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Value of the Oxford classification of IgA nephropathy in children with Henoch–Schönlein purpura nephritis

Ke Xu[1] · Lili Zhang[2,3] · Jie Ding[1] · Suxia Wang[2] · Baige Su[1] · Huijie Xiao[1] · Fang Wang[1] · Xuhui Zhong[1] · Yanming Li[4]

Abstract

Background The widely used International Study of Kidney Disease in Children (ISKDC) classification for Henoch-Schönlein purpura nephritis (HSPN) does not completely correlate with the clinical presentation and long-term prognosis of this disease. Primary IgA nephropathy (IgAN) and HSPN share common features; thus, the Oxford classification of IgAN might be useful in predicting the long-term outcomes of HSPN. However, its value has not been confirmed in children with HSPN.

Methods We selected children with HSPN diagnosed between 2003 and 2015, and reclassified their renal biopsies according to the Oxford classification scoring system. The primary outcome was impaired renal function, and remission of proteinuria and clinical remission were secondary outcomes.

Results We included 104 patients (58 males, 46 females) with a median age of 10 (4–17) years. Mesangial hypercellularity (M1) was strongly associated with proteinuria, and tubular atrophy/interstitial fibrosis (T1&2) and C2 (with crescents in > 25% of glomeruli) were associated with reduced estimated glomerular filtration rate (eGFR) at the time of biopsy. Patients with M1, endocapillary proliferation (E1), segmental glomerulosclerosis (S1), and crescents (C1&2) were more likely to have been treated with high-dose methylprednisolone. At univariate time-dependent analyses, S1 was strongly associated with the primary outcome (p = 0.025), whereas T1&2 was significantly negatively associated with proteinuria remission (p = 0.035) and clinical remission (p = 0.038).

Conclusions Our findings suggest that the Oxford classification is valid for children with HSPN. S and T lesions, which are ignored in the ISKDC classification, can be used to assess renal outcomes of HSPN, and such assessments are not affected by currently available treatments. The value of M, E and C lesions in predicting response to therapy and renal outcome warrants further study.

Keywords Pediatrics · Prognosis · Henoch-Schönlein purpura nephritis · Oxford classification

✉ Jie Ding
djnc_5855@126.com

✉ Suxia Wang
suxiawang@bjmu.edu.cn

1   Department of Pediatric, Peking University First Hospital, Beijing 100034, China

2   Laboratory of Electron Microscopy, Peking University First Hospital, Beijing 100034, China

3   Department of Pathology, Children's Hospital of Hebei Province, Shijiazhuang 050031, China

4   Biostatistics department, University of Michigan, 1415 Washington Heights, Ann Arbor, MI 48109, USA

Introduction

Henoch-Schönlein purpura (HSP) is one of the most common types of vasculitis in children [1]. Renal involvement (Henoch-Schönlein purpura nephritis, HSPN) is the principal cause of morbidity [2]. The risk of progression to chronic kidney disease is reported to be between 5 and 20% in children [3, 4] and approximately 30% in adults [5]. Presently, the International Study of Kidney Disease in Children (ISKDC) classification is widely applied for histologic analysis of HSPN lesions. However, the grading of this classification does not completely correlate with the severity of the clinical presentation and long-term prognosis [6, 7]. Additionally, differences between acute and chronic glomerular lesions, as well as the presence of tubular and interstitial lesions, are not taken into account in this classification [8].

Therefore, a more reliable, useful pathological classification is needed for patients with HSPN to improve individual prognostication and treatment strategies [9, 10].

In 2017, the International IgA Nephropathy Network and Renal Pathology Society proposed the updated Oxford classification of IgA nephropathy (IgAN) based on histological renal features: mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and cellular/fibrocellular crescents (C) [11]. This classification is well defined, reproducible, and applicable [12]. Additionally, extensive research has shown that the predictive value of these five renal features (M, E, S, T, and C) is independent not only of patients' clinical data but also of their age at renal biopsy [13, 14]. Such a classification may also facilitate the discovery of specific histological features that may respond to immunosuppressant therapy [13, 15].

Considering the etiopathogenetic, clinical, and histopathological similarities between HSPN and IgAN [16, 17], the Oxford classification may also have predictive value in children with HSPN (IgA vasculitis) [18]. However, there is only one study in this regard, involving adults, published by Kim et al. in 2014 [19], and whether this classification is applicable to children has not yet been investigated. Thus, we conducted a single-center retrospective study to evaluate the value of the Oxford classification on the clinical manifestation, treatment response and long-term prognosis in children with HSPN.

Methods

Patient selection

Data for 251 children who had a clinical diagnosis of HSPN and underwent renal biopsy from 2003 to 2015 were retrieved. These children underwent renal biopsies for nephritic syndrome, nephrotic range proteinuria, persistent proteinuria ≥ 1 g/day for more than 3 months, and/or renal impairment, and all of their parents provided informed consent. The inclusion criteria were as follows: (1) age at renal biopsy < 18 years; (2) hematuria, proteinuria, and/or renal failure associated with a palpable purpuric eruption with/without abdominal or joint pain; (3) no less than seven glomeruli on the biopsy; and (4) follow-up duration ≥ 12 months. Patients with comorbid diseases that might affect the prognosis of kidney disease were excluded: three patients with hepatitis B virus (HBV) infection, one patient with post streptococcal glomerulonephritis, one patient with renal dysplasia, and one patient with primary nephrotic syndrome. The hospital's Research Ethics Board approved this study (Fig. 1).
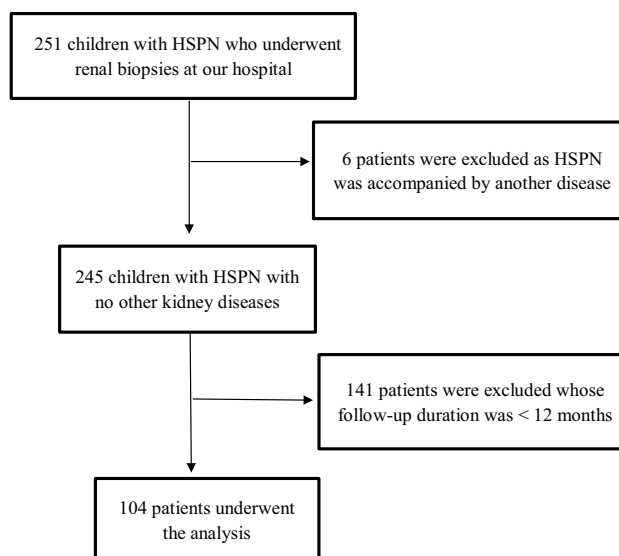

Fig. 1 Flow chart of study enrolment

Clinical data

The estimated glomerular filtration rate (eGFR) was calculated using the Schwartz formula [20]. A constant (K) of 49 for children aged under 13 years and for adolescent girls was used; for adolescent boys, the K value was 62. Children with an eGFR < 90 ml/min per 1.73 m^2 were considered to have renal dysfunction (RD). The mean arterial pressure (MAP) was defined as the diastolic pressure plus one-third of the pulse pressure. Hypertension was defined as blood pressure > 95th percentile for age and sex. Nephrotic-level proteinuria was defined as the presence of proteinuria 3+/4+ or 24-h urine protein > 50 mg/kg per day. Immunosuppressive therapy, which was defined as receiving corticosteroids and/or a cytotoxic agent, was classified into three main types: only corticosteroids, only a cytotoxic agent, and both corticosteroids and a cytotoxic agent.

Outcome measures

The primary outcome of our study was impaired renal function (IRF) defined as a ≥ 50% reduction in initial eGFR or eGFR < 90 ml/min per 1.73 m^2. Furthermore, we included the remission of proteinuria and clinical remission as pre-specified secondary outcomes to evaluate renal outcomes. Remission of proteinuria was defined as three consecutive negative proteinuria results, with/without hematuria, over a 1-month period. Clinical remission was defined as normal renal function and normal urinalysis recorded more than once.

Pathology

All renal biopsy specimens were stained with hematoxylin and eosin, periodic acid-Schiff with silver methenamine and Masson's trichrome. Pathologic findings were reclassified according to the Oxford classification scoring system. C0 was defined as no crescents, C1 as crescents in ≤ 25% of glomeruli, and C2 as crescents in > 25% of glomeruli [11]. Some slides were independently reviewed by two pathologists. The pathologists were blinded to the clinical data.

Statistical analysis

Normally distributed variables were expressed as mean ± standard deviation (SD), and non-normal distributed variables were expressed as median (range). Categorical variables were expressed as number and percentage. Comparisons were based on a t-test for continuous variables and Chi square test or Fisher's exact test for categorical variables. The primary outcome and pre-specified secondary outcomes were analyzed with the Kaplan–Meier method using the log-rank test for comparisons. The starting point for the survival analysis was the time of biopsy. For multivariate analyses, we used the Cox regression model. Variables included in the model were the amount of proteinuria, MAP, and eGFR at the time of renal biopsy and individual variables of the Oxford classification. Results were presented as hazard ratios with 95% confidence intervals. All tests were two-sided, and a p value < 0.05 was considered statistically significant. The inter-observer reproducibility of each pathologic variable between the pathologists was evaluated according to values of the intra-class correlation coefficient (ICC). Statistical analyses were performed using SPSS for Windows, version 19.0.

Results

Patient clinical features

There were 104 patients analyzed in our study. The baseline clinical manifestations of all patients are shown in Table 1. The median age of patients at the time of renal biopsy was 10 (4–17) years, and 44% (46 patients) were female. Renal biopsy was performed at 0.3–76 (median 2) months after disease onset. The median follow-up duration was 40 (12–145) months. All patients accepted different types of immunosuppressive therapy. Four patients were treated with corticosteroids alone, 7 patients were treated with a cytotoxic agent alone, and the other 93 patients received combined corticosteroid and cytotoxic agent treatment, mainly including cyclophosphamide, mycophenolate mofetil, and leflunomide. The age of the subjects and the level of proteinuria in our study were similar to those in a previous study of the Oxford classification among children with IgAN [13], though our study had higher proportions of patients who: were female (44 vs. 25%, p = 0.017), had nephrotic-level proteinuria (55 vs. 27%, p = 0.001), and were receiving immunosuppressants (100 vs. 48%, p < 0.001), as well as higher eGFR values at renal biopsy (161 ± 48 vs. 120 ± 43 ml/min/1.73 m^2).

Table 1 Characteristics of patients at the time of renal biopsy: comparison of our data with the Oxford pediatric cohort

Variables	Our HSPN series (n = 104)	Oxford IgAN series (n = 59)
Clinical features at biopsy		
Median age, years	10 (4, 17)	13 (4, 17.9)
Female gender	46 (44%)	15 (25%)
eGFR, ml/min per 1.73 m^2	161 ± 48	120 ± 43
Proteinuria, g/day	1.7 (0.1 ~ 10.8)	2 (0.5 ~ 7.8)
Nephrotic-level proteinuria	57 (55%)	16 (27%)
MAP, mmHg	82 ± 11	84 ± 10
Massive hematuria	74 (71%)	35 (60%)
Median disease duration at biopsy, months	2 (0.3 ~ 76)	2 (NA)
Treatment		
Immunosuppressive treatment	104 (100%)	28 (48%)
Steroids alone	4 (4%)	18 (31%)
Cytotoxic agents alone	7 (7%)	0
Steroids plus cytotoxic agents	93 (89%)	10 (17%)
High dose methylprednisolone	72 (69%)	NA
Follow-up duration, months	40 (12, 145)	62 (20, 268)

Data are expressed as number (percentage), median (range), or mean ± SD

NA not available

Classification of histologic findings according to the Oxford classification

Pathology information was complete for each pathologic variable in all 104 cases. There was a median number of 20 glomeruli per biopsy (range 7–49). The biopsy specimens of 31 cases were independently reviewed by two pathologists. The ICC scores of each pathologic variable between the pathologists were M (0.742), E (0.723), S (0.623), T (1.000) and C (0.674). Because all of the lesions showed good or very good reproducibility (ICC score > 0.6), the biopsy specimens of the remaining 73 patients were reviewed by one pathologist. In our HSPN cohort, the percentages of glomeruli exhibiting T1&2 and C1&2 were significantly higher compared to pediatric IgAN patients [21–24] (Supplementary Table S1).

Correlation between pathological lesions and baseline clinical features

All patients showed different degrees of hematuria. The clinicopathological correlations at the time of biopsy are summarized in Table 2. The mesangial score was strongly associated with nephrotic-level proteinuria (p = 0.019). Tubular atrophy/interstitial fibrosis and C > 25% were associated with reduced eGFR at the time of biopsy (p = 0.002 and p = 0.038, respectively). No correlation was found between hypertension and pathologic variables (data not shown).

Correlation between pathologic lesions and treatment

All four patients treated with corticosteroids alone showed M0, S0, and T0. Three of these patients (75%) also showed E0 and C0. All seven patients treated with a cytotoxic agent alone showed T0 and C ≤ 25%. Among these 7 patients, there were 6 patients (85.7%) with E0, 5 patients (71.4%) with S0, and 4 patients (58.1%) with M0. Patients with M1, E1, S1 and C1&2 were more likely to have been treated with high-dose methylprednisolone followed by oral treatment with corticosteroids in combination with a cytotoxic agent (Table 2). However, there was no significant difference in the severity of M, E, S, T, and C between patients with and without renin-angiotensin system (RAS) blockade therapy (data not shown).

Follow-up results

Eight patients (7.7%) progressed to the primary outcome IRF after 7–85 months. The median age was 11.5 (6~15) years, and 5/8 patients (62.5%) were female. Nephrotic level proteinuria was present in 7 (87.5%) patients, massive hematuria was present in 6 (75%) patients, and hypertension was present in one (12.5%) patient at the time of biopsy. All 8 patients were given combination therapy with corticosteroids and a cytotoxic agent (7 patients were treated with intravenous high-dose methylprednisolone).

Table 2 Clinicopathological correlations at the time of renal biopsy

	Nephrotic-level proteinuria	p	eGFR	p	MP therapy	p
Mesangial hypercellularity						
M0	22 (43%)		162 ± 41		30 (59%)	
M1	35 (66%)	0.019	160 ± 53	0.861	42 (79%)	0.024
Endocapillary hypercellularity						
E0	42 (55%)		164 ± 51		49 (64%)	
E1	15 (56%)	0.928	154 ± 35	0.374	23 (85%)	0.037
Segmental glomerulosclerosis						
S0	26 (48%)		164 ± 44		31 (57%)	
S1	31 (62%)	0.156	158 ± 52	0.524	41 (82%)	0.007
Tubular atrophy/interstitial fibrosis						
T0	46 (54%)		168 ± 44		56 (66%)	
T1&2	11 (58%)	0.765	131 ± 53	0.002	16 (84%)	0.118
Crescent						
C0	17 (45%)		161 ± 41		18 (47%)	
C1&2	40 (61%)	0.117	161 ± 51	0.955	54 (82%)	< 0.001
C ≤ 25%	45 (51%)		165 ± 45		56 (64%)	
C > 25%	12 (75%)	0.078	138 ± 59	0.038	16 (100%)	0.002

The data are expressed as number (percentage) and mean ± SD

eGFR estimated glomerular filtration rate, *MP* high-dose methylprednisolone

During the follow-up period, 36.5% of the overall study patients (38 patients) developed recurrence of HSPN, 58.7% (61 patients) showed clinical remission, and 77.9% (81 patients) showed remission of proteinuria.

Risk factors for the primary outcome

In the Cox multivariate model, the significant variables associated with the primary outcome were eGFR and proteinuria ($p < 0.05$) at the time of biopsy. Neither MAP nor pathologic lesions were significant variables (Supplementary Table S2). At univariate time-dependent analyses (Kaplan–Meier), regarding the end point of IRF, segmental glomerulosclerosis ($p = 0.025$) impaired renal survival significantly. Mesangial hypercellularity, endocapillary hypercellularity, tubular atrophy/interstitial fibrosis, and crescent scores were not significantly associated with the renal outcome (Figs. 2, 3, 4, 5, 6, 7).

Risk factors for the secondary outcomes

In the Cox multivariate model, eGFR, proteinuria, MAP and pathologic lesions were not significant variables for follow-up proteinuria or clinical remission. The Kaplan–Meier curves for the cumulative risk of proteinuria remission showed that tubular atrophy/interstitial fibrosis was significantly negatively associated with the remission of proteinuria ($p = 0.035$, Fig. 8). Other lesions were not identified as significant variables.

Kaplan–Meier curves for the cumulative risk of clinical remission also showed that tubular atrophy/interstitial fibrosis was significantly negatively associated with clinical
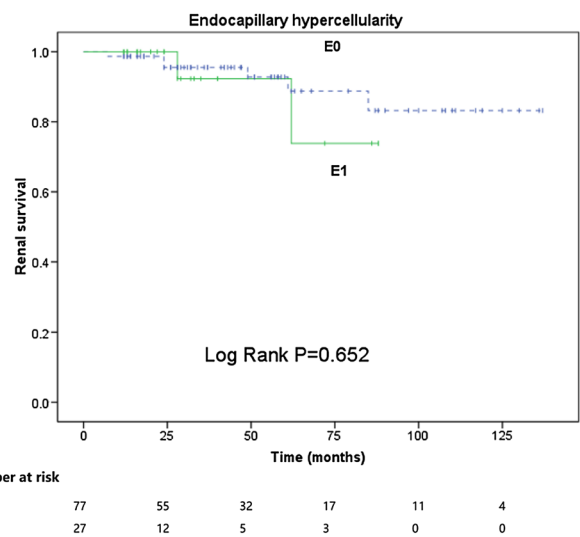
remission ($p = 0.038$, Fig. 9). By contrast, other lesions were not identified as significant variables.

Discussion

Consistent with previous studies [5, 9], our multivariate analysis demonstrated that the eGFR and proteinuria levels at presentation were associated with a poor renal prognosis. Although 58 male patients (56%) were included in our study, more female patients (62.5%) progressed to IRF. These data support the notion that female sex is associated with a poor
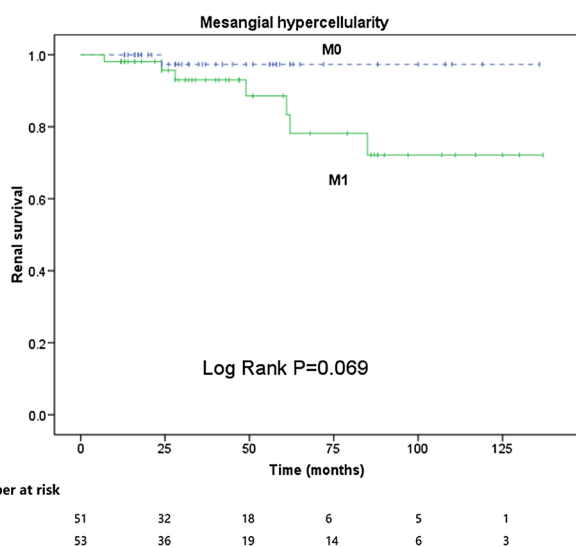
Fig. 3 Renal survival according to endocapillary hypercellularity (E0 or E1), p = 0.652

Fig. 2 Renal survival according to mesangial hypercellularity (M0 or M1), p = 0.069
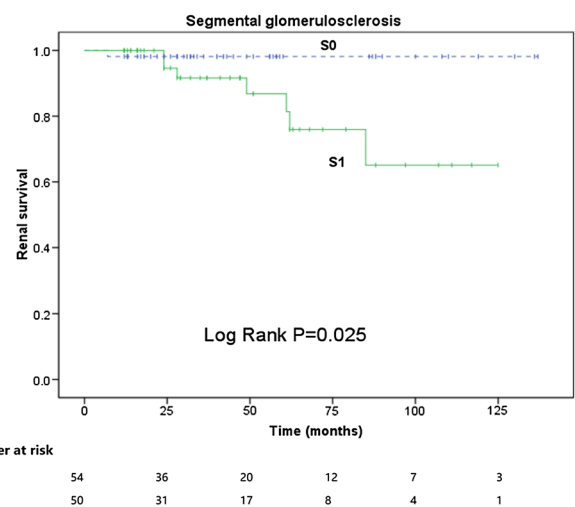
Fig. 4 Renal survival according to segmental glomerulosclerosis (S0 or S1), p = 0.025
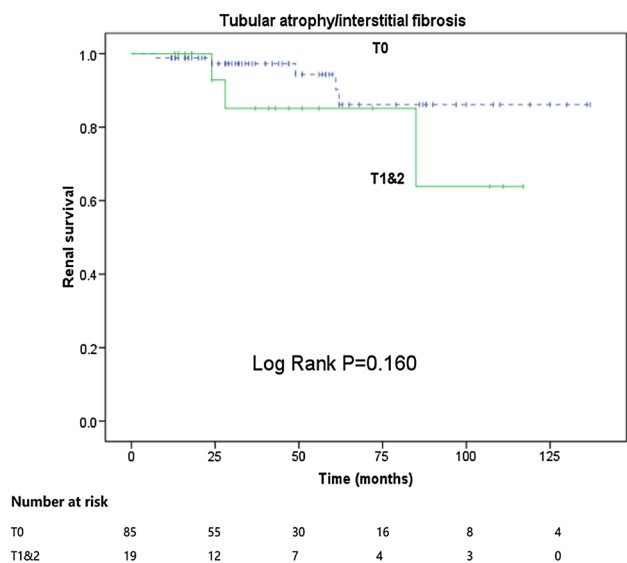
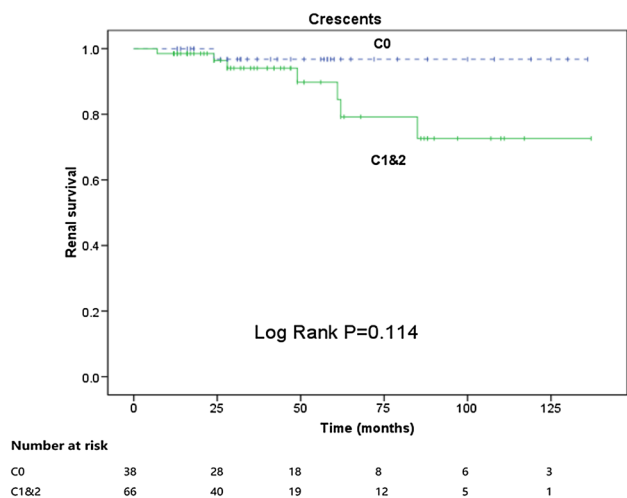**Fig. 5** Renal survival according to tubular atrophy/interstitial fibrosis (T0 or T1&2), p = 0.160

Fig. 6 Renal survival according to crescents (C0 or C1&2), p = 0.114
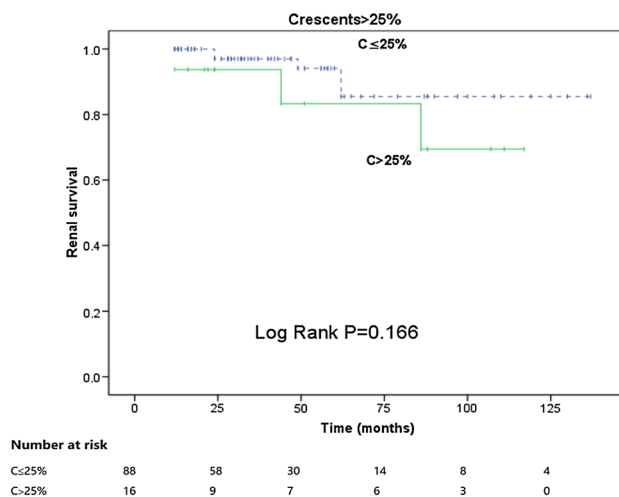

Fig. 7 Renal survival according to glomeruli involved with extracapillary lesions (C ≤ 25% or C > 25%), p = 0.166
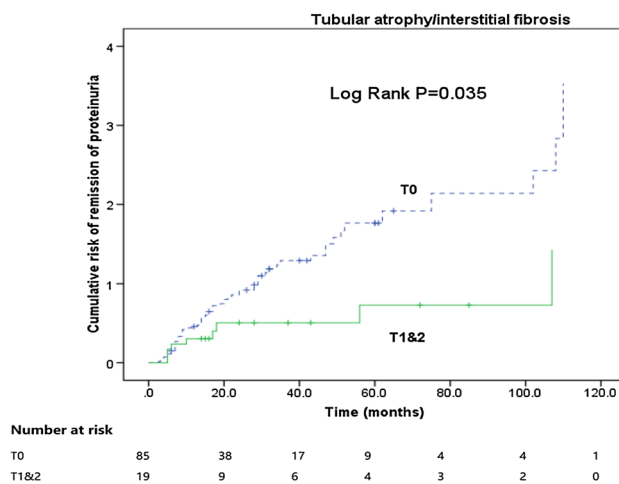

Fig. 8 Cumulative risk of proteinuria remission according to tubular atrophy/interstitial fibrosis (T0 or T1&2), p = 0.035

prognosis [6, 7]. We found that the presence of mesangial hypercellularity was significantly associated with the level of proteinuria at the time of biopsy. More patients with E1, S1, T1, and C1 presented nephritic-level proteinuria than patients without, but the difference was not statistically significant. Children with T1&2 and C > 25% showed a significantly lower eGFR than those without, suggesting that the Oxford classification is associated with initial clinical manifestations.

Although all patients in our study accepted glucocorticoid/immunosuppressive therapy, we identified several renal histologic variables of the Oxford classification system that correlated with the clinical outcome of HSPN: (1) renal

event-free survival was significantly longer in patients with S0 than in those with S1; and (2) patients with T1&2 took longer to achieve remission of proteinuria and clinical remission than those with T0. These findings suggest that S and T could be effective in predicting adverse renal outcomes, as has been reported in other studies [25, 26].

Our results that M1, E1 and C1 were not correlated with renal outcomes are similar to those of Pillebout et al. [5]. These acute lesions are usually transient and do not represent irreversible damage; thus, they may not be associated with long-term outcome. As in other studies, the currently available treatments for HSPN appear to be effective for acute lesions but ineffective for chronic lesions [27, 28]. However, crescents have been related to a poor prognosis of HSPN in previous studies [8, 29]. We also found that
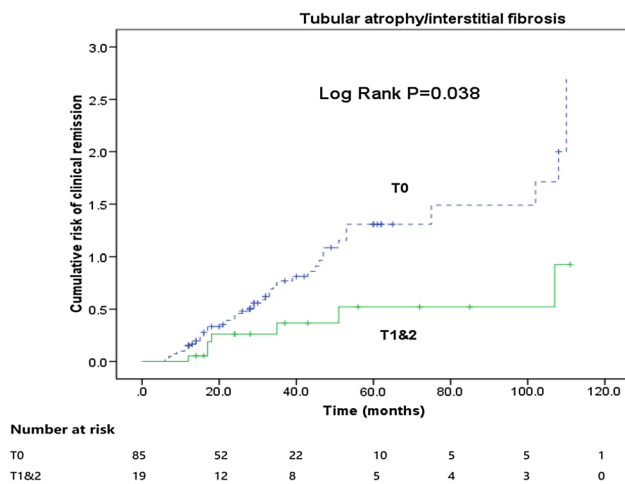
Fig. 9 Cumulative risk of clinical remission according to tubular atrophy/interstitial fibrosis (T0 or T1&2), p = 0.038

mesangial hypercellularity was associated with nephrotic-level proteinuria, which is an important risk factor described by many previous reports [4, 5, 7]. Thus, it is probable that our results may be affected by multiple factors. First, although there were no statistically significant differences, the Kaplan–Meier plots suggested that the renal event-free survival was shorter in patients with M1, E1, T1&2 and C1&2 than in those without, a result that may have been caused by the short follow-up period or the relatively small number of patients with IRF. Second, patients in our study with M1, E1 and C1&2 were more likely to be treated with immunosuppressive drugs, such as high-dose methylprednisolone, during the follow-up period, possibly due to their more severe clinical symptoms. This could explain why crescents were associated with baseline eGFR, but not with eGFR at follow-up, indirectly suggesting that the prompt use of aggressive immunosuppressive treatments might improve the prognosis of these patients, as reported by Niaudet et al. [30]. Thus, whether such acute inflammatory lesions have predictive value requires further study.

There is still some debate regarding the appropriate treatment for HSPN. Some studies have suggested that treatment with steroids and immunosuppressive drugs may be effective for histologically severe HSPN [28, 30]. However, not all studies have confirmed the benefits of multiple combined therapy in patients with HSPN [5, 7]. Due to the retrospective nature of this study and lack of a control group, we did not assess the efficacy of specific treatments in reducing the incidence of renal insufficiency.

Similar to the findings in children with IgAN [13], M1 was associated with nephrotic-level proteinuria. However, we did not detect a predictive value of M1, E1, or C1 for HSPN. Possible reasons for these discrepancies are: (1) HSPN tends to be a self-limited disease, while the

progression of most IgAN cases is chronic [16]; (2) histologically, the presence of crescents was more enhanced in our HSPN patients; and (3) the proportion of patients treated with immunosuppression was higher in our study, likely leading to a better outcome.

Compared to a previous study of adult patients with HSPN, and in agreement with Pillebout et al. [5], our results showed that initial renal failure, the level of proteinuria, interstitial fibrosis and glomerular sclerosis were significant prognostic factors in HSPN. Kim et al. [19] identified endocapillary hypercellularity, tubular atrophy/interstitial fibrosis and crescentic lesions as prognostic factors, which is not completely consistent with our study. More patients accepted immunosuppressive therapy in our study (steroids 93%, with additional immunosuppressants 90%) than in Kim et al.'s study (steroids 61%, with additional immunosuppressants 11%). Additionally, there were more patients with crescents in > 50% of glomeruli in Kim et al.'s study than in ours (33 vs. 4.8%). The outcome of HSPN in adults is poor compared to that in children [6], and the renal pathological chronicity is more severe in adults [31]. Together, these factors may contribute to the observed discrepancies between studies.

Our study has several limitations. First, it was retrospective. Different treatments within the cohort represented a confounding factor. Second, due to loss to follow-up and time limitations, the occurrence of clinical deterioration could have been underestimated. Finally, all the patients in our study agreed to a renal biopsy for severe symptoms at onset, leading to a potential selection bias.

In conclusion, we found mesangial hypercellularity (M1) to be strongly associated with proteinuria at biopsy. T1&2 and C2 were associated with reduced eGFR at biopsy. In addition, we found that segmental glomerulosclerosis and tubular atrophy/interstitial fibrosis, which are ignored in the ISKDC classification, are important prognostic factors and are not affected by the currently available treatments. Furthermore, the Oxford classification may be more relevant to the initial clinical manifestation of HSPN and may help identify histological variables that have independent predictive value for the response to therapy. Large controlled prospective multicenter studies on the prognostic value of the Oxford classification in HSPN patients with a longer follow-up period are needed in the future.

Compliance with ethical standards

Ethical approval Approval was obtained from the clinical research review board of Peking University First Hospital (2016[1227]).

Informed consent For this type of retrospective study using anonymous registry data, formal consent is not required.

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