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A methodological study of 2D shear wave elastography for noninvasive quantitative assessment of renal fibrosis in patients with chronic kidney disease

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Abstract

Purpose To determine the optimal measurement method of 2D shear wave elastography (2D-SWE) for noninvasive quantitative assessment of renal fibrosis in chronic kidney disease (CKD) patients.

Methods A total of 190 CKD patients were enrolled for 2D-SWE of right kidney. The success rates, coefficients of variation (CV), and pathological correlation of different measurement sites, body positions, and depths were compared.

Results (1) Measurement sites: Success rate in the middle part (100%) was higher than that in the lower pole (97.3%, $P>0.05$). CV in the middle part (10.2%) was lower than that in the lower pole (16.4%, $P<0.05$). Pathological correlation of the middle part ($r=-0.452$, $P<0.05$) was higher than that of the lower pole ($r=0.097$, $P>0.05$). (2) Body positions: Success rate in left lateral decubitus position (100%) was higher than that in supine (99.4%, $P>0.05$) and prone position (99.4%, $P>0.05$). CV was lowest (11.9%) and pathological correlation was highest ($r=-0.256$, $P<0.05$) in prone position. (3) Measurement depths: Success rate at depth < 4 cm (100%) was higher than that at depth ≥ 4 cm (98.8%, $P>0.05$). CV at depth < 4 cm (11.1%) was lower than that at depth ≥ 4 cm (14.4%, $P<0.05$). Pathological correlation at depth < 4 cm ($r=-0.303$, $P<0.05$) was higher than that at depth ≥ 4 cm ($r=-0.156$, $P>0.05$).

Conclusion The optimal measurement method of 2D-SWE for renal fibrosis assessment was prone position, renal middle part, and measurement depth < 4 cm.

Keywords 2D shear wave elastography · Noninvasive assessment · Renal fibrosis · Methodological study

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Abbreviations

2D-SWE	2D shear wave elastography
BMI	Body Mass Index
CKD	Chronic kidney disease
CV	Coefficients of variation
eGFR	Estimated glomerular filtration rate
SD	Standard deviation

Introduction

Nowadays, the high prevalence and mortality of CKD have caused a huge social and medical burden [1, 2]. At present, the global prevalence of CKD is about 9.1% [1]. In China, CKD patients in tertiary hospitals account for 4.86% of the total inpatients; the total medical expenditure of all CKD patients in China was 27.646 billion yuan, accounting for 6.50% of the total medical expenditure in 2016 [2]. Renal fibrosis is the main pathological change in the course of CKD [3]. The evaluation of degree of fibrosis has important guiding significance for disease assessment, prognosis judgment, and treatment decisions of CKD.

Renal biopsy and histopathological examination is still the gold standard for evaluating degree of renal fibrosis in CKD patients, but it has some complications such as hemorrhage, infection, vascular fistula, etc. [4, 5], even nephrectomy or death [6]. And it is also unsuitable for long-term and repeated monitoring of CKD because of invasiveness. Therefore, attention has been focused on looking for noninvasive techniques for early monitoring renal fibrosis.

The common clinical indicators for monitoring the progression of CKD mainly include estimated glomerular filtration rate (eGFR), proteinuria, etc., but these indicators have a low specificity in evaluation of the severity of CKD [7–9]. In addition, imaging examination is also a common method in CKD, such as magnetic resonance techniques [10–12]; however, they are also affected by renal blood perfusion, collecting system dilation, tissue edema, etc. Furthermore, these methods indirectly reflect the degree of renal fibrosis through evaluation of renal function, mechanical properties, molecular properties, etc., conducing to certain limitations in the evaluation of CKD.

Ultrasound imaging is a common examination with advantages of real-time, safe, noninvasive, cheap, and high patient acceptance. Conventional ultrasound can provide information reflecting the existence of renal parenchymal injury [13, 14]. However, the correlations between ultrasound parameters and renal fibrosis were not high, so the value of conventional ultrasound in diagnosis and evaluation of CKD was limited.

Fibrosis can directly cause changes in elasticity of organs, which is reflected as increased tissue stiffness [15]. Ultrasound elastography can be used to assess stiffness noninvasively, and has been widely used in clinical evaluation of tissue stiffness. Until now, there have been a certain amount of studies on renal ultrasound elastography, showing that the relationships between renal elasticity and renal fibrosis were usually different or even contradictory [4, 16–18]. There is still no uniform operation standard for renal ultrasound elastography, which may be one of the reasons for the inconsistency of results in the above studies. Therefore, we used 2D-SWE to carry out renal elastography under different measurement sites, body positions, and measurement depths, in an attempt to establish the methodological standards for renal elasticity measurement.

Materials and methods

Subjects

A total of 190 CKD patients were prospectively recruited, who were admitted to the Department of Nephrology of our hospital from April 2019 to March 2021. This study was approved by the ethics committee of our hospital, and all the subjects signed the informed consent. Inclusion criteria for patients in this study were as follows: (1) Patients met the clinical diagnostic criteria for CKD [19] and (2) patients underwent a 2D-SWE examination of their right kidneys. Exclusion criteria were as follows: (1) patients were unable to undergo 2D-SWE or with inadequate or incomplete data collected; (2) the quality of ultrasound images was poor; and (3) the 2D-SWE examination was affected by renal lesions such as calculi, cysts, tumors, hydronephrosis, etc. Characteristics of patients like gender, age, height, weight, and body mass index (BMI) were recorded.

Instruments and methods

(1) *Instruments* SWE examination was performed with a Supersonic Imagine Aixplorer ultrasound system (Aix-en-Provence, France) that was equipped with an XC6-1 convex array probe with a frequency of 1–6 MHz. The size of the elastography sampling box was set as 4 cm × 3 cm, and the diameter of the ROI was set as 4 mm. The elastography scale was displayed in kPa, and the range was fixed from 0 to 80 kPa.
(2) *Shear wave elastography* All patients underwent 2D-SWE examination 1 day before renal biopsy with kidney scanning conditions predetermined by ultrasonic instrument. After micturition, patients were instructed to lie in supine, left lateral decubitus, and prone positions, respectively. All patients first underwent a B-mode renal ultrasound scan, and then the 2D-SWE mode. Patients were required to hold their breath for 3–5 s with the sampling box placed in the middle part and lower pole of renal cortex, respectively. The color elastic images were captured and frozen. In the color imaging area, the circular ROI was placed in the cortex. Then the mean value of renal elastic modulus (unit: kPa) within the ROI (Fig. 1) and measurement depth (the distance between probe and ROI) was recorded. The detection was repeated 5 times under various conditions. A successful measurement was defined as the color-filling area was more than half of the elastic sampling box; full images were obtained within the sampling ROI; the Emin was higher than 0 (an example of successful measurements is shown in Fig. 2; example of unsuccessful measurements are shown in Fig. 3). For the 5 repeated measurements of the same patient, at least 3 successful measurements (i.e., a measurement success rate of more than 60%) were considered to be successful. If a patient's measurements were unsuccessful (i.e., the measurement success rate was less than 60%), the patient's data would be excluded. The mean value of measurements meet-

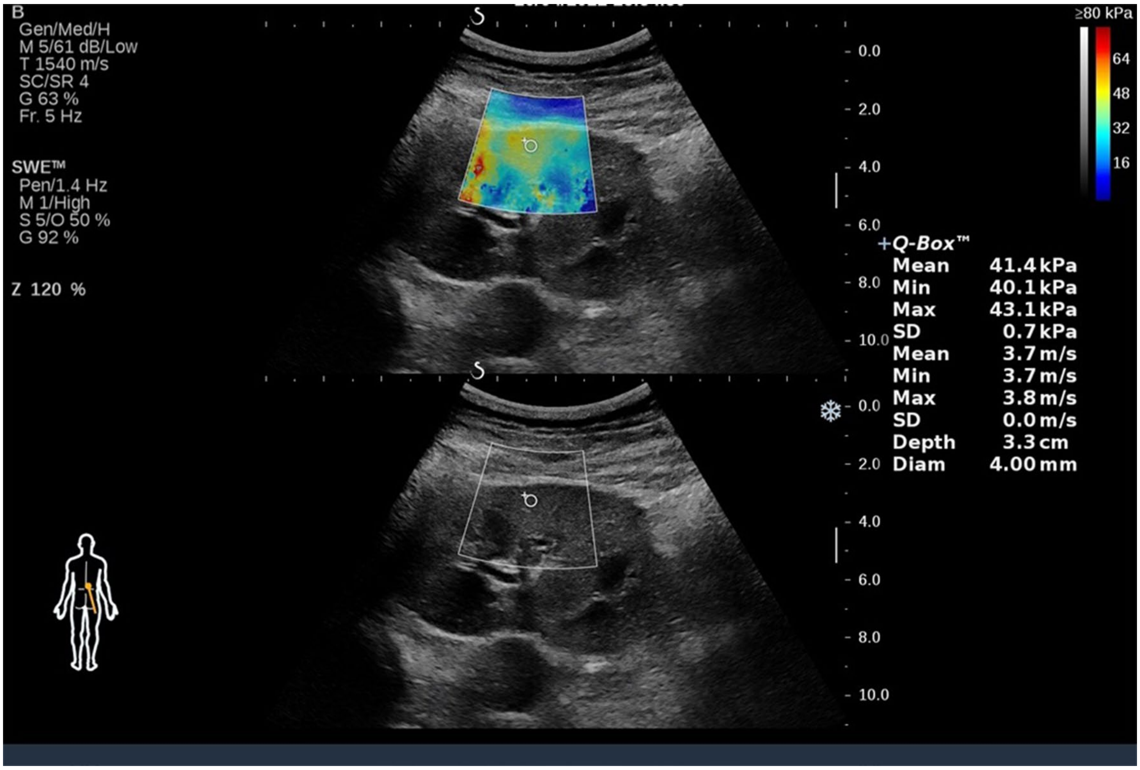

Fig. 1 Real-time 2D-SWE of right kidney in patients with CKD (including fan-shaped sampling box, circular ROI, and Young's modulus of Q-box)

ing the success criteria in these five measurements was taken as the final stiffness for statistical analysis. All patients were examined by the same sonographer with nearly 10 years of conventional ultrasound and more than 5 years of elastography experience. The operator had no knowledge of the patient's clinical data, laboratory test results, etc.

(3) *Renal biopsy* Patients underwent percutaneous needle biopsy of right kidneys guiding by ultrasound with automatic biopsy gun (MG1522 Bard automatic biopsy gun, Bard Company, USA) and matching 16 G biopsy needle. The patients were instructed to lie in prone position and punctured in the lower pole of right kidneys avoiding large vessels. Biopsy specimens obtained were fixed and stained for observation.

(4) *Evaluation of renal fibrosis* All the renal biopsy specimens were analyzed by two pathologists. The degree of renal fibrosis was evaluated based on Katafuchi semi-quantitative scoring system [5, 20]. CKD patients were then classified according to the total scores: mildly impaired (≤ 9 points); moderately impaired (10–18 points); and severely impaired (≥ 19 points). The total score was used to evaluate the degree of renal fibrosis for correlation analysis.

Study design

We studied various impact factors of 2D-SWE in 190 subjects, including measurement site, body position, and measurement depth.

(1) *Study of different measurement sites* The cortical stiffness values of the middle part and lower pole of kidneys were measured in the prone position (since renal needle biopsy was performed in prone position). Evaluation indicators of different measurement sites were compared to select the best measurement site.

(2) *Study of different body positions* The cortical stiffness values of the middle part of kidneys (based on the results of previous part, the best measurement site was the middle part of kidneys) were measured in the supine, left lateral decubitus, and prone positions,

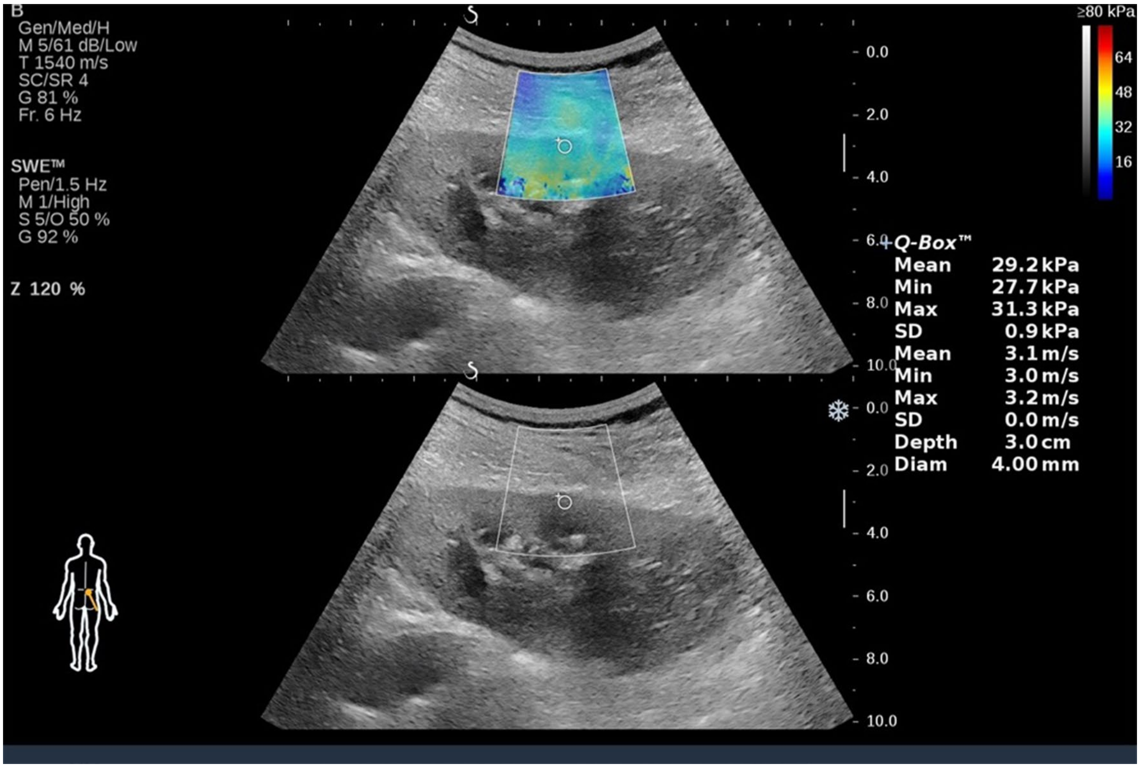

Fig. 2 An example of successful measurements: The color-filling area was more than half of the elastic sampling box; full images were obtained within the sampling ROI; the Emin was higher than 0 (an example of successful measurements)

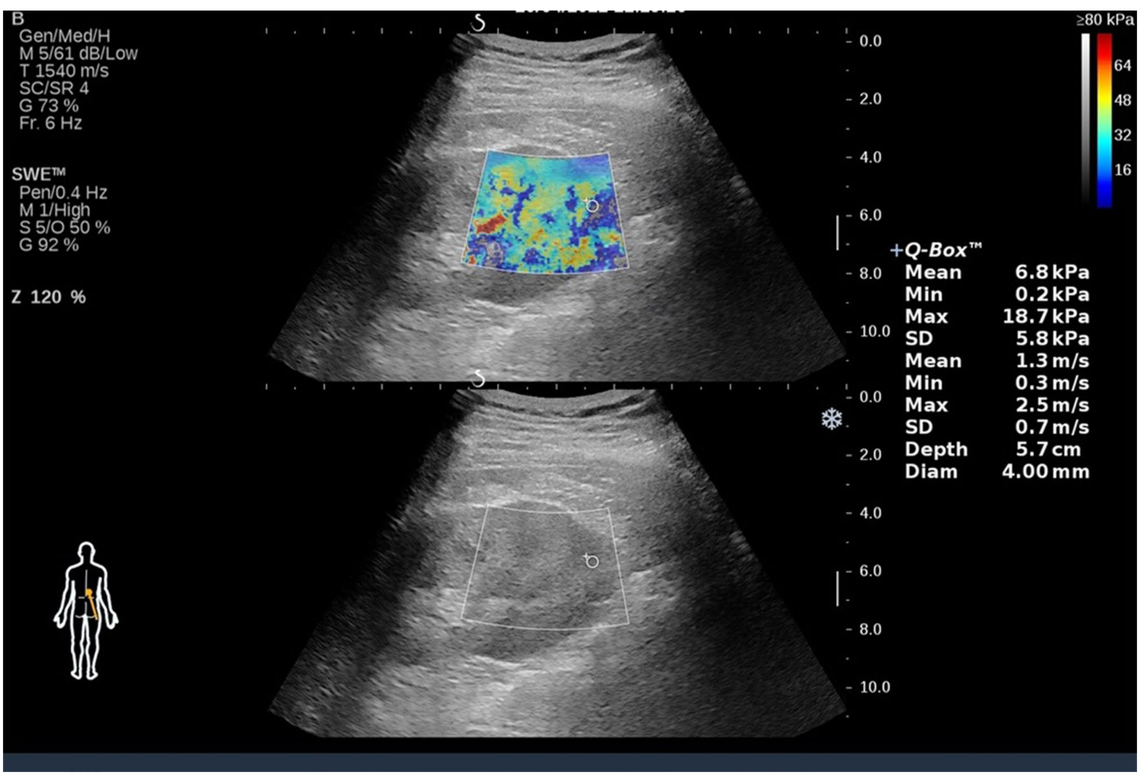

Fig. 3 An example of unsuccessful measurements: The color in the ROI of the 2D-SWE image was not full-filling

respectively. Evaluation indicators of different body positions were compared to select the best body position.

(3) *Study of different measurement depths* The cortical stiffness values of the middle part of kidneys were measured in the prone position (based on the results of previous two parts, the best measurement site and body position were the middle part and the prone position). The measurement depths were divided into two groups (< 4 cm and ≥ 4 cm, the division of depth range was based on early preliminary study) according to the distance from the skin to renal cortex detected. Evaluation indicators of different depth ranges were compared to select the best depth range for measurement.

(4) *Evaluation indicators* Success rate = the number of people successfully measured/the total number of people measured × 100%; coefficient of variation = Standard deviation of 5 measurements of stiffness values/mean of 5 measurements of stiffness values × 100%, expressed in the form of median (25% percentile, 75% percentile); spearman correlation coefficient (*r* value) was used to indicate the correlation between renal stiffness and the total score of renal fibrosis.

Statistical analysis

IBM SPSS Statistics (version 22.0) was used for data analysis. Numerical variables with normal distribution were expressed as mean value and standard deviation (SD), whereas variables with nonnormal distribution were expressed as median (25% percentile, 75% percentile). Nonparametric test was used for comparison between groups. Two independent samples were compared by Mann–Whitney *U* test; multiple independent samples were compared by Kruskal–Wallis one-way ANOVA, and Bonferroni correction was used for pairwise comparison. Chi square test was used for the comparison of two groups of success rates, while chi-square segmentation was used for the comparison of multiple groups of success rates. Correlation between stiffness measured by 2D-SWE and the degree of renal fibrosis was analyzed by Spearman correlation coefficient. $P < 0.05$ was considered statistically significant.

Results

We performed 2D-SWE on the right kidneys in 190 patients with CKD. The characteristics of these patients are shown in Table 1.

Table 1 The characteristics of patients

Characteristics	Mean ± SD
Age (years)	40.4 ± 14.7
Gender, male/female	103/87*
Height (cm)	164.0 ± 8.6
Weight (kg)	65.7 ± 14.1
BMI (kg/m^2)	24.3 ± 4.0

*Data were described in the form of number of males/number of females

Influence of measurement site on 2D-SWE measurement

The inclusion process is shown in Fig. 4. There was no significant difference of the success rate between the middle part and lower pole ($P > 0.05$) (Table 2). The coefficient of variation of each measurement site showed that the five repeated measurements in the renal middle part had better stability ($P < 0.05$) (Table 3).

The correlation analysis is shown in Table 4, Fig. 5 and 6. The correlation between renal stiffness of the middle part and degree of renal fibrosis ($r = -0.452$, $P < 0.05$) was higher than that of the lower pole ($r = 0.097$, $P > 0.05$). Therefore, the stiffness of renal middle part was more correlated with the degree of fibrosis than the lower pole.

Influence of body position on 2D-SWE measurement

The inclusion process is shown in Fig. 7. There was no statistically significant difference in the success rate among the three body positions ($P > 0.05$) (Table 5). As shown in Table 6, renal 2D-SWE had better stability between five repeated measurements when performed in the prone position ($P < 0.05$).

The correlation analysis is shown in Table 7, Figs. 8, 9, and 10. The correlation between renal stiffness and degree of fibrosis was highest in prone position ($r = -0.256$, $P < 0.05$), then in supine position ($r = -0.249$, $P < 0.05$), and lowest in left lateral decubitus position ($r = -0.158$, $P > 0.05$). Therefore, prone position was an ideal body position in terms of pathological correlation.

Influence of depth on 2D-SWE measurement

The inclusion process is shown in Fig. 11. There was no statistically significant difference of the success rate between depth < 4 cm and depth ≥ 4 cm ($P > 0.05$) (Table 8). As shown in Table 9, renal 2D-SWE had better stability

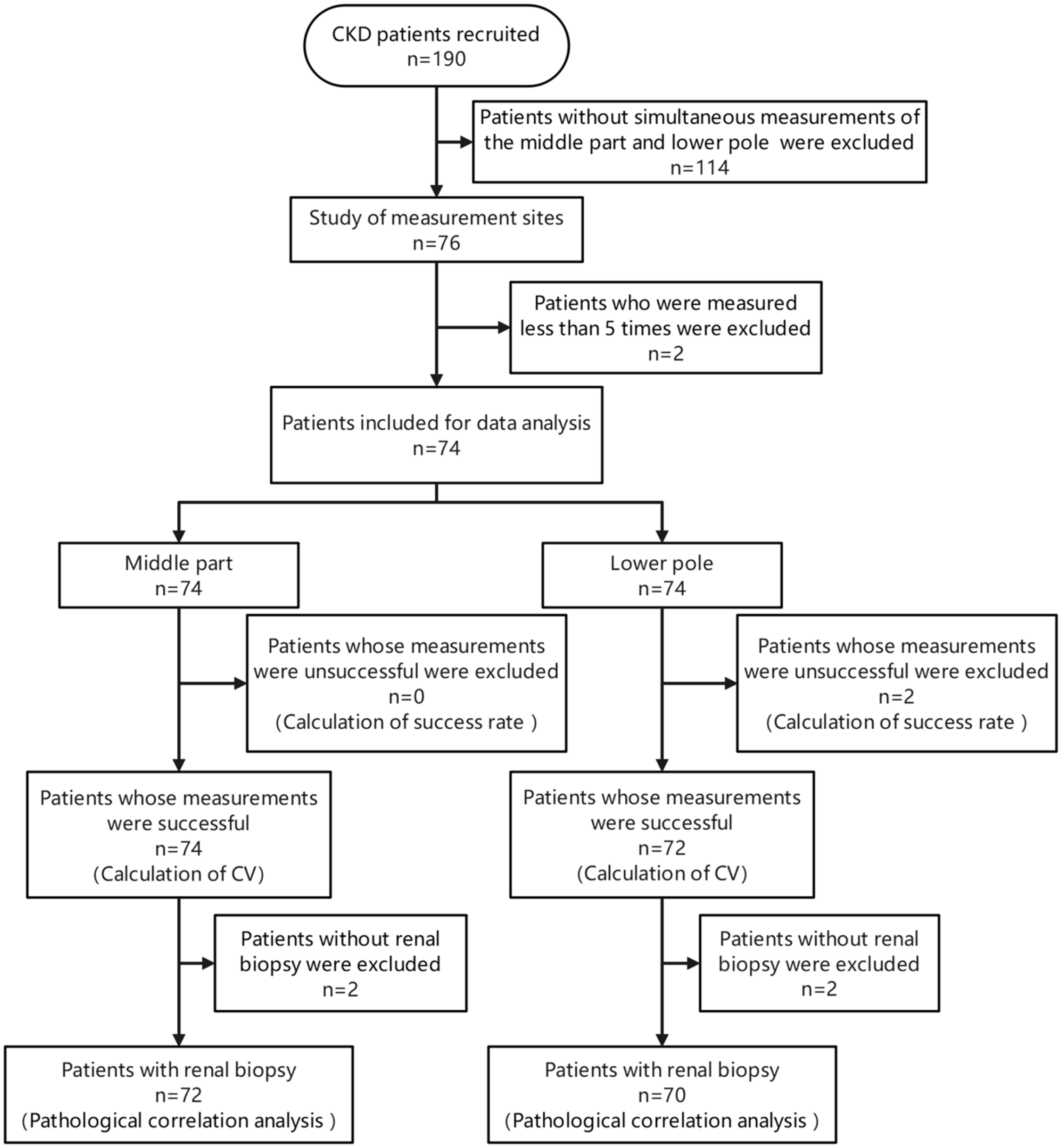

Fig. 4 The inclusion process of study on different measurement sites

Table 2 Influence of measurement site on the success rate of renal 2D-SWE

Measurement site	Number of successfully measured patients	Total number of patients	Success rate (%)
Middle part	74	74	100
Lower pole	72	74	97.3

There was no significant difference of the success rate between the middle part and lower pole

Table 3 Coefficient of variation of each measurement site in CKD patients

Measurement site	Coefficient of variation (%)	P_{25} (%)	P_{75} (%)
Middle part	10.2	7.5	15.2
Lower pole	16.4	13.4	22.9

There was a significant difference of coefficient of variation between the middle part and lower pole

P_{25} was the 25% percentile, P_{75} was the 75% percentile

Table 4 Correlation analysis between renal stiffness and total score of renal fibrosis in each measurement site

Pathological score	Middle part		Lower pole	
	r	*P*	*r*	*P*
Total score	−0.452*	0.000	0.097	0.422

*$P < 0.05$

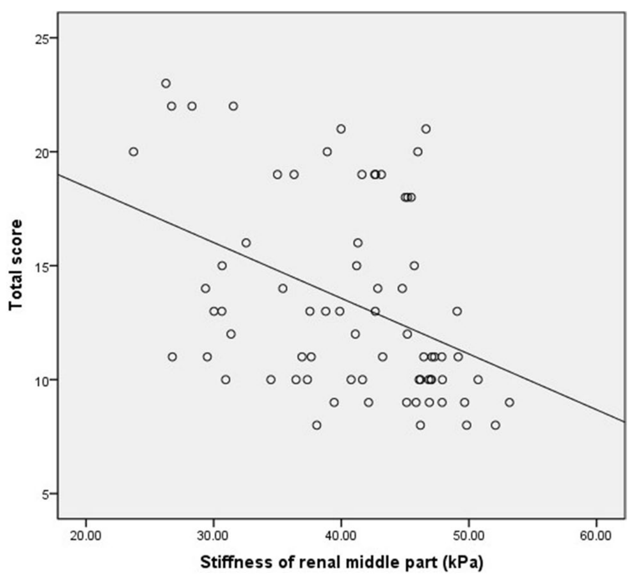

Fig. 5 The correlation between renal stiffness of the middle part and degree of renal fibrosis

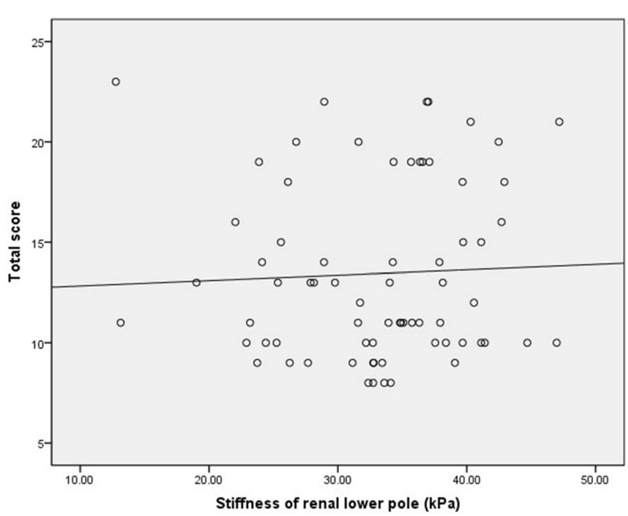

Fig. 6 The correlation between renal stiffness of the lower pole and degree of renal fibrosis

between five repeated measurements when performed at a depth < 4 cm ($P < 0.05$).

The correlation analysis is shown in Table 10, Figs. 12 and 13. The correlation between renal stiffness and fibrosis degree of depth < 4 cm ($r = -0.303$, $P < 0.05$) was higher than that of depth ≥ 4 cm ($r = -0.156$, $P > 0.05$). Therefore, depth < 4 cm was an ideal depth range in terms of pathological correlation.

Discussion

In this study, we analyzed multiple methodological evaluation indicators under different measurement sites, body positions, and measurement depths, and got a comprehensive methodological suggestion, that is, prone position, renal middle part, measurement depth < 4 cm, for 2D-SWE in CKD patients.

Comparing to the results of measurement site in our study, Bob et al. [21] obtained a similar success rate of 98.17% in the renal middle part; Wang et al. [18] obtained a higher CV of 23.0 ± 8.3% when measuring renal stiffness in the middle part of 45 CKD patients, indicating that the stability of renal stiffness measurement in our study was better. Hu et al. [17] showed a similar correlation between middle cortical stiffness and renal fibrosis histological score ($r = -0.511$, $P < 0.001$) in 163 CKD patients.

The higher success rate of renal middle part could be related to its perpendicular relation to ultrasonic wave, better acoustic window, and relatively fixed position. While the measurement of lower pole was often disturbed by the surrounding intestinal gas, simultaneously lower pole was relatively difficult to identify clearly because of its deep position and affection by respiratory movement. Besides, the lower pole had a greater anisotropy, resulting in a larger SWE measurement error.

Comparing to the results of the influence of body position in our study, Bob et al. [21] achieved a similar success rate of 98.17% in renal stiffness measurement in left lateral decubitus position, while Wang et al. [18] measured a higher coefficient of variation of SWE as 23.0 ± 8.3% in 45 CKD patients under lateral decubitus position. Hu et al. [17] measured renal stiffness in 163 patients with CKD in left lateral decubitus position, and the correlation between cortical stiffness and renal fibrosis histological score ($r = -0.511$, $P < 0.001$) was significantly higher than the pathological correlation in each body position in our study. The reasons for the lower correlation in our study need to be further explored.

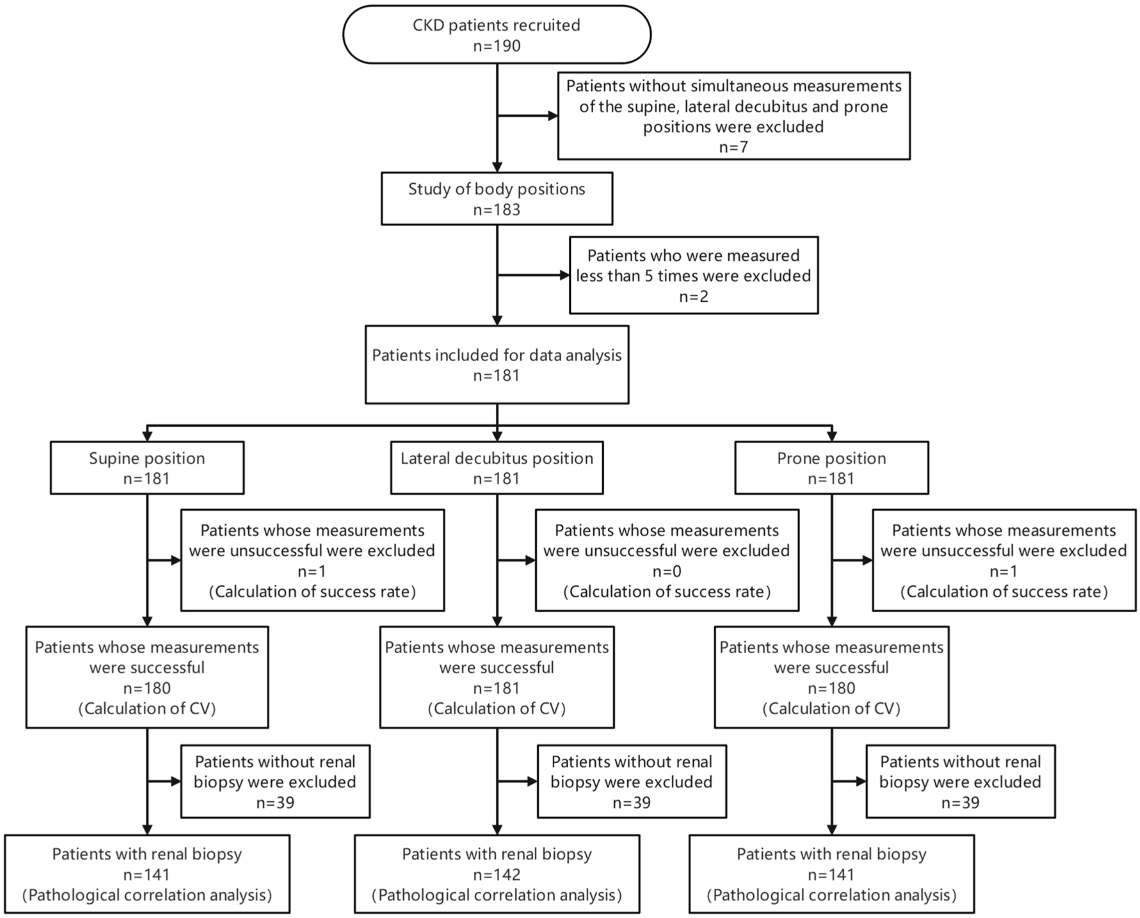

Fig. 7 The inclusion process of study on different body positions

Table 5 Influence of body position on the success rate of renal 2D-SWE

Body position	Number of successfully measured patients	Total number of patients	Success rate (%)
Supine position	180	181	99.4
Left lateral decubitus position	181	181	100
Prone position	180	181	99.4

There was no significant difference in the success rate among the three body positions

Table 6 Coefficient of variation of each body position in CKD patients

Body position	Coefficient of variation (%)	P_{25} (%)	P_{75} (%)
Supine position	13.8[a]	9.3	19.6
Left lateral decubitus position	13.9[b]	9.7	19.8
Prone position	11.9	8.3	17.5

P_{25} was the 25% percentile, P_{75} was the 75% percentile

[a]Means $P < 0.05$ for supine versus prone position

[b]Means $P < 0.05$ for left lateral decubitus versus prone position

The explanation for the results of best body position may be related to that the distance between kidney and body surface varies with the body positions. In supine position, the kidney is relatively far from the body surface due to the shielding of subcutaneous fat and liver. In left lateral decubitus position, the liver moves down due to gravity, so that the position of kidney is relatively shallow with improved ultrasound transmission. In the prone position, there is mainly muscle tissue between kidney and body surface, so it is easy to obtain better ultrasonic imaging. Moreover, the movement of kidney with the breath in prone position is relatively small, so the results of repeated measurements are more stable and the stiffness values measured are more accurate.

Table 7 Correlation analysis between renal stiffness and total score of renal fibrosis in each body position

Pathological score	Supine position		Left lateral decubitus position		Prone position	
	r	*P*	*r*	*P*	*r*	*P*
Total score	− 0.249*	0.003	− 0.158	0.060	− 0.256*	0.002

*$P<0.05$

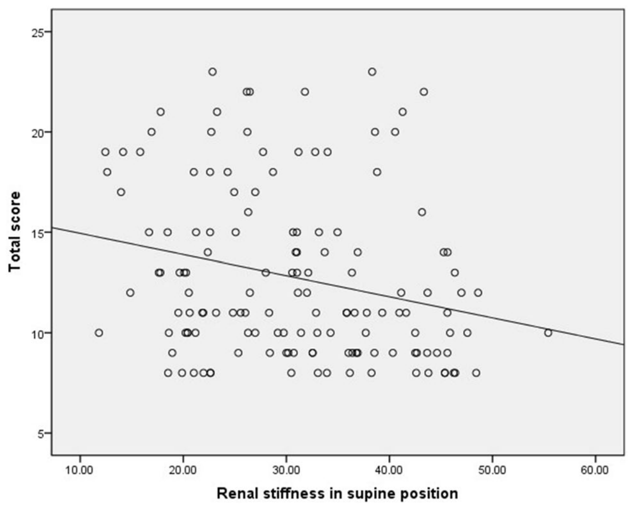

Fig. 8 The correlation between renal stiffness in supine position and degree of renal fibrosis

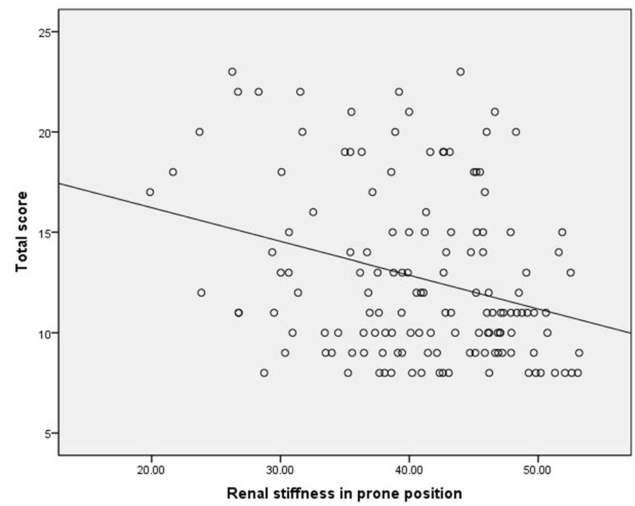

Fig. 10 The correlation between renal stiffness in prone position and degree of renal fibrosis

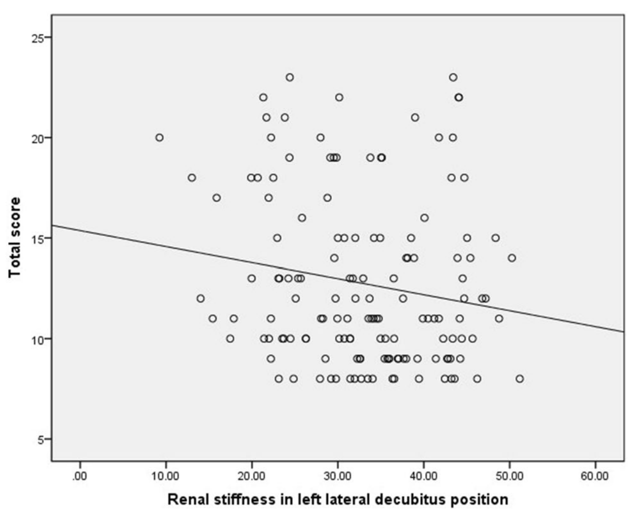

Fig. 9 The correlation between renal stiffness in left lateral decubitus position and degree of renal fibrosis

Our study on the influence of measurement depth on renal 2D-SWE showed that depth < 4 cm had a higher success rate (100%), a lower coefficient of variation (11.1%), and a higher pathological correlation ($r = -0.303$, $P < 0.05$). Due to the lack of similar studies on renal SWE, the results of our study cannot be compared with other studies for the time being.

The success rate was lower with measurement depth increased, which may relate to the greater ultrasound attenuation. In addition, an increased measurement depth usually means obesity; fat can cause more ultrasound energy loss [22], resulting in a lower success rate. Similarly, as the measurement deepens, ultrasound will have a certain degree of attenuation, showing that the shear wave becomes weaker with the increase of depth, which may be the reason for the reduction of stability and accuracy.

In our study, renal elasticity and fibrosis degree were basically negatively correlated under all measurement conditions, which was similar to the results of Asano et al. [23], indicating that renal tissue elasticity gradually decreased with the progression of fibrosis in CKD. This result was in contrast to that found in chronic liver disease, in which the elasticity of liver tissue gradually increased with the progression of liver fibrosis [24]. As for the negative correlation between renal elasticity and fibrosis degree, it may be related to the following factors: (1) Renal fibrosis is not the main influencing factor of renal tissue elasticity in ultrasound elastography [23]. (2) Renal

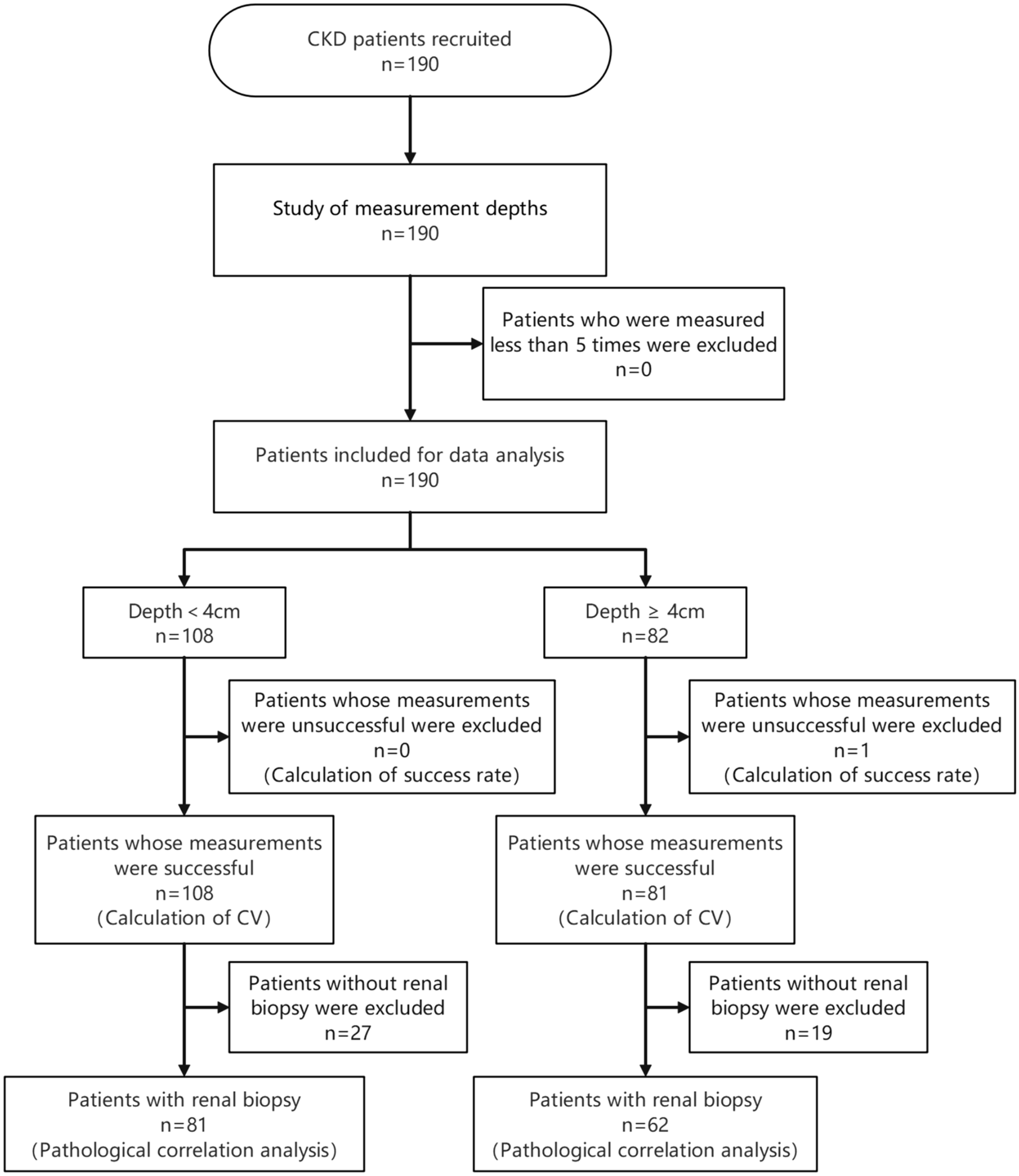

Fig. 11 The inclusion process of study on different measurement depths

Table 8 Influence of measurement depth on the success rate of renal 2D-SWE

Measurement depth	Number of successfully measured patients	Total number of patients	Success rate (%)
Depth < 4 cm	108	108	100
Depth ≥ 4 cm	81	82	98.8

There was no significant difference of the success rate between depth < 4 cm and depth ≥ 4 cm

Table 9 Coefficient of variation of each measurement depth range in CKD patients

Measurement depth	Coefficient of variation (%)	P_{25} (%)	P_{75} (%)
Depth < 4 cm	11.1	7.5	15.2
Depth ≥ 4 cm	14.4	9.1	18.0

There was a significant difference of coefficient of variation between depth < 4 cm and depth ≥ 4 cm

P_{25} was the 25% percentile, P_{75} was the 75% percentile

Table 10 Correlation analysis between renal stiffness and total score of renal fibrosis in each measurement depth range

Pathological score	Depth < 4 cm		Depth ≥ 4 cm	
	r	*P*	*r*	*P*
Total score	− 0.303*	0.006	− 0.156	0.225

$*P < 0.05$

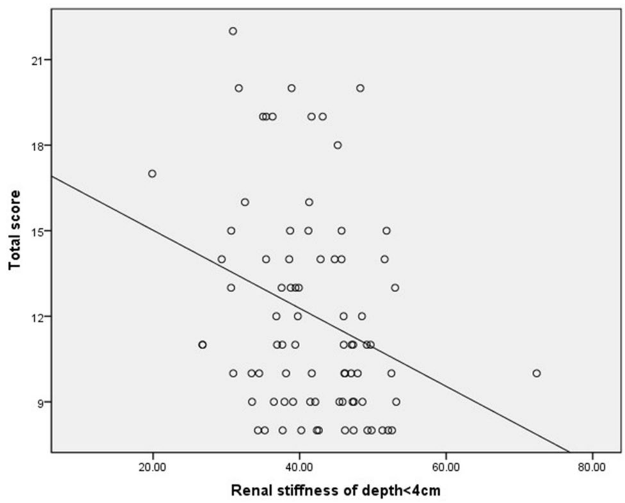

Fig. 12 The correlation between renal stiffness of depth < 4 cm and degree of fibrosis

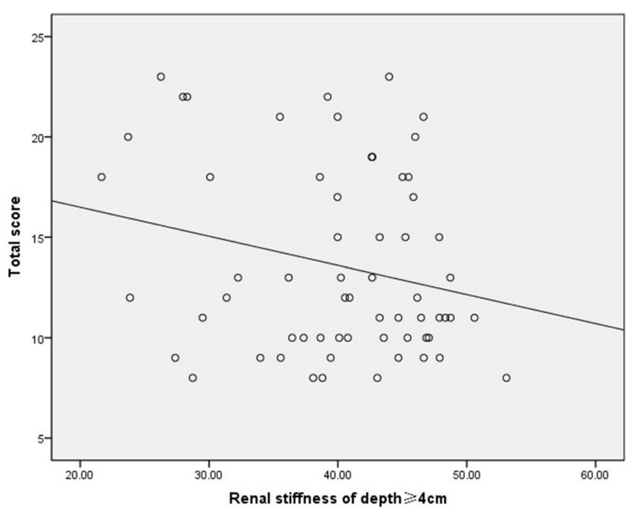

Fig. 13 The correlation between renal stiffness of depth ≥ 4 cm and degree of fibrosis

parenchymal elasticity is not only affected by the degree of renal fibrosis, but also affected by renal blood perfusion, vascular pressure, and urinary flow pressure [23, 25].

This study had the following limitations. First, the sample size of this study was relatively small, which may affect the credibility of the results and need further improvement by expanding the sample size. Second, studies had reported that renal parenchymal stiffness was not only affected by the degree of renal fibrosis, but also affected by renal blood perfusion, vascular pressure, and urinary flow pressure [23, 25]. However, our study did not control these confounding factors, which was not conducive to the correlation analysis of renal stiffness and renal pathological fibrosis degree.

Conclusions

In this study, after a comprehensive evaluation of measurement success rate, coefficient of variation, and pathological correlation, the optimal measurement method of 2D-SWE for noninvasive evaluation of renal fibrosis degree was obtained: prone position, renal middle part, measurement depth < 4 cm.

Author contributions Conceptualization: ZS, YL, YH; Methodology: JC, YH, ZS; Formal analysis and investigation: YL, JC; Writing—original draft preparation: YL; Writing—review and editing: JC, YH, YL, ZS; Resources: ZS; Supervision: ZS, YL, YH.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This is an observational study. The ethics committee at the Fifth Affiliated Hospital of Sun Yat-sen University has confirmed that no ethical approval is required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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