The Spectrum of Biopsy-Proven Glomerular Diseases among Children in China

A National, Cross-Sectional Survey

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Abstract

Background and objectives High-quality epidemiologic data on the spectrum of biopsy-proven glomerular diseases among children are limited. This study aimed to determine the profile of and temporal change in biopsy-proven pediatric glomerular diseases in China.

Design, setting, participants, & measurements We previously conducted a nationwide kidney biopsy survey including 71,151 patients over an 11-year period from January 2004 to December 2014. A total of 7962 children younger than 18 years old from 115 hospitals across China with biopsy-proven glomerular diseases were included in this study. The demographic and clinical variables were extracted from referral records and pathology reports. The composition of pediatric glomerular diseases and clinicopathologic correlations in different sexes, age groups, and regions were assessed. The changing patterns of common glomerulopathies over the study period were examined.

Results Nephrotic syndrome (50%) was the most frequent indication for kidney biopsy in children. Minimal change disease was the most common primary glomerular disease (29%) followed by IgA nephropathy (17%). Henoch–Schonlein purpura nephritis (13%) and lupus nephritis (9%) were the most common secondary glomerular diseases. The proportion of minimal change disease was significant higher in boys (38%) than in girls (13%), whereas lupus nephritis was more prevalent in girls (20%) than in boys (3%). Purpura nephritis (23%) was the major pathologic pattern in younger children (0–12 years old), whereas minimal change disease (33%) was the most common glomerulopathy in adolescents (13–18 years old). The clinicopathologic correlations were slightly different between sexes and age groups. We observed increases in the proportions of minimal change disease, purpura nephritis, and membranous nephropathy over the study period that were contemporaneous with a fall in the proportion of FSGS.

Conclusions The spectrum of glomerular diseases among children varied across sexes, age groups, and regions and changed substantially from 2004 to 2014 in China.

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Introduction

CKD has been recognized as a public health problem worldwide (1–4). The global increase in adult and pediatric patients with CKD is threatening to reach epidemic proportions over the next decade (2,4). World Kidney Day 2016 focused on childhood kidney disease to heighten this field as a priority for clinical and epidemiologic research. Unlike adults, in whom diabetes mellitus and hypertension are responsible for the majority of CKD (5), congenital disorders and GN account for the largest percentage of CKD in children (6). Meanwhile, the etiology of CKD in children varies across races and countries. The North American Pediatric Renal Trials and Collaborative Studies reported that congenital anomalies of the kidney and urinary tract were the most common causes (48%) of CKD in pediatric population, whereas GN accounted for 14% of patients (7). Similar distribution of CKD causes has been reported in studies from other developed countries, such as Italy, Belgian, and Japan (8–10). In contrast, chronic GN is the leading cause of CKD in studies from India, Southeast Asia, Latin America, and sub-Saharan Africa (11–19). Moreover, children with glomerular disease experience a faster progression of CKD than those with congenital disorders, resulting in a relatively higher proportion of GN in patients with ESKD (10,20,21). Children with glomerular diseases make up an important part of pediatric patients, especially in developing countries.

Glomerular disease remains the leading cause of ESKD in China (22,23). The treatment and prognosis of glomerular disease may differ widely on the basis of specific pathologic diagnosis. However, kidney biopsy is much more difficult to perform in children

than in adults due to the smaller size of kidneys and poorer cooperation between pediatric patients and clinicians (24). Thus, it is substantially important to further investigate the composition of biopsy-proven glomerular disease in pediatric patients. More detailed information on the spectrum of pediatric glomerular diseases and their clinicopathologic correlations across different sexes and age groups will contribute to more accurate clinical diagnosis when kidney biopsies are not available and will help to optimize the management of pediatric glomerular diseases. To date, there are only a few small single-centered studies on the composition of glomerular diseases among pediatric patients in China (25). Nationwide epidemiologic data on the spectrum of biopsy-proven glomerular diseases among children are currently limited.

In this study, we aimed to determine the profile of and temporal change in biopsy-proven pediatric glomerular diseases in an 11-year kidney biopsy series from 115 hospitals across China. We also examined the clinicopathologic correlations and the difference of disease composition between sexes, age groups, and regions.

Materials and Methods

Study Population and Data Collection

We previously conducted a multicenter, nationwide, cross-sectional survey of kidney biopsies in China. We collected data from six central pathology laboratories on 75,163 kidney biopsies from 938 local hospitals spanning 282 cities across China over an 11-year period from January 2004 to December 2014 (26). After excluding patients without histologic diagnosis or with fewer than five glomeruli under light microscopy (374), those with repeated biopsies (714), those with kidney graft (250), those with missing demographic or clinical data (927), those diagnosed with isolated tubulointerstitial kidney diseases (1747), and those over 18 years old (63,189), a total of 7962 biopsies were included in this analysis (Supplemental Figure 1). The pediatric patients were divided into two age strata: young children (0–12 years old) and adolescents (13–18 years old).

Nephrologists in local hospitals performed biopsies and filed the standardized referral records, including age, sex, city of residence, date, hospital performing the biopsy, indications of biopsy, clinical diagnosis, and serum creatinine; they sent the biopsy specimens to one of six central laboratories for processing and pathologic diagnosis. eGFR (milliliters per minute per 1.73 m^2) was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation (2009). The indications for kidney biopsy included nephrotic syndrome, AKI, progressive CKD (defined as eGFR≤60 ml/min per 1.73 m^2), proteinuria without nephrotic syndrome, isolated hematuria, and proteinuria with coexisting hematuria. Nephrotic syndrome was defined as proteinuria above 3.5 g/d and serum albumin <30 g/L, whereas proteinuria that did not met the criteria of nephrotic syndrome were defined as proteinuria without nephrotic syndrome or proteinuria with coexisting hematuria.

Data from the pathologic centers were pooled and analyzed at the National Clinical Research Center for Kidney Disease in Guangzhou, China. The Medical Ethics Committee of Nanfang Hospital, Southern Medical University approved the study protocol and waived patient consent.

Histologic Specimens and Diagnosis

Pathologic diagnosis was made on the basis of the detailed histologic features, which included the results of light microscopy, electron microscopy, and immunofluorescence in the pathologic reports. For light microscopy, hematoxylin and eosin staining, periodic acid–Schiff reagent staining, periodic Schiff–methenamine staining, and Masson trichrome solution staining were performed. Congo red and methyl violet staining was performed in specific patients. Immunofluorescence staining for IgA, IgG, IgM, C3, C4, C1q, and κ/λ-light chains was conducted. All of the biopsies have light microscopy and immunofluorescence examination, whereas 76.5% of samples have electron microscope results. The histologic results were interpreted by one of six leading pathologists and extracted from the electronic pathologic reports.

The histologic findings were classified according to *Revised Protocol for the Histological Typing of Glomerulopathy* (27). Histologic diagnoses were classified into one of four major categories: (*1*) primary glomerulopathy, including but not limited to minimal change disease, IgA nephropathy, and FSGS; (*2*) secondary glomerulopathy that is associated with primary diseases, including but not limited to lupus, Henoch–Schonlein purpura, and diabetes; (*3*) hereditary glomerulopathy; and (*4*) unclassified glomerulopathy, such as ESKD of undetermined origin and normal kidney morphology. The classifications of primary and secondary glomerulopathies were made according to the pathologic lesion and clinical comorbidities. For instance, IgA nephropathy without a history of purpura, hepatitis, and other known causes was classified as primary, and obesity-related FSGS was classified as secondary.

Statistical Analyses

All of the data were analyzed by SPSS version 19.0 (SPSS Inc., Chicago, IL). Quantitative data were presented as mean±SD, whereas categorical data were presented as frequencies and percentages. The odds ratios (ORs) of a specific type of glomerulopathy among all patients as well as in different subgroups were estimated by generalized logistic models with adjustment for age, sex, region, the level of the hospital that performed the biopsy, diagnosis center, and indications of biopsy. P value <0.05 was considered to be statistically significant.

Results

Study Population

A total of 7962 children who underwent native kidney biopsy were included in this analysis. Demographic and clinical features of pediatric patients stratified by sex are shown in Table 1. The study population was mainly composed of boys (64%) and adolescents (13–18 years old; 67%), and it was imbalanced in geographic regions, hospital levels, and year of biopsy. The average age of study patients was 13.5±4.1 years old, and the youngest patient was only 2 months old. Most of the patients were from southern China (81%) and tertiary class A hospitals (83%).

Table 1. Demographic and clinical characteristics of 7962 children who underwent kidney biopsy in China from 2004 to 2014

Characteristics	Total, *n*=7962	Sex	
		Boys, *n*=5089	Girls, *n*=2873
Clinical syndrome, *n* (%)			
Nephrotic syndrome	3993 (50)	2858 (56)	1135 (39)
Proteinuria and hematuria	2120 (26)	1190 (23)	930 (32)
Proteinuria	772 (10)	408 (8)	364 (13)
Hematuria	661 (8)	377 (7)	284 (10)
AKI	286 (4)	174 (3)	112 (4)
Progressive CKD[a]	130 (2)	82 (2)	48 (2)
Age, yr, mean (SD)	13.5 (4.1)	13.7 (4.1)	13.1 (4.3)
0–12, *n* (%)	2615 (33)	1551 (31)	1064 (37)
13–18, *n* (%)	5347 (67)	3538 (69)	1809 (63)
Time of kidney biopsy, *n* (%)			
2004–2007	768 (10)	466 (9)	302 (11)
2008–2011	1640 (21)	1065 (21)	575 (20)
2012–2014	5554 (69)	3558 (70)	1996 (69)
Hospital level,[b] *n* (%)			
Tertiary class A	6576 (83)	4168 (82)	2408 (84)
Tertiary class B	666 (8)	442 (9)	224 (8)
Secondary	720 (9)	479 (9)	241 (8)
Region, *n* (%)			
South	6466 (81)	4181 (82)	2285 (80)
North	1496 (19)	908 (18)	588 (20)
Serum creatinine, mg/dl, median (IQR)	0.70 (0.52–0.93)	0.75 (0.57–0.97)	0.59 (0.47–0.82)

All cells except average age and serum creatinine are expressed as *n* (% within the strata). IQR, interquartile range.
[a]Defined as eGFR≤60 ml/min per 1.73 m^2.
[b]According to the Classification of Chinese Hospitals, which is available at https://www.hqms.org.cn/usp/roster/index.jsp.

Nephrotic syndrome (50%) remained the most common indication for kidney biopsy in children over the study period (Supplemental Table 1) followed by proteinuria with coexisting hematuria (26%), proteinuria without nephrotic syndrome (10%), and isolated hematuria (8%). The proportion of nephrotic syndrome in boys (56%) was higher than that in girls (39%). The number of children receiving kidney biopsy has increased over a decade

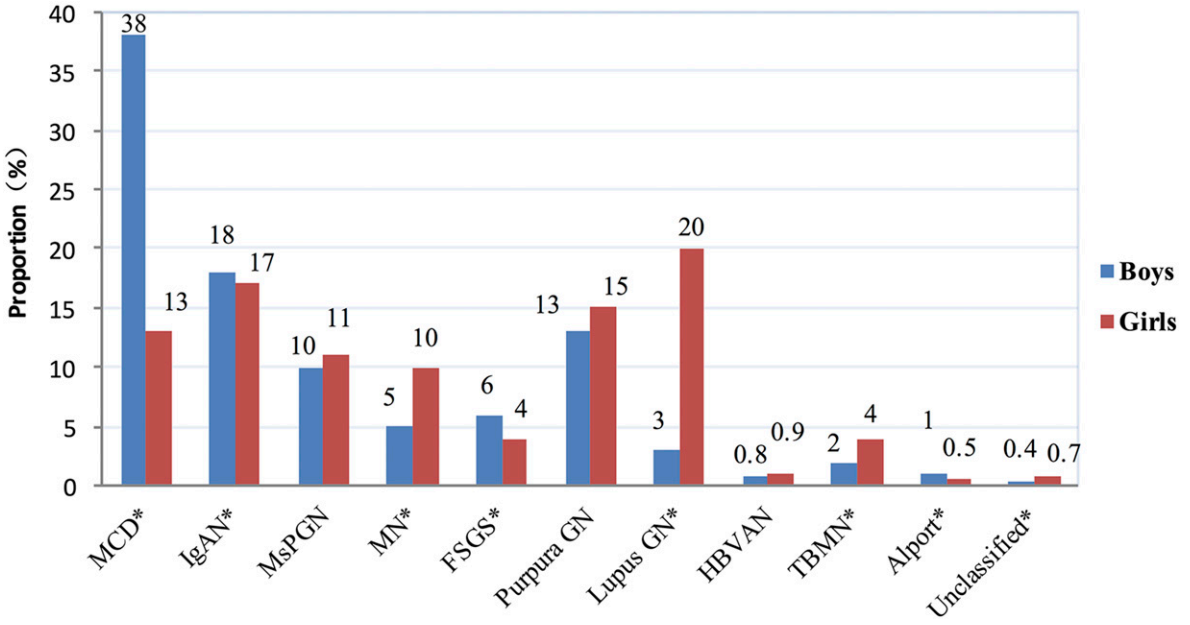

Figure 1. | The composition of major pediatric glomerulopathies is significantly different between boys and girls among 7962 children who underwent kidney biopsy in China from 2004 to 2014. *P* value is calculated in a generalized logistic model to compare the risk of each glomerulopathy (the corresponding proportion among patients with biopsy) in different subgroups with adjustment for age, region, hospital level that performed the biopsy, diagnosis center, and indications of biopsy. Alport, Alport nephropathy; HBVAN, hepatitis B virus-associated nephritis; IgAN, IgA nephropathy; MCD, minimal change disease; MN, membranous nephropathy; MsPGN, mesangial proliferative GN; TBMN, thin basement membrane nephropathy. *P<0.05.

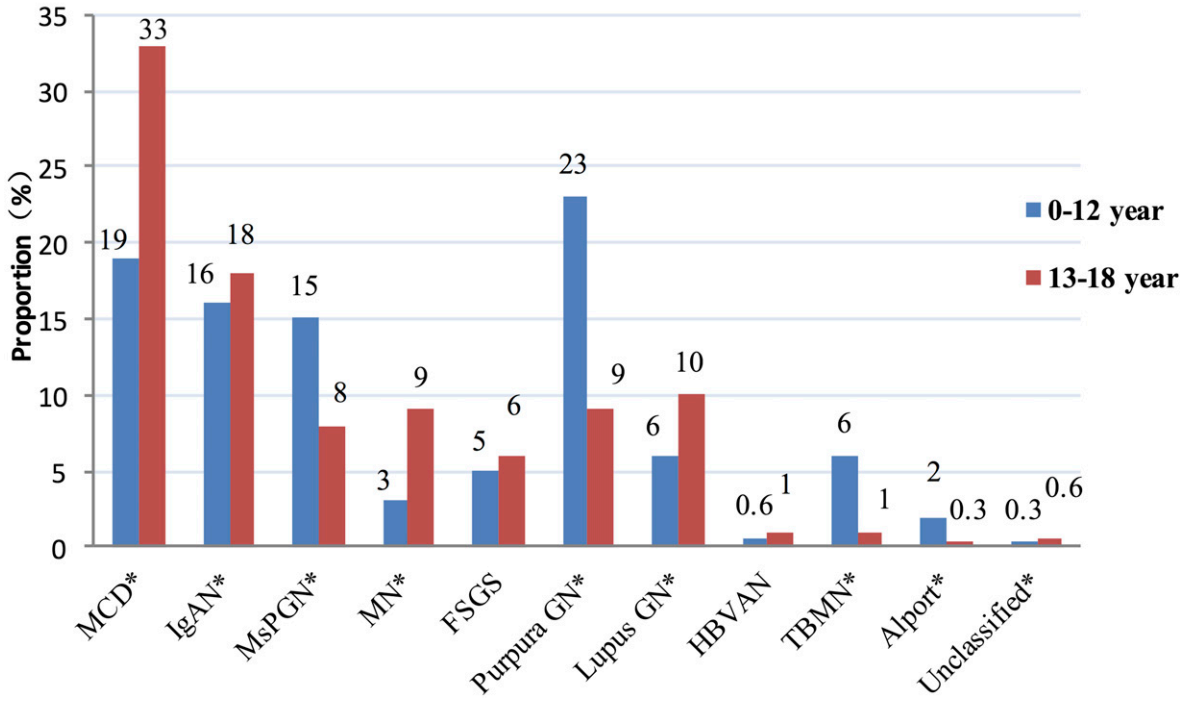

Figure 2. | The composition of major pediatric glomerulopathies is significantly different between young children and adolescents among 7962 children who underwent kidney biopsy in China from 2004 to 2014. *P* value is calculated in a generalized logistic model to compare the risk of each glomerulopathy (the corresponding proportion among patients with biopsy) in different subgroups with adjustment for sex, region, the level of the hospital that performed the biopsy, diagnosis center, and indications of biopsy. Alport, Alport nephropathy; HBVAN, hepatitis B virus-associated nephritis; IgAN, IgA nephropathy; MCD, minimal change disease; MN, membranous nephropathy; MsPGN, mesangial proliferative GN; TBMN, thin basement membrane nephropathy. *$P<0.05$.

progressively; however, the distribution of age and sex has almost stayed stable.

Composition and Secular Pattern of Pediatric Glomerular Diseases

In this study, 5736 (72%) patients were diagnosed with primary glomerular disease, whereas 1885 (23%) had secondary glomerular disease, 299 (4%) had heredity glomerular disease, and 42 (0.5%) had unclassified glomerular disease. Minimal change disease (29%) was the most common primary glomerular disease followed by IgA nephropathy (17%), mesangial proliferative GN (10%), membranous nephropathy (6%), and FSGS (5%). Henoch–Schonlein purpura nephritis (13%) and lupus nephritis (9%) were the two most common secondary glomerular diseases. Thin basement membrane nephropathy and Alport nephropathy were the most common heredity glomerular diseases, accounting for 3% and 0.8% of total pediatric glomerular diseases, respectively.

There were significant differences in the composition of pediatric glomerulopathies between different sex and age groups (Figures 1 and 2). Minimal change disease was the most common glomerulopathy in boys (38%), whereas lupus nephritis was the leading pathologic diagnosis in girls (13%). Compared with boys, girls tended to be less frequently diagnosed with minimal change disease (OR, 0.26; 95% confidence interval [95% CI], 0.23 to 0.30), IgA nephropathy (OR, 0.80; 95% CI, 0.71 to 0.91), FSGS (OR, 0.76; 95% CI, 0.61 to 0.95), and Alport nephropathy (OR, 0.38; 95% CI, 0.21 to 0.69), whereas lupus nephritis (OR, 10.91; 95% CI, 8.92 to 13.33) and membranous nephropathy (OR, 2.88; 95% CI, 2.39 to 3.48) were more frequently diagnosed in girls, even after adjusting for age, region, indications of biopsy, the level of the hospital that performed the biopsy, and diagnosis center. There were no significant sex differences in the proportions of Henoch–Schonlein purpura nephritis (12% versus 15%; $P=0.67$) and hepatitis B virus–associated nephritis (0.8% versus 0.9%; $P=0.51$).

Similarly, minimal change disease (33%) was the most common glomerulopathy in adolescents (13–18 years old), whereas Henoch–Schonlein purpura nephritis (23%) was the major pathologic diagnosis in younger children (0–12 years old). Compared with in the younger patients, significantly decreased odds of purpura nephritis (OR, 0.44; 95% CI, 0.38 to 0.51), thin basement membrane nephropathy (OR, 0.45; 95% CI, 0.32 to 0.62), Alport nephropathy (OR, 0.17; 95% CI, 0.10 to 0.29), and mesangial proliferative GN (OR, 0.75; 95% CI, 0.64 to 0.88) were observed in older children after adjusting for sex, region, indications of biopsy, hospital levels, and diagnosis center. However, the odds of IgA nephropathy (OR, 1.47; 95% CI, 1.28 to 1.68), membranous nephropathy (OR, 3.14; 95% CI, 2.40 to 4.11), lupus nephritis (OR, 2.20; 95% CI, 1.82 to 2.66), and hepatitis B virus–associated nephritis (OR, 1.77; 95% CI, 1.00 to 3.14) were higher in adolescents than that in younger children.

The proportions of major glomerulopathies varied greatly in different geographic regions of China (Supplemental Table 2). Membranous nephropathy was more

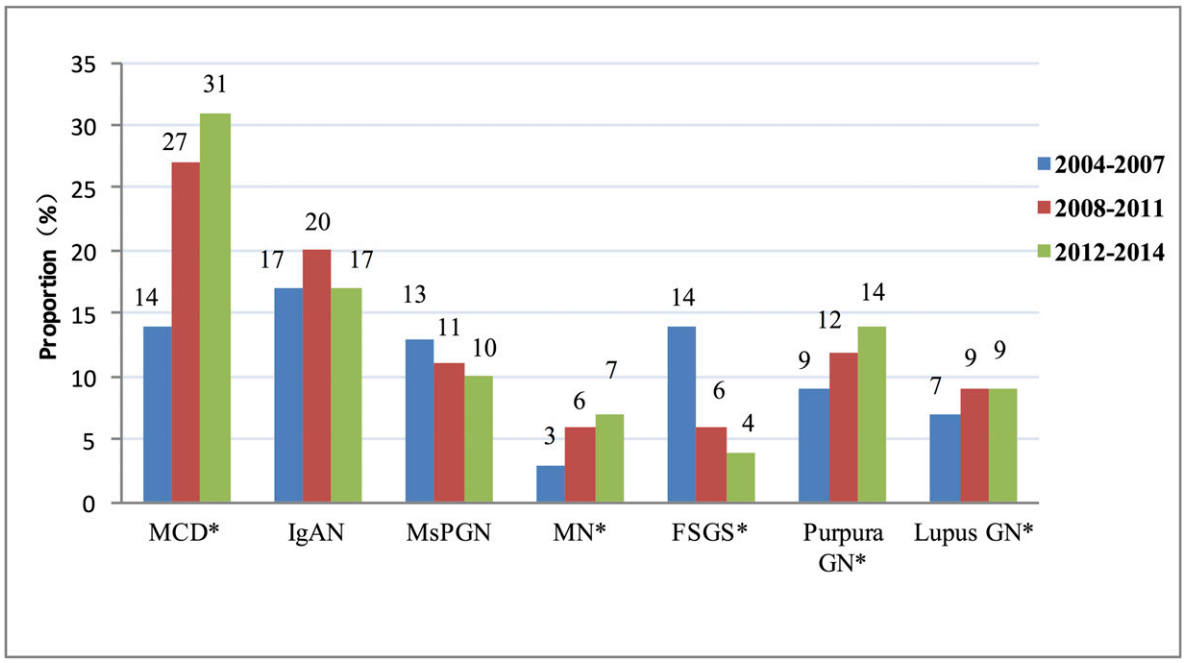

Figure 3. | **The composition of major pediatric glomerular diseases has significantly changed in China from 2004 to 2014.** *P* value is calculated in a generalized logistic model to compare the risk of each glomerulopathy (the corresponding proportion among patients with biopsy) in different subgroups with adjustment for age, sex, region, the level of the hospital that performed the biopsy, diagnosis center, and indications of biopsy. IgAN, IgA nephropathy; MCD, minimal change disease; MN, membranous nephropathy; MsPGN, mesangial proliferative GN. *$P<0.05$.

common in the north of China (5% in the south versus 14% in the north), whereas minimal change disease (30% in the south versus 23% in the north), lupus nephritis (9% in the south versus 7% in the north), and FSGS (6% in the south versus 3% in the north) were more common in southern China ($P<0.05$ for all). There were no significant differences in the proportions of mesangial proliferative GN between regions.

Changing Pattern of Pediatric Glomerular Diseases

IgA nephropathy was the most common pediatric glomerular disease in the period from 2004 to 2007 (diagnosed in 17% of children who underwent kidney biopsy) followed by minimal change disease (14%) and FSGS (14%). During the period from 2008 to 2011, the relative proportion of minimal change disease (27%) surpassed IgA nephropathy (20%) and then, subsequently became the predominant histologic pattern of pediatric glomerular disease (Figure 3). The relative proportions of purpura nephritis and membranous nephropathy increased significantly from 9% and 3%, respectively, in the first period (2004–2007) to 14% and 7%, respectively, in the last period (2012–2014). Meanwhile, the proportion of FSGS showed a significant decreasing trend, starting at 14% in the first period and decreasing to 6% and 4% in the second and third periods, respectively. There was no significant difference in the proportion of mesangial proliferative GN over the study period ($P=0.32$).

Clinicopathologic Correlation of Pediatric Glomerular Diseases

Nephrotic syndrome was the most common indication for kidney biopsy among children with minimal change disease (91%), membranous nephropathy (79%), FSGS (73%), lupus nephritis (39%), and hepatitis B virus–associated nephritis (64%), whereas proteinuria with coexisting hematuria was the most common biopsy indication in patients with IgA nephropathy (48%), mesangial proliferative GN (30%), Henoch–Schonlein purpura nephritis (59%), and Alport nephropathy (43%). Patients with thin basement membrane nephropathy (72%) mainly presented with isolated hematuria (Supplemental Table 3).

The top histologic pattern of different clinical syndromes (indications) stratified by age and sex is shown in Table 2. Minimal change disease was the leading cause of nephrotic syndrome (52%) followed by IgA nephropathy (10%) and membranous nephropathy (10%). IgA nephropathy was the most common etiology of proteinuria with coexisting hematuria (31%) and progressive CKD (30%). Henoch–Schonlein purpura nephritis (25%) was the most common etiology of proteinuria without nephrotic syndrome followed by mesangial proliferative GN (23%) and lupus nephritis (16%). In pediatric patients presenting as isolated hematuria, mesangial proliferative GN (31%), thin basement membrane nephropathy (25%), and IgA nephropathy (21%) were more common than other glomerular diseases. Minimal change disease (28%), lupus nephritis (24%), and endocapillary proliferative GN (11%) were more prevalent in patients with AKI. IgA nephropathy (30%), proliferative sclerosing GN (15%), and FSGS (12%) were the leading causes in patients with CKD.

The clinicopathologic correlations were slightly different between sexes and age groups. For instance, minimal change disease was the most common glomerulopathy leading to AKI in boys (40%), whereas lupus nephritis was the most common etiology of AKI in girls (42%). Thin

Table 2. Most common glomerular disease diagnoses among 7962 children who underwent kidney biopsy in China from 2004 to 2014 by clinical presentation, sex, and age

Clinical Syndrome	Sex		Age Group, yr	
	Boys	Girls	0–12	13–18
Nephrotic syndrome (%)				
Top 1	MCD (62)	MCD (28)	MCD (47)	MCD (54)
Top 2	IgAN (10)	LN (20)	IgAN (13)	MN (12)
Top 3	FSGS (8)	MN (18)	FSGS (10)	IgAN (10)
Proteinuria and hematuria (%)				
Top 1	IgAN (35)	HSPN (27)	HSPN (39)	IgAN (37)
Top 2	HSPN (32)	IgAN (26)	IgAN (22)	HSPN (23)
Top 3	MsPGN (11)	LN (20)	MsPGN (14)	LN (13)
Proteinuria (%)				
Top 1	MsPGN (29)	LN (28)	HSPN (50)	MsPGN (26)
Top 2	HSPN (27)	HSPN (23)	MsPGN (26)	LN (19)
Top 3	IgAN (14)	MsPGN (18)	LN (11)	IgAN (16)
Hematuria (%)				
Top 1	MsPGN (31)	TBMN (32)	MsPGN (36)	IgAN (33)
Top 2	IgAN (28)	MsPGN (32)	TBMN (26)	TBMN (21)
Top 3	TBMN (19)	IgAN (12)	IgAN (16)	MsPGN (20)
AKI (%)				
Top 1	MCD (40)	LN (42)	EPGN (27)	MCD (30)
Top 2	LN (12)	EPGN (13)	MCD (19)	LN (25)
Top 3	FSGS (12)	CrGN (11)	LN (17)	IgAN (8)
Progressive CKD (%)				
Top 1	IgAN (39)	PSGN (21)	IgAN (24)	IgAN (32)
Top 2	FSGS (12)	IgAN (15)	HSPN (16)	PSGN (19)
Top 3	HSPN (11)	LN (15)	FSGS (13)	FSGS (11)

MCD, minimal change disease; IgAN, IgA nephropathy; LN, lupus nephritis; MN, membranous nephropathy; HSPN, Henoch–Schonlein purpura nephritis; MsPGN, mesangial proliferative GN; TBMN, thin basement membrane nephropathy; EPGN, endocapillary proliferative GN; CrGN, crescent GN; PSGN, proliferative sclerosing GN.

basement membrane nephropathy was more prevalent in girls (32%) and younger children (36%) with isolated hematuria. Purpura nephritis (50%) was the leading cause of proteinuria in the younger patients, whereas mesangial proliferative GN (26%) was more common in adolescents with proteinuria.

Discussion

This study presents the first nationwide kidney biopsy series of pediatric patients (age ≤18 years old) in China. Of 7962 patients, 5736 (72%) were identified as having primary glomerular disease, whereas 1885 (24%) had secondary glomerular disease, and 299 (4%) had heredity glomerular disease. Our study provided detailed information on the spectrum of biopsy-proven pediatric glomerular diseases, which varied greatly among sexes, age groups, and regions. We also found significant changes in the disease composition of pediatric glomerular diseases over the study period.

In our series, there was a predominance of boys (68%), which was consistent with previous studies that reported a higher proportion of boys in patients with pediatric glomerulopathy (6,8,25,28). It might be attributable to the higher susceptibility of boys to major glomerular diseases, such as minimal change disease and IgA nephropathy. Supporting this notion, higher risk of minimal change disease and IgA nephropathy in boys compared with girls was observed in our study. Meanwhile, adolescents (76%) accounted for the majority of pediatric patients with glomerular disease, likely due to better acceptability of kidney biopsy in older children.

Minimal change disease was the most common pediatric glomerular disease in our study followed by IgA nephropathy, purpura nephritis, mesangial proliferative GN, and lupus nephritis. The spectrum of pediatric glomerulopathies varies across different countries. Several studies from the United States reported a considerably higher proportion of FSGS in both adult and pediatric glomerular diseases (7,29–32). Mesangial proliferative GN was reported to be the most common glomerulopathy in India (33), whereas IgA nephropathy was reported as the most frequent pattern of pediatric glomerular disease in Korea (34) and Italy (35). In several single-center studies conducted in China (25,36), minimal change disease or IgA nephropathy was identified as the most common pediatric glomerular disease. The variation in the spectrum of pediatric glomerulopathies in studies from different countries may result from the differences in biopsy indications, patient referral, and racial predisposition to different nephropathies (25,37,38). Up to date, there is no standard indication or guideline for kidney biopsies among children. For instance, children with steroid-sensitive nephrotic syndrome or isolated hematuria usually do not undergo kidney biopsy in some hospitals. However, the inconsistency of the disease spectrum within a similar ethnic group (Han Chinese) and study period suggested potential selection bias of study population in previous single-centered studies from China.

We also found that the spectrum of pediatric glomerular diseases varied with age and sex. After adjusting for other

confounders, minimal change disease tended to be more frequently diagnosed in boys, whereas lupus nephritis was more common in girls and adolescents. Regarding minimal change disease, a sex difference was also found among children in the study by Hadidi *et al.* (28). Similarly, numerous studies have shown that adolescent girls had significantly higher risk of lupus nephritis (39–41), which supported our results of sex differences in lupus nephritis. Considering that kidney biopsies are more difficult in children, detailed information on the spectrum and clinicopathologic characteristics of pediatric glomerular diseases among different sexes and age groups will contribute to more accurate clinical diagnosis when kidney biopsies are not available.

Over the 11-year study period, the number of biopsies among children increased by almost tenfold in China, which could be explained by a number of reasons, such as improvement in the safety and accessibility of kidney biopsy; the growing number of hospitals, especially lower-level hospitals, that offer biopsy; the increasing affordability of biopsy; and expansion of pathologic laboratories. To control for the effects of possible confounders in the analysis of the trend in profile change, we adjusted for age, geographic region, sex, clinical syndrome, pathologic laboratory, and hospital level for biopsy in our regression analysis. There were significant changes in the composition of pediatric glomerular diseases over the study period. We observed rises in the proportions of minimal change disease, purpura nephritis, and membranous nephropathy at the same time as a fall in the proportion of FSGS. The increased proportion of minimal change disease over time may be due, in part, to wider access to electron microscopy, leading to a drop in the proportion of "undefined diagnosis" by light microscopy. The rising trend in the proportion of purpura nephritis may be the result of changing referral patterns and attitudes toward biopsy in children with allergic purpura and isolated hematuria. Given that some patients with purpura and asymptomatic urinary abnormalities saw dermatologists rather than nephrologists, the willingness of physicians to refer and to biopsy could alter the biopsy rate and proportion of disease appreciably.

Interestingly, although membranous nephropathy was not a common glomerular disease in children, the proportion of children with membranous nephropathy in our population increased from 3% to 7% during the study period, which was significantly higher than the proportion in Western countries (0.9%–1.2%) (24,35). There were no substantial changes in the criteria for diagnosis or the differentiation of membranous nephropathy over the study period, and >95% of our study population were Han Chinese. Changes in kidney biopsy indication, diagnostic criteria, or genetic variation are unlikely explanations of the changing pattern of membranous nephropathy in our study. Indeed, we have previously reported a similar increasing trend in membranous nephropathy proportion among adults in China, which was partly due to the long-term exposure to air pollution (26). Although the mechanism by which long-term exposure to air pollution increases the risk of membranous nephropathy is still unknown, the adverse effect of air pollution on membranous nephropathy in adults seems likely to be similar to that in the children.

The main strengths of our study were the large sample size and broad coverage of China. The large number of patients, encompassing all age groups and both tertiary and community hospitals, permits a comprehensive evaluation of disease composition and clinicopathologic correlates with respect to glomerular disease in children. Furthermore, we analyzed the age and sex differences in the spectrum of pediatric glomerular diseases with adjustment for important confounders, such as region, hospital level, diagnostic center, and biopsy indications. A limitation of our study is that selection bias of study population is inevitable in all biopsy-based studies. Without a national kidney biopsy registry data in China, we were not able to estimate the true incidence of glomerulopathies in all pediatric patients in China. In addition, we collected the data from routine clinical practice and did not collect data within a prospective research framework. Thus, certain clinical information (*e.g.*, previous treatment, the level of daily urinary protein excretion, and body mass index) was lacking in our study. A national kidney biopsy registry integrated with the clinical information and long-term follow-up would provide more accurate estimates for the disease burden in China and provide valuable insights into the natural history of pediatric glomerular diseases. It may pave the way to tracking patients over time, driving decision support and optimizing the clinical practice, such as we have done for the management of many other chronic diseases (42).

In summary, we provided comprehensive and detailed information on the spectrum of biopsy-proven glomerular diseases among children in China. The composition and clinicopathologic characteristics of pediatric glomerular diseases varied greatly across different sexes and age groups.

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X.X. and F.F.H. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

None.

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