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Original Article

Diagnostic Accuracy of Vibration Controlled Transient Elastography as Non-invasive Assessment of Liver Fibrosis in Patients with Non-alcoholic Fatty Liver Disease

Hossain Salehi[1], Amir Mohammad Salehi[2], Mohammad Ebrahim Ghamarchehreh[1], Elham Khanlarzadeh[2], Masoud Reza Sohrabi[3*]

[1]Research Center for Gastroenterology and Liver Diseases, Baqiyatallah University of Medical Sciences, Tehran, Iran
[2]Student Research Committee, Hamadan University of Medical Sciences School of Medicine, Hamadan, Iran
[3]Department of Community Medicine, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

Abstract

Background: Liver biopsy remain as the gold standard for diagnosing hepatic fibrosis; however, it has some limitations, such as life-threatening complications, low acceptance by the patients, and variations in the related sample. Therefore, there is a need for the development of non-invasive investigations for diagnosing hepatic fibrosis. Vibration-controlled transient elastography (VCTE) is one of these non-invasive methods.

Methods: This study included 73 patients suffering from non-alcoholic fatty liver disease (NAFLD) who were older than 18 years. The patients underwent VCTE at the Baqiatallah and Firoozgar hospitals. Then, they underwent a liver biopsy by an experienced radiologist in the same hospital. A receiver operating characteristic (ROC) curve of different fibrosis stages was used to evaluate the VCTE verification.

Results: VCTE could detect any fibrosis levels (stage 1 and higher) with an area under the ROC curve (AUROC) of 0.381. Moreover, it detected stage 2-4 fibrosis with an AUROC of 0.400, stage 3-4 fibrosis with an AUROC of 0.687, and stage 4 fibrosis with an AUROC of 0.984.

Conclusion: The VCTE has high clinical validity in diagnosing the advanced stages of fibrosis (stages 3, 4) and can be a suitable alternative to the invasive method of liver biopsy with high reliability.

Keywords: Fibrosis, Non-alcoholic fatty liver disease, Elasticity imaging techniques

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Introduction

In 1980, Dr. Ludwig and colleagues defined non-alcoholic fatty liver disease (NAFLD) and its severe form, non-alcoholic steatohepatitis (NASH). Since then, our knowledge of this disease has increasingly grown. NAFLD is one of the most common causes of chronic hepatic disease in several countries. The disease has been increasing in prevalence along with diabetes and obesity, both of which are associated with insulin resistance. Therefore, we are probably facing an epidemic of NAFLD in the near future.[1] NAFLD has a wide clinical range from simple steatosis to NASH, hepatic cirrhosis, and related complications, including portal hypertension (HTN) and hepatocellular carcinoma (HCC). The most important prognostic factor in these patients is advanced fibrosis, leading to cirrhosis and HCC.[2]

The risk of death in patients with NAFLD and NASH is 69% and 86% higher than the normal population of the same age and sex, respectively.[3] Moreover, the overall mortality rate of patients with NAFLD and NASH is 11.77 and 25.56 per 1000 individuals per year, respectively,[4] thus, early detection and estimation of liver fibrosis are important.

Percutaneous liver biopsy is the best standard method available for liver fibrosis assessment; however, it has some limitations, including being invasive, small tissue samples, inter- and intra-observer variations in pathology reports, and potential complications of bile duct injury, hemoperitoneum, and pneumothorax.[5,6] Furthermore, liver biopsy is not a suitable method for monitoring fibrosis progression or response to treatment.[7]

Therefore, the need for non-invasive tools for the accurate assessment of liver fibrosis has been noted by researchers and physicians. An ideal non-invasive method for liver fibrosis assessment should be hepato-specific, easy to perform, reliable, and cost-effective. In addition to fibrosis grading, this potential method should be used for monitoring disease progression, treatment effectiveness, and follow-up with accurate and reliable results.[8,9]

One of the non-invasive imaging techniques is vibration-controlled transient elastography (VCTE), also known as FibroScan. This is a relatively new, fast, safe, reproducible, cost-effective, and available method and can be used in patient screening for liver fibrosis and predicting hepatic

*Corresponding Author: Masoud Reza Sohrabi, Email: sohrab_r@yahoo.com

complications, such as varicosis, HCC, and survival of the patients.[9,10] In VCTE, a probe is placed on the skin in the 9th to 11th intercostal spaces on the right side of the body and using ultrasound, and liver stiffness is measured by the difference in the velocity of elastic waves propagating through the liver tissue in the range of 2.5-75 kPa.[11]

The present study aimed to compare the diagnostic accuracy of VCTE and liver biopsy in detecting liver fibrosis in patients with NAFLD.

Materials and Methods

The present study included 95 patients who had presented to the Fatty Liver Clinic of the Hospital and were older than 18 years. The patients had been diagnosed with fatty liver disease using ultrasound, and had no history of considerable alcohol use (more than 10 and 20 g of daily ethanol for women and men for 2 years, respectively), after obtaining informed consent were willing to participate in the study.

The exclusion criteria were concomitant HIV infection; being affected by hepatitis, such as viral, autoimmune, drug-induced, or other types of hepatitis; hepatic or biliary malignancies; ascites; liver biopsy contraindications (a possibility of uncontrollable hemorrhage); chronic systemic diseases, such as chronic renal failure, severe cardiovascular diseases, and chronic pulmonary diseases; acute infections or sepsis; secondary NAFLD; alcoholism (more than 10 and 20 g of daily ethanol for women and men for 2 years, respectively); a history of liver transplantation; and cholestatic or vascular diseases of the liver. The demographics and laboratory results of the patients were recorded in a specific form. These data included age, sex, weight, height, nutritional behaviors, weekly physical activity and exercise, drug history, and history of major diseases, including hepatitis, diabetes mellitus (DM), HTN, hyperlipidemia, and cardiovascular diseases, as well as laboratory test results, including complete blood count, Fasting blood sugar, hemoglobin A1C, serum iron, total iron-binding capacity, ferritin, Alanine transaminase, aspartate transaminase, alkaline phosphatase, thyroid-stimulating hormone, prothrombin time, international normalized ratio, cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, and insulin levels. Then, 22 patients were excluded from the study because they were affected by other types of hepatitis, such as viral, autoimmune, or drug-induced hepatitis. Finally, 73 patients were included in the study and gave informed consent for participation. The participants first underwent VCTE using M or XL probes (for BMI > 30) by an experienced physician with at least 500 cases of VCTE performed. Following some days, the patients were hospitalized in the gastrointestinal ward. They gave informed consent to undergo a liver biopsy under ultrasound guidance by an experienced radiologist. The samples were sent to the pathology department for histological examination and were evaluated by an experienced pathologist who was blinded to the VCTE results and demographics of the patients. The present study followed the Declaration of Helsinki and was approved by the ethics committee of the Hospital with the ethics code of (IR.UMSHA.REC.1400.373).

Statistical Analysis

The data were analyzed using descriptive statistical indices (mean and ratio) and inferential statistical methods (*t* test and logistic regression). The data analysis was performed using the SPSS software version 22. Moreover, the positive predicted value (PPV), the negative predicted value (NPV), sensitivity (se), specificity (sp), and AUROC curve were used to investigate the diagnostic methods studied. A two-tailed P value < 0.05 was considered significant.

Results

Ninety-five patients with a diagnosis of NAFLD by ultrasound were included in the study. Then, 22 patients were excluded from the study due to hepatitis caused by other causes. Finally, data analysis was performed for 73 patients. The mean age of the participants was 43.19 ± 11.41 years. 45 (61.60%) participants were males, and the rest were females. The basic characteristics of the study participants are presented in Table 1.

Inferential statistics were used to investigate the effect of different factors on the prevalence of liver fibrosis. First,

Table 1. Demographics, biochemical test results, pathology reports, and imaging findings of the study participants.

Demographic	
Age at biopsy, mean (SD)	43.19 (11.41)
Male, n (%)	45 (61.60%)
Female, n (%)	28 (38.40%)
BMI (kg/m^2), median (IQR)	28.70 (4.3)
Diabetes, n (%)	54 (74%)
Metabolic syndrome, n (%)	48 (65.80%)
Biochemical profile	
AST (U/L), median (IQR)	51.0 (38.0)
ALT (U/L), mean (SD)	82.92 (54.15)
AST/ALT ratio, median (IQR)	0.72 (0.43)
ALP (U/L), median (IQR)	186.0 (114)
Triglycerides (mg/dL), median (IQR)	172.0 (114.0)
Total cholesterol (mg/dL), mean (SD)	201.146 (39.158)
HDL (mg/dL), median (IQR)	43.75 (17.25)
LDL (mg/dL), median (IQR)	119.04 (56.75)
Ferritin (mg/dL), median (IQR)	111(103.25)
Histology (fibrosis), n (%)	
0	23 (31.5)
1	26 (35.62)
2	9 (12.33)
3	4 (5.48)
4	11 (15.07)
Imaging	
TE (kPa), median (IQR)	9.4 (7.25)

the patients were divided into two groups (with fibrosis, staging = 1.00, and without fibrosis, staging = 0.00), and the relationship between different factors in these two groups was statistically examined. Tables 2 and 3 summarize the status of the influence of various factors. Since the confidence percentage was considered to be 95, so the factors for which the *P* value reported by SPSS software is less than 0.05 will be effective, and the effects of other factors will not be in the critical range. According to the information, in the use of liver biopsy to diagnose fibrosis, diabetic factors affect the incidence of liver fibrosis, and there is no significant difference in other factors; in other words, these factors do not affect the prevalence of fibrosis.

Of the total of 73 patients, 23 had no evidence of hepatic fibrosis in liver biopsy samples, while 26, 9, 4, and 11 patients had hepatic fibrosis grades 1, 2, 3, and 4, respectively. Using VCTE, it was found that 99 patients had no fibrosis, while 11, 14, 13, and 26 patients were diagnosed with hepatic fibrosis grades 1, 2, 3, and 4, respectively. For further validation, the ROC curve was plotted for each hepatic fibrosis grade (1 to 4) separately (Figure 1).

The related sensitivity, specificity, and area under the ROC curves are presented in Table 4 for each fibrosis grade (Figure 1). Moreover, related PPVs and NPVs are presented in Table 4. We used the cut-off point with the most sensitivity and specificity for liver fibrosis staging; as a result, we identified the cut-off points as 5.7 for any fibrosis, 7.1 for stage 2-4 fibrosis, 9.35 for stage 3-4 fibrosis, and 14.3 for stage 4 fibrosis. VCTE could detect any fibrosis (stage 1 and higher) with an area under the ROC curve (AUROC) of 0.381 (95% CI: 0.258-0.517). Moreover, it detected stage 2-4 fibrosis with an AUROC of 0.400 (95% CI: 0.212-0.588), stage 3-4 fibrosis with an AUROC of 0.687 (95% CI: 0.507-0.881), and stage 4 fibrosis with an AUROC of 0.984 (95% CI: 0.9621.00).

Discussion

Although liver biopsy is the gold standard for hepatic fibrosis assessment and prognosis determination in

Table 3. Comparison of qualitative variables between patients with fibrosis and without fibrosis

Factor		Staging		*P* value
		0	1	
Gender	Male	16	29	0.345
	Female	7	21	
Diabetes	+	5	49	0.0001
	-	18	1	
Metabolic syndrome	+	12	36	0.097
	-	11	14	

Table 2. Comparison of quantitative variables between patients with and without fibrosis

Factor	Staging	Number	Mean	Standard deviation	*P* value
Age	0	23	42.3	12.16	0.673
	1	50	43.6	11.15	
AST	0	23	45.53	22.80	0.277
	1	50	59.30	31.82	
ALT	0	23	81.07	68.42	0.215
	1	50	83.77	46.96	
ALP	0	23	195.45	79.03	0.823
	1	50	199.06	55.66	
TG	0	23	179.65	99.13	0.570
	1	50	194.29	103.18	
HDL	0	23	42.9	12.08	0.60
	1	50	44.3	10.43	
LDL	0	23	131.27	42.43	0.055
	1	50	115.16	27.45	
Cholesterol	0	23	214.78	47.21	0.137
	1	50	194.87	33.54	
Maximum blood pressure	0	23	12.17	1.53	0.958
	1	50	12.21	2.29	
Alanine aminotransferase/aspartate aminotransferase	0	23	0.79	0.63	0.958
	1	50	0.80	0.34	
Ferritin	0	23	114.51	116.4	0.347
	1	50	148.79	150.58	
BMI	0	23	30.184	3.42	0.673
	1	50	28.98	3.46	

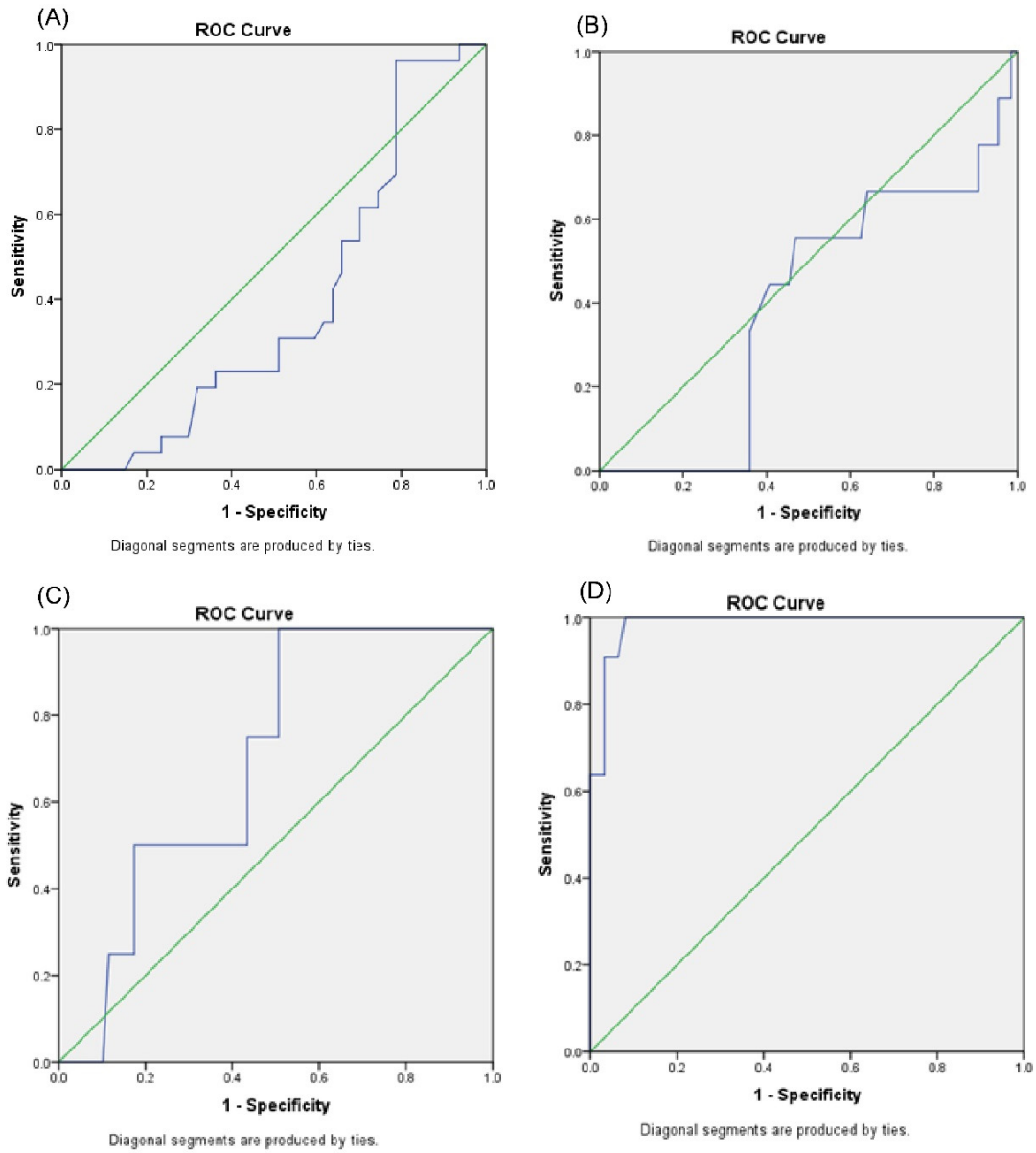

Figure 1. ROC curves for the diagnosis of fibrosis stage (A) 1, (B) 2, (C) 3 and (D) 4 using VCTE.

Table 4. Value of liver stiffness measurements in non-alcoholic fatty liver disease for estimating the stage of liver fibrosis

Fibrosis staging	Cut-off (kPa)	AUROC (95% CI)	Sensitivity	Specificity	NPV%	PPV%
F1 ≤ (n = 50) versus stage 0 (n = 23)	5.7	0.381	96.2	21.3	60	73
F2 ≤ (n = 24) versus stage 0-1 (n = 49)	7.1	0.4	66.7	28.1	71.85	40.38
F3 ≤ (n = 15) versus stage 0-2 (n = 58)	9.35	0.687	75	49.3	97.14	36.8
F4 = (n = 11) versus stage 0-3 (n = 62)	14.3	0.984	100	91.9	100	68.75

patients with NAFLD, several non-invasive alternative methods have been proposed to replace it due to sampling errors, related complications, and lack of acceptance by the patients. Considering the need for serial and lifetime assessments for disease progression detection, decision-making for treatment initiation and response to treatment evaluation, the application of non-invasive methods is of particular importance. Therefore, the methods used for liver stiffness measurement, such as VCTE, have become popular.[11]

The present study intended to compare the diagnostic value of VCTE with liver biopsy in diagnosing hepatic fibrosis in Iranian patients suffering from NAFLD. Our study analyzed four different cut-off points, of which all indicated a high NPV and sensitivity. This is compatible with the results by Yoneda and colleagues who reported the best performance and specificity with a cut-off point of 14.3 kPa.[12] However, it is worth mentioning that the best cut-off point for predicting the fibrosis grade in patients with NAFLD is currently controversial. According to our findings and by comparing them with other studies, it was shown that VCTE has a high NPV for ruling out advanced

fibrosis and cirrhosis (fibrosis grades 3-4).[13,14]

Our results from the ROC curve plotted in fibrosis grades 1 and 2 indicated the low capability of VCTE in diagnosing hepatic fibrosis in early grades compared with biopsy, while in advanced fibrosis and cirrhosis, the related AUROC was close to 100% and ideal. This indicates the extremely high sensitivity of VCTE in diagnosing cirrhosis.

In the present study, we found an AUROC of 0.984, a sensitivity of 100%, and a specificity of 91.9% for cirrhosis diagnosis using the VCTE. However, a study by Park and others reported an AUROC of 0.69, a sensitivity of 62.5%, and a specificity of 66.3% for cirrhosis diagnosis.[15] This difference can be explained by different cut-off points used for the cirrhosis grade.

A meta-analysis by Hashemi and colleagues investigated the diagnostic value of VCTE in diagnosing hepatic fibrosis. The meta-analysis included seven studies with a total of 698 participants and showed the increased sensitivity and specificity of fibrosis diagnosis with increasing grades of hepatic fibrosis.[10] According to the mentioned meta-analysis, the VCTE had sensitivities of 87.5%, 93.7%, and 96.2% and specificities of 78.4%, 91.1%, and 92.2% for diagnosing the hepatic fibrosis grades 2, 3, and 4, respectively. The authors concluded that VCTE could be used to rule out hepatic cirrhosis, although further studies are needed to confirm this conclusion. However, among all non-invasive methods, VCTE has the highest accuracy in cirrhosis detection in patients with NAFLD.[10]

Another meta-analysis by Xiao and colleagues collected and analyzed the data from 2495 patients of different races. The study showed that the AUROC values obtained from M and XL probes, which were 0.87 and 0.86 for advanced fibrosis and 0.92 and 0.94 for hepatic cirrhosis, respectively, were not significantly different. These results are compatible with ours regarding patients with cirrhosis. However, they are incompatible with ours in advanced fibrosis, which can be explained by different study populations and designs.[16]

Various studies on patients with NAFLD have shown a lack of comprehensive and generally accepted algorithms among physicians for the diagnosis and management of fibrosis in patients with NAFLD, which is due to the lack of a strong non-invasive method (alone or in combination with other methods). However, according to the EASL guideline, a combination of several methods, such as VCTE with NFS, can be better than using just one method.[17] Finally, the application of non-invasive methods in primary care can reduce the unnecessary referral of patients with mild disease, help in the early detection of advanced fibrosis,[14] and decrease related costs.[18]

One of the strengths of the present study was that we used a well-characterized cohort of patients with NAFLD undergoing liver biopsy for clinical indications, while the liver biopsy was used as a standard reference to evaluate the imaging results. The liver biopsy was scored using the NASH Clinical Research Network Histologic Scoring System, which is well-validated for NAFLD assessment. Moreover, the procedures and imaging investigations were performed by experienced operators at a research center specialized in clinical and radiological research on NAFLD. Also, it should be noted that the participants were carefully evaluated to exclude other causes of hepatic disease before the inclusion, and the maximum duration between biopsy and VCTE was 10 days, which was very close to the ideal. However, the limitations of the study included the difficult process of patient collection and receiving informed consent for liver biopsy, as well as the limited number of beds for the hospitalization of the patients.

Conclusion

The present study showed that VCTE had an acceptable sensitivity in diagnosing advanced fibrosis and cirrhosis and is an accurate, and reproducible method for assessing liver fibrosis. However, this method has lower diagnostic value for detection of fibrosis in the early grades (grades 1 and 2). Therefore, currently to obtaining better result we need, to use other modalities to distinguish fibrosis levels in patients with NAFLD.

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Competing Interests

The authors declare no conflict of interest related to this work.

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