The profiles of biopsy-proven renal tubulointerstitial lesions in patients with glomerular disease

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Background: Renal tubules and interstitium are vulnerable to injury and play a central role in the progression of various chronic kidney diseases (CKDs). However, high quality epidemiologic study on the profiles of biopsy-proven tubulointerstitial lesions (TILs) is extremely limited.

Methods: We conducted a retrospective renal biopsy series including 62,569 native biopsies at 1,211 hospitals across China from 2015 to 2017. The TILs, including the shedding of tube epithelial, renal tubular atrophy, renal interstitial fibrosis, edema and inflammatory infiltration, were identified from the pathological report. We analyzed the severity and chronicity of TILs stratified by gender, age groups, biopsy indications, and concurrent glomerular diseases. We also examined the correlation between TIL and glomerulosclerosis.

Results: Of 56,880 patients with biopsy-proven glomerular disease, 79.5% had TILs. Renal interstitial inflammatory infiltration was the most common type of TIL (77.7%), followed by renal tubular atrophy (56.0%) and renal interstitial fibrosis (32.8%). Severe and chronic TILs were more common in adults than in children. The three glomerular diseases with the highest proportion of moderate-to-severe and chronic TIL were diabetic nephropathy, immunoglobulin A (IgA) nephropathy and focal segmental glomerulosclerosis. The severity of TILs was moderately correlated with glomerulosclerosis score (r=0.51). Moderate-to-severe and chronic TIL were more common in southern China. After adjusting for age, sex, hospital level, region, biopsy indication and type of concurrent glomerular diseases, adults with renal arteriole injury had a six-fold higher risk of moderate-to-severe TIL [odds ratio (OR), 7.12; 95% confidence interval (CI), 6.42 to 7.91] and a three-fold higher risk of chronic TIL (OR, 4.58; 95% CI, 4.37 to 4.79).

Conclusions: TILs were common in patients with biopsy-proven glomerular disease. The type and severity of TILs varied with age, region and concurrent glomerular diseases. Renal arteriole injury and glomerulosclerosis was associated with a significantly increased risk of TIL.

Keywords: Clinical epidemiology; kidney tubule; pathology injury; glomerulosclerosis; renal arteriole injury

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Introduction

Renal tubules and interstitium are the major components of kidney and susceptible to a variety of injures including hypoxia, proteinuria, systemic disorders, and nephrotoxic drugs. The glomerulus has long been thought the culprit for the progression of chronic kidney disease (CKD), while the renal tubules and interstitium are the victim of injury (1). In recent years, increasing evidence has demonstrated that renal function decline correlates better with tubulointerstitial lesions (TILs) than glomerular injury (2-4). It has been reported that tubular atrophy and fibrosis are better predictors of CKD progression than glomerular pathologic lesions. In patients with focal segmental glomerulosclerosis, the best clinical marker for disease progression is tubulointerstitial inflammation (5,6). Similarly, in patients with immunoglobulin A (IgA) nephropathy, only tubulointerstitial injury was associated with the rate of estimated glomerular filtration rate (eGFR) loss over a follow-up period extending to 35 years (7). Crosstalk between tubulointerstitium and glomerulus may play a pivotal role in the prognosis of patients with primary glomerular lesions (8).

Most epidemiologic studies on renal biopsy have focused on the spectrum of glomerular diseases (9,10). While a few studies focused on isolated tubulointerstitial disease such as acute or chronic tubulointerstitial nephritis (11-14), large and high-quality studies on the profiles of biopsy-proven TILs in patients with glomerular diseases are rather scarce.

In this study, we analyzed the profile of TILs in a renal biopsy series including 62,569 patients from 1,211 hospitals across China and evaluated their correlation with clinical indications and concurrent glomerular diseases. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-1669).

Methods

Study population and data collection

We enrolled a total of 62,569 native renal biopsies from 1,211 hospitals across China from 2015 to 2017. All renal histologic specimens were processed and diagnosed at the Kingmed Pathology Center. The specimens were regularly stained with hematoxylin-eosin, periodic acid-Schiff, periodic acid-silver Metheramine and Masson, and tested for IgA, IgG, IgM, C3, C4, C1q and k/λ–light chains by immunofluorescence assays. Electron microscopic examination was also performed in 86.7% of the samples. The data collected included patients' demographic information, clinical syndrome or diagnosis at biopsy, date and hospital performing the biopsy, histologic diagnosis, detailed histological reports from light microscopy, electron microscopy, and immunofluorescence assays. The Medical Ethics Committee of Nanfang Hospital, Southern Medical University approved the study protocol. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by The Medical Ethics Committee of Nanfang Hospital, Southern Medical University (No.: NFEC-2015-073) and individual consent for this retrospective analysis was waived.

Identification of TILs

Trained nephrologists reviewed the histological reports to identify TILs including both renal tubular lesions and renal interstitial lesions, as well as intrarenal arteriolar lesions. Renal tubular injuries included shedding of tubular epithelium and renal tubular atrophy. Renal interstitial injuries included edema, fibrosis, and infiltration of inflammatory cells. Intrarenal arteriolar lesions included arteriolar hyaline, arterial fibrotic intimal thickening, stenosis of the lumen and necrosis of intrarenal arterioles.

We categorized the severity of TILs based on the degree of spread out of inflammation, fibrosis, and atrophy. We defined focal or multifocal legion (<25% by area), flaky (25–50%), and diffuse (>50%) lesions as mild, moderate, and severe, respectively, with a corresponding score of 1 to 3. Those without TILs were assigned a score of 0. We defined chronic TILs as the existence of any tubular atrophy or fibrosis.

Calculation of the glomerulosclerosis score

The glomerulosclerosis score was calculated according to the percentage of glomeruli with global or segmental glomerulosclerosis (15). Samples with <10%, 10–25%, 26–50%, and >50% of glomeruli with global or segmental glomerulosclerosis were assigned a score from 0 to 3, respectively.

Classification of biopsy indications

The indications for kidney biopsy were classified into one of the following categories in order (from high to low) based on the clinical diagnosis at biopsy: nephrotic syndrome

(NS) with acute kidney injury (AKI), NS, AKI, progressive CKD defined as CKD stage 3-5, proteinuria without NS (PU), and isolated hematuria (HU). For cases that met the definitions of multiple categories, they were assigned to the class with the highest order.

Statistical analyses

We excluded the biopsy cases that had less than five glomeruli under light microscope, without histological diagnosis or glomerular disease, and the repeated biopsy cases. We summarized continuous variables by means ± standard deviation (SD) or median (interquartile range) and categorical variables by count (percentage). We calculated the Spearman's correlation coefficient between the severity of TILs and the glomerulosclerosis score in the total samples as well as stratified by major glomerulopathies. We examined the association between the intrarenal arteriolar lesions and the severity of TILs in children and adults, respectively, using a logistic regression model with adjustment for age, sex, hospital categories, geologic region, biopsy indication and concurrent glomerular diseases. A natural spline term was used for the adjustment of age in the regression model.

A two-sided P value <0.05 was considered statistically significant. All statistical analyses were performed using R version 3.5.0 (16).

Results

Study population

We selected from biopsy series a total of 58,232 independent cases that had 5 or more glomeruli under the microscope with definite pathological diagnosis, including 340 with a combination of two different glomerulopathies, 56,880 with a single glomerulopathy, and 1,012 with isolated tubulointerstitial diseases. The profile of isolated tubulointerstitial diseases was listed in *Table S1*. We subsequently analyzed TILs in the cases that had a single biopsy-proven glomerular disease (*Figure 1*). Because the profiles of glomerulopathy differed significantly between children and adults, we analyzed TILs in children and adults separately.

The demographic and clinical characteristics of the biopsy cases analyzed, including 4,274 children and 52,606 adults, are presented in *Table 1*. The study population was relatively young with an average age of 42 years and split equally in gender. Nearly 80% of the biopsy were performed in the tertiary class A hospitals in China. NS and proteinuria were the most common indications for renal biopsy in both children and adults. The profiles of glomerulopathy differed significantly between children and adults. The most common glomerular diseases in children were minimal change disease, Henoch-Schonlein purpura nephritis and IgA nephropathy, compared to membranous nephropathy, IgA nephropathy, and minimal change disease in adults.

Profiles of TILs in patients with glomerular disease

In our study population, TILs were present in 45.9% and 82.2% of the biopsy cases in children and adults, respectively (*Table 2*). The three most common TILs in children were interstitial inflammatory infiltration, shedding of tubular epithelium, and tubular atrophy, respectively. In adults, interstitial inflammatory infiltration, tubular atrophy and interstitial fibrosis were the most prevalent. Most of TILs were chronic lesions, and accompanied by intrarenal arteriolar lesions that were present in13.3% of children and 66% of adults. The prevalence of chronic TILs and intrarenal arteriole lesions varied with biopsy indication and type of glomerulopathy (*Figure 2*). These lesions were much more common in adults than in children across the whole spectrum of biopsy indications and glomerulopathies, except for diabetic nephropathy, in which almost all cases (>98%) have chronic TILs and intrarenal arteriole. Detailed profiles of TILs stratified by type of glomerulopathy were summarized in *Table S2*. Patients with AKI or progressive CKD were more likely to have chronic TILs as well as intrarenal arteriolar lesions in both children and adults.

Risk factors of moderate-to-severe TILs

In both children and adults, moderate-to-severe TILs were present in about 4% and 15% of cases with and without intrarenal arteriolar lesions, respectively (*Table 3*). After adjusting for other covariates, intrarenal arteriolar lesions were associated with a 7-fold higher odds of moderate-to-severe TILs in both children [odds ratio (OR) 7.49; 95% confidence interval (CI), 5.23 to 10.74] and adults (OR 7.08; 95% CI, 6.38 to 7.87). As expected, the prevalence of moderate-to-severe TILs was much higher in patients with AKI or progressive CKD than those with other biopsy indications. Moderate-to-severe TILs was rare (<1%) in patients with minimal change disease, but very common

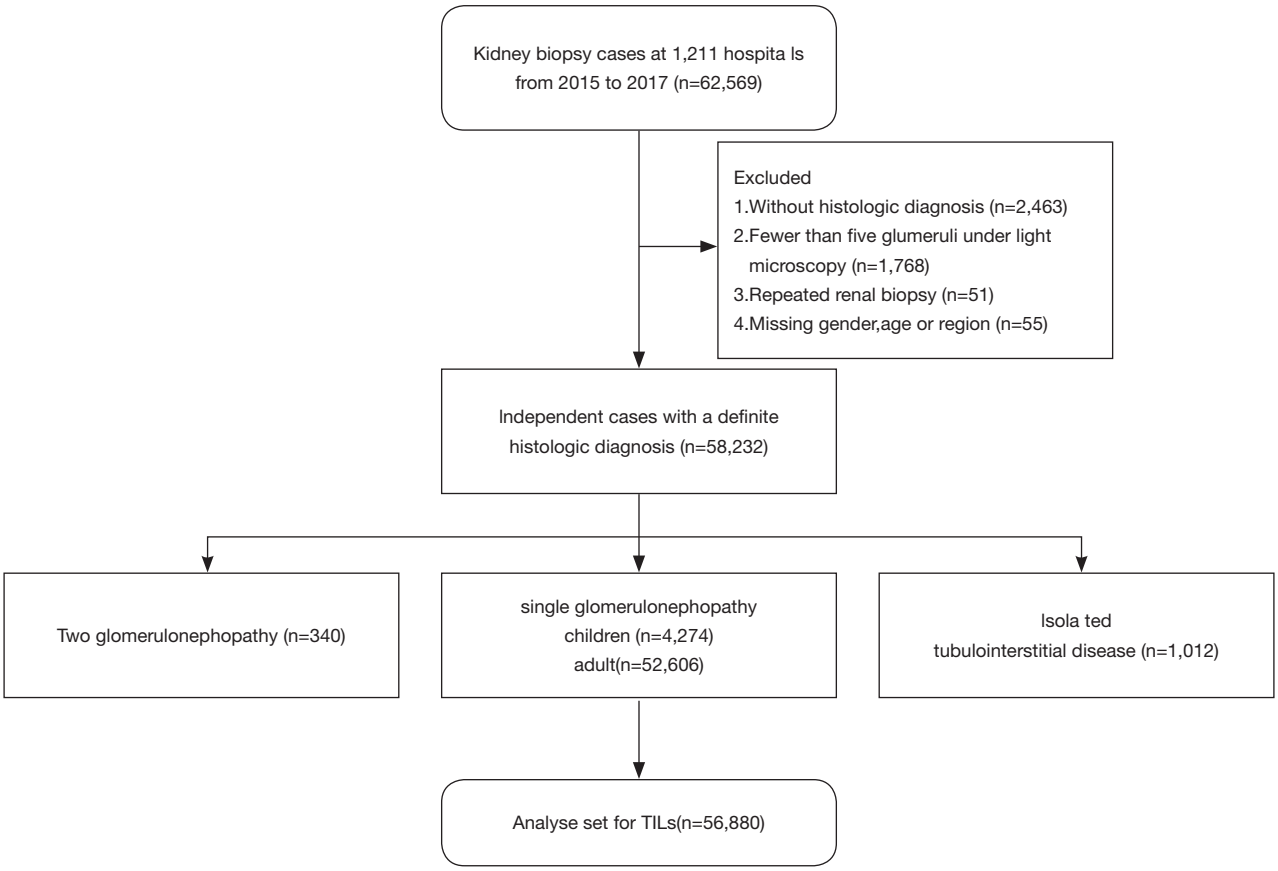

Figure 1 The flow chart of case selection.

(73.9%) in those with diabetic nephropathy. Demographic risk factors of moderate-to-severe TILs included females in children, and males and Southerners in adult. The severity of TILs was also significantly correlated with glomerulosclerosis (r=0.51; 95% CI, 0.50–0.52, *Table S3*), and the highest correlation observed in patients with IgA nephropathy (r=0.59, *Table S4*).

Risk factors of chronic TILs

Chronic TILs were present in 20.6% of children and 66% of adults, most frequently found in patients with IgA nephropathy (82.3%) and diabetic nephropathy (98.3%). In both adult and children, intrarenal arteriolar lesions, AKI, and progressive CKD were associated with a significantly increased risk of chronic TILs after adjusting for other covariates (*Table 4*).

Discussion

To the best of our knowledge, this is the first nationwide study to describe the profiles of biopsy-proven TILs among patients with glomerular disease. Although the biopsy samples in our study came from 1,211 hospitals across China, all the samples were processed and diagnosed histologically at a single pathological laboratory using unified criteria, which minimized the heterogeneity in histological diagnosis. In our study, TILs were more common in adults than in children. Patients with intrarenal arteriolar lesions, glomerulosclerosis, AKI, progressive CKD, or diabetic nephropathy had a significantly increased risk of moderate-to-severe and chronic TILs.

Table 1 Characteristics of the biopsy series in China

Characteristics	All patients (n=56,880)	Children (n=4,274)	Adults (n=52,606)
Age, mean year (SD)	41.7 (16.3)	12.3 (4.0)	44.1 (14.5)
Gender, N (%)			
Male	30,512 (53.6)	2,665 (62.4)	27,847 (52.9)
Female	26,368 (46.4)	1,609 (37.6)	24,759 (47.1)
Biopsy indication, N (%)			
NS	26,366 (46.4)	1,836 (43.0)	24,530 (46.6)
Proteinuria	22,196 (39.0)	1,818 (42.5)	20,378 (38.7)
Progressive CKD[a]	3,354 (5.9)	62 (1.5)	3,292 (6.3)
Hematuria	616 (1.1)	225 (5.3)	391 (0.7)
AKI	468 (0.8)	42 (1.0)	426 (0.8)
NS + AKI	416 (0.7)	33 (0.8)	383 (0.7)
Unknown	3,464 (6.1)	258 (6.0)	3,206 (6.1)
Hospital level, N (%)			
Tertiary class A[b]	44,505 (78.2)	3,762 (88.0)	40,743 (77.4)
Others	12,375 (21.8)	512 (12.0)	11,863 (22.6)
Region, N (%)			
Central	5,728 (10.1)	363 (8.5)	5,365 (10.2)
East	18,975 (33.4)	834 (19.5)	18,141 (34.5)
North	9,519 (16.7)	323 (7.6)	9,196 (17.5)
South	11,071 (19.5)	1,010 (23.6)	10,061 (19.1)
West	11,587 (20.4)	1,744 (40.8)	9,843 (18.7)
Glomerular disease, N (%)			
MN	19,337 (34.0)	233 (5.5)	19,104 (36.3)
IgAN	13,986 (24.6)	814 (19.0)	13,172 (25.0)
MCD	7,353 (12.9)	1,221 (28.6)	6,132 (11.7)
MsPGN	2,825 (5.0)	183 (4.3)	2,642 (5.0)
FSGS	2,526 (4.4)	199 (4.7)	2,327 (4.4)
LN	3,290 (5.8)	341 (8.0)	2,949 (5.6)
HSPN	1,931 (3.4)	922 (21.6)	1,009 (1.9)
DN	1,692 (3.0)	1 (0.0)	1,691 (3.2)
Others	3,940 (6.9)	360 (8.4)	3,580 (6.8)

[a], define as CKD stage 3–5; [b], according to the classification of Chinese hospitals. NS, nephrotic syndrome; CKD, chronic kidney disease; AKI, acute kidney injury; MN, membranous nephropathy; IgAN, IgA nephropathy; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; MsPGN, mesangial proliferative glomerulonephritis; DN, diabetic nephropathy; LN, lupus Nephropathy; HSPN, henoch-schonlein purpura nephritis.

Table 2 TILs and intrarenal arteriolar lesions

Various TILs	All patients, N=56,880 (%)	Children, N=4,274 (%)	Adults, N=52,606 (%)
Renal tubular lesions	40,422 (71.1)	1,420 (33.2)	39,002 (74.1)
Shedding of tubular epithelial	12,489 (22.0)	922 (21.6)	11,567 (22.0)
Renal tubular atrophy	31,843 (56.0)	584 (13.7)	31,259 (59.4)
Renal interstitial lesions	44,237 (77.8)	1,832 (42.9)	42,405 (80.6)
Tubulointerstitial edema	9,399 (16.5)	561 (13.1)	8,838 (16.8)
Renal interstitial fibrosis	18,681 (32.8)	474 (11.1)	18,207 (34.6)
Inflammatory cell infiltration	44,203 (77.7)	1,830 (42.8)	42,373 (80.5)
Intrarenal arteriolar lesions	35,328 (62.1)	569 (13.3)	34,759 (66.1)
Arteriolar hyaline	2,384 (4.2)	9 (0.2)	2,375 (4.5)
Arterial fibrotic intimal thickening	34,666 (60.9)	526 (12.3)	34,140 (64.9)
Stenosis of the lumen	35,268 (62.0)	566 (13.2)	34,702 (66.0)
Necrosis of intrarenal arteriole	45 (0.1)	1 (0.0)	44 (0.1)

TILs, tubulointerstitial lesions.

In our study, male was associated with a slightly increased risk of moderate-to-severe TILs in adults and a decreased risk in children after adjusting for other covariates. The exact mechanisms for these associations are not clear, and it may be caused by unadjusted confounders. For example, adult males are more likely to have hypertension and diabetes and to be exposed to nephrotoxic drugs (17). Such information was not available and hence not included in our association analyses.

The intrarenal arteriolar lesion and glomerulosclerosis are significant contributors of TILs in our study. A previous study reported that the proportions of tubular atrophy, interstitial cell infiltration, and interstitial fibrosis were significantly higher in patients with intrarenal arteriolar lesions than that in the patients without arteriolar lesions (18). Since the peritubular capillaries represent the sole blood supply to the tubules, glomerular scarring that damages the upstream capillary bed could have downstream consequences. Bohle *et al.* (19) found a significant inverse relationship between post-glomerular capillary area and serum creatinine. Obliteration of the peritubular capillary network could lead to reduce blood flow, which results in tubule hypoxia and tubular epithelial cell death and tubular atrophy (20-22). Meanwhile, tubulointerstitial and vessel damage increases the vascular resistance, which leads to drop in the glomerular filtration rate and eventually enters a vicious circle (23). Consistent with previous reports (24-26), the grade of glomerulosclerosis was significantly associated with the severity of TILs in our study, especially in patients with IgA nephropathy.

In our study, the highest prevalence of moderate-to-severe TIL was observed in patients with diabetic nephropathy, followed by IgA nephropathy. It has been reported that activation of renal local complement in patients with diabetic nephropathy contributes to kidney damage, especially tubular interstitial damage (27). Meanwhile, the arterial lesion is common in patients with diabetes which might contribute to the development of TIL. For IgA nephropathy, our results slightly differ from the findings of the previous work from China, in which 38.3% of patients with IgA nephropathy had moderate to severe TIL (28).

It is noteworthy that patients from southern China, mostly Guangdong province, had a 57% higher risk of moderate-to-severe TILs than that from other regions. According to the National Adverse Drug Reaction (ADR) Monitoring System in China, 33.7% of ADR in Guangdong province were potentially caused by inappropriate medication (29), which was the highest among all provinces. In Guangdong, use of Chinese herbal medicine is very common, and the incidence of new or serious ADRs of traditional Chinese herbal injections is significantly higher than the national average (30). We speculate that higher exposure to potentially nephrotoxic drugs may partly

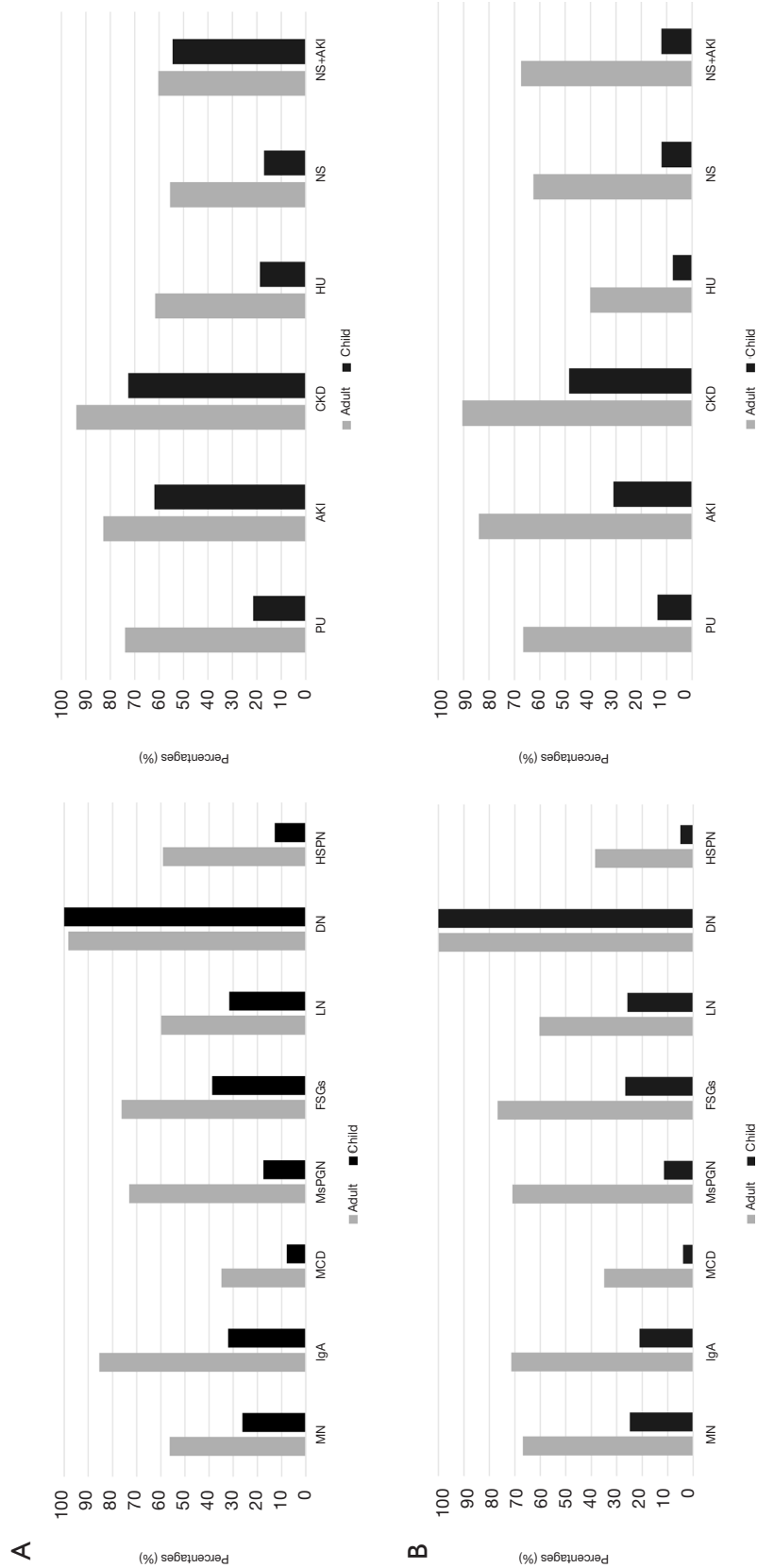

Figure 2 The proportion of biopsies with chronic TILs and intrarenal arteriolar lesions stratified by clinical indications and concurrent glomerulopathy. (A) The proportion of biopsies with chronic TILs stratified by concurrent glomerulopathy (left) and clinical indications (right). (B) The proportion of biopsies with intrarenal arteriolar lesions stratified by concurrent glomerulopathy (left) and clinical indications (right).

Table 3 The risk factors of moderate-to-severe TILs

Variable	Children (N=4,274)				Adults (N=52,606)			
	Total, N	M-to-S TIL[a], N (%)	Unadjusted OR (95% CI)	Adjusted OR[b] (95% CI)	Total, N	M-to-S TIL, N (%)	Unadjusted OR (95% CI)	Adjusted OR[b] (95% CI)
Intrarenal arteriolar lesions								
No	3,705	68 (1.8)	reference	reference	17,847	446 (2.5)	reference	reference
Yes	569	109 (19.2)	12.67 (9.22–17.42)	7.49 (5.23–10.74)	34,759	7,593 (21.8)	10.91 (9.89–12.02)	7.08 (6.38–7.87)
Gender								
Female	1,609	98 (6.1)	Reference	Reference	24,759	3,494 (14.1)	Reference	Reference
Male	2,665	79 (3.0)	0.47 (0.35–0.64)	0.62 (0.43–0.89)	27,847	4,545 (16.3)	1.19 (1.13–1.25)	1.22 (1.15–1.29)
Biopsy indication								
NS	1,836	43 (2.3)	Reference	Reference	24,530	2,007 (8.2)	reference	reference
Proteinuria	1,818	63 (3.5)	1.50 (1.01–2.22)	0.90 (0.55–1.48)	20,378	3,086 (15.1)	2.00 (1.89–2.13)	0.77 (0.71–0.83)
AKI	42	11 (26.2)	14.80 (6.98–31.37)	4.99 (2.06–12.08)	426	254 (59.6)	16.57 (13.58–20.22)	4.87 (3.87–6.12)
CKD	62	30 (48.4)	39.09 (21.83–70.01)	11.63 (5.85–23.14)	3,292	2,051 (62.3)	18.55 (17.05–20.17)	4.74 (4.28–5.26)
HU	225	9 (4.0)	1.74 (0.84–3.61)	1.18 (0.52–2.68)	391	15 (3.8)	0.45 (0.27–0.75)	0.18 (0.11–0.32)
NS + AKI	33	7 (21.2)	11.23 (4.62–27.27)	12.50 (4.03–38.73)	383	110 (28.7)	4.52 (3.61–5.67)	3.73 (2.79–4.99)
Region								
Central	363	9 (2.5)	Reference	Reference	5,365	601 (11.2)	Reference	Reference
South	1,010	65 (6.4)	2.71 (1.33–5.49)	1.92 (0.87–4.22)	10,061	1,880 (18.7)	1.82 (1.65–2.01)	1.55 (1.38–1.75)
North	323	12 (3.7)	1.52 (0.63–3.65)	0.91 (0.35–2.36)	9,196	1,091 (11.9)	1.07 (0.96–1.19)	0.98 (0.86–1.11)
East	834	27 (3.2)	1.32 (0.61–2.83)	0.93 (0.40–2.16)	18,141	2,985 (16.5)	1.56 (1.42–1.71)	1.14 (1.02–1.27)
West	1,744	64 (3.7)	1.50 (0.74–3.04)	0.98 (0.56–1.73)	9,843	1,482 (15.1)	1.41 (1.27–1.55)	1.03 (0.92–1.17)
Glomerular disease								
IgAN	814	53 (6.5)	Reference	Reference	13,172	3,566 (27.1)	Reference	Reference
MN	233	10 (4.3)	0.64 (0.32–1.29)	0.70 (0.32–1.53)	19,104	653 (3.4)	0.10 (0.09–0.10)	0.11 (0.10–0.12)
MCD	1,221	0 (0.0)	0.00 (0.00–Inf)	0.00 (0.00–Inf)	6,132	43 (0.7)	0.02 (0.01–0.03)	0.03 (0.02–0.04)
MsPGN	183	8 (4.4)	0.66 (0.31–1.41)	0.86 (0.37–2.00)	2,642	184 (7.0)	0.20 (0.17–0.24)	0.19 (0.17–0.23)
FSGS	199	16 (8.0)	1.26 (0.70–2.25)	0.90 (0.44–1.81)	2,327	462 (19.9)	0.67 (0.60–0.74)	0.57 (0.51–0.65)
LN	341	29 (8.5)	1.33 (0.83–2.14)	1.12 (0.63–1.98)	2,949	421 (14.3)	0.45 (0.40–0.50)	0.61 (0.54–0.69)
HSPN	922	9 (1.0)	0.14 (0.07–0.29)	0.30 (0.14–0.66)	1,009	75 (7.4)	0.22 (0.17–0.27)	0.43 (0.33–0.55)
DN	1	0 (0.0)	ND	ND	1,691	1249 (73.9)	7.61 (6.78–8.54)	5.89 (5.20–6.67)

[a], M-to-S TIL: moderate-to-severe tubulointerstitial lesions; [b], adjust for age, sex, hospital level, region, biopsy indication and type of concurrent glomerular diseases. NS, nephrotic syndrome; AKI, acute kidney injury; CKD, chronic kidney disease; HU, isolated hematuria; MN, membranous nephropathy; IgAN, IgA nephropathy; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; MsPGN, mesangial proliferative glomerulonephritis; DN, diabetic nephropathy; LN, lupus Nephropathy; HSPN, henoch-schonlein purpura nephritis; OR, odds ratio; CI, confidence interval; ND, not detectable.

Table 4 The risk factors of chronic TILs

Variable	Children (N=4,274)				Adults (N=52,606)			
	Total, N	Chronic TIL[a], N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Total, N	Chronic TIL, N (%)	Unadjusted OR (95% CI)	Adjusted OR[b] (95% CI)
Intrarenal arteriolar lesions								
No	3,705	562 (15.2)	Reference	Reference	17,847	7021 (39.3)	Reference	Reference
Yes	569	318 (55.9)	7.09 (5.87–8.55)	4.67 (3.81–5.75)	34,759	27,689 (79.7)	6.04 (5.80–6.28)	4.58 (4.37–4.79)
Gender								
Female	1,609	359 (22.3)	Reference	Reference	24,759	15,870 (64.1)	Reference	Reference
Male	2,665	521 (19.5)	0.85 (0.73-0.98)	1.11 (0.62–2.28)	27,847	18,840 (67.7)	1.17 (1.13–1.21)	1.34 (1.28–1.40)
Biopsy indication								
NS	1,836	313 (17.0)	Reference	Reference	24,530	13,624 (55.5)	Reference	Reference
Proteinuria	1,818	390 (21.5)	1.33 (1.13–1.57)	0.97 (0.75–1.25)	20,378	15,075 (74.0)	2.28 (2.19–2.37)	1.30 (1.22–1.37)
AKI	42	26 (61.9)	7.91 (4.19–14.91)	4.40 (2.14–9.05)	426	353 (82.9)	3.87 (3.00–4.99)	1.48 (1.12–1.96)
CKD	62	45 (72.6)	12.88 (7.28–22.80)	5.63 (2.96–10.71)	3,292	3,095 (94.0)	12.58 (10.87–14.56)	3.28 (2.80–3.84)
HU	225	42 (18.7)	1.12 (0.78–1.60)	0.81 (0.53–1.23)	391	241 (61.6)	1.29 (1.05–1.60)	0.67 (0.54–0.85)
NS+AKI	33	18 (54.5)	5.84 (2.91–11.71)	5.99 (2.71–13.27)	383	231 (60.3)	1.22 (0.99–1.50)	0.93 (0.73–1.19)
Region								
Central	363	59 (16.3)	Reference	Reference	5,365	3,337 (62.2)	Reference	Reference
South	1,010	248 (24.6)	1.68 (1.23–2.29)	1.72 (1.21–2.46)	10,061	6,871 (68.3)	1.31 (1.22–1.40)	1.24 (1.15–1.35)
North	323	88 (27.2)	1.93 (1.33–2.80)	1.51 (0.99–2.29)	9,196	5,624 (61.2)	0.96 (0.89–1.03)	0.89 (0.82–0.96)
East	834	151 (18.1)	1.14 (0.82–1.58)	1.17 (0.81–1.69)	18,141	12,630 (69.6)	1.39 (1.31–1.48)	1.14 (1.06–1.22)
West	1,744	334 (19.2)	1.22 (0.90–1.65)	1.20 (0.85–1.68)	9,843	6,248 (63.5)	1.06 (0.99–1.13)	0.93 (0.86–1.01)
Glomerular disease								
IgAN	814	261 (32.1)	Reference	Reference	13,172	11,252 (85.4)	Reference	Reference
MN	233	61 (26.2)	0.75 (0.54–1.04)	0.50 (0.34–0.74)	19,104	10,756 (56.3)	0.22 (0.21–0.23)	0.20 (0.19–0.22)
MCD	1,221	97 (7.9)	0.18 (0.14–0.24)	0.17 (0.12–0.24)	6,132	2,138 (34.9)	0.09 (0.09–0.10)	0.15 (0.14–0.16)
MsPGN	183	32 (17.5)	0.45 (0.30–0.68)	0.46 (0.28–0.70)	2,642	1,931 (73.1)	0.46 (0.42–0.51)	0.38 (0.34–0.43)
FSGS	199	77 (38.7)	1.34 (0.97–1.84)	0.85 (0.58–1.26)	2,327	1,773 (76.2)	0.55 (0.49–0.61)	0.47 (0.42–0.53)
LN	341	108 (31.7)	0.98 (0.75–1.29)	0.74 (0.53–1.03)	2,949	1,764 (59.8)	0.25 (0.23–0.28)	0.29 (0.26–0.32)
HSPN	922	118 (12.8)	0.31 (0.24–0.40)	0.46 (0.35–0.61)	1,009	596 (59.1)	0.25 (0.22–0.28)	0.36 (0.31–0.42)
DN	1	1 (100.0)	ND	ND	1,691	1,662 (98.3)	9.78 (6.75–14.16)	4.33 (2.99–6.29)

[a], Chronic TIL: existence of any tubular atrophy or fibrosis; [b], adjust for age, sex, hospital level, region, biopsy indication and type of concurrent glomerular diseases. TILs, tubulointerstitial lesions; NS, nephrotic syndrome; AKI, acute kidney injury; CKD, chronic kidney disease; HU, isolated hematuria; MN, membranous nephropathy; IgAN, IgA nephropathy; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; MsPGN, mesangial proliferative glomerulonephritis; DN, diabetic nephropathy; LN, lupus Nephropathy; HSPN, henoch-schonlein purpura nephritis; OR, odds ratio; CI, confidence interval; ND, not detectable.

contribute to the observed increased risk of moderate-to-severe TIL in patients from southern China (31).

Our study has several limitations. First, we do not have detailed clinical data of the patients such as laboratory indices, comorbidities and medications which may confound our association analyses of moderate-to-severe TILs. However, biopsy indications such as NS, proteinuria and hematuria may serve as a semi-quantitative surrogate for the severity of disease. Second, because our study is cross-sectional we are not able to evaluate the prognosis of TILs. Third, like any association studies, we are not able to make causal inference between TILs and the risk factors. Fourth, the present study only included Chinese population. Whether these results are generalizable to other ethnic population is unknown.

In conclusion, TIL is very frequent in patients with glomerular disease, and its profile varies greatly with age, biopsy indication, and concurrent glomerular disease. Renal arteriolar lesion is associated with a significantly increased risk of TIL. Given the pivotal role of TIL in the progression of kidney disease, more epidemiologic studies are needed to establish the long-term prognostic value of TIL in patients with glomerular disease.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by The Medical Ethics Committee of Nanfang Hospital, Southern Medical University (No.: NFEC-2015-073) and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 The spectrum of isolated tubulointerstitial diseases

Disease	Cases
Acute interstitial nephritis	395
Chronic interstitial nephritis	304
Acute tubular necrosis	182
Subacute interstitial nephritis	86
Multiple myeloma kidney injury	19
Sjogren's syndrome kidney injury	9
Renal interstitial infiltration by tumor cells	6
IgG4-related nephropathy	6
Gitelman syndrome	1
Chronic uric acid nephropathy	1
Subacute tubular necrosis	1
Renal cystic disease	1
Oxalate nephropathy	1

Table S2 The types of TILs stratified by glomerular disease

Pathologic changes	DN, N=1,692	IgAN, N=13,986	FSGS, N=2,526	MN, N=19,337	MCD, N=7,353	MsPGN, N=2,825	LN, N=3,290	HSPN, N=1,931
Renal tubular lesions, n (%)	1,636 (96.7)	12,064 (86.3)	2,159 (85.5)	12,796 (66.2)	3,319 (45.1)	2,070 (73.3)	2,252 (68.4)	907 (47.0)
Shedding of tubular epithelial	76 (4.5)	2,178 (15.6)	739 (29.3)	4,344 (22.5)	1,847 (25.1)	318 (11.3)	1,202 (36.5)	348 (18.0)
Renal tubular atrophy	1,605 (94.9)	10,921 (78.1)	1,679 (66.5)	9,814 (50.8)	1,848 (25.1)	1,901 (67.3)	1,323 (40.2)	636 (32.9)
Renal interstitial lesions, n (%)	1,686 (99.6)	12,531 (89.6)	2,282 (90.3)	14,661 (75.8)	3,437 (46.7)	2,189 (77.5)	2800 (85.1)	1,098 (56.9)
Tubulointerstitial edema	116 (6.9)	2,081 (14.9)	511 (20.2)	2,964 (15.3)	850 (11.6)	207 (7.3)	1,032 (31.4)	238 (12.3)
Renal interstitial fibrosis	1,583 (93.6)	7,245 (51.8)	1,125 (44.5)	3,432 (17.7)	585 (8.0)	918 (32.5)	1,270 (38.6)	271 (14.0)
Inflammatory cell infiltration	1,685 (99.6)	12,525 (89.6)	2,281 (90.3)	14,645 (75.7)	3,430 (46.6)	2,189 (77.5)	2,799 (85.1)	1,098 (56.9)
Intrarenal arteriolar lesions, n (%)	1,688 (99.8)	9,576 (68.5)	1,839 (72.8)	12,817 (66.3)	2,191 (29.8)	1,896 (67.1)	1,869 (56.8)	435 (22.5)
Arteriolar hyaline	1,228 (72.6)	310 (2.2)	118 (4.7)	283 (1.5)	60 (0.8)	184 (6.5)	22 (0.7)	16 (0.8)
Arterial fibrotic intimal thickening	1,683 (99.5)	9,457 (67.6)	1,819 (72.0)	12,527 (64.8)	2,084 (28.3)	1,870 (66.2)	1,828 (55.6)	416 (21.5)
Stenosis of the lumen	1,685 (99.6)	9,563 (68.4)	1,835 (72.6)	12,802 (66.2)	2,177 (29.6)	1,894 (67.0)	1,868 (56.8)	433 (22.4)
Necrosis of intrarenal arteriole	0 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)	0 (0.0)

[a], Chronic TIL: as presence of any tubular atrophy or fibrosis. DN, diabetic nephropathy; IgAN, IgA nephropathy.

Table S3 The TILs lesions stratified by glomerulosclerosis score

Glomerulosclerosis score	Severity of TILs		
	None	Mild	Moderate-to-severe
0	9,674 (40.8)	13,120 (55.4)	897 (3.8)
1	2,539 (10.6)	18,887 (79.1)	2,441 (10.2)
2	75 (1.1)	3735 (57.3)	2,712 (41.6)
3	5 (0.2)	629 (22.4)	2,166 (77.4)

TILs, tubulointerstitial lesions.

Table S4 The correlation between the severity of TILs and glomerulosclerosis stratified by glomerulopathy

Disease	TIL severity[a]	GS score[b]	r[c]	95% CI
IgAN	1.16 (0.59)	1.21 (0.93)	0.59	0.58–0.60
MN	0.80 (0.48)	0.60 (0.64)	0.34	0.33–0.36
MCD	0.49 (0.51)	0.32 (0.49)	0.40	0.38–0.42
MsPGN	0.85 (0.51)	0.81 (0.80)	0.41	0.37–0.44
FSGS	1.10 (0.53)	1.47 (0.80)	0.42	0.38–0.45
LN	1.00 (0.54)	0.54 (0.70)	0.31	0.28–0.34
HSPN	0.62 (0.57)	0.44 (0.64)	0.43	0.38–0.46
DN	1.75 (0.48)	1.40 (0.83)	0.33	0.28–0.37

[a], present as mean (SD); [b], glomerulosclerosis score present as mean (SD); [c], Spearman correlation coefficient. TILs, tubulointerstitial lesions; MN, membranous nephropathy; IgAN, IgA nephropathy; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; MsPGN, mesangial proliferative glomerulonephritis; DN, diabetic nephropathy; LN, lupus Nephropathy; HSPN, henoch-schonlein purpura nephritis.