ORIGINAL ARTICLE

FibroScore for the Non-invasive Assessment of Liver Fibrosis in Chronic Viral Hepatitis

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ABSTRACT

Objective: To evaluate the predictive value of a set of laboratory markers for the assessment of liver fibrosis in chronic viral hepatitis patients.

Study Design: Cross-sectional study.

Place and Duration of Study: Baqai Medical University, Combined Military Hospital, Malir, Karachi, from November 2006 to May 2008.

Methodology: Twenty laboratory parameters were measured in 100 treatment-naïve chronic viral hepatitis patients who also had liver biopsy performed. Descriptive statistics, areas under the ROC's curves, and multivariate logistic regression analysis identified a fibrosis panel, a set of five most useful markers, for the assessment of stages of fibrosis, stage 0 to stage 4. The fibrosis index, FibroScore, consisted of bilirubin, Gamma glutamyl transferase, Hyaluronic acid, alpha 2 macroglobulin, and platelets evaluation.

Results: A score of $\geq$ 0.5 predicted stages 2, 3 and 4, with a sensitivity of 82%, and specificity of 92%. A score $\geq$ 0.5 for stages 3 and 4 had a sensitivity of 85%, and specificity of 89%. At a score of > 0.80, for stages 3 and 4, the sensitivity was 70%, specificity was 97%, and PPV 87% (there was $\geq$ 85% possibility of presence of stage 3 or 4). A score of $\leq$ 0.20 predicted the absence of stages 2, 3, and 4 with a sensitivity of 91%, specificity of 86%, and NPV of 96%. Scores from 0.00 to 0.10 almost certainly ruled out the presence of stages 2-4 (NPV=98%). The areas under the ROC curve were: 0.808 for stage 2; 0.938 for stage 3; and 0.959 for stage 4.

Conclusion: A combination of 5 markers is very useful in predicting various stages of liver fibrosis, and is helpful in the non-invasive assessment of liver fibrosis in chronic viral hepatitis patients.

Key words: *Non-invasive markers. Liver fibrosis. Chronic viral hepatitis. Liver biopsy. FibroScore.*

INTRODUCTION

Chronic viral hepatitis is an important cause of morbidity and mortality in the present day world. About 5% of the world's population or 400 million are chronic carriers of HBV, and more than 3% or about 170 million people are infected with HCV.[1,2] According to a large nationwide survey conducted by the PMRC (Pakistan Medical Research Council), the HBsAg prevalence in the general population in Pakistan was 2.5%, anti-HCV prevalence was 4.9%, with the overall number of persons living with chronic viral liver disease at 11.84 million.[3] It is estimated that by the year 2020-5, there will be three-fold rise in cirrhosis, liver failure, hepatocellular carcinoma, and mortality from HBV and HCV.[4,5]

The prognosis and management of chronic viral hepatitis are dependent on the extent of liver fibrosis. Traditionally, the assessment of fibrosis involves liver biopsy, which has been considered the "gold standard". However, it has some marked limitations. There is a risk of severe adverse events 3/1000, and mortality 1-3/10,000.[6] Sampling/specimen size errors are likely. There may be an inter- and intra- observer variability, and variation of the histopathological staging systems.[7] A 25 mm non-fragmented liver biopsy specimen has about 20% false positive/negative rate for advanced fibrosis when compared to the entire liver as a gold standard[8]; and a specimen of this quality is obtained in less than 50% of all large series.[9] Studies have suggested that cirrhosis can be missed in 10-30% of liver biopsy samples.[7] The risk of complications and limitations of liver biopsy has led researchers to look for other methods to assess the stage of liver fibrosis.

There are two main approaches for the non-invasive assessment of liver fibrosis: blood tests, and imaging techniques (ultrasound elastography [FibroScan] and magnetic resonance elastography). The elastography techniques are emerging and require expensive equipment. Commonly used serum markers such as measurement of: aspartate aminotransferase (AST), prothrombin time, albumin, platelets, or the ratio of AST to alanine aminotransferase (ALT), or platelets,[10] provide assessment of cirrhosis; but in themselves are of limited clinical utility for mild to moderate degrees of

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fibrosis. Similarly, some of the direct markers, such as tissue inhibitor of matrix metalloproteinase - 1, TIMP-1; matrix metalloproteinase - 2, MMP-2; or type III procollagen N peptide, PIIINP; all have low prediction across different stages of fibrosis.[7]

Researchers have combined indirect and direct markers into different panels with enhanced performance, such as Fibrotest (FT), Fibrometer (FM) and Europeon Liver Fibrosis Group (ELFG) assay.[11-13]

The primary aim of this study was to estimate the combination of non-invasive serum markers for assessment of different stages of liver fibrosis as compared to liver biopsy in chronic viral hepatitis patients.

METHODOLOGY

One hundred patients aged between 20 and 55 years, who had liver biopsy performed after informed consent, were consecutively enrolled in this prospective cross-sectional study. The patients were tested positive either with HCV RNA PCR and/or hepatitis B surface antigen, HBsAg. The patients with chronic liver disease other than HBV and HCV, extrahepatic causes of liver fibrosis including cardiovascular, pulmonary, rheumatic diseases, and drugs, cirrhosis as defined by modified Child-Pugh class B and C, prior anti-viral therapy and PCR negative afterwards, and morbid obesity (BMI $\geq$ 30) were excluded. Patients with insufficient liver biopsy specimen and incomplete data on non-invasive markers were also excluded from the final analysis. No patient had history of alcoholism, HIV or liver transplantation. The study protocol was approved by the Board of Advanced Studies and Research, Baqai Medical University, Karachi.

The clinical data included co-morbidities, risk factor profile, history of treatment for chronic viral hepatitis, symptoms of decompensated liver disease, physical examination including BMI, hepatosplenomegaly and stigmata of chronic liver disease. The laboratory parameters included total bilirubin, AST, ALT, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), albumin, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, urea, creatinine, blood glucose random (microlab 200), globulins, immunoglobulin G, PT, INR, APTT (activated partial thromboplastin time) and blood CP (Sysmex KX-21).

Hyaluronic acid (HA), and alpha 2 macroglobulin (A2M) assays were carried out on sera stored at -20°C in batches. The hyaluronic acid assay was performed by an enzyme - linked binding protein assay (Corgenix Inc., CO, USA). Alpha 2 macroglobulin was also determined via an enzyme immunoassay technique (Assaypro, MO, USA). Both assays were carried out according to the manufacturer's recommendations. Overall 20 blood markers were studied.

Ultrasound examination of abdomen was done using the Toshiba ECO-CEE machine, evaluating liver size/echotexture/nodularity, presence or absence of any focal lesion, portal vein diameter and splenomegaly.

Liver biopsy was performed using the 18 gauge liver core biopsy needle (modified Menghini liver aspiration needle), using the subcutaneous intercostal approach after ultrasound abdomen. An adequate specimen was described as containing $\geq$ 6 portal tracts.

All biopsy material slides were stained with haematoxylin, eosin and reticulin stains. The biopsies were interpreted by experienced histopathologists (B.A. and Y.W.). The liver biopsy was scored according to the Knodell HAI classification, and by modified Knodell HAI system (Ishak scoring system). The histopathologists were blinded to the patients' clinical and laboratory profile. Kappa (κ) statistics were used as a measure of interobserver agreement. Following the recommendations of the International Association for the Study of Liver (IASL) panel, the diagnostic line of biopsy report also read the histopathologists' overall visual impression in terms of mild/moderate/severe (extensive) activity and fibrosis.

The statistical analysis was done by logistic regression, area under the receiver operating characteristic (ROC) curves, Kappa (κ) values, and by descriptive statistics: sensitivities, specificities, positive and negative predictive values, likelihood ratios, and diagnostic accuracy. The data followed log normal distribution.

The association between different biochemical markers for the presence or absence of significant fibrosis was assessed in univariate analysis. A 2-sided p-value of less than 0.05 was considered statistically significant. The categorical variables were compared by the chi-square test and expressed as percentages. Continuous variables were compared by the t-test. The quantitative variables were expressed as mean $\pm$ SD, 5% trimmed mean, median, and as interquartile range in box plots 95% confidence intervals were used as a method to measure diagnostic accuracy or variability of statistical results.

The strength of association of individual biochemical markers with significant fibrosis was also assessed by the area under the ROC curve analysis.

The biochemical markers with strong association in univariate analysis, and high area under the ROC curve were then subjected to multivariate analysis. These markers were then combined with age and sex and entered into a forward stepwise logistic regression analysis to determine a probability index ranging from 0 to 1. The dependent variable was the presence or absence of CSF.

Markers with better discriminatory values were also combined into different other logistic regression analyses to develop separate models. These models were then

compared amongst each other by areas under the ROC curve and by descriptive statistics. The model, FibroScore, with fewer variables and the best area under the ROC was then selected. The regression function was:

χ = [- 4.795 + (0.189 x bilirubin) + (0.120 x GGT) + (0.080 x hyaluronic acid) + (0.518 x alpha 2 macroglobulin) - (0.040 x platelets)] with bilirubin expressed in μmol/L; GGT in U/L; hyaluronic acid in μg/L; alpha 2 macroglobulin in g/L; and platelets in 10^9/L.

A central cut off of 0.5 was chosen for the prediction of dependent variable. In addition to this central cut off point, various other points were chosen on either side to predict the presence or absence of different stages of fibrosis. The FibroScore model was also used to predict moderate to severe necroinflammatory activity from no to mild activity.

The statistical software used was Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The patients' demographic and histopathological characteristics are presented in Table I. A total of 100 patients were enrolled in the study, of which 88 were included in the final analysis. Clinically significant fibrosis (CSF) as defined into stages 2, 3 and 4 (F2, F3, F4) was present in 26% patients; and advanced fibrosis, stages 3 and 4 (F3-F4) was present in 23% patients. Moderate necroinflammatory activity was present in 44%, and severe necroinflammatory activity in 6% of patients. The mean length of the biopsy specimen was 1.15 cm (median 1.00 cm), and the interobserver agreement (Kappa, κ coefficient) between the histopathologists was moderate (κ = 0.60) for grading and good for staging (κ = 0.74).

Table I: Demographic and histopathological characteristics.

Characteristic	Mean (SD)(Range)/Percentage
Age (years)	32.43 ± 6.1 (20-53) Median 32
Female	41 (46.6%)
HCV RNA	74 (84%)
HBsAg	13 (14.7%)
Both	01 (1.13%)
Length of biopsy (cm)	Mean 1.15 ± 0.64, Median 1.00
Stage 0 (F0) No fibrosis	26 (29.5%)
Stage 1 (F1) Portal fibrosis	39 (44.3%)
Stage 2 (Ishak) (F2) Portal fibrosis ± septa	03 (3.4%)
Stage 3 (F3) Bridging fibrosis	18 (20.5%)
Stage 4 (F4) Cirrhosis	02 (2.3%)
Clinically significant fibrosis (F2-F4)	23 (26.1%)
Advanced fibrosis (F3-F4)	20 (22.72%)
Minimal activity (0-3)	11 (12.5%)
Mild activity (3-6)	33 (37.5%)
Moderate activity (7-11)	39 (44.3%)
Severe activity (> 11)	05 (5.7%)
Significant activity (Moderate-Severe)	44 (50%)

The association between fibrosis and clinical, liver biopsy, and markers in univariate analysis is shown in Table II. The multivariate model, FibroScore consists of 5 markers: bilirubin, gamma glutamyl transferase (GGT), hyaluronic acid (HA), alpha 2 macroglobulin (A2M), and platelets, Table III.

The FibroScore values (range 0.00-1.00) increased as the fibrosis stage increased. The maximum score was for stage 4 (F4). The small box plot for F4 indicated that the corresponding range for the FibroScore for cirrhosis (F4) was small i.e., 0.99-1.00.

A central cut off of 0.5 was chosen as a differentiation point for clinically significant fibrosis. A score of > 0.5 was seen in 24 of 88 patients (27%). This central cut off point in the model predicted clinically significant fibrosis (F2, F3 and F4) with a sensitivity of 82% (95% CI; 63-93), specificity of 92% (83-96), positive predictive value (PPV) of 79 % (59-90), negative predictive value (NPV) of 93% (85-97), positive likelihood ratio, positive LR of 10.73 (4.53-25.44), negative LR of 0.18 (0.07-0.46), and overall diagnostic accuracy of 89% (95% CI; 81-94). For advanced fibrosis (F3, F4), this cut off of ≥ 0.5 provided sensitivity of 85% (64-94), specificity of 89% (80-94), and the PPV of 71% (51-85), NPV of 95% (87-98), positive LR of 8.25 (3.99-17.05), and negative LR of 0.16 (0.05-0.47).

Increasing the cut off point to ≥ 0.65 for advanced fibrosis (F3-F4) had sensitivity of 80% (58-91), specificity of 95% (87-98), PPV of 84% (62-94), NPV of 94% (85-97), positive LR 17.86 (5.7-55.16), and negative LR 0.20 (0.08-0.50), respectively. Further increasing the cut off to 0.80, for advanced fibrosis, the sensitivity was 70% (48-85), specificity was 97% (89-99), PPV was 87% (64-96), there was > 85% strong possibility of presence of F3 or F4, NPV was 91% (88-96), positive LR 23.8 (5.89-96.05), and negative LR 0.30 (0.15-0.60).

Lowering the cut off to 0.20 predicts the absence of clinically significant fibrosis with a NPV of 96% (88-99), PPV of 70% (52-83), sensitivity of 91% (73-97) and specificity of 86% (75-92), positive LR of 6.59 (3.55-12.25), and negative LR of 0.10 (0.02-0.38). Scores between 0.00 to 0.10 predicted almost 100% certainty of the absence of clinically significant fibrosis (actual NPV 98% of the absence of F2, F3, F4).

The area under the ROC for F2 (stage 2) fibrosis was 0.808 (95% CI; 0.613-0.910), for F3 the ROC was 0.938 (0.888-0.988), and for F4 the ROC was 0.959 (0.893-1.00). The Hepascore values were also computed for the same study population, and in comparison, the area under the ROC for F2 was 0.728 (0.580 - 0.876, p = 0.07), for F3 was 0.851 (0.773 - 0.930, p < 0.0001, Figure 1) and for F4 was 0.912 (0.851 - 0.972, p = 0.02) respectively.

Table II: Clinical, liver biopsy and laboratory parameters vs. fibrosis categories.

Variable	F0-F1	F2-F4	p-value
Age (years)			
Mean	31.2 ± 5.46	35.9 ± 6.88	0.001
5% trimmed mean	31.1	35.5	
Median	31.0	36.0	
BMI			
Mean	23.5 ± 3.38	25.3 ± 4.05	0.031
5% trimmed mean	23.4	25.2	
Median	24.0	24.0	
Female	32 (49.2%)	9 (39.1%)	0.40
Male	33 (50.8%)	14 (60.9%)	-
No to minimal activity (< 3)	11 (16.9%)	0	< 0.0001
Mild activity (3-6)	31 (47.7%)	2 (8.7%)	
Mod activity (7-11)	23 (35.4%)	16 (69.6%)	
Severe activity (> 11)	0	5 (21.7%)	
Bilirubin (μ mol/L)			
Mean	11.2 ± 4.5	13.7 ± 4.7	0.026
5% trimmed mean	10.6	13.0	
Median	10.0	13.0	
ALT (U/L)			
Mean	88.2 ± 37.22	93.6 ± 50.60	0.58
5% trimmed mean	85.7	86.2	
Median	39.0	45.0	
AST (U/L)			
Mean	40.4 ± 12.68	51.6 ± 24.89	0.49
5% trimmed mean	38.8	47.3	
Median	39.0	45.0	
GGT (U/L)			
Mean	33.7 ± 12.1	53.4 ± 22.89	0.001
5% trimmed mean	32.9	50.3	
Median	32.0	48.0	
PT (second)			
Mean	14.3 ± 0.73	15.4 ± 0.99	0.03
5% trimmed mean	14.1	15.4	
Median	14.0	16.0	
Albumin (g/L)			
Mean	43.3 ± 5.45	43.2 ± 4.08	0.95
5% trimmed mean	43.3	43.0	
Median	43.0	42.0	
Urea (mmol/L)			
Mean	4.12 ± 0.73	4.14 ± 0.95	0.89
5% trimmed mean	4.0	4.0	
Median	4.0	4.0	
Globulins (g/L)			
Mean	22.5 ± 7.46	23.1 ± 5.02	0.69
5% trimmed mean	22.2	23.1	
Median	21.0	22.0	
IgG (g/L)			
Mean	13.8 ± 2.61	15.1 ± 2.48	0.040
5% trimmed mean	13.9	15.1	
Median	14.0	15.0	
Hyaluronic acid (μg/L)			
Mean	31.2 ± 16.63	73.9 ± 32.73	< 0.0001
5% trimmed mean	30.0	71.1	
Median	27.0	73.0	
Alpha 2 macroglobulin (g/L)			
Mean	2.3 ± 2.17	3.9 ± 2.36	0.004
5% trimmed mean	2.0	3.7	
Median	2.0	3.0	
Platelets (x 10^9/L)			
Mean	267 ± 45.98	199 ± 45.88	< 0.0001
5% trimmed mean	264	199	
Median	261	201	

Table III: Multiple logistic regression analysis for the prediction of clinically significant fibrosis (F2-F4).

Variables	B (regression co-efficient)	SE	Odds ratio	95% CI odds ratio	p-value
Bilirubin (μmol/L)	0.189	0.096	1.208	1.000 - 1.459	0.051
GGT (U/L)	0.120	0.050	1.128	1.022 - 1.244	0.016
Hyaluronic acid (μg/L)	0.080	0.027	1.084	1.028 - 1.143	0.003
Alpha 2 macroglobulin (g/L)	0.518	0.211	1.678	1.110 - 2.537	0.014
Platelets (10^9/L)	-0.040	0.017	0.960	0.929 - 0.993	0.017

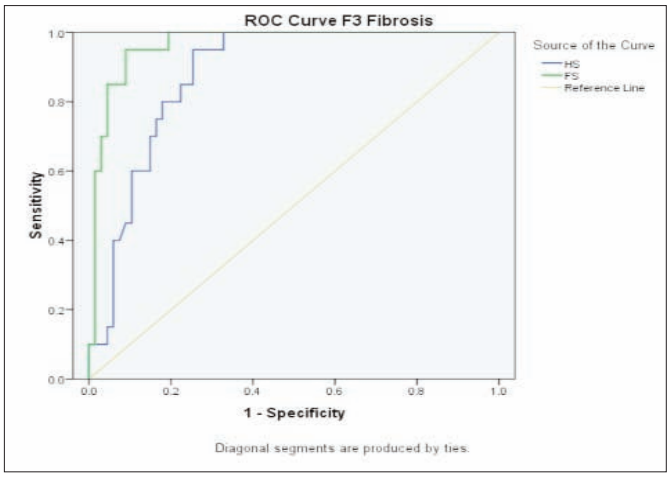

Figure 1: Areas under the ROC curves of FibroScore (FS) and Hepascore (HS) for F3 fibrosis FS AUROC 0.938 (95% CI; .888-.988), HS AUROC 0.851 (.773-.930).

For individual markers, the values of both alpha 2 macroglobulin and hyaluronic acid were significantly higher for stages 2-4 than stages 0-1, p = 0.004 and < 0.0001 respectively. Bilirubin and GGT levels also showed a similar trend. Platelet count was significantly higher at stages 0-1 than stages 2-4, p < 0.0001, Table II, and Figure 2.

The FibroScore was also very useful in differentiating moderate to severe from no to mild necroinflammatory activity. The moderate to severe activity was defined as grade ≥ 7/18, and no to mild activity was considered for grade ≤ 6/18. The area under the ROC curve was 0.790 (0.696-0.884), and the cut off of 0.5 yielded sensitivity of 62% (45-76), specificity of 90% (80-96), PPV of 80% (62-91), NPV of 79% (67-87), positive LR of 6.67 (2.77-16.01), negative LR of 0.42 (0.27-0.65). The activity grades correlated very well with the higher stages of fibrosis. The ALT levels paralleled, and showed statistical significance. The mean ALT level for no to mild activity was 77.88 ± 29.23, and the level for moderate to severe activity was 101.36 ± 47.41, p = 0.007.

DISCUSSION

This study has shown that FibroScore has high predictive value for the diagnosis of liver fibrosis, for advanced stages or even at earlier fibrosis stages. It

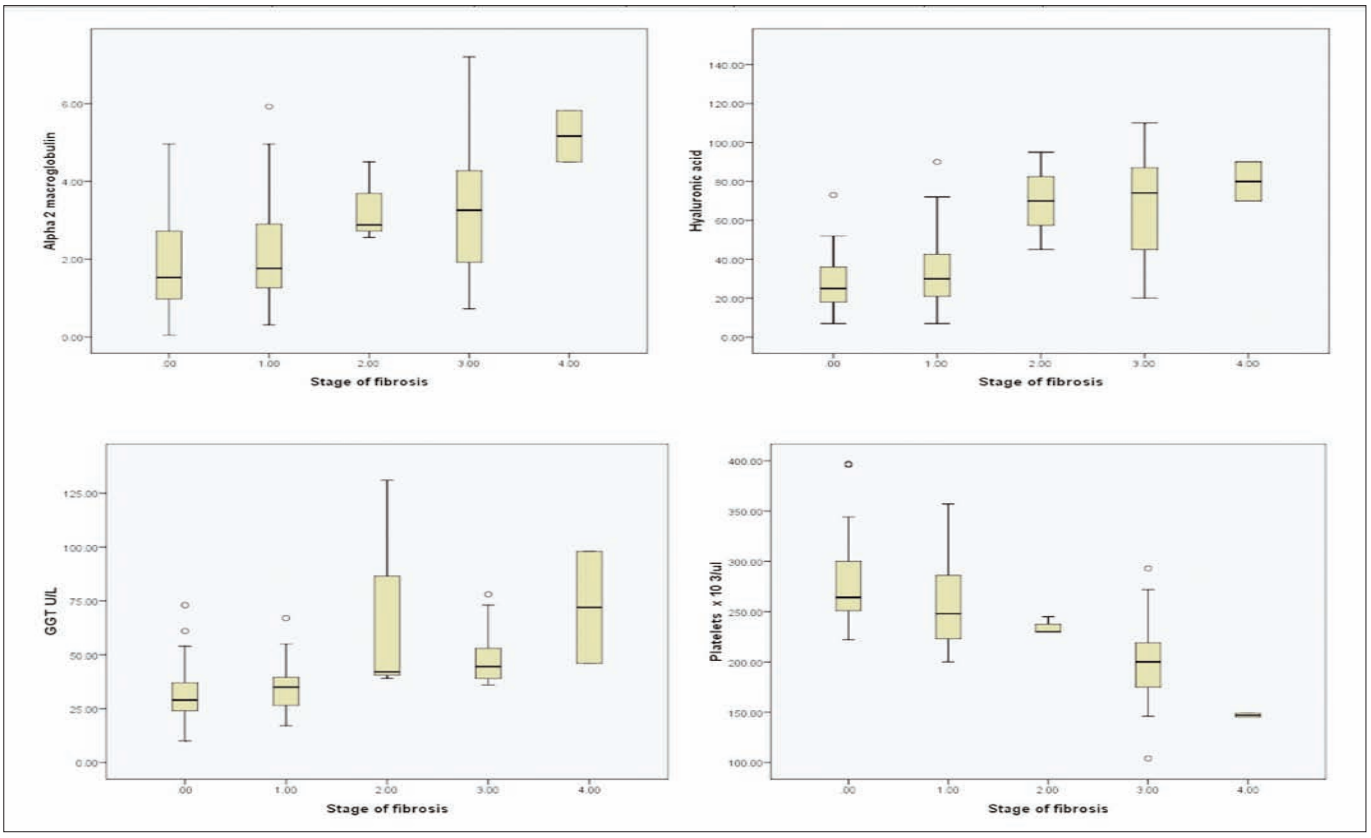

Figure 2: Box plots of alpha-2 macroglobulin, hyaluronic acid, gamma glutamyl transferase, and platelets for different fibrosis stages.

provided a quantitative estimation of individual stages, the higher scores reflecting increased fibrosis.

There have been few local studies describing the role of non-invasive markers, but those were limited in scope.[14]

The overall performance of a fibrosis panel is dependent on many factors. These include: the quality of liver biopsy specimens, underlying prevalence of fibrosis stages, fibrosis stage cut off, intrinsic biological properties of markers, pre-analytic and analytic variability of test components, and population demographics such as alcohol consumption and genetic variation.

To signify the inherent biological properties of test panels, Halfon *et al.*, compared FM and FT based on the misclassification rate. The number of patients misclassified by both test panels was maximum for stage F2 (Metavir system). In patients with stages 2-4 (Metavir) of fibrosis (higher stages of fibrosis), FM had lower proportion of misclassified patients than FT; and vice versa.[15]

In the case of FibroScore, the error rate is mostly in the lower fibrosis score, and less misclassification at advanced stages of fibrosis. It is most likely due to the inherent biological properties of the test components, and is in concordance with other studies.[15] In other words, FibroScore panel will perform better in a population of patients with advanced stages of fibrosis, than vice versa, which is clinically very useful.

Studies have shown a high discordance rate and more misclassified patients for stage F2.[12,15] The misclassification rate has been attributed to the limitations of biopsy itself, suggesting that difficulty in distinguishing F2 from adjacent stages is one of the important causes of misclassification, and this also leads to the underperformance of fibrosis markers.

The performance of a test also depends on the fibrosis stages being compared. The greater the difference between the fibrosis stages being compared (the greater the diagnostic goal), the better will be the observed performance.[15] Poynard and colleagues called it the Spectrum Bias.[16]

In the study by Wai *et al.*, for significant fibrosis (Ishak stages $\geq$ 3), the area under the ROC curve of APRI was 0.80.[10] The area under the ROC curve of APRI for cirrhosis varied from 0.89 to 0.94 in the principal study, which to some extent is comparable to other test panels; for instance FT area under the ROC curve for cirrhosis was 0.923.[11] APRI and FIB-4 (incorporates age, AST, platelets and ALT) have accurately predicted changes in the stage of fibrosis when longitudinally evaluated in chronic hepatitis patients who had liver biopsies performed one year apart.[17] As far as evaluating cirrhosis, the performance of APRI can be compared to the more sophisticated models, but its performance falls for less severe stages of fibrosis. And FS is better in this regard.

The Forn's index consists of age, GGT, platelets, and cholesterol.[18] For significant fibrosis (Scheuer stages 2-4), the area under the ROC varied from 0.86 to 0.81. Forn's index is better at excluding significant fibrosis (NPV 96%), than indicating its presence (PPV 66%). Thus it can be clearly seen that FibroScore is better in this respect.

In the study by Adams *et al.*[19], Hepascore (HS), area under the ROC curve for advanced fibrosis was 0.96, and for cirrhosis was 0.94. In contrast, the FS area under the ROC curve for stage F3 was 0.938, and for F4 (cirrhosis) was 0.959. It can be seen that in the principal study, the area under the ROC curve of HS actually decreased for cirrhosis; whereas in the current study, the area under the ROC curve of FS steadily increased for higher stages of fibrosis including cirrhosis. Moreover, in this study, FS in comparison with HS, has yielded better results for areas under the ROC for different fibrosis stages. This could be attributable to different population characteristics or separate composition of the indices.

The Europeon Liver Fibrosis Group (ELFG) assay consists of age, hyaluronic acid, amino terminal propeptide of type III collagen (PIIINP), and tissue inhibitor of metalloproteinase - 1 (TIMP-1).[13] In a large cohort of patients, for significant fibrosis (Scheuer stages 3-4 vs. stage 0-2) the area under the ROC curve was 0.804 from all causes of chronic liver disease, and 0.773 from patients with chronic hepatitis C. Patel *et al.* evaluated FIBROSpect II panel (FS-II consisting of HA, TIMP-1, and A2M) versus biopsy in chronic hepatitis C patients.[20] FS-II ROC for stages F2-F4 was 0.823, with a sensitivity of 83.5%, specificity of 66.7%, and an accuracy of 80.2%.

Thus, it can be seen that panels with direct markers of liver fibrosis, have lower area under the ROC curve and discriminatory power as compared to FS.

FS consists of both direct and indirect markers. Inclusion of both types adds to the diagnostic performance by limiting variations in the performance of individual markers.

A2M is a large intravascular protease inhibitor, associated with stellate cell activation, whose increased concentration inhibits catabolism of matrix proteins and enhances liver fibrogenesis. Proteomic studies have revealed that high molecular weight component of alpha-2 macroglobulin is preferentially expressed in cirrhosis and moderate fibrosis.[21] Alpha-2 macroglobulin has been the component of all the major test panels of non-invasive markers of liver fibrosis.[11,12,19,20]

Hyaluronic acid is a high molecular weight glycosaminoglycan. During liver injury there is increased hyaluronic acid production by the hepatic stellate cells and decreased clearance by the sinusoidal endothelial cells, because of sinusoidal capillarisation. Of all the direct markers, HA levels have high association with advanced fibrosis and cirrhosis.[22]

In reference to GGT, early cholestasis from bile duct lesions, or the growth factors increase such as hepatocyte growth factor and epidermal growth factor are postulated as the causes for high GGT values in severe fibrosis.[11]

With progression in fibrosis, the increase in bilirubin is likely due to: reduced hepatic excretion from bile duct lesions, and reduced enterohepatic circulation due to portal systemic shunting of blood.

Thrombocytopenia is a commonly encountered haematological condition in chronic liver disease and cirrhosis. In patients without splenomegaly, thrombocytopenia was independently and inversely associated with the stage of fibrosis. Pathogenetic mechanisms postulated for thrombocytopenia include: hypersplenism secondary to portal hypertension, bone marrow suppression (resulting in suppression of megakaryocytes), and aberrations of the immune system resulting in the formation of anti-platelet antibodies and/or immune-complexes that bind to platelets and facilitate their premature clearance.[23]

It was a cross-sectional study and longitudinal evaluation in chronic hepatitis patients should be performed to assess fibrotic changes over time de novo, or in chronic viral hepatitis patients after treatment. Validation against fibro-test should be performed, which is the most validated modality of markers of liver fibrosis.

The role of liver biopsy in diagnosing diffuse parenchymal liver disease is being diminished. With improvement in technology, its days of dominance are being challenged by the non-invasive markers and imaging tests.[24] The non-invasive techniques will continue to be refined and play an important role in the assessment of patients with chronic liver disease in future.[25]

CONCLUSION

It is concluded that FibroScore is a useful index for the assessment of different stages of liver fibrosis in patients with chronic viral hepatitis, and may enhance the future management of patients with chronic viral related liver disease.

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