Anti-PLA2R Antibodies Measured by ELISA Predict the Risk of Vein Thrombosis in Patients With Primary Membranous Nephropathy

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Research Article

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Abstract

Background

Primary membranous nephropathy (PMN) is associated with the highest risk for developing venous thrombosis compared with other nephrotic diseases. The aim of the study was to assess the predictive value of the pathognomonic anti-PLA2R antibody with regard to incidence of venous thrombosis in PMN.

Methods

269 PMN patients with venous thrombosis examination were collected and analyzed. Anti-PLA2R antibodies were detected by commercial enzyme-linked immunosorbent assay. Multivariate Logistic regression was used to detect the independent risk factors for venous thrombosis.

Results

28 patients (10.4%) had venous thrombosis. Patients with venous thrombosis had higher levels of CHOL, LDL, and D-dimer than those without venous thrombosis (P<0.05). Patients with venous thrombosis had significantly lower levels of ALB (23.26 ± 5.24 *vs.* 26.00 ± 6.69 g/L, P=0.037). No significant differences were found in urine proteinuria, SCR, eGFR, platelets and fibrinogen between patients with and without thrombosis. Anti-PLA2R antibody levels in patients with venous thrombosis were significantly higher than in patients without it (P=0.010). In the univariate logistic regression, Ln PLA2R (OR: 1.316; P=0.032), ALB (OR: 0.932; P=0.039), CHOL (OR: 1.189, P=0.015) , and LDL (OR: 1.288，P=0.009) were associated with venous thrombosis. PLA2R-Ab (OR=1.316; 95%CI: 1.024~1.691), and LDL (OR=1.229; 95%CI: 1.012~1.493) were the independent risk factors for venous thrombosis (P<0.05) in multivariate analysis.

Conclusion

Anti-PLA2R antibody was the independent risk factor for venous thrombosis in PMN. Larger prospective studies were warranted to verify the results in future.

Background

Deep vein thrombosis (DVT), renal vein thrombosis (RVT) and pulmonary embolism (PE) are collectively known as venous thromboembolism (VTE), which is a common complication and a major cause of morbidity and mortality in patients with nephrotic syndrome (NS) [1, 2].

The underlying pathophysiological mechanisms of VTE in patients with NS have not been fully elucidated. Hypercoagulability is postulated to due to a variety of elements, including the imbalance of glomerular loss of coagulation factors with increased liver procoagulants synthesis, altered platelet activity, intravascular volume contraction, venous stasis accompanying edema [3, 4]. Proteinuria and serum albumin levels, which reflect the severity of NS, are the most frequently studied VTE risk factors in patients with NS [5–7]. Higher proteinuria and lower serum albumin levels have been suggested to be risk

factors of VTE in some but not all studies [7–10]. Compared with other nephrotic diseases, membranous nephropathy (MN) is associated with the highest risk for developing venous thrombosis, especially renal vein thrombosis [11, 12], even adjusted for gender, proteinuria, and serum albumin by multivariable analysis [13]. The reason for the increased thromboembolic risk in MN has yet to be unraveled.

Identification of antibodies to phospholipase A2 receptor (PLA2R) in 70–80% of adult patients with primary MN (PMN) is the major breakthrough, which shows primary MN is an autoimmune disease [14, 15]. Anti-PLA2R antibodies are highly specific for MN, rarely being detected in other nephropathies, autoimmune diseases, or healthy individuals. Furthermore, a number of studies have shown that PLA2R autoantibodies correlate closely with disease activity and progression [16, 17] and can be used to monitor response to immunosuppressive therapy [18, 19]. Since anti-PLA2R antibodies are considered to be pathogenic for MN, some researchers have postulated the association between anti-PLA2R antibodies and the particularly high VTE risk [13]. Moreover, in our clinical experience, we observed some patients with serum albumin levels around 30 g/L and extremely high levels of anti-PLA2R antibodies had extensive VTE. To the best of our knowledge, there was no clinical study to evaluate whether anti-PLA2R antibody was the risk factor for VTE in patients with PMN till now.

In this study, we added anti-PLA2R antibodies to the common thrombophilic risk factors, such as proteinuria, hypoalbuminemia and serum creatinine, to analyze the predictors of venous thrombosis in a large Chinese PMN cohort.

Methods

Design

We retrospectively analyzed all the in-hospital patients diagnosed with PMN in Provincial Hospital affiliated to Shandong First Medical University between January 2018 and January 2021. The prevalence of venous thrombosis and its risk factors were investigated in this cross-sectional study.

Participants

All the patients diagnosed with PMN were included in this study. The major inclusion criteria in this study included: (1) biopsy-diagnosed PMN; (2) anti-PLA2R antibody-positive patients without renal biopsy. Major exclusion criteria included: (1) secondary forms of MN, such as: systemic lupus erythematosus, hepatitis B virus infection, malignancy, medication, and heavy metal poisoning; (2) without the result of anti-PLA2R antibody test; (3) without a venous examination; (4) use of immunosuppressive drugs prior to the study enrollment; (5) exposure to classic risk factors for venous thrombosis such as antiphospholipid syndrome, major surgery, prolonged immobilization.

The ethics committee of Provincial Hospital affiliated to Shandong First Medical University approved the study.

Venous thrombosis examination

In the local practice, patients with glomerulonephritis would routinely receive renal vascular and lower extremity vascular ultrasounds for venous thrombosis screening. Magnetic resonance venography (MRV) would be performed if the patients had clinical signs and symptoms of cerebral sinovenous thrombosis, such as nausea, vomiting, headache, and dizziness. Computed tomography pulmonary angiography (CTPA) and CT venography (CTV) were not performed unless the patients presented with clinical signs and symptoms of PE, such as dyspnea, hemoptysis, chest pain and syncope. Only 2 PMN patients received CTPA and diagnosed with pulmonary embolism in the study period, and both of them had extensive renal venous and inferior vena cava thrombosis. Since PE was not routinely screened in our patients, we focused on the risks of venous thrombosis in this study. Venous ultrasound was screened by sonologists with 10-year experience in vessel ultrasound.

Data Collection

Clinical data were obtained at the time of venous examination by reviewing the patient's previous medical records, including age, sex, blood pressure measurements, history of smoking, hemoglobin, platelet count, serum albumin, serum lipids profile, plasma fibrinogen, D-dimer, urinalysis, quantification of proteinuria, blood urea nitrogen, serum creatinine, estimated glomerular filtration rate (eGFR), anti-PLA2R antibody, and pathological results. In our cohort, anti-PLA2R antibodies were detected by commercial enzyme-linked immunosorbent assay (ELISA), and the manufacturer’s recommended cut-off value is 20 RU/ml.

Statistical Analysis

Statistical software SPSS 24.0 (SPSS, Chicago, IL) was employed for statistical analysis. Quantitative data were expressed as mean ± SD, median with quartile or number (%). The levels of anti-PLA2R antibody were highly skewed, so natural log transformation was used for the analyses. The correlation between two parameters (nonparametric distributions) was analyzed by Spearman’s rank coefficient of correlation. For comparison of clinical features of patients, t-tests, the Mann–Whitney U-test, and $\chi 2$ test were used. Binary logistic regression with forward-conditional method was applied to identify the potential risk factors for venous thrombosis in patients with PMN. Only variables with $P < 0.05$ in the univariate logistic regression analysis were used in the multiple logistic regression analysis. Results were expressed as odds ratio (OR) with 95% confidence intervals (CI). Statistical significance was considered as $P < 0.05$.

Results

Patient population

A total of 430 in-hospital patients were diagnosed with PMN at Provincial Hospital affiliated to Shandong First Medical University from January 2018 to January 2021, including 423 biopsy-proven PMN and 7 anti-PLA2R antibody positive patients who didn’t receive renal biopsy because of extensive venous thrombosis. 318 of the 430 patients received renal vascular and lower extremity vascular ultrasounds, and venous thrombosis was found in 32 (10.6%) patients. 49 patients were further excluded, 45 of whom

received immunosuppressive treatment prior to the time of venous thrombosis examination, and 4 didn't have the results of anti-PLA2R antibody test. Thus, a total of 269 patients were entered into the final cohort.

General characteristics of the study patients

General clinical profiles of the patients were listed in Tables 1. Of the 269 patients, 97 (36.1%) were females and 172 (63.9%) were males. The mean age of the patients was 47.6 ± 11.7 years. 69.5% (187/269) of the patients had nephrotic-level proteinuria. At a cut-off value of 20 RU/ml for anti-PLA2R autoantibodies, 85.1% (229/269) of the patients had either elevated anti-PLA2R antibody in the serum or enhanced PLA2R in glomeruli. In Spearman's correlation analysis, anti-PLA2R antibodies correlated positively with proteinuria ($r = 0.309$, $P < 0.001$), total cholesterol ($r = 0.209$, $P = 0.001$) and serum creatinine ($r = 0.123$, $P = 0.044$). The anti-PLA2R levels correlated negatively with serum ALB ($r=-0.358$, $P < 0.001$).

Table 1
The clinical parameters of the studied PMN patients

Parameters	n = 269
Gender (male/female)	172/97
Age (mean ± SD) (years)	47.6 ± 11.7
Level of PLA2R Abs (median, quartile) (RU/mL)	46.51 (6.72, 171.39)
<2 (n, %)	29 (10.8)
2–20 (n, %)	75 (27.9)
>20 (n, %)	165 (61.3)
Ln PLA2R Abs (mean ± SD) (RU/mL)	3.58 ± 1.87
Glomerular PLA2R antigen positive (n, %)	185 (68.8)
[a]PLA2R-related MN (n, %)	229 (85.1)
Urinary protein (mean ± SD) (g/24h)	6.47 ± 4.51
Nephrotic proteinuria (n, %)	187 (69.5)
ALB (mean ± SD) (g/L)	25.72 ± 6.60
SCR (mean ± SD) (μmol/L)	68.11 ± 29.93
eGFR (mean ± SD) (mL/min/1.73 m^2)	106.87 ± 19.87
CHOL (mean ± SD) (mmol/L)	8.33 ± 2.58
LDL (mean ± SD) (mmol/L)	5.43 ± 1.91
Combined with DM (n, %)	26 (9.7)
Abbreviations: PMN, primary membranous nephropathy; SD, standard deviation; PLA2R, phospholipase A2 receptor; Abs, antibodies; ALB, albumin; SCR, serum creatinine; eGFR, estimated glomerular filtration rate; CHOL, cholesterol; LDL, low density lipoprotein; DM, diabetes.	
[a]PLA2R-related MN was defined as either positive for serum anti-PLA2R antibody (cut-off value of 20 RU/mL) or glomerular PLA2R antigen.	

Among the studied patients, 28 patients (10.4%) had venous thrombosis. A total of 40 anatomic site venous thrombosis were detected in these patients, and 5 patients had simultaneous venous thrombosis at more than one site. 18 patients had a DVT; 11 patients had a RVT; 9 patients had an inferior vena cava thrombosis; 2 patients had a pulmonary embolism. The clinical characteristics of patients with and without venous thrombosis at the time of vascular ultrasounds examination are shown in Table 2. There were no statistical differences in the distributions of age and sex between patients with and without venous thrombosis. Patients with venous thrombosis had significantly higher levels of cholesterol

(CHOL), low density lipoprotein (LDL), D-dimer, and lower levels of ALB than those without venous thrombosis ($P < 0.05$). No significant differences were found in urine proteinuria, SCR, eGFR, platelets and fibrinogen between patients with and without thrombosis. Anti-PLA2R antibody was highly skewed, in Mann–Whitney U-test anti-PLA2R antibody levels in patients with venous thrombosis were significantly higher than in patients without it ($P = 0.010$). The distributions of Ln anti-PLA2R antibody of the two groups were shown in Fig. 1.

Table 2
Laboratory findings of PMN with or without venous thrombosis

Parameters	With venous thrombosis (n = 28)	Without venous thrombosis (n = 241)	*P* value
Age (mean ± SD) (years)	47.0 ± 11.0	47.7 ± 11.8	0.769
Gender (female, %)	7 (25.0%)	90 (37.3%)	0.220
PLT (mean ± SD) (10^9/L)	281.93 ± 67.47	271.46 ± 63.32	0.419
Ln PLA2R Abs (mean ± SD) (RU/mL)	4.50 ± 1.50	3.47 ± 1.88	**0.006**
Urinary protein (mean ± SD) (g/24h)	7.80 ± 4.10	6.32 ± 4.54	**0.106**
ALB (mean ± SD) (g/L)	23.26 ± 5.24	26.00 ± 6.69	**0.037**
SCR (mean ± SD) (μmol/L)	75.59 ± 18.74	67.24 ± 30.87	**0.163**
eGFR (mean ± SD) (mL/min/1.73 m^2)	102.21 ± 20.12	107.42 ± 19.81	0.190
CHOL (mean ± SD) (mmol/L)	9.50 ± 2.84	8.20 ± 2.52	**0.013**
LDL (mean ± SD) (mmol/L)	6.37 ± 2.29	5.32 ± 1.84	**0.007**
D-dimer (median, quartile) (μg/mL)	1.79 (0.87, 5.90)	0.57 (0.34, 1.11)	**< 0.001**
Fib (median, quartile) (g/L)	4.20 (3.69, 5.29)	4.03 (3.53, 4.79)	0.243
Combined with DM (n, %)	3 (10.7)	23 (9.5)	0.741

Abbreviations: PMN, primary membranous nephropathy; SD, standard deviation; PLT, platelet; PLA2R, phospholipase A2 receptor; Abs, antibodies; ALB, albumin; SCR, serum creatinine; eGFR, estimated glomerular filtration rate; CHOL, cholesterol; LDL, low density lipoprotein; Fib, fibrogen; DM, diabetes.

Risk factors of venous thrombosis in patients with PMN

Results of the univariate and multivariate logistic regression analyzing risk factors for venous thrombosis in PMN were shown in Table 3. Anti-PLA2R antibody was highly skewed, so natural log transformation

was used for the analysis. In the univariate logistic regression, Ln PLA2R (OR: 1.316; *P* = 0.032), ALB (OR: 0.932; *P* = 0.039), CHOL (OR: 1.189, *P* = 0.015), and LDL (OR: 1.288,*P* = 0.009) were associated with venous thrombosis. CHOL was highly colinear with LDL, and then ALB, LDL, and Ln PLA2R were used in the further multivariate logistic regression with forward-conditional method. We found that only PLA2R-Ab (OR = 1.316; 95%CI: 1.024 ~ 1.691), and LDL (OR = 1.229; 95%CI: 1.012 ~ 1.493) were the independent risk factors for venous thrombosis (*P* < 0.05).

Table 3
Risk factors in predicting venous thrombosis in patients with PMN

Parameters	Univariate analysis		Multivariate analysis	
	P value[a]	OR (95%CI)	*P* value	OR (95%CI)
Age	0.768	0.995 (0.962, 1.029)		
sex	0.203	0.559 (0.229, 1.368)		
Ln PLA2RAbs	**0.008**	**1.385 (1.090, 1.760)**	**0.032**	**1.316 (1.024, 1.691)**
ALB	**0.039**	**0.932 (0.871, 0.996)**		
SCR	0.202	1.006 (0.997, 1.015)		
eGFR	0.192	0.988 (0.971, 1.006)		
PLT	0.418	1.002 (0.996, 1.009)		
CHOL	**0.015**	**1.189 (1.034, 1.368)**		
LDL	**0.009**	**1.288 (1.067, 1.556)**	**0.037**	**1.229 (1.012, 1.493)**
Proteinura	0.110	1.066 (0.986, 1.152)		
Combined with DM	0.843	1.137 (0.319, 4.059)		

Abbreviations: PMN, primary membranous nephropathy; PLA2R, phospholipase A2 receptor; Abs, antibodies; ALB, albumin; SCR, serum creatinine; eGFR, estimated glomerular filtration rate; PLT, platelet; CHOL, cholesterol; DM, diabetes.

[a]Only variables with *P* < 0.05 in the univariate logistic regression analysis were used in the multiple logistic regression. CHOL was highly colinear with LDL, CHOL was not used in the multiple logistic regression.

Discussion

Compared with other nephrotic diseases, PMN is associated with the highest risk for developing venous thrombosis [11–13]. The aim of this study was to explore whether the pathognomonic PLA2R autoantibodies contribute to venous thrombosis risk in PMN.

The levels of anti-PLA2R antibody usually decline rapidly after immunosuppressive therapy. Patients who have received immunosuppressive drugs prior to the enrollment were excluded from the study. In this large PMN cohort, venous thrombosis occurred in 10.4% of the paitents, and DVT occurred more frequently than RVT. Although similar to that reported in some cohorts [13, 20], this frequency is substantially lower than that previously reported in studies that used computed tomography angiography or lung ventilation and perfusion scintigraphy for VTEs screening [10, 21]. The frequency and location of VTEs are highly dependent upon the clinical screening modality and intensity. However, the clinical significance of undetected asymptomatic VTE is unknown. The other explanation for the relatively lower prevalence of venous thrombosis was that non-nephrotic patients were also included and accounted for 30.5% in our cohort. Although the prevalence of thrombosis was lower in patients without NS than in patients with it, two venous thrombosis events were indeed detected in patients without NS. Non-nephrotic patients should also be involved to explore the risk predictors of thrombosis in PMN.

In our cohort, we found that hypoalbuminemia, CHOL, and LDL were the risk factors for venous thrombosis in univariate anlaysis. Proteinuria was not the predictive of thrombotic events in this cohort. Anti-PLA2R antibody is an organ-specific autoantibody which targets the kidney podocytes, and is considered to be pathogenic in PMN. The levels of PLA2R autoantibodies correlate closely with disease activity and progression in PMN [16, 17]. In this cross-sectional study, anti-PLA2R antibodies were correlated with proteinuria and hypoalbuminemia. More interestingly, the levels of anti-PLA2R antibody were significantly higher in patients with venous thrombosis than that of patients without venous thrombosis. Moreover, in multivariate logistic regression analysis, anti-PLA2R antibody was the independent risk factor for venous thrombosis, even adjusted for ALB and LDL. The results of our study indicated that anti-PLA2R antibody is superior to albumin and proteinuria in relation to the assessment of the risk of venous thrombosis in PMN.

The high risk of VTE in individuals with nephrotic range proteinuria is assumed to be secondary to loss of anticoagulant proteins. However, microalbuminuria and declined eGFR were also found to be independently associated with increased risk for VTE [22–25]. Pang et al performed urine proteomics of PMN and found that these proteins are mainly involved in immune response and coagulation cascades [26]. These results indicated that there might be direct links between renal injury and thrombosis. The correlation of anti-PLA2R antibody induced renal injury and activation of coagulation deserves further investigation. On the other hand, a recent study demonstrated that MN patients with Th17-mediated inflammation had more VTEs [27]. Th17-immune response is a proinflammatory immune pathway associated with autoimmune diseases [28, 29]. Whether the development of thrombosis will be induced by the activation of autoimmune response against PLA2R is another question for future consideration.

This study has several limitations. First, to explore the role of anti-PLA2R antibody in the thrombosis risk, it would be the best to investigate it in PLA2R-related MN. The optimum cut-off value for the diagnostic accuracy of the commercially available ELISA assay in different populations was still under discussion [30, 31]. Moreover, in patients who are PLA2R antibody negative, the positive staining of the renal biopsy for PLA2R antigen may also disclose PLA2R-related MN [32]. It is hard to accurately define the PLA2R-

related MN. However, in our cohort, using a relatively conservative cut-off value of 20 RU/ml for anti-PLA2R autoantibodies, 85.9% of the patients had either elevated anti-PLA2R antibody in the serum or enhanced PLA2R in glomeruli. That is, PLA2R-related MN accounted for the majority of the population in our cohort. Second, despite the large size of our cohort, there were relatively few events, which might limit the ability to identify predisposing risk factors. Finally, based on a retrospective analysis of passively captured clinical events, our findings may underestimate their true frequency.

Conclusion

In summary, we were the first to explore the risk of anti-PLA2R antibody in the development of venous thrombosis in PMN, and found anti-PLA2R antibody to be the independent risk factor. Larger prospective studies are warranted to verify the results in future.

Declarations

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Authors' contributions

Huizi Zhu and Liang Xu: acquisition of data, analysis, and interpretation of data. Xiang Liu and Bing Liu: acquisition of data, and article revision. Xiaowei Yang and Rong Wang: the conception and design of the study, and text revision.

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Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This retrospective study was approved by the ethics committee of Provincial Hospital affiliated to Shandong First Medical University.

Consent for publication

Not applicable.

Competing interests

None.

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Figures

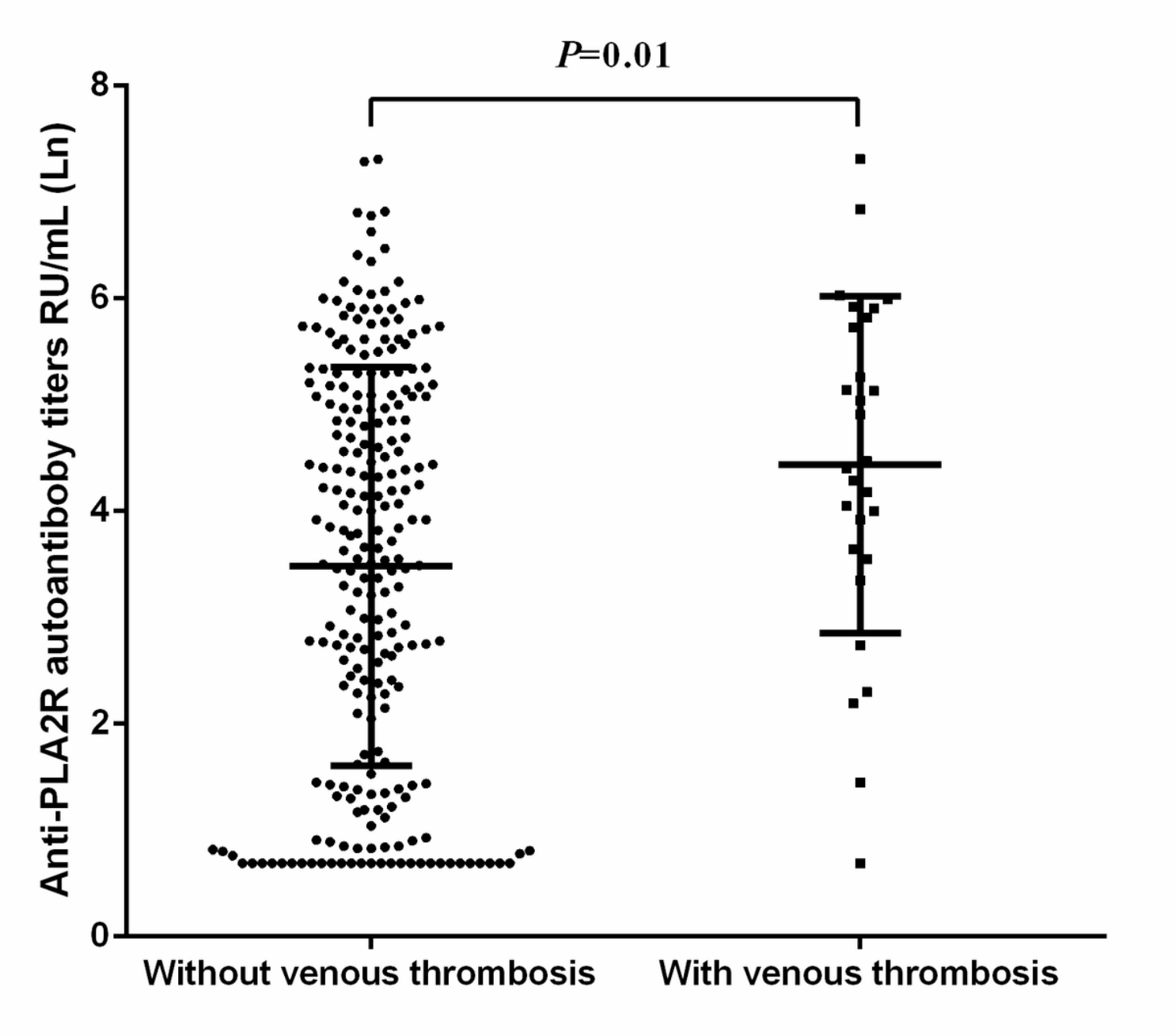

Figure 1

Scatter plot shows the levels of anti-PLA2R antibody in PMN patients with and without venous thrombosis. Anti-PLA2R antibody was highly skewed, so natural log transformation was used for the analysis.