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Original Article

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Economic Benefit of Anti-PLA2R Antibody Testing in the Diagnosis of Membranous Nephropathy: A Single-Center Cost Analysis

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ABSTRACT

Background: This study aimed to evaluate the financial impact of using anti-phospholipase A2 receptor antibody testing instead of kidney biopsy for diagnosing membranous nephropathy.
Methods: A retrospective cross-sectional study was conducted at Gazi University Faculty of Medicine Hospital between November 2022 and January 2024. Seventy adult patients with nephrotic syndrome underwent anti-phospholipase A2 receptor antibody testing using an enzyme-linked immunosorbent assay. The costs of diagnosis based on serology and kidney biopsy were compared.
Results: Among 70 patients, 18 tested positive for anti-phospholipase A2 receptor antibodies. Of these, 13 were diagnosed without a kidney biopsy, leading to a cost reduction of approximately 52 000 Turkish Liras (1300 American Dollars). The total expense for anti-phospholipase A2 receptor antibody testing was significantly lower than that of kidney biopsy, which required hospitalization and procedural costs. If all antibody-positive patients had been diagnosed without a biopsy, the potential savings would have reached 24 000 Turkish Liras (600 American Dollars).
Conclusion: Anti-phospholipase A2 receptor antibody testing provides a cost-effective, non-invasive alternative to kidney biopsy for diagnosing membranous nephropathy. Implementing a serology-first approach in selected cases may significantly reduce healthcare expenditures while maintaining diagnostic accuracy.
Keywords: Cost analysis, diagnosis, membranous nephropathy, nephrotic syndrome, phospholipase A2 receptor

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INTRODUCTION

Nephrotic syndrome is characterized by proteinuria exceeding 3.5 g/day, hypoalbuminemia, edema, and hyperlipidemia.[1] Kidney biopsy remains the gold standard in the diagnosis of glomerular diseases causing nephrotic syndrome. However, it carries risks such as bleeding, pain, hematuria, and the need for hospitalization, thereby increasing both the overall cost and the burden patient.[2,3] In contrast, in certain types of nephritis (e.g.anti neutrophilic cytoplasmic antibody(ANCA)-associated patient burden glomerulonephritis), a diagnosis can often be established with high accuracy using serological markers, without the need for a kidney biopsy.[4]

One of the most common causes of nephrotic syndrome in adults is membranous nephropathy (MN).[5] Membranous nephropathy can be associated with malignancies, drugs, infections, and systemic diseases; however, approximately 80% of cases occur primarily.[6] In the pathogenesis of primary MN, M-type phospholipase A2 receptors located on the podocyte surface and the anti-phospholipase A2 receptor (PLA2R) antibodies formed against them play a crucial role.[7] Anti-PLA2R antibodies are detectable in 50%-80% of patients with primary MN.[8]

Bobart et al[3] demonstrated that in patients with an estimated glomerular filtration rate (eGFR) ≥60 mL/min/

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1.73 m^2 and no identifiable secondary causes of MN, a positive anti-PLA2R antibody test provided sufficient diagnostic certainty to forgo a kidney biopsy, as the biopsy results did not alter clinical management.

Consistent with this, the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guideline for the management of glomerular diseases states that in patients with preserved kidney function who present with nephrotic syndrome and test positive for anti-PLA2R antibodies, kidney biopsy may not be necessary to confirm the diagnosis of MN.[9]

Building on this diagnostic shift, a retrospective cohort study was conducted to assess the economic impact of biopsy-based versus enzyme-linked immunosorbent assays (ELISA)-based diagnosis in MN. By comparing real-world diagnostic costs, the aim was to determine whether a serology-first strategy provides a meaningful financial advantage in clinical practice.

MATERIAL AND METHODS

Study Design

This retrospective cross-sectional study included 70 patients with nephrotic syndrome who presented to the Nephrology Clinic at Gazi University Faculty of Medicine Hospital between November 2022 and January 2024. All patients had anti-PLA2R antibody levels measured at presentation.

Inclusion criteria for the study were: age ≥18 years, availability of complete clinical and laboratory data at both presentation and follow-up visits, and documented serum anti-PLA2R measurements at initial evaluation.

Patients who did not continue care at the institution were excluded.

Data Collection

Patient records provided data on demographic characteristics (age, gender), comorbid conditions, anticoagulant and antiplatelet medication usage, and relevant laboratory parameters, including creatinine levels, estimated glomerular filtration rate (eGFR) calculated via the CKD-EPI 2021 equation, albumin and lipid profiles, quantitative proteinuria, and anti-PLA2R antibody measurements. Complete data were available for all variables specified in the analysis. Anti-PLA2R antibody quantification was performed using ELISA methodology with EUROIMMUN commercial assay kits. Interpretation of anti-PLA2R antibody titers followed standardized cutoffs: values <14 RU/mL were classified as negative, 14-19 RU/mL as borderline, and ≥20 RU/mL as positive.[10]

The cost of anti-PLA2R antibody testing at the center was approximately 400 Turkish Liras (TL)/10 American Dollars ($) per patient during the study period. The overall expense of an uncomplicated percutaneous renal biopsy in Türkiye was around 4000 TL ($100), including 450 TL for single-day hospitalization and 3550 TL for the procedure itself.

A cost analysis was conducted between 2 patient cohorts diagnosed with MN, either by kidney biopsy or ELISA-based serology.

The Gazi University Ethics Committee approved this study on September 5, 2023 (Approval number: E-77082166-604.01.02-813550). The research was conducted according to the Declaration of Helsinki principles. Due to the nature of this study, informed consent was waived by the ethics committee.

This study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Statistical Analysis

Data were analyzed using SPSS version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistics for demographic and clinical characteristics, means and SDs, medians and interquartile ranges for continuous variables, and frequencies and percentages for categorical variables were calculated. The normality of the distribution was assessed using the Shapiro-Wilk test. Normally distributed data were given as mean, and non-normally distributed data were given as median (interquartile range [IQR]).

RESULTS

We enrolled 70 patients presenting with nephrotic syndrome who underwent anti-PLA2R antibody testing. The mean age was 54 ± 17 years. Thirty-seven were male and 33 were female. Anti-PLA2R antibodies were detected in 18 patients (25.7%) (Table 1). Five of the anti-PLA2R antibody-positive patients had diabetes mellitus. None of the patients with positive anti-PLA2R antibodies were considered false positives. Among seropositive individuals, the median serum creatinine was 0.94 mg/dL, and the median estimated glomerular filtration rate (eGFR) was 74.5 mL/min. Median serum albumin and 24-hour proteinuria were 2.8 g/dL and 8650 mg/day, respectively. Comprehensive laboratory parameters are summarized in Table 2.

Among the 18 anti-PLA2R antibody-positive patients, 13 received a diagnosis of MN without the need for kidney biopsy. The remaining 5 underwent kidney biopsy due to suspected

MAIN POINTS

- Anti-phospholipase A2 receptor (PLA2R) test enables non-invasive diagnosis of membranous nephropathy.
- Cost analysis shows significant savings with anti-PLA2R-based diagnosis.
- Adopting antibody testing may reduce the healthcare burden without accuracy loss.

Table 1. General Characteristics of Patients with Nephrotic Syndrome

Age, mean ± SD (years)	54 ± 17
Sex (female/male), (n [%])	33 (47.1%) / 37 (52.9%)
Anti-PLA2R antibody-positivity (n [%])	18 (25.7%)
Presence of diabetes mellitus (n [%])	19 (27.1%)

PLA2R, phospholipase A2 receptor. SD; standart deviation

Table 2. Laboratory Characteristics of Anti-Phospholipase A2 Receptor Antibody–Positive Patients

Creatinine (mg/dL), median (IQR)	0.94 (0.70)
eGFR (CKD-EPI 2021, mL/min/1.73 m^2), median (IQR)	74.50 (59.00)
Albumin (g/dl), median (IQR)	2.80 (0.60)
Anti-PLA2R antibody level (RU/mL), median (IQR)	99.47 (398.03)
Total cholesterol (mg/dL), median (IQR)	278.50 (97.00)
LDL cholesterol (mg/dL), median (IQR)	180.00 (64.25)
Proteinuria (mg/day), median (IQR)	8650.00 (2475.00)

CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, glomerular filtration rate; IQR, interquartile range; LDL, low density lipoprotein; PLA2R, phospholipase A2 receptor.

concomitant rheumatologic disease (n = 2) or delayed serological results (n = 3) (Figure 1). No post-procedural complications were observed, and all patients were discharged following 24 hours of monitoring. Biopsy confirmed the diagnosis of MN in all 5 cases.

Among the 52 patients with negative serum anti-PLA2R antibody results, 10 did not undergo biopsy due to small kidney size, mandatory anticoagulant or antiplatelet use, presumed chronic disease, or patient refusal. The remaining 42 underwent biopsy, and 12 were diagnosed with serum anti-PLA2R-negative MN (Figure 1).

The total cost of testing 70 patients for anti-PLA2R antibodies was approximately 28 000 TL ($700). The cost of the 5 biopsies performed on anti-PLA2R antibody-positive patients was approximately 20 000 TL ($500). Since 13 patients were diagnosed with MN without biopsy, the avoidance of biopsy costs saved approximately 52 000 TL ($1300), resulting in a net savings of 4000 TL ($100) (Figure 2). If the 5 antibody-positive patients had been diagnosed without performing a kidney biopsy, this economic benefit could have increased by 20 000 TL ($500), reaching 24 000 TL ($600).

DISCUSSION

This study hypothesized that the use of anti-PLA2R antibodies for the diagnosis of membranous nephropathy is more cost-effective than kidney biopsy. According to the literature review, this study is the first to conduct a cost analysis of anti-PLA2R antibodies and kidney biopsy in the diagnosis of MN and demonstrates that anti-PLA2R antibodies are cost-effective compared to kidney biopsy in the diagnosis of MN. Using anti-PLA2R antibodies in the diagnosis of MN has provided with approximately 4000 TL ($100) in economic benefit. If a biopsy had not been performed on patients for whom it was conducted despite a positive antibody test, the economic benefit would have increased even more. This finding demonstrates the significant cost advantage of anti-PLA2R antibodies in the diagnosis of MN.

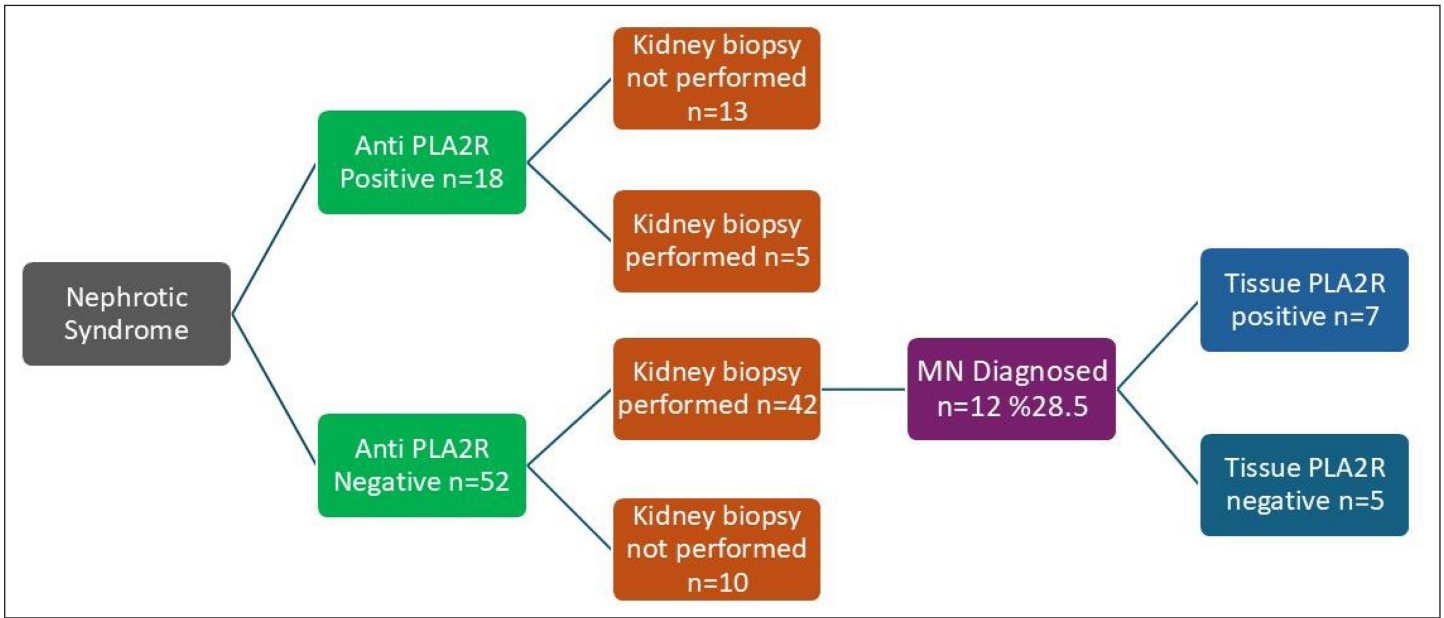

Figure 1. Anti-PLA2R antibody and kidney biopsy analysis. PLA2R, phospholipase A2 receptor.

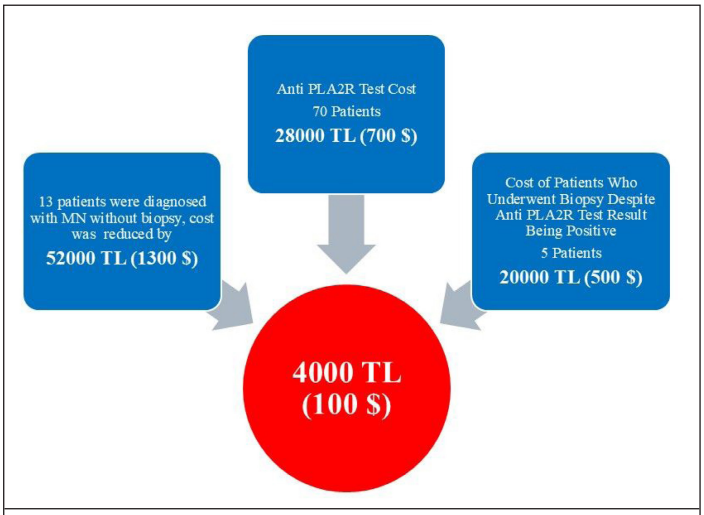

Figure 2. Anti-PLA2R test and kidney biopsy cost analysis. PLA2R, phospholipase A2 receptor; TL, Turkish Lira; $, American Dollar.

Serum anti-PLA2R antibodies are generally detected using immunofluorescence assays (IFA) and ELISA methods. Immunofluorescence assay is a more sensitive method than ELISA. Its sensitivity has been reported as 83% and its specificity as 100%.[11] In a study conducted by Jurubiță and colleagues,[12] using the ELISA method with a cut-off value of 20 RU/mL, the sensitivity of anti-PLA2R antibodies in diagnosing MN was found to be 64%, specificity 94%, positive predictive value 91%, and negative predictive value 75%. In another study conducted by Li and colleagues,[13] again with a cut-off value of 20 RU/mL, the sensitivity of anti-PLA2R antibodies in diagnosing MN was reported as 62.2% and specificity as 91.5%. Although prioritizing the IFA method in diagnosis is necessary, these studies also demonstrate that measuring serum anti-PLA2R antibodies using the ELISA method is highly specific in diagnosing MN.

There is no direct study in the literature regarding the cost analysis of anti-PLA2R antibodies. Ragy and colleagues reported in their study that the average cost of anti-PLA2R antibody measurement in the United Kingdom was £27.[14] In our clinic, the cost of anti-PLA2R antibody measurement is 400 TL ($10). The elimination of the need for hospitalization by the test prevents loss of workforce for both the patient and the caregivers. The repeatability of the test and its ability to show response to treatment also provide indirect economic benefit by reducing unnecessary use of immunosuppressive therapy.[15] All these factors provide a significant economic advantage. The cost analysis conducted in this study also demonstrates that the use of anti-PLA2R antibodies in diagnosis is significantly more cost-effective compared to kidney biopsy.

Kidney biopsy is accepted as the gold standard method for MN diagnosis.[16] In addition to diagnosing the disease, kidney biopsy also provides information on the severity and chronicity of the disease. The measurement of anti-PLA2R antibodies is highly specific for diagnosis,[17] but it cannot provide information on disease severity and chronicity, which biopsy offers. Despite the positive contributions of biopsy in diagnosis and treatment, its disadvantages include being an invasive procedure and the possibility of complications such as post-procedure bleeding.[16] Additionally, kidney biopsy is a costly procedure.[17] In a study conducted by Ragy and colleagues, the cost of an uncomplicated biopsy procedure in England was reported as an average of £774, whereas in Türkiye, it is on average 4000 TL ($100).[14,18] In cases where complications develop after kidney biopsy, these costs can further increase. The hospitalization of patients for the kidney biopsy procedure and their temporary absence from working life also impose additional burdens on the national economy.

The fact that anti-PLA2R antibodies provide a non-invasive diagnostic method protects patients from possible complications associated with biopsy. In patients who are hesitant about kidney biopsy due to potential complications, the measurement of PLA2R antibodies enables accurate diagnosis and the planning of appropriate post-diagnosis treatment.[19] Additionally, anti-PLA2R antibodies can also be used in disease monitoring after diagnosis.[20] The test has several disadvantages. These include its inability to provide information about the chronicity of the disease—unlike kidney biopsy—the relatively low sensitivity of the ELISA method, and the potential for false-negative or false-positive results. Indeed, false-positive results have been reported in diabetic patients in the literature.[20] A false-negative result obtained by the ELISA method may delay the diagnosis and treatment process of MN. In cases where the test result is suspected to be falsely positive or negative, it is recommended to evaluate antibody levels using the indirect immunofluorescence test or to include a kidney biopsy in the diagnostic process.[21] In such cases, the economic benefit provided by the test may also be limited. Although the cost of the IFA method is higher compared to ELISA, it may offer a more meaningful economic advantage in certain patients due to its higher diagnostic accuracy and its ability to eliminate the need for an invasive procedure.

The study supports that anti-PLA2R antibodies are cost-effective in the diagnosis of MN. Furthermore, the fact that the pathology results of all patients who underwent kidney biopsy despite having positive anti-PLA2R antibodies were reported as MN indicates the high specificity of the test. In the literature review, there were no similar studies conducting a comparative cost analysis of anti-PLA2R antibodies and kidney biopsy in the diagnosis of MN, making this study significant in this regard.

This study has several limitations. The first is that its single-center and retrospective design limits the generalizability of the findings to institutions with different clinical practices or cost structures. Multicenter prospective studies are needed to validate the results in more diverse healthcare settings. Another limitation is that evaluating the cost analysis solely based on

procedure and test fees excludes the economic losses due to workforce absenteeism of patients and caregivers, as well as additional expenses incurred due to access to hospital services during hospitalization. Additionally, establishing the diagnosis of MN without performing a biopsy allows the medical team and pathologists to allocate more time to other procedures not included in the cost analysis; not including this gain in the analysis is another limitation of this study. The economic benefit identified in this study is modest; however, considering the limitations in future similar studies and including workforce-related losses in the analysis will enable a more effective cost evaluation. As a result, in such a case, the economic benefit obtained from such analyses may be on a larger scale.

Our study demonstrates that anti-PLA2R antibodies should be included as a cost-effective, non-invasive diagnostic method in the diagnosis of primary MN. The widespread implementation of anti-PLA2R antibody measurements in diagnosis will provide significant benefits for healthcare economics.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Gazi University (Date: 05.09.2023; No.: E-77082166-604.01.02-813550).

Informed Consent: Due to the retrospective nature of this study, informed consent was not obtained from the patients.

Peer-review: Externally peer-reviewed.

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