Research Article

The Clinicopathological Characteristics of Henoch-Schönlein Purpura Nephritis with Presentation of Nephrotic Syndrome

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Keywords

Henoch-Schönlein purpura nephritis · Adult onset · Nephrotic syndrome · Clinicopathological manifestations · Renal outcome

Abstract

Background: Henoch-Schönlein purpura nephritis (HSPN) is a common vasculitis involving the kidneys, with a lower incidence in adults. Meanwhile, nephrotic syndrome (NS) can appear in HSPN. However, the clinicopathological features and renal outcome of adult-onset HSPN presenting with NS (NS-HSPN) have not been well clarified. **Methods:** A total of 191 HSPN patients were prospectively analyzed and comparisons were made between NS-HSPN and non-NS-HSPN. Multivariate Cox regression analysis was carried out to find the unfavorable factors of renal outcome of NS-HSPN. **Results:** Among the 191 patients, 44 (23.0%) had NS-HSPN. Apart from edema and abdominal pain, patients with NS-HSPN tended to have lower levels of erythrocytes and hemoglobin in blood as well as a greater number of erythrocytes in urine ($p < 0.05$). Mesangial proliferation was the most common pathological lesion in HSPN and the rates of crescent formation were significantly different, with 54.5% in NS-HSPN and 33.3% in non-NS-HSPN ($p < 0.05$). Notably, 18.2 and 4.8% of patients reached the composite endpoints in the NS-HSPN and non-NS-HSPN groups, respectively ($p < 0.05$), demonstrating that NS-HSPN patients were more likely to progress to end-stage renal disease and had a worse outcome. We also found that hypertension, estimated glomerular filtration rate (eGFR), cystatin, and tubular atrophy/interstitial fibrosis ($HR > 1$, $p < 0.05$) at onset were correlated with adverse outcome in NS-HSPN. **Conclusion:** NS-HSPN had more severe clinicopathological manifestations and poorer prognosis. The adverse predictors of NS-HSPN principally depend on clinicopathological presentation rather than on different therapies, and hypertension, eGFR, cystatin, and tubular atrophy/interstitial fibrosis can serve as independent risk factors in NS-HSPN.

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Introduction

Henoch-Schönlein purpura (HSP) is a common vasculitis predominantly affecting arterioles, venules, and capillaries [1]. The clinical manifestations of HSP include palpable purpuric rashes, diffuse abdominal pain with or without gastrointestinal bleeding, arthralgia, gross hematuria, and proteinuria [2]. It is generally acknowledged that HSP is a self-limiting disease while the long-term prognosis is principally based on renal involvement, known as HSP nephritis (HSPN). Owing to lower incidence in adults, there is little high-quality research on adult-onset HSPN.

Nephrotic syndrome (NS) is a collection of manifestations including massive proteinuria and hypoalbuminemia, commonly with swelling and/or hyperlipidemia [3]. In clinical practice, we find that NS is relatively less frequent in HSPN; its effect on prognosis has been poorly studied, though it has been proved that NS is associated with unfavorable outcomes in many kidney diseases, such as immunoglobulin A nephropathy, and can indicate severe renal histopathological changes [4]. Consequently, this study was carried out to get more acquainted with the clinicopathological characteristics and prognosis of adult patients suffering from HSPN presenting with NS (NS-HSPN).

Materials and Methods

Inclusion and Exclusion Criteria

In this prospective study, 209 patients with HSPN who had undergone a renal biopsy were recruited from the West China Hospital of Sichuan University in China between October 2010 and June 2017. The diagnosis of HSPN was made when HSP patients had microscopic or gross hematuria and/or proteinuria, further confirmed by renal biopsy [5]. The proposals based on the American College of Rheumatology database and methodology were used as diagnostic criteria of HSP [6]. All patients enrolled in our study were over 14 years old. Nevertheless, patients with other systemic diseases such as liver cirrhosis, malignant neoplasm, systemic lupus erythematosus, etc. were not considered. Additionally, patients whose demographic and laboratory data were not sufficient for our analysis were also excluded. Accordingly, 191 patients with HSPN were analyzed in our study.

Data Collection

General and clinical characteristics were reviewed including age, sex, follow-up duration, time to endpoint, clinical symptoms, systolic blood pressure, diastolic blood pressure, and treatment strategies. Laboratory data comprised excretion levels of 24-h proteinuria, number of erythrocytes in urine (u-RBCs) at high magnification, serum albumin, serum creatinine, uric acid, triglycerides, cholesterol, low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase, aspartate aminotransferase, hemoglobin, platelets, erythrocytes, and leukocytes in blood. Renal pathology data included mesangial proliferation, endocapillary proliferation, segmental glomerulosclerosis, tubular atrophy, interstitial fibrosis, and crescents.

Treatment Regimens

Four pharmacotherapeutic schemes were widely used clinically, including angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) (scheme A), glucocorticoids (scheme B), glucocorticoids combined with immunosuppressants (scheme C), and pulse therapy with methylprednisolone and cyclophosphamide (scheme D). The choice of scheme depended on the severity of disease and the doctor's experience. Patients in scheme A received full-dose ACEI or ARB alone. Patients in scheme B received oral glucocorticoids

daily (0.5–1 mg/kg prednisone) and tapered down gradually. Glucocorticoids combined with immunosuppressive agents, including cyclophosphamide, mycophenolate mofetil, azathioprine, leflunomide, tacrolimus, and cyclosporin, were used in scheme C [7, 8]. Patients in scheme D were treated with intravenous pulse methylprednisolone followed by oral glucocorticoids and sequentially treated with intravenous cyclophosphamide. Optimal renal protective treatments were used in all schemes.

Definitions and Outcome Measurements

The definition of NS was hypoalbuminemia <30 g/L and proteinuria >3.5 g/day. The diagnosis of hypertension was based on standards of the World Health Organization Expert Committee ($>140/90$ mm Hg). Hematuria was defined as u-RBCs >5 at high power. The Chronic Kidney Disease Epidemiology Collaboration formula was used to calculate the estimated glomerular filtration rate (eGFR).

It has been well accepted that immunoglobulin A nephropathy and HSPN share similar pathogenesis and pathology findings. Owing to no standards in pathological classification of adult-onset HSPN, the Oxford classification might be effective to predict the long-term outcomes of HSPN [9]. The definitions of mesangial proliferation, endocapillary proliferation, segmental glomerulosclerosis, tubular atrophy, and interstitial fibrosis are largely referred to the Oxford classification [10–12]. Moreover, crescents were a feature in HSPN which could not be ignored. Therefore, we also collected the pathological data of crescents [13].

The primary endpoint was the composite of a 50% decline in eGFR, end-stage renal disease (ESRD) and/or death. The definition of ESRD was eGFR <15 mL/min/1.73 m² or maintenance renal replacement treatment. Secondary renal outcome was classified as complete remission, partial remission, active renal disease, and renal insufficiency, based largely upon Meadow's criteria [14]. Complete remission was defined as 24-h proteinuria ≤ 0.3 g, with no hematuria and normal renal function. Partial remission was defined as 24-h proteinuria ≤ 1 g, with or without recurrent hematuria. Active renal disease was defined as 24-h proteinuria >1 g or a decreased eGFR level $>10\%$. The definition of renal insufficiency was eGFR <60 mL/min/1.73 m².

Statistical Analyses

Data were analyzed using the IBM SPSS Statistics 22.0 software. Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range, which were compared by Student *t* test or Wilcoxon test. Categorical variables were summarized as numbers and percentages, which were compared by χ^2 test or Fisher exact test. Kaplan-Meier estimation was performed to calculate the survival outcome and rate of endpoint. The crude effects of clinical manifestations and pathological features on renal outcomes were evaluated by multivariate Cox regression analysis. Additionally, all *p* values were two-tailed and statistical significance was reached when *p* was <0.05 .

Results

Demographic Data

A total of 209 patients with HSPN were registered in our medical center, whereas only 191 patients were recruited in our study because of the exclusion criteria. Forty-four patients (23 male and 21 female) were categorized into the NS-HSPN group, while 147 patients (64 male and 83 female) were assigned to non-NS-HSPN group (Fig. 1). Table 1 reveals the demographic data. The age of patients at onset ranged from 14 to 76 years, with a median of 24 years, and the mean follow-up of our cohort was 27 months.

Fig. 1. Flow diagram of patient progress and outcomes. eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HSPN, Henoch-Schönlein purpura nephritis; NS-HSPN, Henoch-Schönlein purpura nephritis presenting with nephrotic syndrome.

Clinicopathological Findings

As presented in Table 1, edema (65.9%, $p < 0.01$) and abdominal pain (40.9%, $p < 0.05$) were significantly more common in the NS-HSPN group ($p < 0.05$), and patients with NS seemed to have higher levels of systolic blood pressure (127.84 ± 20.39 mm Hg, $p = 0.078$) and rates of bloody stools (20.5%, $p = 0.099$). However, no significances were found in age at onset, sex, purpura, gross hematuria, arthralgia, diastolic blood pressure, mean arterial pressure, and hypertension ($p > 0.1$). There were obviously different laboratory findings between those two groups at baseline. Apart from massive proteinuria and hypoalbuminemia, patients with NS-HSPN tended to have lower levels of erythrocytes ($4.52, 3.92\text{--}4.75 \times 10^{12}/\text{L}$, $p < 0.01$) and hemoglobin (123.14 ± 19.69 g/L, $p < 0.01$) in blood as well as a greater number of u-RBCs (103, 13–320/high-power field, $p < 0.05$) and platelets ($260.30 \pm 106.14 \times 10^9/\text{L}$, $p < 0.05$). In addition, median cholesterol was 6.53 mmol/L (4.53–7.48 mmol/L) in the NS-HSPN group and 4.80 mmol/L (3.94–5.78 mmol/L) in the non-NS-HSPN ($p < 0.05$). LDL-C was 3.47 mmol/L (2.59–5.16 mmol/L) versus 2.62 mmol/L (2.11–3.41 mmol/L, $p < 0.05$), respectively. However, we did not find any differences in creatinine, eGFR, uric acid, triglyceride, alanine aminotransferase, aspartate aminotransferase, cystatin, and leukocytes.

Table 1. Clinical manifestations and laboratory data of HSPN patients at baseline

	NS-HSPN (n = 44)	Non-NS-HSPN (n = 147)	p values
Age at diagnosis, years	21 (16–43)	27 (18–44)	0.657
Male/female (%)	23/21 (52.3/47.7)	64/83 (43.5/56.5)	0.307
Skin purpura (%)	41 (93.2)	135 (91.8)	1.000
Edema (%)	29 (65.9)	44 (29.9)	0**
Gross hematuria (%)	3 (6.8)	19 (12.9)	0.419
Arthralgia (%)	11 (25.0)	29 (19.7)	0.451
Abdominal pain (%)	18 (40.9)	36 (24.5)	0.034*
Bloody stools (%)	9 (20.5)	16 (10.9)	0.099
Follow-up, months	18 (12.0–50.0)	19.5 (12.0–34.5)	0.423
SBP, mm Hg	127.84±20.39	122.20±17.93	0.078
DBP, mm Hg	80.7±13.60	78.76±11.34	0.343
MAP, mm Hg	95.67 (84.33–106.33)	93.33 (86.59–102.67)	0.205
Hypertension (%)	14 (31.8)	32 (21.8)	0.171
Proteinuria, g/24 h	5.40 (3.84–8.25)	1.65 (0.80–2.76)	0**
u-RBCs/HPF	103 (13–320)	25 (8–109)	0.021*
Albumin, g/L	24.24±4.79	38.54±5.61	0**
SCr, µmol/L	72.30 (56.90–111.10)	70.25 (57.95–86.70)	0.112
Uric acid, µmol/L	356.92±113.49	337.09±99.89	0.265
eGFR, mL/min/1.73 m ²	112.80 (71.50–131.15)	110.55 (87.13–129.65)	0.525
Triglycerides, mmol/L	1.93±0.92	1.77±1.01	0.341
Cholesterol, mmol/L	6.53 (4.53–7.48)	4.80 (3.94–5.78)	0**
LDL-C, mmol/L	3.47 (2.59–5.16)	2.62 (2.11–3.41)	0**
ALT, IU/L	26.59±18.25	28.46±23.28	0.627
AST, IU/L	23.59±10.13	22.59±8.30	0.405
Cystatin C, mL/L	1.38±0.72	2.90±15.47	0.517
RBCs, ×10 ¹² /L	4.52 (3.92–4.75)	4.69 (4.31–5.14)	0.002**
Hemoglobin, g/L	123.14±19.69	138.05±18.91	0**
Platelets, ×10 ⁹ /L	260.30±106.14	221.54±90.20	0.018*
WBCs, ×10 ⁹ /L	9.62 (6.78–13.74)	8.88 (6.15–11.80)	0.151

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HPF, high-power field; HSPN, Henoch-Schönlein purpura nephritis; LDL-C, low-density lipoprotein cholesterol; MAP, mean arterial pressure; NS-HSPN, Henoch-Schönlein purpura nephritis presenting with nephrotic syndrome; RBCs, erythrocytes; SBP, systolic blood pressure; SCr, serum creatinine; u-RBCs, erythrocytes in urine; WBCs, leukocytes. * $p < 0.05$, ** $p \leq 0.01$.

As presented in Table 2, the most frequent renal pathological lesions in the NS-HSPN group were mesangial proliferation (39/44, 88.6%) and crescents (24/44, 54.5%), while in the non-HSPN group, mesangial proliferation (122/147, 83.0%) and tubular atrophy/interstitial fibrosis (62/147, 42.2%) were the most common lesions. There were remarkable differences in crescent formation, with 24/44 (54.5%) and 49/147 (33.3%) in the NS-HSPN and non-NS-HSPN group, respectively. There were no other significant histopathological characteristics between the two groups.

Treatments

Table 3 shows the principal treatment regimens for the 191 patients enrolled in our study. No patients with NS-HSPN and only 11.6% of non-NS-HSPN patients were treated with ACEI or ARB only. The proportion of glucocorticoids alone, glucocorticoids combined with immunosuppressants, and pulse therapy with methylprednisolone and cyclophosphamide was 25.0, 47.7, and 27.3% in the NS-HSPN group and 44.2, 33.3, and 10.9% in non-NS-HSPN

Table 2. Renal pathological findings of HSPN patients

	NS-HSPN (n = 44)	Non-NS-HSPN (n = 147)	p values
M1/M0 (%)	39/5 (88.6/11.4)	122/25 (83.0/17.0)	0.481
E1/E0 (%)	11/33 (25.0/75.0)	21/126 (14.3/85.7)	0.095
S1/S0 (%)	15/29 (34.1/65.9)	54/93 (36.7/63.3)	0.749
C1/C0 (%)	24/20 (54.5/45.5)	49/98 (33.3/66.7)	0.011*
C0/0–25/>25 (%)	20/10/14 (45.5/22.7/31.8)	97/39/11 (66.0/26.5/7.5)	0**
T1/T0 (%)	15/29 (34.1/65.9)	62/85 (42.2/57.8)	0.337

“1” stands for presence, “0” stands for absence. C, crescents; E, endocapillary proliferation; HSPN, Henoch-Schönlein purpura nephritis; M, mesangial proliferation; NS-HSPN, Henoch-Schönlein purpura nephritis presenting with nephrotic syndrome; S, segmental glomerulosclerosis; T, tubular atrophy/interstitial fibrosis. * $p < 0.05$, ** $p \leq 0.01$.

Table 3. Principal treatments of patients with HSPN

	NS-HSPN (n = 44)	Non-NS-HSPN (n = 147)	p values
ACEI/ARB (%)	0 (0)	17 (11.6)	0.014*
Glucocorticoids (%)	11 (25.0)	65 (44.2)	0.022*
Glucocorticoids + immunosuppressants (%)	21 (47.7)	49 (33.3)	0.082
Pulse therapy with MP and CTX (%)	12 (27.3)	16 (10.9)	0.007**

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CTX, cyclophosphamide; HSPN, Henoch-Schönlein purpura nephritis; MP, methylprednisolone; NS-HSPN, Henoch-Schönlein purpura nephritis presenting with nephrotic syndrome. * $p < 0.05$, ** $p \leq 0.01$.

group, respectively. On the whole, NS patients were treated with more aggressively immunosuppressive treatments.

Outcomes

In our cohort, 7.9% of patients with HSPN progressed to ESRD. Kaplan-Meier survival analysis, shown in Figure 2, indicated that 18.2% (8/44) and 4.8% (7/147) patients reached the combined endpoints in the NS-HSPN and non-NS-HSPN group, respectively ($p < 0.05$). Further information on laboratory data from the last follow-up is provided in Table 4. Comparison between NS-HSPN and non-NS-HSPN patients demonstrated significant differences in creatinine and eGFR ($p < 0.05$). However, statistical significances were not found in proteinuria, u-RBCs, albumin, uric acid, triglyceride, cholesterol, or LDL-C. Notably, patients with NS-HSPN tended to have a higher proportion of renal insufficiency (22.7 vs. 10.9%, $p < 0.05$) and a lower rate of partial remission (20.5 vs. 37.4%, $p < 0.05$), whereas other renal outcomes including rates of complete remission (27.3 vs. 25.2%, $p = 0.779$) and active renal disease (29.5 vs. 26.5%, $p = 0.693$) showed no differences.

Factors of Renal Outcome

Multivariate Cox regression analysis was applied to explore the risk factors in NS-HSPN patients, for the reason that more patients with NS-HSPN would progress to the combined

Table 4. Laboratory data at the last follow-up

	NS-HSPN (n = 44)	Non-NS-HSPN (n = 147)	p values
Proteinuria, g/24 h	0.31 (0.15–0.81)	0.30 (0.19–0.70)	0.129
u-RBCs/HPF	41.89±146.13	25.16±84.23	0.340
Albumin, g/L	42.81±5.74	44.20±4.67	0.102
SCr, µmol/L	75.40 (62.70–116.10)	69.05 (59.15–92.17)	0.014*
Uric acid, µmol/L	371.80±113.30	357.17±92.02	0.383
eGFR, mL/min/1.73 m ²	98.50 (63.65–126.40)	110.15 (86.90–124.43)	0.043*
Triglycerides, mmol/L	1.59±0.90	2.19±7.16	0.586
Cholesterol, mmol/L	4.59 (3.94–6.18)	4.47 (3.92–5.27)	0.269
LDL-C, mmol/L	2.67 (1.80–3.29)	2.46 (2.06–3.07)	0.621
Renal survival			
Complete remission (%)	12 (27.3)	37 (25.2)	0.779
Partial remission (%)	9 (20.5)	55 (37.4)	0.037*
Active renal disease (%)	13 (29.5)	39 (26.5)	0.693
Renal insufficiency (%)	10 (22.7)	16 (10.9)	0.044*

eGFR, estimated glomerular filtration rate; HPF, high-power field; LDL-C, low-density lipoprotein cholesterol; NS-HSPN, Henoch-Schönlein purpura nephritis presenting with nephrotic syndrome; SCr, serum creatinine; u-RBCs, erythrocytes in urine. * $p < 0.05$.

Fig. 2. Kaplan-Meier analysis for the probability of composite endpoint, which was a 50% decline in estimated glomerular filtration rate, end-stage renal disease, and/or death. NS-HSPN, Henoch-Schönlein purpura nephritis presenting with nephrotic syndrome.

endpoints, as presented in Table 5. The results revealed that hypertension (HR 9.615, 95% CI 1.398–66.131, $p < 0.05$), eGFR (HR 1.040, 95% CI 0.999–1.082, $p = 0.058$), cystatin (HR 9.403, 95% CI 1.465–60.334, $p < 0.05$) at onset, and tubular atrophy/interstitial fibrosis (HR 10.218, 95% CI 1.398–66.131, $p < 0.05$) in histopathological features were independent risk factors, and bloody stool (HR 5.402, 95% CI 0.828–35.24, $p = 0.078$) also seemed to be associated with poor outcome, although statistical significance was not found. Nevertheless, sex, age, gross hematuria, edema, treatment strategies, creatinine, and uric acid at onset were not correlated with renal outcome ($p > 0.1$).

Table 5. Cox proportional hazard model of factors associated with renal insufficiency/ESRD in patients with HSPN

	Unadjusted			Adjusted		
	HR	95% CI	<i>p</i> values	HR	95% CI	<i>p</i> values
Bloody stool	3.226	0.766–13.589	0.11	5.402	0.828–35.240	0.078
Hypertension	6.068	1.206–30.518	0.029	9.615	1.398–66.131	0.021*
eGFR	0.995	0.979–1.011	0.532	1.040	0.999–1.082	0.058*
Cystatin C	2.258	1.021–4.997	0.044	9.403	1.465–60.334	0.018*
T	5.626	1.263–25.052	0.023	10.218	1.398–66.131	0.021*

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HSPN, Henoch-Schönlein purpura nephritis; T, tubular atrophy/interstitial fibrosis. * $p < 0.05$.

Discussion

HSPN is a common vasculitis mostly affecting children, with a lower incidence in adults. Meanwhile, less attention has been paid to NS-HSPN and its features are still not quite clear. In order to provide further information of adult-onset HSPN, we prospectively studied patients with HSPN manifested by nephrotic state. It could be easily noted that patients with NS-HSPN were characterized by severe symptoms and poor laboratory findings. Comparable with those reported elsewhere, our results suggest that edema was a common sign of NS-HSPN and hyperlipidemia was another peculiarity, mainly manifested by increased levels of cholesterol and LDL-C instead of triglycerides; it was widely recognized that hypoproteinemia and lower levels of lipoprotein lipase were to blame [3]. Apparently, patients with NS-HSPN were more likely to suffer from anemia in our study, probably caused by transferrin loss and severe hematuria. Above all, our study found that 40.9% of NS-HSPN patients complained of abdominal pain and that 20.5% of NS-HSPN patients had bloody stools, suggesting that gastrointestinal impairment was more common and clinical manifestations are more serious in NS-HSPN.

In our study, histopathological changes were various and renal lesions were more severe in NS-HSPN. It was reported previously that mesangial injury with different degrees of hypercellularity was the basic pathological pattern in children with HSPN [15]. Our study drew a similar conclusion that the majority of renal impairment of HSPN was mesangial proliferation. Furthermore, as is known, crescents usually present the active factor of disease, and there is an important link between crescent formation and rapidly progressive glomerulonephritis. Our study demonstrated that NS-HSPN patients tended to have higher proportions of crescents, revealing that NS-HSPN was an active form of vasculitis. Generally, patients with crescent glomerulonephritis will progress to renal insufficiency rapidly if treated inadequately. Consequently, aggressive treatment is widely used to treat patients with crescent glomerulonephritis with acceptable efficacy, which is the main reason why crescents fail to be a predictor of poor prognosis in many studies, including ours [4, 16]. Meanwhile, it could serve as a reminder that we should treat NS-HSPN patients with severe clinicopathological manifestation timely and radically.

However, it was worth mentioning that our study prominently illustrated the poor prognosis of HSPN, depending on clinicopathological presentation rather than on different therapies. The correlation between NS and unfavorable prognosis was not hard to find in this study. The percentage of renal insufficiency was distinctly higher in NS-HSPN patients, and

they were in a high-risk group that might progress to ESRD. The relationship has been extensively investigated in children by previous studies, and the conclusions that nephrotic state at onset can be regarded as a prognostic factor of adverse renal outcomes have been proposed [17–19]. Thus, more aggressive treatment regimens were tendentiously used to treat patients with NS-HSPN, which might partially explain why there were no differences in renal outcome by different therapies. Moreover, several studies have reported that aggressively immunosuppressive therapy has advantages as to decreasing proteinuria and that it is effective for treating NS-HSPN patients [20–22]. Nevertheless, immunosuppressive treatment was not a significant predictor in our study, and the data of our cohort illustrated that the poor prognosis of HSPN depended on clinicopathological presentation instead of treatment strategies. There is no denying that it is still controversial whether immunosuppressants are superior to glucocorticoids in the treatment of HSPN, which was not recommended by guidelines, and more high-quality research is required to solve this problem [23].

In addition, 7.9% of patients with HSPN in our cohort progressed to ESRD, and 18.2% of NS-HSPN patients reached the study endpoint. On the one hand, the prognosis of our HSPN patients seems to be better than that of Europeans, which might be caused by different races, geographical area, sample size, and other reasons [24–27]. On the other hand, although the fact that patients with NS-HSPN are more likely to progress to ESRD was proved in this study, there seems to be no significant differences in the rate of complete remission, implying that a discrepancy of efficacy existed in treating NS-HSPN. Hence, it is of great importance to find predictors of poor renal outcome, which is sure to benefit clinically and taken as a significant index in the treatment of NS-HSPN.

Thus, further investigation was carried out to explore the risk factors that contributed to NS-HSPN progression. Forty-four HSPN patients with nephrotic state at onset were assessed in isolation. The results of multivariate Cox regression analysis indicated that hypertension, eGFR, cystatin, and tubular atrophy/interstitial fibrosis can serve as independent risk factors in NS-HSPN. Notably, the prognostic indexes were not always consistent in the literature. Previous studies focused on pediatric patients with NS-HSPN proposed that the long-term outcomes principally based on clinical presentation and tubulointerstitial injuries were not relevant to renal outcome [21, 28]. However, our research demonstrated that both clinical manifestation and pathological features could result in poor prognosis, which was consistent with studies whose objects were HSPN patients and that were not able to separate NS-HSPN from non-NS-HSPN [5, 16, 25, 27, 29]. This could be partially explained by two reasons. First, the timing of renal biopsies, different areas, and problems associated with recurrence or progression of NS-HSPN might play a part in the discrepancy. Second, it has been reported that adult and pediatric patients with HSPN have various clinical manifestations and histopathological findings and that adults tend to have worse renal outcome [25, 30]. Thus, we cannot afford to ignore patients of different ages. Surprisingly, we found that cystatin and renal outcome were interrelated in NS-HSPN. Cystatin C, abundantly expressed in extracellular fluids, is a 13-kDa subtype of cystatin with the function of inhibiting cysteine proteinase, which can be identified as a promising factor of renal insufficiency [31]. A recent cohort reported by Feng et al. [28] illustrated that children with NS-HSPN had higher cystatin levels. Another previous study revealed that cystatin was positively correlated with activity index and severity of pathological findings [32]. However, the role that cystatin plays in the pathogenic processes of HSPN is not elucidated yet, and in-depth studies are needed.

Some limitations of our study cannot be neglected. This was a single-center study with moderate sample size, and the patients enrolled were all Chinese. In addition, the follow-up of our study was not very long. All in all, a longer multicenter prospective study with a larger sample is required to help us achieve a better understanding of NS-HSPN in adults.

Conclusion

The prognosis of adult patients with NS-HSPN, characterized by severe symptoms, poor laboratory findings, and histopathological changes, is worse than that of non-NS-HSPN patients. The unfavorable prognosis of HSPN principally depends on clinicopathological presentation rather than on different therapies, and hypertension, eGFR, cystatin, and tubular atrophy/interstitial fibrosis can serve as independent risk factors in NS-HSPN.

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Statement of Ethics

The subjects enrolled in our study gave their informed consent. This study was approved by the Ethics Committee of the West China Hospital of Sichuan University and fully complied with the Helsinki Declaration.

Disclosure Statement

The authors declare no conflicts of interest. This study received no funding.

Author Contributions

The study was designed by Wei Qin. The clinicopathological and follow-up data were collected by Jiaying Tan, Yi Tang, Yicong Xu, Siyu Yan, Yuanyuan Xu, Li Tan, and Zhengxia Zhong. Data analysis was carried out by Jiaying Tan, Li Tan, and Padamata Tarun. All authors listed significantly contributed to this paper. The authors declare that the paper is honest, accurate, and transparent.

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