

Role of CHA₂DS₂-VASc-HS Score as Predictor for Failed Reperfusion After Fibrinolytic in St-Elevation Myocardial Infarction

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Abstract : Background: Recent studies showed that CHA₂DS₂-VASc-HS score can effectively predict longterm outcome, hospitalization and severity in CAD. However, the role of this score in predicting failed reperfusion after fibrinolytic in STEMI patients has not been studied extensively. The main objective of this study was to determine whether CHA₂DS₂-VASc-HS score can predict failed reperfusion after fibrinolytic in STEMI patients.

Methods: A total of 62 patients with STEMI who undergo fibrinolytic at Haji Adam Malik Hospital since October 2017 until November 2018 were recruited in this cross sectional study. We also performed complete blood count and chest x-ray. CHA₂DS₂-VASc-HS score was counted before the fibrinolytic started. After the fibrinolytic was done, we assessed the succesfullness with the decrease of chest pain, resolution of ST segments > 50% and aritmia reperfusion criterias.

Results: The cut-off value of CHA₂DS₂-VASc-HS score was 4 (AUC 0.928, 95% CI 0.861-0.995, p<0.05). The CHA₂DS₂-VASc-HS score \geq 4 group had higher incidence of failed reperfusion. CHA₂DS₂-VASc-HS score \geq 4 is considered to predict the incidence of failed reperfusion with a sensitivity of 91.7%, a specificity of 69.2%, NPV of 85.7% and PPV of 80.4%. Multivariate analysis also showed that CHA₂DS₂-VASc-HS score \geq 4 was an independent factor that could predict the occurrence of failed reperfusion (OR 23.769, p<0.001).

Conclusion: CHA₂DS₂-VASc-HS score is a simple, very useful and easy-to remember bedside score and an inexpensive indicator which can be used as a prognostic marker for failed reperfusion after fibrinolytic in STEMI.

Keyword : CHA₂DS₂-VASc-HS, fibrinolytic, STEMI.

Introduction

Acute ST Segment Elevation Myocardial Infarction (STEMI) is a part of acute coronary syndrome that occurs due to a total blockage of coronary arteries by thrombus formed or released as the body's response to

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arterosclerotic plaque rupture.¹ STEMI patients require revascularization to restore blood flow and myocardial reperfusion, which can be done by pharmacological therapy (fibrinolytic agent) or mechanically, namely Percutaneous Coronary Intervention (PCI) primary. Fibrinolytic is an important reperfusion strategy, especially in places that cannot perform PCI. Fibrinolytic therapy is recommended given within 12 hours of symptom onset in patients without a counter indication if the primary PCI cannot be performed by a team experienced in 120 minutes since the first medical contact.^{2,3} Criteria for successful fibrinolytic can be assessed by reduce chest pain, decrease elevation ST segment more than 50% and find arrhythmias reperfusion such as accelerated idioventricular rhythms.^{4,5}

The CHA₂DS₂-VASc score is a score developed for emboli risk stratification in atrial fibrillation patients. The components of the CHA₂DS₂-VASc score for each letter are the beginning of a certain word, Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke history, Vascular disease, Age between 65 to 74 years, and Sex category (female).^{6,7} Some recent studies have developed the use of the CHA₂DS₂-VASc score in the non-AF population. The study by Kim found that a high CHA₂DS₂-VASc score could provide worse cardiovascular outcomes in patients with acute myocardial infarction.⁸ The study conducted by Cetin found the CHA₂DS₂-VASc-HS score with additional "H" (Hyperlipidemia) and "S" (Smoker) components as well as the Sex category component that prioritized male gender as predictors of CAD severity.⁹ Some components of this scores, namely hypertension, age, diabetes mellitus, male gender, hyperlipidemia and smoking are traditional risk factors for CAD, very important and a prognostic factor in cardiovascular outcome. Clinicians need simple, reliable, easy to use and quantitative tools to identify patient risks and recommend prevention strategies. Furthermore, most CAD patients have at least one risk factor, and if they have more than one risk factor it will increase the risk of CAD and will give a worse outcome.^{10,11}

Seeing the role of the CHA₂DS₂-VASc-HS score in CAD, the aim of this study is to assess the role of the CHA₂DS₂-VASc-HS score in predicting failed reperfusion after fibrinolytic in patients with STEMI.

Method

Population and Study Design

This study is a cross-sectional study conducted at Haji Adam Malik General Hospital in Medan, Indonesia, with permission from the Research Ethics Committee of the Medicine Faculty of University of North Sumatra. The study subjects were patients with acute STEMI admitted to the emergency department (ED) from October 2017 until November 2018. Diagnosis of STEMI based on the diagnostic criteria of ESC. The inclusion criteria were patients with a diagnosis of STEMI with onset of less than 12 hours and received fibrinolytic therapy with tissue plasminogen activator (t-PA;alteplase). ECG records that cannot be read perfectly and patients with contraindications of fibrinolytic therapy were excluded from this study. 12 leads ECG examination was performed at the beginning of admission in emergency unit and 90 minutes from the start of fibrinolytic therapy with a recording speed of 25 mm/s and a scale of 10 mm/mv. In this study, 62 peoples have met the inclusion and exclusion criteria and provided with written informed consent and recruited as subjects.

Study Procedure

Baseline clinical and demographic characteristics including age, sex category, previous history of illness such as diabetes mellitus, hypertension, heart failure, stroke, vascular disease and hyperlipidemia, smoking history, family history of CHD, family history of drug use and also vital sign were completely recorded. The initial important data evaluated were 12 lead ECG at the time of admission in the emergency room of Adam Malik General Hospital and 90 minutes from the start of fibrinolytic therapy. The patient also undergo blood test and chest x-ray. The CHA₂DS₂-VASc-HS score was calculated before the fibrinolytic therapy started. Then based on fibrinolytic results, subjects were divided into two groups, the first group who experienced fibrinolytic failure and the second group who experienced fibrinolytic successful.

Statistic Analysis

All statistical analyses were carried out using the SPSS statistical software. Categorical variables are presented by number or frequency (n) and percentage (%). Numeric variables are presented with mean values

with standard deviations for normally distributed data. The normality test of numeric variables in all study subjects using the Kolmogorov-Smirnov test ($n > 50$). In numeric variables compared with two free samples T test (Two Samples Independent Student's t-test) on normal distributed data or Mann Whitney U Test test if the data is not normally distributed. In categorical variables, an analytical test is performed using chi squared or fisher tests. For variables that were found to be significant in the bivariate analysis test, were included in the multivariate test. Variables found to have significance values with $p < 0.05$ in multivariate analysis are displayed in the form of Odds Ratio (RO) with 95% confidence intervals.

Results

Baseline Characteristics

The study subjects were divided into two groups, which were the group that experienced fibrinolytic failure (36 people, 58.1%) and the group that experienced fibrinolytic successful (26 people, 41.9%). Of the 36 people who experienced failure consisted of 33 men (91.7%) and 3 women (8.3%). The average age was 52 years old in successful group and 54 years in the failure group, but did not reach statistical significance ($p > 0.05$). The average systolic blood pressure at admission in the two groups was not much different and the average heart rate at admission was slightly higher in the failed fibrinolytic group which was 79 times/minute and 70 times/minutes in the successful fibrinolytic.

From the laboratory examination, it was found that there were statistically significant differences between the failed fibrinolytic group and the successful fibrinolytic group in the number of leukocytes, blood glucose and fasting blood glucose. Likewise in the risk factors of coronary heart disease, there was a statistically significant difference in hypertension and diabetes mellitus in both groups. In addition, other risk factors such as smoking, hyperlipidemia and a family history of CAD are more common in the failed fibrinolytic group.

The results of this study also showed that there were statistically significant differences between the failed fibrinolytic group and the successful fibrinolytic in terms of the location of the infarction, the presence of pathological Q waves on the ECG, chest X-ray and congestive heart failure. In the failed group, 27 people (75.0%) were found to have an anterior infarction location, the results of cardiomegaly chest X-ray were 28 people (77.8%), more pathological Q waves in 24 people (66.7%) and heart failure in 19 people (52.8%) compared to the group that experienced successful fibrinolytic with all values of $p < 0.05$. The basic characteristics of the subjects can be seen in table 1.

Table 1. Baseline Characteristics of The Subjects Study

	Reperfusion		<i>p</i>
	Failed n = 36	Successful n = 26	
Age (years)	54.5±8.84	52.0±8.98	0.28
Sex category			0.439
- Male	33 (91.7%)	22 (84.6%)	
- Female	3 (8.3%)	4 (15.4%)	
Systolic blood pressure	129.17 ± 23.345	121.92 ± 17.893	0.190
Heart rate	79.39 ± 14.58	70.88 ± 14.68	0.028*
Body mass index			0.023*
- Normoweight	15 (41.7%)	20 (76.9%)	
- Overweight	12 (33.3%)	4 (15.4%)	
- Obesitas	9 (25%)	2 (7.7%)	
Hypertension	22 (61.1%)	4 (15.4%)	<0.001*
Diabetes Mellitus	25 (69.4%)	8 (30.8%)	0.003*
Smoker	31 (86.1%)	19 (73.1%)	0.2
Hyperlipidemia	36 (100%)	24 (92.3%)	0.172
Family history	9 (25.0%)	2 (7.7%)	0.101

Leucocyte	15521.39 ± 3015.10	13793.08 ± 3280.72	0.036*
Ureum	35.69 ± 42.57	26.38 ± 11.19	0.28
Creatinine	1.23 ± 1.17	1.04 ± 0.44	0.433
Blood glucose	223.0 ± 113.14	163.35 ± 88.42	0.023*
Fasting blood glucose	150.64 ± 66.15	111.81 ± 40.85	0.01*
Post prandial blood glucose	164.03 ± 65.76	139.0 ± 60.42	0.127
Total cholesterol	200.56 ± 37.45	202.35 ± 39.11	0.856
LDL	134.31 ± 35.10	148.73 ± 43.80	0.155
HDL	38.03 ± 9.23	39.81 ± 9.34	0.459
Triglycerida	156.56 ± 47.82	182.19 ± 119.79	0.249
Ckmb	175.83 ± 189.72	110.08 ± 118.42	0.124
Troponin	8.14 ± 10.95	5.18 ± 10.17	0.238
Onset	5.47 ± 2.52	4.42 ± 2.63	0.118
TIMI Risk	3.72 ± 1.32	3.08 ± 1.38	0.068
KILLIP			0.387
- I	33 (91.7%)	22 (84.6%)	
- II	2 (5.6%)	4 (15.4%)	
- III	0 (0%)	0 (0%)	
- IV	1 (2.8%)	0 (0%)	
Infark location			0.02*
- Anterior	27 (75.0%)	12 (46.2%)	
- Non anterior	9 (25.0 %)	14 (53.8%)	
ECG			0.101
- Sinus bradycardia	3 (8.3%)	4 (15.4%)	
- Sinus rhythm	27 (75.0%)	18 (69.2%)	
- Sinus tachycardia	6 (16.7%)	1 (3.8%)	
- AV block	0 (0%)	2 (7.7%)	
- Atrial fibrillation	0 (0%)	1 (3.8%)	
Pathological Q wave	24 (66.7%)	6 (23.1%)	0.001*
Chest X-ray			0.01*
- Cardiomegaly	28 (77.8%)	12 (46.2%)	
- Non cardiomegaly	8 (22.2%)	14 (53.8%)	
CHF	19 (52.8%)	4 (15.4%)	0.003*
Stroke	-	-	-
Vascular disease	3 (8.3%)	0 (0.0%)	0.258

Table 2. Bivariate of CHA₂DS₂VASC-HS score in reperfusion failure

	Failed Reperfusion	Successful Reperfusion	p value
CHA ₂ DS ₂ VASC-HS score	4.81 ± 0.82	3.08 ± 0.74	< 0.001

CHA₂DS₂VASC-HS Score as Predictor of Failed Reperfusion After Fibrinolytic

The mean CHA₂DS₂VASC-HS score in the failed group was 4.81 ± 0.82 and in the group that experienced successful fibrinolytic was 3.08 ± 0.74. The CHA₂DS₂VASC-HS score in the two groups was found to be significantly different with p < 0.001. The relationship of CHA₂DS₂VASC-HS score in reperfusion failure after fibrinolytic can be seen in table 2.

Cutoff of CHA₂DS₂VASC-HS Score in Reperfusion Failure after Fibrinolytic

Using the ROC curve, Area Under the Curve (AUC) can be assessed from the CHA₂DS₂VASC-HS score parameter, which will show the ability of the CHA₂DS₂VASC-HS score as a predictor of failed reperfusion after fibrinolytic in STEMI. In this study, we found AUC 0.928 with p value <0.05. This showed that CHA₂DS₂VASC-HS score were clinically significant as predictors of failed reperfusion after fibrinolytic in STEMI. The cutoff values were found ≥ 4 which were considered can predict failed reperfusion with a sensitivity of 91.7% and specificity of 69.2% (Figure 1) (Table 3).

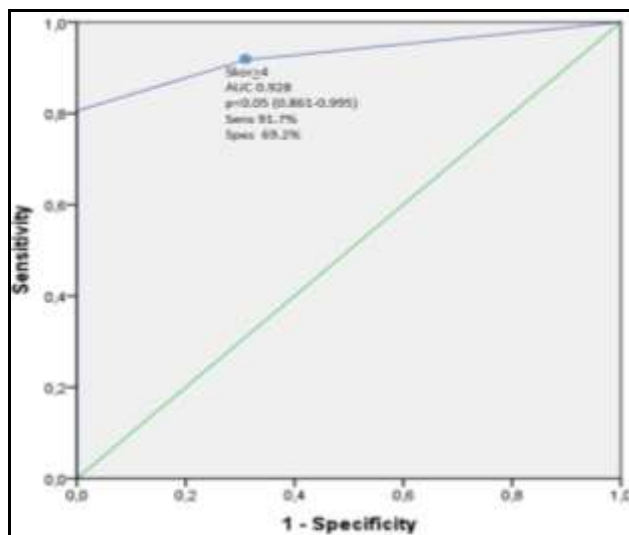


Figure 1. ROC curve of CHA₂DS₂VASC-HS score

Table 3. CHA₂DS₂VASC-HS Score test results based on ROC

Cutoff	Sens	Spes	AUC	p value	95% CI
≥ 4	91.7%	69.2%	0.928	0.05	0.861-0.995

In these 62 subjects, we found 41 people had CHA₂DS₂VASC-HS score ≥ 4 and 21 people had a CHA₂DS₂VASC-HS score < 4 . The subjects in the group with CHA₂DS₂VASC-HS score ≥ 4 had a higher rate of reperfusion failure which was 33 people (80.5%) compared to 8 people (8.3%) who experienced successful fibrinolytic. Whereas there were 18 people (85.7%) in the group with CHA₂DS₂VASC-HS score < 4 experienced successful fibrinolytic compared to 3 people (14.3%) who experienced failed fibrinolytic. CHA₂DS₂VASC-HS score ≥ 4 can predict failed reperfusion after fibrinolytic in STEMI patients with a sensitivity of 91.7%, specificity of 69.2%, negative predictive value (NPV) of 85.7% and positive predictive value (PPV) of 80.4%.

After adjusting admission variables by univariate analysis, we performed multivariate analysis in this study. It was useful to find out which independent variables could be the most dominant and affect the occurrence of reperfusion failure. It showed that there were 2 independent factors that could predict reperfusion failure after fibrinolytic, which were pathological Q wave [OR 6.28 (1.45-27.027), p = 0.014] and CHA₂DS₂VASC-HS ≥ 4 score [OR 23.759 (4.904-115.19), p = <0.001] (Table 4).

Table 4. Multivariate analysis of independent factors as predictor of failed reperfusion

Parameter	P value	OR	Lower	Upper
Pathological Q wave	0.014	6.28	1.45	27.027
CHA ₂ DS ₂ -VASC-HS ≥ 4	<0.001	23.769	4.904	115.19

Relationship between the Criteria for Reperfusion and Fibrinolytic

In this study, we used 3 criterias to determine successfulness of fibrinolytic which were reduction in chest pain, ST segment resolution more than 50% and the presence of arrhythmia reperfusion. Fibrinolytic was success if there were 2 of the 3 criterias. In 36 people who experienced fibrinolytic failure, all experienced a reduction in chest pain (100%), as well as 26 people in the successful group (100%). In 36 people who failed, all of them had ST segment resolution less than 50% (100%), while the resolution of the ST segment more than 50% was found in 26 people who succeeded in fibrinolytic (100%). In the failed group, 1 person (2.8%) had arrhythmia reperfusion and 35 persons (97.2%) did not experience arrhythmia reperfusion, while in the successful group, 8 persons (30.8%) had reperfusion arrhythmia and 18 persons (69.2%) did not experience arrhythmia reperfusion.

Then we wanted to know the correlation between the reperfusion criterias and fibrinolytic. The criteria for chest pain reduction could not be analyze because all samples had a reduction in pain so we could not compare the two groups. In Table 5 showed correlation between the criterias for reperfusion and fibrinolytic. There was a positive correlation of ST segment resolution more than 50% and fibrinolytic with a correlation coefficient (r) was 1.00 and p value < 0.001. Furthermore, there was also a significant positive correlation between arrhythmia reperfusion and fibrinolytic with weak correlation strength (r = 0.392) and p value 0.003.

We also wanted to analyze correlation of the success or failure of the fibrinolytic with the TIMI flow value from the coronary angiography result. There was a significant correlation between TIMI flow and fibrinolytic with strong correlation strength (r = -0.875), significant (p = <0.001) and inverse. It showed that the TIMI flow was higher in the successful fibrinolytic group.

Table 5. Correlation of Reperfusion Criterias and Fibrinolytic

Reperfusion Criterias	Correlation Coefficient	P value
ST segment resolution > 50%	1.00	< 0.001
Arrhythmia reperfusion	0.392	0.003
TIMI flow	-0.875	< 0.001

Discussion

Immediate reperfusion therapy with primary PCI or pharmacology with fibrinolytic agents is indicated for all patients with symptoms occurring within 12 hours with new permanent ST segment elevation or LBBB. If there is no local hospital that has PCI facility, the fibrinolytic therapy is directly selected. After fibrinolytics is given and if possible, the patient can be sent to the hospital with PCI facility.^{1,2}

The basic characteristics of the subjects in this study between the two groups showed no significant differences for the sex category and age of the patients, but significant differences were found in the heart rate. And in the group that experienced failed reperfusion were found to have more risk factors for hypertension, diabetes mellitus, hyperlipidemia, smoking and family history of CAD than those who experienced successful fibrinolytic. As it is known that the risk factors for CAD are hypertension, smoking, hyperlipidemia, diabetes mellitus and older age. Furthermore, many studies showed that older age, hyperlipidemia, hypertension, diabetes, smoking and male sex category will increase cardiovascular risk and can produce worse outcome.^{12,13,14}

Laboratory parameters showed significant differences in blood glucose and fasting blood glucose values, and the location of the anterior infarction was found to experience failed reperfusion as much as 75%. In addition, the longer onset of STEMI were found in the group that experienced failed reperfusion which was 5.47 ± 2.52 hours. Mahendra et al (2016) found that the onset of ≥ 6 hours, hyperglycemia on admission and the location of anterior wall myocardial infarction could be used as predictors of failed fibrinolytic in STEMI patients using streptokinase with a sensitivity value of 53% and specificity 94%.¹⁵ Kocas et al (2015) also found that admission hyperglycemia was an independent predictive factor for failed reperfusion, along with time from symptom onset to fibrinolytic and anterior wall myocardial infarction.¹⁶

The mean CHA₂DS₂-VASc-HS score in the group that experienced failed reperfusion was found to be higher at 4.81 ± 0.82 compared to the successful group of 3.08 ± 0.74 , this difference was statistically significant with $p < 0.001$. This shows that the CHA₂DS₂-VASc-HS score can be used as a predictor of failed reperfusion after fibrinolytic. Many studies have used the CHA₂DS₂-VASc-HS score on coronary heart disease, as the study by Cetin et al (2014) found that the CHA₂DS₂-VASc-HS score > 2 was a predictor of coronary heart disease severity.⁹ The same study was developed by Tasolar et al (2016) also mentioned that the CHA₂DS₂-VASc-HS score > 5 could be a predictor of severity and complexity of coronary artery disease and predictors of major cardiovascular events in NSTEMI patients.¹⁷ Both of these studies were important and significant because the components in the CHA₂DS₂-VASc-HS score which were hypertension, older age, diabetes mellitus, male gender, hyperlipidemia and smoking are very important traditional risk factors for coronary heart disease and are prognostic factors in cardiovascular outcome. Other study also showed that patients with stroke which was one of CHA₂DS₂-VASc-HS components, have a pre clinic of CAD condition and a relationship between coronary and cerebral atherosclerosis.¹⁸ Korkmaz et al (2012) also demonstrated that there was strong relationship between peripheral artery disease (PAD) which also known in CHA₂DS₂-VASc-HS components with CAD.¹⁹ A high CHA₂DS₂-VASc-HS score is estimated to be able to describe increased thrombogenicity and the number of thrombus in STEMI patients and can produce worse outcome.^{20,21}

CHA₂DS₂-VASc-HS score ≥ 4 is considered to be the optimal value in predicting reperfusion failure based on the ROC curve with a sensitivity of 91.7% and specificity of 69.2%. The study subjects in the group with CHA₂DS₂-VASc-HS score ≥ 4 had a higher rate of reperfusion failure compared to the group with CHA₂DS₂-VASc-HS < 4 which was 33 people (91.7%) compared to 3 people (8.3%). This is in line with study conducted by Killic et al. (2018) who obtained CHA₂DS₂-VASc score ≥ 2 and CHA₂DS₂-VASc-HS score ≥ 3 as predictors of failed reperfusion after fibrinolytic with lower sensitivity and specificity compared to this study of 76.1% and 67.6% (AUC 0.764, $p < 0.001$, 95% CI 0.725-0.799). The cutoff value of the CHA₂DS₂-VASc-HS score that is different from the previous study can be caused by the different population and race of the subjects in the study.

Furthermore, after adjusting for other factors affecting failed reperfusion after fibrinolytic, it was obviously found that the CHA₂DS₂-VASc-HS score ≥ 4 remained the dominant factor affecting failed reperfusion after fibrinolytic with OR 23.759 (4,904-115.19), $p = < 0.001$. So it can be concluded that the CHA₂DS₂-VASc-HS score can be used as a predictor of failed reperfusion after fibrinolytic in STEMI patients.

In this study a strong positive correlation was found between ST segment resolution $> 50\%$ and fibrinolytic with correlation coefficient $r = 1.00$ ($p = < 0.001$). Most studies used ST segment resolution criteria $> 50\%$ as a determinant of fibrinolytic successful. Many studies using intracoronary thrombolysis showed a decrease in ST segment elevation after successful myocardial reperfusion with a sensitivity of 73-88% and a specificity of 63-80%. The result of this study was consistent with data from the Gruppo Italiano per Studio della Soprawivenza nell'Infarto Miocardico (GISSI-2) trial, which showed patients with a $> 50\%$ reduction in ST segment elevation 4 hours after given thrombolytic had a better outcome.²² Furthermore, there was also a positive but weak correlation between reperfusion arrhythmias and fibrinolytic action with a correlation coefficient $r = 0.392$ ($p = 0.003$). Arrhythmias is a specific marker of myocardial reperfusion in many experimental studies where arrhythmias that often appear are idioventricular rhythm or slow ventricular tachycardia. Reperfusion arrhythmias appears more frequently in patients who experience successful than those who failed in fibrinolytic.²² This is consistent with this study where reperfusion arrhythmias were found more in the successful group as many as 8 people (30.8%) compared to 1 person (2.8%) in the failed group.

Limitations

The sample in this study was STEMI patients who undergo fibrinolytic therapy, where nowadays the prevalence rate was lower with the development of hospital facility in conducting the primary PCI so that there were difficulties in collecting the minimum number of samples. In addition, the number of samples in this study is smaller than the previous studies and only carried out in one place so that further study is needed with a larger sample size and collaboration with several referral hospitals that have intensive cardiovascular inpatient facility in order to provide more representative results.

Conclusion

CHA₂DS₂-VASc-HS score is a simple, very useful and easy-to remember bedside score and an inexpensive indicator which may be used as a prognostic marker for failed reperfusion after fibrinolytic in patients with STEMI, where the cutoff value obtained from this study was ≥ 4 .

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