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ORIGINAL ARTICLE

Comparison of Transient Elastography and Liver Biopsy in Assessing Fibrosis in Patients with Nonalcoholic Fatty Liver Disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease. Ultrasound-based transient elastography (TE) or TE of the liver is a noninvasive tool for effectively evaluating liver stiffness and fibrosis. The study aimed to compare the accuracy of TE as assessed by Fibroscan with liver biopsy in staging fibrosis in patients with NAFLD. Consecutive NAFLD patients (N = 72) were prospectively enrolled. TE evaluation was performed with Fibroscan and compared with liver biopsy, which is a reference standard. Fibrosis was staged according to the METAVIR scoring system (Meta-analysis of Histological Data in Viral Hepatitis). TE scores and biopsy-related fibrosis stages were correlated. Diagnostic accuracy (sensitivity, specificity, positive and negative predictive values) of TE was evaluated. Data were analyzed using software R v3.6.3. Liver biopsy showed that 36.11% of patients did not exhibit fibrosis, whereas 25, 16.67, 15.28, and 6.94% of patients had stage F1 (portal/mild fibrosis), F2 (periportal/moderate fibrosis), F3 (bridging/severe fibrosis), and F4 (cirrhosis/advanced fibrosis), respectively. TE showed that 50% of patients had cirrhosis, whereas 20.83,15.28, and 13.86% of patients had mild, moderate, and severe fibrosis, respectively. TE had 71% accuracy, 89% sensitivity, and 38% specificity in diagnosing the severity of fibrosis. Hence, it can be implemented as a noninvasive alternative diagnostic tool for understanding the severity of fibrosis in patients with NAFLD. Moreover, it can also be used for quick early diagnosis of NAFLD, reliable staging of fibrosis, and understanding the need for liver transplantation in patients with NAFLD.

Keywords: biopsy; elasticity imaging techniques; fibrosis; liver cirrhosis; nonalcoholic fatty liver disease

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease globally with an estimated prevalence of 20–30% (1, 2). NAFLD is characterized by predominant storage of lipids in hepatocytes and subsequent inflammatory progression, resulting in steatohepatitis, which is not due to alcohol consumption (3). Risk factors for NAFLD include obesity, dyslipidemia, type 2 diabetes mellitus, metabolic syndrome, hypothyroidism, and insulin resistance (4). The histologic spectrum of NAFLD comprises

simple steatosis, nonalcoholic steatohepatitis, fibrosis, and cirrhosis (5). NAFLD is the hepatic manifestation of metabolic syndrome (2).

Early detection of NAFLD and staging of fibrosis are crucial for identifying patients with potentially aggressive fatty liver disease (6). To diagnose NAFLD, patients are clinically, biochemically, and radiographically evaluated. Presently, liver biopsy is the gold standard for distinguishing simple steatosis from nonalcoholic steatohepatitis as well as staging and grading of fibrosis in patients with NAFLD (5). Liver biopsy assesses the prognosis of the disease in response to medical interventions. However, the technique is invasive and expensive and presents sampling errors, potential complications, and inter- and intra-observer variability. Hence, it is impractical for frequent evaluations on a regular basis (5).

Currently, noninvasive techniques that are highly sensitive and specific are being studied extensively (5). These techniques comprise the biological approach using serum biomarkers—including hyaluronic acid, collagen, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST)/ALT ratio, and AST/platelet ratio—as well as the physical approach based on imaging modalities to measure liver stiffness/elasticity, including transient elastography (TE) (7).

TE using FibroScan® is a specialized ultrasound device that assesses liver stiffness sonographically by estimating the velocity of shear wave propagation, which implies that faster the propagation, stiffer the liver tissue (8). To evaluate fibrosis, TE values are further interpreted based on clinical and morphological data. TE is used for the evaluation of patients with numerous liver disorders, including NAFLD, and is preferred by clinicians due to its noninvasiveness, simplicity, and rapid outcomes in an outpatient setting (9).

Herein, we aimed to evaluate and compare the accuracy of simple noninvasive TE and conventional invasive liver biopsy in assessing the degrees of fibrosis in patients with NAFLD.

Materials and Methods

From January 2016 to December 2017, a prospective observational study was conducted including 72 patients with NAFLD attending the outpatient clinic in the Department of Medicine and Gastroenterology services at a tertiary care hospital in Bengaluru. The sample size was calculated as described by Jamali et al. and Charan et al. (10, 11). Written informed consent was obtained from all patients. Patients in the age group of 20–70 years who exhibited deranged liver enzymes and fatty liver—as diagnosed on ultrasound examination—were consecutively included in the study. Exclusion criteria included patients with a history of alcohol consumption of >20 g/day (during the last 5 years); chronic drug use; the presence of hepatitis B, hepatitis C, or HIV; biliary obstruction on ultrasonography; malabsorption; pregnancy; any cardiorespiratory comorbidities; α1-antitrypsin deficiency; and hemochromatosis. Moreover, patients who fulfilled the inclusion criteria but did not provide their consent were also excluded.

Methodology

Demographic characteristics of patients were recorded. TE was performed on the right lobe of the liver through intercostal spaces using FibroScan® (12) with patients lying in the dorsal decubitus position and the right arm in maximum abduction. For each patient, 10 successful acquisitions were performed, the median value was calculated, and the liver stiffness was expressed in kilopascals (kPa). Comorbid conditions, such as diabetes mellitus, hypertension, dyslipidemia, and hypothyroidism, were evaluated and recorded. The patients were further subjected to liver biopsy, and fibrosis was staged from F1 to F4 according to the METAVIR scoring system—a scoring system for grading and staging the histological lesions in NAFLD proposed by Brunt et al. and Pais et al. (13, 14). Subsequently, liver stiffness was correlated with the stages of fibrosis according to liver biopsy. All data were recorded in a structured patient-specific pro forma.

Statistical analysis

Data were analyzed using R software version 3.6.3 and Excel. Categorical and continuous variables are presented in the form of the frequency with percentages and mean (± standard deviation), respectively. Chi-square test was used to analyze categorical data, and Welch analysis of variance with suitable post hoc test was used to compare continuous data. P-value < 0.05 was considered statistically significant.

Results

The mean age of patients was 42.47 ± 17.86 years. Females comprised 63.89% of the sample size. Twenty-six (36.11%) patients were overweight with a body mass index (BMI) of 25.0–29.9 kg/m^2, 18 (25%) were obese (≥30.0 kg/m^2), 14 (19.44%) were underweight (≤18.5 kg/m2), and only 14 (19.44%) had BMI in normal range (18.5–24.9 kg/m^2). On upper GI endoscopy, 41 (56.94%) patients exhibited no varices, whereas 20 (27.78%) and 11 (15.28%) patients exhibited large and small varices, respectively.

Out of 72 patients, 43 (59.6%) patients had diabetes mellitus, 1 (1.9%) patient had hypertension, 34 (46.2%) patients had dyslipidemia, and 19 (26.9%) patients had hypothyroidism. Of the 43 patients with diabetes mellitus, 11 (25.58%), 11 (25.58%), 7 (16.28%), 7 (16.28%), 4 (9.30%), and 3 (6.97%) were suffering from diabetes for years >10, 5–10, 3–5, 1–2, 0, and <1, respectively.

Based on the TE scorecard, it was observed that 36 (50%) patients had a score of >13 (cirrhosis), whereas 15 (20.83%),

Table 1: Correlation between liver biopsy, endoscopy, and Fibroscan

		Fibroscan				P-value
		≤7.5 KPa	7.6–9.9 KPa	10–12.9 KPa	≥13 KPa	
Liver biopsy	F0	10 (38.46%)	5 (19.23%)	4 (15.38%)	7 (26.92%)	0.0465*
	F1	0	0	1 (20%)	4 (80%)	
	F2	2 (18.18%)	2 (18.18%)	3 (27.27%)	4 (36.36%)	
	F3	3 (25%)	2 (16.67%)	1 (8.33%)	6 (50%)	
	F4	0	2 (11.11%)	1 (5.56%)	15 (83.33%)	
Endoscopy	No varices	15 (36.59%)	9 (21.95%)	5 (12.20%)	12 (29.27%)	0.005*
	Small varices	0	2 (18.18%)	0	9 (81.82%)	
	Large varices	0	0	5 (25%)	15 (75%)	

The values represent number of patients (respective percentage). *Denotes statistically significant.

11 (15.28%), and 10 (13.86%) patients had scores of ≤7.5 (mild fibrosis), 7.6–9.9 (moderate fibrosis), and 10–12.9 (severe fibrosis), respectively.

According to the findings of liver biopsy and METAVIR scoring system, 26 (36.11%) patients did not exhibit fibrosis (stage F0), whereas 18 (25%), 12 (16.67%), 11 (15.28%), and 5 (6.94%) were in stage F1 (portal/mild fibrosis), F2 (periportal/moderate fibrosis), F3 (bridging/severe fibrosis), and F4 (cirrhosis/advanced fibrosis), respectively.

The correlation between TE and liver biopsy findings are depicted in Table 1.

Using the chi-square test with simulation in the present study, liver biopsy and TE were found to be significantly associated with each other (P = 0.0465). In addition, we also tried to see the correlation between endoscopy and TE. Here too there was a significant association with each other (P = 0.005).

For evaluating the correlation between liver biopsy, TE, and endoscopy, patients exhibiting stage F0 on liver biopsy, mild fibrosis on TE, and no varices on endoscopy were classified as the "no fibrosis" group. Considering this, 46 patients on liver biopsy, 31 patients on endoscopy, and 57 patients on TE were listed under "yes," whereas 26 patients on liver biopsy, 41 patients on endoscopy, and 15 patients on TE were listed under "no" for evaluating the correlation between the three as shown in Table 2.

A strong correlation was obtained between TE and liver biopsy (P = 0.0143), and no correlation was observed between endoscopy and liver biopsy (P = 0.0659).

Table 3 presents the sensitivity and specificity of TE, compared to liver biopsy.

Compared to liver biopsy, TE was found to have 71% accuracy along with 89% sensitivity and 38% specificity in staging fibrosis in patients with NAFLD.

Table 2: Correlation of Fibroscan and endoscopy with liver biopsy

		Liver biopsy		P-value
		Yes	No	
Fibroscan	Yes	41	16	0.0143*
	No	5	10	
Endoscopy	Yes	23	8	0.0659
	No	23	18	

The values represent number of patients. *Denotes statistically significant.

Discussion

NAFLD is a global health crisis leading to chronic liver diseases worldwide. It is more prevalent in males than females, and the risk of developing NAFLD increases with age (15). Early diagnosis of NAFLD is crucial for better prognosis and improved patient outcome. Liver biopsy is considered as the gold standard for diagnosing fibrosis in patients with NAFLD; however, it is invasive and not always feasible (6). Herein, the present study compared the accuracy of noninvasive TE with that of gold standard invasive liver biopsy for assessing fibrosis in patients with NAFLD.

TE is a quick, noninvasive, and reproducible method. It does not present any discomfort or potential risks to patients. Although the technique has been more widely implemented in the diagnosis of diseases such as chronic hepatitis C, it is not yet fully validated in NAFLD (16).

Table 3: Diagnostic analysis of Fibroscan with liver biopsy

		Liver biopsy		Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
		Fibrosis	No fibrosis					
Fibroscan	Yes	41	16	0.89	0.38	0.71	0.72	0.67
	No	5	10					

The values represent the number of patients.

In the present study, the sensitivity and specificity of TE were 89% and 38%, respectively. Reportedly, as the stages of fibrosis increase, the sensitivity and specificity of the TE increase to better diagnose fibrosis in patients with NAFLD, suggesting that TE can be implemented to exclude liver cirrhosis (16, 17). Nevertheless, future studies are required to confirm this.

Liver stiffness is influenced by histological parameters, including chronic liver inflammation and spontaneous surge in liver enzymes (18). The findings of the present study and other published literature suggest that the reliability and accuracy of TE are altered due to factors such as chronic inflammatory activity, resulting in an overestimation of fibrosis (18). In the present study, TE was more accurate in diagnosing F4 fibrosis, and it overestimated the early stages of fibrosis. This may be attributable to the fact that TE is more strongly related to the degree of fibrosis as compared to the METAVIR scoring system used in liver biopsy findings (19). Compliant with the literature, the present study suggests that TE is as accurate as liver biopsy in staging fibrosis, mainly F4 fibrosis (20).

In patients with NAFLD, higher BMI can negatively alter the results (14, 16, 21). In one study, out of 2114 patients with chronic liver disease, liver stiffness could not be evaluated in 4.5% of patients, and BMI of >28 kg/m^2 was suggested to be the only factor leading to an error in multivariate analysis (22). In obese patients, TE is difficult to perform, because ultrasound vibrations are often attenuated in the subcutaneous tissue. This condition is usually observed in patients with NAFLD (23, 24). In the present study, nearly 43 patients out of 72 exhibited a BMI of >25 kg/m^2, suggesting that BMI interfered with the specificity of TE. Nevertheless, future studies are needed to confirm the hypothesis.

Commonly associated comorbidities, including type 2 diabetes mellitus, dyslipidemia, obesity, and hypertension, are associated with the manifestations of NAFLD (15, 25). Such comorbidities can result in significant morbidity and mortality. In the present study, out of 72 patients, 43 (59.6%) suffered from diabetes mellitus, the most associated comorbidity (26). The presence of comorbidities highlights the unmet requirement of early diagnosis and treatment of these conditions in successfully managing patients with NAFLD. Diagnosing and managing such comorbidities on a large scale can remarkably improve the quality of life of patients with NAFLD (26). Moreover, as observed in the present study, hypothyroidism, hypertension, and dyslipidemia are the emerging contributors to the development of NAFLD.

In the present study, TE was reported to be 71% accurate in detecting the severity of fibrosis. Compliant with the literature, the present study proposes that considering the invasiveness of liver biopsy, TE can be implemented in clinical practice as a noninvasive alternative diagnostic method for assessing the severity of fibrosis in patients with NAFLD (16, 27). This may also be attributable to the major drawbacks of liver biopsy, mainly sampling variability. Often a biopsy specimen 1.5 cm in length and 1.2–2 mm in diameter is adequate for the diagnosis (28). However, sampling is associated with human error and other relevant factors. This sampling variability can potentially alter the staging of fibrosis and diagnosis of patients with NAFLD (14).

TE is a better modality than endoscopy as it can detect cases undiagnosed by endoscopy (29). In addition, as evaluated by Ghamdi et al., in the case of cirrhosis, TE can prognosticate the presence of varices, although it cannot differentiate between the size of varices—small or large (30). However, the present study suggests that TE and endoscopy are significantly correlated in terms of size of varices and degree of severity. This disagreement could be because Ghamdi et al. enrolled patients with cirrhosis only, whereas the present study included patients with varying degrees of fibrosis for a more comprehensive analysis (30).

The findings help hypothesize that endoscopy findings and biopsy findings are poorly correlated in the case of NAFLD (Table 2). Moreover, the sample size included in the present study was remarkably small to make any solid conclusion. Thus, future studies with a larger sample size are required to confirm the correlation between liver biopsy and endoscopy.

After a liver biopsy, nearly 30, 0.3, and 0.01% of patients experience pain, severe complications, and death, respectively (31, 32). Owing to a high prevalence of NAFLD, drawbacks of liver biopsy, and reliability of noninvasive tests, TE is more feasible than liver biopsy; and thus, the TE scoring

system is gaining more clinical preference (14). Due to its invasiveness, limited studies have evaluated the severity of NAFLD and the unsuitability of liver biopsy as a screening technique in patients with NAFLD. The disease demands detailed attention of clinicians because NAFLD serves as a hepatic manifestation of metabolic syndrome and a risk factor for developing extrahepatic diseases (25).

The present study has a few limitations. This was a prospective, observational study with a sample size of 72. Future studies including a larger sample size are required to generalize the findings. Nevertheless, identifying and eliminating potential factors responsible for the overestimation and underestimation of the stages of fibrosis by TE are extremely crucial for validating the process because such factors interfere with the accuracy of the technique (19). The present study also suggests that to improve the accuracy of TE, it should be combined with other noninvasive techniques. The study provides a basis for evaluating the accuracy and efficacy of TE in comparison with liver biopsy. Further research must be conducted to better understand the pathophysiology, diagnosis, and prognosis of NAFLD with respect to TE.

Conclusion

Noninvasive TE can be used as an alternative to invasive liver biopsy in staging fibrosis, mainly advanced fibrosis, and cirrhosis, in patients with NAFLD. Identifying and eliminating factors associated with over-/underestimation of fibrosis is crucial for enhanced accuracy. Considering its noninvasiveness and reproducibility, TE should be performed for better diagnosis and staging of NAFLD and to implement more effective treatment for improved patient outcomes.

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Ethics approval and Consent to Participate

Because the present study was observational, it did not require approval from Institutional Ethics Committee. Patients provided their consent to participate in the study, and their anonymity was maintained throughout the study.

Consent for Publication

Written informed consent was obtained from all participants for publication.

Availability of Data and Material

All data generated or analyzed during this study are included in this article.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

Dr. Bachhav, Dr. Ravikiran, and Dr. Lokesh conceptualized the study. Dr. Bachhav, Dr. Ravikiran, and Dr. Avinash, designed the study. Dr. Patil and Dr. Satyaprakash collected, analyzed, and interpreted the data. Dr. Bachhav and Dr. Ravikiran drafted the manuscript. All authors have approved the submitted version of the manuscript. All authors have agreed to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated and resolved.

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