



Renal elastography measurements in children with acute glomerulonephritis

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Purpose: The aim of this study was to compare the acoustic radiation force impulse elastography (ARFI-e) values of the renal cortical parenchyma in children with acute glomerulonephritis (AGN) and healthy children, and to determine a cut-off point for the diagnosis of AGN.

Methods: This prospective study included 30 children with biopsy-proven AGN and 30 healthy children. All the children underwent renal ARFI-e measurements. Values were obtained from the upper, middle, and lower zones of the right kidney parenchyma. A total of nine ARFI-e measurements (three from each zone) were made. Statistical analyses were conducted of the mean elastography values (MEVs) of the children in both groups.

Results: In the patient group, the MEVs measured from the upper, middle and lower zones of the right kidney were 3.42 ± 0.42 m/s, 3.45 ± 0.45 m/s, and 3.39 ± 0.39 m/s (average, 3.42 ± 0.34 m/s), respectively. In the healthy control group, the MEVs measured from the upper, middle, and lower zones of the right kidney were 2.85 ± 0.63 m/s, 2.85 ± 0.68 m/s, and 2.86 ± 0.66 m/s (average, 2.85 ± 0.57 m/s), respectively. The MEVs in all zones were significantly higher in the patient group than in the healthy group ($P < 0.001$). The cut-off values determined to predict AGN in the upper, middle, and lower zones of the kidney were 2.74 m/s (sensitivity, 96.67%; specificity, 46.67%), 2.71 m/s (sensitivity, 96.67%; specificity, 53.33%), and 2.81 m/s (sensitivity, 93.33%; specificity, 56.67%), respectively.

Conclusion: The ARFI-e technique can be considered as a non-invasive, easily applicable, auxiliary method for the early diagnosis of AGN.

Keywords: Acute glomerulonephritis; Biopsy; Prediction; Shear wave elastography; Ultrasound

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Introduction

Glomerulonephritis (GN) accounts for approximately 10%–15% of childhood glomerular diseases. Associated glomerular inflammation and damage lead to the passage of protein and red blood cells from serum to urine. It is one of the major causes of end-stage renal failure [1].

GN is a preventable risk factor for renal failure and cardiovascular disease [2]. The isolated presence of blood and/or protein in the urine, nephrotic (consisting of proteinuria, edema, and hyperlipidemia) or nephritic (consisting of hematuria and hypertension) syndromes, and acute or chronic kidney failure are clinical manifestations of glomerular involvement [3]. Although it is not fully understood, current evidence suggests that genetic factors, various infectious agents, drugs, and autoimmunity play a



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complex role in the pathogenesis of GN [4].

GN is classified according to etiology (primary or secondary), histopathological type, and clinical features [5]. Focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) are reported as the most common forms of primary GN in childhood, although there may be variations according to geographical and ethnic differences [6–10]. Renal parenchymal needle biopsy is the gold standard for the histopathological diagnosis of GN and can provide guidance in determining the prognosis and selecting the appropriate treatment. However, there may also be complications such as massive bleeding and infection [11].

Gray-scale ultrasound (US) imaging is used to determine kidney size, parenchymal thickness, and echogenicity changes. Although increased parenchymal echogenicity in addition to an increase or decrease of corticomedullary differentiation may be observed in diffuse renal parenchymal diseases, the definitions of these findings can be subjective. Therefore, US findings and the clinical history should be correlated to differentiate possible diagnoses [12,13]. Recently, ultrasound elastography (UE) has been used for further examination of kidney parenchyma. Shear wave elastography (SWE) is a non-invasive UE technique that allows measurements of tissue stiffness. It provides real-time measurements of shear wave velocity (SWV) generated with an acoustic impulse, thereby providing quantitative information about tissue elasticity. Harder tissues have been shown to have higher SWV. The use of UE is increasingly important in the evaluation of liver fibrosis, thyroid nodules, splenic stiffness, prostate lesions, breast lesions, and lymph nodes [14].

However, the anisotropy of the kidney parenchyma is higher than that of the liver due to its double compartment structure of the cortex and medulla, and also due to its rich vascularization. Therefore, the use of elastography for the evaluation of renal diseases is not widespread [15,16]. Some UE studies have evaluated renal parenchymal diseases, but studies specifically of GN in the pediatric population are limited [11]. The aim of this study was to compare SWE values of kidney parenchyma in children with biopsy-proven acute glomerulonephritis (AGN) and in healthy individuals.

Materials and Methods

Compliance with Ethical Standards

This prospective study was approved by the Institutional Ethics Committee of Gaziantep University Medical Faculty in Turkey with the decision number of 2019/388. An informed voluntary consent form was obtained from the parents of all the patients before the procedures were performed.

Patient Population

Patients were randomly selected from children with isolated hematuria and/or proteinuria, acute nephrotic/nephritic syndrome, or acute kidney failure who were referred to the pediatric radiology unit with an indication for renal biopsy between February 1 and August 1, 2019. The study included 30 pediatric patients with histopathologically proven AGN, and a control group of 30 healthy children with normal clinical and laboratory findings. According to the initial treatment protocol of the Pediatric Nephrology Department, all patients received oral steroid therapy before the SWE measurement and biopsy procedure. The right kidney parenchyma of the children in both groups was evaluated first with B-mode US, and then acoustic radiation force impulse elastography (ARFI-e) measurements were obtained. A Tru-Cut biopsy was performed after SWE evaluation of the patients' ipsilateral kidney.

Exclusion Criteria

Patients were excluded from the study if they were not able to cooperate with the procedure, had a history of chronic GN, congenital anomaly or hereditary kidney disease, had been diagnosed with any systemic disease (e.g., diabetes mellitus), urinary infection or urolithiasis, had renal atrophy or parenchymal thinning, or were being followed up due to vesicoureteral reflux or hydronephrosis.

Equipment, Gray-Scale Ultrasonography Procedure, and SWE Techniques

B-mode US and ARFI-e evaluations were made by the single chief resident of the Radiology Department who was blinded to the clinical information about the children. SWE measurements were performed on a Siemens Acuson S2000 (Siemens Medical Solutions, Mountain View, CA, USA) using virtual touch tissue quantification (VTQ) software with a 6C1 HD convex probe. Before the US examination, the children and/or parents were informed about the procedure and instructed what to do and what not to do. In some cases, children were shown cartoons or music clips on mobile phones to keep them immobile during the procedure. After providing optimal cooperation, the patient was positioned in a mild left lateral decubitus position with maximum abduction of the right arm. Right kidney morphology was evaluated first with B-mode US imaging and then point SWE mode was initiated. With the patient holding his or her breath lightly, measurements of the kidney were taken in the longitudinal plane. The ARFI excitation pulse axis was almost perpendicular to the middle zone of the renal cortex, while the pulses sent to the upper and lower polar cortices were from different angles. The maximum depth of the region of interest (ROI) was kept within 5 cm and the operator made every

effort to minimize pressure during the transducer-skin contact. The elastography values were obtained with a constant 10×5 mm rectangular ROI unit, placed in the cortical area of the upper, middle, and lower zones of the kidney, avoiding the capsule and medulla (Fig. 1). A total of nine SWE measurements were made, three from each zone. The mean ARFI-e values were used as representative values. The measurements were repeated if the kidney was moving due to poor breath control or the device did not provide a result. Data were saved digitally. After completion of the procedure, the patient was referred to the biopsy unit on the same day.

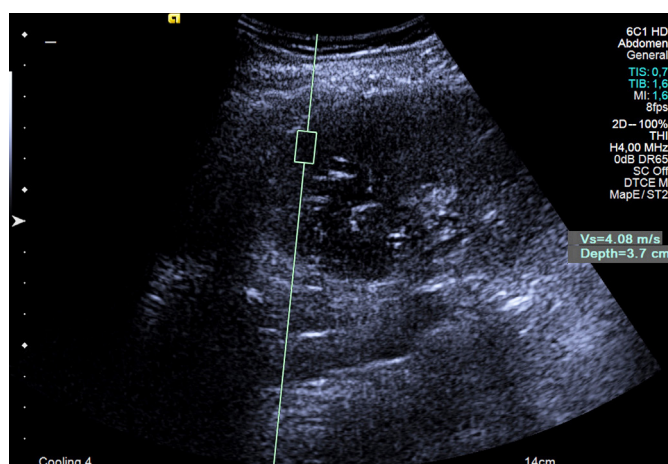
Using the same technique, the SWV of the healthy control group was measured and compared with the data of the AGN patients (Fig. 2).

Statistical Analysis

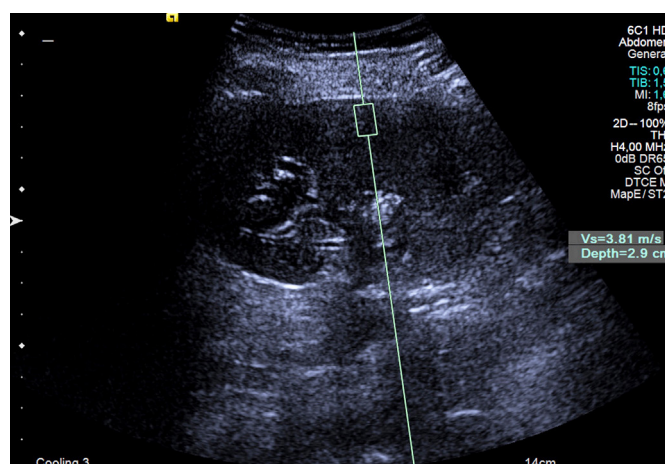
Power analysis using G*Power version 3.1 revealed that a minimum of 26 subjects was required in each group for a significant difference of 1.15 ± 1.45 units to be determined between the patient and

control groups in the renal elastography measurements ($\alpha=0.05$, $1-\beta=0.90$). This number was increased by 15% to take dropouts and exclusions into consideration.

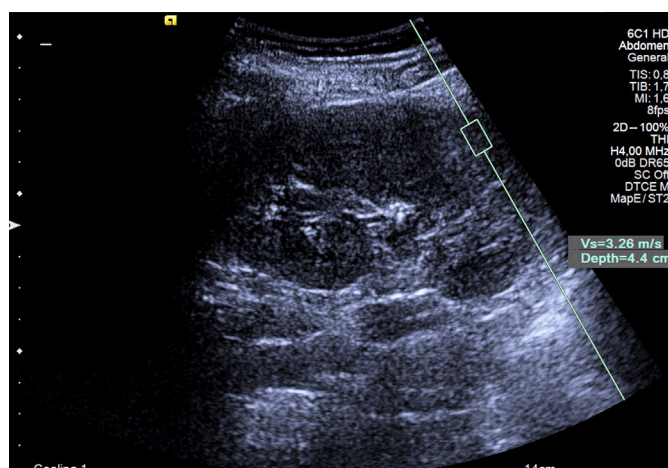
Conformity of the data to a normal distribution was assessed with the Kolmogorov-Smirnov and Shapiro-Wilk tests, and the data showed a normal distribution in both groups ($P>0.05$). The t-test was used to compare mean elastography values by region according to the study group and histopathological results. Analysis of variance (ANOVA) was used to compare mean elastography values obtained from the three zones of the kidney cortex in both groups. According to the histopathological results, *post-hoc* multiple comparisons were made using the Bonferroni and Sidak tests. Correlations between the mean elastography values of the patients and the laboratory findings (blood urea nitrogen [BUN], serum creatinine, and serum albumin) were examined with the Pearson rank correlation test. Receiver operating characteristic (ROC) analysis was used to determine the ARFI-e cut-off values to differentiate AGN from the control group. The analyses were performed using SPSS version 22.0



A



B



C

Fig. 1. Longitudinal view of the right kidney of a patient with acute glomerulonephritis.

A–C. A total of nine acoustic radiation force impulse elastography measurements were made: three each from the upper (A), middle (B), and lower (C) zones.

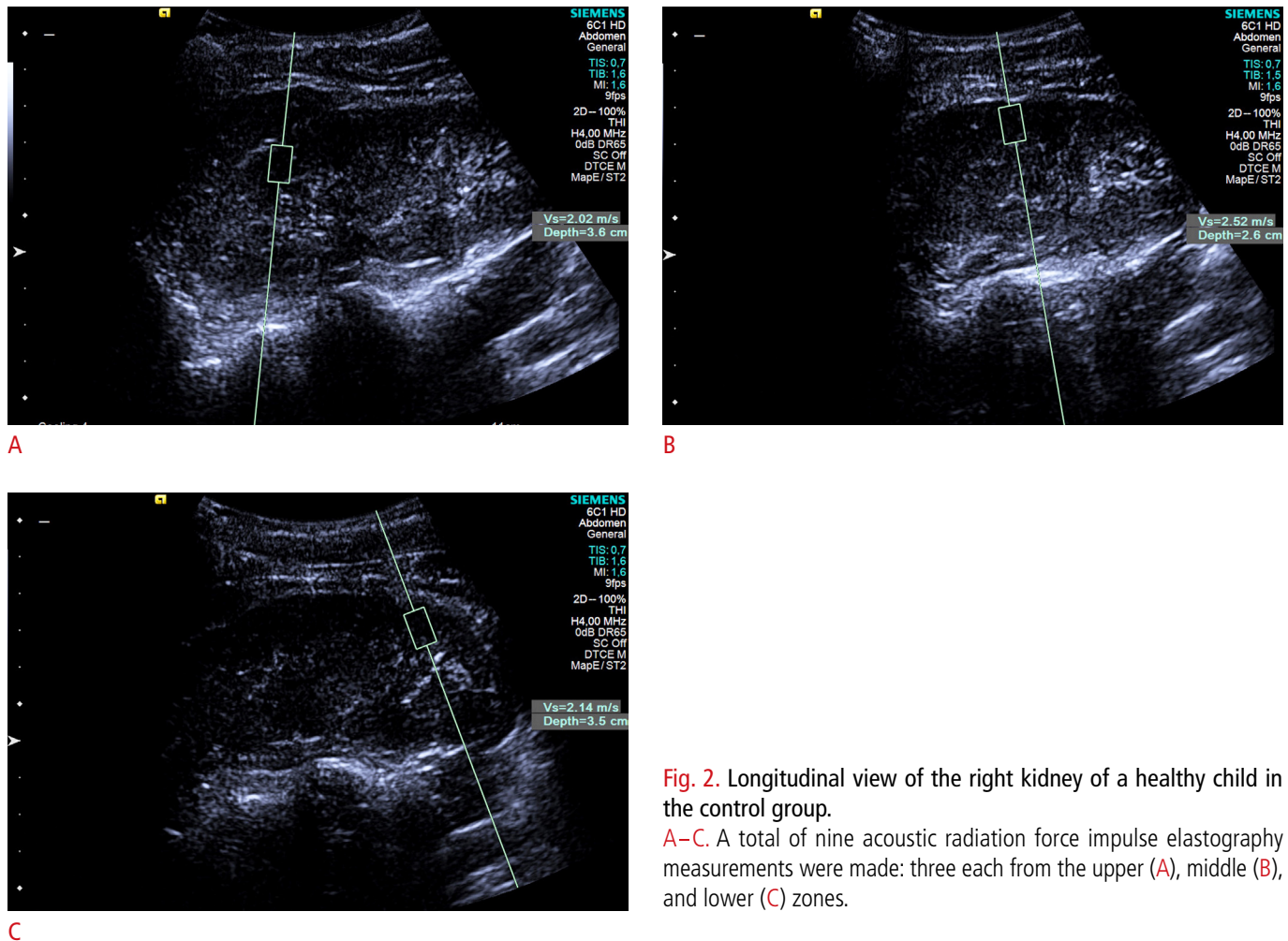


Fig. 2. Longitudinal view of the right kidney of a healthy child in the control group.

A–C. A total of nine acoustic radiation force impulse elastography measurements were made: three each from the upper (A), middle (B), and lower (C) zones.

(IBM Corp., Armonk, NY, USA) and MedCalc (MedCalc Software Ltd., Ostend, Belgium). A P-value <0.05 was accepted as indicating statistical significance.

Results

In total, 60 children were evaluated, comprising 30 patients with AGN and 30 healthy children as a control group. The AGN patient group comprised 14 (46.66%) males and 16 (53.33%) females with a mean age of 8.80 ± 4.48 years (range, 1 to 17 years). The control group comprised 16 (53.33%) males and 14 (46.66%) females with a mean age of 8.43 ± 5.30 years (range, 1 to 15 years). A total of 14 children who did not meet the criteria for the patient and control groups were excluded from the study.

No statistically significant difference was determined between the two groups in terms of mean age or sex ($P > 0.05$ for both).

The demographic characteristics and the mean kidney ARFI-e values of both groups and the last BUN, serum creatinine, and

serum albumin values of the patients (within 5 days before SWE measurements) are shown in Table 1.

ARFI-e Results

The mean ARFI-e measurements of the upper, middle, and lower zones of the kidney cortical parenchyma of the patients were significantly higher than those of the control group ($P < 0.05$) (Table 2).

The best cut-off values of ARFI-e measurements to differentiate AGN from normal for each kidney zone were determined using ROC analysis. The cut-off values for the upper, middle, and lower zones were defined as 2.74, 2.71, and 2.81 m/s, respectively ($P < 0.001$). The area under the curve for each of the above-described regions was 0.754, 0.769, and 0.753, respectively. The detailed ROC analysis results are summarized in Table 3 and the ROC curves are shown in Fig. 3.

The mean SWV values obtained from the three different zones of the kidney cortex in both groups were compared using ANOVA. No statistically significant differences were found between the groups

Table 1. Demographic features and ARFI-e measurement results of the patient and control groups

No.	Patient group						Control group						
	Age (year)	Sex	BUN (mg/dL)	Crea (mg/dL)	Alb (g/dL)	Mean ARFI-e (m/s)			Age (year)	Sex	Mean ARFI-e (m/s)		
						U	M	L			U	M	L
1	3	F	9.81	0.34	3.8	3.39	3.48	3.18	8	F	3.12	2.40	2.56
2	12	F	12.15	0.56	3.9	3.05	3.58	3.79	14	F	3.56	3.43	3.86
3	1	F ^{a)}	25.70	0.15	1.8	3.91	3.66	3.59	7	F	3.31	3.04	2.72
4	7	F ^{a)}	16.54	0.50	3.6	3.22	3.66	3.33	13	M	3.27	4.07	4.42
5	3	F ^{a)}	10.61	0.19	2.2	3.81	3.32	4.02	13	F	2.75	3.52	3.71
6	5	F	28.97	3.57	2.3	2.89	2.67	2.83	2	M	2.93	2.54	2.54
7	13	M	18.22	0.69	3.8	2.43	2.88	2.48	1	M	2.40	2.28	2.04
8	10	M	19.63	0.40	2.1	4.34	4.11	3.43	12	F	2.09	2.71	2.44
9	16	M ^{a)}	14.02	0.56	4.0	3.43	3.09	3.27	13	M	1.54	4.08	3.27
10	12	M	15.42	0.74	4.1	3.66	3.53	3.58	15	M	2.33	2.22	2.49
11	10	M	13.55	0.54	4.0	3.44	4.27	3.39	14	F	2.54	3.31	2.73
12	10	F ^{a)}	90.23	2.25	3.0	3.37	3.69	3.34	2	M	2.20	2.63	2.20
13	2	F ^{a)}	39.30	0.24	2.0	3.41	3.55	3.45	9	M	2.92	3.40	2.90
14	15	F	35.51	3.02	2.8	3.88	3.62	3.18	12	F	3.88	3.20	3.50
15	5	M	8.55	0.19	3.3	2.94	3.47	3.46	12	M	3.19	2.69	3.70
16	7	M	13.08	0.41	4.3	3.57	2.75	2.70	13	F	3.54	3.81	3.74
17	9	F	7.48	0.18	2.7	2.81	3.11	2.86	5	M	3.02	2.65	3.08
18	10	M	7.01	0.58	4.3	3.17	3.49	3.36	15	F	3.91	3.28	3.30
19	6	M	14.95	0.17	3.1	3.12	3.40	3.32	14	M	3.52	3.60	2.89
20	12	F	13.08	0.57	3.9	3.62	3.06	3.66	15	M	3.34	2.61	2.37
21	17	F	7.01	0.47	4.2	3.06	2.89	3.06	14	F	3.52	3.58	3.28
22	12	F	17.80	0.49	4.9	4.21	3.23	3.27	9	M	3.49	3.03	2.81
23	3	M	6.54	0.14	2.6	3.10	2.96	3.08	1	M	2.36	2.26	2.74
24	10	M	12.15	0.48	3.5	3.12	3.22	3.25	4	F	2.15	1.09	1.27
25	2	F	8.41	0.10	1.1	3.66	4.10	3.65	4	M	3.23	2.77	3.27
26	15	M	33.55	1.61	2.7	3.56	4.69	3.90	2	F	2.50	2.67	2.63
27	11	F ^{a)}	78.04	6.11	3.2	3.84	3.54	3.67	1	M	2.57	2.35	2.60
28	8	M ^{a)}	27.10	5.84	3.0	3.29	3.50	3.43	3	F	2.00	2.15	2.19
29	6	M ^{a)}	25.28	0.46	1.8	3.40	3.65	3.87	1	M	2.03	2.33	2.77
30	12	F	7.48	0.26	3.9	3.77	3.20	4.25	5	F	2.21	1.84	1.89

ARFI-e, acoustic radiation force impulse elastography; BUN, blood urea nitrogen; Crea, serum creatinine; Alb, serum albumin; U, upper zone of the right kidney; M, middle zone of the right kidney; L, lower zone of the right kidney; F, female; M, male.

^{a)}Patients diagnosed with focal segmental glomerulosclerosis.

in terms of the zonal elastography values ($P>0.05$).

No correlation was found between the mean SWV values of the three kidney zones of the patients and the laboratory findings (BUN, serum creatinine, and serum albumin) ($P>0.05$).

Histopathological Results

The biopsy results were as follows: nine (30%) FSGS, two (6.67%) Henoch Schönlein purpura nephritis, five (16.67%)

immunoglobulin A nephropathy, four (13.33%) MCD, three (10%) membranoproliferative GN, three (10%) podocyte/slit diaphragm protein mutations, and four (13.33%) lupus (systemic lupus erythematosus) nephritis. Non-significant differences were found in the mean SWV values obtained from the three kidney zones of the patients with FSGS compared to all the remaining patients with other AGN ($P>0.05$). Only the mean SWV values obtained from the upper kidney region of the patients with systemic lupus

erythematous (SLE) nephritis were found to be significantly higher than those of the patients with MCD ($P=0.045$, $F=2.86$).

Discussion

GN is a very important public health problem throughout the world

Table 2. Comparison of ARFI-e measurement values of the patient and control groups according to the selected kidney cortical regions

Kidney regions	No.	Mean±SD (m/s)	P-value
Upper zone cortex			
Patient	30	3.42±0.42	0.001*
Control	30	2.85±0.63	
Middle zone cortex			
Patient	30	3.45±0.45	0.001*
Control	30	2.85±0.68	
Lower zone cortex			
Patient	30	3.39±0.39	0.001*
Control	30	2.86±0.66	

ARFI-e, acoustic radiation force impulse elastography; SD, standard deviation.
*P-values according to the independent t test ($P<0.05$).

and is the most common cause of end-stage renal failure after diabetes and hypertension. According to the 2017 United States Renal Data System data, GN accounts for the etiology of 9.19% of cases of end-stage renal failure. The mortality rate of children with end-stage renal failure is approximately 55–150 times higher than that of the general pediatric population [17,18].

As a non-invasive method, UE provides information about the stiffness of tissues and can be used for further evaluation of the renal parenchyma. This method has been used in the examination of soft tissue tumors, lymphadenopathies, liver fibrosis, thyroid and breast lesions, and studies on its use in many areas are ongoing [19]. Strain elastography is a semi-static and qualitative method, and in this technique, tissue deformation and displacement are measured in response to the force applied [20]. SWE, however, is a dynamic method in which high-power acoustic repulsive radiation force created with the transducer probe is applied to the desired region of the tissue instead of external compression. As a response, shear waves are generated, and the propagation speed of the waves is measured to estimate the tissue elasticity. ARFI-e is a point SWE technique used together with VTQ software, which is a commercial product. In the point SWE technique, a single focal region is selected in a tissue and excited by ARFI to induce shear

Table 3. Receiver operating characteristic curve analysis results according to the selected kidney cortical regions

Kidney cortical regions	Cut-off value (m/s)	Sensitivity (95% CI)	Specificity (95% CI)	AUC	P-value
Upper zone	2.74	96.67 (82.8–99.9)	46.67 (28.3–65.7)	0.754	0.001
Middle zone	2.71	96.67 (82.8–99.9)	53.33 (34.3–71.7)	0.769	0.001
Lower zone	2.81	93.33 (77.9–99.2)	56.67 (37.4–74.5)	0.753	0.001

CI, confidence interval; AUC, area under the curve.

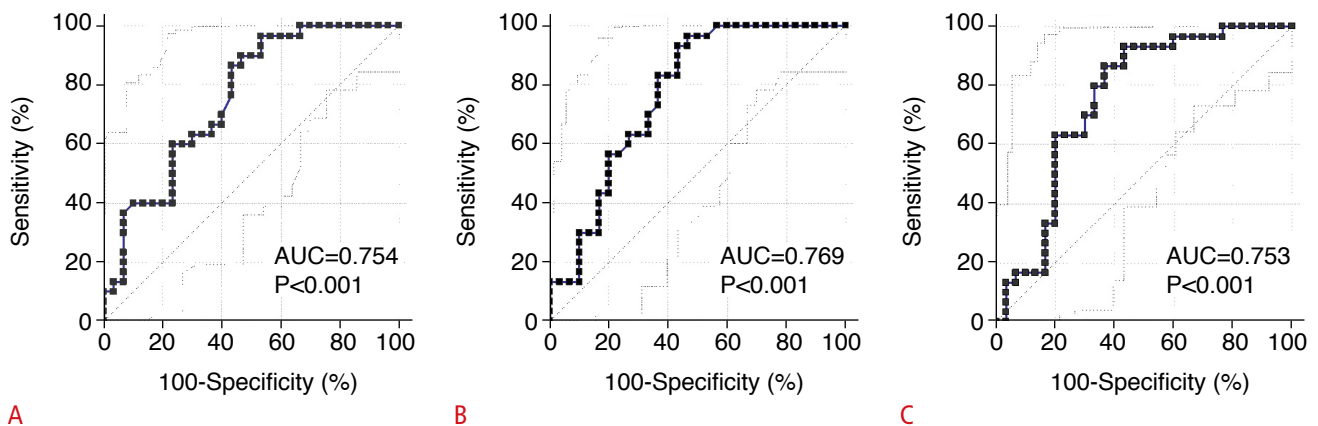


Fig. 3. Receiver operating characteristic curves according to the selected kidney cortical regions. A–C. A differentiate acute glomerulonephritis from normal, the cut-off values of acoustic radiation force impulse elastography measurements for the upper (A), middle (B), and lower zones (C) were defined as 2.74, 2.71, and 2.81 m/s, respectively ($P<0.001$). The area under the curve (AUC) values for these thresholds are shown on the graphs.

waves perpendicular to the plane of excitation. The measured shear wave propagation rate is proportional to the stiffness of the tissue [14,21–23]. Compared to conventional elastography, ARFI-e is more advantageous as it can give an absolute velocimetric value for a particular area of tissues [24]. The aim of this study was to observe the proven effectiveness of SWE and test the advantages of this quantitative method for the estimation or early diagnosis of pediatric AGN.

In a study by Samir et al. [25], the SWE values of the kidney parenchyma in adult patients with chronic kidney disease (CKD) were higher than in the control group. Accordingly, it has been suggested that SWE is a low-cost method that provides additional diagnostic information in CKD [25].

In a study by Cui et al. [24], 76 adult patients with nephropathy were separated into four groups as a non-fibrosis group and mild, moderate, and severe fibrosis groups according to the biopsy results obtained from the right kidney. All four groups were evaluated with the ARFI-e technique, and statistically significantly higher SWV values were observed in groups with fibrosis than in the non-fibrosis group. However, there was no significant difference in SWV values between the groups with fibrosis. Consequently, it was argued that ARFI-e may be useful for the diagnosis of renal fibrosis. The cut-off value to predict renal fibrosis was determined as 1.67 m/s with sensitivity of 86.3% and specificity of 83.3% [24]. Similarly, Leong et al. [26] evaluated renal parenchymal stiffness with SWE in adults with CKD and reported that the SWV values of the patient group were higher than those of the control group.

In contrast to the above-mentioned studies, Bob et al. [15] reported that the ARFI-e measurement values of the patient group were lower than those of the control group in a study of adult patients diagnosed with GN. Similarly, the renal parenchyma was evaluated with ARFI-e in pediatric patients with CKD by Bilgici et al. [27]. The mean SWV values of the patient group were lower than those of the control group [27]. These studies differed from the present study in terms of the included patient population and type or stage of kidney disease.

Xu et al. [11] evaluated 105 children with glomerular disease and 120 healthy children using the point SWE technique and reported that the SWV measurements were significantly higher in the patient group than in the control group. The cut-off value of SWE to predict glomerular disease in children was 1.58 m/s, with a sensitivity of 53.33% and specificity of 85.83%. As a result, it has been suggested that elastography can be used in the early diagnosis of pediatric glomerular diseases [11]. To the best of the authors' knowledge, with the exception of the previous study by Xu et al. [11], no other study has evaluated the renal elastography of pediatric patients with GN. By comparison, it was seen that the

mean SWV values determined in the present study were higher than the values reported in the previous study, in both the patient and control groups. However, this could have resulted from the use of a different US system (Philips Medical Systems, Bothell, WA, USA) and software (Elast PQ).

The cut-off values determined in the above-mentioned studies seem to be quite different from the values determined in the current study. This could be due to differences in the mechanism, time, and severity of the inflammatory process of the renal diseases. Furthermore, differences in operator experience, patient population (children or adults), treatment options or medications, or the use of different devices or techniques can also affect the results of UE measurements. Swollen, edematous parenchyma and stretched renal capsules in AGN can cause increased SWV values as in this study. However, this result could not be explained by renal fibrosis, as fibrosis is the final stage of an inflammatory process involving the kidneys [28].

Due to the complexity of kidney structure and function, there is no validated standard range of values for normal tissue elasticity [29]. Some authors have stated that SWE values obtained from the deeper parenchyma can differ due to the angle between the US emission and the medullary microstructures. It has also been suggested that SWE measurement results in the renal cortex are more reliable than those taken from the medulla [14,16]. Confirming this argument, the zonal elastography differences obtained from the renal cortex in the current study were not significant in the whole study population.

Although there may be geographical and ethnic differences, FSGS and MCD are reported as the most common forms of primary GN in childhood. Studies in different countries have reported an increasing incidence of FSGS [6–10,30]. Similarly, the most common histopathological diagnosis in this study was FSGS, at a rate of 30%. In terms of the mean SWV values obtained from the three kidney zones, the differences between the patients with FSGS and the remaining patients with other AGN were insignificant. Only the mean SWV values obtained from the upper kidney region of the patients with SLE nephritis were found to be significantly higher than those of the patients with MCD ($P=0.045$).

This study has some limitations, primarily the relatively small sample size and the presence of seven different pathological diagnoses, which may affect the reliability of the statistical results. Second, although all patients received oral steroid therapy, the time interval between treatment and the SWE measurement and biopsy procedure varied. Therefore, the possible effects of the varying medication time on tissue elasticity were ignored. Third, possible interobserver or intraobserver variability was not evaluated in the study. Fourth, since there was low specificity of the ARFI-e results in

differentiating AGN from healthy children, the SWE results should be considered when there is high clinical suspicion of AGN. Finally, user dependency, fixed box size, and the sensitivity of the target ROI were other relative limitations of the elastographic examinations.

In conclusion, the ARFI-e technique can be considered a non-invasive, easily applicable, auxiliary method for the early diagnosis of AGN, but due to the differences in the results of renal elastography studies in the literature, more detailed studies are needed on this topic in larger patient groups.

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Conceptualization: Yoğurtçuoğlu B. Data acquisition: Yoğurtçuoğlu B. Data analysis or interpretation: Yoğurtçuoğlu B, Damar Ç. Drafting of the manuscript: Yoğurtçuoğlu B, Damar Ç. Critical revision of the manuscript: Damar Ç. Approval of the final version of the manuscript: all authors.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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