IJKD KIDNEY DISEASES

Long-term Outcomes in Patients with Membranous Nephropathy: A Retrospective Cohort Study in Iran

Seyed Mehdi Hoseini,[1] Neda Najafi,[1] Mitra Mehrazma,[2] Reihane Chegini,[2] Mandana Rahimi,[2] Mohsen Vahedi,[3] Shahrzad Ossareh[1]

[1]Department of Medicine, Nephrology Section, Hasheminejad Kidney Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[2]Department of Pathology, School of Medicine, Hasheminejad Kidney Center, Iran University of Medical Sciences, Tehran, Iran
[3]Department of Biostatistics and Epidemiology, Faculty of Rehabilitation Sciences, Iranian Research Center on Aging, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

Keywords. glomerulonephritis, membranous nephropathy, risk factors, renal insufficiency, survival, Iran, retrospective cohort study

Original Paper

Introduction. Membranous nephropathy (MN) has variable clinical outcomes, ranging from spontaneous remission to slow progression to kidney failure. Since the clinical outcomes of MN have not been studied in a large sample size in Iran, this study was designed to evaluate the outcome of patients diagnosed with MN at Hasheminejad Kidney Center (HKC), Tehran.

Methods. In this retrospective cohort study, 1086 patients with a diagnosis of MN who were biopsied between 1998 and 2018 in HKC were evaluated through a review of medical records for baseline clinical and laboratory characteristics at the time of biopsy and through a review of follow-up charts and phone calls for the evaluation of clinical outcomes. Of these patients, 551 could be followed for clinical outcomes. The composite outcome included kidney loss (hemodialysis, transplantation, or death). The effect of demographic, clinical, laboratory, and pathological variables on kidney survival was determined by the Cox-regression model using SPSS-16 software at a significance level of .05.

Results. Sex ($P < .05$), higher weight ($P < .05$), older age ($P < .001$), hypertension ($P < .001$), higher baseline proteinuria and lower glomerular filtration rate (GFR) at the onset of the disease were associated with kidney failure ($P < .001$). A higher percentage of interstitial fibrosis, tubular atrophy, global sclerosis, and a higher pathological class of membranous nephropathy were significantly associated with disease outcome in the univariate Cox-regression analysis ($P < .001$). Kidney survival rates at 5, 10, and 15 years were 86%, 74%, and 56%; respectively.

Conclusion. Our study suggests that baseline demographic, clinical and laboratory factors affect kidney outcomes. Patients who are considered high-risk based on the criteria listed above may need to be candidates for more aggressive therapy.

IJKD 2023;17:238-44
www.ijkd.org
DOI: 10.52547/ijkd.7373

INTRODUCTION

Glomerular disease is one of the leading causes of chronic kidney disease, hypertension, kidney failure, and death.[1] Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults and the most common pathology among glomerular diseases in several parts of the world, including Iran.[2,3] Membranous

nephropathy manifests itself as nephrotic-range proteinuria with edema in both primary and secondary types. The primary type is usually induced by antibodies against phospholipase A_2 receptors, while the secondary type occurs in the setting of several non-kidney diseases including autoimmune diseases (e.g., lupus erythematosus and autoimmune thyroiditis), infections (e.g., hepatitis B, hepatitis C and malaria), medications (e.g., penicillamine and gold), and malignancies (e.g., colon and lung cancers). Secondary MN is more common in children, especially in the setting of hepatitis and systemic lupus erythematosus. [4] Membranous nephropathy is related to cancer in 20 to 30% of people over the age of 60.[5]

Primary MN, with a best-estimated incidence of 12 cases per million population annually, remains the leading cause of nephrotic syndrome in adults.[6] It has variable clinical outcomes that vary from spontaneous remission to chronic kidney disease and end-stage kidney disease (ESKD). The rate of complete or partial spontaneous remission in nephrotic syndrome is about 30%, which is associated with better kidney survival. However, 30 to 40 percent of patients still progress to ESKD within 5 to 15 years. The efficacy and safety of immunosuppression for the treatment of MN with nephrotic syndrome are controversial.[7] The long-term outcomes of this disease, including patient and kidney survival rates, and the recurrence of the active disease are not well known.[5]

Persistent nephrotic-range proteinuria and high creatinine levels are associated with poor disease outcome.[8] Other biological markers, such as serum beta-2 microglobulin, urinary immunoglobulin G, and high titers of phospholipase A2 receptor antibodies, are associated with a higher risk of developing kidney failure.[9,10]

Kidney survival in patients with severe and progressive MN is improved with immunosuppressive therapies.[11] Immunosuppressive medications are typically administered after 6 to 12 months of follow up, based on the prediction of the risk of progression to kidney failure.[12] However, the risk of kidney failure and death becomes apparent over time.[5] Previous studies, with follow-up periods of 39 to 72 months from the initial manifestation, have not shown a significant effect of the disease on the long-term survival of patients. [7,13-15]

Short-term follow-up may not be able to show the effect of the disease on the patient and kidney survival in a disorder such as primary MN, with a relatively slow progression. Similarly, earlier studies have not shown the effect of disease recurrence on progression to kidney failure, which again can be assumed to be due to the relatively short follow-up period. There is also no information or guidance for the long-term follow-up and treatment of patients in remission.[5]

Since the clinical outcomes of MN and its risk factors have not been studied in a large sample size in Iran, this historical cohort study was conducted on 1086 patients with MN who underwent kidney biopsy between 1998 and 2018 at Hasheminejad Kidney Center (HKC), Tehran.

MATERIALS AND METHODS

Study Design

This retrospective cohort study was performed on all patients with proteinuria diagnosed with MN from 1998 to 2018 in HKC, with at least 6 months of post- biopsy follow-up.

Data Collection

Epidemiological, basic clinical, and laboratory data from the 1086 biopsied patients, diagnosed with MN, were extracted from the HKC glomerulonephritis database with permission. This data included demographic characteristics (age, sex, weight), laboratory results including baseline and last serum creatinine levels, 24-hour proteinuria at the baseline and last follow-up, lipid profile, secondary serologic laboratory tests (ANA, Anti ds-DNA, C3, C4, CH50, P-ANCA, C-ANCA), thyroid stimulating hormone (TSH), and pathological findings (interstitial fibrosis and tubular atrophy (IF/TA) and pathological class of MN.

From the original 1086 patients, follow-up data for 551 patients was available and collected. The biopsy group included all 1086 patients, and the outcome group included 551 patients, consisting of those individuals who had complete baseline and follow up information. The follow-up data were collected after obtaining verbal consent at the hospital outpatient clinic, private offices, and/or phone calls to the patients. Using the WhatsApp mobile application for collecting data via phone calls, the patients were asked to send a picture of their last laboratory test results and medications

to the principal researcher (SMH).

The baseline and last glomerular filtration rate (GFR) were measured by the MDRD formula using the patient's information recorded in the checklist.

One hundred and fifty-five patients were not reached by phone or did not have their recent (in less than 2 years) laboratory data; thus, clinical history was used to categorize the outcome as either kidney loss or possible CKD. Classification of chronic kidney disease based on glomerular filtration rate and albuminuria in patients whose creatinine and protein levels were obtained in follow-up was done based on Kidney Disease Improving Global Outcomes (KDIGO) classification.[16,17]

1- **Complete remission**: Proteinuria < 0.5 g in 24 hours and stable kidney function or reduction of glomerular filtration rate by < 15% and stage 1 or 2 of chronic kidney disease
2- **Partial remission**: At least 50% reduction in proteinuria and proteinuria between 0.5 and 3.5 g in 24 hours
3- **No response**: Proteinuria ≥ 3.5g in 24 hours or no reduction in proteinuria of 50% from the baseline or reduction in glomerular filtration rate ≥ 15% before reduction of proteinuria
4- **Relapse**: Increase in proteinuria to ≥ 3.5g in 24 hours after complete or partial remission
5- **Possible stable chronic kidney disease (without lab data on conservative medication or without medication)**: Patients not undergoing dialysis nor transplanted, with a stable health condition, but with no recent recorded laboratory test, who were not taking any immunosuppressive medication on the last follow-up call or test.
6- **Kidney loss (dialysis, kidney transplantation or death due to renal or non-renal cause)**: Kidney loss was defined as the composite disease outcome.

Data Analysis

Quantitative variables were described by using the mean ± standard deviation, and qualitative variables with relative frequency. Kaplan-Meyer method was used to determine the incidence of long-term disease outcomes. Finally, the Cox-regression model was used to evaluate the simultaneous effect of independent variables on composite disease outcome. Data were analyzed by SPSS 16.0. Chicago, SPSS Inc, 2007, at a significance level of .05.

RESULTS

Demographic and Clinical Features at Kidney Biopsy and Follow-up

The current study included 1086 patients (56.2% males and 43.8% females) with biopsy proven MN. Mean ± SD of age and weight of the patients were 40.80 ± 15.33 years and 73.45 ± 14.59 kg, respectively. Of 1086 patients (biopsy group), 551 were followed, and their outcomes were recorded (outcome group). The follow-up period ranged from 6 to 256 months (median: 77, Interquartile range 88). In the outcome group, 56.4% were male and 43.6% were female. Mean of age and weight of the patients in the outcome group were 41.09 ± 14.79 years and 75.28 ± 15.10 kg, respectively.

In the biopsy group (1086 patients), 35.9% were hypertensive, 78, 8% had nephrotic syndrome, and 16.19% had dysmorphic RBC in urine sediment. In the outcome group (551 patients), 34% were hypertensive, 75.7% had nephrotic syndrome, and 10.17% had dysmorphic RBC in urine sediment.

Laboratory Features

In the biopsy group, the mean baseline serum creatinine level was 1.28 ± 1.21 mg/dL and the mean proteinuria was 6.37 ± 4.51 g/24 hours. The mean ± SD of total cholesterol, total triglyceride and low-density lipoprotein levels were 302.52 ± 114, 245.65 ± 170, and 187.65 ± 94 mg/dL; respectively.

In the outcome group, the mean baseline serum creatinine level was 1.34 ± 1.33 mg/dL and the mean proteinuria was 6.42 ± 4.84 g/24 hours that were not significantly different from the biopsy group. The mean of total cholesterol, total triglyceride and low-density lipoprotein levels were 280.91 ± 114, 227.23 ± 139, and 169.83 ± 88 mg/dL; respectively.

Since the mean values of demographic, clinical, and laboratory results were almost the same between the biopsy and the outcome groups, the study results in the outcome group could be generalizable to all biopsied patients.

Pathological Features in Patients with Clinical Outcome

In the outcome group, detailed pathologic features including pathologic class, global sclerosis and IF/TA were available in 506 patients, based on pathology reports (Table 1).

Table 1. Pathologic Features (IF/TA Staging), Pathologic Class and Global Sclerosis

Variable	Number (%)
IF/TA percentage	
0%	198 (39.1)
< 25	263 (52)
25 to 49	33 (6.5)
≥ 50	12 (2.4)
Pathological class	
Class 1	82 (16.3)
Class 1-2 and 2	326 (64.7)
Class 2-3 and 3	91 (18)
Class 3-4 and 4	5 (1)
Global sclerosis (%)	
0	181 (40.4)
< 25	216 (48.2)
25 to 49	31 (6.9)
≥ 50	20 (4.5)

*Interstitial Fibrosis and Tubular Atrophy

CKD Classification in the Outcome Group

On the basis of the outcome group last GFR and proteinuria, 396 patients were classified for CKD, and 197 patients (49.7%) were in stage 2 of CKD (Table 2). The mean proteinuria in the outcome group was 1193 ± 2101 mg/24 hours (8 to17350 mg/24 hours).

Outcome Summary

The patients in the outcome group were categorized as complete remission (25.2%), partial remission (17.4%), no response or relapse (27.5%), possible stable chronic kidney disease (no lab data available and on conservative medication or without medication) (11%), and kidney loss (composite outcome) in 18.9%, (including hemodialysis [8%], kidney transplantation [3.1%], and death [7.8%]), based on their response to treatment (Table 3). At the end of the follow-up period 447 individuals had kidney survival, accounting for 81.1% of the total population.

Table 2. CKD Classification in Patients with GFR Available on Last Follow-up

GFR categories (mL/min /1.73 m^2)	Number (%)
G1 (≥ 90)	73 (18.4)
G2 (60 to 89)	197 (49.7)
G3[a] (45 to 59)	61 (15.4)
G3[b] (30 to 44)	35 (8.8)
G4 (15 to 29)	21 (5.3)
G5 (< 15)	9 (2.3)

Notes: G1, normal or high; G2, mildly decreased; G3a, mildly to moderately decreased; G3b, moderately to severely decreased; G4, severely decreased; G5, kidney failure.

Table 3. Summary of Disease Outcomes

Outcome	Number (%)
Complete remission	139 (25.2)
Partial remission	96 (17.4)
No response or relapse	152 (27.5)
Possible stable chronic kidney disease	60 (11)
Hemodialysis	44 (8)
Kidney transplantation	17 (3.1)
Death	43 (7.8)
Total	551 (100)

Cox-regression Survival Analysis for Variables and Outcome

There was a significant correlation between independent variables of sex, age, and weight and the composite outcome (kidney loss) in the Cox regression univariate model. The hazard ratio (HR) for males was 1.551. For every five kg of weight gain and each year of increasing age the hazard of kidney loss increased by 0.093 and 0.031, respectively.

The effect of hypertension, proteinuria, GFR, glomerular sclerosis, IF/TA, global sclerosis, and pathological class was significant on composite outcome in the Cox-regression univariate model. The HR for hypertension, proteinuria, progressive CKD stages and pathologic classes were 2.594, 1.061, 2.142, and 2,093; respectively (Table 4).

In the Cox-regression model, after excluding the confounding variables the baseline GFR ($P < .001$), baseline proteinuria ($P < .05$) and IF/TA ($P < .05$) showed a significant effect on composite outcome (Table 5).

According to the life table using the Kaplan-Meier method, the 5-, 10-, and 15-year survival rates for patients with MN were 86%, 73%, and 56%; respectively.

DISCUSSION

In this retrospective cohort study, the relationship between demographic, laboratory, clinical, and pathological variables, and kidney outcome was investigated. According to the findings, in all patients and in patients with the recorded outcome the male-to-female ratio was 1.28, which was consistent with other studies. For example, in studies from China and Japan, male-to-female

Table 4. Univariate Cox-regression Survival Analysis for Variables and Composite Outcome

Variable	Beta	Exp (B)	Exp (B) 95%CI	*P*
Sex	.439	1.551	(1.027, 2.343)	> .05
Age at biopsy	.031	1.031	(1.018, 1.045)	< .001
Weight one fifth	.088	1.093	(1.019, 1.171)	< .05
Hypertension	.953	2.594	(1.752, 3.840)	< .001
Proteinuria one thousandth	.059	1.061	(1.029, 1.093)	< .001
GFR stage	.762	2.142	(1.824, 2.515)	< .001
Cholesterol	-.001	.999	(.997, 1.001)	> .05
Triglyceride	-.001	.999	(.998, 1.001)	> .05
Albumin	-.313	.731	(.436, 1.227)	> .05
IF/TA* percentage	.939	2.559	(1.979, 3.309)	< .001
Global sclerosis percentage	.613	1.847	(1.481, 2.303)	< .001
MN** class	.739	2.093	(1.535, 2.854)	< .001

*Interstitial fibrosis and tubular atrophy
**Membranous nephropathy

Table 5. Multivariate Cox-regression Survival Analysis for Variables and Composite Outcome

Variable	Beta	Exp (B)	Exp (B) 95%CI	*P*
Hypertension	.437	1.549	(.851, 2.818)	> .05
Proteinuria one thousandth	.043	1.044	(1.000, 1.090)	≤ .05
GFR at biopsy	.693	2.000	(1.518, 2.634)	< .001
IF/TA* percentage	.492	1.635	(.995, 2.687)	≤ .05
Global sclerosis percentage	-.113	.893	(.617, 1.293)	> 0.05
MN** class	.155	1.168	(.726, 1.877)	> .05

*Interstitial fibrosis and tubular atrophy
**Membranous nephropathy

ratios were1.5 and 1.65, respectively. [18,19] In North America and Europe the male-to-female ratio were 2, [20,21] while in a Korean study, this ratio was 1.5.[22]

In the present study, sex, age, weight, hypertension, baseline proteinuria, and GFR, as well as pathological findings in biopsy specimens, i.e., the percentage of IF/TA, global sclerosis, and pathological class, had a significant relationship with composite outcome in the univariate Cox-regression model study. In a multivariate Cox-regression study, the baseline GFR, proteinuria, and percentage of IF/TA were associated with the composite outcome.

In the study of Shiiki *et al.*, it was shown that the above-mentioned parameters are also risk factors in Japanese patients in univariate analysis. Male sex and elevated serum creatinine were the predictors of kidney failure in multivariate analysis.[19]

Most clinical studies on idiopathic MN have been performed on Caucasian populations and they have shown that male sex, older age, hypertension, and baseline nephrotic-range proteinuria are independent risk factors for development of ESKD[18,19] Additionally, based on a review study, decreased GFR, and interstitial lesions are the consequence of prior injury due to MN [23] that is concordant with the findings of our study.

In the available studies in Caucasian males, the age more than 50 years, hypertension and massive proteinuria (more than 10 g in 24 hours), as well as high serum creatinine levels, and severe and chronic tubulointerstitial changes, are risk factors for idiopathic membranous nephropathy.[24]

According to the findings of the study conducted by Choi *et al.*, in Korea, older patients had favorable renal outcomes compared to younger patients that contradicts the finding of our study. [22] However, high GFR was a good predictor for renal outcome, that is in agreement with our findings.

In a study from China, reduced GFR and severe, chronic tubulointerstitial lesions were independent risk factors for the outcome of patients with MN. In addition, nephrotic -range proteinuria was also a risk factor for kidney failure. [18] Moreover, a second study conducted in China revealed that patients with older age, lower GFR, and more proteinuria at the time of kidney biopsies were at higher risk for composite outcome including

progression of renal function, ESKD, and death.[25] Our study findings support evidence from the previous studies.

The results of the study by Shiiki *et al.*, showed that male sex, age over 60 years, high serum creatinine (above 1.5 mg/dL) and lower GFR, and severe, chronic tubulointerstitial lesions, were independent risk factors for the outcome of patients with MN. In addition, nephrotic -range proteinuria were the main predictors of progression to kidney failure.[19] In addition, their findings indicate that kidney survival was significantly higher in patients treated with steroids than in those who received conservative therapy alone.[19] It should be noted that in the study by Shiiki *et al.*, only patients with proteinuria in the nephrotic -range were included, while in our study as well as a few other studies, all patients with any amount of proteinuria were included.

Pathological examination of patients with idiopathic MN has shown that patients with higher degrees of tubulointerstitial fibrosis, vascular sclerosis, and secondary focal segmental glomerulosclerosis (FSGS) are older, have higher blood pressure, and have a lower amount of GFR.[26] Although these pathological findings are associated with decreased kidney survival, they cannot predict disease outcomes regardless of clinical variables and are not associated with decreased kidney function or basal proteinuria. In addition, the severity of tubulointerstitial and vascular lesions does not preclude remission in patients receiving immunosuppressive therapy.

In the study by Troyanovet *et al.*, the severity of tubulointerstitial and vascular damage found on light microscopy predicted renal survival.[26] The association between tubulointerstitial disease and vascular lesions and kidney survival was accounted for by lower creatinine clearance at the beginning of the disease and not by a more rapid rate of disease progression or initial proteinuria.[26]

Patients with a greater degree of tubulointerstitial disease, vascular sclerosis, and secondary FSGS were older, had a higher mean arterial pressure, and a lower creatinine clearance at the presentation. Although these histologic features were associated with reduced renal survival, they did not predict this outcome independently of the baseline clinical variables, nor did they correlate with the rate of decline in function or with baseline proteinuria.

In the present study, kidney survival at 5, 10, and 15 years was 86%, 74%, and 56%; respectively. In the study of Shiiki *et al.*, kidney survival at 5, 10, 15, and 20 years were 95.8%, 90.3%, 81.1%, and 60.5%; respectively.[19] Previous studies have shown that East Asian populations have a better prognosis for the disease than Caucasian populations. A national study in Japan have confirmed these results.[19] In the Chinese population, kidney survival at 5, 10, and 15 years were 96.9%, 93.5%, and 86.6%, respectively.[18]

Therefore, the prognosis of idiopathic MN in this study on a group of the Iranian population is more similar to the results presented in the Caucasian population and is not as benign as in the Asian population.

This study had some limitations. A number of patients who had been biopsied in earlier years were not accessible; this led to some missing information in this group. Due to the lack of uniform treatment protocols and inaccessibility to treatment regimens, we could not assess the effectiveness of different types of therapeutic regimens. Also, the lack of access to Antiphospholipase A2 receptor antibodies was another limitation of this study.

CONCLUSION

Male sex, older age, lower GFR, higher baseline proteinuria, and chronic pathological changes including the percentage of IF/TA at biopsy were independently associated with composite outcome. The prognosis and survival of the disease in this Iranian cohort were more similar to the Caucasian population and different from the East Asian population. We recommend early patient assessment for the aforementioned risk factors to identify high-risk candidates for more aggressive treatment.

ETHICAL CONSIDERATIONS

This study was conducted under ethical approval from the local ethics committee of Iran University of Medical Sciences (registration code: IR.IUMS.FMD.REC.1398.393). Verbal consent was obtained at the beginning of the telephone interview from all patients who were asked about the outcome of their disease.

FUNDINGS

None.

ACKNOWLEDGMENT

This study (ID: IR.IUMS.FMD.REC.1398.393) was funded by the Vice-Chancellor of Research and Technology of Iran University of Medical Sciences.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES

1. Alok A, Yadav A. Membranous nephropathy. StatPearls [Internet]. StatPearls Publishing; 2020.
2. Ossareh S, Asgari M, Abdi E, et al. Renal biopsy findings in Iran: case series report from a referral kidney center. International urology and nephrology. 2010;42(4):1031-1040.
3. Ossareh S, Asgari M, Abdi E, et al. Renal biopsy findings in Iran: update of a case series report from a referral kidney center. Oxford univ press great clarendon st, oxford ox2 6dp, england; 2014:457-457.
4. Hoxha E, Reinhard L, Stahl RA. Membranous nephropathy: new pathogenic mechanisms and their clinical implications. Nature Reviews Nephrology. 2022;18(7):466-478.
5. Teisseyre M, Beyze A, Perrochia H, et al. C5b-9 glomerular deposits are associated with poor renal survival in membranous nephropathy. Kidney International Reports. 2023;8(1):103-114.
6. Alan S, Chertow GM, Luyckx V, Marsden PA, Skorecki K, Taal MW. Brenner and Rector's The Kidney E-Book. Elsevier Health Sciences; 2015.
7. McGrogan A, Franssen CF, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrology Dialysis Transplantation. 2011;26(2):414-430.
8. Van den Brand JA, Van Dijk PR, Hofstra JM, Wetzels JF. Long-term outcomes in idiopathic membranous nephropathy using a restrictive treatment strategy. Journal of the American Society of Nephrology. 2014;25(1):150-158.
9. Marx BE, Marx M. Prediction in idiopathic membranous nephropathy. Kidney international. 1999;56(2):666-673.
10. Kanigicherla D, Gummadova J, McKenzie EA, et al. Anti-PLA2R antibodies measured by ELISA predict long-term outcome in a prevalent population of patients with idiopathic membranous nephropathy. Kidney international. 2013;83(5):940-948.
11. Branten AJ, du Buf-Vereijken PW, Klasen IS, et al. Urinary excretion of β2-microglobulin and IgG predict prognosis in idiopathic membranous nephropathy: a validation study. Journal of the American Society of Nephrology. 2005;16(1):169-174.
12. Waldman M, Austin HA. Treatment of idiopathic membranous nephropathy. Journal of the American Society of Nephrology. 2012;23(10):1617-1630.
13. Cattran DC, Feehally J, Cook HT, et al. Kidney disease: improving global outcomes (KDIGO) glomerulonephritis work group. KDIGO clinical practice guideline for glomerulonephritis. Kidney International Supplements. 2012;2(2):139-274.
14. Troyanov S, Wall CA, Scholey JW, Miller JA, Cattran DC, Group FTTGR. Idiopathic membranous nephropathy: definition and relevance of a partial remission. Kidney international. 2004;66(3):1199-1205.
15. Donadio Jr JV, Torres VE, Velosa JA, et al. Idiopathic membranous nephropathy: the natural history of untreated patients. Kidney international. 1988;33(3):708-715.
16. Schieppati A, Mosconi L, Perna A, et al. Prognosis of untreated patients with idiopathic membranous nephropathy. New England Journal of Medicine. 1993;329(2):85-89.
17. Zuo K, Wu Y, Li S-J, Xu F, Zeng C-H, Liu Z-H. Long-term outcome and prognostic factors of idiopathic membranous nephropathy in the Chinese population. Clinical nephrology. 2013;79(6):445-453.
18. Shiiki H, Saito T, Nishitani Y, et al. Prognosis and risk factors for idiopathic membranous nephropathy with nephrotic syndrome in Japan. Kidney international. 2004;65(4):1400-1407.
19. Couser WG. Primary membranous nephropathy. Clinical Journal of the American Society of Nephrology. 2017;12(6):983-997.
20. Kanigicherla DA, Short CD, Roberts SA, et al. Long-term outcomes of persistent disease and relapse in primary membranous nephropathy. Nephrology Dialysis Transplantation. 2016;31(12):2108-2114.
21. Choi J-Y, Chin HJ, Lee H, et al. Idiopathic membranous nephropathy in older patients: Clinical features and outcomes. PloS one. 2020;15(10):e0240566.
22. Wasserstein AG. Membranous glomerulonephritis. Journal of the American Society of Nephrology. 1997;8(4):664-674.
23. Wu Q, Jinde K, Nishina M, et al. Analysis of prognostic predictors in idiopathic membranous nephropathy. American journal of kidney diseases. 2001;37(2):380-387.
24. Xiaofan H, Jing X, Chenni G, et al. New risk score for predicting progression of membranous nephropathy. Journal of Translational Medicine. 2019;17:1-7.
25. Troyanov S, Roasio L, Pandes M, Herzenberg A, Cattran D. Renal pathology in idiopathic membranous nephropathy: a new perspective. Kidney international. 2006;69(9):1641-1648.

Correspondence to:
Shahrzad Ossareh, MD
Professor, Department of Nephrology, Hasheminejad Kidney Center, Iran University of Medical Sciences, Tehran, Iran
Tel: 0098 21 8864 4420
Fax: 0098 21 8864 4441
E-mail: ossareh_s@hotmail.com

Received April 2023
Revised June 2023
Accepted August 2023