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Assessment of Hepatic Fibrosis Using Non-Invasive Aspartate Aminotransferase to Platelets Ratio Index Compared to Hepatic Stiffness Measurements Using Transient Elastography FibroScan®

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ABSTRACT

Background: Transient Elastography FibroScan® and aspartate aminotransferase to platelets ratio index have frequently been evaluated in comparison to liver biopsy for the assessment of liver fibrosis.

Methods: Cross-sectional study to correlate between Aspartate transaminase to platelets ratio index and liver Transient Elastography FibroScan® among patients with liver diseases. Aspartate transaminase to platelets ratio index (in IU/L) and platelet count (expressed as K/ul) were calculated. Transient Elastography FibroScan® scores were obtained and then the patients were categorized into four stages of fibrosis. Baseline characteristic data were obtained for each patient. IBM SPSS V.20 was used to perform a correlation analysis of stiffness score and Aspartate transaminase to platelets ratio index. Moreover, one-way ANOVA was performed to test for differences in Aspartate transaminase to platelets ratio index, platelets, and Aspartate Aminotransferase among different stages of fibrosis.

Results: 235 patients were included: 141 (60%) males and 94 (40%) females. The most common cause of liver disease was chronic viral hepatitis C (38.3%). The majority of patients had mild fibrosis (F0-F1, n = 117 (49.8%)). Eighteen (7.6%) patients had F3, and 62 (26.4%) had cirrhosis (F4). Age > 40 years was associated with higher liver stiffness compared with age ≤ 40 years. There was a profound relationship between stiffness score and Aspartate transaminase to platelets ratio index.

Conclusion: Aspartate transaminase to platelets ratio index is strongly correlated with Transient Elastography FibroScan® in patients with advanced fibrosis and cirrhosis and can effectively categorize mild from advanced fibrosis or cirrhosis.

Keywords

Aspartate transaminase to platelets ratio index; Transient Elastography FibroScan®; Liver stiffness; Hepatic fibrosis; Non-invasive markers

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INTRODUCTION

The treatment and outcome of chronic liver diseases largely depend on the degree and progression of hepatic fibrosis[1]. This is in particular accurate for individuals with chronic viral hepatitis B (CHB), C (CHC) and Non-Alcoholic Fatty Liver Disease (NAFLD) , which are the main causes of chronic liver disease in the world[2-5]. Proper diagnosis and identification of the degree of liver fibrosis is essential as this will determine the prognosis of the disease and the treatment plan[6,7]. Despite its invasiveness and high risk of complications, liver biopsy remained the gold standard test for the diagnosis of liver fibrosis and cirrhosis[8-10]. One of the important disadvantages of performing liver biopsy is the variability in the interpretation that could lead to inaccurate staging in up to 20% of the cases[11,12]. Therefore, a proper non-invasive approach of evaluating hepatic fibrosis is essential[13]. This include clinical examination[14], laboratory tests including serum markers of fibrosis[15-20] .

Transient elastography (FibroScan®[FS], Echosens, Paris, France) is a peculiar, quick, non-invasive, and reproducible test to measure hepatic stiffness[21]. Multiple studies proved that FS can properly stage hepatic fibrosis in patients with chronic hepatitis C[1,22,23].

This study compared the diagnostic accuracy of FS with a routine laboratory tests (Aspartate transaminase to platelets ratio index (APRI)) which was developed by Wai *et al.*[16] in 2003.

Aspartate transaminase to platelets ratio index can be used in the clinic or at the bedside, and in the original study, it was remarkably precise in detecting significant fibrosis and cirrhosis[16]. Several other studies have been conducted to validate APRI[24,25]. Multiple studies had shown that it is very valuable in predicting severe fibrosis in diverse etiologies of liver disease[26,27].

FibroScan® and APRI appear to be very effective in determining the presence or more specifically, the absence of advanced fibrosis or cirrhosis. Using the two validated tests is expected to support the results.

This study was conducted at the hepatology unit of King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia to assess the reliability of the Aspartate Aminotransferase (AST) to platelets index ratio (APRI) in determining the degree of liver fibrosis by comparing it to liver stiffness measurement using Transient Elastography FibroScan®.

METHODOLOGY

This study was conducted using a cross-sectional design.

The team followed the ethical consideration of confidentiality and freedom to participate, and patient consent was obtained. The Faculty of Medicine at King Abdulaziz University provided ethical approval for the study.

Study Population

The target population was male and female patients with known liver disease who had undergone transient elastography using Transient Elastography FibroScan® at the hepatology department of King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia.

The inclusion criteria of this study were as follows: male or female patients who are known to have chronic liver disease and agreed to undergo Transient Elastography FibroScan® examination during the study period from May 2012 to June 2013. All the included patients had a negative history of alcohol use. For patients with chronic hepatitis C, Transient Elastography FibroScan® blood tests were performed as part of the assessment of fibrosis before starting treatment. For patients with chronic hepatitis B, Transient Elastography FibroScan® examination was performed at the time of initial diagnosis or during follow-up. For patients who had AIH, the Transient Elastography FibroScan® examination included in this study was performed at the time of biochemical remission, and all of the AIH patients were on immune suppression with Azathioprine and low-dose prednisolone (5-7.5 mg).

The exclusion criteria were patients who had failed Transient Elastography FibroScan® study or who did not have lab results for AST and platelets available within one month of the study. Moreover, patients with acute liver disease were also excluded.

Demographic data was obtained for each patient(age and sex)and the patients categorized into two age groups: ≤ 40 years and ≥ 41 years.

The cause of the liver disease was obtained from the hospital information system.

Transient elastography (FibroScan®): The FibroScan® device used in this study was a FibroScan® 502 manufactured by echosens in France 2005. FibroScan® was performed by two expert hepatologists from the hepatology unit at King Abdulaziz University Hospital, Jeddah. All the patients were fasting for four hours prior to the FibroScan® examination.

The liver stiffness values corresponding to the different stages of chronic liver disease were as follows: < 7 kPa, F0-F1 (mild fibrosis); 7-9.4 kPa, F2 (moderate fibrosis); 9.5-12.4 kPa, F3 (advanced fibrosis); and ≥ 12.5, F4 (cirrhosis)[1].

Patients were included for whom at least 10 successful readings with a success rate of 70% and an interquantile range less than 30% had been achieved. The stiffness score, measured in kPa, was recorded in addition to the degree of fibrosis (F1-F4).

Aspartate transaminase to platelets ratio index: The data necessary to calculate APRI are AST, which was measured using the Dimension clinical chemistry system (Flex reagent cartridge) and expressed as IU/L; the upper

limit of normal range (ULN), which is 42 IU/L at the lab at King Abdulaziz University Hospital (KAUH); and platelet count, expressed as (K/ul), with a normal range of 15-400. The APRI values were calculated using the formula (AST/ULN)/platelet count x 100[16].

An APRI reading of ≤0.5 was defined as excluding significant fibrosis and a reading of ≥ 1.5 as suggesting significant fibrosis. For cirrhosis, APRI ≤ 1 was considered as excluding cirrhosis and APRI ≥ 2 as suggesting cirrhosis[16].

STATISTICAL METHODS

This study used the IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, NY USA) for data analysis. After calculating descriptive statistics, the Pearson's correlation analysis to determine the correlation between FibroScan® stiffness score and APRI was the applied. One-way ANOVA was used to evaluate the effects of different liver diseases on the fibrosis score and APRI. Receiver operating characteristics (ROC) curve analysis of APRI was performed in the assessment of mild and severe fibrosis.

RESULTS

Twenty-five patients (out of 260) were excluded due to failed FibroScan® exams (12 (4.6%) patients) or lab tests not performed within one month of the FibroScan® exam (13 (5%) patients). 235 patients were included in the final analyses. There were 141 (60%) male patients and 94 (40%) female patients. The mean age was 46.2 ± 15.8 years (range 12-85). The females were older than the males, with a mean age of 48.8 years for females and 45 years for males, but this difference was not statistically significant. The most common cause of liver disease was CHC, and the second most common cause was CHB (Table 1). The mean stiffness score and APRI were 10.5 and 0.53, respectively (SD 11.6 and 0.6 respectively).

Regarding FibroScan® fibrosis grade distribution, most of the patients (n = 117) had mild fibrosis, *i.e.,* F0-F1, and approximately one-quarter had advanced fibrosis (F3) or cirrhosis (F4) (Table 2).

An age of greater than 40 years was associated with significantly higher fibrosis compared with age 40 years or younger (mean 12.74 kPa SD 13.1 and 9.4 kPa SD 10.8, respectively; P = 0.044). There was a significant correlation between age and FibroScan® fibrosis score (r = 0.15, P = 0.022). The stiffness score did not differ between males and females. Similarly, there was a significant correlation between age and APRI (r = 0.223, P = 0.001).

The one-way ANOVA and post hoc analysis revealed that patients with CHB had significantly lower stiffness scores compared with patients with non-alcoholic fatty liver disease (NAFLD) or CHC (P < 0.001; Table 3). Moreover, APRI differed significantly among the different causes of liver disease (P < 0.001).

There was a significant correlation between stiffness score and APRI (r = 0.6 and 0.65 for Pearson's and Spearman's correlation, respectively; P < 0.001 for both; Fig. 1). This correlation was stronger for patients who had

TABLE 1.
Distribution of patients according to gender and the cause of liver disease

Diagnosis	Male	Female	Total	Percentage
Chronic Hepatitis C	44	46	90	39.64%
Chronic Hepatitis B	58	18	76	33.48%
Non-alcoholic Fatty Liver Disease	26	11	37	16.29%
Autoimmune Hepatitis	3	9	12	5.28%
Primary Biliary Cirrhosis	1	2	3	1.32%
Cardiac Cirrhosis	3	0	3	1.32%
Primary Sclerosing Cholangitis	1	2	3	1.32%
Combined CHB and CHC	1	0	1	0.44%
Thalassemia	1	0	1	0.44%
Congenital Liver Fibrosis	1	0	1	0.44%
Total	141	94	235	100%

CHB: Chronic hepatitis B; CHC: Chronic hepatitis C

TABLE 2.
Distribution of patients according to gender and stage of fibrosis

		Fibrosis Stage				Total
		F0-F1	F2	F3	F4	
Gender	Male	68	26	12	35	141
	Female	49	12	6	27	94
Total		117	38	18	62	235

P = 0.6

moderate or advanced fibrosis on FibroScan®. However, for patients who had no or mild fibrosis, the correlation was not significant.

Aspartate transaminase to platelets ratio index was able to effectively distinguish patients with no or mild fibrosis (F0-F1) from those with advanced fibrosis or cirrhosis (F3-F4). It was also effective for distinguishing patients with advanced fibrosis (F3) from those with cirrhosis (F4). However, it was less accurate in distinguishing patients with moderate fibrosis (F2) from patients with advanced fibrosis (F3). Moreover, APRI could consistently differentiate cirrhosis (F4) from all other stages of fibrosis (Fig. 2). The RCO analysis showed that APRI had an AUC of 0.863 in the detection of advanced fibrosis and a much lower AUC of 0.4 in the detection of mild and moderate fibrosis (Fig. 3 and 4).

Two patients who had CHB and discrepancies between the FibroScan® result and HBV viral load underwent percutaneous liver biopsy that showed features of NAFLD, and the stages of fibrosis on the biopsies were consistent with the FibroScan® stages of fibrosis.

TABLE 3.
Comparison of stiffness score between different forms of liver disease using one-way ANOVA

Liver Disease		Mean Difference between the groups and 95% CI	P value	95% Confidence Interval	
				Lower Bound	Upper Bound
CHC compared with other diagnosis	CHB	6.6±	0.001	2.1	11.1
	NAFLD	1.5	0.90	-4.1	7.1
	AIH	-5.6	0.356	-14.4	3.2
CHB compared with other diagnosis	CHC	-6·6	0.001	-11.0696	-2.1
	NAFLD	-5.1	0.10	-11	0.64
	AIH	-12.2	0.003	-21.1	-3.3
NAFLD compared with other diagnosis	CHC	-1.5	0.902	-7.1	4.1
	CHB	5.1	0.10	-0.64	11
	AIH	-7.08986	0.221	-16.6	2.4
AIH compared with other diagnosis	CHC	5.6	0.356	-3.2	14.4
	CHB	12.2	0.003	3.3	21.1
	NAFLD	7.1	0.221	-2.4	16.6

P < 0.001; AIH: Autoimmune hepatitis; APRI: Aspartate transaminase to platelets ratio index; CHB: Chronic hepatitis B; CHC: Chronic hepatitis C; CI: Confidence interval; NAFLD: Non-alcoholic fatty liver disease

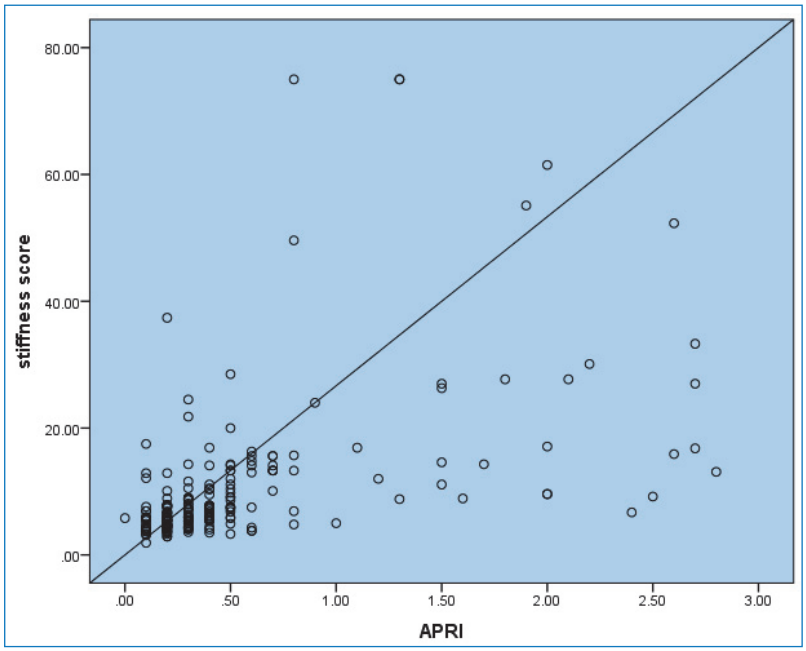

FIGURE 1.
Correlation between FibroScan® stiffness score and aspartate aminotransferase to platelets ratio index. R = 0.6, P < 0.001.

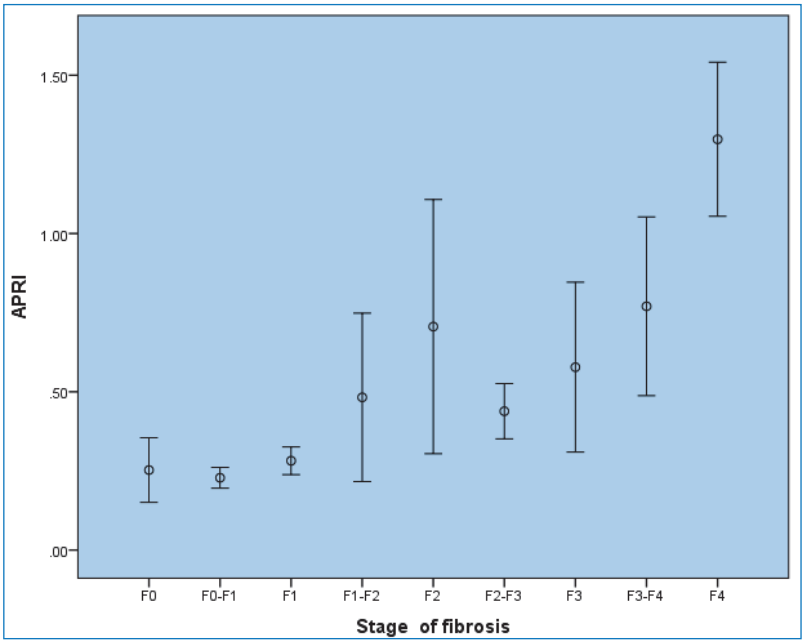

FIGURE 2.
Difference in aspartate aminotransferase to platelets ratio index according to FibroScan® stages of fibrosis. P < 0.001, ANOVA.

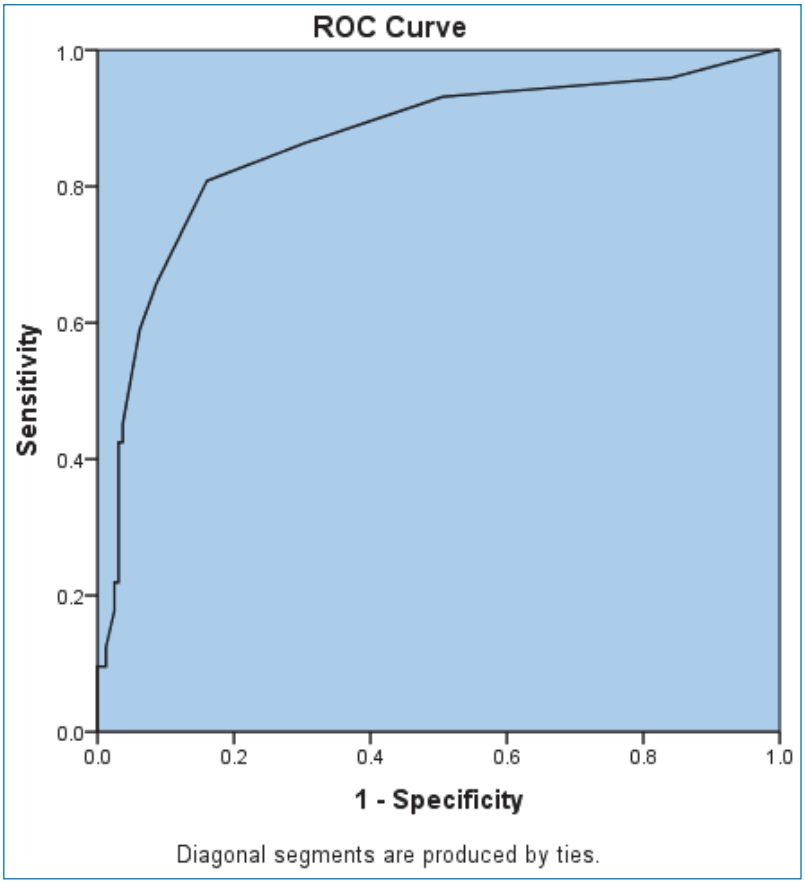

FIGURE 3.
Area under the curve of the receiver operating characteristic analysis of aspartate aminotransferase to platelets ratio index in the detection of transient elastography advance fibrosis > F2. Area under the curve = 0.863.

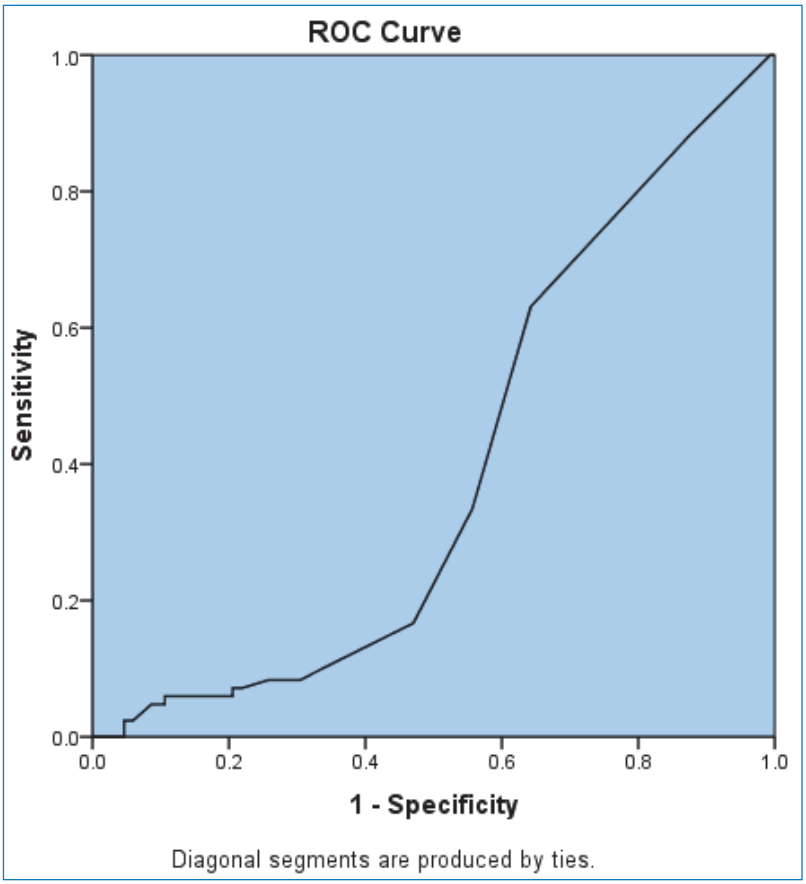

FIGURE 4.
Area under the curve of the receiver operating characteristic analysis of aspartate aminotransferase to platelets ratio index in the detection of mild to moderate fibrosis, F1 and F1-F2. Area under the curve = 0.4.

DISCUSSION

This current study revealed a strong relationship between the FibroScan® and APRI values in patients with moderate or severe fibrosis. These findings indicate that using these two methods together can increase the certainty of defining the degree of fibrosis, especially in patients with viral hepatitis, AIH or NAFLD, as in this cohort. Several previous studies have shown the accuracy of FibroScan® and APRI in the assessment of liver fibrosis[28-31]. Though the study's data is 6-7 years old, the same methods are currently in use and this study can be of value to the current practice.

The precise assessment of the stage of liver fibrosis is important for the prediction of the progression of liver disease, the development of complications and treatment decisions for some liver diseases[1,6,7]. However, in cases of mild to moderate fibrosis, the correlation between the FibroScan® and APRI values was much less evident, partially because both FibroScan® and APRI are more accurate in the detection of advanced fibrosis and cirrhosis. This is similar to the findings of previous studies[31,32]. The FibroScan® test as the reference non-invasive test for liver fibrosis was conducted because multiple studies had validated its utility in the assessment of different forms of liver disease[1,32-34]. Several studies have shown the accuracy of FibroScan® and APRI in the detection of advanced liver fibrosis compared with liver biopsy[1,28-31,33,35]. Aspartate transaminase to Platelets Ratio Index was first evaluated in CHC[16], but subsequent studies evaluated it in other forms of liver disease[28,31,32,34]. Abd El Rihim *et al.*[28] reported a meta-analysis of 23 studies that evaluated FibroScan® and 20 studies that evaluated APRI in the assessment of liver fibrosis. They found that FibroScan® had a sensitivity of 83.4% and a specificity of 92.2 for the detection of F4 fibrosis, whereas APRI had a sensitivity of 66.6% and a specificity of 71.1%. However, APRI was not useful for the detection of early stages of fibrosis[28]. In another meta-analysis of studies of patients with CHC and CHC/HIV co-infection, Lin *et al.*[29] reported area under the curve of the receiver operating characteristic (AUROC) values of 0.77, 0.8, and 0.83 for the detection of significant fibrosis, severe fibrosis and cirrhosis, respectively, in isolated CHC patients. However, APRI was less accurate for detection in cases of CHC/HIV co-infection[29]. In a similar study, Shaheen and Myers[30]obtained similar results for CHC patients but a higher accuracy for APRI detection of cirrhosis in CHC/HIV co-infection. As this sample did not include CHC/HIV co-infected patients, no comparison is possible. Lin *et al.*[36] evaluated APRI in a cohort of patients with CHC and CHB and found that APRI was more accurate in the detection of advance fibrosis and cirrhosis in CHC patients than in CHB patients. They obtained AUROC values for CHC and CHB patients of 0.87 and 0.69, respectively, for advanced fibrosis and of 84 and 0.75,

respectively, for cirrhosis[36]. In a study of CHB patients, Jin *et al.*[35] obtained a higher AUROC value (0.79) for the detection of advanced fibrosis than did Lin *et al.* but a similar AUROC value for cirrhosis. In a study of NAFLD patients, Wong *et al.*[32] used liver biopsy as reference and directly compared FibroScan® to other non-invasive biomarkers. They found that FibroScan® was more accurate than other biomarkers including APRI in the detection of F3 and F4 fibrosis. Similarly, Pathik *et al.*[34] compared liver biopsy with FibroScan® and other non-invasive biomarkers and reported a sensitivity of 0.9 and an NPV of 0.93 for FibroScan® and a sensitivity of 0.7 and an NPV of 0.84 for APRI. One advantage of this study is that it included a large number of patients with different forms of liver disease, including liver diseases that have not been well studied, using FibroScan® and APRI for the assessment of liver fibrosis.

This study showed that patients with AIH had more advanced fibrosis compared with patients with all other forms of liver disease on both FibroScan® and APRI. This is not an unusual finding, as it was previously reported that most AIH patients among Saudis have advanced liver disease, a finding that was also reported by Abdo *et al.*[37,38]. The observation of more advanced fibrosis in CHC patients than in CHB patients can be explained by the fact that most CHB patients are inactive CHB patients with a low chance of fibrosis progression[3,39]. Similarly, the lower degree of fibrosis in NAFLD patients than that in CHC and AIH patients can be attributed to the relatively benign course of NAFLD in most patients[4,40]. However, more recent studies are showing increasing rate of cirrhosis and hepatocellular carcinoma secondary to NAFLD[5]. Castera *et al.*[1] reviewed the cut-off values in FibroScan® scores for the detection of cirrhosis, which were as low as 10.3 in CHB and CHC and 17.3 in cholestatic liver disease. In a meta-analysis of performance, Friedrich-Rust *et al.*[33] showed that different liver diseases had different cut-off values for the defection of advanced fibrosis and cirrhosis.

This data showed that age greater than 40 years was associated with a higher chance of advanced fibrosis. Several studies have shown an effect of older age on the progression of fibrosis[33,41-43]. This finding also represents the ultimate outcome of the progression of liver disease. Moreover, previous reports have shown similar correlations of age with FibroScan® and APRI values[33,34,42].

These findings can help avoid the need for liver biopsy in patients who show agreement between FibroScan® and APRI results regarding the degree of fibrosis. In addition, the two methods can be used to assess liver fibrosis in patients with mild fibrosis, especially NAFLD patients and CHB carriers who do not have clear indications for liver biopsy. These methods can also be used for the assessment of fibrosis during and after treatment, thereby avoiding the risk of complications of repeated liver biopsy. An important future application for the non-invasive assessment of liver fibrosis is follow-up after treatment. This is very difficult to achieve with multiple liver biopsies. However, serial testing can follow baseline FibroScan® and APRI assessment. Several researchers have reported and reviewed the useful clinical applications of FibroScan® as a non-invasive test for the predication of liver events and for follow-up of patients after treatment[44-46].

In this cohort, CHC was the most common cause of chronic liver disease, followed by CHB. This observation is comparable to local data on chronic liver disease from Saudi Arabia, where viral hepatitis is the most common cause of liver disease and related morbidity and mortality in the country[47,48]. The relatively high percentage of NAFLD patients in this cohort is alarming. This high percentage reflects the increasing burden of diabetes, obesity and metabolic syndromes in Saudi Arabia[49,50].

CONCLUSION

The data showed that APRI significantly correlated with FibroScan® in the assessment of severe and moderate fibrosis. It is also shown that APRI could effectively distinguish mild fibrosis from advance fibrosis and cirrhosis. The combined use of FibroScan® and APRI can increase the accuracy of non-invasive assessment of the stage of liver fibrosis.

Limitations of the Study

FibroScan® was used as the reference method for the assessment of liver fibrosis, although FibroScan® has been validated through comparison with liver biopsy in multiple previous studies.

FibroScan® has been shown to have a high failure rate in patients with morbid obesity, but this failure rate is much lower than the rates reported by other investigators.

FibroScan® can give inaccurately high results in patients with acute inflammation; therefore, the patients with acute hepatitis were not included in this study.

In this study, there were small numbers of patients with some liver diseases, such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). These diseases are less prevalent than viral hepatitis and NAFLD in this community.

Up-to-date liver biopsy is still considered the gold standard and the reference for the assessment of liver fibrosis, and in some patients, it will still be needed, as in the case of two of this CHB patients.

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Conflict of Interest

The author has no conflict of interest.

Disclosure

The author did not receive any type of commercial support either in the form of compensation or finances for this study. The author has no financial interest in any of the products devices, or drugs mentioned in this article.

Ethical Approval

Obtained.

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تقييم التليف الكبدي باستخدام مؤشر نسبة انزيم ناقلة امين الاسبارتات إلى الصفائح الدموية مقارنة مع قياسات تليف الكبد باستخدام جهاز المسح الليفي للكبد

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مقدمة: تم تقييم جهاز المسح الليفي ومؤشر نسبة انزيم ناقلة امين الاسبارتات إلى الصفائح الدموية ومقارنتهم مع خزعة الكبد لتقييم تليف الكبد.

الطريقة: دراسة مقطعية للربط بين مؤشر نسبة انزيم ناقلة امين الاسبارتات إلى الصفائح الدموية وجهاز المسح الليفي للكبد بين المرضى الذين يعانون من أمراض الكبد، و تم حساب مؤشر نسبة انزيم ناقلة امين الاسبارتات إلى الصفائح الدموية، كما حصلنا على نتائج جهاز المسح الليفي للكبد و من ثم قمنا بتصنيف المرضى إلى ٤ مراحل للتليف مع الحصول على بيانات المرضى الأساسية، وجرت العمليات الإحصائية باستخدام برنامج SPSS.

النتائج: حوت الدراسة على ٢٣٥ مريض، ١٤١ ذكورا (٦٠٪) ٩٤ إناثا (٤٠٪) و كان التهاب الكبد الفيروسي ج (٣٨٪) الأكثر شيوعا بين مرضى الكبد ، والغالبية من المرضى مصابون بتليف الكبد الخفيف (درجة ٠-١)، (٤٩,٨٪). ثمانية عشر مريضا (٧,٦٪) لديهم تليف من الدرجة الثالثة، و٦٢ مريض (٢٦,٤٪) لديهم تليف من الدرجة الرابعة، وارتبط العمر الأكبر من ٤٠ سنة مع مراحل متقدمة أكثر للتليف مقارنة مع سن أقل من ٤٠ عاما بقيمة احتمالية = ٠,٠٠٤. و قد وجدنا ارتباطا قويا بين درجة التليف ومؤشر نسبة انزيم ناقلة امين الاسبارتات إلى الصفائح الدموية بقيمة احتمالية أقل من ٠,٠٠١ و كان هذا الارتباط واضحا للتليف المتوسط أو المتقدم على جهاز المسح الليفي للكبد.

الخلاصة: يرتبط مؤشر نسبة انزيم ناقلة امين الاسبارتات إلى الصفائح الدموية ارتباطا وثيقاً بنتائج جهاز المسح الليفي للكبد عند المرضى الذين يعانون من التليف المتقدم وتشمع الكبد ، وعلاوة على ذلك يمكن أن يحدد مؤشر نسبة انزيم ناقلة امين الاسبارتات إلى الصفائح الدموية بشكل دقيق درجة التليف الكبدي من نوع التليف المتقدم أو تشمع الكبد.