# Predictors of 30-day Mortality in ST-Elevation Myocardial Infarction (STEMI) Patients

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## ABSTRAK

***Latar belakang:*** *menemukan faktor-faktor lain selain TIMI skor yang dapat dijadikan sebagai predictor mortalitas 30 hari pada pasien ST-elevation myocardial infarction (STEMI) dengan memasukkan variabel laju filtrasi glomerulus dan variabel fraksi ejeksi ventrikel kiri (FEVK) di Rumah Sakit Umum Pusat Nasional (RSUPN) Cipto Mangunkusumo.* ***Metode:*** *studi kohort retrospektif terhadap 487 pasien STEMI yang dirawat di RSUPN Cipto Mangunkusumo pada periode 2004-2013. Besar sampel dihitung dengan menggunakan rumus rule of thumbs. Data diperoleh dari penelusuran rekam medis dan dianalisis secara bivariat dan multivariat menggunakan Cox's Proportional Hazard Regression Model. Setelah itu, sebuah model sistem skor baru dibuat untuk memperkirakan tingkat mortalitas 30 hari pada pasien STEMI. Kemampuan kalibrasi dan diskriminasi dari model sistem skor baru ditinjau dengan menggunakan uji Hosmer-Lemenshow dan AUC (area under receiver operating characteristic curve).* ***Hasil:*** *analisis secara bivariat dan multivariat menunjukkan bahwa hanya dua variabel yang secara statistik bermakna dalam model sistem skor baru yaitu kelas Killip II-IV dan LFG dengan kisaran total skor 0 hingga 4.6. Klasifikasi risiko mortalitas dalam 30 hari pada pasien STEMI adalah tinggi (total skor >3,5; 46,5%), sedang (total skor 2,5-3,5;23,2%), dan rendah (total skor <2,5;5,95%). Dua variable skor ini memiliki kalibrasi (p >0,05) dan diskriminasi (AUC 0.816; IK 95%; 0.756-0.875) yang memuaskan.* ***Kesimpulan:*** *terdapat dua variabel skor baru yang dapat dijadikan sebagai prediktor risiko mortalitas 30 hari pada pasien STEMI, yaitu kelas Killip dan LFG. Dua variabel skor ini memiliki kalibrasi dan diskriminasi yang baik.*

***Kata kunci:*** *prediktor, mortalitas 30 hari, ST-elevation myocardial infarction (STEMI), fraksi ejeksi ventrikel kiri (FEVK).*

## ABSTRACT

***Background:*** *to identify other factors other than the TIMI scores that can be used as predictors of 30-day mortality in STEMI patients by including variables of left ventricle ejection fraction (LVEF) and glomerulus filtration rate (GFR) at Cipto Mangunkusumo National Central General Hospital.* ***Methods:*** *a retrospective cohort study was conducted in 487 STEMI patients who were hospitalized at RSUPN Cipto Mangunkusumo between 2004 and 2013. Sample size was calculated using the rule of thumbs formula. Data were obtained from medical records and analyzed with bivariate and multivariate method using Cox's Proportional Hazard Regression Model. Subsequently, a new scoring system was developed to predict 30-day mortality rate in STEMI patients. Calibration and discrimination features of the new model were assessed using Hosmer-Lemeshow test and area under receiver operating characteristic curve (AUC).* ***Results:*** *bivariate and multivariate analyses showed that only two variables*

*in the new score system model were statistically significant, i.e. the Killip class II to IV and GFR with a range of total score between 0 and 4.6. Thirty-day mortality risk stratification for STEMI patient included high, moderate and low risks. The risk was considered high when the total score was >3.5 (46.5%). It was considered moderate if the total score was between 2.5 and 3.5 (23.2%) and low if the total score was <2.5 (5.95%). Both variables of the score had satisfactory calibration (p > 0.05) and discrimination (AUC 0.816 (0.756-0.875; CI 95%). Conclusion: There are two new score variables that can be used as predictors of 30-day mortality risks for STEMI patients, i.e. the Killip class and GFR with satisfactory calibration and discrimination rate.*

***Keywords:*** *predictor, 30-day mortality, ST-elevation myocardial infarction (STEMI), left ventricle ejection fraction (LVEF).*

## INTRODUCTION

Acute coronary syndrome (ACS) is a global problem considering its staggering morbidity and mortality rate in developed countries as well as in developing countries including Indonesia.[1] Although no nationwide study has been conducted in Indonesia, but the Cipto Mangunkusumo Hospital has some data showing increased hospitalization rate of patients with ACS at the ICCU.[2] Setyawan et al[3] demonstrated that the mortality rate of STEMI patients in RSUPN Cipto Mangunkusumo was 18.6%.

Early and accurate treatment for ACS patients is necessary to reduce mortality rate. Therefore, a mortality risk scoring system should be designed to allow practitioners to predict mortality risk and devise a management plan. At the moment, a mortality risk prediction scoring system known as the Thrombolysis in Myocardial Infarction (TIMI) is widely used.[4] TIMI STEMI score is a simple risk stratification, which consists of parameters obtained directly at hospital arrival.[4] The score has been validated in Indonesia by Setiawan dkk[3] and has shown evidence of calibration and discrimination ability for 30-day mortality prediction with a calibration plot value of 0.98, Hosmer-Lemeshow test value of 0.93, and AUC of 0.801 (0.759-0.844; CI 95%). However, the score is not reliable for high-risk ACS patients with diabetes mellitus and chronic renal failure.[5]

Other parameters include glomerulus filtration rate (GFR) and left ventricle ejection fraction (LVEF), which have been known to affect the prognosis of STEMI patients. Studies done by Gibson et al[6], Akif et al[1], and Selvarajah et al[7] exhibit correlation between high creatinine level and low GFR in STEMI patients as well as TIMI score and increased mortality rate in these patients.[1,6,7] Vivian G Ng et al[8] has proven that 30-day mortality in STEMI patients is correlated with left ventricle dysfunction. The study explains that patients with normal LVEF have lower mortality rate than those with low LVEF. When the In TIME II (2000) study had been completed, these parameters were suggested to be included in TIMI score calculation. Nonetheless, since creatinine test and echocardiography were unfavorable at that time, those parameters were excluded.

We attempted to identify other factors that could be used as 30-day mortality predictors in STEMI patients by including GFR and LVEF, which we considered to be necessary and practical nowadays. These factors were expected to allow more accurate prediction of 30-day mortality rate in STEMI patients.

## METHODS

Study subjects were all STEMI patients who underwent revascularization therapy (PPCI and thrombolytic) and conservative therapy in Cipto Mangunkusumo Hospital, Jakarta and they were followed up. STEMI patients with severe comorbidities, such as acute stroke, hepatic cirrhosis, acute complication of diabetes mellitus, sepsis, chronic inflammation disease, or malignancy were excluded as well as STEMI patients who were pregnant, breastfeeding or without complete medical record. Sample size was calculated using the rule of thumbs formula. A sample size of 484 subjects was necessary to answer our research question. This study has been approved by the Ethics Committee of Faculty of Medicine Universitas Indonesia, reference number 403/H2.F1/ETIK/2014.

### Study Design and Procedure

The design of our study was retrospective cohort, which was based on prognostic studies. Data were collected from medical records of hospitalized patients and 30-day mortality outcome after onset of STEMI was recorded

**Table 1.** Basic and clinical subject characteristics

| Subject Characteristics | Total patient n = 487 | Conservative therapy n = 213 | Reperfusion therapy n = 274 |
|---|---|---|---|
| Sex, male, n (%) | 371 (76.2) | 151 (70.8) | 220 (80.3) |
| Age, n (%) | | | |
| - <65 years old | 363 (74.5) | 143 (67.1) | 220 (80.3) |
| - 65-74 years old | 94 (19.3) | 52 (24.4) | 42 (15.3) |
| - >74 years old | 30 (6.2) | 18 (8.5) | 12 (4.4) |
| Comorbidities, n (%) | | | |
| - Hypertension | 255 (52.4) | 109 (51.2) | 146 (53.3) |
| - Diabetes mellitus | 141 (29) | 59 (27.7) | 82 (29.9) |
| Smoking history, n (%) | | | |
| - Active smoker | 256 (52.6) | 118 (55.4) | 138 (50.4) |
| - Former smoker | 59 (12.1) | 23 (10.8) | 36 (13.1) |
| Dyslipidemia, n (%) | 113 (24.6) | 39 (18.3) | 74 (27) |
| Obesity, n (%) | 163 (33.5) | 53 (24.9) | 110 (40.1) |
| ACS history in family, n (%) | 55 (11.6) | 19 (8.9) | 36 (13.1) |
| Cardiac arrest on arrival, n (%) | 12 (2.5) | 6 (2.8) | 6 (2.2) |
| Systolic blood pressure | | | |
| - Median (minimum, maximum) mmHg | 119 (60.2) | 117 (60.2) | 120 (70.2) |
| Heart rate | | | |
| - Median (minimum, maximum) beats/minute | 84 (30.2) | 90 (30.2) | 82 (46.2) |
| Glomerulus filtration rate, n (%) | | | |
| - ≥60 mL/minute | 303 (62.2) | 118 (55.4) | 185 (67.5) |
| - 30 - <60 mL/minute | 134 (27.5) | 59 (27.7) | 75 (27.4) |
| - <30 mL/minute | 47 (9.7) | 34 (16) | 13 (4.7) |
| - Unknown | 3 (0.6) | 2 (0.9) | 1 (0.4) |
| Infarct location, n (%) | | | |
| - Anterior septal | 147 (30.2) | 69 (32.4) | 78 (28.5) |
| - Anterior lateral | 8 (1.6) | 4 (1.9) | 4 (1.5) |
| - Anterior extensive | 109 (22.4) | 46 (21.6) | 63 (23) |
| - Inferior posterior lateral | 14 (2.9) | 7 (3.3) | 7 (2.6) |
| - Inferior | 93 (19.1) | 37 (17.4) | 56 (20.4) |
| - Inferior posterior | 40 (8.2) | 17 (8) | 23 (8.4) |
| - Inferior lateral | 6 (1.2) | 1 (0.5) | 5 (1.8) |
| - Inferior right | 26 (5.3) | 16 (7.5) | 10 (3.6) |
| - Lateral | 3 (0.6) | 2 (0.9) | 1 (0.4) |
| - Anterior | 39 (8.0) | 13 (6.1) | 26 (9.5) |
| - Unknown | 2 (0.4) | 1 (0.5) | 1(0.4) |
| Killip class, n (%) | | | |
| - Killip class I | 259 (53.2) | 77 (36.2) | 182 (66.4) |
| - Killip class II-IV | 228 (46.8) | 136 (63.8) | 92 (33.6) |
| LVEF, n (%) | | | |
| - ≥ 40% | 308 (63.2) | 115 (54) | 193 (70.4) |
| - < 40 % | 150 (30.8) | 77 (36.2) | 73 (26.6) |

from December 2013 onwards. Main data were TIMI STEMI score and its components, GFR and LVEF, and 30-day mortality rate post STEMI. Basic demographic data such as age, sex, smoking history, dyslipidemia history, and location of infarction were also documented.

### Statistic Analysis

Data were analyzed using SPSS software program version 21.0. Basic data were evaluated using descriptive statistics. To answer our research question, the analysis was carried out with bivariate and multivariate methods using Cox's Proportional Hazard Regression Model. After a new prognostic scoring model was obtained, its calibration and discrimination features were tested using Hosmer-Lemeshow test and by evaluating area under receiver operating characteristic curve (AUC) respectively. Classification based on risk death was constructed. The classification was established using score interval that was obtained from the new scoring system. The model of new scoring system was tested on all data and was compared with the pre-existing TIMI score.

## RESULTS

Our study included 487 subjects with STEMI, in which the number was greater than the estimated necessary sample size as shown on **Table 1**. There were 371 male patients (76.2%) and 116 female patients (23.8%) with age ranging between 28 and 91 years old; while the median of age was 57 year old. There were 247 subjects who received reperfusion therapy and 213 subjects who received conservative therapy.

Bivariate analysis with $p<0.25$ indicated that there was an association between 30-day mortality rate in STEMI patients and several parameters, which were age, systolic blood pressure, heart rate, Killip class, LVEF, and GFR as shown in **Table 2**.

Multivariate analysis, which was conducted on similar parameters, showed that only two statistically significant variables on the Cox's proportional hazard regression model, which were Killip class ($p=0.000$) and GFR ($p=0.004$). Regression coefficient per error standard of each parameter was then rounded up to construct the new scoring system as shown in **Table 3**. The new scoring system for 30-day mortality prediction in STEMI patients is shown in **Table 4**.

The new scoring system classifies the mortality risk into mild risk, moderate risk, and high risk (**Table 5**) based on the following equation:

$$p = \frac{1}{1+\exp(-y)'}$$

in which $y = -4.321 + (3.736 \times \text{total score})$

**Tabel 2.** Bivariate analysis on predictors of 30-day mortality rate in STEMI patients

| Parameters | P value | HR (95%CI) |
|---|---|---|
| Age | | |
| - < 65 years old | Ref | |
| - 65-74 years old | 0.001 | 2.564 (1.443-4.555) |
| ≥75 years old | 0.373 | 1.607 (0.566-4.561) |
| Systolic blood pressure <100 mmHg | 0.008 | 2.276 (1.236-4.912) |
| Heart rate >100x/minute | < 0.001 | 1.643 (1.248-2.164) |
| Killip class II-IV | < 0.001 | 3.466 (2.187-5.494) |
| Comorbidity (diabetes mellitus/ hypertension/angina) | 0.606 | 1.164 (0.654-2.072) |
| Reperfusion therapy >4 hours | 0.711 | 1.213 (0.438-3.361) |
| Anterior infarct location/ left bundle branch block | 0.383 | 1.303 (0.719-2.360) |
| Glomerulus Filtration Rate (GFR) | | |
| - ≥60 mL/minute | Ref | |
| - 30-59 mL/minute | 0.006 | 2.523 (1.300-4.895) |
| - <30 mL/minute | <0.001 | 7.426 (3.789-14.555) |
| Left Ventricle Ejection Fraction (LVEF) <40% | 0.027 | 2.089 (1.087-4.014) |

*Ref: Reference

**Table 3.** Multivariate analysis for prediction score construction

| Variable | Regression coefficient (B) | SE | B/SE | Score | Score rounding up |
|---|---|---|---|---|---|
| Killip class II-IV | 2.344 | 0.4 | 4.82 | 2.38 | 2.4 |
| Glomerulus Filtration rate | | | | | |
| - 30-59 mL/minute | 0.748 | 0.369 | 2.03 | 1.00 | 1.0 |
| - <30 mL/minute | 1.816 | 0.415 | 4.38 | 2.16 | 2.2 |
| Constant | -4.321 | | | | |

**Table 4.** The new scoring system that can be used as 30-day mortality predictor in STEMI patients

| Variables | Score |
|---|---|
| Killip class | |
| - I | 0 |
| - II-IV | 2.4 |
| Glomerulus Filtration Rate (GFR) | |
| - ≥ 60 mL/minute | 0 |
| - 30-59 mL/minute | 1.0 |
| - < 30 mL/minute | 2.2 |

**Table 5.** 30-day mortality prediction score and risk classification

| Score | Risk Classification | Probability (%) |
|---|---|---|
| <2.5 | Low | 5.95 |
| 2.5-3.5 | Moderate | 23.2 |
| >3.5 | High | 46.5 |

Hosmer-Lemeshow test was conducted on the new scoring system to assess its precision. The result showed p>0.05. To assess its discrimination, AUC (area under receiver operating characteristic curve) was used and showed 0.816 (0.756-0.875; CI 95%). These results indicate that the new scoring system has reliable precision and discrimination features.

Internal validation using bootstrap analysis demonstrated statistically significant results (p=0.001). **Figure 1** show an observation-prediction curve based on the new scoring system. Another Hosmer-Lemeshow test was performed and the result showed similar p value (p>0.05) and similar AUC of 0.816 (0.756-0.875; CI 95%).

## DISCUSSION

Our study on the new scoring system in Cipto Mangunkusumo Hospital is a retrospective

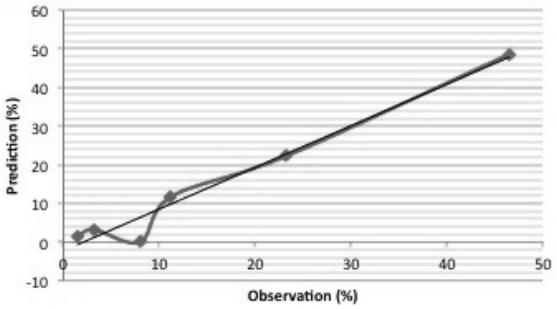


**Figure 1.** An observation-prediction curve based on the new scoring system for 30-day mortality prediction in STEMI patients

cohort study with 487 subjects of STEMI patients in ER. Our study documented 30-day mortality rate in STEMI patients (10.9%), which is higher than the rate found in the In-TIME II (2000) study (6.7%) and EFFECT (2007) study (9.1%). On the other hand, our study shows a slight difference with Selvarajah et al (2012) (11.1%), NRMI 3 (12.6%) and Cipto Mangunkusumo Hospital ICCU study (1990-2007) (12%).[3,4,7,9,10]

Our study has identified ten variables as 30-day mortality predictors in STEMI patients. Eight variables are the original variable used in the In-TIME II (2000) study and two additional variables are LVEF and GFR. We analyzed these two additional variables based on studies done by Vivian Ng et al and Gibson et al.[6,8] The aim of our study is to obtain a new scoring system, which predicts 30-day mortality rate in STEMI patientsin Cipto Mangunkusumo Hospital. Multivariate analysis showed only two variables with statistic significance, which are Killip class and GFR (p<0.05).

Killip class II to IV had p = 0.000 with a hazard ratio of 3.466 (2.187-5.494; CI 95%). The result is similar with results of multivariate analysis in the In TIME II (2000) study, which showed that Killip class II to IV had an OR of 2.3

(1.9-2.7; CI 95%) and 2 points in TIMI STEMI score calculation. GUSTO I and Lee et al11 showed 13.6% mortality rate and OR 2.95 (2.79-3.23; CI 95%) for Killip class II; 32.3% mortality rate and OR 8.91 (7.63-10.40; CI 95%) for Killip class III and 57.8% mortality rate and OR 25.68 (21.96-30.03; CI 95%) for Killip class IV.[11]

Killip class II-IV has strong predictive attribute as 30-day mortality predictor in TIMI score for STEMI patients. Characteristics of Killip class classification represent clinical LVEF function after infarct. Myocardium suffers post-infarct pump function deterioration, which may have similar appearance with heart failure. Such dysfunction causes mortality rate in STEMI patients to increase 3 to 4 times higher than those without myocardial dysfunction.

Our study has also found that GFR is also one of the statistically significant 30-day mortality predictors in STEMI patients (p=0,000). Our result is similar with results of a study conducted by Chan et al[13], which found that there was no significant difference between patients undergoing reperfusion therapy with low GFR and those with normal GFR. Sadeghi et al[14] suggested that patients with low GFR have metabolic-function-related abnormalities including insulin resistance, dyslipidemia, homocysteinemia, hyperuricemia, thrombosis, and oxidative stress. These factors play essential roles in elevating cardiovascular disease risk.

Some variables such as age, diabetes mellitus, angina, hypertension, systolic decrease, heart rate increase, infarct location, and LVEF are statistically insignificant since GFR and Killip class have had taken these variables into account; while MDRD formula calculates GFR with age as a part of the formula.[15-16] GFR directly represents diabetes mellitus and hypertension. Angina, systolic decrease, heart rate increase, infarct location and LVEF are parts of Killip class determination factors.

## CONCLUSION

The new 30-day mortality prediction model in STEMI patients has only two variables, which are Killip class and GFR. The new scoring system has satisfactory calibration and discrimination features as 30-day mortality predictor in STEMI patients.

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