Indonesian Journal of Cardiology
Indonesian J Cardiol 2022:43:56-63
pISSN: 2830-3105 / eISSN: 2964-7304
doi: 10.30701/ijc.1152

Original

Validation and Comparison of Zwolle, TIMI, and GRACE Risk Scores for STEMI Patients Undergoing Primary Percutaneous Coronary Intervention in The Indonesian Population.

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Abstract

Background: Zwolle, TIMI, and GRACE risk scores have been proven to predict major adverse cardiovascular events (MACE) in STEMI patients undergoing primary percutaneous coronary intervention (PCI). However, they developed a long time ago and many advances have been made in the cardiovascular field today. The scores were also developed in the non-Asian majority population and their accuracy for the Indonesian population remains unknown. We aimed to validate and compare these scores for the Indonesian population.

Methods: An analytical observational study was conducted on 193 patients undergoing primary PCI. The Zwolle, GRACE, and TIMI risk scores were calculated for each patient. Then, the risk score validation was carried out with the calibration test using the Hosmer Lemeshow test and the discrimination test using the AUC ROC. Furthermore, the comparisons between the risk scores were carried out using the DeLong test.

Results: The three scores have good results in the Hosmer Lemeshow calibration test ($p > 0.05$). The discrimination test also indicated good results with AUC ROC Zwolle, TIMI, and GRACE risk scores respectively 0.776; 0.782; 0.831 ($p<0.05$). There was no significant difference in the prediction accuracy of the three risk scores in the DeLong test.

Conclusion: The Zwolle, TIMI, and GRACE risk scores had good validity for predicting major adverse cardiovascular events in STEMI patients undergoing primary PCI for the Indonesian population. There was no significant difference in the prediction accuracy of the three risk scores.

(Indonesian J Cardiol. 2022;43:56-63)

Keywords: Risk score, major adverse cardiovascular events, primary percutaneous coronary interventions.

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Introduction

The risk score is a method for predicting patients' prognosis based on the predictors proven to be related to the outcomes. An accurate risk score is essential in ST-elevation myocardial infarction (STEMI) management. Several risk scores have been developed and proven from studies in STEMI to predict both mortality and major adverse cardiovascular events.[1]

The Zwolle risk score was developed from a population of STEMI patients undergoing primary percutaneous coronary intervention (PCI) with the purpose to increase the effectiveness and reduce the cost of treating STEMI patients after primary PCI.[2] The Global Registry of Acute Coronary Events (GRACE) risk score and Thrombolysis in Myocardial Infarction (TIMI) risk score are other risk scores in STEMI patients. Although they were developed based on a larger patient population and more widely known than the Zwolle risk score, those two risk scores were not specifically developed from a population of STEMI patients undergoing primary PCI or included variables related to primary PCI.

All of these risk scores were developed more than ten years ago in which the variables on the score may not be relevant today. Several management aspects have also evolved and can affect the clinical course and patient outcome. The risk score was also developed from a population of North American and European patients and its accuracy to the Asian populations is still unknown, specifically to the Indonesian population.[3–6]

This study was conducted to validate the three risk scores based on the Indonesian population, especially at RSUP Dr. Kariadi Semarang. Risk score validation is a method to test whether a risk score has a good prognostic performance so it is feasible to use.[7,8] We also compared the prediction accuracy performance of the three risk scores to determine the best score to use.

Methods

Subject

This study was an analytical observational study with a retrospective cohort design. Data collection for this study was conducted from December 2019 to July 2020. The research subject was STEMI patients undergoing primary PCI at RSUP Dr. Kariadi Semarang from January 2015 to June 2018 who met the research criteria. The inclusion criteria were STEMI patients with an onset of 12 hours undergoing primary PCI, aged >18 years to 80 years, and undergoing post-primary PCI treatment at RSUP Dr. Kariadi Semarang. The exclusion criteria were those patients known to suffer from cancer or other diseases that became the main cause of death during treatment or had a stroke before or during primary PCI and when medical record data were incomplete.

Study variables

The Zwolle, GRACE, and TIMI risk scores were calculated for each patient based on their medical records. The Zwolle and TIMI risk scores were calculated manually while the GRACE risk score was calculated using the calculator application on the https://www.mdcalc.com/grace-acs-risk-mortality-calculator website. The components and value of each variable between each risk score are shown in the table below. **(Table 1)**

The outcomes assessed were major adverse cardiovascular events (MACE) in the hospital of STEMI patients undergoing primary PCI which is defined as the presence of one of the following six events: post primary PCI lethal arrhythmias (ventricular fibrillation, ventricular tachycardia, asystole, new or persistent high degree AV block requiring pacemaker management, pulseless electromechanical activity);[9] urgent revascularizations; acute lung edema (ALO); cardiogenic shock;[10,11] stroke and mortality.[12] If the patients had more than one major adverse cardiovascular event, they were assigned to a separate group and counted as one event only.

Statistical Analsyis

The risk score validation was carried out by calibration test using the Hosmer Lemeshow test and discrimination test using the area under the receiver operating characteristic curve (AUC ROC) using IBM SPSS Statistics 25. The AUC ROC value of 0.7-0.8 was categorized as acceptable, 0.8-0.9 was excellent, and more than 0.9 was outstanding.[13] To see a comparison of the discrimination ability of each risk score, the DeLong test was carried out using MedCalc.[14]

Table 1. Comparison of risk score variable.

Zwolle risk score	GRACE risk score	TIMI risk score
Killip class • 2 (4 points) • 3-4 (9 points) TIMI flow post • 2 (1 points) • (2 points) Age ≥ 60 (2 points) 3 vessel disease (1 points) Anterior infarction (1 points) Ischemic Time > 4 hours (1 points)	Age Heart rate Systolic blood pressure Creatinine Cardiac arrest at admission ST segmen deviation at ECG Abnormal cardiac enzymes Killip class	Age 65-74/>75 (2/3 points) Systolic blood pressure <100 (3 points) Heart rate >100 (2 points) Killip class II-IV (2 points) Anterior infarction or LBBB (1 points) Diabetes, history of hypertension or history of angina (1 points) Weight < 67 kg (1 points) Time to treatment >4 hours (1 points)
Total score: 0-16	Total score max :372	Total score: 0-14

Results

In the period from January 2015 to June 2018, 241 STEMI patients underwent primary PCI. Of these, 193 patients met the criteria selection of research subjects. There were 48 patients excluded, 35 patients due to incomplete medical records, 7 patients underwent coronary angiography only without intervention, 2 patients aged over 80 years, 2 patients had a stroke before/during primary PCI and 2 patients died during primary PCI. The major adverse cardiovascular events were found in thirty-six patients (18.7%). The description of MACE was mortality in seventeen patients (8.8%), lethal arrhythmias post-primary PCI in eight patients (4.1%), stroke in six patients (3.1%), cardiogenic shock in three patients (1.6%), and two patients had more than one major adverse cardiovascular event (1.0%).

The basic characteristics of the subjects in this study are shown in the table below **(Table 2)**. The average age was 55.76 ± 10.07 years. Most of the subjects were male (80.8%). The majority of research subjects also came in clinical conditions of Killip class 1-2 (91.2%). Based on the location of the infarction, 93 patients (48.2%) had infarction located anteriorly and the rest were located non-anteriorly (51.8%). From laboratory parameters, the average hemoglobin level was 13.92 ± 2.06 g/dl; blood creatinine level was 1.21±0.45 mg/dl, and blood glucose level was 196.37±119.28 mg/dl. A total of 76 patients (39.9%) had 3 vessel diseases from the results of the coronary angiography performed. The average onset was 4.88 ± 2.87 hours, the average door-to-wire crossing was 194.83 ± 115 minutes and the average total ischemic time was 487.74 ± 216.38 minutes.

The validation of the three risk scores was carried out using calibration and discrimination tests. In the calibration test with Hosmer and Lemeshow test, the significance value of the Zwolle risk score was 0.714, of GRACE risk score, was 0.538, and of TIMI risk score was 0.129 which indicated that there was no significant difference between the risk score models and the reality in the observation. The results of this test indicated good calibration ability on these three risk scores. **(Figure 1.)**

In the discrimination test with AUC-ROC, it was found that the Zwolle and TIMI risk scores were in the acceptable category with AUC ROC of 0.776 and 0.782 ($p<0.05$). Meanwhile, the GRACE risk score with an AUC ROC of 0.831 ($p<0.05$) was in the excellent category. Subsequently, the DeLong test was carried out to see if there was a difference in the prediction accuracy between these three risk scores. **(Table 3.)**

In the DeLong test, there was a difference in the AUC ROC area of 0.0491 between the GRACE and TIMI risk scores, but it was not statistically significant ($p=0.1761$). Meanwhile, between the GRACE and Zwolle risk scores, there was a difference in the area of 0.0556 even though it was not statistically significant ($p=0.0816$). An insignificant difference was also found in the comparison of the TIMI and Zwolle risk scores with a difference in the area of 0.00646 ($p = 0.8950$). From these results, there was no significant difference in the prediction accuracy between these three risk scores. **(Table 4.)**

Table 2. Baseline Characteristics.

Variables	All subject (n=193)
Age (year)	55.76±10.07; 56 (22-78)
Female	37 (19.2%)
Systolic blood pressure (mmHg)	121.33±25.49;120 (58-180)
Heart rate (beat/minute)	80.88±23.37; 80 (20-215)
Killip class	
Killip class 1-2	176 (91.2%)
Killip class 3-4	17 (8.8%)
Arrhythmias pre and during primary PCI	27 (14%)
Anterior Infarct	93 (48.2%)
Blood haemoglobin levels (g/dL)	13.92±2.06; 14.2 (6.3-18.7)
Anemia	41 (21.2%)
Leukocyte count (/ml)	13522.33±4208.36; 12900 (6300-29600)
Blood creatinine levels (mg/dl)	1.21±0.45; 1.12 (0.20-4.17)
Blood glucose levels (mg/dl)	196.37±119.28; 154 (60-847)
CAD 3 vessel disease	76 (39.9%)
Symptoms to first medical contact (hour)	4.88±2.87;4 (0.17-12)
Door to wire crossing (minute)	194.83±115.23;162 (55-741)
Total ischemic time duration	
(minute)	487.74±216.38; 456 (107-1404)
(hour)	8.14±3.61; 8 (2-23)
Outcomes	
Major adverse cardiovascular events (MACEs)	36 (18.7%)
Post primary PCI lethal arrhythmia	8 (4.1%)
Stroke	6 (3.1%)
Cardiogenic shock	3 (1.6%)
Mortality	17 (8.8%)
>1 MACEs	2 (1.0%)

Mean±SD; Median (min-max)
n (%)

Table 3. AUC ROC of Risk Scores.

Test Result Variable (s)	Area Under Curve	Std. Error	Asymptotic Sig.	95% Confidence Interval
GRACE Risk Score	0.831	0.040	0.000	0.752-0.910
TIMI Risk Score	0.782	0.049	0.000	0.686-0.879
Zwolle Risk Score	0.776	0.044	0.000	0.689-0.862

Table 4. Comparison of Risk Scores Accuracy.

	Difference between areas	SE	95% CI	Z statistic	Significance level, p
GRACE RS ~ TIMI RS	0.0491	0.0363	-0.022 to 0.120	1.353	0.1761
GRACE RS ~ Zwolle RS	0.0556	0.0319	-0.007 to 0.118	1.741	0.0816
TIMI RS ~ Zwolle RS	0.00646	0.0490	-0.089 to 0.102	0.132	0.8950

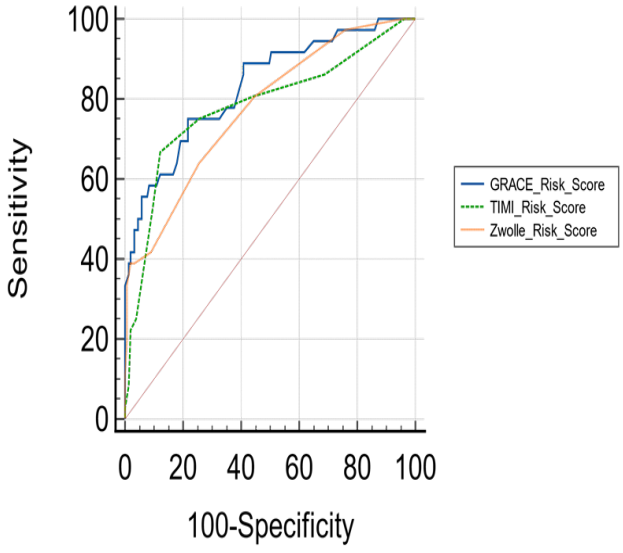

Figure 1. AUC ROC of Risk Scores.

Discussion

In this study, the discrimination and calibration tests were carried out to validate the Zwolle, TIMI, and GRACE risk scores. Furthermore, the DeLong test was performed to analyze the differences in the prediction accuracy of risk scores for the major adverse cardiovascular events during hospitalization. Although the results of the risk score validation varied in several studies in different countries, the results of this study found that all these three risk scores had good results for use in the Indonesian population. Good risk score validation from the Zwolle, TIMI, and GRACE risk scores has also been obtained in previous studies. The study conducted by Tralhao et al. found that the Zwolle risk score had good calibration and discrimination values (C-statistic: 0.937, p<0.001) in a population of 276 patients undergoing primary PCI in Lisbon, Portugal. Abelin et al. also obtained the same result, where in 509 patients undergoing primary PCI in Brazil, the Zwolle risk score had significantly good accuracy with a C-statistic of 0.80 (0.73-0.87). In the same study, the GRACE and TIMI risk scores were also validated and obtained good results with C-statistics for both risk scores of 0.84 (0.78-0.90) and 0.81 (0 .74-0.87).[15] Several issues related to the low proportion of Asians in the development of risk scores and the need for recalibration of risk scores to improve their accuracy were not proven in our study.[16,17]

We also found no significant difference in the prediction accuracy between the three risk scores. These findings were the same as previous studies. The study conducted by Abelin et al. against four risk scores, namely the GRACE, TIMI, Zwolle, and PAMI risk scores, the Zwolle, GRACE, and TIMI risk scores were well-validated with good accuracy value for 30-day mortality outcomes while the PAMI risk score had the worst accuracy compared to the other three risk scores. There was no significant difference related to the accuracy of the risk score between the three risk scores.[15] Another study conducted by Littnerova et al. acquired good validation results for the three risk scores on mortality outcomes in a year (AUC ROC of 0.73-0.85). Meanwhile, for long-term outcomes up to 3 years, the GRACE risk score was more appropriate.[14] Another study conducted by Koziedadzka in 505 patients undergoing primary PCI on mortality outcomes over a longer period of up to 5 years obtained approximately the same prognostic value for these three risk scores, namely the GRACE risk score of 0.742 (0.69-0.79), TIMI risk score of 0.727 (0.67-0.78), and Zwolle risk score of 0.72 (0.67-0.77) while the CADILLAC risk score also validated turned out to have a poor prognostic value of 0.687 (0.63-0.74).[18]

Several reasons can explain the results of this study. Each risk score that has been developed so far has its plus and minus values. The Zwolle risk score was developed from a more specific population, namely STEMI patients undergoing primary PCI. This risk score also included the primary PCI variables such as multivessel disease (MVD) and TIMI flow, as independent predictors of 30-day mortality in addition to demographic, clinical, and ECG variables. However, compared to the TIMI or GRACE risk score, this risk score had a relatively smaller number of development and validation samples. This risk score involving 1.791 patients was derived from the patient registry data and validated with cohort data from 747 other patients.[2]

In contrast, the TIMI risk score was developed based on the patient population at 'An Intravenous nPA for Treatment of Infarcting Myocardium Early II Trial Substudy' namely 14.114 STEMI patients undergoing fibrinolytic and was validated externally in the TIMI 9 trial (c-statistic of 0.746). Although not specifically developed based on the STEMI patients undergoing

primary PCI, the TIMI risk score had been validated with data from the National Registry of Myocardial Infarction 3 (NRMI 3) patients, where this score had good predictive value in patients undergoing reperfusion, both with fibrinolytic (n=23.960; c=0.79) and primary PCI (n=15.348; c=0.80).

The GRACE risk score was also developed from a large sample size. This score development included 11.389 acute coronary syndrome patients and was validated in 3.972 patients from the GRACE registry and 12.142 patients from the Global Use of Strategies to Open Occlude Coronary Arteries IIb (GUSTO-IIb) trial. This large sample size seems to be the statistical advantage of this score. Regarding this sample size, the study conducted by Pate et al. stated that the stability of a clinical prediction model would depend on the size of the development sample. If the sample was too small, the risk score could be overfitted, which caused over-optimistic model performance in the dataset made, but when used in a population outside the population for which it was created, the risk score performance would be poor. On the contrary, a large sample size could increase the accuracy and precision of the assessed parameters.[8,13]

Compared to the Zwolle risk score, the components of the score variables in the TIMI and GRACE risk scores only included demographic components such as age, clinical components, laboratory examination, and ECG components without involving components of the primary PCI variables. In this regard, several studies have proven the essential role of these primary PCI variables.[10,12,19-21] Nevertheless, the primary PCI variables such as multivessel diseases and final TIMI flow in a scoring system were still only components of a model, and their values could be replaced by the predictive values of other variables in risk score models. On top of that, even though it was proven to be significant in several studies, the primary PCI variable had a lower predictive value than other variables. For example, the Zwolle risk score and Westerhout et al. studies showed Killip class, age, or systolic blood pressure as predictors with a greater and more stable hazard ratio (HR) values as good predictors at baseline, two hours, twenty-four hours, and ninety-six hours after patient presentation.[2,19]

There were several limitations in this study. It used a relatively small sample and secondary data, so it depended on the accuracy and completeness of medical records and the accuracy of the hospital information system.

Conclusion

The Zwolle, TIMI, and GRACE risk scores had good validity for predicting major adverse cardiovascular events of STEMI patients undergoing primary PCI in the Indonesian population. There was no significant difference in the prediction accuracy of the three risk scores.

Ethical Approval

This research has ethical approval from Health Research Ethics Committee Dr. Kariadi Hospital, Semarang with ethical clearance reference number No. 190/EC/ KEPK-RSDK/2018.

Finding

No specific funding was provided for this article.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by The Department of Cardiology and Vascular Medicine, Faculty of Medicine, Diponegoro University, and Dr. Kariadi General Hospital Semarang, Central Java, Indonesia.

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