Journal of Izmir Chest Hospital 2023;37(1):16–21
DOI: 10.14744/IGH.2023.44227

RESEARCH ARTICLE / ÖZGÜN ARAŞTIRMA

The Relationship between Platelet Indices and Radiological Involvement in Pulmonary Thromboembolism

Pulmoner Tromboembolide Platelet İndeksleri ile Radyolojik Tutulum Arasındaki İlişki

[1]Kadir Burak AKGÜN
[2]İnan KORKMAZ
[3]Mehmet KARADAĞ

[1]Department of Pulmonary Diseases, Hatay Mustafa Kemal University Faculty of Medicine, Hatay, Türkiye

[2]Department of Radiology, Hatay Mustafa Kemal University Faculty of Medicine, Hatay, Türkiye

[3]Department of Biostatistics and Medical Informatics, Hatay Mustafa Kemal University Faculty of Medicine, Hatay, Türkiye

ORCID ID
KBA : 0000-0002-3017-1025
İK : 0000-0001-6820-8199
MK : 0000-0001-9539-4193

ABSTRACT

Objective: Pulmonary thromboembolism (PTE) is a disease characterized by occlusion of the pulmonary artery and its branches by thrombus material as a result of stasis, hypercoagulability, and/or endothelial damage. Recent studies have focused on platelet (PLT) parameters, mortality of the disease, and its use as a diagnostic parameter. In particular, a significant relationship was found between high mean PLT volume (MPV) values and mortality and disease risk in the meta-analyses. The aim of our study is to examine the relationship between PLT parameters and the severity of radiological involvement.

Material and Methods: The files of patients who were followed up with the diagnosis of pulmonary thromboembolism between 2012 and 2021 were reviewed retrospectively. The patients were radiologically divided into 3 groups: (1) those with major branch involvement, (2) those with segmental branch involvement without major branch involvement, and (3) those with only subsegmental branch involvement. In addition, patients were examined in two separate groups according to whether there was more than 50% of involvement in the main branch radiologically and whether the right ventricle/left ventricle ratio was above 0.9 or not, radiologically. PLT, neutrophil, lymphocyte, platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio, MPV, plateletcrit (PCT), platelet distribution width (PDW), and PLT large cell ratio data in complete blood count measurements taken from patients at the time of diagnosis were also recorded.

Results: There was a significant correlation between rising in PLR and occlusion in the major branch more than 50% (p=0.041). PLT, PDW, PCT, and neutrophil values differed radiologically according to the involvement of major, segment, and subsegment; however, subgroup analyses did not provide the linear difference that we expected in our study.

Cite this article as: Akgün KB, Korkmaz İ, Karadağ M. The Relationship between Platelet İndices and Radiological İnvolvement in Pulmonary Thromboembolism. Journal of Izmir Chest Hospital 2023;37(1):16–21.

Received (Geliş): November 18, 2022 **Revised (Revize):** March 01, 2023 **Accepted (Kabul):** March 10, 2023 **Online (Çevrimiçi):** April 18, 2023
Correspondence author (Sorumlu yazar): Kadir Burak AKGÜN, MD. Hatay Mustafa Kemal Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Hatay, Türkiye.
Tel: +90 544 812 78 28 **e-mail:** kadirburakakgun@gmail.com

Conclusion: An increase in the PLR appears to be associated with radiological weight in pulmonary thromboembolism. We think that the relationship between PLT indices and radiological involvement should be supported by multicenter studies.

Keywords: Hemogram, pulmonary artery, pulmonary thromboembolism.

ÖZ

Amaç: Pulmoner tromboemboli (PTE), staz, hiperkoagülasyon ve/veya endotel hasarı sonucu pulmoner arter ve dallarının trombüs materyaliyle tıkanması ile karakterize bir hastalıktır. Son yıllarda yapılan çalışmalar platelet parametrelerinin, hastalığın mortalitesi ve tanısal bir parametresi olarak kullanımına odaklandı. Özellikle meta-analizlerde yükselmiş ortalama trombosit hacmi (MPV) değerleri ile ölüm ve hastalık riski arasında anlamlı bir ilişki bulundu. Çalışmamızın amacı, trombosit parametreleri ile radyolojik tutulumun şiddeti arasındaki ilişkiyi incelemektir.

Gereç ve Yöntemler: 2012-2021 yılları arasında PTE tanısı ile izlenen hastaların dosyaları retrospektif olarak incelendi. Hastalar radyolojik olarak üç gruba ayrıldı: majör dal tutulumu olanlar, majör dal tutulumu olmayan segmental dal tutulumu olanlar ve sadece subsegmental dal tutulumu olanlar. Ayrıca hastalar radyolojik olarak ana dalda %50'den fazla tutulum olup olmadığına ve radyolojik olarak sağ ventrikül/sol ventrikül oranının 0,9'un üzerinde olup olmadığına göre iki grupta incelendi. Tanı anında hastalardan alınan tam kanda trombosit (PLT), nötrofil, lenfosit, trombosit/lenfosit oranı (PLR), nötrofil/lenfosit oranı (NLR), MPV, prokalsitonin (PCT), trombosit dağılım genişliği (PDW), trombosit büyük hücre oranı (PLCR) verileri de kaydedildi.

Bulgular: PLR'de yükselme ile ana dalda %50'den fazla oklüzyon arasında anlamlı bir korelasyon vardı (p=0,041). Trombosit, PDW, PCT ve nötrofil değerleri majör, segment ve subsegment tutulumuna göre radyolojik olarak farklılık gösterdi; ancak alt grup analizleri çalışmamızda beklediğimiz lineer farkı sağlamadı.

Sonuç: PTE'de PLR'deki artışın radyolojik ağırlık ile ilişkili olduğu görülmektedir. Trombosit indeksleri ile radyolojik tutulum arasındaki ilişkinin çok merkezli çalışmalarla desteklenmesi gerektiğini düşünüyoruz.

Anahtar kelimeler: Hemogram, pulmoner arter, pulmoner tromboemboli.

INTRODUCTION

Pulmonary thromboembolism is a disease characterized by occlusion of the pulmonary artery and its branches by thrombus material. The disease occurs when the thrombus formed in the veins of the upper extremity at a rate of 70% joins the systemic circulation and reaches the pulmonary arteries through the heart. Virchow triad (endothelial damage, hypercoagulability, and stasis) has been suggested in the physiopathology of the disease. Risk factors for the formation of the disease are previous history of venous thromboembolism, immobilization, active cancer disease, trauma, surgery, obesity, heart diseases, and recently COVID-19 disease. D-dimer test has high specificity but low sensitivity for disease diagnosis.[1] Although pulmonary thromboembolism can be diagnosed radiologically, the search for diagnostic parameters continues because sometimes the patient is clinically unavailable and sometimes the technical possibilities are insufficient. In addition, studies on mortality biomarkers are increasing, but they are not used routinely because sufficient clinical data are not available yet. Our study is to examine some platelet (PLT) indices, which have been shown to be associated with mortality in recent years, together with clinical and radiological data and to question their use in our routine practice.

MATERIAL AND METHODS

For the study, the permission of Hatay Mustafa Kemal University Ethics Committee with the decision number 19 was obtained. The study was created by retrospectively scanning the files of 154 patients who applied to Hatay Mustafa Kemal University Medical Faculty Hospital between January 1, 2012, and December 31, 2021, and were followed up with pulmonary embolism (PE). I.26, I26.0, and I26.9 ICD codes are used in data scanning. Age, gender, comorbidities, previous medications, bleeding, and mortality events during the follow-up were recorded from the patient files. Those who used anticoagulants or antiaggregants before, those who received chemotherapy or radiotherapy, and those who had hematological disease were excluded from the study due to the possibility of affecting PLT indices. Computed tomography (CT) scans were performed in the supine position using either the Hitachi Eclos 16 (5 mm slice thickness, 120 kV, 75 mAs) or the 64-slice Toshiba Aquilion (5 mm slice thickness, 120 kV, 25 mAs) units. The simultaneous thorax CT and hemogram data of the patients taken at the time of diagnosis were analyzed by one pulmonologist an one radiologist. Those with hemoglobin values below 10 g/dL were also excluded from the study due to the suspicion of undiagnosed hematological disease. PLT, neutrophil, lymphocyte, platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio (NLR), mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), and platelet large cell ratio (PLCR) data of the patients was recorded. On CT examination, patients were divided into three groups according to (1) major branch involvement, (2) segmental branch involvement without major branch, and (3) subsegmental branch involvement only. In addition, among those with major branch involvement, two separate subgroups were formed: (1) About 50% or more of the major branch diameter involvement and (2) <50% or none of the major branch diameter involvement. All patients were analyzed separately according to whether the right ventricle/left ventricle ratio was above or below 0.9 on CT.

Table 1: Involvement diameter and platelet indices

	Involvement diameter		
	Minimal	Excessive	
	M (Q1-Q3)	M (Q1-Q3)	p
Age (years)	66 (52–72)	72.5 (65–75)	0.374
PLT ($10^3/\mu$L)	223 (175–305)	296.5 (171–302)	0.141
MPV (fL)	9.8 (9.1–10.7)	10.35 (9.8–10.8)	0.406
PDW (ratio)	15.55 (10–16.1)	16.55 (14.8–16.9)	0.187
PCT (%)	0.23 (0.18–0.3)	0.31 (0.17–0.33)	0.183
PLCR (%)	25.85 (20.4–31)	29.7 (24.7–32.7)	0.185
Lymphocyte (μL)	1830 (1110–2420)	3525 (1950–5040)	0.372
Neutrophil (μL)	8230 (5170–10309)	7235 (7090–8850)	0.246
PLR	121.43 (85.94–191.93)	74.61 (59.92–144.77)	**0.041**
NLR	4.39 (1.84–7.81)	2.05 (1.4–6.25)	0.327

P value was obtained from Mann-Whitney U or Student t-Test. M: Median, Q1: Quartile 1 (P25), Q3: Quartile 1 (P75), PLT: Platelet, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit, PLCR: Platelet large cell ratio, PLR: Platelet/lymphocyte ratio, NLR: Neutrophil/lymphocyte ratio

Statistical Analysis

The normal distribution of the data was analyzed using the Shapiro–Wilk test. Mean differences between two groups with normally distributed will be compared by Student's t-test, whereas the Mann–Whitney U-test was will be applied for comparisons of the not normally distributed data. The Kruskal–Wallis test was used for three independent groups for non-normally distributed parameters. Dunn test was used in pairwise comparison analysis after the Kruskal–Wallis test. Descriptive statistics median, quartile 1 (percentile 25), and quartile 3 (percentile 75) values of the parameters were given. The margin of error was $p<0.05$. Statistical analysis of the data was done with the SPSS for Windows version 23 software package.

RESULTS

The mean age of the patients included in the study was 70.5. There were 10 (35.7%) male and 18 (64.3%) female patients. Bleeding event was seen in 5 (17.8%) and in-hospital mortality in 4 (14.3%) patients. Only one patient (3%) developed bleeding that led to mortality. Thrombus was detected in the major branches in 13 (46.4%) of the patients, only subsegmental involvement was observed in 3 (10.7%) of the patients, and the remaining 12 (42.9%) were those with segmental involvement without major branch involvement. Among those with major occlusion, there were 6 (21.4%) patients with more than 50% obstruction and 7 (25%) patients with <50% obstruction. While right ventricular enlargement was observed in 15 (53.6%) patients, it was not detected in the remaining 13 (46.4%) patients.

The relationship between involvement diameter and PLT indices was examined in Table 1. Two groups were formed as those with <50% or no occlusion, "minimal" and those whose thrombus diameter occludes more than 50% in the major branch are "excessive." Involvement diameter minimal individuals' PLR values 121.43 (85.94–191.93) were significantly higher than the excessive group 74.61 (59.92–144.77) ($p=0.041$).

When grouping according to the places of involvement, three groups were formed; these are the major branch group, in which the right and left main pulmonary branches are occluded, the segmental branches group in which the main branches are not occluded but segmental branches are involved; group of subsegmental branches in which only more distal branches are occluded. As shown in Table 2, PLT, PDW, PCT, and neutrophil levels were statistically significantly different between the groups (respectively $p=0.008$, $p=0.048$, $p=0.043$, $p=0.035$). In major branch and only subsegmental branch groups, the PLT and the PWD values were significantly lower than the segmental branch group. However, in the segmental branch group, the PCT values 0.4 (0.27–0.43) was significantly lower than major branch 0.23 (0.16–0.3) and only subsegmental branch 0.22 (0.19–0.3) groups. In the segmental branch group, the neutrophil values were significantly lower than only subsegmental branch groups.

However, there was no expected relationship between the results when subgroup analyses were performed. While designing the study, we planned those with major involvement were the most clinically severe group; those with only subsegmental involvement are the mildest group; and the ones with segment involvement as an intermediate group. In subgroup analysis, although PLT and PCT were highest in the segment group and PDW was the lowest, there was no statistically significant difference in the major and only subsegment groups. In addition, neutrophil count was highest in the segment group and lowest in the only subsegment group. These conflicting results were associated with sample size (especially only subsegment group).

The relationship between bleeding and PLT indices is shown in Table 3. There was no statistical relationship between PLT indices and bleeding events. It was observed that the PLT indexes value of the patients with and without bleeding was similar.

Table 2: Place of involvement and platelet indices

	Place of involvement			
	Major branch	Segmental branch	Only subsegmental branch	
	M (Q1-Q3)	M (Q1-Q3)	M (Q1-Q3)	p
Age(years)	70 (56–73)	52 (26–55)	71 (59–79.5)	0.106
PLT ($10^3/\mu$L)	214[a] (163–295)	431[b] (288–451)	223[a] (183.5–311.5)	**0.008**
MPV (fL)	10.1 (9.8–10.8)	9.2 (8.9–9.9)	9.8 (9.2–10.6)	0.347
PDW (ratio)	16[b] (13.1–16.6)	9.6[a] (9.1–10.6)	15.95[b] (12.75–16.25)	**0.048**
PCT (%)	0.23[a] (0.16–0.3)	0.4[b] (0.27–0.43)	0.22[a] (0.19–0.3)	**0.043**
PLCR (%)	28.4 (26.7–32.7)	19.1 (15.8–23.5)	23.65 (20.7–31.65)	0.054
Lymphocyte (μL)	2010 (1620–2550)	2260 (1930–2890)	1360 (960–2300)	0.292
Neutrophil (μL)	7380[ab] (5500–7890)	4380[a] (3370–10210)	9540[b] (8010–12940)	**0.035**
PLR	85.94 (70.1–115.43)	156.05 (127.43–223.31)	134.92 (96.71–204.05)	0.108
NLR	3.58 (1.72–6.25)	1.51 (1.49–5.29)	5.76 (4.13–9.18)	0.110

P value was obtained from one way ANOVA or Kruskall-Wallis Test. [a,b]: bWithin each row, different letters in superscript indicate significantly different (according to *post hoc* test) (p<0.05). M: Median, Q1: Quartile 1 (P25), Q3: Quartile 1 (P75), PLT: Platelet, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit, PLCR: Platelet large cell ratio, PLR: Platelet/lymphocyte ratio, NLR: Neutrophil/lymphocyte ratio.

In-hospital mortality was directly proportional to age (p=0.029) which showed in Table 4. Mortality increased as MPV, PDW, and PLCR values increased (respectively, p=0.020, p=0.024, and p=0.006).

DISCUSSION

Since hypercoagulability is involved in the pathophysiology of pulmonary thromboembolism, PLT parameters that can be measured in complete blood count have been the focus of attention in recent years. Many studies have examined whether PLT indices can be used as a diagnostic biomarker in PE. In addition, data revealing their relationship with mortality in PE have been presented. The weakness of the studies is that conditions that may impair PLT function are not excluded from the studies. In addition, the fact that the mortality shown in the studies was not associated with common mortal conditions in PE, such as bleeding or cardiogenic shock, prevented the cause-effect relationship from being revealed.

Febra and Macedo found a higher MPV value in patients with acute pulmonary thromboembolism than in the control group

Table 3: Bleeding and platelet indices

	Bleeding		
	Yes	No	
	M (Q1-Q3)	M (Q1-Q3)	p
Age(years)	85 (55–86)	70 (52–72)	0.239
PLT ($10^3/\mu$L)	288 (175–305)	232 (171–302)	0.964
MPV (fL)	10.8 (9.8–11.5)	9.8 (9.1–10.7)	0.135
PDW (ratio)	14.8 (11–15.3)	16 (10.2–16.5)	0.413
PCT (%)	0.27 (0.19–0.36)	0.23 (0.17–0.3)	0.535
PLCR (%)	34.1 (23.1–37.7)	26.7 (21–31)	0.173
Lymphocyte (μL)	2260 (1950–5120)	1860 (1070–2490)	0.154
Neutrophil (μL)	8570 (4640–8850)	7450 (5500–10600)	0.413
PLR	87.69 (61.52–127.43)	115.43 (81.11–191.93)	0.193
NLR	1.72 (1.59–2.37)	4.43 (1.84–7.81)	0.154

P value was obtained from Mann–Whitney U or Student t-test, M: Median, Q1: Quartile 1 (P25), Q3: Quartile 1 (P75), PLT: Platelet, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit, PLCR: Platelet large cell ratio, PLR: Platelet/lymphocyte ratio, NLR: Neutrophil/lymphocyte ratio.

Table 4: In-hospital mortality and platelet indices

	In-hospital mortality		
	Yes	No	
	M (Q1-Q3)	M (Q1-Q3)	p
Age (years)	73.5 (72.5–80)	63.5 (51.5–72)	**0.029**
PLT ($10^3/\mu$L)	302 (236.5–308.5)	223 (173–300)	0.427
MPV (fL)	11.1 (10.8–11.45)	9.8 (9.15–10.25)	**0.020**
PDW (ratio)	16.9 (15.85–16.95)	15.55 (10.1–16.15)	**0.024**
PCT (%)	0.33 (0.26–0.34)	0.23 (0.17–0.3)	0.188
PLCR (%)	34.3 (32.7–36.8)	24.55 (20.7–28.8)	**0.006**
Lymphocyte (μL)	5040 (2985–5080)	1895 (1175.5–2340)	0.209
Neutrophil (μL)	7970 (7090–8955)	7670 (4945–10454.5)	0.769
PLR	60.72 (59.92–122.7)	121.43 (86.82–173.99)	0.126
NLR	1.56 (1.4–5.73)	4.39 (2.11–6.63)	0.186

P value was obtained from Mann–Whitney U or Student t-test. M: Median, Q1: Quartile 1 (P25), Q3: Quartile 1 (P75), PLT: Platelet; MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit, PLCR: Platelet large cell ratio, PLR: Platelet/lymphocyte ratio, NLR: Neutrophil/lymphocyte ratio.

(p<0.00001) in a meta-analysis of 13 studies including 1316 patients and 1112 control groups. This meta-analysis did not provide information on mortality and bleeding events.[2]

In a meta-analysis of 18 studies including 2674 patients and 1192 control groups, Lin et al.[3] found an increase in MPV consistent with the diagnosis of PE (p<0.001) and also found a relationship between the increase in MPV and the mortality of pulmonary thromboembolism patients (p<0.001). This meta-analysis highlighted the heterogeneity between groups and the causes of mortality were not studied.

In a study by Varol et al.[4] in which they examined 107 PE patients and 70 control groups, they found MPV and leukocyte values to be higher and PLT values to be lower in PE patients (respectively; p<0.001; p<0.001; and p<0.001). In addition, PE patients were divided into three groups as high risk, medium risk, and low risk according to blood pressure, echocardiography, and troponin values; they could only show a relationship between right ventricular enlargement and MPV elevation (p<0.001).

In a study by Günay et al.,[5] in which they examined 63 PE patients and 50 control groups; they found higher MPV and PDW values and lower PLT values in the PE group. When they separate the PE group as massive and submassive, the MPV value is higher in the massive group (p=0.001). In this study, we noticed that a third group was not formed as non-massive PE.

We were able to find only one study investigating the relationship between PCT and PE in our PubMed search. Moharamzadeh et al.[6] in a study of 173 suspected PE patients detected PE in 125 of them and took the rest as a control group. The PCT value did not differ statistically in the PE group (p>0.05), and the difference in MPV and PDW values was statistically insignificant (respectively, p>0.05 and p>0.05), inconsistent with the meta-analysis results.

We could not find a study investigating the relationship between PLCR and PE.

In this study, we investigated the relationship of PLT indices with not only mortality but also other clinical conditions in PE disease and analyzed the statistical data. In-hospital mortality was directly proportional to age, MPV, PDW, and PLCR. As the PLR value increased, the ratio of thrombus diameter to vessel diameter increased, but this could not be associated with mortality or severity of radiological involvement. Although we retrospectively analyzed the data of the patients followed up over a 10-year period, the fact that we included only 18% of them due to the exclusion criteria caused a loss of power for our study. There is a need for studies that can use larger patient series and examine the relationship between PLT indices, radiology, and mortality.

Disclosures

Ethics Committee Approval: The study was approved by The Hatay Mustafa Kemal University Non-interventional Clinical Research Ethics Committee (date: 16.06.2022, number: 19).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – K.B.A.; Design – K.B.A., İ.K.; Supervision – K.B.A.; Data Collection and/or Processing – K.B.A., İ.K.; Analysis and/or Interpretation – M.K.; Literature Search – K.B.A.; Writing – K.B.A.; Critical Reviews – İ.K., M.K.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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