Platelet Distribution Width Level in Patients With Systemic Lupus Erythematosus-Associated Pulmonary Arterial Hypertension and its Diagnostic Value

Yuzhu HE, Yikai YU, Shaoxian HU

Department of Rheumatology and Immunology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

ABSTRACT

Objectives: This study aims to compare the platelet distribution width (PDW) level in patients with systemic lupus erythematosus-associated pulmonary arterial hypertension (SLE-PAH) with that in patients with systemic lupus erythematosus alone (SLE-non-PAH) and to evaluate the clinical value of the PDW level in the early diagnosis of SLE-PAH.

Patients and methods: We analyzed 80 SLE-PAH patients (1 males, 79 females; 34.9±12.3 years; range, 19 to 77 years) and 154 sex- and age-matched SLE-non-PAH patients (4 males, 150 females; mean age 36.7±12.4 years; range, 19 to 69 years) hospitalized between June 2011 and April 2018. All patients underwent transthoracic Doppler echocardiography within three months of inclusion in the study. Age, sex, disease course, currently prescribed medications, clinical manifestations, and past history were collected. Pulmonary artery systolic pressure, ejection fraction, white blood cell count, red blood cell count, hemoglobin, platelet count, PDW, mean platelet volume, erythrocyte sedimentation rate, complement 3 (C3), and C4 levels were also obtained.

Results: The PDW level was higher in the SLE-PAH group than that in the SLE-non-PAH group (p=0.023). SLE patients were allocated into high systemic lupus erythematosus disease activity index (SLEDAI) group (SLEDAI score, ≥10) (n=121) or low SLEDAI group (SLEDAI score, <10) (n=113). The PDW level was significantly higher in the high SLEDAI group than that in the low SLEDAI group (p=0.030). The receiver operating characteristic curve was used to evaluate the clinical value of the PDW level in diagnosing PAH in SLE patients. The PDW level was valuable for diagnosing PAH in SLE patients [area under the curve (AUC)=0.591, p=0.023]. The optimal critical value of the PDW level was 14.55 fl. Under these conditions, the sensitivity, specificity, and Youden index were 57%, 63% and 0.20, respectively. For newly diagnosed patients, the PDW level had good diagnostic accuracy, with an AUC of 0.626 (p=0.037). The optimal critical value of the PDW level was 14.65 fl. Under these conditions, the sensitivity, specificity, and Youden index were 66%, 67% and 0.33, respectively.

Conclusion: The PDW level is a good predictor of SLE-PAH, and this parameter is applicable to various clinical settings.

Keywords: Platelet distribution width, predictor, pulmonary arterial hypertension, systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the presence of circulating autoimmune antibodies that damage multiple organs within the cardiovascular system, respiratory system, urinary system, and hematological system.1 Pulmonary arterial hypertension is comprised of a group of diseases characterized by the progressive increase of pulmonary resistance. The prevalence of SLE with pulmonary arterial hypertension (SLE-PAH) is significantly lower than that of the common clinical manifestations of SLE, such as lupus nephritis, arthritis, and hematological system involvement. Regardless, PAH is the third leading cause of death in SLE patients, and it is an independent risk factor for death in this
population. The five-year survival rate of patients with SLE-PAH is much lower than that of patients with SLE alone.\textsuperscript{2,3} Although PAH is not a common complication of SLE, the diagnosis and treatment of SLE-PAH should receive more attention due to its poor prognosis.

The early clinical manifestations of SLE-PAH are not always specific for the disease. Furthermore, there are few studies describing the biomarkers of SLE-PAH, and a lack of reliable biomarkers further complicates the diagnosis of the disease. Timely treatment can lengthen the survival time of SLE-PAH patients, so it is important to identify new biomarkers for the early diagnosis of SLE-PAH.\textsuperscript{4}

Platelet distribution width (PDW) level is an indicator of the heterogeneity in platelet (PLT) size. An elevated PDW level indicates increased PLT activation.\textsuperscript{5,6} Some studies have showed that PDW and mean PLT volume (MPV) are valuable biomarkers of immunological diseases.\textsuperscript{7-9} A previous study has reported an elevated PDW level in SLE patients, as well as a positive correlation between the PDW level and disease severity, suggesting that the PDW level is a predictor of SLE activity.\textsuperscript{10} PLT volume indexes are widely used as predictors of cardiovascular diseases.\textsuperscript{11-14} Recently, Zheng et al.\textsuperscript{15} found that the PDW level was elevated in patients with idiopathic pulmonary arterial hypertension (IPAH). However, to our knowledge, there is no study on the clinical value of the PDW level for diagnosing SLE-PAH. Therefore, in this study, we aimed to compare the PDW level in patients with SLE-PAH with that in patients with systemic lupus erythematosus alone (SLE-non-PAH) and to evaluate the clinical value of the PDW level in the early diagnosis of SLE-PAH.

**PATIENTS AND METHODS**

A total of 80 SLE-PAH patients (1 males, 79 females; 34.9±12.3 years; range, 19 to 77 years) as well as 154 sex- and age-matched SLE-non-PAH patients (4 males, 150 females; mean age 36.7±12.4 years; range, 19 to 69 years) hospitalized at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology between June 2011 and April 2018 were retrospectively analyzed. All patients met the diagnostic criteria for SLE, as revised by the American Society of Rheumatology in 1997 or the International Clinical Collaboration Group for SLE in 2012. Patients aged <16 years or those with a history of recent blood transfusion, recent pregnancy, IPAH, coronary heart disease, congenital heart disease, heart valve disease, chronic obstructive pulmonary disease, hematological system disease, cancer, serious infection, or other connective tissue diseases were excluded. All patients underwent transthoracic Doppler echocardiography within three months of inclusion in the study. The pulmonary artery systolic pressure (PASP) (mmHg) was estimated by tricuspid regurgitation. The PASP in the SLE-PAH group was ≥40 mmHg.\textsuperscript{16} The study protocol was approved by the Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The age, sex, disease course, currently prescribed medications, clinical manifestations, and past history were collected. The PASP, ejection fraction (EF), white blood cell count, red blood cell count (RBC), hemoglobin (Hb), PLT count, PDW, MPV, erythrocyte sedimentation rate (ESR), complement 3 (C3), and C4 levels were also obtained. The severity of SLE was evaluated by the systemic lupus erythematosus disease activity index (SLEDAI).

**Statistical analysis**

When two samples met the conditions of normal distribution and homogeneous variance, the t-test was used and results were described by mean ± standard deviation; otherwise, the Mann-Whitney test was used and results were described by median (25\textsuperscript{th} percentile, 75\textsuperscript{th} percentile). When two samples met the condition of normal distribution, Pearson’s correlation analysis was used; otherwise, Spearman’s correlation analysis was used.

Counting data were presented as percentages. The four-grid table was used to determine whether there was a significant difference in the sample rate between the two groups.

The receiver operating characteristic (ROC) curve was used to evaluate the clinical value of
## Table 1. Comparison of systemic lupus erythematosus-associated pulmonary arterial hypertension group and systemic lupus erythematosus alone group

|                       | SLE-PAH patients (n=80) |                       |                      | SLE-non-PAH patients (n=154) |                       |                      |                      |                           |
|-----------------------|-------------------------|-----------------------|----------------------|-----------------------------|-------------------------|----------------------|----------------------|---------------------------|
|                       | n (%)                   | Mean±SD               | Median               | 25th-75th percentile        | n (%)                   | Mean±SD               | Median               | 25th-75th percentile        | p                  |
| Age (year)            | 34.9±12.3               | 36.7±12.4             | 0.303                | 3.5±3.8                    | 3.7±4.7                 | 0.776                |                      |                           |
| Course (year)         | 99                      |                       | 0.873                | 4                          | 4.7±12.3               |                      |                      |                           |
| Sex                   |                         |                       |                      | 1                          | 4                       |                      |                      |                           |
| Male                  | 1                       | 79                    |                      | 96                         | 62.34                   |                      |                      |                           |
| Female                | 79                      | 150                   |                      | 150                        |                         |                      |                      |                           |
| Glucocorticoid        | 42                      | 52.50                 | 0.147                | 96                         | 62.34                   |                      |                      |                           |
| Diabetes mellitus     | 5                       | 6.25                  |                      | 3                          | 1.95                    | 0.086                |                      |                           |
| Hypertension          | 10                      | 12.50                 | 0.323                | 13                         | 8.44                    |                      |                      |                           |
| PASP (mmHg)           | 66.00                   | 52.25-82.25           | 0.001*               | 28.00                      | 24.00-32.00             | <0.001*              |                      |                           |
| EF (%)                | 66.00                   | 61.25-70.00           | 0.219                | 67.00                      | 64.00-71.00             |                      |                      |                           |
| SLEDAI                | 12.6±6.9                | 10.2±5.9              | 0.005*               | 12.6±6.9                   | 10.2±5.9               |                      |                      |                           |
| Shortness of breath   | 51                      | 63.75                 | <0.001*              | 26                         | 16.88                   | <0.001*              |                      |                           |
| Chest tightness       | 53                      | 66.25                 | <0.001*              | 31                         | 20.13                   | <0.001*              |                      |                           |
| Raynaud’s phenomenon  | 23                      | 28.75                 | 0.034*               | 26                         | 16.88                   | 0.007*               |                      |                           |
| Interstitial lung disease | 15                      | 18.75                 | 0.007*               | 11                         | 7.14                    | 0.007*               |                      |                           |
| ESR (mm/h)            | 44.00                   | 12.00-81.50           | 0.314                | 32.00                      | 16.00-61.00             | 0.314                |                      |                           |
| IgA (g/L)             | 2.64                    | 1.79-3.57             | 0.728                | 2.67                       | 2.04-3.49               | 0.728                |                      |                           |
| IgM (g/L)             | 1.14                    | 1.79-3.57             | 0.577                | 1.19                       | 0.80-1.64               | 0.577                |                      |                           |
| IgG (g/L)             | 22.10                   | 12.73-32.54           | 0.001*               | 16.02                      | 12.28-20.33             | 0.001*               |                      |                           |
| C3 (g/L)              | 0.7±0.4                 | 0.7±0.3               | 0.752                | 0.7±0.4                    | 0.7±0.3                 |                      |                      |                           |
| C4 (g/L)              | 0.1±0.1                 | 0.2±0.1               | 0.040*               | 0.1±0.1                    | 0.2±0.1                 |                      |                      |                           |
| RBC (10^12/L)         | 3.8±1.0                 | 3.7±0.7               | 0.333                | 3.8±1.0                    | 3.7±0.7                 |                      |                      |                           |
| Hb (g/L)              | 110.1±30.2              | 107.5±19.5            | 0.434                | 110.1±30.2                 | 107.5±19.5             | 0.434                |                      |                           |
| PLT (10^9/L)          | 139.00                  | 94.50-215.00          | 0.013*               | 178.00                     | 130.50-228.50          | 0.013*               |                      |                           |
| MPV (fl)              | 9.90                    | 7.70-11.30            | 0.183                | 9.90                       | 7.70-11.30             | 0.183                |                      |                           |
| PDW (fl)              | 14.60                   | 11.90-16.20           | 0.023*               | 14.60                      | 11.90-16.20            | 0.023*               |                      |                           |

SLE: Systemic lupus erythematosus; PAH: Pulmonary arterial hypertension; SD: Standard deviation; PASP: Pulmonary artery systolic pressure; EF: Ejection fraction; SLEDAI: Systemic lupus erythematosus disease activity index; ESR: Erythrocyte sedimentation rate; Ig: Immunoglobulin; C3, C4: Complement 3, 4; RBC: Red blood cell count; Hb: Hemoglobin; PLT: Platelet; MPV: Mean platelet volume; PDW: Platelet distribution width; SLE-non-PAH: Systemic lupus erythematosus alone; * Represents p value <0.05.
the PDW level for diagnosing SLE-PAH. The p value and area under the curve (AUC) were calculated. The sensitivity, specificity, and Youden index corresponding to the best critical value were also calculated. A p value <0.05 was considered statistically significant. The IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA) software was used for statistical analysis.

**RESULTS**

No significant differences in age, disease course, sex ratio, glucocorticoid use ratio, and proportions of diabetes mellitus and hypertension were observed between the SLE-PAH and SLE-non-PAH groups (all p values >0.05). The PASP of the SLE-PAH group was higher than that of the SLE-non-PAH group (p<0.001), whereas there was no difference in the EF between the groups (p=0.219). The SLEDAI score of the SLE-PAH group was significantly higher than that of the SLE-non-PAH group (p=0.005). The incidence rates of shortness of breath, chest tightness, Raynaud’s phenomenon, and interstitial lung disease in the SLE-PAH group were higher than those in the SLE-non-PAH group (all p values <0.05). Thirty-eight patients were allocated into the newly diagnosed SLE-PAH group, whereas 58 patients were allocated into the newly diagnosed SLE-non-PAH group. Newly diagnosed patients had similar clinical characteristics (Tables 1 and 2).

The PDW level as well as the immunoglobulin IgG concentration were higher in the SLE-PAH group than those in the SLE-non-PAH group (all p values <0.05). The serum C4 and PLT values in the SLE-PAH group were lower than those in the SLE-non-PAH group (all p values <0.05). No statistical differences in the ESR and the levels of IgA, IgM, C3, RBC, Hb, and MCV were observed between the SLE-PAH and SLE-non-PAH groups (all p values >0.05). For newly diagnosed SLE patients, the PDW level in the SLE-PAH group was also higher than that in the SLE-non-PAH group (p=0.049). SLE patients were allocated into high SLEDAI group (SLEDAI score, ≥10) (n=121) or low SLEDAI group (SLEDAI score, <10) (n=113). The PDW level in the high SLEDAI group was 14.80 (11.30, 16.00) fL, which was significantly higher than that in the low SLEDAI group of (p=0.030). Newly diagnosed SLE patients were allocated into high SLEDAI group (n=59) or low SLEDAI group (n=36). PDW level in the high SLEDAI group was also higher (0.015) (Tables 1, 2 and 3).

| Table 2. Comparison of initially diagnosed systemic lupus erythematosus-associated pulmonary arterial hypertension patients and systemic lupus erythematosus alone patients |
|---------------------------------------------------------------|
| **SLE-PAH patients (n=38)** | **SLE-non-PAH patients (n=58)** |
| **Age (year)** | 33.6±13.8 | 35.3±12.1 | 0.522 |
| **Course (year)** | 1.00 | 0.08-2.50 | 0.25 | 0.08-1.00 | 0.108 |
| **Sex** | | | | 1.000 |
| Male | 1 | | 2 | |
| Female | 37 | | 56 | |
| **Diabetes mellitus** | 1/38 | 2.63 | 1/58 | 1.72 | 1.000 |
| **Hypertension** | 4/38 | 10.53 | 5/58 | 8.62 | 0.737 |
| **PASP (mmHg)** | 58.50 | 52.00-76.25 | 27.00 | 24.00-32.00 | <0.001* |
| **EF (%)** | 65.50 | 61.00-70.00 | 67.00 | 63.00-71.00 | 0.167 |
| **SLEDAI** | 12.5±6.1 | 9.9±5.5 | 0.002* |
| **PLT (10³/L)** | 136.00 | 83.50-255.75 | 175 | 131.5-207.5 | 0.203 |
| **MPV (fL)** | 9.15 | 7.05-11.05 | 10.3 | 9.3-11.40 | 0.037* |
| **PDW (fL)** | 15.15 | 11.85-16.28 | 13.9 | 11.35-15.05 | 0.049* |

SLE: Systemic lupus erythematosus; PAH: Pulmonary arterial hypertension; SD: Standard deviation; PASP: Pulmonary artery systolic pressure; EF: Ejection fraction; SLEDAI: Systemic lupus erythematosus disease activity index; PLT: Platelet; MPV: Mean platelet volume; PDW: Platelet distribution width; SLE-non-PAH: Systemic lupus erythematosus alone; * Represents p value <0.05.
The ROC curve was used to evaluate the clinical value of the PDW level for diagnosing PAH in SLE patients. The PDW level had certain diagnostic value, with an AUC of 0.591 (p=0.023). The optimal critical value of the PDW level was 14.55 fL. Under these conditions, the sensitivity, specificity, and Youden index were 57%, 63% and 0.20, respectively. For newly diagnosed patients, the PDW level had good diagnostic accuracy, with an AUC of

Table 3. Comparison of platelet distribution width level in high systemic lupus erythematosus disease activity index group with that in low systemic lupus erythematosus disease activity index group

| Grouping                  | All SLE patients (n=234) | Newly diagnosed patients (n=96) |
|---------------------------|--------------------------|--------------------------------|
| SLEDAI ≥10 (n=121)       | SLEDAI <10 (n=113)       | p                               |
| PDW (fL)                 | 14.80                    | 11.30-16.00                    | 12.90  | 11.30-15.20 | 0.030  | 14.8   | 12.30-15.90 | 12.20  | 11.10-15.00 | 0.015  |

SLE: Systemic lupus erythematosus; SLEDAI: Systemic lupus erythematosus disease activity index; PDW: Platelet distribution width; * Represents p value <0.05.

Table 4. Evaluation of diagnostic value for systemic lupus erythematosus-associated pulmonary arterial hypertension of PDW and sUA by receiver operating characteristic curve

| Test variable | AUC   | 95% CI       | Best critical value (fL) | Sensitivity (%) | Specificity (%) | Youden index | p     |
|---------------|-------|--------------|--------------------------|-----------------|-----------------|--------------|-------|
| PDW           | 0.591 | 0.510-0.672  | 14.55                    | 57              | 63              | 0.20         | 0.023*|

Table 5. Evaluation of diagnostic value for systemic lupus erythematosus-associated pulmonary arterial hypertension of PDW and sUA in newly diagnosed patients

| Test variable | AUC   | 95% CI       | Best critical value (fL) | Sensitivity (%) | Specificity (%) | Youden index | p     |
|---------------|-------|--------------|--------------------------|-----------------|-----------------|--------------|-------|
| PDW           | 0.626 | 0.502-0.751  | 14.65                    | 66              | 67              | 0.33         | 0.037*|

AUC: Area under the curve; CI: Confidence interval; PDW: Platelet distribution width; sUA: Serum uric acid; * Represents p value <0.05.

Figure 1. Value of platelet distribution width for diagnosing pulmonary arterial hypertension in systemic lupus erythematosus patients.

Figure 2. Value of platelet distribution width for diagnosing pulmonary arterial hypertension in newly diagnosed systemic lupus erythematosus patients.

PDW: Platelet distribution width.
Platelet Distribution Width Level in Patients With SLE-Associated PAH

0.626 (p=0.037). The optimal critical value of the PDW level was 14.65 fL. Under these conditions, the sensitivity, specificity, and Youden index were 66%, 67% and 0.33, respectively (Tables 4 and 5 and Figures 1 and 2).

**DISCUSSION**

The clinical symptoms of SLE-PAH are not specific to the disease, as similar symptoms have been reported for other rheumatoid, cardiovascular, respiratory, and renal disorders. In addition, there are few reliable biomarkers for the diagnosis of the disease. The aim of this study was to identify a new biomarker for the early diagnosis of SLE-PAH.

In this study, no significant differences in the age, disease course, sex ratio, glucocorticoid use ratio, and proportions of diabetes mellitus and hypertension between the SLE-PAH and SLE-non-PAH groups were noted.

The PDW level, which reflects the size of PLTs, is a predictor of PLT activation. PLT activation, which involves inflammatory cytokines and complements, has been observed in patients with SLE. A previous study has reported an elevated PDW level in SLE patients compared to healthy controls, as well as a positive correlation between the PDW level and disease severity. Therefore, the PDW level may be a reliable marker for the clinical assessment of SLE. Another study has indicated that the PDW level was higher in patients with IPAH than that in healthy controls; thus, the PDW level may also reflect the severity of IPAH.

We found that the PDW level was higher in the SLE-PAH group than that in the SLE-non-PAH group. As discussed above, an elevated PDW level, which was observed in patients with SLE or IPAH, indicates increased PLT activation. In this study, the SLEDAI score, which reflects the severity of SLE, was higher in the SLE-PAH group than that in the SLE-non-PAH group. The PDW level was higher in the high SLEDAI group than that in the low SLEDAI group, suggesting that the PDW level can reflect the severity of SLE at least to some degree. SLE patients with higher disease severity may have greater systemic inflammation, which can lead to PLT activation and an elevated PDW level. Moreover, increased PLT activation can cause thrombosis, which may contribute to vascular changes in patients with pulmonary arterial hypertension. Furthermore, we observed that the PDW level had certain clinical value in the diagnosis of SLE-PAH. For newly diagnosed SLE patients, the PDW level also had good diagnostic accuracy.

Our study had several limitations. Firstly, the PASP was estimated by tricuspid regurgitation. Although a previous study has defined a PASP of 40 mmHg as good cut-off value for the diagnosis of PAH, heart catheterization is the gold standard for PASP measurement. Secondly, the size of the study sample was not large enough, and further studies are needed to validate our findings.

In conclusion, the prognosis of SLE-PAH is poor. Furthermore, many SLE-PAH patients present with clinical symptoms that are not specific to the disease, which contributes to incorrect and missed diagnoses and to the lack of timely treatment. Recently, SLE-PAH research has gained momentum. In this study, we showed that the PDW level has certain clinical value in the diagnosis of SLE-PAH, and this parameter is applicable to various clinical settings. However, further studies are needed to better reflect its value in the early diagnosis of SLE-PAH.

**Declaration of conflicting interests**

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