Ulutas Med J 2017;3(1):13-19
DOI: 10.5455/umj.20170224013949

ORIGINAL ARTICLE OPEN ACCESS

Correlation Between Clot Load Burden with Neutrophil Lymphocyte and Platelet Lymphocyte Ratios in Patients with Acute Pulmonary Embolism

Mehmet Burak Çildağ[1] **Songül Çildağ**[2]

[1] Department of Radiology, Faculty of Medicine, Adnan Menderes University, Aydın, Turkey
[2] Department of Allergy and Clinical Immunology, Adnan Menderes University, Aydın, Turkey

Background: The correlation between neutrophil-lymphocyte ratio (NLR) and acute pulmonary embolism (APE) related mortality, platelet-lymphocyte ratio (PLR) and clinical severity classification of APE were demostrated. Also clot load burden one of the prognostic criteria of pulmonary embolism.

Method: The pulmonary arterial computed tomographic obstruction index ratio (PACTOIR) was calculated in 62 patients diagnosed with APE, retrospectively. Patients were divided into two groups according to their PACTOIR values. NLR and PLR were calculated from the blood samples collected on the day of diagnosis.

Results: Mean PACTOIR, NLR and PLR of all patients with APE were calculated as 23.58%, 4.4 and 186.5, respectively. A positive correlation was observed between PACTOIR and NLR and PLR ($p<0.001$). A statistically significant difference was found between the NLR and PLR levels of low and high PACTOIR groups ($p<0.05$).

Conclusion: A statistically significant correlation was found between PACTOIR and NLR and PLR in patients with APE. According to the findings of our study, NLR and PLR ratios may give an idea about the thrombus load in patients with clinically suspected APE.

Keywords: Acute pulmonary embolism, Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio

Introduction

Symptomatic acute pulmonary embolism (APE) is a major cause of cardiovascular death and morbidity. While there may be clinically asymptomatic subjects, there are also cases resulting in cardiogenic shock and sudden death. The multidetector computed tomography (MDCT) with very thin sections, and low scanning times, has the highest sensitivity and specificity for detecting APE. Computed tomography allows not only detection of the presence of thrombus but also calculation of the pulmonary arterial computed tomographic obstruction index ratio (PACTOIR), which indicates the degree of thrombus in the vascular bed and yields objective results (1).

PACTOIR and right ventricular dysfunction, which is con-sidered to be one of the prognostic criteria of pulmonary embolism, are correlated (1-3).

Corresponding Author: Mehmet Burak Cildag; Radiology Department, Adnan Menderes University, Aydın, Turkey.
E-mail: mbcildag@yahoo.com

Received: Feb 12, 2017 **Accepted**: March 14, 2017
Published: March 28, 2017

Prognostic indicators are also important in APE since they may change the therapeutic approach. Some clinical severity classifications have been made as prognostic indicators in APE (4,5). There are also publications which indicate that biochemical indicators such as troponins, heart-type fatty acid-binding protein, brain natriuretic peptide or N-terminal-proBNP and right ventricular dysfunction may be prognostic factors (6-10). Neutrophil-Lymphocyte Ratio (NLR) is a readily measurable laboratory marker used to evaluate systemic inflammation.Neutrophils are the first elements of inflammation and they play a major role in thrombotic and inflammatory processes (11). There are studies which demonstrate that NLR, and APE-related mortality development are correlated and that Platelet-Lymphocyte Ratio (PLR), another inflammatory marker, and the clinical severity classification of APE are also correlated (12,13).

In this study, we investigated the correlation between PACTOIR, which shows vascular thrombus load and is considered a radiological prognostic indicator in APE,NLR and PLR ratios, which may be laboratory prognostic indicators.

Study Design

This study has been approved by the Local Ethics Committee of Adnan Menderes University School of Medicine. Computed tomography (CT) scans were examined retrospectively for 240 patients who underwent computed tomographic pulmonary angiography at our hospital's Radiology Unit with the suspicion of pulmonary embolism between January 2014 and March 2016. 118 patients were excluded since they had no vascular filling defect which could be APE, 5 patients were excluded due to poor image quality and 22 patients were excluded due to findings consistent with chronic pulmonary embolism. APE was detected in 95 patients by computed tomographic pulmonary angiography. 18 patients were excluded due to malignancy, 10 patients were excluded due to infectious diseases and 5 patients were excluded due to chronic liver disease. As a result, the study was completed with 62 patients who were diagnosed with APE based on computed tomographic pulmonary angiography and started to receive treatment.

Pulmonary CT angiography was performed with a 64-detector MDCT device (Prime Aquilion, Toshiba Medical Systems, Otawara, Japan). Imaging parameters for pulmonary CT angiography were set as 100 kV, 300 mA, 400 ms rotation time, 0.5mm slice thickness, 0.4mm increments, and 64x0.5 mm detector collimation (pitch:0.64). In all patients, APE was diagnosed upon the detection of partial or total intraluminal filling defect in the main pulmonary artery and lobar and segmental bronchi.

Computed tomography slice images in the archive system were evaluated by a radiologist with 14 years of experience. In subjects with detected pulmonary embolism, obstruction rate was calculated separately for each patient based on computed tomographic pulmonary angiography.

PACTOIR calculating method; Pulmonary arteries are subdivided into ten segmental arteries in each lung (three to the upper lobe, two to the middle lobe and lingula, five to the lower lobe). The presence of an embolus in a segmental artery is scored as 1 point, and more proximal emboli are scored a value equal to the number of segmental branches arising from the affected vessel. Each score is multiplied by 1 or 2 according to the estimated degree of vascular occlusion (1=partial occlusion; 2=complete occlusion). A subsegmental embolus is considered an embolus in the corresponding segmental artery, with partial occlusion (scoring 1×1=1). Maximum PACTOIR score is 40. The percentage value is

then calculated as: (n×d)/40×100 [n=score of embolus multiplied by the number of dependent segments; d=degree of obstruction].

Neutrophil, platelet, lymphocyte, white blood cell (WBC) and D-dimer values were obtained from the hospital's archive system, from laboratory tests made on the same day as the patients' computed tomography scans. At our hospital, peripheral blood samples are collected in calcium-EDTA tubes and blood counts are calculated by auto-analyzer. PLR and NLR were calculated from complete blood counts.

Patients included in the study were divided into 2 groups, low PACTOIR group and high PACTOIR group, according to their median PACTOIR values. Neutrophil, platelet, lymphocyte, WBC, NLR, PLR and D-dimer values were compared between the two groups.

Information about the patients' clinical progression was obtained using the hospital's archive system.

Statistical analysis

All statistical analyses were performed using SPSS software, version 18.0 (SPSS Inc. Chicago, IL). Kolmogorov-Smirnov test was used to determine the normality of the distribution of data.For data that was not normally distributed such as patients' PACTOIR value, median and range values were indicated. Kendall's taub correlation coefficients were used for analysis of intercorrelations among the investigated parameters. Mann-Whitney U test was used to compare nonparametric continuous variables in independent groups that were established according to median of PACTOIR. Descriptive data was given as frequencies, percentages, means and standard deviation. P values <0.05 were considered statistically significant.

Results

A total of 62 patients comprising 25 males and 37 females were included in the study, with a mean age of 62.84±17.75. Patients' median PACTOIR, NLR and PLR values were 23.58% (5-60) ,4.4 (1.3-29.5), 186.5 (45.8-768), respectively (Table-1).

Table-1. Laboratory and demographic findings of patients

Gender Male, n (%)	25 (40.3%)
Age[1] (years)	62.84±17.75
PACTOIR[2] (%)	23.5 (5-60)
WBC count[1] (10^3/μL)	10.97±4.56
Neutrophil count[1] (10^3/μL)	8.06±4.46
Lymphocyte count[1] (10^3/μL)	1.56±0.74
Platelet count[1] (10^3/μL)	283±115
NLR[2]	4.4 (1.3-29.5)
PLR[2]	186.5 (45.8-768)
D-dimer[2] (ng/mL)	3425 (318-7477)

PACTOIR: Pulmonary artery computed tomography obstruction index ratio, WBC: White blood cell, NLR: Neutrophil–lymphocyte ratio, PLR: Platelet-lymphocyte ratio, [1] Mean± standard deviation, [2] Median (min-max), n:number of patients.

Based on Kendall's tau-b correlation test, a positive correlation was found between PACTOIR and NLR, PLR, neutrophil and WBC count ($p<0.001$); and a negative correlation was found between PACTOIR and lymphocyte count ($p=0.05$) (Table-2).

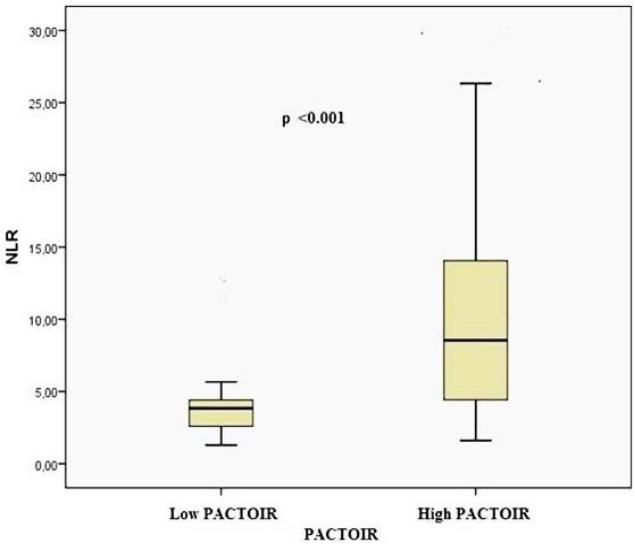
Table-2. Correlation coefficient between PACTOIR and complete blood count

Tests	PACTOIR	
	r	p
NLR	0.373*	p<0.001
PLR	0.344*	p<0.001
Neutrophil	0.381*	p<0.001
Lymphocyte	-0.176*	p=0.05
WBC	0.329*	p<0.001
Platelet	0.117*	p=0.19

*=Correlation Coefficient (r), PACTOIR: Pulmonary artery computed tomography obstruction index ratio, WBC: White blood cell, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio.

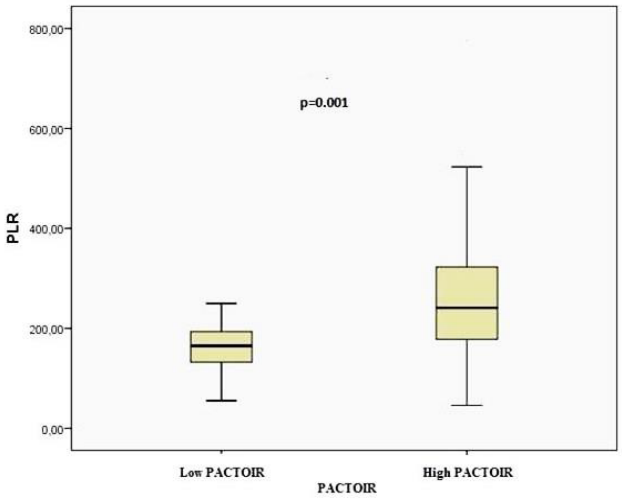
The low PACTOIR group (PACTOIR ≤23.5) and high PACTOIR group (PACTOIR >23.5) identified according to median PACTOIR levels were compared for complete blood parameters by Mann-Whitney U test, a statistically sig-

nificant difference was found between the two groups in WBC, neutrophil, NLR, PLR and D-Dimer levels (p<0.05)(Table-3).



Graph-1. Graph showing a significant difference for NLR between patients with low and high PACTOIR.

Of the patients included in the study, 5 died of acute pulmonary embolism within 1 month following diagnosis. These patients' median PACTOIR, NLR and PLR values were 38% (25-45), 14.57 (3.11-26.32), 394.2 (104-768), respectively. Statistical analysis wasn't performed because of small number of died patients. However, all patients who died were in the high PACTOIR group.



Graph-2. Graph showing a significant difference for PLR between patients with low and high PACTOIR

Discussion

APE is the third disease of vascular origin that causes the most deaths after coronary artery disease and stroke (14,15). Following the development of multi-dedector CT systems, CT pulmonary angiography (CTPA) became the preferred imaging system in the diagnosis of APE. The most important features of CTPA include its ability to show embolism with a fast and non-invasive technique and to offer alternative diagnoses (16). Improvement of multi-dedector CT devices allowed high spatial and temporal resolution. Moreover, with increased arterial opacification quality, both sensitivity

Table-3. Complete blood count parameter in the high and low PACTOIR groups

Parameter	PACTOIR ≤23.5 (n=31)	PACTOIR >23.5 (n=31)	p value
WBC count (10^3/μL)	8.99±2.97	12.95±5.04	**0.001**
Neutrophil (10^3/μL)	6.07±2.6	10.54±4.84	**<0.001**
Lymphocyte (10^3/μL)	1.66±0.63	1.45±0.84	0.15
Platelet (10^3/μL)	260±89	306±134	0.20
NLR	4.1±2.59	9.81±6.96	**<0.001**
PLR	171±86	271±157	**0.001**
D-dimer (ng/mL)	2697±1441	3614±1420	**0.04**

PACTOIR:: Pulmonary artery computed tomography obstruction index ratio, WBC: White blood cell, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, n: number of patients. Statistically significant values are indicated in bold.

and specificity values of CTPA increased, making it the first-line imaging method (17-20). CTPA allows not only detection of presence of thrombus but also calculation of the pulmonary arterial computed tomographic obstruction index ratio (PACTOIR), which indicates the degree of thrombus and yields objective results (1). Severity of thrombosis is determined by using PACTOIR, calculated with the degree of occlusion in the artery and the number of segmental arteries distal to thrombosis. Identification of PACTOIR allows objective evaluation in subjects with APE.

Determining this index also gives an idea about prognosis in patients with APE and may help to shape the treatment plan. In a study investigating clinical course in patients with APE whose PACTOIR values were calculated, it was noted that 83% of patients with a PACTOIR of more than 60% died while 98% of patients with a PACTOIR of less than 60% recovered with treatment (2). In our study, the highest PACTOIR level was 60%. 5/62 patients included in study died of APE. Average PACTOIR value was 38% (25-45) for the patients who died versus 25.5% for all patients in the study.

Aggressive treatments such as endarterectomy and thrombolytic therapy are recommended in hemodynamically unstable subjects with APE. However, the treatment to be administered for hemodynamically stable subjects with right ventricular dysfunction has not been clearly identified. Therefore, clinical and laboratory predictive factors can be used for such cases. Risk classifications have been made for the early mortality risk in APE (4,5). Similarly, some biochemical indicators (troponins, heart-type fatty acid-binding protein, BNP or N-terminal-proBNP), right ventricular dysfunction determined by echocardiography and right ventricular extension determined by computed tomography are significant for mortality risk (6-10). There are studies that show that myeloperoxidase enzymes and reactive oxygen species (ROS) were elevated in subjects with APE and that the IL-6 level and mortality are correlated in APE (21,22). These findings support that endothelial damage and inflammation play a role in APE. Afzal et al. (23) reported that WBC count was increased in APE. It was noted that WBC count was more a prognostic indicator than a diagnostic tool (24). In recent years, it has been claimed that NLR is a better indicator than WBC in indicating inflammation.

Neutrophils are the first elements of inflammation and they play a major role in thrombotic and inflammatory processes. It has been suggested that increased NLR in inflammation might be related to the increased level of steroids in relation to stress and increased apoptosis (11). Kayrak et al. (12) noted that NLR might have prognostic value in APE. Platelet activation and chemokine secretion also plays an important role in APE. There are studies which provide information as to PLR and aggregation and inflammatory process in thromboembolic events (13, 25). Kundi et al. (13) demonstrated that PLR and a simplified version of pulmonary embolism severity index (sPESI) and mortality were correlated in APE.

In this study, we found that PACTOIR values, which indicate the vascular thrombus load and are considered a potential radiological prognostic indicator in APE, are positively correlated with NLR, PLR, neutrophil and WBC counts which may be laboratory prognostic indicators and negatively correlated with lymphocyte counts. Comparison of low PACTOIR and high PACTOIR groups revealed a statistically significant difference between NLR, PLR, Neutrophil and WBC counts. Kayrak et al. (12) identified an NLR value of 9.2 as cut-off value for death and reported the hazard ratio for this value to be 3.6. In a similar study, it was reported that

the mortality rate increased 10.8 times when the NLR cut-off value for death was taken as 5.7 (26). In our study, average NLR was found to be 9.81±6.96 in the high PACTOIR group with a high thrombus load versus 4.1±2.59 in the low PACTOIR group. A significant difference was found between the NLR values of both groups. In the study on PLR levels, Kundi et al. (13) reported that a cut-off value of 149 for PLR was significant for high sPESI scores and that mortality rates were statistically higher beyond this value. In our study, average PLR was found to be 271±157 in the high PACTOIR group versus 171±86 in low PACTOIR group. These results suggest that NLR and PLR values are correlated with PACTOIR, which indicates the thrombus load in the vascular bed.

Limitations of our study include the fact that it is retrospective; the number of patients is small; there are no patients with a PACTOIR value of more than 60%;, information is not available on other inflammatory markers such as C reactive protein (CRP), fibrinogen and myeloperoxidase; and there are no follow-up NLR and PLR values.

In conclusion, NLR and PLR ratios may give an idea about the thrombus load in patients with clinically suspected APE. Also, outcome of patients with APE could estimated according to these parameters.

Acknowledgement

This study was not funded any sources. Both authors declare that there was no conflict of interest.

Reference

1. Qanadli SD, El Hajjam M, Vieillard-Baron A, Joseph T, Mesurolle B, Oliva VL, et al. New CT index to quantify arterial obstruction in pulmonary embolism: comparison with angioraphic index and echocardiography. AJR Am J Roentgenol 2001;176:1415-1420.
2. Wu AS, Pezzulo JA, Cronan JJ, Hou DD, Mayo-Smithet WW. CT Pulmonary Anjiography: Quantification of Pulmonary Embolus as a Predictor of Patient Outcome-Initial Experience. Radiology 2004; 230:831-835.
3. P Apfaltrer, T Henzler, M. Meyer, Roeger S, Haghi D, Gruettner J,et al. Correlation of CT angiographic pulmonary artery obstruction scores with right ventricular dysfunction and clinical outcome in patients with acute pulmonary embolism.European Journal of Radiology 2012;81:2867-71.
4. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005;172:1041–6.
5. Jiménez D, Aujesky D, Moores L, Gómez V, Lobo JL, Uresandi F, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010;170:1383–9.
6. Agterof MJ, Schutgens RE, Snijder RJ, Epping G, Peltenburg HG, Posthuma EF, et al. Out of hospital treatment of acute pulmonary embolism in patients with a low NT-proBNP level. J Thromb Haemost 2010;8:1235–41.
7. Hellenkamp K, Kaeberich A, Schwung J, Konstantinides S, Lankeit M. Risk stratification of normotensive pulmonary embolism based on the sPESI: does it work for all patients? Int J Cardiol 2015;197:162–3.
8. Lankeit M, Jiménez D, Kostrubiec M, Dellas C, Kuhnert K, Hasenfuß G, et al. Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism. Eur Respir J 2014;43:1669–77.
9. Jiménez D, Kopecna D, Tapson V, Briese B, Schreiber D, Lobo JL, et al, for the PROTECT Investigators. Derivation and validation of multimarker prognostication for normo tensive patients with acute symptomatic pulmonary embolism. Am J Respir Crit Care Med 2014;189:718–26.
10. Konstantinides SV, Barco S, Lankeit M, Meyer G. Management of Pulmonary Embolism: An Update. JACC 2016; 67: 976-90.
11. Hotchkiss RS, Karl IE: The pathophysiology and treatment of sepsis. N Engl J Med. 2003; 348:138–150.
12. Kayrak M, Erdoğan Hİ, Solak Y, Akilli H, Gül EE, Yildirim O, et al. Prognostic value of Neutrophil to lymphocyte Ratio in Patients with Acute Pulmonary Embolism: ARetrospective Study. Heart, Lung and Circulation 2014;23:56-62.
13. Kundi H, Balun A,Cicekcioglu H, Cetin M, Kiziltunc E, Cetin ZG, et al. The relation between platelet-to-lymphocyte ratio and Pulmonary Embolism Severity Index in acute pulmonary embolism. Heart & Lung 2015;44 340-343.
14. Giuntini C, Di Ricco G, Marini C, Melillo E, Palla A. Pulmonary embolism: epidemiology. Chest 1995;107:3s-9s.
15. Wittram C, Maher MM, Yoo AJ, Kalra MK, Shepard JA, McLoud TC. CT angiography of pulmonary embolism: diagnostic criteria and causes of misdiagnosis. Radiographics 2004;24:1219-38.
16. Remy-Jardin M, Pistolesi M, Goodman LR, Gefter WB, Gottschalk A, Mayo JR, et al. Management of suspected acute pulmonary embolism in the era of CT angiography: a statement from the Fleischner Society. Radiology 2007;245: 315-29.

17. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35:3033-69.
18. Tresoldi S, Kim YH, Baker SP, Kandarpa K. MDCT of 220 consecutive patients with suspected acute pulmonary embolism: incidence of pulmonary embolism and of other acute or non-acute thoracic findings. Radiol Med 2008;113: 373-84.
19. Ritchie G, McGurk S, McCreath C, Graham C, Murchison JT. Prospective evaluation of unsuspected pulmonary embolism on contrast enhanced multidetector CT (MDCT) scanning. Thorax 2007;62:536-40.
20. Stein PD, Fowler SE, Goodman LR, Gottschalk A, Hales CA, Hull RD, et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med 2006;354:2317-27.
21. Mühl D, Füredi R, Cristofari J, Ghosh S, Bogár L, Borsiczki B, et al. Evaluation of oxidative stress in the thrombolysis of pulmonary embolism.J Thromb Thrombolysis. 2006;22:221-228.
22. Marchena YP, Nieto RJ, Serrano MS, Belinchón Moya O, Cortés Carmona A, Díaz de Tuesta A, et al. Acute-phase reactants and markers of inflammation in venous thrombo embolic disease: correlation with clinical and evolution parameters. An Med Interna. 2006;23:105-110.
23. Afzal A, Noor HA, Gill SA, Brawner C, Stein PD. Leukocytosis in acute pulmonary embolism. Chest 1999;155: 1329-32.
24. Huang CM, Lin YC, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Risk stratification and clinical outcomes in patients with acute pulmonary embolism. Clin Biochem 2011;44:1110-5.
25. Yüksel M, Yıldız A, Oylumlu M, Akyüz A, Aydın M, Kaya H, et al. The association between platelet/lymphocyte ratio and coronary artery disease severity. Anatol J Cardiol 2015; 15:640-7.
26. Soylu K, Gedikli Ö, Ekşi A, Avcıoğlu Y, Soylu Aİ, Yüksel S, et al. Neutrophil-to-lymphocyte ratio for the assesment of hospital mortality in patients with acute pulmonary embolism. Arch Med Sci 2016;12(1):95-100.

How to cite?

Cildag MB, Cildag S. Correlation Between Clot Load Burden with Neutrophil Lymphocyte and Platelet Lymphocyte Ratios in Patients with Acute Pulmonary Embolism. Ulutas Med J. 2017; 3(1):13-19

Doi: 10.5455/umj.20170224013949