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Original Article

Fibro-α score as a simple and useful non-invasive test for predicting significant liver fibrosis in chronic hepatitis C patients

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ABSTRACT

Background and study aims: Non-invasive methods for the assessment of liver fibrosis are clinically important where hepatitis C virus (HCV) is common in Egypt. Our aim was to evaluate the diagnostic performance of a panel of simple blood markers of liver fibrosis in chronic hepatitis C (CHC) patients.

Patients and methods: A total of 199 patients with CHC evaluated for eligibility for antiviral therapy were included. Liver biochemical profile including transaminases, bilirubin, alkaline phosphatase, serum albumin, complete blood count prothrombin time and AFP were estimated. Liver biopsy was done. Statistical analyses were performed by logistic regression and receiver operating characteristic (ROC) curves to assess and compare diagnostic accuracy of blood markers. A stepwise combination algorithm was developed and validated prospectively in 135 additional patients.

Results: α-Foetoprotein (AFP) was the most efficient marker among other markers tested. The areas under the curves (AUCs) of AFP were 0.77 for significant liver fibrosis (F2–F4), 0.75 for advanced liver fibrosis (F3–F4) and 0.76 for liver cirrhosis (F4). The stepwise multivariate discriminant analysis (MDA) selected a novel non-invasive index for discriminating patients with significant liver fibrosis, named Fibro-α score.

Fibro-α score = (1.35 (numeric constant) +AFP (IU ml^{-1}) × 0.009584 + aspartate aminotransferase (AST)/alanine aminotransferase (ALT) × 0.243 − platelet count (×10^9 l^{-1}) × 0.001624).

The Fibro-α score was used for patients with advanced liver fibrosis and liver cirrhosis. The AUCs of Fibro-α score were 0.82 for patients with advanced liver fibrosis and 0.80 for those with cirrhosis. These results were reproduced in a validation study with no significant difference.

Conclusion: While liver biopsy is invasive, expensive and, in some settings, impossible to do, Fibro-α score is simple, cheap, non-invasive and may be useful for predicting significant liver fibrosis.

Introduction

Hepatitis C virus (HCV) infection is gaining increasing attention as a global health crisis. Egypt reports the highest prevalence of HCV worldwide, ranging from 6% to more than 40% among regions and demographic groups [1]. The assessment of the stage of liver fibrosis is essential for prognosis and for deciding on antiviral treatment [2]. The gold standard in assessing the stage of liver fibrosis is the histological evaluation of a liver biopsy. However, the procedure carries a moderate risk of complications, including bleeding and a small risk of death [3,4]. Moreover, because fibrosis is not uniformly distributed in the liver and a biopsy only samples 1/50,000th to 1/30,000th of the liver mass [5,6], cirrhosis is missed in an estimated 15–30% of liver biopsies [7,8]. As liver biopsy is an invasive procedure that is also cost intensive, mostly uncomfortable for the patient and sometimes prone to complication, alternative, simple and non-invasive tests have been developed to reliably assess the stages of liver fibrosis [9,10]. Laboratory markers of liver fibrosis may be the ideal diagnostic tool to assess the grade of fibrosis. They are supposed to provide accurate and reliable results in a simple, fast and cost-effective manner [11]. Individuals with non-significant fibrosis are not likely to develop advanced fibrosis in the short term, even in the light of long-standing disease, and are typically monitored every 3–5 years. Individuals with significant fibrosis are at increased risk of developing cirrhosis and are usually treated [12]. Various non-invasive markers of liver fibrosis have been developed and are now an interesting alternative to liver biopsy to evaluate the severity of liver fibrosis in patients with chronic hepatitis C (CHC); but none of the tests met the expectations, and their superiority to standard clinical evaluation is still

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questionable [13,14]. Ideally, non-invasive alternatives should be simple, cheap, easy to perform, safe, precise, reproducible and validated externally, and capable of differentiating patients in need of therapy [15,16]. Liver fibrosis markers are composed of direct and indirect markers of fibrosis, depending on their relationship with the connective tissue [17]. α-Foetoprotein (AFP) has been widely used as a diagnostic marker for hepatocellular carcinoma, although elevated serum AFP level in patients with CHC has been shown to be a significant independent predictor of the liver fibrosis even in the absence of hepatocellular carcinoma [18]. In the present study, we have developed and evaluated the Fibro-α score based on three simple blood markers that can be easily used by clinicians to predict the stage of liver fibrosis in CHC patients, and we have validated the Fibro-α score in external cohorts.

Patients and methods

The study has been approved by the local ethical committee and all patients included have provided a written consent.

Blood samples

In estimation study, blood samples were taken from consecutive CHC Egyptian patients ($n = 199$) from Tropical Medicine Unit, Mansoura University, Mansoura during the period from January 2008 to December 2009. These presented for consideration for antiviral therapy. Blood samples were collected from all patients, a portion of the blood was treated immediately with potassium-ethylenediaminetetraacetic acid (K-EDTA) for complete blood count and another portion was treated with a citrate solution for prothrombin-INR (international normalised ratio, INR). Sera were separated from the rest of blood samples and tested fresh for liver profile. The blood tests included liver profile including transaminases, bilirubin, alkaline phosphatase and serum albumin, complete blood count, prothrombin time and AFP. Liver profile was measured on an automated biochemistry analyser (Hitachi 902; Roche Diagnostics). Platelet count was performed on an XT 1800

Table 1
Demographic data and laboratory biomarkers of 199 patients with CHC.

Items	Mean ± SD	Range
Male (%)	139 (70%)	
Female (%)	60 (30%)	
Age (years)	43.5 ± 8.42	21–59
Biochemical markers[a]		
AST (U/ml)	68.1 ± 39.5	5–276
ALT (U/ml)	55.9 ± 32.1	13–187
AST/ALT	0.88 ± 0.36	0.41–2.92
Alkaline phosphatase (IU l^{-1})	82.2 ± 43.8	12–213
Total bilirubin (mg dl^{-1})	1.0 ± 0.5	0.6–5.2
Direct bilirubin (mg dl^{-1})	0.23 ± 0.20	0.02–0.80
Albumin (g/L)	43.0 ± 3.9	13.1–50.3
α-Foetoprotein (IU ml^{-1})	5.6 ± 10.5	0.1–87
Haematological markers		
Platelets count ($\times 10^9$ l^{-1})[b]	188 ± 53	17–344
Prothrombin-INR[c]	1.2 ± 0.2	1–1.6
AST/platelet count ratio (APRI)[d]	0.83 ± 0.59	0.11–4.3
Virological marker		
Quantitative PCR (IU ml^{-1})	567 017 ± 1 217901	171–10,872,306

[a] Normal values: Aspartate aminotransferase (AST) up to 40 U ml^{-1}; alanine aminotransferase (ALT) up to 45 U ml^{-1}; alkaline phosphatase 22–92 IU l^{-1}; total bilirubin up to 1 mg dl^{-1}; direct bilirubin up to 0.25 mg dl^{-1}; albumin 38–54 g/l^{-1}; α-foetoprotein up to 5.8 (IU ml^{-1}).
[b] Platelet count 150–400 $\times$ 10^9 l^{-1}.
[c] INR: international normalised ratio.
[d] AST/platelets ratio index = AST level (U ml^{-1})/40 (upper limits of normal)/platelets count 10^9 l^{-1}) $\times$ 100.

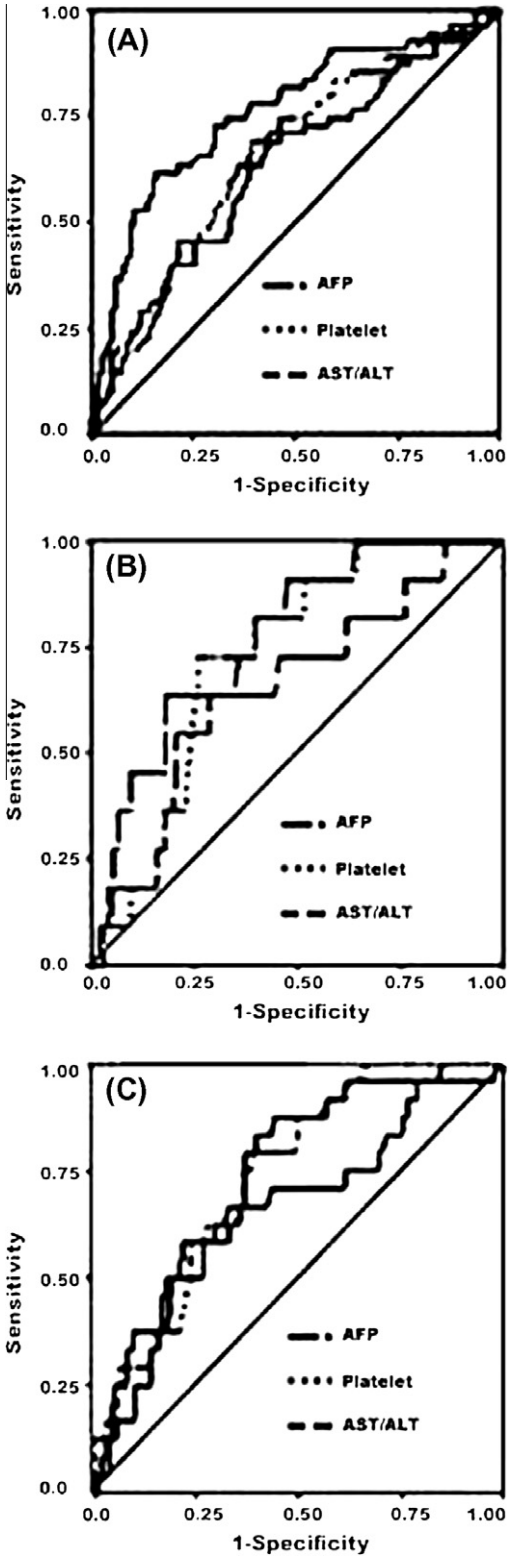

Fig. 1. ROC curves of AST/ALT, platelet count and AFP. (A) For discriminating patients with significant liver fibrosis (F2–F4) from non-significant liver fibrosis (F0–F1); (B) for discriminating patients with advanced liver fibrosis (F3–F4) from non-advanced liver fibrosis (F0–F2); (C) for discriminating patients with liver cirrhosis (F4) from non-liver cirrhosis (F0–F3) in CHC patients. The areas under the ROC curves of AST/ALT, platelet count and AFP for discriminating patients with significant liver fibrosis were 0.64 ($p < 0.003$), 0.67 ($p < 0.0001$) and 0.77 ($p < 0.0001$); for advanced liver fibrosis were 0.66 ($p < 0.012$), 0.74 ($p < 0.0001$) and 0.75 ($p < 0.0\,001$); and for liver cirrhosis were 0.65 ($p < 0.084$), 0.72 ($p < 0.013$) and 0.76 ($p < 0.003$); respectively.