COMPARISON OF GRACE, TIMI RISK SCORES FOR PREDICTION OF MAJOR ADVERSE CARDIAC EVENTS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION, VIETNAM

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Acute myocardial infarction (MI) is one of the leading causes of cardiovascular death and can experience many events during illness. Therefore, many risk prediction scales have been established to stratify patients with acute MI, in which TIMI and GRACE scores are common. We conducted this study to compare the predictability of GRACE and TIMI scores in patients with acute MI within 12 months. A prospective cohort study was performed on 195 patients with acute MI, of which 86 patients had ST elevation (STEMI) and 109 patients without ST elevation (NSTEMI). The study looked at five major events including death, coronary re-intervention, bleeding due to drug use, re-hospitalization, and stroke. As a result, the heart rate in the STEMI group was 83.06 ± 14.78, higher than the heart rate of the NSTEMI group at admission (78.59 ± 10.63), the difference was significant with p = 0.015. The study has not shown the predictive effect of GRACE and TIMI scores on the occurrence of events in patients with acute MI within 12 months. However, the study showed that GRACE can better ability to stratify the risk for the group of subjects that had not yet occurred.

Keywords: TIMI score, Grace score, Acute Myocardial Infarction.

I. INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide. In 2019, CVDs were the leading cause of death worldwide, accounting for 32% of all deaths. Of the people who died from CVDs, 85% died from heart attack or stroke.[1] In particular, acute myocardial infarction (MI) is one of the leading causes of cardiovascular death. 30% of patients will die without treatment, but with timely detection and treatment, mortality can be reduced from 6 to 10%.[1] Patients may experience serious cardiovascular events: death, coronary re-intervention, re-infarction, and stroke. Many studies showed that using predictive and risk stratification models for patients with acute MI is a valuable tool for planning early treatment, intervention or discharge and rehabilitation for patients with acute myocardial infarction.[2,3]

Therefore, many risk prediction models for MI patients have been established to stratify patients with acute MI.[4,5] The risk score showed strong prognostic capacity overall (c = 0.74 vs 0.78 in derivation set) and among patients receiving acute reperfusion therapy (c = 0.79).[6] For patients with ST-elevation myocardial infarction (STEMI), the TIMI score is based on eight clinical indicators obtained upon admission including: Age over 75; SBP < 100 mmHg; heart rate > 100 beats per minutes; Killip degree: II – IV; ST elevation anterior wall or left bundle branch block; history of diabetes, hypertension, angina; weight < 67 kg; time from symptom onset to revascularization > 4 h,

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with a score from 0 to 14. For non-ST elevation myocardial infarction (NSTEMI), TIMI score is based on seven clinical indicators including: age over 65; having 3 or more coronary artery factors; coronary artery stenosis equal to or greater than 50%; at least 2 times of angina in 24 hours; there are ST changes on the electrocardiogram; have elevated cardiac enzymes (Troponin T, I); have been taking aspirin for at least 7 days, scores ranging from 0 to 7.[3] Another scale used by clinicians for patients with acute MI is the global registry of acute coronary events (GRACE), which is based on multinational data to assess risk in all patients with the acute coronary syndrome, has a good prognostic value with c=0.84.[7] GRACE uses 8 variables including: age; Killip grade; SBP; ST changes; have circulatory arrest; Creatinine levels; increased heart enzymes; heart rate and applies to all acute coronary syndromes.[7] This scale has long-term prognostic value and has high practical value. However, applying the scale to different groups of subjects gives different results. These two scales were developed by enrolling patients primarily from countries in North America, South America and Europe, with only Australia and New Zealand providing data from Asian countries to the GRACE registry.[8] TIMI and GRACE are evaluated as good predictors of mortality in patients with acute MI, but predictive of other events such as revascularization, drug-induced bleeding, and strokeis unknown.[9,10] Several studies have compared TIMI and GRACE scores, showing that GRACE scores are a better predictor of major events than TIMI.[11] In Vietnam, there is currently no study on the predictive ability of these two scales on MI patients. Therefore, we conducted this study to compare the predictive power of GRACE and TIMI scores in patients with acute MI within 12 months.

II. MATERIALS AND METHOD

1. Patients

The patient was diagnosed with acute MI according to the fourth global definition. The term MI is used when there is an acute myocardial injury with clinical evidence of acute myocardial ischemia and elevation of troponin with at least one value above the 99th percentile, along with at least one of the following:

- Symptoms of myocardial ischemia.

- Change of new ischemic type diabetes.

- There are pathological Q waves.

- There is new imaging evidence of dysfunctional myocardium or regional movement disturbances in a setting consistent with ischemia.

- Coronary thrombosis was noted during coronary angiography or at autopsy.

- Patients with acute MI were divided into two groups: with ST-segment elevation (STEMI) and without ST-elevation (NSTEMI).

**** Diagnosis of ST-segment elevation on electrocardiogram:***

Patients with J-point ST elevation in at least 2 consecutive leads:

- At leads V2 and V3:

- Male < 40 years old: J 2.5mm

- Male ≥ 40 years old: J 2 mm

- Female: J 1.5 mm

Other leads: J 1 mm

Or new left bundle branch block with angina > 30 min and/or evidence of muscle fibrosis with elevated troponin I levels ≥ 0.1 ng/mL.

**** Diagnosis of NSTEMI:***

Diagnosed in patients with typical angina, troponin I level ≥ 0.1 ng/mL and no detectable ST-segment elevation on the electrocardiogram.

Exclusion criteria

The patient has an event for reasons other than cardiovascular (trauma, traffic accident)

2. Treatment proceduce and monitoring of main cardiovascular events

All patients received anti-UTI drugs with an aspirin 300 mg combined with clopidogrel 300-600 mg or ticagrelor 180 mg. Then, they were given a maintenance dose of clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily in combination with aspirin 80-100 mg daily.

All patients were closely monitored for clinical events, including severity of heart failure (NYHA) and major cardiovascular events, drug-related bleeding events, and other events over a 12-month period

Major cardiovascular events included death, stroke, re-MI, and revascularization of the culprit artery.

Events related to bleeding due to drug use were defined according to the PLATO criteria.

3. Scales used in the study

**** Risk assessment according to the TIMI score***

****For STEMI:***

Based on age over 75; SBP < 100 mmHg; heart rate > 100 beats per minute; Killip degree: II – IV; ST elevation anterior wall or left bundle branch block; history of diabetes, hypertension, angina; weight < 67kg; Time from symptom onset to recanalization > 4 hours.

Low risk = 0 – 3; Medium risk = 4 – 6; High risk = 7 or more.

****For NSTEMI:***

Based on age over 65; have 3 or more coronary artery factors; coronary artery stenosis of greater or equal to 50%; at least 2 episodes of chest pain in 24 hours; there are ST changes on the electrocardiogram; have elevated cardiac enzymes (Troponin T, I); have been taking aspirin for at least 7 days.

Low risk = 0 – 2; Medium risk = 3 – 4; High risk = 5 or more.

*** Risk assessment according to the GRACE score**

Based on age criteria; Killip grade; SBP; ST changes; circulatory arrest; Creatinine levels; increased heart enzymes; heartbeat.

Low risk = 1 - 108; Medium risk = 109 – 140; High risk = 141 – 372.

4. Research location

Vietnam National Heart Institute – Bach Mai Hospital and Hanoi Heart Hospital

5. Research Methods

Prospective cohort study,

Sample size: use the sample size formula to estimate a proportion

$$n = Z^2_{1-\alpha/2} \frac{p\,(1 - p)}{(p.\ \varepsilon)}$$

n: sample size

p: 0,5

$Z_{1-\alpha/2}$: 1,96

ε: 0,15

n=170, plus 15% redundancy.

The total number of patients participating in the study was 195.

6. Research data collection and data processing

Data were gathered from patients' detailed medical history then processed and analyzed with SPSS 16.0 software. ANOVA/Chi-square tests are used to compare and test mean values or ratios between groups.

7. Research ethics

The patients voluntarily participated in the study after receiving full information about the study's purpose. Patient information is kept confidential and used for research purposes only.

III. RESULT

The study was performed on 195 patients with acute myocardial infarction (MI), of which 86 patients had ST elevation (STEMI) and 109 patients had no ST elevation (NSTEMI). Detailed results are presented in Table 1.

Table 1. Characteristics of the study population

Characteristics		STEMI (n=86)	NSTEMI (n=109)	p
Age (year)		64.62 ± 12,511	63.56 ± 10.168	0.516
Sex	Male	68 (79.1%)	82 (75.2%)	0.609
	Female	18 (20.9%)	27 (24.8%)	
History of myocardial infarction		11.6%	27.5%	0.007
History of cardiac catheterization		0%	7.3%	0.01
History of percutaneous coronary intervention		16.3%	30.3%	0.023
History of angina		19.8%	35.8%	0.017
History of heart failure		2 (2.3%)	2 (1.8%)	0.81
History of cerebrovascular accident		2 (2.3%)	4 (3.7%)	0.688
Hypertension		47 (54.7%)	64 (58.7%)	0.662
Diabetes with drug treatment (%)		13 (15.1%)	24 (22%)	0.272
BMI (Kg/m ^{2})		22.09 ± 2.86	22.05 ± 2.79	0.481
Systolic blood pressure (mmHg)		129.59 ± 23.05	136.51 ± 20.54	0.028
Heart Rate (Beats/minute)		83.06 ± 14.78	78.59 ± 10.63	0.015
Killip Degree > II % (%)		2.3 %	1.8 %	0.249
Troponin T*		94.1	5.1	0.002
Glucose (mmol/L)		7.652 ± 3,974	7.195 ± 3.53	0.42
Creatinine (mmol/L)		97.62 ± 45.82	91.45 ± 22.02	0.218
CK* (UI/L) (Median)		310	119	< 0.001
CK – MB* (UI/L) (Median)		35.5	17	< 0.001
Platelet aggregation		25.37	26.62 ± 11.61	0.116
TIMI Score		5.02 ± 1.756	3.42 ± 1.03	**< 0.001**
GRACE Score		114.36 ± 24.85	93.53 ± 22.83	**< 0.001**

Analyzing the results from Table 3.1, we found that the mean age in the 2 groups of patients was quite similar at 64.62 and 63.56 years old (p = 0.516). The heart rate in the STEMI group was 83.06 ± 14.78, higher than the NSTEMI group on admission (78.59 ± 10.63), the difference was statistically significant p = 0.015. The study's subjects tend to be older, most of them were males (76.9%), had high rates of hypertension (56.9%), and many patients were smokers (52.8%). The mean TIMI score of STEMI (5.02 ± 1.756) was higher than NSTEMI (3.42 ± 1.03). The mean GRACE score of the STEMI group was 114.36 ± 24.849, which was higher than the NSTEMI group of 93.53 ± 22,831.

Our study looked at five major events occurring in 12 months including death, revascularization, re-hospitalization, drug-induced bleeding, and stroke as shown in Figure 1.

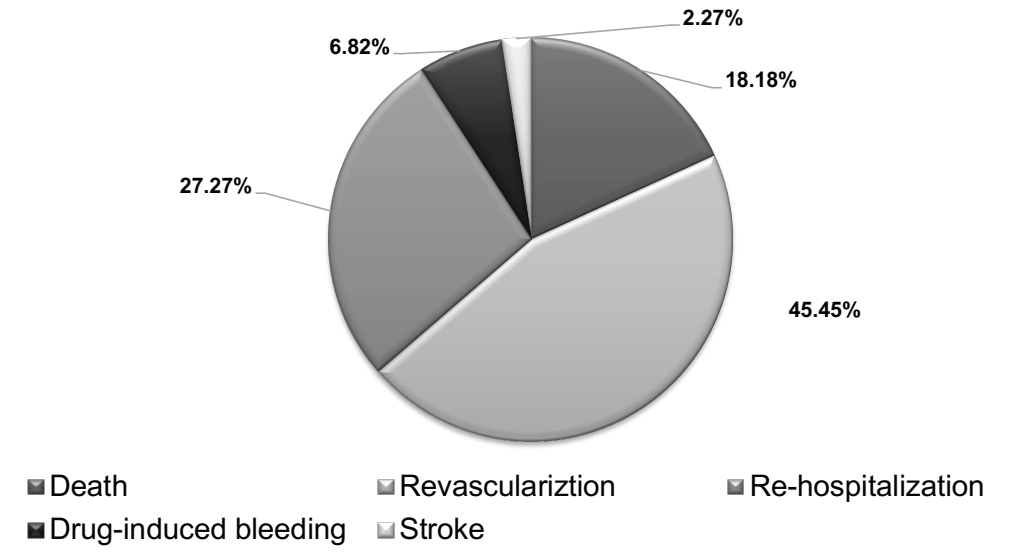

Figure 1. Major adverse cardiac events occurring in study subjects over a 12-month

Period significant events occurring in 44 patients over a 12-month period included death in 8 cases (18.18%), revascularization in 20 cases (45.45%), drug-induced bleeding in 3 cases (6.82%), stroke in 1 case (2.27%), re-hospitalization in 12 cases (27.27%).

The event rates were compared between the two groups ST-segment elevation myocardial infarction and non-ST-elevation myocardial infarction, as shown in Figure 3.2.

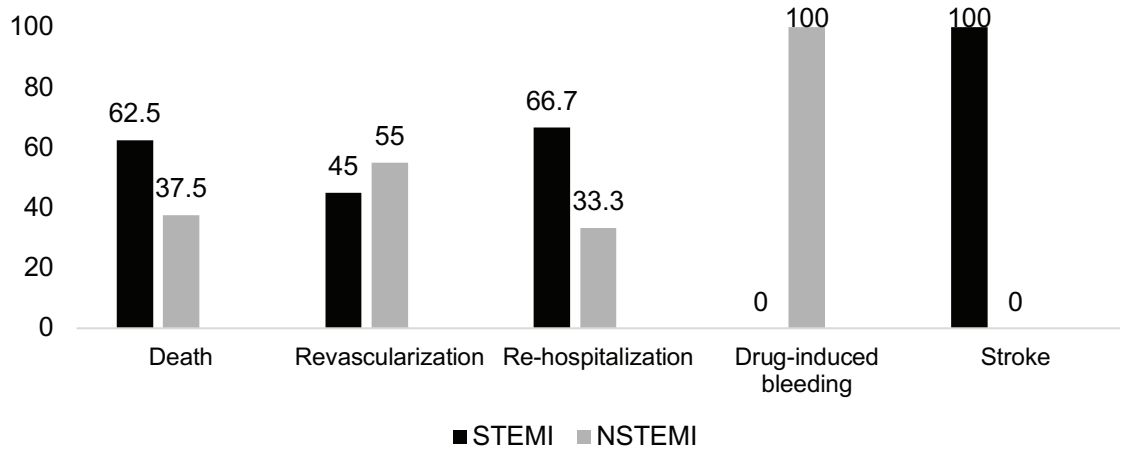

Figure 2. Distribution of major adverse cardiac events rates of the study subjects according to the classification of MI after 12 months

Of the significant events occurring after 12 months, mortality (62.5%) and re-hospitalization were 66.7%, mostly concentrated in the STEMI group. The rates of coronary intervention (55%) and drug-induced bleeding (100%) were more concentrated in the NSTEMI group (Figure 3.2).

1. The predictability of the GRACE score

We continue to analyze the risk stratification ability of this scale with the outcome of events in the patients after 12 months. The results are shown in Table 3.

Table 2. GRACE risk stratification results with major adverse cardiac events

	Type of event	GRACE Score Scale		
		Low risk n (%)	Medium risk n (%)	High risk n (%)
NSTEMI	Dead	3 (100%)	0	0
	Cardiovascular re-intervention	7 (63.6%)	4 (36.4%)	0
	Drug-induced bleeding	2 (66.7%)	1 (33.3%)	0
	Re-hospitalization	4 (100%)	0	0
	Stroke	0	0	0
	Event	16 (76.2%)	5 (23.8%)	0
	No event	63 (71.6%)	23 (26.1%)	2 (2.3%)
STEMI	Dead	0	5 (100%)	0
	Cardiovascular re-intervention	4 (44.4%)	3 (33.3%)	2 (22.2%)
	Drug-induced bleeding	0	0	0
	Re-hospitalization	3 (37.5%)	5 (62.5%)	0
	Stroke	0	1 (100%)	0
	Event	7 (30.4%)	14 (60.9%)	2 (8.7%)
	No event	28 (44.4%)	28 (44.4%)	7 (11.1%)

In 44 cases of events in patients with acute MI, GRACE stratified low risk in 23 cases, medium risk in 19 cases, and high risk in 2 cases (4.55%).

In NSTEMI patients with 21 CV events, GRACE predicted low risk in 16 cases (76.2%) and none at high risk. Of these, 3 deaths were classified as low risk. In patients with STEMI, there were 23 events, GRACE stratified low risk in 7 cases, medium risk in 14 cases, and high risk in 2 cases.

In 44 cardiovascular events, only two were classified as high-risk. In addition, 9 cases without events were classified as high-risk groups.

Regarding the event-free group (n = 151) of the whole study, GRACE stratified low risk 91 cases (60.27%), medium risk 51 cases (33.77%), and high risk 9 cases (5.96%).

2. Predictability of the TIMI score

With the TIMI score, we also analyzed the risk stratification ability of this scale with the outcome of events occurring in the study subjects after 12 months. The detailed results are in Table 3.3.

Table 3. The predictable of the TIMI scale for major cardiovascular events during 12 months of follow-up

	Type of event	TIMI score		
		Low	Medium	High
NSTEMI	Dead	1 (33.3%)	2 (66.7%)	0
	Cardiovascular re-intervention	1 (9.1%)	9 (81.8%)	1 (9.1%)
	Stroke	0	0	0
	Drug-induced bleeing	0	2 (66.7%)	1 (33.3%)
	Re-hospitalization	0	2 (50%)	2 (50%)
	Event	2 (9.5%).	15 (71.4%)	4 (19%)
	No event	14 (15.9%)	63 (71.6%)	11 (12.5%)
STEMI	Dead	0	4 (80%)	1 (20%)
	Cardiovascular re-intervention	2 (22.2%)	4 (44.4%)	3 (33.3%)
	Re-hospitalization	2 (25%)	5 (62.5%)	1 (12.5%)
	Drug-induced bleeding	0	0	0
	Stroke	0	1	0
	Event	4 (17.4%)	14 (60.9%)	5 (21.7%)
	No event	17 (27%)	34 (54%)	12 (19%)
Total	Event	6 (13.6%)	29 (65.9%)	9 (20.5%)
	No event	31 (20.5%)	97 (64.2%)	23 (15.2%)

Analyzing the results from Table 3.3, it was found that in 44 cases of events, 9 cases with high risk level (20.45%), 29 cases with medium risk level, and 6 cases with low risk level.

In the NSTEMI group, the low risk stratification was 02 cases, the average risk was 15 cases, and the high risk was in 4 cases, of which 02 deaths were stratified in the middle-risk group and 01 case at low risk. In the STEMI group, low risk stratification was 04 cases, medium risk 14 cases, and high risk 05 cases. Of which 01 out of 05 deaths were stratified for high risk.

Besides, in 151 cases without events, TIMI stratified high risk in 23 cases, medium risk in 97 cases, and low risk in 31 cases.

3. Comparison the predictability of TIMI and GRACE

We analyzed the univariate correlation between the two scales TIMI and GRADE with the overall risk of 12 months of events. The results are shown in Table 3.4:

Table 4. Regression model of univariate correlation between TIMI and GRACE scores with the 12-month general event of the study subjects

Point ladder	Coefficient β	p	Confidence interval (95%CI)
TIMI	0.175	0.015	0.045 – 0.410
GRACE	0.077	0.939	0.01 – 0.11

The results show that TIMI score is correlated with overall event outcome with p = 0.015 while we have not confirmed the correlation between GRACE and complication outcome at 12 months with p = 0.939.

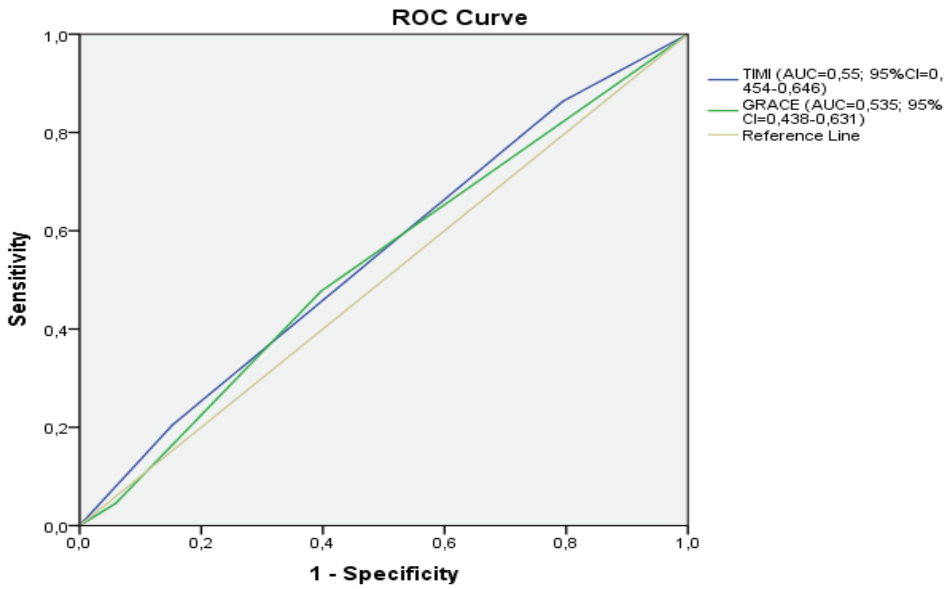

Figure 3. ROC curve for TIMI and GRACE scores for predicting major events when hospitalized

Area under the curve for TIMI score = 0.55 (95%, CI = 0.454 – 0.646, p=0.314) and area under the curve for GRACE score = 0.535 (95 %, CI = 0.438 – 0.631, p=0.483). It was found that TIMI and GRACE scores were not statistically significant in predicting major events in patients with acute MI at 12 months.

IV. DISCUSSION

1. The relationship between group characteristics and predictive stratification ability of TIMI, GRACE

Our study found that the mean TIMI and GRACE scores of the STEMI group were significantly higher than that of the NSTEMI group ($p < 0.05$). Along with that, heart rate, and cardiac enzyme levels (Troponin T, CK, CK-MB) were also higher in the STEMI group than in the NSTEMI group at admission ($p < 0.05$). These results showed a relationship between heart rate, cardiac enzymes and risk score of events in patients with STEMI at hospital admission. It is suggested that, in the STEMI group, when a patient is admitted to the hospital with an elevated heart rate and cardiac enzyme levels, the likelihood that the patient has events is also elevated.

Among the main events occurring after 12 months, the mortality rate was 62.5% and the re-hospitalization rate was 66.7%, concentrated in the STEMI group. The rates of coronary intervention (55%) and drug-induced bleeding (100%) were more concentrated in the NSTEMI group (Figure 3.2). Our results showed that selecting the criteria “Has been used Aspirin within 7 days and has coronary artery history/ risk factors” was reasonable for the TIMI score appropriate to NSTEMI.

2. Accurate risk stratification of the GRACE and TIMI score

The GRACE score is a scoring system that has been objectively studied in patients with acute coronary syndromes with a huge sample size to predict mortality [11]. It was based on eight general endpoints (age, heart rate, systolic blood pressure, creatinine, cardiac arrest on admission, ST elevation, cardiac enzymes, Killip grade) for all patients with acute coronary syndromes without selecting specific, detailed criteria for each type of STEMI or NSTEMI/UA like TIMI, so the risk stratification of GRACE is not close to the actual occurrence of the event. Although GRACE does not accurately predict the risk of events, it does stratify fairly well in the non-event population.

The TIMI score in the study did not show good predictive ability and the risk stratification was inaccurate. TIMI tends to overestimate mortality risk in STEMI patients and underestimate mortality in NSTEMI patients, consistent with findings by Chen et al.[8] In addition, TIMI tends to overestimate the risk of events in study subjects, resulting in a large proportion of cases that are event-free but are classified as high-risk. This affects monitoring, treatment threading, and unnecessary early intervention decisions.

3. Comparison of the predictability of TIMI and GRACE

Our study showed that TIMI had a better predictor of the overall event than GRACE as demonstrated by the risk stratification, specifically in 44 cases of events, the rate of risk stratification is high in TIMI was 20.45%, GRACE was 4.55% (Table 3.3). Based on the ROC curve, TIMI had AUC=0.55 greater than GRACE’s AUC=0.535 (Figure 3.3). This result showed that TIMI was more sensitive than GRACE in predicting significant events in patients with acute MI.

However, in the group of no events, TIMI classified 23 cases (15.2%) into the high-risk group, with an average risk of 97 cases

(64.2%); while GRACE ranked only 9 cases of high risk (5.96%), medium risk of 51 cases (33.77%). Although GRACE was not sensitive to event detection, it stratified better than TIMI in the event-free group.

GRACE was evaluated to be a better predictor of mortality than TIMI by Mendez-Eirín et al, Naqvi et al, Correia et al.[9,10,12] However, in our research, TIMI was more sensitive than GRACE in predicting mortality and overall events. This can be explained that the TIMI score constructed variables related to coronary artery lesions and coronary artery disease risk factors (such as diabetes, hypertension, dyslipidemia, etc ...), criteria that were not included in GRACE. Of the events in this study, 45.45% were coronary revascularization events and all events had high risk factors for coronary artery disease. This result coincides with the TIMI scoring criteria, which makes TIMI a more sensitive assessment of event risk than GRACE. Because objectivity could not be determined, the hypothesis that TIMI predicted events better than GRACE in this study needs to be revisited in a study with a larger sample size.

In summary, our study still objectively indicates that GRACE is more valuable than TIMI in risk stratifying the event-free population. This is consistent with previous studies by Correia et al and Rossi et al.[12,13] We did not collect enough information about the surgical intervention process of each patient for analysis. This may be one of the confounding factors on the study results. However, one of the ways to minimize the confounding factors due to the treatment process, all patients in our study were examined and monitored by the 2 same doctors.

V. CONCLUSION

The study did not show the predictive effect of the two scales GRACE and TIMI on the occurrence of events in patients with acute MI within 12 months. However, the study showed that GRACE's ability to stratify risk for the event-free population was better than the TIMI score. Therefore, we recommend using the GRACE score to monitor patient outcomes after hospital discharge.

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