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ORIGINAL ARTICLE

Platelet distribution width is highly associated with thrombotic events in primary antiphospholipid syndrome

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Abstract

Objective Platelet activation is a possible pathogenic process contributing to thromboembolism in antiphospholipid syndrome (APS), and platelet distribution width (PDW) is associated with platelet activation. The objective of this study was to evaluate the association between platelet indices and thrombotic events in patients with primary APS.

Methods This single-center cross-sectional study included 207 consecutive patients with APS treated at our institution between 2010 and 2019. Results of blood tests were recorded retrospectively from medical records.

Results Of the included patients, 135 (65.2%) were female and 72 (34.8%) were male. They were classified into thrombotic ($n=150$) or non-thrombotic ($n=57$) groups. PDW, mean platelet volume, and large platelet ratio were significantly higher in the thrombotic group. In univariate logistic analysis, PDW was significantly associated with an increased odds of thrombosis [odds ratio (OR) 1.554, 95% confidence interval (CI) 1.289–1.873, $p<0.001$]. In multivariate logistic analysis, PDW and positive lupus anticoagulant (LA) were risk factors for thrombosis. Receiver operating characteristic analysis showed that PDW, combined with a positive LA, was a reliable indicator of thrombosis, with an area under the curve of 0.796 (95% CI 0.728–0.864). The optimal cutoff value for PDW was 12.4 fl, with a sensitivity of 72.0% and specificity of 77.2%. Multivariate logistic regression of PDW tertiles showed that the odds of thrombosis increased abruptly in the highest tertile.

Conclusion This study confirmed the association between PDW and thrombotic events in APS patients, supporting the theory that platelet activation is a crucial mechanism of thrombosis in APS.

Key Points
- *This study is the first to discuss the correlation between PDW and thromboses in patients with APS.*
- *This study provides evidence of the important role of platelet activation in the pathogenesis of APS.*

Keywords Antiphospholipid antibodies · Antiphospholipid syndrome · Platelet distribution width · Platelet indices · Thrombosis · Thrombotic events

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Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies (aPLA), including anticardiolipin (aCL) antibodies, anti-β-glycoprotein I (anti-β2GPI) antibodies, lupus anticoagulant (LA), and non-criteria antiphospholipid antibodies [1]. The main clinical features are venous and arterial thromboses and obstetrical complications (primarily recurrent fetal loss) [2, 3]. APS is a common cause of acquired thrombophilia and is associated with morbidity and mortality secondary to thrombotic events.

The mechanism of thrombosis in patients with APS is not completely clear. Various mechanisms have been proposed (albeit not yet confirmed), including aPLA disruption of fluid-phase coagulation (interference with activation of protein C, interference with annexin A5, and inhibition of fibrinolysis); perturbation of endothelial cells; induction of tissue factor expression on circulating monocytes; and complement activation [4]. Platelets also play a crucial role in hemostasis, thrombosis, and vascular injury and provide a surface with multiple receptors for coagulation reactions [5]. Upon activation, platelets release multiple molecules, including vasoactive and thrombogenic agents, leading to the hypothesis that excessive platelet activation is critical for thrombosis development in patients with APS.

Platelet indices include platelet distribution width (PDW), mean platelet volume (MPV), and large platelet ratio (P-LCR). Previous studies demonstrated increases in MPV and PDW upon platelet activation because of platelet swelling and pseudopodia formation [6]. In APS, multiple prospective studies and a meta-analysis reported significant associations between MPV and thrombotic events, whereas not much evidence could be found to establish a correlation between PDW and clinical manifestations of APS. It is recently reported in a retrospective study that PDW may be a potential marker to predict lupus nephritis [7].

This study aims to evaluate the association between PDW and thrombotic events in patients with primary APS and explore whether PDW is a reliable predictor of thrombosis in these patients.

Materials and methods

Study population

Consecutive patients with primary APS treated at Peking Union Medical College Hospital between January 2010 and December 2019 were evaluated. The diagnosis of APS was based on the 2006 Sydney revised classification criteria. The patients were categorized into thrombotic or non-thrombotic groups according to the presence or absence of previous thrombotic events (the non-thrombotic group included patients with previous obstetric complications). We excluded patients diagnosed with systemic lupus erythematosus (SLE) or other underlying autoimmune diseases (i.e., secondary APS), as well as individuals with acquired thrombophilia from other causes, including nephrotic syndrome, cancer, use of oral contraceptives, and use of hormone replacement therapy. Patients with thrombocytopenia (platelet count $< 50 \times 10^9$/L) were also excluded, as the standard deviation of the PDW measurements could be influenced.

This study was approved by the medical ethics committee of Peking Union Medical College Hospital (approval number: JS-2038). It was conducted in accordance with the Declaration of Helsinki principles and followed the International Conference on Harmonization Guideline for Good Clinical Practice. Written informed consent was obtained from all patients.

Measurement of antiphospholipid antibodies

QUANTA Lite™ ELISA kits (INOVA Diagnostics, Inc., San Diego, CA, USA) were used to measure aCL antibodies and anti-β2GPI antibodies. The cutoff values for positivity were set at > 12 PL IgG-U/mL and > 20 RU/mL, respectively, according to the manufacturer's recommendations. Lupus anticoagulant was detected and measured at the Key Laboratory, according to the International Society on Thrombosis and Hemostasis recommendations. Dilute Russell viper venom time (dRVVT) and activated partial thromboplastin time were determined, with LA considered positive when the dRVVT ratio was > 1.20.

Data collection

Demographic characteristics were recorded at baseline. All patients were examined by rheumatologists. Neurologists and cardiologists were also involved when appropriate, based on disease manifestations. Hematologic parameters, including complete blood count, PDW, MPV, P-LCR, erythrocyte sedimentation rate, and high-sensitivity C-reactive protein (hsCRP) were measured within 60 min of blood collection using an XN-2000 automated hematology analyzer (Sysmex Diagnostics, Kobe, Japan). Platelet indices were recorded at the time of registry. The normal reference range for PDW was 9.0–17.0 fl in our laboratory. Anti-nuclear antibodies, anti-dsDNA, and anti-U1 ribonucleoprotein antibodies were also determined to detect underlying autoimmune diseases. All patients underwent testing for APS and hereditary thrombophilias (e.g., antithrombin, protein C, or protein S deficiency; activated protein C resistance; factor V Leiden mutation). For coagulation tests, patients

were evaluated at least 3 months after a thrombotic event. All thrombotic events were confirmed using vascular ultrasound or other objective imaging modalities.

Statistical analysis

Continuous variables were expressed as median (interquartile range), and categorical variables were expressed as number (percentage). The Shapiro–Wilk test was performed to assess normality. To compare differences between thrombotic and non-thrombotic groups, the Mann–Whitney U test was used for continuous variables. For variables not normally distributed or of unequal variance, the non-parametric Kruskal–Wallis test was applied. To identify potential risk factors that might influence thrombosis occurrence, univariate and multivariate logistic regression analyses were conducted. Receiver operating characteristics (ROC) analysis was performed to determine the sensitivity and specificity with 95% confidence intervals (CIs) at various cutoff values of PDW predictive of thrombosis recurrence. *P* values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS statistics version 26.0 (IBM, Armonk, NY, USA).

Results

A total of 207 patients (135 [65.2%] female, 72 [34.8%] male) were recruited and evaluated (Table 1). Their median age was 35 years (30–40). The thrombotic group included 150 patients (72.5%), and the non-thrombotic group included 57 patients (27.5%). The mean of the number of thrombotic events was 1.72. The number of different kinds of thrombotic events are illustrated in Table 1. There were no significant differences in age, surgery, diabetes mellitus, hypertension, hypercholesterolemia, or smoking status between the two groups.

The antibody profiles and other laboratory characteristics are summarized in Table 2. The PDW, MPV, and

Table 1 Demographic and clinical characteristics

Characteristics	Thrombotic group ($n=150$)	Non-thrombotic group ($n=57$)	*P* value*
Age, years, median (IQR)	34.5 (27–43)	33.0 (30–36)	0.411
Sex, female/male, n	78/72	57/0	< 0.001
Disease duration, years, median (IQR)	2.5 (1.4–4.0)	1.5 (1.2–3.4)	0.020
Surgery, immobilization, or trauma, n (%)	4 (3)	0	0.577
Diabetes mellitus, n (%)	2 (1)	1 (2)	1.000
Hypertension, n (%)	17 (11)	5 (9)	0.770
Hypercholesterolemia, n (%)	6 (4)	1 (2)	0.676
Smoking, n (%)	35 (23)	1 (2)	0.054
BMI, median (IQR)	23.8 (21.5–26.7)	22.1 (20.7–24.0)	0.005
Events of arterial thrombosis, n (%)	75 (46.6)	0	< 0.001
Brain infarction	40 (53.3)		
Coronary arterial thrombosis	12 (16.0)		
Abdominal arterial thrombosis	10 (13.3)		
Arterial thrombosis of lower extremity	11 (14.7)		
Other AT	2 (2.7)		
Events of venous thromboses, n (%)	86 (53.4)	0	< 0.001
DVT	34 (39.5)		
CVST	12 (14.0)		
PE	29 (33.7)		
PVT	6 (7.0)		
Other VT	5 (5.8)		
Pregnancy morbidity, n (%)	17 (11)	57 (100)	< 0.001
Medication			
Aspirin, n (%)	60 (40)	49 (86)	< 0.001
Warfarin, n (%)	83 (55)	1 (2)	< 0.001

BMI, body mass index; *IQR*, interquartile range (25th to 75th percentile); *AT*, arterial thrombosis; *DVT*, deep vein thrombosis; *CVST*, cerebral venous sinus thrombosis; *PVT*, portal venous thrombosis; *VT*, venous thrombosis

*P value based on Mann–Whitney U, Fisher's exact, or Pearson's chi-squared test

P-LCR were significantly higher in the thrombotic group than in the non-thrombotic group: 13.0 fl (11.5–14.9) vs 11.2 fl (10.3–12.3) ($p < 0.001$), 10.7 fl (10.0–11.4) vs 10.0 fl (9.6–10.8) ($p < 0.001$), and 10.7% (10.0–11.4) vs 10.0% (9.6–10.8) ($p < 0.001$), respectively. There were no differences in white blood cell count, hsCRP, or complement component 3 (C3) between groups. Platelet count and hemoglobin were lower in the thrombotic group than in the non-thrombotic group: 206.5×10^9/L (149.5–253.5) vs 243×10^9/L (176.8–287) (p = 0.023) and 143 g/L (128–156) vs 132 g/L (126–141) (p = 0.001), respectively.

Box plots showing the distribution of PDW according to aPLA profiles are presented in Fig. 1. Patients who were positive for aPLA (positive for all three antibodies combined or positive for any of the individual antibodies) had higher levels of PDW.

Age, body mass index, platelet count, PDW, MPV, P-LCR, hemoglobin, hsCRP, and C3 were analyzed in logistic regression. Only age, PDW, and LA were entered in the risk-factor analysis. In both univariate and multivariate logistic regression analyses, PDW and a positive LA appeared to be the most reliable predictors of thrombotic events (Table 3). Age was also a risk factor, showing significance in multivariate analysis but not in univariate analysis.

ROC analysis showed that PDW, combined with positive LA, was a reliable indicator of thrombotic events, with an AUC of 0.796 (95% CI 0.728–0.864) (Fig. 2). The optimal cutoff value for PDW was 12.4 fl, with a sensitivity of 72.0% and a specificity of 77.2%.

We also divided the study population into tertiles according to PDW. Multivariate logistic regression analysis according to tertile showed that PDW was not related to thrombotic events in the lowest two tertiles (Table 4). In contrast, the risk of thrombosis was significantly increased in the highest PDW tertile.

Discussion

This study identified PDW as a potential marker and predictor of thrombosis in patients with APS. PDW not only appeared to be reliable, but it is also accessible and economical. PDW, which reflects variations in platelet volume in a blood sample, was significantly higher in patients with a history of thrombotic events, and PDW was positively associated with the odds of a thrombotic event. PDW > 12.4 fl and a positive LA were identified as prognostic factors of thrombotic occurrence. This association was confirmed when performing multivariate logistic regression of PDW tertiles, as the odds of a thrombotic event abruptly increased in the highest tertile.

Table 2 Laboratory characteristics

Characteristics	Thrombotic group, median (IQR) ($n = 150$)	Non-thrombotic group, median (IQR) ($n = 57$)	*P* value*
Platelet count ($\times 10^9$/L)	206.5 (149.5–253.5)	243 (176.8–287)	0.023
PDW (fl)	13.0 (11.5–14.9)	11.2 (10.3–12.3)	< 0.001
MPV (fl)	10.7 (10.0–11.4)	10.0 (9.6–10.8)	< 0.001
P-LCR (%)	30.3 (24.7–36.3)	25.1 (21.3–31.7)	< 0.001
WBC count ($\times 10^9$/L)	6.17 (4.93–7.55)	6.83 (5.31–8.52)	0.116
Hemoglobin (g/L)	143 (128–156)	132 (126–141)	0.001
hsCRP (mg/L)	0.915 (0.455–1.870)	0.650 (0.305–1.605)	0.124
ESR (mm/h)	6 (3–12)	11 (8–22)	< 0.001
IgG (g/L)	10.95 (9.18–13.28)	10.78 (9.88–13.11)	0.651
IgA (g/L)	1.91 (1.29–2.65)	2.04 (1.58–2.67)	0.256
IgM (g/L)	1.29 (0.81–1.72)	1.68 (1.27–2.34)	< 0.001
C3 (mg/L)	0.986 (0.837–1.123)	0.946 (0.815–1.116)	0.559
Antibody profile, n (%)			
aCL	99 (66)	25 (44)	0.004
Anti-β2GPI	129 (86)	53 (93)	0.168
LA	108 (72)	17 (30)	< 0.001
Double or triple positivity	106 (71)	24 (42)	0.0002

aCL, anticardiolipin; *anti-β2GPI*, anti-β2-glycoprotein I; *C3*, complement component 3; *ESR*, erythrocyte sedimentation rate; *hsCRP*, high-sensitivity C-reactive protein; *Ig*, immunoglobulin; *IQR*, interquartile range; *LA*, lupus anticoagulant; *MPV*, mean platelet volume; *PDW*, platelet distribution width; *P-LCR*, large platelet ratio; *WBC*, white blood cell

[a]Data are median (interquartile range) except where otherwise indicated

*P value based on Mann–Whitney U, Fisher's exact, or Pearson's chi-squared tests

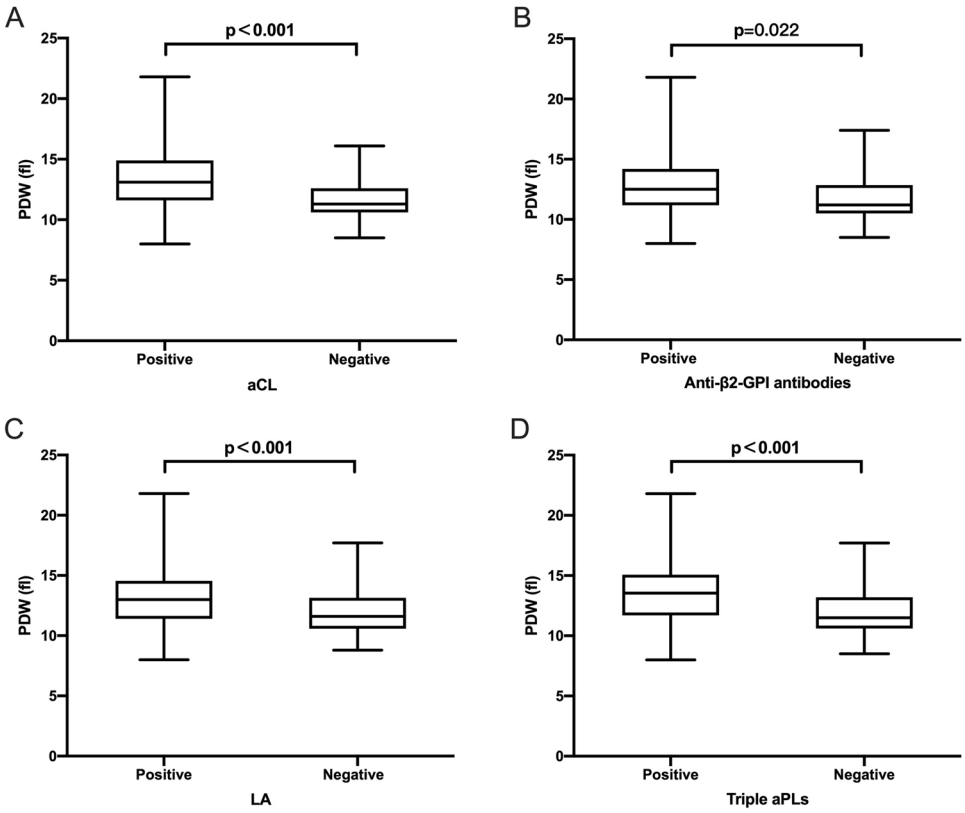

Fig. 1 Box plots showing the distribution of PDW according to aPLA profiles

In this study, we found that older age was associated with the occurrence of thrombotic events. This is consistent with the literature, as increased age has been widely confirmed as a risk factor for thrombosis [8, 9]. Platelets, as the first target in thrombosis, play a pivotal role in the pathologic mechanisms of APS. Wenche et al. [10] reported that platelet activation was significantly higher in APS patients with thrombotic events than in those without thrombotic events. aPLA, especially anti-β2GPI antibodies, have been confirmed to interact with platelets, and it is widely accepted that anti-β2GPI/β2GPI complexes interact with apolipoprotein E receptor 2′ and GPIbα on the surface of platelets to activate platelets by accelerating phosphorylation of p38 mitogen-activated protein kinase [11–13]. Hemoglobin can also interact with GPIbα to induce platelet activation [14]. After activation, membrane ballooning and pseudopod

Table 3 Univariate and multivariate logistic regression analysis of predictors for thrombotic events

Factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.024 (0.996–1.053)	0.089	1.050 (1.015–1.086)	0.005
PDW	1.554 (1.289–1.873)	< 0.001	1.519 (1.236–1.865)	< 0.001
LA	6.050 (3.096–11.825)	< 0.001	6.057 (2.856–12.844)	< 0.001

CI, confidence interval; *LA*, lupus anticoagulant; *OR*, odds ratio; *PDW*, platelet distribution width

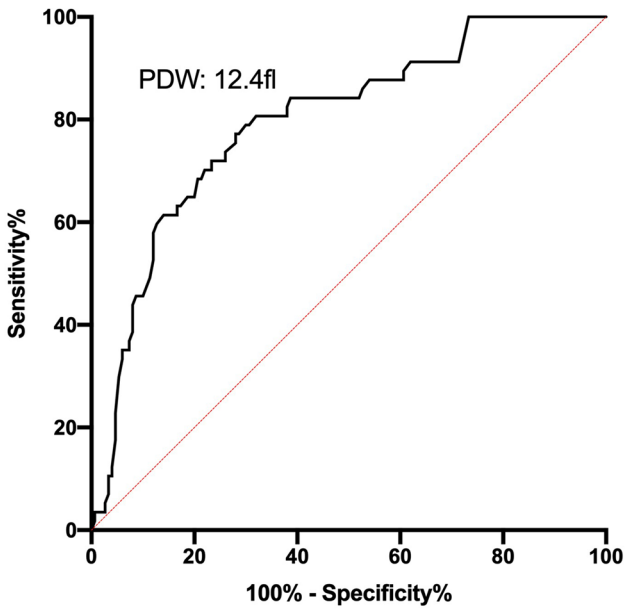

Fig. 2 ROC analysis showing PDW, combined with positive LA, as a reliable indicator of thrombotic events, with an AUC of 0.796 (95% CI 0.728–0.864)

Table 4 Multivariate regression analysis of odds of thrombosis for each PDW tertile

PDW tertiles					
< 11.4 fl		11.4–13.6 fl		> 13.6 **fl**	
OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
1.741 (0.799–3.791)	0.163	1.130 (0.431–2.965)	0.803	6.134 (1.219–30.860)	0.028

PDW, platelet distribution width; *OR*, odds ratio

[a]In this analysis, all covariates presented in Table 3 (age, PDW, and lupus anticoagulant) were adjusted for

formation occur [15], leading to an increased platelet volume. Platelet-derived microparticles (PMP) are vesicles secreted by activated platelets, which express or contain cellular proteins and nucleic acids. Massive release of PMP after activation leads to a decreased platelet volume [16].

Platelet indices may be used to reflect platelet activation. Studies assessing MPV levels in autoimmune diseases have produced contradictory results. Several studies have compared MPV between patients diagnosed with primary APS and healthy controls and found that MPV was significantly increased in primary APS patients with previous thrombotic events [17, 18]. Conversely, another study found lower MPV because of PMP release in SLE patients with aCL antibodies, compared with patients without aCL antibodies [19]. These discrepant results could be explained by differences in platelet activation status. Nevertheless, it is reasonable to deduce that platelet volume variation should increase during platelet activation, as will be reflected in an elevated PDW. As a more stable index compared with MPV, PDW is considered a more specific indicator of platelet activation than MPV [6]. We found that patients that had previous thrombotic events possess higher levels of PDW, which supports the theory that platelet activation plays an important role in the process of thromboses in patients with primary APS.

Changes in PDW have been observed in many diseases [20–22]. However, an association between PDW and aPLA has not been previously described. The association observed in the current study likely represents aPLA-mediated platelet activation. aPLA can mediate platelet activity by interacting with many glycoproteins on platelet membrane. Although the interaction between anti-β2GPI antibodies and platelets has been the most extensively described and confirmed, multiple studies have reported strong associations between LA and clinical manifestations in patients with APS. Several large prospective studies reported that both thrombosis and pregnancy morbidity are more strongly associated with LA than with anti-β2GPI or aCL antibodies [23–25]. Panzer et al. [26] found that platelets with exposed negatively charged phospholipids may contribute to the generation of LA, and activated platelets may have an increased binding affinity for LA. Like anti-β2GPI antibodies, aCL antibodies were also reported to activate platelets via β2GPI, although the exact mechanism remains controversial [27, 28]. The significant differences in PDW between different antibody profiles observed in the current study provide indirect evidence of the differing roles of various aPLA in platelet activation.

This study provides some new insights regarding the correlation between PDW and thromboses in patients with APS. Our findings suggest that PDW could be a simple and reliable marker for thrombotic events in APS. Our results also provide evidence of the important role of platelet activation in the pathogenesis of APS.

This study has some limitations. Its cross-sectional design prohibits conclusions about causal relationships. Furthermore, the sample size is relatively small, which may have contributed to a wider CI, thereby underestimating the association between PDW and thromboses. In addition, it is a single-center study using just one type of automated analyzer. The use of different analyzers may influence the measurements and final results. Changes of clotting index such as international normalized ratio (INR) could indicate the status of coagulation. They could be a confounding factor for thromboses which was not evaluated in our study. Nevertheless, it is hoped that this study will focus more attention on the role of platelet activation in the pathogenesis of APS and increase awareness of a promising marker of thrombotic events that is associated with platelet activation.

Conclusion

This study found that PDW could be a factor associated with thrombotic events in patients with primary APS. As PDW is routinely reported as a part of the complete blood count, it is accessible to most patients throughout the world. Patients with APS who have a positive LA and increased PDW appear to have a higher risk of thrombosis.

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Author contribution Y.S. and J.Z conceived the original idea, and Y.S. wrote the manuscript. H.J. and C.H. helped with the analytic calculations. Both C.H. and M.L. contributed to the final version of this manuscript. X.Z. supervised the project.

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Data availability The data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Ethics approval The study was approved by the medical ethics committee of Peking Union Medical College Hospital (approval number: JS-2038).

Consent to participate Written consent was obtained from all patients.

Consent for publication Written consent for publication was obtained from all participants.

Disclosures None.

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