Journal of Research in Clinical Medicine

J Res Clin Med, 2020, 8: 16
doi: 10.34172/jrcm.2020.016
https://jrcm.tbzmed.ac.ir

TUOMS PRESS

Original Article

The association of mean platelet volume to lymphocyte ratio and no-reflow in patients with myocardial infarction undergoing primary percutaneous coronary intervention

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Article info

Article History:
Received: 17 Mar. 2020
Accepted: 11 Apr. 2020
e-Published: 06 May 2020

Keywords:
- Mean platelet volume to lymphocyte ratio
- No-reflow
- Myocardial infarction
- Primary percutaneous coronary intervention

Abstract

Introduction: The acute coronary events are one of the most common problems which are accounted to higher mortality and morbidity rate around the world. The underlying mechanism is related to occlusion, and the best therapy is to reopen the affected vessels. Many factors can influence the outcomes of percutaneous coronary intervention (PCI).

Methods: This cross-sectional study was conducted on 845 cases with acute myocardial infarction (AMI) undergoing PCI for evaluation of the "No-Reflow" phenomenon who were referred to Shahid Madani hospital in 2018. All demographic, laboratory and angiographic studies were evaluated. The obtained data were recorded and analyzed by SPSS 21.

Results: Among 845 patients with STEMI, the incidence of angiographic no-reflow was 28% (n = 245). The older cases with co-morbid diseases and cardiac-related risk factors were considered as vulnerable to no-reflow after PCI. The other parameters were partially decisive factors for the prediction of no-reflow and mortality rate, such as higher MPV and MPV to lymphocyte ratio.

Conclusion: The coronary artery involvement is a troublesome event because of the established heart risk factors, and sometimes treating it with PCI could be complicated due to no-reflow. The simple predictors (i.e., MPV to lymphocyte ratio) could help us reduce morbidity and mortality.

Introduction

The acute coronary and cerebro-cardiac events as first cardiovascular manifestation have same pathophysiologic mechanisms (i.e., atherosclerosis and thrombosis).[1] The improvement of technology, introducing new and powerful anti-thrombotic treatments may result in increased complexity of percutaneous coronary interventions (PCIs), and consequently, higher intervention risk. Indeed, many patients are suffering from myocardial infarction (MI) after the intervention; especially due to the consequences of decreased blood flow.[2] Although myocardial damage may gradually occur, the formation of platelet plaques in blood circulation could lead to the obstruction of blood supply to the myocardium, and this event is associated with a potentially negative effect on the prognosis of the disease.[3] The primary and delayed prognosis of patients with acute MI are mainly related with three major variables, including left ventricle function, the sensitivity to ventricular arrhythmias and post-reperfusion remained ischemia.[4,5] The no-reflow phenomenon occurs in a significant number of patients with ST-elevation myocardial infarction (STEMI) undergoing primary reperfusion. [6] By remarkable using of primary PCI, it is important to the better diagnosis and treatment of "no-reflow", then, researchers focus on issue which plays a central role in researches for improvement of aforementioned effects. The clinical and laboratory experiences show that "no-reflow" is associated with necrosis of cardiac muscles, which is known as a predictor of mortality.[6-8] Currently, the data of other studies and analysis of controlled clinical trials demonstrate that white blood cell-related indices (e.g., platelet/lymphocyte ratio and neutrophil/lymphocyte ratio) are associated with higher mortality rate, repeated MI, and severe outcomes after acute coronary syndrome (ACS). The inflammation plays a special role in the initiation and progression of atherosclerosis process.[9] Nowadays, the ratio of mean platelet volume to lymphocyte (MPV/lymphocyte) is suggested as a thrombotic and inflammatory marker which has been mainly evaluated in cases with malignant

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tumors.[10] This ratio is followed by inconsistent results. It reflects hemostatic and inflammatory pathways in blood disorders.[11] However, there is a lack of information about the ratio and the association with other undesired events in patients with cardiovascular diseases.[12] Hence, this ratio might have a significant role in the determination of disease severity and response to treatment based on "no-reflow" grading in patients with AMI undergoing PCI. Therefore, we aimed to evaluate this ratio effect on "no-reflow" event in such cases.

Materials and Methods

This cross-sectional study was conducted for evaluation of the "no-reflow" phenomenon in two phases, on 845 cases with AMI undergoing PCI who were referred to Shahid Madani hospital in 2018. Informed consent was obtained from the participants, and the laboratory tests and echocardiographic evaluations were done. The demographic data (including age, weight, etiology of MI, history of hypertension, diabetes mellitus, hyperlipidemia, smoking, renal failure, cardiac surgery, duration of disease, drugs, type of treatment, etc), imaging studies, angiographic findings (e.g., infarcted coronary vessels, the diameter of vessels, length of injury, the ejection fraction (EF) of left ventricle), hospitalization indices (e.g., the first time of inflation symptom of balloon, incidental anti-thrombotic event, clopidogrel loading dose, number of the stents, heparin administration before randomization, and third-degree of supply disorder) and laboratory data (e.g., white blood cell, platelet, creatinine [Cr], erythrocyte sedimentation rate, chain reactive polymerase) were recorded.

Analysis of angiographic study and definition of "no-reflow"

- The coronary angiography was performed based on the standard criteria. The off-line analysis of digital angiograms was done in the central lab by using automated diagnostic systems (blinded operator). The primary PCI (mainly by replacement of stent) and taking care during treatment courses were performed. The anticoagulant drugs (i.e., clopidogrel 600 mg as a loading dose and, following 75 mg/d for minimum four weeks to 6 months and aspirin 200 mg per day by unlimited dose) were administered. The epicardial blood circulation in the area of the infarcted artery and myocardial perfusion rate were graded based on TIMI (thrombolysis in MI). The diagnosis of "no-reflow" is made by the following criteria:
- The documented angiographic re-opening view of obstructed coronary vessels, the successful replacement of stent without any sign of vessel restriction and supply limitation (< 50%), and the obvious no-reflow, spasm or thrombosis.
- The documented angiographic evaluation in view of TIMI <2, or TIMI = 3 with myocardial reperfusion grade = 0 (TMPG) or 1 at least 10 minutes after PCI. TMPG is referred to no entrance of contrast media, and TMPG1 is equivalent to the slow entrance of media or unsuccessful media exiting from vessels. The 50% or more stricture of coronary vessels is known as vessel stricture. If two epicardial vessels are involved more than 50%, this is named to multi-vessel involvement. PCI is considered as successful primary PCI when remained stricture rate based on TIMI grading is < 10%.

The data were analyzed by descriptive methods (mean ± standard deviation and frequency-percentage). Independent samples *t* test and Mann-Whitney U Test were used for the comparison of MPV/lymphocyte ratio when variables were normal and non-parametric, respectively. The normal distribution of data was analyzed using the Kolmogorov-Smirnov test. *P* value < 0.05 was considered statistically significant.

Results

Of 845 patients with STEMI, the incidence of angiographic no-reflow was 28% (n = 245). The demographic, laboratory and angiographic variables are shown in Table 1.

As outlined in this table, the cases in the normal-flow group were younger and had a lower rate of comorbid disease and higher successful history of the prior coronary artery bypass graft. It was more likely that no-reflow has occurred in women with a higher level of Cr, hypercholesterolemia, C-reactive protein (CRP), and platelet to lymphocyte ratio (PLR). In terms of angiographic study, the involvement of multiple vessels, which is resulted in a prolonged time to the placement of balloon, delayed time up to re-opening of occluded vessels and lower TIMI after PCI were observed in the no-reflow group. The stent diameter, Ejection Fraction (EF), and resolution of electrocardiographic changes were higher in the normal-flow group. It meant that there was a significant association with higher MPV to lymphocyte ratio and no-reflow (Table 2).

The univariate and multivariate predictors of no-reflow are listed in Table 3. The multivariate analysis showed that gender, smoking, diabetes mellitus, higher WBC count, serum Cr levels, prolonged time to balloon placement, multi-vessel involvement and chronicity were more powerful predictors for the no-reflow phenomenon.

Discussion

The results of our study demonstrated interesting findings, which show that basic demographic characterization (i.e., age, gender, co-morbid diseases, and smoking), laboratory tests (i.e., higher cholesterol and Cr level, MPV, hs-CRP, MPV to lymphocyte ratio) and angiographic data (i.e., the number of involved arteries, delayed time up to re-opening of occluded vessels, history of anterior MI, TIMI and the characteristics of the stent) have an impact on the no-reflow phenomenon and its incidence in cases with

Table 1. The baseline clinical, laboratory and angiographic variables of studied groups

Variables	Post-procedural coronary flow		*P* value
	Normal re-flow (n = 600)	No-reflow (n = 245)	
Age (y)	56.15 ± 11.33	65.14 ± 10.38	<0.001
Gender (female)	140 (23.3%)	91 (37.1%)	<0.001
Body mass index (kg/m^2)	27.37 ± 4.20	27.90 ± 3.99	0.092
Diabetes mellitus	163 (27.2%)	95 (38.8%)	<0.001
Hypertension	200 (33.3%)	106 (43.3%)	0.006
Active smoker	341 (56.8%)	83 (33.9%)	<0.001
Hypercholesterolemia*	172 (28.5%)	65 (26.8%)	0.531
Prior coronary artery bypass surgery	15 (2.5%)	4 (1.63%)	0.440
Left ventricular ejection fraction (%)	46.95 ± 10.01	40.17 ± 10.58	<0.001
High sensitivity c-reactive protein (mg/L)	8.14 (2.56-10.65)	11.55 (3.90-10.75)	<0.001
White blood cell count (×10^9/L)	11.65 ± 3.47	13.17 ± 4.58	<0.001
Platelet count (×10^9/L)	250 ± 65	244 ± 79	0.455
Hemoglobin (g/dL)	13.45 ± 1.65	14.09 ± 1.98	<0.001
Mean platelet volume (fL)	8.7 (7.6-8.8)	8.5 (8.0-9.4)	<0.001
Lymphocyte count (/mm^3)	1.45 (0.95-1.78)	2.35 (175-3.60)	<0.001
Platelet-to-lymphocyte ratio	95 (69-141)	188 (131-263)	<0.001
Mean platelet volume-to-lymphocyte ratio	3.87 (2.40-4.99)	6.78 (4.79-9.89)	<0.001
Peak troponin-T level (ng/mL)	2999 (810-10000)	5665 (1877-13211)	<0.001
Total cholesterol (mg/dL)	189.7 ± 43.5	192.8 ± 51.3	0.373
Low density lypoprotein cholesterol (mg/dL)	122.1 ± 36.9	123.9 ± 40.1	0.531
High density lypoprotein cholesterol (mg/dL)	40.5 ± 9.1	40.4 ± 10.1	0.888
Triglyceride (mg/dL)	145 (100-201)	122 (83-192)	<0.001
Serum glucose (mg/dL)	155.2 ± 78.1	173.9 ± 90.2	<0.001
Serum creatinine (mg/dL)	0.99 ± 0.20	1.05 ± 0.46	<0.001
Pre-infarction angina	202 (33.6%)	75 (30.6%)	0.391
Pain-to-balloon time (min)	152 (119-245)	363 (181-605)	<0.001
Anterior infarct location	248 (41.3%)	147 (60.0%)	<0.001
Early patency of the infarct-related artery	241 (41.0%)	46 (18.8%)	<0.001
Multi-vessel disease	312 (52.0%)	167 (68.1%)	<0.001
Chronic total occlusion	66 (11.0%)	52 (21.1%)	<0.001
Stent implantation	588 (98.0%)	238 (97.1%)	0.446
Glycoprotein IIb/IIIa inhibitors use	240 (40.1%)	130 (53.0%)	<0.001
P2 y_{12} inhibitor use			
Clopidogrel	461 (76.8%)	195 (79.6%)	0.383
Ticagrelor	126 (21%)	44 (18.9%)	0.317
Prasugrel	13 (2.2%)	6 (2.5%)	0.802
Average stent diameter (mm)	3.23 ± 0.41	3.21 ± 0.43	0.526
Average stent length (mm)	24.9 ± 12.01	32.08 ± 17.9	< 0.001
In-hospital mortality	15 (2.5%)	42 (17.1%)	< 0.001
Pre-hospital medications			
Aspirin	60 (10.0%)	33 (13.5%)	0.144
Renin-angiotensin-aldosterone inhibitor	108 (18.0%)	50 (20.4%)	0.415
Statin	36 (6.0%)	21 (8.6%)	0.052
Beta-blocker	33 (5.5%)	21 (8.6%)	0.098

Table 2. The evaluated data in two groups based on MPV to Lymphocyte ratio

Variables	Mean platelet volume-to-lymphocyte ratio		*P* value
	<4.87 n = 523	≥4.87 n = 322	
Age (years)	56.37 ± 11.93	64.14 ± 12.38	<0.001
Gender (female)	110 (23.03%)	98(30.4%)	<0.001
Body mass index (kh/m^2)	27.97 ± 4.78	28.08 ± 4.49	0.740
Diabetes mellitus	141 (26.9%)	103 (32.0%)	0.117
Hypertension	167 (31.9%)	129 (40.1%)	0.010
Current smoker	316 (60.4%)	132(41.0%)	<0.001
Hypercholesterolemia*	161 (30.8%)	84 (26.1%)	0.191
Prior coronary artery bypass surgery	13 (2.5%)	7 (2.2%)	0.772
Left ventricular ejection fraction (%)	48.05 ± 9.78	43.17 ± 10.64	<0.001
High sensitivity c-reactive protein (mg/L)	9.05 (3.51-10.70)	8.04 (3.56-10.85)	0.807
Hemoglobin (g/dL)	14.79 ± 1.74	13.84 ± 1.72	<0.001
Peak troponin-T level(ng/mL)	2887 (877-11211)	3995 (1610-11000)	0.006
Serum glucose (mg/dL)	146.2 ± 79.8	158.9 ± 81.2	0.089
Serum creatinine (mg/dL)	1.09 ± 0.21	1.11 ± 0.24	0.204
Pre-infarction angina	172 (32.9%)	108 (33.5%)	0.845
Pain-to-balloon time (min)	149 (119-239)	241 (119-422)	<0.001
Anterior infarct location	203 (38.8%)	165 (51.2%)	<0.001
Early patency of the infarct-related artery	219 (41.9%)	99 (30.7%)	<0.001
Post-procedural angiographic no-reflow	31 (5.9%)	100 (31.1%)	<0.001
Multi-vessel disease	261 (49.9%)	200 (62.1%)	<0.001
Chronic total occlusion	47 (9.0%)	55 (17.1%)	0.005
Stent implantation	513 (98.1%)	312 (96.9%)	0.286
Average stent diameter (mm)	3.17 ± 0.41	3.15 ± 0.39	0.483
Average stent length (mm)	25.8 ± 11.9	27.9 ± 14.2	0.021
In-hospital mortality	16 (3.1%)	23 (7.1%)	0.006
Pre-hospital medications			
Aspirin	52 (9.9%)	30 (9.3%)	0.763
Renin-angiotensin-aldosterone inhibitor	82 (15.8%)	67 (20.8%)	0.057
Statin	32 (6.1%)	18 (5.6%)	0.752
Beta-blocker	31 (5.9%)	20 (6.2%)	0.886

STEMI. The higher MPV and lower count of lymphocyte mean enhanced coagulation activity in such patients. On the other hand, it could be explained by long-term decreased perfusion of ischemic heart tissues due to delayed performance of PCI, the more narrow applied stents, and the lowered consumption rate of anticoagulant drugs, which is also reinforced by underlying conditions such as the previous history of hyperlipidemia. This survey suggested the power of the mentioned ratio in the prediction of no-reflow. However, the most important question is "what is the effect of no-reflow on the prognosis of STEMI?". Here, we could state the there is a significant correlation between mortality after MI and the no-reflow phenomenon and this event will be decreased by elimination or eradication of some variables which can play a role in this scenario.

Yildiz et al evaluated the MPV/lymphocyte ratio for the prediction of "no-reflow" in patients with ST-elevation MI (undergoing PCI). TIMI was surveyed in 287 cases who were treated with primary PCI and classified in 3 groups according to PLR. The indices of TIMI were calculated during pre- and post-treatment periods. The cut-off value for MPV/lymphocyte ratio and neutrophil to lymphocyte ratio (NLR) were equal with approximately 160 and 5.9, respectively. The specificity and sensitivity were about 75% and 71%, respectively. These findings showed that the high levels of pre-treatment MPV/lymphocyte ratio and NLR were supposed as important and independent prognostic factors.[11] The other study by Kurtul et al assessed the evaluation of the relationship between MPV/lymphocyte ratio and "no-reflow" after primary PCI. Overall, 520 cases with STEMI were evaluated within 12 hours after onset of symptoms in 2 groups: cases with "normal flow" (TIMI = 3) and "without flow" (TIMI = 0-1 or 2). The results showed that 403 and 117 (22.5%) patients were "normal flow" and " no-reflow", respectively. The second group had significantly higher PLR. The MPV/lymphocyte ratio and total stent length were independent

Table 3. The univariate and multivariate predictors of no-reflow

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age (y)	1.074 (0.969-1.012)	<0.001	1.050 (0.874-1.191)	0.201
Gender (female)	2.034 (1.410-2.970)	<0.001	9.489 (2.087-52.101)	0.003
Active smoker	0.384 (0.242-0.601)	<0.001	0.609 (0.167-2.759)	0420
Hypertension	1.490 (1.132-2.017)	0.009	1.231 (0.421-3.978)	0.905
Diabetes mellitus	1.792 (1.223-2.262)	0.001	2.737 (0.495-15.063)	0.298
Left ventricular ejection fraction	1.101 (0.991-1.002)	<0.001	0.889 (0.702-1.103)	0.211
White blood cell count	1.006 (0.905-0.988)	<0.001	1.132 (0.987-1.421)	0305
Hemoglobin	0.712 (0.525-0.911)	<0.001	0.647 (0.395-0.967)	0.035
Serum creatinine	2.712 (1.425-4.962)	<0.001	2.937 (0.544-36.371)	0.510
High-sensitivity C-reactive protein	1.098 (1.075-1.077)	0.001	1.089 (1.002-1.096)	0.021
Pain-to-balloon time	1.006 (1.004-1.009)	<0.001	1.001 (0.956-1.006)	0.019
Early patency of the infarct-related artery	0.439 (0.184-0.409)	<0.001	0.285 (0..059-1.204)	0.064
Multi-vessel disease	2.053 (1.625-3.258)	<0.001	2.421 (0.783-8.544)	0.197
Average stent length	1.061 (1.013-1.043)	<0.001	1.091 (1.010-1.087)	0.012
Chronic total occlusion	1.994 (1.479-3.012)	<0.001	2.541 (0.283-19.429)	0.458
Anterior infarct location	1.109 (0.179-8.857)	<0.001	8.009 (1.903-36.521)	0.007
Mean platelet volume-to-lymphocyte ratio	1.694 (1.375-1.498)	<0.001	1.597 (1.432-2.078)	<0.001
Serum glucose	1.007 (1.005-1.012)	<0.001	1.011 (0.915-1.088)	0.205

prognostic factors after primary PCI (PPCI) so that pre-intervention ratio could be considered as mainstay cue for the prediction of PPCI outcomes.[13] Currently, it has been suggested that anemia is associated with increased mortality rate, re-infarction and severe consequences after ACS. Lawler et al showed that 4 4519 of 23 3144 cases had anemia who were elderly and had a higher prevalence of diabetes, heart failure, cerebral disease and history of bleeding.[10,14]

Conclusion

The present study showed that no-reflow is an important event which is followed by a higher mortality rate. For having the prognostication value of this phenomenon, the evaluation of contributing simple factors, such as MPV, MPV to lymphocyte ratio and TIMI could help to prevent the no-reflow and resultant mortality.

Conflict of interest

The authors stated that they had no conflict of interest.

Ethical Approval

This study was approved by the ethical committee of Tabriz University of Medical Sciences (No. IR.TBZMED. REC.1398.1271).

Author's Contributions

AS carried out the design and coordinated the study, participated in fundus exams. PD participated in neonate's examinations and follow ups. AAA provide assistance in the design of the study, neonate's examinations and follow ups. AS provided assistance in statistical analysis and manuscript preparation. AAA and PD assisted in data gathering and participated in manuscript editing.

Funding

There was no funding support

Acknowledgements

We would like to thank staffs of Heart Shahid Madani Hospital, Cardiovascular Research for their participation and Author contribution.

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