Clin. Lab. 2026;72:XXX-XXX

ORIGINAL ARTICLE

Platelet Indices and Cholinesterase in Diagnosis and Prognosis of Pulmonary Embolism

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SUMMARY

Background: **This study aimed to investigate the diagnostic and prognostic value of platelet indices (Platelet (PLT), Platelet Distribution Width (PDW), Mean Platelet Volume (MPV) and cholinesterase activity in patients with pulmonary embolism (PE) in the emergency department (ED).**
Methods: **This prospective observational case-control study included 60 patients diagnosed with PE through CT angiography and 40 healthy controls. The platelet indices and cholinesterase levels were measured on admission and day 3. The simplified Pulmonary Embolism Severity Index (sPESI) was calculated for risk stratification. The relationship between these parameters and mortality was analyzed.**
Results: **The mean age was 67.25 ± 17.14 years in the PE group and 64.6 ± 18.12 years in the control group. MPV levels were significantly higher in PE patients compared to controls (10.78 ± 1.05 vs. 10.15 ± 0.96, p = 0.048), while cholinesterase levels were significantly lower (5.54 vs. 7.25, p < 0.001). Among PE patients, those who died had significantly lower cholinesterase levels (3.54 vs. 5.87, p = 0.043) and systolic blood pressure, along with higher lactate levels and sPESI scores compared to survivors. Patients with sPESI scores ≥ 1 had significantly lower cholinesterase levels compared to those with sPESI = 0 (5.08 vs. 7.19, p < 0.001).**
Conclusions: **Our findings suggest that decreased cholinesterase levels and elevated MPV values may serve as promising biomarkers for PE diagnosis. Additionally, low cholinesterase levels appear to be associated with increased mortality risk in PE patients. These parameters, particularly cholinesterase, could potentially enhance current risk stratification tools when integrated with clinical scoring systems.**
(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.250916)

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Manuscript accepted November 12, 2025

KEYWORDS

pulmonary embolism, mean platelet volume, platelet distribution width, cholinesterase, mortality

INTRODUCTION

Pulmonary embolism (PE), which generally occurs due to deep vein thrombosis in the lower extremities, is a recurring condition with high rates of morbidity and mor-

tality [1,2]. If untreated, APE (acute pulmonary embolism) results in death in 25 - 30% of cases, although this rate can be as low as 2 - 8% following appropriate treatment [3]. Although the early diagnosis of PE and the definition of its prognostic markers is desirable, it is complicated due to the presence of PE only being indicated through non-specific symptoms and physical findings such as dyspnea, chest pain, and syncope [4]. Current guidelines for the diagnosis and prediction of the prognosis of PE patients recommend the use of scoring systems such as the revised Geneva and Wells rules, biomarkers such as D-dimer and troponin and, additionally, a more detailed risk rating through methods such as the evaluation of biomarkers, for example B-type natriuretic peptic (BNP), NT-proBNP, troponin, lactate, and copeptin, and the consideration of echocardiographic results, such as right ventricle (RV) overload of pulmonary embolism severity index (PESI) [4-6]. As none of these methods are currently definitive, research continues on a biomarker for early diagnosis, the development of clinical scoring, and the prediction of PE prognosis.

Platelets, which play a significant part in the physiopathology of thrombosis, as well as mean platelet volume (MPV) and platelet distribution width (PDW), which are indicators of platelet activity, are easily measured parameters in complete blood cell count [7,8]. MPV is positively correlated with indicators of platelet activity, including the expression of glycoprotein Ib and glycoprotein IIb/IIIa receptors, and may also be considered a marker of platelet activation [9]. As platelets with high MPV produce more prothrombic substances, such as thromboxane A2, serotonin, b thromboglobulin, as well as p selectin and glycoprotein IIIa, higher MPV values are known to be an independent risk factor and a poor prognostic factor for myocardial infarction and stroke [9-11]. In addition, high MPV is associated with increased venous thromboembolism [12]. It has been established that, as is the case with MPV, PDW can also be used to determine the severity of PE and options for treatment [13].

Cholinesterase enzymes belong to a family of esterases that hydrolyze choline esters and play a role in cholinergic regulation in the body. Among these, acetylcholinesterase is involved in the termination of neurotransmission in the nervous system, while butyrylcholinesterase is synthesized mainly in the liver and circulates in the plasma [14,15]. Acetylcholinesterase (AChE) is expressed in hematopoietic cells and has been shown to play a role in the formation and development of megakaryocytes [14,15]. Serum butyrylcholinesterase, on the other hand, is synthesized in the liver and circulates in the plasma [16].

As it is possible for cholinesterase, MPV, and RDW levels to change during thromboembolic events, a study has been conducted into the effects of cholinesterase, MPV, and RDW on the diagnosis and prognosis of APE.

MATERIALS AND METHODS

Study design and participants

This prospective observational case-control study was conducted between 01.06.2016 and 01.10.2017 in the Emergency Department of a regional hospital which treats 350,000 patients annually. Patients included in the study were over 18 years of age, had been diagnosed with PE following a CT angiography conducted in the emergency room, and had agreed to participate in the study. Patients excluded from the study were under eighteen, had a history of poisoning with organophosphate compounds, were pregnant, had a history of cancer, had previously received radiotherapy, or did not volunteer to participate. The healthy control group was created from hospital staff, as well as from patients' relatives over 18 who visited the emergency department. Informed consent was obtained from the patients included in the study.

Study protocol and data collection

The age, gender, known diseases, used medicines, vital parameters, and laboratory findings of those who came into the ED and were diagnosed with PE, as well as those who were found to be healthy, were noted. Plt, PDW, MPV, cholinesterase, urea, creatine, troponin, sodium, potassium, and d-dimer levels were recorded on the day of diagnosis, and again on the third day, before being evaluated according to the laboratory findings. Wells score was categorized into three groups; low, medium, and high, and the simplified PESI (sPESI) Score was calculated using the age, systolic blood pressure, oxygen saturation, heart rate, chronic cardiopulmonary disease, and history of cancer, before being recorded. The patients were grouped as either hemodynamically stable or unstable, with a patient being considered unstable if systolic BP < 90 mmHg or if vasopressors were needed to achieve BP ≥ 90 mmHg, despite adequate filling status and end-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate). The clinical results of these patients (the duration of their stay in the ED, intensive care and ward hospitalization, and if they had died while in intensive care), were also recorded.

Laboratory measurements

Venous blood samples were collected at admission. Serum butyrylcholinesterase (BChE) activity was measured using an enzymatic colorimetric method with a commercial Beckman Coulter assay kit (REF OSR6114, Beckman Coulter Inc., Brea, CA, USA) on an automated clinical chemistry analyzer. Results were reported in kU/L, and the reference range used in our laboratory was 5.3 - 12.9 kU/L**.**

Platelet indices (PLT, MPV, and PDW) were obtained from complete blood count analysis performed using an automated hematology analyzer. All measurements were performed according to manufacturer recommendations and institutional laboratory standards.

Statistical analysis

Statistical analysis was conducted using SPSS Windows 15.0 software. The fitness of variables to normal distribution was examined using visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov/ Shapiro-Wilk tests) methods. Descriptive analyses were expressed in mean ± SD for normal distribution variables, and in the median and interquartile range (IQR) for non-normal distribution variables. In the comparison of the pulmonary embolism group with the control group, categorical data was compared using the chi-squared or Fischer's exact test, normally distributed variables were compared using the independent samples *t*-test, and non-normally distributed variables were compared using the Mann-Whitney U test. Factors affecting mortality were calculated using either the chi-squared or the Fischer's exact test for categorical variables. Numerical data was compared using the Mann-Whitney U test. Cases with p-values below 0.05 were accepted as being statistically significant.

RESULTS

Of the 79 volunteer patients diagnosed with PE evaluated in the study, nine were diagnosed with cancer, one with organophosphate poisoning, two decided not to participate and four lacked data. Following exclusion of these patients, our study had a total of 100 participants: 60 patients, 25 (41.7%) of whom were male and 35 (58.3%) female, and 40 healthy volunteers (the control group), 18 (45%) of whom were male and 22 (55%) female. The mean age of PE patients was 64.8 ± 21.4, the mean age of the control group was 64.6 ± 18.12, and there were no statistically significant differences (p: 0.350). The cholinesterase level of patients diagnosed with PE was 5.54 (3.81), which was lower than the control group (p: < 0.001). The fundamental characteristics of the participants are provided in Table 1.

The most common accompanying diseases in PE patients were hypertension (33 (55%)), diabetes (29 (48.3%)) and COPD (21 (35%)). The cholinesterase and systolic blood pressure were lower, and lactate and sPESI scores were higher, in PE patients who died compared to those who survived. The factors related to the death and survival of PE patients are given in Table 2. Of the patients with PE, 37 (61.6%) scored higher than 1 in sPESI. The cholinesterase level of those who scored higher in sPESI was 5.08 (3.06) K/µL, and was significantly higher than those whose sPESI score was lower (p: < 0.001). An analysis of the parameters based on sPESI score is provided in Table 3.

The MPV, PDW, PLT, and cholinesterase values measured at admission were compared with the values obtained on the third day of follow-up. MPV, PDW, and cholinesterase levels changed significantly between Day 1 and Day 3 ($p < 0.05$). Cholinesterase levels on Day 3 were lower compared to admission, while platelet count did not show a significant difference. The comparison of these parameters is shown in Table 4.

DISCUSSION

PE in the emergency department is associated with serious morbidity and high rates of mortality [3,4,17]. While a fast and accurate diagnosis in APE is crucial to enable early and effective intervention, the application of an inappropriate thrombolytic therapy can lead to major bleeding and possibly life-threatening conditions such as intracranial and gastrointestinal hemorrhage.

While clinical scorings, such as PESI and sPESI, are used to assess the severity and early mortality risks of PE, these scorings are not at the desired levels for determining the prognosis [17-20]. Therefore, guidelines highlight that utilizing these risk scorings, along with scanning and laboratory examinations in early prognosis prediction, increases the efficiency of clinical scoring systems [4].

The purpose of this study was to consider whether cholinesterase, MPV, and RDW can be used to diagnose and foresee the prognosis of APE. As far as is known, this is the first study to examine cholinesterase, MPV, and RDW levels as diagnostic and prognostic predictors of PE.

Many studies have shown that platelets contain some components of a non-neuronal cholinergic system, with α7 nicotinic acetylcholine receptors (α7nAchR) being found in platelets [14,21,22]. Schedel et al. reported the presence of an autocrine regulation mechanism through the release of cholinesterase stored via the α7nAchR pathway in human platelets and megakaryocytes [23]. A study by Bennet et al. stated that endogenous cholinesterase produced by platelets blocks the activity of platelets for thrombosis [24]. In addition, it has been shown that cholinesterase increases as a result of increased endothelium-derived nitric oxide (NO) and inhibits platelet degranulation by inhibiting P-selectin and glycoprotein IIb/IIIa (GPIIbIIIa) activation [17,24,25]. All of these studies indicate that low levels of cholinesterase can be an activator in thromboembolic events. In support of these studies, this study has demonstrated that cholinesterase levels significantly decreased in patients with PE in comparison with the control group. Shen et al. additionally reported that choline, which occurs after cholinesterase activation, decreased in severe lung damage, which suggests that cholinesterase activity decreases in severe lung damage [26]. Our study supports this conclusion in its finding that cholinesterase levels were lower in PE patients who died than in those who survived.

Meta-analysis by Kohn et al. revealed that sPESI did not exhibit the necessary sensitivity to predict the mortality rate in relation to all causes of death in PE patients, but it was reliable for indicating the suitability of the early discharge of low-risk patients [4,20]. Similarly, Elias et al. reported that sPESI was a reliable indicator for the early discharge of low-risk patients, and

Table 1. The demographic characteristics of pulmonary embolism and control groups.

Variables		Pulmonary Embolism (n = 60)	Control Group (n = 40)	p-value
Age in years		67.25 ± 17.14	64.6 ± 18.12	0.350
Gender	male	25 (41.7%)	18 (45%)	0.088
	female	35 (58.3%)	22 (55%)	
MPV, mean ± SD		10.78 ± 1.05	10.15 ± 0.96	0.048
PDW, median (IQR)		12.6 (2.5)	12.0 (3.5)	0.057
PLT, median (IQR)		216 (90)	215 (62)	0.15
Cholinesterase, median (IQR)		5.54 (3.81)	7.25 (2.36)	< 0.001

Data is presented as mean ± standard deviation (SD), median (25% - 75% quartiles) (IQR: Inter Quantile Range) or n (%). MPV Mean Platelet Volume, PDW Platelet Distribution Width, PLT Platelet count.

Table 2. Comparison of factors related to death and survival with regards to the discharge of pulmonary embolism patients.

Variables	All Critical Diseases	Survival (n = 42)	Mortality (n = 18)	p-value
Age in years, mean ± SD	67.25 ± 17.14	65.5 ± 16.4	78.6 ± 14.8	0.092
Gender, male	35 (58.3%)	25 (59.5%)	10 (55.5%)	0.088
Hypertension	33 (55%)	22 (52.3%)	11 (61.1%)	0.734
Diabetes	29 (48.3%)	19 (45.2%)	10 (55.5%)	0.055
COPD	21 (35%)	13 (30.9%)	8 (44.4%)	0.105
DVT	19	13	6	
Heart failure	18	12	6	
Malignancy	4	1	3	
Creatinine, mg/dL, median (IQR)	1.02 ± 0.23	0.97 ± 0.21	0.99 ± 0.19	0.138
Urine, mg/dL,	46 (33)	42 (29)	48 (31)	0.16
Cardiac troponin, ng/mL	11.5 ± 4.2	10.8 ± 3.1	13.5 ± 6.1	0.039
D-dimer, ng/mL	1,192 ± 862	1,157 ± 742	1,317 ± 742	0.385
Lactate, mmol/L	4.1 ± 2.2	3.1 ± 2.8	5.5 ± 3.2	0.008
Platelet count	216 (90)	198 (82)	231 (71)	0.15
MPV, (9 - 13 fL)	10.78 ± 1.05	10.77 ± 0.94	10.8 ± 1.18	0.24
PDW, (9 - 17 fL)	12.18 (3.5)	11.9 (4.3)	12.6 (2.4)	0.12
Cholinesterase, (4.62 - 11.5 K/µL)	5.54 (3.81)	5.87 (2.64)	3.54 (3.72)	0.043
Heart rate (bpm)	113 ± 25	110 ± 21	115 ± 23	0.091
Systolic blood pressure (mmHg)	107 ± 13	114 ± 12	97 ± 13	0.002
Diastolic blood pressure (mmHg)	67 ± 10	70 ± 7	64 ± 9	0.058
Pulse oximetry (SpO2, %)	88 (83 - 92)	89 (85 - 92)	87 (83 - 91)	0.096
sPESI score	2 (1 - 4)	1 (1 - 2)	2 (2 - 4)	< 0.001

Data is presented as mean ± standard deviation (SD), median and 25th - 75th percentiles (IQR: Inter Quantile Range) or n (%). * p-value < 0.05, COPD chronic obstructive pulmonary disease, DVT deep vein thrombosis, MPV Mean Platelet Volume, PDW Platelet Distribution Width, sPESI simplified Pulmonary Embolism Severity Index.

Table 3. Parameter analysis based on sPESI score.

Variables	sPESI: 0 (n = 23)	sPESI ≥ 1 (n = 37)	p-value
MPV, mean ± SD	1.54 ± 1.06	10.54 ± 1.06	0.85
PDW, median (IQR)	12.2 (3.5)	12.6 (2.5)	0.57
PLT, median (IQR)	206 (90)	219 (82)	0.15
Cholinesterase, median (IQR)	7.19 (3.58)	5.08 (3.06)	<0.001

Data is presented as mean ± standard deviation (SD), median and 25th - 75th percentiles (IQR: Inter Quantile Range) or n (%). * p-value < 0.05, sPESI simplified Pulmonary Embolism Severity Index, MPV Mean Platelet Volume, PDW Platelet Distribution Width, PLT Platelet count.

Table 4. Comparison of patients' laboratory values measured at admission, Day 1, and on Day 3.

Parameter	Reference Range	Day 1 (Admission) Mean ± SD/Median (IQR)	Day 3 Mean ± SD/Median (IQR)	p-value
MPV (fL)	9 - 13	10.77 ± 1.06	10.49 ± 1.04	0.003
PDW (fL)	9 - 17	12.4 (2.6)	11.7 (2.9)	0.027
PLT Count (x 10^3/mm^3)	150 - 450	201 (91)	211 (99)	0.700
Cholinesterase (kU/L)	4.62 - 11.5	5.43 (3.84)	5.08 (3.46)	< 0.001

Comparison of laboratory parameters measured at admission and on Day 3 of follow-up. MPV and PDW are presented as mean ± SD and median (IQR), respectively. Cholinesterase levels decreased significantly on Day 3 compared to admission.

stated that CT, US, and biomarkers can be determined more effectively in identifying high-risk patients with new models integrating into sPESI [4,27]. We found cholinesterase levels to be low both in patients who had died, and in those with high sPESI scores, which suggests that the integration of cholinesterase into sPESI scores could be effective.

A study by Günay et al. conducted with 113 APE patients demonstrated that MPV and RDW were effective in determining diagnosis, severity, and hospitalization duration for PE patients [13]. A meta-analysis by Lin et al. revealed a positive correlation between MPV and PE, and showed that MPV was significantly higher in PE patients than in the control group, and also higher in PE patients who had died than those who survived [28]. Our study also confirmed these studies in its finding that MPV and RDW levels were higher in PE patients than in the control group. This, however, was not associated with mortality.

The study found that cholinesterase levels were statistically significantly lower in patients with PE than in the control group ($p < 0.001$). It was also found that both cholinesterase levels and systolic blood pressure was low, while lactate and sPESI scores were high, in patients who died due to PE. Additionally, cholinesterase level was seen to be significantly lower in patients whose sPESI score was high ($p < 0.001$). In conclusion, these findings suggest that low levels of cholinesterase in ED are predictive indicators for the diagnosis and mortality of PE patients.

There are several possible limitations of our study, the first of which is that racial and ethnic differences occurring within normal ranges cannot be ruled out in a specific population since this was a single-center study. Secondly, the study might be subjected to electoral bias because the sample size was relatively small. It is therefore possible that different findings might be achieved with a larger population.

CONCLUSION

In conclusion, we found that cholinesterase levels decreased in PE patients in the emergency department, that MPV and RDW were promising biomarkers for PE diagnosis, and that cholinesterase levels were lower in patients who died in the early period of PE. It is clear that cholinesterase can be a promising marker in the prediction of mortality for patients with PE, and can also be used with scoring systems. However, larger prospective studies are needed to fully validate these findings.

Acknowledgment:
There is no person, institution or company to acknowledge.

Ethical Approval and Declaration of Helsinki
Approval for this study was obtained from the Necmettin Erbakan University Faculty of Medicine Clinical Research Ethics Committee (Date: 01.06.2016, Decision No.: 2016/611). The study was conducted in accordance with the World Medical Association Helsinki Declaration and Good Clinical Practice Guidelines.

Source of Funds:
No funds have been received for this study.

Data Availability Statement:
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Use of AI:
The authors declared that no AI tool was used.

Declaration of Interest:
The authors declare no competing interests.

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