Value of serum fibronectin for assessment of liver fibrosis in chronic hepatitis C virus patients

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Background
The stage of liver fibrosis is the most important predictive factor for initiation and duration of antiviral treatment, where patients with early fibrosis stages respond to treatment better with a higher sustained virologic response rate. Several noninvasive tests to stage the degree of fibrosis in patients with chronic hepatitis C virus (HCV) infection have been used. No single test is known to have high accuracy and the results of each test must be carefully interpreted. The objective of the study is to evaluate the value of serum fibronectin (FN) as a noninvasive predictor for the assessment of HCV-induced liver fibrosis.

Patients and methods
A total of 100 patients with chronic HCV infection proved by HCV antibodies and HCV RNA preparing for antiviral treatment were exposed to full history, physical examination, and laboratory assessment. Serum FN level and fibroscan were done for all patients. According to the results of fibroscan, the patients were divided into four groups of liver fibrosis and compared.

Results
All patients were proved to have HCV viremia with average PCR of 1990.52 ±3144.29 copies/ml. A statistically significant difference was found as regards FN, fibroscan, and APRI score between patients with fibrosis in comparison to patients without fibrosis. According to fibroscan results, 20 patients were found with fibrosis stage 0, 24 patients with stage 1, 24 patients with stage 2, eight patients with stage 3, and 24 patients with stage 4 (cirrhosis). On comparison of different stages of fibrosis as regards FN level, we found no statistically significant difference between stages. FN have a sensitivity of 67.5% and a specificity of 47.4% with 84.4% positive predictive value.

Conclusion
FN is a good noninvasive marker for the assessment of liver fibrosis in patients with chronic HCV. Larger scale multicenter studies are needed to assess its validity in the detection of fibrosis caused by causes other than HCV.

Keywords:
fibronectin, fibroscan, liver fibrosis

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Introduction

Chronic hepatitis C virus (HCV) infection is the most common cause of chronic liver disease worldwide [1]. Its long-term impact is highly variable and range from minimal histological changes to extensive fibrosis and end-stage cirrhosis which may be complicated by hepatocellular carcinoma (HCC) [2].

It is is estimated that 185 million people or more have been infected with HCV around the world, of whom 350 000 die each year [3]. Most of those people are unaware of their infection and for many of them who are diagnosed, treatment remains unavailable [4].

Egypt has the highest prevalence of HCV in the world. According to the Egyptian demographic health survey HCV prevalence among the 15–59 years age group is estimated as 14.7% [5] and according to WHO, prevalence in Egypt is more than 10% [6].

The stage of liver fibrosis is the most important predictive factor for initiation and duration of antiviral treatment [7], where patients with early fibrosis stages respond better to antiviral treatment with a higher sustained virologic response rate [6].

Liver biopsy is considered the gold standard method for the assessment of fibrosis, but now noninvasive methods are increasingly trying to replace it due to its

invasiveness, high cost, discomfort to patients, increased risk of complications, besides the need for expert histological interpretation [8].

Recently, noninvasive methods used to detect the stage of fibrosis in chronic HCV-infected patients include models incorporating indirect serum markers [routine tests such as platelets count, aspartate transaminase, and alanine transaminase (ALT)], direct serum markers which are components of the extracellular matrix secreted from activated hepatic stellate cells and transient liver elastography [2].

No single test is known to have high accuracy and the results of each test must be carefully interpreted. The most accurate approach for the assessment of fibrosis is to combine the direct biomarkers with transient liver elastography [9].

Fibronectin (FN) is a glycoprotein released from hepatocytes, endothelial, and Kupffer cells. Circulating FN represents a viable marker for the absence or presence of significant liver fibrosis. FN was identified at 90 kDa and quantified in the sera of patients with chronic hepatitis C using enzyme-linked immunosorbent assay (ELISA) [10].

Attallah *et al.* [11] evaluate the diagnostic value of FN as a predictor for liver fibrosis in patients with chronic HCV infection and incorporate it in a novel score called FN discriminant score with APRI score and albumin. They found FN discriminant score-predicted liver fibrosis with a high degree of accuracy and potentially decreasing the number of liver biopsy is required. Erturk *et al.* [12] also assessed the usefulness of FN as a marker of disease severity in acute and chronic viral hepatitis.

Evaluation of liver stiffness by fibroscan is being widely used for the assessment of liver fibrosis in chronic HCV. Fibroscan generates an elastic shear wave that disseminates through the underlying tissue. Shear wave dissemination is monitored by pulse-echo ultrasound acquisition. The velocity of which is directly correlated with stiffness of the tissue [13]. Fibroscan appears to give a precise and a reliable assessment of liver fibrosis or cirrhosis in patients with chronic hepatitis C [14].

Aim of the work

The aim of this work is to study the value of serum FN as a noninvasive marker for the assessment of HCV-induced liver fibrosis.

Patients and methods

Patients

This is a prospective, cross-sectional study that was conducted on 100 adult patients of both sex attending the Specialized Medical Hospital, Mansoura University, Egypt, during the period from January to December 2018 with positive HCV antibodies and/or viremia evidenced by PCR and preparing for antiviral treatment. We excluded patients with chronic hepatitis B virus or HIV, alcoholic liver cirrhosis, cholestatic liver cirrhosis, autoimmune liver cirrhosis, metabolic liver diseases, vascular diseases of the liver, drug-induced liver failure, patients with advanced systemic disease, and patients with decompensated liver cirrhosis or HCC.

Grouping of the patients

This study involved HCV patients which were subclassified according to fibroscan and liver function test.

(1) Group I: coincides with F1 by fibroscan.
(2) Group II: coincides with F2 by fibroscan.
(3) Group III: coincides with F3 by fibroscan.
(4) Group IV: coincides by F4 and compensated cirrhosis.

For all patients the serum level of FN by ELISAtest was assessed and an analysis of the relation between the FN level and the degree of fibrosis and cirrhosis was done.

Methods

History taking

History taking included history of smoking, risk factors for contracting HCV (history of blood transfusion, history of medical or surgical interventions, intravenous drug abuse, and occupational exposure), and symptoms of liver disease.

Clinical examination

General examination includes performance, vital signs, and signs of hepatocellular failure. Local abdominal examination for assessment of the liver, spleen, and detection of ascites was done for all patients.

Investigations

(1) Liver function tests [ALT, aspartate aminotransferase (AST), serum albumin, serum bilirubin (total and direct), alkaline phosphatase, and prothrombin time], creatinine, fasting blood sugar, complete blood count and α-fetoprotein.

(2) Abdominal ultrasound.
(3) Fibroscan.

Sampling

We obtained 5 ml blood sample from each patient and delivered them into a dry tube with a clot activator. The blood samples were centrifuged for 5 min at 3000 rpm, and serum samples were stored at −80°C after transferring to Eppendorf tubes for FN analysis. Analysis of FN using ELISA reader TECAN (Germany) using sunred kits.

Statistical analysis

Data were fed into a computer and analyzed using IBM SPSS software package, version 20.0 (SPSS Inc., Chicago, IL,USA). Quantitative data were described using mean, SD for parametric data and median minimum and maximum for nonparametric after testing the normality using Kolmogrov–Smirnov test. Significance of the obtained results was judged at the 0.05 level and all tests were two-tailed.

The used tests were as follows: one-way analysis of variance test, for parametric quantitative variables, was used to compare between more than two studied groups with post-hoc Tukey test. Student's *t*-test for parametric quantitative variables was used to compare between the studied groups. Mann–Whitney *U*-test was used for nonparametric quantitative variables to compare between two studied groups. Pearson's correlation was used to correlate nonparametric variables within the same group. χ^2-Test was used to compare between categorical variables and Monte-Carlo test was used for correction for χ^2 if more than 25% of cells have a count of less than 5.

Receiver operating characteristic curve was used to calculate validity (sensitivity and specificity) of continuous variables with calculation of best cutoff point; accuracy was calculated using cross tabs.

Ethics

The study protocol was investigated and approved by the medical ethics research team, Faculty of Medicine in Mansoura University. Every case, after guaranteeing privacy, has given informed written consent.

Results

Patient characteristics

The study included 100 patients, 68 men and 32 women with a mean age of 56.9±8.36 years. The laboratory and radiological characteristics of the patients are shown in Table 1. All patients were proved to have HCV viremia with an average PCR of 1990.52±3144.29 copies/ml. DM was found in 30 and hypertension in 14 cases. The patients have an average platelet count of 172.9±57.2 and 30.56±18.40, 32.08±21.11 for ALT and AST, respectively. By ultrasound, liver was normal in 28 cases, coarse in 38 cases, cirrhotic in 18 cases, fatty in 10 cases where focal lesions were detected in two cases. Spleen was normal in 66 patients and splenomegaly was found in 34 patients. Esophageal varices were

Table 1 Descriptive statistics of the studied cases

	N=100	
	Mean±SD	Median (minimunm–maximum)
Age (years)	56.9±8.36	57.5 (35.0–74.0)
DM		
No	68	68.0
Pre-DM	2	2.0
DM	30	30.0
Hypertension		
No	86	86.0
Hypertension	14	14.0
ALT	30.56±18.40	25.5 (10.0–84.0)
AST	32.08±21.11	30.0 (3.0–130.0)
Platelet	172.9±57.2	168.0 (45.0–290.0)
WBC	6.43±1.87	6.40 (1.3–10.3)
Hb	12.51±1.78	12.75 (6.7–16.2)
Albumin	4.07±0.45	4.13 (3.03–4.73)
Bilirubin	1.38±1.53	1.03 (0.30–10.0)
Creatinine	0.85±0.26	0.80 (0.50–1.73)
PCR ($\times 10^3$)	1990.52 ±3144.29	9933.5 (1.723–17190.0)
INR	1.21±0.30	1.12 (1.0–2.70)
Fibronectin	102.95±41.32	93.2 (29.6–214.0)
APRI	0.23±0.17	0.185 (0.01–0.76)
Fib-4	2.54±2.29	1.64 (0.22–11.36)
Fibroscan	10.65±8.4	7.30 (3.0–36.70)
Liver [*n* (%)]		
Normal		28 (28.0)
Cirrhosis		18 (18.0)
Coarse		38 (38.0)
Fatty		12 (12.0)
HCC		4 (4.0)
Spleen [*n* (%)]		
Normal		66 (66.0)
Enlarged		34 (34.0)
Esophageal varices [*n* (%)]		
Present		20 (80.0)
Absent		80 (20.0)
Fibrosis stage [*n* (%)]		
0		20 (20.0)
1		24 (24.0)
2		24 (24.0)
3		8 (8.0)
4		24 (24.0)

APRI, AST to platelet ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, diabetis mellitus; Fib-4, fibrosis-4; Hb, hemoglobin; HCC, hepatocellular carcinoma; INR, international normalized ratio; WBC, white blood cell.

Table 2 Comparison of demographic and laboratory characters between cases with fibrosis and non-fibrosis

	No fibrosis (*N*=20)	Fibrosis (*N*=80)	Test of significance
Age (mean±SD) (years)	58.0±7.57	56.63±8.56	*t*=0.66*P*=0.51
Fibroscan			
Mean±SD	4.22±0.48	12.26±8.63	*z*=6.54*P*<0.001*
Median (minimunm–maximum)	4.1 (3.4–4.9)	8.9 (3.0–36.7)	
ALT			
Mean±SD	29.80±19.98	30.75±18.11	*z*=0.35*P*=0.73
Median (minimunm–maximum)	20.50 (12.0–67.0)	26.0 (10.0–84.0)	
AST			
Mean±SD	27.80±19.4	33.15±21.5	*z*=0.96*P*=0.34
Median (minimunm–maximum)	26.0 (3.0–73.0)	33.0 (5.0–130.0)	
Platelet (mean±SD)	207.6±39.69	164.22±57.79	*t*=3.2*P*=0.002*
WBC (mean±SD)	6.90±1.44	6.32±1.96	*t*=1.25*P*=0.22
Hb (mean±SD)	13.32±0.63	12.30±1.91	*t*=2.35*P*=0.02*
Albumin (mean±SD)	4.41±0.28	3.98±0.45	*t*=4.6*P*<0.001*
Bilirubin			
Mean±SD	0.92±0.64	1.50±1.65	*z*=2.97*P*=0.003*
Median (minimunm–maximum)	0.7 (0.4–2.7)	1.1 (0.3–10.0)	
Creatinine (mean±SD)	0.85±0.35	0.85±0.23	*t*=0.004*P*=0.99
PCR ($\times 10^3$)			
Mean±SD	1988.3±3084.62	1991.1±3178.2	*z*=0.60*P*=0.55
Median (minimunm–maximum)	593.7 (250.0–10 000.0)	1126.0 (1.723–17190)	
INR (mean±SD)	1.08±0.08	1.24±0.33	*t*=2.09*P*=0.039*
Fibronectin			
Mean±SD	85.52±40.35	105.90±41.25	*z*=1.38*P*=0.04*
Median (minimunm–maximum)	93.2 (29.6–185.0)	93.75 (50.0–214.0)	
APRI			
Mean±SD	0.14±0.11	0.247±0.18	*z*=2.9*P*=0.004*
Median (minimunm–maximum)	0.11 (0.05–0.41)	0.2 (0.01–0.76)	
Fib4			
Mean±SD	1.74±1.66	2.74±2.39	*z*=1.86*P*=0.06
Median (minimunm–maximum)	1.236 (0.24–5.93)	2.11 (0.22–11.36)	
DM			
No	12 (60.0)	56 (70.0)	MC*P*=0.46
Pre	0	2 (2.5)	
DM	8 (40.0)	22 (27.5)	
Hypertension			
No	14 (70.0)	72 (90.0)	χ^2=5.32*P*=0.02*
Yes	6 (30.0)	8 (10.0)	

APRI, AST to platelet ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, diabetis mellitus; Fib-4, fibrosis-4; Hb, hemoglobin; HCC, hepatocellular carcinoma; INR, international normalized ratio; MC, Monte-Carlo test; *t*, Student's *t*-test; WBC, white blood cell; *z*, Mann–Whitney *U*-test; χ^2, χ^2-test. *$P<0.05$, Statistically significant.

found in 20 patients, 16 of them were in stage 4 fibrosis (Table 1). In Table 2, we compared demographic, laboratory, and radiological characteristics of patients with fibrosis with patients without fibrosis. A statistically significant difference was found as regards platelet count, hemoglobin level, albumen, bilirubin, international normalized ratio (INR), FN, fibroscan, and AST to platelet ration index (APRI) score between patients with fibrosis in comparison to patients without fibrosis.

Fibrosis scores

We calculated the fibrosis scores for all patients mainly the APRI and Fib-4 where it was 0.23±0.17 and 2.54 ±2.29, respectively (Table 1). According to fibroscan results, 20 patients were found with fibrosis stage 0, 24 patients with stage 1, 24 patients with stage 2, eight patients with stage 3, and 24 patients with stage 4 (cirrhosis). There was a statistically significant difference between patients with fibrosis in comparison to patients without fibrosis as regards APRI score with *P*=0.004 (Table 2).

Fibronectin levels and validity

Serum FN level was measured for all patients and it was 102.95±41.32 on average (Table 1). There was a statistically significant difference between patients with fibrosis in comparison to patients without

Table 3 Fibronectin and fibrosis-4 according to the stage of fibrosis

	Stage of fibrosis					
	0 (*N*=20)	1 (*N*=24)	2 (*N*=24)	3 (*N*=8)	4 (*N*=24)	
Fibronectin (mean±SD)	90.52±40.35	97.16±34.36	103.92±43.37	93.78±9.11	120.66±48.93	F=1.81P=0.13
Fib4 (mean±SD)	1.74±1.66[A]	1.67±0.96[B]	2.15±1.31[C]	3.07±2.07	4.28±3.41[A,B,C]	F=6.34P<0.001*

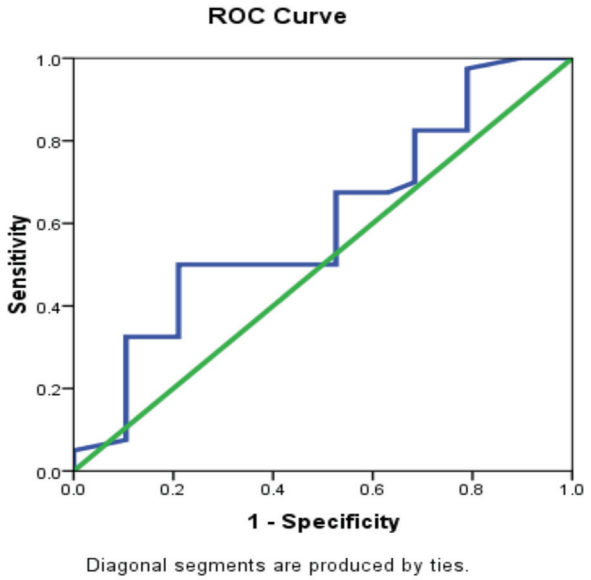
Similar superscripted letters denote significant difference between groups. *F*, one-way analysis of variance test. *P<0.05, statistically significant.

Table 4 Validity of fibronectin in diagnosing fibrosis among the studied cases

	AUC	Cut off point	Sensitivity	Specificity	PPV	NPV	Accuracy
Fibronectin	0.60	85.6	67.5	47.4	84.4	25.7	63.6

AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

Figure 1



Receiver operating characteristic (ROC) curve of fibronectin in differentiating fibrosis among the studied cases.

fibrosis as regards FN level with P=0.04 (Table 2). On comparison of different stages of fibrosis as regards FN level, we found no statistically significant difference between stages (Table 3). Assessment of validity of FN in diagnosing fibrosis is shown in Table 4 where we found that FN has a sensitivity of 67.5% and a specificity of 47.4% with 84.4% positive predictive value (Fig. 1). Table 5 shows the correlation of FN with clinical and laboratory results where FN is strongly correlated with APRI, fibrosis-4, ALT, fibroscans and inversely correlated with platelet count.

Discussion

In chronic HCV infection, assessment of the degree of liver fibrosis represents an important part of patient care and a key for making a decision. The stage of liver fibrosis is the most important prognostic factor in many liver diseases, including hepatitis C where advanced stages of fibrosis have been shown to be associated with progression to decompensated cirrhosis. Besides this, the stage of liver fibrosis is crucial for the selection of antiviral therapy in chronic HCV infection. It may also show the need for further assessments, such as screening for varices and surveillance for HCC [15] (Fig. 2).

Estimation of liver fibrosis can be done by many tools which may be noninvasive and can be divided into imaging modalities and serological markers or invasive, such as the liver biopsy.

As liver fibrosis represents a morphological damage, liver biopsy became the natural gold standard method for estimating the degree of fibrosis. However, due to sampling errors, interobserver variability, invasiveness, and inability to estimate the resolution of fibrosis and monitoring effects of therapeutic agents, some authors believe that liver biopsy should rather be considered the best available standard method [16].

Serum markers of liver fibrosis globally present an alternative cost-effective test to liver biopsy; they are less invasive than liver biopsy without complications. Owing to these advantages they can be measured also repeatedly and used in the follow-up of the process of fibrosis dynamically, for example in clinical practice, to monitor the efficacy of antiviral treatment in the resolution of fibrosis [17].

Our study analyzed serum FN level, biochemical liver function tests, fibroscan, and fibrosis indices of 100 patients with chronic hepatitis C. The average level of FN of our patients was 102.95±41.32. On calculation of APRI and Fib-4 indices, it was 0.23±0.17 and 2.54 ±2.29, respectively (Table 1). According to fibroscan results, we found 20 patients without fibrosis (stage 0), 24 patients with stage 1 fibrosis, 24 patients with stage 2, eight patients with stage 3, and finally 24 patients with stage 4 (cirrhosis).

Table 5 Correlation between serum fibronectin and clinical and laboratory results

	Fibronectin
APRI	
r	0.320**
P	0.001
Fib-4	
r	0.342**
P	0.001
Age/years	
r	–0.050
P	0.620
Fibrosis stage	
r	0.206*
P	0.041
ALT	
r	–0.184
P	0.068
AST	
r	0.364**
P	0.000
PLT	
r	–0.163
P	0.106
Fibroscan	
r	0.299**
P	0.003
WBC	
r	–0.085
P	0.401
HB	
r	–0.124
P	0.220
Albumin	
r	–0.170
P	0.093
Bilirubin	
r	0.141
P	0.165
Creatinine	
r	0.38
P	0.712
PCR	
r	0.209*
P	0.038
INR	
r	–0.066
P	0.516

APRI, AST to platelet ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, diabetis mellitus; Fib-4, fibrosis-4; Hb, hemoglobin; HCC, hepatocellular carcinoma; INR, international normalized ratio; *r*, Pearson's correlation coefficient. WBC, white blood cell. *Significant. **Strongly significant.

We compared patients without fibrosis (stage 0) with other stages of fibrosis (stages 1, 2, 3, and 4), and found a statistically significant difference between the two groups as regards hemoglobin level, platelet count, albumen, bilirubin, INR, APRI, and FN level (Table 2). This seems logic as regards the hemoglobin level, platelet count, albumen, bilirubin, INR, and APRI because these parameters represent both the synthetic and excretory capacity of the liver affected by the presence of fibrosis. These data may also suggest that serum FN level is elevated in patients with liver fibrosis and may serve as a useful marker for differentiating patients with fibrosis from that without fibrosis. This runs parallel to Attallah *et al.* [11] who found that the level of FN is increased significantly with the development of liver fibrosis.

The cause of liver fibrosis is still speculative and many theories describing the relation between fibrosis and FN have been proposed. A number of events that occur chronically and lead to liver fibrosis were postulated such as the accumulation of excess and disorganized extracellular matrix components that lead to loss of normal liver cell functions [18,19]. However, the standard method for the assessment of liver fibrosis remains the liver biopsy [20].

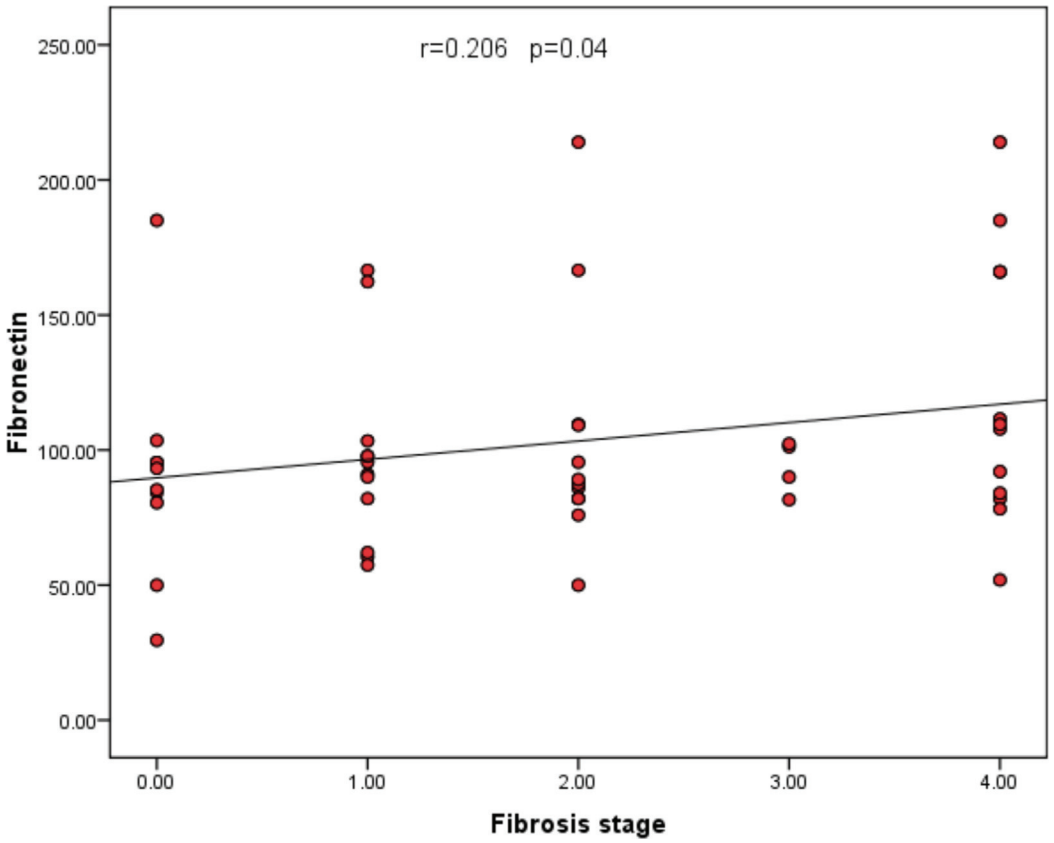
FN is an extracellular matrix noncollagen adhesive protein that plays a crucial role in basal membrane adhesion, intercellular adhesion, clot stabilization, macrophage functions, and fibroblast migration. The form of FN in the plasma is produced by the blood vessel endothelium and hepatocytes are soluble in blood and other body fluids [21].

In our study, the level of FN increases progressively with increasing stage of fibrosis except for stage 3; however, it did not reach a statistical significance (Table 3). The decreased level of FN in stage 3 in our study may be explained by the small number of patients discovered in this stage (eight patients) that might affect the statistical significance. This suggests that FN may be useful in detecting fibrosis regardless of its stage although its level increases with increasing fibrosis.

Junge *et al.* [22] have shown that the level of FN increased significantly with the progression of fibrosis staging but it decreased in patients with liver cirrhosis. This discrepancy as regards the level of FN in cirrhotic patients may be due to the small number of cirrhotics found in our study besides the differences in staging fibrosis in cirrhotic patients without liver biopsy.

Our data show that a significant correlation exists between serum AST and FN levels in contrast to ALT where high FN levels were associated with raised AST (Table 5). This may be in agreement with Erturk *et al.* [12] who noted that serum levels

Figure 2



Fibronectin level in relation to fibrosis stage.

of FN were lower in patients with acute and chronic hepatitis. They found also an inverse relationship between serum AST and ALT levels and serum FN. A decrease in serum FN levels may imply severity of hepatitis as AST and ALT elevation represent damage of hepatocytes. This contrast between the two studies may be related to the underlying cause of acute or chronic hepatitis and also whether those patients were followed up in the post-hepatitis period or not, where serum FN levels may start to increase along with AST with the development of fibrosis. In acute hepatitis, acute damage of hepatocyte may lead to high aminotransferase levels where there is no evidence of fibrosis which may suggest that elevated FN level is correlated with the presence of fibrosis. FN is inversely correlated with platelet count where its level increases with a decrease in platelet count (Table 5). This seems logical as the platelet count enters in the APRI score and decreases in platelet count will elevate the APRI score that means increasing fibrosis.

In our study, FN has sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 67.5, 47.4, 84.4, 25.7, and 63.6%, respectively, with a cutoff value of 85.6 (Table 4 and Fig. 1) in contrast to APRI that has a sensitivity of 25% and accuracy of 54%. These data suggest that patients with FN level above the cutoff value (85.6) are associated with significant fibrosis.

Mehta *et al.* [23] concluded that when we take into account the range of accuracies of biopsy and range of fibrosis prevalence, even in the 'best' scenario an area under the receiver operating characteristic curve of more than 0.90 cannot be achieved even with the perfect serum marker. This perceived limitation in the diagnostic accuracy of noninvasive markers is probably the major cause why these tests have not been adapted in clinical practice on a wide range. To improve the sensitivity and specificity of detection of fibrosis, different scores were introduced such as APRI, fibrosis-4, fibrotest, and others. The introduction of FN in any of these equations may be the area of future studies.

Our study may be limited by some factors such as the small number of patients included in the study that surly do not reflect the general population, lack of correlation with tissue pathology in liver biopsy which remains the gold standard for staging of liver fibrosis, and the underlying etiology of liver fibrosis of patients included in the study which is chronic HCV excluding other causes of fibrosis.

To summarize, FN appears to be a useful marker for the detection of liver fibrosis. However, its usefulness in the staging degree of fibrosis is still debating where its combination with fibroscan or other tests of fibrosis may improve sensitivity of detection of liver fibrosis.

Conclusion

FN is a good noninvasive marker for the assessment of liver fibrosis in patients with chronic HCV. Larger scale multicenter studies are needed to assess its validity in the detection of fibrosis caused by causes other than HCV.

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Conflicts of interest

There are no conflicts of interest.

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