Original paper

FIB-5 versus FIB-4 index for assessment of hepatic fibrosis in chronic hepatitis B affected patients

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Abstract

Aim of the study: Chronic hepatitis B virus (HBV) infection is one of the major health problems worldwide. Use of non-invasive tests for assessment of hepatic fibrosis such as the FIB-4 index could be used to avoid liver biopsy. Another promising noninvasive test, FIB-5, could also be used to detect significant hepatic fibrosis. The aim of the study was to compare the use of FIB-5 and FIB-4 as noninvasive markers to assess chronic HBV-related hepatic fibrosis.

Material and methods: This study was done on 176 chronic HBV patients who underwent liver biopsy. Grading and staging of liver fibrosis was done according to the METAVIR scoring system. FIB-5 and FIB-4 scores were calculated for all patients.

Results: As regards FIB-4 for differentiation between non-significant fibrosis (group I) and significant fibrosis (group II), at a cutoff level of 1.28 with positive predictive value (PPV) 41.4% and specificity 48% while at a cutoff level of 7.08 with PPV 98.8% and specificity 98% for FIB-5.

Conclusions: As regards both scores, the FIB-5 score was more specific than FIB-4 for diagnosing significant from nonsignificant hepatic fibrosis in patients with chronic HBV infection.

Key words: FIB-5, FIB-4, fibrosis, biopsy, chronic HBV.

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Introduction

Liver cirrhosis is a critical complication of chronic liver diseases. Early diagnosis is mandatory for management and surveillance of patients with chronic liver disease. Diagnosis of liver cirrhosis was based mainly on liver biopsy, which is an invasive procedure with rare but potentially life-threatening complications and also prone to sampling errors. Use of non-invasive laboratory and radiological methods has rapidly decreased the use of liver biopsy for diagnosing liver cirrhosis in patients with chronic viral hepatitis. These methods are widely used in many clinical practices and recommended by the European Association for the Study of the Liver (EASL) and international guidelines [1-5]. Non-invasive markers such as FIB-4 use age, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and platelet count. Recently FIB-5 using albumin, alkaline phosphatase (ALP), AST to ALT ratio and platelet count has been used for assessment of liver fibrosis and for predicting severe fibrosis or cirrhosis in patients with chronic hepatitis C infection [6, 7]. FIB-5 and FIB-4 use for assessment of nonsignificant (F0-1) and significant fibrosis (F2-4) in patients with chronic hepatitis B virus (HBV) was the aim of this study.

Material and methods

This cross-sectional study was conducted on 176 patients with chronic HBV infection who were recruited from outpatient clinics of the National Liver Institute Hospital, Menoufia University from June 2016 to May

2018. Written informed consent from each patient in the study especially for liver biopsy, with approval of the local ethical committee, was obtained before starting the data collection. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priority approval by the institution's human research committee. Exclusion criteria of the study included patients coinfected by hepatitis C virus (HCV), hepatitis D virus (HDV) or human immunodeficiency virus (HIV), patients with primary or secondary liver tumors, patients who received any
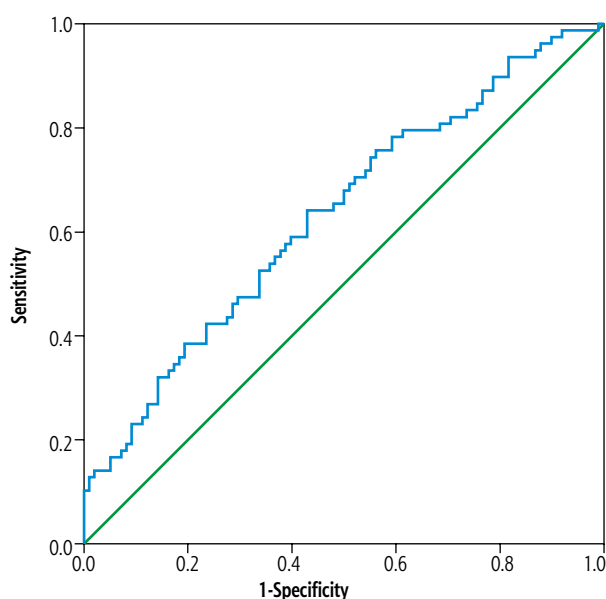
previous antiviral or immunosuppressive medications, and also patients who refused liver biopsy or having any contraindication to undergo liver biopsy and patients with decompensated cirrhosis. All patients in the study were subjected to full history taking, complete physical examination, and laboratory investigations which included: complete blood count, liver function tests and abdominal ultrasound. The FIB-5 score was calculated according to Attallah et al. [7] as follows: albumin (g/l) × 0.3 + platelet count (10^9/l) × 0.05 − alkaline phosphatase (IU/l) × 0.014 + AST/ALT ratio × 6 + 14. The FIB-4 [8] score was calculated as follows: [Age (year) × AST (IU/l)]/[platelet count (× 10^9/l) × ALT (IU/l)$^{1/2}$]. All studied patients were positive for HBsAg for more than six months with a detectable HBV DNA level (IU/l) by real-time polymerase chain reaction (PCR) for diagnosis of chronic HBV infection. Liver biopsy sections were examined histopathologically blindly by an expert pathologist. Stages of fibrosis (F0-4) were assessed according to the METAVIR scoring system [9]. We further divided fibrosis stages into two groups: group I as F0-1 (non-significant fibrosis), and group II as F2-4 (significant fibrosis) [9].

Statistical analysis

Demographic data, clinical, laboratory and virologic data were collected. All patient data were tabulated and processed using SPSS version 22. Pearson correlation was conducted to correlate continuous parameters. Multivariate backward stepwise binary logistic regression analysis with significant fibrosis (F2) – as the dependent factor – was performed to determine how well the FIB-5 test compared to FIB-4 as a diagnostic test which can predict that a patient has nonsignificant (F0-1) or severe fibrosis (F3-4). Efficiency is an overall estimate of a test's ability to classify patients correctly. It is estimated by adding the number of the two correct classifications (true positive and true negative) and dividing by the total number of patients assessed. P-values < 0.05 were considered significant.

Results

As regards liver fibrosis stage by histopathological examination, F0 was found in 1 (0.6%), F1 in 97 (55.1%), F2 in 61 (34.7%), F3 in 9 (5.1%) and F4 in 8 (4.5%) patients (Table 1). There was a statistically significant difference between the two studied groups regarding age ($p = 0.008$). Non-significant fibrosis was diagnosed mostly in younger patients (Table 2). Serum albumin, platelet count, ALP, γ-glutamyl transferase (GGT), prothrombin concentration (PC) and interna-

Table 1. Frequency distribution of all studied patients according to METAVIR scoring system

Stage	Frequency (n)	Percent (%)
F0	1	0.6
F1	97	55.1
F2	61	34.7
F3	9	5.1
F4	8	4.5

Table 2. Baseline characteristics of chronic hepatitis B patients with hepatic fibrosis regards two main classifications ($N = 176$)

Parameters	Non-significant fibrosis (F0-1) (n = 98)	Significant fibrosis (F2-4) (n = 78)	P-value
Age (years)	32.37 (9.23)	36.28 (10.25)	0.008*
Total bilirubin (mg/dl)	0.76 (0.25)	0.81 (0.44)	0.6
ALT (U/l)	35.73 (20.07)	43.79 (30.15)	0.15
AST (U/l)	33.46 (19.83)	39.05 (23.33)	0.12
ALP (U/l)	68.87 (15.68)	96.73 (30.86)	0.00004*
GGT (mg/dl)	29.65 (10.63)	42.38 (21.08)	0.00001*
Albumin (gm/dl)	4.57 (0.43)	4.26 (0.47)	0.00002*
HB (g/dl)	14.9 (10.4)	13.45 (1.51)	0.04*
WBCs (× 10^3/mm³)	6.49 (1.65)	6.34 (1.72)	0.54
Platelets (× 10^3/mm³)	222.66 (51.26)	193.54 (59.09)	0.001*
γ-globulin (g/dl)	1.3 (0.2)	1.53 (0.43)	0.00001*
PC (%)	91.86 (6.74)	87.08 (7.94)	0.00003*
INR	1.08 (0.07)	1.13 (0.08)	0.00002*
HBV DNA level (U/l)	12620011.88 (95725298.66)	622951.35 (2843934.18)	0.48
AST/ALT ratio	1.11 (0.34)	1.12 (0.36)	0.89
FIB-4	1.5 (0.73)	2.11 (1.49)	0.001*
FIB-5	5.83 (1.87)	4.15 (0.94)	0.00001*

ALT – alanine aminotransferase, AST – aspartate aminotransferase, ALP – alkaline phosphatase, GGT – γ-glutamyl transferase, HB – hemoglobin, WBCs – white blood cells, PC – prothrombin concentration, INR – international normalized ratio

Fig. 1. Receiver-operating characteristic (ROC) curve generated by FIB-4 for differentiation between significant and non-significant fibrosis
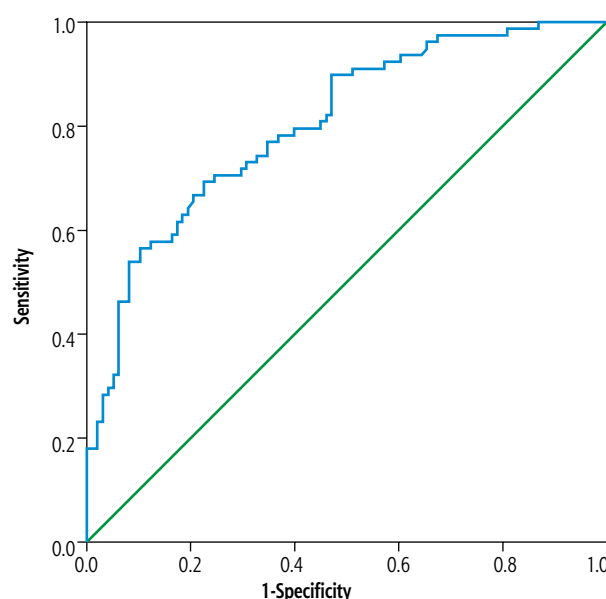
Fig. 2. Receiver-operating characteristic (ROC) curve generated by FIB-5 for differentiation between significant and non-significant fibrosis

tional normalized ratio (INR) were significantly different between groups (Table 2). ALP, albumin, and platelet count decreased in the group of advanced fibrosis. FIB-5 value and FIB-4 significantly differentiated between fibrosis groups ($p = 0.00001$, 0.001 respectively) as shown in Table 2. There was a significant relationship between fibrosis stages and both serum indices. There was a significant increase in the level of FIB-4 as fibrosis progressed from non-significant (F0-1) to significant fibrosis (F2-4). A significant decrease in the level of FIB-5 ($p = 0.00001$) was observed with the progression of fibrosis stages from non-significant to significant fibrosis (Table 2). The area under the curve (AUC) values (p-values) of the serum non-invasive indices are shown in Figures 1 and 2. The AUC of FIB-5 for differentiating non-significant fibrosis from significant fibrosis (as shown in Fig. 2) was 0.8 ($p < 0.01$) and for FIB-4, as shown in Figure 1, it was 0.63 ($p < 0.01$). When compared to liver biopsy, FIB-5 values at a cutoff level 7.08 showed a positive predictive value (PPV) of 98.8% to differentiate between F0, F1 and other fibrosis stages with specificity of 98% and FIB-4 values at a cutoff level of 1.28 showed a PPV of 41.4% to differentiate between F0, F1 and other fibrosis stages with specificity of 48% (Table 3).

Discussion

Liver biopsy is considered the traditional reference standard for fibrosis staging [10]. FIB-5 is a promising noninvasive test used for assessment of hepatic fibrosis [11]. The aim of this study was to compare the use of FIB-5 vs. FIB-4 for the differentiation between significant (F2-4) and non-significant hepatic fibrosis (F0-1) which was conducted on 176 patients with chronic hepatitis B infection. A significant decrease in the level of FIB-5 ($p = 0.00001$) was observed with the progression of fibrosis stages from non-significant (98 patients) to significant fibrosis (78 patients). FIB-5 values at a cutoff level of 7.08 showed a PPV of 98.8% with a specificity of 98% for the differentiation between significant and non-significant fibrosis. This high specificity and PPV compared to the FIB-4 value at a cutoff level of 1.28 with PPV of 41.4% and specificity of 48% are needed for taking treatment decisions in clinical practice. In this study, the AUROC of FIB-4 to differentiate significant (F2-4, $n = 78$) from non-significant fibrosis (F0-1, $n = 98$) was 0.63, with a sensitivity of 70.5%. The negative predictive value (NPV) was 70% and the PPV was 41.4%. Better results

Table 3. Performance characteristics of both fibro fast (FIB-5) and FIB-4 to differentiate between F0, F1 and other fibrosis stages ($N = 176$ cases)

	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	SE	95% CI
FIB-4 (1.28)	0.63	70.5	48.0	41.4	70.0	0.04	0.55-0.72
FIB-5 (7.08)	0.80	23.1	98.0	98.8	46.2	0.03	0.74-0.87

AUC – area under the curve, PPV – positive predictive value, NPV – negative predictive value, SE – standard error

were reported by Li *et al.* [12]. They obtained multiple meta-analysis evaluated the performance of FIB-4 in HBV mono-infected patients with 12 studies on 1908 patients and 10 studies on 2105 patients with the AUROCs ranging between 0.74 and 0.81 at a cutoff value between 1.45 and 1.62 and they concluded that the FIB-4 index is of great value for detecting significant fibrosis and also cirrhosis in HBV infected patients but its accuracy is suboptimal in exclusion of fibrosis and cirrhosis. Kim *et al.* [13] studied 575 patients with chronic HBV; they found that APRI and FIB-4 scores were not suitable to be used in clinical practice for assessment of hepatic fibrosis according to the Ishak staging system in chronic hepatitis B patients. Chayanupatkul *et al.* [14] concluded that the FIB-4 ROC curve value of 0.652 was suitable for diagnosing liver cirrhosis. Yin *et al.* [15] found that the best cutoff level of FIB-4 in identifying cirrhosis was > 2. The FIB-5 score in differentiation between significant and non-significant fibrosis in the present study differs from FIB 4 due to the presence of serum albumin, which was closely one of the synthetic functions of the liver, and also alkaline phosphatase, which represents hepatocellular integrity and excretory liver function [11, 13]. FIB-5 is an easy, inexpensive, non-invasive, accurate and bedside test that could be used in clinical practice, and this needs further multiple studies on a large number of patients to confirm our results.

Conclusions

FIB-5 is a sensitive non-invasive test that might be used for diagnosis of significant and non-significant fibrosis in patients with chronic HBV infection. FIB-5 can help to decrease the use of liver of biopsies, which is an invasive procedure and needs to be avoided in clinical practice, and this is the main ultimate goal of the study. FIB-5, with a cutoff point of 7.08, could be considered as a good and applicable marker. This will further need a large number of patients to be included in more studies to confirm it.

Acknowledgements

Disclosure

The authors declare no conflict of interest.

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