

Shear Wave Elastography in the Evaluation of Renal Parenchymal Stiffness in Patients With Chronic Kidney Disease: A Meta-Analysis

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Abstract

Background: Chronic kidney disease (CKD) is a progressive loss of renal function, mainly due to hypertension, diabetes, and primary kidney disease. The histopathological findings are that of glomerulosclerosis, tubulointerstitial fibrosis and loss of renal parenchyma characterized. Therefrom, CKD can lead to higher morbidity and mortality. Patients with CKD have multiple risk factors, and the prevention work is complicated and arduous. Therefore, it is important to quantify the severity of CKD. The aim of this study is to investigate the value of shear wave elastography (SWE) in the evaluating renal parenchymal stiffness in patients with CKD.

Methods: We carried out the systematic search of databases for publications in PubMed, Embase and Cochrane Library on SWE evaluating renal fibrosis in patients with CKD. The Endnote X9, STATA 16, Review Manager 5.3 and other software were used to sort out documents, extract, integrate and analyze data.

Results: The outcomes were utilized to appraise the diagnostic accuracy of SWE and diagnose the CKD with renal fibrosis. A total of 405 patients were enrolled and their data analysis results were as follows: summary of sensitivity (S-SEN) 84% (95% confidence interval (CI): 80-87%); specificity (S-SPE) 80% (95% CI: 76-84%); summary of DLR (digital light radiography) positive (DLR-P) 4.29 (95% CI: 3.43 - 5.37); and DLR negative (DLR-N) 0.20 (95% CI: 0.16 - 0.25). The corresponding areas under the curves of diagnostic odds ratio (DOR) and summary receiver operating characteristic curve (SROC) were 21.50 (95% CI: 14.69 - 31.46) and 89% (95% CI: 86-92%), respectively.

Conclusions: SWE is highly accurate and has clinical significance for evaluating renal fibrosis, especially when the shear modulus value is used as the threshold.

Keywords: Shear wave elastography; Chronic kidney disease; Meta-analysis

Introduction

Chronic kidney disease (CKD) is an important cause of an increasing epidemiologic burden and a major health burden all over the world [1]. More than 500 million of 6.4 billion people have different types and different stages of kidney diseases in the whole world. It is predicted that by 2030, the number of patients requiring dialysis or transplantation due to renal failure will exceed 2 million [2, 3]. CKD caused 1.2 million deaths worldwide in 2017. More than 1 million CKD patients die of cardiovascular diseases every year in China, accounting for the first cause of death [4-7]. During the course of the disease, the mechanisms contributing to CKD consist of the rarefaction, destruction, necrosis of the capillary network, chronic hypoxia and inflammation [8], resulting in CKD progression with parenchymal fibrosis, tubulointerstitial atrophy and sclerosis of the glomerular compartment (Fig. 1).

These structural abnormalities detected by traditional gray-scale ultrasound imaging cannot be objectively quantified [9]. Although the accuracy of percutaneous renal biopsy is rather high, the puncture and invasive diagnosis may easily lead to complications [10]. Therefore, a reliable noninvasive technique is needed to detect the renal fibrosis in patients with CKD, as well as evaluate treatment response [11]. Shear wave elastography (SWE) is a noninvasive, low-cost, fast, quantitative and real-time short-time ultrasound technique for assessing renal stiffness. SWE is a focused acoustic energy pulse used to generate microstructure displacement and shear waves that propagate perpendicularly to the main ultrasonic beam. The ultrasonic scanner is able to monitor the tissue displacement as the shear waves move through the tissue and measure the time to peak displacement and recovery time. Quantification of rigid (Young's modulus (YM)) propagation velocity within tissues is measured at local tissues with meters per second (m/s) to kilopascals (kPa).

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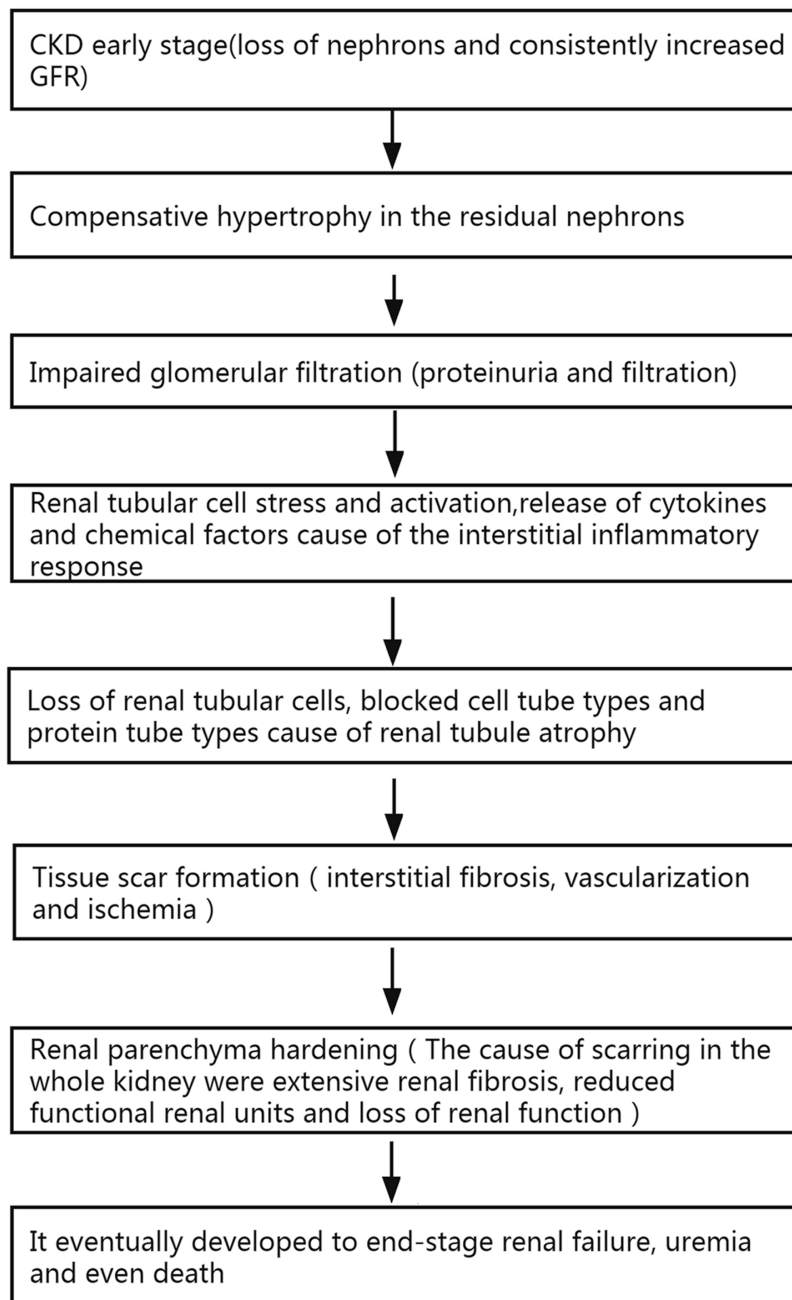


Figure 1. Relationship or mechanisms between renal parenchyma stiffness, fibrosis, impaired renal function, and mortality. CKD: chronic kidney disease; GFR: glomerular filtration rate.

The shear wave velocity of pathological tissue increases, and the hardness of pathological tissue may be significantly higher than that of normal tissue. It is a potential tool to reduce the need for kidney biopsies. Many studies [12-14] have confirmed that the SWE technology has highly application value in evaluating tissue fibrosis and many applications in the evaluation of liver fibrosis, breast mass hardness, and thyroid mass hardness. When using SWE to measure the elastic modulus of renal parenchyma in CKD patients in real time, quantitative analysis of absolute kidney stiffness information can objectively assess the CKD

with renal stiffness, thereby opening up a new approach to the evaluation of CKD fibrosis.

Materials and Methods

The present Hand Institutional Review Board approved the waiver. This study was carried out in accordance with the ethical standards of the responsible body on human subjects as well as the Declaration of Helsinki.

Search protocol

Databases of PubMed, Embase and Cochrane Library were searched for the use of SWE to assess CKD fibrosis up to April 26, 2021. Mesh strategies and free words were used for searching in the database: “chronic kidney failure” OR “kidney disease” OR “kidney failure” OR “chronic kidney disease” OR “kidney failure, chronic” OR “renal insufficiency, chronic” OR “kidney stiffness” OR “renal parenchymal stiffness” OR “kidney elasticity” AND “elasticity imaging techniques” OR “acoustic radiation force impulse imaging” OR “elastographies” OR “fibros-can” OR “ultrasonically” AND “elastance” AND “image”. In order to search the entire document as much as possible, the retrieval method in this study is in combination of subject terms with free words, network retrieval with manual retrieval, and a second review of the retrieved related documents. Then the two investigators independently screened according to the standard that is used to analyze the diagnostic ratio than literature.

Study and data selection

Inclusion criteria are: 1) The types of literature mainly include the published diagnostic tests on SWE evaluation of CKD; 2) The research object is CKD caused by various reasons; 3) The research method is to use SWE to detect the severity of renal fibrosis; 4) The literature provides the original data and we can directly/indirectly calculate the sensitivity, specificity, false negatives, false positives and other data.

Exclusion criteria are: 1) The diagnosis of CKD/renal insufficiency is not clear; 2) The data are incomplete; 3) Repeated publications that are within the same main research literature.

Data extraction and quality assessment

According to the established standards, the two investigators independently screened relevant database documents and extracted the data. The extracted data include authors, the year published in journals and publications, samples, research location, etiology, average age, and gender. Data are related to SWE and diagnostic tests for renal insufficiency diseases, as well as the calculation of the sensitivity and specificity, the number of true positives, false positives, true negatives, and false negatives. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool is used to assess the data quality [15]. Disagreements were resolved through discussions between the two investigators. Case selection, trial evaluation, diagnostic criteria and risk assessment are included in the study.

Statistical analysis

The main meta-analysis software for extracted data includes STATA 16 (Stata Corp., University of Texas College, USA) and Review Manager 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). They are used to calculate the pooled sensitivity (S-SEN), specificity

(S-SPE), pooled positive likelihood ratio (PLR-P), negative likelihood ratio (PLR-N), diagnostic odds ratio (DOR) and 95% confidence interval (95% CI), and summary receiver operating characteristic curve (SROC) and area under the curve (AUC) [16, 17]. The S-SEN and S-SPE forest maps were constructed using SWE to assess the accuracy of renal fibrosis. A DOR ROC chart was drawn to determine the threshold effect. The heterogeneity test was performed by Cochrane-Q and I^2 statistic. If inconsistency ($I^2 \geq 25\%$ and $P < 0.05$), DOR is considered heterogeneous, and the random effects model is selected. Otherwise, the fixed effects mode shall be selected.

Results

Literature searches

A total of 1,306 English documents were searched in the relevant literature database, and those duplicate articles were deleted. After completing detailed manual review, 16 articles met the inclusion and exclusion criteria. After a detailed manual review, the duplicates and documents that did not meet the inclusion criteria were eliminated. Finally, there were six documents in line with the inclusion criteria. See Figure 2 for the literature screening process and results of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) research guide. The main features of meta-analysis in the study were included in Table 1 [18-23].

Study characteristics

Six studies were included in the meta-analysis, including 405 patients, aged between 23 and 79 years. The etiology was divided into CKD, idiopathic nephrotic syndrome (INS) and immunoglobulin A nephropathy (IgAN). In these studies, there are some [18-22] YM values that were used to evaluate the degree of renal fibrosis in CKD patients. The results of the studies indicate that the YM value is higher as the CKD condition progresses. It should be pointed out that in the study by Grosu et al, the hardness of the kidney was evaluated by shear wave velocity (SWV) on an ultrasound machine [23]. The results showed that the two-dimensional (2D)-SWE value of CKD was significantly higher than that of the healthy group, and patients with reduced estimate the glomerular filtration rate (GFR) have higher SWV values. Compared with normal kidneys, the cut-off values of the six studies found that the SWE diagnostic threshold of CKD renal insufficiency is lower, while the cut-off value of autoimmune nephropathy is higher [24] (Table 2 [18-23]). In addition, Radulescu et al [19] studied the high diagnostic threshold of SWE mainly because most of the CKD patients selected for the study were stage 4 and 5 CKD patients.

Methodological quality assessment

According to the methodological assessment of the QUADAS-2 checklist, all studies were prospective and well designed, indi-

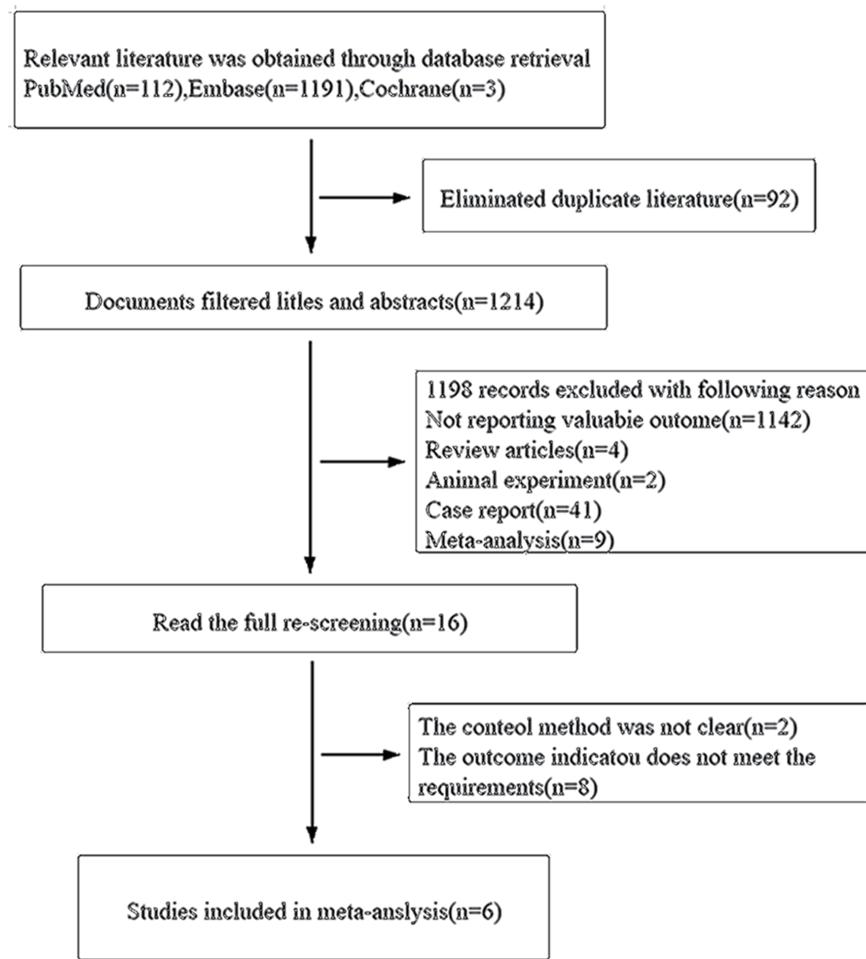


Figure 2. Screening processes of document and results.

cating good quality of inclusion studies. Patients have been included in all studies continuously; laboratory tests and/or clinical diagnosis were used as the reference criteria. The risk of case selection, trial evaluation, diagnostic criteria and clinical applicability was low. The outcomes were shown in Figure 3.

Meta-analysis

Figure 4 shows the preliminary analysis of the S-SEN ($I^2 =$

0.00%, $Q = 4.81$, $P = 0.44 (> 0.1)$) and S-SPE ($I^2 = 44.36%$, $Q = 8.99$, $P = 0.11 (> 0.1)$). It revealed that there was no significant heterogeneity. The S-SEN, S-SPE and DOR were 84% (95% CI: 80-87%), 80% (95% CI: 76-84%) and 21.50 (95% CI: 14.69 - 31.46), respectively. PLR-P was 4.29 (95% CI: 3.41 - 5.37) and PLR-N was 0.20 (95% CI: 0.16 - 0.25), of which the PLR-P was greater than 4 and the PLR-N was less than 0.3, providing “strong” diagnostic evidence. The area under the SROC curve was 0.89 (95% CI: 86-92%), which suggested high diagnostic accuracy. Fagan diagram was drawn

Table 1. Characteristics and Diagnostic Performance of Included Studies of CKD Fibrosis

Studies included	Country	Averaged age (range)	Sample size	Etiology	Sensitivity	Specificity
Leong et al, 2018 [18]	Malaysia	55	106	Chronic kidney disease	0.803	0.795
Radulescu et al, 2018 [19]	Romania	62.875 (48 - 79)	32	Chronic kidney disease	0.875	0.65
Samir et al, 2015 [20]	America	61 (56 - 70)	25	Chronic kidney disease	0.80	0.75
Yang et al, 2020 [21]	China	46.9 (23.0 - 68.0)	120	INS disease	0.817	0.933
Turgutalp et al, 2020 [22]	Turkey	40.2 ± 11.3	30	IgAN disease	0.890	0.900
Grosu et al, 2021 [23]	Romania	57.5 ± 13.4	92	Chronic kidney disease	0.892	0.769

CKD: chronic kidney disease.

Table 2. The Diagnostic Threshold (kPa) of SWE in Fibrosis With Chronic Kidney Disease

Etiology	SWE	Studies included
Chronic kidney disease	YM = 4.31 kPa	Leong et al, 2018 [18]
Chronic kidney disease	YM = 22.95 kPa	Radulescu et al, 2018 [19]
Chronic kidney disease	YM = 5.3 kPa	Samir et al, 2015 [20]
INS disease	YM = 7.96kPa	Yang et al, 2020 [21]
IgAN disease	YM > 15 kPa	Turgutalp et al, 2020 [22]
Chronic kidney disease	SWV < 1.47 m/s	Grosu et al, 2021 [23]

SWE: shear wave elastography; INS: idiopathic nephrotic syndrome; IgAN: immunoglobulin A nephropathy; SWV: shear wave velocity; kPa: kilopascals.

according to Bayes principle. After the test, the PLR-P increased to 52% from 20%, while the PLR-N decreased to 5% (Figs. 5 - 8).

Publication bias

The Deeks’ funnel chart was used to detect in publication bias. The P value was 0.53 and all studies were distributed on both sides of the regression line, indicating no obvious deviation in

publications (Fig. 9).

Discussions

At present, the incidence of CKD is very high worldwide. However, regardless of the underlying cause, the progression of CKD includes substantial fibrosis, tubular interstitial atrophy, and glomerular compartment sclerosis. CKD is a common cause of kidney fibrosis, associated with the severity of

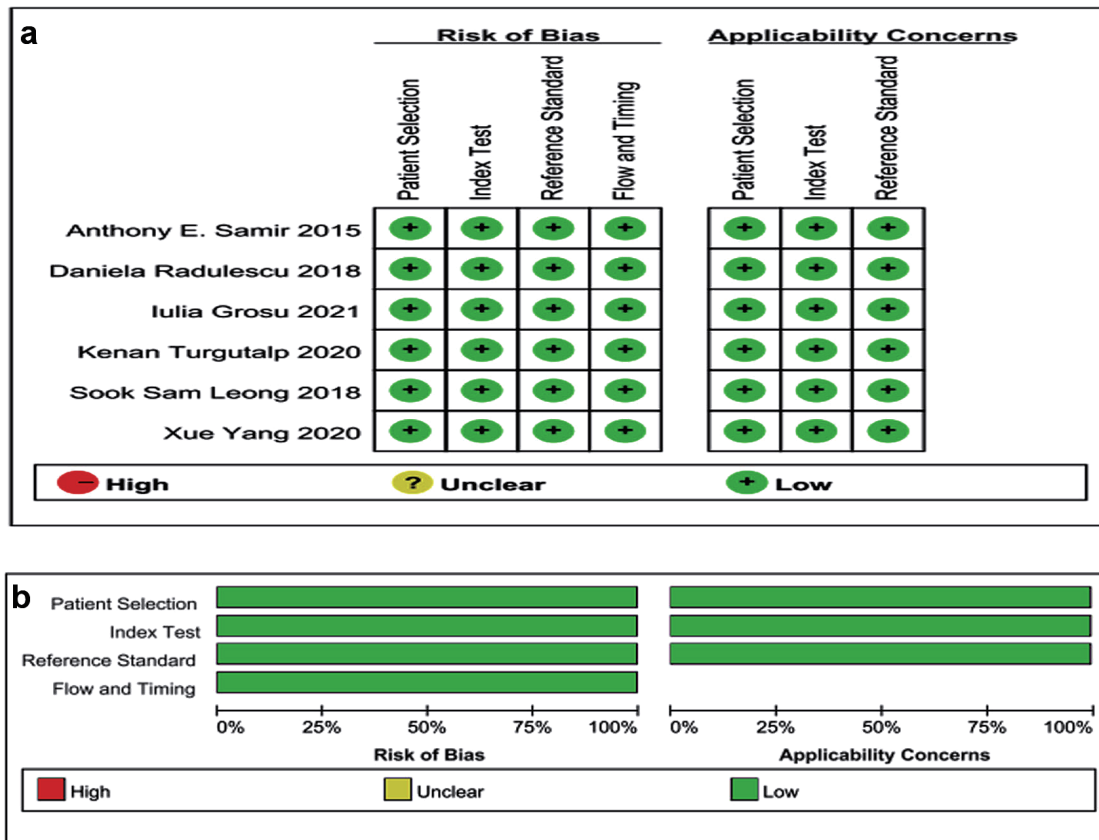


Figure 3. Quality assessment of the studies according to QUADAS-2. QUADAS: Quality Assessment of Diagnostic Accuracy Studies.

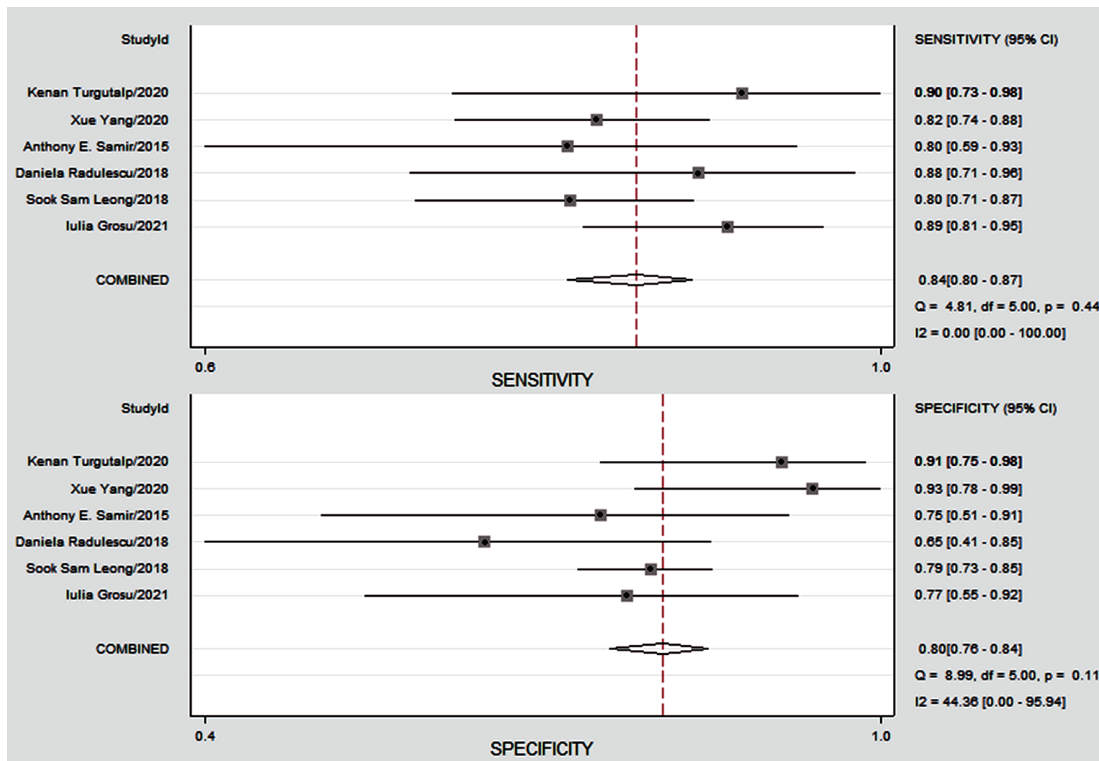


Figure 4. The Forest plots showing diagnostic performance estimates (sensitivity and specificity) of CKD fibrosis. CKD: chronic kidney disease; CI: confidence interval.

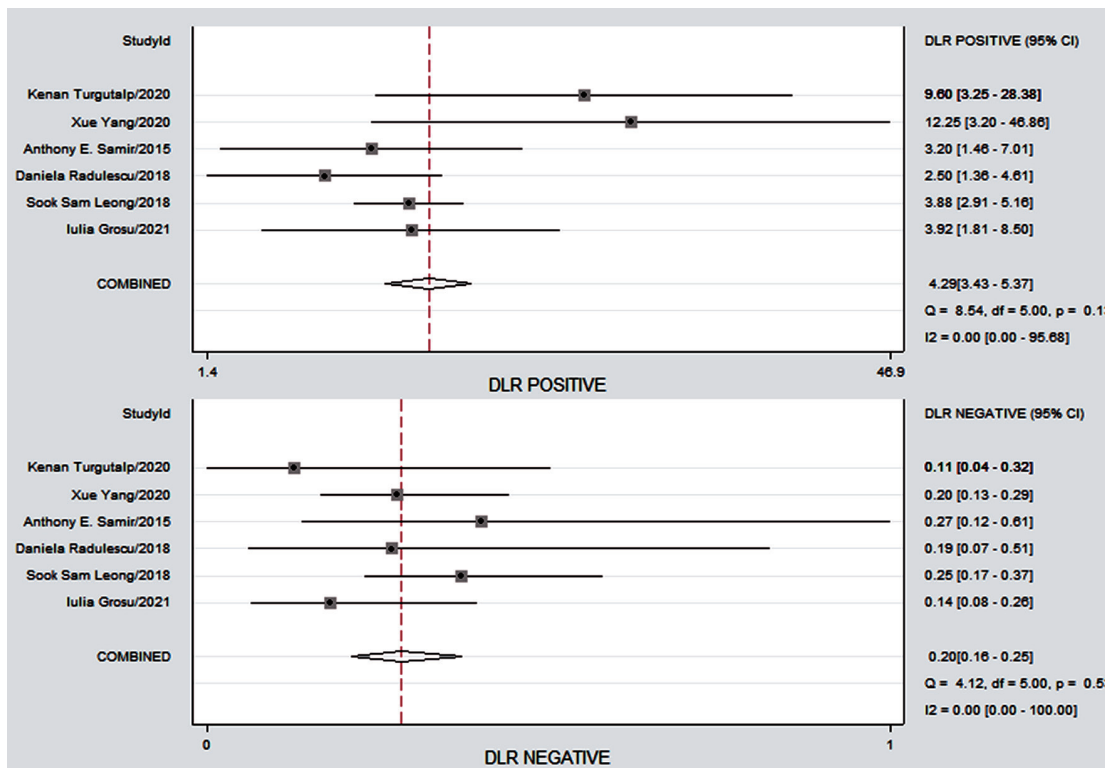


Figure 5. The Forest plots demonstrating the study specificity of SWE on the right y axis in the evaluation of CKD fibrosis. CKD: chronic kidney disease; SWE: shear wave elastography; CI: confidence interval; DLR: digital light radiography.

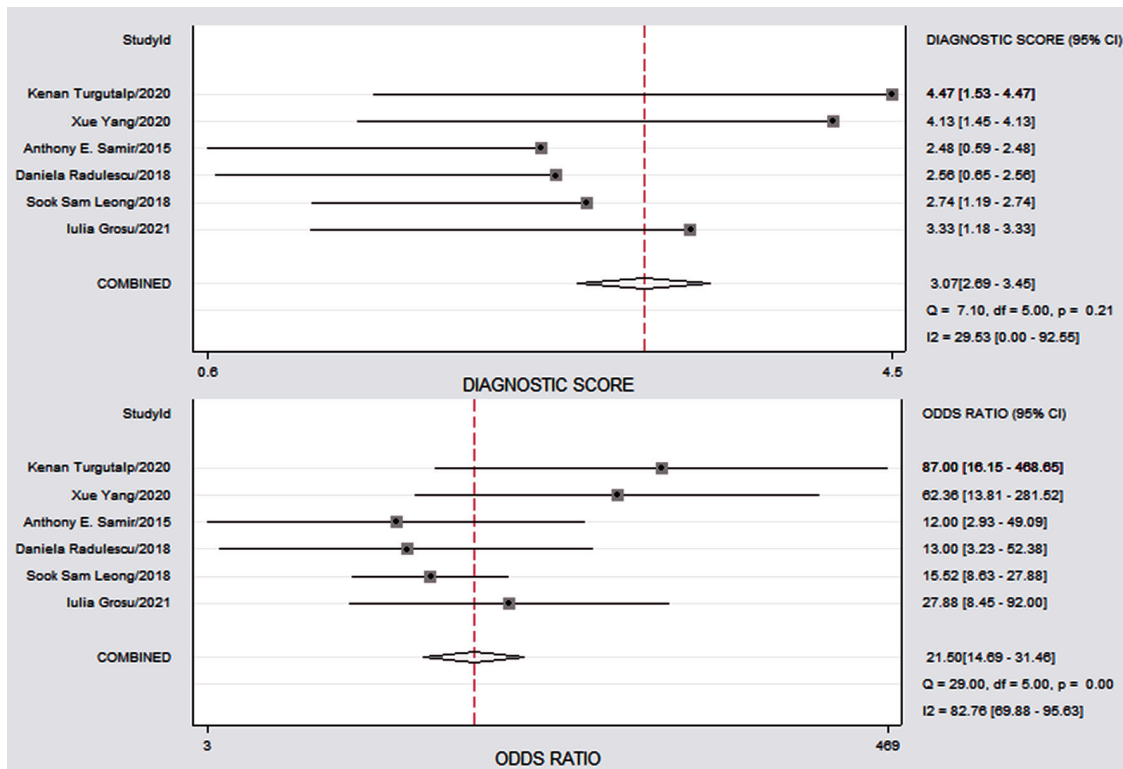


Figure 6. The Forest map plot designed to demonstrate study-specific CKD of SWE on the right y axis in assessment. CKD: chronic kidney disease; SWE: shear wave elastography; CI: confidence interval.

the disease [25-27]. The histological examination of kidney biopsy specimens is currently the only clinical histological evaluation method for renal fibrosis. Invasiveness is associated with specific risks of surgery and the risk of sampling errors [20]. The detection mainly relies on biomarkers in medical practice. SWE generates shear waves through sensors and measures tissue stiffness noninvasively. Existing human and animal studies have shown a correlation between the SWE estimation of renal YM and the presence of CKD or fibrosis [20, 28, 29].

With the development of noninvasive quantitative technology and the rapid development of diagnostic techniques in the field of liver fibrosis, renal elastography technology has become available. As the incidence of CKD increases, the application of elastography may be of critical value in the assessment of tissue stiffness. This study has collected the domestic and foreign researches on the diagnosis of CKD by SWE technology. When extracting data, we collected according to uniform standards the literature that involves and summarizes the same quantitative parameters. The analysis of the diagnostic value of SWE summarizes in the diagnosis of CKD with fibrosis, and provides strong evidence for SWE in the study of CKD with renal stiffness in the future.

Meta-analyses showed that in six studies, SWE imaging techniques assessed the sensitivity and specificity of tissue stiffness in 80.0-89.2% and 65.0-93.3%. The efficacy of SWE imaging technology in assessing tissue stiffness is judged from a single study. It is not easy. The sensitivity and specificity by meta-analysis are 84% (95% CI: 80-87%) and 80% (95% CI:

76-84%). The DOR is 21.50 (95% CI: 14.69 - 31.46) and the SROC curve is 89% (95% CI: 86-92%), indicating that the application of elastography technology has a higher value in the evaluation of chronic kidney fibers. The results of Leong et al [18] show that YM measurements are significantly correlated with estimated glomerular filtration rate (eGFR), serum creatinine and urea, which is consistent with our results. SWE can achieve equivalent S-SEN and S-SPE, which shows that SWE is a truly valuable imaging method for evaluating renal fibrosis. Mehmet Sami et al [30] use SWE to evaluate the fibrosis of CKD in a study, and the results shows a highly correlation with the elasticity measurement of fibrosis patients in renal biopsy (P = 0.046). Likelihood ratio (LR) is a comprehensive indicator that reflects the diagnostic value of diagnostic experiments [31, 32]. In our study, PLR-P is 4.29 (95% CI: 3.43 - 5.37) and PLR-N is 0.20 (95% CI: 0.16 - 0.25), providing “strong” diagnostic evidence. In this study, it is found that the AUC of chronic renal fibrosis exceeds 89%, indicating that SWE can accurately assess different causes of renal fibrosis and has highly diagnostic performance.

The SWE cannot accurately and quantitatively assess renal fibrosis, which will lead to an increase in P-SEN and a decrease in P-SPE. The results are consistent with the study of Sia et al [33]. A large number of published research results [34-36] show that kidney stiffness of the estimated value seems to increase with increasing in the CKD stage. The strong correlation with histological markers of fibrosis indicates that the observed difference is due to renal parenchymal stiffness. In the meta-analy-

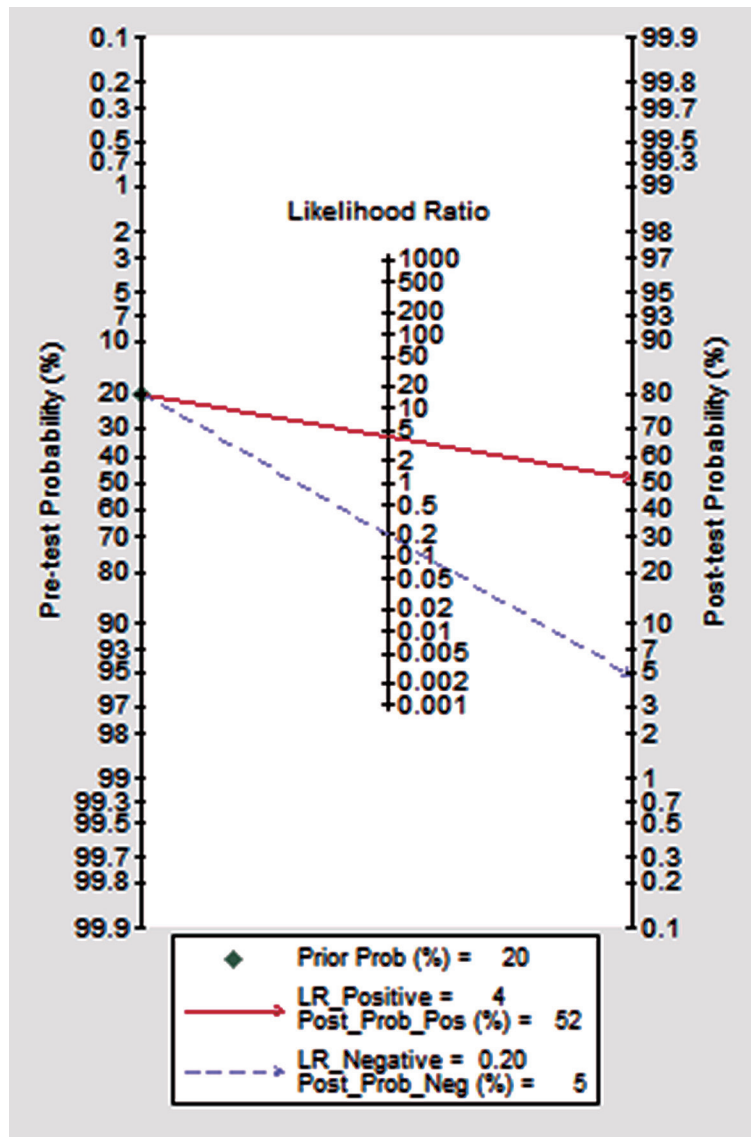


Figure 7. The SROC curve: midas tp fp fn tn, es (x) plot SROC2 graph. SROC: summary receiver operating characteristic curve; LR: likelihood ratio.

sis, studies with low sample sizes are included and no subgroup analysis is performed. Therefore, extensive analysis and multiple subgroup analysis are needed to assess the diagnostic value of SWE in the diagnosis of CKD fibrosis in future studies.

The meta-analysis with the P-SEN ($I^2 = 0.00\%$) and P-SPE ($I^2 = 44.367\%$) of the forest plot 95% CI shows a moderate degree of heterogeneity. The main reason is maybe due to the different staging and grouping study design and patient characteristics of CKD. Secondly, it is related to the threshold of each individual study. There are multiple confounding factors in the study object.

Limitations of this study include: 1) Shear modulus is a new imaging technique for evaluating tissue stiffness, and the stiffness measurement of the kidney is affected by factors such as anisotropy and blood perfusion rate; 2) In some research projects, CKD patients had not clinically undergone renal bi-

opsy, and the stage of CKD was not accurately determined; 3) There are differences between the two investigators in the evaluation of renal stiffness, as well as the ultrasound equipment used in the literature. Different manufacturers and models may cause large differences in the measured values. However, due to the limited sample size of the included literature, it is impossible to conduct the subgroup analysis based on the sources of heterogeneity in this aspect of the data; 4) We also use known imperfect eGFR reference standards to estimate the severity of CKD. There are no kidney biopsy data available to quantify the histological fibrosis.

In short, this study shows that SWE has a highly performance in evaluating the hardness of CKD, especially when using a higher shear modulus threshold, which can provide a reference for clinical judgment and has a great application prospect. Nonetheless, this result still needs to be approved.

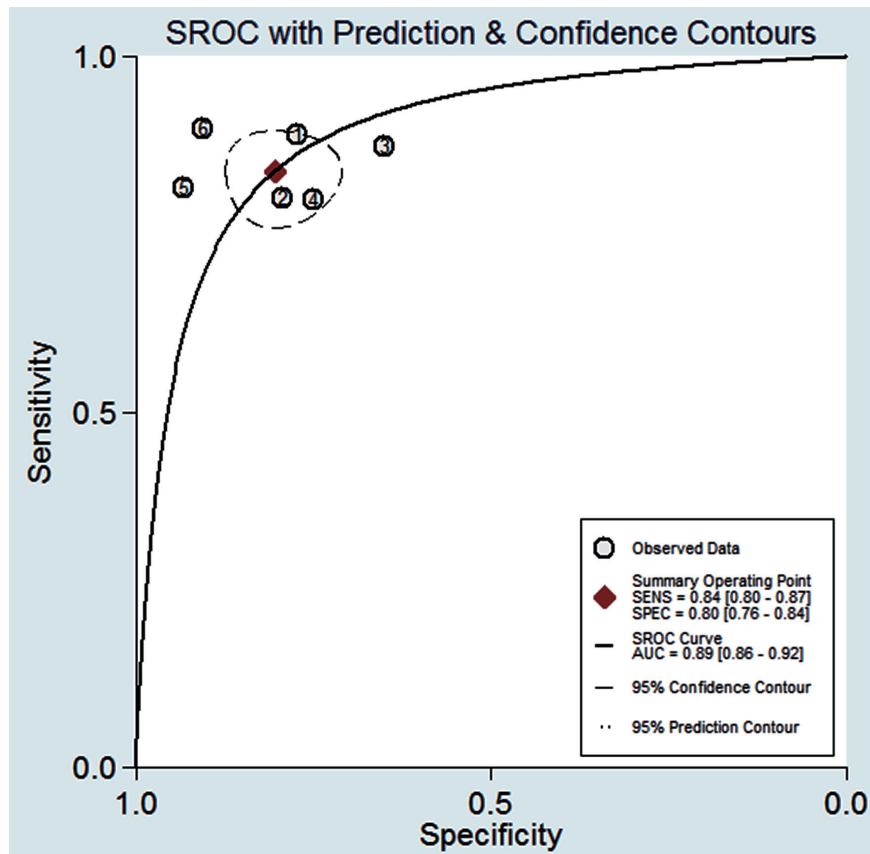


Figure 8. The Fagan's nomogram for SWE illustrating post-test probability with a fixed pre-test probability of 20% for CKD. CKD: chronic kidney disease; SWE: shear wave elastography; SEN: sensitivity; SPE: specificity.

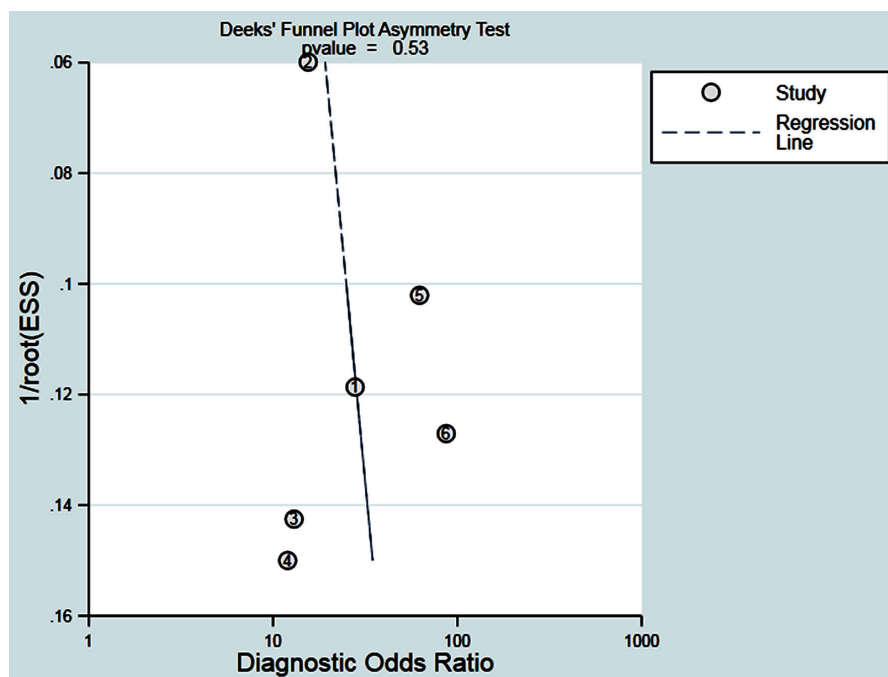


Figure 9. The Deeks funnel plot is a bias-odd detection of the published results, all distributed on both sides of the regression lines, indicating that no significant deviations were found.

Larger multi-center studies and longitudinal follow-up are needed to conduct a more comprehensive evaluation to assess the development of CKD more accurately.

Conclusions

The meta-analysis shows that SWE is accurate in diagnosing renal fibrosis. However, as mentioned above, due to the various causes of renal fibrosis, different renal stiffness may be produced. Therefore, the diagnostic critical threshold needs to be adjusted under the specific case. The institute involves a limited number of researches, and it is necessary to further study the relationship between the tissue elasticity and the severity of renal fibrosis.

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Financial Disclosure

None to declare.

Conflict of Interest

The authors disclose no conflict of interest.

Informed Consent

Informed consent was waived in this manuscript.

Author Contributions

Xian Ling Mo (chief physician) and Hui Yan Meng (deputy chief physician) independently screened according to the standard that can analyze the diagnostic ratio than literature, had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design, acquisition, analysis, or interpretation of data: Xian Ling Mo, Hui Yan Meng, Yan Yan Wu, Xue Yan Wei, Zong Ke Li, and Su Qin Yang. Drafting of the manuscript: Xian Ling Mo. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Xian Ling Mo. Administrative, technical, or material support: Xian Ling Mo and Hui Yan Meng. Supervision: Xian Ling Mo.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

CKD: chronic kidney disease; SWE: shear wave elastography; S-SEN: summary sensitivity; S-SPE: summary specificity; DLR: digital light radiography; DLR-P: DLR positive; DLR-N: DLR negative; PLR-P: positive likelihood ratio; PLR-N: negative likelihood ratio; DOR: diagnostic odds ratio; SROC: summary receiver operating characteristic curve; AUC: area under the curve; INS: idiopathic nephrotic syndrome; IgAN: immunoglobulin A nephropathy; SWV: shear wave velocity; kPa: kilopascals; YM: Young's modulus; QUADAS: Quality Assessment of Diagnostic Accuracy Studies; eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate; LR: likelihood ratio

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