Non-glomerular Tip Lesion Focal Segmental Glomerulosclerosis as a Negative Predictor in Idiopathic Membranous Nephropathy*

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[Abstract] Objective: To assess the significance of focal segmental glomerulosclerosis (FSGS) variants on clinicopathological characteristics and short-term outcomes in idiopathic membranous nephropathy (IMN) patients. Methods: The clinicopathological data of 146 IMN patients diagnosed between December 2016 and March 2019 in our center were collected and analyzed. These patients were divided into the pure IMN group, IMN with glomerular tip lesion (GTL) group, and IMN with non-GTL FSGS group. Results: The IMN with non-GTL FSGS and IMN with GTL groups both had higher proportions of patients with hypertension, lower serum albumin, and severe proteinuria, while the IMN with non-GTL FSGS group additionally showed higher blood pressure and serum cholesterol, and lower serum IgG than the IMN group (all \( P<0.05 \)). As for pathology, the IMN with non-GTL FSGS group had higher proportions of patients with acute tubular injury and moderate to severe chronic injuries than the IMN group (all \( P<0.05 \)). In the IMN, IMN with GTL, and IMN with non-GTL FSGS groups, the overall one-year remission rates were 81.6%, 76%, and 58.8%, respectively. Furthermore, the IMN with non-GTL FSGS group showed the lowest cumulative incidence to reach remission within one year. Multivariate Cox logistic analysis demonstrated that higher level of serum anti-M-type phospholipase A2 receptor antibody and the existence of non-GTL FSGS lesion were independent predictors for no remission in IMN patients. Conclusion: The non-GTL FSGS lesion was a novel negative predictor in IMN and should be taken into account in the management of IMN.

Key words: idiopathic membranous nephropathy; focal segmental glomerulosclerosis; glomerular tip lesion

Idiopathic membranous nephropathy (IMN), identified as an autoimmune disease, is a common cause of primary nephrotic syndrome in adults. The natural course of IMN differs widely among patients, thus varying from spontaneous remission to end-stage kidney disease (ESKD)[1, 2]. In the past decade, the incidence and the morbidity of IMN has gradually increased in China[3] probably due to environmental pollution. Hence, it is critical to identify the factors that influence the prognosis of IMN patients, so to develop appropriate treatment plans.

Numerous prior studies have concluded that persistent heavy proteinuria[4–7], high serum titer of an anti-M-type phospholipase A2 receptor (anti-PLA2R) antibody[8, 9], age over 50 years old[10–12], male[10, 11], and high level of serum creatinine or low level of the estimated glomerular filtration rate (eGFR) at the time of diagnosis or within five years[5, 10, 12–14] were important predictors for progression to ESKD in IMN patients. Moreover, certain histopathological features, including chronic tubulointerstitial injuries[5–7, 10, 12–15] and the histological stage[16] were also found to be associated with poor long-term outcomes. The significance of focal segmental glomerulosclerosis (FSGS) lesion presented in IMN patients was thus investigated, but the results still remained conflicting[7, 12, 14, 15, 17]. However, previous studies tended to regard the FSGS lesion as a whole to assess its impact on IMN patients, while studies focusing on different FSGS variants were lacking.

Glomerular tip lesion (GTL) is one morphologic...
variant of FSGS, and is characterized by segmental lesions involving the tip domain of the glomeruli (near the origin of the proximal tubule) accompanied by synechia or a confluence of podocytes with parietal or tubular epithelial cells[18]. GTL occurs in both primary and secondary FSGS forms, including membranous nephropathy (MN), immunoglobulin A (IgA) nephropathy, diabetic nephropathy, and chronic kidney transplant rejection[19, 20]. Most studies reported patients with GTL had a good response to steroids[21–23]. They had the highest remission rates (57%), and 5-year renal survival rates (78%) among all FSGS variants[23]. In general, patients with GTL had a better prognosis than those with other FSGS variants. Thus, we supposed IMN with GTL to be benign as well.

In this retrospective study, we analyzed the clinicopathological baseline data and one-year follow-up data of the patients diagnosed as biopsy-proven IMN with and without different FSGS variants, therefore aiming to assess the significance of the FSGS variants on the clinicopathological features and short-term outcomes in IMN patients.

1 MATERIALS AND METHODS

1.1 Patients and Treatments

The research protocol was approved by the Medical Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. Written informed consents were obtained from each participating patient.

In total, there were 1024 patients diagnosed as biopsy-proven MN between December 2016 and March 2019 in our center. The enrolled patients had to fulfill the following inclusion criteria: (1) diagnosed as biopsy-proven IMN; (2) the clinical, laboratory, and pathological data at diagnosis were complete except for the anti-PLA2R antibody; and (3) the one-year outpatient follow-up data were complete. We excluded patients as follows: (1) atypical membranous nephropathy, showing atypical pathological findings, such as cell proliferation, electron dense deposits in multisites, and mostly a “full house” pattern in immunofluorescence, but without definite etiology; (2) secondary causes of membranous nephropathy, such as autoimmune diseases, neoplasia, infection, or exposure to certain drugs; and (3) a medication history of steroids or immunosuppressive agents before the renal biopsy. There were 146 patients finally included in the study (fig. 1). From the combined FSGS lesions, we divided the patients into three groups: IMN with no FSGS lesion group (fig. 2A), IMN with GTL group (fig. 2B), and IMN with non-GTL FSGS group (fig. 2C).

The therapeutic regimens were mainly determined by the severity of proteinuria, the titer of anti-PLA2R antibody, and eGFR. Most patients with proteinuria <8 g/day, anti-PLA2R antibody titer <50 RU/mL, and eGFR ≥60 mL/min/1.73 m² were given non-immunosuppressive therapy, while the others with no contraindications received corticosteroids and immunosuppressive agents like cyclophosphamide or tacrolimus.

1.2 Data Collection

We collected the clinical and pathological data of the enrolled patients. The clinical data included

![Fig. 2 The light microscopic patterns of the lesions of the three groups](image)

A: IMN with no FSGS lesion; B: IMN with GTL; C: IMN with non-GTL FSGS lesion (PASM; magnification: 400×). FSGS: focal segmental glomerulosclerosis; GTL: glomerular tip lesion; IMN: idiopathic membranous nephropathy
the basic information (age, sex, and blood pressure), and laboratory examinations, such as hemoglobin, serum albumin, serum creatinine, blood urea nitrogen, uric acid, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and anti-PLA2R antibody. Routine clinical and biochemical variables were measured by standardized methods on autoanalyzers. The serum anti-PLA2R antibody was measured by an enzyme-linked immunosorbent assay using a validated commercial kit (Euroimmun AG, Germany) according to the manufacturer’s instructions. The urinary protein excretion was quantified by 24-h urinary protein or estimated protein excretion rate (ePER). The ePER was calculated by multiplying the protein-creatinine ratio (PCR) by the estimated creatinine excretion rate (eCER), which was obtained using Fotheringham’s formula\textsuperscript{24}. The eGFR was calculated using the modified glomerular filtration rate estimating equation for Chinese patients\textsuperscript{25}.

All kidney biopsy specimens were examined by immunofluorescence, light microscopy, and electron microscopy. Renal tubular atrophy, interstitial fibrosis, vascular intimal fibrosis, and hyaline degeneration were scored according to the area involved: no lesions, mild (<25%), moderate (25%–50%), and severe (>50%). Glomerular lesions were classified into four stages by referring to Ehrenreich and Churg staging\textsuperscript{26}. The severity of the above-mentioned pathological changes in the IMN with GTL group was between the other two groups, albeit insignificant. Moreover, the patients in the IMN with GTL group had the highest proportions of patients with hypertension, while the IMN with non-GTL FSGS group ranked second (all \(P<0.05\)) than those in the IMN group. Patients in the IMN with GTL group and IMN with non-GTL FSGS group showed lower levels of serum albumin \(P=0.009\) and \(P=0.002\), respectively) and higher levels of 24-h urinary protein excretion \(P=0.005\) and \(P=0.006\), respectively) than those in the IMN group. Among the three groups, the IMN with GTL group had the highest proportions of patients with hypertension, while the IMN with non-GTL FSGS group ranked second (all \(P<0.05\)). There were no significant differences in terms of other parameters.

### 2 RESULTS

#### 2.1 Clinical and Laboratory Parameters

A total of 146 patients were enrolled in the study. The baseline clinical parameters among the three groups are summarized in table 1. Eighty-seven patients (59.6%) were in the IMN group, 25 patients (17.1%) in the IMN with GTL group, and 34 patients (23.3%) in the IMN with non-GTL FSGS group. The patients in the IMN with non-GTL FSGS group had higher systolic blood pressure \((P=0.004)\), diastolic blood pressure \((P=0.002)\) and serum total cholesterol \((P=0.028)\), and lower serum IgG level \((P=0.048)\) than those in the IMN group. Patients in the IMN with GTL group and IMN with non-GTL FSGS group showed lower levels of serum albumin \((P=0.009\) and \(P=0.002\), respectively) and higher levels of 24-h urinary protein excretion \(P=0.005\) and \(P=0.006\), respectively) than those in the IMN group. Among the three groups, the IMN with GTL group had the highest proportions of patients with hypertension, while the IMN with non-GTL FSGS group ranked second (all \(P<0.05\)). There were no significant differences in terms of other parameters.

#### 2.2 Pathological Parameters

The renal pathological data are listed in table 2. A significantly higher proportion of patients in the IMN with non-GTL FSGS group had acute tubular injury \((P<0.05)\) and moderate to severe chronic injuries, including renal tubular atrophy \((P<0.01)\), interstitial fibrosis \((P<0.01)\), and vascular intimal fibrosis \((P<0.05)\) than the IMN group. The severity of the above-mentioned pathological changes in the IMN with GTL group was between the other two groups, albeit insignificant. Moreover, the patients in the IMN with GTL group and IMN with non-GTL FSGS group had a higher proportion of segmental sclerosis than those in the IMN group \((P<0.01)\). Regarding the pathological stages, 31 (35.6%) patients in the IMN group, 12 (48%) patients in the IMN with GTL group, and 19 (55.9%) patients in the IMN with non-GTL FSGS group were in the advanced stage, but displayed no significant difference in distribution. There were also no significant differences in terms of the proportion of global sclerosis and other parameters.

#### 2.3 Treatment Response at One-year

After diagnosis, 125 out of 146 (85.6%) patients received corticosteroids and immunosuppressive
agents for more than six months, including 19 patients who were initially given supportive treatment. Twenty-one (14.4%) patients had sustained supportive treatment only. There was no significant difference in the distribution of the treatment among the three groups of patients.

### Table 1 Comparison of the clinical parameters among the three groups

| Clinical parameters | IMN (n=87) | IMN+GTL (n=25) | IMN+non GTL FSGS (n=34) |
|---------------------|------------|----------------|-------------------------|
| Age (years)         | 50±11      | 52±13          | 47±14                   |
| Gender (male/female)| 57/30      | 21/4           | 23/11                   |
| Duration (months)   | 1 (0.9–5)  | 1 (0.37–2)     | 1.5 (0.63–3.75)         |
| Nephrotic syndrome, n (%) | 66 (75.9%) | 23 (92%)       | 30 (88.2%)              |
| Hypertension, n (%) | 38 (43.7%) | 15 (60.0%)     | 24 (70.6%)**            |
| SBP (mmHg)          | 129±19     | 136±16         | 141±15*                 |
| DBP (mmHg)          | 82±11      | 86±11          | 89±9#                   |
| Hemoglobin (g/L)    | 131±16     | 129±16         | 131±16                  |
| Serum albumin (g/L) | 25.0 (22.0–28.2) | 19.1 (17.6–20.7) | 17.3 (16.1–21.3)§      |
| Anti-PLA2R positive, n (%) | 68 (80%)** | 18 (85.7%)*    | 28 (90.3%)**            |
| Anti-PLA2R titer (RU/mL) | 72 (26–185) | 67 (25–125)    | 86 (41–237)             |
| Proteinuria (g/24 h) | 5.2 (3.5–8.0) | 8.0 (4.6–9.1)  | 7.6 (5.8–9.9)§         |
| SBP (mmHg)          | 73.4±20.9 | 73.4±20.9      | 79.8±30.5               |
| DBP (mmHg)          | 5.0 (0.72–1.73) | 1.0 (0.63–1.45) | 0.95 (0.52–1.27)        |
| Blood urea nitrogen (mmol/L) | 346±96.7 | 397±72.0       | 436±86.0                |
| Total cholesterol (mmol/L) | 7.1 (5.5–8.4) | 7.8 (6.9–8.5) | 8.2 (6.5–9.7)§          |
| HDL-C (mmol/L)      | 2.1 (1.5–3.1) | 1.7 (1.3–2.5)  | 2.1 (1.4–4.4)           |
| LDL-C (mmol/L)      | 1.35 (1.16–1.63) | 1.35 (1.20–1.73) | 1.30 (1.03–1.66)        |
| Serum IgG (mg/dL)   | 6.08 (4.82–7.66) | 5.20 (4.03–6.53) | 5.01 (3.65–5.93)*       |
| Serum IgM (mg/dL)   | 1.21 (0.72–1.73) | 1.0 (0.63–1.45) | 0.95 (0.52–1.27)        |
| Serum IgA (mg/dL)   | 1.87 (1.42–2.46) | 2.08 (1.75–2.81) | 2.45 (1.97–3.01)        |
| Serum C3 (mg/dL)    | 8.0 (0.81–1.12) | 0.91 (0.83–0.95) | 0.96 (0.83–1.09)        |
| Serum C4 (mg/dL)    | 0.26 (0.21–0.29) | 0.25 (0.22–0.30) | 0.29 (0.21–0.32)        |

*P<0.05, **P<0.01 vs. the IMN group; §P<0.05 vs. the IMN with GTL group. *Serum anti-PLA2R antibodies were positive in 68 out of 85 patients in the IMN group, 18 out of 21 patients in the IMN with GTL group, and 28 out of 31 patients in the IMN with non-GTL FSGS group. There were 9 patients lacking the measurement of the serum anti-PLA2R antibody titer.

IMN: idiopathic membranous nephropathy; GTL: glomerular tip lesion; FSGS: focal segmental glomerulosclerosis; SBP: systolic blood pressure; DBP: diastolic blood pressure; anti-PLA2R: anti-M-type phospholipase A2 receptor; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol

### Table 2 Comparison of the pathological parameters among the three groups

| Pathological parameters | IMN (n=87) | IMN+GTL (n=25) | IMN+non GTL FSGS (n=34) |
|-------------------------|------------|----------------|-------------------------|
| Acute tubular injury, n (%) | 10 (11.5%) | 5 (20.0%) | 11 (32.4%)*            |
| Interstitial edema, n (%) | 55 (63.2%) | 19 (76.0%) | 21 (61.8%)             |
| Tubular atrophy (≥25%), n (%) | 21 (24.1%) | 9 (36.0%) | 21 (61.8%)*            |
| Interstitial fibrosis (≥25%), n (%) | 5 (5.7%) | 3 (12.0%) | 10 (29.4%)*            |
| Vascular intimal fibrosis (≥25%), n (%) | 8 (9.2%) | 5 (20.0%) | 10 (29.4%)*            |
| Vascular hyaline change (≥25%), n (%) | 8 (9.2%) | 4 (16.0%) | 7 (20.6%)              |
| Number of glomeruli, n | 20 (16–28) | 21 (15–29) | 19 (13–26)             |
| Proportion of global sclerosis (%) | 4.8 (0.0–8.3) | 4.3 (0.0–9.6) | 5.5 (2.2–14.7)         |
| Proportion of segmental sclerosis (%) | 0* | 5.6 (3.2–14.0) | 7.0 (3.3–10.7)*        |
| PLA2R deposit, n (%) | 83 (95.4%) | 24 (96.0%) | 32 (94.1%)             |
| C3 deposit, n (%) | 62 (71.3%) | 20 (80.0%) | 21 (61.8%)             |
| C1q deposit, n (%) | 30 (34.5%) | 8 (32.0%) | 12 (35.3%)             |
| C4 deposit, n (%) | 7 (8.0%) | 2 (8.0%) | 3 (8.8%)              |
| IgA deposit, n (%) | 7 (8.0%) | 2 (8.0%) | 4 (11.7%)              |
| IgM deposit, n (%) | 6 (6.6%) | 1 (4.0%) | 2 (5.9%)              |
| Pathological stage I/II, n (%) | 56 (64.4%) | 13 (52.0%) | 15 (44.1%)             |
| Pathological stage III/IV, n (%) | 31 (35.6%) | 12 (48.0%) | 19 (55.9%)             |

*P<0.05, **P<0.01 vs. the IMN group. There were only 5 patients with segmental sclerosis in the IMN group.

IMN: idiopathic membranous nephropathy; GTL: glomerular tip lesion; FSGS: focal segmental glomerulosclerosis; PLA2R: M-type phospholipase A2 receptor
The proteinuria excretion decreased remarkably after one year in all groups (all \( P < 0.001 \)), but the levels of proteinuria in the IMN with GTL group and IMN with non-GTL FSGS group still exceeded that of the IMN group, especially the IMN with non-GTL FSGS group (\( P < 0.05 \)). The serum albumin levels of the three groups increased significantly (all \( P < 0.001 \)), but there were no significant differences among the three groups. In addition, no significant changes were found in the serum creatinine levels of the three groups after one year, and there were no significant differences among the three groups as well (table 3).

The Kaplan-Meier analysis revealed a significant difference in the cumulative incidence to attain CR or PR among the three groups (\( P = 0.009 \)), which was significantly lower in the IMN with non-GTL FSGS group than in the IMN group (\( P = 0.002 \)) and IMN with GTL group (\( P = 0.035 \)) (fig. 3). In the IMN group, IMN with GTL group, and IMN with non-GTL FSGS group, the overall one-year remission rates were 81.6%, 76%, and 58.8%, respectively. The IMN with non-GTL FSGS group had the lowest remission rate (both \( P < 0.05 \)). The one-year CR was 41.4%, 20%, and 20.6%, respectively. The comparable CR in the latter two groups were lower than that in the IMN group (both \( P < 0.05 \)) (fig. 4).

### 2.4 Risk Factors of No Remission in IMN Patients

The risk factors for poor treatment response in IMN patients were analyzed by the Cox univariate regression analysis (table 4). The results showed that higher initial levels of anti-PLA2R antibody, 24-h proteinuria and serum creatinine, lower eGFR, the existence of the overall FSGS lesion and non-GTL FSGS lesion, and moderate to severe vascular intimal fibrosis were risk factors for no remission. In the multivariate analysis model 1 in which we considered GTL and non-GTL FSGS lesion as a whole, higher titer of serum anti-PLA2R antibody was the only significant risk factor for no remission. However, in model 2, we regarded GTL and non-GTL FSGS lesion as individuals, and demonstrated that the titer of serum anti-PLA2R antibody was still a risk factor (\( P = 0.030 \)), while the non-GTL FSGS lesion became a new independent risk factor for no remission (\( P = 0.034 \) (table 5).
In recent years, many studies have reported the clinicopathological characteristics of IMN with FSGS lesion, but whether the FSGS lesion affected the prognosis of IMN patients still remained controversial, as some researchers suggested the FSGS lesion to be an independent risk factor for renal outcomes[9,12,15,17], while others doubted this[7,14]. Most of these studies focused on the predictive value of the overall FSGS lesion rather than the pathological variants of FSGS on clinical outcomes. Given the previous studies indicating GTL, one of the FSGS variants, tended to have a benign clinical outcome[21,23], we divided the FSGS lesion into the GTL and non-GTL FSGS lesion for the first time to investigate their impacts on the clinicopathological characteristics and the short-term outcome of IMN patients, and to find whether the prognosis of IMN patients with GTL was favorable.

In our cohort, 59 out of 146 (40.4%) IMN patients had FSGS lesion, which was similar to the previous detective rates[14,17]. The proportions of the patients with GTL and non-GTL FSGS lesion in all IMN patients were 17.1% and 23.3%, respectively.

### Table 4 Cox univariate regression analysis for the predictive factors of CR or PR

| Parameters                                      | HR (95%CI) | P-value |
|-------------------------------------------------|------------|---------|
| IMN without FSGS                                | 1 (Reference) |         |
| IMN combined with non-GTL FSGS                  | 0.503 (0.303–0.836) | 0.008   |
| IMN combined with all types of FSGS             | 0.690 (0.468–1.016) | 0.060   |
| Anti-PLA2R antibody (increased by 1 RU/mL)      | 0.880 (0.758–0.998) | 0.022   |
| 24-h proteinuria (increased by 1 g/24 h)        | 0.930 (0.869–0.995) | 0.034   |
| Serum creatinine (increased by 1 μmol/L)        | 0.977 (0.960–0.995) | 0.069   |
| eGFR (increased by 1 mL/min/1.73 m²)            | 1.019 (1.009–1.065) | 0.048   |
| Vascular intimal fibrosis (≥25%)                | 0.428 (0.194–0.944) | 0.035   |

All covariates with P<0.1 (other covariates with P≥0.1 were excluded).

CR: complete remission; PR: partial remission; CI: confidence interval; HR: hazard ratio; IMN: idiopathic membranous nephropathy; GTL: glomerular tip lesion; FSGS: focal segmental glomerulosclerosis; anti-PLA2R: anti-M-type phospholipase A2 receptor; eGFR: estimated glomerular filtration rate

### Table 5 Cox multivariate regression analysis for the predictive factors of CR or PR

| Parameters                                      | HR (95%CI) | P-value |
|-------------------------------------------------|------------|---------|
| Model 1: GTL and non-GTL FSGS as a whole        |            |         |
| IMN without FSGS                                | 1 (Reference) |         |
| IMN combined with all types of FSGS             | 0.812 (0.502–0.999) | 0.132   |
| Sex (ref. men)                                  | 0.817 (0.510–1.310) | 0.401   |
| Age (increased by 1 year)                       | 0.988 (0.965–1.012) | 0.327   |
| Anti-PLA2R antibody (increased by 1 RU/mL)      | 0.929 (0.717–0.997) | 0.039   |
| 24-h proteinuria (increased by 1 g/24 h)        | 0.925 (0.781–1.0) | 0.068   |
| eGFR (increased by 1 mL/min/1.73 m²)            | 1.011 (0.987–1.015) | 0.471   |
| Tubular atrophy (≥25%)                          | 0.802 (0.621–1.860) | 0.540   |
| Intertstitial fibrosis (≥25%)                    | 1.310 (0.625–2.743) | 0.474   |
| Vascular intimal fibrosis (≥25%)                | 0.719 (0.637–1.337) | 0.548   |
| Model 2: GTL and non-GTL FSGS as individuals    |            |         |
| IMN without FSGS                                | 1 (Reference) |         |
| IMN combined with GTL                           | 0.793 (0.627–1.094) | 0.416   |
| IMN combined with non-GTL FSGS                  | 0.679 (0.452–0.903) | 0.034   |
| Sex (ref. men)                                  | 0.812 (0.459–1.217) | 0.501   |
| Age (increased by 1 year)                       | 0.918 (0.871–1.112) | 0.412   |
| Anti-PLA2R antibody (increased by 1 RU/mL)      | 0.917 (0.870–1.132) | 0.030   |
| 24-h proteinuria (increased by 1 g/24 h)        | 0.919 (0.810–1.301) | 0.071   |
| eGFR (increased by 1 mL/min/1.73 m²)            | 1.021 (0.990–1.139) | 0.518   |
| Tubular atrophy (≥25%)                          | 0.871 (0.612–1.271) | 0.570   |
| Intertstitial fibrosis (≥25%)                    | 1.172 (0.614–1.890) | 0.601   |
| Vascular intimal fibrosis (≥25%)                | 0.810 (0.712–1.216) | 0.471   |

Adjusted for sex, age, tubular atrophy (≥25%), and interstitial fibrosis (≥25%).*P<0.05.

CR: complete remission; PR: partial remission; CI: confidence interval; HR: hazard ratio; IMN: idiopathic membranous nephropathy; GTL: glomerular tip lesion; FSGS: focal segmental glomerulosclerosis; anti-PLA2R: anti-M-type phospholipase A2 receptor; eGFR: estimated glomerular filtration rate
that GTL accounted for a considerable proportion of the overall FSGS lesions, which was close to the total of the other variants. In terms of the clinical features, we demonstrated that IMN patients with FSGS lesion had higher blood pressure, lower serum albumin, and severer proteinuria, which was consistent with the previous studies as well[7, 9, 12, 17, 27]. Furthermore, the clinical manifestations of the IMN patients with GTL were less severe than those with non-GTL lesion, which were albeit mostly insignificant. An interesting finding of our study was that proteinuria in IMN patients with GTL was more severe. Some researchers have believed that a vast leakage of proteinuria is present before GTL, so GTL may be merely a non-specific response of the glomerulus to the high flow rate protein-rich filtrate, which perhaps illustrates our finding[19, 28]. Pathologically, previous studies have demonstrated that IMN patients with FSGS lesion were prone to presenting severe tubulointerstitial and vascular lesions[7, 9, 12, 17, 26], which was confirmed by our study, as we observed a remarkably high proportion of IMN patients with FSGS lesion who had moderate to severe tubular atrophy, interstitial fibrosis, and vascular intimal fibrosis, as well as acute tubular injury, especially patients with non-GTL FSGS lesion.

Since accumulating evidence has suggested the remission of proteinuria could be a surrogate endpoint for predicting long-term renal outcomes[30, 31], we took the remission of proteinuria as an endpoint event. We revealed that the comparable CR in IMN patients with GTL and non-GTL FSGS lesion was lower than that in IMN patients with no FSGS, thus supporting FSGS as a risk factor for no remission[9, 12, 15, 17]. In addition, IMN patients combined with GTL had a higher remission rate than those with non-GTL FSGS lesion, in accordance with our initial assumption, which proposed a benign prognosis with GTL. Furthermore, we demonstrated that higher level of serum anti-PLA2R antibody and the presence of non-GTL FSGS lesion but not the overall FSGS lesion were independent risk factors for no remission of proteinuria in IMN patients within one year. Additionally, prior studies concluded that persistent heavy proteinuria[6-7], age over 50 years old[10-12], male[10, 11], high level of serum creatinine or low eGFR[5, 10, 12-14], chronic tubulointerstitial injuries[5-7, 10, 12, 15], and histological stage[16] were important predictors for poor long-term outcomes, while these factors were found to have no significant association with the short-term outcome in our study, which was possibly due to the short follow-up period and the surrogate endpoint event.

In addition, there were several limitations in our study. Firstly, for some patients lacking a measurement of 24-h proteinuria during the follow-up, we used ePER instead, which was certified to have no significantly different bias from the 24-h collection[22]. Secondly, the study was limited to the insufficient follow-up duration of only one year. Hence, it was unlikely for us to regard ESKD or 50% reduction in eGFR as an endpoint event since the progress of renal function in IMN patients was relatively slow. Thirdly, this study relied on data of retrospective analysis from a single center with a relatively small sample size. Thus, further studies with an enlarged sample size from multiple centers and prolonged follow-up period would be necessary to verify our findings.

In conclusion, the clinical manifestations and pathological changes of IMN patients combined with non-GTL FSGS lesion were prone to be more severe. The existence of non-GTL FSGS lesion could be a significant predictor for poor renal outcome in IMN patients and should be taken into account in the management of IMN.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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