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## Research Article

# Performance of the GRACE 2.0 and EPICOR risk scores for predicting 1-year postdischarge mortality in Vietnamese patients with acute coronary syndrome

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GRACE 2.0, EPICOR, mortality risk scores, acute coronary syndrome, Vietnamese.

**ABSTRACT**

We aimed to determine the performance of the Global Registry of Acute Coronary Events (GRACE) risk score version 2.0, and the long-term follow up of antithrombotic management patterns in acute coronary syndrome patients (EPICOR) risk score for predicting 1-year postdischarge mortality in patients with acute coronary syndrome (ACS) in Vietnam. A prospective cohort study was conducted on 455 patients who were discharged with an ACS diagnosis from two hospitals in Can Tho, and one in Ho Chi Minh City. Online simplified EPICOR and GRACE 2.0 calculators were used to assess the expected risk of death. We compared the performance of predicting 1-year mortality between GRACE 2.0 and EPICOR risk scores by using the Hosmer-Lemeshow test, the area under the curve (AUC), and the De-Long test. The proportions of low-risk group, moderate-risk group, and high-risk group for GRACE were 31%, 42%, and 27%, respectively. Actual mortality rates for the low, medium and high-risk groups were 3.6%, 9.4%, and 19.4%. The proportions of low-risk and high-risk patients for EPICOR were 92.0% and 8.0%, respectively. The actual mortality rate of the high-risk group was 31.4%, and of the low-risk group 8.6%. Hosmer-Lemeshow test results of the GRACE 2.0 and EPICOR were 0.337 and 0.001, respectively. The AUC results of the GRACE 2.0 and EPICOR were 0.703 and 0.752 respectively, and the De-Long test with  $p = 0.0532$ . In conclusion, the GRACE 2.0 was better than EPICOR in predicting 1-year postdischarge mortality in Vietnamese patients with ACS.

**1. INTRODUCTION**

Ischemic heart disease (IHD) is the major cause of mortality worldwide, with an increasing trend from 7.3 million in 2007 to 8.93 million in 2017<sup>1</sup>. IHD remains a health challenge for the public in developing countries. Acute coronary syndrome (ACS) is the main factor that leads to IHD deaths<sup>2</sup>. For ACS treatment international guidelines recommended using a combination of antiplatelet agents, anticoagulants, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers<sup>3-5</sup>. The pharmacological medication significantly reduced the in-hospital and postdischarge mortality of ACS<sup>6-8</sup>. However, ACS patients had

different medical histories, physical examinations, and electrocardiographic and biochemical cardiac marker data. These factors also affect ACS risk stratification.

ACS risk stratification plays an important role in disease management<sup>4</sup>. It helps physicians to classify ACS patients as well as to choose an appropriate management strategy to limit short-term and long-term events<sup>5</sup>. There are many models of risk stratification for ACS. The GRACE score is an effective model to predict in-hospital and postdischarge deaths<sup>9-13</sup>. Until now, the GRACE score has been the most popular model and is recommended in international guidelines<sup>4,14</sup>. The GRACE score has 2 versions. The GRACE 1.0 was designed in 2000 to estimate in-hospital and 6-month postdischarge mortality<sup>9,10</sup>. The GRACE 2.0 was updated by Fox KA *et al.* to heighten the performance of GRACE 1.0. A more modern tool, the GRACE 2.0 is more accurate than the old version in predicting short and long-term mortality<sup>11,12</sup>.

The EPICOR is a new risk score, designed to calculate one-year mortality in survivors<sup>15,16</sup>. The validated research of the EPICOR score is a new study conducted on an international cohort<sup>16</sup>. There have previously been no studies to estimate the performance of EPICOR in Vietnam. In this study we compared the GRACE 2.0 and EPICOR risk scores on a Vietnamese cohort. According to S. Pocock *et al.*, it would be useful to compare directly the GRACE 2.0 and EPICOR risk models in an independent cohort of ACS patients followed after hospital discharge<sup>16</sup>. Therefore, the aim of this study was to determine the performance of GRACE 2.0 and EPICOR risk scores for predicting 1-year postdischarge mortality in Vietnamese patients with ACS.

## 2. MATERIALS AND METHODS

### 2.1. Study population

This prospective cohort study was conducted in patients discharged with a diagnosis of ACS from two public hospitals in Can Tho City and one public hospital in Ho Chi Minh City. We calculated the sample size for estimating a single proportion of the high-risk group in the study population with 5% absolute precision and 95% confidence. Assuming a high-risk group proportion of 50% and a 15% loss to follow-up, we should recruit at least 443 patients. Patients included as eligible were admitted

between January and October 2015 and survived during hospitalization with one of the following discharge diagnoses (according to coding of the International Classification of Diseases, 10<sup>th</sup> revision (ICD-10)): unstable angina (I20.0), acute myocardial infarction (I21) consisting of non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI), or subsequent myocardial infarction (I22)<sup>17</sup>, after receiving a complete treatment. Patients were followed for one year after discharge. The follow-up period ended in October 2016. We excluded patients for whom relevant data were missing or who had initially been admitted to another hospital. The research was approved by the institutional review boards and is in line with Vietnamese regulations. For all participants the relevant data were recorded, and the mortality risk calculated and classified by GRACE and EPICOR risk scores.

### 2.2. Study design and data analysis

The GRACE 2.0 score was calculated by assigning the appropriate number of points for each of the 8 factors: age, heart rate, systolic blood pressure, serum creatinine concentration or renal failure, cardiac arrest at admission, ST-segment deviation, elevated cardiac biomarkers of necrosis, and Killip class or diuretic usage<sup>13</sup>. We calculated by using an online calculator <http://www.gracescore.org/WebSite/WebVersion.aspx>. Patients were classified into three risk groups: low, medium and high-risk groups. The GRACE 2.0 score was categorized using common cut-off points: <4% (low-risk), 4%-12% (medium risk) and >12% (high-risk)<sup>18</sup>.

The EPICOR score consists of the following factors: age, gender, ACS subtype, ejection fraction at hospital admission, serum creatinine at admission, hemoglobin and fasting blood glucose at admission, interventions during admission, EuroQol-5D (EQ-5D) score upon discharge (to characterize current health status), cardiac complications in hospital, history of chronic obstructive pulmonary disease (COPD) or other chronic lung disease, history of peripheral vascular disease, and on diuretic at discharge<sup>16</sup>. The EPICOR score was calculated using <http://www.acsrisk.org/calculator>. Patients were divided into 6 groups according to risk: groups 1 - 4 were regarded as low-risk (mortality risk < 6.3%), group 5 (mortality risk > 6.3 %) and group 6 (mortality risk > 18.2%) were regarded as high-risk<sup>16</sup>.

### 2.3. Statistical analysis

After classifying the risk of death in 1 year by GRACE and EPICOR risk scores, we evaluated the accuracy of two risk scores by two indicators: calibration and discrimination. The calibration was described using the Hosmer-Lemeshow test<sup>19</sup>. A *p*-value less than 0.05 was considered to be a statistically significant difference between the prediction and actual rate, indicating a poor prediction capacity of the model. The assessment of discrimination capacity was calculated by the AUC<sup>20</sup>. The AUC of a model with good discrimination was more than 0.7. We used the De-Long test to compare the AUC for the two risk scores and determine whether there was any difference between the two scores<sup>21</sup>. Statistical analysis was performed

using SPSS 22, MedCalc version 18.5, and Microsoft Excel 2010.

### 3. RESULTS

A total of 455 patients with ACS were included in the analysis. Their mean age was  $67.6 \pm 13$  years (range 55 to 81 years), and 79.9% had health insurance. The majority of patients were male (58.9%) and had hypertension (77.6%). One hundred and eighty-seven (41.1%) patients underwent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), and two hundred and sixty-eight (58.9%) had no invasive procedure. The majority of patients had a discharge diagnosis of unstable angina and non-ST-segment elevation ACS (NSTEMI) (76.9%) (Table 1).

**Table 1.** Characteristics of the study population.

Description	Number of patients (N = 455)	Percentage (%)
Age $\geq$ 65	265	58.2
Male	268	58.9
Health Insurance	362	79.9
Number of patients died	47	10.3
<b>In-hospital invasion</b>		
PCI or CABG	187	41.1
Non-invasive	268	58.9
<b>Discharge diagnosis</b>		
Unstable angina/NSTEMI	350	76.9
STEMI	105	23.1
<b>Medical history and comorbidities</b>		
Hypertension	353	77.6
Dyslipidemia	110	24.2
Diabetes	88	19.3
Heart failure	65	14.3
Renal failure	33	7.3
Smoking	161	35.4

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

We compared some characteristics of the groups of those patients who died and those who survived (Table 2). In the group of patients who died, the majority were  $> 65$  years old (80.9%). The rate of mortality in patients with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) was lower than in patients who had not undergone invasive procedures. The rate of heart failure (34%) and renal failure (23.4%) was significantly higher in patients who died than in the group who survived. The proportion of hypertension (89.4 %) tended to be statistically higher in the group who died. Table 2 gives an insight into the

risk factors of ACS.

The proportion of low-risk, moderate-risk, and high-risk groups for GRACE was 31%, 42%, and 27% respectively. The actual mortality rates for the low, medium and high-risk groups were 3.6%, 9.4%, and 19.4%. The proportion of low-risk and high-risk patients for EPICOR was 92.0% and 8.0%, respectively. The actual mortality rate of the high-risk group was 31.4% and of the low-risk group 8.6%. The proportion of risk categories for the GRACE 2.0 and EPICOR scores is shown in Table 3. The results of the performance of the GRACE 2.0 and the EPICOR are shown in Figure 1 and Table 4.

**Table 2.** Characteristics of death and survival patients.

	Group of death patients n (%)	Group of survival patients n (%)	p-value
<b>Number of patients</b>	47 (10.3)	408 (89.7)	
<b>Characteristic</b>			
Older than 65	38 (80.9)	227 (55.6)	0.001
Male	26 (55.3)	242 (59.3)	0.598
Health Insurance	38 (80.9)	324 (79.8)	0.865
<b>In-hospital invasion</b>			
PCI or CABG	9 (19.1)	178 (43.6)	0.001
Non-invasive	38 (80.9)	230 (56.4)	0.001
<b>Discharge diagnosis</b>			
Unstable angina/ NSTEMI	40 (85.1)	310 (76.0)	0.160
STEMI	7 (14.9)	98 (24.0)	0.160
<b>Medical history and comorbidities</b>			
Hypertension	42 (89.4)	311 (76.2)	0.041
Dyslipidemia	6 (12.8)	104 (25.5)	0.054
Diabetes	10 (21.3)	78 (19.1)	0.723
Heart failure	16 (34.0)	49 (12.0)	< 0.001
Renal failure	11 (23.4)	22 (5.4)	< 0.001
Smoking	17 (36.2)	144 (35.3)	0.905

ACS, acute coronary syndrome, CABG, coronary artery bypass grafting; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

**Table 3.** The proportion of risk categories for GRACE 2.0 and EPICOR risk scores.

	GRACE 2.0 score n (%)	EPICOR score n (%)
<b>Group of risk category (N= 455)</b>		
Low risk	139 (31.0)	420 (92.0)
Intermediate risk	192 (42.0)	-
High risk	124 (27.0)	35 (8.0)
<b>Actual mortality rate</b>		
Low risk	5 (3.6)	36 (8.6)
Intermediate risk	18 (9.4)	-
High risk	24 (19.4)	11 (31.4)

GRACE, global registry of acute coronary event; EPICOR, long - term follow up of antithrombotic management patterns in acute coronary syndrome patients.

**Table 4.** The calibration and discrimination capacity of GRACE 2.0 and EPICOR in one-year mortality ACS prediction.

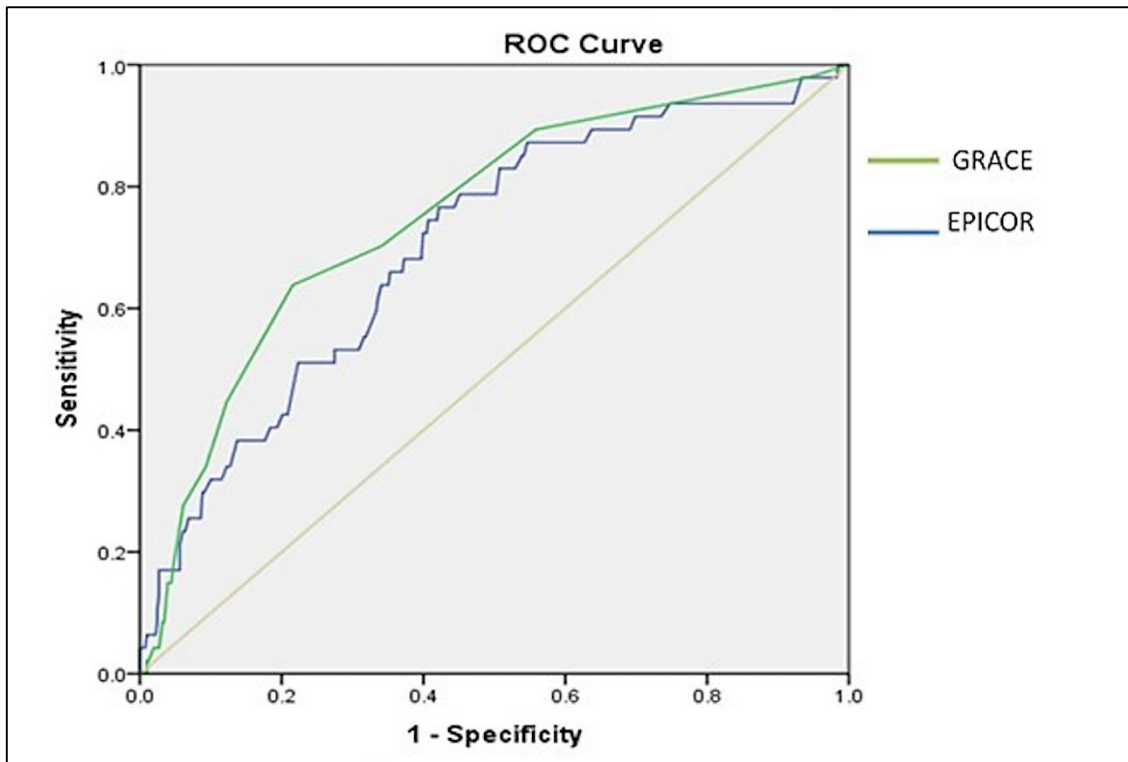
	Hosmer - Lemeshow (p) test (The calibration)	The area under the curve AUC (95% CI) (The discrimination)	De - Long test
<b>GRACE 2.0</b>	0.337	0.703 ( $p < 0.001$ )	$p = 0.0532$
<b>EPICOR</b>	0.001	0.752 ( $p < 0.001$ )	$p = 0.0532$

AUC, the area under the curve; 95% CI, confidence interval; GRACE, global registry of acute coronary event; EPICO, long - term follow up of antithrombotic management patterns in acute coronary syndrome patients.

#### 4. DISCUSSION

Generally, this prospective cohort study gave an insight into the performance of EPICOR as compared with GRACE 2.0. The mean patient age in this sample ( $67.6 \pm 13$ ) was similar to that in another study in The United States<sup>3</sup>. Age is an important risk factor in GRACE and EPICOR scores<sup>11,16</sup>; in fact, Pocock *et al.* demonstrated age to be the leading factor causing the mortality in

the EPICOR score<sup>16</sup>. The higher age led to a higher rate of mortality in ACS<sup>22</sup>. The rate of survival patients who had undergone invasion procedures was significantly higher than the rate of mortality patients because the early invasive procedure reduced mortality, recurrent risk and complications<sup>23,24</sup>. In this study, the rate of patients who had interventions tends to be significantly lower than in other research<sup>14,16</sup> because of the economic situation of the patients



**Figure 1.** AUC of GRACE 2.0 and EPICOR risk cores.

and inadequate techniques for invasion in one hospital. Rates of hypertension, heart failure and renal failure in the mortality group were significantly higher than in the survivor group. Hypertension increases the risk of sudden death, coronary spasms, and coronary thrombosis<sup>25</sup>. Heart failure and renal failure are also two risk factors of ACS to calculate the GRACE 2.0 score<sup>18</sup>. Therefore, these factors could raise the prognosis of mortality.

According to categorization of the GRACE 2.0 score, the percentages of patients in the low-risk group, the moderate-risk group, and the high-risk group were 31%, 42%, and 27%, respectively. Overall, the majority of patients was in the moderate risk groups. This result was similar to the findings of Akyuz et al. 2016<sup>18</sup> and Bekler et al.<sup>26</sup>. According to the EPICOR score, more than 90% of patients were in the low-risk group and no more than 10% were in the high-risk group. The results of risk stratification between EPICOR and GRACE 2.0 scores were different. This was explained by the difference in the classification of the two risk scores. In addition, there were a number of different factors in the calculation of the two scores. The EPICOR score needs to investigate ejection fraction upon admission, cardiovascular complications during hospital stay, etc.<sup>16,18</sup> Both the GRACE 2.0 and EPICOR scores showed that the actual mortality

rate of patients in the high-risk group was higher than in the other groups. The basic analysis of this study showed that discrimination was not a statistical difference. However, the calibration ability of the GRACE 2.0 score was better than that of the EPICOR score.

In our study, the Hosmer-Lemeshow test results of GRACE 2.0 and EPICOR scores were 0.337 and 0.001, respectively. The calibration compared the predicted and observed mortality rates. The results showed a satisfactory calibration capacity of the GRACE 2.0 score ( $p = 0.337 > 0.05$ ); thus, there was no difference between the predicted value and actual results of death events within one year after the discharge of patients with ACS. This showed the relevance of the GRACE 2.0 score for the study population. Other research has also provided evidence for the good performance of GRACE 2.0. The study of L.C. Correia et al. (2014) reported the ability to adjust the GRACE 2.0 score as  $p = 0.08$ <sup>22</sup>. In 2015, Akyuz et al. assessed the calibration ability of the score on each different risk group (classified by GRACE 2.0 score); the Hosmer-Lemeshow results of the GRACE 2.0 score for low, medium and high-risk patients were 0.66, 0.75, and 0.96, respectively<sup>18</sup>. In contrast, our results of the EPICOR score as indicated by the Hosmer-Lemeshow test did not correspond with the study population ( $p = 0.001 < 0.05$ ). Because of the low

calibration, the EPICOR score was not valid with this population. However, the previous study of Pocock demonstrated the excellent calibration ability of the EPICOR score<sup>16</sup>. The EPICOR score was not suitable for this study because of the sensitivity of the population used for the model sensitivity of the population with the model. Another reason was that we were not able to record the EuroQol-5D (EQ-5D) score in all patients of the sample, although this factor was allowed to be omitted<sup>16</sup>. Both GRACE 2.0 and EPICOR scores were capable of discriminating well, with AUCs of 0.703 and 0.752, respectively. The AUC of the GRACE 2.0 score in this study was lower than that in the research of Huang *et al.*, 2016 (0.77)<sup>13</sup>. The sample sizes of the two studies were not significantly different. The difference in the prognostic capacity of the GRACE 2.0 scores between the studies may be due to the characteristics of the study population.

When comparing the discriminatory ability of the GRACE 2.0 score in this study with the original validation study of the GRACE 2.0 score<sup>13</sup>, we found the discriminatory ability of the GRACE 2.0 score in the original study to be better ( $0.83 > 0.703$ ). This could be explained because the population in the original study was 7 times larger than our study sample. The EPICOR score had good ability to discriminate (AUC = 0.752). When we compared our study with the original study - the study to establish and build the EPICOR score - the AUC of the EPICOR score in this study was lower ( $0.752 < 0.81$ )<sup>16</sup>. In general, the discriminatory ability of the EPICOR score tends to be better than the GRACE 2.0 score (0.752 compared with 0.703). However, the De-Long test result had  $p = 0.0532$ ; this showed that between GRACE 2.0 and EPICOR scores there was no difference in the ability to distinguish. Based on the ability to calibrate and distinguish between GRACE 2.0 and EPICOR scores, the GRACE 2.0 was suitable for predicting mortality within one year after discharge in patients in the study cohort who had acute coronary syndrome.

Generally, GRACE 2.0 is a popular, simple, effective scale to estimate the risk of death in patients with ACS in hospital and postdischarge. The factors of GRACE 2.0 easy to collect from preclinical and clinical data of patients in hospital. Moreover, this risk score has been validated through many large-scale studies. Our study also demonstrates the good quality of this risk score about predicting one-year mortality. On the other hand, GRACE 2.0 is not specific for one-year mortality and it does not

contain any information about the medical history and health status of patients at hospital discharge and postdischarge. EPICOR risk score includes these factors in the calculation, and it is specific for a one-year mortality estimation. However, these factors can be missed or incorrect because they are provided by patients. A small number of studies have validated this new risk score<sup>11, 12, 15, 16</sup>.

Some limitations of our study should be considered. Data were collected from only three hospitals in Vietnam. However, the sample was adequate for assessing calibration and discrimination. Results could, however, differ in different countries and with different ethnicities. Therefore, the difference in the performance of EPICOR score between this study and the research of Pocock *et al.* can be attributed to the study sample. The GRACE 2.0 score is just one of many risk-stratification tools. We could not conclude that this was the best model to predict one-year mortality in ACS patients. In future studies, we should compare the GRACE 2.0 score with other scores to determine the most suitable score. That we were unable to record the EuroQol-5D (EQ-5D) score in this population could explain the poor performance of the EPICOR score.

This research can be regarded as the first study to compare the GRACE 2.0 and EPICOR risk scores in the same population. Our study found the GRACE 2.0 score to be a good model for predicting one-year mortality in Vietnamese patients with ACS. In the future, to have a better assessment and find the most suitable standard for Vietnam, we need to conduct comparative research on GRACE, EPICOR and another score (such as the thrombolysis in myocardial infarction -TIMI) related to the rate of mortality in one year.

## 5. CONCLUSIONS

A significant difference was found between the performance of the GRACE 2.0 and EPICOR risk scores. In this study, the GRACE 2.0 score was more accurate for predicting one-year mortality after discharge in patients with acute coronary syndrome, compared to the EPICOR score. The GRACE 2.0 score is an effective tool for estimating one-year mortality risk in Vietnam.

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**Conflict of interests**

There are no competing interests.

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