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CHA_2DS_2-VASc score predicts the slow flow/no-reflow phenomenon in ST-segment elevation myocardial infarction patients with multivessel disease undergoing primary percutaneous coronary intervention

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Abstract

ST-segment elevation myocardial infarction (STEMI) patients with multivessel disease (MVD) have a higher incidence of slow-flow/no-reflow (SF-NR) phenomenon during primary percutaneous coronary intervention (PPCI) than those with single vessel disease. Currently, no effective tools exist to predict the risk of SF-NR in this population. The present study aimed to evaluate whether CHA_2DS_2-VASc score can be used as a simple tool to predict this risk.

This study consecutively included STEMI patients hospitalized in Beijing Anzhen Hospital from January 2005 to January 2015. Among these patients, 1032 patients with MVD were finally enrolled. Patients were divided into SF-NR (+) group and SF-NR (–) group according to whether SF-NR occurred during PPCI. SF-NR was defined as the thrombolysis in myocardial infarction (TIMI) grade ≤2.

There were 134 patients (13%) in the SF-NR (+) group. Compared with the SF-NR (–) group, patients in the SF-NR (+) group are elder, with lower left ventricular ejection fraction and higher CHA_2DS_2-VASc score. Multiple logistic regression analysis indicated that CHA_2DS_2-VASc score ≥3 (odds ratio [OR], 2.148; 95% confidence interval [CI], 1.389–3.320; $P = .001$), current smoking (OR, 1.814; 95% CI, 1.19–2.764; $P = .006$), atrial fibrillation (OR, 2.892; 95% CI, 1.138–7.350; $P = .03$), complete revascularization (OR, 2.307; 95% CI, 1.202–4.429; $P = .01$), and total length of stents ≥40 mm (OR, 1.482; 95% CI, 1.011–2.172; $P = .04$) were independent risk factors of SF-NR. The incidence of SF-NR in patients with CHA_2DS_2-VASc score ≥3 was 1.7 times higher than that in patients with CHA_2DS_2-VASc score <3. Additionally, patients with CHA_2DS_2-VASc score ≥3 plus ≥2 risk factors have 3 times higher incidence of SF-NR than those with CHA_2DS_2-VASc score ≥3 plus 0 to 1 risk factor.

CHA_2DS_2-VASc score ≥3 can be used as a simple and sensitive indicator to predict SF-NR phenomenon and guide the PPCI strategy in STEMI patients with MVD.

Abbreviations: AF = atrial fibrillation, CRP = C-reaction protein, IVUS = intravenous ultrasound, LVEF = left ventricular ejection fraction, MVD = multivessel disease, PPCI = primary percutaneous coronary intervention, SF-NR = slow flow/no-reflow, STEMI = ST-segment elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction.

Keywords: CHA_2DS_2-VASc score, multivessel disease, percutaneous coronary intervention, slow flow/no-reflow phenomenon, ST elevation myocardial infarction

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1. Introduction

The primary goal of therapeutic strategy for acute ST-segment elevation myocardial infarction (STEMI) is restoration of myocardial blood flow as soon as possible. Based on the latest guidelines, primary percutaneous coronary intervention (PPCI) was recommended as the preferred reperfusion strategy markedly reducing morbidity and mortality.[1] Besides the benefits of this strategy, a serious complication known as slow flow/no-reflow phenomenon (SF-NR) phenomenon was happened in several cases with poor prognosis and survival.[2] Although the PCI technology is constantly improving, the incidence of SF-NR in PPCI is still as high as 2.3% to 41%.[3] Compared with patients with single vessel disease, those with multivessel disease (MVD) experienced >2 times higher risk of SF-NR occurrence.[4] MVD patients undergoing PPCI are high-risk groups for SF-NR. Therefore, it is very important to predict the risk of SF-NR before PPCI in these patients.

Clinical and laboratory findings indicate that SF-NR is related to capillary bed embolism, ischemic injury, vascular endothelial dysfunction, and other factors.[5] Several studies reported blood cell count, thrombus grade, and left ventricle function were associated with the occurrence of SF-NR. However, there is still a lack of widely accepted risk stratification scoring system for the prediction of SF-NR.

Some parameters included in the CHA_2DS_2-VASc score, such as congestive heart failure, hypertension, and diabetes are closely related to microvascular dysfunction and SF-NR phenomenon.[6–8] Recently, some studies have suggested that CHA_2DS_2-VASc is associated with SF-NR in MI patients undergoing PCI.[9,10] However, it is still unclear its role in predicting SF-NR in STEMI patients with MVD. Therefore, the present study was undertaken to investigate the association between CHA_2DS_2-VASc score and SF-NR in STEMI patients with MVD before PPCI.

2. Methods

2.1. Study population

We continuously enrolled STEMI patients hospitalized in Beijing Anzhen Hospital from January 2005 to January 2015. The cohort initially recruited 2328 STEMI patients receiving PPCI. One thousand two hundred ninety six patients were excluded from this study, including incomplete information (N=1), percutaneous transluminal coronary angioplasty (N=185), single vessel disease (N=844), and bare metal stents implanted (N=266). After screening, a total of 1032 patients with MVD were included. Patients were assigned to SF-NR (+) group (N=134) and SF-NR (–) group (N=898) according to whether SF-NR phenomenon occurred during PPCI (Fig. 1). Baseline and PPCI data were obtained from medical records. The study was approved by the Ethics Committee of Beijing Anzhen Hospital (No. 2018055X).

2.2. Definition

STEMI was diagnosed in the presence of prolonged chest pain (>30 minutes) with ST-segment elevation of 0.2 mV in ≥2 adjacent leads on standard Electrocardiogram. MVD was defined as ≥70% angiographic diameter stenosis in at least 1 non-infarct-related epicardial coronary arteries or left main coronary artery stenosis >50% according to coronary angiography. In order to identify the SF-NR phenomenon, thrombolysis in myocardial infarction (TIMI) flow score was used and classified as follows: TIMI 0, no antegrade blood flow is present; TIMI I, possible blood flow is present; TIMI II, definite blood flow with incomplete perfusion is present; TIMI III, complete perfusion is present.[11] We define NR as TIMI flow grade 0–1 and SF as a TIMI grade=2. All the angiograms were evaluated for TIMI score and the imaging information were assessed by 2 cardiologists with >5 years of clinical experience. Any discrepancies were resolved by consensus and consultation with a third cardiologist. The CHA_2DS_2-VASc score is based on a point system and the highest score was 9 points. It was calculated as follows: 1 point each is assigned for recent congestive heart failure, a history of hypertension, a history of diabetes mellitus, age 65 to 74 years, vascular disease and sex category (women). Two points are assigned for a history of stroke or transient ischemia attack and age ≥75 years. Congestive heart failure (especially moderate to severe systolic left ventricular dysfunction) was defined as left ventricular ejection fraction (LVEF) ≤40% on admission. Vascular disease was defined as the prior occurrence of myocardial infarction, peripheral arterial disease, and complex aortic plaque.

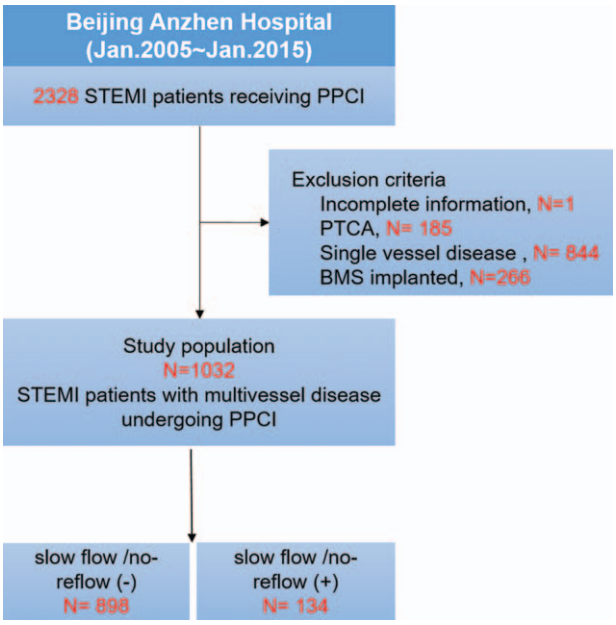

Figure 1. Flowchart of study population. BMS=bare metal stents, PPCI=primary percutaneous coronary intervention, PTCA=percutaneous transluminal coronary angioplasty, STEMI=ST elevation myocardial infarction.

2.3. Outcomes

The clinic event of the present study was the occurrence of SF-NR during PPCI. We also evaluated the major adverse cardiac events (MACE) (a composite of stroke, non-fatal myocardial infarction, repeat revascularization, and all-cause death) at 1 year by Kaplan–Meier analysis with log-rank test.

2.4. Follow up

Patients were followed-up by telephone interviews between December 2016 and January 2017. All of MACE were reconfirmed by reviewing the documentation of the patients who were followed up in our hospital. For the patients who were

treated elsewhere, we contacted the treating physician to get the medical records.

2.5. Statistical analysis

Data are expressed as mean ± standard deviation for continuous data with a normal distribution, median (interquartile range) for continuous variables with a skewed distribution and percentages for categorical variables. Quantitative variables are compared with Student *t* test or Mann–Whitney *U* test. Categorical variables between groups were compared with Chi-squared test. Multiple logistic regression was used to determine the independent risk factors of SF-NR. Variables that could be a predictor of SF-NR phenomena ($P < .05$) in univariate regression analyses were entered the multivariable logistic regression model. The survival rate at 1 year was assessed using Kaplan–Meier analysis with log-rank test. Two-tailed tests were applied in all statistical tests and a *P* value of .05 was considered as significant. All statistical processes were performed with the Statistical Package for the Social Sciences 25.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Baseline characteristics

Among 1032 STEMI patients with MVD, 13.0% (134/1032) patients had SF-NR during PPCI. We compared the characteristics of demographic, clinical, and laboratory parameters of the SF-NR (+) group and the SF-NR (–) group (Table 1). There were no significant differences between the 2 groups in terms of sex, previous coronary heart disease, hypertension, diabetes, and cerebrovascular disease. Compared with the SF-NR (–) group, patients in the SF-NR (+) group were older (61.2 ± 10.9 vs 58.9 ± 10.5, $P = .01$) with lower LVEF (52.0 ± 9.5% vs 54.9 ± 9.4%, $P = .02$) and higher rates of smoking (70.9% vs 61.6%, $P = .04$), AF (5.2% vs 1.8%, $P = .01$) as well as CHA_2DS_2-VASc ≥3 (29.1% vs 18.4%, $P = .004$). According to the laboratory results, the levels of admission hemoglobin, serum creatinine, estimated glomerular filtration rate, and high-sensitivity CRP showed no significant differences between the 2 groups. Whereas, the level of B-type natriuretic peptide in the SF-NR (+) group was higher than that in the SF-NR (–) group (743.6 ± 2197.8 vs 223.8 ± 487.6, $P = .01$).

3.2. Angiographic data

The mean time from the onset of symptomatic to PPCI was 8 hours. According to angiographic data, 395 (44.0%) patients was diagnosed with anterior wall myocardial infarction (MI), 441 (49.1%) patients with inferior wall MI, 12 (1.3%) patients with lateral wall MI, and 50 (5.6%) patients with multiple wall MI in the SF-NR (+) group. No statistical significance was showed in the number of diseased vessels between the 2 groups (2.5 ± 0.5 vs 2.5 ± 0.5, $P = .92$). We also analyzed the PPCI procedure data and found that the rate of complete revascularization (10.4% vs 4.8%, $P = .01$)

Table 1

Demographics characteristic of slow flow/no-reflow (–) versus slow flow/no-reflow (+).

Variables	Slow flow/no-reflow (–) (N = 898)	Slow flow/no-reflow (+) (N = 134)	*P* value
Age, y	58.9 ± 10.5	61.2 ± 10.9	.01*
Gender, male, n (%)	733 (81.6%)	103 (76.9%)	.19
Smoking, n (%)	553 (61.6%)	95 (70.9%)	.04*
CHA_2DS_2-VASc score ≥3	165 (18.4%)	39 (29.1%)	.004*
LVEF[a] (%)	54.9 ± 9.4	52.0 ± 9.5	.02*
Time from symptom onset to PPCI[b], h	8.0 ± 12.5	7.8 ± 9.8	.23
Hospital stay, d	8.1 ± 3.5	8.9 ± 4.4	.07
Previous MI[c], n (%)	50 (5.6%)	6 (4.5%)	.60
Previous PCI,[d] n (%)	60 (6.7%)	13 (9.7%)	.20
Hypertension, n (%)	365 (40.6%)	55 (41.0%)	.93
Diabetes mellitus, n (%)	246 (27.4%)	31 (23.1%)	.30
Atrial fibrillation, n (%)	16 (1.8%)	7 (5.2%)	.01*
Cerebrovascular disease, n (%)	41 (4.6%)	11 (8.2%)	.07
Infarct area, n (%)			.64
Anterior wall	395 (44.0%)	51 (38.1%)	
Inferior wall	441 (49.1%)	73 (54.5%)	
Lateral wall	12 (1.3%)	2 (1.5%)	
Multiple wall	50 (5.6%)	8 (6.0%)	
Biochemical tests			
Estimated glomerular filtration, mg/dL	105.8 ± 55.5	100.0 ± 33.5	.18
Hemoglobin, g/ld.	135.2 ± 19.7	135.1 ± 23.4	.95
High sensitivity CRP,[e] ng/mL	11.7 ± 12.0	16.7 ± 39.5	.53
BNP,[f] pg/mL	223.8 ± 487.6	743.6 ± 2197.8	.01*
Serum creatinine, mg/dL	77.6 ± 23.3	81.5 ± 30.4	.34

Data are n/N (%) or median (IQR).

[a] LVEF = left ventricular ejection fraction.

[b] PPCI = primary percutaneous coronary intervention.

[c] MI = myocardial infarction

[d] PCI = percutaneous coronary intervention

[e] CRP = C-reactive protein BNP, B-type natriuretic peptide

[f] BNP = B-type natriuretic peptide

* Means significant *P* value.

Table 2

Primary percutaneous coronary intervention data of slow flow/no-reflow (–) versus slow flow /no-reflow (+).

PPCI[a] data	Slow flow /no-reflow (–) (N = 898)	Slow flow/ no-reflow (+) (N = 134)	*P* value
Complete revascularization, n (%)	43 (4.8%)	14 (10.4%)	.01*
Thrombus aspiration, n (%)	522 (58.2%)	87 (64.9%)	.14
Number of lesion vessels	2.5 ± 0.5	2.5 ± 0.5	.92
Number of stents implanted	1.4 ± 0.6	1.4 ± 0.7	.77
Mean stent diameter, mm	3.0 ± 0.4	3.0 ± 0.5	.33
Total length of stents ≥40 mm, n (%)	267 (29.7%)	52 (38.8%)	.03*

[a] PPCI = primary percutaneous coronary intervention.
* Means significant *P* value.

and total length of the stents ≥40 mm (38.8% vs 29.7%, $P = .03$) were higher in the SF-NR (+) group compared with the SF-NR (–) group. However, no statistically significant differences were showed in regarding to the rate of thrombus aspiration (64.9% vs 58.2%, $P = .14$), the average of stent diameter (3.0 ± 0.5 vs 3.0 ± 0.4, $P = .33$), and the number of stents implanted (1.4 ± 0.7 vs 1.4 ± 0.6, $P = .77$) between 2 groups (Table 2). Perioperative medication with glycoprotein IIb/IIIa inhibitors, nitroglycerin, and calcium channel blockers could prevent or reverse SF-NR during PPCI. In our study, 220 patients received glycoprotein IIb/IIIa inhibitors, 630 patients received nitroglycerin, and 205 patients received diltiazem.

3.3. Outcomes of SF-NR

A total of 11 deaths (1.06%) occurred during index hospitalization. We found that 8 deaths occurred in the SF-NR (+) group (0.9%) and 3 deaths occurred in the SF-NR (–) group (2.2%). We further compared the mid- and long-term prognosis between the SF-NR (+) group and the SF-NR (–) group through survival analysis. The results showed that the 1-year cumulative survival rate in the SF-NR (–) group (91.2%) was higher than that in the SF-NR (+) group (88.1%). Although there was no statistical difference in the 1-year MACE event rate between the 2 groups (log-rank test $P = .12$), the occurrence of MACE was higher in the SF-NR (+) group than that in the SF-NR (–) group (Fig. 2).

3.4. Risk factors of SF-NR

Univariate logistic regression analysis showed that CHA_2DS_2-VASc ≥3, current smoking, complete revascularization, AF, and total stent length ≥40 mm had a significant impact on the occurrence of SF-NR during PPCI. Subsequent multivariate regression analysis showed that CHA_2DS_2-VASc ≥3 (odds ratio [OR]: 2.148; 95% confidence interval [CI]: 1.389–3.320; $P = .001$), smoking (OR 1.814; 95% CI, 1.19–2.764; $P = .006$), AF (OR, 2.892; 95% CI, 1.138–7.350; $P = .03$), complete revascularization (OR, 2.307; 95% CI, 1.202–4.429; $P = .01$), and total stent length ≥40 mm (OR, 1.482; 95% CI, 1.011–2.172; $P = .04$) are 5 independent risk factors for SF-NR phenomenon (Table 3).

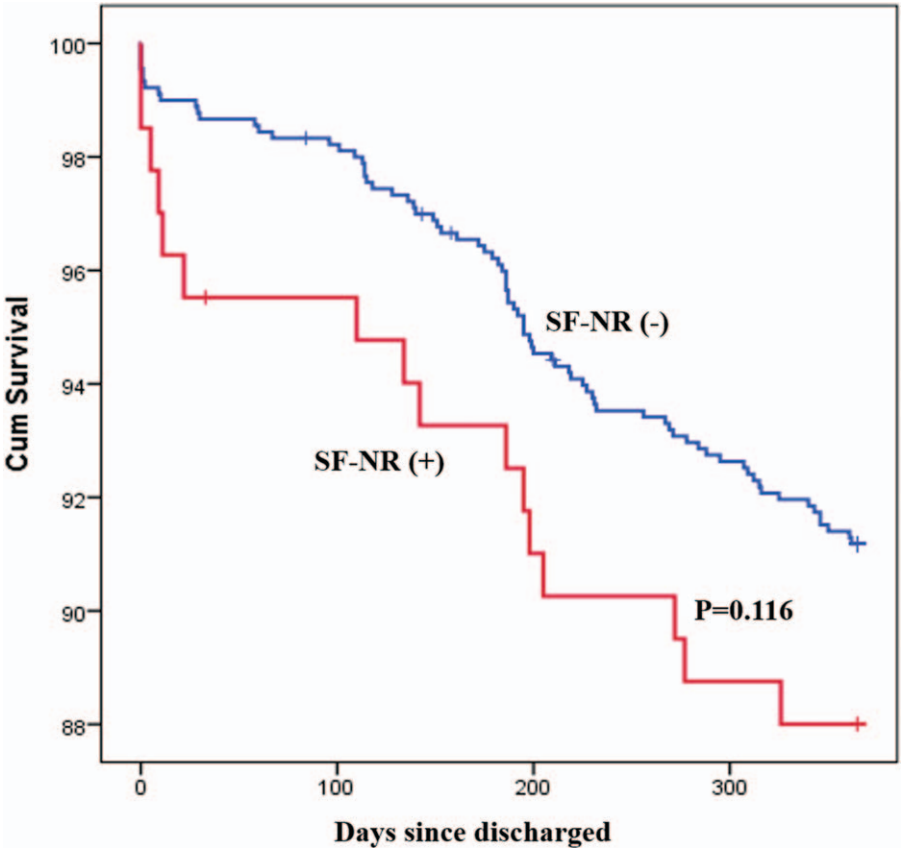

Figure 2. Survival rate of patients with or without slow flow/no-reflow. SF-NR = slow flow/no-reflow.

Table 3

Univariate and multivariate binary logistic regression of predictors for slow flow /no-reflow.

	Univariate			Multivariate		
Variable	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Female vs male	1.337	0.865–2.067	.19			
Smoking	1.520	1.022–2.259	.04*	1.814	1.19–2.764	.01*
CHA_2DS_2-VASc score ≥3	1.824	1.211–2.746	.004*	2.148	1.389–3.320	.001*
Atrial fibrillation	3.038	1.226–7.529	.02*	2.892	1.138–7.350	.03*
Time from symptom onset to PPCI[a]	0.997	0.983–1.015	.87			
Diabetes mellitus	0.798	0.520–1.223	.30			
Infarct area						
Inferior vs anterior	1.282	0.874–1.880	.20			
Lateral vs anterior	1.291	0.281–5.932	.74			
Multiwall vs anterior	1.239	0.556–2.761	.60			
Complete revascularization	2.320	1.232–4.367	.01*	2.307	1.202–4.429	.01*
Thrombus aspiration	1.330	0.910–1.942	.14			
Number of lesion vessels	1.017	0.718–1.442	.92			
Number of stents implanted	1.044	0.785–1.388	.77			
Mean stent diameter	0.777	0.513–1.176	.23			
Total length of stents ≥40 mm	1.499	1.029–2.182	.04*	1.482	1.011–2.172	.04*

[a] PPCI = primary percutaneous coronary intervention.
* Means significant *P* value.

In patients with CHA_2DS_2-VASc <3, the incidence of SF-NR phenomenon was 11.47%. In patients with CHA_2DS_2-VASc ≥3, the incidence of SF-NR phenomenon was 19.12%. If the patient's CHA_2DS_2-VASc ≥3 and combined with 0 to 1 other risk factors (including smoking, AF, complete revascularization, total stent length ≥40 mm), the incidence of SF-NR phenomenon reached 14.53%. If the patient's CHA_2DS_2-VASc ≥3 and combined with ≥2 other risk factors, the incidence of SF-NR phenomenon reaches 43.75%, which is 3 times of that combined with 0 to 1 other risk factors (Fig. 3).

4. Discussion

In the current study, we found that CHA_2DS_2-VASc score ≥3 was a simple and sensitive predictor of SF-NR phenomenon. Smoking, the history of AF, complete revascularization and

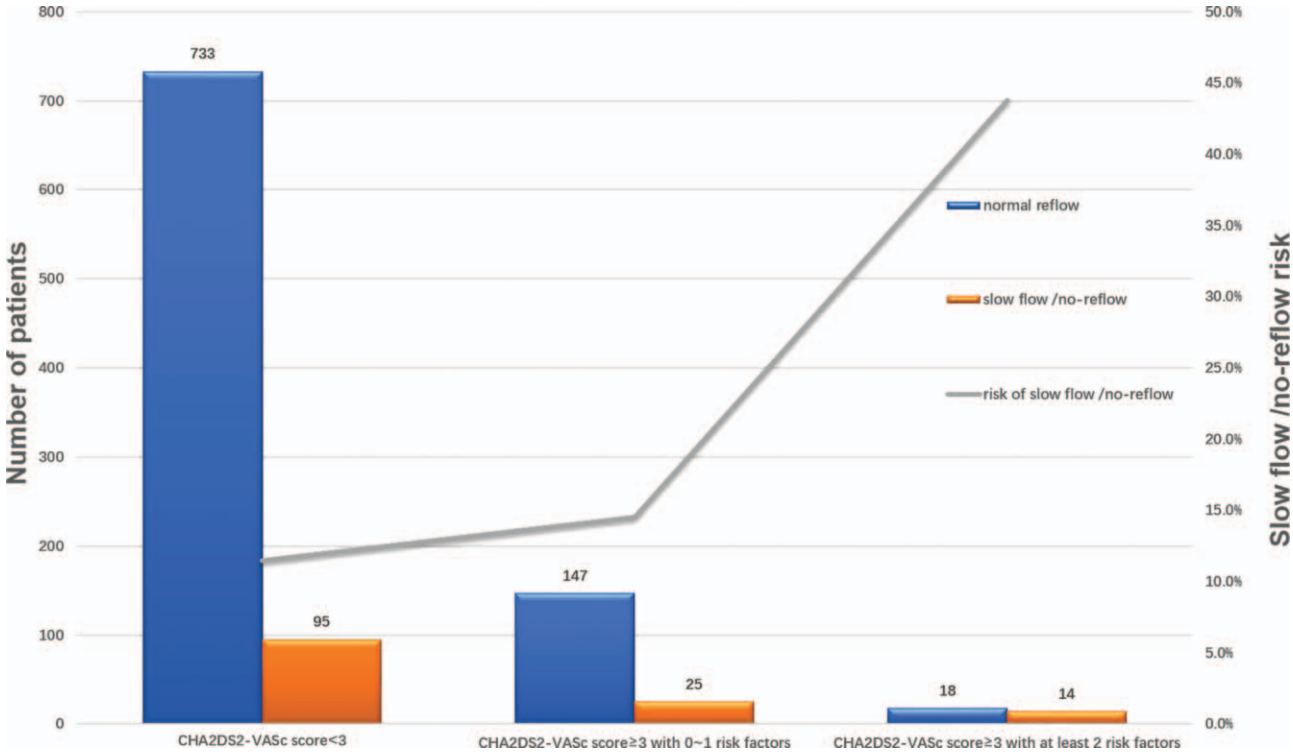

Figure 3. Risk of slow flow/no-reflow.

total stent length ≥40 mm were other 4 risk factors of SF-NR phenomenon. When the patient with CHA_2DS_2-VASc ≥3 plus ≥2 risk factors, physicians should actively implement a treatment strategy to prevent SF-NR occurring.

SF-NR phenomenon occurs at a frequency of 5% to 50% among patients undergoing PPCI.[12,13] Our study findings were in agreement with the SF-NR prevalence. It is associated with adverse mid- and long-term clinical outcomes.[14,15] Similarly, in our study, patients with SF-NR phenomenon had higher in-hospital and 1-year mortality, although no statistical significance was attained. To prevent the occurrence of SF-NR during PPCI, factors associated with a high probability of SF-NR must be anticipated. Some pathophysiological changes have been described as underlying mechanisms of SF-NR including endothelial injury, plugging of capillaries by microthrombi, and inflammation due to generation of free radicals as well as complement activation.[16] In clinical research, the total stent length >20 mm, smoking and history of AF were closely related to SF-NR.[17,18] In accordance with previous studies, in our study, patients with SF-NR had a higher incidence of smoking, history of AF, and total length of stent (mm) ≥40 mm than those with normal blood flow.

Microvascular obstruction due to distal remobilization, thrombosis, and microvascular spasm have been proposed as contributors for SF-NR.[19] All the paraments in CHA_2DS_2-VASc score were important risk and prognostic factors for cardiovascular disease. Several parameters of CHA_2DS_2-VASc score were also showed to be related with microvascular dysfunction. Diabetes mellitus has been proved to be associated with impaired coronary microvascular function following PCI due to the tendency of endothelial vasoconstriction and thrombosis.[6,7,20] Similarly, hypertension, congestive heart failure, and female sex were also showed to be the risk factors of microvascular dysfunction.[8–21] Some recently published studies investigated the role of CHA_2DS_2-VASc scores in patients with acute coronary syndrome. Bozbay et al[22] showed that the CHA_2DS_2-VASc score was a predictor of adverse events in STEMI patients. Açikgöz et al[23] demonstrated that the CHA_2DS_2-VASc score was an independent predictor of stent thrombosis. There are also several studies that investigated the relationship between the CHA_2DS_2-VASc score and SF-NR phenomenon in STEMI patients. Two retrospective studies suggested that the CHA_2DS_2-VASc score was associated with a higher risk of SF-NR phenomenon and in-hospital mortality rates in patients who received PPCI due to STEMI.[10–24] Mirbolouk et al[25] demonstrated that the CHA_2DS_2-VASc score was an independent predictor of SF-NR phenomenon in 398 STEMI patients. Many items in the CHA2DS2-VASc score overlap with the risk factors that cause SF-NR during PPCI. In this study, we demonstrated for the first time that the incidence of SF-NR in patients with CHA_2DS_2-VASc score ≥3 was 1.7 times higher than that in patients with CHA_2DS_2-VASc score <3. CHA_2DS_2-VASc score was an independent predictor of SF-NR phenomenon in STEMI patients with MVD who received PPCI.

The selection of complete or culprit-only revascularization in STEMI patients with MVD is still uncertain. Although the 2018 ESC guidelines give a class IIb recommendation for immediate revascularization of a non-culprit artery in patients with multiple or critical stenosis lesions.[26] However, a recently published meta-analysis showed that complete revascularization did not decrease the risk of all-cause mortality for STEMI patients with MVD undergoing PPCI.[27] In addition, Iqbal et al[28] showed that revascularization of bystander non-culprit increased the level of coronary micro-embolization and the rate of re-infarction during hospitalization resulting in the occurrence of SF-NR phenomenon. In this study, we discovered that complete revascularization was an independent predictor of SF-NR phenomenon in STEMI patients with MVD. For those patients who had higher risk of SF-NR, physicians need to individualize care regarding the selection of myocardial revascularization strategy before PPCI. From the perspective of prevention, identifying the patients at risk of SF-NR phenomenon before PPCI might be helpful for medical decision making.

4.1. Limitation

However, there are some limitations in this article. First, as this was a retrospective, observational study, selection bias was certainly existed. However, we used multivariate analyses to minimize the bias from different baseline characteristics. Second, some laboratory parameters such as high sensitivity CRP and B type natriuretic peptide were random missing in records, which might have some influence on the results of the analysis. However, we performed mean imputation method to deal with the random missing data and partly reduce its adverse impact. Finally, our study did not apply intravenous ultrasound (IVUS) or fractional flow reserve to all patients. Therefore, we are not able to quantitatively assess plaque content, thrombus burden, and collect the detail information of microvascular function. The following diagnostic test could pay more attention on these indexes.

5. Conclusions

SF-NR is still a significant challenge for PPCI in STEMI patients with MVD. Identifying patients at risk of SF-NR before PPCI may be beneficial from the perspective of prevention. In this study, we discovered that CHA_2DS_2-VASc score ≥3 can be used as a simple and sensitive indicator to predict SF-NR phenomenon and guide the PPCI strategy in STEMI patients with MVD. Further pertinent diagnostic tests are needed to test our results before it uses in clinical.

Author contributions

Conceptualization: Shao-Ping Nie.
Data curation: Xin Huang, Wen Zheng, Xue Dong Zhao.
Formal analysis: Xin Huang, Wen Zheng.
Software: Wen Zheng.
Supervision: Shao-Ping Nie.
Writing – original draft: Xin Huang.
Writing – review & editing: Wen Zheng, Shao-Ping Nie.

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