

# Can The Neutrophil to Lymphocyte Ratio, Determined in The Whole Blood Count, Be Used as A Mortality Marker in Patients with Pulmonary Thromboembolism ?

Tam Kan Sayımında Belirlenen Nötrofil/Lenfosit Oranı Pulmoner Tromboemboli Hastalarında Mortalite Belirteci Olarak Kullanılabilir Mi?

Fahrettin Turna<sup>1</sup>, Asim Enhoş<sup>2</sup>

<sup>1</sup> Sakarya University, Education and Resarch Hospital, Department of Cardiology, Sakarya, Turkey

<sup>2</sup> Bezmialem Foundation University, Faculty of Medicine, Department of Cardiology, Istanbul, Turkey

Yazışma Adresi / Correspondence:

**Asim Enhoş**

Bezmialem Foundation University, Faculty of Medicine, Department of Cardiology, Adnan Menderes Avenue, Vatan Street, 34093, Fatih/Istanbul TURKEY

T: +90 530 600 74 18 E-mail : [asimenhos@hotmail.com](mailto:asimenhos@hotmail.com)

Geliş Tarihi / Received : 04.06.2020 Kabul Tarihi / Accepted : 28.08.2020

Orcid :

Fahrettin Turna <https://orcid.org/0000-0003-3483-9456>

Asim Enhoş <https://orcid.org/0000-0002-7479-7783>

( Sakarya Tıp Dergisi / Sakarya Med J 2020, 10(3):422-429 ) DOI: 10.31832/smj.747828

## Abstract

Objective	Acute pulmonary thromboembolism (APTE) is one of the life-threatening cardiovascular diseases. Following the diagnosis, it has a broad range of severity and a wide spectrum. Its mortality and morbidity vary depending on its clinical scope and the site of involvement. Neutrophil / lymphocyte ratio (NLR) has previously been studied in many cardiovascular disease processes as an indicator of inflammation and marker of mortality. The aim of our study is to determine the correlation between NLR and the 30-day mortality in APTE.
Materials and Methods	160 APTE patients who applied to the emergency department of Bağcılar Education and Research Hospital between January 2011 and June 2013 were determined retrospectively and hemogram parameters at the time of application were recorded. It was ensured in the selection of patients that all patients had a final diagnosis supported by computed tomography. APTE patients; It was divided into two groups in terms of those who died (n:28) and survived (n:120) within 30 days. Low, medium and high risk APTE patients in both groups were compared in terms of NLR. The utility of NLR as a marker of mortality was investigated in patients with pulmonary embolism
Results	NLR was significantly higher in the deceased group ( $11.40 \pm 4.24$ vs $18.33 \pm 9.06$ , $p < 0.001$ ). It had 57 % sensitivity and 89 % specificity for prediction of mortality (Area Under Curve: 0.736, 95% CI: 0.619–0.853, $p < 0.001$ ) in patients with pulmonary embolism. In the multivariate logistic regression analysis; NLR was found to be significant independent predictor of the 30-day mortality (Odds: 1.132 (1.031-1.243, CI 95%), $p=0.009$ ).
Conclusion	NLR plays a strong role in determining 30-day mortality in APTE patients.
Key Words	Leukocyte Count; Pulmonary embolism; Mortality

## Abstract

Amaç	Akut pulmoner tromboemboli (APTE) hayatı tehdit eden kardiyovasküler hastalıklardan biridir. Teşhisi takiben, geniş bir ciddiyet aralığı ve spektrumu vardır. Mortalitesi ve morbiditesi klinik kapsama ve tutulum yerine bağlı olarak değişir. Nötrofil / lenfosit oranı (NLR) daha önce birçok kardiyovasküler hastalık sürecinde inflamasyon ve mortalite belirteci olarak incelenmiştir. Çalışmamızın amacı, APTE'de NLR ile 30 günlük mortalite arasındaki korelasyonu belirlemektir.
Gereç ve Yöntemler	Ocak 2011 - Haziran 2013 tarihleri arasında Bağcılar Eğitim ve Araştırma Hastanesi acil servisine başvuran hastalardan 160 APTE hastası retrospektif olarak saptandı ve başvuru sırasında hemogram parametreleri kaydedildi. Hasta seçiminde tüm hastaların bilgisayarlı tomografi ile desteklenen kesin tanı alması sağlandı. APTE hastaları; 30 gün içinde ölen (n: 28) ve hayatta kalan (n: 120) olarak iki gruba ayrıldı. Her iki gruptaki düşük, orta ve yüksek riskli APTE hastaları NLR açısından karşılaştırıldı. Pulmoner emboli hastalarında NLR'nin mortalite belirteci olarak kullanımı araştırıldı.
Bulgular	Ölen grupta NLR anlamlı olarak daha yüksekti ( $11.40 \pm 4.24$ e karşı $18.33 \pm 9.06$ , $p < 0.001$ ). Pulmoner emboli hastalarında NLR; mortalite tahmini için % 57 duyarlılığa ve % 89 özgüllüğe (Eğri altındaki alan: 0.736, % 95 CI: 0.619-0.853, $p < 0.001$ ) sahipti. Çok değişkenli lojistik regresyon analizinde; NLR'nin 30 günlük mortalitenin anlamlı bağımsız prediktörü olduğu bulunmuştur (Odds Oranı: 1.132 (1.031-1.243, GA% 95), $p = 0.009$ ).
Sonuç	NLR, APTE hastalarında 30 günlük mortalitenin belirlenmesinde güçlü bir rol oynamaktadır.
Anahtar Kelimeler	Lökosit Sayısı; Pulmoner emboli; Mortalite

## INTRODUCTION

Acute pulmonary thromboembolism (APTE) is a relatively common cardiovascular emergency resulting from the occlusion of the pulmonary artery bed with thrombus coming from systemic veins at varying rates. Venous thromboembolic disease is the third most common cardiovascular disease after acute coronary syndromes and stroke.<sup>1</sup> About a third of the patients die within the first 3 years, and about half of the patients experience long-term dyspnea and limited functional capacity.<sup>2</sup>

A correlation between APTE and myocardial infarction and cardiovascular conditions such as stroke was recently reported.<sup>3,4</sup> The reported high risk of PTE in obese individuals, smokers and patients affected by systemic hypertension or metabolic syndrome has refreshed the interest shown in the correlation between arterial thromboembolism and venous thromboembolism (VTE).

APTE is a cardiovascular disease with a current mortality rate of 7-15%. The difficulties in its diagnosis and treatment options varying according to the risk classifications increase the prognostic importance of the disease. Hemodynamic imbalance and right ventricular dysfunction are the most common prognostic markers.

As we know from the Virchow's triad; inflammation, endothelial injury and hypercoagulability play a role in the formation of thrombus.<sup>5</sup> The elevation in inflammation indicators supports the increased probability for thrombus formation. The correlation of increased white blood cell (WBC) count with mortality, recurrence, and comorbid conditions has been proved.<sup>6</sup> It was emphasized in recent years that peripheral neutrophil / lymphocyte ratio (NLR) may be a better indicator of inflammation compared to the WBC count.<sup>7</sup> In cases where inflammation, such as acute coronary syndrome, acute inflammatory diseases and cancer, play a significant role in the pathogenesis of the disease, the NLR has been found to be determinant in the prognosis and severity of these diseases. Acute pulmonary

embolism is the cornerstone of thrombotic diseases, and its common pathophysiology with atherothrombotic diseases has been reported. Starting from here, we investigated the value of NLR in predicting the 30-day mortality in patients diagnosed with APTE using also other prognostic markers in this study.

## MATERIALS AND METHODS

### Patient population

160 patients who applied to the Bagcilar Education and Research Hospital emergency department between January 2011 and June 2013 and were diagnosed with pulmonary embolism using pulmonary computed tomographic angiography have been taken from the registry system with the diagnosis code I26. After applying the exclusion criteria, 148 patients were analyzed. 28 patients died (9 in high, 17 in medium, 2 in low risk groups) and 120 patients survived (16 in high, 64 in medium, 40 in low risk groups) in 30 days.

### Exclusion Criteria

Patients with haematological disorders (WBC < 3\*10<sup>3</sup>/L or > 20\*10<sup>3</sup>), infectious, inflammatory, autoimmune and neoplastic disease history, and conditions that may affect results such as immune suppressive therapy were not included in the study. Blood results and clinical data obtained at the time of first admission to the hospital were analysed.

### Study protocol

Our study was designed as a cross-sectional, descriptive study. Patients diagnosed with the ICD-10 code I26 were screened from the hospital's electronic database. Following the pre-screening, the data of the patients with a final pulmonary embolism diagnosis according to the computed tomographic pulmonary angiography were reached from the system. Required laboratory data were obtained from the hospital's database. Clinical data at the time of arrival at the hospital, demographic information, comorbid conditions and vital findings were reached from the patient admission files. By contacting the patients or their

first-degree relatives through the telephone system, information was obtained regarding one-month mortality and morbidity. Study was approved by the Bezmialem Vakif University non-Interventional research ethics committee with the number 3840 on 06.03.2020 and the study was conducted in accordance with ethical principles described by the Declaration of Helsinki.

### **Radiological imaging**

Philips Brilliance 64-detector computed tomography device was used for computed tomographic pulmonary angiography. Intravenous contrast agent injection with multi section tomography (Philips BRILLIANCE 64-detector) was carried out using an automatic injector. Examinations were performed to include lungs from apex to diaphragm. All patients were given 80-100 ml of the agent (350-400/100 mg/ml non-ionic contrast agent) with a size 18 or 20 branule from the forearm vein at an injection rate of 4-5 ml/second for a total of 16-20 seconds. After starting to inject the contrast agent, the device begins screening when it catches the contrast agent density with the real time sections taken from the pulmonary artery level. Pitch value was determined at 0.75-0.825, section thickness was determined at 1 mm and the obtained images were set to be recombined at 0.6 mm intervals. The sections were analysed in parenchyma and mediastinum windows, and the main, lobar, segmental and subsegmental arteries and parenchyma areas were examined in the images. The diagnosis established by the radiologist was accepted in the evaluation of computed tomographic pulmonary angiography.

### **Biochemical and hematological measurements**

Prior to the computed tomographic pulmonary angiography, complete blood count, biochemical evaluation, and cardiac markers and d-dimer measurement tests were performed on patients. Samples were taken from the antecubital vein into vacuum tubes (2 ml) containing ethylenediaminetetraacetic acid (EDTA) for the automatic complete blood count, into serum separation tubes (10 ml) with gel clot activator for the biochemistry and cardiac markers,

and into coagulation tubes (2 ml) containing 3.2% citrate for the d-dimer, and samples were studied within 1 hour. Complete blood counts were performed using Siemens Diagnostics Advia 2120 hemogram device. Siemens Diagnostics Advia-1800 biochemistry analyser was used for the biochemistry parameters. Siemens Diagnostics Advia Centaur XP immunoassay analyser was used for the analysis of Troponin I. The Vidas enzyme-linked immunosorbent assay (ELISA) kits were used for the d-dimer evaluation.

### **Statistical analysis**

Mean±standard deviation and median were used for continuous variables, while percentage was used for categorical variables. Normal distribution was tested using a single sample Kolmogorov-Smirnov test and skewness-kurtosis test. Test of the differences between two independent groups (Unpaired t test) was used to test the difference between the continuous variables with normal distribution between patient and control groups. Mann-Whitney U test was applied for variables not suitable for the normal distribution. Pearson Chi square, Fisher exact probability test and Continuity correction (Yate Correction) test were used to test the categorical variables.

Variables which were  $p < 0.05$  in univariate analyses (age, history of cerebrovascular disease, hypotension, NLR, monocyte count, Red cell distribution width (RDW), urea level, Aspartate aminotransferase (AST), red blood cell (RBC) count, syncope at the time of application) were included in the multivariate analysis. Multivariate logistic regression analysis (using the Backward stepwise method) was used to determine the independent predictors of mortality in pulmonary embolism in the course of the one-month follow-up. ROC analysis was used to determine the cut-off value. P value  $< 0.05$  was considered significant for all tests. Statistical Package for the Social Sciences (SPSS version 11.0, SPSS Inc., Chicago, IL, USA) was used.

## RESULTS

The demographic, clinical and laboratory characteristics of the patients are shown in tables 1, 2 and 3. The patients were divided into two groups - those who died (28 patients) and those who survived (120 patients) in the period of 30-day. There was a significant difference between the groups in terms of age, history of cerebrovascular disease, having applied to the clinic with syncope, WBC (white blood cell count), neutrophil count, lymphocyte count, monocyte count, RBC, RDW, urea level, troponin level and NLR (8,[23] vs 4,[26] p <0.001).

Symptoms	n(%)
Shortness of breath ,n(%)	133 (89.86%)
Pain in chest ,n (%)	87 (58.78%)
Hemoptysis, n(%)	4 (2.70%)
Syncope / presyncope, n(%)	30 (20.27%)

	Died n: 28	Survived n: 120	P
Age, year (mean± SD)	74.27 ± 12.35	61.12± 15.67	<0.001
Gender (female),n(%)	17 (60.71%)	64 (53.33%)	0.535
Gender (male),n(%)	11 (39.29%)	56 (46.66%)	0.628
DM,n(%)	11 (39.29%)	33 (27.50%)	0.249
Hypertension,n(%)	10 (35.7%)	58 (48.33%)	0.291
CAD,n(%)	2 (7.14%)	14 (11.66%)	0.525
CRF,n(%)	2 (7.14%)	7 (5.83%)	1.000
CVD,n(%)	5 (17.85%)	6 (5.00%)	<b>0.046</b>
HF ,n(%)	4 (14.23%)	12 (10.00%)	0.741
COPD ,n(%)	2 (7.14%)	17 (14.16%)	0.529
Smoking,n(%)	5 (17.85%)	30 (25.00%)	0.464
Immobilization,n(%)	13 (46.42%)	26 (30.00%)	0.123
DVT,n(%)	19 (67.85%)	52 (43.33%)	0.077
Use of alcohol,n(%)	0 (0%)	3 (2.50%)	1.000
BMI,(mean ± SD)	27.39±5.12	28.17±5.46	0.414

Mean ± standard deviation was used for continuous variables and percentage was used for categorical variables.  
DM: Diabetsmellitus, CAD: Coronary artery disease, CRF: Chronic renal failure, CVD: Cerebrovascular disease, HF: Heart failure, DVT: Deep vein thrombosis, BMI: Body mass index,COPD: Cronic Obstructive Pulmonary Disease, SD: Standart Deviation

	Died	Survived	P
WBC (x103/L), (mean±SD)	14.23 ± 7.12	10.57 ± 3.25	<b>0.004</b>
RBC (x103/L),(mean±SD)	4.68 ±0.51	4.07±0.6	<b>0.042</b>
Hemoglobin (gr/dl), (mean±SD)	11.35±1.58	12.21±2.14	0.083
Platelet count (x103/L)	264,[1007]	243,[483]	0.459
Neutrophils (%)	81,[88]	72,[62]	< <b>0.001</b>
Lymphocytes (%)	9,[41]	17,[48]	< <b>0.001</b>
NLR	8,[23]	4,[26]	< <b>0.001</b>
Monocytes (%)	5.4,[26]	6.3,[13]	0.023
RDW	15,[9]	14,[13]	0.017
MPV, (mean±SD)	9.13±1.32	8.92±1.41	0.378
Glucose (mg/dl)	151,[287]	119,[311]	0.273
Urea (mg/dl)	45,[154]	37,[128]	<b>0.008</b>
Creatinine (mg/dl), (mean±SD)	0.91±0.28	0.90±0.41	0.693
AST (U/L)	32,[306]	25,[586]	<b>0.042</b>
ALT (U/L)	24,[243]	22,[482]	0.975
Sodium (mmol/L), (mean±SD)	137.97±9.12	140.32±3.86	0.158
Potassium(m-mol/L),(mean±SD)	4.32±0.71	4.43±0.59	0.627
D - dimer (ng/mL)	4113,[9158]	4606,[9468]	0.990
Troponin I ng/mL	0.14,[4.98]	0.02,[6]	<b>0.007</b>
Saturation O2(%),(mean±SD)	88.8±9.1	91.2±7.9	0.132
PO2 (mmHG)	61,[126]	68,[386]	0.201
PCO2 (mmHG)	30,[28]	32,[29]	0.569

Mean ± standard deviation, median, range (in parentheses) were used for continuous variables.  
WBC: White bloodcell, RBC: Red blood cells, NLR: Neutrophil count / lymphocyte ratio, RDW: Red cell distribution width; MPV: Mean platelet volume, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SD: Standart Deviation

There was no significant difference between the groups in terms of the right ventricular loading measured by computed tomographic pulmonary angiography (table 4).

	Died	Survived	P
LV (mm)	46.35±7.08	47.01±5.87	0.460
RV (mm)	43.14±5.75	42.91±7.11	0.613
RV/LV	0.95±0.21	0.94±0.17	0.231

Mean ± standard deviation was used for continuous variables.  
LV: Left ventricular, RV: Right ventricular

In the multivariate Cox regression analysis; age (Odds: 1.056 (1.011-1.1003, GA 95%),  $p=0.014$ ), syncope at the time of application (Odds: 3.232 (1.051-9.943, GA 95%),  $p=0.04$ ) and NLR were the independent predictors of the 30-day mortality rate (Odds: 1.132 (1.031-1.243, GA 95%),  $p=0.009$ ) (Table 5).

	Odds Ratio	Confidence Interval (%95)	P
Age	1.056	1.011-1.103	<b>0.014</b>
NLR	1.132	1.031-1.243	<b>0.009</b>
Syncope	3.232	1.051-9.943	<b>0.041</b>

NLR: Neutrophil to lymphocyte ratio

A receiver operating characteristic(ROC) curve was generated for sensitivity and specificity, and the respective areas under the curve (AUCs) were used to investigate the predictive value of NLR for prediction of 30-day mortality for APTE. NLR cutoff of 7.87 predicts 30-day mortality for APTE with a sensitivity of 57 % and a specificity of 89 % . (AUC: 0.736, 95% CI: 0.619–0.853,  $p < 0.001$ ) (figure 1)

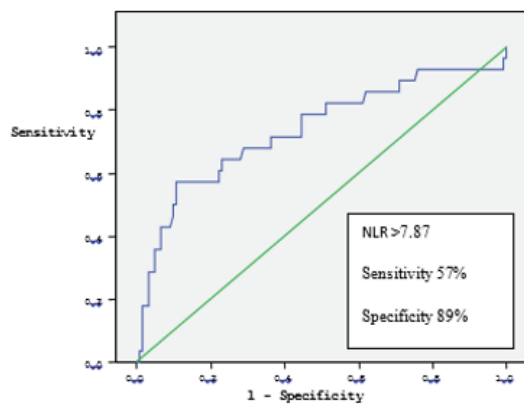


Figure 1: ROC analysis (AUC: 0.736,  $p < 0.001$ , 95% CI [0.619-0.853]) Neutrophil/lymphocyte ratio (NLR) cut off of 7.87 predicts 30-day mortality for acute pulmonary thromboembolism (APTE).

ROC receiver operating characteristic, AUC area under the curve

When the correlation of the groups with the NLR was analysed according to the risk classification specified in the European Cardiology Association guide;<sup>8</sup>

- i) No significant differences were found between the patients who died and survived in terms of NLR in the patient group with syncope and right ventricular dilation and/or troponin (+). (high risk group)
- ii) A significant difference was found between the patients who died and survived in terms of NLR in the patient group with right ventricular dilation and/or troponin (+) without syncope. (moderate risk group)
- iii) A significant difference was found between the patients who died vs. survived in terms of NLR in the patient group without syncope or right ventricular dilation and without troponin (-). (low risk group) (table 6).

Table 6. The correlation of NLR with basic risk markers in complete blood count in acute pulmonary thromboembolism

Risk markers	Died	Survived	P
Syncope and right ventricular dilation and/or troponin (+)	9 (32%) NLR: 5.7;[22]	16 (13%) NLR: 4.7;[10]	0.014
Right ventricular dilation and/or troponin (+)	17 (60%) NLR: 8.7;[20]	64 (53%) NLR: 3.9;[21]	< 0.001
No syncope or right ventricular dilation and without troponin (-)	2 (7%) NLR: 9.5 ± 2.1	40 (33%) NLR: 4.6;[26]	0.037

Mean ± standard deviation, median, range (in parentheses) were used for continuous variables, and percentage was used for categorical variables.  
NLR: Neutrophil to lymphocyte ratio

## DISCUSSION

NLR detected in the complete blood count at the time of admission in patients with a final diagnosis of APTE was investigated in our study. In the deceased group, NLR was significantly higher. NLR was able to predict short-term mortality independently from troponin and right ventricular loading. In addition, the NLR cutoff of 7.87 predicts 30-day mortality for APTE with a sensitivity of 57 % and a specificity of 89 %. In previous studies, NLR was reported as a good marker in predicting 1-month mortality in acute pulmonary embolism.<sup>9-12</sup> Even though similar results were

obtained in our study, our results had different aspects compared to these studies. Our study included pulmonary embolism markers and troponin and right ventricular loading findings which are used in the risk classification, and arrived at the conclusion that the NLR can be used as a mortality marker in the moderate and low risk groups instead of the high risk group through pulmonary embolism risk classification. Additionally, in one of the previous studies, the blood gas analysis mentioned in their limitations was also included in our study and no statistically significant differences were found.

Today thromboembolic and atherothrombotic diseases are among the leading causes of death in the world and in our country.<sup>13</sup>

In the recent years, the role of biomarkers reflecting inflammation and inflammatory conditions in atherothrombotic diseases and their association with adverse events has been investigated in many studies. The role of inflammation is investigated not only in terms of the progression of thromboembolism, and acute and chronic forms of the disease, but also in terms of the prognosis and survival rates of the disease. Markers related to inflammation are handled in a rather wide spectrum. Some biomarkers such as white blood cells, acute phase reactants, adhesion molecules, and cytokines have been used to investigate the inflammatory response in our body and to what extent it is stimulated. The most commonly investigated marker in this respect is C-reactive protein (CRP), which is synthesized in the liver and is an acute phase reactant. The WBC and its subtypes, which are the most basic cells of inflammation, are held responsible for undesirable conditions in cardiovascular diseases and are used as a marker of the inflammatory condition.<sup>14</sup> It was previously shown that an increase in neutrophil levels in acute atherothrombotic conditions is associated with the prevalence and short term prognosis of myocardial damage.<sup>15</sup> In addition to the neutrophil increase in acute coronary syndrome, lymphopenia, which is seen due to acute stress, is a condition that

reflects acute changes in the immune system. The increase in apoptosis with lymphocyte migration and its drainage to the lymphatic system is effective in the lymphopenia mechanism.<sup>16</sup> It was also shown in previous studies that lymphopenia is associated with the stress-related cortisol release and is one of the early results following acute coronary syndrome.<sup>17</sup>

In the recent years, an index that reflects both neutrophils increasing according to the acute state of inflammation and lymphopenia that takes place following acute physiological stress has been used. This index, obtained by the ratio of neutrophils and lymphocytes, has been used in conjunction with other inflammatory markers in studies and has been found to be a good indicator of the inflammatory condition.<sup>18</sup>

It has been shown that the NLR is associated with the progress of atherosclerosis in coronary arteries, and is an independent predictor of unsuccessful reperfusion with CRP following undesired in-hospital conditions and primary percutaneous intervention in acute myocardial infarction.<sup>19</sup>

It has been reported that NLR leads to a 23% increase in the risk of undesirable cardiovascular conditions in the long term in a 4-year follow-up of patients with ST elevation myocardial infarction.<sup>20</sup>

Venous stasis, endothelial damage, genetic and acquired prothrombotic factors and inflammation play a role in the formation, progress, organization or recanalization of thrombus. Among these, the importance of inflammation has especially gained currency in the recent years. In this study, we identified that NLR can predict 30-day mortality independently from acute right ventricular loading and troponin values, which are markers of right ventricular damage.

### **Limitations of Study**

Our main limitations are that our study is not a prospective study, it is single-centred, the effect of the treatment on the process could not be clearly analysed, and the number of patients is limited. Since the study is retrospective, it prevents us from regarding the correlation between NLR and mortality as a cause and effect relationship.

### **CONCLUSION**

NLR has a prognostic significance in complete blood cell count for 30-day mortality in patients diagnosed with APTE. Especially as distinct from the previous series, the fact that the predictive value is significant in the moderate and low risk group patients rather than the high risk group patients in the subgroup analysis adds a different value to our study. In this context, the role of NLR, which is widely used in our daily practice and determined by leukocyte count and leukocyte subgroup analysis, which is a very simple, feasible and cheap test, should be confirmed by prospective, larger, randomized studies.

**Study was approved by the Bezmialem Vakif University non-Interventional research ethics committee with the number 3840 on 06.03.2020.**



## Kaynaklar

1. Yamada N, Nakamura M, Ito M. Current status and trends of right ventricular disjunction of acute pulmonary thromboembolism. *Circ J*. 2011;75(12):2731-8.
2. Konstantinides SV, Barco S, Rosenkranz S, Lankeit M, Held M, Gerhardt F, et al. Late outcomes after acute pulmonary embolism: rationale and design of FOCUS. a prospective observational multicenter cohort study. *J Thromb Thrombolysis*. 2016; 42(4):600-609.
3. Becattini C, Agnelli G, Prandoni P, Silingardi M, Salvi R, Taliani MR et al. A prospective study on cardiovascular events after acute pulmonary embolism. *Eur Heart J*. 2005 Jan;26(1):77-83.
4. Sørensen HT, Horvath-Puho E, Pedersen L, Baron JA, Prandoni P. Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study. *Lancet*. 2007 Nov 24;370(9601):1773-9.
5. Bagot CN, Arya R. Virchow and his triad: a question of attribution. *Br J Haematol*. 2008 Oct;143(2):180-90.
6. Monreal M, Trujillo-Santos J. Lessons from VTE registries: the RIETE experience. *Best Pract Res Clin Haematol*. 2009 Mar;22(1):25-33.
7. Zahorec R. Ratio neutrophil to lymphocyte counts- rapid and simple parameter of systemic inflammation and stres in critically ill. *Bratisl Lek Listy* 2001; 102(1):5-14
8. Adam Torbicki, Chairperson (Poland), Arnaud Perrier (Switzerland), Stavros Konstantinides (Germany), Giancarlo Agnelli (Italy), Nazzeno Galie` (Italy), Piotr Pruszczyk (Poland), et al. Guidelines on the diagnosis and management of acute pulmonary embolism, *European Heart Journal* (2008) 29, 2276-2315
9. Kayrak M, Erdoğan HI, Solak Y, Akilli H, Gül EE, Yildirim O, et al. Prognostic value of neutrophil to lymphocyte ratio in patients with acute pulmonary embolism: a retrospective study. *Heart Lung Circ*. 2014 Jan;23(1):56-62.
10. Farah R, Nseir W, Kagansky D, Khamisy-Farah R, et al. The role of neutrophil-lymphocyte ratio, and mean platelet volume in detecting patients with acute venous thromboembolism. *J Clin Lab Anal*. 2020 Jan;34(1):e23010.
11. Ma Y, Mao Y, He X, Sun Y, Huang S, Qiu J, et al. The values of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in predicting 30 day mortality in patients with acute pulmonary embolism. *BMC Cardiovasc Disord*. 2016 Jun 4;16:123.
12. Soyulu K, Gedikli Ö, Ekşi A, Avcıoğlu Y, Soyulu AI, Yüksel S, et al. Neutrophil to lymphocyte ratio fort he assessment of hospital mortality in patients with acute pulmonary embolism. *Arch Med Sci*. 2016 Feb 1;12(1):95-100.
13. Gotto AM Jr. Role of C-reactive protein in coronary risk reduction: focus on primary prevention. *Am J Cardiol*. 2007 Mar 1;99(5):718-25
14. Furman MI, Becker RC, Yarzebski J, Savegeau J, Gore JM, Goldberg RJ. Effect of elevated leukocyte count on in-hospital mortality following acute myocardial infarction. *Am J Cardiol*. 1996 Oct 15;78(8):945-8.
15. Kirtane AJ, Bui A, Murphy SA, Barron HV, Gibson CM. Association of peripheral neutrophilia with adverse angiographicoutcomes in ST-elevation myocardial infarction. *Am J Cardiol*. 2004 Mar 1;93(5):532-6.
16. Omar M, Tanrıverdi O, Cokmert S, Oktay E, Yersal O, Pilancı KN, et al. Role of increased mean platelet volume (MPV) and decreased MPV/platelet count ratio as poor prognostic factors in lung cancer. *Clin Respir J*. 2018 Mar;12(3):922-929.
17. Thomson SP, Gibbons RJ, Smars PA, V J Suman, R V Pierre, P J Santrach, et al. Incremental value of the leukocyte differentialand the rapid creatine kinase-MB isoenzyme for the early diagnosis of myocardial infarction. *Ann Intern Med*. 1995 Mar 1;122(5):335-41.
18. Gibson PH, Cuthbertson BH, Croal BL, Rae D, El-Shafei H, Gibson G, et al. Usefulness of neutrophil/lymphocyte ratio as predictor of new-onset atrial fibrillation after coronary artery bypass grafting. *Am J Cardiol*. 2010 Jan 15;105(2):186-91.
19. Kalay N, Dogdu O, Koc F, Yarlioglu M, Ardic I, Akpek M, et al. Hematologic parameters and angiographic progression of coronary atherosclerosis. *Angiology*. 2012 Apr;63(3):213-7.
20. Akpek M, Kaya MG, Lam YY, Sahin O, Elcik D, Celik T, et al. 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. *Am J Cardiol*. 2012 Sep 1;110(5):621-7