conclusion: The results suggest that the combined risk score is a simple and efficient method of prediction of composite endpoint.

Introduction

The need to risk stratify acute coronary syndrome (ACS) is widely accepted. Early risk stratification plays a central role, as the benefits of aggressive and costly treatment strategies seem to be proportional to the risk of adverse clinical events. Recently, many risk score algorithms were derived from clinical trials, such as the thrombolysis in myocardial infarction (TIMI)-11¹ and the Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trials, which had restricted entry criteria. Patients with comorbidities such as renal impairment were often excluded. In contrast, Global Registry of Acute Coronary Events (GRACE)² hospital discharge prediction model for 6-mo mortality (GRACE score) was developed from a multinational registry involving all subsets of ACS including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). The GRACE score derived from clinical parameters at the time of hospital discharge was found to accurately predict mortality at 6 mo and may have broader applicability in the longer term. Different risk scores are

now available based on initial clinical history, electrocardiogram (ECG), and laboratory tests that enable early risk stratification on admission.

The clinical parameters from the TIMI-11B¹ trial and GRACE² research were used in daily clinical practice. TIMI flow grade (TFG) provides a gold standard for comparison of the various methods of evaluating the efficacy of reperfusion. This study was designed to compare the prognostic value of clinical risk score, TFG, and combined risk score on outcome of ACS in order to understand whether or not the prognostic value of combining clinical risk score and TFG (namely combined risk score) on outcome of ACS could be improved.

Materials and Methods

Study Population and Clinical Characteristics

Patients with ACS undergoing coronary angiographies following coronary stent implantation as appropriate in our hospital from December 2004 to June 2006 were enrolled. Inclusion criteria:³ (1) STEMI: defined as having ST-segment elevation ≥ 1 mm in 2 contiguous leads (or ≥ 2 mm in V_1

to V₃ leads) or new left bundle branch block together with chest pain for >30 minutes and/or evidence of myonecrosis with elevated troponin T; (2) NSTEMI: defined as non-ST-segment elevation on ECG despite elevated troponin T and chest pain for >30 minutes; (3) Unstable angina: defined as ischemic chest pain lasting more than 30 minutes with no evidence of myonecrosis or ST-elevation. Patients who had severe renal insufficiency (serum creatinine ≥ 445 $\mu\text{mol/L}$), coronary stenosis less than 50%, and pacemaker implanted were excluded from this study.

This study protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing University of Medical Sciences (Chongqing, China), and all patients provided written informed consent prior to operation.

Methods of Assessment

Demographic characteristics, vital signs, physical examination, severity and number of vessels with lesions, and the number of stents implanted were recorded. Pragmatic parameters derived from the TIMI-11B trial and GRACE research were used to calculate the clinical risk score which including (1) age 65 years or older; (2) at least 3 risk factors for coronary artery disease; (3) history of acute myocardial infarction or percutaneous coronary intervention or heart failure; (4) severe angina pectoris (at least 2 anginal events in prior 24 hours); (5) ST-segment deviation on electrocardiogram at presentation; (6) use of aspirin in prior 7 days or use of unfractionated heparin intravenously within 24 hours together with (7) serum creatinine (>133 $\mu\text{mmol/L}$ defined as positive). Assigning value of 1 when one of the clinical parameter noted above was present and 0 when it was absent; sum of total score represents clinical risk score for each patient.

The TFG of each patient before stent implantation was evaluated by reviewing the CD recorded intraoperatively (the speed of playing the disc was 14 frames/second) according to the standard described by Braunwald et al.⁴ Left anterior descending branch, left circumflex branch, and the right coronary artery were evaluated as target vessels. The TFG of the target vessel with more severe lesions was evaluated when multivessel diseases were present. Assigning risk score of 3 to TFG 0, 2 to TFG 1, 1 to TFG 2, and 0 to TFG 3, sum of the clinical risk score and the risk score of TFG were expressed as the combined risk score.

Receiver operating characteristic curves (ROCs) were constructed using the clinical risk score, TFG, or combined score and each endpoint, respectively, thus the accuracy of prognostic value of each method expressed as area under the curve (AUC) can be calculated.

Management

All operations were finished on a digital angiographic machine INNOVA2000 (GE Company, Fairfield, CT). Selection of indications and timing of the operations were

conducted according to the European Society of Cardiology (ESC) and Chinese guidelines for percutaneous coronary intervention (PCI)^{5,6} at the discretion of the treating physicians and integrating their own experiences.

Management after operation was at the discretion of treating physicians according to the guidelines.^{6,7}

Protocol of Follow-Up and Endpoints

All patients were followed by telephone and/or visiting outpatient clinics monthly. Lipid profile of each patient was recorded according to the guidelines.⁸ When patients died, the time and cause of death was noted accurately. Recurrent angina and reinfarction were recorded based on classic symptoms, ECG, and biomarkers of cardiac necrosis. The primary endpoint of this study included cardiac death and noncardiac death; the secondary endpoint consisted of non-fatal stroke, reinfarction, heart failure, and recurrent angina.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation (SD) and categorical variables were expressed as frequency or percentage. Logical regression (chi-square test and the Hosmer and Lemeshow test) was performed to estimate the goodness of fit of the clinical risk score, TFG, and combined risk score. Statistical analysis was performed with SPSS version 13.0 (SPSS Inc., Chicago, IL) and MedCalc version 9.2 (MedCalc Software, Mariakerke, Belgium). For all comparisons, 2-sided *p* value of <0.05 was considered statistically significant. When appropriate, confidence intervals (CIs) were calculated, with a 95% confidence level.

Results

Baseline Characteristics

There were 268 patients (STEMI: 96 [35.82%], NSTEMI: 57 [21.27%], and UA: 115 [42.91%]) enrolled excluding 11 patients who had been lost to follow-up. The mean follow-up time was 11.41 ± 5.33 mo. The baseline characteristics and the methods are shown in Table 1. The distribution of lesions is shown in Table 2.

The minimum and maximum of clinical risk score was 1 and 6, respectively, with a mean value 3.32 ± 1.17 . The distribution of preoperative TFG was as followed: there were 43 (16.04%) patients who had TIMI 0 grade; 62 (23.13%) patients who had TIMI 1 grade; 94 (35.07%) patients who had TIMI 2 grade; 69 (25.74%) patients who had TIMI 3 grade. The minimum and maximum of combined risk score was 1 and 9, respectively, associated with a mean value 4.62 ± 1.72 .

There were 11 (4.10%) patients who reached the primary endpoint, of whom 8 (2.99%) experienced cardiac death; 3 (1.12%) experienced noncardiac death. There were 23 (8.58%) patients who reached the secondary endpoints including 3 (1.12%) patients who had a nonfatal stroke; 6 (2.24%) patients who had reinfarction; 3 (1.12%) patients

Table 1. Method of Clinical Risk Score

Clinical Parameters	Score
Age >65 y	1
Risk factors for CAD	
Family history of Hypertension/DM/Hypercholesterolemia	1
History of AMI/PCI/HF	1
Severe angina pectoris	1
ST-segment deviation on ECG	1
Use of aspirin in prior 7 d/UHF	1
Serum creatinine (>133 μ mol/L)	1
Abbreviations: AMI, acute myocardial infarction; CAD, coronary artery disease; DM, diabetes mellitus; ECG, electrocardiograph; HF, heart failure; PCI, percutaneous coronary intervention; UHF, unfractionated heparin.	

who had heart failure, and 11 (4.10%) patients who had recurrent angina.

The Results of Goodness of Fit of Clinical Risk Score, TFG, and Combined Risk Score

Clinical risk score, TFG, and combined risk score had goodness of fit with composite endpoint, as demonstrated by the probability values of the Hosmer and Lemeshow test with a chi-square of 4.794, 6.085, and 3.914, respectively, which were 0.187, 0.056, and 0.562, correspondingly. Similarly, values of chi-square were 0.355, 4.108, and 0.676, respectively, associated with *p* values which were 0.949, 0.128, and 0.984, correspondingly, for the primary endpoint. With respect to the secondary endpoint, the values of chi-square were 6.534, 5.700, and 3.708, respectively; the corresponding probabilities were 0.088, 0.058, and 0.592.

Comparison of Prognostic Value on Each Endpoint

Evaluating composite endpoint using the clinical risk score, TFG, and combined risk score, the AUC of the clinical risk score was 0.722 (95% CI = 0.664 ~ 0.775); 0.774 (95% CI = 0.719 ~ 0.822) for TFG; 0.805 (95% CI 0.752 ~ 0.850) for the combined risk score. In pair-wise comparisons, the *p* values were 0.427 (the clinical risk score vs the TFG), 0.016 (the clinical risk score vs the combined risk score), and 0.418 (the TFG vs the combined risk score; Figure 1). Prognostic values on the primary endpoint measured as the AUC of individual curve were 0.685 (95% CI = 0.625 ~ 0.740) for the clinical risk score; 0.798 (95% CI = 0.745 ~ 0.844) for the TFG; and 0.808 (95% CI = 0.755 ~ 0.853) for the combined risk score. The *p* values were 0.324 (the clinical risk score vs the TFG), 0.053 (the clinical risk score vs the combined risk score), and 0.888 (the TFG vs the combined risk score) in pair-wise comparisons (Figure 2).

Table 2. Baseline Characteristics and Management

General State of Health	
Sex (Male)	211 (78.73%)
Age (Mean $\pm$ SD), y	67.57 $\pm$ 9.88
Diabetes n (%)	68 (25.37%)
Hypertension n (%)	163 (60.82%)
SBP (mm Hg)	137.65 $\pm$ 24.76
DBP (mm Hg)	76.66 $\pm$ 13.44
TC (mmol/L)	4.75 $\pm$ 1.12
HDL (mmol/L)	1.29 $\pm$ 0.33
LDL (mmol/L)	2.56 $\pm$ 0.93
Cr (μ mol/L)	95.20 $\pm$ 32.32
Medications	
Aspirin	229 (85.45%)
ACEI/ARB	157 (58.58%)
β -blocker	126 (47.01%)
LMWH	184 (68.66%)
Statins	233 (86.94%)
ADP receptor antagonist	225 (83.96%)
CCB	110 (41.04%)
Nitrates	202 (75.37%)
Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ADP, adenosine diphosphate; ARB, aniotensin receptor blockers; CCB, calcium channel blockers; Cr, creatinine; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LMWH, low molecular weight heparin; SBP, systolic blood pressure; TC, total cholesterol.	

Similarly, with respect to the secondary endpoint, the AUC of the clinical risk score was 0.721 (95% CI = 0.663 ~ 0.774); 0.737 (95% CI = 0.680 ~ 0.788) for the TFG; 0.776 (95% CI = 0.721 ~ 0.824) for the combined risk score. The *p* values in pair-wise comparisons were 0.837 (the clinical risk score vs the TFG), 0.161 (the clinical risk score vs the combined risk score), and 0.393 (the TFG vs the combined risk score), with no significant difference (Figure 3).

Discussion

In this study, it was demonstrated that the clinical risk score, the TFG, and the combined risk score can be used to accurately predict the outcome of acute coronary syndrome.

Figure 1. Pair-wise comparisons of prognostic value of different risk score on the composite endpoint. Abbreviation: TFG, thrombolysis in myocardial infarction flow grade.

Figure 3. Pair-wise comparisons of prognostic value of different risk score on the composite endpoint. Abbreviation: TFG, thrombolysis in myocardial infarction flow grade.

Figure 2. Pair-wise comparisons of prognostic value of different risk score on the composite endpoint. Abbreviation: TFG, thrombolysis in myocardial infarction flow grade.

The combined risk score can more accurately predict the composite endpoint.

The clinical risk score was used to predict efficiently the immediate and long-term outcome of acute coronary syndrome. Analyzing the immediate outcomes of 5124 patients with UA and NSTEMI using the parameters from the TIMI-11B trial including the 6 parameters noted above, together with the elevated marker of myocardial necrosis and prior coronary stenosis of 50% or more, Antman and colleagues⁹

Table 3. Distribution of Lesions

Distribution of Lesions (n = 268)			
Single vessel disease n (%)	101 (37.69%)		
Double vessels disease n (%)	99 (36.94%)		
Multivessel disease n (%)	68 (25.37%)		
	PS n (%)	MS n (%)	DS n (%)
LAD	137 (51.12%)	78 (29.10%)	3 (1.12%)
LCX	54 (20.15%)	76 (28.35%)	4 (1.49%)
RCA	65 (24.25%)	70 (26.12%)	17

Abbreviations: DS, distal segment; LAD, left anterior descending; LCX, left circumflex; MS, middle segment; PS, proximal segment; RCA, right coronary artery.

found that the TIMI risk score was directly correlated to the cardiovascular events. Furthermore, studying the long-term mortality of the 1,057 patients with ACS consisted of NSTEMI: 39%, STEMI: 39%, and UA: 22% using method of GRACE research, Tang et al.³ found that the TIMI risk score can accurately predict the long-term outcome of ACS. However, some of these parameters cannot be obtained immediately, especially, in the hospitals of China. Additionally, studying the relationship of renal insufficiency and the outcome of the percutaneous coronary intervention in 5,397 patients who had ACS, Best et al¹⁰ found that the renal insufficiency was the strongest predictor of mortality and

cardiovascular events. The prevalence of dyslipoproteinemia, disorders of coagulation, severe hypertension, and complex lesions in patients with ACS complicating renal insufficiency, the prognoses of these patients are not as good as anticipated. Therefore, the pragmatic parameters including serum creatinine are selected to predict the outcome of ACS in this study, and the prognostic value of the clinical risk score on the composite endpoint, the primary endpoint, and the secondary endpoint are 0.722, 0.685, and 0.721, respectively, which are slightly lower than that (0.81 ~ 0.82) reported by Tang et al.³ The reason may be the sample size in this study is smaller than that of their study. But, it is higher than that (AUC = 0.585, 95% CI = 0.539 ~ 0.631) reported by de Araújo Gonçalves et al.,¹¹ in which they studied the outcomes of consecutive 460 ACS patients without ST-segment elevation at 1 year using parameters derived from the PERSUIT, TIMI, and GRACE trials.

TFG is often used to predict the outcome of ACS, especially of acute myocardial infarction after thrombolysis therapy. Gibson et al.¹² found CTFC (corrected TIMI frame count—frame count of infarct artery divided by the ratio of its frame count to that of the mean values for the noninfarct arteries) was an independent predictor of hospital mortality of patients included in the TIMI-4, TIMI-10A, and TIMI-10B trials when they studied the relationship of the corrected 90 minutes TFG and mortality. In this study, the prognostic values of the TFG on the composite endpoint, the primary endpoint, and the secondary endpoint in this group are 0.774, 0.798, and 0.737, respectively. The sensitivities to the all endpoints are more than 70%.

It is different that invasive methods in combination with a noninvasive one were used to predict outcome of ACSs in this study, and the renal function was considered simultaneously. The composite endpoint can be more accurately predicted with the combined risk score, demonstrated by the *p* value (*p* = 0.016) in pair-wise comparison, even if the prognostic values on the primary endpoint and the secondary endpoint are not significant. Synergistic effect of clinical risk score and TFG on prognosis of ACS could improve the sensitivity of the combined risk score on each endpoint. Karpaliotis et al.¹³ found that there was a stronger correlation existing between the TFG and mortality in patients who have higher TIMI risk score. The complexities of lesions may be exacerbated with the increase of the clinical risk score. Therefore, the outcomes of these patients are poorer than that of the patients whose clinical risk score are lower. It is probable that the prognostic value of the combined risk score on each endpoint could be improved with the sample of study increase.

Conclusions

The clinical risk score, the TFG, and the combined risk score can be used to accurately predict the outcomes of

ACS. The method incorporating the TFG and the clinical risk score may be more precise. The clinical risk score could be one of the efficient means of outcome assessment and primary risk assessment of patients with ACS in the emergency department and in the community hospitals in China.

References

1. Antman EM, McCabe CH, Gurfinkel EP, Turpie AG, Bernink PJ, et al.: Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation*. 1999;100:1593–1601.
2. Steg PG, Goldberg RJ, Gore J, Fox KA, Eagle KA, 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;90:358–363.
3. Tang EW, Wong CK, Herbison P, et al.: Global Registry of Acute Coronary Events (GRACE) hospital discharge risk score accurately predicts long-term mortality post acute coronary syndrome. *Am Heart J*. 2007;153:29–35.
4. Braunwald E, Douglas P, Zipes, Peter Libby, O. Robert, Stephan Achenbach, et al.: ST-elevation myocardial infarction: Management. In: *Heart Disease Textbook of Cardiovascular Medicine*. 7th ed. Philadelphia: W.B. Saunders Company. 2001. p 2162–2164.
5. Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, et al.: Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J*. 2005;26:804–847.
6. Chinese Medical Association of Cardiology Branch: Guidelines for percutaneous coronary interventions. *Modern Practical Medicine*. 2004;16:55–64.
7. Van de Werf F, Ardissino D, Betriu A, Cokkino DV, Falk E, et al.: Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J*. 2003;24:28–66.
8. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143–3421.
9. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, et al.: The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA*. 2000;284:835–842.
10. Best PJ, Lennon R, Ting HH, Bell MR, Rihal CS, et al.: The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol*. 2002;39:1113–1119.
11. de Araújo Gonçalves P, Ferreira J, Aguiar C, Seabra-Gomes R: TIMI, PURSUIT, and GRACE risk scores: Sustained prognostic value and interaction with revascularization in NSTEMI-ACS. *Eur Heart J*. 2005;26:865–872.
12. Gibson CM, Murphy SA, Rizzo MJ, Ryan KA, Marble SJ, et al.: Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. Thrombolysis In Myocardial Infarction (TIMI) Study Group. *Circulation*. 1999;99:1945–1950.
13. Karpaliotis D, Turakhia MP, Kirtane AJ, Murphy SA, Kosmidou I, et al.: Sequential risk stratification using TIMI risk score and TFG among patients treated with fibrinolytic therapy for ST-segment elevation acute myocardial infarction. *Am J Cardiol*. 2004;94:1113–1117.