Acta Cardiologia Indonesiana (*Vol 2 No. 2)*: 39-46

Prediction of Failed Fibrinolytic Using Scoring System in ST Elevation Myocardial Infarction Patients

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Abstract

Background: ST elevation myocardial infarction (STEMI) is the most common acute coronary syndrome in adults, and requiring immediate reperfusion. Primary percutaneous coronary intervention (PCI) is the main reperfusion therapy, but because of many limitations, fibrinolytic is often chosen. Fibrinolytic have high failure risk, so it is important to be able to predict whether this therapy will fail or not. This research aim to create a scoring system to predict failed fibrinolytic in STEMI patients.
Methods: This is retrospective cohort study using medical records data from Dr. Sardjito General Hospital in Yogyakarta, recorded in June 2014-December 2015. The population was STEMI patients that reperfused with streptokinase regiment. Determination of failed fibrinolytic was using the difference in the ST segment elevation of the pre and post fibrinolytic electrocardiogram (ECG). The clinical variables of subjects were recorded. The statistical analysis was done and scoring system was constructed.
Results: A total of 105 patients with mean age of 57.82±9.59 years were included in this study. Subjects with failed fibrinolytic was 53 patients (50.5%). Several variables were independently associated with failed fibrinolytis, i.e. the onset of ≥ 6 hours, hyperglycemia, and the location of anterior infarction (OR = 11.3, p = 0.000; OR = 6.11, p = 0.003 and OR = 10.5, p = 0.001, respectively). After scoring system was constructed, it was found that score ≥ 2 predict failed fibinolytic, with 53% sensitivity and 94% specificity.
Conclusions : Scoring system consisting of onset ≥ 6 hours, hyperglycemia in arrival, and anterior infarct location, can be used to predict failed fibrinolytic in STEMI patients using streptokinase with 53% sensitivity and 94% specificity.

Keywords: failed fibrinolytic scoring, fibrinolytic; STEMI; streptokinase

Background

ST elevation myocardial infarction (STEMI) is the most common acute coronary syndrome in adults. This disease is mainly caused by intracoronary thrombosis after atherosklerotic plaque rupture in coronary artery. Mortality rate in 24 hours in STEMI is 30%, whereas 5-10% survived patients will die after 1 year. The presence of ST segment elevation in electrocardiogram (ECG) signals active transmural damage. Without immediate reperfusion therapy, the damage will develop into irreversible myocardial necrosis, which indicated by the presence of Q waves on ECG. This necrosis can evolve into heart failure and become a substrate for lethal arrhytmia events.[1]

Thrombus occlusion will persist in most of STEMI patients. Timely reperfusion therapy is the most effective step in restoring the balance between oxygen supply and demand in myocardium. There are two ways of reperfusion, ie with primary percutaneous coronary intervention (PCI), or fibrinolytic therapy. Primary PCI is the preferred reperfusion strategy if it can be done within 120 minutes of first medical contact in PCI uncapable hospitals, or 90 minutes on PCI capable hospitals. In Indonesia, only a few hospitals have this facility. Therefore there are limitations in conducting timely primary PCI, fibrinolytic therapy remains an important reperfusion strategy in STEMI patients.[2] In a study by Fibrinolytic Therapy Trialist (FTT) group

showed that administration of fibrinolytic therapy prevents 20-30 deaths in 1000 patients with mortality reduction of 25%.[3]

One of the shortcoming of fibrinolytic therapy is the presence of treatment failure. Fibrinolytic therapy have success level that depends on the fibrinolytic drug used. Until now, one of the most commonly used drug is streptokinase, which has a low success rate of 60-68%.[4] While in failed fibrinolytic patients, emergency rescue PCI should be done immediately. Therefore, it is important to be able to estimate the chance of failed fibrinolytic in STEMI patients that was done fibrinolytic using streptokinase.

There are various kinds of predictors that can predict the failure of fibrinolytic therapy, but to determine the prognosis of fibrinolytic therapy using the predictors are quite complicated. Scoring system is an easy way to facilitate determination of the prognosis of a disease or therapy.[5] However, until now author did not find a scoring system to predict the failure of fibrinolytic therapy.

Methods

This is retrospective cohort study using medical records data from Dr. Sardjito General Hospital in Yogyakarta, recorded in June 2014-December 2015. The subjects of thise study was STEMI patients that were undergone reperfusion strategy with streptokinase regiment. Determination of failed fibrinolytic was using the difference in the ST segment elevation of the pre and post fibrinolytic electrocardiogram (ECG) based on ACC/AHA criteria. Several demography, clinical and laboratory parameters of the subjects were recorded and analyse as predictors of failed fibrinolytic.

Statistical analysis was performed with bivariate and multivariate analysis and scoring system with weight value calculation was constructed. A p value < 0.05 was considered as statistical significance.

This research is a non-experimental research so that there is no specific intervention on the subject. This study was using secondary data from patients medical records. This study did not influence patient's disease management. This study was conducted after approval from the ethics committee of the Faculty of Medicine Universitas Gadjah Mada, Yogyakarta, Indonesia.

Result

The retrieval of data was based on medical records in the period of June 2014 to December 2015. Total subjects who met the inclusion criteria were 120 patients. A total of 15 patients were excluded because there is a bundle branch block in ECG or premature cessation of fibrinolytic.

An ECG assessment was performed by two observers who first tested the Kappa

Table 1. Characteristics of STEMI patients that was done fibrinolytic using streptokinase regiment

Variables	Value (n=105)
Sex, n(%)	
Male	95 (90.5%)
Female	10 (9.5%)
Age (years old), mean±SD	57.82 ± 9.59
Elderly (> 75 years old), n(%)	6 (5.7%)
Clinical	
Hypertension, n (%)	48 (45.7%)
Diabetes, n (%)	17 (16%)
Not smoker, n (%)	23 (21.9%)
Killip class > 1, n (%)	20 (19%)
Onset	
≥ 6 hours, n (%)	29 (27.6%)
< 6 hours, n (%)	76 (72.4%)
Laboratory examination	
Leukocytosis/neutrophilia, n (%)	88 (83.8%)
Hyperglycemia, n (%)	26 (24.8%)
Blood glucose, mean±SD	171 ± 75.97
Increased creatinine level : n (%)	42 (40%)
Creatinine level, mean±SD	1.38 ± 0.75
Electrocardiography	
Anterior infarction, n (%)	60 (57.1%)
Failed fibrinolytic; n (%)	53 (50.5%)

Table 2. Bivariate analysis of STEMI patients that was done fibrinolytic using streptokinase regiment

Variables	Fibrinolytic		p value
	Failed n = 53	Successful n = 52	
Male sex, n (%)	47 (49.5%)	48 (50.5%)	0.527
Elderly (> 75 years old), n (%)	4 (66.7%)	2 (33.3%)	0.410
Hypertension, n (%)	30 (62.5%)	18 (37.5%)	0.024*
Diabetes, n (%)	11 (64.7%)	6 (33.3%)	0.200*
Not smoker, n (%)	14 (60.9%)	9 (9.1%)	0.260
Killip class > 1, n (%)	15 (75%)	5 (25%)	0.015*
Onset ≥ 6 hours, n (%)	24 (82.8%)	5 (17.2%)	0.000*
Leukocytosis / neutrophilia, n (%)	45 (51.1%)	43 (48.9%)	0.760
Hyperglycemia, n (%)	20 (76.9%)	6 (23.1%)	0.002*
Increased creatinine level, n (%)	23 (54.8%)	19 (45.2%)	0.470
Anterior infarction, n (%)	39 (65%)	21 (35%)	0.001*

*statistically powerful to be included in multivariate analysis

suitability value. From the interobserver Kappa test performed we obtained a value of 0.85, which means that there was a very strong conformity between ECG observer. This study showed that there was 53 (50.5%) subjects who have failed fibrinolytic. The number of subjects who had an anterior infarction was 60 (57.1%). Table 1 showed the characteristics of subjects.

The subjects was divided into two groups, i.e. those who had failed fibrinolytic and those who had successful fibrinolytic. The bivariate analysis was conducted to find factors that can affect the result of fibrinolytic. In bivariate analysis, factors that have statistically significant differences in both groups were hypertension, diabetes, Killip class, onset, hyperglycemia, and anterior infarct location (shown in table 2).

To examine the relationship between various independent variables on fibrinolytic failure, multivariate analysis was done by using logistic regression, with the inclusion criteria those who had p value <0.25. Based on multivariate analysis, the onset ≥ 6 hours, hyperglycemia, and the anterior infarction were associated independently with failed fibrinolytic (OR = 11.3, p = 0.000; OR = 6.11, p = 0.003 and OR = 10.5, p = 0.001, respectively). Table 3 shows the multivariable analysis.

To determine the scoring system, first we performed the analysis and calculation of the weight value (score) from each independent predictors associated with fibrinolytic failure. From the calculation we found score is 1 for each predictors (table 4).

By looking at the score that has been obtained, scoring system based on probability may now be established. Ths scoring system model is based on the score of probability. From the calculation results, when the subject has an onset ≥ 6 hours, hyperglycemia, or infarct

Table 3. Multivariate analysis of failed fibrinolytic predictors

Predictors	p value	OR	95% Confidence Interval
ypertension	0.074	2.43	0.92 - 6.44
Diabetes	0.26	2.00	0.89 - 2.05
Killip > 1	0.53	1.55	0.40 - 6.02
Onset ≥ 6 jam	0.000*	11.3	3.30 - 38.9
Hyperglycemia	0.005*	6.11	1.86 - 20.0
Anterior infarction	0.002*	10.5	1.93 - 14.4

FIBRINOLYTIC PATIENTS SCORING CARD
BASED ON PROBABILITY

Patient name :
Complete data below. Use (V) mark in the box corresponding to the patient's condition.

Predictor	Yes	No	Patient score
STEMI onset ≥ 6 hours	1	0	
Hyperglycemia on arrival	1	0	
Anterior infarction	1	0	
Total score			

Note:

Total score	Failed fibrinolytic probability (%)
0	12 %
1	48 %
2	97 %
3	99 %

Figure 1. Scoring card based on probability of subjects to get a failed fibrinolytic

location, each have score of 1. The probability is then calculated for each subject have failed fibrinolytic uses regression equation (table 5).

Moreover, we can set up a scoring system based on the value of the cutoff point. This scoring system model is derived from the value of sensitivity and specificity chart based on probability. Figure 1 and 2 were the scoring system chart based on probability as well as cut-off point.

Discussion

In this retrospective study, we investigated the predictors associated with fibrinolytic failure in 105 patients. Although fibrinolytic is one of the option for reperfusion in STEMI, but more than a third of patients do not respond well to this therapy and follow-up actions should be done in the form of rescue PCI.[5] Determination of fibrinolytic results in this study is using ST segment resolution. Some literature suggests that ST segment resolution is better to determine prognosis, and may be more a marker of reperfusion failure when compared with TIMI flow. TIMI flow only see the blood flow in the epicardial coronary, while the ST segment is also reflects microvascular blood flow.[6] For this reason, we use the ST segment resolution < 50% as fibrinolytic failure criteria.

Table 4. Calculation of the weight value (score) from each independent predictors associated with fibrinolytic failure

Predictors	B	SE	B/SE	[B/SE]/x	Score
Onset ≥ 6 jam	2.5	0.64	3.91	1.4	1
Hyperglycemia	1.74	0.61	2.85	1.0	1
Anterior infarction	1.58	0.52	3.03	1.1	1

FIBRINOLYTIC PATIENTS SCORING CARD
BASED ON CUTOFF POINT

Patient name :
Complete data below. Use (V) mark in the box corresponding to the patient's condition.

Predictor	Ya	Tidak	Skor pasien
☐ STEMI onset ≥ 6 hours	1	0	
☐ Hyperglycemia on arrival	1	0	
☐ Anterior infarction	1	0	
Total score			

Note:
Fibrinolytic therapy will fail if the patient had a total score of ≥ 2
Fibrinolytic therapy will succeed if the patient had a total score of ≤ 1

Figure 2. Scoring card based on cut-off value of subjects to get a failed fibrinolytic

In this study, the use of fibrinolytic streptokinase is failed in 53 patients (50.5%). This is consistent with the existing literature and guidelines, that said streptokinase had a failure rate in nearly half of STEMI patients.[5] This study found factors that do not affect fibrinolytic failures are gender, age, smoking history, value of leukocyte / neutrophil, and creatinine. In addition to the above factors, factors that predict failure of fibrinolytic but not independently are hypertension, diabetes and Killip class > 1, while independent predictor factors are the onset of STEMI ≥ 6 hours, hyperglycemia, and locations involving anterior infarction.

Gender was not a confounding factor in this study. In bivariate analysis, gender did not affect the results of fibrinolytic (p = 0.53). This is consistent with four previous studies, which reflected that although the literature said that men are more prone to the "no-reflow" phenomenon, but in clinical practice is rare to have fibrinolytic failure. Male make up the majority of the study subjects (90.5%). This is consistent with previous studies in which female experience less STEMI that was done fibrinolytic. Research by Sinkovic et al.[7] showed that male consist of 78 of the 106 subjects (73%). Other studies had similar results where men make up 60%, 82%, and 70% of subjects, respectively.[8,9,10]

This study shows that advanced age is not related to the failed fibrinolytic (p = 0.41). This is consistent with prior research.[7,10]. The different

Table 5. Calculation of the probability (p) of each score based on a logistic regression

Patient's score (S)	Constant (A)	Coefficient (B)	y_0 = BxS	y = A+B	$p = \frac{1}{1+\exp(-y)}$
0	-2	1.908	0	-2	0.12
1	-2	1.908	1.908	-0.092	0.48
2	-2	1.908	5.816	3.816	0.97
3	-2	1.908	7.724	5.724	0.99

results expressed by other study, where the older age correlated positively with fibrinolytic failure, but not independently,[9] so it can be concluded that in general the elderly only have indirect effect on fibrinolytic results. This result have clinical implications, namely in elderly STEMI patients who will be given fibrinolytic, we can consider other factors than failed reperfusion, for example, the risk of bleeding or stroke risk.

Only a small proportion (21.9%) patients have no history of smoking in this study. Smoking history are not predictor of failed fibrinolytic in this study (p = 0.26). Kocas et al.[10] found similar result, with the percentage of subjects who had a smoking history is 34.4% in the group of successful fibrinolytic and 55.4% in the group failed fibrinolytic (p = 0.08). This is contradicting with Rosencher et al.[9], that found history of smoking was an independent predictor of successful fibrinolytic (OR = 1.75, p = 0.003). This difference is due to the basic characteristics of the subject in our research, where most subject have a history of smoking, which shows that smoking is still a problem that can not be separated from the life of the populations. This problem is a challenge for medical practitioners and stakeholders to improve health promotion efforts in reducing the prevalence of this traditional cardiovascular risk factors.

Leukocyte / neutrophil and creatinine values was not predictor of failed fibrinolytic in this study (p = 0.76; p = 0.47). Increased creatinine level in arrival has proven to be an independent predictor of 30-day mortality in patients with STEMI. [11] Therefore, when predicting the failure of fibrinolytic, should not wait for these laboratory parameters. We expect this result to accelerate time to treatment in patients who was given fibrinolytic.

Hypertension affects the failed fibrinolytic, but not independently in this study. Bivariate analysis get results of p = 0.024, while univariate get results of p = 0.074. The different results obtained by several studies who found that hypertension has no effect on the outcome of fibrinolytic.[7,9,10]

A Killip class > 1 have effect on fibrinolytic failure, but not independently in this study. Bivariate analysis got results of p = 0.015, while univariate get results of p = 0.53. The different results obtained by Rosencher et al.[9] and Kocas et al.[10] who found that Killip class has no effect on the outcome of fibrinolytic. This result suggests that the presence of heart failure that occurs arrival might only indirectly affect the results of fibrinolytic, which is because in this study, heart failure is almost entirely in patients with infarction in the anterior leads.

History of diabetes have effect on fibrinolytic failure, but not independently. Bivariate analysis get results of p = 0.2, were univariate get results of p = 0.26. This is consistent with previous research.[10] The different results showd other study who found that diabetes is a predictor of failure of fibrinolytic.[8] The results of this study may be because the majority (14 of 17) of patients with diabetes have hyperglycemia on admission, but less than half of patients who experience hyperglycemia is diabetic (12 of 26 patients).

Onset STEMI ≥ 6 hours was an independent predictor of fibrinolytic failure in this study. This is consistent with several previous studies. Research by Rosencher et al.[9] showed that onset fibrinolysis ≤ 1 hour is an independent predictor of the success of fibrinolytic (OR = 1.76, p = 0.006). Kocas et al.[10] also mention that there are significant differences between the onset of STEMI with fibrinolytic failure, where the subject who experienced failure had a mean onset time of 180 minutes compared to having successful fibrinolysis who had 150 minutes. Sinkovic et al.[7] have different result in which STEMI onset is not related to the results of fibrinolytic. In another study, in patients with STEMI performed primary PCI, the onset ≥ 6 hours has been identified as an independent predictor of failure of reperfusion.[12]

These results provide clinical implications which is STEMI patients who arrive late at the hospital should be given extra attention when determining the reperfusion strategy.

Hyperglycemia was an independent predictor of fibrinolytic failure in this study (p = 0.005). This result fit in research conducted by Kocas et al.[10] where arrival hyperglycemia is an independent predictor of fibrinolytic failure. Increase in blood sugar is frequent in patients treated with STEMI, with a prevalence of 14-50%.[10,13]. In this study, the prevalence of hyperglycemia amounted to 24.8%. Although several studies have been looking for the effects of hyperglycemia on the cardiovascular system, there has been no consensus on the definition of acute hyperglycemia in patients with STEMI. Some studies such as Wahab et al.[13] and Kocas et al.[10] was using criteria based on guidelines from the American Diabetes Association, which is> 198 mg/dL, but in our study we use criteria based on the guidelines of PERKENI i.e. ≥ 200 mg/dL.[14] The results in this study also indicates that while diabetes is one of the traditional cardiovascular risk factors and the phenomenon of "no-reflow", but in patients with STEMI and given fibrinolytic, it is preferred to use random blood sugar tests.

Infarction involving anterior is an independent predictor of fibrinolytic failure in this study. This is consistent with other research where anterior infarcts is a predictor of failure fibrinolytic.[9] However, other study have different result that state although STEMI patients who failed fibrinolytic have more that involving anterior infarction, infarct location not associated statistically with fibrinolytic failure.[10]

These three independent predictors of failed fibrinolysis, namely onset ≥ 6 hours, hyperglycemia, and anterior infarct location can easily be checked in STEMI patients that will be given fibrinolytic. Only by anamnesis, a simple laboratory examination, and ECG, clinicians can estimate the results of fibrinolytic. To further simplify and accelerate the predictions, clinicians may use a scoring system that has been created. In this study, the scoring system have sensitivity of 53% and a specificity of 94% in predicting the failure of fibrinolytic. The results support the research hypothesis that the scoring system is capable to predict failed fibrinolytic in STEMI patients.

Study Limitations

This study was done retrospectively, so it has a lower level of evidence than a prospective study. Some of the variables examined in this study was derived from previous studies. Other variables not examined in this study were the body mass index and door to needle time, due to the limitations in the data in medical record.

Conclusion

A scoring system consisting of onset ≥ 6 hours, hyperglycemia in arrival, and anterior infarct location, can be used to predict failed fibrinolytic in STEMI patients using streptokinase regiment, with 53% sensitivity and 94% specificity. Failed fibrinolytic was predicted in patient who had score of at least 2, with a probability of 97%.

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