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Letter to the Editor

LETTER TO THE EDITOR

Risk factors of venous thromboembolism in anti-PLA2R-positive and -negative primary membranous nephropathy

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Antibody to the phospholipase A2 receptor (anti-PLA2R) is identified as a pathogenic and prognostic marker in primary membranous nephropathy (PMN) [1, 2]. Increased risk of venous thromboembolism (VTE) in PMN has been demonstrated repeatedly ever since this association was first highlighted during the early 1980s [3, 4]. The significant risk factors of VTE in PMN with anti-PLA2R status considered remain to be established. Recent studies published in preprint form, such as a retrospective observational study from China of 269 PMN patients by Zhu *et al.* [5], suggest anti-PLA2R-positivity itself as an independent risk factor for VTE in PMN {odds ratio [OR] 1.32 [95% confidence interval (CI) 1.02–1.69], $P < .05$} through a multivariate analysis adjusting for serum albumin and low-density lipoprotein. In that study, the anti-PLA2R antibody demonstrated superior predictive value for VTE events in PMN over serum albumin and proteinuria.

We conducted an observational study retrospectively using data collected from our department between October 2015 and September 2021. Patients included in this study were those ≥18 years of age who had biopsy-diagnosed new-onset or relapsed PMN and anti-PLA2R direct immunofluorescent assay testing following PMN diagnosis. Those with secondary causes of membranous nephropathy, previous kidney transplantation or where iatrogenic causes such as major surgery or prolonged immobilization led to VTE were excluded. Patients were then grouped according to anti-PLA2R status and the presence or absence of VTE events during follow-up.

Various demographic, clinical and laboratory parameters relating to comorbidities, risk prediction scores and investigation results were selected *a priori*. Table 1 describes data recorded at the time of PMN diagnosis. Higher serum cholesterol levels were found among anti-PLA2R-positive PMN patients with VTE events. In the anti-PLA2R-negative group, higher serum cholesterol levels, lower serum albumin levels, increased 24-h proteinuria and proteinuria:albumin ratios were observed among patients with VTE events.

Multivariate regression analysis determined associations between each selected parameter and VTE events during study follow-up for both groups. Table 2 presents the distribution of adjusted ORs from multivariate regression analysis. For each 1 mmol/L increase in cholesterol level, serum cholesterol is demonstrated to be significantly associated with VTE in both the anti-PLA2R-positive [OR 1.42 (95% CI 1.12–1.72), $P < .05$] and anti-PLA2R-negative groups [OR 1.45 (95% CI 1.15–1.76), $P < .05$]. Serum albumin for each 1 g/L increase in albumin level [OR 0.72 (95% CI 0.49–0.96), $P < .05$], 24-h proteinuria for each 1 g increase in 24-h proteinuria [OR 1.33 (95% CI 1.03–1.63), $P < .05$] and proteinuria:albumin ratio for each 1 unit increase in proteinuria:albumin ratio [OR 1.32 (95% CI 1.04–1.59), $P < .05$] were shown to be significantly associated with VTE within the anti-PLA2R-negative group.

Our findings suggest serum cholesterol, serum albumin and proteinuria may present as important risk prediction markers of VTE in PMN, dependent on anti-PLA2R status. Serum

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Table 1. Demographic, clinical and laboratory data in anti-PLA2R-positive and negative PMN patients with and without VTE events during study follow up

	Anti-PLA2R-positive PMN ($n = 39$)			Anti-PLA2R-negative PMN ($n = 31$)		
Characteristics	VTE ($n = 8$)	No VTE ($n = 31$)	*P*-value	VTE ($n = 4$)	No VTE ($n = 27$)	*P*-value
Age (years), mean ± SD	53.0 ± 9.2	60.1 ± 4.9	.464	52.0 ± 20.1	66.3 ± 8.4	.133
Gender (female), *n* (%)	2 (25.0)	21 (67.8)	<.05	2 (50.0)	12 (44.4)	.850
Hypertension, *n* (%)	5 (62.5)	15 (48.4)	.512	1 (25.0)	16 (59.3)	.260
Diabetes mellitus, *n* (%)	0 (0)	7 (22.6)	.171	0 (0)	6 (22.2)	.402
Atrial fibrillation, *n* (%)	4 (50.0)	13 (41.9)	.700	1 (25.0)	9 (33.3)	.803
CHA_2DS_2-VASC ≥3, *n* (%)	5 (62.5)	11 (35.5)	.201	2 (50.0)	11 (40.7)	.752
BMI >30, *n* (%)	4 (50.0)	14 (45.2)	.818	1 (25.0)	6 (22.2)	.874
Malignant disease, *n* (%)	1 (12.5)	7 (22.6)	.598	1 (25.0)	6 (22.2)	.874
Hormone treatment or contraceptive pill, *n* (%)	1 (12.5)	3 (9.68)	.798	0 (0)	4 (14.8)	.558
Albumin (g/L), mean ± SD	25.6 ± 3.4	26.5 ± 5.5	.141	19.3 ± 5.6	25.6 ± 5.2	<.05
24-h proteinuria (g), mean ± SD	9.1 ± 4.3	7.9 ± 3.6	.105	14.7 ± 13.6	7.7 ± 9.2	<.05
Proteinuria:albumin ratio, mean ± SD	3.7 ± 2.0	3.2 ± 1.8	.433	8.4 ± 12.4	3.4 ± 4.4	<.05
Creatinine (µmol/L), mean ± SD	124.8 ± 37.9	134.9 ± 81.7	.0804	158.0 ± 95.6	158.8 ± 138.9	.113
eGFR (mL/min/1.73 m^2), mean ± SD	54.5 ± 20.1	52.6 ± 21.6	.396	45.3 ± 23.1	51.4 ± 24.7	.215
Cholesterol (mmol/L), mean ± SD	8.9 ± 3.2	6.3 ± 1.9	<.05	6.8 ± 3.2	6.0 ± 2.7	<.05
Triglycerides (mmol/L), mean ± SD	2.5 ± 1.3	2.3 ± 1.4	.0986	2.4 ± 0.9	1.8 ± 0.7	.881
IgG (g/L), mean ± SD	3.8 ± 1.2	4.4 ± 1.8	.768	6.9 ± 2.1	5.7 ± 3.3	.227

BMI, body mass index; eGFR, estimated glomerular filtration rate; IgG, immunoglobulin G.

Table 2. Multivariate regression analysis between selected parameters and VTE events in patients with anti-PLA2R-positive and negative PMN

	Anti-PLA2R-positive PMN		Anti-PLA2R-negative PMN	
Characteristics	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age, for each 1 year increase in age	1.11 (0.87–1.35)	.423	1.19 (0.93–1.45)	.435
Female gender	1.27 (0.90–1.65)	.579	1.31 (0.97–1.64)	.275
Hypertension	1.18 (0.85–1.50)	.248	1.26 (0.94–1.57)	.119
Diabetes mellitus	1.10 (0.75–1.46)	.398	1.09 (0.80–1.39)	.301
Atrial fibrillation	1.25 (0.96–1.54)	.441	1.17 (0.88–1.45)	.612
CHA_2DS_2-VASC ≥3	1.16 (0.88–1.43)	.207	1.24 (0.92–1.56)	.218
BMI >30	1.18 (0.88–1.49)	.539	1.11 (0.84–1.39)	.393
Malignant disease	1.07 (0.71–1.43)	.0884	1.10 (0.77–1.43)	.239
Hormonal treatment or contraceptive pill	1.08 (0.73-1.44)	.379	1.05 (0.71–1.38)	.177
Albumin, for each 1 g/L increase in albumin level	0.85 (0.57–1.13)	.0841	0.72 (0.49–0.96)	<.05
24-h proteinuria, for each 1 g increase in 24-h proteinuria	1.20 (0.91–1.49)	.0902	1.33 (1.03–1.63)	<.05
Proteinuria:albumin ratio, for each 1 unit increase in proteinuria:albumin ratio	1.21 (0.90–1.51)	.187	1.32 (1.04–1.59)	<.05
Creatinine, for each 1 µmol/L increase in creatinine	1.14 (0.82–1.46)	.255	1.16 (0.88–1.45)	.472
eGFR, for each 1 mL/min/1.73m^2 increase in eGFR	0.90 (0.61–1.19)	.303	0.92 (0.59–1.25)	.415
Cholesterol, for each 1 mmol/L increase in cholesterol level	1.42 (1.12–1.72)	<.05	1.45 (1.15–1.76)	<.05
Triglycerides, for each 1 mmol/L increase in triglyceride level	1.15 (0.87–1.44)	.291	1.18 (0.91–1.44)	.538
IgG, for each 1g/L increase in IgG	0.81 (0.49–1.13)	.106	0.87 (0.56–1.18)	.0995

BMI, body mass index; eGFR, estimated glomerular filtration rate; IgG, Immunoglobulin G.

cholesterol itself presents as a significant risk factor for VTE in PMN regardless of anti-PLA2R status. Dysregulation of cholesterol metabolism is commonly observed in patients with nephrotic syndrome including PMN and contributes toward mesangial cell proliferation, podocyte and tubulointerstitial damage [6–8]. Consequently, these patients have increased cardiovascular and VTE risks [9]. In contrast, low serum albumin and increasing proteinuria were significant risk factors for VTE in the anti-PLA2R-negative group only. Surprisingly, this was not the case for anti-PLA2R-positive patients. Hypoalbuminemia and proteinuria are established risk factors of VTE in nephrotic syndrome, although the mechanisms remain incompletely understood [10].

Taken together with available data, these results suggest that the mechanisms underlying VTE in PMN may be more complex than previously thought. Our findings should inform further recommendations within this topic, if confirmed in larger cohorts and other ethnic groups. This may have future implications for risk assessment and risk calculation of thrombosis in clinical practice for the PMN population.

CONFLICT OF INTEREST STATEMENT

A.W. is a member of the *CKJ* editorial board. The results presented in this article have not been published previously in whole or in part.

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