Introduction: There have been few studies comparing younger and older adults with membranous nephropathy. The objective of this study was to compare younger and older patients with membranous nephropathy, in terms of the clinical, etiological, remission, and survival data. Method: This was a retrospective study of patients with membranous nephropathy who underwent renal biopsy between 2009 and 2017. Results: We included 214 patients with membranous nephropathy. At diagnosis, 169 (79%) of those patients were <60 years of age and 45 (21%) were ≥60 years of age. There was a predominance of males in both groups. The degree of proteinuria and the prevalence of hematuria did not differ significantly between the groups. However, the median serum creatinine level was higher in the ≥60-year group as was the prevalence of hypertension. Of the patients evaluated, 36 (16.8%) had secondary membranous nephropathy. Although the proportions of infectious and autoimmune causes were comparable between the two groups, neoplastic etiologies were more common in the ≥60-year group. A total of 86 in the <60-year group and 25 in the ≥60-year group were followed long term, and partial or complete remission was achieved in 68.5% and 68.0% of the younger and older patients, respectively. However, whom progressed to requiring dialysis eight (9.3%) were in the <60-year group patients and eight (32.0%) of the ≥60-year group patients (p = 0.0045). Conclusion: Despite having worse renal function at diagnosis, older patients with membranous nephropathy appear to have remission rates comparable to those of younger patients with the disease, which demonstrates the benefits of seeking diagnosis and treatment.

Glomerulopathy is the third leading cause of chronic kidney disease (CKD) requiring dialysis, in Brazil and worldwide, the first and second leading causes being diabetic kidney disease and hypertension, respectively [1]. Among the various types of glomerulopathy, membranous nephropathy (MN) is notable because it is one of the main etiologies of nephrotic syndrome in adults without diabetes [2].
Nephrotic syndrome is the indication for approximately 35.5% of all renal biopsies, regardless of patient age. The main etiology of nephrotic syndrome in children under 10 years of age is minimal change disease, whereas it is MN in individuals over 30 years [3–5]. Most epidemiological studies that involve renal biopsy show MN to be the main glomerulopathy diagnosed in older adults [4, 5]. In one such study, Cameron [4] evaluated patients with nephrotic syndrome who were over 60 years of age. The author found that the main etiology was MN, which was identified in 35% of the cases, followed by minimal change disease, in 16%, and amyloidosis, in 12%.

Approximately 70% of cases of MN are associated with the antibody against the M-type phospholipase A2 receptor (PLA2R), which is expressed on podocytes, and 20% are associated with secondary causes, including infection, autoimmune diseases, medications, and neoplastic etiologies, the last being more common in older individuals [6].

Studies evaluating MN in different age groups, especially studies comparing young people with older people, are scarce. In a multicenter study conducted in Japan, Yamaguchi et al. [7] identified 171 patients with primary MN, of whom 90 (52.6%) were under 65 years of age, 40 (23.4%) were 65–70 years of age, and 41 (24%) were ≥71 years of age. The authors found that serum albumin was lower, and serum creatinine and the incidence of pleural effusion were higher in both of the older age groups. The authors also found that the rate of complete remission was comparable across the age groups, although the patients ≥71 years of age were statistically more likely to be hospitalized for infection. Cattran et al. [8] evaluated 323 patients with primary MN, comparing those <60 years of age and ≥60 years of age, and observed a predominance of White males in both groups. The authors found that creatinine clearance was significantly lower in the older patients, although they detected no difference between the two groups in terms of the progression to CKD or death.

The renal survival of patients with MN, with the use of various treatments that we have today, still varies from 5 to 20% of complete remission of the disease, 25 to 50% of a partial remission, and 10 to 25% that progress to stage V of CKD [2]. Treatment includes initial supportive care such as blood pressure control, salt restriction, use of medications that block the renin-angiotensin-aldosterone system, combating smoking, combating obesity, and dyslipidemia [2, 9]. Patients with indication to start immunosuppression are those who, after 6 months of the initial treatment described above, persist with proteinuria ≥4 g/day, or those who at any time presented complications of the nephrotic syndrome or loss of creatinine clearance [9]. The quantification of anti-PLA2R seems to have a predictive value of disease remission when in low serum titers or in decline over the months of monitoring [10].

The objective of the present study was to evaluate the epidemiological profile of patients with MN diagnosed at a single center. We determined the proportional distribution by the age group (<60 years of age and ≥60 years of age), comparing the age groups in terms of clinical data, renal histology, etiology (primary or secondary), and evolution during the follow-up.

Methods

This was a retrospective study of data obtained from the medical records of all patients diagnosed with MN after renal biopsy, between 2009 and 2017, at the Hospital das Clínicas, in the city of São Paulo, Brazil. The patients were followed in the Nephrology Department of the Hospital, where the clinical, epidemiological, biochemical, and renal biopsy data were evaluated.

Inclusion Criteria

Patients aged 18 years and over, both sexes, who underwent renal biopsy with a diagnosis of MN within the established period, were included in the study. The division of groups into younger and older was defined according to law n° 10,741 of the Ministry of Health of Brazil, where the elderly is considered from the age of 60 years or more.

Exclusion Criteria

Patients for whom the medical records were incomplete were excluded, as were those for whom the renal biopsy sample was deemed insufficient, less than nine glomeruli. We also excluded patients who had previously been diagnosed with systemic lupus erythematosus (SLE) or were diagnosed with SLE on the basis of the renal biopsy findings. Patients with SLE were excluded because such patients typically have a long history of disease and immunosuppression.

Laboratory Analysis

The following parameters were evaluated at the time of renal biopsy: 24 h proteinuria, by the automated colorimetric method; urinalysis; serum creatinine, by the kinetic colorimetric method; estimated glomerular filtration rate (eGFR) [11], as calculated with the CKD Epidemiology Collaboration equation; complement C3 and C4, by the immunoturbidimetric method, with reference values of 90–180 mg/dL and 10–40 mg/dL, respectively; serology for hepatitis B, hepatitis C, and HIV; the Venereal Disease Research Laboratory test result; antinuclear factor; rheumatoid factor; serum proteins, by immunofixation; anti-DNA antibodies; and blood pressure. Hematuria was defined as the presence of ≥10 red blood cells per field in two urinalyses; hypertension was defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or both [12]; and CKD was defined as an eGFR ≤60 mL/min/1.73 m² for more than 3 consecutive months [13].
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Findings were inconclusive. Cases (those in which the microscopy or immunofluorescence. Electron microscopy was performed in only a few cases). Under light microscopy were the presence of glomerular crescents, tubulointerstitial alterations, and vascular lesions, whereas immunoglobulin deposition and complements were analyzed by immunofluorescence. The variables analyzed considered representative and were analyzed under light microscopy but excluded from the final analysis. At the end of the follow-up period, which varied among cases, the patients were evaluated to determine whether the MN was in remission. Complete remission was defined as a serum creatinine level equal to or lower than the baseline level, with proteinuria below 0.3 g/day, and partial remission was defined as a serum creatinine level ≤25% higher than the baseline level, with proteinuria 0.3–3.5 g/day. Patients who did not meet any of those criteria were categorized as nonresponders.

### Statistical Analysis
Continuous variables were expressed as mean and standard deviation or as median and interquartile range as appropriate, whereas categorical variables were expressed as absolute and relative frequencies. Two-group differences, for continuous variables, were identified by the unpaired Student’s t test or the Mann-Whitney test, as appropriate. For categorical variables, those differences were identified by the Fisher’s exact test. To assess the risk of progressing to dialysis, we performed a multivariate analysis using binary logistic regression. Values of statistical significance were considered when p < 0.05. The statistical analysis was performed with GraphPad Prism software, version 6.0 (GraphPad Software, Inc., San Diego, CA, USA).

### Ethics
The study was approved by the Ethics Committee of Hospital das Clinicas de São Paulo, number 4,327,317. As this is a retrospective study that only evaluated medical records, the ethics committee was asked to release the use of informed consent, which was supported by this committee. Research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

### Results
During the study period, a total of 232 patients were diagnosed with MN by renal biopsy at the Hospital das Clinicas. Eighteen patients were excluded: 13 because they had SLE (previously diagnosed or diagnosed at the time of renal biopsy); and five because their medical records were incomplete or because the renal biopsy sample was insufficient. Therefore, the sample comprised 214 patients with biopsy-proven MN. In the sample as a whole, the mean age at diagnosis was 45.70 ± 15.71 years (range, 13–83 years). Of the 214 patients evaluated, 133 (62.1%) were male and 134 (62.6%) were White. Only 1 patient (0.46%) was Asian. The median serum creatinine level was 1.00 mg/dL (0.80–1.79), the median serum albumin level was 1.88 g/dL (1.30–2.60), and the median level of proteinuria was 6.00 g/day (3.15–8.84). Hematuria was identified in 77 (35.9%) of the patients. At diagnosis, 106 patients (49.5%) had a history of hypertension, seven (3.2%) had a history of diabetes mellitus, and three (1.4%) had a family history of glomerular disease.

We found that 36 (16.8%) of the 214 patients had secondary MN. Among those 36 patients, men accounted for 61.1% (n = 22), the mean age was 48.58 ± 14.42 years, the mean proteinuria was 5.90 ± 3.61 g/day, the mean serum albumin level was 2.12 ± 0.83 g/dL, the median serum creatinine level was 1.15 mg/dL (0.84–2.15), and hematuria was identified in 22 (61.1%) of the patients. At diagnosis, 106 patients (49.5%) had a history of hypertension, seven (3.2%) had a history of diabetes mellitus, and three (1.4%) had a family history of glomerular disease.

### Table 1. Etiology of secondary membranous nephropathy

| Etiology                        | n (%)  |
|--------------------------------|--------|
| Infection, n (%)               |        |
| Hepatitis B                    | 5 (13.9) |
| Syphilis                       | 5 (13.9) |
| Schistosomiasis                | 3 (8.3)  |
| HIV                            | 3 (8.3)  |
| Hepatitis C                    | 2 (5.6)  |
| Tuberculosis                   | 1 (2.8)  |
| HIV + hepatitis B              | 1 (2.8)  |
| Solid tumors, n (%)            |        |
| Lung cancer                    | 2 (5.6)  |
| Prostate cancer                | 2 (5.6)  |
| Duodenal adenocarcinoma        | 1 (2.8)  |
| Carcinoma of the tongue        | 1 (2.8)  |
| Breast cancer                  | 1 (2.8)  |
| Kidney cancer                  | 1 (2.8)  |
| Autoimmune disease, n (%)      |        |
| Rheumatoid arthritis           | 3 (8.3)  |
| Antiphospholipid antibody syndrome | 1 (2.8) |
| Hematologic cancer, n (%)      |        |
| Non-Hodgkin lymphoma           | 1 (2.8)  |
| Acute myeloid leukemia         | 1 (2.8)  |
| Hematologic disease, n (%)     |        |
| Aplastic anemia                | 1 (2.8)  |
| Beta-thalassemia minor         | 1 (2.8)  |
cases (55.5%); solid tumors, in eight (22.2%); rheumatologic diseases, in four (11.1%); hematologic cancer, in two (5.5%); aplastic anemia, in one (2.8%); and beta-thalassemia minor, in one (2.8%). One patient with MN secondary to syphilis was also diagnosed with Alport syndrome, by genetic studies and electron microscopy of the renal biopsy sample.

At diagnosis, 45 (21%) of the 214 patients were ≥60 years of age, with a mean age of 67.51 ± 6.25 years, and 169 (79%) were <60 years of age, with a mean age of 39.89 ± 11.89 years. As can be seen in detail in Table 2, there were no significant differences between the ≥60-year group and the <60-year group in terms of the proportion of males, the median level of proteinuria, the median serum albumin level, or the prevalence of hematuria. However, the mean serum creatinine at diagnosis was higher in the ≥60-year group, as was the prevalence of hypertension.

The proportions of infectious and autoimmune causes of MN were comparable between groups (Table 2). However, the proportion of neoplastic causes (solid tumors + hematological cancer) was higher in the ≥60-year group than in the <60-year group – 11.1% versus 2.9% (p = 0.02).

Under light microscopy, beyond the observation of membrane spikes and thickening of the glomerular capillary walls, we identified some degree of interstitial fibrosis in 66 (30.8%) of the 214 biopsy samples, acute tubular necrosis (ATN) in 53 (24.7%), vascular involvement in 34 (15.8%), tubulointerstitial nephritis in five (2.3%), glomerular crescents in four (1.8%), glomerulosclerosis in three (1.4%), and collapsing glomerulopathy in one (0.46%). There were no statistically significant differences between the two age groups in terms of the light microscopy findings (Table 3).

Among the patients with ATN, the median serum creatinine at diagnosis was 1.55 mg/dL (0.75–2.38) in the ≥60-year group and 1 mg/dL (0.78–1.38) in the <60-year group (p = 0.22), with an improvement of serum creatinine levels during the follow-up just in 6.2 and 13.5% in these patients, respectively. Interstitial fibrosis renal involving ≥30% occurred in 5 patients in the ≥60-year group and eight in the <60-year group (p = 0.11), four in

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**Table 2. Comparison between the age groups, at diagnosis, and during follow-up**

| Characteristic | Age group | p value |
|---------------|-----------|---------|
|               | ≥60-year  | <60-year |       |
|               | (n = 45)  | (n = 169) |       |
| Male, n (%)   | 30 (66.6) | 102 (60.3) | 0.43  |
| Age, years, mean±SD | 67.51±6.25 | 39.89±11.89 | <0.0001 |
| Type of MN, n (%) | | | |
| Primary       | 36 (80.0) | 142 (84.0) | 0.46  |
| Secondary     | 9 (20.0)  | 27 (16.0)  | 0.32  |
| Hematuria, n (%) | 19 (42.2) | 58 (34.3)  | 0.56  |
| Proteinuria (g/day), median (IQR) | 6.0 (3.3–8.0) | 6.2 (3.0–9.0) | 0.09  |
| Serum albumin (g/dL), median (IQR) | 1.70 (1.40–2.20) | 2.00 (1.30–2.75) | 0.0011 |
| Baseline serum creatinine, mg/dL, median (IQR) | 1.50 (1.00–2.36) | 1.00 (0.75–1.40) | <0.0001 |
| Initial eGFR, mL/min/1.73 m², median (IQR) | 47.9 (28.1–81.7) | 87.4 (58.1–115.6) | 0.0011 |
| Hypertension, n (%) | 32 (71.1) | 74 (43.7)  | 0.03  |
| Etiology of secondary MN, n (%) | | | |
| Infectious    | 3 (6.6)   | 17 (10.0)  | 0.43  |
| Autoimmune    | 1 (2.2)   | 3 (1.7)    | 1     |
| Neoplastic    | 5 (11.1)  | 5 (2.9)    | 0.02  |
| Nonneoplastic hematologic | 0 (0) | 2 (1.1) | 1 |
| Follow-up, years, median (IQR) | 4 (2–7) | 1 (2–6) | 0.55 |
| Complete remission, n (%) | 10 (40.0)* | 50 (58.1)† | 0.10 |
| Partial remission, n (%) | 7 (28.0)† | 9 (10.4)† | 0.02 |
| Final eGFR ≤60 mL/min/1.73 m², n (%) | 10 (40.0)* | 23 (26.7)† | 0.05 |
| Dialysis, n (%) | 8 (32.0)* | 8 (9.3)† | 0.0045 |
| Death, n (%) | 0* | 4 (4.6)† | 0.05 |

MN, membranous nephropathy; eGFR, estimated glomerular filtration rate. * (n = 25). † (n = 86).
the first group, and three in the second group progressed to dialysis.

Of the 4 patients with glomerular crescents (Table 3), three had idiopathic disease and one had hepatitis B. Two of those patients were in the <60-year group and showed complete remission after treatment with calcineurin inhibitors. Of the two in the ≥60-year group, one had hepatitis B; both of those patients progressed to dialysis within 3 to 4 years, without undergoing immunosuppressive therapy.

The 1 patient with collapsing glomerulopathy was a young man with a serum creatinine level of 1.37 mg/dL and proteinuria of 6 g/day at diagnosis, without any other secondary disease. That patient responded well to immunosuppressive therapy: at the end of follow-up, he had a serum creatinine level of 0.95 mg/dL and no proteinuria.

Immunofluorescence data were unavailable for 7 patients (Table 3). Of the remaining 207 patients, in addition to the data on IgG and C3 deposit in a capillary loop granular pattern, 25 (12.1%) had C1q deposits and only eight had secondary MN, of various etiologies: syphilis, in two; rheumatoid arthritis, in two; schistosomiasis, in two; hepatitis B, in one; and aplastic anemia, in one. Monoclonal immunoglobulin deposition in renal tissue was identified in 9 patients (4.3%), six with kappa and three with lambda light chain. Only in three, all kappa light chain, they were found a secondary etiology: one with acute myeloid leukemia, one with beta-thalassemia minor, and one with rheumatoid arthritis. The unidentifiable forms were categorized as idiopathic, rather than as gammopathies of renal significance, because none of the remaining patients had paraprotein in their blood or urine. Immunoglobulin A (IgA) deposits occurred in 22 patients (10.6%): one had syphilis; one had acute myeloid leukemia; one had aplastic anemia; one had schistosomiasis; and 18 had no underlying diagnosis. The proportion of these deposits between the older and younger groups has not shown any difference (Table 3).

Electron microscopy was performed in 5 patients: one with syphilis; one with C1q deposition; one with IgA deposition; one with deposition of C1q and IgA; and one with low serum C4. The electron microscopy findings did not add pertinent data to the diagnosis in any of those cases.

A total of 111 patients (86 in the <60-year group and 25 in the ≥60-year group) were followed for a relevant length of time – over a median follow-up period of 4 years (2–6). At the end of follow-up, the median serum creatinine level was 1.21 mg/dL (0.88–2.71) and 16 patients (14.4%) had progressed to dialysis. Four patients (3.6%) died during the follow-up. Complete remission of MN was achieved in 60 patients (54.0%), and partial remission was achieved in 16 (14.4%).

Of the 25 patients in the ≥60-year group who were followed long term, eight (32%) progressed to dialysis, compared with eight (9.3%) of the 86 patients in the <60-year group, a statistically significant difference (p = 0.0045; Table 2). However, there was no statistical difference between the two groups in terms of the proportion of patients who, at the end of follow-up, had an eGFR ≤60 mL/min/1.73 m² (p = 0.05; Table 2).

Table 4 shows the comparison between patients who progressed to dialysis, n = 16, versus those who did not,
demonstrating that the patients in the former group were older, however with a mean age of 53.94 ± 13.59 years, versus 46.11 ± 15.01 years for the latter group \( (p = 0.03) \). In addition, the group of patients who progressed to dialysis had more proportion of men, a significantly higher median baseline serum creatinine, lower GFR, and a significantly greater proportion of patients with hypertension at diagnosis. The presence of interstitial fibrosis, a significantly greater proportion of patients with vascular involvement seen on renal histology, and a lower use of immunosuppressant were also significant findings in patients who progressed to dialysis (Table 4). However, after analyzing these data by binary logistic regression, there was no statistically significant correlation with the dialysis outcome.

Of the 25 patients in the ≥60-year group, 10 (40%) achieved a complete response and seven (28%) achieved a partial response, compared with 50 (58.1%) and nine (10.4%), respectively, of the 86 patients in the <60-year group. Although there was no statistical difference between the two groups in terms of the rate of complete response, a partial response was significantly more common in the ≥60-year group \( (p = 0.02) \). Table 2 summarizes the data regarding the evolution of the patients, by age group.

Treatment regimens in both groups were quite varied. Table 5 details these treatments and the responses in the older and younger groups.

If we define spontaneous remission as partial or complete remission that occurs without the use of an immunosuppressant, that occurred in seven (28%) of the 25 pa-
tients in the ≥60-year group and in 15 (17.4%) of the 86 patients in the <60-year group, with no statistical difference between the two age groups (p = 0.24) (Table 5).

In our sample, all deaths occurred in the <60-year group. Of the 4 patients who died, only one had received immunosuppressive therapy (with prednisone and cyclophosphamide), subsequently evolving to death from sep- sis. Of the three other deaths, two occurred after dialysis and one was attributed to pulmonary thromboembolism.

Discussion

In individuals over 40 years of age, which was the mean age of the patients evaluated in this 8-year study, MN is the leading cause of nephrotic syndrome. It is noteworthy that 66 (30.8%) of the 214 patients had primary MN with hematuria, corresponding to 37.1% of the 178 patients with primary MN. That is surprising, given that a review of the topic showed hematuria to be almost exclusively associated with secondary MN and quite rare in the primary form of the disease, occurring in less than 25% [14, 15].

With the increase in life expectancy in recent years, the concept of old age has changed. Individuals were previously considered elderly if they were over 60 years of age, but that threshold has gradually been shifting upward [16]. Older individuals typically have chronic ailments and are more susceptible to acute events. In such individuals, renal biopsy has helped improve diagnostic accuracy and the quality of treatment. In our sample, patient characteristics at diagnosis were similar between the two age groups, except for the fact that serum creatinine levels were higher in the ≥60-year group, as was the proportion of patients with a history of hypertension, findings that are in keeping with those of other studies [3–5]. Therefore, early diagnosis and prompt treatment are especially important in older individuals suspected of having MN, given that comorbidities such as hypertension make it more likely that patients with MN will progress to CKD.

Approximately 15% of the patients in our study sam- ple were referred for dialysis, and that proportion was higher in the ≥60-year group. Therefore, advanced age could be considered predictive of a poor outcome. However, in a study conducted by Tu et al. [17], the multivariate analysis showed that terminal renal failure was associated only with male gender and hypoalbuminemia. In the univariate analysis of our data, in addition to the age factor, patients who progressed to dialysis had more extensive interstitial renal fibrosis, which could have been responsible for higher serum creatinine levels at diagnosis. Hypertension and vascular involvement were also more common among the patients who progressed to dialysis. Because only a small number of patients in our sample progressed to dialysis, it was not possible to perform a multivariate analysis. However, interstitial fibrosis and hypertension, which were identified at diagnosis in some of our patients, can be considered risk factors for renal failure, regardless of the age of the patient.

Menn-Josephy H et al. [18] evaluated the degree of interstitial fibrosis on renal biopsy and its primary outcome, the initiation of dialysis. As expected, the authors found that the group of patients with interstitial fibrosis occupying ≥50% of the biopsy sample progressed most rapidly to CKD requiring dialysis, the mean time from biopsy to dialysis being 1.2 years in that group, compared with 6.5 years and 10 years, respectively, for the groups in which fibrosis occupied 25–49% and 0–24% of the sample (p < 0.001), regardless of the age of the patients. Although unable to provide an explanation, the authors identified a group of patients in which interstitial fibrosis occupied ≥80% of the renal biopsy sample and who did not progress to dialysis over 10 years of follow-up [18]. Despite those renal histology data, the treatment is currently based on the degree of proteinuria and on the serum lev- els of anti-PLA2R antibodies, at diagnosis and over time [9].

After the discovery that anti-PLA2R antibodies constitute a marker of MN, it became possible not only to make the diagnosis but also to monitor the response to treat- ment by performing serial measurements of anti-PLA2R antibody levels. However, neither serum nor tissue levels of anti-PLA2R antibodies were addressed in the present study because it was a retrospective study of data collect- ed at a time when such measurements were not yet part of the routine investigation of glomerulopathy.

Other light microscopy findings in the present study included ATN, as well as, more rarely, glomerular cres- cents and collapsing glomerulopathy. Although ATN has not been widely addressed in the literature, it was identi- fied in nearly 25% of the patients in our sample, albeit with few biochemical repercussions. In a 9-year study conducted in the USA [19], the authors evaluated 14,800 biopsies and found the prevalence of MN with glomerular crescents to be only 0.1%. Those authors found that, among the patients with anti-PLA2R antibody-positive MN, only one had the primary form, the remaining pa- tients having the secondary form, which was associated with malignancy, hepatitis C, or, most commonly, auto-
immune disease, mainly antineutrophil cytoplasmic antibody. In our sample, there were 4 MN cases with crescent and only one of those cases was associated with a secondary cause (hepatitis B).

The immunofluorescence data related to the deposition of C1q, IgA, and monoclonal immunoglobulin, which occurred, respectively, in 12.0%, 10.6%, and 4.3% of the patients in our sample, alert us to the need to screen for secondary forms. However, the fact that we did not find such deposition in some patients makes us question what could have been involved in the pathogenesis of MN in those cases. In our patients with syphilis, schistosomiasis, rheumatoid arthritis, or aplastic anemia, the deposition of C1q was more often associated with secondary causes than was that of IgA. Rocha et al. [20] identified a predominance of IgG kappa deposition among patients with MN, as well as finding that 9 of the 28 patients evaluated had the secondary form of the disease, which was associated with lymphoproliferative disease in 6 of those nine patients. Their findings are similar to ours.

The reported etiology of solid tumors associated with MN varies widely [8]. However, only 10 (4.6%) of the patients in our sample were diagnosed with malignancy before or at the end of follow-up, although that proportion was higher in the patients ≥60 years of age. That low prevalence of malignancy associated with MN underscores the fact that cancer screening should not be routinely performed, except in elderly patients, smokers, individuals with a family history of cancer, and individuals presenting with warning signs or symptoms [9].

Partial or complete remission is reported in 30–70% of cases of MN, and the 10- and 15-year rates of progression to end-stage renal disease are approximately 35% and 41%, respectively [21, 22]. After a median follow-up period of 4 years, partial and complete remission was observed in 14.4% and 54.0% of the patients in our sample. Although the rate of complete remission was comparable between the two age groups, the rate of partial remission was higher among the patients ≥60 years of age. Those data indicate that early diagnosis and prompt treatment of MN will have a positive effect, regardless of patient age.

Recent studies with a randomized treatment protocol have a mean age of patients close to 50 years, therefore not considering a higher age group. In these protocols, the frequency of complete or partial remission is very variable, analyzed over 12 months, and depending on the medication used [23, 24]. In one of the studies, RI-CYC-LO, after 3 years of follow-up, complete and partial remission was achieved in 85% of the rituximab group and 73% of the cyclophosphamide group. However, in this study, the percentage of partial remission was higher than complete remission [24].

Our study has some limitations, not the least of which is the fact that it was a retrospective, single-center study. In addition, as previously mentioned, data related to anti-PLA2R antibody levels were not available. However, by virtue of the sheer size of the patient sample evaluated, our results provide relevant information for clinical practice. In addition, we believe that studies such as ours will serve as points of comparison for future studies of MN evaluating the levels of anti-PLA2R antibodies and other autoantibodies. Such studies could show the real change that the introduction of these markers has brought about in relation to the evolution and long-term renal function of patients with the disease.

Conclusion

In the present study, we emphasize that at the clinical presentation of the patients, in addition to proteinuria, hematuria occurred frequently even in primary forms of the disease. The association with secondary causes occurred in less than 20%, regardless of age, except for the rate of MN associated with neoplasia, which was higher (albeit still low) in the ≥60-year group. The most relevant aspect of the renal biopsy data was the deposition of C1q, IgA, and monoclonal IgG, as well as the presence of cellular crescents in a minority of patients, many of whom had primary MN, with no difference between the two age groups. The older patients, despite having worse renal function at diagnosis and more referral for dialysis during the follow-up, had remission rates comparable to those of the younger patients. Requiring dialysis was associated with more extensive renal fibrosis and hypertension at diagnosis, probably regardless of age. So, this cohort demonstrated the benefits of seeking diagnosis and treatment for MN in any age.

Statement of Ethics

The study was approved by the Ethics Committee of Hospital das Clínicas de São Paulo (number 4,327,317). As this is a retrospective study that only evaluated medical records, the ethics committee was asked to release the use of informed consent, which was supported by this committee. Research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.
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**Author Contributions**

Renata Paula Martins Brandão Paulo and Cristiane Bitencourt Dias were responsible for data collection and analysis, as well as for the initial writing of the article. Lecticia Barbosa Jorge, Luis Yu, and Viktoria Woronik were responsible for reviewing the entire data analysis and reviewing the article for publication. All of the authors have also read and approved the manuscript in its present form and have agreed to its submission to the *Kidney and Blood Pressure Research*.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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