Prognostic Importance of Increased Right Ventricular Afterload in Orthotopic Liver Transplantation Recipients With Endstage Cirrhosis

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ORIGINAL ARTICLE

Relationship Between Prodromal Angina Pectoris and Neutrophil-to Lymphocyte Ratio in Patients With ST Elevation Myocardial Infarction

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Background The aim of this study was to investigate the relationship between prodromal angina (PA) with neutrophil-to-lymphocyte ratio (NLR) in patients with ST-segment elevation myocardial infarction (STEMI).

Methods The study group included 145 patients with STEMI who underwent emergency coronary angiography (CA) within 24 hours of symptom onset. Data were collected regarding whether patients had experienced PA before acute myocardial infarction. Seventy-three (73) patients (50.3%) had prodromal angina. Prodromal angina positive and negative groups were compared for demographic characteristics, complete blood count parameters including NLR, blood biochemistry parameters and left ventricular ejection fraction (LVEF).

Results Neutrophil count, NLR, and troponin I levels were significantly higher in the PA negative group. LVEF after reperfusion and lymphocyte count were lower in the PA negative group. In multivariate regression analysis, NLR ($\beta = -0.419$, $p < 0.001$) and LVEF ($\beta = 0.418$, $p < 0.001$) were found to be significantly associated with the presence of PA in STEMI patients.

Conclusions Absence of PA was significantly and independently associated with increased NLR and impaired LVEF after reperfusion, and increased NLR was found as a significant predictor for both lack of PA and impaired LVEF in STEMI patients.

Keywords Neutrophil-to-lymphocyte ratio • Prodromal angina • ST-segment elevation myocardial infarction

Introduction

It has been shown that inflammation plays an important role in the development and course of cardiovascular diseases [1]. Myocardial ischaemia/reperfusion injury is, in fact, an inflammatory process characterised by recruitment of neutrophils into the ischaemic myocardium [2].

Discovery of the ischaemic preconditioning phenomenon has focussed attention on the ability of the myocardium to protect itself. It has been well demonstrated in animal models that brief ischaemic episodes preceding prolonged coronary occlusion cause a significant reduction of infarct size [3]. Prodromal angina (PA), defined as chest pain episodes limited to the 24 hours before infarction, could be regarded as

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the clinical correlate of ischaemic preconditioning [4–8]. It has been demonstrated that ischaemic preconditioning has anti-inflammatory effects [9–11].

Neutrophil-to-lymphocyte ratio (NLR) is a non-specific, frequently used marker for acute inflammatory response. Increased NLR has been associated with impaired left ventricular function and adverse outcomes in patients with acute myocardial infarction (AMI) [12–15]. However, no studies, to date, have investigated the relationship between NLR with the presence/absence of PA in AMI cases.

In this study, we aimed to investigate the relationship between PA and NLR in patients with ST-segment elevation AMI (STEMI).

Materials and Methods

Study Design

The patients who were admitted to our hospital with STEMI, and underwent emergency coronary angiography (CA) after diagnosis between March and July 2014 were included in our study. The local ethics committee of Ankara Numune Education and Research Hospital approved the study protocol, and all patients provided their written informed consents.

ST-segment elevation was considered when the patients had symptoms of AMI for 30 minutes, accompanied by >1 mm (0.1 mV) ST-segment elevation in two consecutive leads. The diagnosis was later confirmed by an increase in troponin I level.

Prodromal angina was defined as typical chest pain episode(s) that persisted <30 minutes either at rest or during effort ≤24 hours before the onset of AMI. Patients with active infectious or inflammatory diseases (n = 10), haematologic disorders (n = 5), severe renal or liver disease (n = 25), previous stroke (n = 5), rheumatologic diseases (n = 4), diabetes mellitus (n = 35), malignancy (n = 3), previous myocardial infarction and non-STEMI (NSTEMI) (n = 45) were excluded from the study. After evaluation for inclusion and exclusion criteria, 145 patients with STEMI remained for final analysis (Figure 1).

Complete blood counts and differentials were studied from the peripheral venous blood samples obtained on admission of the patients to the emergency department. Blood samples were collected in calcium-ethylenediaminetetraacetic acid (EDTA) tubes. Blood counts were measured with an auto-analyser. Neutrophil-to-lymphocyte ratio was calculated as the ratio of neutrophils to lymphocytes in the peripheral blood. Other routine laboratory parameters were

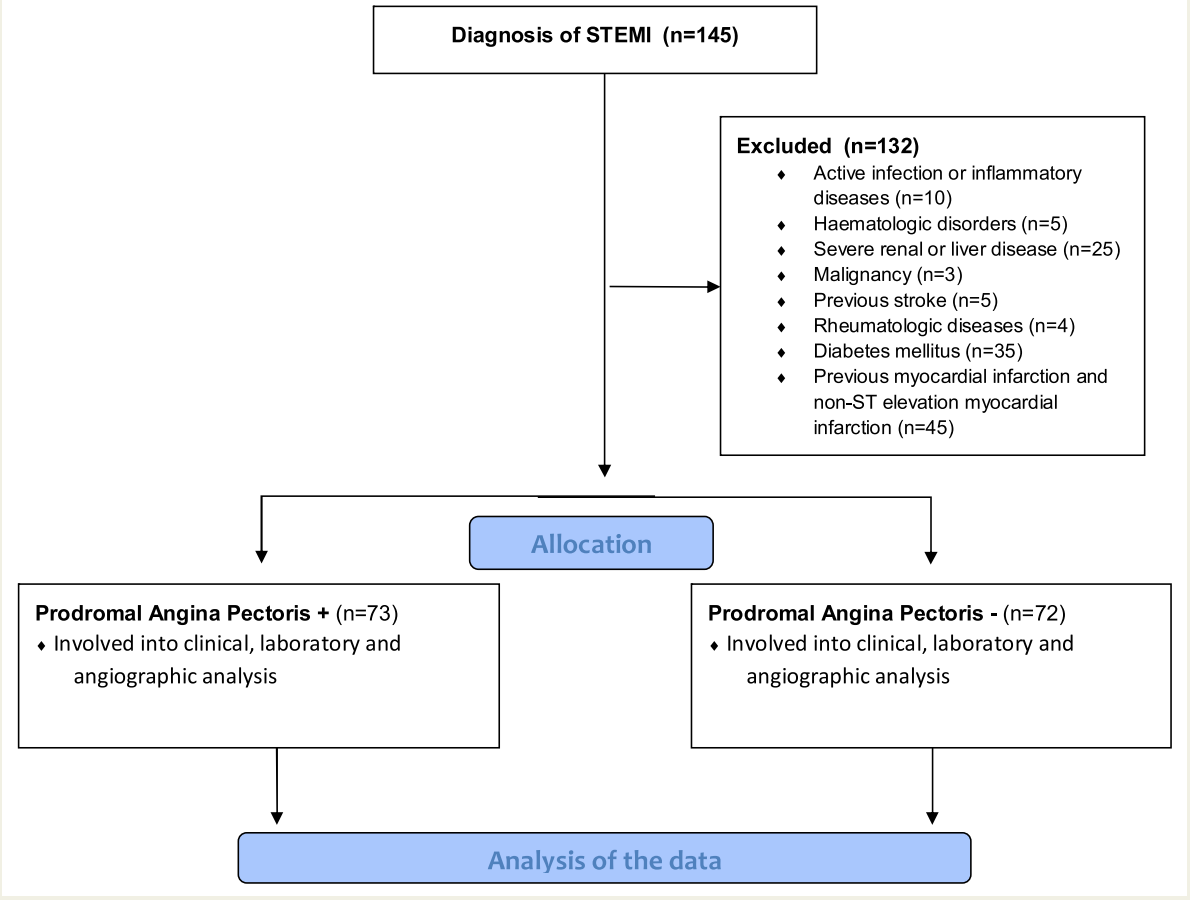

Figure 1 Participant selection process to the present study.

also measured in our hospital's laboratory, from the blood samples obtained on admission of the patients.

Transthoracic echocardiography was performed within 72 hours of hospital admission. Left ventricular ejection fraction (LVEF) was calculated using Simpson's method.

The patients were asked whether they had PA before AMI. Then they were divided into two groups as the ones that had PA (PA positive group) and the ones did not have PA (PA negative group). All study data were recorded in a study form including status of PA, blood tests, echocardiography findings and CA data.

All patients were orally pretreated with acetyl salicylic acid 300 mg. STEMI patients were given 600 mg clopidogrel at the time of diagnosis, and before CA. Baseline CA was performed through the femoral artery by standard Judkins technique with 6 or 7 F catheters using the Siemens Axiom (Siemens Axiom Artis Zee 2011; Siemens Healthcare, Erlangen, Germany) Sensis XP. Coronary angiography and balloon dilation/stent application were performed within 60 minutes after admission of the patients.

Statistical Analysis

SPSS 22.0 statistical software (IBM Corp., Armonk, NY, USA) was used to perform statistical analysis. Kolmogorov–Smirnov test was used to examine the distribution pattern of data. Continuous variables were presented as median and interquartile range (IQR) or mean ± standard deviation (SD). The effects of age, LVEF, smoking, mean corpuscular volume (MCV), NLR; white blood cell (WBC), neutrophil, lymphocyte, monocyte and platelet counts; and levels of haemoglobin, peak troponin I, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), creatinine, stent size, and total bilirubin on PA were computed in univariate analysis. Variables that had unadjusted p value <0.10 in logistic regression analysis were identified as potential risk markers (WBC, lymphocyte and neutrophil counts, NLR, LVEF, troponin I level), and they were included in the multiple logistic regression analysis. A p value <0.05 was considered as statistically significant at a confidence interval of 95%.

Receiver operating characteristics (ROC) curve was used to show the sensitivity and specificity of NLR, and the optimal cut-off value for predicting PA.

Results

The baseline clinical characteristics and laboratory parameters of the study population are presented in Table 1. There were 145 patients in the study group, 73 of them (50.3%) with PA. Gender, age, smoking status, levels of total cholesterol,

Table 1 Baseline characteristics of the patients with and without prodromal angina.

		Overall n = 145 (100%)	Negative n = 72 (49.7%)	Positive n = 73 (50.3%)	P-value
Gender	Male, n (%)	111 (100%)	53 (47.7%)	58 (52.3%)	0.41
	Female, n (%)	34 (100%)	19 (55.9%)	15 (44.1%)	0.22
Age, years		60.6 ± 14	62 ± 14	59 ± 15	0.21
Left ventricular ejection fraction, %		48 (40–60)	42 (37–50)	50 (45–60)	<0.001*
Smoking, n (%)		88 (60.6%)	45 (51.2%)	43 (49.8%)	0.26
White blood cellcount, $10^3/\mu L$		9.2 ± 6.3	11.6 ± 4.1	7.2 ± 4.2	<0.001*
Haemoglobin, g/dL		14.1 (12.6–15.5)	14 (12.1–15.2)	14.2 (13–16)	0.32
Neutrophil count, $10^3/\mu L$		8.46 ± 3.80	9.2 ± 3.9	5.86 ± 3.88	<0.001*
Lymphocyte count, $10^3/\mu L$		1.79 ± 1.15	1.60 ± 1.16	2.29 ± 1.32	<0.001*
Monocyte count, $10^3/\mu L$		0.8 ± 0.04	0.8 ± 0.01	0.08 ± 0.01	0.74
Peak troponin I, ng/ml		25 (5–51)	27 (6.8–51)	20 (3.2–50)	<0.001*
Platelet count, $10^3/mm^3$		220 (192–257)	218 (198–266)	225.5 (184–255)	0.44
Mean corpuscular volume, fL		87 (83.7–90)	86 (82–89)	88 (84–90)	0.15
Neutrophil-to-lymphocyte ratio		4.5 (2.8–8.2)	7.9 (3.9–10.4)	3.4 (2.1–5.5)	<0.001*
Total cholesterol, mg/dL		193 ± 44	191 ± 43	196 ± 45	0.56
Low density lipoprotein, mg/dL		122 ± 39	122 ± 41	122 ± 37	0.96
High density lipoprotein, mg/dL		41 ± 13	42 ± 13	40 ± 16	0.73
Creatinine, mg/dL		0.98 ± 0.07	0.97 ± 0.06	1.07 ± 0.09	0.32
Total bilirubin, mg/dL		0.56 ± 0.33	0.55 ± 0.33	0.57 ± 0.33	0.87
Anterior infarct location, n %		42 (58.3%)	44 (61.1%)	38 (52.1%)	0.16
Time-to-reperfusion (h)		4.2 ± 1.9	4.2 ± 2.4	4.0 ± 1.8	0.25
Stent diameter, mm		3 (2.75–3)	3 (2.5–3)	3 (2.5–3)	0.65
Stent length, mm		15 (12.5–18)	15 (13–18)	15 (12–19)	0.38

*p value is statistically significant.

LDL, HDL, creatinine and total bilirubin, monocyte count, haemoglobin (Hb), platelet count, MCV, stent length and stent diameter were similar between PA positive and negative groups.

Peak troponin I levels, WBC counts, NLR, and neutrophil counts were significantly higher in the PA negative group. On the other hand, LVEF and lymphocyte counts were significantly higher in the PA positive group (Table 1). The comparison of NLR levels between PA positive and negative groups is also shown in Figure 2.

When six variables found significantly different between PA positive and negative groups on univariate analysis (Table 1) (peak troponin I level, WBC count, NLR, neutrophil count, LVEF, and lymphocyte counts) were included in a multivariate analysis, NLR ($\beta = -0.419$, $p < 0.001$) and LVEF ($\beta = 0.418$, $p < 0.001$) were found to be independently associated with the presence of PA (Table 2).

Finally, ROC analysis was performed to determine the cut-off value of NLR to predict the absence of PA. The cut-off value of NLR to predict absence of PA in all study populations on admission was found as 4.5, with 73.8% sensitivity and 68.1% specificity (area under the curve 0.750, $p < 0.001$, Figure 3).

Then, the patients were divided into two groups on the basis of NLR cut-off value 4.5. Patients with NLR $\geq$ 4.5 were older when compared to the patients with NLR < 4.5 ($p = 0.014$). In addition, WBC count, peak troponin I level, and the number of patients with PA were significantly higher in NLR $\geq$ 4.5 group, but LVEF was significantly lower (Table 3).

Discussion

In this study, we have shown that STEMI patients without PA had higher NLR values on admission, and lower LVEF after reperfusion.

Previous studies have shown that preconditioned myocytes tolerate ischaemia by reducing energy demand, preserving ATP and slowing down the development of the osmotic load and acidosis. The clinical correlate of ischaemic preconditioning is PA; it delays cardiac myocyte death, and has a cardioprotective effect against ischaemic injury before reperfusion. Murry et al. were the first to show the phenomenon of ischaemic preconditioning [3], and they reported that intermittent periods of coronary ischaemia separated by periods of reperfusion preceding more prolonged myocardial ischaemia resulted in a significant cardioprotective effect [16].

After this study, several clinical studies reported that PA occurring shortly before the onset of AMI had a cardioprotective effect. In the percutaneous coronary intervention era, the presence of PA was found to be related to smaller infarct

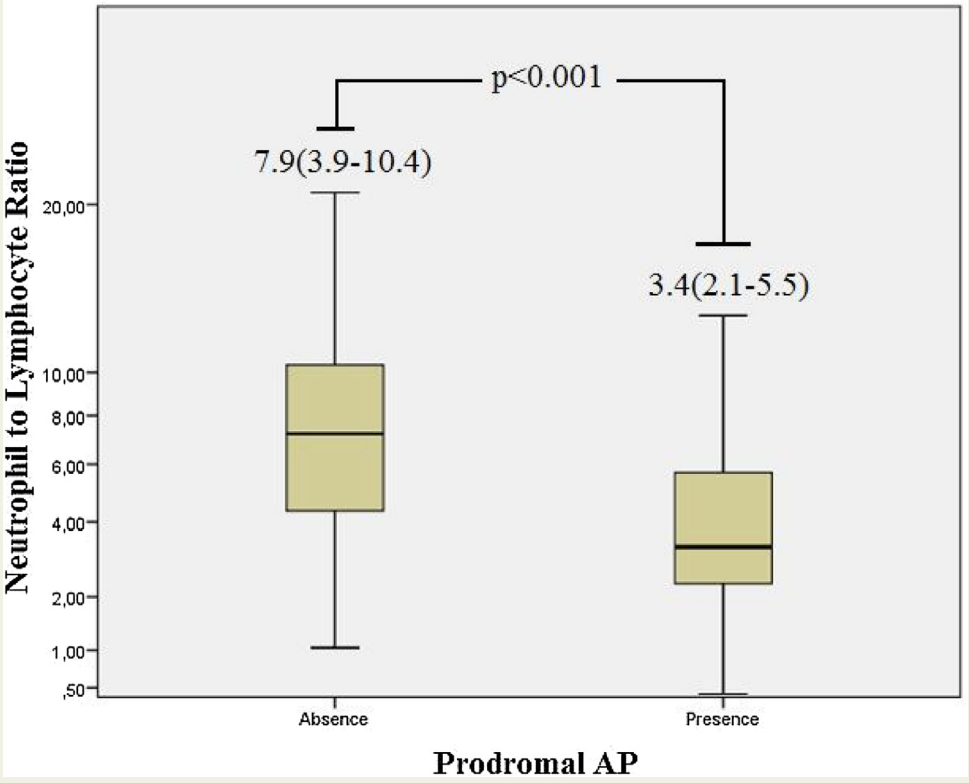

Figure 2 Graph demonstrating significant differences for neutrophil-to-lymphocyte ratio in prodromal angina positive and negative patients.
Abbreviation: AP, angina pectoris.

Table 2 Multiple logistic regression analysis showing the relationship of the prodromal angina with neutrophil-to-lymphocyte ratio and left ventricular ejection fraction.

Paramerters	Standardised Coefficients Beta	P-value
White blood cell count (/μL)	−0.002	0.14
Lymphocyte count (/μL)	−0.002	0.24
Neutrophil count (/μL)	−0.076	0.068
Neutrophil-to lymphocyte ratio	−0.419	<0.001
Left ventricular ejection fraction (%)	0.418	<0.001
Troponin I (ng/ml)	0.116	0.15

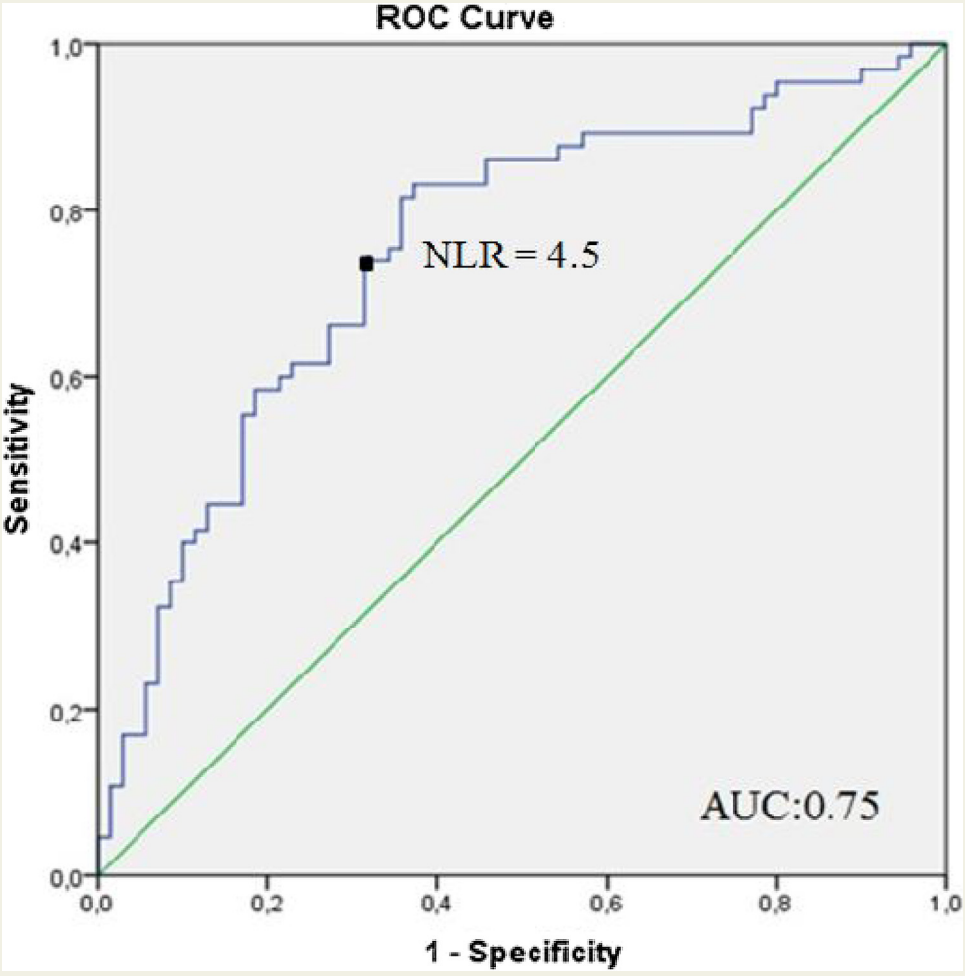

Figure 3 Receiver-operating characteristic (ROC) curve analysis of neutrophil-to- lymphocyte ratio (NLR) data for prodromal angina.
Abbreviation: AUC, area under the curve.

size [17,18], improved left ventricular function, and favourable short- and long-term prognosis after AMI [7,8].

Inflammatory reaction plays an important role in myocardial ischaemia/reperfusion injury [12]. Release of inflammatory cytokines and aggregation and infiltration of inflammatory cells are the key steps in inflammation. Ischaemic injury seems to be induced, in part, by neutrophil activation, and previous studies reported the link between neutrophils and ischaemia/reperfusion injury. Removal of neutrophils or drug inhibition of neutrophil activity has been shown to reduce ischaemia/reperfusion injury [19,20]. Studies have also shown that low lymphocyte counts are associated with more severe coronary artery disease in the settings of stable angina and poor prognosis in patients with AMI [21,22]. In fact, NLR has a stronger

Table 3 Clinical characteristics of the study patients in relation with the NLR values in patients with ST-segment elevation myocardial infarction.

	Overall (n = 145) (100%)	NLR ≥ 4.5 (n = 74) (51%)	NLR < 4.5 (n = 71) (49%)	P-value
Patients with PA, n (%)	73 (50.3)	50 (67.5)	23 (32.3)	<0.001
Age, years	61 ± 14	64 ± 14	58 ± 12	0.014
Female, n (%)	34 (24)	17 (24)	17 (24)	0.850
White blood cell count, $10^3/\mu L$	9.2 ± 6.3	11.9 ± 4.8	7.4 ± 3.2	0.012
Platelet count, $10^3/mm^3$	220 (192–257)	218 (187–251)	226 (193–265)	0.390
Peak troponin I, mg/dL	25 (5–51)	35 (12–51)	11 (2.5–41)	0.045
Left ventricular ejection fraction, (%)	48 (40–60)	45 (37–50)	55 (45–60)	<0.001

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PA, prodromal angina.

predictive value since it is measured by proportioning two inflammatory markers, neutrophils and lymphocytes.

Recently, Alfakry et al. reported that high serum neutrophil markers, namely myeloperoxidase, matrix metalloproteinase (MMP)-8, tissue inhibitor of metalloproteinase (TIMP)-1 concentrations, and MMP-8/TIMP-1 ratio reflected increased risk of recurrent acute coronary syndrome, especially in patients without periodontal disease and not receiving anti- microbial medication [23]. Later, it was shown that NLR was associated with the severity and complexity of stable and unstable angina as reflected by SYNTAX and Gensini scores [21,24,25]. Neutrophil-to-lymphocyte ratio was also found to be associated with the severity of chronic heart failure in patients with idiopathic dilated cardiomyopathy [26]. It was also reported that increased NLR was a predictor for large infarct size and impaired LV function after reperfusion therapy in patients with AMI [27]. Kurtul et al. showed that increased NLR is independently associated with risk of contrast-induced nephropathy in non-ST-segment elevation acute coronary syndrome patients treated by percutaneous coronary intervention [28].

As seen in the aforementioned studies, NLR has been studied in a number of cardiovascular diseases, but no studies up to date investigated the relationship between PA and NLR in patients with STEMI. Therefore, we hypothesised that increased NLR might have a relationship with absence of prodromal AP based on the pathophysiological roles of the ischaemic preconditioning and inflammation in AMI, and found lower NLR values on admission, and higher LVEF after reperfusion in STEMI patients with PA.

STEMI often occurs because of plaque rupture or erosion, which is called vulnerable plaque. Vulnerable plaques were thought to represent a mild to moderate luminal stenosis in the past [29]. Previous studies revealed that mild to moderate coronary lesions exhibited a higher risk for AMI than anatomically and physiologically severe lesions [30,31]. Inflammation is associated with more positive remodelling and less angiographic stenosis but is associated with more plaque rupture and more rupture-stimulated thrombus formation of the ruptured plaque [31]. As we know, NLR is not only elevated due to the stress of the acute MI (lymphopaenia) but also elevated inflammatory status (neutrophilia) in the setting of STEMI. If NLR is only elevated due to the stress of the AMI then all big infarcts will have higher NLR than smaller infarcts. In addition, it would have been better if we could have pre-MI NLR levels, but we could not assess whether NLR was elevated before MI. Given that elevated NLR during STEMI is related to the absence of PA according to our study results, we can speculate that its mechanism is that PA has an anti-inflammatory effect or that increased plaque inflammation (as reflected by NLR) might be related to less severe stenosis before AMI and therefore less PA.

The mechanisms of the relationship between absence of PA and increased NLR are not clear. The most probable mechanism is anti-inflammatory effect of PA reducing neutrophil accumulation, and attenuating neutrophil-mediated ischaemia/reperfusion injury. Therefore, it is possible that neutrophilic inflammation, and hence NLR, decreases in the presence of PA. In addition, our results indicated a better LVEF after reperfusion in STEMI patients with PA and lower NLR.

Our study has some limitations. First, this is a single centre and non-randomised study that included a relatively small patient group. The effect of PA on the abortion of STEMI, which was most likely to occur in patients in the very early group, was not assessed. We could not reach the data related to the bad infarct area such as collaterals on initial CA and thrombolysis in myocardial infarction (TIMI) flow post percutaneous coronary intervention (PCI). Lastly, NLR was not compared with other inflammatory markers, such as C-reactive protein, interleukin 6, fibrinogen or myeloperoxidase.

Conclusions

To the best of our knowledge, this is the first study in the literature showing the relationship between absence of PA and increased NLR. Our findings suggested that a significant relationship between lack of PA and impaired LVEF after

reperfusion, and increased NLR was found as an independent predictor for both lack of PA and impaired LVEF in STEMI patients. Neutrophil-to-lymphocyte ratio could be used as a simple and easy-to-obtain marker for clinical risk assessment in STEMI patients on their admission to hospital.

Acknowledgements

All authors have substantial contributions to conception and design, or acquisition of data, and analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published.

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