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FULL PAPER

Shear wave elastography in the evaluation of renal parenchymal stiffness in patients with chronic kidney disease

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Objective: To investigate the use of shear wave elastography (SWE)-derived estimates of Young's modulus (YM) as an indicator to detect abnormal renal tissue diagnosed by estimated glomerular filtration rate (eGFR).
Methods: The study comprised 106 chronic kidney disease (CKD) patients and 203 control subjects. Conventional ultrasound was performed to measure the kidney length and cortical thickness. SWE imaging was performed to measure renal parenchymal stiffness. Diagnostic performance of SWE and conventional ultrasound were correlated with serum creatinine, urea levels and eGFR.
Results: Pearson's correlation coefficient revealed a negative correlation between YM measurements and eGFR (r = −0.576, p < 0.0001). Positive correlations between YM measurements and age (r = 0.321, p < 0.05), serum creatinine (r = 0.375, p < 0.0001) and urea (r = 0.287, p < 0.0001) were also observed. The area under the receiver operating characteristic curve for SWE (0.87) was superior to conventional ultrasound alone (0.35–0.37). The cut-off value of less or equal to 4.31 kPa suggested a non-diseased kidney (80.3% sensitivity, 79.5% specificity).
Conclusion: SWE was superior to renal length and cortical thickness in detecting CKD. A value of 4.31 kPa or less showed good accuracy in determining whether a kidney was diseased or not.
Advances in knowledge: On SWE, CKD patients show greater renal parenchymal stiffness than non-CKD patients. Determining a cut-off value between normal and diseased renal parenchyma may help in early non-invasive detection and management of CKD.

INTRODUCTION

Chronic kidney disease (CKD) is a progressive loss of kidney function whose cause is mainly due to hypertension, diabetes and primary renal disorders. As CKD progress, it results in widespread tissue scarring, which subsequently leads to the destruction of kidney parenchyma and end-stage renal failure. The pathologic damage is irreversible and can lead to morbidity and mortality.

CKD has been described as a worldwide public health issue. In USA, the prevalence of kidney failure requiring renal replacement therapy was projected to increase from 340,000 in 1999 to 651,000 in 2010.[1] A similar situation was observed in Malaysia where in 2014, there were 34,767 Malaysians undergoing dialysis, a 2.5-fold increase from 2005.[2] As such, screening and early detection of CKD is important so that measures can be taken to arrest its progression to end-stage disease, which is expensive to treat.

In the past, conventional methods have been used to detect and evaluate renal disorders. These include CT, MRI, conventional ultrasound and biochemical analysis of blood samples. However, these methods carry their own risks, such as radiation exposure and the administration of iodinated contrast medium in CT scans. Conventional renal ultrasound is often used in the initial evaluation because it is safe, easy and inexpensive to perform. Renal ultrasound features, such as increased parenchymal echogenicity and decreased renal size and parenchymal thickness can be easily assessed. Parenchymal echogenicity is a commonly used marker for nephropathy. However, this marker is subjective, not quantitative and often fails to detect renal abnormality.

Thus, conventional renal ultrasound is generally uninformative in evaluating the progression of CKD.[3]

Currently, CKD is divided into five severity-based stages based on the estimated glomerular filtration rate (eGFR), which is calculated from serum creatinine values using one of several formulas. Yet, there are clinical situations where eGFR results may become inconsistent and misleading, such as during acute changes in kidney function, high dietary protein intake, extreme body size and severe liver disease.[4]

Histology of the kidney affects its mechanical properties, particularly the amount of fibrosis in the parenchyma. As such, renal biopsy remains the gold standard for assessing fibrosis with histological techniques. This invasive process may cause post biopsy complications, such as bleeding. Thus, there is huge interest in developing non-invasive methods to accurately evaluate nephropathy.

Shear wave elastography (SWE) is an emerging ultrasound technique used to measure tissue stiffness. A real-time short-duration acoustic push pulse is used to generate shear waves that propagate perpendicular to the main ultrasound beam. When the waves hit the targeted tissue, the tissue is "pushed" in the direction of propagation, causing it to temporarily deform or displace. The ultrasound scanner can monitor the tissue displacement, measuring the time-to-peak displacement and the recovery time. Shear wave velocity increases in diseased tissues, which can be significantly stiffer than normal ones. The parameters are expressed in pressure units of kilopascals (kPa) and velocity (m s^{-1}).

Variations of SWE have been used to study breast, thyroid, prostate and liver diseases.[5–8] SWE has been observed to enhance B-mode ultrasound findings and potentially improve the detection of tissue abnormality and selection of patients for fine needle aspiration biopsy.[7]

Several nephrology studies have utilised SWE to evaluate renal parenchymal elasticity. Nevertheless, these studies have yielded conflicting results. Hassan et al[9] reported that cortical stiffness was inversely correlated with eGFR. Although Bob et al[10], Cui et al[11] and Hassan et al[9] have defined optimal cut-off values for their control groups, their sample sizes were relatively small.

Studies regarding the effectiveness of SWE in detecting renal parenchymal stiffness would, therefore, be of interest. In this study, we aim to investigate whether SWE-derived estimates of tissue Young's modulus (YM) could be used as an indicator to distinguish between normal and abnormal renal parenchymal tissue, compared with using conventional ultrasound.

METHODS AND MATERIALS

Patient selection

The study protocol was proposed in accordance with the Declaration of Helsinki and approved by the medical ethics committee of the University of Malaya Medical Centre (MECID. No: 201743-5108). Written informed consent was obtained from all participants.

Data were obtained from 309 adults (167 males, 142 females, mean age 55), who had been referred to the Department of Biomedical Imaging, University of Malaya Medical Centre, from July 2016 to August 2017 for routine conventional abdominal ultrasound. The control group comprised 203 subjects (104 males, 99 females) who did not have any clinical signs of renal disease.

The inclusion criteria of the control subjects were as follows: subjects with eGFR of >90(ml min^{-1}/1.73 m^2), serum creatinine of 44–71 μmol l^{-1} and serum urea of 3.2–8.2 mmol l^{-1}. Exclusions were done in the following scenarios: those who had thin renal parenchymal thickness, those with a renal cortex to skin surface depth of more than 8 cm, those who refused to participate in this research and those who could not control their breathing according to the sonographer's instructions during the SWE procedure.

The CKD group comprised of 106 patients (63 males, 43 females) receiving treatment at the Nephrology Clinic, Department of Medicine, University of Malaya Medical Centre. Their inclusion criteria were as follows (minimum of 2 simultaneously): those with abnormal eGFR (<90 ml^{-1}min/1.73 m^2), those with deranged serum creatinine (>71 μmol l^{-1}) and those with deranged serum urea (>8.2 mmol l^{-1}). The exclusion criteria of patients in the diseased group were the same as those in the control group. The eGFR values (ml min^{-1}/1.73 m^2) were calculated using the CKD Epidemiology Collaboration equation.[12] Classification of CKD stages were based on these eGFR values (Table 1).[1]

Image acquisition

Difference between CKD subgroups

Conventional ultrasound and SWE imaging were performed using an ultrasound scanner (Epiq 7, Philips, Bothell, Washington) equipped with SWE software (ElastPQ, Philips, Bothell, Washington). A curved array transducer (C5-1, frequency range: 1.0–5.0 MHz) (Philips, Bothell, Washington) was used. All ultrasound examinations were performed by the same sonographer (LSS, 10 years experience).

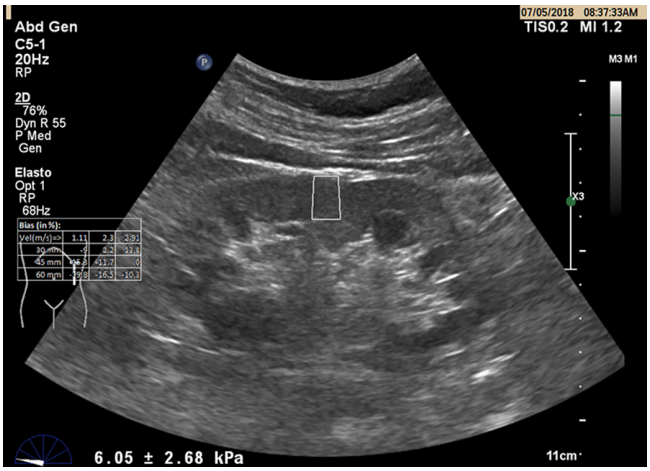
Patients were placed in a lateral decubitus position. A routine conventional ultrasound was performed on both kidneys. Bipolar length and cortical thickness of the kidneys were measured. The

Table 1. Classification for stages of CKD

Classification of CKD based on eGFR	
Stage	eGFR (ml min^{-1}/1.73 m^2)
1	≥90
2	60–89
3	30–59
4	15–29
5	<15

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Figure 1. Measurement of shear wave elastography estimates of Young's modulus in a kidney. The ROI box was positioned at the midregion of the right renal cortex. (ROI, region of interest).



long diameter of the kidney was determined as the maximum longitudinal dimension in coronal section. Kidney cortical thickness was measured from the outer border of the renal cortex to the outer border of the medullary pyramid.

Using the ElastPQ software, imaging was focused on the long axis view of the kidneys with the transducer placed parallel, without any pressure. The patients were told to hold their breath.

With the image stabilised, a region of interest (ROI) with a fixed size of $0.5 \times 0.8 \times 0.02$ cm^3 was placed in the renal cortex, excluding the renal medulla and sinus, to measure the SWE estimates of renal YM in kPa. Effective stiffness values were measured five consecutive times at the midregion of the kidneys on each side, with shear wave travel oriented perpendicular to the radially arranged tubular system. The mean value for each kidney was recorded (Figure 1).

Intra- and interobserver reliability

31 subjects from the control group participated in the intra- and interobserver reliability studies of YM measurements from SWE imaging. Stiffness values were measured five times at the midregion of the kidneys and the mean values were recorded. For interobserver reliability, SWE imaging was performed by the first sonographer (LSS, 10 years experience) and then repeated by a second sonographer (SM, 5 years experience) on the same day. Both sonographers were blinded to each other's SWE imaging results. Each subject was scanned repeatedly by both sonographers with a 2 day interval to avoid recall bias.

Pre- and post-void studies

The 31 subjects from the control group also participated in the pre- and post-void studies. SWE imaging was performed on the subjects with a full bladder. Each subject was examined again on the same day after bladder emptying. Stiffness values were measured five times at the midregion of the kidneys during pre- and post-void studies. SWE imaging were performed by LSS on these 31 subjects.

Influence of ROI location on YM measurements

SWE imaging with two ROI box locations were performed on 31 patients from the diseased group. Once the stiffness values were acquired in the midregion of the kidneys, a repeat SWE imaging was performed at the upper pole of the kidneys, orienting the shear wave travel path parallel to the radially arranged tubular system. SWE imaging was performed by LSS on these 31 patients.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences software (IBM Corporation, v. 21.0, Armonk, NY). Continuous data were expressed as the mean (± standard deviation). The mean YM, renal length and parenchymal thickness among diseased and control groups were analysed using one-way analysis of variance and the Tukey *post hoc* test. Correlations between SWE and conventional ultrasound parameters with age, serum creatinine, eGFR and serum urea were analysed using Pearson's correlation coefficient ($p \leq 0.05$). The diagnostic performance of SWE imaging and conventional ultrasound in distinguishing the diseased group from the control group was assessed by receiver operating characteristic (ROC) curves. The optimal cut-off values for the prediction of the control group was chosen to maximise the sum of sensitivity and specificity. Statistical tests were performed on the data collected and significance levels were declared at $p \leq 0.05$.

Intraclass correlation coefficients (ICCs) were used to evaluate the intra- and interobserver reliability of the YM measurements. The degree of agreement was quantified as either poor (ICC < 0.40), fair to good (ICC 0.40–0.75) or excellent (ICC > 0.75). Paired *t*-test was used to assess YM measurements for the pre- and post-void study. Wilcoxon rank sum test was used to assess YM measurement at different ROI locations.

RESULTS

Patient and control subject characteristics

A total of 309 adults comprises 106 patients and 203 control subjects were assessed. The demographic features of patients and control subjects at different stages of renal function based on eGFR as well as the aetiology of CKD are presented in Tables 2 and 3.

Relationship between SWE and conventional ultrasound measurements with age, creatinine and urea levels

Pearson's correlation coefficient revealed a moderate negative linear correlation between YM measurements and eGFR ($r = -0.576$, $p < 0.0001$). Weak positive linear correlations between YM measurements with age ($r = 0.321$, $p < 0.0001$), serum creatinine ($r = 0.375$, $p < 0.0001$) and serum urea ($r = 0.287$, $p < 0.0001$) were observed.

In comparison with SWE imaging, kidney length and cortical thickness obtained sonographically showed no significant correlation with age, eGFR, serum creatinine or serum urea.

Table 2. Demographic features of the patients and control subjects

Parameter	Control group	Diseased groups (n = 106)			
	eGFR >90 (n = 203)	eGFR 60–89 (n = 57)	eGFR 30–59 (n = 35)	eGFR 15–29 (n = 10)	eGFR <15 (n = 4)
Age (years)	50.94 ± 12.71	65.05 ± 11.12	66.34 ± 10.40	65.00 ± 12.63	59.5 ± 13.78
Weight (kg)	65.90 ± 14.34	65.85 ± 15.42	68.19 ± 13.01	70.50 ± 12.95	56.67 ± 5.16
Height (cm)	162.00 ± 8.51	162.05 ± 9.98	162.18 ± 10.45	162.50 ± 7.13	156.00 ± 5.37
BMI	24.88 ± 4.52	25.08 ± 5.44	26.03 ± 4.79	26.68 ± 4.57	23.24 ± 1.13
eGFR (ml min^{-1}/1.73m^2)	91.00 ± 0.44	77.20 ± 10.14	48.00 ± 11.45	21.50 ± 5.26	11.75 ± 4.62
Serum creatinine (μmol l^{-1})	62.05 ± 14.41	83.60 ± 14.30	124.89 ± 30.10	250.20 ± 66.48	432.75 ± 153.66
Serum urea (mmol l^{-1})	4.24 ± 3.74	5.05 ± 1.44	8.38 ± 5.12	13.89 ± 3.64	17.25 ± 6.92
YM (kPa)	3.55 ± 1.59	7.61 ± 6.09	11.61 ± 6.88	10.06 ± 5.72	12.75 ± 5.63
Kidney length (cm)	10.31 ± 1.22	9.76 ± 1.18	9.98 ± 1.18	9.36 ± 0.85	9.70 ± 1.54
Cortical thickness (cm)	0.94 ± 0.17	0.83 ± 0.15	0.83 ± 0.15	0.84 ± 0.14	0.83 ± 0.22

BMI, body mass index; eGFR, estimated glomerular filtration rate; YM, Young's modulus.

There was no significant difference in renal length or cortical thickness in the diseased and control groups, but a significant difference was found in YM measurements as determined by one-way analysis of variance (F = 90.188, $p < 0.0001$). Tukey *post hoc* test revealed that the YM measurements were lower in the group that had higher eGFR. The test also showed that it was difficult to distinguish between CKD 3, 4 and 5 based on their YM measurements due to the large variance within the groups.

Comparison between SWE imaging with conventional ultrasound

SWE imaging and conventional ultrasound between control and patient groups were analysed using ROC curves. The area under the ROC curve for SWE (0.87) was larger than that of kidney length and cortical thickness measured using conventional ultrasound (Table 4). We obtained a YM measurement cut-off value of 4.31 kPa, of which a value less or equal to this suggested a non-diseased kidney. This yielded a sensitivity and specificity of 80.3% and 79.5%, respectively (Figure 2).

Reproducibility of YM measurements

The ICC of the first and second readers were 0.839 [95% confidence interval (CI): 0.734–0.903) and 0.758 (95% CI: 0.600–0.854), respectively. For interobserver reliability, the ICC was 0.687 (95% CI: 0.473–0.807). This indicates that the YM measurements had fair to good interobserver reliability and excellent intraobserver reliability.

Table 3. Aetiologies of CKD

Diagnosis	Number
Obstructive uropathy	18
Malignancy	3
Diabetic nephropathy	21
Hypertension	30
Diabetic nephropathy/hypertension	26
IgA nephropathy	3
Unknown diagnosis	5

CKD, chronic kidney disease.

YM measurements from pre- and post-void study

A paired-sample *t*-test showed that there was no significant difference in YM measurements of the renal cortices between empty and full bladder states.

YM measurements from different ROI location

Wilcoxon rank sum test showed that the median difference of YM measurements between upper pole and midregion ROI box locations was significant ($p < 0.0001$), with the upper pole (2.52 kPa) showing lower YM values than the midregion of the kidney (6.57 kPa)

DISCUSSION

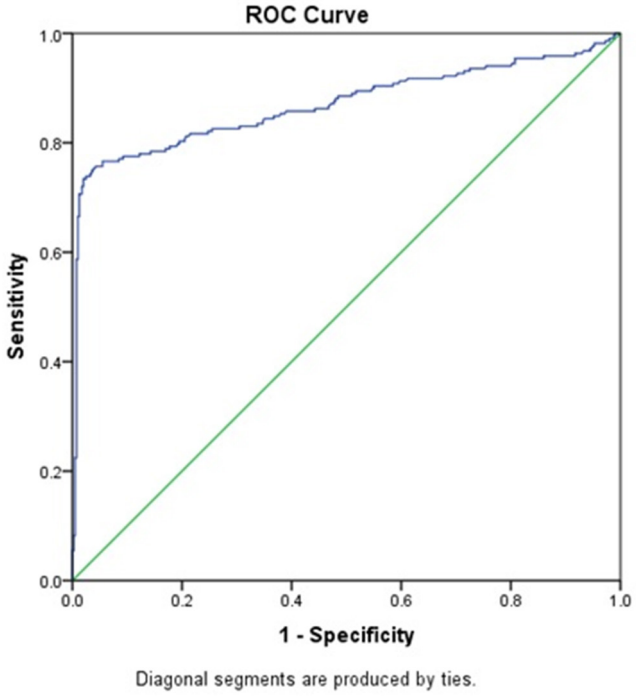
In this study, we first investigated the relationship of SWE and conventional ultrasound with age and laboratory tests. The YM measurements significantly correlated with age and this observation was supported by Yang et al.[13] This was due to the development of glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriosclerosis as kidneys aged. However, Samir et al[4] recently reported no significant correlation between YM measurement and age. One explanation for this might be the

Table 4. Diagnostic accuracy of SWE imaging and conventional ultrasound in the control group

	Control group	
	AUC	p-value
YM measurements (kPa)	0.870	<0.0001
Kidney length (cm)	0.351	<0.0001
Cortical thickness (cm)	0.374	<0.0001

AUC, area under curve; SWE, shear wave elastography.

Figure 2. ROC curve of YM in distinguishing between diseased and control groups, AUC = 0.87, cut-off = 4.31 kPa, sensitivity 80.3% and specificity 79.5%. AUC, area under the curve; ROC, receiver operating characteristic; YM, Young's modulus.



relatively small sample size in the latter study, which only had 20 adults in the control group and 25 adults in the diseased group.

Tubulointerstitial renal fibrosis, a progressive detrimental connective tissue deposition in the kidney parenchyma, appeared to be the leading cause in renal function deterioration. Progressive interstitial damage results in declining GFR, indicating an inverse correlation between serum creatinine and GFR.[14] Hyperfiltration may also cause interstitial damage at the glomerulus, leading to tubulointerstitial injury as plasma proteins are forced out into the tubule and urine.[15] Protein reuptake at the tubules may result in the development of inflammation and fibrosis. As the degree of fibrosis increases, the affected tissue area becomes stiffer, allowing shear waves generated by a transducer to propagate quickly.[16,17] The GFR was inversely related to the degree of renal fibrosis, which in turn is directly related to the propagation of shear waves. Our results concur with this, where YM measurements significantly correlated with eGFR, and serum creatinine and urea.

However, opposing results were demonstrated by Guo et al[18] where they found a positive relationship between shear wave velocity (SWV) and eGFR, and a negative relationship between SWV and serum creatinine. The reason for these differences remains unclear.

In SWE for liver disease, it was reported that estimates of tissue YM, measured in kPa, showed higher values for higher degrees of fibrosis.[19,20] Feng et al[19] observed that liver stiffness positively correlated with histological grading score (F0-F4), with a higher score indicating more severe fibrosis. Their research concluded that the F4 group showed significantly higher elastic YM compared with the other groups. Similar results were demonstrated in our study, whereby the control group showed significantly lower YM measurements than the CKD group.

This is also in accordant with previous research findings in which SWV measurement was negatively correlated with eGFR grading.[21,22] However, we noticed that the mean YM measurement for CKD patients (eGFR 15–29) was lower compared with the eGFR 30–59 subgroup. This discrepancy could be due to the small number of patients in eGFR 15–29 subgroup (n = 10), as most of the patients in this subgroup had to be excluded due to thin renal parenchymal thickness compared with the eGFR 60–89 (n = 57) and eGFR 30–59 (n = 35) subgroups.

Age-associated loss of kidney function and reduction in kidney size has been recognized for decades.[23] However, our results showed no significant correlation between kidney length or cortical thickness with age. One explanation for this might be the prevalence of CKD in our sample did not increase with age but with other risk factors such as obesity, hypertension and diabetic nephropathy. Bipolar length of the kidney has also been used as a predictor of CKD. However, according to Sanusi et al[24] kidney length is not an accurate predictor of kidney abnormality as compared to kidney volume. In our results, we showed that conventional ultrasound had no correlation between kidney length or cortical thickness and laboratory tests.

According to Lucisano et al[25] the morphostructural changes occurring in CKD do not strictly correlate with GFR. Similar to our results, Xu et al[21] reported that there was no significant difference in the renal length between diseased and control groups. Hu et al[26] also reported that renal length and parenchymal thickness, when compared to SWE, have a weaker correlation with serum creatinine and eGFR. According to our study's maximum area under the ROC curve, a YM measurement of less or equal to 4.31 kPa was determined as a diagnostic indicator of normally functioning renal parenchyma with a sensitivity of 80.3% and a specificity of 79.5%, superior to conventional ultrasound parameters.

Although the results of SWE is encouraging, the limitations of this new technique should be taken into account, such as the location of the ROI in SWE, bladder distention and intra- and interobserver variation in the assessment of kidney stiffness. In this study, we repeated YM measurements by the same operator to eliminate intraobserver variation and different operators to eliminate interobserver variation.

We obtained a fair to good interobserver reliability and excellent intraobserver reliability. The intraobserver reliability obtained is higher than in published studies on renal stiffness measurements by means of acoustic radiation force impulse imaging, in which the reported ICCs was 0.709.[26] One possibility could be that both operators in our study were more experienced in the field of ultrasonography as well as SWE imaging.

For routine conventional kidney ultrasound, patients are required to have a full bladder during the scan in order to demonstrate the bladder wall and to exclude bladder masses. However, an overly-distended bladder with transmitted backpressure might give a false positive for obstructive hydronephrosis.[27] A study by Sohn et al[28] stated that increased pelvic pressure due to hydronephrosis could increase renal parenchymal stiffness. They reported that median SWVs in kidneys with high-grade hydronephrosis were higher than those in normal kidneys.

In our study, we repeated the SWE measurements on 31 subjects from the control group with an empty and distended bladder. Our results showed no significant difference in the YM measurements between a distended bladder and empty bladder. This could be due to the overly distended bladder causing only mild splaying of the pelvicalyceal system, but not hydronephrosis that may alter the stiffness of the renal parenchyma.

It is known that kidney tissue is anisotropic, hence, the properties are not the same in all axis orientations.[29] Sending ultrasound beams in different axes on these structures (loops of Henle and vasa recta within the medulla, collecting ducts within cortex and medulla) might lead to different elasticity values due to the difference in the way the shear waves propagate.[30] Accordingly, our results showed a significant difference in YM measurements when the position of the ROI was changed, effectively altering the beam-to-tissue orientation. In view of the fact that the ROI box location significantly influenced YM measurements, a fixed location should be determined during image acquisition in order to obtain reliable and reproducible results, especially when establishing normal limits of stiffness of a particular tissue. As such, we recommend placing the ROI box at the midregion of the kidney during image acquisition as this position easily allows exclusion of the renal medulla and sinus.

There are several limitations in our study. First, the ROI size could not be reduced to sample smaller volume. . This study was not suitable for patients with thin renal parenchymal thickness. Second, we used the known reference standard of eGFR only to estimate CKD severity. No biopsy data for histological quantification was involved as patients with CKD were not clinically indicated for renal biopsy. The lack of histological quantification will be addressed in the next step of our study. In view of the maximum detection depth of only 8 cm, the SWE method could not be used on obese patients and patients with hepatomegaly or splenomegaly. The sensitivity to breathing movement artefact was also one of the challenges encountered in obtaining reliable measurements.

SUMMARY

We observed that SWE was superior to conventional ultrasound in the assessment of CKD. We used a cut-off value of 4.31 kPa to distinguish between diseased from normal kidneys. Despite its limitations, SWE-derived estimates of renal stiffness is an effective, low-cost tool for non-invasive method to provide extra diagnostic information in CKD.

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