Original Article

Noninvasive assessment of pediatric glomerular disease: multimodal ultrasound

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Background: Traditional 2-dimensional (2D) ultrasound is a noninvasive method in the assessment of glomerular disease. Ultrasound elastography shows promise in evaluating renal fibrosis, which plays a key role in glomerular disease progression. However, research in pediatric cohorts is limited. This study aimed to assess the diagnostic efficacy of multimodal ultrasound in pediatric patients with glomerular disease.

Methods: Pediatric patients undergoing kidney elasticity examination were recruited. Participants were categorized into a control group, nephritic group, and nephrotic group based on clinical presentation and pediatric nephrologist diagnosis. The nephritic group included cases with hematuria, proteinuria, kidney function impairment, and potentially edema or hypertension. The nephrotic group included cases with nephrotic syndrome. All participants underwent multimodal ultrasound of the right kidney to obtain 2D parameters, hemodynamic parameters, and elasticity values. Sound touch quantification (STQ) is a new shear wave elastography (SWE) technology that has been used in clinical applications in recent years. In this study, it was used to obtain kidney elasticity values. The diagnostic efficacy of multimodal ultrasound was evaluated through receiver operating characteristic (ROC) curve analysis. Logistic regression was further utilized to investigate the combined diagnostic efficacy of multiple parameters.

Results: This study included 154 females and 187 males with ages ranging from 4 to 16 years (mean age: 9.78±3.20 years). Cortical STQ and medullary STQ exhibited lower sensitivity but higher specificity. In logistic regression modeling, multimodal ultrasound showed good diagnostic performance. Between the nephritic group and the control group, the ROC curve yielded an area under the curve (AUC) of 0.71 [95% confidence interval (CI): 0.64–0.77]; sensitivity, 58.10%; specificity, 76.26% (P<0.01). Between the nephrotic group and the control group, the ROC curve yielded an AUC of 0.75 (95% CI: 0.69–0.82); sensitivity,

75.26%; specificity, 62.59% (P<0.01).

Conclusions: Ultrasound elastography demonstrates potential in detecting glomerular disease. Multimodal ultrasound can serve as a noninvasive approach for assessing glomerular disease, exhibiting good diagnostic performance.

Keywords: Glomerular disease; pediatric; multimodal ultrasound; ultrasound elastography

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Introduction

In children, glomerular disease accounts for 5–14% of chronic kidney disease (CKD) and 15–29% of end stage kidney disease (1). Unlike in developed countries, where congenital anomalies of the kidney and urinary tract are the most common cause, glomerulonephritis is the main cause of CKD in developing countries. In China, glomerular disease is the leading cause of end stage renal disease (2). Glomerular disease can lead to two different urinary and clinical patterns: nephritic and nephrotic. Nephritic glomerular disease is often asymptomatic with hematuria and mild proteinuria. However, significant or complete glomerular invasion can lead to heavy proteinuria (which may be in the nephrotic range), edema, hypertension, and kidney function impairment. Nephrotic glomerular disease involves heavy proteinuria and lipiduria. When urinary protein levels reach nephrotic-range proteinuria (≥200 mg/mmol creatinine or ≥1,000 mg/m^2/day) along with hypoalbuminemia (<3.0 g/dL) or edema, nephrotic syndrome (NS) develops (3). Different glomerular pathologies produce different clinical behavior, determining treatment approach and prognosis in pediatric patients.

Kidney biopsy represents the diagnostic gold standard. However, biopsy is invasive with risks including *de novo* hematuria, perinephric hematoma, infection, and arteriovenous fistula (4). Smaller kidney size and poor cooperation in children further challenge biopsy feasibility relative to adults (5).

In clinical practice, urinalysis and ultrasound are standard assessments for glomerular disease. In urinalysis, urine occult blood (UOB) and urine protein are important markers that can indicate renal impairment (6,7). The presence of red blood cells and/or protein in the urine indicates underlying structural damage to the kidneys. Abnormal urinalysis findings and renal function test results are suggestive of underlying kidney damage. However, hematuria and proteinuria can occasionally be physiological, such as after intense exercise. Traditional 2-dimensional (2D) ultrasound is utilized primarily to measure kidney size and evaluate renal echogenicity. Color Doppler ultrasound allows for assessment of renal hemodynamic parameters. Changes in kidney volume and cortical thickness correlate with impairment of renal function. Decreased renal blood perfusion contributes to kidney failure. However, these ultrasound findings may not be evident in the early stages of renal disease. Ultrasound elastography was previously used to differentiate between benign and malignant tumors. In recent years, ultrasound elastography has gradually been applied to evaluate inflammation and fibrosis in the liver (8,9). The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines on the clinical use of elastography provide a comprehensive overview of renal elastography applications and limitations. These guidelines highlight the ongoing debates regarding the influence of fibrosis and perfusion on elastography measurements in the kidney, emphasizing the need for further research in this area. In the kidney, ultrasound elastography has shown promise in predicting kidney fibrosis (10,11). A systematic review and meta-analysis (11) reported that shear wave elastography (SWE) is a good technique for diagnosing mild and severe renal fibrosis, and a fair technique for moderate fibrosis. Additionally, a study of 75 CKD patients found that Young's modulus correlates significantly with renal histological fibrosis (12). These previous studies have confirmed the feasibility of using ultrasound elastography to assess renal fibrosis, which plays a crucial role in glomerular disease.

Prior studies have demonstrated correlations between kidney Young's modulus values and renal fibrosis (13-16). However, there is limited data in pediatric cohorts. In this study, we hypothesize that ultrasound elastography helps in identifying pediatric patients with glomerular disease,

and multimodal ultrasound examination aids in improving the diagnostic efficacy of glomerular disease. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1126/rc).

Methods

This prospective study was registered in the Chinese Clinical Trial Registry (registration No. ChiCTR2400079883). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Board of The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (No. 2022-K-314-02). Informed consent was provided by all the patients.

Population

We recruited 341 pediatric patients in The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University from January 2023 to December 2023. All of these patients underwent kidney elasticity examination and had complete clinical data available. The cohort included 154 females and 187 males with ages ranging from 4 to 16 years (mean age 9.78±3.20 years). Patients were classified into three groups: control group, nephritic group, and nephrotic group. Group classification was primarily based on the diagnosis made by pediatric nephrologists, taking into account the patient's current clinical presentation and laboratory test results (17).

The inclusion criteria for each group were defined as follows:

- Control group: (I) age: 4–16 years; (II) asymptomatic urinary abnormalities, defined as subnephrotic-range proteinuria and/or microscopic hematuria without evidence of renal damage.
- Nephritic group: (I) age: 4–16 years; (II) abnormal findings in urinalysis (hematuria or/and proteinuria); (III) laboratory examinations found kidney function impairment; (IV) potentially edema or hypertension.
- Nephrotic group: (I) age: 4–16 years; (II) abnormal findings in urinalysis (hematuria or/and proteinuria) and urinary protein levels reach nephrotic-range proteinuria; (III) hypoalbuminemia; (IV) potential edema or hyperlipidemia.

The exclusion criteria for all groups were patients with kidney tumors, congenital genitourinary abnormalities, or history of kidney operations.

In cases of mixed nephritic-nephrotic presentation, patients were classified under the nephrotic group if they exhibited nephrotic-range proteinuria and hypoalbuminemia, as these are considered defining features of NS. All participants in this study were hospitalized patients at the time of evaluation. The majority of patients were admitted following their initial outpatient clinic visit after the first discovery of symptoms, representing cases at or near disease onset. However, it is important to note that a subset of patients, particularly those with chronic glomerular disease or NS, were evaluated during hospital re-admission due to recent disease relapse. For patients with conditions known to have periods of remission, such as minimal change disease, we ensured that evaluations were conducted during active disease phases. In cases of nephritic syndrome, which can have a dynamic clinical course, we aimed to evaluate patients during acute presentations or exacerbations.

Estimated glomerular filtration rate (eGFR) calculation:

The Schwartz's formula [2009]: eGFR =41.3 × (height/serum creatinine) was adopted in this research to calculate the eGFR in the disease groups (18).

Ultrasound examination

Mindray Resona 7T and Mindray Resona 9T ultrasonic diagnostic apparatus (Mindray, Shenzhen, China) were applied in this study. All scans were conducted by two ultrasound specialists with over 5 years of experience in ultrasound elastography. They used the same equipment to perform measurements on the same patient in sequence. The scanning protocol was as follows: first, each participant was placed in the prone position on the examination table. Kidney sizes were measured in 2D gray scale model by using SC5-1 and L9-3 probes. Kidney volumes were calculated using the formula: kidney volume = height × weight × length × $\pi/6$ (19). Second, in Doppler mode, the right renal artery hemodynamic parameters of peak systolic velocity and resistance index (RI) were obtained. Third, in elastography mode, sound touch quantification (STQ) was performed using a 5 mm × 5 mm region of interest (ROI) placed separately in the renal cortex and medulla in the middle portion of the right kidney (*Figures 1*,*2*). STQ is a new SWE technology used to calculate the elastic modulus of tissues by measuring the speed of shear wave propagation, thereby reflecting tissue stiffness. In recent years, STQ has been gradually applied in clinical practice including in the liver, kidneys, and tendons (20-22). When

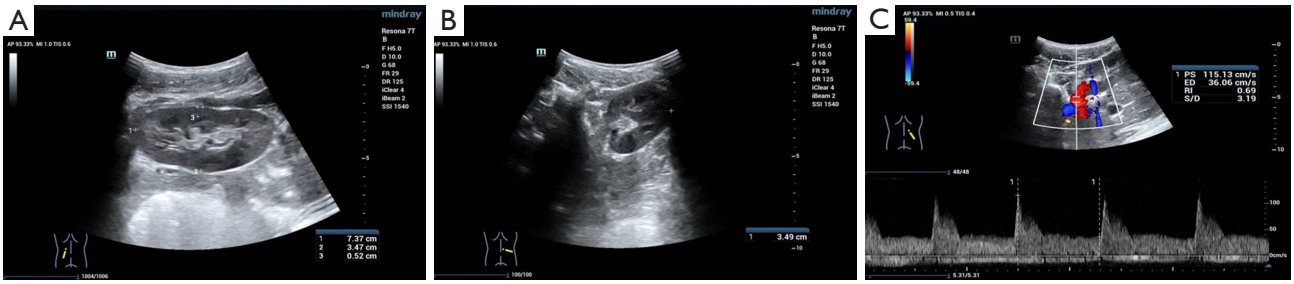

Figure 1 Renal ultrasound examinations. (A,B) Measurement of renal size and cortical thickness using two-dimensional grayscale ultrasound. (C) Doppler ultrasound measurement of right renal artery hemodynamic parameters including peak systolic velocity and resistance index. PS, peak systolic velocity; ED, end-diastolic velocity; RI, resistance index; S/D, peak systolic velocity/end-diastolic velocity.

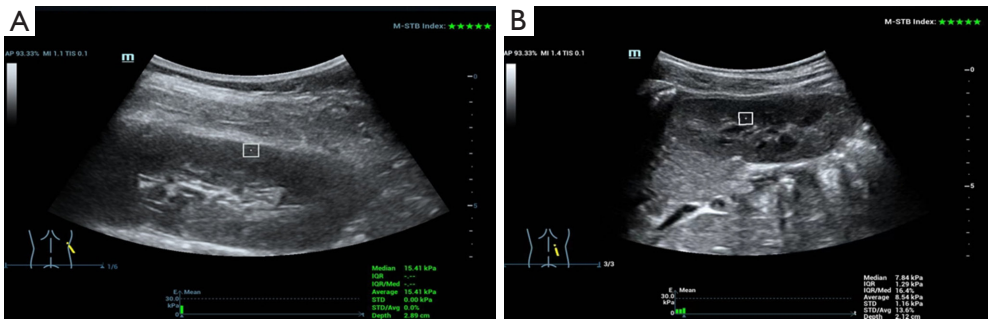

Figure 2 Renal elastography. (A) Measurement of renal cortical elasticity value using STQ. Region of interest is placed in the cortex. (B) Measurement of renal medullar elasticity values using STQ. Region of interest is placed in the medulla. The box in the figure represents the position and size of the ROI under the STQ mode. STQ, sound touch quantification; M-STB index, the motion stability index; IQR, interquartile range; ROI, region of interest; Med, median; Avg, average; STD, standard deviation.

measuring the elasticity of the renal cortex, it is important to ensure that the ROI (5 mm × 5 mm) is completely located within the renal cortex, avoiding placement outside the renal capsule and within the renal pyramids. When measuring the renal medulla, the ROI (5 mm × 5 mm) should be positioned as much as possible within the renal pyramids, avoiding placement within the renal cortex and renal sinus. A total of six measurements were acquired in both the cortex and medulla, during breath holds by the participant. The motion stability (M-STB) index located in the upper right corner of the screen should be no less than four stars. The final elasticity values represent the mean of six measurements, with the interquartile range (IQR)-to-median ratio (IQR/M) between measurements less than 30% (calculated automatically by Mindray Resona).

Statistical analysis

Data analysis was performed using the software SPSS 24.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 9.0 (GraphPad Software, San Diego, CA, USA). Normality testing was conducted on all measurement data using the Kolmogorov-Smirnov normality test. Normally distributed measurement data were presented as mean ± standard deviation. Non-normally distributed measurement data and qualitative data were presented as median and interquartile quartile. The reproducibility between two different operators was assessed with intraclass correlation coefficient (ICC). One-way analysis of variance (ANOVA) with Bonferroni *post-hoc* test was used for multiple comparisons of normally distributed data. Non-parametric Kruskal-Wallis test with Nemenyi *post-hoc* test was used for multiple comparisons of non-normally distribute data and qualitative data. Correlation analysis was performed using Pearson or Spearman rank correlation test. Logistic regression analysis was conducted for multivariate parameter analysis. Area under the receiver operating characteristic (ROC) curve (AUC) with 95% confidence interval (CI) was used to assess

diagnostic performance. A P value <0.05 was considered statistically significant.

Results

A total of 341 pediatric patients were included in this study. The cohort comprised 139 patients in the control group (76 males, 63 females, mean age 9.60±3.17 years), 105 patients in the nephritic group (45 males, 60 females, mean age 9.99±3.01 years), and 97 patients in the nephrotic group (66 males, 31 females, mean age 9.80±3.44 years). In the control group, 66 had nutcracker syndrome and 73 had simple hematuria or/and postural proteinuria. In the nephritic group, 68 had purpura nephritis, 17 had primary immunoglobulin A nephropathy (IgAN), 6 had lupus nephritis, 5 had chronic glomerular nephritis, 3 had acute nephritic syndrome, 3 had mesangial proliferative glomerulonephritis, 2 had C3 glomerulopathy, and 1 had acute post-streptococcal glomerulonephritis. In the nephrotic group, 81 had primary NS, 8 had minimal change NS, 3 had Alport syndrome, 2 had lupus nephritis, 2 had autoimmune glomerulonephritis, and 1 had primary IgAN.

There were no statistically significant differences in age among the three groups (P>0.05). The mean body mass index (BMI) of the nephrotic group (18.26±3.66 kg/m^2) was higher than that of the control group (17.03±3.11 kg/m^2) (P<0.05). There was no statistically significant difference in BMI between the nephritic group (17.68±3.49 kg/m^2) and the control group or between the nephritic group and the nephrotic group (P>0.05).

Laboratory tests

Various serological and urinary parameters were compared between groups (*Table 1*). Levels of urine protein, serum uric acid, urinary N-acetyl-beta-D-glucosaminidase (NAG), urinary albumin, urinary α1-microglobulin (Uα1-MG), urinary immunoglobulin G (IgG), urinary transferrin, and 24-hour urinary protein quantification in the nephrotic group were higher than those in the nephritic group and the control group. Total protein, serum albumin, and serum globulin in the nephrotic group were lower than those in the nephritic group and the control group. Ceruloplasmin and α1 acid glycoprotein (AAG) were reduced in the nephrotic group relative to the nephritic group. UOB, blood urea nitrogen (BUN), and β2-microglobulin (β2-MG) were elevated in the nephrotic group compared to the control group. Prealbumin and 24-hour urinary calcium in the nephrotic group were lower than those in the control group. Serum albumin and eGFR in the nephritic group were lower than that in the control group. Qualitative urine protein, UOB, serum globulin, BUN, NAG, C-reactive protein (CRP), urinary albumin, urinary IgG, urinary transferrin, 24-hour urinary protein quantification, haptoglobin, ceruloplasmin, and AAG in the nephritic group were higher than those in the control group. There were no other statistically significant differences in laboratory parameters among these three groups.

Ultrasound examination

In our study, multimodal ultrasound approach was utilized to evaluate the kidney, incorporating 2D grayscale imaging, Doppler ultrasound, and elastography (*Table 2*, *Figures 3*,*4*). Kidney volume was increased in the nephritic and nephrotic groups compared to the control group. Cortical STQ and medullary STQ values were also increased in the nephritic and nephrotic groups compared to the control group (*Figure 5*). Furthermore, cortical thickness in the nephrotic group was greater than that in the control group. Renal artery RI was reduced in the nephrotic group relative to the control group. There were no other statistically significant differences in ultrasound parameters among the three groups.

ICC

In our study, the measurement of cortical STQ and medullary STQ was conducted by two different operators. The ICC results showed good reproducibility between two different operators (*Table 3*).

Correlations between renal elasticity value and laboratory tests

As renal elastography values may serve as a potential indicator of kidney injury, we evaluated the correlation between elastography findings and other laboratory parameters in patients with glomerular diseases (*Table 4*). We found that renal cortical STQ correlated with UOB, serum albumin, prealbumin, serum creatinine, serum uric acid, urinary creatinine, urinary albumin, 24-hour urine creatinine quantification, 24-hour urine calcium, ceruloplasmin, AAG, and haptoglobin. Renal medullary STQ correlated with 24-hour urine creatinine quantification

Table 1 Results of laboratory tests

Variables	Control	Nephritic	Nephrotic	P value
eGFR (mL/min/1.73 m^2)	127.61±35.89	114.28±30.91*	120.50±33.66	<0.05
Urine protein†	0 [0, 1]	1 [0, 2]*	3 [2, 3.5]*#	<0.01
UOB†	1 [0, 1]	2 [1, 3]*	2 [1, 3]*	<0.01
Total protein (g/L)	70.54±4.57	68.94±7.13	51.20±12.52*#	<0.01
Serum albumin (g/L)	45.63±2.90	42.31±5.66*	30.38±10.17*#	<0.01
Serum globulin (g/L)	24.90±3.28	26.34±4.96*	20.81±3.81*#	<0.01
Prealbumin (mg/L)	219.00 [185.00, 249.00]	207.00 [169.00, 271.00]	173.00 [141.15, 244.50]*	<0.01
Serum uric acid (μmol/L)	330.49±93.18	344.28±114.62	398.82±126.06*#	<0.01
Serum creatinine (μmol/L)	40.40 [33.40, 51.70]	43.80 [36.40, 55.85]	39.90 [33.40, 52.50]	0.11
BUN (mmol/L)	4.60 [4.09, 5.40]	5.10 [4.20, 6.22]*	5.00 [4.20, 6.65]*	<0.05
β2-MG (μg/L)	131.00 [81.00, 211.00]	142.00 [76.65, 249.00]	204.00 [95.00, 390.00]*	<0.05
Urinary creatinine (mmol/L)	10.24 [6.52, 16.33]	10.31 [6.74, 15.02]	12.70 [7.21, 17.09]	0.16
NAG (U/L)	6.59 [4.40, 11.11]	10.64 [6.10, 18.70]*	49.10 [22.80, 79.30]*#	<0.01
CRP (mg/L)	1.40 [1.00, 2.79]	2.80 [1.31, 5.56]*	1.82 [1.33, 2.99]	<0.01
Urinary albumin (mg/L)	11.00 [6.20, 28.90]	111.00 [17.60, 749.00]*	5,660.00 [1,320.00, 8,640.00]*#	<0.01
Uα1-MG (mg/L)	4.80 [4.00, 8.45]	6.40 [4.00, 17.85]	45.80 [16.35, 89.95]*#	<0.01
Urinary IgG (mg/L)	7.40 [3.60, 15.60]	13.60 [5.40, 69.85]*	157.00 [39.35, 348.50]*#	<0.01
Urinary transferrin (mg/L)	2.00 [2.00, 2.24]	6.76 [2.00, 37.95]*	383.00 [81.45, 809.50]*#	<0.01
24-hour urinary protein quantification (g/24-hour)	0.07 [0.05, 0.11]	0.22 [0.07, 0.57]*	2.93 [1.06, 5.95]*#	<0.01
24-hour urinary creatinine quantification (mmol/24-hour)	5.71 [3.66, 8.37]	5.46 [4.06, 7.67]	5.36 [3.88, 7.66]	0.90
24-hour urinary calcium (mmol/24-hour)	1.37 [0.63, 2.02]	1.14 [0.60, 2.19]	1.04 [0.43, 1.70]*	<0.05
Haptoglobin (g/L)	54.90 [4.07, 89.80]	90.20 [39.95, 141.00]*	97.60 [31.18, 151.18]*	<0.01
Ceruloplasmin (g/L)	24.70 [0.37, 29.40]	27.00 [19.81, 36.25]*	21.18 [11.60, 29.40]#	<0.01
AAG (g/L)	50.10 [1.01, 63.60]	68.00 [50.10, 101.00]*	36.30 [27.74, 56.63]#	<0.01

Data are presented as mean ± standard deviation or median [interquartile range]. †, the values 0–4 represent the degree of UOB and urine protein: 0, negative; 1, (+); 2, (++); 3, (+++); and 4, (++++). *, compared to the control group, P<0.05. #, compared to the nephritic group, P<0.05. eGFR, estimated glomerular filtration rate; UOB, urine occult blood; BUN, blood urea nitrogen; β2-MG, β2-microglobulin: NAG, N-acetyl-beta-D-glucosaminidase; CRP, C-reactive protein; Uα1-MG, urinary α1-microglobulin; urinary IgG, urinary immunoglobulin G; AAG, α1 acid glycoprotein.

and haptoglobin; however, these were weak correlations.

Diagnostic performance of multimodal ultrasound parameters and logistic regression modeling

We attempted to explore the diagnostic performance of ultrasound parameters. Ultrasound parameters that were statistically significant between groups were evaluated by ROC curve analysis (*Table 5*). Our elastography results revealed significant differences between the control group and both the nephritic and nephrotic groups. For distinguishing the control group from the nephritic group, the optimal cut-off value for cortical STQ was 21.15 kPa, with a sensitivity of 48.57% and a specificity of

Table 2 Results of ultrasound parameters

Variables	Control	Nephritic	Nephrotic	P value
Volume (mL)	67.89±23.83	79.89±29.58*	83.89±36.70*	<0.01
Cortical thickness (mm)	6.09±1.14	6.39±1.21	6.75±1.30*	<0.01
Artery peak systolic velocity (m/s)	1.05±0.24	1.02±0.30	0.99±0.27	0.24
Artery resistance index	0.68±0.07	0.68±0.11	0.65±0.10*	<0.05
Cortical STQ (kPa)	17.44±4.25	20.61±7.00*	21.21±8.55*	<0.01
Medullary STQ (kPa)	10.69±2.76	11.84±3.62*	11.93±3.88*	<0.01
Cortical/medullary STQ rate	1.68±0.43	1.77±0.45	1.80±0.51	0.12

Data are presented as mean ± standard deviation. *, compared to control group, P<0.05. STQ, sound touch quantification.

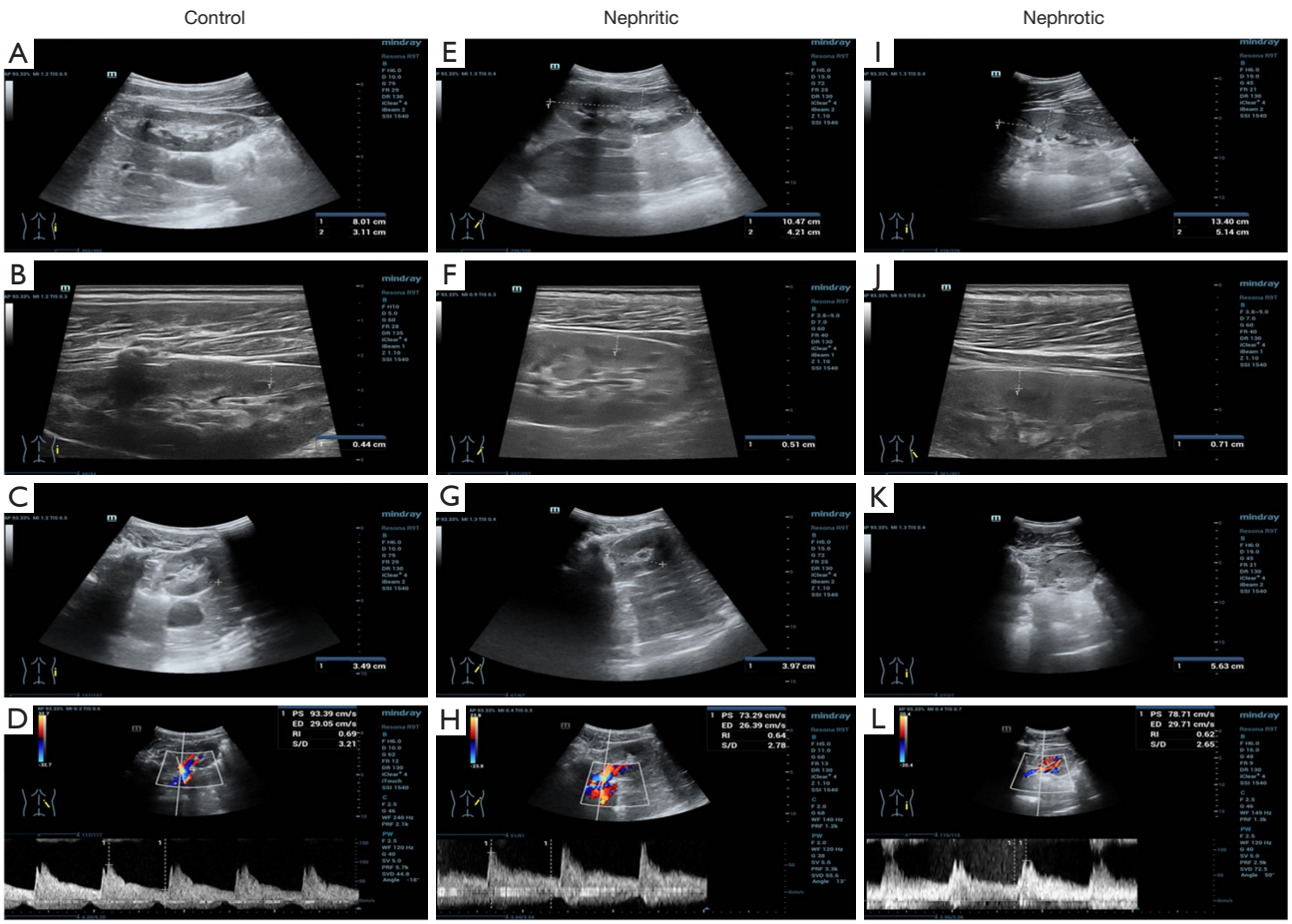

Figure 3 Renal ultrasound examinations were performed on participants. Control: 6 years old, female, the right kidney volume (A,C), cortical thickness (B), and renal artery hemodynamic parameters (D). Nephritic: 9 years old, male, the right kidney volume (E,G), cortical thickness (F), and renal artery hemodynamic parameters (H). Nephrotic: 15 years old, male, the right kidney volume (I,K), cortical thickness (J), and renal artery hemodynamic parameters (L). PS, peak systolic velocity; ED, end-diastolic velocity; RI, resistance index; S/D, peak systolic velocity/end-diastolic velocity.

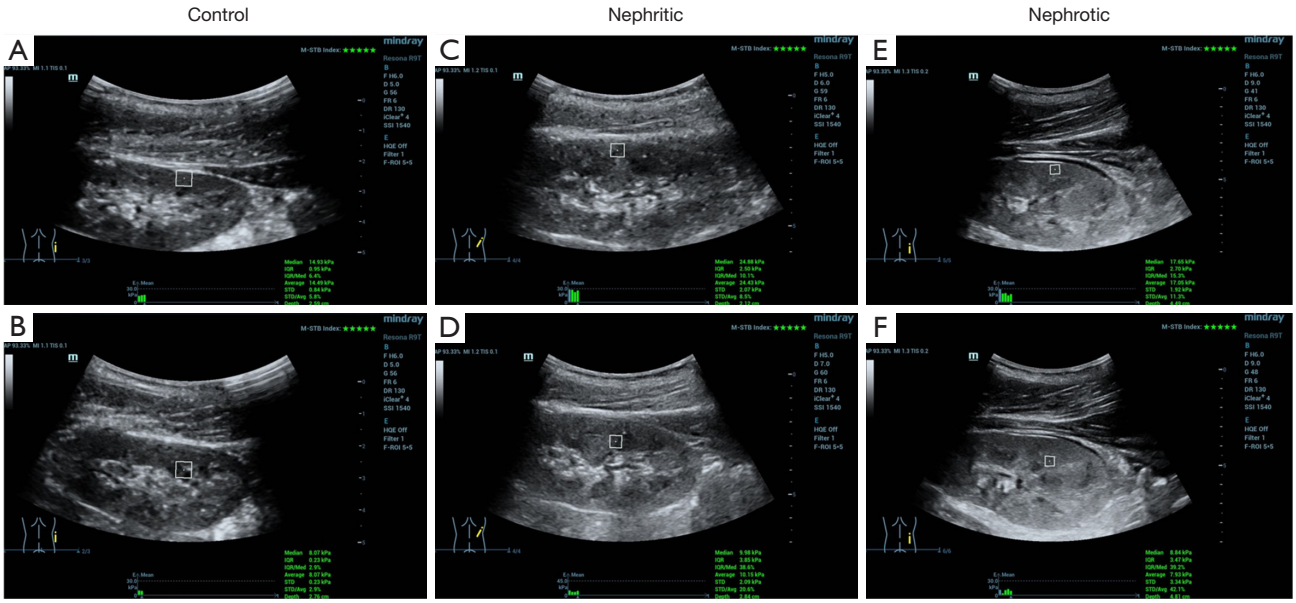

Figure 4 Renal elastography were performed on participants. Control: 6 years old, female, cortical STQ (A) and medullary STQ (B). Nephritic: 9 years old, male, cortical STQ (C), and medullary STQ (D). Nephrotic: 15 years old, cortical STQ (E), and medullary STQ (F). The box in the figure represents the position and size of the ROI under the STQ mode. M-STB index, the motion stability index; IQR, interquartile range; Med, median; Avg, average; ROI, region of interest; STQ, sound touch quantification; STD, standard deviation.

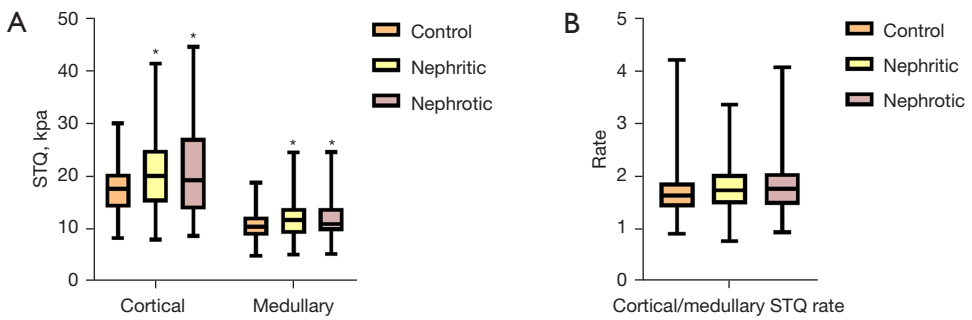

Figure 5 Box plot of renal elasticity results. (A) Box plots showed cortical STQ and medullary STQ in the control group, nephritic group, and nephrotic group; (B) box plots showed cortical/medullary STQ rate. *, compared to control group, P<0.05. STQ, sound touch quantification.

Table 3 Intraclass correlation coefficient

Variables	Cortical STQ (kPa)			Medullary STQ (kPa)		
	Control	Nephritic	Nephrotic	Control	Nephritic	Nephrotic
Operator 1	17.44±4.25	20.61±7.00	21.21±8.55	10.69±2.76	11.83±3.62	11.93±3.88
Operator 2	16.66±3.52	18.83±5.87	19.15±5.71	9.44±2.82	10.67±3.69	10.61±3.88
ICC	0.92	0.91	0.83	0.90	0.95	0.94

Data are presented as mean ± standard deviation. ICC, intraclass correlation coefficient; STQ, sound touch quantification.

Table 4 The correlation of renal elasticity value and laboratory test

Renal elastography value	Cortical STQ		Medullary STQ	
	r	P value	r	P value
eGFR	0.04	0.62	0.06	0.43
Urine protein	0.08	0.16	0.02	0.68
UOB	0.16	<0.01*	0.08	0.17
Total protein	–0.10	0.06	–0.05	0.32
Serum albumin	–0.11	<0.05*	–004	0.52
Serum globulin	–0.05	0.33	–0.08	0.15
Prealbumin	–0.15	<0.01*	–0.09	0.11
Serum uric acid	–0.12	<0.05*	–0.08	0.16
Serum creatinine	–0.16	<0.01*	–0.07	0.17
BUN	0.07	0.23	0.06	0.31
β2-MG	0.07	0.20	–0.02	0.65
Urine creatinine	–0.15	<0.01*	–0.07	0.18
NAG	0.01	0.81	0.01	0.90
CRP	0.09	0.09	0.10	0.07
Urinary albumin	0.11	<0.05*	0.09	0.10
Uα1-MG	0.04	0.47	0.02	0.79
Urinary IgG	0.06	0.29	0.04	0.48
Urinary transferrin	0.11	0.05	0.07	0.18
24-hour urine protein quantification	0.03	0.60	0.03	0.56
24-hour urine creatinine quantification	–0.31	<0.01*	–0.21	<0.01*
24-hour urine calcium	–0.12	<0.05*	0.01	0.82
Haptoglobin	0.21	<0.01*	0.12	<0.05*
Ceruloplasmin	0.16	<0.01*	0.10	0.06
AAG	0.11	<0.05*	0.08	0.16

*, P<0.05. eGFR, estimated glomerular filtration rate; UOB, urine occult blood; BUN, blood urea nitrogen; β2-MG, β2-microglobulin; NAG, N-acetyl-beta-D-glucosaminidase; CRP, C-reactive protein; Uα1-MG, urinary α1-microglobulin; IgG, immunoglobulin G; AAG, α1 acid glycoprotein; STQ, sound touch quantification.

81.29% (AUC =0.63, 95% CI: 0.56–0.71). The medullary STQ cut-off value was 11.64 kPa (sensitivity 51.43%, specificity 67.39%, AUC =0.59, 95% CI: 0.51–0.66). For differentiating the control group from the nephrotic group, the cortical STQ cut-off value was 24.43 kPa (sensitivity 30.93%, specificity 97.84%, AUC =0.60, 95% CI: 0.52–0.67), whereas the medullary STQ cut-off was 12.44 kPa (sensitivity 40.21%, specificity 77.54%, AUC =0.59, 95% CI: 0.51–0.66). For discriminating between the nephritic group and the control group, cortical STQ had the highest AUC. When comparing the nephrotic group and the control group, cortical thickness exhibited the greatest AUC. In addition, we further investigated the diagnostic efficacy of multimodal ultrasound parameters using multivariate logistic regression analysis. For differentiating the control group and the nephritic group, we included cortical STQ, medullary STQ, and volume in the logistic regression model. Cortical STQ and volume were

Table 5 Metrics of diagnostic efficacy

Variables	Cutoff value	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Control group *vs*. nephritic group				
Cortical STQ (kPa)	21.15	48.57	81.29	0.63 (0.56–0.71)
Medullary STQ (kPa)	11.64	51.43	67.39	0.59 (0.51–0.66)
Volume (mL)	61.16	71.43	45.65	0.61 (0.53–0.68)
Control group *vs*. nephrotic group				
Cortical STQ (kPa)	24.43	30.93	97.84	0.60 (0.52–0.67)
Medullary STQ (kPa)	12.44	40.21	77.54	0.59 (0.51–0.66)
Volume (mL)	58.91	76.29	42.75	0.62 (0.55–0.69)
RI	0.69	73.20	47.48	0.61 (0.54–0.69)
Cortical thickness (mm)	6.65	50.52	73.38	0.65 (0.58–0.72)

STQ, sound touch quantification; RI, resistance index; AUC, area under the curve; CI, confidence interval.

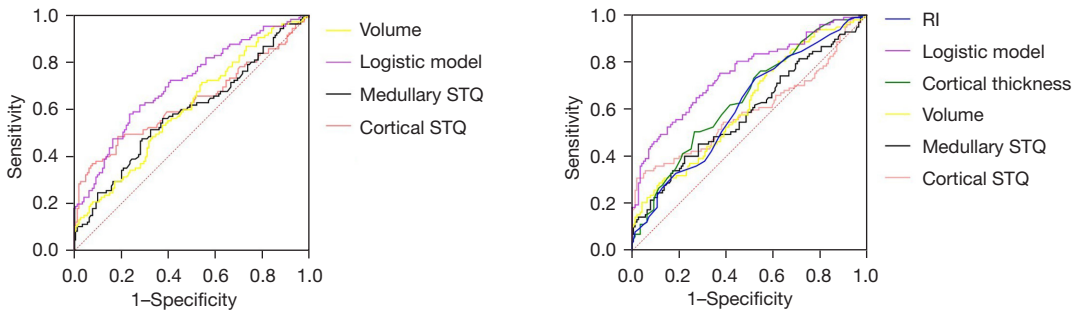

Figure 6 Results of the ROC curves. Left receiver operating characteristic curves for differentiation between control group and nephritic group with logistic modeling, volume, cortical STQ and medullary STQ (P<0.01, P<0.01, P<0.01, and P<0.05). Right ROC curves for differentiation between control group and nephrotic syndrome group with logistic modeling RI, cortical thickness, volume, cortical STQ, and medullary STQ (P<0.01, P<0.01, P<0.01, P<0.01, P<0.05, and P<0.05). ROC, receiver operating characteristic; STQ, sound touch quantification; RI, resistance index.

statistically significant predictors in the regression modeling (P<0.01). The modeling equation y=–4.33 + 0.14 × cortical STQ + 0.02 × volume yielded an AUC of 0.71 (95% CI: 0.64–0.77), sensitivity of 58.10%, and specificity of 76.26%. When comparing the control group and the nephrotic group, we included cortical STQ, medullary STQ, volume, cortical thickness, and RI in the logistic regression model. Cortical STQ, volume, and RI were significant variables (P<0.05). The regression modeling y=–2.01 + 0.15 × cortical STQ + 0.02 × volume – 4.83 × RI yielded an AUC of 0.75 (95% CI: 0.69–0.82), sensitivity of 75.26%, and specificity of 62.59%. The results of the univariate and multivariate logistic regression analyses are shown in *Figure 6*.

Discussion

In glomerular diseases, chronic inflammation from sustained injury can promote renal fibrosis. The progression of fibrosis results in pathological manifestations including glomerulosclerosis, tubulointerstitial fibrosis, and arteriolosclerosis. Renal fibrosis represents a major determinant of kidney failure. Considering the poor prognosis of CKD, early diagnosis and timely intervention are critical.

In this study, we reviewed pediatric patients with varying clinical presentations of glomerular disease. In the nephritic group, acute inflammatory phase indicators were higher

compared to those in the control group. Serum albumin was lower and urinary protein excretion was higher than they were in the control group. This aligned with the pathological mechanism of glomerulonephritis, in which immune-mediated damage to the glomeruli disrupted the filtration function of glomeruli (23,24). In the nephrotic group, urinary protein excretion continued to increase, whereas serum proteins continued to decrease. The acute inflammatory phase indicators exhibited no statistically significant differences between the control group and the nephrotic group. Compared to the nephritic group, the nephrotic group had lower acute inflammatory phase indicators and serum proteins but higher urinary protein excretion and serum uric acid. Inflammation in the nephrotic group appeared to be chronic rather than acute (25). The persistent chronic inflammation may contribute to ongoing damage to the glomerular filtration barrier, resulting in heavy proteinuria.

In traditional 2D gray-scale ultrasound, kidney volume and cortical thickness have been used to evaluate kidney injury. As renal function declines, enlargement of kidney volume and cortical thickness is observed. However, in end-stage renal disease, the kidneys undergo atrophy. In our study, we found kidney volume was higher in the nephritic and nephrotic groups compared to the control group. Previous research had confirmed that the changes in kidney size were associated with renal impairment and histological changes in the kidney (26). Similar to the results of laboratory tests, the increases in kidney volume in the nephritic and nephrotic groups in our study also indicated kidney damage. Renal cortical thickness was increased only in the nephrotic group compared to the control group. Cortical thickness was more closely related to eGFR than renal length in CKD (27). The nephritic group typically presented earlier and had a shorter disease course compared to the nephrotic group. This might explain why cortical thickness was not increased in the nephritic group in our study. However, there were no statistically significant differences in kidney volume or cortical thickness between the nephritic group and the nephrotic group. This might be because structural changes in the kidney were not markedly different between these two groups. Compensatory increases in kidney volume or cortical thickness typically occurred in patients with a longer disease duration. In this study, most pediatric patients were still in the early stages of the disease. Compared to the control group, kidney volume had high sensitivity (71.40%, 76.29%) but low specificity (45.65%, 42.75%) for identifying the nephritic group and the nephrotic group, respectively. In contrast, renal cortical thickness had low sensitivity (50.52%) but high specificity (73.38%) for identifying the nephrotic group compared to the control group. Overall, kidney volume and cortical thickness could be useful indicators to detect renal impairment.

It is important to note that, unlike liver elastography, there is currently no widely accepted standard for kidney elasticity values in normal children. As highlighted by studies such as that by Cetiner *et al.* on liver elastography, which presented percentiles for normal values, similar comprehensive data are lacking for kidney elastography (28). This gap in the literature is partly due to variations in elasticity values between different devices and imaging techniques, making direct comparisons between studies challenging. The application of elastography in renal assessment is complicated by several factors, including the influence of renal blood flow, hydration status, and the heterogeneous structure of the kidney. These factors, as discussed in the EFSUMB guidelines, contribute to the ongoing debate about the interpretation and reliability of renal elastography measurements, particularly in pediatric populations.

In this study, we found that the renal cortical STQ and medullary STQ in the nephritic group and the nephrotic group were higher than they were in the control group. In previous studies, kidney elasticity values in patients with glomerular disease (biopsy-proven) were higher than those in healthy individuals and correlated with renal fibrosis (29-32). However, in the early stages of glomerular disease, renal biopsy indications may not be met, or patients may refuse the procedure. Therefore, the application value of ultrasound elastography in early-stage glomerular disease lacks direct clinical evidence, especially in pediatric patients. In this study, the majority of patients were in the early stages of glomerular disease, with eGFR values still within the normal range. The result is consistent with the conclusions from previous studies, which suggested that kidney elasticity values could help identify early-stage glomerular disease. There were no statistically significant differences in ultrasound elastic parameters between the nephritic group and the nephrotic groups. Serum creatinine, BUN, and eGFR were all within normal ranges in both groups, with no statistically significant differences observed between the groups. This implied that the degree of renal impairment was similar between the two groups. Moreover, the ROI in this study was fixed in the middle portion of the right kidney, which might overlook elasticity changes

in other parts of the kidney. In future studies, it could be worthwhile to consider measuring elasticity in multiple regions of the kidneys. These might help explain why there were no statistically significant differences in ultrasound elastic parameters. We also noted that some previous studies found that Young's modulus value decreased with kidney impairment (33,34). Renal histology is complex. In addition to fibrosis, renal blood flow is also a key factor influencing renal elasticity (35). Hypoperfusion in the kidney decreases renal stiffness (36). Different elastography techniques and equipment could also contribute to varying results. Compared to the control group, cortical STQ and medullary STQ had low sensitivity (48.57%, 51.43%) but high specificity (81.29%, 67.39%) for identifying the nephritic group. Compared to the control group, cortical STQ and medullary STQ also had low sensitivity (30.93%, 40.21%) but high specificity (97.84%, 77.54%) for identifying the nephrotic group. Although the sensitivity is modest, the relatively high specificity, particularly in differentiating the nephrotic group from controls, suggests that ultrasound elastography is reliable in ruling out disease when present, even if it might miss some cases. Overall, cortical STQ and medullary STQ could also serve as markers of renal impairment.

The higher cut-off values for both cortical and medullary STQ in the nephrotic group compared to the nephritic group suggest that NS may be associated with greater tissue stiffness. However, the moderate sensitivity and specificity of these measures indicate that although elastography provides valuable information, it should be used in conjunction with other clinical and laboratory findings for optimal diagnostic accuracy. Additionally, we found that cortical STQ correlated with some laboratory parameters that indicate kidney damage, including UOB, serum creatinine, urinary albumin, and others. Medullary STQ correlated with 24-hour urine creatinine quantification and haptoglobin. But these correlations were very weak. This result suggested that changes in renal STQ were not strongly associated with changes in renal function. Renal elasticity values reflected the stiffness of the kidneys and were related to their structure. In the early stages of glomerular diseases, structural changes in the kidneys might not align with functional changes. Therefore, even though the correlation was weak, ultrasound elastography might still provide complementary information that contributes to a more comprehensive assessment of the kidneys. Moreover, in our study, the eGFR of pediatric patients was normal and these parameters were not further stratified. Further studies are needed to elucidate this correlation in more detail. Stratifying patients by eGFR and degree of proteinuria could help determine if cortical and medullary STQ correlate more strongly with laboratory markers of kidney damage in certain subgroups.

In clinical practice, ultrasound examinations are commonly used as non-invasive, convenient, and cost-effective screening tests for glomerular kidney disease. Therefore, we evaluated the efficacy of multimode ultrasound for the diagnosis of glomerular kidney diseases. Logistic regression modeling showed that the combination of cortical STQ and volume had 58.10% sensitivity and 76.26% specificity for differentiating between the nephritic group and the control group. The combination of cortical STQ, volume, and RI had 75.26% sensitivity and 62.59% specificity for differentiating between the nephrotic group and the control group, respectively. Although the AUC of multimodal ultrasound performed better than other ultrasound parameters alone (kidney volume, cortical thickness, cortical STQ, medullary STQ, or RI), there is room for improvement. Future research could consider several measures to improve the diagnostic performance of the model, such as incorporating more parameters, increasing the sample size, and utilizing machine learning algorithms.

There were some limitations in this study. Firstly, this was a single-center study conducted over a 1-year period, which may limit the generalizability of our findings to broader populations. The patient demographics, clinical practices, and environmental factors specific to our hospital might not be representative of other healthcare settings or geographical regions. Future research should involve multi-center studies with extended time frames to better validate these findings across a more diverse population. Secondly, our control group, consisting of patients with asymptomatic urinary abnormalities rather than healthy controls, presents a limitation. This selection was made to ensure the availability of comprehensive clinical data by using hospitalized patients as study participants. Ethical considerations also influenced this decision, as certain invasive procedures and ultrasound elastography may not be ethically justified for completely healthy individuals. We acknowledge that this choice might introduce bias and potentially affect the interpretation of our results. Thirdly, most patients in our study had normal eGFR, indicating the need to recruit more patients with impaired eGFR for a more comprehensive analysis. Fourthly, although renal biopsy remains the gold standard for diagnosing glomerular

disease, ethical considerations and the strict indications for renal biopsy in pediatric patients prevented us from obtaining biopsy data for all participants. This limitation is common in pediatric studies of this nature, where the risks of an invasive procedure must be carefully weighed against the potential benefits. Fifthly, our study encompassed a broad age range (4–16 years), and ideally, kidney volumes should be presented in relation to age/length-related normal values. However, the current lack of comprehensive, percentile-based reference data for kidney volume in Chinese children across different age groups precluded such an analysis. Lastly, the ROI selection for elastography was limited to the midportion of the right kidney. Elasticity values of the left kidney and different regions within the kidneys were not evaluated, which might impact the comprehensiveness of the findings.

Future multicenter studies are needed to establish reference values for kidney shear wave elasticity in normal children, similar to the approach taken by Cetiner *et al.* for liver elastography (28). In our upcoming research, we will aim to contribute to this effort by establishing such reference values based on the Mindray system.

Conclusions

Ultrasound elastography can serve as an indicator reflecting kidney damage. The established cut-off values for cortical and medullary STQ (21.15 and 11.64 kPa for nephritic syndrome; 24.43 and 12.44 kPa for NS, respectively) may serve as reference points for clinicians when interpreting elastography results in pediatric patients with suspected glomerular diseases. Multimodal ultrasound has better diagnostic efficacy than other ultrasound parameters alone.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1126/coif). L.W. reports that this research was partly supported by Clinical Research Foundation of the Second Affiliated Hospital of Wenzhou Medical University (No. SAHoWMU-CR2019-05-213), and the Huadong Medicine Joint Funds of the Zhejiang Provincial Natural Science Foundation of China (No. LHDMY24H280003). The other authors have no conflicts of interest to declare.

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 Ethics Board of The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (No. 2022-K-314-02). Informed consent was provided by all the patients.

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