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Original Research Article

A STUDY TO EVALUATE THE CORRELATION AND OUTCOMES OF CLINICOPATHOLOGY AND CLINICAL PROFILE IN ADULT MEMBRANOUS NEPHROPATHY

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ABSTRACT

Background: Membranous nephropathy (MN) is a common cause of adult nephrotic syndrome with variable clinical presentation and outcomes. This study aimed to evaluate the correlation between clinicopathological features and clinical outcomes in adult patients with membranous nephropathy.

Materials and Methods: A total of 51 biopsy-proven adult MN patients admitted to the Department were included. Clinical characteristics, laboratory parameters, histopathological findings, treatment regimens, and outcomes were analyzed. Patients were categorized into primary and secondary MN groups, and factors associated with remission and renal impairment were evaluated.

Results: Approximately one-third of patients were aged 30–39 years, followed by 23.53% in the 40–49-year age group. Edema was present in nearly 75% of patients, hypertension in almost half, and diabetes in 7%. Primary MN accounted for 80.39% of cases, while 19.61% were secondary MN. The modified Ponticelli regimen was used in 60.78% of patients. Among primary MN patients treated with the modified Ponticelli regimen, complete remission was achieved in 58.06%. Hematuria was significantly associated with secondary MN ($p = 0.01$). Laboratory parameters were generally lower in primary MN compared to secondary MN, except for eGFR and total cholesterol, though differences were not statistically significant. C1q staining was significantly more common in secondary MN ($p < 0.0001$). Remission rates differed significantly among treatment regimens ($p < 0.0001$), with higher remission rates observed in secondary MN, likely due to treatment directed at the underlying cause. Absence of diabetes was the only significant predictor of remission ($p = 0.02$). Regarding renal function, 31.37% had mildly reduced kidney function, 23.52% had moderate reduction without symptoms, 17.64% had moderate reduction with symptoms, 7.84% had severe reduction, and 3.92% had very severe reduction. Renal impairment developed in 11.76% of patients. Hypertension and diabetes were significant predictors of renal impairment ($p = 0.03$ and 0.04, respectively), and UPCR was the single most significant predictor ($p = 0.003$). Complications occurred in approximately 15% of patients with primary MN, while no complications were observed in secondary MN.

Conclusion: Primary MN constituted the majority of cases. Younger age of onset, female gender, hematuria, and positive C1q staining were significant predictors of secondary MN. Secondary MN demonstrated higher remission rates, with absence of diabetes being a key predictor of remission. Hypertension, diabetes, and elevated UPCR were significant indicators for the development of renal impairment. Complications were observed exclusively in primary MN patients.

Keywords: Ponticelli Drug Regimen, eGFR, Renal Impairment, nephropathy, Glomerulopathy.

INTRODUCTION

Membranous nephropathy (MN) is a common cause of primary glomerular disease and one of the leading etiologies of nephrotic syndrome in adults.[1] Primary (idiopathic) membranous nephropathy accounts for approximately 75–80% of cases. Advances in understanding its pathogenesis have established MN as a kidney-specific autoimmune disease, with nearly 70% of affected patients demonstrating circulating antibodies against the M-type phospholipase A2 receptor (PLA2R), a podocyte surface antigen.[2,3]

The remaining 20–25% of MN cases are secondary to identifiable causes, including systemic autoimmune disorders such as systemic lupus erythematosus, chronic infections such as hepatitis B and C, malignancies, and drug exposure.[2] The clinical course of primary MN is variable. Approximately one-third of patients achieve spontaneous remission, another one-third continue to exhibit persistent proteinuria with stable renal function, and nearly 40% progress to end-stage renal disease over time.[4] In addition to progressive renal dysfunction, patients with MN have an increased risk of morbidity and mortality due to thromboembolic and cardiovascular complications.[5]

Management strategies for MN are guided by the severity of proteinuria and the risk of disease progression. Patients with low-risk disease and minimal proteinuria are typically managed conservatively with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or a combination of both. Although these agents reduce proteinuria, they do not significantly alter disease progression. Patients with moderate- to high-risk disease require immunosuppressive therapy, including corticosteroids, alkylating agents, calcineurin inhibitors such as cyclosporine A and tacrolimus, or combination regimens such as the modified Ponticelli protocol.[6] Emerging therapies, including adrenocorticotropic hormone and B-cell–depleting agents such as rituximab, have shown promising results in recent studies; however, optimal therapeutic selection remains challenging.

Membranous nephropathy also poses a significant challenge in the post-transplant setting, with reported recurrence rates of up to 40% following renal transplantation. Given the heterogeneity in clinical presentation, pathology, and outcomes, there is a need for region-specific data.

The objective of this study is to analyze the clinicopathological characteristics and clinical outcomes of membranous nephropathy in the study population, addressing the existing gap in comprehensive local data.

MATERIALS AND METHODS

Study Setting and Design: This prospective observational study was conducted in the Department of Nephrology, Narayana Medical College & Hospital, Nellore.

Study Period: The study was carried out over a period of 18 months following approval from the Institutional Ethics Committee.

Study Population and Sample Size: The study included all adult patients admitted to the Department of Nephrology with biopsy-proven membranous nephropathy (MN) who fulfilled the inclusion and exclusion criteria during the study period. A total of 51 patients were enrolled using a convenience sampling technique.

Inclusion Criteria

- Age between 18 and 75 years
- Both male and female patients
- Biopsy-proven membranous nephropathy
- Willingness to provide written informed consent

Exclusion Criteria

- Pregnant patients
- Patients unwilling to participate
- Patients with end-stage renal disease (eGFR<30 mL/min/1.73 m²)
- Patients not willing to provide informed consent

Study Procedure: Patients fulfilling the inclusion criteria were enrolled after obtaining written informed consent. A detailed clinical history was obtained, including symptoms such as edema, oliguria, abdominal distension, joint pain, early morning stiffness, skin rash, photosensitivity, breathlessness, weight loss, loss of appetite, hemoptysis, hematemesis, vomiting, altered bowel habits, and swelling. History of jaundice, blood transfusion, drug intake, and comorbid conditions such as hypertension and diabetes mellitus were documented.

A thorough clinical examination was performed, including blood pressure measurement in all four limbs and complete systemic examination. Hypertension was defined as blood pressure ≥140/90 mmHg.

Laboratory and Imaging Evaluation: All patients underwent routine urine examination, including assessment for proteinuria, red and white blood cells, and casts. Urine protein–creatinine ratio (UPCR) was measured. Hematological investigations included hemoglobin levels, total leukocyte count, differential count, and peripheral smear examination.

Biochemical investigations included fasting blood sugar, blood urea, serum creatinine, serum electrolytes, and lipid profile. Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft–Gault formula and expressed as mL/min/1.73 m². Liver function tests, including serum bilirubin and liver enzymes, were performed.

Urine and blood samples were collected for culture and sensitivity testing, and blood samples were

screened for malarial parasites. Viral serology screening for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus was performed in all patients. Where indicated, additional serological tests such as antinuclear antibody, anti–double-stranded DNA antibodies, and complement levels were evaluated.

Imaging studies included chest X-ray (posteroanterior view), electrocardiography, upper gastrointestinal endoscopy, stool examination for occult blood, abdominal ultrasonography, and renal ultrasonography to assess kidney size, cortical echogenicity, and corticomedullary differentiation. Selected patients underwent computed tomography of the chest, prostate-specific antigen testing (males), and mammography (females) to evaluate for secondary causes.

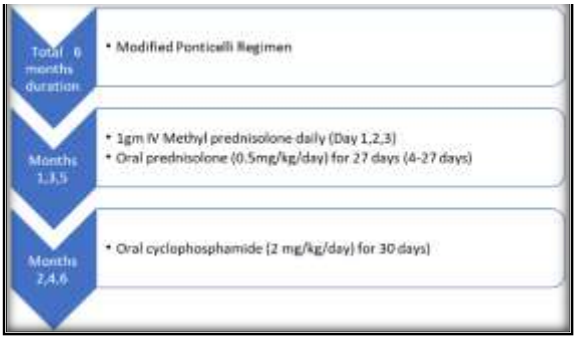
Histopathological Evaluation: Renal biopsy specimens were analyzed for histopathological features including C1q staining, interstitial nephritis, and tubular atrophy. Based on clinical, serological, and histopathological findings, patients were classified into primary or secondary membranous nephropathy. Secondary MN cases were further categorized according to the underlying etiology.

Treatment and Follow-up: Patients with primary MN were treated according to KDIGO guidelines. Those eligible received the Modified Ponticelli regimen, and treatment outcomes, including remission rates and renal function, were assessed during follow-up.

Modified Ponticelli Regimen: The Modified Ponticelli regimen consisted of cyclical corticosteroids and cyclophosphamide administered over six months:

- Months 1, 3, and 5: Intravenous methylprednisolone 1 g daily for 3 days (Days 1–3), followed by oral prednisolone at 0.5 mg/kg/day for 27 days (Days 4–30).
- Months 2, 4, and 6: Oral cyclophosphamide at 2 mg/kg/day for 30 days

Figure showing the modified Ponticelli Regimen:



Treatment Protocols: Patients with primary membranous nephropathy (MN) who were deemed unsuitable for immunosuppressive therapy after risk stratification were managed with NIAT regimen, a non-immunosuppressive anti-proteinuric treatment approach for MN. This regimen primarily focused on supportive therapy aimed at reducing proteinuria and preserving renal function.

Patients diagnosed with secondary membranous nephropathy were treated according to the NIH regimen, with therapy directed toward the underlying etiology in addition to supportive renal care.

All patients were followed up regularly. Clinical, biochemical, and histological parameters were compared between patients who achieved remission and those who did not. Patients who progressed to advanced stages of kidney disease, including end-stage renal disease (ESRD), were identified, and factors predictive of disease progression were analyzed.

Statistical Analysis: Data were entered into a structured proforma and analyzed using descriptive and inferential statistical methods. Continuous variables were expressed as mean ± standard deviation (SD) with minimum and maximum values, while categorical variables were presented as frequency and percentage. Intergroup comparisons of continuous variables were performed using analysis of variance (ANOVA). Categorical variables were compared using the Chi-square test. A p-value < 0.05 was considered statistically significant, and all statistical tests were conducted at a 5% level of significance.

RESULTS

A total of 51 biopsy-proven membranous nephropathy patients were included in the study. Approximately one-third of the study population belonged to the 30–39 years age group, followed by 23.53% in the 40–49 years group. Patients aged 20–29 years and 50–59 years each constituted 17.65%, while those aged 60 years and above accounted for less than 10% of the cohort. Both genders were equally represented.

Clinically, edema was observed in approximately 75% of patients, hypertension was present in nearly half of the study population, and diabetes mellitus was noted in 7% of patients. Primary MN constituted 80.39% of cases, whereas 19.61% were classified as secondary MN.

Regarding treatment modalities, 60.78% of patients received the Modified Ponticelli regimen, 19.61% were managed with the NIAT regimen, and all secondary MN cases were treated using the NIH regimen. Among patients with primary MN who received the Modified Ponticelli regimen, complete remission was achieved in 58.06% of cases.

Among the study population, age and gender showed a significant association with the type of membranous nephropathy. Primary MN was diagnosed at a significantly later age compared to secondary MN (mean age: 43.2 years vs 29.8 years, respectively), and this difference was highly statistically significant ($p < 0.0001$). Male predominance was observed in primary MN, with

58.53% of cases occurring in males, whereas male involvement in secondary MN was significantly lower (20%), and this association was statistically significant (p = 0.01). Hematuria was found to be significantly associated with secondary MN (p = 0.01). Remission rates differed significantly across treatment regimens, with a statistically significant difference observed between regimens (p<0.0001). The NIAT regimen demonstrated significantly higher remission rates compared to the Modified Ponticelli regimen.

Table 1: Clinical and laboratory parameters and C1Q staining according to primary and secondary disease

	Primary (n=41)	Secondary (n=10)	P value
Clinical parameters			
Male Gender	24 (58.53%)	2 (20%)	0.01
Edema	32 (78.04%)	7 (70%)	0.3
Diabetes	3(7.3%)	1 (10%)	0.32
HTN	18 (43.90%)	5 (50%)	0.37
Hematuria	22 (53.65%)	9 (90%)	0.01
Age	43.2 ± 11.9	29.8 ± 7.08	<0.0001
Laboratory parameters			
Hb	11.6±1.76	11.23 ± 1.86	0.5
Upcr	3.26 ± 1.9	3.69 ± 2.01	0.55
Sr. Creatinine	1.11 ± 0.5	1.53 ± 0.87	0.17
Egfr	70.52 ± 24.08	63 ± 33.91	0.52
Sr.Albumin	3.07 ± 0.95	3.62 ± 0.73	0.06
Total Cholesterol	209.24 ± 63.15	195.7 ± 62.74	0.05
RBS	131.92 ± 55.88	148.70 ± 67.20	0.47
C1Q staining			
1+	4 (9.75%)	4 (40%)	8 (15.68%)
2+	1 (2.43%)	3 (30%)	4 (7.84%)
3+	0 (0%)	3 (30%)	3(5.88%)
N	36 (87.80%)	0	36 (70.58%)

Table 2: Clinical parameters according to remission

	Remission (n=25)	No remission (n=16)	P value
Gender - Male	16 (64%)	8 (50%)	0.19
Edema	18 (72%)	14 (87.5%)	0.13
Diabetes	0	3 (18.75%)	0.02**
HTN	9 (36%)	9 (56.25%)	0.11
Hematuria	14 (53.84%)	12 (75%)	0.12
Age	40.47 ± 11.73	46.43 ± 11.93	0.09
Lab Profile			
Hb	11.90±1.65	11.04 ± 1.38	0.8
Upcr	3.32 ± 1.80	3.12 ± 2.06	0.74
Sr. Creatinine	1.08 ± 0.45	1.14 ± 0.58	0.7
eGFR	72.46± 23	68.26 ± 25.82	0.58
Sr.Albumin	2.77 ± 0.81	3.30 ± 0.99	0.06
Total Cholesterol	205.50 ± 64.31	210.38 ± 64.3	0.8
RBS	118.38 ± 33.50	152.0 ± 75.98	0.05

Table 3: Clinical parameters of Renal Impairment

	Renal Impairment (n=6)	Stable Renal Function (n=45)	P value
Gender - Male	3 (50%)	23 (51.11%)	0.99
Edema	6 (100%)	33 (73.33%)	0.09
Diabetes	2 (33.33%)	2 (4.44%)	0.04**
HTN	5 (83.33%)	18 (4%)	0.03**
Hematuria	4 (66.66%)	27(60%)	0.3
Age	41.66 ± 8.16	40.44 ± 12.88	0.75
Lab Profile			
Hb	10.76 ±1.27	11.63 ± 1.81	0.18
Upcr	1.64 ± 1.05	3.57 ± 1.89	0.003**
Sr. Creatinine	1.14 ± 0.94	1.20 ± 0.56	0.8
eGFR	77.71 ± 29.7	67.89 ± 25.7	0.46
Sr.Albumin	3.22 ± 1.03	3.17 ± 0.93	0.91
Total Cholesterol	231.53 ± 114.48	203.266 ± 53.65	0.57
RBS	215.00 ± 94.35	124.57 ± 42.65	0.06

Table 4. Complications in primary MN cases

Complications	Frequency	Percentage
DIDM	2	4.87
Leukopenia	1	2.43
LRTI	3	7.31
No	35	85.36
Grand Total	41	100

Renal Function and Outcomes: Assessment of renal function among the study population showed that 15.68% of patients had normal kidney function. Mildly reduced renal function was observed in 31.37% of patients. Moderate reduction without symptoms was seen in 23.52%, while moderate reduction with symptoms was noted in 17.64% of cases. Severe reduction in kidney function was present in 7.84%, and very severe reduction or kidney function insufficient to support bodily needs was observed in 3.92% of patients.

During follow-up, renal impairment developed in 11.76% of the study population. Urine protein–creatinine ratio (UPCR) emerged as the only significant predictor of renal impairment in patients with membranous nephropathy ($p = 0.003$).

Complications were observed in approximately 15% of patients with primary membranous nephropathy, whereas no complications were reported among secondary MN cases.

DISCUSSION

In the present study, the majority of patients belonged to the 30–39 years age group, followed by those aged 40–49 years, with fewer patients at the extremes of age. The mean age was 40.5 ± 12 years, indicating that membranous nephropathy (MN) predominantly affects individuals in early to middle adulthood in our population. This finding is comparable to the study by Subramanian et al. (2020), which reported a median age of 34 years among adult patients, though their cohort included a wider age range extending into pediatric patients.[7]

Gender distribution in the present study showed equal representation of males and females, contrasting with several earlier reports demonstrating male predominance. For instance, Liang et al. (2023) reported a male-to-female ratio of 1.39:1.[8] The absence of a strong male predominance in our cohort may reflect regional or referral-based variations.

Clinically, edema was present in approximately three-fourths of patients, while hypertension was observed in nearly half, and diabetes mellitus was seen in only 7% of cases. These findings are broadly consistent with prior studies, although the prevalence of hypertension in our study was lower than that reported by Hemanth Kumar et al. (2022), where 65% of patients were hypertensive.[9] Variability in comorbidity burden may reflect differences in population characteristics and duration of disease at presentation.

In the present study, primary MN constituted 80.39% of cases, with secondary MN accounting for 19.61%, findings comparable to Subramanian et al., who reported 76% primary and 24% secondary MN. In contrast, Liang et al. reported exclusively idiopathic MN, likely reflecting differences in study design and exclusion of secondary causes.

Regarding treatment, 60.78% of patients received the Modified Ponticelli regimen, while 19.6% of primary MN patients were managed with NIAT, and secondary MN patients received NIH regimen. Treatment distribution differed from studies such as Liang et al., where various immunosuppressive and conservative regimens were employed, emphasizing the heterogeneity of therapeutic approaches across centers.

In our cohort, 58.06% of primary MN patients treated with the Modified Ponticelli regimen achieved complete remission, while patients managed with NIAT showed higher remission rates (70%), with a statistically significant difference between regimens ($p<0.0001$). These findings align with existing literature demonstrating higher remission rates with immunosuppressive therapy compared to conservative management, as reported by Liang et al. and Hemanth Kumar et al., though direct comparison is limited due to differences in patient selection and risk stratification.

Age and gender were significantly associated with disease type. Primary MN was diagnosed at a later age (mean 43.2 years) compared to secondary MN (mean 29.8 years), and male predominance was more pronounced in primary MN, whereas secondary MN showed significantly lower male involvement. Hematuria and positive C1q staining were significantly associated with secondary MN, consistent with immune-complex–mediated secondary causes such as lupus nephritis.

With respect to predictors of remission, absence of diabetes mellitus emerged as the only significant clinical predictor in our study. Laboratory parameters did not significantly predict remission, in contrast to Liang et al., who identified UPCR as a predictor, and Hemanth Kumar et al., who found baseline proteinuria to be significantly lower among responders. These differences highlight the multifactorial nature of remission and the influence of population-specific factors.

Renal function assessment showed that while a substantial proportion of patients had mild-to-moderate reduction in kidney function at presentation, chronic kidney disease developed in 11.76% during follow-up. Hypertension, diabetes mellitus, and elevated UPCR were significant

predictors of renal impairment, with UPCR being the strongest independent predictor, underscoring the importance of proteinuria control in MN. Similar observations have been reported in previous studies emphasizing proteinuria as a key determinant of long-term renal outcomes.

Complications were observed in approximately 15% of patients with primary MN, whereas no complications were noted in secondary MN cases, possibly reflecting closer etiological targeting and shorter disease duration in secondary MN.

CONCLUSION

The present study demonstrates that primary membranous nephropathy constitutes the majority of MN cases, with secondary MN accounting for nearly one-fifth of patients. Younger age at onset, female gender, hematuria, and positive C1q staining were significant predictors of secondary MN. Higher remission rates were observed in secondary MN, and absence of diabetes mellitus was a significant predictor of remission. Chronic kidney disease developed in 11.76% of patients, with hypertension, diabetes, and elevated UPCR serving as significant predictors of renal impairment. Complications were observed exclusively among patients with primary MN. These findings emphasize the importance of comprehensive clinicopathological evaluation and individualized risk-based management in membranous nephropathy.

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