Point Shear Wave Elastography for Assessing Liver Stiffness in Chronic Liver Diseases of Different Etiologies Compared to Biopsy

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ABSTRACT **Background:** Point shear-wave elastography (pSWE) is a new method to assess the degree of liver fibrosis. It has been shown to be effective in detecting stiffness in viral hepatitis.

Objectives: To determine the feasibility of pSWE for assessing liver stiffness and fibrosis in liver diseases of different etiologies.

Methods: This prospective single-center study included a population of adult patients with chronic liver diseases from different etiologies, who were scheduled for liver biopsy, and a control group of healthy adults who prospectively underwent pSWE. Ten consecutive pSWE measurements of the liver were performed using a Philips iU22 ultrasound system. Stiffness degree was compared to liver biopsy results. Fibrosis degree was staged according to METAVIR scoring system.

Results: The study group was comprised of 202 patients who underwent liver biopsy and pSWE test and a control group consisting of 14 healthy adults who underwent pSWE for validation. In the study group, the median stiffness was 5.35 ± 3.37 kilopascal (kPa). The median stiffness for F0–1, F2, F3, and F4 as determined by liver biopsy results were 4.9 kPa, 5.4 kPa, 5.7 kPa, and 8 kPa, respectively. The median stiffness in the control group was 3.7 ± 0.6 kPa. Subgroup analyses were conducted for viral hepatitis vs. non-viral hepatitis and steatohepatitis vs. non-steatohepatitis groups.

Conclusions: pSWE is a reproducible method for assessing liver stiffness and is in a linear relationship with fibrosis degree as seen in pathology. Compared with patients with non-significant fibrosis, healthy controls showed significantly lower values.

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In the last decade, several noninvasive imaging modalities for assessment of liver fibrosis have been developed and are increasingly replacing liver biopsy [1]. Noninvasive assessment of hepatic fibrosis can be done with serologic tests or imaging. Serologic tests are desirable due to their noninvasive nature and potential wide availability. These tests detect byproducts of degradation or synthesis of collagen, or assess the effect of fibrosis on hepatocytes function. Unfortunately, serum tests are not reliable because non-hepatic related inflammation can contribute to false-positive test results, and serum levels are affected by clearance rates, which may be impaired due to sinusoidal endothelial cell dysfunction or impaired biliary excretion [2].

Ultrasound elastography is one of the most accurate imaging methods [3-6]. It calculates liver stiffness by measuring the propagating velocity through the liver of acoustically induced mechanical shear waves, a process termed shear wave elastography. The speed of shear waves traveling through the liver is faster in stiffer fibrotic livers than in normal livers. A number of proprietary elastography technology embodiments have been developed by different manufacturers of elastography equipment, including acoustic radiation force impulse imaging (ARFI) and dynamic shear wave elastography (SWE) [2].

One such shear wave imaging modality is point shear wave elastography (pSWE). The longest and most experienced pSWE product is VTQ® (Siemens. AG, Erlangen, Germany) followed by ElastPQ® (Philips, USA). More recently pSWE methods have become available from many other companies [7].

In this modality, the operator can select the depth at which liver elasticity is evaluated by placing a measuring box (The size depends on the manufacturer.) in the right liver lobe (segment VII or VIII) via an intercostal approach and with the transducer at 90° in relation to the liver capsule in an area free of large vessels. In a pSWE study using VTQ® to measure shear wave speed (SWS) [8], the best correlation with histological fibrosis was observed for measurements performed 1–2 cm and 2–3 cm beneath the liver capsule (0.675 and 0.714, respectively), but in up to 15% of cases, measurements could not be obtained if performed 2–3 cm under the liver capsule [7].

pSWE has proven to have an excellent intraoperator and interoperator reproducibility for liver elastography assessment in both healthy subjects and patients with chronic liver disease [7, 9-14].

Bota and colleagues [15] evaluated factors that influenced the correlation of SWS assessed by VTQ® with histological fibrosis in a cohort of 106 chronic hepatitis C patients. In univariate and multivariate analysis, an interquartile range/median (IQR/M) ≥ 30% was associated with a discordance of at least two stages of fibrosis between SWS and histological fibrosis. Using ElastPQ®, Ferraioli and co-authors [16] suggested that an IQR/M ≤ 30% is the most important quality criterion, whereas the number of measurements seems not to affect the performance, provided that they are at least five. Thus, the compliance with quality criteria may increase the diagnostic accuracy of pSWE [15]. Quality parameters have been described for other manufacturers as well [7,17].

The performance of this type of shear wave elastography is promising [18-21], but it is not as widely validated as transient elastography (TE) or ARFI-based approaches [2].

The aim of our study was to investigate the yield of pSWE in chronic liver diseases of different etiologies by comparing the elastography results to liver biopsy pathology results, the gold standard method.

PATIENTS AND METHODS

The patient population included adults over 18 years of age with suspected chronic liver disease of any etiology scheduled to undergo a liver biopsy. The patients were referred from the liver unit at a single university hospital. The study was approved by the institutional ethics committee. Patients were prospectively recruited to perform a pSWE after signing an informed consent.

Exclusion criteria included patients under 18 years old and those with portal vein thrombosis, right heart failure, or hepatocellular carcinoma, or patients who did not plan to undergo liver biopsy. Demographic and clinical data, laboratory and pathological results were gathered for each patient.

Liver biopsies were conducted after 6 hours of fasting. The place of the biopsy was determined during an ultrasound examination. Biopsies were performed by a senior hepatologist (the first author), with more than 3 years of experience using a 16 G full core biopsy needle (BioPence™, Argon medical devices, USA), placed in formalin and sent to pathology. Patients were followed for at least 6 hours and discharged if there were no complications.

The pSWEs ultrasound examinations were performed by ultrasound technicians and interpreted by specialists in radiology with more than 10 years of experience. The tests were performed using a Philips IU22 ultrasound system (Bothell, Seattle, USA) using a 1-5 MHz transducer with the patient in a supine position. Patients were asked to hold their breath while the measurements were being taken. Measurements were conducted in at least 10 regions of interest (ROI) on the upper right lobe of the liver, segments 7–8 about 1–2 cm below the diaphragm. Measurements were electronically calculated in kilopascal (kPa) and the median, mean, and standard deviation values were presented.

Pathological and elastography data were reported by separate operators in a double-blind manner. Elastography results were compared to the pathologic tests by the hepatologists.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). Descriptive statistics in terms of mean ± standard deviation, median, percentiles, and ranges presented to the whole parameters in the study. The normal distribution of the quantitative parameters was tested by Kolmogorov Smirnov test. Parametric and non-parametric tests were used.

Differences between groups (hepatitis B virus (HBV)/ hepatitis C virus (HCV), non-alcoholic steatohepatitis (NASH), stage of fibrosis) in the median of PSWE were tested by *t*-test, Mann-Whitney U test, Anova and Kruskal–Wallis tests. The relation between laboratory parameters and the PSWE were tested by Pearson correlation or Spearman's rho correlation. A receiver operating characteristic (ROC) curve was used to describe the relationship between the sensitivity and the false positive rate for different values of pSWE (stiffness) in the identification of patient at risk for fibrosis stage. Area under the curve with 95%confidebnce interval (95%CI) was presented. $P < 0.05$ was considered as significant.

RESULTS

Between January 2014 and February 2017, 202 patients with suspected liver disease of any origin were included in the study, 103 (51%) of them were females. Demographic data is presented in Table 1. The most common diagnosis on liver biopsy was cryptogenic (49 patients (24%) followed by viral hepatitis 42 (22.8%), non- alcoholic fatty liver disease (NAFLD) 36 (17.8%), autoimmune hepatitis 21 (10.4%), and primary biliary cholangitis 8 (4%), overlap 6 (3%), Wilson's disease, drug induced liver injury 4 patients each (2%), sarcoidosis 3 (1.5%) and other etiology was seen in 5 patients (2.5%). Biopsies were normal in 11.4% of the patients.

Ninety-seven patients (48%) had fibrosis degree F=0. F1 and F2 were seen in 33 patients each (16.4%), F3 in 26 patients (12.9%), and 12 patients (6%) had F4 fibrosis. The inflammation degree was A0 in 21 patients (10.4%), A1 in 56 (27.9%), A2 85 (42.3%), A3 37 (18.4%), and A4 in two patients (1%). Data of one patient were missing.

The stiffness degrees in elastography were compared to the fibrosis degree in pathology [Table 2]. There was a direct correlation between the results obtained in elastography and pathology: $R = 0.45$, $P < 0.001$ by Spearman's rho correlation [Figure 1].

The cutoff for each fibrosis stage was set based on the median stiffness degree. For fibrosis F ≤ 2 (clinically insignificant fibrosis), the stiffness degree with the highest sensitivity and specificity was 5.4, 95%CI 0.67–0.82, area under the ROC

Table 1. Demographic, laboratory, and histo-pathologic data

	All patients (n=202)	Non-viral (n=160)	HBV/HCV (n=42)	*P* value
Age	44.2 ± 12.9	45.7 ± 13.1	38.6 ± 11.1	*P* = 0.002
BMI	26.6 ± 4.8	27.0 ± 4.8	25.1 ± 4.9	*P* = 0.03
Gender: female	99 (49%)	80 (50.0%)	19 (45.2%)	*P* = 0.61
Country of origin Israel Former Soviet Union Other	 113 (56%) 73 (36%) 15 (8%)	 102 (63.7%) 46 (28.7%) 12 (7.5%)	 11 (26.8%) 27 (65.9%) 3 (7.3%)	*P* < 0.0001
Hypertension	7 (3.5%)	5 (3.1%)	2 (4.8%)	*P* = 0.64
Diabetes	4 (2%)	4 (2.5%)	0	*P* = 0.58
Hyperlipidemia	3 (1.5%)	3 (1.9%)	0	*P* = 1.00
Alcohol abuse	1 (0.5%)	0	1 (2.4%)	*P* = 0.21
*HIV	0	0	0	
*ALT (U/L)	64 (35–110)	66 (36–110)	51.5 (35–76)	*P* = 0.14
*ALP (U/L)	102 (65–155)	108 (78–155)	78 (65–105)	*P* < 0.0001
*Bilirubin (mg/dl)	0.69 (0.5–0.96)	0.69 (0.5–0.9)	0.69 (0.55–0.96)	*P* = 0.61
Albumin (g/l)	4.35 ± 0.52	4.33 ± 0.55	4.41 ± 0.38	*P* = 0.38
Creatinine (mg/dl)	0.78 ± 0.19	0.78 ± 0.19	0.76 ± 0.18	*P* = 0.53
INR	0.99 ± 0.09	0.99 ± 0.09	0.99 ± 0.07	*P* = 0.65
PLT (K/μL)	226.6 ± 62.4	227.9 ± 64.9	221.9 ± 51.8	*P* = 0.58
Fibrosis score by biopsy F0 F1 F2 F3 F4	 97 (48.3%) 33 (16.4%) 33 (16.4%) 26 (12.9%) 12 (6.0%)	 82 (51.6%) 22 (13.8%) 29 (18.2%) 17 (10.7%) 9 (5.7%)	 15 (35.7%) 11 (26.2%) 4 (9.5%) 9 (21.4%) 3 (7.1%)	*P* = 0.06
Inflammation A0 A1 A2 A3 A4	 21 (10.4%) 56 (27.9%) 85 (42.3%) 37 (18.4%) 2 (1.0%)	 21 (13.2%) 45 (28.3%) 65 (40.9%) 26 (16.45) 2 (1.3%)	 0 11 (26.2%) 20 (47.6%) 11 (26.2%) 0	*P* = 0.08

*Median 25–75%

ALP = alkaline phosphatase, ALT = alanine aminotransferase, BMI = body mass index, HBV/HCV = hepatitis B virus/hepatitis C virus, HIV = human immunodeficiency virus, INR = international normalized ratio, PLT = platelets

curve (AUC) 0.744. For F3 and F4 the median stiffness degree was 5.765 (95%CI 0.74–0.89) and 8.5 (0.91–0.98), respectively, and the AUC for F3 and F4 was 0.82 and 0.95, respectively.

A sub group analysis included patients with viral hepatitis compared to non-viral hepatitis. In our cohort there were 42 patients with viral hepatitis (B or C), and 160 patients with non-viral hepatitis. Patients with viral hepatitis were younger (mean age 38.6 ± 11.1 years vs. 45.7 ± 13.1) and with lower body mass index (BMI) (25.1 ± 4.9 vs. 27.0 ± 4.8). There was no difference in stiffness degree between viral and non-viral hepatitis in different metavir scores [Figure 2A].

Another sub group analysis included patients with non alcoholic fatty liver disease (NAFLD) (36 patients) vs. non-NAFLD (166 patients). The former group had higher BMI (30.3 ± 4.9 vs. 25.8 ± 4.4, $P < 0.0001$) and more of them suffered from diabetes mellitus (8.3% vs. 0.6%, $P = 0.018$). No difference was seen in age, male rate, hypertension, or hyperlipidemia prevalence. Lower stiffness degree was seen in F0, F1, and F4 in the NAFLD group compared to non-NAFLD, ($P = 0.004$ and 0.042, respectively) but not in F2 and F3 ($P = 0.75$ and 0.33, respectively) [Figure 2B].

A control group of 14 healthy adults underwent the elastography test, and a comparison was made with the patients group.

Table 2. Stiffness degree on elastography for every fibrosis degree on pathology

Fibrosis degree	N	Mean	Median	Minimum	Maximum
F0	97	5.33	4.87	3	14
F1	33	5.72	5.11	4	11
F2	33	6.40	5.69	4	15
F3	26	8.46	7.01	4	26
F4	12	13.09	12.82	9	18
Total	201	6.44	5.37	3	26

The mean and average stiffness seen in healthy controls were significantly lower than the group of the patients with METAVIR score 0 and 1, mean PSWE score 3.4 (range 3.3–4.1) kPa vs. 4.9 (range 4.2–6) kPa, $P = 0.001$.

DISCUSSION

Our results show that pSWE is a highly reliable study to determine liver fibrosis, in different etiologies when compared to liver biopsy as a gold standard. Ferraioli et al. [10] showed that pSWE is a reliable test in 134 patients with viral hepatitis. However, their study was conducted only on patients with viral hepatitis. Samir et al. [20] studied 136 patients, mainly with viral hepatitis and autoimmune hepatitis, and reported similar results.

pSWE is a recently developed method that is part of the second generation of ultrasound elastography methods. These methods differ from the first-generation TE in several aspects, including the generation of shear waves within the organ by a focused ultrasound beam and the capability of focusing the beam at different locations within the organ under ultrasound image guidance. These properties should improve the feasibility of stiffness measurements in obese patients and patients with ascites. They may also improve the accuracy of pSWE relative to TE. Compared to TE, routine ultrasound systems with an elastography software are advantageous in allowing the evaluation of other features that are complementary to stiffness like those aiding in the diagnosis of cirrhosis and they can be used to screen for focal liver lesions [10,22,23].

To the best of our knowledge, this is the first study to assess the feasibility of pSWE to determine the fibrosis degree in every cause of liver fibrosis. This study is also the largest pSWE study performed so far. We have shown a linear correlation between the stiffness degree in pSWE and the fibrosis seen in liver biopsy, with high sensitivity and specificity [Table 3]. Moreover, we have shown no difference between stiffness degrees in viral vs. non-viral hepatitis. This test is useful for any etiology of liver disease and not just for viral hepatitis.

Figure 1. Point shear wave elastography score in different METAVIR stages according to biopsy
IQR = interquartile range, kPa = kilopascal, PSWE = point shear wave elastography
$R = 0.45$, $P < 0.001$ by Spearman's rho correlation

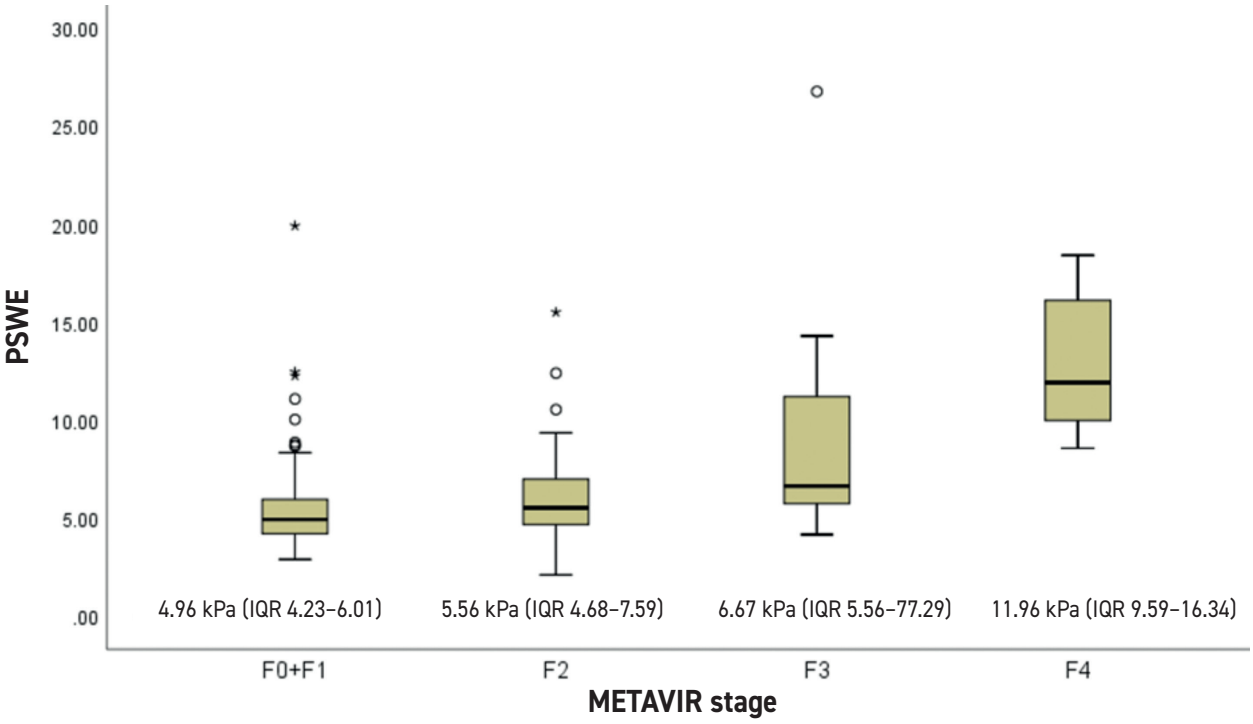


Figure 2A. Viral vs. non-viral hepatitis stiffness in different METAVIR groups
HBV/HCV = hepatitis B virus/hepatitis C virus, PSWE = point shear wave elastography

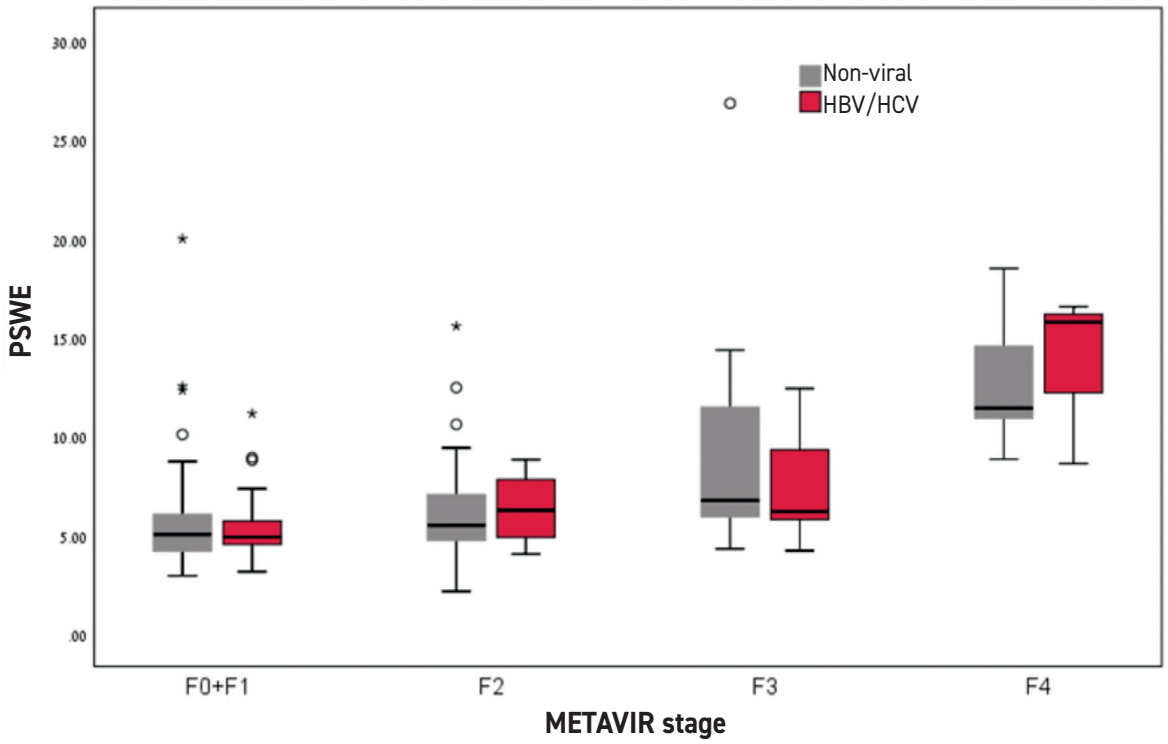
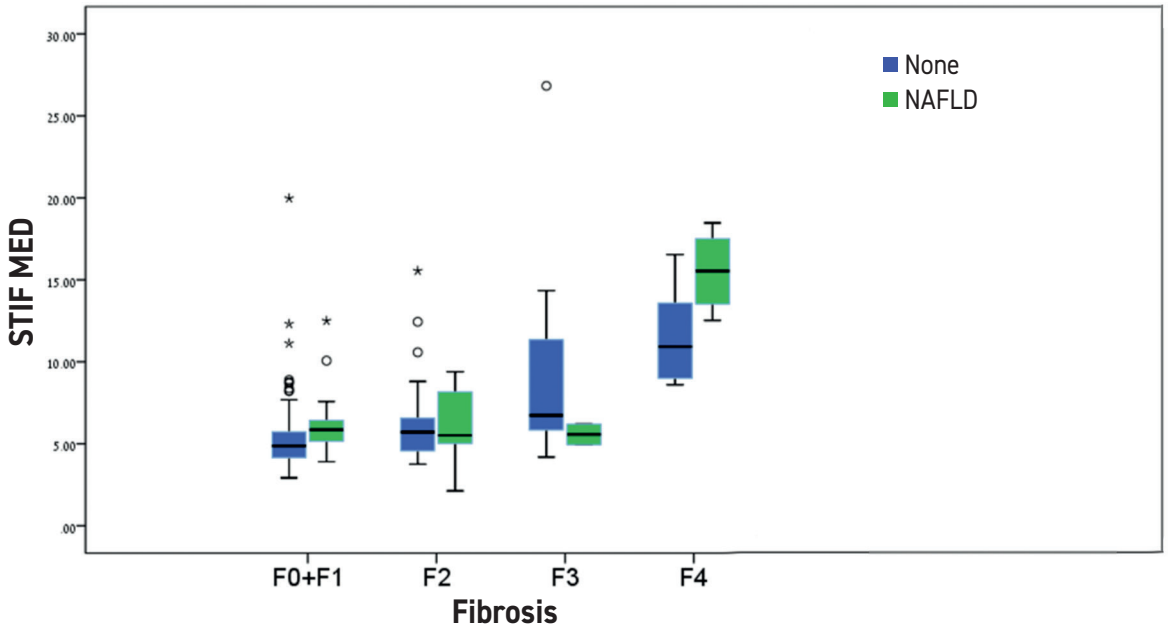


Figure 2B. Stiffness degree in different METAVIR stages, comparison between NAFLD vs. non-NAFLD
NAFLD = non-alcoholic fatty liver disease. STIF MED = median stiffness



However, higher stiffness degree was seen in F0+F1 and F4 in the NAFLD group, compared to non-NASH/NAFLD. This finding might raise a question about the test reliability in the group of NAFLD. However, the number of patients in the F3 and F4 NAFLD group was very low (2 and 4, respectively). Previous studies suggested that the fibrosis stage in patients with steatohepatitis should be assessed using a different scale (Brunt's classification) [24].

Ebinuma et al. [25] found that the degree of steatosis did not affect the elastography measurements using acoustic radiation force impulse (ARFI). This finding can be explained by the different technique and the small numbers of patients in the studies by Brunt and Ebinuma.

In our study, the stiffness degree obtained on pSWE in healthy subjects was significantly lower than in patients with non-significant fibrosis (F0-F1). Similar results were seen in previous studies [10]. Based on these results, physicians may select patients who need further evaluation or follow-up for chronic liver disease.

LIMITATIONS

This study has several limitations. It is a single center study. The elastography studies were conducted about 20 minutes after the biopsies, which could have some influence on the stiffness degree.

CONCLUSIONS

pSWE is a highly reliable method to evaluate liver fibrosis of any etiology and highly correlated to the gold standard liver biopsy.

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Kahlil Gibran (1883–1931), Lebanese-American poet and artist