Neutrophil/Lymphocyte Ratio as a Predictor of In-Hospital Major Adverse Cardiac Events, New-Onset Atrial Fibrillation, and No-Reflow Phenomenon in Patients with ST Elevation Myocardial Infarction

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ABSTRACT

BACKGROUND: Neutrophil/lymphocyte (N/L) ratio represents the balance between neutrophil and lymphocyte counts in the body and can be utilized as an index for systemic inflammatory status. The no-reflow phenomenon is defined as inadequate myocardial perfusion through a given segment of the coronary circulation without angiographic evidence of mechanical vessel obstruction. Systemic inflammatory status has been associated with new-onset atrial fibrillation (NOAF) as well as no-reflow.

AIM: To evaluate the predictive value of N/L ratio for in-hospital major adverse events, NOAF, and no-reflow in patients with ST elevation myocardial infarction (STEMI).

PATIENTS: Two hundred consecutive patients with STEMI presenting to Alexandria Main University Hospital and International Cardiac Center Hospital, Alexandria, Egypt, from April 2013 to October 2013 were included in this study.

METHODS: Laboratory investigation upon admission included complete blood count with mean platelet volume (MPV) and N/L ratio, and random plasma glucose (RPG) level. The results of coronary angiography indicating the infarct-related artery (IRA), initial thrombolysis in myocardial infarction (TIMI) flow in the IRA, and the TIMI flow after stenting were recorded. The patients were studied according to the presence of various clinical and laboratory variables, such as age, gender, pain-to-balloon time, location of the infarction, RPG level and complete blood count including N/L ratio and MPV on admission, and initial TIMI flow in the IRA. They were also evaluated for the final TIMI flow after the primary percutaneous coronary intervention, incidence of NOAF, and the incidence of in-hospital major adverse cardiac events (MACE).

RESULTS: The incidence rate of no-reflow, NOAF, and in-hospital MACE was 13.2%, 8%, and 5%, respectively, with cardiac death as the predominant form of in-hospital MACE. The group of no-reflow, NOAF, and/or MACE showed significantly older age (62.29 ± 7.90 vs 56.30 ± 10.34, $P = 0.014$), longer pain-to-balloon time (15.90 ± 7.87 vs 6.08 ± 3.82 hours, $P < 0.001$), higher levels of RPG, N/L ratio (8.19 ± 3.05 vs 5.44 ± 3.53, $P < 0.001$), and MPV (11.90 ± 2.09 vs 8.58 ± 1.84 fL, $P < 0.001$) on admission. After adjustment of confounding factors, the independent predictors of NOAF, no-reflow, and in-hospital MACE were higher N/L ratio (odds ratio [OR] = 3.5, $P = 0.02$) and older age (OR = 3.1, $P = 0.04$).

CONCLUSIONS: Older patient age, longer pain-to-balloon time, hyperglycemia, higher N/L ratio, and MPV on admission are useful predictive factors for the occurrence of no-reflow postprimary percutaneous coronary intervention, NOAF, and/or in-hospital MACE. N/L ratio is a new strong independent predictor of no-reflow, NOAF, and/or in-hospital MACE in patients with STEMI. The use of this simple routine biomarker may have a potential therapeutic implication in preventing NOAF and improving prognosis in STEMI revascularized patients.

KEYWORDS: STEMI, no reflow, NOAF

CITATION: Wagdy et al. Neutrophil/Lymphocyte Ratio as a Predictor of In-Hospital Major Adverse Cardiac Events, New-Onset Atrial Fibrillation, and No-Reflow Phenomenon in Patients with ST Elevation Myocardial Infarction. *Clinical Medicine Insights: Cardiology* 2016:10 19–22 doi: 10.4137/CMC.S35555.

TYPE: Original Research

RECEIVED: October 19, 2015. **RESUBMITTED:** December 22, 2015. **ACCEPTED FOR PUBLICATION:** January 04, 2016.

ACADEMIC EDITOR: Thomas E. Vanhecke, Editor in Chief

PEER REVIEW: Four peer reviewers contributed to the peer review report. Reviewers' reports totaled 688 words, excluding any confidential comments to the academic editor.

FUNDING: Authors disclose no external funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

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Introduction

ST elevation myocardial infarction (STEMI) remains one of the leading causes of death globally.[1] The main goal of the treatment of acute myocardial infarction is the early restoration of patency of the culprit artery. This could be achieved by either fibrinolysis or primary percutaneous coronary intervention (PPCI).[2] The no-reflow phenomenon is defined as inadequate myocardial perfusion through a given segment of the coronary circulation without angiographic evidence of mechanical vessel obstruction.[3] It can be caused by the variable combination of four pathogenetic components, namely, distal embolization, ischemic injury, reperfusion injury, and susceptibility of coronary microcirculation to injury. No-reflow has been documented in 30% of patients after thrombolysis or mechanical intervention for acute myocardial infarction.[4] No-reflow implies abnormal tissue perfusion.

Patients with persistent no-reflow are more prone to develop in-hospital major adverse cardiac events (MACE) and congestive heart failure early after myocardial infarction

and demonstrate progressive left ventricular cavity dilatation in the convalescent stage of the infarction.[3]

Several key pathophysiological processes, usually in combination, are believed to be responsible for this phenomenon, such as distal embolization of atherothrombotic debris, thrombus formation, and endothelial dysfunction of the distal arteriolar and capillary bed, including endothelial desquamation and microcirculatory vasospasm.[5]

Recently, neutrophil/lymphocyte (N/L) ratio was found to be a strong predictor of adverse outcomes after PPCI.[6] However, its underlying mechanism remains unknown. It may be due to atherosclerosis, which is an inflammatory process, and inflammatory biomarkers have been identified as useful predictors of clinical outcomes.

The N/L ratio has been evaluated as a new predictor of cardiovascular risk.[7] Previous studies have shown that inflammation acts as a facilitator in the induction of supraventricular tachycardia, and a recent study has shown that increased inflammatory markers may have a role in predicting atrial tachycardia in selected patients.[8]

This study aimed to determine the relation between N/L ratio and the occurrence of in-hospital MACE, new-onset atrial fibrillation (NOAF),[9] and no-reflow in patients with STEMI.

Patients and Methods

This study included 200 STEMI patients treated with PPCI, who were analyzed as part of a prospective study conducted in the Faculty of Medicine of Alexandria Main University Hospital and International Cardiac Center Hospital, Alexandria, Egypt, from April 2013 to October 2013.

According to European Society of Cardiology guidelines, inclusion criteria were patients with STEMI eligible for PPCI, while the exclusion criteria were patients who underwent previous coronary artery bypass grafting or patients who underwent previous PCI and had in-stent restenosis.

All PCI procedures were done using a transfemoral approach. The use of aspiration devices, balloon predilatation, and the type of stent and also the use of glycoprotein IIb/IIIa inhibitors were based on the decision of the acting physician.

The patients were studied according to the presence of various clinical and laboratory variables, such as age, gender, risk factors, absence of preinfarction angina, pain-to-balloon time, location of the infarction, plasma glucose level and complete blood count including N/L ratio and mean platelet volume (MPV) on admission, as well as initial thrombolysis in myocardial infarction (TIMI) flow in the infarct-related artery (IRA) and the final TIMI flow after the PPCI.

All blood samples were withdrawn at hospital admission.

Patients were observed to detect the occurrence of any in-hospital MACE or NOAF. Our research complied with the principles of the Declaration of Helsinki. Patients gave their written, informed consent to participate in the research, which was approved by the Ethics Committee of the Faculty of Medicine – Alexandria University.

Table 1. Distribution of the two studied groups.

	NO	%
Normal (Group A)	165	82.5
No-reflow, hospital MACE or NOAF (Group B)	35	17.5

Results

The patients were divided into two groups according to the final TIMI flow after the PPCI and the incidence of in-hospital MACE or NOAF, as listed in Tables 1 and 2. Group A had a normal flow after PPCI and did not have in-hospital MACE or NOAF. Group B either had no-reflow after PPCI or experienced in-hospital MACE or NOAF.

The two groups were well matched regarding the baseline clinical characteristics of age and sex distribution (Table 3).

There was no statistically significant difference between the two groups regarding the incidence of diabetes hypertension or dyslipidemia (Table 4).

Regarding smoking in Group A, 87 (52.5%) patients are current smokers, 6 (4%) patients are exsmokers, and 72 (43.4%) patients are nonsmokers; and in Group B, 15 (42.9%) patients are current smokers, 2 (4.8%) patients are exsmokers, and 18 (52.4%) patients are nonsmokers.

In Group A, 28 (17.2%) patients had family history of ischemic heart disease, as did 3 (9.5%) patients in Group B.

The number of patients in Killip I class was 138 (83.8%) in Group A and 27 (76.2%) in Group B. The number of patients in Killip II class was 17 (10.1%) in Group A and 5 (14.3%) in Group B. The number of patients in Killip III class was 2 (1%) in Group A and 2 (4.8%) in Group B. The number of patients in Killip IV class was 8 (5.1%) in Group A and 1 (4.8%) in Group B.

With respect to electrocardiogram (ECG) diagnosis, 120 (72.7%) patients presented with anterior STEMI in Group A and 23 (66.7%) patients in Group B. In Group A, 35 (21.2%) patients presented with inferior STEMI, as did 10 (28.6%) patients in group B. Ten (6.9%) patients presented with lateral STEMI in Group A and 2 (4.7%) patients in Group B (Table 4).

Patients in Group A had longer pain-to-balloon time (6 ± 3.8 hours) than patients in Group B (15.9 ± 7.8 hours), a statistically significant difference ($P < 0.001$; Table 5).

Table 2. Distribution of patients in Group B.

GROUP B	N = 35	%
No-reflow	27	76.2
In-hospital MACE		
Cardiac death	10	28.6
MI	0	0.0
Stent thrombosis	0	0.0
Target vessel revascularization	0	0.0
NOAF	24	68.6

Table 3. Comparison between the two studied groups according to diabetes, hypertension, and smoking.

	GROUP A (N = 165)		GROUP B (N = 35)		χ^2	*P*
	NO	%	NO	%		
Diabetes						
Non diabetic	103	62.6	15	42.9	2.803	$^{MC}P = 0.094$
Diabetic	62	37.4	20	57.1		
Hypertension	80	48.5	12	33.3	1.602	0.206
Smoking						
Non smoker	72	43.4	18	52.4	0.560	0.454
Smoker	87	52.5	15	42.9	0.648	0.421
Ex-smoker	6	4.0	2	4.8	0.023	$^{FE}P = 1.000$
Dyslipidemia	90	54.5	25	71.4	2.021	0.155
Family history	28	17.2	3	9.5	0.760	$^{FE}P = 0.521$
Previous ACS	32	19.2	5	14.3	0.279	$^{FE}P = 0.762$

Abbreviations: FE, Fisher's exact test; MC, Monte Carlo test; χ^2, chi-squared test.

Also, there were statistically significant differences in laboratory results on admission between the two groups (Table 6).

In Group A, the median of random plasma glucose on admission was 150 mg/dL (range = 358 mg/dL), while in Group B the median was 280 mg/dL (range = 336 mg/dL; $P < 0.001$).

Patients in Group A had a statistically lower mean neutrophil/lymphocyte ratio (5.44 ± 3.53) than patients in Group B (8.19 ± 3.05; $P < 0.001$). Receiver-operating characteristic curve analysis showed that N/L ratio >4.6 predicts no-reflow, in-hospital MACE, or NOAF with 90.4% sensitivity and 51.5% specificity.

The mean MPV in Group A was 8.58 ± 1.84 fL, while, in Group B, it was 11.9 ± 2.09 fL ($P < 0.001$).

Discussion

In a variable proportion of patients presenting with ST segment elevation myocardial infarction, ranging from 5% to 50%, PPCI achieves epicardial coronary artery reperfusion but not myocardial reperfusion, a condition known as

Table 4. Comparison between the two studied groups according to ECG.

	GROUP A (N = 165)		GROUP B (N = 21)		χ^2	*P*
	NO	%	NO	%		
ECG						
Anterior MI	120	72.7	23	66.7	0.313	0.576
Lateral MI	10	6.9	2	4.7	0.334	$^{FE}P = 0.628$
Inferior MI	35	21.2	10	28.6	0.538	$^{FE}P = 0.565$

Abbreviations: χ^2, chi-squared test; FE, Fisher's exact test.

Table 5. Comparison between the two studied groups according to pain-to-balloon time.

	GROUP A (N = 165)	GROUP B (N = 35)	*Z*	*P*
Pain-to-balloon time				
Min.–Max.	1.0–19.0	1.0–30.0	4.999*	<0.001*
Mean ± SD	6.08 ± 3.82	15.90 ± 7.87		
Median	5.0	17.0		

Notes: *Z*, *Z* for Mann–Whitney test. *Statistically significant at $P \leq 0.05$.

no-reflow. Of note, no-reflow is associated with a worse prognosis at follow-up. Several recent studies have shown that biomarkers and other easily available clinical parameters can predict the risk of no-reflow and can help in the assessment of multiple mechanisms of the phenomenon. Several therapeutic strategies have been tested for the prevention and treatment of no-reflow.

In our study, patients in Group B had a statistically higher N/L ratio compared with patients in Group A (a mean of 8.19 ± 3.05 vs 5.44 ± 3.53, $P < 0.001$). Receiver-operating characteristic curve analysis of results revealed that N/L ratio >4.6 predicts no-reflow or in-hospital MACE with 90.4% sensitivity and 51.5% specificity.

This higher N/L ratio in the no-reflow group supports the theory of microvascular injury, via elastases released by neutrophils after PPCI, as a cause of no-reflow. Leukocytes could become trapped in coronary capillaries and venules early after coronary reperfusion, and plugging of enhanced leukocytes in the microcirculation may end with no-reflow phenomenon.[5]

Patients with thrombus formation were found to have significantly higher N/L ratio than those without thrombus

Table 6. Comparison between the two studied groups according to laboratory results (on admission).

	GROUP A (N = 165)	GROUP B (N = 35)	TEST OF SIG.	*P*
Plasma glucose				
Min.–Max.	84.0–442.0	104.0–440.0	*Z* = 3.377*	0.001*
Mean ± SD	186.38 ± 84.65	275.29 ± 104.11		
Median	150.0	280.0		
N/L ratio				
Min.–Max.	1.20–24.0	2.80–13.0	*Z* = 3.665	<0.001*
Mean ± SD	5.44 ± 3.53	8.19 ± 3.05		
Median	4.50	8.0		
MPV				
Min.–Max.	5.0–13.0	5.90–15.0	*t* = 7.320*	<0.001*
Mean ± SD	8.58 ± 1.84	11.90 ± 2.09		
Median	8.20	12.20		

Notes: *t*, Student's *t*-test; *Z*, *Z* for Mann–Whitney test. *Statistically significant at $P \leq 0.05$.

formation. Li et al found that N/L ratio was independent predictive of thrombus formation in the IRA, and thrombus formation in the IRA was the only predictor of no-reflow/slow flow during PCI.[6] Two distinct mechanisms may explain this observation: neutrophilia as a reflection of systemic inflammatory status and consequently increased cardiovascular risk or lymphopenia as a reflection of the acute stress presented by acute coronary syndrome.[10,11]

Akpek et al reported that 37% of patients had no-reflow post PCI and 63% had TIMI 3 flow assessed by post PPCI TIMI flow grade.[12] They also reported that patients with no-reflow had significantly higher N/L ratio (4.6 ± 1.7 vs 3.1 ± 1.9, $P < 0.001$). They found that patients with N/L ratio >3.3 developed no-reflow, with 74% sensitivity and 83% specificity. They also reported that patients with no-reflow had higher incidence of in-hospital MACE: cardiac death 7%, reinfarction 5%, and in-stent thrombosis 5%.

In this study, we focused on assessing the relationship between N/L ratio and the development of NOAF in patients undergoing PPCI for acute STEMI. We found that there was a significant correlation between N/L ratio and NOAF and that N/L ratio >4.6 predicts no-reflow, in-hospital MACE, or NOAF with 90.4% sensitivity and 51.5% specificity.

Chavarria et al also found that patients who developed AF ($n = 40$, 13.8%) had higher postcatheterization N/L ratios at 48 hours than those who did not develop AF (median 5.23 vs 3.00, $P = 0.05$).[13] Furthermore, in a study conducted by Aydın et al, patients with documented supraventricular tachycardia showed significantly higher N/L ratio values compared with control subjects.[14] The limitations of this study are the relatively small sample size compared with large studies published in the literature, such that larger studies are needed to validate our results, and the lack of multivariate statistical analysis, which might have affected the results.

Conclusion

Patients with high N/L ratio on admission are more susceptible to developing no-reflow, NOAF, and/or in-hospital MACE after PPCI. Special care should be given to these patients to decrease the incidence of NOAF and adverse cardiac events after PPCI.

Author Contributions

Conceived and designed the experiments: SW, MS, ML. Analyzed the data: SW, MS, ML. Wrote the first draft of the manuscript: SW, MS, ML. Contributed to the writing of the manuscript: SW, MS, ML. Agree with manuscript results and conclusions: SW, MS, ML. Jointly developed the structure and arguments for the paper: SW, MS, ML. Made critical revisions and approved final version: SW, MS, ML. All authors reviewed and approved of the final manuscript.

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