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Research Article

Role of APRI and FIB4 as a Non Invasive Tests for Assessment of Liver Fibrosis in Chronic HCV Infection

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Abstract

Background: Liver biopsy is considered the reference method for assessing hepatic fibrosis in chronically infected hepatitis C virus (HCV) patients, but unfortunately has many complications.

Aim: This study aimed to assess the role of the aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis 4 (FIB-4) tests as non-invasive alternatives to liver biopsy.

Methods: Our study recruited 757 patients with a median age of 42.6 ± 10.3 years. All patients underwent liver biopsy for fibrosis stage estimation, and the APRI and FIB-4 tests were performed. The liver biopsies were scored using the METAVIR system: 13 patients were F0 (1.7%), 356 (47%) were F1, 227 (30%) were F2, 160 (21%) were F3, and 1 (0.1%) was F4.

Results: For predicting fibrosis stages F ≥ 3, APRI and FIB-4 had a specificity of 90% at cut-off values of 1.1 and 2.7, respectively and a specificity of 95% at cut-off values of 1.67 and 3.3 respectively. The area under the receiver operating characteristic curve (AUC) was 0.663 (95% confidence interval [CI], 0.617 - 0.709) for APRI and 0.673 (95% CI, 0.627 - 0.719) for FIB-4. For predicting F ≥ 2, APRI and FIB-4 had a specificity of 90% at cut-off values of 0.94 and 2.4 respectively, a specificity of 95% at cut-off values of 1.14 and 2.7 respectively. The AUC was 0.642 (95% CI, 0.603 - 0.681) for APRI and 0.676 (95% CI, 0.638 - 0.714) for FIB-4.

Conclusion: For accurate non-invasive assessment of liver fibrosis stage, taking higher cut-off values for APRI and FIB-4 is recommended to improve their specificities.

Keywords: *APRI; FIB4; Liver Fibrosis; HCV*

Introduction

Chronic hepatitis C virus currently represents a major public health problem in Egypt. Its prevalence rates are estimated to be between 10% and 15% [1].

Historically, HCV has been treated by the administration of a combination of interferon and ribavirin for 24 - 48 weeks, depending on the genotype and the response to treatment, with a sustained virological response (SVR) reaching up to 50%for genotype 4 (the most common HCV genotype in Egypt).

The development of oral direct antiviral agents (DAAs) has revolutionized HCV treatment in the past3 years. DAAs have replaced interferon-ribavirin combinations, with an SVR reaching up to 100% for all genotypes [2].

Assessing fibrosis with a high degree of accuracy remains crucial for predicting HCV disease progression and outcomes [3]. The reference method for accurately assessing the stage of hepatic fibrosis is the liver biopsy, with tissue staging using the Ishak [4] or METAVIR [5] scoring systems. Unfortunately, this method has its disadvantages, as it is subject to inter-observer variability and sampling error, leading to inaccurate staging. Additionally, there are health risks related to the procedure including bleeding, infection, post-procedure pain, and

ascites leakage and it is contraindicated in cases of bleeding disorders [6-8]. These disadvantages have driven researchers to formulate non-invasive alternative tests to accurately assess hepatic fibrosis.

Aim of the Study

The aim of our study was to verify the ability of APRI and FIB-4 calculations based on simple, frequently requested tests to discriminate between different stages of hepatic fibrosis and to determine whether these laboratory tests can replace liver biopsy in a significant proportion of patients.

Study design

Our study is a single-centre, prospective study that performed in the Internal Medicine Department of the Kasr Alainy hospital Cairo university. Our study recruited patients with chronic HCV who were referred for liver biopsy during the period from 2014 to 2016. HCV was diagnosed prior to referral by the presence of HCV antibodies and confirmed by HCV-RNA quantitative assay. The exclusion criteria were focal hepatic lesions, acute hepatitis, coinfection with hepatitis B virus (HBV) or HIV or other liver comorbidities and treatment experience.

The following items were fulfilled for all participating patients:

1. A full detailed medical history was taken regarding their illness, including age, address, telephone number, history of drug intake, and any associated comorbidities, e.g., diabetes, along with a full clinical examination.
2. The following tests were performed:
    a. Liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, gamma-glutamyl transferase), serum albumin, total protein, serum bilirubin (total, direct), complete blood count, and prothrombin time.
    b. HCV total antibodies by ELISA, HCV-RNA by quantitative assay using PCR, HBsAg, HBcAb total and HIV antibodies.
    c. The APRI values were calculated using the following formula: (AST/upper limit of normal AST)/platelet count (10^9) × 100.
    d. The FIB-4 values were calculated automatically using the following formula: age (years) - AST [U/l]/ (platelets [10^9/l] - (ALT [U/l])1/2).
    e. Liver biopsy: Two experienced radiologists performed ultrasound-guided liver biopsies to decrease the risk of complications. Biopsies were taken using a 14-G true-cut needle and required a length of at least 20 mm. Two well-trained and experienced hepatopathologists blinded to the results of the non-invasive tests reviewed all biopsies (double read) to categorize the fibrosis using the METAVIR scoring system, as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, few septa; F3, numerous septa without cirrhosis; F4, cirrhosis [1].

Compliance with the study

All included patients were compliant with our study.

Consent of the patients

The protocol was accepted by the ethical committee, and we obtained a written consent before inclusion.

Statistical analysis

All patient data were collected using Excel 2010. Data were processed using SPSS version 20 for Windows 2010. The Pearson chi-square test was used to calculate the P value when both table variables were quantitative. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. Receiver operating characteristic (ROC) curves were applied for calculating the area under the curve (AUC), sensitivity and specificity for the tests used. Cut-off values were also calculated. $P > 0.05$, $P < 0.05$ and $P < 0.001$ was considered not significant, significant and highly significant, respectively.

Results

The current study included 757 patients with a mean age of 42.6 ± 10.3 years. There were 470 males (62.1%) and 287 females (37.9%). As per the liver biopsy assessment,13 patients were scored as F0 (no fibrosis), 356 (47%) as F1 (mild fibrosis), 227 (30%) as F2 (moderate fibrosis), 160 (21%) as F3 (moderate to severe fibrosis) and 1 (0.1) as F4 (cirrhosis), as shown in table 1.

Sex	Frequency (%)
Male	470 (62.1)
female	287 (37.9)
METAVIR F	
F0	13 (1.7)
F1	356 (47)
F2	227 (30)
F3	160 (21)
F4	1 (0.1)
METAVIR A	
A0	44 (5.8)
A1	480 (63.4)
A2	146 (19.3)
A3	69 (9.1)
A4	18 (2.4)
Steatosis	
0	384 (50.7)
1	261 (34.5)
2	104 (13.7)
3	8 (1.1)

Table 1: *Show the percentage of patients in the fibrosis and steatosis stages.*

Significant differences were found between the fibrosis stages (METAVIR, F) in the albumin level and the platelet count, suggesting early hepatic synthetic dysfunction before the development of cirrhosis. Significant differences were also found in AST, ALT, APRI and FIB-4, supporting their role in predicting F ≥ 3, as shown in table 2 and figure 1 and 2.

METAVIR F	0, 1, 2	3, 4	P value
Age, years	41.6 ± 10.4	46.4 ± 8.9	0.000
Bilirubin total, mg/dl	0.8 (0.6 - 0.9)	0.8 (0.7 - 1.1)	0.001
AST, U/L	36 (23-55.7)	48 (32 - 74)	0.000
ALT, U/L	38 (21 - 61)	53 (31 - 82)	0.000
AST/ALT	1.0 (0.8 - 1.2)	1.04 (0.8-1.2)	0.818
Albumin, gm/dl	4.1 (3.8 - 4.4)	3.9 (3.6 - 4.2)	0.000
Alkaline Phosphatase, U/L	116 (87.2-155)	115 (88-142)	0.555
PT, sec	12.7 ± 0.7	12.9 ± 0.7	0.003
PC, %	88.7 ± 9	86 ± 9.9	0.000
INR	1.0 (1.0 - 1.1)	1.1 (1.0 - 1.15)	0.013
Hb	13.9 ± 1.6	13.4 ± 1.5	0.001
TLC	6012 (4800 - 7375)	5800 (4750 - 1694)	0.214
Platelets	207538 ± 64803	190583 ± 65251	0.003
APRI	0.4 (0.3 - 0.7)	0.7 (0.4 - 1.1)	0.000
FIB4	1.1 (0.8 -1.7)	1.2 (1.7-2.6)	0.000
BMI, Kg/m^2	27 ± 4.5	29 ± 4.9	0.000
HAI score	5.6 ± 2.1	11 ± 1.2	0.000

Table 2: *Shows comparison between F0, 1, 2 and F3, 4 as regard different variables.*

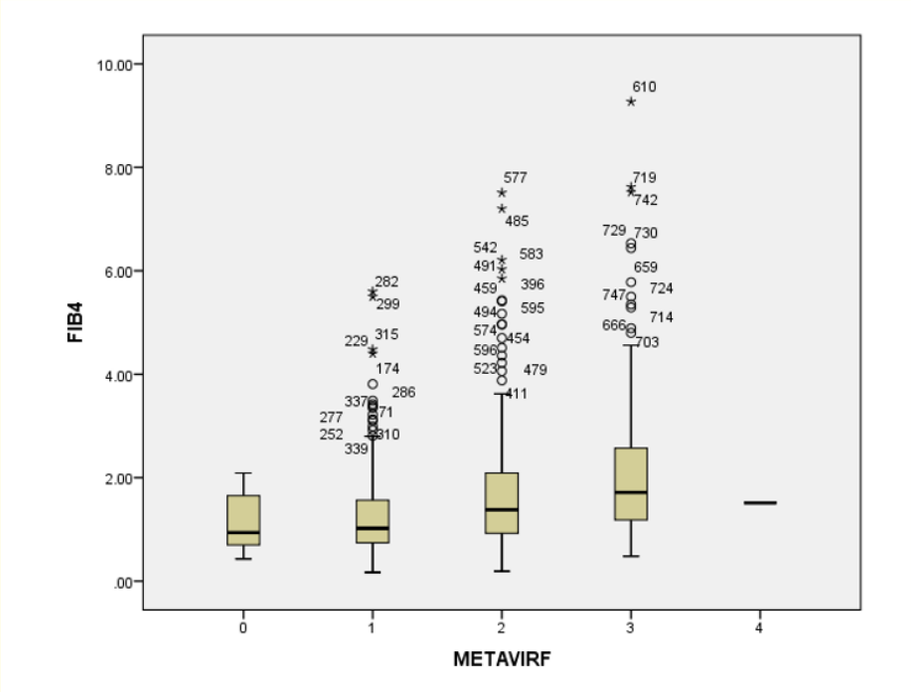

Figure 1: *Shows levels of FIB4 in different stages of Fibrosis stages.*

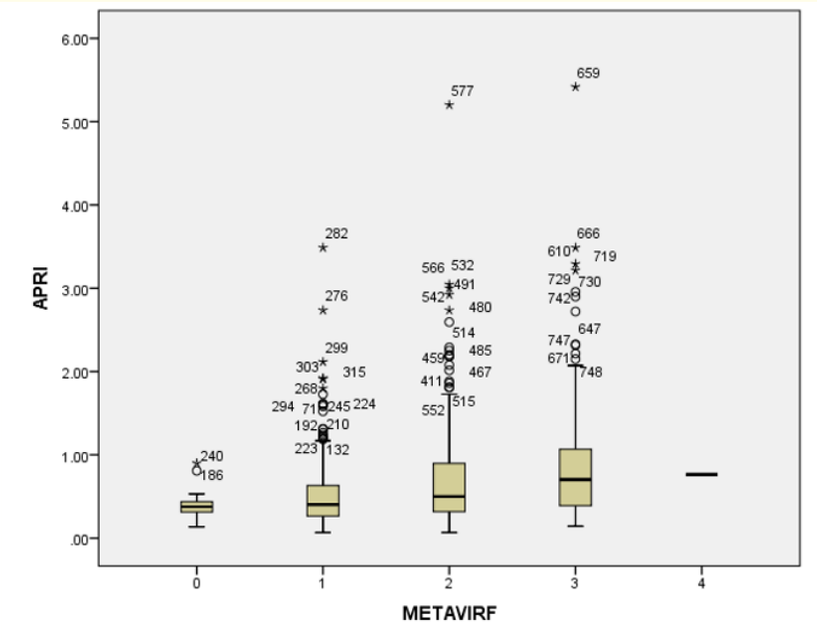

Figure 2: *Shows levels of APRI in different stages of Fibrosis stages.*

For the prediction of fibrosis stage F ≥ 3, APRI had a specificity of 90% and 95%at a cut-off value of 1.1 and 1.67 respectively, while FIB-4 had a specificity of 90% and 95% at a cut-off value of 2.7 and 3.3 respectively, as shown in table 3. The AUC for differentiating se-

vere (F3-F4) from mild-to-moderate fibrosis (F0-F2) was 0.663 (95% confidence interval [CI] 0.617 - 0.709) for APRI and 0.673 (95% CI, 0.627 - 0.719) for FIB-4. There was a significant difference in the AUCbetweenFIB-4 and APRI (P < 0.001), as shown in table 4 and figure 3.

	Cutoff	Sensitivity	Specificity
APRI	0.56	62	65
	0.69	51	73
	1.1	22	89
	1.14	22	90
	1.67	11	95
FIB4	1.3	68	60
	1.6	54	70
	2.7	24	90
	3.3	14	95

Table 3: *Show different cutoff values of APRI and FIB4 and their sensitivity and specificity to differentiate fibrosis stage F0, 1, 2 VS 3, 4.*

Test Result Variable (s)	Area	95% Confidence Interval	
		Lower Bound	Upper Bound
APRI	.6630	.6170	.7090
FIB4	0.673	.6270	.7190

Table 4*: Show area under the ROC curve of APRI and FIB4 and 95% Confidence Interval to differentiate fibrosis stage F0, 1, 2 VS 3, 4.*

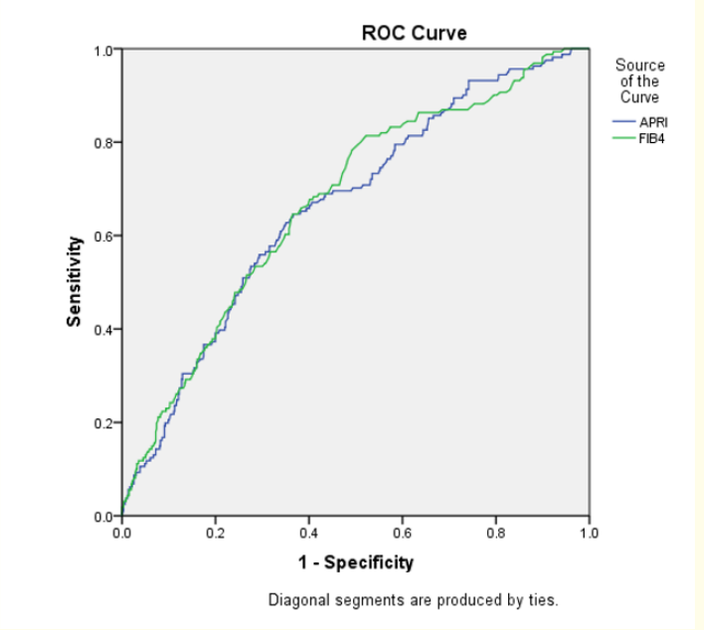

Figure 3: *Show ROC curve of APRI and FIB4 and their sensitivity and specificity to differentiate fibrosis stage F0, 1, 2 VS 3, 4.*

In our study, for the prediction of F ≥ 2, APRI had a specificity of 90% and 95% at a cut-off value 0.94 and 1.14 respectively, while FIB-4 had a specificity of 90% and 95% at a cut-off value 2.4 and 2.7 respectively, as shown in table 5. The AUC for distinguishing moderate to severe (F2-F4) from mild fibrosis (F0-F1) was 0.642 (95% confidence interval [CI], 0.603 - 0.681) for APRI and 0.676 (95% CI, 0.638 - 0.714) for FIB-4. There was a significant difference in the AUC between FIB-4 and APRI (P < 0.001) as shown in table 6 and figure 4.

	Cutoff	Sensitivity	Specificity
APRI	0.47	60	60%
	0.56	51%	70%
	0.94	27	90
	1.14	19	95
FBI	1.26	64	64
	1.4	55	70
	2.4	25	90
	3.7	20	95

Table 5: *Show different cutoff values of APRI and FIB4 and their sensitivity and specificity to differentiate fibrosis stage F0, 1 VS 2, 3, 4.*

Test Result Variable (s)	Area	95% Confidence Interval	
		Lower Bound	Upper Bound
APRI	0.642	.6030	.6810
FIB4	.6760	.6380	.7140

Table 6*: Show area under the ROC curve of APRI and FIB4 and 95% Confidence Interval to differentiate fibrosis stage F0, 1 VS 2, 3, 4.*

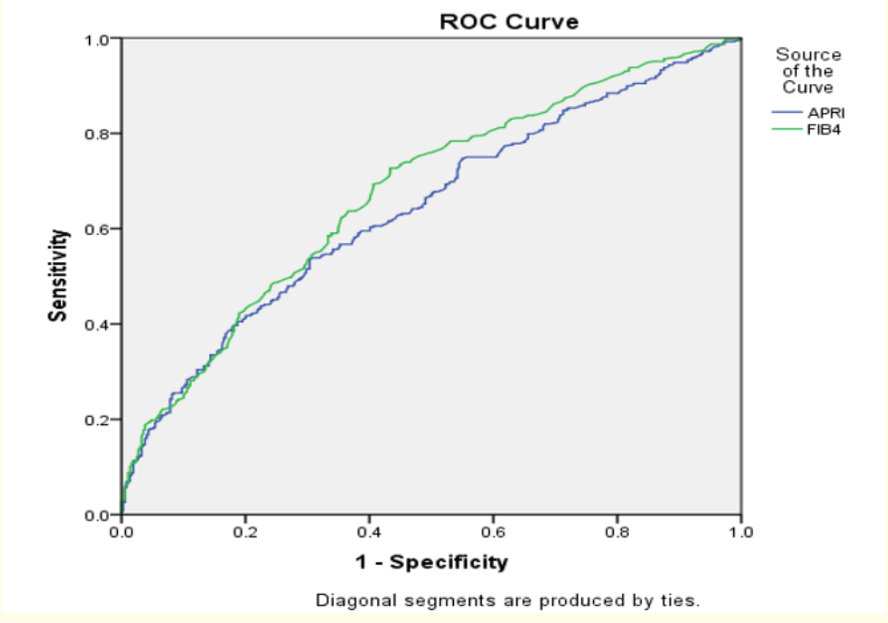

Figure 4: *Show ROC curve of APRI and FIB4 and their sensitivity and specificity to differentiate fibrosis stage F0, 1 VS 2, 3, 4.*

Discussion and Conclusion

Individuals with severe fibrosis or cirrhosis require screening for hepatocellular carcinoma (HCC) and gastro-oesophageal varices. In most instances, the recommended duration of treatment is also longer [9,10].

In some areas with limited resources and facilities (e.g. qualified well-trained doctors and budgeted health-care services), there is a need to prioritize treatment by giving precedence to those who will experience maximum benefits (i.e. METAVIR F ≥ 2). Moreover, those

who achieved SVR following treatment with DAAs should be screened for HCC if their METAVIR score is ≥ 3. However, in those who failed to achieve SVR with DAAs, the choice of DAA for retreatment depends on whether the METAVIR score is ≥ 3. Thus, assessing fibrosis with a high degree of accuracy is essential in both treatment-naïve and treatment-experienced patients.

Non-invasive tests to stage the degree of hepatic fibrosis include tests incorporating direct and indirect serum biomarkers and vibration-controlled techniques, e.g. transient elastography. No test alone is known to have a high level of accuracy [11].

Non-invasive test results have shown marked discrepancies among studies due to variable parameters, such as cut-off values, age, gender and number of included patients; the absence of moderately accurate results has also been observed in patients with intermediate fibrosis stages [12,13]. In clinical practice, the accurate detection of fibrosis stage is not usually needed, as knowing the stage itself is less valuable than knowing whether the patient has mild or severe hepatic fibrosis [14]. Liver biopsy should be performed in indeterminate cases. Hepatic biopsy and non-invasive tests should be used as an integrated and complementary system to enable a more efficient assessment [15].

APRI is a simple non-invasive test for evaluating hepatic fibrosis [16]. Many meta-analyses have shown that the range of APRI cut-off values for detection of different fibrosis stages is wide. The APRI cut-off value to detect F ≥ 2 ranges from 0.5 to 1.5, while that for detecting F ≥ 3 ranges from 0.5 to 2, with an optimal threshold of 1, with 64% specificity and 61% sensitivity [17].

FIB-4 is a more complex score than APRI for evaluating hepatic fibrosis. Several studies have shown that a cut-off of 1.26 for F ≥ 2 had a sensitivity and specificity of 64 and 75%, respectively [18]. For F ≥ 3, the optimal threshold ranged between 1.45 and 1.81 [19-21].

In our study, the sensitivity and specificity of APRI and FIB-4 to differentiate between severe fibrosis or cirrhosis versus lower grades of fibrosis were largely dependent on the cut-off value. Taking lower cut-off values increased the sensitivity but decreased the specificity and vice versa. Therefore, in the absence of an accurate estimation of the fibrosis stage by a standard liver biopsy, predicting METAVIR F ≥ 3 based on non-invasive tests, such as APRI and FIB-4, requires higher cut-off values to provide better specificity.

As previously mentioned, the prediction of fibrosis stage F ≥ 2 is crucially important in some areas with limited resources to prioritize treatment for patients with moderate to severe fibrosis [12].

It is worth mentioning that for the prediction of F ≥ 2, taking lower cut-off values will increase the sensitivity at the expense of the specificity, thereby allowing the earlier treatment of patients with lower degrees of fibrosis. Thus, we suggest the application of national cut-off values based on the available resources, national economic state and HCV infection burden in the community.

Our study complements a prospective study performed by Romanas., *et al.* that estimated the relationship of APRI and FIB-4 with the fibrosis stage in 140 patients with chronic HCV infection. To detect F ≥ 3, they found the APRI and FIB-4 cut-off values to be 1.28 and 2.28 respectively, with a sensitivity of 77.8% and 84.4% and a specificity of 78.5% and 81.7%, respectively. To detect F ≥ 2, the APRI and FIB-4 cut-off values were 1.12 and 1.63, with a sensitivity of 72.1% and 82.4% and a specificity of 78.6% and 75.7%, respectively [22].

The FIB-4 test was evaluated in 847 patients with chronic HCV infection. FIB-4 values higher than 3.25 had a PPV of 82.1% to confirm the existence of significant fibrosis (F3-F4), with a specificity of 98.2%. Values lower than 1.45 had an NPV of 94.7% for the exclusion of severe fibrosis, with a sensitivity of 74.3% [23].

Our study was consistent with a series of 847 liver biopsies performed in HCV patients; FIB-4 testing allowed the accurate detection of patients with severe fibrosis and cirrhosis (F3-F4), with an AUC of 0.85 (95% CI, 0.82 - 0.89) and 0.91 (95% CI, 0.86 - 0.93) respectively. A FIB-4 value < 1.45 had an NPV of 94.7% for excluding severe fibrosis, with a sensitivity of 74.3%. A FIB-4 value higher than 3.25 had a PPV of 82.1% for confirming the presence of significant fibrosis (F3-F4), with a specificity of 98.2% [24].

The results of our study are similar to the results obtained from a larger cohort study performed on 2372 HCV-infected patients in the US whose fibrosis stage distribution by biopsy was the following: F0, 267 (11%); F1, 555 (23%); F2, 648 (27%); F3, 394 (17%); and F4, 508 (21%). The mean APRI and FIB-4 values significantly increased with increasing fibrosis levels (P < 0.05). The AUC for discriminating severe (F3-F4) from mild-to-moderate fibrosis (F0-F2) was 0.80 (95% CI, 0.78 - 0.82) for APRI and 0.83 (95% CI, 0.81 - 0.85) for FIB-4 [25].

In another retrospective study including 1473 chronic HCV patients, the AUC of FIB-4 for the detection of significant fibrosis (F2), advanced fibrosis (F3), and cirrhosis (F4) was 0.816, 0.827 and 0.849 respectively, compared with that of APRI, which was 0.799, 0.791 and 0.802, respectively. The AUC of FIB-4 was significantly greater than that of APRI for patients with advanced fibrosis and cirrhosis, respectively ($P < 0.0001$). They concluded that FIB-4 more accurately predicts severe fibrosis and cirrhosis than APRI in chronic HCV patients [26].

However, a meta-analysis including 40 studies and a total of 8739 chronic HCV patients showed that the AUC of the APRI for the diagnosis of F2 or more was 0.77 and for diagnosis of ≥ F3 was 0.80 and for cirrhosis (F4) was 0.83 [27]. This meta-analysis concluded that the best cut-off value for detection of significant fibrosis was 0.7, which have a sensitivity of 77% and specificity of 72%. For the diagnosis of cirrhosis, the optimal cut-off was 1.0, which have a sensitivity of 76% and a specificity of 72% [27].

When we compared our results with those of the previously mentioned studies, we concluded that when considering the APRI or FIB-4 tests for assessing fibrosis stage, we should take higher cut-off values to increase the specificity of these tests. Combining these tests with other non-invasive tests, e.g. elastography, whenever possible would provide better accuracy. Lastly, in some cases, taking a liver biopsy in the case of inconclusive results and the absence of contraindications may be mandatory.

We realize that our study has some shortcomings, one of which is comparing only 2 non-invasive tests without combination with vibration-controlled tests, e.g. transient elastography, to conclude whether the combination of different non-invasive liver fibrosis tests could increase of the diagnostic accuracy of predicting different stages of fibrosis.

Another shortcoming is the small number of F4 (one) and F0 (13) patients. From another point of view, the large numbers of patients in the F1, F2 and F3 stages strengthened the differentiation of intermediate stages of fibrosis in our study without the diluting effect of the extremes of the fibrosis spectrum.

Moreover, our study has some strengths. The current study is the first prospective single-centre study in Egypt including a relatively high number of patients forming a homogeneous group that did not include treatment-experienced patients with chronic hepatitis C.

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