RESEARCH ARTICLE

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Evaluation of Clinical Findings and Treatment Outcomes of Patients with Primary Membranous Nephropathy: A Single Center Experience

Primer Membranöz Nefropatili Hastaların Klinik Bulgularının ve Tedavi Sonuçlarının Değerlendirilmesi: Tek Merkez Deneyimi

ABSTRACT

Objective

Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in non-diabetic white adults. The primary aim of our study was to compare the demographic and clinical characteristics, treatment outcomes, and the occurrence of remission in patients with primary MN.

Materials and Methods

Our study included 35 patients diagnosed with primary MN between January 2012 and January 2021. Based on risk classification, patients were distributed across low, moderate, high, and very high-risk groups. All patients were treated under Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.

Results

The mean age of our patients was 55.9±10.8 years, and 71.4% were male. At diagnosis, almost all patients (97.1%) had nephrotic-level proteinuria. In the risk classification of the patients with MN, 13 (37.1%) patients were low risk, 11 (31.4%) patients were moderate risk, 8 (22.9%) patients were high risk, and 3 (8.6%) patients were in the very high-risk group. The overall remission (OR) rate at the end of the first year was 68.6%. The mean age of patients who achieved remission was 52.8±10.5, while the mean age of patients who did not achieve remission was 62.9±8.4 (p=0.008). The most commonly used immunosuppressive (IS) agent that combined with steroids was cyclophosphamide (65.7%), followed by calcineurin inhibitors (45.7%).

Conclusion

High OR rates were observed at the end of the first year of MN treatment. IS treatment applied to MN patients may contribute to early remission.

Key Words

Membranous nephropathy, Remission, Immunosuppressive treatment, Proteinuria

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ÖZ

Amaç

Membranöz nefropati (MN), diyabetik olmayan beyaz yetişkinlerde nefrotik sendromun en yaygın nedenidir. Çalışmamızın temel amacı, primer MN tanısı alan hastaların demografik ve klinik özelliklerini, tedavi sonuçlarını ve remisyon oluşumunu karşılaştırmaktır.

Gereç ve Yöntemler

Çalışmamıza, Ocak 2012 ile Ocak 2021 arasında primer MN tanısı alan 35 hasta dahil edilmiştir. Hastalar risk sınıflandırmasına dayalı olarak düşük, orta, yüksek ve çok yüksek risk grubu olarak sınıflandırıldı. Tüm hastalar, Böbrek Hastalığı: Sonuçların İyileştirilmesi (KDIGO) kılavuzları altında tedavi edilmiştir.

Bulgular

Hastalarımızın ortalama yaşı 55,9±10,8 yıl olup, çoğunluğu (%71,4) erkekti. Tanı anında hastaların neredeyse tamamında (%97,1) nefrotik seviyede proteinüri mevcuttu. MN için yapılan risk sınıflandırmasında, 13 (%37,1) hasta düşük risk grubunda, 11 (%31,4) hasta orta risk grubunda, 8 (%22,9) hasta yüksek risk grubunda ve 3 (%8,6) hasta çok yüksek risk grubunda yer aldı. İlk yıl sonunda genel remisyon oranı %68,6 idi. Remisyon elde eden hastaların ortalama yaşı 52,8±10,5 iken, remisyon elde edemeyen hastaların ortalama yaşı 62,9±8,4 idi (p=0,008). Steroidlerle birlikte en yaygın kullanılan immünosupresif (IS) ajan, siklofosfamid (%65,7) olup, bunu kalsinörin inhibitörleri (%45,7) takip etti.

Sonuç

Tek merkezli çalışmamızda, literatürle tutarlı olarak MN tedavisinin ilk yılı sonunda yüksek genel remisyon oranları gözlemlenmiştir. MN hastalarına uygulanan IS tedavi, erken remisyona katkıda bulunabilir.

Anahtar Kelimeler

Membranöz nefropati, Remisyon, İmmünosupresif tedavi, Proteinüri

INTRODUCTION

The most prevalent cause of idiopathic nephrotic syndrome in non-diabetic adults worldwide is membranous nephropathy (MN), with an incidence of about 30%, and it increases up to 40% in adults over 60 years old (1, 2). Approximately 75-80% of cases are renal-limited (primary MN), while the remaining cases are associated with conditions such as malignancies, autoimmune/collagen vascular diseases, infections, and drugs/toxins (secondary MN). In MN, characteristic morphological findings include glomerular basement membrane thickening accompanied by subepithelial immune deposits containing immunoglobulins and complement. The antigens present within the localized antigen-antibody complexes in MN may originate from endogenous podocytes or systemic sources. These antigens become lodged in podocytes, leading to the activation of immune-mediated damage (3). Most cases of primary MN are mediated by antibodies against the M-type phospholipase A2 receptor (anti-PLA2R) (85%), thrombospondin type 1 domain-containing 7A (THSD7A) (3-5%), Semaphorin-3b, exostosin-1A/1B and neural epidermal growth factor-like 1 (4).

Clinical presentation is similar in both primary and secondary forms of the disease, often manifesting with symptoms of nephrotic syndrome (edema, hypoalbuminemia, proteinuria, hyperlipidemia, and lipiduria), microscopic hematuria (30-40%), hypertension (10-20%), and venous thromboembolic events. The progression of MN displays significant heterogeneity, with one-third of untreated patients, particularly those exhibiting low or absent anti-PLA2R levels, undergoing spontaneous remission (5, 6). Another third progresses to end-stage renal disease (ESRD) within ten years, while the remaining individuals develop non-progressive chronic kidney disease (CKD). Higher proteinuria, serum creatinine, and anti-PLA2R levels at diagnosis are well-known prognostic factors for renal survival, and current guidelines recommend tailoring treatment in primary MN according to these factors (7).

Although the KDIGO 2012 and 2021 glomerulonephritis (GN) guidelines attempt to find a global consensus on the treatment of MN, a disease-specific treatment is yet to be established. Due to the limited treatment options and varying approaches among centers, there is a need for local centers' experiences to contribute to consensus building and improving prognosis in disease management. This study aims to evaluate the clinical outcomes of primary MN patients managed at our center, in comparison with their demographic and laboratory characteristics.

MATERIALS and METHODS

Study Population

Our study evaluated the records of 450 patients diagnosed with GN via renal biopsy between January 2012 and January 2021. It was determined that 45 of these patients were diagnosed with MN. All patients with MN underwent a comprehensive evaluation to exclude secondary causes, consistent with established guidelines (8). This evaluation included screening for hepatitis B and C viruses, human immunodeficiency virus, treponemes in syphilis, systemic lupus erythematosus, and potential drug-related etiologies such as nonsteroidal anti-inflammatory drugs. In addition, cancer screening was performed based on age and national guidelines, incorporating imaging techniques such as chest X-ray or computed tomography scans and tests like prostate-specific antigen in males over 50–60 years of age. By systematically excluding secondary MN, we ensured that our cohort primarily represented cases of primary disease. Patients with a follow-up period of less than one year (n=7) and those diagnosed with secondary MN (n=3) were excluded from the study. Eventually, 35 patients diagnosed with primary MN were included in this study.

The MN diagnosis was made based on characteristic findings from a kidney biopsy. Light microscopy typically shows diffuse thickening of the glomerular basement membrane (GBM) without significant hypercellularity; in advanced stages, GBM "spikes" may be seen among immune deposits and chronic sclerosing changes. Immunofluorescence microscopy confirms the diagnosis by demonstrating a diffuse granular IgG and C3 staining pattern throughout the GBM (4).

Data Collection

The patients' demographic, clinical, and laboratory data at diagnosis were retrospectively analyzed. Parameters such as gender, age at diagnosis, and accompanying comorbidities were examined. Besides, biochemical parameters, including albumin, estimated glomerular filtration rate (eGFR), serum creatinine, white blood cell count, platelet count, hemoglobin, 24-hour urine protein levels, and active urine sediment at diagnosis were also analyzed. The presence of five or more red blood cells (RBC) per high power field (HPF) in urine analysis was defined as hematuria. The clinical and laboratory findings of the patients were evaluated to determine risk groups for MN.

Treatment and Renal Response

In our clinic, patients diagnosed with MN were treated according to the 2012 and 2021 KDIGO guidelines throughout the follow-up period (7, 9). We initiate treatment by taking into account the potential toxicity of immunosuppressive drugs used in the treatment of primary MN and the high probability of spontaneous remission, especially in patients in the low-risk group. So, we do not initiate immunosuppressive (IS) therapy in our patients with MN if they have nephrotic syndrome with normal eGFR or unless at least one risk factor for disease progression is severe or present complications of nephrotic syndrome (e.g., AKI, infections, thromboembolic events) have occurred. Patients diagnosed with MN in 2021 and after that were treated according to the current GN guidelines, with treatment tailored to their risk groups. In addition, all patients diagnosed with MN were routinely given the maximum tolerated ACE inhibitor or ARB dose unless contraindicated.

Complete remission (CR) was defined as a reduction in 24-hour urine proteinuria to <300 mg/day within 6-12 months after the initiation of treatment, along with stabilization or improvement in measured kidney function. If the proteinuria level did not meet the criteria for a CR, a partial remission (PR) was defined as at least a 50% reduction in proteinuria, along with a decrease in 24-hour urine protein excretion to <3.5 g/day and stable serum creatinine levels. All patients achieving PR or CR were defined as overall remission (OR). The IS treatments and responses of the patients during the follow-up period were also examined.

Statistical Analysis

The study evaluated the normal distribution of variables using visual methods such as histograms and probability graphs, as well as analytical methods, including Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics presented numerical data with normal distribution as mean and standard deviation, data without normal distribution as median (minimum-maximum values), and nominal data as count and percentage. Numerical variables with normal distribution were compared between two groups using the independent samples t-test, while those without normal distribution were analyzed using the Mann-Whitney U test. Nominal data were compared using Chi-square analysis and Fisher's exact test. The statistical significance level was set at a threshold of $p<0.05$. Data analysis was performed using the SPSS version 25.0 (Chicago, USA) software package.

RESULTS

The study comprised 35 patients diagnosed with primary MN through kidney biopsy, with a median follow-up duration of 3 (1-18) years. At the time of diagnosis, the patients had a mean age of 55.9±10.8 years, and 10 (28.6%) were female. Seventeen (48.5%) of the patients had a known history of hypertension, and 5 (14.3%) had a diagnosis of diabetes mellitus. At diagnosis, the median serum creatinine level was 0.9 (0.5-6.4) mg/dL, and the eGFR was 98 (10-128) ml/min/1.73 m². Active urine sediment was detected in 14 (40%) patients, and 97.1% had nephrotic-level proteinuria. The serum albumin level was 2.8 (1.4-3.7) g/dL, and the 24-hour urine proteinuria level was 9957±5183 mg/day. In the risk classification for MN, 13 (37.1%) patients were found to be in the low-risk group, 11 (31.4%) in the moderate-risk group, 8 (22.9%) in the high-risk group, and 3 (8.6%) in the very high-risk group.

The demographic, clinical and laboratory data at the time of diagnosis were analyzed for patients who achieved remission within the first year and those who did not. In the first year, 24 out of 35 patients (68.6%) achieved OR, while 11 (31.4%) did not. The average age of patients who achieved remission was 52.8±10.5 years, while the average age of those who did not was 62.9±8.4 years (p=0.008). The median follow-up duration was 4 (1-18) years for patients who achieved remission and 1.5 (1-6) years for those who did not (p=0.016). Although 75% of the patients in the remission group were in the low and moderate-risk categories, the risk distribution between the groups was similar (p=0.498). No differences were found between the groups regarding gender, comorbidities, laboratory values at the time of diagnosis, or treatment modalities. In the first year after diagnosis, serum creatinine and eGFR values were better in patients who achieved OR [0.85 (0.79-1.25) mg/dl vs. 1.97 (0.9-3.2) mg/dl (p=0.02) and 93 (68-107) ml/min/1.73 m2 vs. 37 (21-88) ml/min/1.73 m2 (p=0.009), respectively]. Similarly, patients who achieved OR in the first year had better serum creatinine 0.85 (0.79-1.25) mg/dl vs. 1.97 (0.9-3.2) mg/dl (p=0.004) and eGFR 93 (68-107) ml/min/1.73 m2 vs. 37 (21-88) ml/min/1.73 m2 (p=0.006) values at the last follow-up visits. However, the proportion of patients with ESRD at the last follow-up was similar between groups (p=0.092). Clinical and laboratory features of patients with MN are shown in Table I.

Table I. Clinical and laboratory findings of patients with membranous nephropathy

	Total n=35 (100%)	**Non- remission** n=11 (31.4%)	**Overall Remission in first year** N=24 (68.6%)	P
Age (years)	55.9±10.8	62.9±8.4	52.8±10.5	**0.008**
Female, n (%)	10 (28.6%)	1 (9.1%)	9 (37.5%)	0.089
Disease duration (years)	3 (1-18)	1.5 (1-6)	4 (1-18)	**0.016**
HT, n (%)	17 (48.5%)	6 (54.4%)	11 (45.8%)	0.909
DM, n (%)	5 (14.3%)	3 (27.3%)	2 (8.3%)	0.166
CAD, n (%)	3 (8.5%)	1 (9.1%)	2 (8.3%)	0.691
Serum creatinine (mg/dL)	0.9 (0.5-6.4)	1.1 (0.63-6.4)	0.9 (0.5-3.2)	0.268
eGFR (ml/min/1.73 m^2)	98 (10-128)	83 (10-115)	103 (24-128)	0.163
Uric acid (mg/dL)	5.5±0.98	5.5±0.9	5.6±1.1	0.796
Total protein (g/dL)	5±0.88	4.8±0.8	5.1±0.9	0.371
Albumin (g/dL)	2.8 (1.4-3.7)	2.4 (1.6-3.3)	2.9 (1.4-3.7)	0.472
Total cholesterol (mg/dL)	314±106	309±97	316±112	0.873
LDL (mg/dL)	215±75	214±69	216±79	0.958
Triglycerides (mg/dL)	226±111	276±117	259±111	0.674
WBC count (x10^3/µL)	7.85±1.5	7.9±1.34	7.8±1.65	0.945
Hemoglobin (g/dL)	13.5±1.8	13.6±2.4	13.5±1.5	0.954
Platelet count (×10^3/µL)	268±69	274±86	265±62	0.736
Active urine sediment, n (%)	14 (40%)	6 (54.5%)	8 (33.3%)	0.206
Proteinuria (mg/24 h)	9957±5183	12686±6531	8707±3997	0.084
Nephrotic proteinuria, n (%)	34 (97.1%)	10 (90.9%)	24 (100%)	0.314
Risk classification, n (%)				
Low	13 (37.1%)	3 (27.3%)	10 (41.7%)	0.498
Moderate	11 (31.4%)	3 (27.3%)	8 (33.3%)	
High	8 (22.9%)	3 (27.3%)	5 (20.8%)	
Very High	3 (8.6%)	2 (18.2%)	1 (4.2%)	
Treatments, n (%)				
RAAS blockers	33 (94.2%)	10 (90.9%)	23 (95.8%)	0.536
Steroids	26 (74.2%)	8 (72.7%)	18 (75%)	0.597
CNI	16 (45.7%)	5 (45.5%)	11 (45.8%)	0.983
CYC	23 (65.7%)	8 (72.7%)	15 (62.5%)	0.424
MMF	3 (8.6%)	1 (9.1%)	2 (8.3%)	0.691
Rituximab	3 (8.6%)	1 (9.1%)	2 (8.3%)	0.691
First year				
Serum creatinine (mg/dL)	0.9 (0.8-1.38)	1.4 (0.9-2.8)	0.9 (0.75-1.05)	**0.02**
eGFR (ml/min/1.73 m^2)	92 (63-110)	57 (22-104)	105 (80-113)	**0.009**
Last Follow-up visit				
Serum creatinine (mg/dL)	0.96 (0.8-1.72)	1.97 (0.9-3.2)	0.85 (0.79-1.25)	**0.004**
eGFR (ml/min/1.73 m^2)	76 (48-106)	37 (21-88)	93 (68-107)	**0.006**
ESRD, n (%)	2 (5.7%)	2 (18.2%)	0 (0%)	0.092

CAD: Coronary artery disease, **CNI:** Calcineurin Inhibitors, **CYC:** Cyclophosphamide, **DM:** Diabetes Mellitus, **eGFR:** estimated glomerular filtration rate, **ESRD:** End stage renal disease, **HT:** Hypertension, **LDL:** Low-density lipoprotein, **MMF:** Mycophenolate mofetil, **RAAS:** Renin Angiotensin Aldosterone System, **WBC:** White blood cell

The remission status of the patients at the 6th and 12th months was examined according to their risk categories. In the low-risk group (n=13), five patients (38.5%) achieved PR at six months, but none achieved CR. By the 12th month, eight patients (61.5%) had achieved PR, and two patients (15.4%) had achieved CR. In the moderate-risk group (n=11), six patients (54.5%) achieved PR at six months, with no patients achieving CR. By the 12th month, eight patients (72.7%) had achieved PR, but none had achieved CR. In the high-risk group (n=8), two patients (25%) achieved PR, and one patient (12.5%) achieved CR at six months. By the 12th month, four patients (50%) had achieved PR, and one patient (12.5%) had achieved CR. In the very high-risk group (n=3), no patients had achieved PR or CR at six months. Also, none of these patients achieved PR by the end of the first year, but one patient (33.3%) had achieved CR (Figure 1).

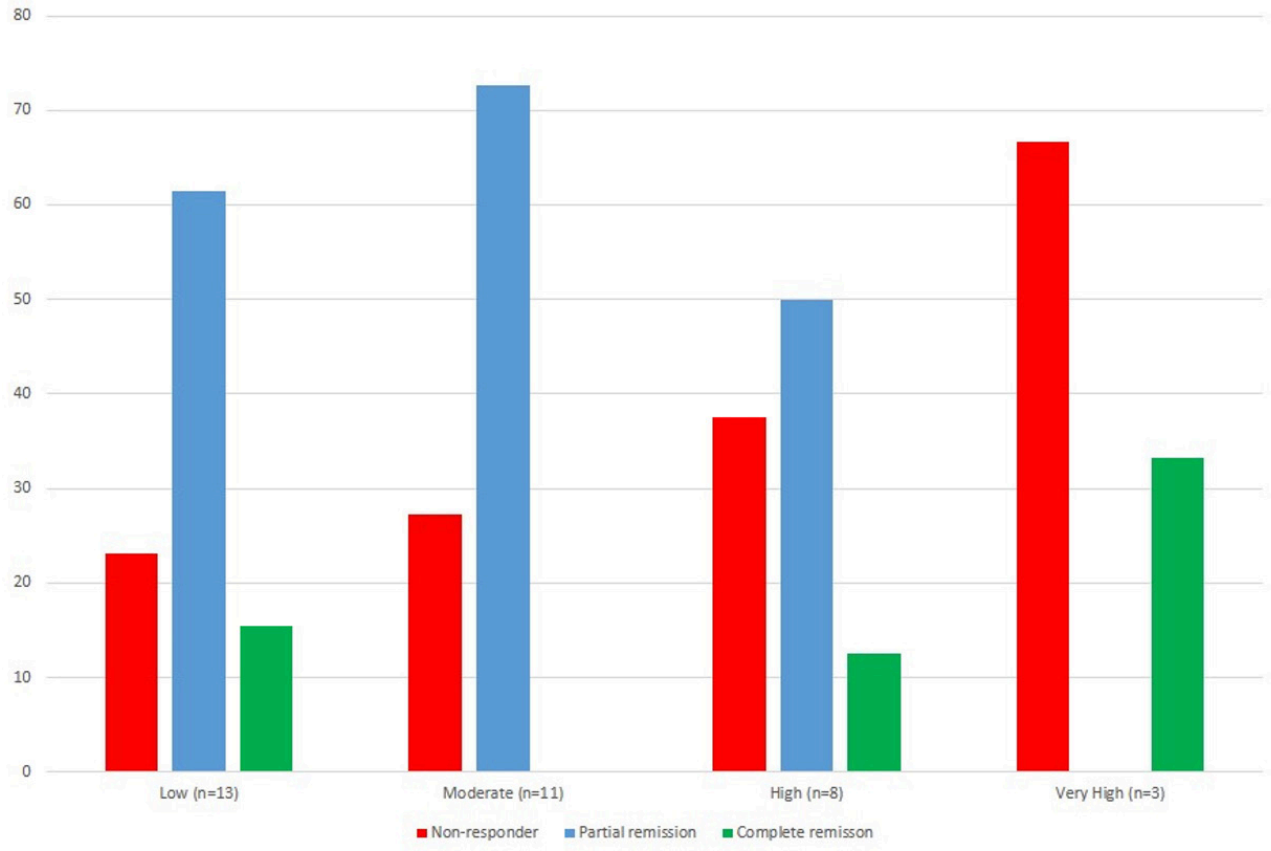

Figure 1. Remission rates at first year in membranous nephropathy patients according to risk classification

The IS treatments received by patients according to their risk groups were analyzed. In the low-risk group, seven patients (53.8%) received cyclophosphamide, and six (46.2%) received a calcineurin inhibitor. In the moderate-risk group, seven (63.6%) patients received cyclophosphamide, four (36.4%) received a calcineurin inhibitor, and three (27.3%) patients received rituximab. Six (75%) patients in the high-risk group received cyclophosphamide, and 5 (62.5%) received a calcineurin inhibitor. In the very high-risk group, all three patients (100%) received cyclophosphamide, and one patient (33.3%) received a calcineurin inhibitor (Table II).

Table II. Distribution of the immunosuppressive therapies according to membranous nephropathy classification

	Low (n=13)	Moderate (n=11)	High (n=8)	Very- High (n=3)
CNI	6 (%46.2)	4 (%36.4)	5 (%62.5)	1 (%33.3)
CYC	7 (%53.8)	7 (%63.6)	6 (%75)	3 (%100)
Rituximab	0 (%0)	3 (%27.3)	0 (%0)	0 (%0)

CNI: Calcineurin inhibitors, CYC: Cyclophosphamide

DISCUSSION

In this study, we have analyzed patients' general characteristics and remission status after being diagnosed with MN. Patients who achieved OR in the first year were observed to be younger at the time of diagnosis and had longer total follow-up durations. The remission rates at the 12th month were higher in low- and moderate-risk patients. Besides, patients who achieved the OR had better kidney function in the first year and last follow-up visits.

MN is recognized as a prevalent cause of nephrotic syndrome in adults. It exhibits a broad spectrum of onset ages and often reaches its peak incidence during the fifth to sixth decades of life (10). Primary MN is an organ-specific autoimmune disease, accounting for approximately 80% of cases. The characteristic features under light microscopy include non-inflammatory glomerular lesions with glomerular basement membrane thickening in Jones silver stain and granular IgG and complement deposits observed along the capillary walls in immunofluorescence. In addition, the absence of predominant IgG4 and C1q in IF indicates primary MN (11). Under electron microscopy, typical widespread podocyte foot process effacement and subepithelial immune deposits are observed. Pathological findings such as glomerular scarring (segmental and global glomerulosclerosis) and the severity of tubulointerstitial disease have been associated with poor renal outcomes in patients with MN (12, 13).

The clinical course of primary MN exhibits significant variability, including the potential for spontaneous remission, relapse, or progression to severe nephrotic syndrome, ultimately leading to ESRD. Traditionally, around one-third of patients experience spontaneous remission without necessitating IS treatments (4). Therefore, before commencing IS agents, it is compulsory to evaluate complications, such as progressive renal function decline or venous thromboembolism, to avoid unnecessary employment and mitigate associated adverse effects. KDIGO recommends assessing patients using clinical and laboratory criteria-including serum creatinine, eGFR, urine protein-to-creatinine ratio, serum albumin, and anti-PLA2R antibodies and stratifying them into low, moderate, high, or very high-risk categories based on their risk of progressive renal function deterioration (7).

In our study, the leading clinical presentation and indication for kidney biopsy in 97.1% of our patients diagnosed with MN was a nephrotic syndrome, and this rate is higher than the rate of 81.7% in the TSN-GOLD study (14). Besides, the OR rate at the end of the first year was 68.6%. Three-quarters of the patients who achieved remission were in the low and moderate-risk groups. Similarly, in a study by Jiang et al., the OR rate in the first year in patients with idiopathic MN was 73.7% (15). Also, they demonstrated that baseline urine protein was independently associated with worsening kidney function (≥30% eGFR decrease or ESRD). In another study from South Africa, 94.6% and 80.8% of all idiopathic MN patients had not achieved OR at the 12th and 24th months, respectively (16). Only 41.9% of patients had achieved remission at the last follow-up. This condition may be attributed to the fact that only 46.9% of the patients in this study received IS therapy. In addition, it has been known that APOL1 genetic susceptibility is associated with worse pathological findings in idiopathic MN in patients of African descent and also plays a role in clinical response (17). Racial differences may be an additional and reasonable explanation for the differences observed between our cohort and these studies. The epigenetic role in this variability warrants further investigation.

Several risk factors have been identified as indicators of poor prognosis in MN, including reduced kidney function at diagnosis, persistent hypertension, male sex, proteinuria levels at presentation, hypoalbuminemia, hyperlipidemia, and advanced glomerular damage with chronic tubulointerstitial fibrosis observed in renal biopsy (18). Our study found that patients who achieved OR in the first year were younger at the time of diagnosis than those who did not. Polanco et al. have shown that spontaneous remission is more common in younger patients with MN (5). Conversely, advanced age is an independent risk factor for worsening kidney function, infection, and all-cause mortality in MN patients (19). Although the small sample size limited the ability to detect some statistically significant differences between the two groups, it is noteworthy that baseline proteinuria levels and the proportion of male patients were higher in those who did not achieve remission compared to those who achieved remission ($p=0.084$ and $p=0.089$, respectively). This trend may require further evaluation in larger cohorts.

Besides, we found that patients who achieved remission in the first year had better kidney function in the first year and at the last follow-up visits. A multicenter study from Italy also demonstrated that patients with MN who achieved complete and partial remission had a better probability of patient and renal survival when compared to patients with persisting nephrotic syndrome (20). Although there was no difference in the ESRD rates in our patients, this condition may be due to our small sample size.

In this study, the initial IS treatments included the combination of alkylating agents (65.7%) or calcineurin inhibitors (45.7%) with steroids as an alternative first-line treatment. Although interest in rituximab has been increasing recently, only 8.6% of our patients received rituximab. It may be related to the treatment protocols in our study, which were predominantly administered according to the previous KDIGO guidelines (9). A systematic review has highlighted that using IS treatment for primary MN in adults likely reduces the number of patients progressing to ESRD by approximately 40% and increases the number of patients achieving CR compared to no treatment, supportive treatment, or steroids alone (21). Therefore, the combination of IS therapy with steroids may reduce

disease activity and have short- and long-term benefits in limiting potential kidney damage. However, it should also be noted that IS therapy could be associated with more adverse events and hospital admissions (22).

The limitations of the study arise from its single-center and retrospective design. The study's sample size was restricted to a single center, containing a relatively small patient cohort. Consequently, we could not specify the subgroups for treatment regimens and responses due to the limited sample size. In addition, as the patient population exclusively represented ethnic groups from our country, the generalizability of our findings to other ethnicities is constrained. Last, the absence of routine testing for serum anti-PLA2R levels in our clinic limited our ability to explore potential differences between patient subgroups.

CONCLUSION

In this single-center study, we observed high OR rates at the end of the first year of MN treatment, consistent with existing literature. The use of IS treatment in MN patients may contribute to achieving early remission. However, our findings should be further validated through prospective, multicenter studies.

Ethics Committee Approval

The study's design and procedures have received approval from our institution's local ethics committee Ankara Etlik City Hospital No. 1 Clinical Research Ethics Committee,Protocol ID: 2023-076, Date: 05.04.2023). This study was prepared based on the master's/doctoral thesis titled "Evaluation of clinical, pathological findings and treatment outcomes of patients with membranous nephropathy: Single-center experience" which was presented/completed in 2023 under the supervision of Prof. Dr. Ebru Gok Oguz.

Informed Consent

This endorsement aligns with the principles of the Declaration of Helsinki and complies with ethical standards for human experimentation. Due to the study's retrospective nature and the fact that all procedures were conducted as part of routine care, informed consent was not required.

Author Contributions

Concept – G.C.K., E.G.O.; Design - G.C.K., E.G.O., O.F.A. Supervision - E.G.O., O.F.A., M.D.A.; Data Collection and/or Processing - G.C.K., E.G.O., O.F.A.; Analysis and/ or Interpretation - G.C.K., E.G.O., O.F.A.; Literature Search - G.C.K., E.G.O., O.F.A.; Writing Manuscript - G.C.K., E.G.O., O.F.A, M.D.A.; Critical Review - E.G.O., O.F.A, M.D.A.

Conflict of Interest

The authors have no conflict of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

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