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CHA2DS2 - Vasc Score Predict No Reflow Phenomenon in Primary Percutaneous Coronary Intervention

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Abstract

Purpose: ST-Elevation Myocardial Infarction is the most acute manifestation of Coronary artery disease, with substantial morbidity and mortality. Early reperfusion (re-establishing the blood flow in the occluded artery) is the most effective way to preserve the viability of the ischaemic myocardium and limit infarct size. Early diagnosis of STEMI is crucial to initiate appropriate treatment and should ideally be made within 10 minutes of first medical contact. This study aimed to evaluate the CHA2DS2-VASc score as a simple tool for predicting the no-reflow among patients with STEMI who underwent primary percutaneous coronary intervention.

Methodology: This was a case-control study which was conducted on 100 patients, diagnosed with acute STEMI and underwent primary PCI, who was admitted to Cardiology Department, Benha University Hospital and National Heart Institute. Patients were classified into two groups, control and no-flow, according to their final angiographic TIMI flow rates resulting from primary PCI. The control group: 78 patients with TIMI flow rate >2. The no-reflow group: 22 patients with TIMI flow rate ≤2, despite mechanical reopening of the infarct-related artery in patients without dissection of the coronary artery.

Findings: In this study, LVEF was significantly lower in patients with no-reflow compared to patients with normal TIMI flow (p <0.001), but LVEDV was significantly higher (p =0.01). There was no significant difference in LVESV between patients with no-reflow compared to patients with normal TIMI flow. CHA2DS2VASC score was significantly higher in patients with no-reflow compared to patients with normal TIMI flow (p <0.001). CHA2DS2VASC score is a significant predictor of occurrence of no reflow phenomenon (AUC: 0.689, p =0.006). At a cut off value of ≥ 2it has a sensitivity of 68.2%, specificity of 58.9%, PPV of 31.9% and NPV of 86.8%.

Recommendation: The study suggest that the CHA2DS2-VASc score can be an independent predictor of no-reflow phenomenon in patients undergoing primary PCI. As a simple and easy-to-calculate score, it might be a useful assessment tool to predict no-reflow phenomenon before primary PCI interventions in patients with STEMI. Thus we recommend using CHA2DS2-VASc score as it is very simple and a quick tool to predict no-reflow before primary PCI

Keywords: *CHA2DS2, VASc score, no reflow phenomenon, primary percutaneous coronary intervention*

INTRODUCTION

In patients with ST-segment elevation myocardial infarction (STEMI), the purpose of primary percutaneous coronary intervention (PCI) is immediate return of normal blood flow in the infarct-related artery. Nevertheless, no-reflow phenomenon is a major challenging disadvantage of this procedure. No-reflow is defined as inadequate myocardial perfusion despite mechanical reopening of the culprit lesion with PCI. This phenomenon is related to higher incidence of complications, and short- and long-term morbidity and mortality in acute STEMI patients (**1**). This phenomenon occurs in 0.6% to 5% of elective PCIs, but a higher incidence has been reported in patients who underwent primary PCI. A multifactorial and complex pathophysiology has been suggested for mechanism of this event. Unfortunately, there is no widely accepted risk stratification method for the prediction of this complication (**2).**

As one of the serious complications of PPCI, no reflow phenomenon can aggravate myocardial ischemia and increase MI size and the incidence of heart failure, in addition to also being an independent predictor of short- and long-term adverse prognosis. The exact mechanism of no-reflow phenomenon (NRP) is still not fully understood, but the mainstream view is that microvascular obstruction, including ischemic injury, reperfusion injury, microvascular dysfunction, and distal microvascular embolization, is the main pathological basis of NRP (**3).**

CHA2DS2-VASc score is a clinical predictor of thromboembolism events and is recommended in clinical guidelines for oral anticoagulant therapy in patients with nonvalvular atrial fibrillation. The components of this score are related to atherosclerosis, vascular spasm and microvascular dysfunction similar to common risk factors of the no-reflow (**4).** The aim of this work was to evaluate the CHA2DS2-VASc score as a simple tool for predicting the no-reflow among patients with STEMI who underwent primary PCI.

PATIENTS AND METHODS

Study Population

This prospective study included 100 patients with a diagnosis of acute STEMI and underwent primary PCI, who were admitted to Cardiology Department, Benha University Hospital and National Heart Institute, in the period from (March 2022 to March 2023).

Ethical Consideration

An informed consent was obtained from patients before enrollment in the study. An approval from Research Ethics Committee in Benha Faculty of Medicine was obtained.

Inclusion Criteria

Patients with ST-Segment Elevation Myocardial Infarction (STEMI) with symptoms onset less than twelve hours who underwent successful reperfusion either by thrombolytic therapy in the 1st 12h from onset of symptoms or in the first 24 hours from onset of symptoms for Primary PCI. Patients with STEMI were those presenting with typical chest pain for myocardial infarction of at least 30 minutes duration and less than 12 hours, with ECG showing new ST segment elevation at the J point in two contiguous leads with the cut-off point ≥ 0.1mV in all leads on the 12–lead ECG other than leads V2 and V3 with cut-off points ≥ 0.2 mV in men ≥40years ; ≥ 0.25mV in men< 40years or ≥ 0.15mV in women and with elevated cardiac enzymes (troponin) **(5).**

Exclusion Criteria

Patients with preexisting cardiomyopathy. Moderate and severe valvular heart disease. Patients with late presentation after symptom onset (more than 12 hours from onset of chest pain). Patients with atrial fibrillation, paced rhythms or other conditions that may hamper the quality of obtained echocardiographic data.

On admission all patients were subjected to the following;

Full history: Including history of cigarette smoking, systemic hypertension, diabetes mellitus, hyperlipidaemia, family history of premature coronary artery disease (CAD) and past history of CAD or previous PCI. Hypertension was defined as a systolic pressure ≥ 140 mmHg and/or a diastolic pressure ≥ 90 mmHg **(6);** a history of hypertension was noted in patients using anti-hypertension medications. Type II diabetes was noted in patients who met the 1999 WHO diagnosis criteria **(7).** Smoking was defined as smoking for six months or longer, and a smoking index was calculated as the number of daily cigarettes × years of smoking **(8).** A family history of early CAD was recorded in patients where it was first diagnosed in the father at ≤ 55 or the mother at ≤ 65 years of age **(6).**

1. **Physical examination**:
   - Hemodynamics including pulse, temperature, blood pressure and central venous pressure.
   - Full cardiac examination.
   - Full systemic examination for other associated medical or surgical problems.
   - Body weight and height, for calculation of body mass index, **BMI = weight (kg) / [height (m)]² (9).**

2. **Standard 12-lead ECG:**

ECG was done on admission.

3. **Laboratory investigation:**
   - Random blood sugar
   - Cardiac enzymes (CK, CK –MB, and LDH) were estimated on admission, post intervention 6 hourly in the first 24hours and then once daily till normalization, troponin analysis was done as well.
   - Coagulation profile including prothrombin time (PT), Prothrombin concentration (PC), & partial thromboplastin time (PTT).
   - Kidney function tests including blood urea and serum creatinine.
   - Liver function tests including serum total bilirubin, serum direct bilirubin, serum albumin, ALT, AST and Serum electrolytes including serum sodium and potassium.

4. **Transthoracic echocardiograghy (TTE)**

To assess left ventricular ejection fraction (LVEF) by simpthon's method, left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and regional wall motion abnormalities before hospital discharge

5. **The CHA2DS2-VASc score**

The CHA2DS2-VASc score was the sum of 1 point each for the presence of congestive heart failure, hypertension, diabetes mellitus, age of 65 to 74 years, female sex, and vascular diseases (history of MI, peripheral arterial disease, or complex aortic plaques) and 2 points for age ≥ 75 years and a history of stroke or transient ischemic attack (TIA). **(10)**

Study Groups

The study population was divided into two groups of control and no-flow according to their final angiographic TIMI flow rates resulting from primary PCI; the control group included 78 patients with TIMI flow rate >2. The no-reflow group included 22 patients with TIMI flow rate ≤2, despite mechanical reopening of the infarct-related artery in patients without dissection of the coronary artery.**(11)**

Definition of the TIMI flow grades was as follows:

- Grade 0 refers to no flow at all after the culprit lesion.
- Grade 1, the contrast material flow after occlusion site but fails to opacify the entire artery.
- Grade 2 refers to opacification of the entire artery distal to the obstruction point, however the flow is slower than normal,
- Grade 3 refers to normal coronary flow.**(10)**

Statistical Analysis

The collected data were tabulated and analyzed using SPSS version 24 software (SPSS Inc, Chicago, ILL Company). Categorical data were presented as number and percentages. Quantitative data were expressed as mean ± standard deviation, median and range. Student "t" test was used to analyze normally distributed variables among 2 independent groups. Regression analysis was used to investigate risk of association. ROC curve was used to detect cutoff values with optimum sensitivity and specificity. The accepted level of significance in this work was stated at 0.05 (P <0.05 was considered significant).

RESULTS

Table 1: Demographic characteristics of the studied groups

		Normal flow (n =78)	No-reflow (n =22)	P value
Age (years)	Mean ± SD	57.87 ± 10.54	64.05 ± 6.47	0.011*
	Range	30 - 78	49 - 74	
Gender	Male	59 (76%)	14 (64%)	0.285
	Female	19 (24%)	8 (36%)	
BMI (kg/m^2)	Mean ± SD	27.41 ± 2.66	29.5 ± 2.56	0.001*
	Range	21 - 32	26 - 35	

*SD: Standard deviation, BMI: Body mass index, * statistically significant as p value ≤0.05.*

Age and BMI were significantly higher in patients with no-reflow compared to patients with normal TIMI flow (p =0.011, 0.001 respectively), but there was no significant difference in gender between them.

Table 2: Clinical history of the studied groups

	Normal flow (n =78)	No-reflow (n =22)	P value
Hypertensive	31 (40%)	15 (68%)	0.028*
Diabetic	17 (22%)	9 (41%)	0.098
Hyperlipidemic	15 (19%)	10 (45%)	0.023*
History of CHF	2 (3%)	1 (5%)	0.529
History of CAD	12 (15%)	9 (41%)	0.016*
History of Stroke	7 (9%)	6 (27%)	0.035*
Family history of CAD	11 (14%)	5 (23%)	0.336
Cigarette smoker	29 (37%)	5 (23%)	0.308

*CAD: Coronary artery disease, CHF: Congestive heart failure *statistically significant as p value ≤0.05.*

Regarding clinical history of the studied groups, patients with hypertension, hyperlipidemia, history of CAD, and history of stroke in no-reflow group were significantly higher compared to normal TIMI flow group (p =0.028, 0.023, and 0.016 respectively). There was no significant difference in number of patients with diabetes mellitus, patients with history of CHF, patients with family history of CAD, and patients who were on cigarette smoking between no-reflow group and normal TIMI flow group.

Table 3: Hemodynamics data of the studied groups

		Normal flow (n =78)	No-reflow (n =22)	P value
SBP (mmHg)	Mean ± SD	124.49 ± 16.68	135.23 ± 14.6	0.007*
	Range	95 - 175	115 - 165	
DBP (mmHg)	Mean ± SD	76.41 ± 9.18	87.27 ± 9.97	<0.001*
	Range	60 - 95	75 - 110	
HR (beat/min)	Mean ± SD	74.86 ± 13.97	80.32 ± 15.49	0.117
	Range	52 - 104	56 - 104	

*SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, *statistically significant as p value ≤0.05.*

SBP and DBP were significantly higher in patients with no-reflow compared to patients with normal TIMI flow, but there was no significant difference in HR between them.

Table 4: Cardiac markers in the studied groups

		Normal flow (n =78)	No-reflow (n =22)	P value
CK-MB (ng/L)	Mean ± SD	49.14 ± 61.71	95.36 ± 100.27	<0.001*
	Range	5 - 369	12 - 475	
Troponin (ng/L)	Mean ± SD	1.81 ± 3.97	5.41 ± 12.74	0.034*
	Range	0 - 30	0 - 61	

*SD: Standard deviation, CK-MB: Creatine kinase-MB, *statistically significant as p value ≤0.05.*

CK-MB and troponin were significantly higher in patients with no-reflow compared to patients with normal TIMI flow (p <0.001, =0.034).

Table 5: Transthoracic echocardiography before hospital discharge in the studied groups

		Normal flow (n =78)	No-reflow (n =22)	P value
LVEF (%)	Mean ± SD	58.97 ± 14.48	42.18 ± 5.86	<0.001*
	Range	28 - 95	26 - 53	
LVESV (mL)	Mean ± SD	44.53 ± 11.4	43.32 ± 13.7	0.676
	Range	27 - 63	24 - 70	
LVEDV (mL)	Mean ± SD	151.4 ± 34.78	178.23 ± 63.14	0.01*
	Range	76 - 229	59 - 309	

*SD: Standard deviation, LVEF: Left-ventricle ejection fraction, LVESV: Left-ventricle end systolic volume, LVEDV: Left-ventricle end diastolic volume, *statistically significant as p value ≤0.05.*

Regarding echocardiography before hospital discharge in the studied groups, LVEF was significantly lower in patients with no-reflow compared to patients with normal TIMI flow (p <0.001), but LVEDV was significantly higher (p =0.01). There was no significant difference in LVESV between patients with no-reflow compared to patients with normal TIMI flow.

Table 6: CHA2DS2VASC score in the studied groups

		Normal flow (n =78)	No-reflow (n =22)	P value
CHA2DS2VASC score	Median (IQR)	1 (1 – 2)	2 (1 – 4)	<0.001*
	Range	0 – 4	0 – 5	

*IQR: Interquartile range, *statistically significant as p value ≤0.05.*

CHA2DS2VASC score was significantly higher in patients with no-reflow compared to patients with normal TIMI flow (p <0.001).

Table 7: Diagnostic accuracy of CHA2DS2VASC to predict no reflow phenomenon in primary percutaneous coronary intervention

	Cut off	AUC	Sens.	Spec.	PPV	NPV	p value
CHA2DS2VASC score	≥ 2	0.689	68.2%	58.9%	31.9%	86.8%	0.006*

AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value
**statistically significant as p value ≤0.05.*

CHA2DS2VASC score is a significant predictor of occurrence of no reflow phenomenon (AUC: 0.689, p =0.006). At a cut off value of ≥ 2it has a sensitivity of 68.2%, specificity of 58.9%, PPV of 31.9% and NPV of 86.8%.

Table 8: Univariate and multivariate logistic regression of CHA2DS2VASC score elements for the prediction of no reflow phenomenon in primary percutaneous coronary intervention

	Univariate regression analysis		Multivariate regression analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age 65-74	2.31(0.849 – 6.272)	0.101	-	-
Female gender	1.77 (0.646 – 4.876)	0.266	-	-
Hypertension	3.25 (1.889 – 8.878)	0.022*	3.51 (1.911 – 10.327)	0.023*
Congestive heart failure	1.81(0.156 – 20.94)	0.635	-	-
Diabetes mellitus	2.48 (0.908 – 6.791)	0.076	-	-
Stroke	3.8 (1.125 – 12.856)	0.032*	2.36 (0.610 – 9.161)	0.213
Vascular disease	3.81(1.333 – 10.872)	0.012*	3.82 (1.194 – 12.278)	0.024*

AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value
**statistically significant as p value ≤0.05.*

In univariate regression analysis, Hypertension (OR: 3.25, p value =0.022), stroke (OR: 3.8, p value =0.032), and vascular disease (OR: 3.81, p value =0.012) were significant predictors of no reflow phenomenon. But age 65-74 years, female gender, congestive heart failure, and diabetes mellitus were not. In Multivariate regression analysis, hypertension (OR: 3.51, p value =0.023), and vascular disease (OR: 3.82, p value =0.024) were significant predictors of no reflow phenomenon. But stroke not.

DISCUSSION

In this study, males were 14 (64%) and female were 8 (36%) in no-reflow group. In contrary to these results, a previous study reported that young women with STEMI are more likely than similarly aged men to have reperfusion delays and that the female sex is associated with NRP (12). This may be due to several factors, such as differences in plaque composition and thrombotic activity between men and women and a higher prevalence of microvascular disease in women than in men. A meta-analysis of 27 studies found that the male sex is an independent predictor of NRP (13).

According to Zhang et al. (14) who aimed to find a simple but effective risk stratification method for the prediction of NRP, male sex was revealed to be an independent predictor of NRP. This may be because male patients are more likely to smoke and suffer from obesity

than female patients. This study showed that, age was significantly higher in patients with no-reflow compared to patients with normal TIMI flow (p =0.011). This agreed with Fajar et al. (13) who aimed to investigate the no reflow risk factors after percutaneous coronary intervention in ST elevation myocardial infarction patients. Their demographic and clinical characteristics found that age was proven to be associated with the risk of no reflow. Advancing age is one of the major risk factors for cardiovascular disease because aging has the significant role in the development of vascular endothelial dysfunction and stiffening of large elastic arteries (15).

The current study showed that, SBP and DBP were significantly higher in patients with no-reflow compared to patients with normal TIMI flow, but there was no significant difference in HR between them. In contrast, Mirbolouk et al. (10) who aimed to evaluate the effectiveness of CHA2DS2-VASc score in predicting no-reflow phenomenon. CHA2DS2-VASc score is a risk stratification method to estimate the risk of thromboembolism in patients with atrial fibrillation. They revealed that lower systolic blood pressure (SBP) and diastolic blood pressure (DBP) is correlated with increased risk of no-reflow independently. It might be related to reduction of coronary arterial perfusion pressure due to decreased blood pressure.

Furthermore, Fajar et al. (13) found that elevated heart rate was associated with the risk of no reflow. Recently, it has been known that higher heart rate above 70 beats per minute is known as an independent risk factor for the development of HF (16). The study found patients with hypertension, hyperlipidemia, history of CAD, and history of stroke in no-reflow group were significantly higher compared to normal TIMI flow group (p =0.028, 0.023, and 0.016 respectively).

In addition, Mirbolouk et al. (10) reported that, hyperlipidemia was more prevalent in those with no-reflow than in the control group. The current study revealed that, CK-MB and troponin were significantly higher in patients with no-reflow compared to patients with normal TIMI flow (p <0.001, =0.034). Zhang et al. (14) demonstrated that CK-MB is independent predictor of NRP. Fajar et al. (13) reported that, their laboratory findings also found that elevated CK was associated with the risk of no reflow.

In this study, LVEF was significantly lower in patients with no-reflow compared to patients with normal TIMI flow (p <0.001), but LVEDV was significantly higher (p =0.01). There was no significant difference in LVESV between patients with no-reflow compared to patients with normal TIMI flow. Similarly, Mirbolouk et al. (10) reported that, patients with the no-reflow had significantly lower mean left ventricle ejection fraction compared to the control group.

Moreover, Fajar et al., (13) reported that, their findings suggested that low LVEF was proven to be associated with no reflow. The study also revealed that, CHA2DS2VASC score was significantly higher in patients with no-reflow compared to patients with normal TIMI flow (p <0.001). In this study, CHA2DS2VASC score is a significant predictor of occurrence of no reflow phenomenon (AUC: 0.689, p =0.006). At a cut off value of ≥ 2it has a sensitivity of 68.2%, specificity of 58.9%, PPV of 31.9% and NPV of 86.8%.

This is in harmony with Mirbolouk et al. (10) who reported that, the mean CHA2DS2-VASc score was 1.6 ± 1.4 and it was significantly higher in the no-reflow group compared to the control group (3 ± 1.4 versus 1.1 ± 1.1, P < 0.001). This also agreed with Gürbak et al. (17) who aimed to investigate the relationship between the CHA2DS2-VASc score and no-reflow phenomenon after SVG PCI in patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS). They reported that the CHA2DS2-VASc score (P <0.001) was significantly higher in no-reflow group.

This agrees with several studies, Mirbolouk et al. (10) who declared the usefulness of CHA2DS2–VASc score in predicting no-reflow phenomenon after primary PCI in STEMI patients. Moreover, they reached a cut-off value of ≥2 for predicting no-reflow possibility in these patients and Ipek et al (18) which evaluated the predictive power of CHA2DS2-VASc score in 1781 patients with STEMI who underwent primary PCI. Furthermore, Zhang et al. (14) demonstrated that the $CHADS_2$, CHA_2DS_2-VASc, score was independent predictor of NRP after PPCI in patients with STEMI. In addition, Gürbak et al. (17) reported that, receiver operating characteristics analysis showed that a CHA2DS2-VASc score of 4 predicted no-reflow phenomenon with 67.9% sensitivity and 69.3% specificity.

Several previous studies have shown that the CHA_2DS_2-VASc score is a predictor of the severity of coronary artery disease (19, 20). Moreover, Bozbay et al. (21) showed that the CHA2DS2-VASc score was a predictor of adverse events in STEMI patients. Li et al. (22) also reported that the CHA_2DS_2-VASc score is a powerful predictor of major adverse cardio-cerebral vascular events in patients with acute MI, while Wang et al. (23) found that deaths after long-term illnesses, cardiac deaths, and non-fatal strokes were significantly higher in patients with a CHA_2DS_2-VASc score of > 2 than in patients with a lower CHA_2DS_2-VASc score.

In univariate regression analysis, hypertension (OR: 3.25, p value =0.022), stroke (OR: 3.8, p value =0.032), and vascular disease (OR: 3.81, p value =0.012) were significant predictors of no reflow phenomenon. But age 65-74 years, female gender, congestive heart failure, and diabetes mellitus were not. In Multivariate regression analysis, hypertension (OR: 3.51, p value =0.023), and vascular disease (OR: 3.82, p value =0.024) were significant predictors of no reflow phenomenon. But stroke not. Similarly, Iwakura et al. (24) did not find diabetes mellitus as a predictor in spite of demonstrating an association between hyperglycemia and no-reflow.

Moreover, Zhang et al. (14) demonstrated that a history of stroke/TIA, and vascular disease are associated with NRP and that the CHA_2DS_2-VASc score is an independent predictor of NRP. The multivariate regression analysis did not reveal diabetes mellitus to be a predictor of NRP. Kim et al. (25) reported that, there is an association between abnormal vascular function and stroke. On the other hand, Congestive heart failure, hypertension and ischemic cardiomyopathy, as well as age 65-74 years and age ≥75were predictors of no-reflow in previous studies (26; 18).

This finding is not similar to Mirbolouk et al. (10), multivariate analysis showed that diabetes mellitus and peripheral arterial disease are associated with no-reflow during primary PCI. After multivariate analysis there was no significant relationship between no-reflow and female gender and stroke. They showed that lower stent diameter can predict no-reflow. Based on their findings grade 0 TIMI flow rate at initial angiography also was an independent predictor of no-reflow similar to another previous study (27).

Many of the risk factors such as hypertension, diabetes mellitus and female gender are associated with microvascular dysfunction (28). A recent study has confirmed that the CHA_2DS_2-VASc score is an independent predictor of NRP (29), and a recent meta-analysis revealed that male sex, a family history of coronary artery disease, and smoking are also associated with NRP (13). Previous studies have identified various predictors of NRP. For example, Bayramoglu et al. (30) and Mazhar et al. (31) found that advanced age, lower-left ventricular ejection fraction, stent length of ≥20 mm, thrombus burden, Killip class ≥3, and longer pain-to-balloon time are independent predictors of NRP. Similarly, anterior infarctions, (32) hypertension, dyslipidemia, a history of smoking, and a history of tobacco use have also been shown to be associated with NRP (33).

CONCLUSION

Findings suggest that the CHA2DS2-VASc score can be an independent predictor of no-reflow phenomenon in patients undergoing primary PCI. As a simple and easy-to-calculate score, it might be a useful assessment tool to predict no-reflow phenomenon before primary PCI interventions in patients with STEMI.

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