

The Value of Peripheral Blood Cell Ratios in Primary Membranous Nephropathy: A Single Center Retrospective Study

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Background: Primary membranous nephropathy (PMN) is a common cause of nephrotic syndrome in adults. Forty percent of the patients continue to progress and eventually develop into chronic renal failure. Although phospholipase A2 receptor (PLA2R) is the major antigen of PMN, the clinical features do not often parallel with the antibody titers. Therefore, it is significant to find relative credible markers to predict the treatment response.

Methods: One hundred and eighteen PMN patients were recruited. The response to treatment was defined as ALB \geq 30g/L at 6 months and complete remission (CR) or not at the end of the follow-up. Renal outcome endpoint was defined as 50% or more Cr increase at the end.

Results: The patients with poor treatment effects had numerically higher platelet-lymphocytes ratio (PLR). For patients with CR or not, the difference was near to statistic significant ($P=0.095$). When analyzing CR or not, the fitting of the binary logistic regression model including both PLA2R Ab titer and PLR (Hosmer–Lemeshow test: $\chi^2=8.328$, $P=0.402$; OR (PLA2R Ab titer) = 1.002 (95% CI 1.000–1.004, $P=0.042$); OR (PLR) = 1.006 (95% CI 0.999–1.013, $P=0.098$) was markedly better than that with only PLA2R Ab titer (Hosmer–Lemeshow test: $\chi^2=13.885$, $P=0.016$). The patients with renal function deterioration showed significantly higher monocyte-lymphocyte ratio (MLR) (0.26 (0.22–0.31) vs 0.18 (0.13–0.22), $P=0.012$).

Conclusion: PMN patients with poor treatment response tended to have higher PLR at the time of renal biopsy, and a higher MLR was associated with poor renal outcomes. Our findings suggested that PLR and MLR might be used to predict treatment efficacy and prognosis for PMN patients, respectively.

Keywords: membranous nephropathy, peripheral blood cell ratios, platelet-lymphocytes ratio, monocyte-lymphocyte ratio, treatment response, outcome

Introduction

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults and can be primary or secondary. The antigenic target of antibodies in 70% of primary cases is phospholipase A2 receptor (PLA2R).¹ The specificity of PLA2R Ab for the lesion of MN nears 100%.² Yet, the correlation between antibody levels and clinical features in primary MN (PMN) is not intuitive, as changes in antibody levels tend to precede and predict clinical changes but with a significant lag time.³ Early in the humoral immune response, low concentrations of autoantibody would engage podocyte antigen and rapidly be removed from the circulation, limiting detection by conventional clinical assays. The rapid elimination of low levels of PLA2R Ab from the circulation due to antigen binding has been termed the “sink hypothesis” and results from a very high affinity of PLA2R Ab for the N-terminal epitope in PLA2R.^{3–}

⁹ Therefore, it is significant to find relative credible markers to predict the response to treatment in patients with PMN. Accumulating data has begun to emerge that MN is associated with high inflammatory burden.^{10,11} Recently,

several studies have reported that some peripheral blood cell ratios, especially neutrophil–lymphocyte ratio (NLR), monocyte–lymphocyte ratio (MLR), platelet–lymphocyte ratio (PLR), and systemic immune-inflammation index (SII, calculated by platelet count \times neutrophil count/lymphocyte count) serve as valuable biomarkers of inflammatory conditions and prognosis. For example, elevated NLR has been reported in inflammatory bowel disease,¹² diabetes mellitus,¹³ gastrointestinal conditions,¹⁴ thyroiditis,¹⁵ and SARS CoV-2 infection.¹⁶ In addition, thyroid conditions,¹⁷ gastrointestinal diseases,¹⁴ cancer,¹⁸ diabetes mellitus,¹⁹ irritable bowel disease,²⁰ and Covid-19 infection²¹ are characterized with high PLR levels in blood. Finally, MLR is suggested as a disease marker in malignancy,²² diabetic nephropathy,²³ functional bowel conditions,²⁰ frailty,²⁴ gastrointestinal conditions,¹⁴ and Covid-19 infection.²¹ Therefore, studying these markers in membranous nephropathy makes sense due to common inflammatory pathway.

However, to our knowledge, limited studies have focused on evaluating the involvement of these markers in PMN, as well as their predictive value for treatment and progression in PMN. Therefore, the aim of this study was to evaluate whether the peripheral blood cell ratios at the renal biopsy were associated with the therapeutic effects in PMN patients.

Materials and Methods

Study Population

We retrospectively analyzed 168 patients with nephrotic syndrome (NS) and biopsy-proven PMN²⁵ in Renal Division of Capital Medical University Affiliated Beijing Friendship Hospital from 2018 to 2019. Among them, 5 patients who received corticosteroids or other immunosuppressive therapy before the renal biopsy and 45 patients who were followed up for less than 1 year were excluded from this study. Finally, the remaining 118 patients were recruited for our following analysis (Figure 1). This study protocol was reviewed and approved by Ethics Committee of Beijing Friendship Hospital, approval number 2021-P2-269-01, and the written informed consents were not required.

Demographic, Clinical, and Laboratory Information

Baseline demographic and clinical information of age, sex, serum albumin and creatinine (ALB and Cr), 24-h urinary protein (UTP), and laboratory data, including white cells (WBC), neutrophils (NE), lymphocytes (LY), and platelets (PLT), were collected from the initial medical records at the renal biopsy. PLA2R Ab titer was determined a validated quantitative ELISA test kit (EUROIMMUN, Lübeck, Germany).²⁶ NLR, MLR, PLR, and were calculated. All renal biopsy specimens were reviewed and graded by independent pathologists who were blinded to the patients' information. The response to treatment was defined as ALB \geq 30g/L at 6 months and complete remission (CR) or not at the end of the

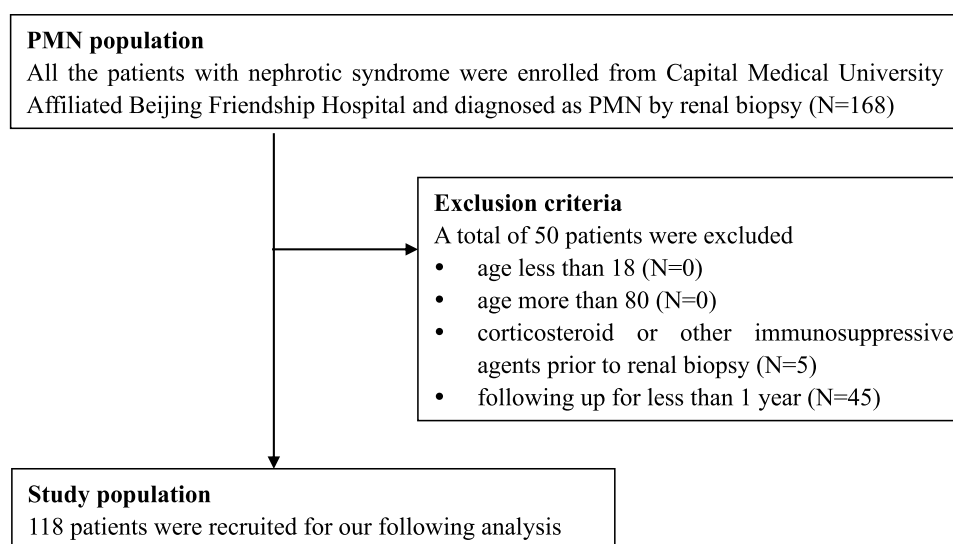


Figure 1 Flow diagram of the study population selection.

Abbreviation: PMN, primary membranous nephropathy.

follow-up visit. According to the two indices of therapeutic effects, respectively, the patients were divided into two groups (Improved ALB group/Control group, and CR group/Control group). Renal outcome endpoint was defined as 50% or more Cr increase at the end of the follow-up.

Statistical Analysis

Skewness and Kurtosis test were used to conduct normality analyses. Quantitative variables were expressed as the mean \pm SD for normally distributed data or median and interquartile range (IQR) for nonnormally distributed data, and categorical data were represented as absolute frequencies or percentages. Continuous data for two groups were compared by the independent-samples *t*-test or the Mann–Whitney *U*-test when appropriate, while the chi-square test was performed for categorical data. Binary logistic regression models were used to estimate the relationship between indicators and treatment responses. Receiver operating characteristic (ROC) curves were generated to evaluate the predictive performance of indicators for renal outcomes. Statistical analysis was performed by SPSS software (version 22.0; SPSS, Chicago, IL, USA). Figures were produced by GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA). A two-sided $P < 0.05$ was considered statistically significant.

Results

Characteristics of the Patients

Among the 168 PMN patients, 118 patients were recruited for the following analysis. The 118 enrolled patients showed comparable demographic and clinical features with the 168 PMN patients (Table 1). Among the enrolled patients, the average age was 52.9 ± 12.1 years old at the time of renal biopsy, 70 (59.3%) were male and 48 (40.7%) were female. A total of 75 (63.6%) patients presented with positive serum PLA2R Ab, whose median titer was 99.23 (IQR 63.32–262.96) RU/mL. At the time of renal biopsy, the median 24-h proteinuria was 3.72 (IQR 2.04–5.48) g, the mean serum ALB was 24.6 ± 5.7 g/L, and the median serum Cr was 66.6 (57.0–78.0) μ mol/L. Ninety-eight (83.1%) patients received corticosteroids and/or other immunosuppressive therapy. The median follow-up was 33.0 (IQR 22.5–39.0) months. At 6 months, serum ALB was elevated to more than 30g/L in 78 (66.1%) patients. At the end of the follow-up, 75 (63.6%) patients achieved CR. Seven (5.9%) patients had a 50% or more Cr increase at the end of the follow-up.

Comparison of Improved ALB Group and Control Group

Compared to control group, PMN patients with $ALB \geq 30$ g/L at 6 months had lower PLA2R Ab positive rate and titer, less UTP, higher serum ALB levels, and less C3 deposit along the glomerular basement membrane (GBM) at the time of renal biopsy (Table 2). There were no significant differences in all the peripheral blood cell ratios between the groups

Table 1 Comparison of the Included and Excluded PMN Patients

Characteristic	PMN Patients n=168	Included n=118	Excluded n=50	P value ^a
Gender (male/female)	99/69	70/48	29/21	0.873
Age (years)	53.6 \pm 12.5	52.9 \pm 12.1	55.5 \pm 13.7	0.251
PLA2R Ab titer (RU/mL)	47.25 (0.00–129.02)	58.13 (0.00–155.97)	30.00 (0.00–86.27)	0.206
UTP (g)	3.61 (2.01–5.34)	3.72 (2.04–5.48)	3.14 (1.71–5.23)	0.317
ALB (g/L)	24.2 \pm 5.6	24.6 \pm 5.7	23.1 \pm 5.4	0.150
Cr (μ mol/L)	67.3 (57.8–80.8)	66.6 (57.0–78.0)	70.6 (61.2–91.5)	0.101
NLR	2.00 (1.52–2.78)	2.01 (1.51–2.70)	1.95 (1.52–3.00)	0.522
MLR	0.18 (0.14–0.24)	0.18 (0.14–0.22)	0.19 (0.14–0.27)	0.231
PLR	121.54 (92.27–167.84)	121.06 (91.66–161.41)	125.24 (95.05–208.48)	0.142
SII	484.57 (384.21–715.27)	480.30 (351.07–700.76)	507.73 (306.96–813.33)	0.505

Note: ^aP value was used to indicate the differences between the included and excluded PMN patients.

Abbreviations: PMN, primary membranous nephropathy; UTP, 24-h urinary protein at baseline; ALB, serum albumin at baseline; Cr, serum creatinine at baseline; NLR, neutrophil–lymphocyte ratio; MLR, monocyte–lymphocyte ratio; PLR, platelet-to-lymphocyte ratio at baseline; SII, systemic immune-inflammation index.

Table 2 Comparison of Improved ALB Group and Control Group

Characteristic	Improved ALB Group n=78	Control Group n=40	P value
Gender (male/female)	43/35	27/13	0.195
Age (years)	53.4±12.0	52.0±12.4	0.563
PLA2R Ab (±)	43/35	32/8	0.008 ^a
PLA2R Ab titer (RU/mL)	42.86 (0.00–90.51)	106.26 (34.21–274.34)	0.001 ^a
UTP (g)	3.21 (1.69–5.13)	4.24 (2.87–6.08)	0.011 ^b
ALB (g/L)	26.0±5.6	21.9±5.0	<0.001 ^c
Cr (μmol/L)	69.8±23.0	71.5±18.7	0.668
Neutrophil (×10 ⁹ /L)	4.11±1.40	4.29±1.75	0.550
Lymphocyte (×10 ⁹ /L)	2.05±0.70	2.13±0.81	0.569
Monocyte (×10 ⁹ /L)	0.37±0.13	0.39±0.17	0.291
Platelet (×10 ⁹ /L)	239.55±81.41	267.08±113.40	0.132
NLR	1.96 (1.51–2.69)	2.20 (1.51–2.92)	0.710
MLR	0.18 (0.14–0.22)	0.19 (0.12–0.23)	0.676
PLR	119.70 (89.83–156.78)	121.26 (92.34–180.61)	0.535
SII	476.71 (345.53–635.76)	480.70 (369.57–818.00)	0.488
IgG IFA	3.3±0.5	3.4±0.5	0.440
C3 IFA	1.0 (1.0–2.0)	2.0 (1.0–3.0)	0.029 ^b
Immunosuppressive therapy (yes/no)	56/22	33/7	0.201

Notes: ^a*P*<0.01; ^b*P*<0.05; ^c*P*<0.001.

Abbreviations: PLA2R Ab, PLA2R Ab qualitative test; UTP, 24-h urinary protein at baseline; ALB, serum albumin at baseline; Cr, serum creatinine at baseline; Neutrophil, peripheral blood neutrophil count; Lymphocyte, peripheral blood lymphocyte count; Monocyte, peripheral blood monocyte count; Platelet, peripheral blood platelet count; NLR, neutrophil–lymphocyte ratio; MLR, monocyte–lymphocyte ratio; PLR, platelet-to-lymphocyte ratio at baseline; SII, systemic immune-inflammation index; IFA, semiquantitative direct immunofluorescence analysis of renal biopsy samples; IgG, immunoglobulin G; C3, complement C3.

(Table 2). Binary logistic regression models revealed that only ALB at the renal biopsy was independently associated with ALB levels at 6 months (Hosmer–Lemeshow test: $\chi^2=6.123$, *P*=0.633; OR=0.867 (95% CI 0.799–0.941, *P*=0.001)).

Comparison of CR Group and Control Group

Compared to control group, PMN patients with CR at the end of the follow-up had lower PLA2R Ab positive rate and titer at the time of renal biopsy (Table 3), and they also tended to have lower PLR (*P*=0.095) (Table 3). However, when only PLA2R Ab titer was included into the analysis of binary logistic regression models, the fitting was not satisfying (Hosmer–Lemeshow test: $\chi^2=13.885$, *P*=0.016). In contrast, when both PLA2R Ab titer and PLR were included, the fitting was significantly improved (Hosmer–Lemeshow test: $\chi^2=8.328$, *P*=0.402). PLA2R Ab titer was identified as the independently correlate of CR (OR (PLA2R Ab titer) = 1.002 (95% CI 1.000–1.004, *P*=0.042)); OR (PLR) = 1.006 (95% CI 0.999–1.013, *P*=0.098).

Characteristics of the Patients with Cr Increase

At the end of the follow-up, 7 patients had a 50% or more serum Cr increase. They were all male and had higher Cr levels and higher MLR at the renal biopsy (Table 4). Unsurprisingly, 7 patients had worse treatment response (Table 4). We additionally performed ROC curve analysis and calculated the area under the ROC curve (AUC) to evaluate the association of renal outcomes with Cr and MLR. MLR showed the larger AUC (MLR: 0.784 (95% CI 0.577–0.990, *P*=0.012); Cr: 0.754 (95% CI 0.520–0.988, *P* = 0.024)) (Figure 2).

Discussion

As well known, PMN is an autoimmune disease directed against podocytes. PLA2R is the major antigen of PMN in adults. However, the clinical remission does not often parallel with the immunological remission. The same titer of antibody may be observed in the early stages of the disease or in patients undergoing remission.⁵ Therefore, there is a need to find some biomarkers to evaluate patients' inflammatory and immune status and then make treatment decision.

Table 3 Comparison of CR Group and Control Group

Characteristic	CR Group n=75	Control Group n=43	P value
Gender (male/female)	42/33	28/15	0.332
Age (years)	54.0±11.9	50.9±12.4	0.181
PLA2R Ab (±)	41/34	34/9	0.008 ^a
PLA2R Ab titer (RU/mL)	43.46 (0.00–90.30)	91.15 (30.69–255.77)	0.002 ^a
UTP (g)	3.73 (1.79–5.15)	3.71 (2.69–5.86)	0.305
ALB (g/L)	25.3±5.5	23.4±5.9	0.082
Cr (μmol/L)	68.2±15.7	74.1±29.0	0.149
Neutrophil (×10 ⁹ /L)	4.07±1.35	4.32±1.79	0.405
Lymphocyte (×10 ⁹ /L)	2.12±0.76	2.02±0.69	0.494
Monocyte (×10 ⁹ /L)	0.38±0.13	0.37±0.16	0.814
Platelet (×10 ⁹ /L)	244.75±73.26	267.47±109.62	0.181
NLR	1.92 (1.53–2.69)	2.22 (1.51–2.96)	0.328
MLR	0.18 (0.14–0.23)	0.19 (0.12–0.22)	0.625
PLR	117.83 (88.13–155.97)	130.42 (100.00–178.33)	0.095
SII	452.86 (350.00–615.07)	520.63 (351.43–824.44)	0.168
IgG IFA	3.3±0.5	3.4±0.5	0.440
C3 IFA	1.5 (1.0–3.0)	1.5 (1.0–2.1)	0.831
Immunosuppressive therapy (yes/no)	55/20	34/9	0.486

Note: ^aP<0.01.

Abbreviations: CR, complete remission; PLA2R Ab, PLA2R Ab qualitative test; UTP, 24-h urinary protein at baseline; ALB, serum albumin at baseline; Cr, serum creatinine at baseline; Neutrophil, peripheral blood neutrophil count; Lymphocyte, peripheral blood lymphocyte count; Monocyte, peripheral blood monocyte count; Platelet, peripheral blood platelet count; NLR, neutrophil–lymphocyte ratio; MLR, monocyte–lymphocyte ratio; PLR, platelet-to-lymphocyte ratio at baseline; SII, systemic immune-inflammation index; IFA, semiquantitative direct immunofluorescence analysis of renal biopsy samples; IgG, immunoglobulin G; C3, complement C3.

Table 4 Characteristics of Patients with a 50% or More Cr Increase

Characteristic	Patients with Cr Increase n=7	Other Patients n=111	P value
Gender (male/female)	7/0	63/48	0.040 ^a
Age (years)	59.0 (37.0–66.0)	55.0 (47.0–61.0)	0.686
PLA2R Ab (±)	5/2	70/41	1.000
PLA2R Ab titer (RU/mL)	88.34 (0.00–151.66)	51.78 (0.00–164.92)	0.653
UTP (g)	5.15 (2.81–8.12)	3.71 (2.00–5.36)	0.356
ALB (g/L)	18.4 (16.7–35.2)	24.5 (20.5–28.2)	0.245
Cr (μmol/L)	95.8 (69.1–123.0)	65.4 (56.5–77.2)	0.024 ^a
Neutrophil (×10 ⁹ /L)	4.69 (2.89–7.44)	3.77 (3.26–4.82)	0.319
Lymphocyte (×10 ⁹ /L)	1.98 (1.34–2.40)	2.03 (1.54–2.53)	0.536
Monocyte (×10 ⁹ /L)	0.41 (0.29–0.74)	0.35 (0.28–0.44)	0.814
Platelet (×10 ⁹ /L)	238.00 (209.00–313.00)	241.00 (204.00–280.00)	0.181
NLR	2.96 (1.79–3.50)	1.99 (1.48–2.66)	0.087
MLR	0.26 (0.22–0.31)	0.18 (0.13–0.22)	0.012 ^a
PLR	130.42 (121.51–178.33)	118.25 (90.00–160.34)	0.390
SII	756.00 (315.93–1266.17)	471.59 (351.43–663.08)	0.181
IgG IFA	3.0 (3.0–4.0)	3.0 (3.0–4.0)	0.892
C3 IFA	2.0 (1.0–3.0)	1.5 (1.0–2.1)	0.640
Immunosuppressive therapy (yes/no)	6/1	83/28	0.824
Improved ALB at 6 months (yes/no)	2/5	76/35	0.044 ^a
CR at the end of follow-up (yes/no)	0/7	73/36	0.001 ^b

Note: ^aP<0.05; ^bP<0.01.

Abbreviations: PLA2R Ab, PLA2R Ab qualitative test; UTP, 24-h urinary protein at baseline; ALB, serum albumin at baseline; Cr, serum creatinine at baseline; Neutrophil, peripheral blood neutrophil count; Lymphocyte, peripheral blood lymphocyte count; Monocyte, peripheral blood monocyte count; Platelet, peripheral blood platelet count; NLR, neutrophil–lymphocyte ratio; MLR, monocyte–lymphocyte ratio; PLR, platelet-to-lymphocyte ratio at baseline; SII, systemic immune-inflammation index; IFA, semiquantitative direct immunofluorescence analysis of renal biopsy samples; IgG, immunoglobulin G; C3, complement C3; CR, complete remission.

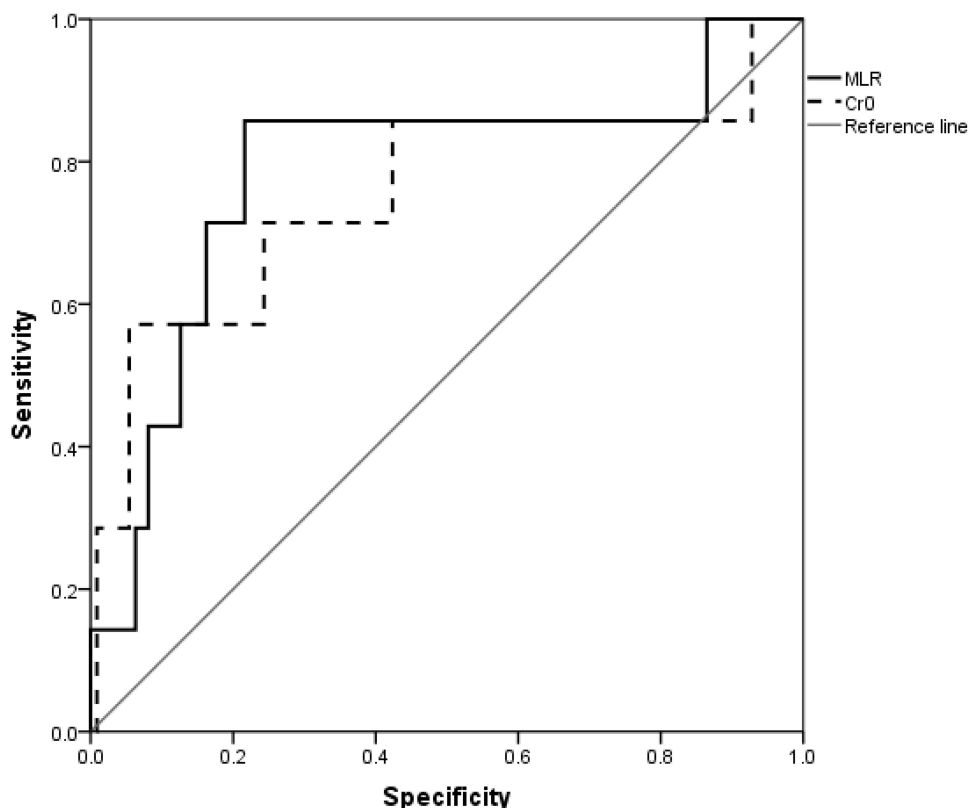


Figure 2 Receiver operating characteristic (ROC) curves showing the sensitivity and specificity of MLR and Cr at renal biopsy for renal outcomes. MLR had the larger area under the curve (AUC=0.784) than Cr (AUC=0.754).

Abbreviations: MLR, monocyte-lymphocyte ratio; Cr0, serum creatinine at baseline.

In this study, we retrospectively compared several peripheral blood cell ratios in PMN patients with different treatment response. The results suggest that PLR might be a promising candidate to predict the effect of treatments, and that MLR may be associated with poor renal outcomes.

In-vitro and in-vivo studies have elucidated the origin of activated circulating platelets, which display numerous membrane receptors and release multiple biologically active substances from their granules that can regulate cellular interactions and contribute to immune, inflammatory, and thrombotic diseases.^{27–29} Circulating platelets can also interact with erythrocytes, neutrophils, and lymphocytes in the vessel lumen at sites of vascular damage.^{30,31} PLR has been believed as an informative marker revealing shifts in platelet and lymphocyte counts due to inflammatory and prothrombotic states.³² Some studies showed that PLR could be potentially valuable in the accurate evaluation of inflammatory activity,³² and others demonstrated that high PLR was associated with venous thrombosis.³³ Particularly, emerging evidence suggests that PLR has also been proposed as a marker for kidney diseases.³⁴ In this study, we found that the patients with poor treatment effects, whose serum ALB levels were less than 30g/L at 6 months or who did not reach CR at the end of the follow-up, had numerically higher PLR. Especially for patients with CR or not, the difference was near to statistically significant. It is more noteworthy that when analyzing CR or not, the fitting of the binary logistic regression model including both PLA2R Ab titer and PLR was markedly better than that with only PLA2R Ab titer. PMN is an autoimmune disease as well as the pathology type with the highest incidence of thrombotic events in nephrotic syndrome.³⁵ Our findings give a vital clue to determine treatment response of PMN patients at the time of renal biopsy. Besides serum ALB levels and PLA2R Ab, PLR at baseline might be a potential and good addition. This is intriguing, given that even in patients who respond to therapy, improvement of proteinuria only occurs after months, which imposes long trials of at least 2 years when testing the effectiveness of drugs.⁵ Kazan et al³⁶ reviewed retrospectively 39 patients with low and moderate risk PMN and reported that the non-remission patients had significantly higher SII and pan-

immune-inflammation value (calculated as (platelet count \times neutrophil count \times monocyte count)/lymphocyte count), which partly supported our findings. Larger studies are needed to demonstrate our hypothesis.

In the present study, only 7 (5.9%) patients had a 50% or more Cr increase at the end, which was far less than those reported by previous researches.⁹ The relatively short investigation period may be an important cause as 63.6% patients achieved CR during the median 33-month follow-up period, which was consistent with other studies.⁹ A study, whose mean duration of follow-up was 6.2 ± 3.2 years, showed that 59.6% patients reached renal endpoint (end-stage renal disease).³⁷ Their results also revealed that both high NLR and PLR predicted poor long-term renal survivals in PMN patients, while MLR was not analyzed. In our study, the patients with Cr increase indeed tended to have higher NLR, but the difference did not reach the statistic significant ($P=0.087$) (Table 4). In contrast, higher MLR was significantly associated with renal function deterioration. Various metabolic stimuli lead to an increase in monocytes. These monocytes differentiate into macrophages and create an inflammatory state.³⁴ Some kidney macrophages have been demonstrated to be able to promote kidney fibrosis.³⁸ The prognostic value of MLR for PMN patients deserves further investigation by larger and longer-time studies.

Finally, although immunosuppressive agents did not display any beneficial effects on whether treatment response or renal outcomes in the present study, we cannot negate the value of immunosuppressive therapy in PMN patients, especially high-risk ones. We did not analyze specific therapeutic programs, and some patients were given immunosuppressive agents after several months but not at the renal biopsy. The heterogeneity could hamper treatment efficacy evaluation.

The current study has some limitations. First, the sample size was small and the follow-up duration was short, which contributed to too few endpoint events, so a Cox proportional hazards analysis could not be conducted. Second, we only recruited PMN patients from a single center, and validation studies in other independent PMN cohorts are needed in the future.

Conclusions

Taken together, we found that PMN patients with poor treatment response tended to have higher PLR at the time of renal biopsy, and a higher MLR was associated with poor renal outcomes. Our findings suggested that PLR and MLR might be used to predict treatment efficacy and prognosis for PMN patients, respectively.

Data Sharing Statement

The datasets used during the current study are available from Wen-hu Liu on reasonable request.

Statement of Ethics

This study protocol was reviewed and approved by Ethics Committee of Beijing Friendship Hospital, approval number 2021-P2-269-01, and Ethics Committee of Beijing Friendship Hospital waived the need for informed consent based on the following reasons: (1) the purpose of the study was important; (2) the possible risk to patients was not higher than the minimum one; (3) the waiver of informed consent would not adversely affect the rights and health of patients. (4) the patients' privacy and personal identity information were well protected. The protocol of the study is compliant with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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