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Research

Diagnostic and Prognostic Value of Anti-Phospholipase A2 Receptor Antibodies in Patients with Membranous Nephropathy

Membranöz Nefropatili Hastalarda Anti-Fosfolipaz A2 Reseptör Antikorlarının Tanısal ve Prognostik Değeri

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ABSTRACT

Objective: This study aimed to evaluate the diagnostic and prognostic significance of anti-phospholipase A2 receptor (PLA2R) in primary membranous nephropathy (PMN) patients and determine the most appropriate cut-off value.

Methods: Between June 2022 and June 2023, 74 patients who were followed up with PMN, secondary MN, non-MN nephrotic syndrome and 15 healthy volunteers were included. Anti-PLA2R antibody levels were evaluated by enzyme-linked immunosorbent assay (ELISA) (EUROIMMUN, Lübeck, Germany). Receiver operating characteristic (ROC) curve analysis was performed.

Results: The ELISA kit showed sensitivity of 30% and specificity of 100% when the cut-off value of 20 relative units (RU)/mL was used. According to the ROC curve analysis, the cut-off value was found to be 1.19 RU/mL. When using this value, sensitivity was 66.6% and specifity was 72.7%. However when cut-off value was used 2 RU/mL, sensitivity and specifity was 46.6% and 100%, respectively. Only part of PMN patients were antibody positive; all other groups were negative. All PMN patients were antibody positive at diagnosis; and as for patients with active disease 25% were positive and 25% were borderline. Whereas for patients with complete and partial remission and 18.8% of these were antibody positive. Anti-PLA2R positive patients had higher mean proteinuria and lower mean albumin. Anti-PLA2R positive PMN patients had lower mean hemoglobin and hematocrit values.

Conclusion: Anti-PLA2R may be helpful in diagnosis in PMN patients when secondary causes are well excluded at the time of diagnosis and also be helpful in predicting progression during follow-up.

Keywords: Antibody, enzyme-linked immunosorbent assay, phospholipase A2 receptor, primary membranous nephropathy, proteinuria

ÖZ

Amaç: Bu çalışmada, primer membranöz nefropatili (PMN) hastalarda anti-fosfolipaz A2 reseptörünün (PLA2R) tanısal ve prognostik öneminin değerlendirilmesi ve en uygun eşik değerin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Haziran 2022 ile Haziran 2023 tarihleri arasında, PMN, sekonder MN, MN dışı nefrotik sendrom tanısı ile takip edilen 74 hasta ile 15 sağlıklı gönüllü çalışmaya dahil edildi. Anti-PLA2R antikor düzeyleri enzim bağlantılı immünosorbent test (ELISA) yöntemiyle (EUROIMMUN, Lübeck, Almanya) değerlendirildi. Alıcı çalışma özelliği (ROC) eğrisi analizi yapıldı.

Bulgular: ELISA kiti, 20 göreceli/bağıl birimler (RU)/mL eşik değeri kullanıldığında %30 duyarlılık ve %100 özgüllük göstermiştir. ROC eğrisi analizine göre, eşik değeri 1,19 RU/mL olarak bulunmuştur. Bu değer kullanıldığında duyarlılık %66,6 ve özgüllük %72,7 olmuştur. Ancak eşik değeri 2 RU/mL kullanıldığında duyarlılık ve özgüllük sırasıyla %46,6 ve %100 olmuştur. PMN hastalarının sadece bir kısmı antikor pozitifti; diğer

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ÖZ

tüm gruplar negatifti. Tüm PMN hastaları tanı anında antikor pozitifti; aktif hastalığı olan hastaların %25'i pozitif, %25'i ise sınırda idi. Tam ve kısmi remisyonda olan hastaların ise %18,8'i antikor pozitifti. Anti-PLA2R pozitif hastaların ortalama proteinüri değerleri daha yüksek, ortalama albümin değerleri ise daha düşüktü. Anti-PLA2R pozitif PMN hastalarının ortalama hemoglobin ve hematokrit değerleri daha düşüktü.

Sonuç: Anti-PLA2R, tanı anında sekonder nedenler iyi bir şekilde dışlandığında PMN hastalarında tanıya yardımcı olabilir ve ayrıca takip sürecinde progresyonu tahmin etmede de faydalı olabilir.

Anahtar Kelimeler: Antikor, enzim bağlantılı immünosorbent test, fosfolipaz A2 reseptör, primer membranöz nefropati, proteinüri

INTRODUCTION

Membranous nephropathy (MN) is defined histopathologically by immune complex deposition along the outer basement membrane and by thickening of the glomerular capillary walls. As an autoimmune glomerular disease, MN may arise at any age, yet remains the most frequent cause of nephrotic syndrome among adults. Primary MN (PMN) is predominantly idiopathic. If it is due to a known etiological cause, it is called secondary MN (SMN) (1).

The association of phospholipase A2 receptor (PLA2R) with MN was first reported in 2009. PLA2R currently represents the most commonly recognized autoantigen in MN (1-4). This molecule is a 185-kDa glycoprotein of the mannose receptor family, and the antibodies against it are mainly immunoglobulin G4 (IgG4) (5,6).

PLA2R-associated MN accounts for approximately 80% of PMN cases. PMN constitutes 70-75% of MN diagnoses identified on biopsy; thus, PLA2R-associated MN represents 55% of all MN cases overall (7).

Studies show that anti-PLA2R may be an important biomarker for diagnosing PMN, assessing treatment response, and predicting prognosis. In this way, serologic tests hold potential as a non-invasive alternative to biopsy, which is currently considered the gold standard in diagnosing MN (1,5-7).

Immunofluorescence (IFT) and enzyme-linked immunosorbent assay (ELISA) tests have been used to measure anti-PLA2R antibodies. IFT has high sensitivity and specificity. However, the results of IFT are not quantitative. For that reason, the ELISA tests are mainly used for determining quantitative antibody titres (1,2). The ELISA test is more convenient because more samples can be run at a time and it provides objective and quantitative results (8-10).

This study aimed to determine anti-PLA2R antibody levels and positivity rates using a commercial ELISA kit (EUROIMMUN, Lübeck, Germany) and to identify the most appropriate cut-off value for this kit. The relationship between this antibody and both disease activity and prognostic parameters of the disease was also evaluated.

METHODS

Ethics Committee Approval

Ethical approval for the study was granted by the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (approval no: 2022/120, date: 30.06.2022). The authors declared that the study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each participant included in this study.

Study Design

This cross-sectional investigation included 74 adult patients diagnosed and followed up at the Karadeniz Technical University Faculty of Medicine Nephrology Clinic between June 2022 and June 2023**,** and 15 healthy adult volunteers who served as the control group. The control group had neither kidney disease nor autoimmune disease. Among the 74 patients, 30 were diagnosed with PMN by biopsy after excluding secondary causes, 10 with SMN, and 34 with non-MN nephrotic syndrome. All PMN patients were examined to exclude secondary causes such as autoimmune diseases (antinuclear antibodies, anti-double stranded deoxynucleic acid, etc.), hepatitis (hepatitis B virus, hepatitis C virus), malignancy, and other diseases, in order to correctly diagnose PMN. Disease activity was classified as active disease, partial remission, or complete remission. Complete remission was defined as proteinuria <0.3 g/24 hours and normal serum albumin. Partial remission was defined as proteinuria <3.5 g/24 hours and a >50% reduction from baseline. Active disease was defined as the absence of the above conditions. PLA2R levels were evaluated according to disease activity. All kidney biopsies were evaluated in the same pathology laboratory. Patients' demographic information and laboratory results were obtained from the hospital information system (HIS). Serum specimens were collected from both the patient population and healthy control participants for analysis and were stored at -80 °C until the study day. Anti-PLA2R levels were quantified by ELISA.

Measurement of Anti-PLA2R

Serum samples were thawed at room temperature after being retrieved from the deep freezer. Anti-PLA2R antibody

concentrations were quantified using a commercial ELISA kit (EUROIMMUN, Lübeck, Germany) that employs purified human recombinant PLA2R antigen and a calibration curve prepared from five standards [2, 20, 100, 500, and 1500 relative units (RU)/mL]. Positivity for the antibody was evaluated based on the manufacturer's recommended cut-off values: values <14 RU/mL were interpreted as negative, values from ≥14 to <20 RU/mL as borderline, and those ≥20 RU/mL as positive.

To identify the optimal cut-off value, receiver operating characteristic (ROC) curve analysis was performed on ELISA results, using the pathological renal biopsy findings as the gold standard. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the anti-PLA2R IgG ELISA test were calculated at different cut-off values, including 40 RU/mL, 14 RU/mL, and 2 RU/mL (as used in other studies), as well as the cut-off values recommended by the manufacturer and derived from ROC curve analysis (11).

Biochemical Parameters

Clinical biochemistry test results indicating disease activity were collected from the HIS. Urine total protein, urine creatinine, urine albumin, glucose, creatinine, albumin, blood urea nitrogen, estimated glomerular filtration rate, low-density lipoprotein, high-density lipoprotein, alanine aminotransferase, cholesterol, triglycerides, total calcium, potassium, sodium, hemoglobin, and hematocrit values were analyzed. In this study, the lowest values that our devices (AU5800 and AU680, Beckman Coulter, Japan) could measure, 0.5 mg/dL for urine albumin and 1 mg/dL for urine total protein, were used. 24 hours urine samples were used to calculate proteinuria levels. Patients were divided into two groups according to proteinuria level: <3.5 g/day and >3.5 g/day.

Study Analysis

Statistical Analysis

All statistical analyses were conducted using SPSS software version 24.0 (SPSS Inc., Chicago, IL, USA). Categorical variables are presented as frequencies and percentages, whereas continuous variables are summarized using appropriate descriptive statistics, including mean, standard deviation (SD), median, and range. The distribution of numerical data was evaluated. For variables not conforming to a normal distribution, comparisons were performed with the Mann-Whitney U or Kruskal-Wallis tests, as appropriate. Associations between categorical variables were assessed using the Pearson chi-square test. Spearman's rank correlation analysis was applied to examine relationships between non-normally distributed continuous variables. The diagnostic performance of antibody levels measured by the ELISA kit in predicting PMN was evaluated using ROC curve analysis. A p-value below 0.05 was considered statistically significant.

RESULTS

This study included 89 individuals, 15 of whom were healthy volunteers. The mean age of the 74 patients was 44.1 years (SD: 12.7; range 21-65); 40 (54.1%) were male. Thirty patients (40.5%) had PMN, 10 (13.5%) had SMN, and 34 (45.9%) had non-MN nephrotic syndrome. Of the 10 SMN patients, five had hypertensive nephropathy, two had systemic lupus erythematosus, one had IgM nephropathy, one had anti-neutrophil cytoplasmic antibodies-associated glomerulonephritis, and one had infection-related glomerulonephritis. Of the 34 non-MN patients, 13 had IgA nephropathy, 11 had focal segmental glomerulosclerosis, 5 had membranoproliferative glomerulonephritis, 2 had minimal change disease, 1 had renal amyloidosis, and 1 had post-streptococcal glomerulonephritis. The mean age of PMN patients was 46.9 years (SD: 11.6; range 21-63); 18 (60%) were male. The mean age of SMN patients was 46.6 years (SD: 11.7; range 28-63); 3 (30%) were male. The mean age of non-MN nephrotic syndrome patients was 41.0 years (SD: 13.5; range 21-65); 19 (55.9%) were male.

Patient characteristics are presented in Table 1. Of the 30 PMN patients, 29 (96.7%) had received immunosuppressive therapy, while one (3.3%) had not. The numbers of patients receiving therapy, either alone or in combination, were as follows: 28 (93.3%) received steroids; 22 (73.3%) received cyclosporine A; two (6.7%) received tacrolimus; two (6.7%) received mycophenolate mofetil; one (3.3%) received azathioprine; and one (3.3%) received cyclophosphamide.

Anti-PLA2R antibody was positive in 9 of 30 PMN patients, whereas it was negative in all patients with SMN, in those with non-MN nephrotic syndrome, and in healthy volunteers. In one of the PMN patients, the anti-PLA2R antibody result was borderline. In this study, mean anti-PLA2R antibody levels were 31.8±55.3 RU/mL in patients with PMN, 1.1±0.09 RU/mL in patients with SMN, 1.1±0.1 RU/mL in patients with non-MN nephrotic syndrome, and 1.1±0.1 RU/mL in the healthy volunteers.

Among the 30 patients with PMN, four (13.3%) were enrolled at diagnosis, and all four had positive anti-PLA2R results (32.66, 119.2, 104.4, and 204 RU/mL, respectively).The remaining 26 patients (86.7%) were evaluated during follow-up. Of these, four had active disease; one was anti-PLA2R positive and another was borderline. Seventeen patients

Table 1. The features of the patients

	PMN (n=30) (mean±SD)	SMN (n=10) (mean±SD)	Non-MN (n=34) (mean±SD)	p
BUN (mg/dL)	21.8±10.2	21.8±13.5	18.1±10.2	0.11
Creatinine (mg/dL)	1.1±0.8	1.1±0.7	1.1±0.6	0.99
Urine total protein (mg/dL)	145.8±173.7	52±58.6	98.2±132.3	0.18
Albumin (g/L)	35.4±6.5	39.6±3.7	38.6±6.7	0.08
Hemoglobin (g/dL)	13.3±1.7	12.6±1.7	13.9±1.5	0.09
Hematocrit (%)	40.4±4.7	37.7±4.5	41.7±4.4	0.05
eGFR (mL/min/L)	82.4±36.2	79.9±35.2	85.7±34.8	0.79
Proteinuria (gr)	3±3.2	1.6±1.8	2.4±3.3	0.12

p<0.05 indicates statistical significance
BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, PMN: Primary membranous nephropathy, SD: Standard deviation, SMN: Secondary membranous nephropathy

were in partial remission, four of whom were anti-PLA2R positive. The remaining five patients were in complete remission, and all were anti-PLA2R negative (Figure 1).

The ELISA kit manufacturer's recommended cut-off value for anti-PLA2R antibody was 20 RU/mL. Using this cut-off value, sensitivity and specificity were 30% and 100%, respectively. ROC curve analysis (area under the curve=0.706 and p=0.003) determined a cut-off value of 1.19 RU/mL (Figure 2). The sensitivity, specificity, PPV, and NPV of the anti-PLA2R IgG ELISA test at different cut-off values are shown in Table 2.

The mean values of parameters related to glomerular disease activity were compared between patients who were anti-PLA2R IgG ELISA-positive and those who were anti-PLA2R IgG ELISA-negative. Anti-PLA2R antibody-positive patients had significantly higher mean proteinuria (p=0.015) and significantly lower mean albumin (p=0.010) levels than antibody-negative patients (Table 3).

Among those with positive anti-PLA2R IgG results, 44.4% had proteinuria levels <3.5 g/day and 55.6% had proteinuria levels >3.5 g/day. Among the patients with negative anti-PLA2R IgG results, 81.2% had proteinuria levels <3.5 g/day and 18.8% had proteinuria levels >3.5 g/day. Proteinuria levels differed significantly (p=0.027) between patients with positive and negative anti-PLA2R IgG ELISA results.

Differences in mean hemoglobin (p=0.030) and hematocrit (p=0.039) values between ELISA-confirmed anti-PLA2R IgG-positive and -negative individuals with PMN were statistically significant, whereas no significant differences were found in other parameters. The mean hemoglobin value of anti-PLA2R antibody positive patients was 12.3±1.3 and the mean hemoglobin value of negative patients was 13.9±1.7. The mean hematocrit value of anti-PLA2R antibody positive patients was 37.6±3.9, while the mean hematocrit value of negative patients was 41.7±4.7. The mean hemoglobin and

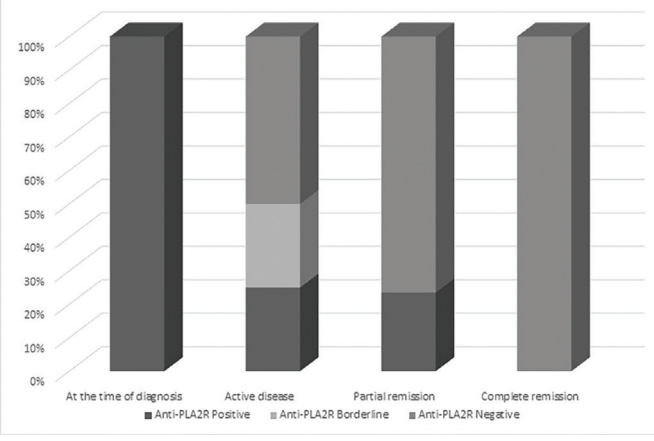

Figure 1. Anti-PLA2R positivity according to disease stages in 30 PMN patients
PMN: Primary membranous nephropathy, PLA2R: Phospholipase A2 receptor

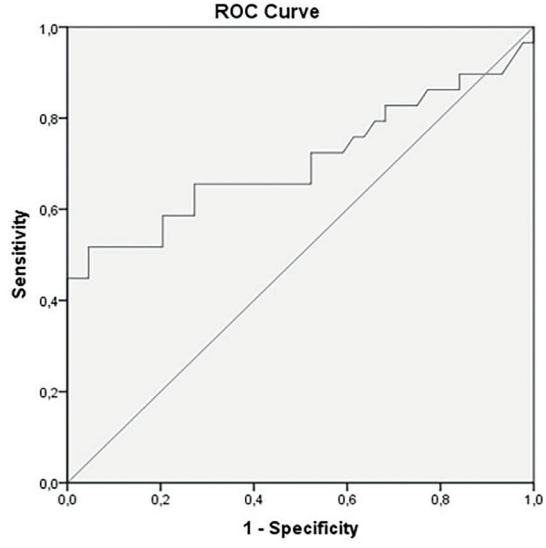

Figure 2. ROC curve analysis
ROC: Receiver operating characteristic

Table 2. Sensitivity, specificity, PPV and NPV of the test at different cut-off values

Cut-off value	Sensitivity	Specificity	PPV	NPV
40 RU/mL	20%	100%	100%	64.7%
20 RU/mL	30%	100%	100%	67.6%
14 RU/mL	33.3%	100%	100%	68.7%
2 RU/mL	46.6%	100%	100%	73.3%
1.19 RU/mL	66.6%	72.7%	62.5%	76.2%

NPV: Negative predictive value, PPV: Positive predictive value

hematocrit values of anti-PLA2R IgG-positive PMN patients were significantly lower than those of anti-PLA2R IgG-negative PMN patients (Table 4).

DISCUSSION

As a chronic immune-mediated glomerular disease, MN remains the predominant cause of nephrotic syndrome among adults. Accurate diagnosis of MN, effective treatment planning, and prognosis assessment are crucial. Anti-PLA2R antibodies are hypothesized to help differentiate primary

Table 3. Comparison of mean values of parameters associated with glomerular disease activity in patients with positive and negative anti-PLA2R IgG ELISA test

	Anti-PLA2R positive (mean±SD)	Anti-PLA2R negative (mean±SD)	p
BUN (mg/dL)	23.4±11.1	19.4±10.6	0.214
Creatinine (mg/dL)	1.1±0.6	1.1±0.7	0.913
eGFR (mL/min/L)	79.6±39.5	85±34.2	0.620
Albumin (mg/dL)	32.3±5.8	38.2±6.3	0.010
Proteinuria (gr)	3.6±2.1	2.4±3.2	0.015

p<0.05 indicates statistical significance
BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, PLA2R: Phospholipase A2 receptor, SD: Standard deviation, ELISA: Enzyme-linked immunosorbent assay, IgG: Immunoglobulin G

Table 4. Results of biochemical clinical parameters according to anti-PLA2R ELISA test in patients with PMN

	Anti-PLA2R positive (mean±SD)	Anti-PLA2R negative (mean±SD)	p
Urine total protein* (mg/dL)	171.9±147.9	129±188.9	0.140
Urine creatinine (mg/dL)	50.1±25.6	51.3±21.9	0.835
Urine albumin† (mg/dL)	125.4±119.7	95.7±156	0.127
Proteinuria (gr)	3.6±2.1	2.8±3.7	0.127
Glucose (mg/dL)	91.2±24.4	98.1±40.9	0.417
BUN (mg/dL)	23.4±11.1	20.4±9.8	0.472
Creatinine (mg/dL)	1.1±0.6	1.1±0.9	0.908
eGFR (mL/min/L)	79.6±39.5	86.4±34.2	0.594
Albumin (g/L)	32.3±5.8	37±6.6	0.069
LDL‡ (mg/dL)	115.4±40.1	147.8±62.1	0.153
HDL‡ (mg/dL)	68.3±41.1	64.2±16.5	0.532
Cholesterol‡ (mg/dL)	215.5±78.5	242.1±80.7	0.340
Triglyceride‡ (mg/dL)	159.3±55.5	150.2±79.8	0.417
Total calcium (mg/dL)	8.8±0.6	9.2±0.4	0.153
Potassium (mEq/L)	4.3±0.4	4.5±0.4	0.199
Sodium (mEq/L)	137.8±3.4	139±1.4	0.365
ALT (U/L)	23.2±16.3	19.6±8.3	0.799
Hemoglobin (g/dL)	12.3±1.3	13.9±1.7	0.030
Hematocrit (%)	37.6±3.9	41.7±4.7	0.039

p<0.05 indicates statistical significance
*Urine total protein of one patient was less than 1 in HIS, †: Urine albumin of five patients was less than 0.5 in HIS, ‡: LDL, HDL, cholesterol and triglyceride values of two patients could not be used in the study as it was not available
ALT: Alanine aminotransferase, BUN: blood urea nitrogen, eGFR: Estimated glomerular filtration rate, HDL: High density lipoprotein, LDL: Low density lipoprotein, PLA2R: Phospholipase A2 receptor, SD: Standard deviation, HIS: Hospital information system, ELISA: Enzyme-linked immunosorbent assay, PMN: Primary membranous nephropathy

MN from secondary forms of the disease. In addition to the diagnosis, these antibodies have been found to be useful in treatment decisions, assessment of clinical response, and prediction of prognosis (1,12,13).

Despite the cross-sectional design of the study, clinical characteristics were comparable across the PMN, SMN, and non-MN nephrotic syndrome groups, and there were no statistically significant differences ($p>0.05$) (Table 1). Using the manufacturer's recommended cut-off (20 RU/mL), anti-PLA2R positivity was detected only in PMN patients and not in other patient groups or healthy volunteers. These results indicate high specificity and high PPV. Accordingly, when secondary causes (e.g., autoimmune diseases, infections such as hepatitis, or malignancy) are carefully excluded, anti-PLA2R positivity may reduce the need for biopsy in MN patients in line with Kidney Disease: Improving Global Outcomes (KDIGO) 2021 (14). However, biopsy decisions should still be individualized. This may allow rapid diagnosis of MN and may reduce the risk of biopsy-related complications (4). These findings are consistent with Kim et al. (15), who reported negative anti-PLA2R results in SMN, non-MN nephrotic syndrome, and healthy controls.

The optimal cut-off value for the anti-PLA2R ELISA has not yet been standardized (4). In studies using the commercial ELISA kit (EUROIMMUN, Lübeck, Germany), anti-PLA2R positivity rates reported in PMN vary across populations. Differences across studies may reflect immunosuppressive therapy (IST) status, the presence of other target antibodies [e.g., thrombospondin type 1 domain-containing 7A (THSD7A)], *PLA2R* gene polymorphisms, and the interval between diagnosis and testing (11). Using the 20 RU/mL cut-off, positivity has been reported as 50% in Japanese patients, 62.2% in Chinese patients, 25% in Australian patients, and 48.5% in Greek patients (11,16). In our study, positivity at 20 RU/mL was 30% among PMN patients, closely similar to the rate reported in Australian patients.

Several factors may contribute to low or undetectable anti-PLA2R levels in patients with PMN. Anti-PLA2R may be negative when serum is collected during immunologic remission or while the patient is receiving IST. In addition, antibodies other than anti- PLA2R (e.g., THSD7A or other not-yet-identified antibodies) may contribute to the pathogenesis (8,17). In our study, anti-PLA2R was negative in some PMN patients; this may be explained by the factors mentioned above.

In our study, all four patients evaluated at the time of diagnosis, before initiation of IST, were anti-PLA2R positive, whereas anti-PLA2R was negative in all patients who were in complete remission and had normal proteinuria during follow-up (Figure 1). These findings support the view that anti-PLA2R may be a diagnostic and prognostic marker, particularly in patients who have not yet received treatment. KDIGO 2021 notes that anti-PLA2R levels >50 RU/mL may indicate high risk for progression and recommends monitoring antibody levels every 3-6 months. Decreasing antibody levels can predict clinical remission (14). In our study, the finding that all patients in complete remission were anti-PLA2R negative supports this. In addition, antibody seroconversion under IST may indicate a reduced risk of relapse. Therefore, anti-PLA2R monitoring may be a useful marker for predicting treatment response and determining the treatment plan.

Several studies have shown that the sensitivity, specificity, PPV, and NPV of ELISA assays vary according to the cut-off value used. Liu et al. (11), determined the cut-off value of 2.6 RU/mL by ROC analysis in Chinese patients and showed that increasing the cut-off increased specificity and PPV, whereas sensitivity and NPV decreased. Similarly, an Italian study reported sensitivity and specificity values of 61.1% and 99.7% at a cut-off of 20 RU/mL; lowering the cut-off to 14 RU/mL slightly increased sensitivity (63.5%) while maintaining high specificity. Alternatively, an ROC-derived cut-off of 2.7 RU/mL resulted in 83.3% sensitivity and 95.1% specificity (18). In our study, ROC analysis determined 1.19 RU/mL as the optimal cut-off (sensitivity 66.6%, specificity 72.7%, PPV 62.5%, NPV 76.2%). Applying a higher cut-off of 2 RU/mL reduced sensitivity to 46.6% but increased specificity to 100%. At a cut-off of 1.19 RU/mL, the risk of missed diagnoses decreases, and negative results more confidently rule out PMN; however, the increased risk of false- positive results may complicate diagnosis. At a cut-off of 2 RU/mL, diagnostic confidence increases, although some cases may be missed. In general, a higher cut-off may better reflect true clinical activity during follow-up. Nevertheless, the limited sample size restricts diagnostic reliability in our study. Larger studies are needed.

Anti-PLA2R antibody levels and proteinuria are widely used markers for prognostic assessment in MN (10). Previous studies have shown that anti-PLA2R antibodies are associated with disease activity and prognosis (19,20). Radice et al. (20) reported a linear association between anti-PLA2R positivity and higher proteinuria as well as lower serum albumin levels, and also demonstrated that anti-PLA2R antibody levels correlate with disease activity as assessed by proteinuria and other biomarkers. Consistent with these findings, anti-PLA2R-positive patients in our study had higher mean proteinuria ($p=0.015$) and lower mean serum albumin ($p=0.010$). Proteinuria >3.5 g/day is commonly

used to define nephrotic proteinuria and is routinely used to monitor MN activity (21-23). Our findings also showed a significant difference in proteinuria between anti-PLA2R-positive and anti-PLA2R-negative groups (p=0.027); anti-PLA2R positivity was more frequent among patients with nephrotic-range proteinuria. These results support the use of anti-PLA2R antibodies as a prognostic indicator with respect to proteinuria, a marker of disease activity. While Akiyama et al. (24) reported lower albumin in antibody-positive PMN patients, in our study, significantly lower hemoglobin and hematocrit values were also observed in anti-PLA2R-positive patients, whereas most other laboratory parameters did not differ significantly between groups.

The prognosis of PMN is heterogeneous: approximately one-third of patients achieve spontaneous remission, one-third have persistent proteinuria with stable renal function, and one-third progress to end-stage renal failure (21). Anemia is a serious complication in chronic renal failure and has been associated with high proteinuria (25,26). The combination of higher proteinuria and lower hemoglobin and hematocrit observed in anti-PLA2R-positive patients may be relevant to progression to chronic renal failure. Finally, detection of anti-PLA2R antibodies before the onset of proteinuria and before pathological diagnosis has been reported (27), further supporting their clinical importance and the need for additional studies.

Study Limitations

Our study had limitations. First, the number of patients was relatively low compared with those in other studies. Furthermore, because this was a cross-sectional study and because of financial difficulties, we were unable to follow up with patients; therefore, the relationship between remission/relapse rates and anti-PLA2R antibodies could not be determined.

CONCLUSION

In our study, a positive anti-PLA2R result using the manufacturer's recommended cut-off value may help to rule in PMN and reduce the need for biopsy, whereas a negative result may still require biopsy for confirmation. ROC curve analysis identified 1.19 RU/mL as the optimal cut-off; however, overall diagnostic performance in our dataset was better at 2 RU/mL. Anti-PLA2R positivity was associated with higher proteinuria and lower hemoglobin and hematocrit, suggesting that this antibody may have prognostic value and be linked to progression to chronic renal failure. Larger prospective studies are needed to clarify the clinical significance of anti-PLA2R antibody levels in MN.

ETHICS

Ethics Committee Approval: Ethical approval for the study was granted by the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (approval no: 2022/120, date: 30.06.2022).

Informed Consent: Informed consent was obtained from each participant included in this study.

FOOTNOTES

This work was presented at the 7th National Congress of Clinical Microbiology, Muğla, Türkiye, in 2023.

This work is also included in Mustafa Erdem Sarp's thesis.

Authorship Contributions

Surgical and Medical Practices: M.E.S., R.K.K., Concept: M.E.S., I.B., G.B., N.K., R.K.K., E.Ö., F.A., Design: M.E.S., I.B., G.B., N.K., R.K.K., E.Ö., F.A., Data Collection or Processing: M.E.S., R.K.K., Analysis or Interpretation: M.E.S., I.B., G.B., Literature Search: M.E.S., I.B., G.B., N.K., R.K.K., E.Ö., F.A., Writing: M.E.S., I.B., G.B.

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