



A clinicopathological comparison between IgA nephropathy and Henoch–Schönlein purpura nephritis in children: use of the Oxford classification

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Abstract

Background There is controversy over whether IgA nephropathy (IgAN) and Henoch–Schönlein purpura nephritis (HSPN) are the same diseases. This study focuses on the clinicopathological comparison between HSPN and IgAN in children.

Methods Children with IgAN and HSPN who had a diagnostic renal biopsy were enrolled. This study collected the clinical data of patients at biopsy, re-evaluated the pathological lesions of patients according to the Oxford Classification (MEST-C), and made a retrospective comparison between IgAN and HSPN on different stratifications of the course (Tc) and proteinuria.

Results A total of 142 children with IgAN and 57 children with HSPN were enrolled. Various stratification showed the same result, which suggested that IgAN showed more mesangial proliferation (M). HSPN showed more segmental glomerulosclerosis in the Tc > 12 m group than IgAN (S 60.0% vs. 9.10%, $P = 0.008$). In the non-nephrotic-range and nephrotic-range proteinuria group, there were no significant differences in MEST-C scores between IgAN and HSPN.

Conclusion M is more common in IgAN. HSPN had more S than IgAN over the course of more than 12 months. These results indicate the differences in the pathogenesis in IgAN and HSPN. We propose early biopsy and active treatment of HSPN within 12 months to delay the development of chronic lesions.

Keywords IgA nephropathy · Henoch–Schönlein purpura nephritis · Children · Kidney biopsy · The Oxford classification · Clinicopathological

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Introduction

IgA nephropathy (IgAN) is one of the most prevalent types of glomerulonephritis, which is characterized by recurrent hematuria and proteinuria with precursor infection. Henoch–Schönlein purpura (HSP) is the most frequently

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detected form of vasculitis in children. About 30–60% of patients with HSP develop nephritis (HSPN) with urinary abnormalities and/or renal impairment [1]. IgAN and HSPN share the same histological feature of predominant glomerular deposits of IgA, mostly represented by the subclass IgA1 [2]. Due to the similarity in their pathology, there is controversy over whether IgAN and HSPN are the same diseases. Meadow et al. believed that IgAN was a kind of HSPN without rash [3], while other researchers considered that IgAN differs from HSPN [4].

Over the past decade, many studies have indicated that aberrantly glycosylated IgA1 is necessary for the development of both diseases [5–7]. Despite the same oriented pathogenesis, IgAN differs from HSPN in clinical manifestation and pathology [8–10]. However, previous studies that focused on the comparison between IgAN and HSPN did not use the same pathological classification for the assessment of histological lesions of these two diseases. Also, these studies overlooked the fact that the time from the onset of renal involvement to biopsy and proteinuria may have an influence on the histological lesions.

The Oxford Classification for IgAN includes mesangial proliferation (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and cellular/fibrocellular crescents (C). On the basis of the consideration that the Oxford Classification covers more chronic lesions than the ISKDC standard for HSPN and the great value of MEST-C in predicting the prognosis of the disease, we evaluated the pathological lesions according to the updated Oxford Classification (MEST-C) in both IgAN and HSPN [11, 12]. In addition, we made a comparison between IgAN and HSPN at a different time from the first time to find urinary abnormalities to biopsy and different levels of proteinuria. Therefore, this study focuses on the clinicopathological association between HSPN and IgAN in children on different stratifications.

Methods

Patients

This study performed a retrospective investigation of the clinical records from pediatric patients, age < 18 years, diagnosed with IgAN or HSPN through renal biopsy, at the department of nephrology in Beijing Children's Hospital between January 2013 and January 2018. The diagnosis of IgAN was based on the presence of IgA as the sole or predominant immunoglobulin in the glomerular mesangium without any systemic disease, such as HSPN, systemic lupus nephritis [13]. HSPN was defined as palpable purpura without platelet reduction or coagulation dysfunction, renal involvement (e.g., proteinuria, hematuria, and renal failure),

as well as one or more manifestations such as abdominal pain, arthritis/arthralgia, and tissue biopsy revealing IgA deposits [14]. Exclusion criteria for HSPN were patients with thrombocytopenic purpura, other systemic diseases, acute post-streptococcal glomerulonephritis, or any other primary and secondary glomerulonephritis. All patients with IgAN and HSPN underwent a renal biopsy. The renal biopsy indications of our institution are atypical or severe glomerulonephritis, steroid-resistant or frequent recurrence of nephrotic syndrome, persistent hematuria or proteinuria, secondary glomerular diseases (HSPN, lupus nephritis, etc.), diseases that diagnosis depends on renal biopsy (IgAN, Alport syndrome, etc.) and suspected renal parenchymal hypertension. In addition, all the renal biopsies had been provided with informed consent by the patients' parents. The results of which were confirmed by two pathologists and were re-evaluated according to the Oxford Classification. Both the pathologists are blinded to the clinical data of the enrolled patients. When the two pathologists scored differently, the third pathologist would re-score the target and the results would depend on the third pathologist.

This study was approved by the Ethics Committee of the Beijing Children's hospital (Reference number: 2018183). The Ethics Committee specifically stated that informed consent was not necessary, because this study was retrospective and the data were analyzed anonymously.

Clinical data

All clinical parameters of patients were collected at biopsy. These included age at biopsy, age at the first time of abnormal urinalysis (age at T_{Ab-U}), the time from the first time of abnormal urinary test to renal biopsy, sex, weight, height, inducement, presence of clinical symptoms (purpura, abdominal pain, arthralgia, and edema), systolic and diastolic blood pressure (SBP/DBP), albumin (ALB), serum creatinine (Scr), glomerular filtration rate (eGFR), serum immunoglobulin A (sIgA), serum complement 3 (sC3), 24-hour urine protein (24 h urine protein), total score of Oxford Classification (MEST-C) [11] and immunosuppressive therapy before biopsy. The eGFR was estimated using the new Schwartz formula [15]. All patients were divided into the following four clinical types according to the laboratory results: (1) isolated hematuria (urine erythrocyte > 5/HPF and proteinuria < 150 mg/24 h), (2) minimal proteinuria ($150 \text{ mg/24 h} \leq \text{proteinuria} < 25 \text{ mg/kg}$), (3) moderate proteinuria ($25 \text{ mg/kg} \leq \text{proteinuria} < 50 \text{ mg/kg}$), and (4) massive proteinuria ($\text{proteinuria} \geq 50 \text{ mg/kg}$). The inducement is defined as symptoms of upper respiratory tract infection (such as sneezing, sore throat, cough, and fever) or heterologous protein allergy within 2 weeks prior to the first time of the abnormal urinary test of IgAN or HSPN. The immunosuppressive therapy before biopsy includes

corticosteroids and/or a cytotoxic agent such as cyclophosphamide, cyclosporin A, mizoribine, mycophenolate mofetil, and tacrolimus. The reasons for immunosuppressive treatments before renal biopsy were severe abdominal symptom or arthralgia before HSP developed to HSPN and the nephrotic-range proteinuria or nephrotic syndrome in HSPN and IgAN.

In this study, the time from the first time of abnormal urinalysis to renal biopsy was defined as the course (Tc). We stratified the patients according to the Tc and the degree of proteinuria. We chose 3 months and 12 months as different standards of course stratification. All patients with IgAN and HSPN were separately divided into the group given a course of no more than 3 months ($Tc \leq 3$ m group), the group given a course of more than 3 months but no more than 12 months group ($3\text{ m} < Tc \leq 12$ m group), and the group given a course of more than 12 months ($Tc > 12$ m group). The degree of proteinuria was determined on the basis of whether the level of nephrotic-range proteinuria was reached. Nephrotic-range proteinuria (N-p) was defined as urinary total protein over 50 mg/kg/day on 24 h urine sampling, while non-nephrotic-range proteinuria (n-N-p) was defined as urinary total protein less than 50 mg/kg/day on 24 h urine sampling.

Pathological data

In this study, each patient underwent a renal biopsy. Biopsy tissues were fixed in 10% neutral formaldehyde. Within 1 week after a biopsy, these tissues were stained using four methods, including hematoxylin–eosin staining (HE), periodic acid–Schiff stain (PAS), Masson trichrome staining, and periodic acid–silver methenamine (PASM) and Masson staining (PASM–Masson). Light microscopy (LM) was used to observe and evaluate the histopathological lesions. The assessment of the biopsy specimens with a minimum of eight glomeruli was confirmed by two pathologists, and it was re-evaluated according to the Oxford Classification [11].

Statistical methods

Statistical analysis was performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). For continuous variables, data with normal distribution are presented as the mean \pm standard deviation and the independent *t* test was used for comparisons between these variables. However, variables with non-normal distribution revealed by the Shapiro–Wilk test are presented as the median and interquartile range (IQR), and they were compared using the Wilcoxon rank-sum test. Dichotomous variables were compared using the Chi-squared test, and the course-group and the proteinuria group comparisons using the Cochran–Mantel–Haenszel Chi-squared test (CMH Chi-squared test). Ranked variables including the *T* score and the *C* score were analyzed using

the Mann–Whitney *U* test. *P* values < 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 199 patients were enrolled in this study. The total number of patients comprised 142 patients with IgAN (71.4%), of whom 84 were male (59.2%), and 57 patients with HSPN (28.6%), of whom 30 were male (52.6%). One patient with IgAN and two patients with HSPN had no test results with respect to 24 h urine protein, so only 141 patients with IgAN and 55 patients with HSPN were enrolled on proteinuria stratification (Table 2). There were 100 patients (70.4%) in the $Tc \leq 3$ m group, 20 patients (14.1%) in the $3\text{ m} < Tc \leq 12$ m group and 22 patients (15.5%) in the $Tc > 12$ m group in IgAN. There were 35 patients (61.4%) in the $Tc \leq 3$ m group, 12 patients (21.1%) in the $3\text{ m} < Tc \leq 12$ m group and 10 patients (17.5%) in the $Tc > 12$ m group in HSPN. The comparison of the clinical presentation and biopsy findings at biopsy between IgAN and HSPN is provided in Table 1. No significant differences were found between IgAN and HSPN in terms of age at the onset of renal involvement, age at biopsy, course and clinical types. However, IgAN was more likely to show with inducement (49.30% vs. 24.56%, $P = 0.001$) and edema (40.14% vs. 22.81%, $P = 0.022$), while purpura (0 vs. 100.00%, $P < 0.001$), abdominal pain (7.04% vs. 40.35%, $P < 0.001$) arthralgia (1.41% vs. 24.56%, $P < 0.001$) and immunosuppressive therapy before biopsy (43.96% vs. 73.68%, $P < 0.001$) were more often seen in HSPN. There were no differences between IgAN and HSPN in ALB, eGFR, sIgA, sC3, 24 h urine protein, and total score of MEST-C.

Comparison of clinicopathological parameters between IgAN and HSPN on different stratifications

No significant differences in MEST-C scores were found between IgAN and HSPN in both the $Tc \leq 3$ m group and $3\text{ m} < Tc \leq 12$ m group (Fig. 1). Interestingly, in the $Tc > 12$ m group, HSPN showed more S than IgAN (60.0% vs. 9.10%, $P = 0.008$) (Fig. 1). IgAN showed no significant differences in ALB, eGFR, or 24 h urine protein with HSPN in any of the three groups (Fig. 2). In the non-nephrotic-range proteinuria group, HSPN had lower Alb than IgAN (36.40 [IQR 31.20–39.60] vs. 39.25 [IQR 33.93–41.78], $P = 0.01$), and there were no significant differences in MEST-C scores in this group (Table 2). There were no significant differences between IgAN and HSPN in nephrotic-range proteinuria group (Table 2).

Table 1 Comparison between clinico-pathological features of IgAN and HSPN

	IgAN (<i>n</i> = 142)	HSPN (<i>n</i> = 57)	<i>P</i>
Age at T _{Ab-U} (years)	9.63 (6.67–11.66)	9.25 (7.81–11.75)	0.77
T _c (month)	2.00 (1.00–6.00)	2.00 (1.00–8.17)	0.52
Age at biopsy (years)	10.13 ± 21.95	10.21 ± 2.58	0.86
Sex (male/female)	84/58	30/27	0.40
Inducement (%)	49.30	24.56	0.001
Purpura (%)	0	100.00	<0.001
Arthralgia (%)	1.41	24.56	<0.001
Abdominal pain (%)	7.04	40.35	<0.001
Edema (%)	40.14	22.81	0.02
Clinical types			0.68
Isolated hematuria (%)	6	9	
Minimal proteinuria (%)	40	39	
Moderate proteinuria (%)	21	21	
Massive proteinuria (%)	33	31	
SBP (mmHg)	110.00 (102.00–119.00)	114.00 (104.25–120.00)	0.34
DBP (mmHg)	70.00 (61.50–76.00)	70.00 (61.25–77.00)	0.82
Albumin (g/L)	36.10 (27.43–40.75)	35.90 (28.30–38.80)	0.38
eGFR (ml/min/1.73m ²)	109.39 (88.84–125.82)	114.20 (94.39–131.14)	0.06
Serum IgA (g/L)	2.08 (1.46–2.85)	2.32 (1.61–2.97)	0.30
Serum C3 (g/L)	0.97 (0.88–1.12)	0.94 (0.79–1.06)	0.16
24-hour urine protein (g/kg/day)	28.47 (11.87–81.99)	24.15 (9.32–60.81)	0.27
Treatment before biopsy (%)	42.96	73.68	<0.001
Total score of MEST-C	3.00 (2.00–4.00)	3.00 (2.00–4.00)	0.97

IgAN IgA nephropathy, HSPN Henoch–Schönlein purpura nephritis, T_c the time from the first time of abnormal urinalysis to renal biopsy, SBP systolic blood pressure, DBP diastolic blood pressure, eGFR estimated glomerular filtration rate, TC total cholesterol, M mesangial proliferation, E endocapillary hypercellularity, S segmental glomerulosclerosis, T tubular atrophy/ interstitial fibrosis, C cellular/ fibrocellular crescents

In addition, CMH Chi-squared tests for all kinds of stratification showed the same result, which suggested IgAN showed more M (Fig. 3).

Comparison of clinicopathological parameters between different levels of proteinuria in IgAN or HSPN

Relative to the patients of non-nephrotic-range proteinuria, IgAN with nephrotic-range proteinuria showed lower ALB (20.00 [IQR 24.60–31.70] vs. 39.25 [IQR 33.93–41.78], $P < 0.001$), higher total score of Oxford Classification (3.00 [IQR 3.00–4.00] vs. 3.00 [IQR 2.00–4.00], $P = 0.03$), and more C ($Z = -2.316$, $P = 0.021$) (Table 2). On using stepwise logistic regression to estimate the likelihood of non-nephrotic-range vs. nephrotic-range proteinuria with the course and MEST-C, only C ($P = 0.017$) remained significant (Suppl. S1).

Compared with the non-nephrotic-range proteinuria, HSPN with nephrotic-range proteinuria had a shorter course (1.00 [IQR 0.69–2.00] vs. 3.00 [IQR 1.00–10.00],

$P = 0.02$) and lower ALB (27.95 [IQR 24.60–34.88] vs. 36.4 [IQR 31.20–39.60], $P < 0.001$) (Table 2). On using stepwise logistic regression to estimate the likelihood of non-nephrotic-range vs. nephrotic-range proteinuria with the course and MEST-C, none of the variables remained significant (Suppl. S2).

Discussion

To the best of our knowledge, this is the first study to make a clinicopathological comparison between IgAN and HSPN with the Oxford Classification used in HSPN. The Oxford Classification for IgAN is well defined, reproducible, and applicable. Thus, considering the advantage of the Oxford Classification, we re-evaluated the histological lesions of IgAN and HSPN according to the Oxford Classification and made a clinical and pathological comparison between IgAN and HSPN based on the Oxford Classification.

In view of the similarities of IgAN and HSPN in clinical and histological lesions [16, 17], this classification may

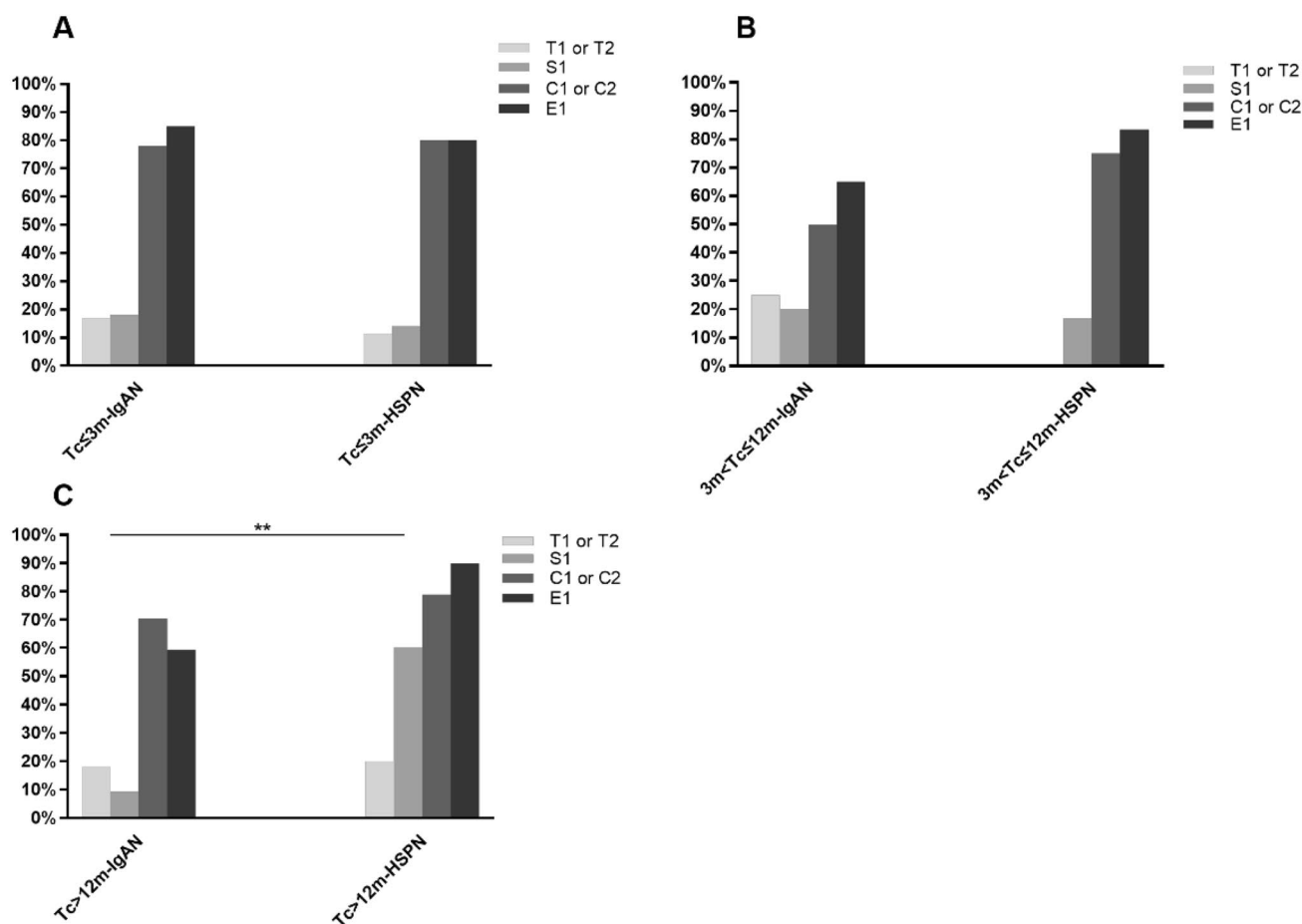


Fig. 1 The comparison in ESTC of IgAN and HSPN in different stratification. *IgAN* IgA nephropathy, *HSPN* Henoch–Schönlein purpura nephritis, *E* endocapillary hypercellularity, *S* segmental glomerulosclerosis, *T* tubular atrophy/interstitial fibrosis, *C* cellular/fibrocellular crescents, *Tc* the time from the first time of abnormal urinalysis to

renal biopsy. No difference between IgAN and HSPN in the Tc of no more than 3 months group (a) and the course of more than 3 months but no more than 12 months group (b). In the course of more than 12 months group, IgAN showed less S than HSPN (c). $**P < 0.01$

also have predictive value for severity and outcome in children with HSPN [18]. Recently, several studies suggested that this classification, especially the S and T lesions which are ignored in the ISKDC classification, was also useful in predicting long-term outcomes of HSPN [19–22]. However, whether the Oxford Classification is applicable for HSPN remains unclear and needs further study.

A retrospective study of a comparative analysis from Japan suggested that IgAN showed more M than HSPN in the children group [10]. The results of this study showed M to be more common in IgAN irrespective of the course and degree of proteinuria. Based on the multiple-hit pathogenesis of IgAN and HSPN [5, 23], the activation of mesangial cells may depend on the level of the mesangial Gd–IgA1 complex and its constituents, particularly their Gd–IgA1 content. The finding that M was more common in IgAN might indicate the difference in the pathogenesis of activation of mesangial cells in IgAN and HSPN. However, it is

unknown whether the pathogenesis differs between IgAN and HSPN, so further study should focus on the mesangial Gd–IgA1 complex and its constituents in the two diseases. In addition, the IgA nephropathy classification working group suggested that the most powerful predictive factor in children and young subjects is M1 [11]. However, validation studies of the Oxford Classification in China indicated that only T had an independent predictive value in Chinese children [24]. Prospective studies with larger sample sizes are warranted to determine the predictive value of M in IgAN and HSPN and to assess whether more M in IgAN implies a difference in the prognosis of IgAN and HSPN.

Observations reported in previous studies suggested that E and C were more common in HSPN, while T and S were more common in IgAN [2, 12]. Hiroyuki Komatsu et al. found no difference of focal segmental glomerulosclerosis between pediatric IgAN and HSPN [10]. However, this study showed that HSPN had more S than IgAN in the Tc > 12 m

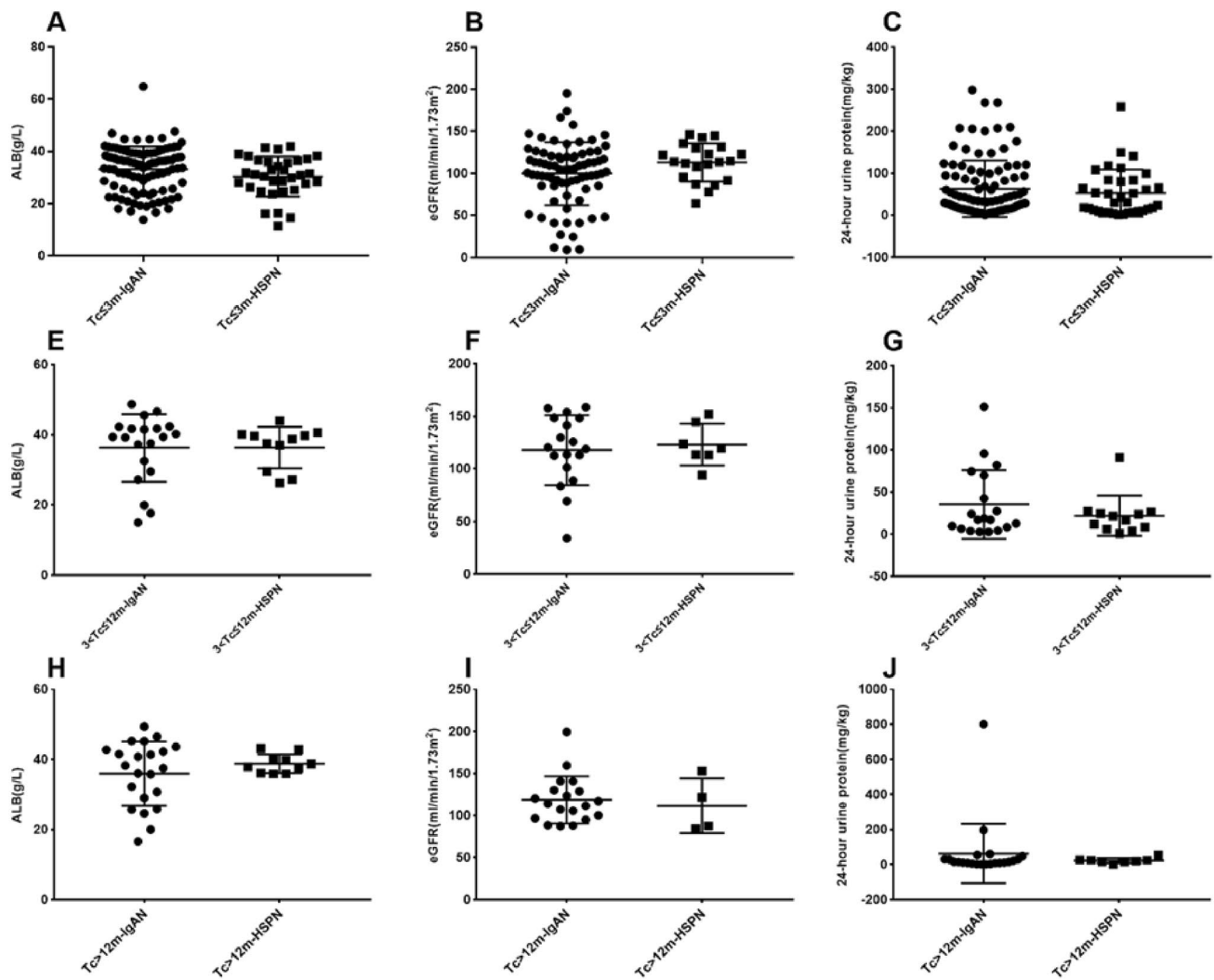


Fig. 2 The comparison in ALB, eGFR and 24-hour urine protein between IgAN and HSPN. *IgAN* IgA nephropathy, *HSPN* Henoch–Schönlein purpura nephritis, *eGFR* estimated glomerular filtration rate, *Tc* the time from the first time of abnormal urinalysis to renal

biopsy. No significant differences of ALB (a, e, h), 24 h-proteinuria (b, f, i) and eGFR (c, g, j) between IgAN and HSPN in all three course stratification

group, but there was no difference in MEST-C between the two diseases in the $Tc \leq 3$ m group and the $3\text{ m} < Tc \leq 12$ m group. In this study, we found that immunosuppressive therapy before the renal biopsy was more often seen in children with HSPN (73.68% vs. 43.96%, $P < 0.001$). Several studies suggested that the currently available treatments for HSPN appear to be effective for acute lesions but ineffective for chronic lesions [25, 26]. But, interestingly, we found that HSPN showed more S than IgAN in the $Tc > 12$ m even though more children with HSPN received immunosuppressive therapy before the renal biopsy. Thus, our data imply that the process of S lesion in HSPN may be faster than that in IgAN. However, the reasons for these different results between this study and the previous may be higher age of patients in the previous study and ignorance towards the

influence of the course. Recently, several studies have identified that S lesions could be used to assess renal outcomes of HSPN [22, 27]. Moreover, although there is a lack of convincing large randomized controlled studies proving the effect of immunosuppressive therapy, several single-center studies have indicated that treatment can improve the histological and clinical outcome in pediatric HSPN [28, 29]. Therefore, we propose early biopsy and more active treatment of HSPN within 12 months to delay the process of chronic lesions.

In this study, we compared IgAN and HSPN in different degrees of proteinuria and we found that both IgAN and HSPN showed more C with nephrotic-range proteinuria. However, in the logistic regression analysis, the association between nephrotic-range proteinuria and crescents was only

Table 2 Comparison between IgAN and HSPN in different level of proteinuria

	Non-nephrotic-range proteinuria		Nephrotic-range proteinuria		P_1	P_2	P_3	P_4
	IgAN ($n=94$)	HSPN ($n=37$)	IgAN ($n=47$)	HSPN ($n=18$)				
Tc (month)	2.00 (1.00–7.00)	3.00 (1.00–10.00)	1.50 (1.00–3.00)	1.00 (0.69–2.00)	0.68	0.32	0.02	0.01
Albumin (g/L)	39.25 (33.93–41.78)	36.40 (31.20–39.60)	20.00 (24.60–31.70)	27.95 (24.60–34.88)	0.01	0.12	<0.001	0.002
eGFR (mL/min/1.73 ²)	108.22 (88.80–124.79)	114.51 (109.40–126.86)	114.24 (86.32–134.51)	113.36 (87.60–142.86)	0.10	0.80	0.63	0.59
Total score of MEST-C	3.00 (2.00–4.00)	3.00 (2.00–4.00)	3.00 (3.00–4.00)	3.00 (3.00–4.00)	0.78	0.67	0.03	0.36
M (0/1)	2/92	2/35	0/47	2/16	0.68	0.07	0.55	0.83
E (0/1)	21/73	8/29	9/38	2/16	0.93	0.69	0.66	0.57
S (0/1)	80/14	28/9	37/10	14/4	0.20	1.00	0.34	1.00
T(0/1/2)	79/14/1	33/4/0	36/7/4	16/1/1	0.44	0.29	0.22	0.92
C(0/1/2)	31/57/6	10/25/2	10/27/10	1/15/2	0.73	0.75	0.02	0.06

IgAN IgA nephropathy, HSPN Henoch–Schönlein purpura nephritis, Tc the time from the first time of abnormal urinalysis to renal biopsy, eGFR estimated glomerular filtration rate, M mesangial proliferation, E endocapillary hypercellularity, S segmental glomerulosclerosis, T tubular atrophy/interstitial fibrosis, C cellular/fibrocellular crescents. P_1 non-nephrotic-range proteinuria IgAN vs. non-nephrotic-range proteinuria HSPN, P_2 nephrotic-range proteinuria IgAN vs. nephrotic-range proteinuria HSPN, P_3 non-nephrotic-range proteinuria IgAN vs. nephrotic-range proteinuria IgAN, P_4 non-nephrotic-range proteinuria HSPN vs. nephrotic-range proteinuria HSPN

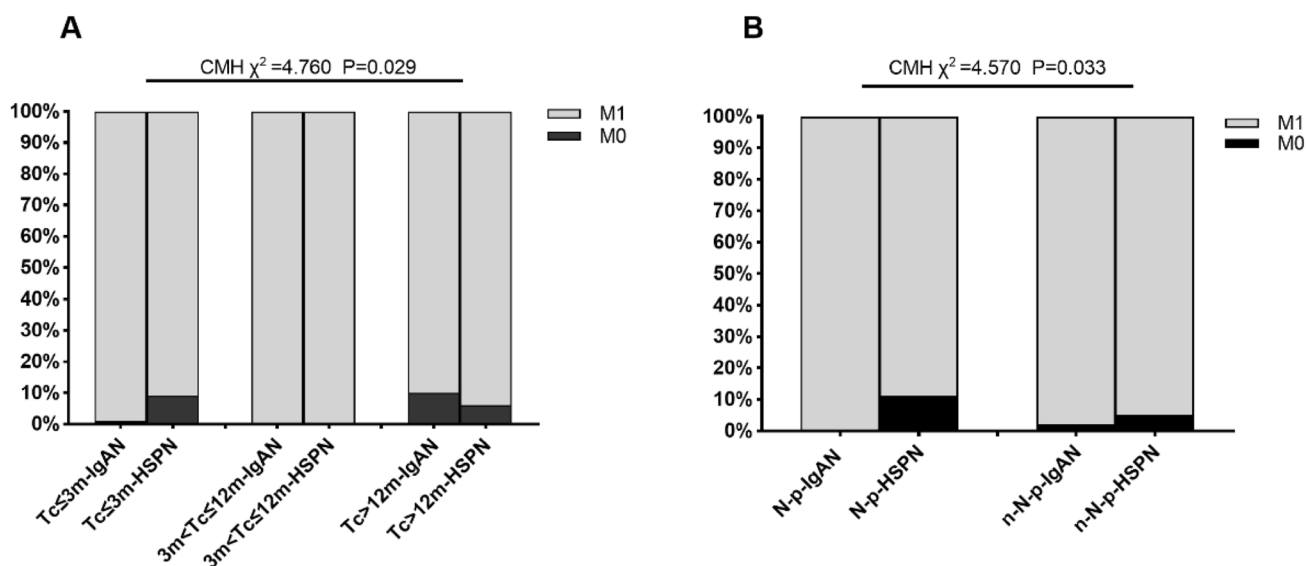


Fig. 3 The comparison in M of IgAN and HSPN. IgAN IgA nephropathy, HSPN Henoch–Schönlein purpura nephritis, N-p nephrotic-proteinuria, n-N-p non-nephrotic-proteinuria. Comparison on the stratification by course (a). Comparison on the stratification by proteinuria (b)

detected in IgAN but not in HSPN. Similarly, a recent study on IgAN indicated that patients with proteinuria > 0.50 g/day showed more S and T, while patients with proteinuria 0.31–0.50 g/day exhibited higher proportions of C [29]. In addition, Imke Hennies et al. suggested that there were no differences of histological lesions between nephrotic-range and non-nephrotic-range proteinuria in children with HSPN [30]. Further studies are needed to assess the pathological mechanism behind proteinuria in IgAN and HSPN.

This study has some limitations. This was a single-center retrospective study with a small sample size, which lacked data on the prognosis of diseases. Thus, large-scale, multicenter prospective studies are needed to overcome these limitations.

In conclusion, M is more common in IgAN. HSPN showed more S than IgAN over the course of more than 12 months. These results indicate the differences in the pathogenesis of IgAN and HSPN. Moreover, we propose

early biopsy and active treatment of HSPN within 12 months to delay the development of chronic lesions.

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Compliance with ethical standards

Conflicts of interest The authors declare that no conflicts of interest exist.

Ethical approval The study was approved by the ethics committee of Beijing Children's Hospital, China. The Ethics Committee specifically stated that informed consent was not required because this study was retrospective and the data analyzed anonymously.

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