Original article

Validation of the GRACE score for prognosis in Indian patients with acute coronary syndromes

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KEY WORDS

Acute coronary syndromes
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ABSTRACT

Aim: To validate the global registry of acute coronary events (GRACE) score in acute coronary syndromes (ACS) patients and study its angiographic correlation.**Methods and results:** Two-hundred and thirty-five ACS patients were studied for the combined endpoint of all-cause in-hospital mortality and non-fatal infarction/reinfarction. We tested the predictive accuracy of the composite GRACE score using the receiver operating characteristics (ROC) curve.Lower systolic blood pressure (SBP) (odds ratio [OR] 7.93, $P=0.005$), ST-segment deviation (OR 7.79, $P=0.02$) and cardiac biomarker positivity (OR >6.52 , $P=0.01$) were significantly associated with events. Serum creatinine >1.4 mg/dL showed a trend towards statistical significance (OR 4.14, $P=0.05$), whereas age >50 years (OR 3.62, $P=\text{not significant [NS]}$) and Killips class 4 (OR 2.71, $P=\text{NS}$) showed good association. The best value for predicting events was a GRACE score of ≥ 217 and these patients were more likely to have double/triple vessel disease ($P=0.0009$). The C statistic for the GRACE score was 0.75.**Conclusion:** Higher GRACE score predicts in-hospital events and more severe angiographic coronary artery disease (CAD).

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Introduction

Acute coronary syndrome (ACS) is the commonest diagnosis at admission to a coronary care unit (CCU). It covers a broad spectrum of patients including those with unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). As newer and more effective therapeutic options become available, it is equally important to target the right treatment to the right patient. Yet, some contemporary data suggests that more aggressive therapy is not necessarily targeted at high-risk patients.¹ Hence, there is a need for an efficient risk prediction tool to optimise treatment.

While a risk score has to be comprehensive, it should also be simplistic for maximum usability. A number of multivariate prognostic models have been developed in patients with

STEMI² and with ACS without ST-elevation.^{3,4} These have been derived from or validated in clinical trial databases and often do not reflect real time practice, due to selection bias. The global registry of acute coronary events (GRACE) score⁵ has been developed from registry data and accounts for newer prognostic variables which were not previously considered. Moreover, it is applicable across all cases of ACS.

This study aims to validate the GRACE score and assess its prognostic value in patients of ACS admitted to our hospital.

Materials and methods

Study population

This was a prospective study of 235 consecutive patients of ACS admitted to the CCU at St. John's Medical College and Hospital between September 2007 and May 2008. It included

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all patients presenting with chest pain or other symptoms suggestive of ACS, with the most recent episode occurring within 24 hours of admission. A diagnosis of ACS was made using symptoms, electrocardiogram (ECG) changes, and cardiac biomarkers (Troponin T/I or CPK-MB). Patients were recruited irrespective of planned revascularisation.

All patients received standard treatment as per guidelines, including aspirin, clopidogrel, anticoagulants (unfractionated heparin [UFH]/low molecular weight heparin [LMWH]), thrombolytics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors/ARB, and statins. In addition, glycoprotein (GPIIb–IIIa) inhibitors, aldosterone antagonists, and second line antianginals were used as indicated. Some of the patients underwent coronary angiogram (CAG) and revascularisation wherever feasible.

Risk score

Risk assessment was done using the GRACE score. The score was calculated using a programme downloaded from the site of the GRACE project. The variables that constitute the GRACE score⁵ are:

1. Age
2. Heart rate
3. Systolic blood pressure (SBP)
4. Serum creatinine
5. Killip class
6. Cardiac arrest at admission
7. Elevated cardiac markers
8. ST-segment deviation.

Endpoint

Patients were followed up for the combined endpoint of all-cause mortality and non-fatal myocardial infarction (MI). In cases of STEMI, reinfarction beyond 24 hours was considered as an event and was defined according to ACC/AHA guideline criteria as⁶

- i. Either re-elevation of the CPK-MB levels above the upper limit of normal and increased by at least 50% of the previous value or
- ii. Appearance of new Q waves on the ECG.

A secondary analysis correlating the GRACE score to the severity of coronary artery disease (CAD) on angiogram was also performed.

Statistical analysis

Descriptive statistical analysis has been carried out. Chi-square test and Fisher Exact test has been used whenever the data is presented in terms frequency, and student *t*-test has been used to test significance when the results are presented as mean $\pm$ standard deviation (SD). Odds ratio (OR) and its confidence interval (CI) have been computed for event of interest. Multivariate logistic regression analysis has been used to

Figure 1 Patient distribution across the acute coronary syndrome spectrum. NSTEMI: non-ST-elevation myocardial infarction, STEMI: ST-elevation myocardial infarction, UA: unstable angina.

assess the risk factors for predicting the event. A *P* value <0.05 was considered statistically significant. Receiver operating characteristics (ROC) curve analysis has been performed to know the predictive value of GRACE score for predicting the event.

The statistical software namely SPSS 11.0, MedCalc 9.0.1, Stata 8.0, Systat 11.0, and Effect Size calculator were used for the analysis of the data.

Results

A total of 235 patients were analysed. One hundred and eight of these patients were admitted with a diagnosis of STEMI while 127 patients had non-ST-elevation ACS (Figure 1).

A total of 21 (9.1%) patients had an event, i.e. death or MI. Of these, 16 were in the STEMI group and five in the unstable angina/NSTEMI group.

Baseline characteristics

The baseline characteristics of these patients (Table 1) are shown. Majority of the patients were male (73.1%) and the mean age of the cohort was 59.5 years. Of the conventional risk factors, diabetes mellitus (DM) and hypertension (HTN) were most common. C-reactive protein was done in 154 patients. Other biochemical findings are also shown.

We did a univariate (Table 2) as well as multivariate (Table 3) analysis for assessing the risk associated with these baseline characteristics and then assessed the predictive accuracy of the composite GRACE score.

Factors affecting prognosis

Age

As the age increased, the chance of an event occurring also increased (Figure 2). In the multivariate analysis, age >50 years

Table 1
Baseline characteristics.

Variable	Number/average (%)
Age	59.5
Sex	
Male	172 (73.1)
Female	63 (26.8)
Risk factors	
Diabetes mellitus	125 (53.1)
Hypertension	137 (58.2)
Smoking	70 (29.7)
Dyslipidaemia	74 (31.4)
Family history of IHD	18 (7.6)
Previous history of	
IHD	70 (29.7)
PCI	12 (5.1)
CABG	6 (2.5)
Myocardial infarction	10 (4.2)
Peripheral arterial disease	14 (5.9)
TIA/stroke	12 (5.1)
Previous treatment	
Aspirin	55 (23.4)
Clopidogrel	46 (19.5)
Beta-blockers	46 (19.5)
ACEIs	33 (14.0)
ARB	18 (7.6)
CCB	12 (5.1)
Statin	49 (20.8)
Nitrates	4 (1.7)
Admission findings	
Heart rate (bpm)	86.96
Systolic BP (mmHg)	136.44
Diastolic BP (mmHg)	85.33
Killips class	
I	126 (53.6)
II	59 (25.1)
III	40 (17)
IV	10 (4.2)
LVEF	
<40	31 (13.1)
≥40	204 (86.9)
In-hospital treatment	
Aspirin	229 (97.4)
Clopidogrel	230 (97.8)
GPIIb–IIIa inhibitor	17 (7.2)
LMWH/unfractionated heparin	220 (93.6)
Thrombolysis	45/108 (45.3)
Beta-blocker	178 (75.7)
ACEI	185 (78.7)
ARB	18 (7.6)
Statin	235 (100)
CAG	125 (53.1)
Revascularisation	41 (17.4)
Lipids	
Total cholesterol (mg/dL)	167.87
LDL (mg/dL)	104.54
HDL (mg/dL)	34.63
Triglycerides (mg/dL)	149.26
Serum creatinine (mg/dL)	1.34
C-reactive protein >0.5	91/154 (59)

ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin-receptor blocker, BP: blood pressure, CABG: coronary artery bypass graft, CAG: coronary angiogram, GP: glycoprotein, HDL: high-density lipoprotein, IHD: ischaemic heart disease, LDL: low-density lipoprotein, LMWH: low molecular weight heparin, LVEF: left ventricular ejection fraction, PCI: percutaneous coronary intervention, TIA: transient ischaemic attack.

showed very good association with the occurrence of death/MI (OR 3.62, $P=0.072$).

Systolic blood pressure

Mean SBP in the patients with events was 121.24 ± 27.67 mmHg and in those without events was 137.93 ± 32.27 mmHg and this difference was statistically significant ($P=0.023$). In the multivariate analysis, decreasing SBP was associated with events (OR 7.93, $P=0.005$).

Heart rate

Mean heart rate (HR) in the study population was 86.96 bpm. In the patients, with and without events it was 88.29 ± 16.14 bpm and 86.83 ± 20.71 bpm, respectively and this was not statistically significant.

Killips class

There was a steady increase in the likelihood of an event with worsening Killips class at presentation (Figure 3). 20% of patients in class IV had an event and this was strongly associated with a worse prognosis (OR 2.71, $P=NS$) when compared to patients presenting in any other class.

Serum creatinine

The average serum creatinine in the general population was 1.34 mg/dL while in those with events it was 1.57 mg/dL. 14.5% of patients with serum creatinine >1.4 mg/dL suffered an event while only 7.4% of patients with serum creatinine ≤1.4 mg/dL reached the endpoint. This showed a trend towards statistical significance (OR 4.14, $P=0.05$).

ST-segment deviation

All events except one occurred in patients with ST-segment deviation (elevation/depression >0.5 mm). Patients with ST-segment deviation were significantly more likely to have an event (OR 7.79, CI 1.02–59.35). As expected, patients with ST-segment elevation had a worse prognosis in both univariate (OR 5.12, $P=0.002$) and multivariate analysis (OR 12.12, $P=0.011$).

Cardiac biomarkers

All patients with a positive cardiac biomarker within 6 hours of admission were compared with those with a negative marker. All the events occurred in patients with positive cardiac biomarkers (Cardiac Troponins/CPK-MB). Thus, cardiac biomarker positivity was significantly associated with events (OR >6.52, $P=0.01$).

Table 2

Univariate analysis for association of risk factors with event (death/myocardial infarction).

Risk factors	Event: absent (n=214) No (%)	Event: present (n=21) No (%)	P value	OR	95% CI
Age > 50 yr	162 (75.7)	17 (80.95)	0.738	0.84	0.31–2.28
Sex					
Male	155 (72.4)	17 (80.9)	0.400	1.61	0.52–5.05
Female	59 (27.6)	4 (19.1)	0.400	0.62	0.19–1.93
Diabetes mellitus	116 (54.2)	9 (42.9)	0.320	0.63	0.26–1.57
Hypertension	126 (58.9)	12 (57.1)	0.877	0.93	0.38–2.30
Dyslipidaemia	70 (32.7)	5 (23.8)	0.404	0.64	0.23–1.63
Smoking	64 (29.9)	6 (28.6)	0.898	0.94	0.35–2.52
Previous history of IHD/CAG/CABG/PCI	68 (31.8)	4 (19.1)	0.227	0.51	0.16–1.56
Family history of IHD	16 (7.5)	2 (9.5)	0.667	1.30	0.28–6.09
TIA/stroke	11 (5.1)	1 (4.8)	1.000	0.92	0.11–7.52
Peripheral arterial disease	12 (5.6)	2 (9.5)	0.362	1.77	0.37–8.51
ST-depression	67 (31.3)	4 (19.1)	0.243	0.52	0.17–1.59
ST-elevation	97 (45.3)	17 (80.9)	0.002**	5.12	1.66–15.74
ST-depression+elevation	154 (71.9)	20 (95.2)	0.020*	7.79	1.02–59.35
Cardiac biomarkers	163 (76.2)	21 (100)	0.010*	>6.52	–
Killips	8 (3.7)	2 (9.5)	0.221	2.71	0.53–13.68
Total cholesterol >200 mg/dL	51 (23.8)	3 (14.3)	0.422	0.53	0.15–1.88
LDL >100 mg/dL	110 (51.4)	10 (47.6)	0.741	0.86	0.35–2.11
HDL <40 mg/dL	159 (74.3)	17 (80.9)	0.502	1.47	0.47–4.56
Triglycerides >150 mg/dL	82 (38.3)	7 (33.3)	0.653	0.80	0.31–2.08
Serum creatinine	41 (19.2)	7 (33.3)	0.154	2.11	0.81–5.56
Ejection fraction <40	25 (11.7)	6 (28.6)	0.041*	3.02	1.07–8.81
C-reactive protein >0.5	83/139 (59.7)	8/15 (53.3)	0.633	0.77	0.26–2.25
GRACE ≥217	85 (39.7)	15 (71.4)	0.005**	3.79	1.42–10.17

CABG: coronary artery bypass graft, CAG: coronary angiogram, CI: confidence interval, HDL: high-density lipoprotein, IHD: ischaemic heart disease, LDL: low-density lipoprotein. OR: odds ratio, PCI: percutaneous coronary intervention, TIA: transient ischaemic attack.

Other factors

Other factors which showed a very good association with events in the multivariate analysis included male sex (OR 2.54, $P=NS$), a past history of HTN (OR 2.26, $P=NS$), dyslipidaemia (OR 4.46, $P=NS$), and a family history of ischaemic heart disease (IHD) (OR 5.67, $P=NS$). A higher diastolic BP at admission was associated with events. In addition, the ejection fraction (EF) on echocardiogram also strongly predicted chances of death/MI with a lower EF conferring a worse prognosis.

GRACE score as a prognostic tool

As the GRACE score increased, the likelihood of a patient developing an event (death/MI) also increased (Figure 4). The mean $\pm$ SD was 204.73 ± 72.77 .

Patients who reached an endpoint had an average score of 260.38 while in those who did not reach endpoint the score was 199.27; the best cut-off value for predicting events was a score of 217.

The area under curve (AUC) for the GRACE score was 0.752 (Figure 5) which represents a good discriminatory accuracy.

Correlation of GRACE score with coronary angiography

A total of 125 patients (53.9%) underwent coronary angiography. 45/100 (45%) patients with a GRACE score of ≥ 217 underwent the procedure while 80/135 (59.25%) patients who had a score of < 217 underwent the procedure. Those patients with a score of < 217 were significantly more likely to have normal/non-obstructive/single vessel disease than patients with score of ≥ 217 , who were more likely to have double/triple vessel disease ($P=0.0009$).

Discussion

This study of patients of ACS at our centre, confirms the prognostic value of several baseline characteristics reported in other studies. It further corroborates the GRACE registry findings that the GRACE score is a good tool to predict in-hospital death/MI across all cases of ACS.

In our study, increasing age showed a very good association with events and patients aged > 50 years were at a high-risk. A low cut-off age (50 years) to compare prognosis was

Table 3

Multivariate logistic regression analysis for predicting the event (death/myocardial infarction).

Risk factors	Logit coefficient	SE	Wald	P value	Adj OR
Age > 50 yr	1.29	0.73	3.11	0.078 ⁺	3.62
Sex: male	0.93	0.89	1.09	0.296	2.54
Diabetes mellitus	−0.39	0.71	0.30	0.585	0.68
Hypertension	0.81	0.74	1.20	0.273	2.26
Dyslipidaemia	1.50	1.04	2.08	0.150	4.46
Smoking	−0.41	0.76	0.29	0.587	0.66
Previous history of IHD/CAG	−3.24	1.63	3.97	0.046 [*]	0.04
Family history of IHD	1.73	1.07	2.63	0.105	5.67
TIA/stroke	0.60	1.37	0.19	0.663	1.82
Peripheral arterial disease	−0.25	1.37	0.03	0.858	0.78
Pulse rate	−0.01	0.02	0.22	0.638	0.99
Systolic BP	−0.06	0.02	7.93	0.005 ^{**}	0.94
Diastolic BP	0.10	0.04	7.75	0.005 ^{**}	1.11
Total cholesterol > 200 mg/dL	−1.82	1.13	2.58	0.108	0.16
LDL > 100 mg/dL	−0.18	0.74	0.06	0.805	0.83
HDL < 40 mg/dL	0.12	0.78	0.02	0.880	1.13
Triglycerides > 150 mg/dL	0.19	0.74	0.07	0.796	1.21
Serum creatinine (> 1.4)	1.42	0.75	3.59	0.050 [*]	4.14
Ejection fraction < 40%	1.42	0.81	3.04	0.081 ⁺	4.14
ST-depression	0.01	0.91	0	0.992	1.01
ST-elevation	2.50	0.98	6.53	0.011 [*]	12.12
Aspirin	1.38	1.65	0.70	0.401	3.98
Statin	0.73	1.44	0.26	0.610	2.09
Beta-blocker	−0.44	1.07	0.17	0.679	0.64
ACEI/ARB	1.03	0.94	1.20	0.274	2.80

*Statistically significant, **highly statistically significant, +strong association tending towards statistical significance. ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin-receptor blocker, BP: blood pressure, CAG: coronary angiogram, HDL: high-density lipoprotein, IHD: ischaemic heart disease, LDL: low-density lipoprotein. OR: odds ratio, PCI: percutaneous coronary intervention, SE: standard error, TIA: transient ischaemic attack.

Figure 2 Event occurrence with increasing age.

taken considering the fact that CAD occurs in Indians at a younger age.^{7,8} In the GRACE registry, age has been shown to be a statistically significant predictor of events for every 10 years increase in age (OR 1.7/decade).

Like in the GRACE registry (OR 1.4 for every 10 mmHg decrease), our study also showed that a lower SBP at admission is significantly associated with more events.

In this study, a patient presenting in a higher Killips class was at higher risk for death/MI with the highest risk for

Figure 3 Events according to Killips class.

Killips class IV. In the GRACE study also, increasing Killips class predicted worse prognosis (OR 2/class).

An increasing serum creatinine level has been shown to be prognostically significant in a number of studies.^{9,10} In the GRACE registry, the risk increased for every 1 mg/dL increase in serum creatinine, while in our study, patients with an initial level > 1.4 mg/dL had a worse prognosis showing a trend towards statistical significance.

ST-segment deviation and positive cardiac biomarkers have long been shown to predict events in cases of ACS. In GRACE

Figure 4 Events in various quartiles of GRACE score.

Figure 5 Receiver operating characteristics (ROC) curve for GRACE score for predicting event.

Figure 6 GRACE score correlation with angiographic findings. DVD: double vessel coronary artery disease, SVD: single vessel coronary artery disease, TVD: triple vessel coronary artery disease.

registry also, ST-segment deviation (OR 1.8) and positive cardiac markers (OR 1.6) predicted worse prognosis. Our analysis was consistent with these findings and showed statistical significance in predicting events when both these variables were assessed.

One other component of the GRACE score, i.e. presentation of heart rate did not reach statistical significance in our study, although the patients with events had a marginally higher average heart rate. In the GRACE registry, increasing HR was associated with worse outcome (OR 1.3/30 beats/min increase). Cardiac arrest at presentation as a prognostic variable could not be assessed as only one patient had a cardiac arrest at presentation.

When the GRACE score was used in this cohort, a score of 217 represented the best cut-off value to predict death/MI. The C statistic for the score in the GRACE registry was 0.84 while in our study it was slightly lower but achieved a good discriminatory value (AUC=0.752). Thus it has been shown to be a good prognostic tool to predict death/MI.

It has been reported in various studies that the patients at high-risk are very often less likely to undergo intervention.¹¹ In our study, 45% of patients with a score ≥ 217 underwent CAG while 59.25% of patients with score < 217 underwent the procedure. Patients with a higher risk score were significantly more likely to have more severe disease than those with a lower score.

Traditionally, ACS have been classified as those with ST-elevation and those without ST-elevation and risk scores have been developed separately for the two categories. However, very often the patients of ACS represent a continuum and may be difficult to categorise into either group. The GRACE score is common for all cases of ACS. The GRACE score incorporates newer prognostic variables like serum creatinine and cardiac arrest at presentation which have been shown to be most important in a Medicare database of patients with acute MI (AMI).¹⁰ Moreover, the GRACE score has been developed from registry data and thus is more representative of the general population as compared to scores which have been developed from clinical databases. These clinical databases may suffer from selection bias due to exclusion of high-risk patients like those with coronary heart failure (CHF) or raised serum creatinine.¹²

The GRACE model can be downloaded from the GRACE registry site in a format that can be used on computer as well as Personal Digital Assistants (PDA).

Important to a prognostic score are accuracy, generalisability, and ease of use. The GRACE score fulfills these criteria and also includes newer prognostic variables.

Limitations

On account of a smaller database and fewer events as compared to large studies, some prognostic variables may not have reached statistical significance despite showing good association with events. Risk stratification is a continuous process and in actual practice, may require a recalculation of the score during hospital stay for a more dynamic assessment.

Conclusion

Baseline characteristics that constitute the GRACE score independently predict adverse events. As validated in this study, the GRACE score correlates well with the in-hospital events. Moreover, increasing GRACE score correlated with a more severe disease on CAG. The GRACE score can thus be used in all cases of ACS to predict prognosis and to guide the management by identifying the patients at high-risk who are likely to benefit from aggressive management.

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