



## RESEARCH ARTICLE

## Higher Neutrophil/Lymphocyte ratio is a reliable laboratory marker for predicting the lower rate of complete revascularization following primary percutaneous coronary intervention

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### Abstract

**Introduction:** There is a growing recognition that neutrophil / lymphocyte (N/L) ratio can provide a reliable inflammatory index as an estimation of the reperfusion success in the coronary artery disease.

**Aim** of this study is to estimate if a meaningful relationship exists between neutrophil / lymphocyte ratio and the success of coronary reperfusion after primary percutaneous coronary intervention.

**Patients and Methods:** 47 adult patients were included in the study. They were classified into 2 groups based on post intervention thrombolysis in myocardial infarction (TIMI): Group 1 with sufficient reperfusion (TIMI III, TIMI II) and Group 2 with insufficient reperfusion (TIMI 0, TIMI I). All the 47 patients had undergone primary percutaneous coronary intervention (PCI). Estimation of the success of reperfusion by the TIMI flow together with echocardiographic assessment and calculation of wall motion score index was performed in the 1st day and 3rd month of admission.

**Results:** Patients with insufficient final coronary flow had highly significant elevated N/L ratios ( $11.9619 \pm 1.1864$  vs.  $4.9835 \pm 0.70985$ ,  $P=0.000$ ) and decreased lymphocyte count ( $952.92 \pm 309.284$  vs.  $1390.27 \pm 343.583$ ,  $P=0.000$ ).

**Conclusion:** Higher N/L ratio should be considered as new lab marker for predicting both the lower rate of complete revascularization (TIMI 0, TIMI 1) and the higher incidence of complications after primary percutaneous coronary intervention.

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## INTRODUCTION

The integral role of inflammation in stable and unstable coronary artery disease (CAD) has been recognized. Depending on this pathophysiology, many inflammatory indicators were developed to assess the severity of coronary artery disease and to acquire prognostic information (Kurtul A, Murat SN et al., 2015).

There is a growing recognition that neutrophil / lymphocyte (N/L) ratio can provide a reliable inflammatory index to be used in the coronary artery disease for estimation of the reperfusion success and for prognostic stratification (Yarnell JW, Baker IA et al., 1991).

The poor coronary reperfusion after primary percutaneous coronary intervention expressed as no-reflow phenomenon or failed resolution of the ST segment in electrocardiography is associated with increased inflammatory status (Barron HV, Cannon CP et al., 2000).

Some investigators believe that the neutrophil / lymphocyte ratio can be correlated to the no-reflow phenomenon and used as indicator of poor coronary reperfusion. Some studies examined this issue. However, a convincing demonstration of this relationship has still to be proved. Few studies are in fact available, often characterized by samples with a limited number of patients, or comprising particular ethnic groups (Huang G, Zhong XN et al., 2009).

### **Aim of the work**

The aim of the study is to estimate if a meaningful relationship exists between neutrophil / lymphocyte ratio and the success of coronary reperfusion after primary percutaneous coronary intervention.

### **Patients and Methods**

This study was carried out in Cardiology Department of Zagazig University Hospitals. Approval for the study was obtained from institutional review board (IRB), Faculty of Medicine-Zagazig University. Authors declare no conflict of interests. Study started in November 2013 and ended by September 2014.

#### **Patients**

The study included 47 adult patients. Informed consents were obtained from all of them to use their samples for research and analysis. They were classified into 2 groups:

Group 1 with sufficient reperfusion (TIMI III, TIMI II)

Group 2 with insufficient reperfusion (TIMI 0, TIMI I)

#### **Inclusion criteria:**

All patients undergoing primary percutaneous coronary intervention within 12 hours of ST elevation myocardial infarction.

#### **Exclusion criteria:**

- 1- Previous myocardial infarction
- 2- Malignancy
- 3- Congestive heart failure
- 4- Liver cell failure
- 5- Patients receiving corticosteroid therapy
- 6- Patients who had undergone previous coronary artery bypass grafting surgery (CABG) or percutaneous coronary intervention (PCI)

#### **Steps of performance and techniques used:**

- 1- Complete history taking
- 2- Clinical examination
- 3- Primary percutaneous coronary angiography
- 4- Calculation of neutrophil / lymphocyte ratio
- 5- Conventional Transthoracic Echodoppler study
- 6- The neutrophil lymphocyte ratio was correlated to the TIMI scores & to the echo findings of each group

### **Statistical Analysis**

The data were tabulated and statistically analyzed using Microsoft Office Excel 2010, and Statistical Package for Social Sciences version 21 (SPSS: An IBM Company).

- A. Descriptive statistics: Data were summarized using the arithmetic mean, standard deviation (SD), median and range for numerical variables. The frequency, distribution and percentage were calculated for categorized variables.
- B. Comparative Statistics: Student's (t) test was used for comparisons between quantitative variables and the Chi square test ( $\chi^2$ ) test for comparisons between qualitative variables.

### **Results**

Our study was performed during the period from November 2013 to September 2014 in Cardiology Department, Faculty of Medicine, Zagazig University. We recruited 47 patients who had been admitted to the coronary care unit with chest pain and provisional diagnosis of acute MI, all were proved to have STEMI (ST elevated myocardial infarction) based on electrocardiographic and biochemical data. All the 47 patients had undergone primary PCI. Estimation of the success of reperfusion by the TIMI flow together with echocardiographic assessment and calculation of wall motion score index was performed in the 1st day and 3rd month of admission.

The mean age of the patients was  $56.62 \pm 11.26$  years, 42 patients (89.4%) were males and 5 (10.6%) were females, 16 patients (34%) were hypertensive, 19 patients (40.4%) were diabetic, 29 patients (61.7%) were current smokers and 2 patients (4.3%) gave positive family history of premature CAD. The patients were directed to primary PCI with 28 (59.6%) patients diagnosed with anterior STEMI, 12 (25.5%) inferior and 7 (14.7%) as either septal, posterior or extensive anterior.

Patients were divided into two groups: Group (1): with sufficient reperfusion (TIMI III, TIMI II) and Group (2): with insufficient reperfusion (TIMI 0, TIMI I).

Demographic data and risk factors in both groups table (1):

Group (1) consisted of 25 patients with a mean age of  $56.05 \pm 9.43$  years old, 22 males (88%) and 3 females (12%), 10 patients (81.8%) were hypertensive, 10 patients were diabetic (40%), 19 patients (76%) were smokers and 1 patient (4%) gave positive family history of premature CAD and

Group (2): consisted of 22 patients with a mean age of  $58.05 \pm 8.08$  years old, 20 males and 2 females (90.9% and 9.1% respectively), 6 patients (27.3%) were hypertensive, 9 patients (40.9%) were diabetic, 10 patients (45.5%) were smokers and 1 patient (4.5%) gave positive family history of premature CAD.

There was no significant difference between the two groups regarding age, gender, hypertension, diabetes, family history or smoking ( $p > 0.05$ ).

Clinical and electrocardiographic findings in both groups table (2):

Group 1:

At admission the systolic blood pressure (SBP) was  $123.2 \pm 22.862$  mmHg, the diastolic blood pressure (DBP) was  $72.8 \pm 10.214$  mmHg, the heart rate (HR) was  $97.4 \pm 24.838$  and the ECG before the revascularization showed initial ST-segment elevation (ST1) of  $4.4 \pm 2.198$  mm in comparison with  $1.68 \pm 1.069$  mm elevation 2 hours after the revascularization (ST2).

Group 2:

At admission the systolic blood pressure (SBP) was  $117.73 \pm 21.142$  mmHg, the diastolic blood pressure (DBP) was  $68.64 \pm 9.902$  mmHg, the heart rate (HR) was  $97.64 \pm 35.838$  and the ECG before the revascularization showed initial ST-segment elevation (ST1) of  $4.318 \pm 1.809$  mm in comparison with  $2.5909 \pm 1.7904$  mm elevation 2 hours after the revascularization (ST2).

Echocardiographic findings in both groups table (3):

Group 1:

The initial echocardiographic assessment at day 1 after primary PCI showed ejection fraction (EF-1) to be  $57.68 \pm 5.785$  % while the wall motion score index (WMSI-1) was  $1.2080 \pm 0.12557$ . While the follow up echocardiography 3 months later showed the change of ejection fraction (EF-3) into  $56.1250 \pm 5.7507$  % and the wall motion score index (WMSI-3) into  $1.2 \pm 0.12854$ .

Group 2:

The initial echocardiographic assessment at day 1 after primary PCI showed ejection fraction (EF-1) to be  $41.00 \pm 4.242$  % while the wall motion score index (WMSI-1) was  $1.94 \pm 0.24815$ . While the follow up echocardiography 3 months later showed the change of ejection fraction (EF-3) into  $43.33 \pm 3.77$  % and the wall motion score index (WMSI-3) into  $1.828 \pm 0.2777$ .

CBC findings in both groups Table (4):

Group 1: The laboratory findings in the patients with TIMI I and TIMI 0 showed the neutrophil count (N) to be  $6.842 \pm 1.655$  / $\mu$ L while the lymphocyte count (L) was  $1.390 \pm 0.343$  / $\mu$ L. The neutrophil / lymphocyte ratio (N/L) was  $4.9835 \pm 0.7098$  while the platelet count (Plt) was  $208.227 \pm 7.680$  / $\mu$ L.

Group 2: The laboratory findings in the patients with TIMI II and TIMI III showed the neutrophil count (N) to be  $11.406 \pm 3.736$  / $\mu$ L while the lymphocyte count (L) was  $0.952 \pm 0.309$  / $\mu$ L. The neutrophil / lymphocyte ratio (N/L) was  $11.9619 \pm 1.1864$  while the platelet count (Plt) was  $244.080 \pm 6.578$  / $\mu$ L.

## Discussion

Myocardial infarction is one of the main causes of mortality in the world which is mainly treated with fibrinolytic drugs and primary percutaneous coronary intervention (PCI) (Keeley EC and Grines CL 2005).

Up-to-date cardiology guidelines recommend mechanical techniques to restore coronary flow and reestablish myocardial perfusion in patients presenting with STEMI (Camm AJ, Lip GY et al. 2012). Despite improvements in the techniques and materials used, the performance of primary PCI fails to normalize the coronary flow and myocardial perfusion in some of these patients. This phenomenon described as no-reflow is associated with an increased mortality as well as morbidity (Soylu K, Yuksel S et al. 2013). The aim during primary PCI is to achieve TIMI III flow in the occluded artery. However, this target is semi-quantitative and not objective. The improvement in the management of patients with ST-segment elevation myocardial infarction (STEMI), characterized by early diagnosis and treatment of the acute event, improved management of complications and general availability of pharmacological and mechanical therapies has significantly reduced cardiac mortality and morbidity (De Luca L, Tomai F et al. 2010). Studies have suggested possible mechanisms for no-reflow phenomenon such as endothelial ischemic damage, microvascular obstruction, leukocyte occlusions, and mechanical compression due to interstitial oedema, reactive oxygen radicals and coagulation (Turkmen S, Dogdu O et al. 2013).

Research also demonstrated the relationship of inflammation to no reflow. It is reported that N/L ratio and CRP had a significant and positive correlation with no-reflow in STEMI patients treated with PCI (Akpek M, Kaya M et al. 2012). The present study was conducted on 47 patients admitted by acute STEMI candidate for reperfusion therapy by primary PCI, careful history was taken, laboratory tests including CBC, serum creatinine, cardiac enzymes, lipid profile, random blood sugar and echocardiographic assessment were done 1 day and three month after the reperfusion.

In our study, patients with insufficient final coronary flow (group2) had highly significant elevated N/L ratios ( $11.9619 \pm 1.1864$  vs.  $4.9835 \pm 0.7098$ ,  $P=0.000$ ) and decreased lymphocyte count ( $0.952 \pm 0.309$  vs.  $1.390 \pm 0.343$ ,  $P=0.000$ ). This suggested a relationship between the inflammatory response and leukocyte occlusions of the coronaries. This was concordant with (Sen N, Afsar B et al. 2013); this goes with the fact that there is a strong and well investigated association between thrombotic and inflammatory pathways in acute coronary syndromes. Leukocytosis is a common finding in acute STEMI that reflects the infiltration of WBCs into necrotic tissue in response to ischemia and reperfusion. In particular, neutrophils are the first leukocytes to be found in the damaged myocardial area. Procoagulants are secreted locally by leukocytes that contribute to oxidative and proteolytic injury. Furthermore, the distal embolization of leukocytes and platelet-leukocyte aggregates may reduce downstream micro vascular perfusion and contribute to thrombosis and widespread myocardial inflammation (Kurtul A, Yarlioglu M et al. 2014). The prognostic role of leukocytes is supported by observations from thrombolysis trials that identified leukocyte count as a predictor of short- and long-term adverse clinical outcomes, whereas elevated neutrophil count is significantly associated with myocardial infarct extension and the early development of congestive heart failure (Rashidi F, Rashidi A et al. 2008; Han YC, Yang TH et al. 2013; Zazula E, Denise A et al. 2008). It was also demonstrated that the neutrophil/lymphocyte ratio is a strong independent predictor of success of reperfusion after ST elevation myocardial infarction treated with very early revascularization (Shen XH, Chen Q et al. 2010; Bhat T, Teli S et al. 2013). The N/L ratio can provide strong prognostic information as concluded from the previous findings. This is also supported by the findings made by (Duffy BK, Gurm HS et al. 2006; Misumida N, Kobayashi A et al. 2015). The N/L ratio is a useful marker to predict 12-month MACE and death in patients with STEMI who have undergone primary PCI (Huang B, Yang Y 2014; Sawant AC, Adhikari P et al. 2014). A concordant finding was made by (Ulucan S., Keseler A., et al. 2014), this concluded that The N/L ratio, an inexpensive and easily measurable laboratory variable, is independently associated with the development of no reflow and in-hospital MACEs in patients with ST-segment elevation myocardial infarction undergoing primary PCI. Our study showed no statistical difference between the study groups regarding the heart rate, systolic and diastolic blood pressures. This was concordant with the results observed by (Maden O, Kacmaz F et al. 2009) but this was discordant with the results in the (APEX-AMI) study that showed a demarked difference regarding these parameters in between the study groups. This may be attributed to the very large number of patients involved in the APEX-AMI study in comparison with the others that will allow the difference to be statistically sound (APEX AMI Investigators, Armstrong PW et al. 2007). In the present study there was no statistical significant difference among the study groups as regard the platelet count. This is discordant with (Lai HM, Chen QJ et al. 2015; Karahan Z, Uçaman B et al. 2015; Sarli B, Baktir AO et al. 2013). This could be attributed to the parameter measured to express the role of the platelets in our study was the platelet count while in the other studies the platelet volume was measured and used to explore the platelet function and role in the no reflow phenomenon. In the present study there was no statistical significant difference among the study groups as regard age, sex, smoking, hypertension, obesity and family history. This was concordant with previous studies (Cecchi E, Liotta AA et al. 2009; Celik T, Turhan H et al. 2015). This was explained in our study by small sample size, which makes our study not powered to detect the difference, short term follow up period and random selection of cases according to capability of our primary PCI center. Regarding the Echocardiographic findings of the study conducted; a significant difference between the study groups in the ejection fraction (EF) measured one day after reperfusion, ejection fraction after 3 months and wall motion score index (WMSI) measured in both times with a better findings in the group 1 (TIMI III, TIMI II) than that in the group 2 (TIMI I, TIMI 0). These predicted findings are concordant with the findings by (Vakili H, Sadeghi R et al. 2014; Wang CH, Xie XJ et al. 2011). Also (Galasko GIW, Basue S et al. 2015) found that the EF measured only 48 hours after the acute MI was significantly higher in patients with good reperfusion criteria. But this is discordant with such large-scale studied as TEAM or GUSTO that have not found significant changes in LVEF in the period between 90 minutes and 1- to 2- week after AMI (Lepper W, Hoffmann R et al. 2000). The short term follow up period conducted in all of the proposed studies may be the accepted explanation. On the other hand, the wall motion score index provides powerful prognostic information after acute myocardial infarction and the predictive power of wall motion score index is greater than the Ejection fraction (Møller E., Hillis S. Oh JK et al. 2003). Although the results were obtained from a single medical center (Zagazig University Hospitals) with small

sample size and short term follow up period, our study confirm that the N/L ratio can be used as an inexpensive easy parameter to assess the reperfusion after primary PCI and as a strong prognostic marker.

### **Conclusion:**

The present study showed that admission higher N/L ratio in patients presented by acute STEMI was associated with more severe CAD, lower ST-segment resolution, lower rate of complete revascularization (TIMI 0, TIMI 1) and higher incidence of complications. Higher N/L ratio should be considered as new lab marker for predicting the success rate of reperfusion of the coronaries and as a prognostic factor as well.

**Recommendation:** The present study recommends the use of neutrophil/ Lymphocyte ratio as a predictor of outcome after reperfusion and as a prognostic factor with future studies on a large sector of patients and long term follow up period at different centers.

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