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Membranous glomerulonephritis: a retrospective study on prognostic outcome

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Abstract

Background: Membranous glomerulonephritis (MGN) is one of the most common causes of nephrotic syndrome in non-diabetic adults, accounting for up to one-third of biopsy diagnostics in some regions. A watchful waiting strategy has been adopted to accurately assess the success of MGN. In this study, we predict prognostic risk factors for primary MGN patients for effective intervention.

Materials and Methods: This is a retrospective study design involving 125 biopsy-proven MGN subjects on follow-up from January 2012 to October 2019 in Hospital Serdang and Hospital Kuala Lumpur, Malaysia.

Result and Conclusion: After the median follow-up of 36 (15.0-57.0) in months, 26 (20.8%) consisting of 17 (13.6%) primary MGN and 9 (7.2%) secondary MGN subjects achieved complete remission while 17 (13.6%) and 10 (8.0%) of primary and secondary MGN subjects respectively achieved spontaneous remission. Subjects with nephrotic range proteinuria have 2.917 odds more at risk of primary MGN while subjects with hypertension have 2.417 odds risk of primary MGN compared to those with no hypertension at presentation. Multiple logistic regression models retained only factors directly associated with MGN with only nephrotic range proteinuria associated with primary MGN. Those with nephrotic range proteinuria were 3.04 times the odds of primary MGN when compared with those without nephrotic syndrome (95% C. I = 1.089, 8.472).

The nephrotic syndrome could be used to determine the prognosis in patients with primary MGN especially those at risk of end-stage renal disease.

Keywords: Membranous glomerulonephritis; remission; nephrotic syndrome; chronic kidney disease, end-stage renal diseases.

Introduction

One of the leading causes of nephrotic syndrome in non-diabetic adults, accounting for up to one-third of biopsy diagnoses in some areas (1). The time frame between the manifestation of cancer and the diagnosis of MGN is between the ages of 52 and 65 years, respectively (2). Patients may undergo remission or have chronic proteinuria without developing renal dysfunction or may develop an end-stage renal disease (ESRD). Thirty per cent renal survival was reported in patients who were not in remission, 100% in those who were in complete remission, and greater than 70% in those who were in partial remission (3,4).

A watchful waiting strategy has been adopted to accurately assess the progress of MGN. This entails measuring urinary protein and creatinine clearance every 24 hours for at least 6 months and comparing the results to nephrotic range proteinuria levels (5).

At present, there is not enough data on the prognosis of patients with nephrotic syndrome secondary to membranous nephropathy. Nevertheless, reduction in proteinuria is related to achieving remission in primary MGN (6,7). In addition, studies were conducted on the same patients to determine the prognosis using M-type phospholipase A2 receptors (M-PLA2R) and Thrombospondin domain-containing type 7 A (THSD7A) demonstrated a direct relationship with proteinuria (8). In this study,

we predict prognostic risk factors for primary MGN patients for effective intervention. In addition, clinicians will benefit from this prediction tool in assessing the risk variables directly linked to primary MGN patients and determining who need more intensive therapies and regular follow-up.

2. Materials and Method

2.1 Study design

This is a retrospective study design involving biopsy-proven primary MGN on follow-up from January 2012 to October 2019 in Hospital Serdang and Hospital Kuala Lumpur, Malaysia. Ethical approval was obtained from the National Medical Research Register (NMRR-18-3245-44092). To ensure confidentiality of the data collected in the proforma, each subject was coded and blinded to its clinical data.

2.2. Methodology

2.2.1. Data collection

Patients' information was obtained from the library information system in Hospital Serdang and Kuala Lumpur as shown in figure 1. Electron microscopy was used to classify the biopsy as either primary or secondary MGN. Besides, clinical parameters were used to rule out secondary involvement (MGN with associated chronic conditions such as hepatitis B virus infection, diabetes nephropathy, malignancy, and lupus nephritis type V). In contrast, those with no known associated conditions were considered primary MGN.

One hundred and twenty-five patients were diagnosed with MGN from January 2012 to October 2019 at hospitals in Serdang and Kuala Lumpur. General information such as age, sex and contacts of subjects were obtained from the hospitals' databases.

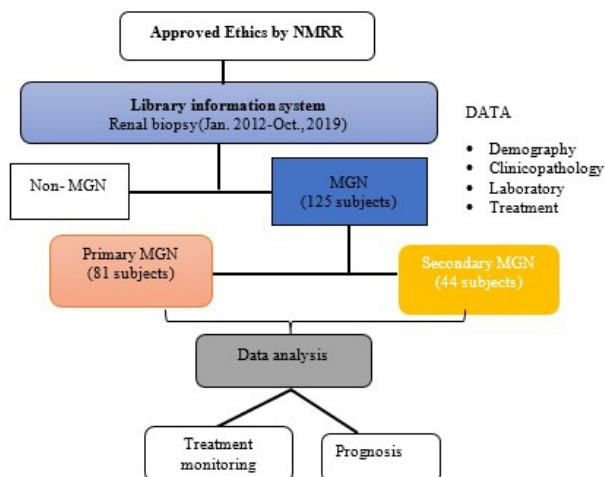


Figure 1: Flow chart of events from ethical approval to data analysis.

2.2.2. Cut-off points value for laboratory parameters

Complete remission and no remission were defined as 0.03g/mmol and > 0.03g/mmol, respectively, according to Kidney Disease Improving Global Outcome (KDIGO) (9). Serum albumin levels of 35g/L were considered low, while serum urea and creatinine levels of 2.76-8.07mmol/L and 44-80 mol/L, respectively. The Estimated Glomerular Filtration Rate (eGFR) was defined as follows: > 90, 60-89, 45-59, 30-44, 15-29 and 15mL/min/1.73m² for normal, chronic kidney disease stage I (CKD 1), CKD 2, CKD 3, CKD 4 and CKD 5 respectively, calculated using the CKD-EPI Creatinine 2009 Equation.

2.3. Data Analysis

The data was analysed using IBM SPSS statistics for the MacBook (SPSS version 25.0). Normally distributed continuous variables were expressed as mean SD, while non-normally distributed variables were expressed as median (interquartile). Simple and multiple regression analyses were conducted to determine the factors associated with MGN, validated by the ROC curve. At $p < 0.05$, differences were considered statistically significant.

3. Results

3.1. General characteristics of subjects

3.1.1 Socio-demographic characteristics of subjects.

The median age at diagnosis was 45.0 (29.5-58.5) years. Figure 2 shows that primary MGN was the most common, accounting for 81 (63.2%) of all MGN, while lupus nephritis was the most common cause of secondary MGN, responsible for 23.2% of all MGN. Other causes of secondary MGN include hepatitis B virus infection (4%), hepatitis C virus infection (0.4%),

diabetes mellitus (1.6%), malignancy (3.6%) and others like sarcoidosis, rheumatoid arthritis, and drugs.

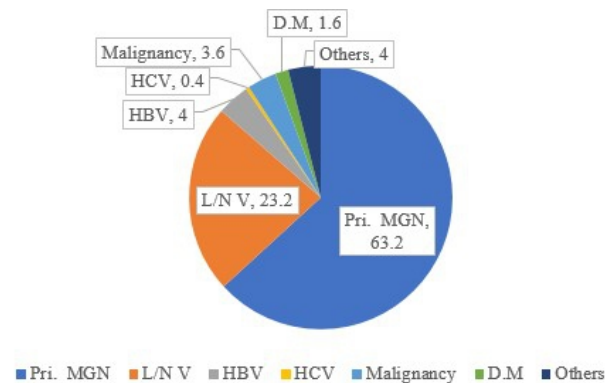


Figure 2: Percentages of primary MGN and secondary MGN with a detailed aetiological proportion.

Table 1 depicts a strong association between MGN and age at diagnosis. In contrast to primary MGN, which was associated with subjects aged 50-60 years ($\chi^2 = 19.940$, $p = 0.001$), secondary MGN is associated with subjects aged 30 years ($p = 0.001$). In addition, females were significantly associated with secondary MGN 33 (51.6%) ($\chi^2 = 14.391$, $p < 0.001$). Secondary MGN was more associated with Malay ethnic group 34 (45.9%) ($\chi^2 = 9.787$, $p = 0.007$). Primary MGN was significantly associated with other ethnic groups 19 (86.4%) and the Chinese population 22 (75.9%).

Table 1. Association between socio-demographic factors and MGN

Variables	Primary MGN n=81(%)	Secondary MGN n=44(%)	χ^2	*P-value
Age at Diagnosis (years)			19.940	0.001*
≤ 30				
31-40	13(38.2)	21(61.8)		
41-50	13(65.0)	7(35.0)		
51-60	10(58.9)	7(41.1)		
61-70	24(88.9)	3(11.1)		
> 70	11(73.3)	4(26.7)		
	10(83.3)	2(16.7)		
Gender:			14.391	<0.001*
Male	50(82.0)	11(18.0)		
Female	31(48.4)	33(51.6)		
Ethnicity:			9.787	0.007*
Malay	40(54.1)	34(45.9)		
Chinese	22(75.9)	7(24.1)		
Others	19(86.4)	3(13.6)		

Categorical variables were expressed in frequencies (percentage) and compared by chi-square value (χ^2), significance level $p < 0.05$

3.1.2. Clinico-pathological parameters of subjects (n=125) at presentation

Nephrotic range proteinuria and haematuria were seen among 63 (72.4%) and 14 (66.7%) primary MGN subjects respectively. Table 2 shows 47 (74.6%) primary MGN and 16 (25.4%) secondary MGN presented with hypertension.

The urea test at presentation was high among 20.0% and 6.4% of subjects with primary and secondary MGN respectively, while

67 of the 125 subjects presented with high creatinine levels, most of whom (53 of 67) belonged to primary MGN. Low albumin levels at presentation were seen in 45.6% of primary MGN subjects and 20.0% of secondary MGN subjects. For eGFR level at presentation, 26 of the 125 subjects had a moderately high level of eGFR while 16 of the 125 had a severely high level of eGFR, whereas the UPCr Index at presentation was very high in 63% and 16% of subjects with primary and secondary MGN. Nephrotic range proteinuria was found to be more significantly associated with primary MGN 63 (72.4%) than secondary MGN 24 (27.6%) ($\chi^2 = 7.273$, $p = 0.007$), whereas haematuria 14, (66.7%) was found to be more associated with primary MGN ($\chi^2 = 5.351$, $p = 0.025$). Likewise, hypertension and serum creatinine were more associated with primary MGN ($\chi^2 = 7.273$, $p = 0.021$) and ($\chi^2 = 12.953$, $p = 0.001$) respectively. Compared to secondary MGN, moderately and severely low eGFR were more significantly associated with primary MGN ($\chi^2 = 8.128$, $p = 0.043$).

Table 2. Association between clinicopathological data and MGN

Variables	Primary MGN n=81(%)	Secondary MGN n=44(%)	χ^2	P-value
Nephrotic range proteinuria:			7.273	0.007*
Absent	18(47.4)	20(52.6)		
Present	63(72.4)	24(27.6)		
Haematuria:			5.351	0.025*
Absent	67(64.4)	37(35.6)		
Present	14(66.7)	7(33.3)		
Hypertension:			7.273	0.021*
Absent	34(54.8)	28(45.2)		
Present	47(74.6)	16(25.4)		
Albumin (g/L):			2.321	0.128
Low	57(69.5)	25(30.5)		
Normal	24(55.8)	19(44.2)		
Creatinine (μmol/L):			12.953	< 0.001*
Normal	28(48.3)	30(51.7)		
High	53(79.1)	14(20.9)		
Urea (mmol/L):			2.360	0.124
Normal	56(60.9)	36(39.1)		
Abnormal	25(75.8)	8(24.2)		
UPCr Index (g/mmol):			5.223	0.073
Normal	10(45.5)	12(54.5)		
Moderately High	20(62.5)	12(37.5)		
Severely High	51(71.8)	20(28.2)		
eGFR (mL/min/1.73m²):			8.128	0.043*
Normal	30(51.7)	28(48.3)		
Mild	19(76.0)	6(24.0)		
Moderate	20(76.9)	6(23.1)		
Severe	12(75.0)	4(25.0)		

Categorical variables were expressed in frequencies (percentage) and compared by chi-square (χ^2), urine protein creatinine index (UPCr Index), estimated Glomerular Filtration Rate (eGFR) normal ≥ 90 , mild = 60-89 (mL/min/1.73m²), moderate=30-59 (mL/min/1.73m²), high= < 30 (mL/min/1.73m²), significant level $p < 0.05$ *

3.2. The outcome of subjects (n=125) at the end of follow-up

Table 3 shows the outcome of subjects at the end of follow-up. After the median follow-up of 36 (15.0-57.0) months, 26 (20.8%) consisting of 17 (13.6%) primary MGN and 9 (7.2%) secondary MGN subjects achieved complete remission with immunosuppressive therapy while 17 (13.6%) and 10 (8.0%) of primary and secondary MGN subjects respectively achieved complete remission without immunosuppressive therapy. Of the total subjects that achieved partial remission, 47 (36.6%), 26 (20.8%) were of the primary type, while 21 (16.8%) belonged to the secondary MGN. In addition, 21 (16.8%) and 4 (3.2%) belong to both primary and secondary MGN, yet to achieve remission.

Primary MGN subjects were responsible for 55 (44.0%) of the high-risk eGFR 88 (70.4%) while the remaining were due to

secondary MGN.

Table 3. Subjects (n= 125) outcome at the end of follow-up

Variable	Primary		Secondary	
	Frequency/Median	Percentage/Interquartile	Frequency/Median	Percentage/Interquartile
Follow-up (months)	39.0	17.5-59.5	27.5	13.0-49.8
Remission				
Complete (with IT)	17	13.6	9	7.2
Complete (without IT)	17	13.6	10	8.0
Partial	26	20.8	21	16.8
No remission	21	16.8	4	3.2

Immunosuppressive therapy (IT)

3.3. Risk factors for primary MGN

Table 4 shows the results of a multivariate logistic analysis of factors associated with MGN among subjects on follow-up at Hospital Serdang and Hospital Kuala Lumpur. Following univariate logistic regression, the multiple logistic regression was done to determine the factors that are directly linked to primary MGN. In this case, only nephrotic range proteinuria was directly associated with primary MGN. Therefore, subjects with nephrotic range proteinuria had 3.04 times the odds of primary MGN compared to those without nephrotic range proteinuria (95% C. I = 1.089, 8.472).

Table 4: Multivariate logistic regression analysis of factors associated with primary MGN.

Variables	B -Coefficient	S. E	AOR	C. I (95%)	p-value
Age at diagnosis:					0.175
≤ 30					
31-40	0.449	0.699	1.57	0.398-6.164	0.521
41-50	0.301	0.686	1.35	0.352-5.185	0.661
51-60	1.756	0.758	5.79	1.308-25.593	0.021
61-70	1.324	0.805	3.76	0.776-18.203	0.100
> 70	1.458	0.984	4.30	0.624-29.561	0.139
Gender:					
Male			1.00		
Female	-0.935	0.485	0.39	0.152-1.015	0.054
Ethnicity:					0.099
Others			1.00		
Malay	-1.695	0.867	0.18	0.034-1.004	0.051
Chinese	-0.952	0.952	0.39	0.060-2.494	0.317
Nephrotic syndrome:					
Absent			1.00		
Present	1.111	0.523	3.04	1.089-8.472	0.034*
Hypertension					
Absent			1.00		
Present	-0.089	0.501	1.09	0.410-2.910	0.858

S. E= standard error, C. I= confidence interval, AOR= Adjusted Odd Ratio, significant value < 0.05*

4. Discussion

4.1. General characteristics of the subjects

The proportion of primary and secondary MGN varies from one region to another, most reported within 70-80% and 20-30% for primary and secondary MGN respectively (10-14). In addition, the male to female for MGN was 2-3:1 in favour of men in most studies. These values are slightly in contrast with the values obtained from this study, which put the proportion of MGN at 63.4% and 36.6% for both primary and secondary MGN, respectively, and a male to female ratio of 1:1.1 with a slight female predominant. The reason may not be unconnected to the

high prevalence of lupus nephritis in Malaysia (15). While primary MGN was thought to be common among Caucasians and Southeast Asians globally, it was reported more frequently among Malay and Chinese in Malaysia (15,17-19) (5,16).

Studies have shown that patients with advanced age, low albumin, haematuria, abnormal creatinine, urea and eGFR are at risk of progressing to ESRD (24-26). Like other studies (18,20), this study also demonstrated that nephrotic syndrome was the most common presentation among adults with MGN. Haematuria was also a common presentation, especially among individuals with the nephritic-nephrotic syndrome (21-23), while hypertension was seen mostly as a complication when there is renal compromise or in the acute form of MGN, occurring in up to 30% of cases (9,22) similar as in this study where it was reported in 37.6% of subjects with primary MGN.

It is important to note that the urine protein creatinine index (UPCr Index) was considered a prognostic laboratory parameter for MGN because the nephrotic syndrome is the most common presentation and, therefore, a low UPCR Index is associated with good prognosis (remission) and vice versa (9,27).

Treatment of MGN patients depends on the type and presentation. Patients with lower eGFR and UPCR Index were considered low risk and therefore benefited from supportive therapy or watchful waiting techniques (5). Immunosuppressive therapy is initiated only when there is a high risk of progression to ESRD, as evidenced by a creatinine level doubling within 6 months of presentation, a UPCR Index > 8g/g, and persistence proteinuria (28). Hence, the reason why most of the subjects in this study received either supportive therapy or nothing. Furthermore, it is important to delay the immunosuppressive therapy by 6 months since it was reported that one-third of patients with primary MGN can achieve remission within 6 months. This claim can be supported by this study where 21.6% of the total 125 subjects achieved remission without any immunosuppressive therapy and another study by Perrine Jullien, *et al.*, (2017) where 22% achieved spontaneous remission (28).

4.2. Predictors of MGN

Although most of the clinical presentations of MGN (especially primary MGN) are not specific, there are some specific clinical presentations, including laboratory parameters associated with the severity of kidney disease as mentioned earlier. Nephrotic syndrome, especially in adults, was found to be a major risk factor for the primary MGN in this study. The finding supported the idea that nephrotic syndrome is the most common symptom and is also linked to remission (6).

5. Conclusions

Nephrotic syndrome is the most common presentation in primary MGN and could be used to determine the prognosis in patients with primary MGN. This will assist in early intervention, thereby preventing or reducing the rate of progression of primary

MGN patients to ESRD.

6. Limitation of the studies

The study is retrospective in nature, which makes access to certain information such as survival analysis very difficult since the follow-up period was not uniform.

7. Author Contributions:

The conceptualization of this study was done by Sadiq Mu'azu Maifata and Fauzah Abd Ghani.; methodology, Sadiq Mu'azu Maifata and Fauzah Abd Ghani; validation, Nor Fadhlin Zakaria., Fauzah Abd Ghani and Rafidah Hod; formal analysis, Sadiq Mu'azu Maifata; investigation, Nor Fadhlin and Sadiq Mu'azu Maifata; resources, Fauzah Abd Ghani; data curation, Sadiq Mu'azu Maifata.; writing—original draft preparation, Sadiq Mu'azu Maifata; writing—review and editing, Nor Fadhlin Zakaria, Rafidah Hod and Fauzah Abd Ghani; visualization, Sadiq Mu'azu Maifata; supervision, Fauzah Abd Ghani, Rafidah Hod and Nor Fadhlin Zakaria; project administration, Fauzah Abd Ghani; funding acquisition, Fauzah Abd Ghani and Nor Fadhlin Zakaria.

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