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Original Article

Gastroenterol Res. 2022;15(5):232-239

Diagnostic Accuracy of Elastography and Liver Disease: A Meta-Analysis

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Abstract

Background: Ultrasound-based transient elastography (TE) is a non-invasive alternative to liver biopsy for the staging of hepatic fibrosis due to various chronic liver diseases. This meta-analysis aims to assess the diagnostic accuracy of TE for detecting liver cirrhosis (F4) and severe fibrosis (F3) in patients with chronic liver diseases, in comparison to the gold standard liver biopsy.

Methods: A systematic search was performed using PubMed search engine following Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines from inception to May 2021. The meta-analysis studies evaluating the diagnostic accuracy of TE for severe fibrosis and cirrhosis were identified. We conducted a meta-meta-analysis to generate pooled estimates of the sensitivity, specificity, and diagnostic odds ratios (ORs) for F3 and F4 fibrosis stage.

Results: We included five studies with a total of 124 sub-studies and 20,341 patients in our analysis. Three studies have reported the diagnostic accuracy of TE in detecting F3/severe fibrosis stage and found 81.9% pooled sensitivity (95% confidence interval (CI): 79.9-83.7%; $P < 0.001$) ($I^2 = 0\%$), 84.7% pooled specificity (95% CI: 81.3-87.6%) ($I^2 = 81\%$; $P = 0.02$). All five studies reported the diagnostic accuracy of TE in detecting F4/liver cirrhosis stage. We found 84.8% pooled sensitivity (95% CI: 81.4-87.7%) ($I^2 = 86.4\%$; $P < 0.001$), 87.5% pooled specificity (95% CI: 85.4-89.3%) ($I^2 = 90\%$; $P < 0.001$) and pooled diagnostic OR (41.8; 95% CI: 3.9 - 56.5) ($I^2 = 87\%$; $P < 0.001$).

Conclusions: Ultrasound-based TE has excellent diagnostic accuracy for identifying cirrhosis and liver fibrosis stages 3. Future studies should focus on estimating the diagnostic accuracy of other fibrosis stages in chronic liver disease patients. This will eventually decrease the risk associated with invasive liver biopsy.

Keywords: Transient elastography; Liver cirrhosis; Liver fibrosis; Diagnostic accuracy; Liver biopsy

Manuscript submitted July 18, 2022, accepted September 19, 2022
Published online October 19, 2022

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doi: https://doi.org/10.14740/gr1557

Introduction

Liver cirrhosis is one of the most common causes of death worldwide. In Latin America, 2.7% of deaths are due to liver cirrhosis [1]. It is the end stage of progressive liver fibrosis, where the morphology of hepatocytes is distorted. The etiology of liver cirrhosis can be a toxic, infectious, allergic, autoimmune, or vascular process or an inborn error of metabolism [2, 3]. Among these causes, alcoholic liver disease is the most common cause [3]. Globally around 10.6 million prevalent cases of decompensated cirrhosis and about 112 million prevalent cases of compensated cirrhosis [4] are identified in 2017. In the USA, 0.15% of the population is estimated to have liver cirrhosis [5].

There are structural consequences of chronic liver diseases. The persistent continued inflammation of hepatocytes stimulates a complex activation process that includes excess

synthesis and deposition of type 1 collagen by activated hepatic stellate cell (HSC), among others extracellular matrix and increased cell proliferation leading to fibrogenic response [6]. Fibrosis can be reversed if detected early enough, and the underlying liver disease that caused the development of fibrosis can be cured or treated. If fibrosis is left untreated, it can lead to cirrhosis and liver cancer [7]. Accurate assessment of the severity of liver fibrosis and a reliable diagnosis of cirrhosis are important steps for the management of patients with chronic liver diseases, as they provide information that guides therapeutic decisions [8, 9].

Liver biopsy is the gold standard for the staging of fibrosis and diagnosis of cirrhosis; however, diagnostic accuracy is correlated with the length of the biopsy specimen [10]. Liver biopsy remains a costly and invasive procedure that requires physicians and pathologists to be sufficiently trained, in order to obtain adequate and representative results which limits the use of liver biopsy for mass screening [11]. Sampling errors and risk of complications are other limitations for the use of liver biopsy. Recently introduced transient elastography (TE) is a non-invasive test to determine the staging of hepatic fibrosis and stiffening of the liver due to scarring. It allows examination of 100 times more significant volume of liver tissue as compared to a liver sample obtained through liver biopsy. Different shear wave-based elastography methods are available, including TE, point shear wave elastography, and two-dimensional shear wave elastography (2D-SWE). The most extensively evaluated elastography method for liver stiffness is TE (FibroScan; Echosens, Paris, France) [11, 12].

It involves using a transducer on the end of a US probe, which transmits 50 MHz pressure waves, and the resultant "shear wave" velocity is measured. This shear wave velocity correlates with liver stiffness and helps estimate the stage of liver fibrosis [5]. It is also used to predict the complications caused by cirrhosis like portal hypertension and has excellent patient acceptance [5, 13]. It can monitor dynamic changes of liver fibrosis, especially in hepatitis C and hepatitis B, during antiviral or anti-fibrotic treatment [14, 15]. Some studies have evaluated 2D-SWE in patients infected with chronic hepatitis B (n = 226 and n = 303) and revealed diagnostic accuracies according to area under receiver operating characteristic (AUROC) levels of 88-92%, 93-95%, and 95-98% for significant fibrosis, severe fibrosis, and liver cirrhosis, respectively [16, 17]. In one study, 2D-SWE was compared to TE, and the diagnostic accuracies were significantly superior to TE for all fibrosis stages [16].

Materials and Methods

Literature search strategy

In this meta-meta-analysis, we aim to evaluate the diagnostic accuracy of TE in diagnosing liver fibrosis stage 3 and 4 in patients with chronic liver disease compared to liver biopsy (gold standard). A systematic search was performed following Preferred Reporting Items for Systematic reviews and Meta-Analyze (PRISMA) guidelines [18] from inception to May 2021. The meta-analysis studies were searched using PubMed with keywords (("point shear wave elastography" (title/abstract) OR "transient elastography" (title/abstract) OR "Fibroscan" (title/abstract) OR "transient sonoelastography" (title/abstract) OR "two dimensional shear wave elastography" (title/abstract)) AND ("non-alcoholic fatty liver disease" (title/abstract) OR "nonalcoholic steatohepatitis" (title/abstract) OR "fatty liver" (title/abstract) OR "liver fibrosis" (title/abstract) OR "cirrhosis" (title/abstract) OR "chronic liver disease" (title/abstract) OR "hepatitis" (title/abstract)) (Fig. 1).

Study selection and data extraction

Abstracts and full-length articles for meta-analysis studies which have availability of data were reviewed and data were collected for quantitative analysis. Kriti Agarwal and Anusha Chidharla independently screened all of the identified studies and assessed full texts to determine eligibility. Any disagreement was resolved through consensus with Preeti Malik.

We have included meta-analysis studies which have evaluated the diagnostic accuracy of TE in detecting fibrosis stage 3 and 4 according to METAVIR or other systems which can be transformed to METAVIR compared with gold standard biopsy in chronic liver disease patients. Studies published in non-English language, animal studies, randomized clinical trials, non-full text and those comparing different elastography methods without comparing with liver biopsy were excluded.

The following data variables were extracted: author's name, study year, sample size, studies included in the meta-analysis, type of chronic liver disease, and type of elastography as described in Table 1 [19-23].

Statistical analysis

We used the Review Manager version 5.3 software (https://training.cochrane.org/online-learning/core-software/revman) and Open METAXL for analysis. We performed a random effects model irrespective of heterogeneity to estimate the pooled sensitivity, specificity and diagnostic odds ratio (OR) and their respective 95% confidence interval (95% CI). I^2 values of 25%, 50%, and 75% represented low, medium, and high heterogeneity. $P < 0.05$ was considered statistically significant. The Newcastle-Ottawa Scale (NOS) scale was used to estimate the risk of bias among studies. We calculated the true positive, false positive, true negative and false negative of each study based on the reported sensitivity and specificity.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

We screened 55 publications, out of which 10 full-text articles

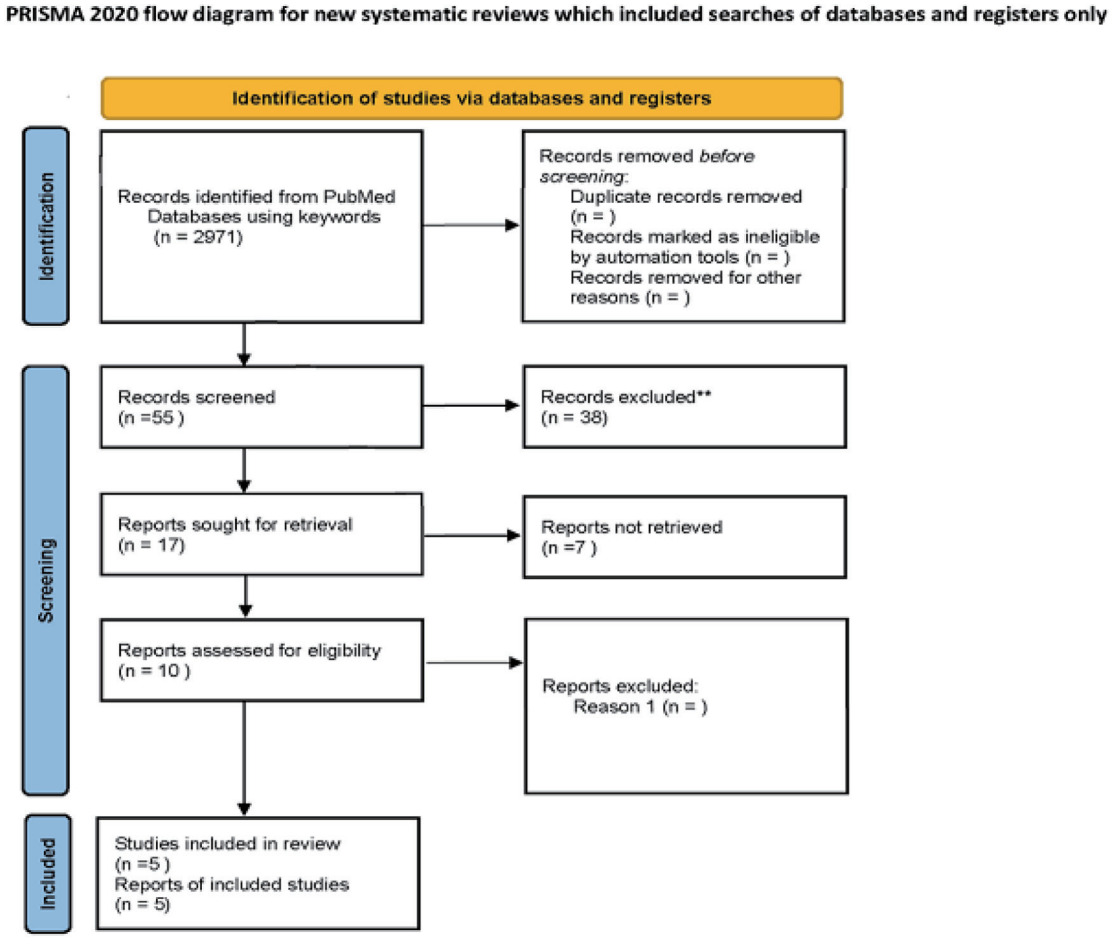

Figure 1. Flow diagram of literature search and study selection process of included studies.

were assessed for eligibility using inclusion and exclusion criteria. Five meta-analysis studies were excluded because they were not in English and did not compare the diagnostic accuracy of elastography with biopsy. After detailed assessment, as of May 20, 2021, a total of five meta-analysis studies were selected to evaluate the diagnostic accuracy of TE. The flow diagram of the search result Is shown in Figure 1.

Stage F3

Three out of the five meta-analysis studies were included in the meta-meta-analysis to evaluate the diagnostic accuracy of TE for staging liver fibrosis F ≥ 3 (severe fibrosis). We found 81.9% pooled sensitivity (95% CI: 79.9-83.7%; P < 0.001) (I^2 = 0%) and 84.7% pooled specificity (95% CI: 81.3-87.6%) (I^2

Table 1. Characteristics of Studies Included

Study	Study year	Sample size	Studies included in meta-analysis	Type of chronic liver disease	Type of elastography
Geng et al [19]	2016	10,204	57	Liver cirrhosis: AIH, hepatitis B and C, NAFLD, ALD, NASH, HCC	Transient elastography
Ying et al [20]	2016	4,255	24	Hepatitis C	Transient elastography
Nguyen-Khac et al [21]	2018	1,026	10	Alcohol-related liver disease	Transient elastography
Li et al [22]	2015	4,386	27	Chronic hepatitis B	Transient elastography
Adebajo et al [23]	2011	470	6	Hepatic fibrosis due to recurrent HCV	Ultrasound-based transient elastography

AIH: autoimmune hepatitis; NAFLD: nonalcoholic fatty liver disease; ALD: alcoholic liver disease; NASH: nonalcoholic steatohepatitis; HCC: hepatocellular carcinoma; HCV: hepatitis C virus.

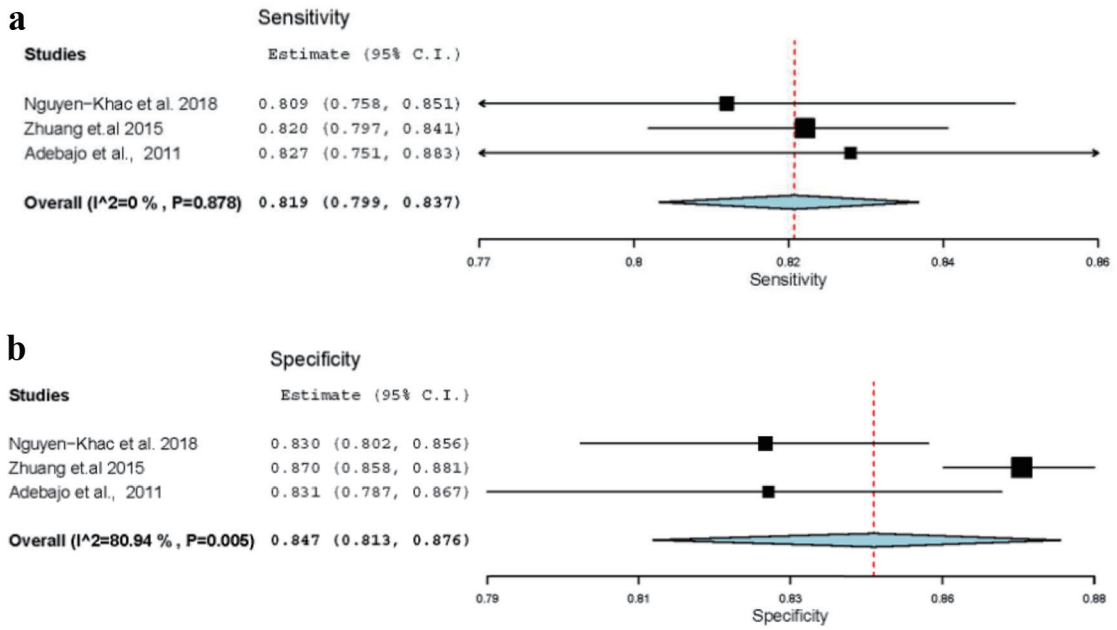

Figure 2. (a) Sensitivity of stage F3. (b) Specificity of stage F3.

= 81%; P = 0.02) (Fig. 2a, b).

Stage F4: sensitivity, specificity and diagnostic odds ratio

Five meta-analysis studies have reported the performance of transient elastography in detecting fibrosis stage 4/liver cirrhosis. We found 84.8 % pooled sensitivity (95% CI: 81.4-87.7%) (I^2 = 86.4%; P < 0.001), 87.5% pooled specificity (95% CI: 85.4-89.3%) (I^2 = 90%; P < 0.001) and pooled diagnostic OR (41.8; 95% CI: 3.9 - 56.5) (I^2 = 87%; P < 0.001) (Fig. 3a-c).

Discussion

This meta-meta-analysis evaluated diagnostic accuracy of TE

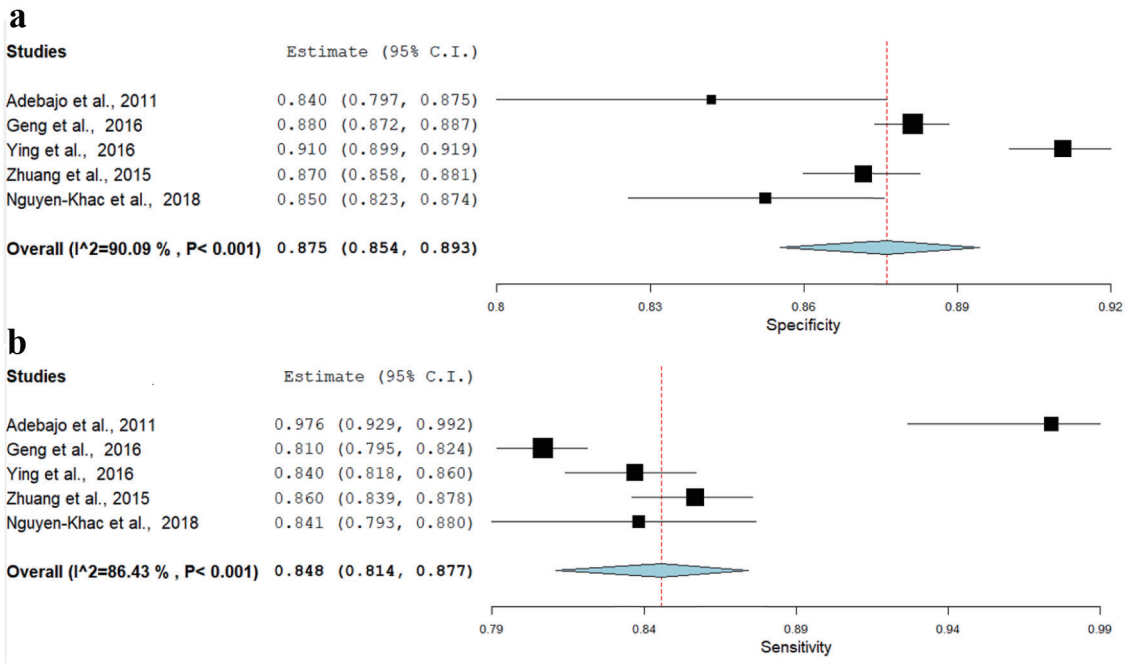

Figure 3. (a) Sensitivity of stage F4. (b) Specificity of stage F4. (c) Diagnostic odds ratio of stage F4.

in detecting F4 stage of liver fibrosis compared to gold standard liver biopsy in patients with chronic liver disease. We included five studies with a total of 124 sub-studies and 20,341 patients in our analysis. Three studies have reported the diagnostic accuracy of TE in detecting F3/severe fibrosis stage and found 81.9% pooled sensitivity (95% CI: 79.9-83.7%; P < 0.001) (I^2 = 0%) and 84.7% pooled specificity (95% CI: 81.3-87.6%) (I^2 = 81%; P = 0.02). All five studies which were included in our meta-meta-analysis reported the diagnostic accuracy of TE in detecting F4/liver cirrhosis stage. We found 84.8% pooled sensitivity (95% CI: 81.4-87.7%) (I^2 = 86.4%; P < 0.001), 87.5% pooled specificity (95% CI: 85.4-89.3%) (I^2 = 90%; P < 0.001) and pooled diagnostic OR (41.8; 95% CI: 3.9 - 56.5) (I^2 = 87%; P < 0.001). Our findings indicate that TE has high diagnostic performance for detecting liver fibrosis stages 3 and 4. This supports the use of TE as an alternative to invasive methods like liver biopsy for assessing advanced stages of chronic liver disease and avoiding its complications/limitations.

There are few studies supporting our results such as Qi et al's study which found that sensitivity, specificity, and diagnostic OR of TE at F4 in chronic hepatitis B (CHB) infection was 78%, 84%, and 14.44, respectively [24]. Similarly, Zhang et al's study used TE for predicting a negative predictive value in advanced fibrosis and cirrhosis in CHB were 92.4% and 98.7%, respectively [25]. Meta-analysis by Talwalkar et al included nine studies and showed a pooled estimate for sensitivity 87% and for specificity 91% in patients with stage 4 fibrosis suggesting good performance of TE which is similar to our findings [26]. Tsochatzis et al included 40 studies and found that the sensitivity and specificity were dependent on the degree of fibrosis [27]. They found that for F2 stage disease, the sensitivity and specificity were 79% and 78%, respectively, whereas for cirrhosis they were 83% and 89%. They also determined that accuracy of TE as evaluated by post-test biopsy was 78% for F2 stage disease and 88% for cirrhosis. Our study also points towards similar results by showing higher diagnostic accuracy in detecting fibrosis at the F4 stage compared to F3 stage.

The meta-analysis of Stebbing et al included 22 studies and found that the sensitivity was 71.9%, specificity was 82.4% for significant fibrosis (≥ F2) and they were 84.5% and 94.7%, respectively, for cirrhosis [28]. Friedrich-Rust et al performed a meta-analysis that assessed the overall performance of TE for diagnosing liver fibrosis and they also analyzed what factors influence the accuracy [29]. They included 50 studies and found that the mean AUROC curve varied depending on the severity of the fibrosis; the AUROC for significant fibrosis (F ≥ 2) was 0.84, for severe fibrosis (F ≥ 3) was 0.89, and for cirrhosis (F ≥ 4) was 0.94. Factors that influenced AUROC were underlying liver disease, scoring system used, and country. Another systematic review and meta-analysis was done by Adebajo et al, comparing TE with liver biopsy for the detection of significant fibrosis (five studies) and cirrhosis (five studies) in patients with recurrent hepatitis C virus (HCV) after liver transplant. The results yielded excellent TE estimates of the sensitivity and specificity for detecting cirrhosis (F ≥ 4) and good estimates for detecting significant fibrosis (F ≥ 2) [23].

Elastography mainly aims at imaging the stiffness of the liver. The various types of elastography include quasi-static method elastography, vibro-acoustography, and TE. TE uses the acoustic force; therefore, it might slightly displace the tissue from its focal point [30]. A study done by Burriel et al has mentioned that TE has an overall 12% chance of being a cost-effective intervention for the European and Asian population [31]. TE is non-invasive and easy to use, and can be done repeatedly [32]. However, there are several limitations of TE which include minimal anatomic orientation, limited depth of penetration, and patient positioning requirements [33, 34]. Shear wave propagation is also attenuated by fluid and adipose tissue [33, 35]. Hence, these limitations may result in failed examinations in patients who are obese, who have anatomic distortions, ascites, and elevated central venous pressures [36]. Factors associated with unreliable results included body mass index (BMI) > 30 kg/m^2, age > 52 years, female sex, operator inexperience, and type 2 diabetes mellitus [33].

Even though liver biopsy is the standard gold test, there are disadvantages associated like hemorrhage and blood transfusion due to bleeding and mortality risk [37]. In addition, it also depends on the pathologist; the chance of error rate in disease staging is 20% [38].

TE measures the shear wave speed through the liver which reflects liver stiffness and not actual amount of fibrosis in the liver. Hence, conditions which increase the stiffness of the liver independent of fibrosis will result in an increased liver stiffness measurement (LSM) and will result in a falsely high estimate of liver fibrosis. LSMs are falsely high in acute hepatitis during alanine transaminase (ALT) flares, hepatic congestion and cholestasis, leading to variability of optimal cut-off levels for the diagnosis of fibrosis and cirrhosis in different etiologies of liver disease. Also, there are differences in the optimal cut-off values reported in different studies [39].

Among the technical limitations, the inclusion of non-parenchymal tissue, such as gallbladder, blood vessels, and bile ducts, alters measurement velocity. Another one is the depth of measurement, as the 2 - 7 cm is ideal for measurement [40]. A study done by Lesmana et al at the F2 stage shows the lower sensitivity (60.3%) and specificity (63.6%) of TE [41].

The tissue response to a known mechanical stimulus forms the principal basis for elastography. This stimulus can be static, quasistatic, or dynamic depending on the tissue being studied. Dynamic stimulus-based techniques like US-based shear wave elastography and magnetic resonance (MR) elastography which typically use vibrations in the range of 20 - 500 Hz and study the properties of the waves produced by the vibrations propagating through the tissues. Chronic liver disease leads to the accumulation of collagen fibers leading to fibrosis and resulting in increased liver parenchymal stiffness. As there is faster propagation of mechanical waves through stiffer tissue which resists deformation, this change in this mechanical property helps differentiate normal liver parenchyma from fibrotic liver and cirrhosis.

Limitations of the study

There were not enough meta-analysis studies done to evaluate the diagnostic performance for F0-F2 fibrosis stages. Hence,

we could not provide strong evidence of diagnostic accuracy of fibrosis stage F0-F2. Additionally, meta-analyses included in the study have included various chronic liver disease which might explain the heterogeneity in the results. Among the technical limitations of elastography is the inclusion of non-parenchymal tissue, such as gallbladder, blood vessels, and bile ducts, alters measurement velocity. Another one is the depth of measurement, as the 2 - 7 cm is ideal for measurement [40]. A study done by Lesmana et al at the F2 stage shows the lower sensitivity (60.3%) and specificity (63.6%) of TE [41]. However, more studies or meta-analyses are required before any definitive conclusion can be drawn. Despite the limitations our meta-meta-analysis shows higher diagnostic accuracy of TE in detecting liver cirrhosis and severe fibrosis compared to liver biopsy.

Future directions of liver elastography

Liver elastography is an emerging and dynamic research modality which can be used repeatedly over a period of time due to its non-invasive nature. It has a prognostic significance in determining long-term survival in patients with chronic hepatitis. Further studies are being undertaken to determine pre-fibrosis liver stiffness which could be beneficial with earlier diagnosis and treatment in high-risk individuals [42]. There is evidence in patients with hemochromatosis for use of TE with serum ferritin algorithms to accurately determine severe fibrosis [43]. There is also active research for the use of elastography in characterization of liver tumors [44, 45].

Conclusion

Novel elastography is an emerging new technique for the better diagnosis and management of the patients with chronic liver disease. Our study focused on the accuracy of TE in diagnosing F3 and F4 stages of liver fibrosis and we found TE showed promising results in detecting advanced stages of liver fibrosis comparable to gold standard liver biopsy. Given the limitations of biopsy like sampling error, invasiveness and associated complications, elastography has recently emerged as the modality of choice to accurately determine liver fibrosis, before it leads to development of cirrhosis and also monitoring of the conditions like HCV, hepatitis B virus (HBV), and nonalcoholic fatty liver disease (NAFLD). But the study of TE has its limitations and technical challenges like lack of standardization of diagnostic threshold across manufacturers, operator and patient dependency, different fibro scan cut off for different chronic liver disease and limited diagnostic accuracy of the F0-F2 stage.

Additional studies are required to determine standardization and to assist with early diagnosis and prompt treatment. Use of elastography is being incorporated into decision making for quantification of the extent of fibrosis and treatment of liver disorders to prevent progression. There is need for collaboration of manufacturers, national societies, and researchers to work together in overcoming the limitations. Hence, these non-invasive techniques can be used for early detection of advancing liver disease.

Acknowledgments

None to declare.

Financial Disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

None to declare.

Informed Consent

The data used in this study are deidentified and collected from the studies published online thus informed consent or IRB approval was not needed for this study.

Author Contributions

Conceptualization: Preeti Malik, Shreejith Pillai, and Kriti Agarwal. Methodology: Preeti Malik and Kriti Agarwal. Acquisition of data: Anusha Chidharla, Kriti Agarwal and Preeti Malik. Formal analysis and investigation: Preeti Malik. Writing original draft preparation: Preeti Malik, Shreejith Pillai, Kriti Agarwal, Salwa Abdelwahed, Renu Bhandari, Abhishek Singh, Anusha Chidharla, Kajal Patel, Priyanka Singh, and Pritika Manaktala. Writing review, critical feedback, and editing: Rizwan Rabbani, Thoyaja Koritala, and Sachin Gupta. Resources and supervision: Thoyaja Koritala and Sachin Gupta.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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