

Research Article

King's Score, FI, FibroIndex and Lok Index Predict METAVIR Stage of Fibrosis among Chronic HCV Mono-infected Patients

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Abstract

Background: Liver biopsy is the best predictor for the assessment of liver fibrosis/cirrhosis. However, the need exists for non-invasive and accurate methods for staging liver fibrosis without exposing patients to the potential harms of the biopsy. The current study assesses the reliability of four recently introduced, non-invasive biomarkers: King's score, Fibrosis Index (FI), FibroIndex and Lok index in predicting hepatic fibrosis/cirrhosis in patients with chronic HCV infection versus METAVIR stage.

Patients and methods: Eighty-one HCV mono-infected patients who underwent liver biopsy and blood sampling were included. Liver fibrosis was staged (F0-4) and required laboratory tests were performed. King's score, Fibrosis Index (FI), FibroIndex and Lok index were calculated and their Receiver Operating Curves (ROCs), sensitivities, specificities, predictive values and accuracies were evaluated.

Results: There were 14, 47 and 20 patients at F0-F1, F2-F3, and F4 groups. Platelet count, prothrombin time, AST, ALT, serum albumin, gamma globulin, and all non-invasive biomarkers demonstrated significant statistical differences. From ROCs FI and FibroIndex were good for predicting significant fibrosis and excellent for cirrhosis. King's score and Lok index were fair for predicting significant fibrosis and good for cirrhosis. King's Score was the most reliable for prediction of cirrhosis (100% accuracy). FI diagnosed 90% of cirrhotic patients with high accuracy (94.1%). Lok Index and FibroIndex diagnosed 80% and 70% of cirrhotic patients.

Conclusions: This study verified the utility of King's Score, FI, FibroIndex and Lok Index in estimating the stage of hepatic fibrosis/cirrhosis in HCV infected patients as opposed to METAVIR scoring.

Keywords: FI; FibroIndex; Lok Index; King's Score; META- VIR Scoring

Abbreviations:

HCV : Hepatitis C virus

INR : International normalized ratio

AST : Aspartate aminotransferase

ALT : Alanine aminotransferase

ROC : Receiver-operating characteristic

PPV	:	Positive predictive value
NPV	:	Negative predictive value
AUROC	:	Area under the receiver-operating characteristic
METAVIR	:	Meta-analysis of Histologic Data in Viral Hepatitis
ISI	:	International specificity index

Introduction

Globally, an estimated 130-170 million persons are living with Hepatitis C Virus (HCV) infection. This chronic form of this infection is associated with sizable morbidity and mortality. More than 350 000 deaths are attributed to HCV infection each year, mostly due to liver cirrhosis and hepatocellular carcinoma. The epidemiology and burden of HCV infection varies throughout the world, with country-specific prevalence ranging from < 2% to >10% [1]. Egypt is believed to have the highest burden of hepatitis C in the world, being estimated at 14.7% among the 15-59 years age group, [2] and as high as 42% in some regions [3].

Although liver biopsy is the best predictor for the stage of liver fibrosis, biopsy is invasive, costly and is associated with discomfort and risk of major complications (0.3%-0.5%), including death (0.03%-0.1%). Furthermore, it is subjected to sampling error; interpretation variability or underestimation of underlying cirrhosis, especially when biopsy specimens are small or fragmented. Thus, the need exists for a non-invasive and accurate method for diagnosing the stage of liver fibrosis or cirrhosis without exposing patients to the harms of biopsy [4-6]. Several investigators have reported non-invasive approaches for the quantitative diagnosis of liver fibrosis and cirrhosis, comprising single routine laboratory tests, serum fibrosis markers, indices based on multiple tests, radiological imaging, and elastography [7].

Although transient elastography is the most validated non-invasive diagnostic approach for cirrhosis among HCV infected patients, it may be difficult to obtain a reliable examination, especially in obese patients and with other conditions that increase liver stiffness [8,9]. The ideal non-invasive approach must be simple, readily available, reliable, inexpensive, safe, and well validated. It must also be useful in assessing the progression of liver disease [10]. Despite the diversity of non-invasive tests and indices, inconsistent results and low diagnostic accuracies were reported for these tests when evaluated in different study populations with inconsistent results [8,11,12,13].

The current study aimed to assess the reliability of four recently introduced, less investigated non-invasive biomarkers of hepatic fibrosis namely King's score, Fibrosis Index (FI), FibroIndex and Lok index in predicting the stage of hepatic fibrosis/cirrhosis in patients with chronic HCV infection versus histopathological stage detected by METAVIR scoring [F0-4]. Results are presented

as the mean±Standard Deviation (SD), counts and percentages when appropriate. The sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), diagnostic accuracy and the Area Under the Receiver Operating Curve (AUROC) characteristic of each non-invasive biomarker were calculated based on liver biopsy as a reference.

Patients and Methods

Patient selection

Patients included in this study had been diagnosed clinically to bear symptomatic HCV infection, confirmed by positive HCV antibody assay and detectable HCV-RNA by qualitative Polymerase Chain Reaction (PCR). They were referred by general practitioners, private specialists or public general hospitals for liver biopsy and staging before starting medical treatment. Eighty-one HCV mono-infected Egyptian patients, who did not suffer from additional causes of chronic liver disease (HIV and/or HBV co-infection, metabolic liver diseases, hepatocellular carcinoma, prior liver transplantation) as confirmed by standard clinical, serological, biochemical, and radiological criteria were selected to be enrolled in this study. Patients with clinically decompensated liver cirrhosis were excluded from the study.

Liver biopsy was performed for all patients prior to antiviral or antifibrotic therapy. Concomitant blood sample was taken at the same time of liver biopsy and stored at -80°C for performing laboratory tests that allow the calculation of non-invasive biomarkers of liver fibrosis for all patients. All procedures were followed in accordance with the current revision of the Helsinki declaration, and all participants gave informed consent [14].

Liver biopsies

Percutaneous liver biopsies were taken under ultrasonographic guidance using an 18-20gauge tru-cut needles (GMSS.N, Ghat-wary Medical, Egypt) and samples ≥ 15 mm in length were collected and processed with standard techniques. Formalin-fixed, paraffin-embedded liver biopsy specimens were cut into 4- μ m sections and stained with Hematoxylin and Eosin (H&E), reticulin, Masson trichrome and Periodic Acid-Schiff (PAS). Each biopsy sample was scored after examination of at least three histological H&E-stained sections and the corresponding special stains. Biopsy samples in which the liver capsule was identified were staged using all but a 1-mm sub-capsular rim of tissue and biopsy specimens with at least six portal fields were considered representative. Assessment of biopsies for fibrosis were performed without knowledge of the results of laboratory tests [15]. METAVIR scoring system was applied on a scale of 0-4: F0, no fibrosis; F1, portal fibrosis without septa (bridge of connective tissue between two portal tracts, a portal tract and a centrilobular vein, or between two centrilobular veins); F2, few septa; F3, numerous septa without

cirrhosis; F4, cirrhosis (liver tissue is mutilated by nodular fibrosis that delineates hepatocyte nodules) [16]. For statistical analysis, the F0 and F1 were considered insignificant fibrosis; F2-F3 were considered significant fibrosis and stage F4 as cirrhosis [11].

Laboratory testing

HCV-RNA qualitative real time PCR assay was performed using Roche Molecular Diagnostics-Ampliprep/Cobas TaqMan HCV test (detects >60 IU/mL in serum). Complete hemogram including platelet count ($\times 10^9/L$) was done using electronic blood cell counter (Beckman Coulter cell counter), and prothrombin time was routinely determined (in seconds) using standard laboratory techniques. International Randomized Ratio (INR) of prothrombin time was calculated as: (Prothrombin time [test]/Prothrombin time [normal]) ISI. Serum spectrophotometric assay (Roche Hitachi 912@spectrophotometer, Diamond Diagnostics, USA) was performed for AST using the AST (GOT) detection kit (Roche, catalog number: 11876848216) and for ALT using the ALT (GPT) detection kit (Roche, catalog number: 11876805216). Serum electrophoresis was used to evaluate serum albumin and gamma globulin (g/dL). The following Normal Values (NV) were used: AST, NV = 0-42 IU/mL; ALT, NV = 0-42 IU/mL; serum albumin, NV=3.3-5.7 g/dL; gamma globulin, NV= 0.5-1.4 g/dL; platelet count, NV = 150-450/ $10^9/L$ and normal prothrombin range was 11-12.5 seconds; ISI (International Sensitivity Index), NV=1.2 and INR, NV = 0.88-1.1.

Calculation of the non-invasive biomarkers

On the basis of the aforementioned routine laboratory tests in addition to age of the patient at the time of liver biopsy, we calculated four non-invasive biomarkers for predicting liver fibrosis or cirrhosis (King's score, FibroIndex, Fibrosis Index (FI) and Lok index) for each of the fibrosis groups: insignificant fibrosis, significant fibrosis and cirrhosis, based on the formulas originally described, [7,17,18] in Table1.

Fibrosis bio-marker	Calculation formula
King's Score [17,18]	Age (years) \times AST (IU/L) \times INR / platelets ($10^9/L$)
Fibrosis Index (FI) [18]	8- 0.01 \times platelets ($10^9/L$) - albumin (g/dl)
FibroIndex [7,17]	1.738-0.064 (platelets [$10^9/L$]) +0.005(AST [IU/L]) + 0.463(gamma globulin [g/dl])

Lok index [17,18]	- 5.56 - 0.0089 \times platelet ($10^9/L$) + 1.26 \times AST/ALT ratio + 5.27 \times INR
AST: Aspartate aminotransferase; INR: International Randomized Ratio; ALT: Alanine aminotransferase	

Table 1: Non-invasive fibrosis biomarkers composed of routine laboratory parameters and their calculation formulas.

Statistical analyses

Data obtained were processed using Statistical Package in Social Science (SPSS) version 16.0 for Windows (SPSS Inc., Chicago, USA). Patient characteristics were given as mean \pm Standard Deviation (SD) or counts, and percentages as appropriate. Quantitative data were analyzed using the Kruskal Wallis test, whilst likelihood ratio was used to compare qualitative data. Spearman's rank correlation coefficient (r) was calculated to measure the relationship between variables. A value of $p \leq 0.05$ was considered statistically significant. Receiver Operating Characteristic (ROC) curves were constructed to determine the optimum cut-off values for each biomarker. The diagnostic values of tests were compared by the area under the receiver operating curve (AUROC) and their corresponding 95% Confidence Intervals (CI). To evaluate diagnostic performance of non-invasive fibrosis tests, sensitivity; specificity; PPV; and NPV were calculated. Accuracy was represented using the terms sensitivity and specificity, and was calculated as the following equation: True Positive (TP) + True Negative (TN)/ total number of patients. Graphics were constructed using the Excel program [19].

Results

The clinicopathological characteristics of the patients and the results of standard laboratory tests at the time of liver biopsy are summarized in Table 2. This study included eighty-one chronic HCV patients (44 males and 37 females) with a mean age (\pm SD) of 52.8 (± 6)-years. According to the METAVIR scoring system, the severity of liver fibrosis was staged as follows: 14.7% either had no fibrosis or had stage 1 fibrosis (F = 0, 1; in fibrosis); 58% had stage 2 or 3 fibrosis (F = 2, 3; significant fibrosis); and 24.7% had cirrhosis (F = 4) (Table 2). The age difference between groups was statistically insignificant. Platelet count and serum albumin tended to decrease with advancing fibrosis stage ($p < 0.001$ for both), whilst prothrombin time, AST, ALT and gamma globulin increased with a rising fibrosis stage ($p < 0.001$, < 0.001 , 0.003 , < 0.001 respectively), imparting a highly significant difference between groups.

Variable	Total (n=81)	METAVIR fibrosis/cirrhosis groups			P value
		F0-F1 (n=14, 14.7%)	F2-F3 (n=47, 58%)	F4 (n=20, 24.7%)	
Gender; n (%)					
Male	44(54.3%)	10 (22.7%)	25(56.8%)	9(20.5%)	0.3
Female	37(45.7%)	4(10.8%)	22(59.5%)	11(29.7%)	
Age (mean±SD)	52.8±6	52.1±4	52±6.3	55.1±5.9	0.14
AST (mean±SD)	71.3±40.7	55.9±21.9	62.3±30.2	103.4±54.7	<0.001*
ALT (mean±SD)	66.2±37.4	55±26.5	59.2±31.4	90.4±47.0	0.003*
Albumin (mean±SD)	3.6±0.6	4.1±0.2	3.7±0.5	3.1±0.5	<0.001*
Gamma globulin (mean±SD)	1.4±0.14	1.2±0.04	1.4±0.08	1.6±0.08	<0.001*
Platelet count (mean±SD)	153.3±38.9	187.4±14.7	151.3±39.5	134.2±34.6	<0.001*
Prothrombin time (mean±SD)	12.76±1.615	12.07±1.26	12.8±1.6	13.34±1.71	<0.001*

n: number; SD: Standard Deviation; * a statistically significant value if $p \leq 0.05$.

Table 2: Clinicopathological and laboratory characteristics of the study population (n =81) and comparison of variables with the METAVIR stage of fibrosis and cirrhosis.

Table 3 compares the four tested non-invasive indices used for predicting liver fibrosis stage among the studied METAVIR fibrosis/ cirrhosis groups: F0-F1, F2-F3 and F4. There were significant statistical differences among groups in regard to all tests ($p < 0.001$ for King's Score, Fibrosis Index and FibroIndex and 0.004 for the Lok Index), with the mean values for all of the calculated non-invasive indices and scores being higher with significant fibrosis and consequently with cirrhosis.

Non-invasive fibrosis biomarkers	METAVIR Fibrosis & cirrhosis groups			P value
	F0-F1 (n=14, 14.7%)	F2-F3 (n=47, 58%)	F4 (n=20, 24.7%)	
King's Score (mean±SD)	20.3±9.6	32.1±21.7	64.9±45.3	< 0.001*
Fibrosis Index (FI) (mean±SD)	1.9±0.2	2.8±0.7	3.5±0.6	< 0.001*
FibroIndex (mean±SD)	-9.4±1.0	-6.9± 2.5	-5.6±2.2	< 0.001*
Lok Index (mean±SD)	0.73±0.5	1.2±0.9	2.0±1.6	0.004*

Table 3: Comparison of non-invasive fibrosis biomarkers with the METAVIR stages of fibrosis and cirrhosis among the study population (n =81).

Receiver operating characteristic (ROC) curves evaluating the diagnostic accuracies of King's Score, Fibrosis Index (FI), FibroIndex and Lok Index were constructed to discriminate subjects with significant fibrosis or cirrhosis. FI and FibroIndex revealed high AUROCs ranging from 0.848 to 1.0 and were good for diagnosis of significant fibrosis (Figure 1) and excellent for diagnosis of cirrhosis (Figure 2) when compared to insignificant fibrosis. For the same diagnostic purpose, King's score and Lok index had lower though paralleled AUROCs ranging from 0.611 to 0.871, being relatively fair for predicting significant fibrosis (Figure 1) and good for predicting cirrhosis (Figure 2) versus insignificant fibrosis.

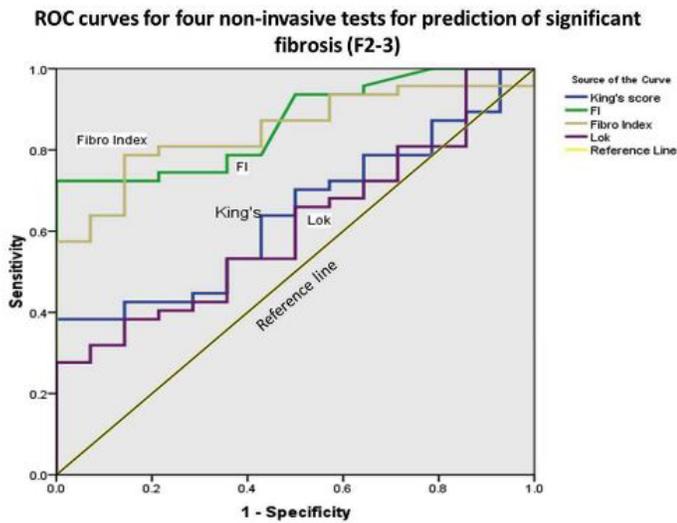


Figure 1: Receiver Operating Characteristic (ROC) curves of the four non-invasive tests for prediction of significant fibrosis (F2-3) versus insignificant fibrosis (F0-F1) according to the METAVIR system in 81 patients with chronic HCV. Areas under the curves (AUROCs) of four non-invasive tests for prediction of significant fibrosis at asymptotic confidence interval = 95% were 0.643 for King's score; 0.867 for FI; 0.848 for FibroIndex; and 0.611 for Lok Index.

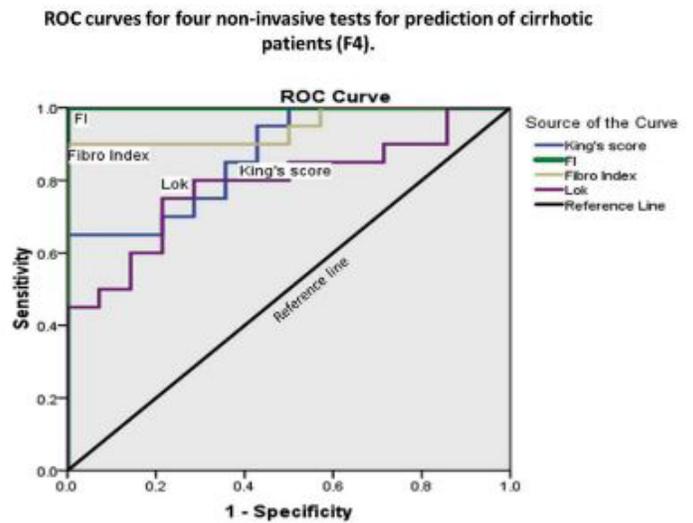


Figure 2: Receiver Operating Characteristic (ROC) curves of four non-invasive tests for prediction of cirrhosis (F4) versus insignificant fibrosis (F0-F1) according to the METAVIR system in 81 patients with chronic HCV. Areas under the curves (AUROCs) of four non-invasive tests for prediction of cirrhosis at asymptotic confidence interval = 95% were 0.871 for King's score; 1.0 for FI; 0.946 for FibroIndex; and 0.789 for Lok Index.

To depict the diagnostic performance of each non-invasive fibrosis biomarker, sensitivity, specificity, PPV, NPV and accuracy were calculated compared to stage of fibrosis using categories and cut-off values as originally described (Table 4). King's Score was the most reliable non-invasive test for prediction of cirrhosis. We found that the optimal cut-off value for King's Score to diagnose cirrhosis and exclude significant fibrosis was 2.345, with a perfect sensitivity, specificity, PPV and NPV and accuracy (100%). At a cut-off value of -7.745, Fibrosis Index (FI) was able to diagnose 90% of cases with high accuracy (94.1%), sensitivity (90%), specificity (100%) and PPV (100%) but the NPV of this index was slightly lower (87.8%) as compared to King's score. At their optimal cut-off values, Lok Index and FibroIndex diagnosed efficiently 80% and 70% of cirrhotic patients respectively. Both indices demonstrated a relatively high PPV for cirrhosis (80% for the former and; 82.4% for the later) at the same cut-off levels. However, their diagnostic accuracies were lower than King's score and FI (76.5% and 73.5% respectively) due to the lower sensitivities, specificities and NPVs for excluding non-cirrhosis and predicting cirrhosis.

Non-invasive biomarker	Cut- off value	Number (%)	Sensitivity	Specificity	PPV	NPV	Accuracy
King's Score	2.345	20 (100%)	100%	100%	100%	100%	100%
Fibrosis Index (FI)	-7.745	18 (90%)	90%	100%	100%	87.8%	94.1%
FibroIndex	31.437	14 (70%)	70%	78.6%	82.4%	64.7%	73.5%
Lok Index	0.9114	16 (80%)	80%	71.4%	80%	71.4%	76.5%

PPV: Positive Predictive Value; NPV: Negative Predictive Value

Table 4: Diagnostic accuracies, sensitivities, specificities and predictive values of the four non-invasive fibrosis biomarkers according to their cut-offs for the diagnosis of cirrhosis (F4).

Discussion

In the absence of an alternate gold standard to liver biopsy, it is difficult to assess the actual number of false positive and false negative liver biopsies as the accuracy of liver biopsy is sometimes hampered by the sampling errors or the inadequate quality of the biopsies.⁵ Hence, several studies on the prediction of liver fibrosis/cirrhosis among Chronic Hepatitis C (CHC) virus infected patients were published during the past 10 years [5,9].

In this study of 81 well-characterized patients with CHC, we investigated four recently described non-invasive indices that can reliably predict the histological stage of liver fibrosis/cirrhosis. With the development of liver cirrhosis, the synthetic function in the liver decreases [9] For this reason, we selected a set of non-invasive tests combining objective biologically plausible variables comprising age, platelet count, AST, ALT, serum albumin, gamma globulin and International Randomized Ratio (INR) of prothrombin time. For emphasis, platelet count is known to correlate with the degree of portal hypertension and with hepatic function and reduced thrombopoietin synthesis [20] Similarly, INR, is related to hepatic synthetic function, so it worsens with progression of fibrosis and hepatocyte loss. Serum levels of AST and ALT are usually elevated in CHC. Notably, an AST/ALT ratio above 1 correlates with the presence of cirrhosis, as a result of delayed AST clearance relative to ALT or of mitochondrial injury associating advanced liver disease [21,22]. Moreover, the characteristic abnormality of serum proteins in CHC and advanced cirrhosis, including falling albumin and elevated gamma globulin concentrations [5,8,23], were as well relied upon.

The mean age of our patients as well as the sex distribution matched with that of Gökcan et al. [24] (51.7±11.6-years) with no statistical difference among groups. Yet, the distribution of METAVIR fibrosis stages among our study group was divergent from that recorded by Bota et al. [17] As compared to the previous study, we had lower frequency of significant fibrosis (58% versus 76.4%) and higher frequency of cirrhotic patients (24.7% versus 14.2%). Meanwhile, our distribution of fibrosis stages matched with Cross et al. [25] who included a percentage of 22% cirrhotic patients in their study. In accordance to our results, a series of previous studies demonstrated a direct and significant correlation between the calculated values of King's Score, Fibrosis Index (FI), FibroIndex and Lok Index as compared to different METAVIR stages [7,17,26-28].

For comparative purposes, many non-invasive biomarkers associated with an AUROC of 0.70 to 0.80 are classified as fair, AUROC of 0.80 to 0.90 are classified as good and those above 0.90 are described as excellent for diagnosis when compared with liver biopsy [29]. Additionally, the cut-off values were chosen in our study that would produce a minimal misclassification error.

King's Score was introduced by Cross et al. on 2009 [25]. They reported AUROCs for predicting of significant fibrosis and cirrhosis of 0.79 and 0.91 (respectively). In the former study, King's Score of greater than or equal to 16.7 predicted cirrhosis, as compared to Ishak score, with 86% sensitivity, 80% specificity and a high NPV of 96%. According to Cross et al. [25] King's Score is an accurate index for predicting cirrhosis in CHC patients. The diagnostic accuracy of this scoring model was established in a later study [30]. We assessed King's Score using ROC curves and an AUROC of 0.643 was found for the prediction of significant fibrosis and 0.871 for cirrhosis. Strikingly, at the best cut-off value obtained in this study (2.345), King's Score predicted cirrhosis with an accuracy of 100%. Comparatively, Bota et al. [17] obtained 90% sensitivity, 97.8% NPV, and 76.4% accuracy for predicting cirrhosis using King's Score compared to Knodell score as a reference value. In comparison to other non-invasive tests, the high NPV for King's Score recorded in different studies, [17,24,25,30] improves its utility in determination of patients with mild fibrosis and in the differentiation of significant fibrosis from cirrhosis, providing prognostic data without the need for a liver biopsy. Our observation is in agreement with previous reports; however, using different histopathological staging systems of fibrosis in different studies as well as inclusion of different numbers of cirrhotic patients elicited some differences among the results.

In the current study, Fibrosis index (FI) was a good to excellent non-invasive test for prediction of significant fibrosis and cirrhosis (AUROCs; 0.867 and 1.0 respectively). Using our best cut-off value, FI had 90% sensitivity and 100% specificity with 94.1% accuracy for diagnosis of cirrhosis. Our results came to support the data obtained by Ahmad et al. [28] who demonstrated that FI had a high AUROCs (0.979-1.00) in discriminating different fibrosis stages with a high sensitivity (95.2%), specificity (94%), PPV and NPV for predicting cirrhosis using their proposed new cut-off value. Similar to our mean FI values, Ohta et al. [26] had median levels of FI in F0-1, F2- F3, F4 of 1.8, 2.7, 3.6 respectively and these values, correlated significantly with the histological fibrosis stage. In the aforementioned study, the AUROC for discrimination between insignificant and significant fibrosis was 0.850 and that for discriminating cirrhosis from non-cirrhosis was 0.976. At a cut-off value of 3.30 and more, Ohta et al. [26] demonstrated a sensitivity of 67.7%, and specificity of 97.9% for prediction of cirrhosis with overall accuracy of 95.4%. These data reflect the ability of FI to distinguish between respective fibrosis stages from insignificant fibrosis to cirrhosis with acceptable accuracy with agreement among different studies.

Among our group of patients, FibroIndex correctly classified 70% of cirrhotic patients with an overall accuracy of 73.5%, but it had a low sensitivity and limited NPV. AUROCs were 0.848 for prediction of significant fibrosis and 0.946 for cirrhosis at the

present study. According to published studies, [7,29] the areas under the ROC curves of the FibroIndex for predicting significant fibrosis and cirrhosis were 0.83 and 0.86 respectively. It had high specificity and PPV in identifying patients with significant or severe fibrosis. However, its sensitivity was limited and not sufficient to recruit patients who need treatment [7]. Moreover, direct comparisons showed no superiority of Fibroindex over other tests for both significant fibrosis and cirrhosis detection [29]. Although the present study showed that FibroIndex performed well in the prediction of significant fibrosis and cirrhosis, we agree with Koda et al. [7] that FibroIndex is not an adequate tool to be used alone, but it may serve as an adjunct along with other fibrosis markers due to its low sensitivity.

Using their original formula, Lok et al. [5] detected an AUROC of 0.79 for Lok index in diagnosing cirrhosis with two cut-off points introduced; 0.2 to rule out cirrhosis and 0.5 to confirm cirrhosis. For Lok Index, we were able to detect AUROCs of 0.611 for prediction of significant fibrosis and 0.789 for cirrhosis. Meanwhile, we used an optimal cut-off value of 0.9114 to diagnose efficiently 80% of cirrhotic patients using this index with an overall accuracy of 76.5%. Several other studies used this index for estimation of liver cirrhosis. For example, Masuzaki and colleagues [31] studied 386 chronic hepatitis C patients for determining the diagnostic accuracy of Lok index in comparison with the other non-invasive indices and they reported an AUROC of 0.692 for diagnosis of cirrhosis. The corresponding AUROC for detection of cirrhosis using Lok index was 0.79 in a study by Ydreborg et al. [9] Another study by Şirli et al. [27] classified correctly 91.3% of patients as having or not having cirrhosis using Lok index. In contrast to Şirli et al. [27] who approved an excellent predictive value for Lok index for cirrhosis, we agree with Castera et al. [32] who reported that this index has just a reasonable performance with an AUROC of 0.81 for diagnosis of cirrhosis. Nonetheless, none of the previous studies assessed the performance for Lok index in prediction of significant fibrosis.

It has been noticed that, comparison of studies performed on the non-invasive biomarkers of liver fibrosis is a difficult task. AUROCs for a specific biomarker were shown to fluctuate in a range among different studies. This means that AUROCs obtained in different studies should not be compared directly, but a unifying correction for the stage distribution should be performed first [13]. Moreover, variation in the optimal cut-off values was a perplexing issue. Our study had some potential limitations including the limited sample size and the relative complexity of formulas, requiring access to a calculator or computer.

In summary, our ROCs demonstrated that, Fibrosis Index (FI) and FibroIndex are good in diagnosing significant fibrosis and excellent for cirrhosis, while King's Score and Lok index are fair for predicting significant fibrosis and good for cirrhosis. King's Score was the most reliable biomarker for diagnosis of cirrhosis.

FI diagnosed most cirrhotic patients with high accuracy. Yet Lok and FibroIndex had a lower though satisfactory diagnostic utility. Consistent with our findings, a comprehensive review, confirmed that non-invasive biomarkers can help to identify HCV-infected patients with significant fibrosis, with somewhat greater accuracy for identifying cirrhosis than insignificant fibrosis.²⁹ We agree with Baranova et al.¹³ that non-invasive biomarkers could be recommended as pre-screening tools to narrow down the patients' population transferred for liver biopsy.

Disclosure

No relevant financial affiliations or conflicts of interest to disclose.

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