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Original Article

Short-Term Outcomes in Membranous Nephropathy: Insights from A Single Study Center

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Abstract

Objective: To determine the short-term outcomes of membranous nephropathy (MN) in patients visiting outpatient department of nephrology, Bahawal Victoria Hospital, Bahawalpur.

Methods: Patients of either gender and any age, having renal biopsy proven MN, visiting outpatient department of nephrology between October 2021 to August 2024, and treated for a minimum duration of 6 months were analyzed. All of the patients underwent a systematic physical examination, and detailed information about their medical history was gathered. Patients were then subjected to necessary baseline investigations. Follow up visits were planned every month and final outcome was labeled after 6 months treatment.

Results: In a total of 178 patients with MN, the mean age was 32.25±12.86 years. There were 117 (65.7%) male patients. The mean duration of symptoms was 7.80±13.04 months. Most frequent types of treatment advised were conservative and cyclical regimens used in 80 (44.9%), and 33 (18.5%) patients, respectively. Post-treatment, 74 (41.6%) patients had complete proteinuria remission, 93 (52.2%) partial remission, whereas 11 (6.2%) patients had nephrotic proteinuria progression. Post-treatment proteinuria status was having significant association with duration of symptoms (p=0.003), baseline proteinuria (p<0.001), baseline serum albumin (p=0.024), baseline progression risk score (p=0.001), and treatment types (p=0.001). Post-treatment, 134 (75.3%) patients did not report renal dysfunction.

Conclusion: This study emphasizes the importance of baseline parameters and treatment modalities in predicting and influencing post-treatment outcomes in MN, providing valuable insights for more targeted and effective patient care. Favorable short-term outcomes were reported in vast majority of patientswith membranous nephropathy.

Keywords: Membranous nephropathy, Nephrotic proteinuria, Proteinuria, Serum albumin, Serum creatinine.

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Introduction

Membranous nephropathy (MN), an autoimmune condition, arises when the circulating autoantibodies attack the glomerular pododcytes.[1] In adults, nephrotic syndrome (NS) primarily occurs due to MN. NS is the most common (80%) manifestation of idiopathic membranous nephropathy (IMN) in adults, with sub-nephrotic proteinuria accounting for the remaining cases.[2] MN is characterized by manifesting spontaneous remissions and relapses in its progression, showing spontaneous complete healing in around 20% of the cases, along with an occurrence of 15-20% in partially recovered patients.[3] Besides, in the majority of cases (70-80%), phospholipase A2 receptor (PLA2R) autoantibodies are detected.[4]

PersistentNS is commonly treated with immunosuppressant medications while other approaches involving multiple regimens (methylprednisolone, cyclosporine, chlorambucil, cyclophosphamide, tacrolimus, and recently rituximab) are also popularly used for the treatment of IMN.[5,6] The maintenance and preservation of renal function for a longer period of time have been observed using corticosteroids and alkylating agents in combination.[7] Currently, the use of rituximab has become popular as it shows long-term safety and fewer chances of relapse, compared with alkylating

agents and calcineurine inhibitors, which are more likely to cause nephrotoxicity.[8] Rituximab is not as cost-effective as other available treatments, and hence, healthcare professionals frequently need to employ a multi-drug strategy while considering the patient's adverse effects, rate of remission, and financial concerns as well. Keeping all this in mind, we planned this study with the objective of determining the short-term outcomes of MN in patients visiting outpatient department of nephrology of Bahalwal Victoria Hospital, Bahawalpur.

Methods

This prospective cohort study was carried out at the Department of Nephrology, Bahawal Victoria Hospital, Bahawalpur, Pakistan, from November 2021 to August 2024. Approval from the "Institutional Ethical Committee" was obtained for this research. Patients of either gender and any age, having renal biopsy proven MN, visiting outpatient department of nephrology and treated for a minimum period of 6 months were analyzed. The exclusion criteria were patients having secondary causes of NS. Informed as well written consents were taken from all study participants after briefing them the aims of this study and ensuring the confidentiality of their data.

All of the patients underwent a systematic physical examination, and detailed information about their medical history was gathered. Patients were then subjected to necessary baseline investigations. All patients underwent an ultrasound-guided kidney biopsy, and the specimen was examined under light microscopy and immunofluorescence. Whenever indicated, special investigations were carried out, like complement levels C3 and C4, hepatitis-B Ag, anti-hepatitis C virus, human immunodeficiency virus, and anti-nuclear antibodies. Wherever possible, PLA2R levels were also measured. The patients were treated as perinstitutional treatment protocols. Treatment options included conservative treatment (ACE-I/ARBs with diuretics for 6 months), continuous regimen (steroids+oral cyclophosphamide), cyclical regimen (steroids at 1, 3, 5 months and oral cyclophosphamide at 2,4,6 months), modified cyclical regimen (steroids at 1, 3, and 5 months with IV cyclophosphamide at 2, 4, 6 months), Rituximab, or steroids plus calcineurin inhibitors.

Follow up visits were planned every month and final outcome was labeled after 6 months treatment. The primary outcome was complete remission, partial remission or neophrotic proteinuria progression. Complete remission was defined as reductionin proteinuria to <0.30 g/day, along with normal serum albumin (≥3.5 g/dl) and satble kidney functions. Partial remission was labeled as reduction of proteinuria below 3.5 g/day along with ≥50% reduction from baseline with stable kidney function. Nephrotic protein was termed as proteinuria ≥3.5 g/day. Secondary outcome were based on renal functioning. No renal dysfunction was labeled as serum creatinine < 1.1 mg/dl. Dysfunction but improved if serum creatinine ≥1.1 mg/dl but reduction in serum creatinine from baseline. Worsening of renal functioning was labeled if serum creatinine increased from baseline. Data analysis was performed using "IBM-SPSS Statistics", version 26.0. The categorical variables were analyzed using chi-square test. P value ≤0.05 was considered statistically significant.

Results

In a total of 178 patients with MN, the mean age was 32.25±12.86 years (ranging between 11-65 years), while 116 (65.2%) patients were aged between 21-49 years. There were 117 (65.7%) male and 61 (34.3%) female patients. The mean duration of symptoms was 7.80±13.04 months (ranging between 1-96 month). Table-1 is showing baseline characteristics of MN patients.

Table 1: *Demographic and clinical characteristics of membranous nephropathy patients*

		Frequency (%)
Age (years)	<21	37 (20.8)
	21-49	116 (65.2)
	≥50	25 (14.0)
Gender	Male	117 (65.7)
	Female	61 (34.3)
Duration of symptoms (months)	≤6	133 (74.7)
	12-Jul	21 (11.8)
	>12	24 (13.5)
Diagnosis by biopsy		178 (100)
Anti-PLA2R antibody	Negative	20 (11.2)
	Not done	120 (67.4)
	Positive	38 (21.3)
Proteinuria (g/day)	<3.5	33 (18.5)
	3.5-10	111 (62.4)
	>10	34 (19.1)
Serum albumin (g/dl)	<2.0	87 (48.9)
	2.0-3.5	85 (47.8)
	>3.5	6 (3.4)
Renal dysfunction		62 (34.8%)
Progression risk score	High	68 (38.2)
	Low	36 (20.2)
	Moderate	74 (41.6)

Most frequent types of treatment advised were conservative and cyclical regimens used in 80 (44.9%), and 33 (18.5%) patients, respectively. Figure I is showing distribution of treatment types in patients with MN.

Post-treatment, 74 (41.6%) patients had complete proteinuria remission, 93 (52.2%) partial remission, whereas 11 (6.2%) patients had nephrotic proteinuria progression. Table-2 is showing comparison of baseline characteristics and treatment given with respect to post-treatment proteinuria findings. Post-treatment proteinuria status was having significant association with duration of symptoms (p=0.003), baseline proteinuria (p<0.001), baseline serum albumin (p=0.024), baseline progression risk score (p=0.001), and treatment types (p=0.001) as shown in table-2.

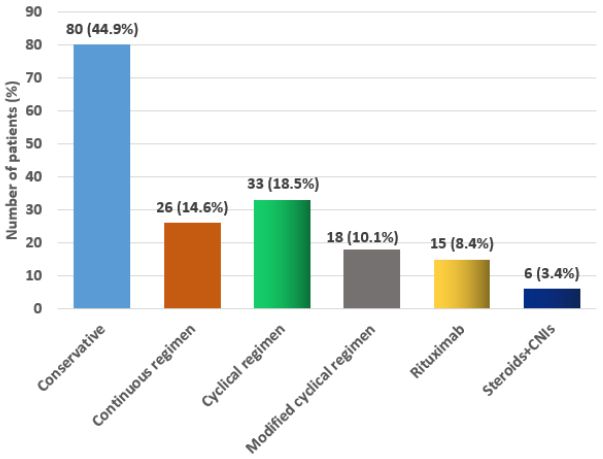

Figure I: *Treatment types in patients with membranous nephropathy*

Table 2: *Comparison of post-treatment proteinuria remission status with baseline characteristics and treatment given*

Characteristics		Complete remission	Partial remission	Nephrotic proteinuria	P-value
Age (years)	<21	18 (24.3)	17 (18.3)	2 (18.2)	0.399
	21-49	50 (67.6)	59 (63.4)	7 (63.6)	
	≥50	6 (8.1)	17 (18.3)	2 (18.2)	
Gender	Male	50 (67.6)	58 (62.4)	9 (81.8)	0.398
	Female	24 (32.4)	35 (37.6)	2 (18.8)	
Duration of symptoms (months)	≤6	63 (85.1)	59 (63.4)	11 (100)	0.003
	12-Jul	8 (10.8)	16 (17.2)	-	
	>12	3 (4.1)	18 (19.4)	-	
Baseline Proteinuria (g/day)	<3.5	24 (32.4)	7 (7.5)	2 (18.2)	<0.001
	3.5-10	47 (63.5)	60 (64.5)	4 (36.4)	
	>10	3 (4.1)	26 (28.0)	5 (45.5)	
Baseline Serum albumin (g/dl)	<2.0	26 (35.1)	56 (60.2)	5 (45.5)	0.024
	2.0-3.5	44 (59.5)	35 (37.6)	6 (54.5)	
	>3.5	4 (5.4)	2 (2.2)	-	
Baseline renal dysfunction		19 (25.7%)	38 (40.9)	5 (45.5)	0.092
Baseline Progression risk score	High	25 (33.8)	38 (40.9)	5 (45.5)	0.001
	Low	26 (35.1)	8 (8.6)	2 (18.2)	
	Moderate	23 (31.1)	47 (50.5)	4 (36.4)	
Treatment types	Conservative	34 (45.9)	40 (43.0)	6 (54.5)	0.001
	Continuous regimen	8 (10.8)	16 (17.2)	2 (18.2)	
	Cyclical regimen	23 (31.1)	10 (10.8)	-	
	Modified cyclical regimen	3 (4.1)	15 (16.1)	-	
	Rituximab	6 (8.1)	6 (6.5)	3 (27.3)	
	Steroids+ CNIs	-	6 (6.5)	-	

Post-treatment, 134 (75.3%) patients were not having renal dysfunction whereas, 33 (18.5%) had serum creatinine above 1.1 mg/dl but improved, 4 (2.2%) had their serum creatinine worsened, whereas remaining 7 (3.9%) needed hemodialysis. Post-treatment proteinuria renal dysfunction status revealed significant association female gender (=0.028), baseline proteinuria (p<0.001), baseline serum albumin (p<0.00), baseline renal dysfunction (p<0.001), baseline progression risk score (p<0.001), and treatment types (p<0.001) as shown in table-3.

Discussion

The study focused on analyzing outcomes in membranous nephropathy (MN) among 178 patients, revealing a range of significant findings. We found that 65.2% MN patients were agedbetween of 21 to 49

Table 3: *Comparison of post-treatment renal functioning status with baseline characteristics and treatment given*

Characteristics		Post treatment renal functioning				P-value
		No dysfunction	Dysfunction but improved	Worsening	Hemodialysis	
Age (years)	<21	29 (21.6)	6 (18.2)	2 (50.0)	-	0.464
	21-49	88 (65.7)	21 (63.6)	2 (50.0)	5 (71.4)	
	≥50	17 (12.7)	6 (18.2)	-	2 (28.6)	
Gender	Male	82 (61.2)	29 (87.9)	2 (50.0)	4 (57.1)	0.028
	Female	52 (38.8)	4 (12.1)	2 (50.0)	3 (42.9)	
Duration of symptoms (months)	≤6	92 (68.7)	30 (90.9)	4 (100)	7 (100)	0.053
	12-Jul	24 (17.9)	-	-	-	
	>12	18 (13.4)	3 (9.1)	-	-	
Baseline Proteinuria (g/day)	<3.5	24 (17.9)	-	4 (100)	5 (71.4)	<0.001
	3.5-10	91 (67.9)	18 (54.5)	-	2 (26.6)	
	>10	-	15 (45.5)	-	-	
Baseline Serum albumin (g/dl)	<2.0	66 (49.3)	21 (63.6)	-	-	<0.001
	2.0-3.5	64 (47.8)	12 (36.4)	2 (50.0)	7 (100)	
	>3.5	4 (3.0)	-	2 (50.0)	-	
Baseline renal dysfunction		31 (23.1%)	26 (78.8)	-	5 (71.4)	<0.001
Baseline Progression risk score	High	36 (26.9)	27 (81.8)	-	5 (71.4)	<0.001
	Low	28 (20.9)	2 (6.1)	4 (100)	2 (28.6)	
	Moderate	70 (52.2)	4 (12.1)	-	-	
	Conservative	70 (52.2)	4 (12.1)	4 (100)	2 (28.6)	
Treatment types	Continuous regimen	22 (16.4)	2 (6.1)	-	2 (28.6)	<0.001
	Cyclical regimen	27 (20.1)	6 (18.2)	-	-	
	Modified cyclical regimen	9 (6.7)	9 (27.3)	-	-	
	Rituximab	3 (2.2)	12 (36.4)	-	-	
	Steroids+ CNIs	3 (2.2)	-	-	3 (42.9)	

years. Our findings are very similar to what Hashmi et al in a local study revealed about the mean age of patients with MN at the time of diagnosis (34.9±16.8 years).[9] Study by Kumar et al from India found that the mean age of patients with glomerulonephritis was higher (43.0±14.6 years) than what we noted but 52.4% patients were aged between 30-50 years which is aligned to what we described.[10]

This study shows that treatment modalities predominantly included conservative approaches, adopted by 44.9% of patients, followed by cyclical regimens in 18.5% of cases. This preference for conservative management might reflect the clinical status, perceived efficacy or patient preferences in treatment strategies for MN. Post-treatment, 41.6% patients had complete proteinuria remission, 52.2% partial remission, whereas 6.2% patients had nephrotic proteinuria progression. Collectively, complete or partial remission was noted in 93.8% patients in our cohort. He et al from china analyzing 474 cases of primary MN reported 95.6% to have complete or partical remisssion and our findings stand aligned with this contemporary data.[11] Lower remission rates have been observed by Jha et al (32% for total remission and 40% for partial remission)[12] and Ram et al (at 9 months, a 31% complete remission rate and a 46.5% partial remission rate).[13] Ramachandran et al mentioned that 6.7% of the patients experienced relapse with oral cyclophosphamide, which was comparable to our findings.[14] Higher relapse rates of 23% and 30%, respectively, were found in other trials from India's Jha et al and Japan's Eriguchi et al.[12,15]

Qin et al examined 408 cases and noted that individuals who attained remission were comparatively younger than those who did not respond, a trend which we did not observe in this study.[16] Our study also highlighted the potential predictive value of various baseline parameters in determining the response to treatment and subsequent outcomes in MN.This also suggests a multifaceted interplay among various baseline indicators and treatment strategies in influencing outcomes post-MN treatment.[17,18] Further exploration into the predictive value of baseline parameters in determining treatment responses and subsequent outcomes may offer insights into personalized approaches for managing MN.Overall, this study contributes valuable insights into the clinical landscape of MN, emphasizing the significance of baseline indicators and treatment modalities in predicting post-treatment outcomes, thereby highlighting avenues for more targeted and effective management strategies.

Single center study design with relatively short follow up evaluation was some of the limitations of this study. We were also unable to evaluate eGFR in the current cohort which would have added very valuable insights to the present research.

Conclusion

This study emphasizes the importance of baseline parameters and treatment modalities in predicting and influencing post-treatment outcomes in MN, providing valuable insights for more targeted and effective patient care. Favorable short-term outcomes were reported in vast majority of patients with membranous nephropathy. Further comparative studies assessing personalized management strategies based on the baseline predictors are warranted to optimize therapeutic approaches in MN.

Ethical Approval: The IRB/EC approved this study via letter no 1226/DME/QAMC Bahawalpur dated October 25, 2021.

Conflict of Interest: *None*

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Authors' Contribution

RK, SIM, QMA: Conception

MTR, AS: Design of the work

MKI, AA: Data acquisition, analysis, or interpretation

MKI, AA, MTR, AS: Draft the work

RK, SIM, QMA: Review critically for important intellectual content

All authors approve the version to be published

All authors agree to be accountable for all aspects of the work

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