Cite as: Liaqat M, Siddique K, Yousaf I, Bacha R, Farooq SMJ, Gilani SM: Comparison between shear wave elastography and serological findings for the evaluation of fibrosis in chronic liver disease. J Ultrason 2021; 21: e186–e193. doi: 10.15557/JoU.2021.0030.

Submitted: 12.11.2020
Accepted: 11.03.2021
Published: 16.08.2021

Comparison between shear wave elastography and serological findings for the evaluation of fibrosis in chronic liver disease

Mahjabeen Liaqat[1], Kashif Siddique[2], Imran Yousaf[3], Raham Bacha[1], S. Muhammad Yousaf Farooq[1], Syed Amir Gilani[1]

[1] Radiology, The University of Lahore, Pakistan
[2] Radiology, Shaukat Khanum Hospital, Pakistan
[3] Radiology, Shalamar Hospital, Pakistan
Correspondence: Dr. Mahjabeen Liaqat, e-mail: im.mahjabeen111@gmail.com

DOI: 10.15557/JoU.2021.0030

Keywords
APRI, FIB-4, liver fibrosis, chronic liver disease, shear wave elastography

Abstract

Aim: In this study, we sought to examine the optimal cutoff values for predicting different stages of liver fibrosis, and to determine the level of agreement between shear wave elastography and aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 index (FIB-4) scores in patients with chronic liver disease. **Methodology:** A descriptive, cross-sectional study was performed at the Radiology Department of Shaukat Khanum Memorial Hospital Lahore from 1 Jun 2019 until 1 June 2020. FIB-4 and APRI scores were determined by the following formula: FIB-4 = (age × AST) ÷ (platelet count × (√ (ALT)) and APRI = (AST÷AST upper limit of normal) ÷ platelet × 100. Data was analyzed with the help of SPSS version 24.0 and Microsoft Excel 2013. **Results:** Eighty individuals were conveniently selected, of which 62.5% were men and 37.5% were women. The mean age of the subjects was 43.47 SD ± 13.85 years. APRI and FIB-4 scores predicted F4 patients using the cutoff values of 0.47 (Sn. 72%, Sp. 70%) and 1.27 (Sn. 78%, Sp. 73%), respectively. The cutoff values of 0.46 for APRI and 1.27 for FIB-4 predicted F3–F4 patients (Sn. 74% and 77%; Sp. 76% and 76%), respectively. To predict F1–F4 compared to F0, the cutoff value was 0.34 (Sn. 68%, Sp. 75%) for APRI, while the cutoff value for FIB was 0.87 (Sn. 72%, Sp. 75%). The findings suggest that FIB-4 shows better diagnostic accuracy than APRI. **Conclusion:** This study provides optimal cutoff values for different groups of fibrosis patients for both serum markers. Also, the diagnostic accuracy of FIB-4 for predicting liver fibrosis was found to be superior to APRI in all disease stages.

Introduction

Liver cirrhosis is a major cause of death and disability globally[1]. Studies have shown that 6–7% of the adult population without a known liver disease have liver fibrosis, typically associated with non-alcoholic fatty liver disease[2,3]. In this study, the following stages of fibrosis were defined: F0–F1: <7, F2: 7–8.9, F3: 9–11.9, and F4: ≥12 kPa, as these cutoff values have been adopted by the Greek National Insurance Program[4]. Those with no risk factors had only a 0.4% prevalence of significant liver fibrosis.

Traditionally, liver biopsy was considered as the 'gold standard' in the identification and examining of liver fibrosis and cirrhosis[5]. Liver histological scoring systems including Ishak, Knodell, Sheuer and METAVIR are used to assess liver architecture and fibrosis[6]. However, the technique is constrained by its invasiveness, risk of complications, and high costs[7]. These confines of liver biopsy have prompted research to identify noninvasive methods of evaluating the stages of liver fibrosis.

Noninvasive liver tests (NILTs) can generally be divided into three categories: simple or indirect serum markers, direct serum markers, and imaging modalities[8]. The most widely used imaging modality is transient elastography (TE) or FibroScan (Echosens, Paris)[4]. Later in the mid-1990s, elastography was introduced for the evaluation of stiffness and elasticity of soft tissues by giving external pressure[9]. It is an alternative technique to biopsy, as it is both safe and noninvasive[10].

Elastography can be done with an ultrasonic transducer in combination with shear wave techniques such as TE, point shear wave elastography (pSWE), and two-dimensional shear wave elastography[11,12]. The main restriction of TE in clinical practice is the high amount of uninterpretable outcomes[13]. Shear wave elastography (SWE) is an innovative method that is based on shear waves applied on a diagnostic ultrasound system[14]. SWE has the benefit of being able to image liver stiffness in real time because the shear waves are generated by ultrasonographic pulse pushes. Real-time imaging is used, so that masses and large vessels can be identified and avoided. Moreover, the SWE image is directed by a higher frame-rate B-mode image. The method could provide a more accurate score of fibrosis staging resulting from the SWE and B-mode image direction[15]. Several serological tests have been established to identify liver fibrosis. The aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 index (FIB-4) scoring are the most extensively used compound substitutes for detecting progressive fibrosis[16]. Uroš Karić *et al*. concluded in their study that FIB-4 was superior to APRI in distinguishing severe fibrosis. FIB-4 has been found to be very useful in identifying patients without advanced liver disease, particularly if other noninvasive methods are unavailable[17].

We conducted this study to thoroughly compare the performance of ultrasound-based SWE with routine serological markers, the APRI and FIB-4, for evaluating liver fibrosis in patients with chronic liver disease.

Methodology

This descriptive, cross-sectional study was performed using a convenient, non-probability sampling technique in the Radiology Department of Shaukat Khanum Hospital, Lahore. In the study, we planned to evaluate the images and medical records for SWE and serological findings to compare the extent of liver fibrosis, based on these two techniques (SWE and serological findings). According to the study design, we included all patients who underwent ultrasound SWE in the period from 1 June 2019 until 1 June 2020. Patients after liver transplant, technically unfit, i.e. severely obese or unable to lie flat on their back, and those with fluid build-up in the abdomen (ascites) were excluded from the study based on adopted exclusion criteria. Toshiba (Aplio 400) unit with 5 MHz broadband (C5-1) curved array transducer was used. The procedure was performed under the supervision of a radiologist familiar with US-SWE techniques. To examine the liver, the regions of interests (ROIs) were placed at least 1 cm underneath the liver capsule to avoid reverberation artifacts. The ROI sample box was a small area with a fixed stature of 12 mm that could move up to 8 cm deep from the skin surface; the size of the box was modified automatically from 5 mm near the surface of the transducer to 9.3 mm at a depth of 8 cm. The sample box was positioned with care to elude vascular structures. The rate of the generated SW (m/s) is calculated by observing tissue disarticulation over time. The measured velocities could afterwards be transformed to measure stiffness (kPa) using two constants, Young modulus, and tissue density.

The ultrasound examination was done either with light breathing or with a short breath-hold. Individually, a total of 15 distinct velocity measurements were achieved in patients across the liver using sub-costal and/or intercostal approaches, 10 in the right lobe and 5 in the left lobe. Most measurements were taken at a depth of 3–5 cm. The entire US (SWE) examination took 10–15 minutes to perform, and there was no need for sedation. There were dietary restrictions of about 8 to 12 hours prior to each examination.

The patients to be included in the study were identified through the health information system. The FIB-4 score was determined using the following formula: FIB-4 = (age × aspartate aminotransferase (AST)) ÷ (platelet count × (√ alanine transaminase (ALT)), and the APRI score was calculated with the formula: APRI = (AST÷AST upper limit of normal) ÷ platelet × 100. The overall concordance and disagreement between serological markers and SWE were analyzed.

Data analysis was performed with the help of Statistical Package for the Social Sciences version 24.0, and Microsoft Excel 2013. Qualitative data, e.g. gender, SWE (ordinal), was presented in the form of frequencies and their respective percentages. Demographic data, e.g. age, AST, ALT, platelet count, elastographic values, and the APRI/FIB-4 score, were expressed in the form of mean ± standard deviation. A ROC curve was generated to show the connection/trade-off between clinical sensitivity and specificity for every possible cutoff in liver fibrosis between SWE and serological findings.

The guidelines and principles established by the ethics committee were followed while conducting the study, and the rights of the participants were duly respected. All information and data collection were kept confidential. The participants were informed that there were no shortcomings or risks associated with the procedure of the study. The subjects were not exposed to any harm or danger. They were also notified that they were free to withdraw at any time throughout the course of the study.

Results

A total 80 individuals were conveniently selected for the study, of which 50 (62.5%) were men, and 30 (37.5%) were women. The mean age of the subjects was 43.47 SD ± 13.85 years, with the minimum age being 5.0 and the maximum being 70.0 years. The mean values of ALT, AST, and platelet count APRI, FIB-4, elastographic mean and elastographic median value with their maximum and minimum values were also noted, i.e. 61.34 SD ± 86.23 (min. 5.0, max. 485.0), 56.25 SD ± 52.2 (min. 14.0, max. 343.0), 239.0 SD ± 113.88 (min. 12.0, max. 556.0), 0.77 SD ± 0.837 (min. 0.104, max. 5.417), 2.288 SD ± 3.42 (min. 0.06, max. 26.09), 17.8 SD ± 17.89 (min. 4.3, max. 109.7), and 18.1 SD ± 18.0 (min. 4.4, max. 106.9), respectively. A comparison of the descriptive variables of APRI and FIB-4 for 5 stages of liver fibrosis is shown in (Tab. 1, Tab. 2). For the implementation of APRI score in the likelihood of F4 patients consistent with SWE, we assumed F0, F1, F2 and F3 as one group, and F4

Tab. 1. *Multiple comparisons for the descriptive variable APRI in 5 stages of liver fibrosis*

Mean difference among various stages of fibrosis with the help of multiple comparison test						
Stages of fibrosis (I)	**Stages of fibrosis (J)**	**Mean FIB-4 values difference (I-J)**	**Std. error**	**Sig.**	**95% Confidence interval**	
					Lower bound	**Upper bound**
F0	F1	0.2500	0.3077	0.419	–0.3629	0.863
	F2	0.1939	0.3446	0.575	–0.4926	0.880
	F3	–0.3533	0.5329	0.509	–1.415	0.708
	F4	–0.2625	0.2752	0.343	–0.8107	0.286
F1	F0	–0.2500	0.3077	0.419	–0.8629	0.363
	F2	–0.0561	0.3159	0.860	–0.6855	0.573
	F3	–0.6033	0.5149	0.245	–1.629	0.422
	F4	–0.5125*	0.2383	0.035	–0.9873	–0.038
F2	F0	–0.1939	0.3446	0.575	–0.8805	0.493
	F1	0.0561	0.3159	0.860	–0.5734	0.686
	F3	–0.5473	0.5378	0.312	–1.618	0.524
	F4	–0.4564	0.2844	0.113	–1.023	0.110
F3	F0	0.3533	0.5329	0.509	–0.7083	1.415
	F1	0.6033	0.5149	0.245	–0.4223	1.629
	F2	0.5473	0.5378	0.312	–0.5240	1.618
	F4	0.0908	0.4961	0.855	–0.8975	1.079
F4	F0	0.2625	0.2752	0.343	–0.2857	0.811
	F1	0.5125*	0.2383	0.035	0.0377	0.987
	F2	0.4564	0.2844	0.113	–0.1101	1.023
	F3	–0.0908	0.4961	0.855	–1.079	0.898

* The mean difference is significant at the 0.05 level.
Std. – standard; Sig. – level of significance; F0 – liver fibrosis stage 0; F1 – liver fibrosis stage 1; F2 – liver fibrosis stage 2; F3 – liver fibrosis stage 3; F4 – liver fibrosis stage 4

Tab. 2. *Multiple comparisons for the descriptive variable FIB-4 in 5 stages of liver fibrosis*

Mean difference among various stages of fibrosis with the help of multiple comparison test						
Stages of fibrosis (I)	**Stages of fibrosis (J)**	**Mean FIB-4 values difference (I-J)**	**Std. error**	**Sig.**	**95% confidence interval**	
					Lower bound	**Upper bound**
F0	F1	1.876	1.261	0.14	–0.635	4.388
	F2	1.415	1.412	0.32	–1.397	4.228
	F3	1.268	2.183	0.56	–3.082	5.617
	F4	–0.204	1.128	0.86	–2.451	2.042
F1	F0	–1.876	1.261	0.14	–4.388	0.635
	F2	–0.461	1.295	0.72	–3.040	2.118
	F3	–0.609	2.109	0.77	–4.811	3.593
	F4	–2.081*	0.976	0.04	–4.026	–0.136
F2	F0	–1.415	1.412	0.32	–4.228	1.397
	F1	0.461	1.295	0.72	–2.118	3.040
	F3	–0.148	2.203	0.95	–4.537	4.241
	F4	–1.620	1.165	0.17	–3.941	0.702
F3	F0	–1.268	2.183	0.56	–5.617	3.082
	F1	0.609	2.109	0.77	–3.593	4.811
	F2	0.148	2.203	0.95	–4.241	4.537
	F4	–1.472	2.033	0.47	–5.521	2.577
F4	F0	0.204	1.128	0.86	–2.042	2.451
	F1	2.081*	0.976	0.04	0.136	4.026
	F2	1.620	1.165	0.17	–0.702	3.941
	F3	1.472	2.033	0.47	–2.577	5.521

* The mean difference is significant at the 0.05 level.
Std. – standard; Sig. – level of significance; F0 – liver fibrosis stage 0; F1 – liver fibrosis stage 1; F2 – liver fibrosis stage 2; F3 – liver fibrosis stage 3; F4 – liver fibrosis stage 4

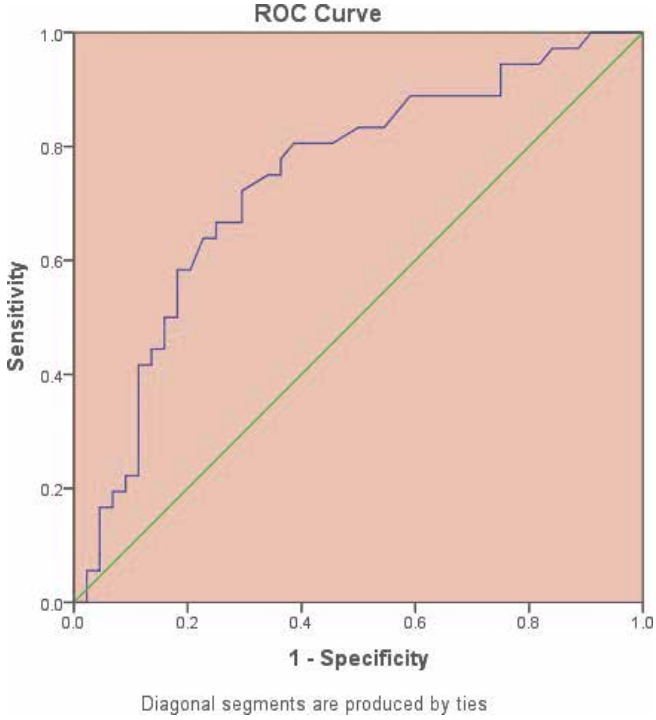

Fig. 1. *Area under receiver operator curve for performance of APRI score in the prediction of F4 patients based on SWE*

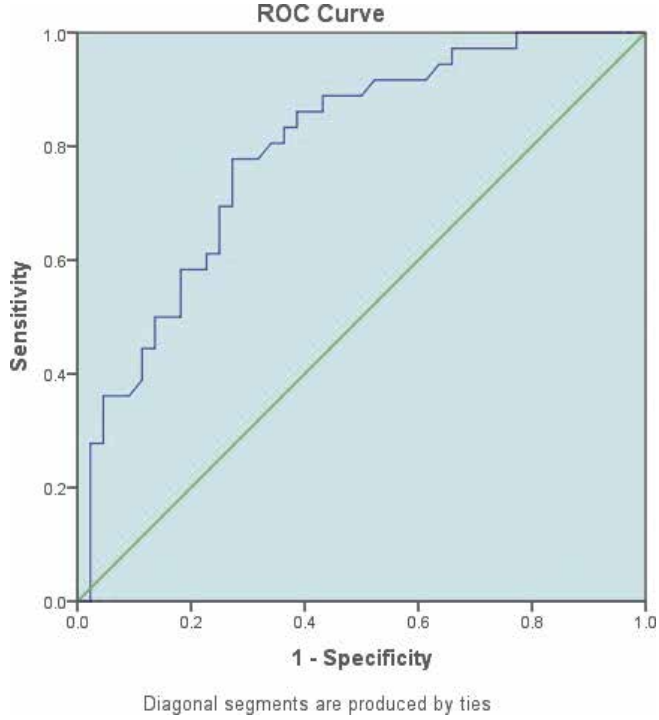

Fig. 2. *Area under receiver operator curve for performance of FIB-4 score in the prediction of F4 patients based on SWE*

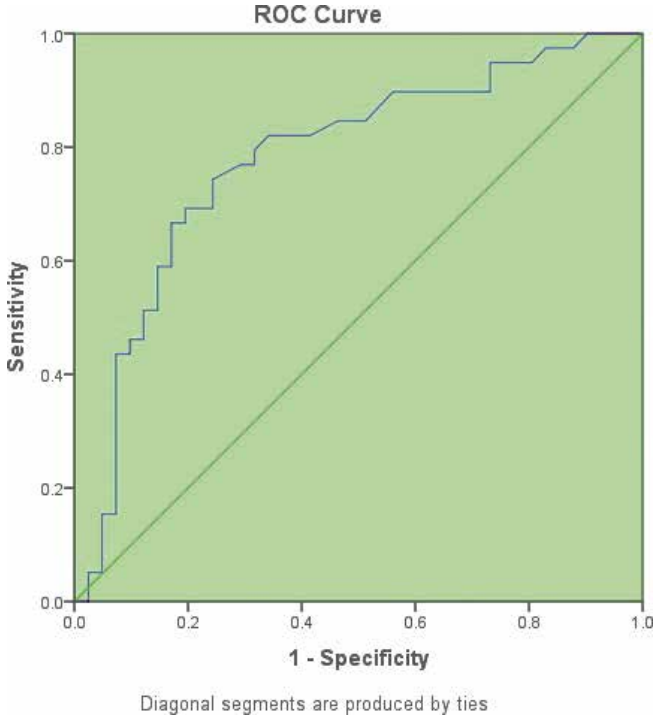

Fig. 3. *Area under receiver operator curve for performance of APRI score in the prediction of F3–F4 based on SWE*

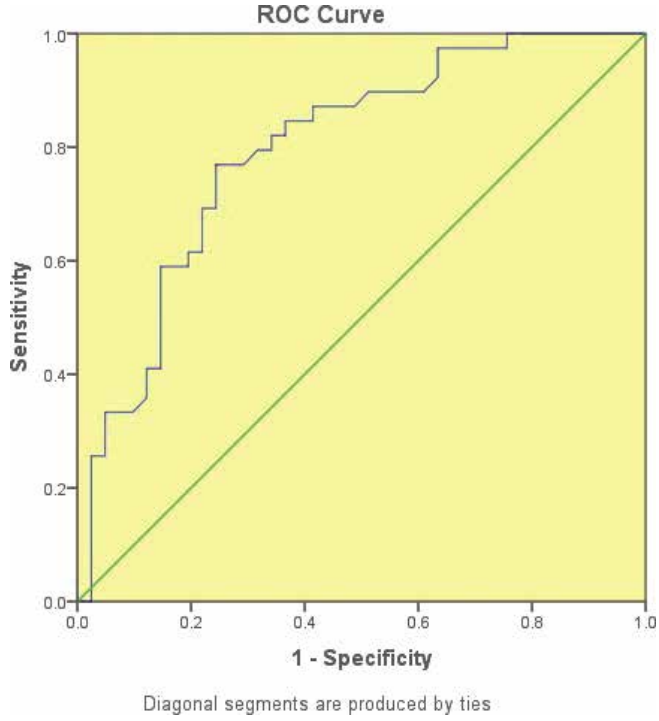

Fig. 4. *Area under receiver operator curve for performance of FIB-4 score in the prediction of F3–F4 patients based on SWE*

as another group; then the area under the receiver operator characteristic curve (AUROC) was 0.74 (95% CI 0.63–0.85; p <0.001). With the optimal APRI cutoff value of >0.46, we found F4 fibrosis having a sensitivity of 0.72 (72%) and specificity of 0.70 (70%) (Fig. 1). For the implementation of FIB-4 score in the likelihood of F4 patients consistent with SWE, we assumed F0, F1, F2 and F3 as one group, and F4 as another group; then AUROC was 0.795 (95% CI 0.698–0.89; p <0.001) With the optimal FIB-4 cutoff value of >1.27, we found F4 fibrosis having a sensitivity of 0.78

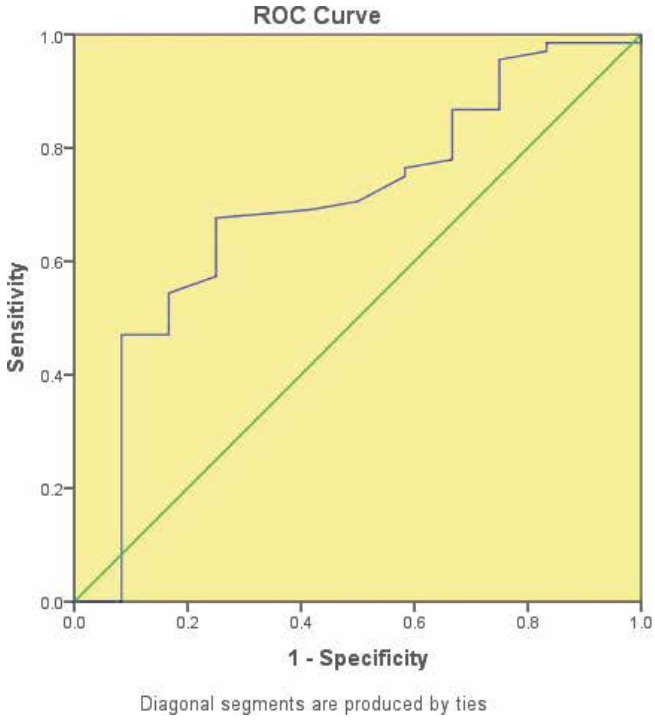

Fig. 5. *Area under receiver operator curve for performance of APRI score in the prediction of F1–F4 patients based on SWE*

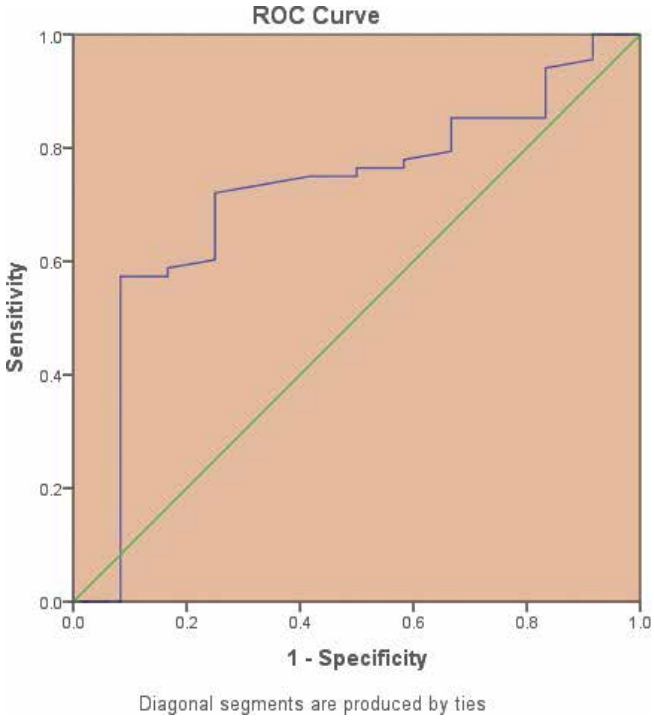

Fig. 6. *Area under receiver operator curve for performance of FIB-4 score in the prediction of F1–F4 patients based on SWE*

(78%) and specificity of 0.73 (73%) (Fig. 2). For the implementation of APRI score in the likelihood of F3–F4 patients consistent with SWE, we assumed F0, F1 and F2 as one group, and F3 and F4 in another group; then AUROC was 0.78 (95% CI 0.67–0.88; $p< 0.001$). With the optimal APRI cutoff value of >0.46, we found F4 fibrosis having a sensitivity of 0.74 (74%) and specificity of 0.76 (76%) (Fig. 3). For the implementation of FIB-4 score in the likelihood of F3–F4 patients consistent with SWE, we assume F0, F1 and F2 as one group, and F3–F4 in another group; then AUROC was 0.80 (95% CI 0.70–0.90; $p <0.001$). With the optimal FIB-4 cutoff value of >1.27, we found F4 fibrosis having a sensitivity of 0.77 (77%) and specificity of 0.76 (76%) (Fig. 4). For the implementation of APRI score in the likelihood of F1–F4 patients consistent with SWE, we assumed F0 as one group, and F1 F2, F3 and F4 as another group; then AUROC was 0.70 (95% CI 0.54–0.86; $p <0.001$). With the optimal APRI cutoff value of >0.34, we found F4 fibrosis having a sensitivity of 0.68 (68%) and specificity of 0.75 (75%) (Fig. 5).

The implementation of F4 score in the likelihood of F1–F4 patients consistent with SWE, if we assume F0 as one group, and F1 F2, F3 and F4 as another group, then AUROC was 0.72 (95% CI 0.56–0.87; $p <0.001$). With the selected FIB-4 optimal cutoff value of >0.87, we found F4 fibrosis having a sensitivity of 0.72 (72%) and specificity of 0.75 (75%) (Fig. 6).

Discussion

Although liver biopsies are commonly used for investigative purposes, the method also has a number of limitations, such as being invasive and costly. Also, it may bring about sampling errors and inter-and intra-observer variations in considering hepatic fibrosis. Real-time SWE is an innovative, noninvasive practice to evaluate liver fibrosis by assessing liver stiffness (Fig. 7). These confines of the liver biopsy have encouraged research for noninvasive approaches in the assessment of liver fibrosis. SWE is an innovative practice that is grounded on shear waves implemented on an investigative ultrasound method. This technique could end result in a more precise score of fibrosis stages bring about the SWE and B-mode image direction[18]. We evaluated the diagnostic performance of the APRI and FIB-4 scores accompanying SWE in determining the stages of fibrosis (F0–F4). The main benefit of biochemical noninvasive scores (APRI and FIB-4) in considering liver fibrosis is that they are generally available at a low cost, and are very easy to perform. Though, SWE measurement is not far and wide existing owing to technical and practical field together with its unusual cost, on the other hand its use is not widespread in low- and mid-income nations[18,19], whereas APRI and FIB-4 scores have been shown to be quite reliable for evaluating liver fibrosis[20]. However, authentication in different patients is still required.

Liver biopsy has been extensively regarded as the gold standard for the assessment of liver fibrosis, though it has been nearly completely replaced by noninvasive approaches that measure liver stiffness (LS), such as transient elastography (TE)[21,22], or biochemical markers and scoring systems[18,23]. In the present study, we compared two noninvasive techniques, SWE and serological findings, for the evaluation of fibrosis grading in chronic liver disease (CLD), and observed an agreement between SWE and serological findings (APRI and FIB-4 scores) for the estimation of fibrosis grading in CLD. A total of 80 individuals were evaluated.

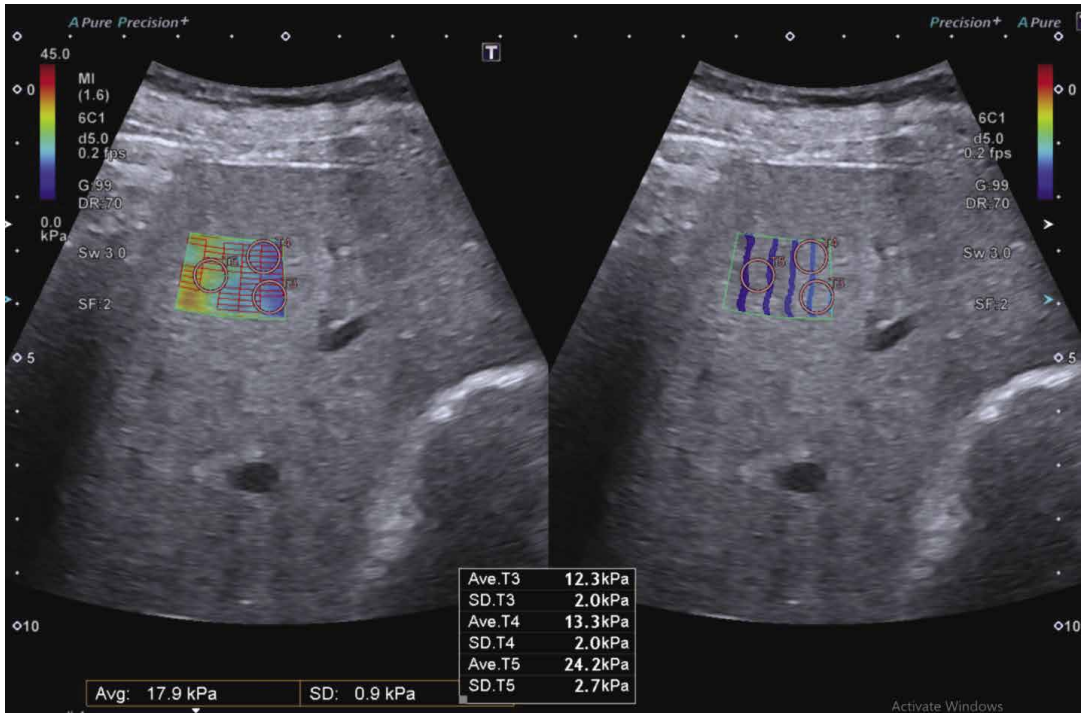

Fig. 7. *SWE image showing liver fibrosis stage F4 with average median value of liver stiffness of about 17.9 kpa*

The associations of the patient's individual characteristics at different fibrosis stages were assessed by using the one-way ANOVA or chi-square test, as suitable.

Nikolaos Papadopoulos *et al*. evaluated APRI/FIB-4 scores compared with TE-liver stiffness in detecting significant fibrosis or cirrhosis (F3 or F4). In that study, the authors retrospectively enrolled 575 patients with CHC who underwent TE-LS, and found that both scores projected F4 patients adequately. This also shows that FIB-4 is a suitable evaluation for ruling out noncirrhotic patients[24].

A pilot study was conducted in 2012 by Giovanna Ferraiolion *et al*. on real-time SWE for considering liver fibrosis in CH-C. The purpose of that study was to assess the diagnostic precision of real-time SWE in the evaluation of liver fibrosis in patients with chronic hepatic cirrhosis, in comparison with transient elastography, by using the histologic METAVIR classification as the reference system. In that study, real-time SWE measurements were compared with TE values in severe fibrosis and cirrhosis. Real-time SWE validated a significant improvement in the detection of significant fibrosis when compared with T-elastography[15]. Another study was done by Lun-Gen Lu *et al*. in 2003 on grading and staging of hepatic fibrosis and its correlation with noninvasive investigative considerations. The goal of that study was to see the sights of the grades and stages of pathology and also their relationship with hepatic fibrosis and noninvasive indicative factors. It was concluded that the categorizing and staging of liver fibrosis are interconnected with serum markers, Doppler ultrasound, computed tomography (CT) scan and/or magnetic resonance imaging (MRI). The combinations of the above-stated noninvasive factors were recognized to be relatively sensitive and specific in determining liver fibrosis. The sensitivity, specificity and accuracy values were 80.36%, 86.67%, and 81.10%, respectively[25]. In our study we compared two noninvasive techniques, ultrasonographic SWE with two biomarkers i.e. APRI and FIB-4.

In the present study, we found different cutoff values for APRI and FIB-4 in different groups of fibrosis to distinguish their optimal cutoff values according to AUROC, and the diagnostic accuracies (sensitivity and specificity) of APRI and FIB-4 (normal AST level up-to 40 IU/L) for predicting the performance of APRI and FIB-4 accompanying ultrasound SW elastography. In a similar type of study, Yi-Hao Yen *et al*. in 2018 examined the optimum cutoff values of the two compound surrogates for envisaging cirrhosis by the AST level according to the AUROC analysis results differentiating cirrhotic (F4) from noncirrhotic (F0–F3). They concluded that the ideal cutoff values of both APRI and FIB-4 to predict cirrhosis graded by AST levels could be more practicable as compared with the single cutoff values offered in a foregoing research paper[26].

Conferring to former findings, APRI and FIB-4 were associated with the international normalized ratio, albumin level and necroinflammatory score[27,28]. Additionally, the positive correlations of APRI and FIB-4 with necroinflammatory score also kept our theory that the use of APRI and FIB-4 causes a possibility of overrating the fibrosis stage due to the influence of necroinflammatory activity on transaminases[29,30] and the indicative precision of FIB-4 foreseeing liver fibrosis was found to be equivalent to or superior to that of APRI[31]. Even so, the objective of our study was to estimate the competence of the serological findings for the progressive fibrosis by comparing ultrasonographic SWE.

Conclusions

The systematic accuracy of FIB-4 for predicting liver fibrosis was found to be equivalent to or superior to that of APRI for all stages of liver fibrosis. The study also provided optimal cutoff values for different groups of fibrosis for both serum markers, which could be more practicable to compare with the distinct cutoff values suggested in foregoing studies.

Recommendations

- In this study, we only determined an agreement between SWE and serological findings (APRI and FIB-4 scores) for the evaluation of fibrosis grading in patients with chronic liver disease. For further evaluation, biopsy as a reference method can be added to allow further detailed analysis, and future studies are needed to explore this important area of research.
- For more accurate results and satisfying optimal cutoff values, a larger sample size must be selected.
- Clinical data collected from patients can be included in data analysis, such as the reason for the FibroScan examination (etiology), FibroScan date, reading, IQR, date of blood tests, FIB-4, APRI, and comorbidities (DM, HTN).
- The study analyzed the overall concordance and disagreement between the serological markers and FibroScan findings. Subgroup analysis can also be performed for advanced fibrosis, no fibrosis, and indeterminate categories.
- The study duration was fixed, however for further evaluation and detailed analysis the duration of the study can be extended.

Limitations

- In this study, we only determined an agreement between two noninvasive procedures, i.e. SWE and serological findings (APRI and FIB-4 scores) for the evaluation of fibrosis grading in patients with chronic liver disease.
- The sample size was too small for a more accurate analysis of results and satisfying optimal cutoff values.
- The study included no subgroup analysis for advanced fibrosis, no fibrosis, and indeterminate categories.
- The study duration was fixed, hence there was no further evaluation and detailed analysis of liver disease.

Acknowledgments

I am very thankful to my Creator and Prophet (S.A.W.W) for the completion of this study. I would like to express gratitude to my supervisor and co-supervisor for their support throughout the period of the study and their extra-ordinary help and guidance during data collection and support in practical sessions.

I would like to thank my Biostatistician, our worthy Dean, and I am also grateful to Dr. Waqas Ahmad and all the members of the scientific research committee and staff at the Radiology Department of Shaukat Khanum Hospital, Lahore, Pakistan.

Conflict of interest

Authors do not report any financial or personal connections with other persons or organizations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

References

1. Ginès P, Graupera I, Lammert F, Angeli P, Caballeria L, Krag A *et al.*: Screening for liver fibrosis in the general population: a call for action. Lancet Gastroenterol Hepatol 2016; 1: 256–260.
2. Dong D, Yin L, Qi Y, Xu L, Peng J: Protective effect of the total saponins from Rosa laevigata michx fruit against carbon tetrachloride-induced liver fibrosis in rats. Nutrients 2015; 7: 4829–4850.
3. Weiskirchen R, Tacke F: Liver fibrosis: from pathogenesis to novel therapies. Dig Dis 2016; 34: 410–422.
4. Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M *et al.*: Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005; 128: 343–350.
5. Denzer U, Arnoldy A, Kanzler S, Galle PR, Dienes HP, Lohse AW: Prospective randomized comparison of minilaparoscopy and percutaneous liver biopsy: diagnosis of cirrhosis and complications. J Clin Gastroenterol 2007; 41: 103–110.
6. Crossan C, Tsochatzis EA, Longworth L, Gurusamy K, Davidson B, Rodríguez-Perálvarez *et al.*: Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. Health Technol Assecc 2015; 19: 1–410.
7. Spengler EK, Loomba R: Recommendations for diagnosis, referral for liver biopsy, and treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Mayo Clin Proc 2015; 90: 1233–1246.
8. Nobili V, Vizzutti F, Arena U, Abraldes JG, Murra F, Pietrobattista A *et al.*: Accuracy and reproducibility of transient elastography for the diagnosis of fibrosis in pediatric nonalcoholic steatohepatitis. Hepatology 2008; 48: 442–448.
9. Tyagi S, Kumar S. Clinical applications of elastography: an overview. Int J Pharma Bio Sciences 2010; 1: 1–8.
10. Manzoor I, Bacha R, Gilani SA: Diagnostic accuracy of sonoelastography in different diseases. J Ultrason 2018; 18: 29–36.
11. Guo Y, Parthasarathy S, Goyal P, McCarthy RJ, Larson AC, Miller FH: Magnetic resonance elastography and acoustic radiation force impulse for staging hepatic fibrosis: a meta-analysis. Abdom Imaging 2015; 40: 818–834.
12. Singh S, Venkatesh SK, Loomba R, Wang Z, Sirlin C, Chen J *et al.*: Magnetic resonance elastography for staging liver fibrosis in non-alcoholic fatty liver disease: a diagnostic accuracy systematic review and individual participant data pooled analysis. Eur Radiol 2016; 26: 1431–1440.
13. Castéra L, Foucher J, Bernard PH, Carvalho F, Allaix D, Merrouche W *et al.*: Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. Hepatology 2010; 51: 828–835.
14. Friedrich-Rust M, Nierhoff J, Lupsor M, Sporea I, Fierbinteanu-Braticevici C, Strobel D *et al.*: Performance of acoustic radiation force impulse imaging for the staging of liver fibrosis: a pooled meta-analysis. J Viral Hepat 2012; 19: e212-e219.
15. Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Filice G, Filice C *et al.*: Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology 2012; 56: 2125–2133.
16. Udompap P, Sukonrut K, Suvannarerg V, Pongpaibul A, Charatcharoenwitthaya P: Prospective comparison of transient elastography, point shear wave elastography, APRI and FIB-4 for staging liver fibrosis in chronic viral hepatitis. J Viral Hepat 2020; 27: 437–448.

17. Karic U, Pesic-Pavlovic I, Stevanovic G, Korac M, Nikolic N, Radovanic--Spurnic A *et al.*: FIB-4 and APRI scores for predicting severe fibrosis in chronic hepatitis C-a developing country's perspective in DAA era. J Infect Dev Ctries 2018; 12: 178–182.
18. Afdhal NH, Bacon BR, Patel K, Lawitz EJ, Gordon SC, Nelson DR *et al.*: Accuracy of fibroscan, compared with histology, in analysis of liver fibrosis in patients with hepatitis B or C: a United States multicenter study. Clin Gastroenterol Hepatol 2015; 13: 772–779. e1–3.
19. Vergniol J, Foucher J, Terrebonne E, Bernard P-H, le Bail B, Merrouche W *et al.*: Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. Gastroenterology 2011; 140: 1970–1979.e1–3.
20. Shiha G, Ibrahim A, Helmy A, Sarin SK, Omata M, Kumar A *et al.*: Asian-Pacific Association for the Study of the Liver (APASL) consensus guidelines on invasive and non-invasive assessment of hepatic fibrosis: a 2016 update. Hepatol Int 2017; 11: 1–30.
21. Sandrin L, Fourquet B, Hasquenoph J-M, Yon S, Fournier C, Mal F *et al.*: Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003; 29: 1705–1713.
22. Tapper EB, Cohen EB, Patel K, Bacon B, Gordon S, Lawit E *et al.*: Levels of alanine aminotransferase confound use of transient elastography to diagnose fibrosis in patients with chronic hepatitis C virus infection. Clin Gastroenterol Hepatol 2012; 10: 932–937. e1.
23. Chou R, Wasson N: Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. Ann Intern Med 2013; 158: 807–820.
24. Papadopoulos N, Vasileiadi S, Papavdi M, Sveroni E, Antonakaki P, Dellaporta E *et al.*: Liver fibrosis staging with combination of APRI and FIB-4 scoring systems in chronic hepatitis C as an alternative to transient elastography. Ann Gastroenterol 2019; 32: 498–503.
25. Lu L-G, Zeng M-D, Wan M-B, Li C-Z, Mao YM, Li J-Q *et al.*: Grading and staging of hepatic fibrosis, and its relationship with noninvasive diagnostic parameters. World J Gastroenterol 2003; 9: 2574–2578.
26. Yen Y-H, Kuo F-Y, Kee K-M, Chang K-C, Tsai M-C, Hu TH *et al.*: APRI and FIB-4 in the evaluation of liver fibrosis in chronic hepatitis C patients stratified by AST level. PLoS One 2018; 13: e0199760.
27. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J *et al.*: Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006; 43: 1317–1325.
28. Houot M, Ngo Y, Munteanu M, Marque S, Poynard T: Systematic review with meta-analysis: direct comparisons of biomarkers for the diagnosis of fibrosis in chronic hepatitis C and B. Aliment Pharmacol Ther 2016; 43: 16–29.
29. European Association for Study od Liver; Asociacion Latinoamericana pana el Estudio del Higado: EASL-ALEH Clinical Practice Guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015; 63: 237–264.
30. Sheth SG, Flamm SL, Gordon FD, Chopra S: AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. Am J Gastroenterol 1998; 93: 44–48.
31. Kamimoto Y, Horiuchi S, Tanase S, Morino Y: Plasma clearance of intravenously injected aspartate aminotransferase isozymes: evidence for preferential uptake by sinusoidal liver cells. Hepatology 1985; 5: 367–375.