ORIGINAL ARTICLE

Monocyte to large platelet ratio as a diagnostic tool for pulmonary embolism in patients with acute exacerbation of chronic obstructive pulmonary disease

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KEY WORDS

blood platelets, chronic obstructive pulmonary disease, monocytes, pulmonary embolism

ABSTRACT

INTRODUCTION A higher prevalence of pulmonary embolism (PE) has been noted among patients with chronic obstructive pulmonary disease (COPD), particularly in those with acute exacerbations of COPD (AECOPD). Due to a similar clinical presentation and the lack of highly specific laboratory tests, there is a common overuse of computed tomography pulmonary angiography (CTPA). The introduction of an additional, simple, and inexpensive diagnostic tool to help in the diagnosis of PE in patients with AECOPD would be of special interest for everyday clinical practice.

OBJECTIVES The aim of the study was to assess the usefulness of the monocyte to large platelet ratio (MLPR) as a diagnostic tool for PE in patients with AECOPD.

PATIENTS AND METHODS We performed a retrospective evaluation of patients with AECOPD and suspicion of PE who underwent CTPA. The MLPR was investigated as a marker of thrombosis. Receiver operating characteristics (ROC) curve analyses were preformed to measure the accuracy of the MLPR in comparison with CTPA results and to identify the cutoff value for the MLPR.

RESULTS A total of 101 patients (56 men and 45 women; median age, 72 years; range, 37–94 years) were included in the study. The MLPR showed an excellent accuracy in comparison with CTPA results: the area under the ROC curve was 0.945 (95% confidence interval [CI], 0.904–0.986). The MLPR was characterized by a good accuracy of qualitative test parameters, with high sensitivity (100%; 95% CI, 79.6–100) and specificity (85.7%; 95% CI, 75.9–92.6).

CONCLUSIONS The MLPR measurement appears to be a reliable, simple, inexpensive, and widely available test that may help in the differential diagnosis of PE in patients with AECOPD.

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INTRODUCTION Pulmonary embolism (PE) is a common disorder associated with significant morbidity and mortality.[1,2] Moreover, according to recent estimates in the Polish population, there has been an alarming increase in the number of patients with PE.[3]

There is evidence for a higher prevalence of PE among patients with chronic obstructive pulmonary disease (COPD),[4,5] in particular those with acute exacerbations of COPD (AECOPD).[6,7] Aleva et al[8] reported a pooled prevalence of PE in unexplained AECOPD of 16.1%.

COPD may contribute to pulmonary vascular alterations, including medial wall thickening and muscularization of the arterioles.[9,10] Moreover, the higher prevalence of pulmonary hypertension in patients with COPD may contribute to increased vascular resistance of the pulmonary vascular beds, as well as stagnation of blood flow.[11,12] PE has been shown to increase the rate of

deaths from COPD in the year following the episode of PE.[13,14]

Due to the similar clinical presentation, and the fact that routine laboratory tests do not allow the exclusion or confirmation of acute PE,[15,16] the detection of PE with coexisting AECOPD is still a diagnostic challenge. Therefore, the development of a new diagnostic tool that would help in the diagnosis of PE in this patient group may be of special interest for everyday clinical practice.

Physiologically, monocytes play a crucial role in innate immunity and the development of tissue macrophages and dendritic cells. They are also important for coagulation processes.[17] Monocytes appear to be the major source of blood tissue factor, which is the key element of the coagulation cascade and occurs in 2 forms: as a transmembrane protein, which can be activated during vascular wall damage and exposure of subendothelial tissues to circulating elements in blood, and as a splice variant in a soluble form.[17] During AECOPD, monocytes can express increased amounts of tissue factor following stimulation by hypoxia, C-reactive protein, or lipopolysaccharides, among others.[18-21] McGilvray et al[22] reported that tissue factor can also be expressed by monocytes that have transmigrated across the endothelium to the sites of extravascular inflammation, and that it acts both to focus and amplify the inflammatory response. The authors suggested that an extravascular focus of infection or inflammation can promote both intravascular thrombosis and extravascular fibrin deposition during the process of adhesion and transmigration across the endothelial barrier. Monocyte-bound tissue factor has also been found to be present at elevated levels in patients with deep vein thrombosis (DVT).[23] Moreover, Granger et al[24] reported that highly purified human blood monocytes are capable of extracellular trap release in response to several stimuli, and that these monocyte extracellular traps demonstrate procoagulant activity, which broadens the range of the thrombogenic properties of monocytes.

Another important mechanism linking monocytes and inflammation with thrombus generation is the platelet–monocyte crosstalk leading to monocyte–platelet aggregation. P-selectin is a transmembrane protein that resides within the α-granule membrane of unstimulated platelets[25] and is translocated to the surface membrane on platelet activation.[26,27] Platelets can bind via P-selectin to the leukocyte receptor P-selectin glycoprotein ligand 1 (PSGL-1).[28] Although both platelet–monocyte and other peripheral blood leukocyte–platelet interactions are mediated by PSGL-1 and P-selectin, a more prolonged and stable binding to monocytes was observed.[29] Platelet activation seems to be the key aspect of the pathophysiology of monocyte–platelet aggregates. Bournazos et al[29] reported that binding of activated platelets triggers proinflammatory responses in monocytes, while the binding of unstimulated platelets did not affect receptor expression, cytokine production, NF-κB activation, chemotactic responses, or apoptosis. The authors suggested that high levels of P-selectin on the surface of activated platelets or binding of multiple platelets by monocytes may be required to trigger monocyte activation via PSGL-1.[29] Platelet activation is evident in acute PE and correlates with the severity of right ventricular dysfunction.[30]

There is also a considerable body of evidence supporting the correlation of platelet function with platelet volume. Thompson et al[31] reported a more rapid and more complete aggregation with increased platelet size and suggested that large platelets may be functionally more important than smaller ones. The authors showed that large platelets had greater density, higher enzymatic activity of lactate dehydrogenase, a higher number of dense bodies per platelet and per cubic micron of platelet volume. Finally, they demonstrated greater serotonin uptake and release with increased thrombin concentrations. Moreover, Mannucci et al[32] observed that platelet aggregation appeared to selectively involve large platelets.

Increased values of the mean platelet volume (MPV) in patients with acute PE were observed.[33-35] Sevuk et al[34] reported that serial measurements of MPV and platelet distribution width (PDW), as well as percent change in MPV and PDW, appear to be useful markers for predicting the occurrence of acute PE in patients with a first episode of acute proximal DVT. Varol et al[33] also revealed that MPV was independently correlated with right ventricular dimension. Moreover, Kostrubiec et al[36] found MPV to be an independent predictor of early death in acute PE.

Considering the above evidence concerning the role of monocytes and large platelets, as well as the platelet–monocyte crosstalk, in thrombus formation, we aimed to assess the value of the peripheral blood monocyte to large platelet ratio (MLPR) for the diagnosis of PE in patients with AECOPD. To our knowledge, this is the first report analyzing this novel parameter.

PATIENTS AND METHODS This was a retrospective analysis of de-identified data collected in the digital database of AECOPD of the Department of Pneumology and Allergy and the Department of General and Oncological Pulmonology of the Medical University of Lodz in Łódź, Poland. Therefore, there was no need to obtain the approval of an ethics committee.

The study was conducted in a population of patients admitted to the hospital between November 2007 and May 2017 due to AECOPD and suspicion of PE. All included patients had moderate to high probability of PE according to the Wells score and the revised Geneva score.[37] A plasma D-dimer value below 500 μg/l was considered negative; however, in cases of a high clinical probability of PE, such a result did not exclude

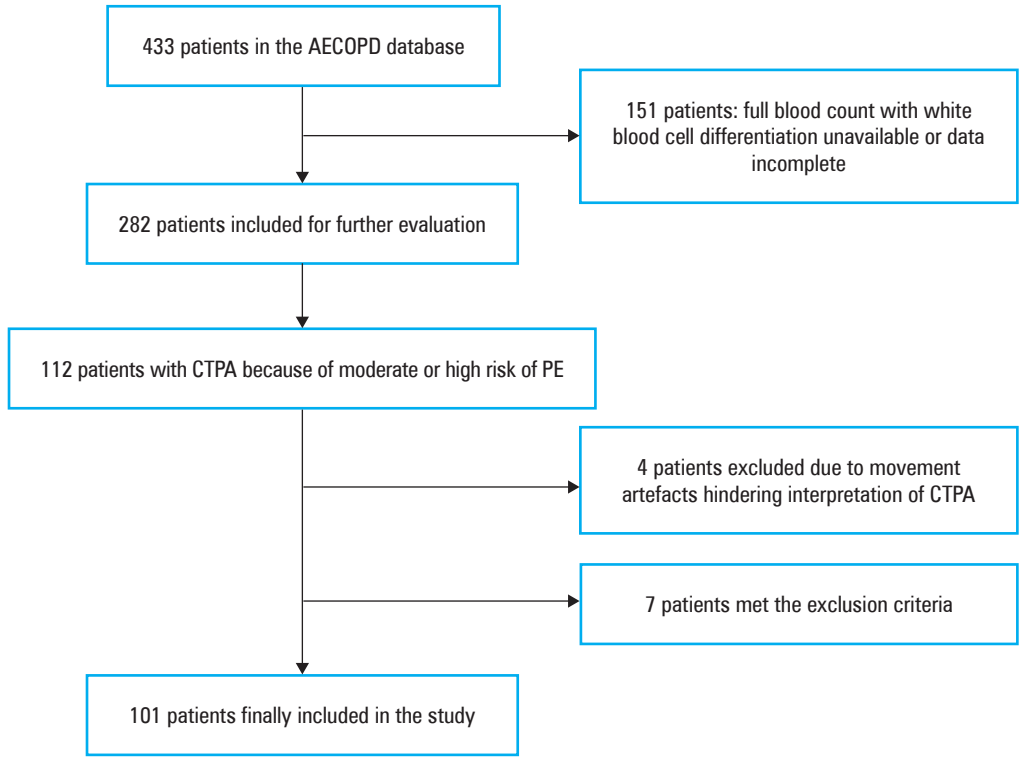

FIGURE 1 Flow chart of patient selection for inclusion in the study Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism

a patient from further examination. The diagnosis of PE was confirmed by computed tomography pulmonary angiography (CTPA). The interpretation was made by a senior radiologist, and PE was diagnosed when embolic material was directly visualized or when vessel truncation implied the presence of occlusion.

Only patients with the results of full blood count and white blood cell differentiation, measured before the treatment of suspected PE, were included. Venous blood was collected by venipuncture into tubes with ethylenediaminetetraacetic acid as an anticoagulant. The sample was immediately transferred to a laboratory and was examined with an automated hematology analyzer. The cell count and size were assessed using the electrical impedance method.

The exclusion criteria were as follows: a history of any myeloproliferative disorder, myelofibrosis, Glanzmann thrombasthenia, May–Hegglin anomaly, Bernard–Soulier syndrome, suspicion of disseminated intravascular coagulation, blood transfusion in the last 2 months, and administration of any anticoagulant drug at a therapeutic dose. Additionally, patients with acute coronary syndrome, pulmonary edema, or pneumothorax were excluded, as well as those who required either invasive or noninvasive ventilation, and were directly transferred to an intensive care unit.

The MLPR was calculated as follows: MLPR = (monocyte absolute count) / LPC × 100%, where LPC is the large platelet count. LPC can be calculated by multiplying the platelet count (PLT) by the platelet–large-cell ratio (PLCR): LPC = (PLT × PLCR) / 100.

Continuous data were presented as mean with SD or median with interquartile range (IQR), depending on data distribution. The area under the receiver operating characteristic (ROC) curve (AUC) was presented as the result and 95% confidence interval (CI), while the accuracy of the qualitative test parameters was presented as point estimates or percentages (sensitivity and specificity) and 95% CIs.

ROC analyses were preformed to measure the accuracy of the MLPR in comparison with CTPA results and to identify the cutoff value for the MLPR for further analyses. An AUC greater than 0.9 was considered as excellent; 0.8 to 0.9, as very good; 0.7 to 0.8, as good; 0.6 to 0.7, as average; and below 0.6, as poor.[38]

Two-way tables were created for the diagnosis of PE by CTPA using the MLPR as a diagnostic test to assess the apparent prevalence, true prevalence, sensitivity, specificity, positive and negative predictive values, likelihoods, and diagnostic accuracy. The ROC curves for the MLPR measurement and D-dimer test were compared using the DeLong test. Agreement between the diagnosis of PE by MLPR and CTPA thresholds was assessed by the Cohen κ coefficient.

Continuous variables were compared using the Welch's *t* test for normally distributed data and the Wilcoxon rank sum test with continuity correction for data with a nonnormal distribution. Categorical variables were compared using the χ^2 test with Yates correction, if appropriate. For a more accurate analysis of factors influencing the MLPR value, a multivariable logistic regression was used. A *P* value of less than 0.05 was considered significant.

TABLE 1 Baseline clinical data according to the occurrence of pulmonary embolism

Parameter	PE not confirmed (n = 77)	PE confirmed (n = 24)	Total (n = 101)	*P* value
Age, y	74 (64–79)	64.5 (58.5–77.75)	72 (62–79)	0.1
HR, bpm	88 (70–100)	88.5 (68.25–106.25)	80 (70–100)	0.61
D-dimer, µg/l	2550 (1042.53–4284.3)	3677.61 (936.5–7012.5)	2597.99 (1020.84–4696.13)	0.37
WBC, G/l	8.4 (6.62–9.9)	10.34 (7.77–12.02)	8.54 (7.01–10.84)	0.047
Monocytes, G/l	0.66 (0.51–0.85)	0.91 (0.8–1.09)	0.7 (0.57–0.92)	<0.001
Monocytes, %, mean (SD)	8.11 (3.06)	9.93 (5.11)	8.54 (3.71)	0.11
CRP, mg/l	11.2 (3.86–53.3)	25.9 (12.24–63)	12.64 (4.13–56.58)	0.14
PLT, G/l, mean (SD)	286.48 (118.75)	202.67 (67.1)	266.56 (114.19)	<0.001
MPV, fl	10 (9.5–10.5)	9.3 (9–10.48)	10 (9.2–10.5)	0.1
PDW, fl	11.7 (10.6–12.45)	10.5 (9.9–12.33)	11.5 (10.18–12.45)	0.13
PCT, %	0.26 (0.22–0.34)	0.21 (0.17–0.24)	0.25 (0.2–0.32)	0.001
PLCR, %	26 (21–30)	20 (18–28.5)	24 (20–30)	0.07
LPC, G/l	66.08 (56.26–89.25)	43.43 (39.05–49.35)	59.01 (44.1–79.05)	<0.001
MLPR	1.02 (0.75–1.31)	2.04 (1.92–2.39)	1.15 (0.88–1.89)	<0.001
pH	7.44 (7.42–7.46)	7.44 (7.41–7.47)	7.44 (7.42–7.46)	0.92
PaO_2, mm Hg	60.7 (51–66.5)	64.7 (52.3–77)	60.75 (50.45–67.38)	0.17
SaO_2, %	90.9 (84.45–94.1)	93.1 (86.95–96)	91.55 (84.85–94.65)	0.18
$PaCO_2$, mm Hg, mean (SD)	36.93 (9.14)	36.22 (6.82)	36.76 (8.62)	0.69
HCO_3^-, mmol/l	23.75 (21.43–26.33)	22.8 (20.95–26.8)	23.6 (21.15–26.4)	0.72
BE, mmol/l, mean (SD)	0.15 (4.76)	0.1 (3.55)	0.14 (4.48)	0.96

Data are presented as median (IQR) unless otherwise stated.

Abbreviations: BE, base excess; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, heart rate; IQR, interquartile range; LPC, large platelet count; MLPR, monocyte to large platelet ratio; MPV, mean platelet volume; PaO_2, partial pressure of oxygen dissolved in arterial blood; $PaCO_2$, partial pressure of carbon dioxide dissolved in arterial blood; PCT, plateletcrit; PDW, platelet distribution width; PLCR, platelet–large-cell ratio; PLT, platelet count; WBC, white blood count; others, see FIGURE 1

TABLE 2 Comorbidities according to the occurrence of pulmonary embolism

Comorbidity	PE confirmed (n = 24)	PE not confirmed (n = 77)	Total (n = 101)	*P* value
DVT	5 (20.8)	2 (2.6)	7 (6.9)	0.01
Malignancy	4 (16.67)	13 (16.88)	17 (16.83)	1
Arterial hypertension	9 (37.5)	44 (57.14)	53 (52.48)	0.09
AF[a]	5 (20.8)	10 (12.99)	15 (14.85)	0.54
Arrhythmia other than AF[b]	3 (12.5)	2 (2.6)	5 (4.95)	0.16
IHD	5 (20.8)	28 (36.36)	33 (32.67)	0.16
History of MI	2 (8.3)	14 (18.18)	16 (15.84)	0.4
CHF	5 (20.8)	25 (32.47)	30 (29.7)	0.28
Cardiac stimulator	4 (16.67)	3 (3.9)	7 (6.9)	0.07
Diabetes mellitus	3 (12.5)	12 (15.58)	15 (14.85)	0.97
Chronic kidney disease	4 (16.67)	9 (11.69)	13 (12.87)	0.77
History of stroke	2 (8.3)	4 (5.19)	6 (5.94)	0.94
History of pulmonary embolism	2 (8.3)	4 (5.19)	6 (5.94)	0.94
History of DVT	3 (12.5)	5 (6.49)	8 (7.92)	0.6
Obesity	3 (12.5)	5 (6.49)	8 (7.92)	0.6
Varices	1 (4.2)	2 (2.6)	3 (2.97)	1

Data are presented as number (percentage) of patients.

a First detected on admission, paroxysmal, persistent, or permanent

b On admission or in medical history

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; DVT, deep vein thrombosis; IHD, ischemic heart disease; MI, myocardial infarction; others, see FIGURE 1

The results were analyzed using the R software for MacOS (R Core Team [2016]. R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS A total of 101 patients were enrolled to the study (56 men and 45 women; median age, 72 years; range, 37–94 years). The flow chart of patient selection for inclusion in the study is presented in FIGURE 1.

In 24 patients (23.76%), PE was confirmed by CTPA. In 70.83% of the patients, central PE was detected, and in 29.17%, peripheral PE (including subsegmental PE in 57.14%). The baseline clinical data and comorbid diseases according to the occurrence of PE are presented in TABLES 1 and 2, respectively. Smoking history was not associated with the occurrence of PE (88% of former smokers and 12% of active smokers; χ^2 <0.001, P = 1.0). No difference was found between sexes (χ^2 = 0.11, P = 0.7).

The MLPR measurement demonstrated excellent accuracy in comparison with CTPA results: the AUC was 0.945 (95% CI, 0.904–0.986) (FIGURE 2A).

The D-dimer test showed poor accuracy in comparison with CTPA results: the AUC was 0.564 (95% CI, 0.414–0.713). The DeLong test revealed a difference between the ROC curves for the MLPR measurement and D-dimer test (Z = 4.9063, P <0.001) (FIGURE 2B).

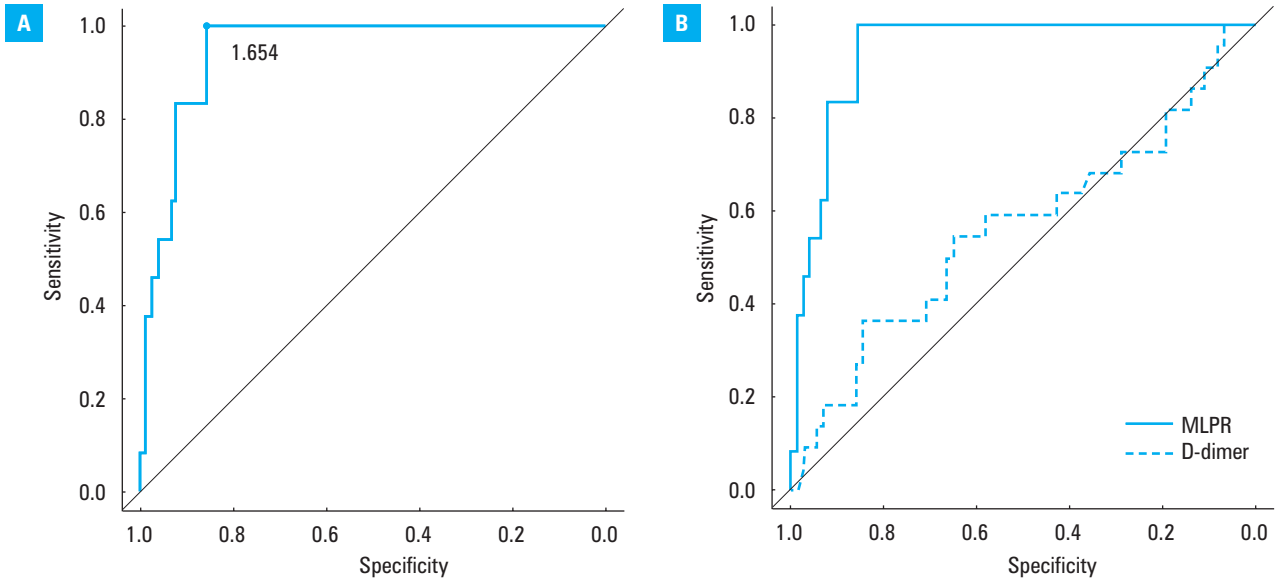

FIGURE 2 **A** – a receiver operating characteristic (ROC) curve for the monocyte to large platelet ratio (MLPR) against computed tomography pulmonary angiography results with a marked cutoff point; **B** – comparison of the ROC curves for MLPR measurement and D-dimer test

The MLPR of 1.654% showed the best sensitivity (100%; 95% CI: 79.6–100) and specificity (85.7%; 95%CI: 75.9–92.6). This cutoff value yielded 24 true positive results (23.8%), 11 false positive results (10.9%), and 66 true negative results (65.3%).

The apparent prevalence was 0.35 (95% CI, 0.26–0.45), the true prevalence was 0.24 (95% CI, 0.16–0.33), and the negative and positive predictive values were 1 (95% CI, 0.92–1.00) and 0.69 (95% CI, 0.51–0.83), respectively. The likelihood for a positive test result was 7 (95% CI, 4.05–12.1). Finally, the diagnostic accuracy was 0.89 (95% CI, 0.81–0.94). The Cohen κ coefficient indicated a good agreement between the MLPR measurement and CTPA results (κ = 0.74; 95% CI, 0.6–0.89).

The clinical data of patients according to the cutoff value of 1.654% for the MLPR are presented in **TABLE 3**.

Of the included patients, 21.31% suffered from infective AECOPD, of whom 65.57% had coexisting pneumonia. Neither the infective nature of AECOPD nor pneumonia seemed to affect the MLPR values (W = 978, $P = 0.09$ and W = 370, $P = 0.3$, respectively). Moreover, we did not show differences in a similar analysis according to the cutoff value of the MLPR ($\chi^2 = 2.73$, $P = 0.1$ and $\chi^2 = 0.71$, $P = 0.4$ respectively).

In a qualitative analysis, the χ^2 test identified only DVT to be associated with higher MLPR values ($\chi^2 = 6.4$, $P = 0.01$) (**TABLE 4**). The multivariable logistic regression analysis demonstrated that type 2 diabetes ($P = 0.03$), congestive heart failure ($P = 0.04$), and chronic kidney disease ($P = 0.01$) were factors influencing the MLPR values.

DISCUSSION The results of our study confirm the utility of a new diagnostic tool that may assist the diagnosis of PE in patients with AECOPD. The MLPR measurement demonstrated an excellent accuracy in diagnosing PE, using CTPA results as a reference. The MLPR was characterized by a good profile of the variables describing the accuracy of qualitative test parameters, including high sensitivity and specificity, in the analyzed population. We hypothesize that the MLPR indirectly reflects the role of the relationships between platelets and monocytes in thrombus formation; it may be a surrogate marker of thrombosis and assist the differential diagnosis of PE in patients with AECOPD. Additionally, because the absolute monocyte count and PLCR are commonly measured in clinical practice, the MLPR may be routinely calculated and any additional costs would therefore be negligible. This makes this parameter a cost-effective biomarker that could be widely used in everyday clinical practice.

In our study, patients with PE showed decreased platelet count and plateletcrit with a significantly lower LPC. It is possible that when large platelets are involved in thrombus formation, their numbers in circulating blood decrease. This observation also complies with evidence for a more rapid and complete aggregation with an increased platelet size, and shows that platelet aggregation may selectively involve large platelets.[31,32] On the other hand, we observed a higher absolute monocyte count in patients with PE. Similar observations were reported by Rezende et al[39] in venous thrombosis. These observations, as well as evidence concerning the role of monocytes[17-24] and platelet–monocyte crosstalk[17,28] in thrombus formation, constitute the rationale for developing the MLPR and assessing its usefulness for diagnostic purposes.

In contrast, the D-dimer test appeared to be of limited value in diagnosing PE in the analyzed population, and studies concerning the use of D-dimer in AECOPD are inconsistent. Li et al[40]

TABLE 3 Clinical data according to the cutoff value of 1.654% for the monocyte to large platelet ratio

Parameter	MLPR		*P* value
	<1.654% (n = 66)	>1.654% (n = 35)	
Age, y	75 (64–79)	65 (61–77.5)	0.17
HR, bpm	80 (70–96.25)	80 (70–105)	0.57
D-dimer, µg/l	2160 (1053.37–4630)	3270 (980–5830)	0.48
WBC, G/l	8.35 (6.56–9.88)	9.44 (7.66–11.69)	0.06
CRP, mg/l	10.74 (3.45–52.85)	17.7 (9.3–60.25)	0.12
PLT, G/l, mean (SD)	301.26 (118.9)	201.14 (67.64)	<0.001
MPV, fl	10.15 (9.6–10.58)	9.4 (9–10.25)	0.02
PDW, fl	11.8 (10.8–12.8)	10.9 (9.85–11.85)	0.03
PCT, %	0.27 (0.23–0.35)	0.19 (0.15–0.25)	<0.001
pH	7.44 (7.42–7.46)	7.44 (7.42–7.46)	0.93
PaO_2, mm Hg	60.75 (54.88–66.83)	60.15 (47.23–74.4)	0.82
SaO_2, %	91.4 (87.9–94.48)	92.1 (82.33–94.65)	0.76
$PaCO_2$, mm Hg, mean (SD)	36.94 (9.09)	36.42 (7.79)	0.77
HCO_3^-, mmol/l	24 (21.9–26.4)	21.95 (20.63–26.3)	0.21
BE, mmol/l, mean (SD)	0.04 (4.59)	0.32 (4.35)	0.77

Data are presented as median (IQR) unless otherwise stated.

Abbreviations: see **TABLE 1**

TABLE 4 Monocyte to large platelet ratio depending on the presence of comorbidities and divided according to the cutoff value (continued on the next page)

Comorbidity	MLPR, n (%)		χ^2	*P* value	MLPR, median (IQR)	*P* value
	<1.654% (n = 66)	>1.654% (n = 35)				
DVT						
Yes	1 (1.52)	6 (17.14)	6.4	0.01	2.08 (1.93–3.18)	0.002
No	65 (98.48)	29 (82.86)			1.13 (0.86–1.8)	
Malignancy						
Yes	11 (16.67)	6 (17.14)	0.004	0.95	1.02 (0.91–1.89)	1
No	55 (83.33)	29 (82.86)			1.2 (0.88–1.87)	
Arterial hypertension						
Yes	39 (59.09)	14 (40)	3.34	0.07	1.13 (0.94–1.66)	0.49
No	27 (40.91)	21 (60)			1.28 (0.67–1.98)	
AF[a]						
Yes	8 (12.12)	7 (20)	1.12	0.29	1.44 (0.97–1.93)	0.5
No	58 (87.88)	28 (80)			1.14 (0.88–1.85)	
Arrhythmia other than AF[b]						
Yes	1 (1.52)	4 (11.43)	2.9	0.09	1.94 (1.75–1.95)	0.16
No	65 (98.48)	31 (88.57)			1.15 (0.87–1.85)	
IHD						
Yes	23 (34.85)	10 (28.57)	0.41	0.52	1.18 (0.89–1.71)	0.62
No	43 (65.15)	25 (71.43)			1.14 (0.87–1.94)	
History of MI						
Yes	11 (16.67)	5 (14.29)	0.1	0.76	1.2 (0.96–1.78)	0.86
No	55 (83.33)	30 (85.71)			1.15 (0.86–1.92)	
CHF						
Yes	22 (33.33)	8 (22.86)	1.2	0.27	1.15 (0.9–1.63)	0.6
No	44 (66.66)	27 (77.14)			1.27 (0.88–1.92)	
Cardiac stimulator						
Yes	3 (4.55)	4 (11.43)	0.78	0.38	1.65 (1.11–1.73)	0.61
No	63 (95.45)	31 (88.57)			1.13 (0.87–1.88)	

TABLE 4 Monocyte to large platelet ratio depending on the presence of comorbidities and divided according to the cutoff value (continued from the previous page)

Comorbidity	MLPR		χ^2	*P* value	MLPR, median (IQR)	*P* value
	<1.654%, n (%) (n = 66)	>1.654%, n (%) (n = 35)				
Diabetes mellitus						
Yes	8 (12.12)	7 (20)	1.12	0.28	1.15 (0.96–1.79)	0.83
No	58 (87.88)	28 (80)			1.16 (0.88–1.93)	
Chronic kidney disease						
Yes	6 (9.09)	7 (20)	1.55	0.21	1.75 (0.89–2.04)	0.13
No	60 (90.91)	28 (80)			1.14 (0.88–1.82)	
History of stroke						
Yes	4 (6.06)	2 (5.71)	0	1	1.09 (0.59–1.56)	0.41
No	62 (93.94)	33 (95.29)			1.15 (0.88–1.9)	
History of PE						
Yes	4 (6.06)	2 (5.71)	0	1	0.97 (0.9–1.74)	0.87
No	62 (93.94)	33 (95.29)			1.18 (0.88–1.88)	
History of DVT						
Yes	3 (4.55)	5 (14.29)	1.79	0.18	1.8 (0.98–2.05)	0.25
No	63 (95.45)	30 (85.71)			1.15 (0.87–1.85)	
Obesity						
Yes	5 (7.58)	3 (8.57)	<0.001	1	1.14 (1.02–1.83)	0.5
No	61 (92.42)	32 (91.43)			1.18 (0.86–1.89)	
Varices						
Yes	2 (3.03)	1 (2.86)	<0.001	1	1.22 (1.11–1.88)	0.5
No	64 (96.97)	34 (97.14)			1.15 (0.88–1.89)	
Smoking						
Active	8 (12.12)	4 (11.43)	0	1	1.08 (0.92–1.94)	0.97
Ex-smoker	58 (87.88)	31 (88.57)			1.18 (0.88–1.86)	

a First detected on admission, paroxysmal, persistent, or permanent

b On admission or in medical history

Abbreviations: see **TABLES 1** and **2**

reported a frequency of PE of 10.3% in a series of 522 patients with AECOPD, and recommended that patients with AECOPD admitted to the hospital should be considered for the presence of PE if they demonstrate the following risk factors: immobilization lasting 3 days or longer, lower extremity edema, and D-dimer levels of 2000 μg/l or higher. Fruchter et al[7] revealed higher D-dimer levels in patients with venous thromboembolism (VTE)/PE than in those with AECOPD alone; however, this study was a retrospective analysis of a relatively small group of patients, and VTE/PE was excluded by imaging modalities only in patients with positive D-dimer test results. Hypothetically, it is also possible that VTE/PE was present and not detected in some patients with low D-dimer levels.

Shapira-Rootman et al[14] reported positive D-dimer test results in 29 patients, of whom 8 patients (27.6%) had PE detected by CTPA and 1 patient with confirmed PE showed normal D-dimer levels. The authors reported a sensitivity of the D-dimer test of 88.9% and a specificity of 42.5%,[14] which confirms our observations that D-dimer testing has limited diagnostic value in excluding PE in the population of patients with AECOPD. This can be explained mainly by the fact that age, smoking status, or comorbidities specific to this group of patients may also influence D-dimer values.[41] In our study, age and smoking status were found to have no significant effect on the MLPR; however, the multivariable logistic regression analysis demonstrated the significant effect of type 2 diabetes, congestive heart failure, and chronic kidney disease. This finding needs to be confirmed in a prospective study.

If our results are replicated, the use of the MLPR might have significant clinical implications. The common overuse of CTPA for diagnosing PE, particularly in emergency departments, is controversial.[42] Besides the obvious benefits associated with the increasing rate of PE diagnoses, the decreased number of CTPA procedures may result in a lower occurrence of potential complications such as radiation harms, allergies, and contrast-induced nephropathy. In addition, the increasing costs and potential delays to care[43-45] underline the need for an additional,

simple, and inexpensive diagnostic tool to assist in the diagnosis of PE in everyday clinical practice. We believe that the MLPR might be a reliable tool in a differential diagnosis of PE in patients with AECOPD. Moreover, it might prove useful in decision making about using CTPA in this patient group. It might also help reduce the extent of CTPA overuse and thus the risk of potential complications. Finally, it might be cost-effective and contribute to reducing potential delays to care delivery.

Our study has several limitations. First, as a retrospective study, it did not include data on potential confounding factors. Although we assessed the utility of the MLPR in the diagnosis of PE, we hypothesize that the increased values of this parameter are not specific to the presence of thrombus in lung arteries only, but that they are associated with thrombotic incidents in general. This issue should be addressed in future research. Another issue is that after the exclusion of PE, our patients did not undergo a further diagnostic workup for other types of thrombotic events. Another significant limitation is a high prevalence of subsegmental PE (57.14% of the patients with peripheral PE), while an unequivocal diagnosis of acute PE may be reached when thromboemboli are visualized at least in segmental arteries on CTPA.

To sum up, the current work is the first report to assess the utility of the MLPR in the diagnosis of PE. The MLPR measurement appears to be a reliable, simple, inexpensive, and widely available test that may help in the differential diagnosis of PE in patients with AECOPD. However, burdened by significant limitations, the study should be considered only as hypothesis-generating about the potential routine use of the MLPR in the diagnosis of PE in daily clinical practice.

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