

Retrospective Investigation of the Factors Associated with Remission in Patients Diagnosed Primary Membranous Glomerulonephritis

PRİMER MEMBRANÖZ GLOMERÜLONEFRİT TANILI HASTALARDA REMİSYON İLE İLİŞKİLİ FAKTÖRLERİN RETROSPEKTİF OLARAK İNCELENMESİ

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ABSTRACT

Introduction: The present study aims to investigate the demographic, clinical, and pathological characteristics of patients followed up with a diagnosis of primary membranous glomerulonephritis (MGN) and the effects of the treatments applied on remission.

Methods: Sixty patients older than 18 years of ages, whose primary MGN diagnosis was confirmed by kidney biopsy and followed for at least 12 months between 2006 and 2012 were included in the study. The patients were divided into 3 groups according to the state of remission. The groups were compared in terms of their demographic, clinical, laboratory, and histopathological findings.

Results: Of the patients, 37 (63%) were male, the mean age was 55.7±14.8 years. While 44 (73.3%) patients were followed up with immunosuppressive treatment, 16 (26.7%) patients were followed only with conservative treatment. A high level of proteinuria ($p=0.002$) and male gender dominance were found in the group that received immunosuppressive therapy ($p=0.01$). A total of 18 (29.6%) patients had complete remission at the end of 12 months. Partial remission occurred in 30 (50%) of the patients. Female gender ($p=0.02$) and receiving immunosuppressive therapy ($p=0.01$) were independent factors associated with the development of complete or partial remission; the presence of lower glomerular sclerosis ($p=0.03$) was associated with complete remission. We did not find any relationship between the intensity of immune deposition and the state of being in remission.

Conclusion: Female gender and the presence lower glomerulosclerosis are indicators of good prognosis in primary MGN. In addition, immunosuppressive therapy positively affects the prognosis.

Keywords: Membranous Glomerulonephritis, Prognosis, Proteinuria, Remission.

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ÖZ

Amaç: Bu çalışma, primer membranöz glomerülonefrit (MGN) tanısı ile takip edilen hastaların demografik, klinik ve patolojik özelliklerini ve uygulanan tedavilerin remisyona etkisini araştırmayı amaçlamaktadır.

Gereç ve Yöntem: Çalışmaya 2006-2012 yılları arasında en az 12 ay takip edilen ve böbrek biyopsisi ile primer MGN tanısı konan 18 yaş üstü altmış hasta dahil edildi. Hastalar remisyona göre 3 gruba ayrıldı. Gruplar demografik, klinik, laboratuvar ve histopatolojik bulgular açısından karşılaştırıldı.

Bulgular: Hastaların 37'si (%63) erkek olup, yaş ortalaması 55,7±14,8 yılıdır. 44 (%73,3) hasta immünyüpresif tedavi ile takip edilirken, 16 (%26,7) hasta sadece konservatif tedavi ile takip edildi. İmmünyüpresif tedavi alan grupta yüksek düzeyde proteinüri ($p=0,002$) ve erkek cinsiyet hakimiyeti saptandı ($p=0,01$). Hastaların 18'i (%29,6) 12.ay sonunda tam remisyona ($<0,2$ g/gün) girdi. Hastaların 30'unda (%50) kısmi remisyona meydana geldi. Kadın cinsiyet ($p=0,02$) ve immünyüpresif tedavi alma ($p=0,01$), tam veya kısmi remisyona gelişimi ile ilişkili bağımsız faktörlerdir; daha düşük glomerüler skleroz varlığı ($p=0,03$) tam remisyona ile ilişkilendirildi. İmmün deposit birikimi ile remisyona olma durumu arasında herhangi bir ilişki bulunamadı.

Sonuç: Primer MGN'de kadın cinsiyeti ve düşük oranda glomerüloskleroz varlığı iyi prognoz göstergeleridir. Ayrıca immünyüpresif tedavi prognozu olumlu etkilemektedir.

Anahtar Kelimeler: Membranöz Glomerulonefrit, Prognoz, Proteinüri, Remisyon

Membranous glomerulonephritis (MGN) is an immune complex nephropathy characterized by glomerular basement membrane thickening as a result of subepithelial immunoglobulin G storage (1). The etiology of the disease is unknown in approximately 75% of adult patients diagnosed with MGN, and is defined as primary MGN (idiopathic) (2). In situ immune complexes are formed due to the presence of antibodies against podocyte proteins. This issue has been determined to cause MGN. In 70% of the adult patients, phospholipase A2 receptor (PLA2R) on podocytes has been demonstrated as a target antigen in primary MGN (3). PLA2R appears to be a causative antigen of primary MGN in most of adults (4-5) and some pediatric populations (6). In the group in which etiologies such as infections, tumors, autoimmune diseases, drug use, or exposure to toxic agents are detected, the disease is called secondary MGN (7). Primary MGN is one of the most common causes of nephrotic syndrome in adults (2- 8). The disease is mostly seen in men in their 40s and 50s (9). The course of the disease is highly variable.

Proteinuria goes into spontaneous remission in approximately one-third of patients, permanent proteinuria is observed in one-third, and end-stage renal failure develops within 5-15 years in the remaining one-third (10-11).

In recent studies, persistent proteinuria at the nephrotic level, high creatinine level, increased β 2-microglobulin, α 1-microglobulin, and higher the anti-phospholipase A2 receptor antibody in serum have been reported as indicators associated with the prognosis of the disease (12-13). In addition, morphological changes in kidney tissue such as glomerulosclerosis draw attention as factors affecting the prognosis of patients with MGN. However, significant differences are observed in the results of the study (14). Although these indicators are associated with the prognosis of the disease, new indicators are needed as these are not perfect indicators for prognosis.

The relationship between the clinical features, renal functions, renal histopathological findings, and the

treatment received by the patients with the prognosis of the disease was retrospectively investigated in this study.

MATERIAL AND METHOD

This study was carried out by retrospectively examining the files of 92 patients who were diagnosed with MGN by kidney biopsy for the first time in the Division of Nephrology of the Department of Ege University between 2006 and 2012. Patients who did not participate in regular follow-up and whose data were incomplete or who were diagnosed with secondary MGN (such as lupus nephritis, and crescentic glomerulonephritis) were not included in the study. A total of 60 patients older than 18 years of age, who were diagnosed with primary MGN and followed-up for at least 12 months, were included in the study. The study was conducted with the approval of the Ethics Committee of Clinical Trials of the Faculty of Medicine of Ege University (Approval No. 13-5.1/5)

The data of the patients at baseline, 3rd month, 6th month, and 12th month periods were recorded from medical charts. The demographic, clinical, and laboratory data included gender, age, concomitant diseases, blood pressure, presence of peripheral edema, serum creatinine level, basal creatinine clearance level, presence of hematuria, the amount of protein excretion in 24-hour urine, serum albumin, globulin, uric acid, total cholesterol, triglyceride, and hemoglobin values.

All renal biopsy samples were routinely examined by light microscopy and immunofluorescence microscopy. In all biopsies, immunoglobulin G (IgG), IgA, IgM, C3, kappa and lambda were detected by immunofluorescence staining. Kidney biopsy specimens were re-evaluated by expert nephropathologists in the Department of Pathology, Faculty of Medicine, Ege University. Biopsy specimens were re-evaluated and scored histopathologically in terms of glomerular number, global glomerulosclerosis, segmental glomerulosclerosis and severity of tubulointerstitial fibrosis. The percentage of glomerular sclerosis detected in kidney biopsy samples were scored as 0 (0-4%), 1 (5-24%), 2 (25-49%), 3 (50-99%). Presence of segmental sclerosis was defined as absent (0) or present (1). In addition, presence of interstitial fibrosis and tubular atrophy was scored as none (0), mild (1), moderate (2) and

severe (3) by semiquantitative basis. The intensity of the staining in immunofluorescence analysis was scored as 0, 1, 2, 3, and 4, representing very weak, weak, moderate, strong, and very strong, respectively. C4d staining in immunohistochemistry was evaluated as focal or diffuse granular staining of glomerular basement membrane.

The patients were divided into low-risk (<4 g/day), medium risk (4-8 g/day), and high risk (>8 g/day) groups according to their protein excretion amounts, and only conservative or conservative and immunosuppressive treatments were started according to the risk groups. Conservative treatment included angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor antagonists (ARBs), statins for dyslipidemia, hypoproteic diet, salt restriction, and diuretics as needed. The immunosuppressive treatment group consisted of only those receiving glucocorticoid (n:15) and glucocorticoid-cyclophosphamide (n:29) treatments. At the end of the 12th month, treatment responses were determined according to the amount of proteinuria in 24-hour urine.

Accordingly, patients with a proteinuria level <0.2 g/day were grouped as those who had complete remission, 0.2-2 g/day as those who had partial remission, and > 2 g/day as those who did not have remission. The demographic, clinical, laboratory, and histopathological data of the patients were compared between the groups.

Statistical Analysis

The SPSS 27.0 (IBM Corporation, Armonk, New York, United States) program was used in the analysis of variables. The conformity of univariate data to normal distribution was evaluated by the Shapiro-Wilk Francia test, while the variance homogeneity was evaluated with the Levene test. The Independent-Samples T-test was used together with the Bootstrap results in comparing two independent groups with each other according to the quantitative data. The Pearson Chi-Square and Fisher's Exact tests were used with the Monte Carlo Simulation method in comparing categorical variables with each other, while column ratios were compared with each other and expressed according to the Benjamini-Hochberg corrected p-value results. The Logistic Regression Test was used together with the Enter Method and Bootstrap results to

determine the cause-effect relationship of the categorical response variable with the explanatory variables. The quantitative variables were expressed as Mean \pm Standard deviation, while categorical variables were shown as n (%) in the tables. Variables were analyzed at a confidence level of 95%, and a p-value of less than 0.05 was considered significant.

RESULTS

Of the 60 patients included in the study, 37 (63%) were male, 23 (37%) were female, and the mean age was 55.7 \pm 14.8 years. As to comorbid diseases, 10 patients (16.6%) had type 2 diabetes mellitus and 26 patients (46%) had hypertension. At admission, 53 (88%) patients had peripheral edema. In laboratory findings, the mean serum creatinine level was 1.14 \pm 0.82 mg/dL, uric acid was 6.0 \pm 1.4 mg/dL, albumin was 2.77 \pm 0.72 g/dL, globulin was 2.7 \pm 0.5 mg/dL, protein excretion in 24-hour urine was 6.08 \pm 3.61 g/day and mean creatinine clearance was 85.6 \pm 50.4 ml/min. Hypogammaglobulinemia was also detected in 21 (35.6%) patients (Table 1).

Table 1. General characteristics of the patients

Diagnosis Age (year)*	55.7 \pm 14.8
Gender (male), n (%)	37 (63)
Edema, n (%)	53 (88)
Hypertension, n (%)	26 (46)
Type 2 diabetes mellitus, n (%)	10 (16,6)
Hypogammaglobulinemia, n (%)	21 (35,6)
Creatinine (mg/dL)*	1.1 \pm 0.8
Uric acid (mg/dL)*	6.0 \pm 1.4
Albumin (g/dL)*	2.8 \pm 0.7
Globulin (g/dL)*	2.7 \pm 0.5
Total Cholesterol (mg/dL)*	290.9 \pm 103.1
Triglyceride (mg/dL)*	220.8 \pm 120.8
Hemoglobin (g/dL)*	12.6 \pm 2.0
Protein in 24-hour urine (g/day)*	6.1 \pm 3.6
Creatinine clearance (ml/min)*	85.6 \pm 50.4

*Mean \pm Standard deviation

When the patients were grouped according to the amount of protein excretion, it was found that 20 patients (32.8%) were in the low-risk group, 28 patients (46%) were in the medium-risk group, and 12 patients (20.7%) were in the high-risk group.

More than 10 glomeruli were detected under a light microscope 91.7% of kidney biopsy specimens. The mean glomerular sclerosis rate was 12%. Glomerular sclerosis scores were 0 (none) in 23 patients (38.3%), 1 (mild) in 26 (43.3%), 2 (moderate) in 5 (8.3%), and 3 (severe) in 6 (10%) patients. 28.3% of the patients also had focal segmental glomerulosclerosis (FSGS). Tubular atrophy was found 51.6% of the patients at the time of diagnosis, whereas 42% percent of the patients had interstitial fibrosis. No severe tubular atrophy or interstitial fibrosis was detected. Mean IgG staining intensity score was above 3 (strong/very strong) in 68% of the patients. Only three biopsy (5%) showed significant IgA deposition along with IgG and C3. Significant staining of IgM deposition (score > 2) was found in 2 patients. Significant C3 deposition was found in 67% of the biopsy specimens. Diffuse granular C4d staining was found in 91% of the patients. All biopsy samples showed both lambda and kappa deposition in immunofluorescence staining.

Of the patients, 44 (73.3%) were followed up with immunosuppressive treatment, while 16 (26.7%) were followed up only with conservative treatment. There was no significant difference between the treatment groups in terms of age, the presence of hypertension, serum creatinine, serum albumin levels, the percentage of glomerular sclerosis, segmental sclerosis, interstitial fibrosis, and tubular atrophy and the degree of immune depositions ($p > 0.05$). However, frequency of males ($p = 0.01$) and proteinuria level ($p = 0.002$) at the time of diagnosis were higher in the group receiving immunosuppressive therapy compared to the patients receiving conservative treatment (Table 2).

Table 2. Comparison of demographic, clinical, and laboratory data of the treatment groups.

	Immunosuppressive treatment group, (n=44)	Conservative treatment group, (n=16)	P
Diagnosis Age (year)*	55.0±15.1	57.6±14.1	0.542 †
Gender (male), n (%)	32 (73)	6 (38)	0.013 †
Hypertension, n (%)	17 (39)	10 (63)	0.111 †
Glomerular sclerosis, n (%)*	11.4±15.2	13.6±16.1	0.623 †
IF staining intensity score			
IgG	2.7± 1.1	3.0 ±0.9	0.46
IgA	0.4 ±0.8	0.3 ± 0.8	0.75
IgM	0.7 ± 0.9	0.6 ± 0.8	0.82
C3	1.8 ±1.0	1.3 ±1.1	0.11
C4d positivity (%)	90	92	0.82
FSGS (%)	15 (34)	4 (25)	0.540 ‡
Tubular atrophy (%)			
None	19 (43)	10 (62)	0.26 †
Mild	23 (52)	6 (38)	
Moderate	2 (5)	-	
Interstitial fibrosis (%)			
None	11(25)	5 (31)	0.87 †
Mild	26 (59)	9 (56)	
Moderate	7 (16)	2 (13)	
Serum Creatinine (mg/dl)*	1.2±0.9	0.9±0.3	0.261 †
Serum albumin (g/dl)*	2.7±0.7	3.1±0.7	0.056 †
Proteinuria (g/day)*	6.9±3.7	3.7±1.7	0.002 †

†Independent Samples T-test (Bootstrap), † Pearson Chi-Square Test (Monte Carlo), ‡ Fisher's Exact Test (Monte Carlo) *Mean ± Standard deviation, FSGS: Focal segmental glomerulosclerosis, IF: immunofluorescence

Of the 60 patients, 18 (30%) had complete remission at the end of the 12th month, while 14 (31.7%) of them were in the immunosuppressive treatment group and 4 (22%)

were in the conservative treatment group. When the patient groups with and without complete remission were compared in terms of age, gender, hypertension, FSGS,

serum creatinine and albumin levels, the amount of proteinuria in 24-hour urine and status of receiving immunosuppressive therapy, no statistical difference was found between the groups ($p>0.05$). However, the mean

glomerular sclerosis rate was found to be lower in the patient group who had complete remission ($p=0.008$) (Table 3).

Table 3. Comparison of demographic, clinical, and laboratory data of patient groups with and without complete remission.

	Group with complete remission, (n=18)	Group without complete remission, (n=42)	P
Diagnosis Age (year)*	51.0± 4.7	56.7±13.4	0.181 ^t
Gender (male), n (%)	9 (50)	30(71)	0.144 ^c
Hypertension, n (%)	6 (33)	21(50)	0.326 ^c
Type 2 diabetes mellitus, n (%)	2 (11)	8 (19)	0.708 ^f
Glomerular sclerosis n (%)*	3.3±4.5	15.0±16.6	0.008 ^t
FSGS, n (%)	2 (13)	12 (29)	0.201 ^t
Tubular atrophy n (%)			
None	9 (50%)	20 (48%)	0.63 ^c
Mild	9 (50%)	18 (43%)	
Moderate	0	4 (9%)	
Interstitial fibrosis n (%)			
None	7 (39%)	12 (29%)	0.14 ^c
Mild	11 (61%)	21(50%)	
Moderate	0	9 (21)	
IF staining intensity score			
IgG	3.0 ±1.0	2.7± 1.0	0.49
IgA	0.1 ±0.5	0.4 ±0.9	0.18
IgM	0.5 ±0.7	0.7 ±0.9	0.37
C3	1.6 ±1.1	1.6 ±1.1	0.93
Diffuse granular C4d positivity (%)	93	89	0.78
Creatinine (mg/dl)*	0.8±0.2	1.3±1.0	0.062 ^t
Albumin (g/dl)*	2.8±0.7	2.9±0.2	0.674 ^t
Proteinuria (g/day)*	6.2±4.1	6.1±3.1	0.942 ^t
Immunosuppressive treatment, n(%)	15 (82)	31 (74)	0.561 ^f

IF: immunofluorescence

Moreover, the intensity of immune depositions was not significantly different between patients with and without complete remission.

Partial remission occurred in 30 (50%) of the patients. Of these patients, 24 (54.5%) were in the immunosuppressive treatment group, and 6 (37.5%) were in the conservative treatment group. While 38 (87.8%) patients in the immunosuppressive treatment group had complete or partial remission, 10 (61.5%) patients in the conservative treatment group had complete or partial remission.

When the group who had complete or partial remission and the group who did not have remission were compared in terms of similar parameters, it was found that patients who had received immunosuppressive therapy mostly had complete or partial remission (p=0.002) (Table 4).

Table 4. Comparison of the demographic, clinical, and laboratory data of the patient group with complete or partial remission and the group without remission.

	Complete and partial remission group, (n=48)	Group without remission (n=12)	P
Diagnosis Age (year)*	55.3±15.3	58.2±12.7	0.606 ^t
Gender (male), n (%)	29 (58.0)	8 (80.0)	0.291 ^c
Hypertension, n (%)	20 (44.4)	6 (60.0)	0.490 ^c
Type 2 diabetes mellitus, (%)	6 (12.0)	4 (60.0)	0.052 ^f
Glomerular sclerosis n (%)*	5.6±4.3	10.1±9.2	0.125 ^t
FSGS, n (%)	8 (16.6)	5 (41.7)	0.060 ^f
Tubular atrophy (%)			
None	22 (46%)	7 (58%)	0.34 ^c
Mild	24 (50%)	3 (25)	
Moderate	2 (4%)	2 (17%)	
Interstitial fibrosis (%)			
None	13 (27%)	3 (25%)	0.87 ^c
Mild	27 (56%)	6 (50%)	
Moderate	8 (17%)	3 (25%)	
IF staining intensity score			
IgG	2.8 ±1.0	2.7± 0.9	0.79
IgA	0.3 ±0.8	0.3 ±1.0	0.86
IgM	0.6 ±0.8	1.1 ±1.6	0.26
C3	1.7 ±1.1	1.5 ±0.8	0.65
Diffuse granular C4d positivity (%)	95	80	0.68
Creatinine (mg/dl)*	1.1±0.9	1.2±0.6	0.787 ^t
Albumin (g/dl)*	2.7±0.7	2.9±0.8	0.491 ^t
Proteinuria (g/day)*	6.2±3.6	6.1±3.4	0.918 ^t
Immunosuppressive treatment, n (%)	41 (82.0)	3 (30.0)	0.002 ^f

^t Independent Samples T-test (Bootstrap), ^c Pearson Chi-Square Test (Monte Carlo), ^f Fisher’s Exact Test (Monte Carlo)

*Mean ± Standard deviation, FSGS: Focal segmental glomerulosclerosis, IF: immunofluorescence

In terms of baseline age, creatinine, serum albumin and proteinuria, there were no significant differences between patients with complete or partial remission and the patients without remission. However, the frequency of glomerular sclerosis and focal segmental sclerosis at baseline were slightly lower in patients with complete or partial remission compared to the patients without remission. On the other hand, the degree of tubular atrophy and interstitial fibrosis was found similar. The intensity of immune depositions was not significantly different between patients with and without complete or partial remission.

In the multivariate analysis, it was determined that the percentage of glomerular sclerosis lower than 25% was the determinant for remission ($p=0.037$). In addition, female gender ($p=0.021$) and immunosuppressive therapy ($p=0.014$) were independent factors for complete or partial remission (Table 5).

Table 5. Factors associated with remission.

	Odds Ratio	95% C.I. for Odds ratio		P
		Lower	Upper	
Gender (female)	6.480	1.529	74.145	0.021
Immunosuppressive therapy	8.935	1.342	59.504	0.014
Glomerular sclerosis ratio (<%25)	5.741	2.034	48.603	0.037

Multiple Logistic Regression (Method=Enter), C.I.: Confidence interval

DISCUSSION

In this study, it was found that female gender and the presence of a low rate of glomerular sclerosis in renal biopsy are associated with good prognosis in primary MGN patients and receiving immunosuppressive therapy was a factor that increased remission compared to the conservative treatment.

Studies conducted so far have reported that women had higher levels of remission as a result of a specific treatment in primary MGN disease when compared to men (15). In a study by Pan et al. (16), it was

reported that MGN was seen 2 times more frequently in men than in women. In a study by Chen et al. (17), however, the disease was similarly reported to be more common in men. Similar to the literature, approximately two-thirds of the patients in the present study were male, and female gender was shown to be a good prognostic factor for the development of complete or partial remission.

In a study by Tsai et al. (18), it has been reported that high baseline serum creatinine levels, high levels of proteinuria, and low glomerular filtration rates are poor prognosis findings in primary MGN. In a study by Xiaofan et al. (19), however, advanced age at the time of diagnosis, low glomerular filtration rate, and severe proteinuria have been reported as independent risk factors indicating a poor prognosis. In another study, it was reported that there was a relationship between serum creatine level, proteinuria and creatine clearance, and MGN prognosis (20). However, in a study by Ancak Shiiki et al. (21) including 949 patients, it was reported that advanced age and high serum creatinine levels were not associated with a poor prognosis. In a similar study by Chen et al. (22), it was reported that there was no relationship between advanced age, serum creatinine level, urine protein excretion, serum albumin level, glomerular filtration rate, and serum uric acid level, and the development of short-term remission. Similar to the literature, age and serum creatinine level, serum protein level, proteinuria level, and creatine clearance were not found to affect the development of remission in the present study.

Most MGN cases were normotensive at the time of diagnosis. However, hypertension can be seen in 10-20% of the patients. In a study by Chen et al. (22), it was reported that there was no relationship between hypertension and the development of remission. Similar to the literature, it was shown in the present study that there was no relationship between the presence of hypertension and the development of remission.

In a recent study, it has been shown that the presence of FSGS is associated with a poor prognosis in patients with MGN (23, 24). In a study by Chen et al. (25), FSGS and tubulointerstitial damage were reported to be independent risk factors indicating a poor prognosis. In the

present study, unlike the literature, it was found that there was no relationship between FSGS and the degree of tubulointerstitial damage at baseline biopsy and the development of remission. However, it was shown that those with a rate of glomerulosclerosis lower than 25% were 5.7 times more likely to enter remission than patients with a high rate of glomerulosclerosis. Some studies have shown that immune complex deposition is associated with prognosis (14, 26, 27). Recently, it was reported that glomerular IgM deposition, which is common in MGN, was an independent risk factor for decreased renal function (28). Rarely, MGN associated with dominant subepithelial IgA deposition was reported as case reports, its clinical features and outcome need to be investigated (29). In this study, no correlation was found between immune complex deposition and prognosis in our cohort. In addition, it is not possible to reach clear conclusion due to the low number of cases with IgA or IgM dominant immune deposition.

Conservative treatment is recommended in patients with low-risk primary MGN according to the KDIGO guideline because of poor prognosis findings of severe proteinuria and persistent proteinuria, while immunosuppressive therapy is recommended for patients with nephrotic syndrome or persistent proteinuria (30, 31). In a meta-analysis of 1,025 patients, when compared with conservative treatment or steroids alone, alkylated agents (cyclophosphamide or chlorambucil) alone or in combination with steroids have been reported to increase the rate of partial or complete remission (32). In a study involving 348 primary MGN patients, complete remission was found in 29% and partial remission in 39% of the patients during an average of 5 years of follow-up. The time to enter complete remission was reported as 30 months, and the time to enter partial remission as 23 months (33).

In the present study, the degree of proteinuria was significantly higher and serum albumin was slightly lower in patients receiving immunosuppressive therapy compared to the patients without receiving any immunosuppressive treatment. At the end of the 12th month, one-third of the patients had complete remission. Complete and partial remission rates were higher in the immunosuppressive treatment group compared to the conservative group (87.8% and 61.5%). It was shown that

those who received immunosuppressive therapy had an 8.9-fold better remission compared to those who did not.

Being a retrospective study, a low number of cases, and a short follow-up period are limitations of the present study. The other limitation was the inability to evaluate PLA2R antibody levels in blood and renal tissue samples. It is considered that these limitations do not change the reliability of the results found. We excluded cases of secondary MGN based on clinical and laboratory data.

In conclusion, for primary MGN patients, being female and having a low rate of glomerulosclerosis in renal biopsy at the time diagnosis are good prognosis indicators. Besides, immunosuppressive treatment in addition to conservative treatment increases the likelihood of remission of the disease. It is considered that larger retrospective studies as well as prospective studies are needed to show the prognosis of primary MGN disease with simple and reliable markers.

Conflict of interest

The authors have declared that no conflict of interest exists.

REFERENCES

1. Seitz-Polski B, Dolla G, Payre C, Girard CA, Polidori J, Zorzi K, et al. Epitope spreading of autoantibody response to PLA2R associates with poor prognosis in membranous nephropathy. *J Am Soc Nephrol.* 2016; 27: 1517–1533.
2. Radice A, Trezzi B, Maggiore U, Pregnotato F, Stellato T, Napodano P, et al. Clinical usefulness of autoantibodies to M-type phospholipase A2 receptor (PLA2R) for monitoring disease activity in idiopathic membranous nephropathy (IMN). *Autoimmun Rev.* 2016; 15: 146–154.
3. Beck LH, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med.* 2009;361(1):11-21.
4. Akiyama S, Akiyama M, Imai E, Ozaki T, Matsuo S, Maruyama S. Prevalence of anti-phospholipase A2 receptor antibodies in Japanese patients with

- membranous nephropathy. *Clin Exp Nephrol*. 2015;19(4):653-60.
5. Du Y, Li J, He F, Lv Y, Liu W, Wu P, et al. The diagnosis accuracy of PLA2R-AB in the diagnosis of idiopathic membranous nephropathy: a meta-analysis. *PLoS One* 2014;9:e104936
 6. Cossey LN, Walker PD, Larsen CP. Phospholipase A2 receptor staining in pediatric idiopathic membranous glomerulopathy. *Pediatr Nephrol* 2013;28:2307-11.
 7. Hoxha E, Harendza S, Pinnschmidt HO, Tomas NM, Helmchen U, Panzer U, et al. Spontaneous remission of proteinuria is a frequent event in phospholipase A2 receptor antibody-negative patients with membranous nephropathy. *Nephrol Dial Transplant*. 2015; 30: 1862-1869.
 8. Lee T, Derebail VK, Kshirsagar AV, Chung Y, Fine JP, Mahoney S, et al. Patients with primary membranous nephropathy are at high risk of cardiovascular events. *Kidney Int*. 2016; 89: 1111-1118.
 9. Bally S, Debiec H, Ponard D, Dijoud F, Rendu J, Julien Fauré J, et al. Phospholipase A2 receptor-related membranous nephropathy and mannan-binding lectin deficiency. *J Am Soc Nephrol*. 2016; 27: 3539-3544.
 10. Roccatello D, Sciascia S, Di Simone D, Solfietti L, Naretto C, Fenoglio R, et al. New insights into immune mechanisms underlying response to Rituximab in patients with membranous nephropathy: a prospective study and a review of the literature. *Autoimmun Rev*. 2016; 15: 529-538.
 11. Morita M, Mii A, Shimizu A, Yasuda F, Shoji J, Masua Y, et al. Glomerular endothelial cell injury and focal segmental glomerulosclerosis lesion in idiopathic membranous nephropathy. *PLoS One*. 2015;10:e0116700.
 12. Zuo K, Wu Y, Li SJ, Xu F, Zeng CH, Liu ZH. Long-term outcome and prognostic factors of idiopathic membranous nephropathy in the Chinese population. *Clin Nephrol*. 2013; 79: 445-453.
 13. Hoxha E, Thiele I, Zahner G, Panzer U, Harendza S, Stahl RA. Phospholipase A2 receptor autoantibodies and clinical outcome in patients with primary membranous nephropathy. *J Am Soc Nephrol*. 2014; 25: 1357-1366.
 14. Zhang XD, Cui Z, Zhang MF, Wang J, Zhang YM, Qu Z, et al. Clinical implications of pathological features of primary membranous nephropathy. *BMC Nephrol*. 2018;19(1):215.
 15. Zhang BO, Cheng M, Yang M, Han S, Zhang YH, Shi HG, et al. Analysis of the prognostic risk factors of idiopathic membranous nephropathy using a new surrogate end-point. *Biomed Rep*. 2016; 4: 147-152.
 16. Pan X, Xu J, Ren H, Zhang W, Xu Y, Shen P, et al. Changing spectrum of biopsy-proven primary glomerular diseases over the past 15 years: a single-center study in China. *Contrib Nephrol*. 2013; 181 :22-30.
 17. Chena X, Chenb Y, Ding X, Zhou Y, Lv Y, Li D, et al. Baseline proteinuria level is associated with prognosis in idiopathic membranous nephropathy. *Renal failure*. 2019; 41: 363-369.
 18. Tsai SF, Wu MJ, Chen CH. Low serum C3 level, high neutrophil-lymphocyte-ratio, and high platelet-lymphocyteratio all predicted poor longterm renal survivals in biopsyconfirmed idiopathic membranous nephropathy. *Sci Rep*. 2019; 9: 6209.
 19. Xiaofan H, Jing X, Chenni G, Yifan W, Xialian YU, Li L, et al. New risk score for predicting progression of membranous nephropathy. *J Transl Med*. 2019;17: 41 <https://doi.org/10.1186/s12967-019-1792-8>.
 20. Alfaadhel T, Cattran D. Management of membranous nephropathy in western countries. *Kidney diseases*. 2015; 1(2): 126-37.
 21. Shiiki H, Saito T, Nishitani Y, Mitarai T, Yorioka N, Yoshimura A, et al. Prognosis and risk factors for idiopathic membranous nephropathy with nephrotic syndrome in Japan. *Kidney Int*. 2004; 65(4): 1400-1407.
 22. Chen J, Fu X, Sun Y, Zhang S, Xie H, Lin H. High urinary interleukin-8 levels is associated with poor prognosis in idiopathic membranous nephropathy. *Internal Medicine Journal*. 2018; 48(2): 207-209.

23. He HG, Wu CQ, Ye K, Zeng C, Huang YY, Luo SW, et al. Focal segmental glomerulosclerosis, excluding atypical lesion, is a predictor of renal outcome in patients with membranous nephropathy: a retrospective analysis of 716 cases. *BMC Nephrol.* 2019; 20: 328. <https://doi.org/10.1186/s12882-019-1498-4>
24. Huh H, Lee H, Lee JP, Kim DK, Oh S, Oh YK, et al. Factors affecting the long-term outcomes of idiopathic membranous nephropathy. *BMC Nephrol.* 2017; 18: 104. <https://doi.org/10.1186/s12882-017-0525-6>
25. Chen Y, Tang L, Feng Z, Cao X, Sun X, Liu M, et al. Pathological predictors of renal outcomes in nephrotic idiopathic membranous nephropathy with decreased renal function. *J Nephrol.* 2014; 27(3): 307–316.
26. Gökçe E, Ünlü M, Yıldız S, Cavdar C, Sarioglu S, Camsarı T. Association of Presence and Quantity of C4d with the Severity of Kidney Injury in Primary Membranous Nephropathy. *Turk Nephrol Dial Transplant.* 2017;26: 290–297.
27. 27. Oto OA, Demir E, Mirioglu S, Dirim AB, Ozluk Y, Cebeci E, et al. Clinical significance of glomerular C3 deposition in primary membranous nephropathy. *J Nephrol.* 2021;34: 581–587.
28. 28. Zhu-Yu X, Na-Ya H, Ya-Gui Q, Xiong-Hui C, Zhi-Jian L, Wei C, et al. Clinical characteristics and outcomes of idiopathic membranous with glomerular IgM deposits. *Clin and Exp Med*, 2021. Oct 26. [doi:10.1007/s10238-021-00768-y](https://doi.org/10.1007/s10238-021-00768-y)
29. 29. Sawamura M, Komatsuda A, Kaga H, Saito A, Yasuda T, Wakui H, et al. Membranous nephropathy with solitary polyclonal IgA deposition: A case report and literature review. *Clin Nephrol Case Stud.* 2019: 7:60-65.
30. Chen X, Chen Y, Shi K, Lv Y, Tong H, Zhao G, et al. Comparison of prognostic, clinical, and renal histopathological characteristics of overlapping idiopathic membranous nephropathy and IgA nephropathy versus idiopathic membranous nephropathy. *Sci Rep.* 2017; 7: 11468. [doi:10.1038/s41598-017-11838-1](https://doi.org/10.1038/s41598-017-11838-1).
31. Hladunewich MA, Troyanov S, Calafati J, Cattran DC. The natural history of the non-nephrotic membranous nephropathy patient. *Clin J Am Soc Nephrol.* 2009; 4: 1417–1422.
32. Perna A, Schieppati A, Zamora J, Giuliano GA, Braun N, Ramuzzi G. Immunosuppressive treatment for idiopathic membranous nephropathy: a systematic review. *Am J Kidney Dis.* 2004; 44(3): 385-401.
33. Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC. Idiopathic membranous nephropathy: definition and relevance of a partial remission. *Kidney Int.* 2004; 66(3): 1199-205.