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ORIGINAL ARTICLE

Correlation Between Point Shear Wave Elastography and Liver Function Tests as A Predictor of Liver Fibrosis in Patients with Nonalcoholic Fatty Liver Disease

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ABSTRACT

Aim: of this study is to correlate between point shear wave elastography(pSWE) and liver function tests (LFTs) to predict liver fibrosis in patients with non-alcoholic fatty liver disease (NAFLD).

Materials and methods: this study is a cross sectional study conducted in Ultrasound Clinic in Suleymaniya city. The duration of the study was through the period from 1st of November, 2018 to 30th of June, 2019 on 50 NAFLD patients. After confirming NAFLD diagnosis, the patients were referred to Ultrasound Clinic to complete Point Shear Wave Elastography (PSWE).

Results: showed a mean PSWE of NAFLD patient was 4.12±0.87 Kpa; 18% of them had high PSWE (> 4.6). Elastography fibrosis score was distributed to F0 (82%), F1 (6%), F2 (8%) and F3 (4%). The Aspartate Aminotransferase Platelet Ratio Index (APRI) fibrosis scores were distributed to F0 (48%), F1-3 (48%) and F4 (4%), There was a highly significant association between elastography fibrosis score and APRI fibrosis score of NAFLD patients ($p<0.001$), There was no significant association between elastography fibrosis score and Aspartate Aminotransferase/Alanine Aminotransferase (AST/ALT) values of NAFLD patients ($p=0.5$).

Conclusion: this study showed that the point shear wave elastography is a valuable noninvasive diagnostic technique for predicting significant liver fibrosis among patients with non-alcoholic liver fatty diseases and there is significant correlation between APRI score and pSWE score.

The current gold standard in the diagnosis and staging of liver fibrosis is liver biopsy. Point shear wave elastography is among the noninvasive procedures to assess liver fibrosis.

Keywords: Non-alcoholic fatty liver disease, Point shears wave elastography, Liver fibrosis.

INTRODUCTION

Liver fibrosis is a progressive disease , so its early diagnosis leading to early clinical intervention that may slow down or stop progression to cirrhosis[1]. Many chronic liver diseases end with liver fibrosis. One of them Non-alcoholic fatty liver disease (NAFLD) is. NAFLD is associated with overweight and insulin resistance. Chronic metabolic conditions such as diabetes and degenerative conditions like atherosclerosis also may leads to pathological changes in the biochemical profile of the liver that lead to liver fibrosis[2]. NAFLD is a wide term covering form simple non-alcoholic fatty liver (NAFL), in which there is pure hepatosteatosis only, mild inflammatory process and non-alcoholic steatohepatitis (NASH). The existence of these three histopathological features, i.e., steatosis, inflammation and ballooning (swollen hepatocytes), is required for NASH, which also covers the most progressive forms of NAFLD, fibrosis, cirrhosis and HCC[3].

Diagnosis of liver fibrosis in NAFLD: - consist of noninvasive and invasive methods the non invasive method consist of laboratory and ultrasonic diagnosis As the liver biopsy is an invasive method, over the last years there has been a growing requirement to encourage noninvasive tools to diagnose and stage liver fibrosis. Aspartate Aminotransferase Platelet Ratio Index (APRI) is a laboratory marker that has been shown to have some value in staging liver fibrosis but is lower to liver biopsy[4]. As diabetes, obesity, old age, platelet count ≤ 200 × 109/L, and Aspartate Aminotransferase/Alanine Aminotransferase (AST/ALT) ratio ≥ 0.8 are risk factors of advanced fibrosis (≥ F3) in patients with NAFLD, there are many scoring systems found to predict fibrosis, mostly based on these variables. Of these, APRI index & AST/ALT ratio[4], The AST to ALT ratio is useful index for distinguishing nonalcoholic steatohepatitis from alcoholic liver disease[5], The APRI have acceptable accuracy for the assessment of liver fibrosis in patients with Chronic Hepatitis C (CHC) and NAFLD, but not in those with Chronic Hepatitis B (CHB)[6].

Ultrasonic diagnosis of liver fibrosis in NAFLD: Ultrasound (US) is an acceptable first-line screening machine for NAFLD patients due to its availability and safety. The different gray levels in an ultrasound image reflect acoustic properties of different tissue structures, such as the attenuation of acoustic waves, speed of sound, and acoustic impedance. NAFLD patient's liver appears brighter in an ultrasound B mode image relative to the adjacent kidney or spleen, and the attenuation is larger in severe cases, often obscuring the hepatic and portal vein walls. The sensitivity and specificity of ultrasound for detecting NAFLD have ranged from 60–94% and 84–95%, respectively, in various studies, with the sensitivity being lower when the degree of NAFLD is mild. Previous studies proposed different scoring systems for diagnosing NAFLD [7].

US have many limitations such as : relatively low acuity , its operator-dependency with variable inter- and intra-observer agreement for steatosis being confirmed in some studies though demolished by others and the low accuracy in sever obesity where sensitivity is lowered to 49.1% and specificity to 75%, though with positive predictive value still as high as 95%, Regrettably , B-mode US is inaccurate in detecting fibrosis, it is only with the recent development of US techniques assessing liver

stiffness that it has been possible to quantitate liver fibrosis non-invasively and predict its complications early[8].

Ultrasound based elastography: The imaging modality that estimate the elasticity of liver structure, which is directly associated with the fibrosis staging . The most widely used method is transient elastography (TE), which allows to estimate the elasticity of a portion of liver parenchyma that is around 100 times greater than that examined by liver biopsy, and validated in many studies to have sensitivity and specificity somewhat proximal to liver biopsy [7,9].

Principles of Elastography: Elastography, first mentioned by Ophir et al in 1991[10], describes the noninvasive measurement of tissue mechanical properties such as elasticity, which describes the resistance to changing of a tissue to an applied force. In quantitative elastography methods, the stress is applied via shear-wave propagation, generated transiently, for example, via single mechanical impulse, or dynamically, for example, via continuous application of acoustic waves. Variable elastographic methods are present. Quantitative US elastography methods include transient elastography (TE) and acoustic radiation force impulse (ARFI) techniques such as point shear-wave elastography (pSWE) and two- dimensional (2D) shear-wave elastography (SWE)[11].

Acoustic Radiation Force Impulse (ARFI) principle: Acoustic Radiation Force Impulse (ARFI) imaging is a mode for evaluation of mechanical features of the tissue, without manual compression, by measuring the shear wave speed induced by acoustic radiation and propagating in the tissue. This method has been presented by Siemens and is available on Acuson S2000 and S3000 ultrasound diagnostic imaging devices (Issaquah, WA, USA), and on the Philips diagnostic imaging device developed (Bothell, WA, USA).

This quantitative technique gives a single uni-dimensional measurement of tissue elasticity like the FibroScan, although the measurement area can be positioned on a two-dimensional B mode image. The region is rectangular measuring 1 × 0.5 cm ,The shear wave velocity is presented in meters per second (m/s) or in kPa through Young's modulus $E = 3 (vS^2.\rho)$, where E is Young's modulus, vS is the shear wave velocity and ρ is the density of the tissue[12]

Advantages of ARFI:

- ARFI is present in a conventional ultrasound diagnostic imaging device, which allows the combination, in one exam, of quantitative elastography after a complete morphological ultrasound examination of the liver.
- Easley select the depth measurement, unlike the FibroScan.
- It is an easy, fast, painless technique.
- Results are available after a few seconds.
- Good diagnostic performance: although still undergoing assessment this technique has already appeared in many publications.

Limitations of ARFI: -

- Different cutoff values of fibrosis grading are available, according to the vendors so comparison between different vender is not usable.
- The elasticity measurement is not in real time.
- Only one acquisition can be taken at a time.
- The measurement region is a small, predetermined area, the size of which cannot be changed.
- The available publications using ARFI is less than those using FibroScan
- The technique has not been validated as extensively as transient elastography (FibroScan)[13]

Diagnostic performance of pSWE in assessing liver fibrosis in NAFLD: NASH is a widespread problem in the United States due to the increasing obesity and NAFLD. Liver fibrosis is the commonest complications in NAFLD patients, which motivates the need for a noninvasive technique for detection liver fibrosis and will be of major interest for clinicians and in terms of public health perspective[14]. A former study in NAFLD patients found that pSWE performed very well when diagnosing fibrosis stage F3–F4 and F4, with AUC greater than 0.97 (Fig 5). a series of studies have reported similar high accuracy in diagnosing fibrosis and differentiating NASH from simple steatosis. In a comparative study of pSWE and TE, no significant difference was found, although pSWE achieved a significantly higher reliability rate[11].

Invasive diagnosis: - Liver Biopsy (LB): - NAFLD term covering a spectrum of histological findings from uncomplicated steatosis, steatosis with inflammation and steatohepatitis [nonalcoholic steatohepatitis (NASH) the latter can advance to cirrhosis and hepatocellular carcinoma. NASH is currently accepted as the hepatic manifestation of the set of cardiovascular risk factors collectively known as metabolic syndrome. In 1999 a system for histologic grading and staging for NASH was proposed; this was revised by the NASH Clinical Research Network in 2005 for the entire spectrum of lesions in NAFLD, including the lesions and patterns of pediatric NAFLD, and for application in clinical research trials. Diagnosis remains distinct from grade and stage. A recent European proposal separates steatosis from activity to derive a numeric diagnosis of NASH. Even though there have been promising progression in non-invasive testing, these tests are not yet detailed enough to replace the full range of findings provided by liver biopsy evaluation. Limitations of biopsy are known, but liver biopsy remains the "gold standard" for determination of amounts of necroinflammatory activity, and location of fibrosis, as well as remodeling of the parenchyma in NASH[15], Moreover, liver biopsy is an invasive technique that is not well accepted by patients, small sample size bias and is not an ideal method for following patients[9].

Design, Settings & Sampling: - This study is a cross sectional study conducted in Ultrasound Clinic in Sulaymaniyah city. The duration of study was through the period from 1st of November, 2018 to 30th of June, 2019. All patients with non-alcoholic fatty liver diseases (NAFLD) underwent PSWE examination and liver function tests and some other laboratory investigations (illustrated in the questionnaire) , the inclusion criteria were Age from 18 years to 70 years, bright echogenic liver on ultrasound scanning (increased liver/kidney echogenicity), while exclusion criteria were alcoholic patients, also patients with viral hepatitis, autoimmune hepatitis, Wilson's disease, hemochromatosis and patients refused to participate.

A sample of 50 NAFLD patients was selected after

eligibility to inclusionand exclusion criteria.

Data collection: - The data collection was carried out by the researcher through direct interview with selected patients and filling in a prepared questionnaire. The questionnaire was designed by a gastroenterologist (experience of 5 years), researcher and supervisor (has experience of 1.5 year in pSWE).

After taking full history and examination of NALFD patients and calculating their body mass index (BMI), mean BMI were analyzedaccording to international BMI category:

1. underweight < 18.5kg/m^2
2. normal (18.5 kg/m^2 - 25 kg/m^2)
3. overweight (25 kg/m^2 - 30 kg/m^2)
4. obesity ≥ 30 kg/m^2 as obesity[16].

All the patient sent for the laboratory investigations as described in the questioner. AST/ALT were calculated for all the patients, mean AST to ALT ratios of the patient were analyzed to three groups according to 0.7, 0.9, and 1.4 cutoff values (no fibrosis, mild fibrosis, cirrhosis, respectively)[5], APRI score was calculated using a formula APRI = [(AST level/ULN of AST)/platelet counts (10^9/L)] × 100. A score of < 0.5 was graded as F0, 0.5-1.5 as F1- F3 and >1.5 as F4[1].

After that the patients were referred to perform pSWE using ultrasound machine AFFINITI 70 G Philips 2014 with EPQ software (release 3.0.3), the pSWE were accomplished by the supervisor.

The pSWE were performed for the patients after being fasting for at least 4 hours[17], ultrasound based pSWE exam done after selecting the best acoustic window, a region of interest (ROI) is placed in an area of the liver perpendicular to the liver capsule, taking care not to include large vasculature or biliary structures. An intercostal imaging approach targeting segments 7 or 8 of the liver. At least ten validated measurements are taken while the patient suspends respiration (taking in consideration IQR/median ratio is < 30%), automatic median value generated by the ultrasound software EPQ.

Interpretation of liver fibrosis by point shear wave elastography were done according to Philips vendor cutoff value in kPa divided the patients into five groups: -

1. No fibrosis (F0 < 4.6 KPa).
2. Mild fibrosis (F1 4.6-5.6 KPa).
3. Moderate fibrosis (F2 5.7-7 KPa).
4. Marked fibrosis (F3 7.1-12 KPa).
5. Cirrhosis (F4 > 12 KPa) was used to establish the elastography grade[1].

Ethical considerations: -

1. An approval was taken from General Directorate of Health – Suleymaniya
2. An oral informed consent was taken from patients.

Statistical analysis: - The data of patients were analyzed by application of Microsoft excel program and Statistical Package for Social Sciences (SPSS) version 23. Outcomes of analysis were arranged in scales variables (means & standard deviation) and in categorical variables. Chi square test was used for comparison between categorical data (Fishers exact test applied when expected variable was less than 20% of total). The level of significance (p value) was set as ≤ 0.05.

RESULTS

In present study, 50 non-alcoholic fatty liver diseases (NAFLD) patients were included with mean age of 44.5±10 years; 28% of them were less than 40 years age, 38% of them were in age group 40-49 years, 24% of them were in age group 50-59 years and 10% of them were 60 years age and more. Males NAFLD patients were equal to females NAFLD patients with male to female ratio as 1:1. in Mean weight of NAFLD patients was 89.5±19.1 Kg and mean height of them was 1.69±0.08 m, while mean BMI of NAFLD patients was 31.6±6 Kg/m^2; 16% of NAFLD patients had normal BMI, 26% of them were overweight and 58% of them were obese. All these findings were shown in All these findings were shown table 1.

Table 1: Demographic characteristics of NAFLD patients.

Variable	No.	%
Age mean±SD (44.5±10 years)		
<40 years	14	28.0
40-49 years	19	38.0
50-59 years	12	24.0
≥60 years	5	10.0
Total	50	100.0
Gender		
Male	25	50.0
Female	25	50.0
Total	50	100.0
Weight mean±SD (89.5±19.1 Kg)		
Height mean±SD (1.69±0.08 m)		
BMI mean±SD (31.6±6 Kg/m^2)		
Normal	8	16.0
Overweight	13	26.0
Obese	29	58.0
Total	50	100.0

Mean ALT of NAFLD patients was 73.4±59.3 U/L; 50% of them had high ALT. Mean AST of NAFLD patients was 58.5±89.9 U/L; 64% of them had high AST. Mean upper limit normal of AST was 37.2±2.6 U/L. Mean platelets count of NAFLD patients was 228.4±50.6 x10^9/L; only one patient had low platelets count All these findings were shown in table 2.

Table 2: laboratory investigations of NAFLD patients.

Variable	No.	%
ALT mean±SD (73.4±59.3 U/L)		
Normal	25	50.0
High	25	50.0
Total	50	100.0
AST mean±SD (58.5±89.9 U/L)		
Normal	18	36.0
High	32	64.0
Total	50	100.0
ULN-AST mean±SD (37.2±2.6 U/L)		
Platelets count mean±SD (228.4±50.6 x10^9/L)		
Normal	49	98.0
Low	1	2.0
Total	50	100.0

Mean PSWE of NAFLD patients was 4.12±0.87 Kpa; 18% of them had high PSWE. Elastography fibrosis score was distributed to F0 (82%), F1 (6%), F2 (8%) and F3 (4%). All these findings were shown in table 3.

Table 3: Point shear wave elastography fibrosis scores of NAFLD patients.

Variable	No.	%
PSWE mean±SD (4.12±0.87 Kpa)		
Normal	41	82.0
High	9	18.0
Total	50	100.0
Elastography fibrosis score		
F0 < 4.6 KPa	41	82.0
F1 (4.6 – 5.6) KPa	3	6.0
F2 (5.7 – 7) KPa	4	8.0
F3 (7.1 – 12) KPa	2	4.0
F4 > 12 KPa	0	0
Total	50	100.0

There was a highly significant association between elastography fibrosis score and APRI fibrosis score of NAFLD patients (p<0.001). as shown in table 4.

Table 4: correlation between elastography fibrosis score and APRI fibrosis score of NAFLD patients.

Variable	F0 APRI	F1-3 APRI	F4 APRI	P <0.001*s
F0 pSWE	22	19	0	
F1 pSWE	0	3	0	
F2 pSWE	2	2	0	
F3 pSWE	0	0	2	

* Fishers exact test, S=Significant.

There was no significant association between elastography fibrosis score and AST/ALT values of NAFLD patients (p=0.5). as shown in table 5.

Table 5: correlation between elastography fibrosis score and AST/ALT ratio in NAFLD patients.

Variable	No fibrosis	Mild fibrosis	cirrhosis	P
F0 pSWE	17	24	0	NS
F1 pSWE	2	1	0	
F2 pSWE	1	3	0	
F3 pSWE	0	2	0	

* Fishers exact test, NS=Not Significant.

Only three NAFLD patients have liver biopsy before the laboratory investigations and pSWE done for them and result are consistent with laboratory and pSWE result as shown in table 6.

Table 6: pSWE, AST/ALT ratio and APRI score and histological results.

Biopsy result	AST/ALT ratio	APRI score	pSWE
F0	0.5	0.6	3.71
F0	0.5	0.3	3.39
F1	0.8	0.9	5.3

DISCUSSION

Liver fibrosis is a commonest complication in majority of chronic liver diseases. An accurate staging of fibrosis is mandatory, especially for prognosis, disease management, treatment indication and long-term follow-up. Point shear wave elastography (PSWE) is one of the non-invasive method in assessing liver fibrosis[1,2,18].

Our study showed age range (40-49) years with higher incidence of NAFLD and equal incidence between male and female, Consistently, Shiobhan et al, study in South Korea how stated that the mean age of the NAFLD study participants was 50 years (range, 20-74 years) and 52.2% were male[19]. Although Mark Benedict et al, stated that the role of gender in the development of NAFLD has been met with differing conclusions in the literature. Several studies provide data to suggest a higher prevalence in males while others proposed the opposite. However, according to Lonardo et al, epidemiological review, NAFLD is more common in men and has been shown to increase in those who are younger to middle aged with a decline noted after the age of 50-60 years[20].

In current study, obese patients accounting about 58% of sample size. This finding is in disagreement with results of Manopriya et al[21] review study in India which revealed that NAFLD was more common in obese (91%),this may be due to his large sample size , racial and probably ethnic factors .

In recent study only 2% patients have low platelet count, and this not matching the result of Das S K et al, which documented that platelet count were significantly reduced among NAFLD patients[22], this may be due to small sample size and the fact that 82% of our NAFLD patients were within (F0) category.

Our study showed that 40% of patients have normal AST/ALT ratio and 60% have high AST/ALT ratio, this supported by Darius Sorbi et al, in USA stated that abnormal AST to ALT ratio are suggestive of NASH[5].

Current study revealed that 52% having high APRI score value, these findings are confirmed by Yusuf Yilmaz et al , in Turkey who stated that the APRI shows an acceptable accuracy for the assessment of liver fibrosis in patients with NAFLD[6].

Elastography fibrosis score in current study was distributed to F0 (82%), F1 (6%), F2 (8%) and F3 (4%), these results are not similar to the results of Masato Yoneda et al, in` Japan in which the categorization of NAFLD patients according to the elastography fibrosis score was F0(25%), F1(31%), F2(12%), F3(6%) and F4(9%)[23] , and this inconsistency due to Yoneda use another vender so there will be a difference in categorization as each vender has its own cutoff values and the majority of our NAFLD patients are within F(0) category (simple steatosis) were the fibrosis is not developed yet.

Current study revealed a highly significant association between elastography fibrosis score and APRI fibrosis score of NAFLD patients (p<0.001), this finding is similar to the results of Mark et al, study in Singapore which found a significant correlation between pSWE and APRI score and this emphasizing the important role of pSWE among NAFLD with abnormal APRI score[24].

Current study showed no significant association between pSWE fibrosis score and AST/ALT ratio (p=0.5), this result validated by Qian Li et al , in USA found that among NASH patients they may have normal AST/ALT ratio[25].

In this study only three patients had LB in which pSWE grades are matching those of their LB grades, this emphasizing the role of pSWE as a noninvasive tool for assessment of liver fibrosis in NAFLD.

The main limitations were the absence of liver biopsy, relatively small sample size, limited number of published articles using pSWE among NAFLD patients and there is no

standardized fibrosis score among different ultrasound vendors as each vendor has it[s] own elastography fibrosis score.

CONCLUSION

- NAFLD patients with abnormal APRI score are highly suggestive to have abnormal pSWE.
- There is no significant correlation between pSWE and AST/ALT ratio.

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