Comparison of Two-Dimensional Shear Wave Elastography and Point Shear Wave Elastography for Assessing Liver Fibrosis

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Research article

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Abstract

Background: Progressive liver fibrosis may result in cirrhosis, portal hypertension, and hepatocellular carcinoma (HCC). We performed a meta-analysis to compare liver fibrosis staging in chronic liver disease patients using two-dimensional shear wave elastography (2D-SWE) and point shear wave elastography (pSWE).

Methods: PubMed, Web of Science, and Cochrane Library databases were searched until September 30th 2019 for studies evaluating the diagnostic performance of 2D-SWE and pSWE for assessing liver fibrosis. Pooled sensitivity, specificity, positive and negative likelihood ratios, diagnostic odds ratios, and area under receiver operating characteristic curve (AUC) were estimated using the bivariate random effects model.

Results: Eighteen studies with 3,082 patients were included in the analysis. The pooled sensitivities of 2D-SWE and pSWE were significantly different for the detection of significant fibrosis (0.83 vs. 0.70, $P < 0.001$) and advanced fibrosis (0.89 vs. 0.78, $P < 0.05$), but not for detection of cirrhosis (0.87 vs. 0.83, $P > 0.05$). The pooled specificities of 2D-SWE and pSWE were not significantly different for detection of significant fibrosis (0.83 vs. 0.83, $P > 0.05$), advanced fibrosis (0.80 vs. 0.85, $P > 0.05$), or cirrhosis (0.84 vs. 0.88, $P > 0.05$).

Conclusions: Both 2D-SWE and pSWE have high sensitivity and specificity for detecting each stage of liver fibrosis. 2D-SWE has higher sensitivity than pSWE for detection of significant fibrosis and advanced fibrosis. Large-scale and multi-center studies are needed to directly compare 2D-SWE and pSWE.

Background

Liver fibrosis is an injury-healing response that is characterized by excess extracellular matrix accumulation. Without intervention, fibrosis can develop into cirrhosis, and in some cases eventually progress to hepatocellular carcinoma (HCC) [1]. Thus, it is important to detect fibrosis as early as possible. The main causes of liver fibrosis include viral hepatitis, chronic alcohol abuse, and drug abuse [2]. Liver biopsy is the gold standard for diagnosis of liver fibrosis; however, drawbacks include its invasiveness, sampling error, and risks of hemorrhage and infection. Consequently, a large amount of research is devoted to developing noninvasive methods for diagnosing and staging liver fibrosis.

Various methods of elastography have been developed and examined for assessing liver fibrosis. Transient elastography, a general method of elastography, has been proposed for assessment of liver fibrosis [3]. The technique measures liver stiffness using a dedicated device, that includes an amplitude modulation mode for organ localization [4].

Point shear wave elastography (pSWE) uses a regular ultrasonic probe to emit a single pulse of acoustic radiation to generate a shear wave, and then detects the shear wave propagation velocity [4]. Study has indicated that pSWE is quite accurate for measuring liver stiffness, and the method is widely used

clinically [5]. Two-dimensional shear wave elastography (2D-SWE) is a relatively new method for assessing liver fibrosis. 2D-SWE measures the velocity of elastic shear waves, and estimates the stiffness of a region of interest based on a Doppler-like effect, which is related to the elasticity of the tissue [4].

Many studies have indicated that 2D-SWE and pSWE are superior to transient elastography for measuring liver stiffness and fibrosis [6–10]. 2D-SWE produces image mapping at various locations within a user-selected region of interest (ROI), while pSWE produces a point measurement centered in a small ROI; thus, 2D-SWE has a larger ROI than that of pSWE[4]. This difference suggests that 2D-SWE might outperform pSWE. It also has been reported that pSWE is inaccurate in the detection of early and intermediate fibrosis [11, 12]. Based on current studies, it is not clear is one method is superior to the other for assessing liver fibrosis.

Thus, the purpose of this study was to perform a meta-analysis comparing 2D-SWE with pSWE for assessing liver fibrosis.

Methods

Study Design and Search Strategy

PubMed, Web of Science, and Cochrane Library databases were searched until September 30th 2019 for studies evaluating the diagnostic performance of 2D-SWE and pSWE for assessing liver fibrosis. The search terms included “two-dimensional shear wave elastography” OR " 2-D shear wave elastography” OR “2D-SWE” OR “elasticity imaging techniques” OR “acoustic radiation force impulse imaging” OR “point shear wave elastography” OR “ARFI” OR “pSWE” AND “liver fibrosis” OR “cirrhosis”.

Inclusion and Exclusion Criteria

Criteria for inclusion in the meta-analysis were: 1) Study examined the diagnostic performance of 2D-SWE or pSWE for assessing liver fibrosis; 2) Study used the Metavir scoring system as the reference standard; 3) Study provided sensitivity and specificity data, and the number of patients with different fibrosis stages, so that the true positive, false positive, true negative, and false negative rates could be calculated to form 2×2 contingency tables; 4) The study was published in an international journal, and the language was English. Exclusion criteria were 1) The diagnostic value of 2D-SWE or pSWE was not reported; 2) The report had incomplete data, or liver biopsies were not performed; 3) The report was a review or a meta-analysis; 4) The report was an animal study, or involved children (< 18 years of age) [13, 14]. Abstracts, correspondence letters, and author comments were also excluded.

Data Extraction

Two reviewers independently extracted data from the included studies, including the names of the authors, the year of publication, country the study was performed in, etiology of liver fibrosis, number of patients, patient age and sex, and reported sensitivity, specificity, and area under the receiver operating characteristic curve (AUC). F ≥ 2 represented significant fibrosis, F ≥ 3 represented advanced fibrosis, and F = 4 represented cirrhosis.

Study Quality Assessment

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS–2) tool [15] was used to evaluate the quality and risk of bias of the included studies.

Statistical Analysis

We constructed 2×2 contingency tables according to the classification of F ≥ 2, F ≥ 3 and F = 4. The primary analysis was the diagnostic accuracy of 2D-SWE and pSWE for detecting significant fibrosis (F ≥ 2), and the secondary analysis was the diagnostic accuracy of 2D-SWE and pSWE for detecting advanced fibrosis (F ≥ 3) and cirrhosis (F = 4).

Pooled sensitivity, specificity, positive and negative likelihood ratios (PLR, NLR), diagnostic odds ratios (DORs), and AUC were calculated using the bivariate random effects model. Heterogeneity among the included studies was assessed with I^2 statistic for each of the pooled estimates [16], and judged to be substantial if I^2 was > 50% [17]. To investigate the causes of heterogeneity, threshold effects and subgroup analyses were done. Threshold effects were explored by examining the linear correlation between the sensitivity and false-positive rate (Spearman's correlation coefficient), and were considered substantial if the value was > 0.6 [18]. Subgroup analysis, using a random effects model, could account for heterogeneity. Publication bias was assessed using Deeks' funnel plot asymmetry test, and a value of P < 0.10 indicated significant small-study bias[19]. Statistical analysis was performed using Stata 12.0.

Results

Literature Search

A total of 2,537 articles were identified from the database searches, and 2,478 articles were excluded because they did not investigate 2D-SWE or pSWE, were reviews, no full text were available, or they were pediatric or animal studies. Another 41 articles were excluded because the data included was not sufficient construct 2×2 contingency tables or Metavir scores were not reported. Finally, 8 studies that examined 2D-SWE [9, 20–26] and 10 studies that examined pSWE [27–36] were included in the meta-analysis. A flow diagram of study selection is shown in Figure 1.

Characteristics of the Included Studies

The 8 2D-SWE studies included a total of 1,435 patients, and the 10 pSWE studies included a total of 1,647 patients. The general characteristics of the included studies are presented in Table 1 and Table 2, and the results of the study quality assessment are shown in Figure 2.

Diagnostic Accuracy

Primary analysis

Eight and night set of data respectively were included for detection of significant fibrosis ($F \geq 2$) with 2D-SWE and pSWE. The pooled sensitivity, specificity, PLR, NLR, and DOR of 2D-SWE for detecting significant fibrosis were 0.83 (95% confidence interval [CI]: 0.79, 0.86), 0.83 (95% CI: 0.79, 0.87), 5.0 (95% CI: 4.1, 6.1), 0.20 (95% CI: 0.17,0.25), and 24 (95% CI: 18, 32), respectively (Table 3, Figure 3A). The pooled sensitivity, specificity, PLR, NLR, and DOR of pSWE for detecting significant fibrosis were 0.70 (95% CI: 0.66, 0.73), 0.83 (95% CI: 0.76, 0.89), 4.2 (95% CI: 2.9, 6.2), 0.36 (95% CI: 0.33, 0.41), and 12 (95% CI: 7, 18), respectively (Table 3, Figure 3B).

There was a significant difference in the pooled sensitivity of 2D-SWE and pSWE (0.83 vs. 0.70, $P < 0.001$), but no difference in the pooled specificity (0.83 vs. 0.83, $P > 0.05$). The AUC was 0.90 for 2D-SWE, and was 0.75 for pSWE (Table 3).

Secondary analysis

There was a significant difference in the pooled sensitivity of 2D-SWE and pSWE for detection of advanced fibrosis (0.89 vs. 0.78, $P < 0.05$), but no difference in the pooled specificity (0.80 vs. 0.85, $P > 0.05$). In addition, there were no differences in the pooled sensitivity or specificity of 2D-SWE and pSWE for detection of cirrhosis. The AUCs of 2D-SWE and pSWE for the diagnosis of advanced fibrosis were 0.89 and 0.87, respectively, and for the diagnosis of cirrhosis were 0.92 and 0.85, respectively, (Table 3).

Assessment of Heterogeneity

In the primary analysis, pSWE exhibited significant heterogeneity for specificity ($I^2 > 50\%$), but not for sensitivity ($I^2 < 50\%$), while there was no significant heterogeneity of 2D-SWE with respect to sensitivity ($I^2 < 50\%$) or specificity ($I^2 < 50\%$).

Diagnostic Threshold Effects

In the primary analysis, theSpearman's correlation coefficient for 2D-SWE and pSWE were calculated to be 0.286 (P = 0.493) and 0.350 (P = 0.356), respectively, which indicated no substantial threshold effect.

Subgroup Analysis

For 2D-SWE, the sensitivity was significantly higher in studies not specific to a viral infection etiology as compared to studies that only included patients with a viral etiology of the fibrosis (0.84 vs. 0.83, respectively, P < 0.05), in studies with patients < 50 years old compared to those with patients > 50 years old (0.83 vs. 0.82, respectively, P <0.05), and in studies with more males compared to those with fewer males (0.83 vs. 0.82, respectively, P < 0.05). For pSWE, the sensitivity was significantly higher in studies from Western countries compared to Asian countries (0.72 vs. 0.69, respectively, P <0.05), in studies not specific to a viral infection etiology as compared to studies that only included patients with a viral etiology of the fibrosis (0.74 vs. 0.69, respectively, P <0.05), in studies with patients < 50 years old compared to those with patients > 50 years old (0.74 vs. 0.68, respectively, P < 0.05) and in studies with more males compared to those with fewer males (0.71 vs. 0.70, respectively, P < 0.05) (Table 4).

Assessment of Publication Bias

In the primary analysis, low likelihoods of publication bias for 2D-SWE (P = 0.76) and pSWE (P = 0.13) were observed, based on funnel plot asymmetry tests (Figure 4A and 4B). In the secondary analysis, low likelihoods of publication bias were observed for 2D-SWE (P = 0.54) and pSWE (P = 0.22) for the diagnosis of advanced fibrosis (Figure 4C and 4D). High likelihoods of publication bias were observed for 2D-SWE (P = 0.01) and pSWE (P = 0.10) for the diagnosis of cirrhosis (Figure 4E and 4F).

Discussion

Progressive liver fibrosis can lead to cirrhosis, portal hypertension, and HCC. Early detection of fibrosis is critical to prevent or delay the development of chronic liver disease. Significant fibrosis (F≥2) is typically considered a hallmark of the progressive form of liver disease [37]. Diagnosis of advanced fibrosis (F ≥ 3) or cirrhosis (F = 4) is also essential because these patients should be screened for portal hypertension and HCC [38]. Many previous studies have shown that 2D-SWE and pSWE are superior to general elastography6–10]. However, there are a lack of directly comparisons of 2D-SWE and pSWE for assessing different stages of liver fibrosis. A recent study reported that 2D-SWE is comparable to pSWE in cirrhotic patients [39].

Our results showed that both 2D-SWE and pSWE had high sensitivity and specificity for detecting all stages of liver fibrosis. We also found that both 2D-SWE and pSWE exhibited excellent diagnostic performance, AUC values of 0.75–0.92. However, our results indicated that 2D-SWE has higher sensitivity than pSWE for detection of significant fibrosis and advanced fibrosis.

In a subgroup analysis of 2D-SWE, the method was found to have significantly higher sensitivity in studies in which the etiology was not specific to a viral infection, in those with patients < 50 years old, and in those with more males. In a subgroup analysis of pSWE, the method was found to have significantly higher sensitivity in studies from Western countries, studies in which the etiology was not specific to a viral infection, in those with patients < 50 years old, and in those with fewer males. This result suggests that both 2D-SWE and pSWE have higher sensitivity for the detection of significant fibrosis when the etiology is not limited to viral infection and when patients are < 50 years old.

This study has some limitations. The main limitation is that there were no studies that directly compared 2D-SWE and pSWE, which leads to very different cut-off values. In addition, the number of the included studies was limited. Furthermore, most of the included studies were from Asian countries. Thus, large-scale, well-designed, and multi-center studies that directly compare 2D-SWE and pSWE are needed to give more accurate results.

Conclusions

Our results indicate that both 2D-SWE and pSWE exhibit high sensitivity and specificity for detecting each stage of liver fibrosis, and 2D-SWE has higher sensitivity than pSWE for detection of significant fibrosis and advanced fibrosis. Large-scale, well-designed, and multi-center studies are needed to directly compare 2D-SWE and pSWE.

Abbreviations

2D-SWE: two-dimensional shear wave elastography; pSWE: point shear wave elastography; AUC: area under receiver operating characteristic curve; PLR: positive likelihood ratios; NLR: negative likelihood ratios; DORs: diagnostic odds ratios; F≥2: significant fibrosis; F≥3: advanced fibrosis; F = 4: cirrhosis

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the correspondingauthor on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Research concept and design: XZ and YM;

Assessment of quality and collection of data: XZ;

Data analysis: XZ, JR and XW;

Writing original manuscript: XZ and JR;

Critical revision of the article: XZ and RD.

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Tables

Table 1. Characteristics of the included 2D-SWE studies

Authors and year	Country	Etiology	N	Age	Males, %	Cut-off values	SE (□)	SP (□)	AUROC
Jin 2019	China	Chronic hepatitis B	68	58	80.9	F≥2 >10kPa	71.74	86.36	0.86
						F=4 >11.6kPa	68	79.07	0.811
Park 2019	Korea	Chronic hepatitis B	63	50.8± 8.9	58.7	F≥2 >6.7kPa	84.1	68.4	0.843
						F=4 >9.5kPa	77.8	80	0.816
Tamami 2018	Japan	Chronic hepatitis C	233	65.5± 10.7	63.09	F≥2 1.56m/s	85.3	85.5	0.915
						F≥3 1.72m/s	88.8	83.8	0.94
						F=4 1.93m/s	91.4	90.8	0.949
Sanghyeok 2017	Korea	Chronic liver disease*	96	47.6± 15.9	53	F≥2 9.1kPa	81	92	-
						F≥3 9.3kPa	94	73	-
						F=4 11.1kPa	88	69	-
Zeng 2017	China	Autoimmune liver disease	114	45.6	21	F≥2 9.7kPa	81.7	81.3	0.85

						F≥3 13.2kPa	83	74.6	0.85
						F=4 16.3kPa	87	80.2	0.86
Zeng 2017	China	Chronic hepatitis B	257	36.7±9.4	77.4	F≥2 7.1kPa	88.89	76.38	0.882
						F≥3 8.3kPa	89.66	76.84	0.917
						F=4 11.3kPa	93.55	87.25	0.926
Wu 2016	China	Chronic hepatitis B	437	35.8	76.4	F≥2 8.2kPa	78.16	85.28	0.903
						F=4 11.25kPa	91.8	84.31	0.926
Zheng 2015	China	Chronic liver disease#	167	37.49	71.2	F≥2	85.7	73.9	0.86
						F=4	91.2	79.7	0.93

* chronic liver disease: 21 hepatitis B, 22 hepatitis C, 17 alcoholic liver disease, 11 NAFLD, 8 autoimmune liver disease and 17 other liver diseases.

chronic liver disease: hepatitis B, hepatitis C, alcoholic liver disease, autoimmune liver disease, drug-induced liver disease and unclassified liver disease (no exact number).

Table 2. Characteristics of the included pSWE studies

Authors and year	Country	Etiology	N	Age	Males, %	Cut-off values	SE (□)	SP (□)	AUROC
Leong 2019	Malaysia	NAFLD	100	57.1± 10.2	46	F≥2 6.98kPa	75.6	61.0	0.72
						F≥3 7.02kPa	75.8	58.2	0.69
						F=4 11.52kPa	75.0	92.7	0.79
Iranna 2019	India	alcoholic liver disease	50	41± 9.81	100	F=4 1.87m/s	83	76	0.83
Gani 2017	Indonesia	Chronic liver disease*	43	47.37	72.1	F≥2 1.32 m/s	68	80	0.773
						F≥3 1.32 m/s	82	73	0.785
						F=4 1.71 m/s	80	85	0.856
Li 2017	China	Chronic hepatitis B	126	48.3 ±9.3	64.3	F≥2 1.59 m/s	67.57	88.46	0.861
						F≥3 1.74 m/s	87.5	85.11	0.941
						F=4 1.92 m/s	85	92.45	0.945
Liu 2016	China	Chronic	157	34.34	61.15	F≥2	74.5	84.7	0.851

		hepatitis B				1.41 m/s			
						F≥3	75.5	84.7	0.854
						1.57 m/s			
						F=4	90	93.5	0.965
						1.74 m/s			
Lin 2016	China	Chronic liver disease#	60	51.8	67	F≥2	52.8	95.8	0.733
						1.53 m/s			
						F≥3	87.5	97.7	0.957
						1.66 m/s			
						F=4	58.3	90.4	-
						1.98 m/s			
Kiani 2016	France	alcoholic liver disease	82	43.8 ± 10	84.15	F≥2	82.4	83.3	0.87
						1.63 m/s			
						F≥3	82.4	78.5	0.86
						1.84 m/s			
						F=4	92.3	81.6	0.89
						1.94 m/s			
Silva 2014	Brazil	Chronic hepatitis C	51	53.80	35	F≥2	67.9	87	0.82
						0.86 m/s			
						F=4	66.7	92.9	0.89
						1.71 m/s			
Fierbinteanu 2013	Romania	NAFLD	64	49.69	43.75	F≥2	84.8	90.3	0.944
						1.165 m/s			
						F≥3	86.4	95.2	0.982

						1.480 m/s			
						F=4 1.635 m/s	91.7	92.3	0.984
Sporea 2012	Romania	Chronic hepatits C	914	55.7 ±13.1	46.3	F≥2 1.33 m/s	69.1	79.8	0.792
						F≥3 1.43 m/s	74.8	81.5	0.829
						F=4 1.55 m/s	84.3	76.3	0.842

*chronic liver disease: 14 hepatitis B and 29 hepatitis C.

chronic liver disease: 3 hepatitis B, 47 hepatitis C and 10 nonalcoholic steatohepatitis.

Table 3. Meta-analysis results of 2D-SWE and pSWE for diagnose of significant fibrosis, advanced fibrosis and cirrhosis

Fibrosis	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratios	AUROC
2D-SWE						
F ≥2 (significant fibrosis)	0.83 (0.79, 0.86)	0.83 (0.79, 0.87)	5.0 (4.1, 6.1)	0.20 (0.17,0.25)	24 (18, 32)	0.90 (0.87, 0.92)
F≥3 (advanced fibrosis)	0.89 (0.85, 0.92)	0.80 (0.75, 0.84)	4.4 (3.6, 5.5)	0.13 (0.10,0.19)	33 (21, 53)	0.89 (0.86, 0.91)
F=4 (cirrhosis)	0.87 (0.80, 0.92)	0.84 (0.78, 0.88)	5.3 (3.7,7.6)	0.16 (0.10,0.26)	34 (15,74)	0.92 (0.89, 0.94)
pSWE						
F ≥2 (significant fibrosis)	0.70 (0.66, 0.73)	0.83 (0.76, 0.89)	4.2 (2.9, 6.2)	0.36 (0.33,0.41)	12 (7, 18)	0.75 (0.71, 0.79)
F ≥3 (advanced fibrosis)	0.78 (0.74, 0.81)	0.85 (0.78, 0.90)	5.1 (3.5,7.6)	0.26 (0.21,0.32)	20 (11, 35)	0.87 (0.84, 0.92)
F=4 (cirrhosis)	0.83 (0.77, 0.88)	0.88 (0.83, 0.92)	7.2 (5.0, 10.5)	0.19 (0.13,0.26)	39 (22, 68)	0.85 (0.82, 0.88)

Table 4. Sensitivity estimates for each subgroup for detection of significant fibrosis

Subgroup	Pooled sensitivity for 2D-SWE	P value	Pooled sensitivity for pSWE	P value
Country		-		0.02
Asian	-		0.69(0.63, 0.76)	
Western	-		0.72(0.62, 0.82)	
Etiology		<0.001		<0.001
Specified to virus infenction	0.83(0.79, 0.87)		0.69(0.64, 0.73)	
Not specified to virus infeciton	0.84(0.78, 0.89)		0.74(0.66, 0.81)	
Age		<0.001		<0.001
≥50	0.82(0.76, 0.89)		0.68(0.62, 0.74)	
<50	0.83(0.79, 0.88)		0.74(0.68, 0.80)	
Gender		0.02		<0.001
Male≥50%	0.83(0.80, 0.87)		0.70(0.63, 0.76)	
Male<50%	0.82(0.71, 0.92)		0.71(0.65, 0.78)	

Figures

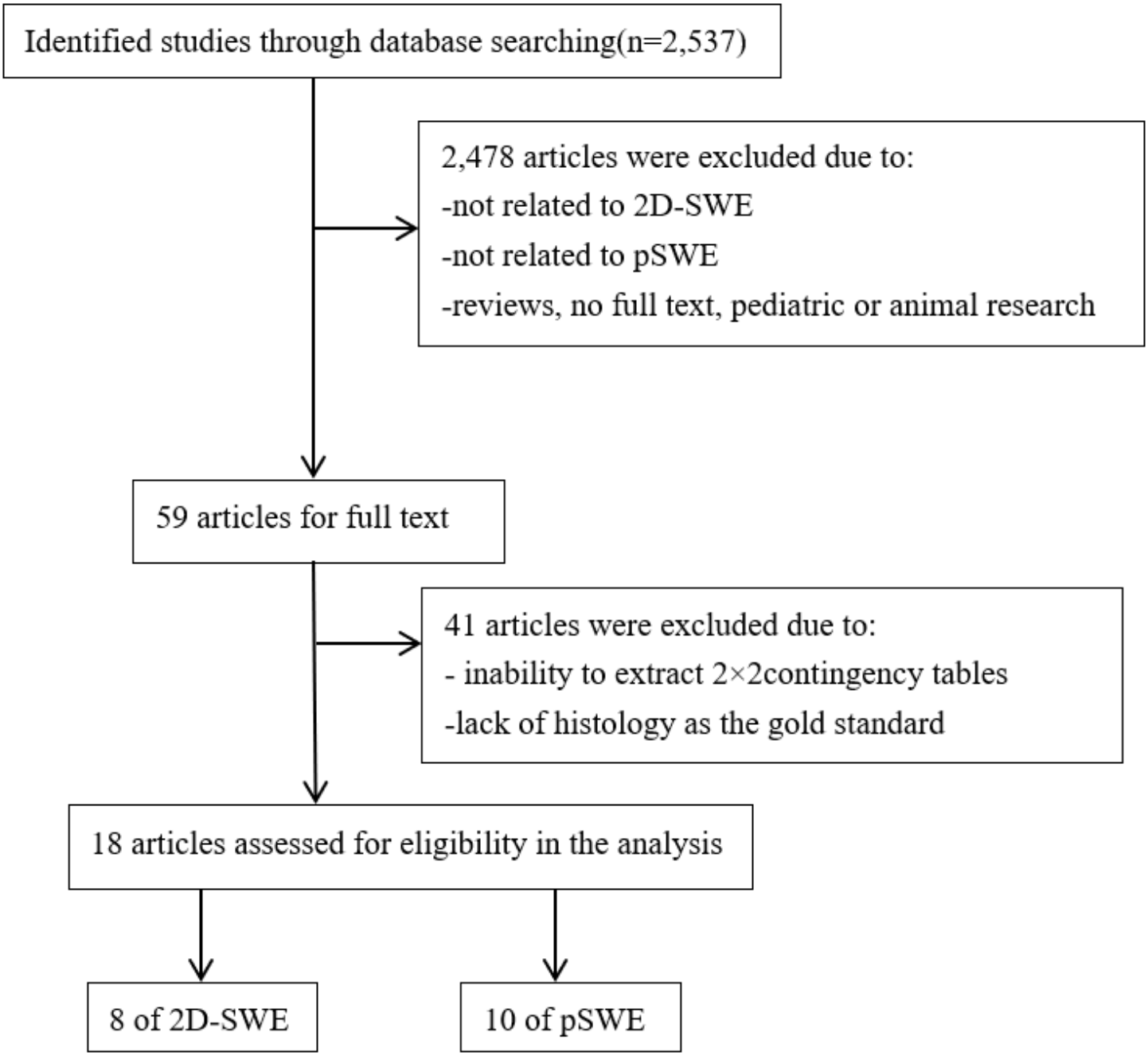

Figure 1

Flow diagram of study selection.

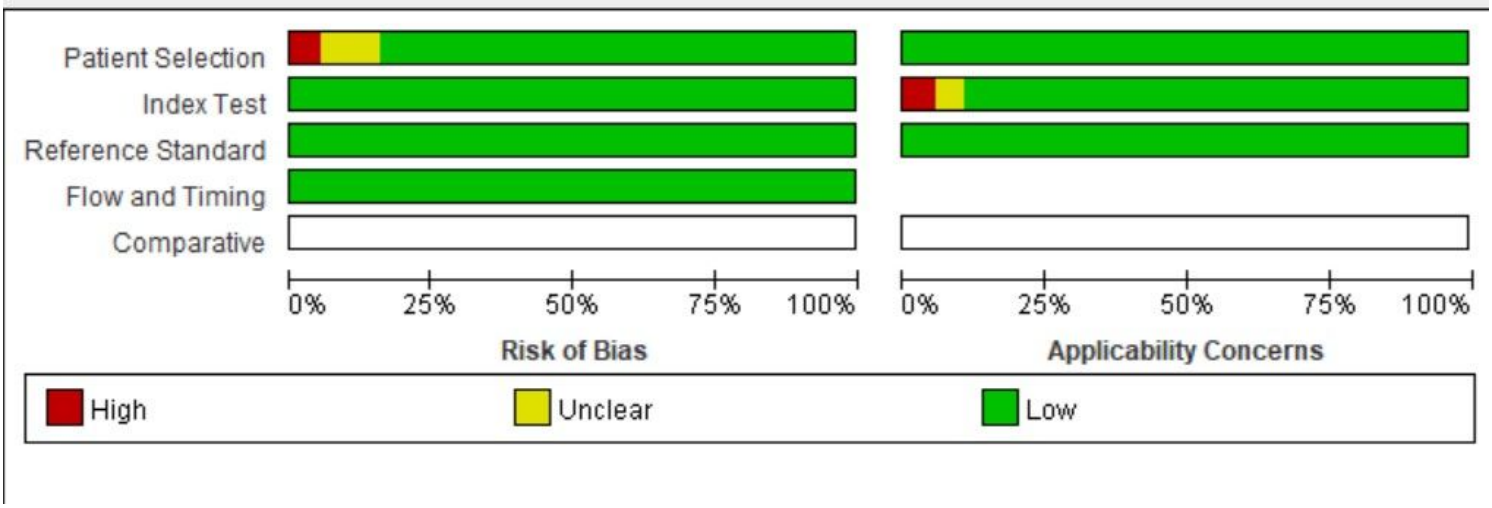

Figure 2

Quality of the included studies according to the revised Quality Assessment for Studies of Diagnostic Accuracy tool (QUADAS-2).

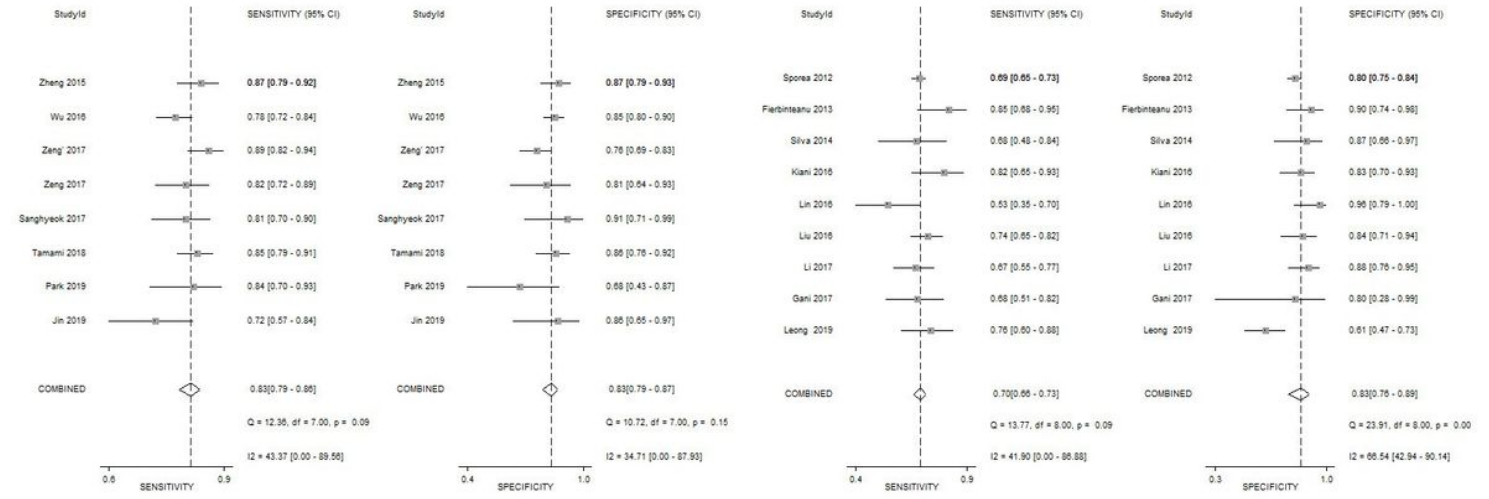

Figure 3

Forest plots of sensitivity and specificity for the detection of significant fibrosis (F ≥ 2) with A) 2D-SWE and B) pSWE.

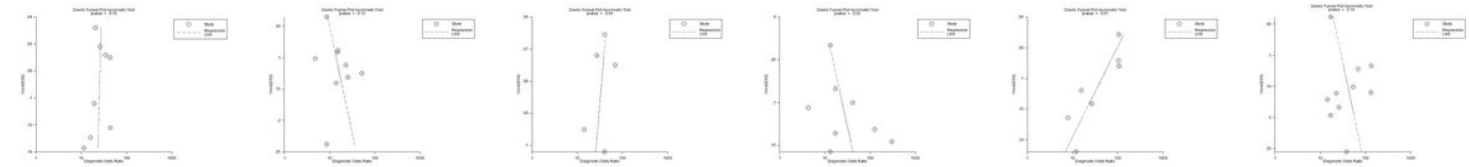

Figure 4

Funnel plots for 2D-SWE and pSWE.

Supplementary Files

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- PRISMAchecklist.doc