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Evaluation of fibrosis regression using FIB-5 score in HCV and HBV positive patients after treatment and virus suppression respectively

Tasneem G.H. Abd-Elazeem[1], Ahmed A.G. Afify[1], Essam A.H. Soliman[1], Fatma A.M. Mahmoud[1*]

[1] Tropical Medicine Department, Faculty of Medicine, Fayoum University, 63514 Fayoum, Egypt.

* Correspondence: Fatma A.M. Mahmoud, Fam03@fayoum.edu.eg; Tel.: (002) 01006744665.

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Abstract:

Introduction: Background: Chronic liver disease (CLD) is a major cause of morbidity and mortality worldwide. Assessment of liver fibrosis (LF) via the utilization of noninvasive tests (NITs) has been emerging nowadays. These NITs, FIB-4 and FIB-5, have adequate predictive positive value (PPV) for the diagnosis of nil or minimal fibrosis up to advanced fibrosis.

Aim of study: To detect fibrosis regression after HCV treatment and HBV suppression using the FIB-5 score and evaluate the accuracy of the FIB-5 score as a validated NIT of fibrosis compared to FIB-4.

Subjects and Methods: This is a prospective study on 100 patients with chronic hepatitis, 50 HCV patients who received direct-acting anti-viral drugs (DAAs) about 5 years ago and achieved sustained virological response (SVR), and 50 HBV patients with undetected viremia who are still on treatment according to the national program for treatment of HCV and Egyptian guidelines for HBV treatment, respectively.

Results: The sensitivity and specificity tests for FIB-5 level post-treatment in the diagnosis of fibrosis regression in HCV patients were 88.2% and 63.6%, respectively, at a cutoff value of -14.695. The sensitivity and specificity tests for FIB-5 level post-treatment in the diagnosis of fibrosis regression in HBV patients were 57.1% and 94.4%, respectively, at a cutoff value of -8.68.

Conclusion: FIB-5 is both a specific and sensitive test to assess fibrosis regression in chronic hepatitis patients after and during treatment.

Keywords: Chronic Liver Disease; Liver Fibrosis; Cirrhosis; FIB-4; FIB-5.

1. Introduction

Chronic liver disease (CLD) is a major cause of morbidity and mortality worldwide, with 2 million individuals dying of liver disease a year [1]. The most common culprits are chronic hepatitis B virus (HBV), hepatitis C virus (HCV), nonalcoholic fatty liver disease (NAFLD), and alcohol-associated liver disease (ALD) [2].

Liver fibrosis (LF) is an ongoing chronic liver condition that develops as a result of the wound healing response following a long-standing liver injury. The liver parenchyma undergoes architectural re-modeling, including fibrillar extracellular matrix (ECM) accumulation with nodular regeneration. If left undiagnosed and untreated, it ends in loss of normal liver function, cirrhosis, liver failure, hepatocellular carcinoma (HCC), and eventually death [3].

Treatment of the aforementioned underlying cause of the liver disease leads to prevention of the progression to cirrhosis and even causes regression of the fibrogenic process. Hence, antiviral treatment for HCV and HBV infection has been established as a means to stabilise and even reverse disease progression [4].

Fibrosis reversal differs from fibrosis regression; the word reversal of cirrhosis is used to indicate complete restoration of normal architecture after the establishment of cirrhosis, while regression of fibrosis or cirrhosis means that the fibrosis content is less than earlier [5].

Histopathological examination by liver biopsy (LB) is still the golden reference for the assessment of LF. However, it is limited by its invasive nature [6], poor acceptance by both patient and doctor, availability, cost, intra- and inter-observer variability, and sampling errors, which cause nearly 24% of false negatives for cirrhosis [7, 8].

Assessment of LF via the utilization of noninvasive tests (NITs) has been emerging nowadays. Initially, it began with chronic viral hepatitis and now involves all other causes of CLD. These markers are noninvasive in nature, cheap, have nearly no problems, and have few sampling errors. Measurements can be done repeatedly, thus allowing supervision of the disease's progression or regression [5].

Consequently, NITs have been developed, such as the AST-to-platelet ratio index (APRI), the Forns test and Fibro-Test [9], and FIB-4, which utilises age, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet count; and recently, FIB-5, using albumin, alkaline phosphatase (ALP), AST-to-ALT ratio, and platelet count, has been used for detecting LF and predicting severe fibrosis or cirrhosis [10].

All of these NITs have adequate predictive positive value (PPV) for the diagnosis of nil or minimal fibrosis up to advanced fibrosis [9].

2. Subjects and methods

2.1. Subjects

We performed a prospective study on 100 patients with chronic hepatitis as a cause of CLD to assess fibrosis regression, 50 HCV patients who received DAAs about 5 years ago and achieved SVR, and 50 HBV patients with undetected viremia who are still on treatment according to the national program for treatment of HCV and Egyptian guidelines for HBV treatment, respectively.

Inclusion criteria

Patients with positive HCV antibodies (HCV-Abs) and Hepatitis B surface antigen (HBsAg), and those received treatment at least five years ago with available contact phone numbers and laboratory data were included.

Exclusion criteria

Patients with negative HCV antibodies and negative HBsAg without treatment received within the previous five years were excluded.

2.2. Methods and data gathering

Data collection

The patient's data was collected from each patient medical record. That included their full medical history; diabetes mellitus (DM), hypertension (HTN), dyslipidemia, current medications, and the virus status post-treatment. Details of the treatment were received by the patient and guardians. Other clinical characteristics included the clinical evaluation, waist circumference (WC), waist hip ratio (WHR), and signs of decompensated liver failure ie, ascites, lower limb edema and jaundice. Normal WC were considered at 85 cm for males and 80 cm for females. WHR was considered at 0.90 for males and 0.80 for females. Obesity was considered when WC and WHR are above these normal values [11]. Furthermore, the data included revision of pre-treatment laboratory data and calculation of pretreatment FIB-4 and FIB-5. Abdominal ultrasound was performed for all patients.

Routine laboratory investigations

That included Alfa-feto protein (AFP), complete blood count (CBC), lipid profile (serum triglycerides, serum cholesterol, HDL-C and LDL-C), liver function tests (alanine aminotransferase ALT), (and aspartate aminotransferase AST), (alkaline phosphatase ALP and serum albumin) to calculate FIB-4 and FIB-5.

Calculation of FIB-4 and FIB-5 scores

As regard fibrosis-4 index (FIB-4 index), mild to significant fibrosis were considered

from 1.45 to 3.25 and advanced fibrosis ≥ 3.25 [12]. For FIB-5, there was no validated cut-off values for fibrosis staging and it differ according to the primary liver pathology; cut-off values differ in NAFLD when compared with chronic hepatitis.

2.3. Statistical analysis

All statistical calculations will be done using Microsoft Excel version 16 and SPSS. Categorical variables will be presented as number (%) and compared by Chi-squared test. Normal distribution of continuous variables was evaluated by the Kolmogorov-Smirnov test. Normally or non-normally distributed continuous parameters were described as mean (standard deviation) or as median (interquartile range, IQR).

3. Results

HCV patients had higher levels of AFP both before and after treatment when compared with the HBV group. In the HCV group, FIB-4 before treatment and post-treatment was 2.38±2.63 and 3.86±5.13, respectively. FIB-5 before treatment and post-treatment was -11.08±5.05 and -15.78±9.31, respectively, with a change of 4.70 ±8.03. In the HBV group, FIB-4 before treatment and post-treatment was 1.93±2.68 and 2.20±2.32, respectively. FIB-5 before treatment and post-treatment was -11.23±4.31 and -14.13±6.95, respectively, with a change of -2.90±6.5 (**Table 1**).

Table 1: Comparison of laboratory data and NITs of fibrosis (AFP, FIB-4, and FIB-5) between HCV and HBV groups of patients.

Item		**Mean ± SD**	
		HCV group (50 patients)	**HBV group** (50 patients)
AFP	Before treatment	72.59± 334.94	3.87± 2.76
	After treatment	147.90± 325.41	2.06± 0.98
FIB-4	Before treatment	2.38± 2.63	1.93± 2.68
	After treatment	3.86 ± 5.13	2.20± 2.32
FIB-5	Before treatment	-11.08 ±5.05	-11.23 ±4.31
	After treatment	-15.78 ± 9.31	-14.13± 6.95
	FIB-5 change	-4.70- ± 8.03	-2.90- ± 6.5

As regards fibrosis regression, we used the validated FIB-4 score as a reference, and patients were divided accordingly into fibrosis regression and non-fibrosis regression groups, as shown in **Table 2**.

Table 2: Fibrosis regression of the studied group patients according to FIB-4 score.

			Count (%)
Fibrosis regression	Yes		31/100 (31%)
		HCV	17/50 (34%)
		HBV	14/50 (28%)
	No		69/100 (69%)
		HCV	33/50 (66%)
		HBV	36/50 (72%)

The sensitivity and specificity tests for FIB-5 level post-treatment in the diagnosis of fibrosis regression in HCV patients were 88.2% and 63.6%, respectively, at a cutoff value of -14.695. FIB-5 change pre- and post-treatment at a cutoff of -2.485 carries sensitivity and specificity of 94.1% and 81.8%, respectively (**Figure 1A**).

The sensitivity and specificity tests for FIB-5 level post-treatment in the diagnosis of fibrosis regression in HBV patients were 57.1% and 94.4%, respectively, at a cutoff value of -8.68. FIB-5 change pre- and post-treatment at a cutoff of -1.305 carries sensitivity and specificity of 64.3% and 94.4%, respectively (**Figure 1B**).

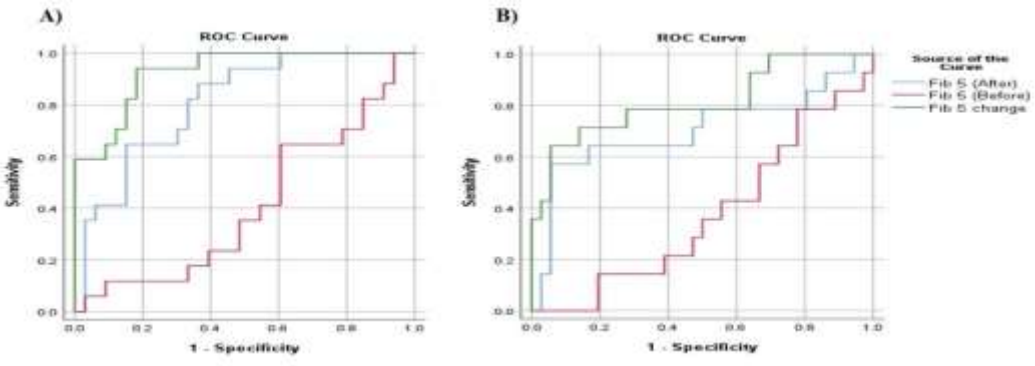

Figure 1: ROC curve of sensitivity and specificity of FIB-5 level post-treatment in the diagnosis of fibrosis regression in A) HCV and B) HBV patients.

4. Discussion

The study recruited 100 patients; 50 of them were HCV-Abs positive, and the other 50 were HBs-Ag positive. All HCV patients achieved SVR, and HBV patients had undetected viremia. To our knowledge, gradual reduction and potentially reversal of fibrosis occur over the course of 5–10 years, so we selected patients with a mean of 5.09 ± 1.55 years post-treatment [13].

When reviewing the demographic data of the current study population, there was a male predominance; males were 65/100 (65%), with a mean age of 49.12 ± 12.08 years for the whole study group. Regarding medical history, we found that DM, HTN, and dyslipidemia were the associated co-morbidities. Clinically and according to WHR, 59% of our patients had truncal obesity, and this goes on with obesity and related dyslipidemia mentioned above [14].

Regarding the clinical examination, we found that 95% of our study group showed no signs of hepatic decompensation, while 2% of them had ascites and lower limb oedema, 1% had ascites, 1% had jaundice, and 1% had lower limb oedema only. This could be explained by the fact that one patient developed HCC post-DAAs with further decompensation [15].

Regarding US findings in our patients, 95% of patients had a bright, textured liver with a regular outline, and 96% had an average splenic size. This was in agreement with the fact that more than half of our patients were obese with HS and could develop metabolically associated fatty liver disease (MAFLD) [16].

Regarding mean FIB-4 scores before and after treatment for the whole study groups, they were 2.16± 2.66 and 3.03± 4.05 “significant to advanced fibrosis,” respectively, denoting un-expected fibrosis progression, but the elevated scores could be explained by other factors affecting the patients, such as dyslipidemia. However, mean FIB-5 scores before and after treatment for the whole study groups were -11.15±4.67 and -14.95±8.21, respectively, denoting fibrosis regression matching AFP but not FIB-4 levels [17].

From the fore-mentioned data, we performed an ROC curve to assess both the sensitivity and specificity of FIB-5 as a NIT for fibrosis assessment. In the HCV cohort, we found that FIB-5 at the cut-off of 14.695 post-treatment carries a sensitivity and specificity of 88.2 and 63.6%, respectively. While in HBV patients, the sensitivity and specificity of FIB-5 as a NIT of fibrosis assessment. We found that FIB-5 at a cut-off of -8.68 post-treatment carries a sensitivity and specificity of 57.1 and 94.4%, respectively [18].

Conclusion

CLD is a major cause of morbidity and mortality worldwide, with two million individuals dying of liver disease each year. The most common culprits are chronic HBV, chronic HCV, NAFLD, and ALD. This study recruited 100 patients with a history of chronic hepatitis: 50 HCV patients who received and finished DAAs and 50 HBV patients on treatment according to the national program for treatment of HCV and Egyptian guidelines for HBV treatment. Sensitivity and specificity tests for FIB-5 level post-treatment in the diagnosis of fibrosis regression in HCV patients were (88.2% and 63.6%, respectively) at a cutoff value of -14.695, while sensitivity and specificity tests for FIB-5 level post-treatment in the diagnosis of fibrosis regression in HBV patients were (57.1% and 94.4%, respectively) at a cutoff value of -8.68. To conclude, FIB-5 is both a specific and sensitive test to assess fibrosis regression in chronic hepatitis patients after and during treatment.

Ethical approval and consent to participate: The study was reviewed by the Faculty of Medicine Research Ethical Committee. The researcher informed the participants about the objectives of the study. The examination and investigations that were done. Also, the confidentiality of their information and their right not to participate in the study were considered (Approval number: M561).

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Conflicts of Interest: The authors declare no conflict of interest.

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