

Platelet distribution width as a prognostic factor in patients with COPD – pilot study

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Background: Platelets may actively participate in inflammation in COPD. Platelet distribution width (PDW), a measure of platelets' volume heterogeneity, may increase in platelets' activation. We hypothesized that PDW may be a marker of hypercoagulation, which plays a significant role in conditions associated with worse survival of patients with COPD, eg, acute myocardial infarction and other forms of ischemic heart disease.

Methods: Retrospective analysis of 79 patients. Variables were compared after grouping patients according to the upper normal limit of PDW, using Welch's *t*-tests or Mann–Whitney *U*, and chi-square tests. Survival in the two groups was compared using the Kaplan–Meier method and Cox proportional hazards regression.

Results: Ten patients presented values of PDW above 16 fL, which was the upper limit of normality for our laboratory. Compared to patients with normal PDW, they had lower forced expiratory flow between 25% and 75% of vital capacity (FEF 25–75) – 35% of reference value vs 57% ($P=0.003$) and peak expiratory flow – 39% vs 54% ($P<0.001$). The median survival of patients with elevated PDW was 743 days compared to those with normal PDW (1,305 days) ($P=0.025$). The adjusted HR was 4.59 (95% CI: 1.1, 19.19; $P=0.04$).

Conclusion: Our analysis indicates that elevated PDW is associated with reduced survival of patients with COPD. If our data are to be confirmed, PDW may be used as an inexpensive and repeatable prognostic tool in COPD.

Keywords: COPD, PDW, platelets, inflammation, survival

Background

Increasing evidence suggests that the pathophysiology of COPD is characterized by the interaction between several factors, including local and systemic inflammation.^{1,2} IL-6 plays a central role in the inflammatory process underlying COPD, with increased concentrations reported in plasma, sputum, and exhaled breath of patients with COPD, especially during exacerbations.^{3–7} IL-6 stimulates the synthesis of acute phase proteins, but also affects platelet count by stimulating the differentiation of megakaryocytes into platelets and possibly by stimulating thrombopoietin production.^{8–12}

It has been shown that platelets actively participate in inflammation in several conditions.¹³ Upon activation, platelets release chemokines from their α -granules such as MIF, CXCL4, CXCL7 or CXCL5 which play a role in inflammatory processes.¹⁴ CXCL5 is a chemokine of potential importance in regulation of lung inflammation, by modulating neutrophil transepithelial and transendothelial migration and accumulation in the airspace.¹⁵ Furthermore, platelets regulate MMPs' activity which significantly contributes to inflammation. Platelets regulate MMPs both directly by secretion of the proteases and their inhibitors, and indirectly by influencing the behavior of other cells such as neutrophils and monocytes.¹⁶ Platelet-derived CD40L, which is shed from the

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platelet surfaces by MMPs, induces MT-1-MMP, MMP-1, MMP-2, and MMP-9 on endothelial cells.^{17,18} There is evidence proving the role of these MMPs in the pathophysiology of COPD.^{19–23}

The routinely available indices which describe platelets' morphology and function are the platelet count (PLT), the platelet-to-lymphocyte ratio (PLR), the mean platelet volume (MPV), and the platelet distribution width (PDW). Thrombocytopenia was associated with poor outcomes in acute exacerbations of COPD.²⁴ On the other hand, thrombocytosis may be associated with increased short- and long-term mortality after exacerbations.²⁵ PLR describes the correlation between changes in levels of platelets and lymphocytes. PLR has been reported to play a significant role in cardiovascular diseases,^{26,27} diabetic ketoacidosis,²⁸ and numerous neoplasms.^{8,12,29–40} MPV reflects changes in either the level of platelet stimulation or the rate of platelet production.⁴¹ It has been assessed as an inflammatory marker in several diseases.^{42–44} COPD patients, during acute exacerbation and in stable phase, have lower MPV compared with healthy controls, and the MPV increases once patients have recovered from exacerbation.⁴⁵ PDW is an index of platelets' volume heterogeneity⁴⁶ and may increase in platelets' activation.⁴⁷ The role of PDW has been assessed in several conditions, such as acute gangrenous appendicitis, carotid artery stenosis, coronary artery disease, angina pectoris, idiopathic pulmonary hypertension, ovarian torsion, and preeclampsia.^{48–56} PDW can serve as useful prognostic factor for long-term mortality in patients with acute myocardial infarction and was found to be an independent risk factors for cardiovascular mortality.⁵⁷ Because hypercoagulation may play a significant role in conditions associated with worse survival of patients with COPD,^{58,59} we hypothesized that PDW may be associated with survival in these patients. The objective of this study was to evaluate the mortality rate of patients with COPD with and without an abnormal PDW.

Methods

From the electronic archive of the Campus Bio-Medico Hospital in Rome, Italy, between March 2006 and December 2014, we identified 288 patients with post-bronchodilator forced expiratory volume in 1 second to forced vital capacity ratio (FEV_1/FVC) <0.7 and for whom information on vital status could be obtained from the regional death registry. Subsequently, we selected patients with a blood cell count performed within 2 weeks of the index spirometry (N: 92).

We excluded patients with conditions that, based on the available evidence, may affect PDW: acute exacerbation of COPD, any active acute inflammation, connective tissue disorder, diabetic ketoacidosis, recent history of myocardial infarction, end-stage renal disease, history of any active malignancy, and hematological system diseases, or blood transfusion in the last 2 months.

Demographic data, medical history, and routine laboratory measurements, including white blood count, neutrophils, lymphocytes, PLT, MPV, and PDW, were collected from the digital database of medical records of Campus Bio-Medico di Roma.

Pulmonary function tests (PFTs) including vital capacity (VC), FVC, FEV_1 , FEV_1/FVC ratio, forced expiratory flow between 25% and 75% of VC (FEF 25–75), peak expiratory flow (PEF), total lung capacity (TLC), and residual volume, were collected from the digital database of medical records of Campus Bio-Medico di Roma. PFTs were performed with the water-bell volume spirometry device between March 2006 and December 2012 by the same technician. All lung function parameters were measured according to the American Thoracic Society/European Respiratory Society guidelines.^{60–63}

Continuous data are presented as the mean with 95% CI, except survival that was presented as median. Variables were compared after grouping patients according to the laboratory upper limit of PDW, using *t*-test for normally distributed continuous data, and Mann–Whitney *U* test for not normally distributed continuous data. Categorical variables were compared using chi-square test with Yates' continuity correction.

Survival analysis was performed after grouping patients according to the laboratory normal limit for PDW values. Kaplan–Meier analysis and log-rank test were used to compare survival curves. Multivariable analyses were performed using Cox proportional hazards regression to adjust for age, comorbidities, and FEV_1 .

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

The protocol of the study was approved by the Ethics Committee of the Campus Bio-Medico University.

Results

Seventy-nine patients met the inclusion criteria. The flow chart of sample selection is reported in Figure 1. Most patients

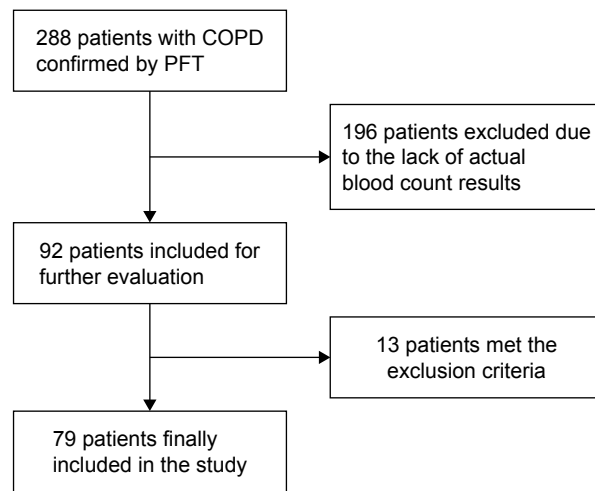


Figure 1 Flow chart of patient selection for inclusion in the study.
Abbreviation: PFT, pulmonary function test.

were GOLD stage II (49.4%), ex-smokers (62.5%), and had comorbidities (90%). Mean age of the study population was 73.6 (95% CI: 72.32, 74.95). The overall male-to-female ratio was 1.93:1. The means of baseline values of the study population are presented in Table 1.

Ten patients presented values of PDW above 16 fL, which was the upper limit of normality for our laboratory. There were no differences in age and gender distribution between the groups. Participants with higher PDW showed significantly lower FEF 25–75 and PEF values compared to those with normal PDW – both in absolute values, and expressed as percent of reference value (Table 2).

Patients with high PDW had worse survival compared to patients with normal PDW, with a median survival time of 743 days compared to 1,305 days of patients with normal PDW (Figure 2). Log rank test showed significant differences between groups (chi-square = 4.9; $P=0.025$). Abnormal PDW values were associated with an RR of death of 3.18 (95% CI 0.6, 7.79; $P=0.07$). The HR for unadjusted Cox regression was 4.34 (95% CI: 1.072, 17.6; $P=0.04$) and HR after adjustment for gender, age, comorbidities, and FEV₁% was 4.59 (95% CI: 1.1, 19.19; $P=0.04$).

Discussion

In our study, we found that elevated PDW was associated with increased risk for mortality in COPD patients. This result was confirmed after adjustment for age, comorbidities, and FEV₁%, suggesting that in our sample PDW was an independent risk factor for mortality.

Activation of platelets causes morphological changes, including pseudopodia formation. Pseudopodium formation

Table 1 Baseline values of the study population

Parameter	Mean	95% CI
WBC ($\times 10^3/\mu\text{L}$)	7.06	6.63, 7.49
Neutrophils ($\times 10^3/\mu\text{L}$)	4.26	3.89, 4.63
Lymphocytes ($\times 10^3/\mu\text{L}$)	2.08	1.87, 2.3
Platelet count ($\times 10^3/\mu\text{L}$)	224.1	202.58, 245.55
MPV (fL)	10.91	10.69, 11.13
PDW (fL)	13.36	12.9, 13.8
PLR	123.13	108.82, 137.44
Pre-bronchodilator		
VC (L)	2.49	2.3, 2.67
FVC (L)	2.47	2.28, 2.65
FVC (%)	76.09	72, 80.17
FEV ₁ (L)	1.47	1.33, 1.6
FEV ₁ (%)	59.29	54.92, 63.67
FEV ₁ /FVC	0.59	0.57, 0.61
FEF 25–75 (L/s)	0.7	0.62, 0.78
FEF 25–75 (%)	36.1	32.35, 39.86
PEF (L)	3.68	3.32, 4.04
PEF (%)	45.57	41.62, 49.52
Post-bronchodilator		
VC (L)	2.7	2.52, 2.89
FVC (L)	2.68	2.5, 2.87
FVC (%)	82.78	78.84, 86.73
FEV ₁ (L)	1.62	1.48, 1.75
FEV ₁ (%)	65.29	60.9, 69.67
FEV ₁ /FVC	0.6	0.57, 0.62
FEF 25–75 (L/s)	0.996	0.89, 1.1
FEF 25–75 (%)	54.5	47.37, 61.62
PEF (L)	4.01	3.66, 4.36
PEF (%)	51.91	46.66, 57.16
TLC (L)	4.89	4.63, 5.15
RV (L)	2.42	2.27, 2.57
	Number of patients	Percent (%)
Comorbidities	71	89.9
Respiratory	14	17.7
Cardiovascular	63	79.7
Mental	9	11.4
Endocrine system	11	13.9
Central nervous system	10	12.7
Diabetes mellitus type 2	18	22.8
Other	47	59.5
Smoking history		
Smoker	18/72 ^a	25
Non-smoker	9/72 ^a	12.5
Ex-smoker	45/72 ^a	62.5
GOLD		
I stage	20	25.3
II stage	39	49.4
III stage	17	21.5
IV stage	3	3.8

Note: ^aSmoking history was reported in 72 records.

Abbreviations: FEF 25–75, forced expiratory flow between 25% and 75% of vital capacity; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; MPV, mean platelet volume; PDW, platelet distribution width; PEF, peak expiratory flow; PLR, platelet-to-lymphocyte ratio; RV, residual volume; TLC, total lung capacity; VC, vital capacity; WBC, white blood count.

Table 2 Functional and demographic parameters of the study population according to upper limit of PDW values

Parameter	PDW ≤ 16 (fL)	PDW > 16 (fL)	Mean difference	Comparison result	
	n=69	n=10		95% CI	P-value
	Mean	Mean			
Age (years)	73.57	74.1			0.64 ^a
WBC (×10 ³ /μL)	7.05	7.15			0.89 ^a
Neutrophils (×10 ³ /μL)	4.28	4.14	0.15	-0.97, 1.26	0.8
Lymphocytes (×10 ³ /μL)	2.05	2.26			0.63 ^a
Platelet count (×10 ³ /μL)	229.94	183.5	46.44	-17.74, 110.63	0.15
MPV (fL)	10.68	12.52	-1.84	-2.36, -1.32	<0.001
PLR	125.34	107.89			0.42 ^a
VC (L) ^b	2.67	2.9	-0.23	-0.79, 0.32	0.4
FVC (L) ^b	2.65	2.89	-0.24	-0.8, 0.32	0.4
FVC (%) ^b	82.64	83.8	-1.17	-13.1, 10.76	0.85
FEV ₁ (L) ^b	1.59	1.82	-0.23	-0.65, 0.18	0.26
FEV ₁ (%) ^b	64.69	69.37	-4.68	-17.9, 8.54	0.48
FEV ₁ /FVC ^b	0.6	0.57			0.2 ^a
FEF 25–75 (L/s) ^b	1.04	0.69	0.35	0.11, 0.59	0.007
FEF 25–75 (%) ^b	57.27	35.4	21.87	8.16, 35.58	0.003
PEF (L/s) ^b	4.13	3.17	0.96	0.32, 1.61	0.005
PEF (%) ^b	53.85	38.54	15.31	6.82, 23.78	<0.001
TLC (L)	4.9	4.79	0.11	-0.64, 0.88	0.76
RV (L)	2.39	2.65			0.25 ^a
	Number of patients and percent n=69	Number of patients and percent n=10			P-value
Gender					0.51
Male	44 (63.77%)	8 (80%)			
Female	25 (36.23%)	2 (20%)			
Smoking history	63	9			0.91
Smoker	15 (23.81%)	3 (33.3%)			
Non-smoker	8 (12.7%)	1 (11.1%)			
Ex-smoker	40 (63.49%)	5 (55.6%)			
GOLD stages of airway obstruction					0.90
I	16 (23.19%)	4 (40%)			
II	35 (50.72%)	4 (40%)			
III	15 (21.74%)	2 (20%)			
IV	3 (4.35%)	0			
Comorbidities					
Respiratory	13 (18.84%)	1 (10%)			0.81
Cardiovascular	55 (79.71%)	8 (80%)			0.98
Mental	8 (11.59%)	1 (10%)			0.88
Endocrine system	9 (13.04%)	2 (20%)			0.92
Central nervous system	10 (14.49%)	0			0.44
Diabetes mellitus type 2	16 (23.19%)	2 (20%)			0.82
Other	40 (57.97%)	7 (70%)			0.7

Notes: ^aP-value for Mann–Whitney *U* test. ^bPost-bronchodilator values.

Abbreviations: FEF 25–75, forced expiratory flow between 25% and 75% of vital capacity; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; MPV, mean platelet volume; PDW, platelet distribution width; PEF, peak expiratory flow; PLR, platelet-to-lymphocyte ratio; RV, residual volume; TLC, total lung capacity; VC, vital capacity; WBC, white blood count.

enhances platelet–surface interactions (adhesion) and platelet–platelet interaction (cohesion).⁶⁴ Progressively activated platelets with pseudopodia formation have heterogeneous size, and PDW may increase.⁴⁷ The association

of PDW with survival may be hypothetically linked with hypercoagulation, which plays a significant role in conditions associated with survival in COPD, eg, acute myocardial infarction and other forms of ischemic heart disease.^{58,59}

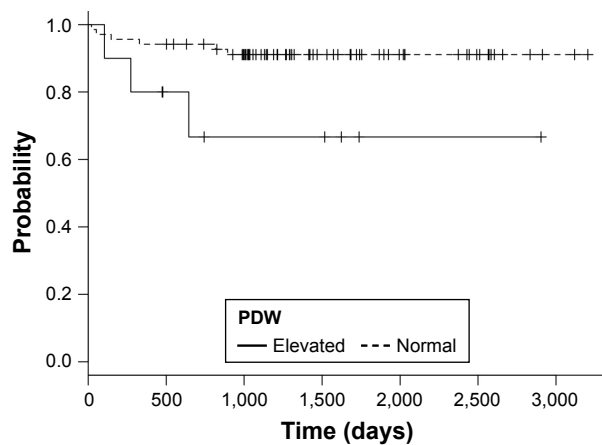


Figure 2 Kaplan–Meier curves for normal and elevated PDW values.
Abbreviation: PDW, platelet distribution width.

According to Wang et al, elevated PDW is a risk factor for pulmonary embolism and may be observed in COPD patients with this condition.⁶⁵

Our results are in line with other evidence which shows that PDW may be a marker of COPD exacerbations,⁶⁶ while patients with stable COPD do not seem to have higher PDW compared to controls.⁶⁷ Furthermore, the use of antiplatelet drugs was associated with improved survival in oxygen-dependent COPD patients.⁶⁸

While we excluded patients with diseases with an obvious impact on PDW or inflammation, in our sample, comorbidities were common, eg, prevalence of diabetes mellitus was 23%. Makhlouf et al showed that COPD patients with diabetes mellitus had significantly higher PDW compared to healthy controls, but there was no difference in PDW between COPD patients with and without diabetes mellitus.⁶⁹

We found significantly lower values of FEF 25–75 and PEF among patients with elevated PDW. This is a novel finding in a population of patients with COPD. Indeed, FEF 25–75 reflects the expiratory flows in peripheral airways, whereas PEF is strictly dependent upon the strength of expiratory muscles. Thus, these findings, though preliminary in nature, suggest that higher PDW, as a marker of inflammatory and hypercoagulable status, is linked to lung metabolism/inflammation and sarcopenia. Unfortunately, we lacked additional information, such as breath pattern analysis and direct measurement of respiratory muscle strength, to test this hypothesis. However, we think that it is unlikely that PDW per se has any direct effect on pulmonary function. The associations that we have found are most likely due to platelet morphology acting as a marker for some other biological process, such as inflammation. Due to the retrospective character of our study, causal relationship

cannot be verified, and our results must also be interpreted in light of the fact that both of these parameters have limited clinical value in COPD, while we found no difference in spirometric parameters known to have important prognostic significance (FEV₁, FVC). Measurement of FEF 25–75 does not contribute to clinical decision making.⁷⁰ PEF is recorded in the first tenth of a second of forced expiration, while FEV₁ continues to record forced expiration for a further 0.9 s, therefore FEV₁ records what happens to expired air after peak flow is reached. It is in this component of forced expiration that the changes characteristic of COPD are observed.⁷¹

There are some limitations of our study that need to be taken into account. Our sample size is relatively small and we could not fully investigate the relationship between PFT and PDW. Furthermore, our study is a retrospective analysis and we have to be aware of a risk of selection bias.

Conclusion

Our pilot analysis shows that PDW is associated with survival in patients with COPD. As it can be simply and rapidly measured from routine blood examination, should our results be confirmed in larger samples, it may prove to be a widely available, inexpensive, and repeatable prognostic marker. Furthermore, it might contribute to the characterization of the phenotypic variability of COPD.

Author contributions

AJB – study conception, design, and coordination, acquisition of data, analysis, and interpretation of data, statistical analysis, drafting of manuscript; CP – study conception, design, and coordination, acquisition of data, analysis and interpretation of data, statistical analysis, drafting of manuscript; WJP – contributed to the design of the study, analysis, and interpretation of data, critical revision; RAI – study design and coordination, analysis and interpretation of data, critical revision, drafting of manuscript. All authors edited and approved the final version of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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