

Diagnostic Accuracy of Transient Elastography for Staging Liver Fibrosis in Autoimmune Hepatitis: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: As a non-invasive method, transient elastography (TE) has been used for staging fibrosis in many different liver diseases. However, in the stage of autoimmune hepatitis (AIH) fibrosis, the diagnostic criteria for transient elastography has not been established.

Aim: This study used summary receiver operating characteristics (SROC) to assess transient elastography for diagnosing and stage liver fibrosis in patients with autoimmune hepatitis.

Methods: Electronic databases and conference abstracts were searched, and studies were identified to evaluate the diagnostic accuracy of TE in AIH patients for staging fibrosis $F \geq 2$, $F \geq 3$ and $F = 4$ with liver biopsy as a reference standard. The SROC curve and the bivariate models were performed to evaluate the diagnostic accuracy of TE. Methodological quality was assessed with Quality Assessment of Diagnostic Accuracy Studies 2 tools.

Results: Seven studies with a total of 469 patients were enrolled in the meta-analysis. The summary sensitivity of transient elastography for staging fibrosis $F \geq 2$, $F \geq 3$ and $F = 4$ were 0.83 (95% CI, 0.75–0.88), 0.81 (95% CI, 0.72–0.88) and 0.88 (95% CI, 0.79–0.93), respectively, and the summary specificity were 0.84(95% CI, 0.76–0.90), 0.90 (95% CI, 0.79–0.95) and 0.94 (95% CI, 0.86–0.97), respectively.

Conclusions: TE performs well to diagnose liver fibrosis in AIH patients.

Keywords: Transient Elastography, Autoimmune Hepatitis, Liver Fibrosis.

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INTRODUCTION

Autoimmune hepatitis (AIH) is an unsolved progressive inflammatory liver disease, characterized by hypergammaglobulinemia, circulating autoantibodies, and lymphoplasmocytic infiltration with interface hepatitis. This disease may begin with acute hepatitis and may be expected to result in liver cirrhosis, liver cancer, liver failure even or death[1]. Treatment with corticosteroids

alone or in combination with other immunosuppressive agents is effective and early diagnosis can result in near-normal life expectancy. Untreated patients, can make progress towards cirrhosis and liver failure[2]. However, about one-third of patients have developed severe fibrosis and cirrhosis at the time of diagnosis.[3] Therefore, it is of importance to discriminate liver fibrosis and cirrhosis in AIH patients.

Liver biopsy has traditionally been considered as the gold standard for the evaluation of liver fibrosis stage. Nevertheless, liver biopsy has many unavoidable shortcomings, such as the risk of complications, sampling error and inter-observer variability, most importantly, as an invasive method, liver biopsy is unfeasible in clinical practice for the purpose of regular dynamic monitoring liver fibrosis stage [4]. Consequently, it is necessary to establish an accurate non-invasive diagnostic method to rate AIH progression.

Several non-invasive methods for discriminating liver fibrosis and cirrhosis have been applied in clinical practice, aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis index based on four factors (FIB-4) were used to predict fibrosis stage in chronic liver disease [5]. However, the reliability of these methods to detect stages of liver fibrosis and cirrhosis in AIH patients is still uncertain. Biochemical markers can reflect the treatment effect, but they cannot apply to diagnosis fibrosis stage in liver disease[6].

Transient elastography (TE, Fibroscan; Echosens, Paris, France) is a new non-invasive diagnostic method developed in the last decade to assess liver stiffness [7]. Numerous studies have evaluated the diagnostic accuracy of this technology in many different liver diseases[8]. While several meta-analyses have previously been conducted in patients with viral hepatitis, meta-analyses performed in AIH patients were rarely reported. In the present study, we utilized SROC model to assess the diagnostic accuracy of TE for staging liver fibrosis in AIH patients with liver biopsy as a reference standard.

METHODS

Literature Search Strategy

A systematic literature search was conducted by two independent authors to evaluate the performance of TE for the diagnosis of liver fibrosis in autoimmune hepatitis. Since the first clinical data of TE were published in 2003, electronic databases PubMed Embase and Cochrane library were searched from January 2003 to August 2019. Chinese databases Wanfang Data was also searched from January 2003 to August 2019. Articles in English or Chinese were included in this study. The search strategy was performed with the following form: 1. Autoimmune hepatitis or autoimmune liver disease or AIH; 2. Fibroscan or Transient Elastography; 3. 1 and 2.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: (1) studies evaluated the performance of TE for the staging of liver fibrosis in AIH; (2) AIH patients were enrolled

in the study; if the primary study enrolled patients with different liver diseases, data for AIH patients were reported separately; (3) liver biopsy was performed as the reference standard for staging fibrosis according to METAVIR or other pathological systems that can be transformed to METAVIR; (4) the number of cases ≥ 30 ; (5) necessary data were provided to calculate the true-positive, false-positive, true-negative, and false-negative results for fibrosis stage $F \geq 2$, $F \geq 3$ or $F = 4$; Exclusion criteria were as follows: (1) animal studies; (2) duplicate publications; and (3) reviews, letters, and editorials.

Data Extraction

The following data were extracted from the included studies: first author, year of publication, country or region of origin, sample size, the grouping of patients, epidemiological and laboratory characteristics, cutoff stage used, true-positive, false-positive, true-negative, and false-negative results from TE for staging fibrosis, and methodological quality. If individual studies without sufficient data for meta-analysis, we sent emails to the authors for more details. In the case of non-response from the authors after two emails, the studies were excluded.

Assessment of Methodological Quality

Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess the quality of the included studies. Software Review Manager (version 5.3, The Nordic Cochrane Centre, Copenhagen, Denmark) was used to present the result of QUADAS assessment. Each study's risks of bias and concern for applicability were rated as yes, no, or unclear for each domain[9]. If there was at least one 'no' or 'unclear' response to a question about a given domain, we scored the risk for bias as high or unclear respectively.

Statistical Analysis

The present study calculated the true positive, false positive, true negative and false negative of each study based on the reported sensitivity, specificity, positive predict value and negative predict value. Then we used METAN and MIDAS modules in the STATA statistical software (version 14.0; StataCorp LP, College Station, TX, USA) to perform the meta-analysis. Spearman correlation analysis was used to assess threshold effect between the sensitivity and the specificity. Descriptive statistics were also used to analyze cut-off values.

Publication Bias

MIDAS modules with STATA 14.0 were used to evaluate publication bias. Linear regression of log odds ratios as a test for funnel plot asymmetry was performed and with $P < 0.1$ for the slope coefficient indicating significant asymmetry.

Methods for Heterogeneity

Heterogeneity between studies was evaluated by forest plot and $Q-I^2$ statistic. Forest plots were used to assess the heterogeneity graphically. In $Q-I^2$ statistic, an I^2 value of $> 50\%$ was considered to represent substantial significant heterogeneity.

RESULTS

Study Selection and Description

346 references were yielded through the initial literature search, 237 articles were excluded because of duplication between different databases, 69 articles were excluded by abstracts, 14 articles were excluded by reading full-text, 10 articles had insufficient data for the evaluation of diagnostic accuracy, and we failed to obtain data from the corresponding authors by e-mail, the number of cases <30 in 2 studies, 7 articles were repeated in the same database,

one article was excluded due to use different standard of liver histology assessment, after a detailed review of these articles, 6 full-text articles comprising 7 studies with a total of 469 patients were finally included[10-15], the flow diagram of the study selection process was shown in Figure 1. The characteristics of each study were presented in Table 1, and the data of diagnostic accuracy in original studies were shown in Table 2. The quality of the included studies as evaluated according to the QUADAS-2 criteria were shown in Figure2. One study was considered to have an unclear risk of bias in patient selection because patients with autoimmune hepatitis-primary biliary cholangitis overlap syndrome were included, there were unclear risk of index test and low applicability concerns in all included studies, the quality of studies in other domains was good. Overall, the quality of the evidence was considered to be moderate.

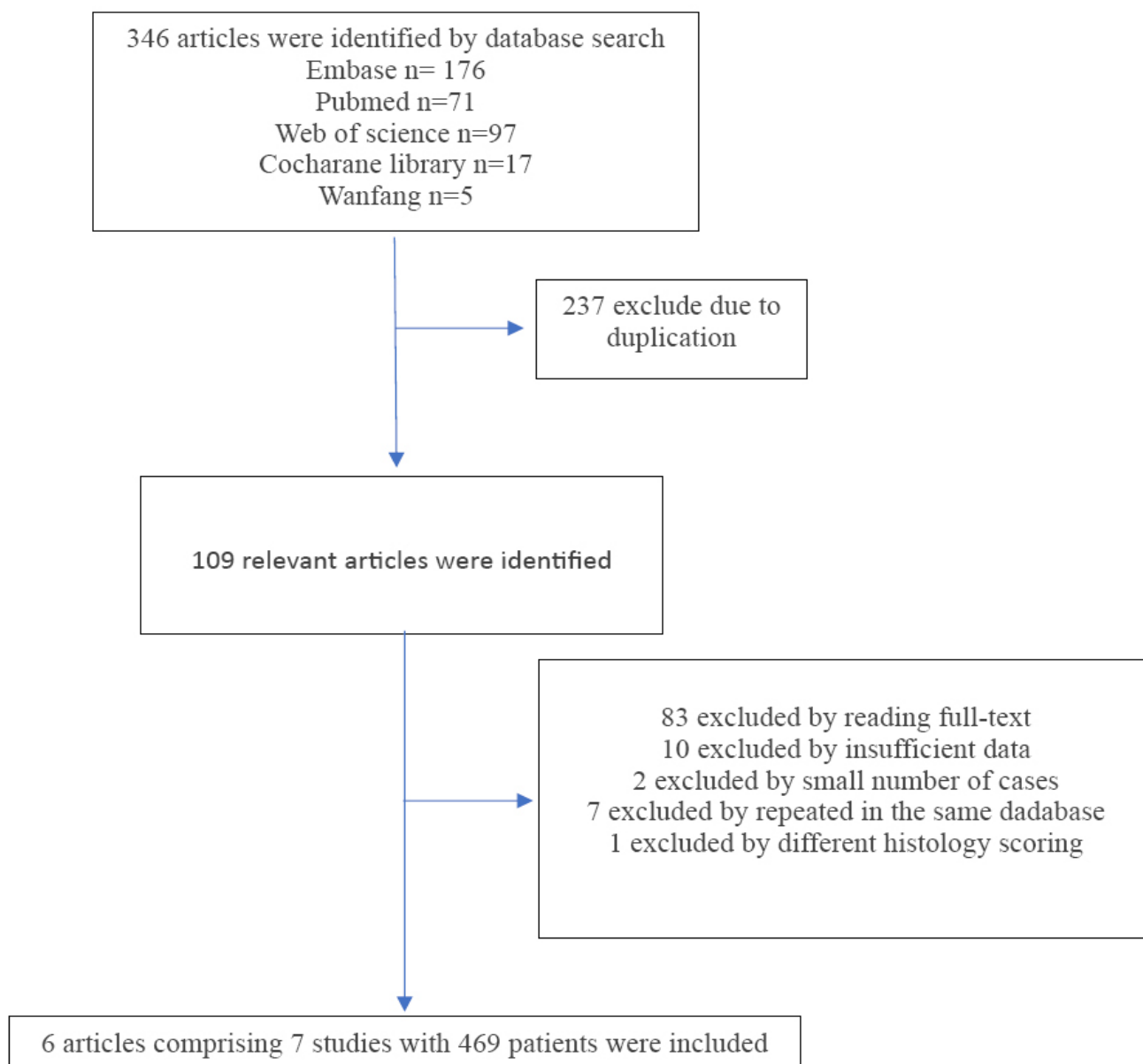


Figure 1. Shows the flow diagram of the study selection

Table 1. Shows the flow diagram of the study selection

Study	Year	County	N	Language	Mean Age (years)	Male (%)	Mean BMI (kg/m ²)	Mean ALT (U/L)	Mean IgG(G/L)	Scoring system	Study Design
Xu	2016	China	100	English	45.0	19.0	NA	131.5	193	Metavir	Prospective
Guo	2017	China	108	English	46.5	195	23.52	146.5	17.1	Metavir	Retrospective
Wu	2018	China	70	English	46.6	15.7	NA	185.6	17.0	Metavir	Retrospective
Anastasiou	2016	Germnay	53	English	47.3	41.5	NA	006.4	18.4	Metavir	Retrospective
Hartl	2016	Germnay	34	English	53.0	180	NA	48.5	13.7	Desmet & Scheuer	Prospective
lart	2016	Germnay	60	English	520	17.0	NA	35.0	12.9	Desmet & Scheuer	Retrospective
Zhou	2018	China	44	Chinese	53.0	13.6	227	86.5	NA	Desmet & Scheuer	Retrospective

BMI Body mass index ALT alanine aminotserferage IgG Immunoglobuline G

Table 2. Data diagnostic accuracy of the studies included in the meta analysis

Study	F \geq 2				F \geq 3				F=4			
	Sen (%)	Spe (%)	Cut-off value(Kpa)	AUROC	Sen (%)	Spe (%)	Cut-off value(Kpa)	AUROC	Sen (%)	Spe (%)	Cut-off value(Kpa)	AUROC
Xu	82.1	87.5	6.45	0.878	80	84	8.75	0.883	87	89.6	12.5	0.914
Guo	84.6	76.7	6.27	0.885	79.6	85.2	8.18	0.897	87.5	88.1	12.67	0.878
Wu	90.2	77.8	6.55	0.837	84.4	92.1	10.5	0.91	100	88.9	14.45	0.966
Anastasiou	61.4	88.9	10.05	0.779	58.6	83.3	12.1	0.739	81.8	92.9	19	0.842
Hartl	82	67	5.8	0.77	73	91	10.4	0.82	83	100	16	0.92
Hartl*	94	75	5.8	0.89	89	100	10.4	0.96	92	100	16	0.97
Zhou	93.9	90.9	NA	0.945	87	90.5	NA	0.941	87.5	91	NA	0.93

Sen, sensitivity, Spe, specificity. AUROC, area under reciever operating chareacteristic curve

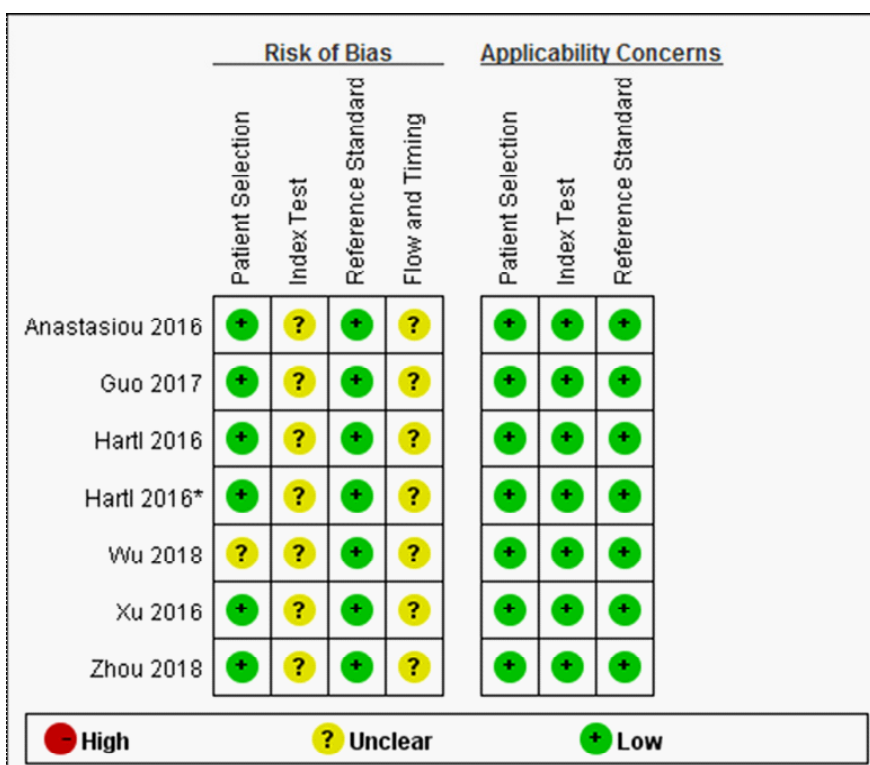


Figure 2. Shows methodological quality summary according to the QUADAS-2

TE for the diagnostic accuracy of liver fibrosis in AIH

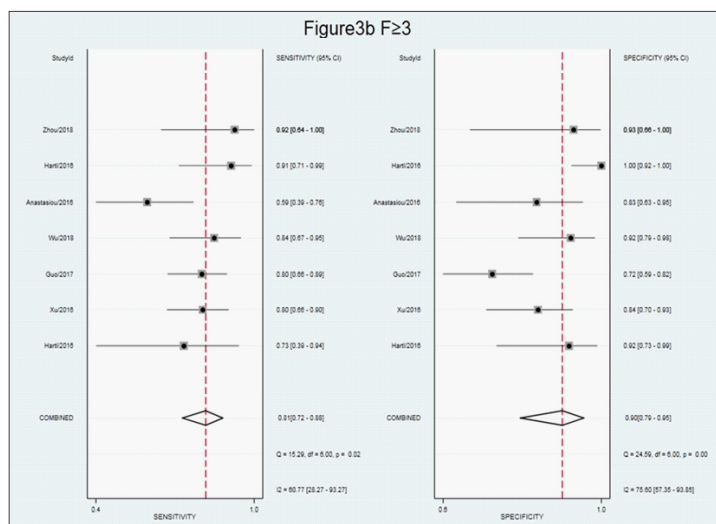
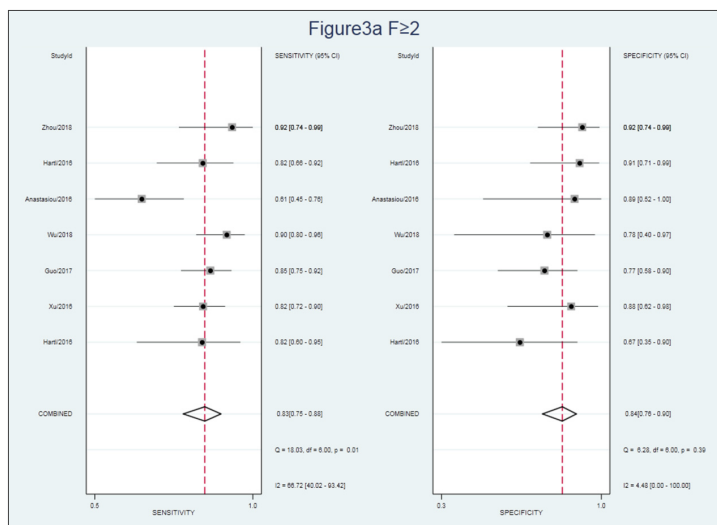
7 studies with 348 patients were included in the present meta-analysis to assess the diagnostic accuracy of TE for staging liver fibrosis $F \geq 2$ in AIH. The spearman correlation test showed no threshold effect between the sensitivity and the specificity ($r_s = -0.036$, $P = 0.939$). The summary sensitivity was 0.83 (95% CI, 0.75–0.88) (heterogeneity $I^2 = 66.72\%$, $p = 0.01$), and the summary specificity was 0.84 (95% CI, 0.76–0.90) (heterogeneity $I^2 = 4.48\%$, $p = 0.39$). Diagnostic Odds Ratio was 25 (95% CI, 13–47). The SROC curve AUC (area under curve) was 0.87 (95% CI, 0.84–0.90). 6 studies provided the cut-off values, which ranged from 5.80 to 10.05 kPa with weighted mean value of 6.90kPa.

7 studies with 212 patients were included to assess the diagnostic accuracy of TE for staging liver fibrosis $F \geq 3$ in AIH. The spearman correlation test showed no threshold effect between the sensitivity and the specificity ($r_s = 0.679$, $P = 0.094$). The summary sensitivity was 0.81 (95% CI, 0.72–0.88) (heterogeneity $I^2 = 60.77\%$, $p = 0.02$), and the summary specificity was 0.90 (95% CI, 0.79–0.95)

(heterogeneity $I^2 = 75.60\%$, $p < 0.001$). Diagnostic Odds Ratio was 39 (95% CI, 12–124). The SROC curve AUC (area under curve) was 0.90 (95% CI, 0.87–0.92). 6 studies provided the cut-off values, which ranged from 8.18 to 12.10 kPa with weighted mean value of 9.60 kPa.

7 studies with 96 patients were included to assess the diagnostic accuracy of TE for staging liver fibrosis $F = 4$ in AIH. The spearman correlation test showed no threshold effect between the sensitivity and the specificity ($r_s = -0.309$, $P = 0.500$). The summary sensitivity was 0.88 (95% CI, 0.79–0.93) (heterogeneity $I^2 = 0.00\%$, $p = 0.89$), and the summary specificity was 0.94 (95% CI, 0.86–0.97) (heterogeneity $I^2 = 59.37\%$, $p = 0.02$). Diagnostic Odds Ratio was 104 (95% CI, 35–311). The SROC curve AUC (area under curve) was 0.89 (95% CI, 0.86–0.92). 6 studies provided the cut-off values, which ranged from 12.50 to 19.00 kPa with weighted mean value of 14.58 kPa.

Figure 3a-c presented forest plots of summary sensitivities and specificities. The summary receiver operating characteristic curves for $F \geq 2$, $F \geq 3$, and $F = 4$ were shown in Figure 4a-c. The summary data of diagnostic characteristics for $F \geq 2$, $F \geq 3$, and $F = 4$ were presented in Table 3.



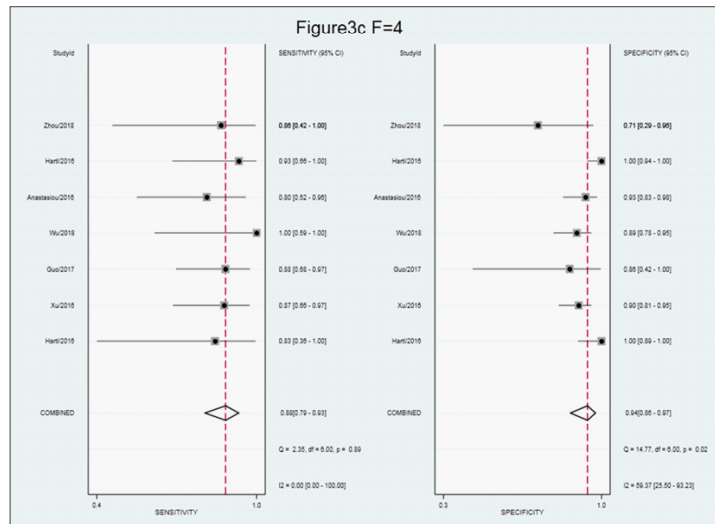
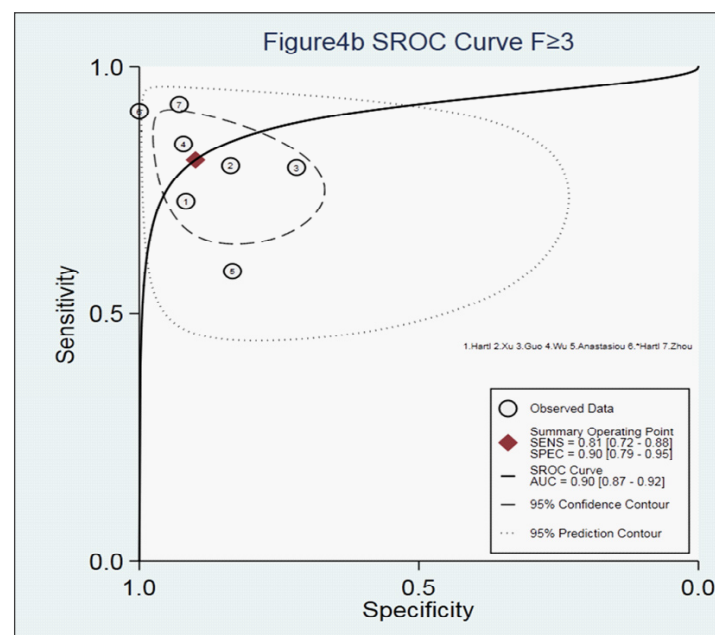
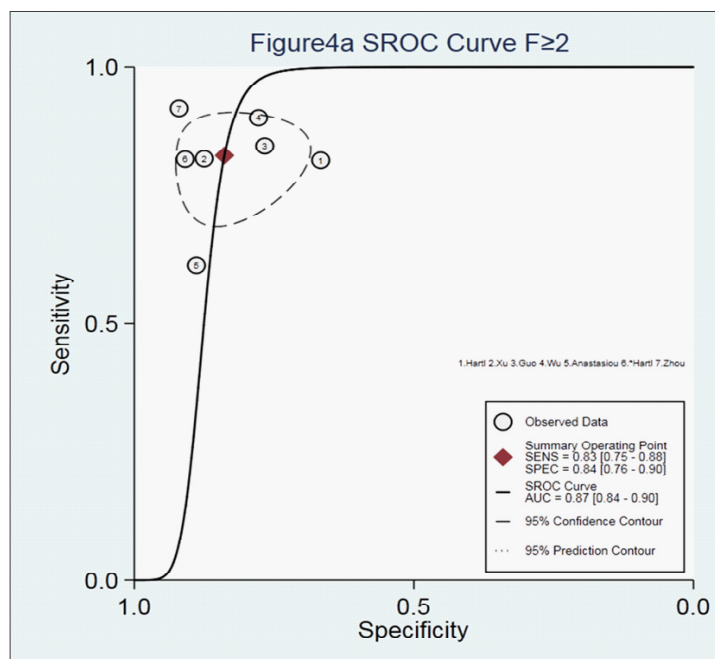


Figure3(a-c). shows forest plots of summary sensitivities and specificities.



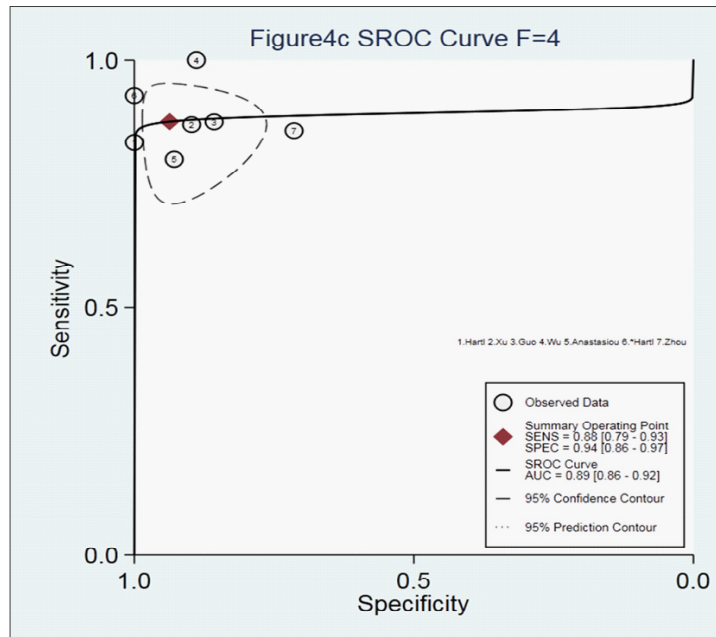


Figure 4 (a-c). shows the summary receiver operating characteristic curves for $F \geq 2$, $F \geq 3$, and $F = 4$

Table 3. Summary of diagnostic characteristics for fibrosis stage

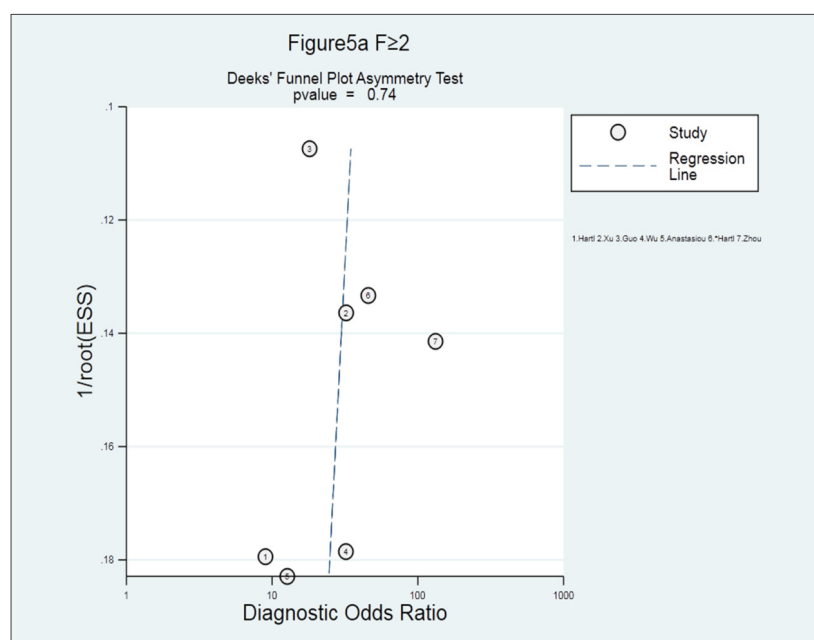
Cut-off value	Sensitivity	Specificity	DOR	AUROC
$F \geq 2$	6.90kPa	0.83 (95% CI, 0.75–0.88)	0.84 (95% CI, 0.76–0.90)	25 (95% CI, 13–47)
$F \geq 3$	9.60kPa	0.81 (95% CI, 0.72–0.88)	0.90 (95% CI, 0.79–0.95)	39 (95% CI, 12–124)
$F = 4$	14.58kPa	0.88 (95% CI, 0.79–0.93)	0.94 (95% CI, 0.86–0.97)	104 (95% CI, 35–311)

DOR: Diagnostic odds ratios; AUROC: Area under receiver operating characteristic

Publication Bias

In the MIDAS models for STATA, the results of publication bias analysis were shown in Figure 5a-c. There was no

significant publication bias according to Deeks' Funnel Plot Asymmetry Test ($F \geq 2$, $P = 0.74$; $F \geq 3$, $P = 0.41$; $F = 4$, $P = 0.69$ respectively).



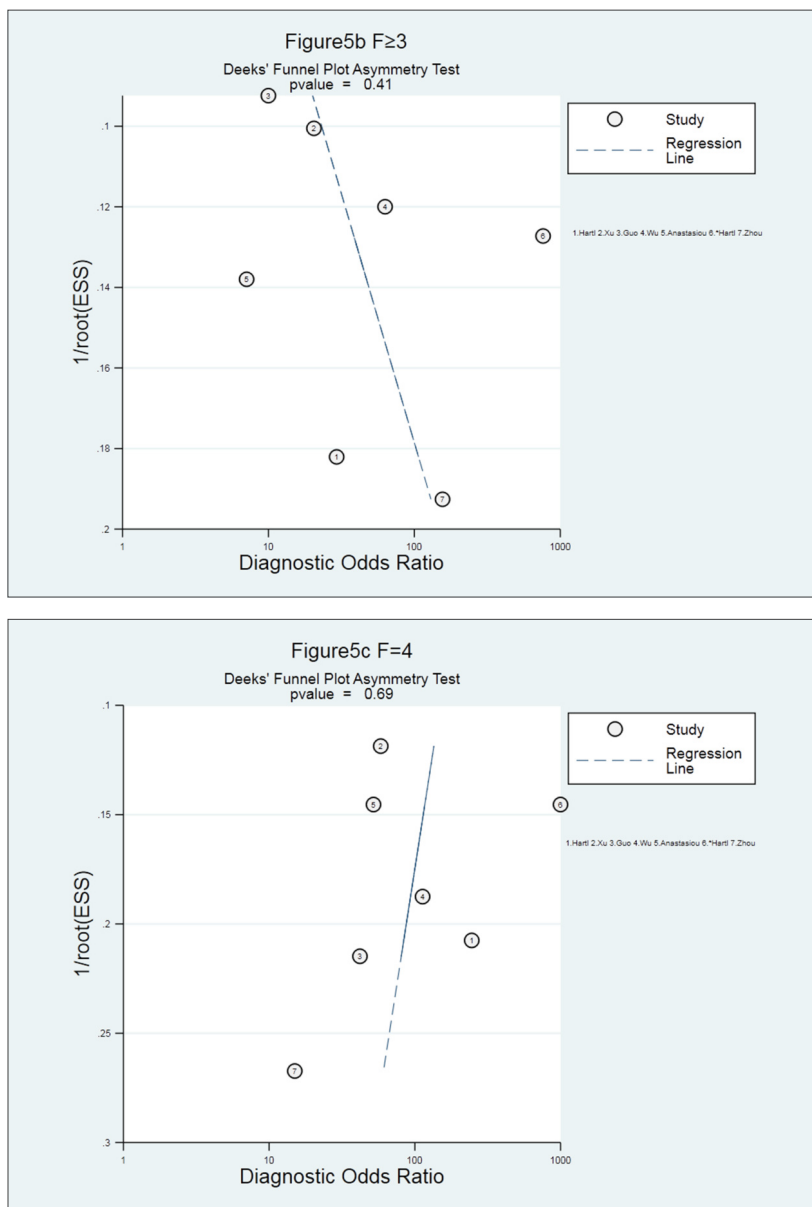


Figure 5(a-c). shows the results of publication bias

DISCUSSION

The present study demonstrates that, as a non-invasive method, TE can provide a reliable detection of liver fibrosis in AIH patients and reduce the complications caused by liver biopsy. TE has been used in the diagnosis of many different liver diseases and performed well in some original studies. Especially in viral hepatitis, TE has been introduced into the guidelines of World Health Organization (WHO) and European Association for the Study of the Liver (EASL) as a liver fibrosis staging technique[16, 17]. Due to the limited evidence, European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) did not issue guidelines on AIH[18]. The diagnostic accuracy of TE is still needed to be further evaluated as compared with liver biopsy in AIH patients.

7 studies were included in our research, 6 studies including only patients with autoimmune hepatitis, 1 study including

patients with autoimmune hepatitis-primary biliary cholangitis overlap syndrome. The results of our meta-analysis demonstrated that TE performed well when staging liver fibrosis F \geq 2, F \geq 3 and F = 4 in AIH patients with the summary sensitivity 0.83, 0.81, 0.88, the summary specificity 0.84, 0.90, 0.94 respectively. The values of summary specificity for diagnosing fibrosis stage F \geq 2, F \geq 3 and F = 4 are higher than that of summary sensitivity, which indicated that the currently approved cut-off values performed better when ruling disease out rather than confirming diagnosis. Furthermore, we used MIDAS model to evaluate the SROC curve AUC of TE in detecting liver fibrosis and the SROC curve AUC were 0.87, 0.90 and 0.89 for fibrosis stage F \geq 2, F \geq 3 and F = 4, respectively, which showed a good performance of TE for staging liver fibrosis in AIH patients. The meta-analysis of hepatitis B and hepatitis C reported by Tsochatzis et al showed that the summary sensitivity of TE for discriminating

liver fibrosis stage $F \geq 2$, $F \geq 3$ and $F = 4$ were 0.79, 0.82 and 0.83 and the summary specificity were 0.78, 0.86 and 0.89 respectively [19]. However, our meta-analysis indicated that TE performed a slightly better staging of autoimmune hepatitis fibrosis than viral hepatitis, we only included seven studies. The weighted mean cut-off values of TE for diagnosing liver fibrosis in AIH patients in our study were 6.90 kPa for fibrosis stage $F \geq 2$, 9.64 kPa for $F \geq 3$, and 14.58 kPa for $F = 4$ respectively. In a meta-analysis of chronic hepatitis B reported by Li. Y et al., the weighted mean cut-off values of TE were 7.2 kPa for fibrosis stage $F \geq 2$, 9.4 kPa for $F \geq 3$ and 12.2 kPa for $F = 4$ respectively[20], the cut values for diagnosing fibrosis stage $F \geq 2$, $F \geq 3$ in both studies are similar, the cut-off value for diagnosing fibrosis stage $F = 4$ is higher than the report of Li. Y. Because of no optimal statistical method, we simply used weighted means to summarize the optimal cut-off values. Additionally, due to lack of enough studies, we could not analyze the diagnostic accuracy of TE at the cut-off values in each original study. The cut-off values for discriminating liver fibrosis $F \geq 2$, $F \geq 3$ and $F = 4$ in AIH ranged from 5.80 to 10.05 kPa, 8.18 to 12.10 kPa and 12.50 to 19.00 kPa respectively. Obviously, the cut-off of values for detecting liver fibrosis $F \geq 2$, $F \geq 3$ were overlapped. Therefore, the stage of liver fibrosis stages $F \geq 2$, $F \geq 3$ may be prone to misdiagnosis. A study reported by Kim, J. K et al indicated that the cut-off of $LS \geq 9.1$ kPa had 94.4% sensitivity and 100% specificity for predicting fibrosis stage $F \geq 3$, the cut-off of $LS \geq 10.4$ kPa had 100% sensitivity and 100% specificity for fibrosis stage $F = 4$, however, only 15 patients analyzed in this study, we excluded this article from the meta-analysis[21]. In order to solve this problem, a studies reported by Vigano M et al used two cut-off values for discriminating liver fibrosis stage, the higher value was used to include patients in the diagnosis while the lower one was used to exclude the false positive cases [22]. However, TE cannot completely replace liver biopsy, since the gray area (between positive and negative values) still exists in this method. Generally, this method reported by Vigano M can improve the diagnostic accuracy to a certain extent, but it is still necessary to further expand the sample size to get a consensus for cut-off values in liver fibrosis $F \geq 2$, $F \geq 3$. Compared with the cut off values for discriminating liver fibrosis $F \geq 2$, $F \geq 3$, the range of cut-off values for detecting liver fibrosis $F = 4$ were not overlapped, however, due to wider range of the values, it is difficult to perform a statistical analysis. Future research can use the cut-off values extracted from the meta-analysis, and the diagnostic accuracy of TE at different cut-off values can be analyzed accordingly. It seems to be more reliable to confirm the optimal cut-off values in this method.

Another meta-analysis of hepatitis B reported by Chon et al, which used the weighted mean cut-off values of TE for assess fibrosis stage, the values were 7.9 kPa for fibrosis stage $F \geq 2$, 8.8 kPa for $F \geq 3$ and 11.7 kPa for $F = 4$ [23]. The weighted mean cut-off values for staging fibrosis $F \geq 3$, $F = 4$ in our study are slightly higher than that of Chon's report. It is worth nothing that compared with reports of Li. Y and Chon, the weighted mean cut-off value for $F = 4$ was higher in our study. In a pediatric study of Behairy et al, higher values of liver stiffness measurement were in AIH (16.15 ± 7.23 kPa) compared to chronic hepatitis C virus (HCV) groups (7.43 ± 1.73 kPa)[24]. On the one hand, it may be associated with a low level of fibrosis and a low rate of progression in HCV patients[25], on the other hand, hepatic inflammation of AIH has been identified as a potential confounding factor leading to false positives in TE values, even without significantly elevated liver enzymes, pathological examinations showed that a considerable proportion of patients with AIH were still in inflammatory activity[26]. Sustained immune clearance disorder may be related to the above phenomenon. Hartl et al reported that after 6 months of treatment, TE could better evaluate cirrhosis compared with short-term treatment. After 6 months of immunosuppressive therapy, residual liver inflammation may no longer affect the accuracy of TE, utilizing the cut-off values of 16 kPa, the diagnostic accuracy for cirrhosis ($F=4$) was excellent [14]. Future studies can be focused on the cut-off values of each stage of liver fibrosis in AIH patients after long-term treatment.

There are several limitations in our meta-analysis that should be taken into consideration. First, our study included a report on autoimmune hepatitis-primary biliary cholangitis overlap syndrome, which was considered to have an unclear risk of bias in patient selection. A specific clinical characteristic of AIH includes an association with other autoimmune diseases of the body [27], clinical features of AIH might be similar to primary biliary cirrhosis (PBC), these diseases may coexist leading to overlap syndromes[28]. A study included different etiologies of intrahepatic cholestasis indicated that inflammation and bile stasis are similar in these diseases and the difference in the pathophysiologic cause will not affect the results of liver stiffness measurement markedly[29], cut-off values for staging fibrosis $\geq F2, \geq F3$, and $F4$ were 6.7, 9.4, and 14.0 kPa, which were similar to our study. Second, the impact of inflammation (such as ALT level) on diagnostic accuracy could not be evaluated due to insufficient data. Elevated serum aminotransferase levels, can increase liver stiffness may be misdirected as fibrosis even or cirrhosis. In this situation, the lower cut-off values are not reliable for cirrhosis. The higher level of aminotransferase, the

higher the cut-off values required [30]. At last, significant heterogeneity was found among the individual studies for several fibrosis stages. Heterogeneity may arise from difference of biopsy protocols, pathological systems, and patient treatment status or a combination of these factors.

In conclusion, TE showed good performance for the diagnosis of liver fibrosis stage in AIH. Future studies with larger sample sizes are needed to confirm the cut-off values for different levels of inflammation and different treatment status.

Conflict of Interest

The authors declare that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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