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Behaviour of the neutrophil to lymphocyte ratio in young subjects with acute myocardial infarction

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particular in coronary artery disease and acute myocardial infarction (AMI). Now we examined this parameter in subjects with juvenile myocardial infarction at the initial stage and after 3 and 12 months. We enrolled 123 young subjects (112 men and 11 women, mean age 39.4 ± 5.8 yrs) with AMI. The time interval between the AMI onset and the investigation was 13 ± 7 days. The mean value of NLR observed in young AMI subjects was significantly increased compared to normal controls ($N = 1.817 \pm 0.711$; young AMI subjects = 2.376 ± 0.873, $p < 0.0001$). NLR does not discriminate STEMI (2.427 ± 0.878) and non STEMI (2.392 ± 0.868) or diabetics (2.604 ± 1.000) and non diabetics (2.324 ± 0.853), but it differentiates smokers (2.276 ± 0.853) and non smokers (2.837 ± 1.072). NLR at the initial stage is not correlated with the number of cardiovascular risk factors or with the extent of the coronary disease. In this study we found a significant decrease of neutrophil count at 3 and 12 months later AMI without any significant variation of lymphocyte and consequently we observed a decrease in NLR at these two intervals of time in comparison with the initial stage. Despite some limitations present in this study, it is interesting to underline that also in juvenile myocardial infarction this low-cost haematological marker may be considered together with other inflammatory indicators.

Keywords: Juvenile myocardial infarction, leukocyte count, neutrophil/lymphocyte ratio

1. Introduction

Leukocyte (WBC) count is an independent predictor of acute myocardial infarction (AMI) and elevated levels of WBCs seem to be correlated with a worse outcome, more complications and a more extensive necrosis [3, 25, 26]. In subjects with coronary artery disease (CAD) WBC count is correlated with smoking, arterial hypertension, diabetes mellitus, and apolipoprotein B [40]. As it is known, leukocytes play a pivotal role in atherosclerosis development because their activation is associated with impaired rheological properties, increased expression of adhesion molecules, and overproduction of cytokines, proteolytic enzymes and reactive oxygen species (ROS) [25]. Leukocyte subtypes are correlated with some cardiovascular risk factors: glucose level and arterial hypertension were correlated with neutrophils, uric acid with neutrophils and monocytes, while smoking affected all the subtypes [28]. An elevated neutrophil count correlates with higher risk of ischemic events [26] and with AMI mortality [37]. The role of neutrophils in atherosclerosis is well known: primed neutrophils infiltrating vascular wall release ROS, cytokines, myeloperoxidase, and elastase promoting

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plaque instability [12, 37]. The inflammatory status influences the neutrophil rheology and these cells, become more rigid, may obstruct the smaller vessels and induce ischemia [37].

The relative lymphocyte count is related to survival in CAD subjects [38]. Lymphopenia has been suggested as a prognostic indicator in ischemic heart disease [35] considering that, in subjects hospitalized for acute chest pain, a low relative lymphocyte count is a predictor of cardiovascular mortality and late myocardial infarction [38]. Lymphopenia might be caused by the activation of the adrenal axis with an increased cortisol and cathecolamine release [38], by a reduced lymphocyte production, a tissue redistribution or an increased apoptosis, which is correlated with plaque instability in atherosclerotic lesions [36]. The lymphocytes modulate the inflammatory response and T lymphocytes, producing interferon γ, seem to regulate the smooth muscle cell proliferation into the vascular wall [23].

In the last decade the neutrophil to lymphocyte ratio (NLR) has been investigated in cardiovascular disorders and it has been suggested as a prognostic factor in CAD [19]. NLR is negatively correlated with the myocardial perfusion, as demonstrated in subjects with known or suspected CAD underwent a cardiac positron emission tomography [48], and significantly correlated with the CAD severity [2]. In subjects with stable chronic CAD, NLR is an independent predictor of cardiac death, in most cases due to AMI [39]. A recent meta-analysis showed that NLR level is a predictor of all-cause mortality and of major adverse cardiac events (MACE) in subjects undergoing angiography or cardiac revascularization, mainly after AMI [47]. Cho et al. have demonstrated that subjects with high NLR had a worse clinical outcome and higher mortality rates at 1 month and 6 months after percutaneous coronary intervention (PCI) compared to those with a low NLR [13]. In STEMI subjects Nunez et al. observed an elevated WBC count at the time of hospitalization, that decreased after 12–24 hours, an increased neutrophil count at 12–24 hours after the admission, with a simultaneous reduction in lymphocyte count; therefore the maximum level of NLR has been found at 12 to 24 hours and it has been correlated with mortality increase [35]. An increasing rate of in-stent thrombosis, non-fatal MI and cardiovascular mortality has been correlated with the NLR increase [27], as well as the frequency of ventricular tachyarrytmias is associated with higher levels of NLR [20], which is considered a predictor of in-hospital and of 12-months MACEs and deaths after STEMI [22]. Sen et al. have studied STEMI subjects undergoing primary PCI observing that an increased NLR is correlated with a more frequent coronary no-reflow event [43]. Also other authors [27, 41, 45] found a higher prevalence of no-reflow after PCI in subjects with increased NLR.

In non-STEMI subjects, higher NLR has been associated with a greater prevalence of atrial fibrillation and heart failure, a lower left ventricular ejection fraction and grater rates of coronary artery bypass grafting [5]. The average NLR results the best predictor of short- and long-term survival compared to other leukocyte parameters, such as neutrophil or lymphocyte count [5], probably because this ratio is less altered by other conditions, such as dehydration or over-hydration [4]. Lee et al. have demonstrated that the NLR value at the admission is an independent predictor of 1-year reinfarction and mortality in diabetic subjects with AMI [29].

Considering that up to now there are no literature data regarding the evaluation of the NLR in juvenile myocardial infarction and also that NLR is an easily measurable laboratory parameter, the aim of our study was to examine the NLR in subjects with juvenile AMI at the initial stage and after 3 and 12 months later. This study is a part of our scientific project identified as “Sicilian Study on Juvenile Myocardial Infarction”.

2. Subjects and methods

In this study we examined 123 young subjects (112 men and 11 women) with recent acute myocardial infarction, aged <46 years; the mean age was 39.4 ± 5.8 yrs. The time interval between AMI onset

and the investigation was 13 ± 7 days. The diagnosis of myocardial infarction was made on the basis of clinical picture, electrocardiography, blood testing (creatine kinase, troponin and myoglobin) and ecocardiography.

In each subject we examined the presence of the principal cardiovascular risk factors, including current smoking habits, family hystory of CAD, hypercholesterolemia, arterial hypertension, and diabetes mellitus. Family hystory consisted in any first-grade relative with clinical manifestation of CAD at age <55 yrs. Hypercholesterolemia was determined as a total cholesterol level >220 mg/dl and/or the us of lipid lowering drugs. The diagnosis of arterial hypertension was based on blood pressure measurements taken on two separate occasions with the patient in a seated position after 15 minutes of rest. The mean values of these measurements were considered. Arterial hypertension was defined as a systolic blood pressure >140 mmHg and/or a diastolic blood pressure >90 mmHg and/or the use of anti-hypertensive drugs. Diabetes mellitus was defined as a fasting blood glucose level >126 mg/dl during the initial stage (13 ± 7 days after the AMI onset); otherwise diabetes was suspected on the basis of the use of hypoglicemic agents. According to the number of cardiovascular risk factors, the young AMI subjects were subdivided into 3 groups: 39 of them had 0 to 1 risk factor, 41 had 2 risk factors and 43 had 3 to 5 risk factors. 92 subjects had STEMI and 31 had non-STEMI.

In each subject the ejection fraction (EF) was evaluated by echocardiography at the time of the admission. The mean EF in the whole group of AMI subjects was $54.63 \pm 7.28\%$. There was no significant difference in EF between STEMI (54.05 ± 7.68) and non-STEMI (56.14 ± 6.00) subjects.

Coronary angiography was performed only in 105 young AMI subjects. In the other cases the subject declined his consent or the angiographic evaluation was not carried out because of the long distance between the hospital in which the AMI was diagnosed and the angiographic unit of the universitary center. The 105 subjects in which coronary angiography was effected were subdivided into 3 groups on the basis of the extent of coronary lesions: 23 subjects did not show any significant coronary stenosis, 47 had a single-vessel disease (defined as a stenosis >70% in one coronary artery), and 35 had a multi-vessel disease that is a stenosis >70% in at least 2 coronary vessels. No subject had previous manifestations of coronary artery disease or other comorbidities.

83 young subjects with AMI were also examined at 3 months while only 66 were examined at 12 months.

The study was approved by the Ethical Committee. Blood samples were collected by venous puncture from the antecubital vein and immediatly transferred to glass tube anticoagulated with EDTA-k3. White blood cell, neutrophil and lymphocyte counts were obtained using an automated blood cell counter while the neutrophil/lymphocyte ratio was calculated.

The same parameter was evaluated in a control group including 116 subjects (87 men and 29 women, mean age 30.16 ± 7.03 yrs) without any sign of acute or chronic vascular diseases (history, physical examination, laboratory and instrumental test); 81 of these subjects were non smokers, while 35 were smokers.

3. Statistical analysis

Data were expressed as means $\pm$ s.d. The statistical difference between STEMI and non-STEMI, diabetics and non-diabetics, and smokers and non-smokers was evaluated according to the Student t test for unpaired data. The difference between the groups of AMI subjects subdivided according to the number of cardiovascular risk factors and to the number of stenosed coronary vessels was explored using the one-way analysis variance (ANOVA) model while for frequencies we employed the Fisher exact test. The correlation between EF and NLR was examined using the linear regression; the same statistical analysis was effected for the study of the correlation between age and NLR. The difference

among the NLR value at the initial stage of AMI and at 3 and 12 months later was examined employing the Student *t* test for paired data.

4. Results

First of all it must be underlined that the mean value of NLR found in young AMI subjects is increased in comparison with that observed in the control group ($N = 1.817 \pm 0.711$; young AMI subjects = 2.376 ± 0.873, $p < 0.0001$). Examining the possible difference between men and women, we found that NLR value was elevated in young AMI males in comparison with healthy men ($p < 0.001$); no difference was noted between healthy women and young AMI females, as well as between young AMI men and women.

At the initial stage no significant difference in NLR was observed between STEMI (NLR 2.427 ± 0.878) and non-STEMI (NLR 2.392 ± 0.868) as well as no difference was found between diabetics ($n = 17$; NLR 2.604 ± 1.000) and nondiabetics ($n = 107$; NLR 2.324 ± 0.853). A significant difference ($p < 0.01$) was observed instead between smokers ($n = 101$; NLR 2.276 ± 0.795) and non smokers ($n = 22$; NLR 2.837 ± 1.072).

Subdividing the young AMI subjects according to the number of cardiovascular risk factors no difference was observed among the 3 groups regarding the NLR (Table 1). Similarly, subdividing the young AMI subjects according to the number of stenosed coronary vessels there was no difference among the 3 groups (Table 1).

Subsequently we subdivided the whole group of AMI subjects into two subgroups according to the median value (2.197) of NLR: low NLR and high NLR. In these 2 subgroups no statistical difference regarding the main cardiovascular risk factors (Table 2) or the involved coronary vessels (Table 2) was observed.

No correlation was found between age and NLR in the entire group of young AMI subjects ($r = -0.061$) and in normal controls ($r = -0.057$). There was no correlation between EF and NLR in the whole group ($r = -0.021$) nor in the subgroups of STEMI ($r = 0.032$) and non-STEMI ($r = -0.186$) subjects.

In the young AMI subjects we noted a significant decrease of the NLR at 3 months (Table 3) and at 12 months (Table 3) in comparison with the initial stage.

Table 1

Means ± S.D. of neutrophil count, lymphocyte count and NLR in AMI patients subdivided according to the number of risk factors (A) or to the number of stenosed coronary vessels (B)

A	0–1 risk factor ($n = 39$)	2 risk factors ($n = 41$)	>2 risk factors ($n = 43$)	F
Neutrophil count (N/mmc)	5423 ± 1895	5427 ± 1442	5642 ± 1817	0.22
Lymphocyte count (N/mmc)	2352 ± 680	2419 ± 575	2547 ± 675	0.98
NLR	2.453 ± 1.025	2.340 ± 0.718	2.340 ± 0.875	0.22
B	No coronary lesions ($n = 23$)	1 stenosed vessel ($n = 47$)	2–3 stenosed vessels ($n = 35$)	F
Neutrophil count (N/mmc)	5710 ± 2048	5410 ± 1611	5871 ± 1530	0.78
Lymphocyte count (N/mmc)	2412 ± 590	2431 ± 697	2477 ± 619	0.08
NLR	2.485 ± 0.991	2.366 ± 0.814	2.485 ± 0.848	0.25

NLR = neutrophil/lymphocyte ratio.

Table 2
Distribution of risk factors (A) and stenosed coronary vessels (B) in AMI patients subdivided according to NLR

A	Low NLR ($n=62$)	High NLR ($n=61$)
0–1 risk factor	18 (29%)	21 (34,4%)
2 risk factors	22 (35,5%)	19 (31,2%)
>2 risk factors	22 (35,5%)	21 (34,4%)
B	Low NLR ($n=50$)	High NLR ($n=55$)
No coronary lesions	11 (22%)	12 (21,8%)
1 stenosed vessel	24 (48%)	23 (41,8%)
2–3 stenosed vessels	15 (30%)	20 (36,4%)

Table 3
Means ± S.D. of neutrophil count, lymphocyte count and NLR in AMI patients at baseline and after three months (A), at baseline and after 1 year (B)

A ($n=83$)	Baseline	After 3 months
Neutrophil count (N/mmc)	5502 ± 1681	$4745 \pm 1668^{***}$
Lymphocyte count (N/mmc)	2460 ± 676	2404 ± 595
NLR	2.363 ± 0.833	$2.038 \pm 0.701^{***}$
B ($n=66$)	Baseline	After 1 year
Neutrophil count (N/mmc)	5550 ± 1892	$4814 \pm 1725^{**}$
Lymphocyte count (N/mmc)	2459 ± 689	2397 ± 561
NLR	2.358 ± 0.822	$2.113 \pm 0.932^{*}$

$^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ vs Baseline (Student's 't' test for unpaired data).

5. Conclusive considerations

In our opinion the evaluation of the NLR reflects especially the systemic inflammatory response to the infarcted myocardium. This assumption is confirmed by the fact that in adult AMI subjects some authors [1, 27] have described a significant and positive correlation between hs-CRP and NLR; the same positive correlation was also observed in a healthy US cohort [44]. Unfortunately, we have no data regarding the relationship between NLR and CRP in these young AMI subjects.

In this group of young AMI subjects the NLR could not be considered a prognostic indicator for the subsequent mortality or a marker of early risk stratification, but only an useful index to evaluate together with other parameters, such as haemorheological determinants, plasma markers of platelet and neutrophil activation, oxidative stress, elastase and protein oxidation (previously examined by our group in juvenile myocardial infarction) [7–11, 30–33].

As it is known, the NLR reflects the balance between two different pathways considering that the neutrophils are responsible for the active and non specific inflammatory response while the lymphocytes are involved in the regulation of the immune system [5].

Our data show that this haematological index does not discriminate STEMI and non-STEMI subjects as well as diabetics and nondiabetics. Regarding this last aspect, the literature data seem to be contrasting; in fact, while some authors found a difference in NLR in relation to the diabetic disease [5, 29, 35], others did not point out this trend [13, 22, 24, 27, 43]. In our small survey this ratio differentiates smokers and non smokers and this datum seems to agree with the findings of several authors [5, 13, 22, 35], but it is different from which observed by others [24, 27, 43].

The results found in this study show that the NLR is not correlated to the number of cardiovascular risk factors nor to the extent of coronary disease.

Our findings in any case are not comparable because, up to now, there are no data concerning the behaviour of this parameter in juvenile myocardial infarction.

As it is known, in young adults AMI has a low incidence that varies between 2% and 10% according to different surveys [14, 15, 17, 34, 49]. In the last years many papers have regarded the acute coronary syndromes [18, 42] and the myocardial infarction in young patients [6, 21] although in these reports the age considered has been respectively of 35 years [42], of 40 years [6, 18], and between 30 and 54 years [21].

Juvenile myocardial infarction has specific risk factors, clinical, angiographic, and prognostic characteristics. Regarding the prognostic characteristics, the follow up carried by us till 18 months has evidentiated that, among AMI subjects included in the subgroup of low NLR, 5 subjects developed a new ischemic event, 3 subjects a heart failure and 3 subjects underwent revascularization, while among those included in the subgroup of high NLR 8 subjects developed a new ischemic event, 3 subjects a heart failure and 4 subjects underwent revascularization. Employing the Fisher exact test, the incidence of each complication is not statistically different between these two subgroups (low and high NLR).

As previously noted by our group in two small groups of young AMI subjects [8, 33], in whom we have examined the behaviour of the polymorphonuclear membrane fluidity and of the cytosolic calcium content at baseline and after *in vitro* activation at the initial stage and after 12 months, also in this study we found a significant decrease of neutrophil count at 3 and 12 months later AMI without any significant variation of lymphocyte count, and consequently we observed a significant decrease in NLR at these two intervals of time in comparison with the initial stage. This trend is probably due to the reduction of the inflammatory status degree accompaning acute myocardial infarction.

This study shows some limitations. The first regards the number of young AMI subjects enrolled for this research. The second is imputable to the fact that it is a retrospective study. The third limitation is ascribable to the circumstance that the first determination of the NLR was effected during the initial stage and not during the acute phase of the AMI. For this last reason we have not examined the relationships between troponin or creatin kinase and NLR.

Despite these limitations, it is interesting to underline that this low-cost haematological marker may be examined together with other inflammatory indicators in juvenile myocardial infarction.

NLR seems to give more information if compared with the total leukocyte count. In addition, NLR seems to predict the no-reflow phenomenon in AMI subjects undergoing a primary coronary revascularization, as described by other authors [27, 41, 43, 45], although we did not studied this phenomenon.

NLR is influenced by diet plus physical exercise [47] and in fact in overweight adolescents a four week diet and physical exercise intervention caused a significant reduction in the NLR. This finding is important considering the long life expectancy of these young AMI subjects.

In conclusion, in this study, that is only an aspect of the Sicilian Study on Juvenile Myocardial Infarction, we have examined the behaviour of NLR showing that its increase is not influenced by the number of cardiovascular risk factors nor by the extent of coronary involvement. We believe that this low-cost haematological parameter is an usefull inflammatory marker accompanying myocardial infarction.

This research complies with the requirement for ethical publication in Clinical Hemorheology and Microcirculation as published in Clin Hemorheol Microcirc. 2010;44(1):1–2.

References

[1] M. Akpek, M.G. Kaya, Y.Y. Lam, O. Sahin, D. Elcik, T. Celik, A. Ergin and C.M. Gibson, Relation of neutrophil/lymphocyte ratio to coronary flow to in-hospital major adverse cardiac events in patients with ST-elevated myocardial infarction undergoing primary coronary intervention, *American Journal of Cardiology* **110** (2012), 621–627.

[2] Y. Arbel, A. Finkelstein, A. Halkin, E.Y. Birati, M. Revivo, M. Zuzut, A. Shevach, S. Berliner, I. Herz, G. Keren and S. Banai, Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography, *Atherosclerosis* **225** (2012), 456–460.
[3] A.H. Ates, U. Canpolat, H. Yorgun, E.B. Kaya, H. Sunman, E. Demiri, A. Taher, T. Hazirolan, K. Aytemir, L. Tokgözoglu, G. Kabakçi and A. Oto, Total white blood cell count is associated with the presence, severity and extent of coronary atherosclerosis detected by dual-source multislice computed tomographic coronary angiography, *Cardiology Journal* **18** (2011), 371–377.
[4] B. Azab, M.A. Shariff, R. Bachir, J.P. Nabagiez and J.T. McGinn Jr., Elevated preoperative neutrophil/lymphocyte ratio as a predictor of increased long-term survival in minimal invasive coronary artery bypass surgery compared to sternotomy, *Journal of Cardiothoracic Surgery* **8** (2013), 193.
[5] B. Azab, M. Zaher, K.F. Weiserbs, E. Torbey, K. Lacossiere, S. Gaddam, R. Gobunsuy, S. Jadonath, D. Baldari, D. McCord and J. Lafferty, Usefulness of neutrophil to lymphocyte ratio in predicting short- and long-term mortality after non-ST-elevation myocardial infarction, *American Journal of Cardiology* **106** (2010), 470–476.
[6] R. Bhardwaj, A. Kandoria and R. Sharma, Myocardial infarction in young adults-risk factors and pattern of coronary artery involvement, *Nigerian Medical Journal* **55** (2014), 44–47.
[7] G. Caimi, B. Canino, E. Incalcaterra, E. Ferrera, M. Montana and R. Lo Presti, Behaviour of protein carbonyl groups in juvenile myocardial infarction, *Clinical Hemorheology and Microcirculation* **53** (2013), 297–302.
[8] G. Caimi, E. Hoffmann, B. Canino, M. Montana, F. Dispensa, E. Incalcaterra, M.F. Casciolo, A. Catania and R. Lo Presti, Polymorphonuclear leukocyte membrane fluidity and cytosolic Ca(2+) content in young adults with acute myocardial infarction. Evaluation at the initial stage and after 12 months, *Clinical Hemorheology and Microcirculation* **31** (2004), 41–47.
[9] G. Caimi, E. Hoffmann, M. Montana, B. Canino, F. Dispensa, A. Catania and R. Lo Presti, Haemorheological pattern in young adults with acute myocardial infarction, *Clinical Hemorheology and Microcirculation* **29** (2003), 11–18.
[10] G. Caimi, E. Hoffmann, M. Montana, E. Incalcaterra, B. Canino and R. Lo Presti, Beta-thromboglobulin and platelet factor 4 in juvenile myocardial infarction, *Clinical and Applied Thrombosis and Hemostasis* **13** (2007), 108–119.
[11] G. Caimi, E. Hoffmann, M. Montana, E. Incalcaterra, F. Dispensa, T. D'Amico, B. Canino and R. Lo Presti, Plasma markers of platelet and polymorphonuclear leukocyte activation in young adults with acute myocardial infarction, *Clinical Hemorheology and Microcirculation* **32** (2005), 67–74.
[12] F. Carbone, A. Nencioni, F. Mach, N. Vuilleumier and F. Montecucco, Pathophysiological role of neutrophils in acute myocardial infarction, *Thrombosis and Haemostasis* **110** (2013), 501–514.
[13] K.H. Cho, M.H. Jeong, K. Ahmed, D. Hachinohe, H.S. Choi, S.Y. Chang, M.C. Kim, S.H. Hwang, K.H. Park, M.G. Lee, J.S. Ko, D.S. Sim, N.S. Yoon, H.J. Yoon, Y.J. Hong, K.H. Kim, J.H. Kim, Y. Ahn, J.G. Cho, J.C. Park and J.C. Kang, Value of early risk stratification using hemoglobin level and neutrophil-to-lymphocyte ratio in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention, *American Journal of Cardiology* **107** (2011), 849–856.
[14] L. Choudhury and J.D. Marsh, Myocardial infarction in young patients, *American Journal of Medicine* **107** (1999), 254–261.
[15] M. Doughty, R. Mehta, D. Bruckman, S. Das, D. Karavite, T. Tsai and K. Eagle, Acute myocardial infarction in the young–The University of Michigan experience, *American Heart Journal* **143** (2002), 56–62.
[16] R. Dragu, S. Khoury, R. Zuckerman, M. Suleiman, D. Mutlak, Y. Agmon, M. Kapeliovich, R. Beyar, W. Markiewicz, H. Hammerman and D. Aronson, Predictive value of white blood cell subtypes for long-term outcome following myocardial infarction, *Atherosclerosis* **196** (2008), 405–412.
[17] M. Egred, G. Viswanathan and G.K. Davis, Myocardial infarction in young adults, *Postgraduate Medical Journal* **81** (2005), 741–745.
[18] M.R. Esteban, S.M. Montero, J.J. Sánchez, H.P. Hernández, J.J. Pérez, J.H. Afonso, C.R. Pérez, B.B. Díaz and A.C. de León, Acute coronary syndrome in the young: Clinical characteristics, risk factors and prognosis, *Open Cardiovascular Medicine Journal* **25** (2014), 61–67.
[19] A.J. Fowler and R.A. Agha, Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography–the growing versatility of NLR, *Atherosclerosis* **228** (2013), 44–45.
[20] S. Ghaffari, M. Nadiri, L. Pourafkari, N. Sepehrvand, A. Movasagpoor, N. Rahmatvand, M. Rezazadeh Saatloo, M. Ahmadi and N.D. Nader, The predictive value of total neutrophil count and neutrophil/lymphocyte ratio in predicting In-Hospital mortality and complications after STEMI, *Journal of Cardiovascular and Thoracic Research* **6** (2014), 35–41.
[21] A. Gupta, Y. Wang, J.A. Spertus, M. Geda, N. Lorenze, C. Nkonde-Price, G. D'Onofrio, J.H. Lichtman and H.M. Krumholz, Trends in acute myocardial infarction in young patients and differences by sex and race, 2001 to 2010, *Journal of American College of Cardiology* **64** (2014), 337–345.

[22] Y.C. Han, T.H. Yang, D.I. Kim, H.Y. Jin, S.R. Chung, J.S. Seo, J.S. Jang, D.K. Kim, D.K. Kim, K.H. Kim, S.H. Seol and D.S. Kim, Neutrophil to lymphocyte ratio predicts long-term clinical outcomes in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention, *Korean Circulation Journal* **43** (2013), 93–99.

[23] G.K. Hansson, J. Holm, S. Holm, Z. Fotev, H.J. Hedrich and J. Fingerle, T lymphocytes inhibit the vascular response to injury, *Proceedings of the National Academy of Sciences of the U S A* **88** (1991), 10530–10534.

[24] J. He, J. Li, Y. Wang, P. Hao and Q. Hua, Neutrophil-to-lymphocyte ratio (NLR) predicts mortality and adverse-outcomes after ST-segment elevation myocardial infarction in chinese people, *International Journal of Clinical and Experimental Pathology* **7** (2014), 4045–4056.

[25] M. Hoffman, A. Blum, R. Baruch, E. Kaplan and M. Benjamin, Leukocytes and coronary heart disease, *Atherosclerosis* **172** (2004), 1–6.

[26] B.D. Horne, J.L. Anderson, J.M. John, A. Weaver, T.L. Bair, K.R. Jensen, D.G. Renlund and J.B. Muhlestein, Intermountain heart collaborative study group, Which white blood cell subtypes predict increased cardiovascular risk? *Journal of the American College of Cardiology* **45** (2005), 1638–1643.

[27] M.G. Kaya, M. Akpek, Y.Y. Lam, M. Yarlioglues, T. Celik, O. Gunebakmaz, M. Duran, S. Ulucan, A. Keser, A. Oguzhan and M.C. Gibson, Prognostic value of neutrophil/lymphocyte ratio in patients with ST-elevated myocardial infarction undergoing primary coronary intervention: A prospective, multicenter study, *International Journal of Cardiology* **168** (2013), 1154–1159.

[28] S.A. Kocaman, A. Sahinarslan, T. Kunak, S. Balcioğlu, M. Cetin, M. Cemri, T. Timurkaynak, B. Boyaci and A. Cengel, The particular interactions of the traditional cardiovascular risk factors with different circulating specific leukocyte subtype counts in blood: An observational study, *Anadolu Kardiyoloji Dergisi* **11** (2011), 573–581.

[29] G.K. Lee, L.C. Lee, E. Chong, C.H. Lee, S.G. Teo, B.L. Chia and K.K. Poh, The long-term predictive value of the neutrophil-to-lymphocyte ratio in type 2 diabetic patients presenting with acute myocardial infarction, *QJM* **105** (2012), 1075–1082.

[30] R. Lo Presti, A. Catania, T. D'Amico, M. Montana, M. Caruso and G. Caimi, Oxidative stress in young subjects with acute myocardial infarction: Evaluation at the initial stage and after 12 months, *Clinical and Applied Thrombosis and Hemostasis* **14** (2008), 421–427.

[31] R. Lo Presti, T. D'Amico, M. Montana, B. Canino, A. Romano and G. Caimi, Platelet activation markers in long-term follow-up of young subjects with acute myocardial infarction, *Clinical Hemorheology and Microcirculation* **35** (2006), 527–528.

[32] R. Lo Presti, M. Montana, E. Hoffmann, T. D'Amico, G. Amodeo and G. Caimi, Elastase in young subjects with acute myocardial infarction: Evaluation at the initial stage and after 12 months, *Clinical Hemorheology and Microcirculation* **35** (2006), 375–377.

[33] R. Lo Presti, M.G. Tozzi Ciancarelli, E. Hoffmann, E. Incalcaterra, B. Canino, M. Montana, T. D'Amico, A. Catania and G. Caimi, Persistence of the altered polymorphonuclear leukocyte rheological and metabolic variables after 12 months in juvenile myocardial infarction, *Clinical Hemorheology and Microcirculation* **35** (2006), 227–230.

[34] P. Morillas, V. Bertomeu, P. Pabón, P. Ancillo, J. Bermejo, C. Fernández and F. Arós, PRIAMHO II investigators, characteristics and outcome of acute myocardial infarction in young patients. The PRIAMHO II study, *Cardiology* **107** (2007), 217–225.

[35] J. Núñez, E. Núñez, V. Bodí, J. Sanchis, G. Miñana, L. Mainar, E. Santas, P. Merlos, E. Rumiz, H. Darmofal, A.M. Heatta and A. Llàcer, Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction, *American Journal of Cardiology* **101** (2008), 747–752.

[36] J. Núñez, J. Sanchis, V. Bodí, E. Núñez, L. Mainar, A.M. Heatta, O. Husser, G. Miñana, P. Merlos, H. Darmofal, M. Pellicer and A. Llàcer, Relationship between low lymphocyte count and major cardiac events in patients with acute chest pain, a non-diagnostic electrocardiogram and normal troponin levels, *Atherosclerosis* **206** (2009), 251–257.

[37] B. ó Hartaigh, J.A. Bosch, G.N. Thomas, J.M. Lord, S. Pilz, A. Loerbroks, M.E. Kleber, T.B. Grammer, J.E. Fischer, B.O. Boehm and W. März, Which leukocyte subsets predict cardiovascular mortality? From the ludwigshafen risk and cardiovascular health (LURIC) study, *Atherosclerosis* **224** (2012), 161–169.

[38] S.R. Ommen, R.J. Gibbons, D.O. Hodge and S.P. Thomson, Usefulness of the lymphocyte concentration as a prognostic marker in coronary artery disease, *American Journal of Cardiology* **79** (1997), 812–814.

[39] A. Papa, M. Emdin, C. Passino, C. Michelassi, D. Battaglia and F. Cocci, Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease, *Clinica Chimica Acta* **395** (2008), 27–31.

[40] M. Rasouli, V. Nesarhosseini, A.M. Kiasari, S. Arab, R. Shariati, D. Kazemi, N. Daneshpour and S. Heidari, The multiplicative interactions of leukocyte counts with some other risk factors enhance the prognostic value for coronary artery disease, *Cardiology Journal* **18** (2011), 246–253.

[41] D.Y. Sahin, M. Gür, Z. Elbasan, A. Yıldız, Z. Kaya, Y.K. Içen, A. Kıvrak, C. Türkoğlu, R. Yılmaz and M. Caylı, Predictors of preinterventional patency of infarct-related artery in patients with ST-segment elevation myocardial infarction: Importance of neutrophil to lymphocyte ratio and uric acid level, *Experimental and Clinical Cardiology* **18** (2013), e77–81.

[42] A.W. Schoenenberger, D. Radovanovic, J.C. Stauffer, S. Windecker, P. Urban, G. Niedermaier, P.F. Keller, F. Gutzwiller and P. Erne, AMIS plus investigators, Acute coronary syndromes in young patients: Presentation, treatment and outcome, *International Journal of Cardiology* **5** (2011), 300–304.

[43] N. Sen, B. Afsar, F. Ozcan, E. Buyukkaya, A. Isleyen, A.B. Akcay, H. Yuzgecer, M. Kurt, M.F. Karakas, N. Basar, E. Hajro and M. Kanbay, The neutrophil to lymphocyte ratio was associated with impaired myocardial perfusion and long term adverse outcome in patients with ST-elevated myocardial infarction undergoing primary coronary intervention, *Atherosclerosis* **228** (2013), 203–210.

[44] N. Shah, V. Parikh, N. Patel, N. Patel, A. Badheka, A. Deshmukh, A. Rathod and J. Lafferty, Neutrophil/lymphocyte ratio significantly improves the framingham risk score in prediction of coronary heart disease mortality: Insights from the national health and nutrition examination survey-III, *International Journal of Cardiology* **171** (2014), 390–397.

[45] S. Turkmen, O. Dogdu, K. Tekin, Z. Kucukdurmaz, C.E. Cagliyan, S. Sarikaya, H. Yucel, H. Karapinar, B. Ozkan, O.K. Uysal, A. Basara, E. Sancaktar and A. Yilmaz, The relationship between neutrophil/lymphocyte ratio and the TIMI flow grade in patients with STEMI undergoing primary PCI, *European Review for Medical and Pharmacological Sciences* **17** (2013), 2185–2189.

[46] R. Wang, J.P. Chen and W.H. Chen, Diet and exercise improve neutrophil to lymphocyte ratio in overweight adolescents, *International Journal of Sports Medicine* **32** (2011), 982–986.

[47] X. Wang, G. Zhang, X. Jiang, H. Zhu, Z. Lu and L. Xu, Neutrophil to lymphocyte ratio in relation to risk of all-cause mortality and cardiovascular events among patients undergoing angiography or cardiac revascularization: A meta-analysis of observational studies, *Atherosclerosis* **234** (2014), 206–213.

[48] B.A. Williams and M.E. Merhige, Association between neutrophil-lymphocyte ratio and impaired myocardial perfusion in patients with known or suspected coronary disease, *Heart and Lung* **42** (2013), 436–441.

[49] F.H. Zimmerman, A. Cameron, L.D. Fisher and G. Ng, Myocardial infarction in young adults: Angiographic characterization, risk factors and prognosis (Coronary Artery Surgery Study Registry), *Journal of American College of Cardiology* **26** (1995), 654–661.