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Application of the Oxford MEST-C Classification in Pathological Classification of Henoch-Schönlein Purpura Nephritis in Children

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[Abstract]

Objective: To explore the evaluation and application of the Oxford classification in Henoch-Schönlein purpura nephritis (HSPN), so as to provide a more refined classification and guidance for the diagnosis and treatment of pediatric HSPN.

Methods: A retrospective study was conducted on the clinical and pathological data of children hospitalized in the Department of Nephrology of our hospital and diagnosed with HSPN by renal biopsy between October 2018 and November 2023. Their pathological specimens were evaluated according to both the International Study of Kidney Disease in Children（ISKDC classification）

and the Oxford classification, and the results were statistically analyzed.

Results: 1. The study found no statistically significant differences in proteinuria changes among the M1E0, Type IIIa, and Type IIIb classifications at the three observation time points of 3, 6, and 9 months. 2. The application of the Oxford classification to HSPN can reflect its clinical features and prognosis: M lesions are associated with quantitative proteinuria; T lesions and C lesions are associated with urinary RBC count; and the severity of C lesions correlates with quantitative proteinuria and urinary red blood cells.

Conclusions: The Oxford classification can be applied to the pathological assessment of children with HSPN, and is more conducive to determining the timing of medication, guiding clinical treatment, and evaluating prognosis.

Keywords: Henoch-Schönlein purpura nephritis in children, Oxford classification, pathological classification

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Henoch-Schönlein purpura nephritis (HSPN) is one of the most common secondary kidney diseases in children and the most common systemic vasculitic disease in children.[1] Renal involvement is one of the most important factors affecting the long-term prognosis of Henoch-Schönlein purpura.[2] Renal biopsy pathological examination is the gold standard for determining the degree of renal injury and provides a basis for disease diagnosis, treatment, and prognosis.[3]

The currently commonly used pathological grading standards were established by the ISKDC in 1974 and the Nephrology Group of the Chinese Medical Association Pediatrics Branch in 2000.[4] The specific grades are: Grade I, minor glomerular abnormalities; Grade II, pure mesangial proliferation: a. focal segmental, b. diffuse; Grade III, mesangial proliferation with <50% glomerular crescent formation and/or segmental lesions (sclerosis, adhesion, thrombosis, necrosis), and the mesangial proliferation may be: a. focal segmental, b. diffuse; Grade IV, lesions same as Grade III, with 50%–75% of glomeruli accompanied by the above lesions, divided into: a. focal segmental, b. diffuse; Grade V, lesions same as Grade III, with >75% of glomeruli accompanied by the above lesions, divided into: a. focal segmental, b. diffuse; Grade VI, membranoproliferative glomerulonephritis.[1]

The Oxford classification of IgA nephropathy was first proposed by an international consensus organization in 2009.[5],[6] It was initially mainly used in adults, and is now gradually being adopted in children with IgA nephropathy as well.[7] The Oxford classification, originally based on the MEST score, was later updated to the MEST-C score with the addition of a crescent dimension (C0, C1, C2): mesangial hypercellularity (M0, M1), endocapillary hypercellularity (E0, E1), segmental glomerulosclerosis or adhesion (S0, S1), tubular atrophy/interstitial fibrosis (T0, T1, T2), and later crescent formation (C0, C1, C2) was added.[8]

Pediatric Henoch-Schönlein purpura nephritis (HSPN), also known as IgA vasculitis with nephritis (IgAVN), is generally considered to be the same disease as IgA nephropathy (IgAN) with different clinical manifestations, sharing the same pathogenesis,[9] and the two are similar in clinical and pathological aspects. Currently, there is no unified international standard for the pathological classification of Henoch-Schönlein purpura nephritis. Compared with the ISKDC classification, the Oxford classification takes into account both acute and chronic lesions of the glomeruli and tubulointerstitium, provides a more comprehensive assessment of the degree of renal injury, and also has certain value in predicting disease prognosis.[10–15] A biopsy study of HSPN found that an Oxford classification score of E1 could predict the initial improvement in renal function after

immunosuppressive therapy.[10] S1, T2, and C2 were proposed to be independently associated with longitudinal decline in renal function in IgAN patients, and targeted therapeutic management of the disease can delay the progression of renal function decline.[13] A retrospective study in the United States classified the pathology of children with HSPN according to different classifications and compared the predictive relationships between the ISKDC classification and the Oxford classification pathology and clinical manifestations and indicators. The results found that S1 accurately predicted the composite outcome of hypertension, CKD, and proteinuria in different cohorts of children with HSPN, suggesting that S and T can be used to predict renal prognosis in children with HSPN.[14] The proportion of crescents (C) is a high-risk factor for HSPN progression,[11] and can predict the long-term renal outcome of HSPN patients.[12]

To explore the significance of applying the Oxford classification in pediatric Henoch-Schönlein purpura nephritis, including its value in predicting disease outcomes and providing targeted guidance for treatment management, this study took children hospitalized in the Department of Nephrology of our hospital from October 2018 to November 2023 who were diagnosed with HSPN by renal biopsy as the research subjects, reclassified their pathological results according to the

Oxford classification, collected data on renal function before and at staged intervals after biopsy, treatment regimens, treatment outcomes, and analyzed the application of the Oxford classification in pediatric HSPN.

I. Research Methods

1. Research Subjects

This study was a single-center, retrospective cohort study. Data from a total of 100 children hospitalized in the Department of Nephrology of our hospital from October 2018 to November 2023 who were diagnosed with HSPN by renal biopsy were collected.

1.1 Inclusion Criteria:

(1) Onset age ≤ 18 years old; (2) Patients with newly diagnosed and previously untreated primary HSPN;(3) The guardians of the participants provided written informed consent and agreed to cooperate with scheduled diagnosis, treatment, laboratory examinations and long-term follow-up; (4) No severe impairment of important organ functions such as heart and lung.

1.2 Exclusion Criteria:

(1) Children who had received hormones, immunosuppressants, biological agents or other immunity-affecting medications within 2 years before disease onset; (2) Children with other concurrent kidney diseases; (3) Children with clinical manifestations of HSPN secondary to other diseases; (4) Children with other immune diseases or immunodeficiency diseases; (5) Children with severe infection, tumors, or other major diseases affecting immune function and organ function; (6) Children receiving long-term nephrotoxic drugs or treatments; (7) Age >18 years; (8) Presence of mental illness or other conditions that may interfere with the study results.

2. Data Collection

The data collected included the children's age, sex, diagnosis, 24-hour urine protein (24HUP), urinary red blood cell count (/HPF), renal function before renal biopsy, including blood urea nitrogen (BUN), serum creatinine (Scr), and serum uric acid (SUA), biopsy date, renal biopsy pathological findings, renal function at 3, 6, and 9 months after biopsy, use of hormones and immunosuppressants, complications, infection status, and treatment outcomes. The pathological findings of all study participants were reclassified according to the Oxford classification..

4. Statistical Methods

SPSS 27.0 software (IBM, IL, USA) was used for analysis. Measurement data conforming to normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$), and non-normally distributed measurement data were expressed as median (P25, P75). Differences between normally distributed data were compared using the t-test, and differences between non-normally distributed data were compared using the Mann-Whitney U test. Correlation between two sets of data was analyzed using Spearman analysis. The chi-square test was used to analyze whether there was an association between classification and urine protein negativity. $P<0.05$ was considered statistically significant.

5.This study was reviewed and approved by the Ethics Committee of Hebei Children's Hospital (approval number 202407-47).

II. Results

1. General Data, Pathological Results, and Clinical Data

During the study, 12 children were lost to follow-up, and 88 children were ultimately included in the study. General data are shown in Table 1. Children with HSPN who presented with massive proteinuria (>50 mg/kg/24h) and still had massive proteinuria after 4 weeks of prednisone (2 mg/kg) treatment, or who did not reach the level of massive proteinuria but had urine protein persistently greater than 0.5

g/24h after 8 weeks of full-dose hormone therapy, underwent renal biopsy .Among the children pathologically diagnosed with HSPN, 50 were male (56.8%) and 38 were female (43.2%), with a median age of 10 years (4, 16) (see Table 1). According to the ISKDC classification, none of the 88 patients were classified as grade Ⅴ or Ⅵ. The proportions of patients with grade Ⅰ, Ⅱa, Ⅱb, Ⅲa, Ⅲb, Ⅳa and Ⅳb were 4.5% (4 cases), 5.6% (5 cases), 6.8% (6 cases), 34.2% (31 cases), 41.0% (36 cases), 3.4% (3 cases) and 2.3% (2 cases), respectively. Among them, 1 case showed endocapillary proliferative lesion. According to the Oxford classification, M1, E1, S1, T1, T2, C1, and C2 accounted for 57.9% (51 cases), 22.7% (20 cases), 31.8% (28 cases), 21.6% (19 cases), 20.5% (18 cases), 57.9% (51 cases), and 20.5% (18 cases) of patients, respectively. Among them, children with grade I, IIa, and endocapillary proliferative type received hormone therapy alone, while the remaining children were treated with tacrolimus combined with hormones. In terms of complications, 25% (22 cases) of children had joint swelling and pain, and 26.1% (23 cases) had abdominal purpura, presenting as abdominal pain, vomiting, and gastrointestinal bleeding. In terms of clinical characteristics, 5 indicators were included: 24h proteinuria, urinary red blood cells/HP, and renal function (BUN, Scr, SUA). Renal function indicators were monitored before renal biopsy and at 3, 6, and 9 months after biopsy.

Table 1 Basic Clinical Characteristics of Pediatric Patients

Clinical Characteristics	Number of Cases	Percentage %
Sex		
Male	50	56.8
Female	38	43.2
Hormone added	88	100.0
Immunosuppressant added	78	88.6
Urine protein negativity	85	96.5
Complications		
Joint swelling and pain	22	25.0
Abdominal purpura	23	26.1
Concurrent infection		
Respiratory tract infection	82	93.1
Urinary tract infection	9	10.2
Intestinal infection	3	3.4

Before and after renal biopsy, the clinical indicators included blood urea nitrogen (BUN), serum creatinine (Scr), serum uric acid (SUA), 24-hour urine protein excretion, and urinary red blood cell (RBC) count per high-power field (HPF). BUN, Scr and SUA were normally distributed and are presented as mean ± standard deviation, whereas 24-hour urine

protein excretion and urinary RBC count were not normally distributed and are presented as median (P25, P75).The BUN levels were 4.03 ± 1.28, 4.98 ± 1.34, 5.14 ± 1.35 and 5.11 ± 1.35 mmol/L, respectively. The Scr levels were 41.13 ± 12.26, 53.23 ± 13.30, 47.92 ± 13.88 and 46.80 ± 10.67 μmol/L, respectively. The SUA levels were 244.42 ± 77.79, 262.50 ± 74.20, 288.56 ± 76.34 and 301.31 ± 68.74 μmol/L, respectively. The urinary RBC count was 54.5 (15.12, 172.93)/HPF, and the 24-hour urine protein excretion was 1.80 (0.96, 3.12) g.

Urine protein negativity was defined as: urine protein quantification <0.15 g/24h. Twelve patients were lost to follow-up, and whether urine protein turned negative was unknown. A total of 3 patients were known to have not achieved urine protein negativity, accounting for a small proportion. In the ISKDC classification, IIIa/IIIb accounted for the largest proportion, among which 2 cases did not achieve urine protein negativity (3.1%), and 1 case of type IV did not achieve negativity (20%). Grades I and IIa/IIb all successfully achieved urine protein negativity. In the Oxford classification, among those classified as M0 and M1, 1 case (2.7%) and 2 cases (4.8%) did not achieve protein negativity, respectively; 3 cases (4.4%) with E0 did not achieve urine protein negativity, while all E1 cases achieved negativity; 1 case (1.7%) with S0 did not achieve negativity; among T0 and T1/T2, 1 case (2.0%) and 2 cases (5.4%) did not

achieve negativity, respectively; all C0 cases achieved negativity, and 3 cases (4.3%) with C1/C2 did not achieve negativity. (See Table 2)

Table 2 Distribution of ISKDC and Oxford Pathological Classifications

Pathological Classification	Number of Patients (Percentage of Total Patients %)	Final Urine Protein Negativity (Percentage of Patients in This Type)
ISKDC Classification		
Ⅰ	4（4.5）	4（100）
Ⅱa/Ⅱb	5（5.6）/6（6.8）	11（100）
Ⅲa/Ⅲb	30（34.1）/36（41.0）	64（96.9）
Ⅳa/Ⅳb	3（3.4）/2（2.3）	4（80.0）
Oxford Classification		
M0	37（40.0）	36（97.3）
M1	51（57.9）	49（96.1）
E0	68（77.3）	65（95.6）
E1	20（22.7）	20（100）
S0	60（68.1）	59（98.3）
S1	28（31.8）	26（92.9）
T0	51（57.9）	50（98.0）
T1/T2	19（21.6）/18（20.5）	35（94.6）
C0	19（21.6）	19（100）
C1/C2	51（57.9）/18（20.5）	66（95.7）

Among the proportions of Oxford classification within each ISKDC classification: for ISKDC grade I patients, M0 was present in 3 cases (75%), M1 in 1 case (25%), and the remaining E, S, T, and C classifications were

all M0, S0, T0, C0; in IIa/IIb, the Oxford classification proportions were M0 (6, 54.5%), M1 (5, 45.5%), E0 (11, 100%), E1 (0, 0%), S0 (10, 90.9%), S1 (1, 9.1%), T0 (8, 72.7%), T1/2 (3, 27.3%), C0 (11, 100%), C1/2 (0, 0%); in IIIa/IIIb, the Oxford classification proportions were M0 (27, 40.3%), M1 (40, 59.7%), E0 (51, 76.1%), E1 (16, 23.9%), S0 (42, 62.7%), S1 (25, 37.3%), T0 (38, 56.7%), T1/2 (29, 43.3%), C0 (1, 2.9%), C1/2 (65, 97.1%); in IVa/IVb, M1, T1/2, and C1/2 were all 5 cases, accounting for 100%, E0 (2, 40%), E1 (3, 60%), S0 (3, 60%), S1 (2, 40%). The higher the traditional grade, the greater the proportion of M1, E1, S0, T1/2, and C1/2 in the Oxford classification.

2. Correlation Between Oxford Classification Pathological Indicators and Laboratory Tests

This study included five clinical indicators: BUN, Scr, UA, urinary RBC count, and 24HUP, expressed as mean (maximum, minimum). Comparisons were made between M0 and M1, E0 and E1, S0 and S1, T0 and T1/2, C0 and C1/2, and C1 and C2 to determine whether there were differences in clinical indicators. The results found that M1 was associated with 24HUP; the mean urine protein quantification of M1 was greater than that of M0, with statistical significance between the two groups ($P<0.05$), while BUN, Scr, UA, and urinary RBC count showed no significant correlation. Between E0 and E1, and between S1 and S0,

there was no significant correlation in BUN, Scr, UA, ERY, or 24HUP. T0 was associated with ERY; the mean of T1/T2 was less than that of T0, with statistical significance between the two groups (P<0.05), while the remaining indicators showed no correlation. C1/C2 was associated with ERY; the urinary RBC count of C0 was less than that of C1/C2, with statistical significance (P<0.05), while the remaining indicators showed no correlation. Some studies have shown that the proportion of crescents is associated with disease progression. Here, the same tests were performed between C1 and C2. Between C1 and C2, it was found that C2 was correlated with both urinary RBC count and 24HUP; the urinary RBC count and 24HUP of C2 were both greater than those of C1, with statistical significance between the two (P<0.05) (see Tables 3–5). M1 was correlated with 24HUP, and C2 was correlated with both urinary RBC count and 24HUP, suggesting that the Oxford classification is conducive to the quantitative grading of pathological injury and corresponds to clinical phenotypes such as proteinuria and renal function impairment.

Table 3 Correlations of Oxford Pathological Indices with Laboratory Tests

Pathological Index	Blood Urea Nitrogen mmol/L	Creatinine μmol/L	Uric Acid μmol/L	Urinary RBC count (/HPF)	24h Urine Protein g
M0	3.8（2.29,9.16）	36.86（21,71）	227.19（120,412）	119.34（1,949.3）	1.65（0.40,9.61）

M1	4.09（1.92,7.21）	43.65（11,71）	254.02（108,486）	158.19（4,1788）	2.68（0.26,12.25）
P value	0.27	0.328	0.283	0.839	0.004
E0	4.04（1.97,7.21）	40.08（21,71）	238.68（108,486）	149.75（1.28,1144）	2.00（0.26,12.25）
E1	4.87（3.64,9.64）	44.17（26,71）	262.26（120,428）	187.54（1,1788）	3.76（0.50,9.61）
P value	0.487	0.358	0.176	0.638	0.106

Table 4 Correlations of Oxford Pathological Indices with Laboratory Tests

Pathological Index	Blood Urea Nitrogen mmol/L	Creatinine μmol/L	Uric Acid μmol/L	Urinary RBC count (/HPF)	24h Urine Protein g
S0	3.99（1.92,9.16）	40.52（21,70）	241.4（123,428）	169.3（1,1788）	2.39（0.26,9.61）
S1	4.10（2.10,7.21）	42.43（11,71）	250.4（108,486）	134.（4.4,773）	2.42（0.3,12.25）
P value	0.448	0.957	0.385	0.975	0.936
T0	4.05（1.97,9.16）	38.78（11,71）	240.5（108,412）	97.64（1,773）	2.34（0.26,9.61）
T1/T2	3.99（1.97,7.21）	44.35（21,71）	250（120,486）	242（1.28，1788）	2.48（0.3,12.25）
P value	0.73	0.043	0.635	0.020	0.839

Table 5 Correlations of Oxford Pathological Indices with Laboratory Tests

Pathological Index	Blood Urea Nitrogen mmol/L	Creatinine μmol/L	Uric Acid μmol/L	Urinary RBC count (/HPF)	24-h Urinary Protein(g)
C0	3.69(1.97,9.16)	37.78（24,71）	228.07（108,392）	95.91（2,923.7）	2.64（0.26,9.61）
C1/C2	4.11(1.92,7.21)	41.99（11,71）	248.32（120,486）	174.39（1,1788）	2.34(0.30,12.25）
P value	0.236	0.408	0.578	0.026	0.668
C1	3.96(1.92，7.21)	40.62（21,71）	235.64（120,412）	101.33（1,490）	1.86（0.30,8.43）
C2	4.57（3.20,6.83）	45.94（11,69）	285.56（153,486）	385.48（6.9,1788）	3.71(0.48,12.25）
P value	0.828	0.383	0.313	0.015	0.007

Note: P<0.05 was considered statistically significant.

3. Oxford Classification and ISKDC Classification and Time to Negativity

In this study, the M1E0 subtype of the Oxford classification accounted for a relatively large proportion (38 cases, 43.1%). Type IIIa and IIIb in the ISKDC classification accounted for 34.1% and 41.0%, respectively (see above). To explore the association between the Oxford classification subtypes (M1E0, IIIa, IIIb) and urinary protein negativity, urinary protein was monitored at 3, 6, and 9 months after renal biopsy. A chi-square test was performed to examine the association. The results are shown below.

Tab 6 Cross-table of negative cases within the third month

Group		Negative	Not Negative	Total
M1E0	Count	11	27	38
	Proportion	28.9%	71.1%	100%
IIIa	Count	6	24	30
	Proportion	20.0%	80.0%	100%
IIIb	Count	6	30	36
	Proportion	16.7%	83.3%	100%
Total	Count	23	81	104
	Proportion	22.1%	77.9%	100%

Tab 7 The situation of turning negative within the third month and the Chi-square test by typing

	Value	df	Asymptotic Significance (2-sided)

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	1.728[a]	2	.421
Likelihood Ratio	1.708	2	.426
Linear-by-Linear Association	1.615	1	.204
Valid Cases	104		

[a]. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 6.63.

Table 8 Crosstabulation of urinary protein negative conversion within 6 months

Group		Negative	Not negative	Total
M1E0	Count	20	18	38
	Proportion	52.6%	47.4%	100%
IIIa	Count	14	16	30
	Proportion	46.7%	53.3%	100%
IIIb	Count	21	15	36
	Proportion	58.3%	41.7%	100%
Total	Count	55	49	104
	Proportion	52.9%	47.1%	100%

Table 9 Chi-square test for negative conversion status and histological subtype within 6 months

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	.895[a]	2	.639
Likelihood Ratio	.897	2	.639
Linear-by-Linear Association	.228	1	.633
Valid Cases	104		

[a]. 0 cells (0.0%) have expected count less than 5. The minimum expected

count is 14.13.

Table 10 Crosstabulation of urinary protein negative conversion within 9 months

Group		Negative	Not negative	Total
M1E0	Count	29	9	38
	Proportion	76.3%	23.7%	100%
IIIa	Count	22	8	30
	Proportion	73.3%	26.7%	100%
IIIb	Count	31	5	36
	Proportion	86.1%	13.9%	100%
Total	Count	82	22	104
	Proportion	78.8%	21.2%	100%

Table 11 Chi-square test for negative conversion status and histological subtype within 9 months

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	1.832[a]	2	.400
Likelihood Ratio	1.915	2	.384
Linear-by-Linear Association	1.207	1	.311
Valid Cases	104		

[a]. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 6.35.

The results showed that there was no significant association between the histological subtypes (M1E0, IIIa, IIIb) defined by the Oxford classification and ISKDC classification and urinary protein negative

conversion at 3, 6 and 9 months after renal biopsy (P＞0.05). This finding may be attributed to limited sample size, differences in treatment regimens among children, age and other confounding factors. The Oxford classification is considered applicable for pathological classification in children with HSPN.

III. Discussion

Henoch-Schönlein purpura is one of the common secondary glomerular diseases in pediatrics, and renal biopsy is the gold standard for determining the degree of renal injury. Clinically, the clinical manifestations of children are not parallel to the degree of renal pathological injury; renal pathology actually better reflects the degree of lesions and expected prognosis. The traditional ISKDC classification grades according to the degree of glomerular injury and fails to take into account interstitial and vascular injury, while the Oxford classification comprehensively takes into account the assessment of glomerular, interstitial, and vascular injury and is considered an independent prognostic indicator, with independent value in predicting renal outcomes.

The HSPN guidelines classify clinically according to the patient's clinical manifestations: (1) isolated hematuria type; (2) isolated proteinuria type (24h urine protein quantification <50 mg/kg); (3) hematuria and

proteinuria type; (4) acute nephritis type; (5) nephrotic syndrome type; (6) rapidly progressive nephritis type; (7) chronic nephritis type. It is completely identical to pediatric IgAN.[18],[19]

In 2009, the international consensus organization, in order to identify specific pathological features, thereby accurately predicting the risk of renal disease progression in IgA nephropathy and improving the prognosis of individual patients, collected sequential clinical data from 265 adults and children with IgA nephropathy, with a median follow-up of 5 years. All patients' renal biopsies were scored by pathologists blinded to clinical data, and through an iterative process, four reproducible variables were established: (1) mesangial hypercellularity score, (2) segmental glomerulosclerosis, (3) endocapillary hypercellularity. Crescent incidence at enrollment was low and was not proposed.[6] Since then, this classification has gradually been applied in clinical practice. In subsequent research work, some researchers found the prognostic role of crescents in a larger study cohort in 2016, so the crescent score was added to the classification, forming the Oxford classification currently widely used for IgAN and becoming one of the disease prognosis predictors.[18] Because HSPN and IgAN are considered to be pathologically similar and represent different manifestations of the same disease,[9] HSPN has a higher rate of acute attacks but fewer cases

progressing to malignant outcomes such as renal failure.[19]

Some researchers have applied the Oxford classification to HSPN and found that the Oxford classification is also applicable to pediatric HSPN and also has certain significance in predicting disease prognosis and guiding treatment.[8,14,20–24]

Currently, there is a lack of multicenter large-sample pathological classification controlled studies. Crescents and interstitial lesions are key factors affecting prognosis and differences in research results. Renal biopsy can only reflect instantaneous renal injury. A unified pathological classification standard can dynamically assess disease prognosis, and because HSPN and IgAN are pathologically homologous with different clinical phenotypes, a unified Oxford classification system is also conducive to conducting precise comparative research on the two types of diseases at the levels of diagnosis, treatment, and prognosis.[27] In this study, the M1E0 type, IIIa type, and IIIb type, which accounted for the largest proportions, were observed for urine protein negativity at the three observation time points of 3, 6, and 9 months, respectively, with no significant statistical difference. Excluding other factors, it is believed that the Oxford classification can be applied to the pathological classification of children with HSPN and does not affect the diagnosis, treatment, and prognosis assessment during the course of the disease.

The traditional ISKDC classification only evaluates glomeruli, with standard qualitative assessment, weak clinical correlation, and insufficient prognostic evaluation. The Oxford classification uses five quantitative indicators, taking into account glomerular, interstitial, and crescent injury. S and T can predict renal disease risk, and the pathological and clinical indicators match well, which can guide individualized treatment, is suitable for multicenter research, and is more suitable for evaluating prognosis in pediatric HSPN. Chan Ho Kim et al.[21] were the first to evaluate whether the Oxford classification of IgAN can be used for the long-term prognosis of HSPN by evaluating 61 HSPN patients with ISKDC classification and Oxford classification, respectively. The final renal outcome was defined as glomerular filtration rate beginning <60 ml/min/1.73m², or a ≥30% decrease in glomerular filtration rate from baseline or end-stage renal disease. The renal survival rates of E1 and T1/T2 in the Oxford classification were lower than those of E0 and T0, and E1 and T1/T2 were independently associated with reaching the primary outcome and were independent risk factors for predicting renal endpoint events. In this study, M1 was associated with 24HUP, suggesting that the more obvious the proliferation, the more severe the glomerular filtration barrier injury, and the higher the proteinuria level usually; C2 was associated with urinary RBC count,

suggesting that the presence or absence of acute crescent injury in the glomeruli corresponds more to the degree of positive urine occult blood and microscopic red blood cell count. However, the Oxford classification still needs to combine M, E, S, T, and C indicators to jointly assess disease severity and prognosis; a single indicator can only reflect local pathological changes. The renal event-free survival of patients with <50% crescents was significantly longer than that of patients with ≥50% glomerular crescents, but the extent of crescents was not an independent risk factor. Adam Jimenez[25] in the United States used logistic regression and receiver operating characteristic curves to analyze the ability of MEST-C to predict the composite outcome of hypertension (age/sex/height blood pressure ≥95th percentile), CKD (estimated glomerular filtration rate <90 mL/min/1.73m^2), or proteinuria (urine protein to creatinine ratio >0.2 mg/mg), including 32 children with HSPN who underwent renal biopsy. The results suggested that S1 accurately predicted the composite outcome of hypertension, CKD, and proteinuria in different cohorts of children with HSPN in the United States. Due to the small sample size, further verification is still needed. Xu Ke[20] from Peking University First Hospital reclassified 104 children with HSPN diagnosed by renal biopsy according to the Oxford classification. The primary outcome was impaired renal function, and proteinuria remission and clinical remission were secondary outcomes. It was found that

mesangial hypercellularity (M1) was closely related to proteinuria, and tubular atrophy/interstitial fibrosis (T1/T2) and C2 (≥25% of glomeruli with crescents) were associated with reduced estimated glomerular filtration rate (eGFR) at biopsy. In univariate time-dependent analysis, S1 was closely related to the primary outcome, while T1/T2 was significantly negatively correlated with proteinuria remission and clinical remission. The results also suggested that S and T lesions in the Oxford classification can be used to evaluate the renal outcome of HSPN and are not affected by currently available treatment methods. This study is basically consistent with its main conclusions but also has some differences. Our observations suggest that M1 is associated with elevated 24h urine protein, and severe crescents C2 suggest aggravated renal injury, which is consistent with the conclusion of that study that C2 is associated with baseline eGFR reduction; in addition, this study stratified and compared C1 and C2 subgroups, and the results suggested that C2 is simultaneously accompanied by higher urinary red blood cells and urine protein, supplementing the evidence for the association between severe crescents and hematuria and proteinuria. However, our research results also have different findings: first, due to different renal function evaluation indicators, the Xu Ke team core used eGFR. This study only followed up for 9 months, and no children showed eGFR decline. Only BUN, Scr, and uric acid were selected to evaluate

short-term renal function. The results suggested that the above indicators had no statistical association with various MEST-C pathological indicators. Second, the conclusions regarding S lesions are inconsistent. The Xu Ke study showed that S1 is a risk factor for long-term renal function impairment. In the short-term follow-up of this study, there was no difference in various clinical indicators between the S0 and S1 groups, which is considered to be due to the short follow-up duration. Wang Meiqiu[14] from Jinling Hospital of Southern Medical University conducted a retrospective study of 877 children with HSPN in 2021, which is the largest series reported in this type of literature so far. The outcome was defined as chronic kidney disease with an estimated glomerular filtration rate <90 mL/min/1.73m^2. The results showed that S and T in the Oxford classification, which are ignored by the ISKDC classification, can be used to predict the renal prognosis of children with HSPN and are independent risk factors for renal outcomes. Combining the above literature conclusions and our research results, the core advantages of the Oxford classification over the ISKDC classification lie in standardized diagnosis, strong pathological-clinical correlation, and clear prognostic and treatment guidance. The ISKDC classification is mostly based on pathological morphological description, lacking unified judgment standards, with large diagnostic differences among different medical centers, and weak correlation with clinical indicators and prognosis;

while the Oxford classification, through five standardized indicators—M (mesangial proliferation), E (endocapillary hypercellularity), S (segmental sclerosis/adhesion), T (tubular atrophy/interstitial fibrosis), and C (crescents)—achieves quantitative grading of pathological injury, can accurately correspond to clinical phenotypes such as proteinuria and renal function impairment, and each indicator can independently predict the risk of disease progression, enabling the formulation of individualized treatment plans, and is also conducive to the development of multicenter clinical research and data integration.

The long-term prognosis of children with HSP depends on the degree of renal injury. HSPN is its most severe manifestation. Delayed treatment of renal damage may lead to the disease progressing to CKD or even renal failure, causing irreversible consequences.[26],[27] Therefore, children with renal injury should be actively identified and treated. The accurate and comprehensive judgment of renal injury by the Oxford classification has relatively positive significance for the diagnosis, treatment, and prognosis of children.[28] Recently, Julian[29] studied the renal histology of IgAN and IgAVN and believed that IgAN is mostly characterized by glomerulosclerosis and tubular atrophy, while the latter is mostly considered to be characterized by endocapillary hypercellularity and increased crescents. Although the disease development processes of the

two are considered different, the Oxford classification can similarly help predict the long-term prognosis of both. According to the pathological characteristics of the two, it is speculated that the evaluation indicators E, T, and C in the Oxford classification are meaningful for predicting the prognosis of children. Sean J Barbour et al.[30] collected 262 patients with HSPN, including adults and children, from 23 centers in Europe and North America, and evaluated the correlation between the Oxford classification and eGFR/proteinuria at biopsy. The research results confirmed some speculations, showing that the renal outcome of patients is determined by clinical risk factors as well as endocapillary hypercellularity (E) and fibrous crescents. Katharina[31] et al. studied the outcomes of children with HSPN after immunosuppression through a multicenter, relatively large-sample study, and concluded that some clinical features, such as age, lower eGFR at onset, hypertension, and histological features such as tubular atrophy and segmental sclerosis, are predictors of poor outcomes.

This study used urine protein negativity time and changes in renal function as prognostic speculation, and believes that M, T, and C in the Oxford classification can reflect some clinical indicators. The extent of mesangial cell proliferation has a certain relationship with urine protein quantification; interstitial lesions and crescents affect urinary red blood

cell indicators; and the extent of crescent lesions is related to urine protein and urinary red blood cell indicators. Pathological classification is closely related to clinical indicators, and clinical features also predict the treatment outcome of children. In summary, the application of the Oxford classification to children with HSPN is feasible. Compared with the ISKDC classification, it provides prediction relative to the clinical manifestations of children, facilitates targeted basic treatment, more comprehensively evaluates the degree of renal injury, and can predict disease prognosis and guide targeted treatment of the disease. This study is a single-center study, with a certain bias in pathological classification, and the proportion of children with final urine protein non-negativity is small, so the analysis has certain limitations. This study is a single-center retrospective study, with limited sample size, observation time points, and follow-up time. It only observed short-term urine protein indicators, and there are deficiencies in long-term eGFR dynamic monitoring and other renal outcomes and disease prognosis evaluation data. Including some data limited by incomplete information and other reasons, further confirmation by multicenter large-sample long-term cohort studies is needed.

IV. Conclusion

Based on the clinical manifestations of children combined with the

Oxford classification, renal pathological prediction is provided, which can be applied to the pathological assessment of children with HSPN, and is more conducive to the quantitative grading of pathological injury, the formulation of individualized treatment plans, and the development of multicenter clinical research and data integration.

Conflict of Interest: All authors declare no conflict of interest.

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