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Combining clinical predictors to better predict for the no-reflow phenomenon

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Abstract. – OBJECTIVE: We aimed to determine whether the combination of a CHA2DS2-VASc score (C: Congestive Heart Failure, H: Hypertension, A2: Age ≥ 75 years, D: Diabetes mellitus, S: Stroke history, V: Vascular disease, A: Age ≥ 65 years, Sc: Sex category) and pre-percutaneous coronary intervention (PCI) thrombus load score was more sensitive at detecting the no-reflow phenomenon compared to the CHA2DS2-VASc score alone or to the thrombus load score alone in patients with acute ST-elevation myocardial infarction (STEMI) who had underwent primary PCI (PPCI).

PATIENTS AND METHODS: 497 patients with acute STEMIs were divided into two groups: no-reflow group (n: 194) and control group (n: 303). The Thrombolysis In Myocardial Infarction (TIMI) flow grading and Myocardial Blush Grade (MBG) were used together to define angiographic no-reflow as TIMI flow < 3 (with any MBG grade) or TIMI flow 3 with MBG 0 or 1. Successful reperfusion was defined as TIMI flow 3 with MBG 2 or 3.

RESULTS: CHA2DS2-VASc score was significantly higher in the no-reflow group than in the control group (2 [1-4] *vs.* 1 [0-3], $p < 0.001$]. Compared with the control group, the no-reflow group had a higher pre-PCI thrombus score (5 [4-5] *vs.* 4 [3-5], $p = 0.001$]. Compared with the CHA2DS2-VASc score alone, the combined use of the pre-PCI thrombus score and the CHA2DS2-VASc score was associated with significant improvements in the ability to predict no-reflow (AUC) (0.65 *vs.* 0.60, $p < 0.05$). The addition of the pre-PCI thrombus score to the CHA2DS2-VASc score was related to a significant net reclassification improvement of 6.7% ($p = 0.047$) and an integrated discrimination improvement of 0.036 ($p < 0.05$).

CONCLUSIONS: We have found that the combination of a CHA2DS2-VASc score and a pre-PCI thrombus load score was more sensitive in detecting the no-reflow phenomenon than only a CHA2DS2-VASc score in patients who underwent PPCIs for STEMIs.

Key Words:
CHA2DS2-VASc score, No-reflow, Primary coronary intervention, ST elevation, Myocardial infarction, TIMI thrombus load score.

Introduction

Acute ST elevation myocardial infarction (STEMI) is a serious clinical presentation of coronary artery disease that requires early diagnosis and treatment. It occurs due to a total occlusion of the epicardial coronary arteries, and primary percutaneous coronary intervention (PPCI) is an effective treatment strategy recommended by current guidelines[1,2]. No-reflow is defined as inadequate coronary perfusion within the myocardium despite a successful mechanical PCI procedure in the occluded artery[3]. The prevalence of no-reflow varies according to the subgroup of patients studied, occurring in up to 60% of patients undergoing PCI[4-6]. No-reflow is an independent predictor of the morbidity and mortality of patients with STEMIs, inhibiting the positive impact of acute revascularization treatments in the early period[7-9]. The underlying pathogenic mechanisms of no-reflow are not completely understood, but it may occur as a result of a distal atherothrombotic embolism, an endothelial injury, an ischemic injury, a reperfusion injury, a vasospasm, local platelet activation, or a combination of any of these[10-14].

Previous studies[15,16] demonstrate various predictors and suggest many risk factors, but there is no clear risk algorithm for detecting no-reflow. Some studies show that the thrombus load of the culprit lesion that caused the STEMI is associated with no-reflow[17,18]. The TIMI thrombus grade is a useful method for classifying the thrombus load of culprit lesions. The latest studies focus especially on CHA2DS2-VASc (C: Congestive Heart Failure, H: Hypertension, A2: Age ≥ 75 years, D: Diabetes mellitus, S: Stroke history, V: Vascular disease, A: Age ≥ 65 years, Sc: Sex category) scores for predicting no-reflow[19]. This score was originally developed to identify atrial fibrillation (AF) patients at risk of thromboembolic events[20]. It has been shown that the predictive value of the CHA2DS2-VASc

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scoring system for the no-reflow phenomenon is not good enough, especially in low-risk patients. For this reason, we designed this study assuming that the no-reflow phenomenon could be predicted at a higher rate using combination of the CHA2DS2-VASc scoring system and the TIMI thrombus load scoring system.

Patients and Methods

Patients

A total of 497 patients with acute STEMIs who underwent PPCI between January 2014 and December 2014 were included in the study. Patients were divided into 2 groups, the no-reflow group (194 patients) and the control group (303 patients) according to their post-PCI no-reflow status. Patients who had coronary artery bypass grafts (CABGs), other acute coronary syndromes, were treated with only balloon angioplasty, or underwent emergency coronary bypass surgery were excluded from the study. Detailed laboratory examinations were obtained from the patients' charts, such as hemogram, blood glucose levels, lipid panels, liver and kidney function tests, 12-lead electrocardiography, and clinical and demographical characteristics. In this retrospective study, we received approval from the Ethics Committee to use patient data registered at our Hospital (the Ethics Committee number: 37).

Definition of Acute STEMI

Patients who had chest pain for more than 30 min with ≥ 1 mm ST segment elevation of at least 2 contiguous leads or who had a new left bundle branch block (LBBB) were considered to have acute STEMIs[21].

CHA2DS2-VASc Score Calculation

CHA2DS2-VASc scores were calculated for each patient according to the definition of Lip et al[22].

Thrombus Load Scoring

The thrombus load of the culprit lesion was calculated according to the definition of Gibson et al[23]. The TIMI classification relies on the angiographic assessment of the presence of a thrombus and its relative size, utilizing a simple score ranging from grade 0 (no thrombus) to grade 5 (very large thrombus content that completely occludes vessel flow). The TIMI thrombus classification is categorized as follows: G0 indicates no angiographic evidence of thrombus or no thrombus; G1 indicates a possible thrombus is present; G2 is a small thrombus, meaning there is a definite thrombus whose dimensions are at most 1/2 the vessel's diameter; G3 is a moderate thrombus, meaning there is a definite thrombus whose greatest linear dimension is > 1/2 but is < 2 vessel diameters; G4 is a large-sized thrombus, meaning there is a definite thrombus whose largest linear dimension is > 2 vessel diameters; G5 indicates total occlusion.

TIMI Flow Grade Calculation

The TIMI grade flow is classified as follows: TIMI-0 indicates there is no antegrade flow beyond the point of occlusion, TIMI-1 indicates there is a faint antegrade coronary flow beyond the occlusion with an incomplete filling of the distal coronary bed, TIMI-2 indicates there is delayed or sluggish antegrade flow with complete filling of the distal territory, and TIMI-3 indicates normal flow with complete filling of the distal territory[24].

Myocardial Blush Grade Calculation

The myocardial blush grades were defined as follows: grade 0 indicates no myocardial blush or contrast density, grade 1 indicates minimal myocardial blush or contrast density, grade 2 indicates moderate myocardial blush or contrast density but less than that obtained during an angiography of a contralateral or ipsilateral non-infarct-related coronary artery, and grade 3 indicates normal myocardial blush or contrast density comparable with that obtained during an angiography of a contralateral or ipsilateral non-infarct-related coronary artery[25].

TIMI flow grading and MBG were used together to define angiographic no-reflow as TIMI flow < 3 (with any MBG grade) or TIMI flow 3 with MBG 0 or 1. Successful reperfusion was defined as TIMI flow 3 with MBG 2 or 3.

Coronary Angiography and Primary PCI

Standard coronary angiography was performed through the femoral artery. Patients were given 300 mg acetyl salicylic acid and 600 mg clopidogrel (300 mg for ≥75-year-olds). Before the study, 100 u/kg of unfractionated heparin (UFH) was administered, but if the patient had received 1 mg/kg of enoxoparin at least 8 hours earlier a 0.3 mg/kg IV of enoxoparin was administered.

Table I. Baseline characteristics of the study population.

Variable	Control group (n=303)	No-reflow (n=194)	*p*-value
Age, year (mean±SD)	61.6±12.3	63.6±13.3	0.086
Female n (%)	81 (27)	68 (34)	0.056
History of HF n (%)	59 (20)	59 (30)	0.006
Hypertension n (%)	109 (36)	87 (45)	0.058
Diabetes mellitus n (%)	83 (28)	53 (27)	0.941
Hyperlipidemia n (%)	89 (25)	14 (29)	0.816
Vascular disease n (%)	14 (5)	18 (9)	0.042
Prior stroke/TIA n (%)	0 (7)	3 (2)	0.031
MI localization			0.017
Anterior n (%)	113 (37)	92 (47)	
Non-anterior n (%)	189 (63)	103 (53)	
CHA2DS2-VASc score	1 (0-3)	2 (1-4)	<0.001
Thrombus classification	4 (3-5)	5 (4-5)	<0.001

HF; heart failure, TIA; transient ischemic attack, MI; myocardial infarction.
CHA2DS2-VASc score and thrombus classification were presented as median (minimum-maximum).

For patients with a huge thrombus load, thrombus aspiration was performed, and a tirofiban infusion regiment was administered. All calculations and scorings were made by two independent cardiologists.

Statistical Analysis

Continuous variables were presented as mean±SD or medians with ranges, and categorical variables were expressed as percentages. Variables were compared by a two-tailed Student's t-test for continuous variables of normal distribution or by the Mann-Whitney U test for continuous variables of non-normal distribution. x^2-test was used for categorical variables. The effect of various variables on no-reflow was calculated by univariate regression analysis. In these analyses, variables with unadjusted $p < 0.1$ were identified as confounding factors and were included in multivariate regression analyses to determine the independent predictors of no-reflow. The predictive values of the CHA2DS2-VASc score alone and a combination of the pre-PCI thrombus score and the CHA2DS2-VASc score were estimated by comparing the areas under the receiver operating characteristic curve. DeLong's test was used to compare the AUC from each of the models 26, which were analyzed by use of the Analyze-it software program. In addition, the increased discriminative value after the addition of the pre-PCI thrombus score to the CHA2DS2-VASc score was also estimated using net reclassification improvement (NRI) and integrated discrimination improvement (IDI)[27]. All statistical tests were two-tailed, and a $p < 0.05$ was considered statistically significant. All analyses were performed using SPSS version 15 (SPSS Inc., Chicago, IL, USA).

Results

The mean age was 62±13 years, and 29.9% of patients were female. The median CHA2DS2-VASc score was significantly higher in the no-reflow group than in the control group (2 [1-4] *vs.* 1 [0-3], $p < 0.001$). The no-reflow group had a higher pre-PCI thrombus score compared with the control group (5 [4-5] *vs.* 4 [3-5], $p = 0.001$). The no-reflow group had a higher prevalence of vascular disease (9% *vs.* 5%, $p = 0.042$) and more frequent heart failure (30% *vs.* 20%, $p = 0.006$). Other clinical variables were not significantly different in both groups. Clinical characteristics of the patients were shown in Table I. White blood cell count (WBC) was higher in the no-reflow group (12.6±4.1 *vs.* 11.3±3.8[109/L], $p = 0.001$). The no-reflow group had significantly higher mean platelet volume (MPV) at admission compared with the control group (8.8±1.4 *vs.* 8.5±1.5 [fL], $p = 0.007$). Hemoglobin levels were significantly lower in the no-reflow group than in the control group (12.9±2.1 *vs.* 13.4±1.9, $p = 0.006$). Laboratory findings in both groups were presented in the Table II. Multivariate analyses showed that WBC, MPV hemoglobin levels, CHA2DS2-VASc scores, and pre-PCI thrombus scores were significantly associated with no-reflow. The rate of patients aged ≥ 75 years was higher in the no-reflow group compared with the control group (25%

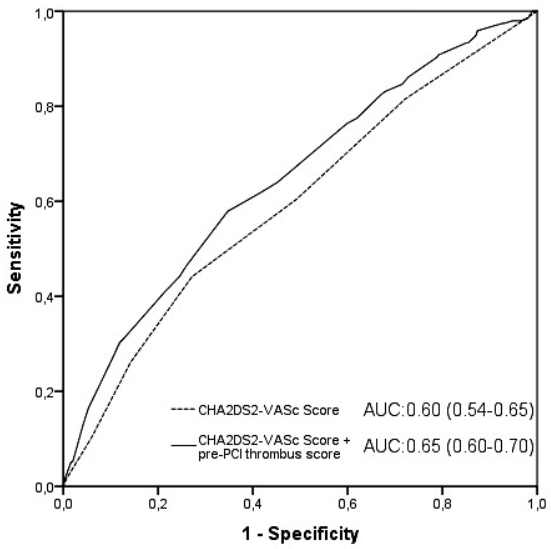

Figure 1. Compared with the CHA2DS2-VASc score alone, combined use of the pre-PCI thrombus score and CHA2DS2-VASc score.

vs. 16%, $p = 0.017$). Univariate and multivariate regression analysis for no-reflow were shown in Table III. Compared with the CHA2DS2-VASc score alone, the combined pre-PCI thrombus score and CHA2DS2-VASc score was associated with significant improvements in the ability to predict no-reflow (AUC: 0.65 *vs.* 0.60, $p < 0.05$) (Figure 1). The addition of the pre-PCI thrombus score to the CHA2DS2-VASc score was related to a significant NRI of 6.7% ($p = 0.047$) and an IDI of 0.036 ($p < 0.05$). Results of the NRI and IDI statistics analyses were presented in the Table IV.

Discussion

In the present study, we evaluated the CHA2DS2-VASc score, the thrombus load score, and the combined CHA2DS2-VASc score and thrombus load score for predicting the no-reflow phenomenon in patients with STEMIs who underwent PPCIs. We found that the combination of a CHA2DS2-VASc score and a thrombus load score is a better predictor for no-reflow compared to each single score. To our knowledge, this is the first study to evaluate the combination of the CHA2DS2-VASc score and thrombus load score. In the literature, many studies have demonstrated that using the CHA2DS2-VASc score alone or the thrombus load score alone were predictors for no-reflow[17,19]. The no-reflow phenomenon is defined as an acute reduction of coronary blood flow in a related vessel without any vessel obstruction, dissection, spasm, or thrombosis and can cause left ventricular dysfunction, malign arrhythmias, cardiogenic shock, or death[14,28]. Some studies[29,30] proved that thrombosis, distal embolization, and microvascular dysfunction were the main mechanisms in the pathogenesis of no-reflow according with ischemic injury, vasospasm, and reperfusion injury. Several previous studies have investigated the prognostic information of no-reflow, but they

Table II. Laboratory results of the study groups.

Variable	Control Group (n:303)	No-Reflow Group (n:194)	*p*-value
Age, year (mean±SD)	61.6±12.3	63.6±13.3	0.086
Female n (%)	81 (27)	68 (34)	0.056
History of HF n (%)	59 (20)	59 (30)	0.006
Hypertension n (%)	109 (36)	87 (45)	0.058
Diabetes mellitus n (%)	83 (28)	53 (27)	0.941
Hyperlipidemia n (%)	89 (25)	14 (29)	0.816
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Prior stroke/TIA n (%)	0 (7)	3 (2)	0.031
MI localization			0.017
Anterior n (%)	113 (37)	92 (47)	
Non-anterior n (%)	189 (63)	103 (53)	
CHA2DS2-VASc score	1 (0-3)	2 (1-4)	<0.001
Thrombus classification	4 (3-5)	5 (4-5)	<0.001

HDL; high-density lipoprotein, LDL; low-density lipoprotein, MPV; mean platelet volume, SCr; serum creatinine, WBC; white blood cell. SCr and triglycerides were presented as median (minimum-maximum). Glucose, Total cholesterol, LDL cholesterol, HDL cholesterol, Hemoglobin, MPV, Platelet count, and WBC were presented as mean±SD. *Comparison was made using Mann-Whitney U test at $p < 0.05$.

Table III. Univariate and multivariate regression analysis for no-reflow.

	Univariate analyses		Multivariate analyses	
Variables	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Age (per 1 year)	1.01 (0.99-1.02)	0.087		
Male (*vs*. female)	1.46 (0.99-2.16)	0.056		
History of HT	1.43 (0.99-2.06)	0.058		
History of DM	0.99 (0.66-1.48)	0.941		
History of HF	1.79 (1.18-2.71)	0.006		
History of stroke/TIA	1	0.999		
Vascular disease	2.09 (1.02-4.31)	0.045		
Age ≥ 75 years	1.90 (1.20-3.03)	0.008		
Age 65-74.5 years	1.36 (0.87-2.10)	0.174		
Creatinine	1.01 (0.97-1.05)	0.554		
Hemoglobin (per 1 g/dl)	0.88 (0.80-0.97)	0.006	0.91 (0.82-1.01)	0.062
MPV	1.21 (1.05-1.39)	0.008	1.15 (1.00-1.32)	0.049
WBC	1.08(1.03-1.14)	0.001	1.09 (1.03-1.15)	0.001
CHADS-VASCs score	1.24 (1.11-1.39)	< 0.001	1.25 (1.09-1.42)	< 0.001
Pre-PCI thrombus score	1.35 (1.15-1.59)	< 0.001	1.32(1.11-1.57)	0.002

OR, Odds ratio; CI, confidence interval; MPV; mean platelet volume, HT; hypertension, DM; diabetes mellitus, HF; heart failure, TIA; transient ischemic attack; white blood cell, PCI; percutaneous coronary intervention.

showed a variety of results. Clinical variables that are independently associated with the development of no-reflow include older age, prolonged interval from symptom onset to admission for STEMIs, cardiogenic shock, heart failure, lesion length ≥ 20 mm, and inappropriate stent diameter[31,32]. CHA2DS2-VASc scores are used to detect the risk of thromboembolisms and strokes in patients with non-valvular atrial fibrillation[20]. After PPCI, it has been shown that microvascular reperfusion is impaired due to endothelial vasoconstriction and thrombosis in diabetic patients[33]. Similarly, microvascular perfusion fails during no-reflow. Hypertension diabetes mellitus and female gender, which are components of the CHA2DS2-VASc score, are also known as risk factors for microvascular dysfunction in coronary circulation[34,35]. CHA2DS2-VASc scores involve atherosclerosis, heart failure, and peripheral vascular disease, which are also known as risk factors for no-reflow. We have found that vascular disease history (9% *vs*. 5%, $p = 0.042$) and a history of heart failure was more frequent in the no-reflow group (30% *vs*. 20%, $p = 0.006$). Additionally, a high CHA2DS2-VASc score is associated with high hospital mortality rates in STEMI patients[36]. Although a number of drugs[37] and devices are trying to treat the no-reflow phenomenon, no standard treatment strategy has been found yet. Since interventions have a low success rate after the development of no-reflow in patients with STEMIs who underwent PPCI, the main strategy is to prevent the development of no-reflow. The TAPAS (Thrombus Aspira-

Table IV. Reclassification of acute STEMI patients who patients experienced the no-reflow phenomenon or who did not experience.

	CHA2DS2-VASc score pre-PCI thrombus score Low risk	CHA2DS2-VASc with High risk	Total
Patients with no-reflow			
Low risk	123	20	143
High risk	10	41	51
Total	133	61	194
Patients without no-reflow			
Low risk	246	15	261
High risk	20	22	42
Total	266	37	303

tion during Percutaneous Coronary Intervention in Acute Myocardial Infarction) study, which was focused on reducing distal embolization, found that thrombus aspiration with catheters is an effective option, but the TASTE (Thrombus Aspiration in STEMI in Scandinavia) study has shown no benefit of this technique[38,39]. Opening the occluded vessel with balloons and stents often results in distal embolization of the thrombus. Carrik et al[32] reported that deferred stenting in PPCI reduced no-reflow in high-risk STEMI patients. If no-reflow occurs after PPCI, it is a really dismal condition for patients, and treatment is difficult and challenging. Therefore, a method needs to be developed for early identification of no-reflow in catheterization laboratories. However, there is no available method that estimates the development of no-reflow in patients with low risk. Neither the CHA2DS2-VASc score nor the pre-PCI thrombus load calculation alone can detect no-reflow in low-risk patients. In our study, we showed that a combined CHA2DS2-VASc score and TIMI thrombus load score is more effective in predicting no-reflow in low-risk STEMI patients.

Conclusions

The occurrence of no-reflow during PPCI of acute STEMI patients increases morbidity and mortality. So, detecting the risk of no-reflow before PCI is important. In this study, we found that the combined CHAD2S2-VASc and pre-PCI thrombus load scores were more effective than only pre-PCI thrombus load scores or only CHADS2VASC scores, especially in low risk STEMI patients. This study needs to be supported by prospective studies that have many more participants. Prospective and large-scale studies are needed to get better clarify this issue.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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