Validation of the GRACE Risk Score to Predict in-Hospital Mortality in Patients with ST Segment Elevation Myocardial Infarction in Thailand

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Background: *The GRACE risk score (GRS) is a validated risk score to predict mortality in acute coronary syndrome patients. However, data on the use of the GRS in Asian patients are limited. The authors assessed the validity of this risk score in a contemporary cohort of patients with ST segment elevation myocardial infarction (STEMI) admitted to a tertiary care hospital in Thailand.*

Material and Method: *From June 1, 2008 through May 31, 2010, 209 consecutive patients with STEMI were prospectively enrolled. The GRS was calculated for each patient. Patients were stratified into three GRACE risk tertiles: high, intermediate and low risk groups. In-hospital mortality rate was assessed and compared to the GRS predicted mortality.*

Results: *The mean GRS was 161 $\pm$ 46.2 and the overall in-hospital mortality was 12.4%. Using the GRS, 103 (49.3%) patients were stratified to the high-risk group ($\geq$ 155 points), 59 (28.2%) patients to the intermediate-risk group (126-154 points) and 47 (22.5%) patients to the low-risk group ($\leq$ 125 points). The observed in-hospital mortality rate was 23.3% (95% CI 16.2-32.3) in the high-risk group and 3.4% (95% CI 0.94-11.5) in the intermediate-risk group. None of the patients in the low risk group died, 0% (95% CI 0-7.9) ($p < 0.001$, low risk vs. high risk; $p = 0.001$ intermediate risk vs. high risk)*

Conclusion: *Use of the GRS in STEMI patients for predicting in-hospital mortality was validated. At the author's institute, the GRS is a useful tool to predict in-hospital death in STEMI patients.*

Keywords: *Acute coronary syndrome, ST-segment elevation myocardial infarction, GRACE, Risk stratification*

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Acute coronary syndrome (ACS) is a significant public health problem worldwide, including Thailand. Data from the Thai ACS registry in 2007 demonstrated that 40% of ACS patients are diagnosed with ST segment elevation myocardial infarction (STEMI) and the in-hospital mortality rate was alarmingly high at 17%[1,2].

STEMI patients are candidates for reperfusion therapy either by thrombolytic therapy or primary percutaneous coronary intervention (PCI) to restore flow in the occluded infarct related artery. Both the United States and European guidelines for the management of patients with ACS recommend that highest risk patients should receive the most aggressive therapy[3,4]. Therefore, prompt identification of high-risk patients at the time of presentation is a crucial step. Although patient's clinical characteristics may be associated with increased risk for adverse outcomes, clinicians must take into account multiple factors all together to accurately assess risk. Risk prediction models for patients with STEMI are considered fundamental tools to aid clinicians in the process of risk stratification.

An ideal risk prediction model must be reliable, accurate, simple to use and it must be representative of the population to which it is to be applied. Many multivariate models have been developed to predict mortality of STEMI patients by identifying independent clinical predictors and quantifying their relative contribution to mortality risk. The GRACE (Global Registry of Acute Coronary Events) investigators have published models derived from the GRACE registry to predict mortality in-hospital as well as at 6 months[5-7]. The GRACE risk score (GRS) is a wildely used model which was developed and validated to predict death in the whole spectrum of ACS patients. It is a predictive logical model which uses eight prognostic variables: age, pulse rate at presentation, systolic blood pressure at presentation, serum creatinine level at presentation,

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Killip classification, ST-segment changes on presenting electrocardiogram, elevated cardiac biomarker and cardiac arrest on admission[6]. Points are scored according to set variables for each element and the sum of the points can be simply calculated using a mobile electronic device which then equates to the GRS. Three risk categories were established using the cutoff points set out in the GRACE study. Predicted in-hospital mortality is < 2% in low-risk, 2-5% in intermediate-risk and > 5% in high-risk patient categories.

Other STEMI risk scores such as the TIMI STEMI risk score[8], PAMI[9] and CADILLAC models[10] were developed from patients that met clearly defined specific enrollment criteria in randomized clinical trials which tend to exclude high-risk patients. In contrast, the GRS was derived from an unselected ACS population from a "real world" multinational registry[6]. Hence, the GRS has a more generalized application in daily clinical practice.

The GRACE population comprised of patients from 14 countries including Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Spain, the United Kingdom and the United States. Notably, Asian countries did not participate in GRACE. Moreover, most published risk models are based on Western populations, thus their application to local populations should ideally be validated before incorporation into clinical use. Recently, Chan MY et al, has reported that the GRACE score under estimated in-hospital mortality in a multi ethnic Asian cohort of ACS patients from Singapore[11]. The present study was undertaken to determine whether the GRS can reliably predict in-hospital mortality in a contemporary Thai population with STEMI.

Material and Method

The present study is a single-center, non-comparative prospective registry. From June 1, 2008 through May 31, 2010, data from all patients aged 18 years old and older who presented within 24 hours of STEMI to our institute were collected prospectively and consecutively. STEMI was diagnosed by having elevated biochemical markers of myocardial necrosis and ECG changes demonstrating either 1) ST-segment elevation $\geq$ 1 mm in two consecutive leads or 2) new or presumed new left bundle branch block.

Data collection

Patient's data on clinical, demographic, treatment and in-hospital outcome were collected by cardiac nurses and/or cardiologists. Data were transcribed onto standard data forms and subsequently to a web-based database. Demographic variables included gender and age. Dyslipidemia, diabetes, hypertension, current tobacco use and family history were used to characterize risk factors. Diabetes was diagnosed when the patient's fasting plasma glucose was 126 mg/dl or higher on at least two occasions or there was the presence of a history of diabetes treated either with dietary control or ant diabetic medication. Hypertension was defined as systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg or a previous diagnosis of hypertension. Dyslipidemia was diagnosed when total cholesterol was > 200 mg/dL, LDL cholesterol > 130 mg/dL, HDL cholesterol < 40 mg/dL or if there was a previous diagnosis of dyslipidemia and/or when currently being treated with a lipid lowering agent. Current tobacco use was defined by the habitual use of tobacco within 1 month of index hospital admission. Congestive heart failure included patients with Killip Class II or III. Killip class II was defined as bibasilar rales in < 50% of lung fields or presence of an S3 gallop whereas Killip class III was defined as bibasilar rales in > 50% of lung fields. Cardiogenic shock (Killip class IV) was defined as symptomatic hypoperfusion with systolic blood pressure < 90 mmHg.

The GRS to predict in-hospital mortality was calculated for each individual patient. Patients were stratified into three GRACE risk tertiles using the cutoff points set out in the GRACE study. A GRS > 155 points defines high-risk, 126-154 points defines intermediate-risk and < 126 points defines the low-risk category. GRACE predicted in-hospital mortality is < 2% in low-risk, 2-5% in intermediate-risk and > 5% in high-risk patient categories. In-hospital all-cause mortality rate was assessed and compared to the GRS predicted mortality.

The protocol was approved by the hospital ethics committee and is in accordance with the Declaration of Helsinki. Informed consent was obtained from every patient.

Statistical analysis

The outcome measure for the GRS was all-cause mortality during the index hospitalization. The Chi-square test was used to determine the association between GRACE risk tertiles and observed mortality rate in each group. Quantitative variables are presented as mean (standard deviation) or median (P25, P75). Qualitative variables are expressed as frequencies and

percentages with a 95% confidence level. The one way ANOVA test and Kruskal-Wallis H test were used as applicable in order to compare the GRACE risk tertiles and the Kolmogorov-Sminov test was used to check normality of data. For all comparisons, p-value of 0.05 (two-tailed) was considered statistically significant. Data were analyzed with PASW Statistics V.18.0 (IBM Corporation, New York, USA).

Results

During the 2-year period, 209 patients with STEMI were enrolled. The mean GRS was 161 ± 46.2. According to the calculated GRS, patients were categorized into three risk tertiles 103 (49.3%) patients were assigned to the high-risk group (> 155 points), 59 (28.2%) patients to the intermediate-risk group (126-154 points) and 47 (22.5%) patients to the low-risk group (< 125 points) (Table 1).

The baseline characteristics of the patients are shown in Table 2. The mean age was 59.6 years old and 74.6% were males. Patients in the high-risk group were significantly older than the other group. Although males were predominant, the high-risk group had a higher percentage of females than the other groups. There was a high prevalence of diabetes, hypertension and dyslipidemia. Up to 60% of the low-risk patients were current smokers whereas the high-risk patients had a significantly lower percentage of current smokers. By electrocardiography, 59.2% were anterior infarcts and 40.8% were inferior infarcts with no significant differences among the risk tertiles. Table 3 demonstrates the variables used to calculate the GRS.

Presence of multivessel coronary disease, the utilization of an intra-aortic balloon counter pulsation and in-hospital coronary artery bypass graft surgery were significantly greater in the high-risk group. There were no significant differences in the rate of primary PCI among the groups, whereas fibrinolytic therapy

Table 1. Risk tertiles of patients categorized by the GRACE risk scores

	GRACE risk score Mean (points) ± SD	n (%)
Low risk ≤125 points	110.3 ± 9.8	47 (22.5%)
Intermediate risk 126-154 points	139.1 ± 8.1	59 (28.2%)
High risk ≥155 points	196.9 ± 38.8	103 (49.3%)
Total	161 ± 46.2	209

Table 2. Baseline characteristics categorized by tertiles of the GRACE risk score

	Low risk n = 47	Intermediate risk n = 59	High risk n = 103	Total patients n = 209	p-value
Male, n (%)	41 (87.2)	49 (83.1)	66 (64.1)	156 (74.6)	0.002[1]
Age (years), mean ± SD	48.3 ± 8.7	57.1 ± 9.3	66.3 ± 12.6	59.6 ± 13.0	< 0.001[2]
Diabetes mellitus, n (%)	12 (25.5)	13 (22)	41 (39.8)	66 (31.6)	0.039[3]
HTN, n (%)	20 (42.6)	35 (59.3)	72 (69.9)	127 (60.5)	0.006[4]
Current tobacco use, n (%)	28 (59.6)	28 (47.5)	30 (29.1)	86 (41.1)	0.001[1]
Dyslipidemia, n (%)	28 (59.6)	36 (61)	63 (61.2)	127 (60.8)	0.623
Previous MI, n (%)	5 (10.6)	4 (6.8)	20 (19.4)	29 (13.9)	0.062
Previous PCI, n (%)	4 (8.5)	3 (5.1)	14 (13.6)	2 (10)	0.230
Previous CABG, n (%)	1 (2.1)	0	3 (2.9)	4 (1.9)	0.598

Pair wise comparision

[1] low risk vs. high risk and int risk vs. high risk, $p < 0.05$

[2] low risk vs. int risk and low risk vs. high risk and int risk vs. high risk, $p < 0.05$

[3] int risk vs high risk, $p < 0.05$

[4] low risk vs high risk, $p < 0.05$

HTN: hypertension, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft surgery

Table 3. Variables of the GRS categorized by tertiles of the GRACE risk score

	Low risk n = 47	Intermediate risk n = 59	High risk n = 103	Total patients n = 209
Heart failure, n (%)	1 (2.1%)	4 (6.5%)	59 (57.3%)	64 (30.6%)
Killip classification, mean ± SD	1 ± 0.1	1.1 ± 0.3	2.3 ± 1.2	1.6 ± 1.0
Cardiogenic shock, n (%)	0 (0%)	2 (3.4%)	25 (24.3%)	27 (12.9%)
Cardiac arrest, n (%)	0 (0%)	0 (0%)	21 (20.4%)	21 (10.0%)
SBP (mmHg), mean ± SD	148.8 ± 24.6	131.9 ± 28.9	119.6 ± 53.7	129.6 ± 43.7
HR (bpm), mean ± SD	75.3 ± 15.6	78.8 ± 16.5	83.8 ± 36.9	80.5 ± 28.4
Cr (mg/dL), mean ± SD	0.97 ± 0.19	1.01 ± 0.28	1.636 ± 1.48	1.31 ± 1.10

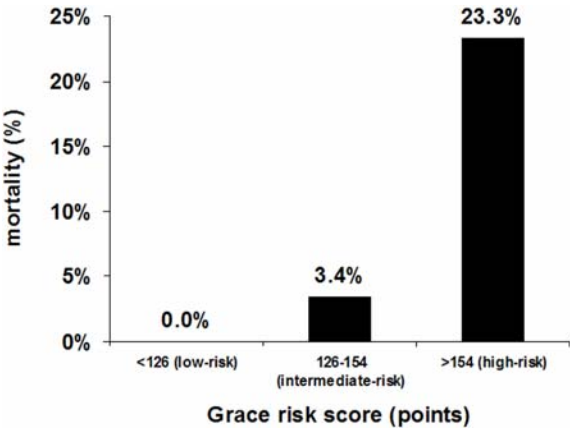
SBP: systolic blood pressure, HR: heart rate, Cr: creatinine

Table 4. In-hospital manangement by GRACE risk tertiles

	Low risk n = 47	Intermediate risk n = 59	High risk n = 103	Total patients n = 209	p-value
Primary PCI, n (%)	26 (55.3)	34 (57.6)	66 (64)	126 (60.3)	0.152
Thrombolytic therapy, n (%)	19 (40.4)	16 (27.1)	16 (15.5)	51 (24.4)	0.002*
DTB time(minutes), median (P25,P75)	145 (101,201)	102 (81,177)	112 (93,141)	112 (91,173)	0.272
DTN time(minutes), median (P25,P75)	60 (50,73)	40 (35,90)	68 (54,82)	60 (45,76)	0.237
IABP placement, n (%)	2 (4.3)	5 (8.5)	32 (31.1)	39 (18.7)	< 0.001*
Multivessel CAD, n (%)	14 (38.9)	25 (51.0)	60 (64.5)	99 (55.6)	0.007*
LVEF (%), mean ± SD	59 ± 12.0	56.8 ±12.4	46.2 ± 13.5	52.1 ± 14.1	< 0.001*
In-hospital CABG, n (%)	0 (0)	2 (3.4)	10 (9.7)	12 (5.7)	0.032*

*High risk vs. other groups

PCI: percutaneous coronary intervention, DTB: Door to balloon time, DTN: Door to needle time, IABP: intra-aortic balloon pump, CAD: corornary artery disease, LVEF: left-ventricular ejection fraction, CABG: coronary artery bypass graft surgery



Low risk vs. high risk p < 0.001, intermediate risk vs. high risk p = 0.001

Fig. 1 In-hospital mortality rate according to GRACE risk score tertiles

was significantly less frequently administered in the high-risk tertile (Table 4).

The overall in-hospital mortality was 12.4%. The in-hospital mortality rate (Fig. 1) was 23.3% (95% CI 16.2-32.3) in the high-risk group and 3.4% (95% CI 0.94-11.5) in the intermediate-risk group. None of the patients in the low risk group died, 0% (95% CI 0-7.9). (p < 0.001, low risk vs. high risk; p = 0.001 intermediate risk vs. high risk). The observed mortality rate in each tertile was significantly associated with the GRS predicted in-hospital mortality.

Discussion

In the present study, the GRS was an excellent predictor of in-hospital mortality. The in-hospital mortality rate in the high-risk group was extremely high at 23.3%. The intermediate-risk group had a mortality rate of 3.4%, whereas none of the patients in the low risk group died. GRS predicted in-hospital mortality is

< 2% in low-risk, 2-5% in intermediate-risk and > 5% in high-risk patient categories. The observed in-hospital mortality rate in each risk tertile was significantly associated with the GRS that was calculated from characteristics on initial presentation. To our knowledge, this is the first study to validate the use of the GRS in Thai patients with STEMI.

Risk prediction models are designed to identify high-risk patients who benefit the most from aggressive target care. The GRS was developed from an unselected ACS population from a "real world" multinational registry thus representing the broad spectrum of ACS patients[6]. In contrast, the TIMI STEMI risk score[8], PAMI[9] and CADILLAC risk models[10] were developed from patients that met specific enrollment criteria in randomized clinical trials. Thus, the GRS has a more generalized application to patients seen in daily clinical practice and has been validated in many populations of the world including English, Welsh, Canadian and Spanish, ACS populations[12-14]. Nevertheless, Chan MY et al, has reported that the GRACE score underestimated in-hospital mortality in a multiethnic Asian cohort of ACS patients from Singapore[11]. Therefore, validation of risk models with in the local population to which it is to be applied is essential before incorporation into daily clinical use.

Although the patients in the present study more frequently received reperfusion therapy and primary percutaneous coronary intervention, the in-hospital mortality (12.4%) was higher compared to GRACE (8%). Nevertheless, this was lower than the mortality in STEMI patients from the Thai ACS registry (17%)[1,2]. The cause of higher mortality is potentially because the author's institute is an academic referral center and 20% of the STEMI patients were referrals. Thus, the patients may have higher risk profiles than patients treated at community hospitals. This is verified by the high percentage of diabetic patients (31.6% vs. GRACE 21%), patients with cardiac arrest (10% vs. GRACE 1.5%) and with cardiogenic shock (12.9% vs. GRACE 7%) on presentation. Furthermore, disparities in health care delivery systems and socioeconomic status could potentially result in different patient's outcomes.

Presentation with congestive heart failure, cardiogenic shock, cardiac arrest and serious cardiac arrhythmias were significant predictors of in-hospital mortality similar to GRACE. However, history of diabetes, hypertension and dyslipidemia were not associated with increased mortality, presumably due to the limited number of patients. Current tobacco use tended to predict lower mortality as was observed in GRACE. Because high risk patients more frequently had history of previous MI and revascularization, they may have previously received tobacco cessation counselling and quit smoking before the index MI. Supporting this explanation is the finding that significantly fewer patients in the high-risk tertile were current smokers.

Limitations

An important limitation is the limited number of patients in the present study. Data were collected from a single-center academic tertiary care hospital that may not represent all hospitals and medical systems in Thailand. Although risk stratification at the time of hospital presentation is of value, the process of risk stratification should be dynamic and continuously revised based on the patient's clinical course.

Conclusion

In the present study, use of the GRS in STEMI patients for predicting in-hospital mortality was validated in a contemporary cohort of patients with STEMI. These data should encourage physicians to use this risk stratification tool for the appropriate management and treatment of patients with STEMI. Those with higher risk scores should be treated with more aggressive strategies.

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Potential conflicts of interest

None.

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การใช้ GRACE risk score เพื่อพยากรณ์อัตราการเสียชีวิตในโรงพยาบาลของผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันชนิด ST segment ยกในประเทศไทย

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***ภูมิหลัง**: GRACE risk score (GRS) เป็นเครื่องมือที่ใช้อย่างแพร่หลาย สำหรับประเมินความเสี่ยงที่จะเสียชีวิตของผู้ป่วยภาวะกล้ามเนื้อหัวใจขาดเลือดเฉียบพลัน อย่างไรก็ตามข้อมูลการใช้ GRS ในผู้ป่วยเชื้อชาติเอเชียมีจำกัด การศึกษานี้เป็นการประเมินการใช้ GRS ในผู้ป่วยภาวะกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันชนิด ST-segment ยก (ST segment elevation myocardial infarction, STEMI) ที่รักษาไว้ในโรงพยาบาลระดับตติยภูมิแห่งหนึ่งในประเทศไทย*

***วัสดุและวิธีการ**: การศึกษานี้เป็นโครงการศึกษาไปข้างหน้าในผู้ป่วยทุกรายที่มีอาการมาภายใน 24 ชั่วโมง ตั้งแต่วันที่ 1 มิถุนายน พ.ศ. 2551 ถึงวันที่ 31 พฤษภาคม พ.ศ. 2553 มีผู้ป่วยจำนวน 209 ราย ทุกรายได้รับการคำนวณหาค่า GRS และแบ่งผู้ป่วยเป็น 3 กลุ่ม ตามค่า GRS เป็นกลุ่มความเสี่ยงสูง, ปานกลางและต่ำ อัตราที่ผู้ป่วยเสียชีวิตในโรงพยาบาลได้รับการเปรียบเทียบกับค่าอัตราเสียชีวิตที่ประเมินจากค่า GRS*

***ผลการศึกษา**: โดยรวมค่า GRS โดยเฉลี่ยอยู่ที่ 161 ± 46.2 และอัตราการเสียชีวิตของผู้ป่วยในโรงพยาบาลร้อยละ 12.4 เมื่อใช้ค่า GRS สามารถแบ่งผู้ป่วย 103 (ร้อยละ 49.3) ราย เป็นกลุ่มความเสี่ยงสูง (ค่า ≥ 155 คะแนน), ผู้ป่วย 59 (ร้อยละ 29.2) ราย เป็นกลุ่มความเสี่ยงปานกลาง (ค่าคะแนน 126-154) และ 47 (ร้อยละ 22.5) ราย เป็นกลุ่มความเสี่ยงต่ำ (ค่าคะแนน ≤ 125) อัตราเสียชีวิตในโรงพยาบาลเป็นดังนี้ กลุ่มเสี่ยงสูง 23.3% (95% CI 16.2-32.3), กลุ่มเสี่ยงปานกลาง 3.4% (95% CI 0.94-11.5) และในกลุ่มเสี่ยงต่ำไม่มีผู้ป่วยเสียชีวิตเลย (95% CI 0-7.9) (p < 0.001 กลุ่มเสี่ยงต่ำเทียบกับเสี่ยงสูง; p = 0.001) กลุ่มเสี่ยงปานกลางเทียบกับกลุ่มเสี่ยงสูง)*

***สรุป**: ในโรงพยาบาลของผู้นิพนธ์ GRS เป็นเครื่องมือที่มีประโยชน์ในผู้ป่วย STEMI สำหรับประเมินโอกาสเสียชีวิตในโรงพยาบาล*