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FIB-4 INDEX:

DIAGNOSTIC VALIDITY FOR PREDICTING HEPATIC FIBROSIS IN SOUTH EAST ASIAN PATIENTS OF CHRONIC HEPATITIS C VIRUS (HCV) GENOTYPE 3 INFECTION

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ABSTRACT… Objectives: To assess the diagnostic validity of FIB-4 for predicting hepatic fibrosis in patients of chronic hepatitis C genotype 3. **Study Design:** Cross-sectional study. **Setting:** Department of Gastroenterology and Hepatology, Isra University Hospital, Hyderabad through convenient sampling. **Period:** June 2013 to June 2014. **Methods:** Diagnostic validity of FIB-4 index for predicting hepatic fibrosis was determined by measuring sensitivity, specificity, positive productive, negative predictive value, and compared these parameters with liver biopsy. The liver histology was determined by METAVIR score. **Results:** A total 115 patients were enrolled with mean and SD of age was 39.6 ± 9.3 years. Dividing FIB-4 index into three categories as <1.45, 1.45 - 3.25, and >3.25; by using the Obuchowski method the AUROC was 0.93 (with 95% CI 0.91, 0.95). When dividing the FIB-4 index in to three categories as <1.45, 1.45 - <2.25 and >2.25; the AUROC by using Obuchowski method was 0.87 (with 95% CI 0.83, 0.91). Similarly for the diagnosis of Cirrhosis (F = 4 METAVIR) on the predictive value of the non-invasive test FIB-4 while using Obuchowski method the AUROC was 0.85 (with 95% CI 0.83, 0.87). **Conclusion:** The FIB-4 index is a simple, inexpensive, non-invasive, and a quick test for predicting liver fibrosis in patients of chronic Hepatitis C genotype 3.

Key words: Liver biopsy, Metavir, Non-invasive, Cirrhosis, Fibrosis, Pakistan.

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INTRODUCTION

Hepatitis C virus (HCV) infection has been attributed one of the most important causes of chronic liver disease and liver cirrhosis among Pakistani population and its prevalence continues to rise.[1] The prevalence of HCV related chronic liver disease is estimated to be around 70%.[2,3] Timely diagnosis and early management of this chronic disease is very crucial in overall better outcome of the patients and to prevent the development of HCV related CLD associated complications. Since its diagnosis, clinicians and researchers aimed to provide best medical treatment to reduce overall burden of this disease but a tremendous change in the treatment has been observed since 10 years. The therapy of CLD is now improved so much since single pills has been replaced with combination therapy. There are so many reasons which affect the response of treatment such as extent of liver fibrosis.[4-5] These patients are more prone to end up with end stage liver disease than those whose liver is not fibrosed.[6-7] Up till now liver biopsy has been regarded as gold standard test for histological staging and grading in CHC.[8] It is an invasive and costly procedure, which causes economical burden on patients and also patient may suffer from certain complications associated with this invasive procedure ranging from 0.09% to 2.3%.[9] Therefore, it is utmost of importance that clinician should be able to identify the patient's stage of liver fibrosis and would be a great help for determining the extension of CLD.[12] Recently a pivotal study AIDS Pegassys Ribavirin International Co-infection Trial (APRICOT) has designed a non-invasive parameter based calculation method through which one can predict the fibrosis of liver.[13] It can be calculated as: age of the cases (Years) x Aspartate aminotransferase (AST) [IU/L]) / (Platelets [10^9]) x (Alanine aminotransferase (ALT) [IU/l] $^{1/2}$).[14] Liver fibrosis is excluded if the cut off value is <1.45 with a sensitivity of 74.3% and a specificity of 80.1%, and if the cut off value

is >3.25 indicate positive liver fibrosis (sensitivity 37.6% and specificity 98.2%).[15]

The aim behind this study was to assess the diagnostic validity of FIB-4 index for predicting hepatic fibrosis in patients of CHC Genotype 3 at Isra university hospital, Hyderabad.

MATERIALS AND METHODS

A cross sectional, hospital based study was conducted through convenient sampling technique from June 20013 to June 2014 at department of Gastroenterology & Hepatology, Isra university hospital, Hyderabad, Pakistan.

Inclusion Criteria

The cases of either gender were enrolled in this study when they were treatment naïve and suffering from CHC genotype 3. They were to be more than 16 years of age with compensated liver disease, having detectable HCV RNA level after getting informed consent.

Exclusion Criteria

The cases were excluded from entering into this study when absolute neutrophil count < 1500/ mm^3; platelets count <70000/mm; Hb. < 11.0 g/ dl for females and <12.o g/dl for males; serum Creatinine level > 1.5 times the upper limit of normal; concurrent HBV and HIV infections; HCV infection other than genotype 3; evidence of decompensate liver disease; severe psychiatric disease; significant co morbid illness that would preclude HCV therapy and previous treatment with interferon and/or ribavirin; history of alcohol consumption; presence of other liver disorders such as autoimmune hepatitis, nonalcoholic steatohepatitis, α1-antitrypsin deficiency, haemochromatosis, pregnant women, and Wilson's disease.

FIB4 Index

This was calculated as age of the cases (in years) x aspartate aminotransferase (AST) [IU/L]) / (Platelets [10^9]) x (alanine aminotransferase (ALT) [IU/l] $^{1/2}$).

Diagnosis of HCV Infection

Cases were regarded with active HCV infection when HCV RNA was detectable in their serum.

Diagnostic Validity of FIB-4 Index

Diagnostic validity of FIB-4 for predicting hepatic fibrosis was determined by measuring the sensitivity, specificity, positive productive value and negative predictive value according to their respective formulas by using 2×2 contingency table where as taking liver biopsy a gold standard test for the diagnosis of hepatic fibrosis. For analysis the patients were categorized into 5 METAVIR classes F0 (no fibrosis); F1 (mild fibrosis); F2 (moderate fibrosis); F-3 (severe fibrosis); F4 (cirrhosis).

Cut off Values of FIB4 Index

The cut off value of <1.45 was taken for negative predictive value to exclude hepatic fibrosis. A cut off value of >3.25 was taken for positive predictive value to predict severe hepatic fibrosis (F3) or cirrhosis (F4).

Laboratory Investigations

All the blood reports were done in the laboratory of our center. Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) were being done on Hitachi 902 by Roche USA, usual upper normal values are ≤40 U/L and ≤45 U/L for males and ≤ 34 U/L and ≤34 U/L for females, respectively; Complete Blood Count (CBC) done by using Nihon Japan Kohden auto analyzer; HCV antibodies (Anti HCV) done on Architect 1000SR by Abbott, Germany. HCV RNA by PCR and Genotyping was done on m2000 sp Abbott real time system by Max-Planck-Ring 2 65205-Wiesbaden Germany. Liver biopsy was done by per cutaneous fine needle aspiration biopsy using 16 G × 90 mm Univer (Japan) disposable lumber puncture needle with K-3 lancet point. Tissue cores of at least 30 mm length were obtained to decrease the likelihood of sampling error. Samples were put immediately in a biopsy jar and sent to a tertiary care center situated in the city of Karachi. It was reported by two independent histopathologists, being experts in liver histopathology who reported the grading of the inflammatory activity and staging of the fibrosis according METAVIR scoring system. The reporting histophathologist were unaware

of each other's reporting in order to lessen the reporting bias. All the other reports were done at our center's main laboratory.

Data Collection Procedure

The purpose, procedure, and benefit of the study were discussed with each case entering into the study. An informed written consent was taken form each case before selection. A separate performa was filled for individual cases. The data was recorded about demography and the laboratory investigations. Complete Blood Count (CBC), AST, ALT, alkaline phosphatase, prothrombin time (PT) & International Normalized Ratio (INR), serum albumin, serum bilirubin, liver biopsy, HCV RNA by PCR, and genotyping were done on the same day. Calculation of FIB-4 index according to fore mentioned formula was recorded.

Data Analysis Procedure

Discrete variables like gender and histology stages were presented in frequencies and percentages, whereas continuous variables were presented as Mean ± SD. Cross tabulation was performed to compare FIB-4 index results with METAVIR stages. Chi - square and independent t-test were applied where ever needed for statistical significance. The derived values for FIB-4 were assessed via the generalization of the area under the receiver operating characteristic (AUROC) curves and calculating by Obuchowski method, where 1.0 indicates perfect discrimination and a score of 0.5 indicates a random prediction. The 2×2 contingency table was used to calculate the sensitivity, specificity, positive predictive value and negative predictive values for the derived FIB-4 index to determine the significance of pre specified cutoff values, FIB-4 value of <1.45 to exclude hepatic fibrosis and FIB-4 value of >3.25 to predict severe hepatic fibrosis. All data were entered and analyzed by using SPSS version 16. P value less than 0.05 was considered statistically significant.

RESULTS

During the study period 115 patients full filled the inclusion criteria and were enrolled under the study. Of these, 115 cases, 69 (60%) were males and 46 (40%) were females, with a mean (± SD) of age was 39.6 ± 9.3 years. When comparing baseline data with METAVIR score, all variables had significant association ($p < 0.05$) except gender and weight ($p > 0.05$); the comparison between different study variables and METAVIR scores is shown in Table-I.

***** P-values are statistically significant
Represented in n(%)
Represented in Mean + SD

Figure-1 classifies METAVIR fibrosis stages on the basis of their severity levels, no fibrosis (F0), mild (F1), moderate (F2), and extensive (F3), and cirrhosis (F4). Majority (N = 41, 36.5%) of the cases presented at stage of F3.

Figure-2 shows three main categorization of FIB-4 index, <1.45, 1.45 – 3.25, and >3.25.

Variables	Total (N = 115)	F0-F1-F2 (N = 67)	F3-F4 (N = 48)	P-Value
Male	69 (60%)	41	28	0.757
Female	46 (40%)	26	20	
Age	39.59 + 9.32	38.06 + 9.33	41.73 + 9.007	0.037*
Weight	65.60 + 17.50	63.15 + 14.65	69.02+ 20.53	0.076
BMI	26.26 + 6.13	25.16 + 5.35	27.79 + 6.84	0.022*
Platelets	228.91 + 89.54	253.30 + 99.20	194.88 + 59.97	<0.001*
ALT	86.60 + 78.94	65.18 + 60.041	116.50 + 92.116	<0.001*
AST	72.53 + 69.58	50.06 + 47.84	103.90 + 82.49	<0.001*

Table-I. Comparison between study variables and metavir scores

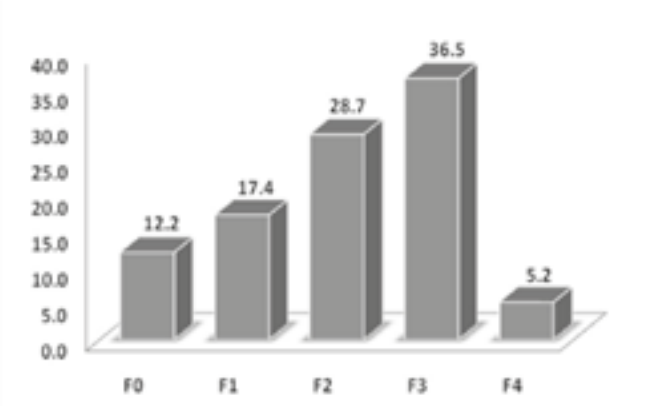

Figure-1. Bar graph showing severity of fibrosis with 5 metavir classes

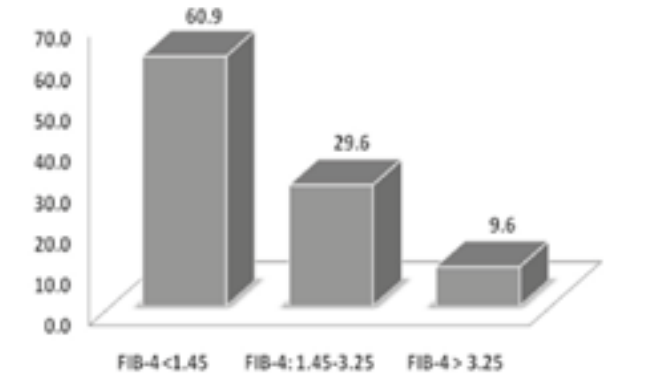

Figure-2. Fib-4 index showing as bar graph

Dividing FIB-4 index into three categories as <1.45, 1.45 - 3.25, and >3.25, the AUROC for severe fibrosis (> F2) was 0.78 (with 95% CI 0.68, 0.87) when calculating by Obuchowski method the AUROC was 0.93 (with 95% CI 0.91, 0.95). When dividing the FIB-4 index in to three categories as <1.45, 1.45 - <2.25 and >2.25 the AUROC for severe fibrosis (> F2) was 0.78 (with 95% CI 0.69, 0.87) while using Obuchowski method the AUROC was 0.87 (with 95% CI 0.83, 0.91). Assuming FIB-4 index as continuous variable the AUROC was 0.82 (with 95% CI 0.75, 0.89) and through Obuchowski method the AUROC was 0.81 (with 95% CI 0.69, 0.92) Table-II, Figure-3, & 4.

Similarly for the diagnosis of Cirrhosis (F = 4 METAVIR) on the predictive value of the non-invasive test FIB-4 is given in Table-II. While the FIB-4 index divided into three categories as <1.45, 1.45 - 3.25 and >3.25 The AUROC for cirrhosis (F=4) was 0.73 (with 95% CI 0.54, 1.00) and calculating by Obuchowski method the AUROC was 0.86 (with 95% CI 0.84, 0.88). When dividing the FIB-4 index with three categories as <1.45, 1.45 - <2.25 and >2.25 The AUROC for advance fibrosis (F=4) was 0.80 (with 95% CI 0.60, 1.00) while using Obuchowski method the AUROC was 0.85 (with 95% CI 0.83, 0.87). If taking FIB-4 index as continuous variable AUROC was 0.80 (with 95% CI 0.65, 0.94) and through Obuchowski method the AUROC was 0.16 (with 95% CI 0.11, 0.20) Table-III. Here Obuchowski gives a low estimates as compare to conventional method due to very few subjects gathered in to cirrhosis category (F=4) Table-III, Figure-3, & 4.

Cut Off of FIB-4	AUROC	SE	95% CI	P-value	Se	Sp	PPV	NPV	LR+	LR-
FIB-4 < 1.45[1]	0.78	0.05	0.68, 0.87	< 0.0001	82.1%	68.8%	73.3%	78.6%	263.1%	26.0%
FIB-4 < 1.45[1] (Obuchowski)	0.93	0.01	0.91, 0.95	< 0.0001	--	--	--	--	--	--
FIB-4 < 2.25[2]	0.78	0.05	0.69, 0.87	< 0.0001	98.5%	35.4%	94.4%	68.0%	152.5%	4.2%
FIB-4 < 2.25[2] (Obuchowski)	0.87	0.02	0.83, 0.91	< 0.0001	--	--	--	--	--	--
FIB-4[3]	0.82	0.04	0.75, 0.89	< 0.0001	--	--	--	--	--	--
FIB-4[3] (Obuchowski)	0.81	0.06	0.69, 0.92	< 0.0001	--	--	--	--	--	--

Table-II. Predictive value of the non-invasive test (i.e. Fib-4) for the presence of significant fibrosis (f > 2 metavir i.e. Severe fibrosis):

1. FIB-4 index divided into three categories <1.45, 1.45 - 3.25 and >3.25
2. FIB-4 index divided into three categories <1.45, 1.45 - <2.25 and >= 2.25
3. FIB-4 index (continuous data)

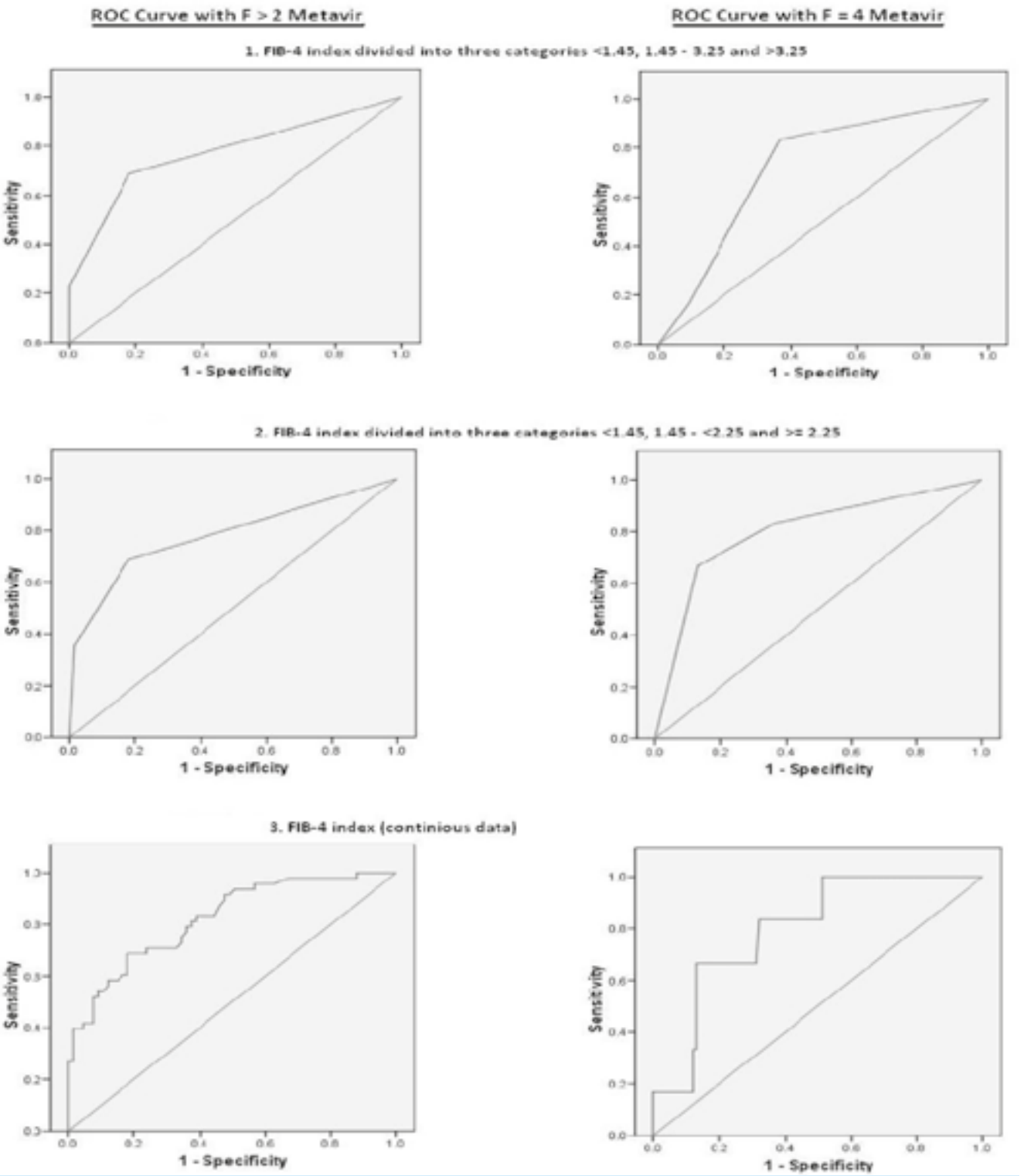

Figure-3. Auroc curves for the prediction of severe fibrosis (f > 2 metavir) and cirrhosis (f = 4 metavir) for the evaluation of diagnostic validity of non-invasive test fib-4

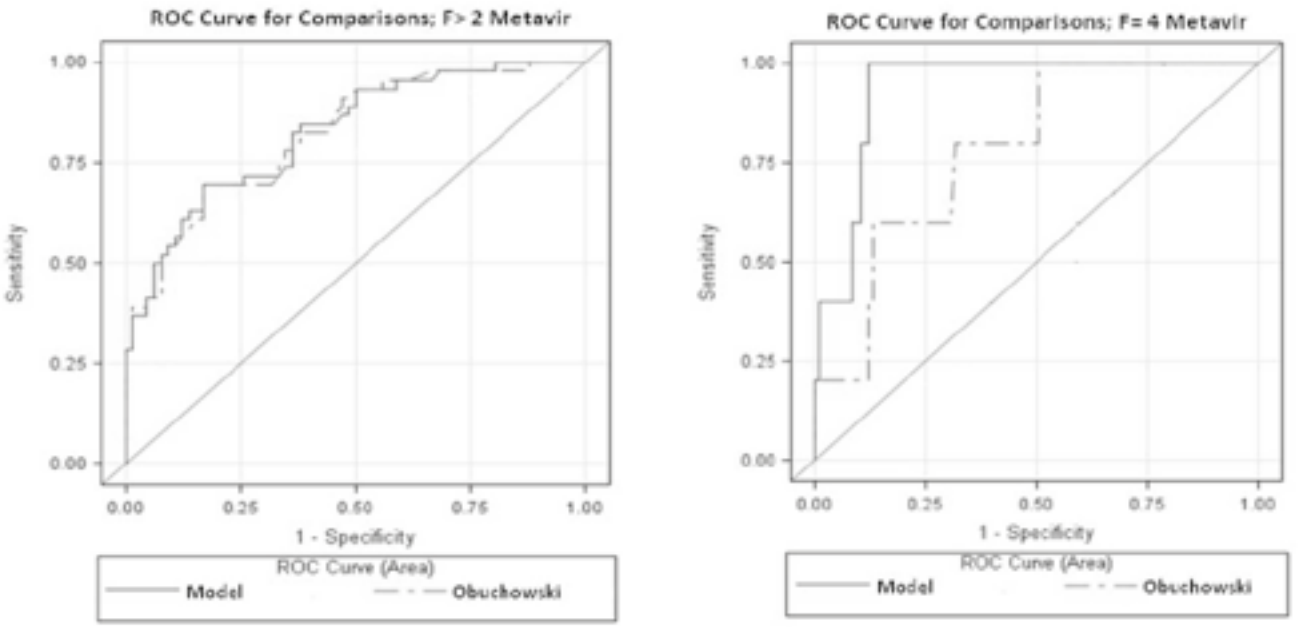

Figure-4. Comparison of roc curves by conventional and obuchowski method for the prediction of severe fibrosis (f > 2 metavir) and cirrhosis (f = 4 metavir) for the diagnostic validity of non-invasive test fib-4

Cut Off of FIB-4	AUROC	SE	95% CI	P-value	Se	Sp	PPV	NPV	LR+	LR-
FIB-4 < 1.45[1]	0.73	0.09	0.54, 0.91	0.06	63.3%	83.4%	11.1%	98.6%	381.3%	44.0%
FIB-4 < 1.45[1] (Obuchowski)	0.86	0.01	0.84, 0.88	< 0.0001	--	--	--	--	--	--
FIB-4 < 2.25[2]	0.80	0.10	0.60, 1.00	0.013	87.2%	66.7%	22.2%	97.9%	261.9%	19.2%
FIB-4 < 2.25[2] (Obuchowski)	0.85	0.01	0.83, 0.87	< 0.0001	--	--	--	--	--	--
FIB-4[3]	0.80	0.07	0.65, 0.94	0.014	--	--	--	--	--	--
FIB-4[3] (Obuchowski)	0.16	0.02	0.11, 0.20	< 0.0001	--	--	--	--	--	--

Table-III. Predictive value of the non-invasive test (i.e. Fib-4) for the presence of significant fibrosis (f = 4 metavir i.e. Cirrhosis):

1. FIB-4 index divided into three categories <1.45, 1.45 - 3.25 and >3.25
2. FIB-4 index divided into three categories <1.45, 1.45 - <2.25 and >= 2.25
3. FIB-4 index (continuous data)

DISCUSSION

Interferon based combination therapy has changed the overall outcome in CHC patients. Its efficacy is dependent upon the number of factors including stage of fibrosis and presence or absence of cirrhosis. Liver biopsy, which is not free of complications, causes anxiety to the patients and also to the treating physicians[16], sampling error may result in wrong histological staging, is invasive and a costly procedure. Majority of a Pakistani population belong to a low to middle social class and they even do not have an access to basic necessities of life. Furthermore, higher illiteracy level made worsening of ongoing situation and people do not afford healthcare causing delayed presentation of patients and liver biopsy could not be performed at that time because of both of the underlying reasons[17] by

Pakistan Society of Gastroenterology (PSG) in patients of CHC.[18] That is why there are lots of other non-invasive procedures introduced to benefit such kind of patients and to clinically predict underlying presence of liver fibrosis.[19] In majority of the models various biochemical markers of fibrosis are used that may not be readily available and not part of routine laboratory investigations. Models using routine tests[20,21,22] seem to perform well. Significant fibrosis and cirrhosis can be predicted noninvasively with accuracy in number of treatment naive patients suffering from CHC.[23]

The present study showed age, BMI, Platelets, AST, and ALT as significant independent variables predicting severe fibrosis (F3) and cirrhosis (F4) on univariate analysis. Of these AST, ALT, platelet count and age are the four components for calculating FIB-4 index. Previously age was used as a surrogate marker of disease duration, the advanced the age, more advanced the fibrosis particularly when knowledge about the exact time of disease onset lacked[24]. Because value of FIB-4 index >3.25 increases with increase in age and the diagnostic accuracy of this value may decrease in elderly patients. Therefore, age as a variable in the elderly can generate excessively high FIB-4 index, leading to misclassification of mild to moderate fibrosis (F0-F2) into a FIB-4 index >3.25. However, mean age of the cases under the present study was 39.6 ± 9.3 years relatively younger patients and there was less likelihood of the misclassification of METAVIR scores, this was comparable with the results of the study conducted by Vallet Pichard et al[15], where in relatively older patients were enrolled with mean age of 44 ± 12 years. Platelet count has been regarded to have an inverse relation with the severity of portal hypertension and advanced fibrosis.[25] Elevated ALT is associated with liver parenchyma injury; whereas AST in part is related to its delayed clearance[26] or mitochondrial injury due to advanced fibrosis.[27] These findings are also consistent in the previously conducted studies[23,28] including APRICOT.[13] The FIB-4 index was easy to use; its calculation was swift and simple. Thus FIB-4 index may become non invasive test of immense importance in countries like Pakistan. The discordance between results of non invasive markers and liver biopsy has been reported by Poynard et al.[29] In their study they have observed that patients failure rate of diagnosis with liver biopsy is seven times higher than biomarkers.

In the present study the AUROC for severe fibrosis (> F2) was 0.78 (with 95% CI 0.68, 0.87) when calculating by Obuchowski method the AUROC was 0.93 (with 95% CI 0.91, 0.95). It correctly predicted severe fibrosis and cirrhosis (METAVIR F3, F4, this was comparable with the results of the study conducted by, A study conducted by Vallet Pichard and his colleagues has confirmed underlying liver fibrosis if the FIB-4 index is more than 3.2.

This showed that in almost 79 % of cases the FIB-4 index could replace the biopsies for the exclusion of extensive fibrosis.

CONCLUSION

The FIB-4 index is a simple, accurate, inexpensive and a quick method for the diagnosis and exclusion of extensive liver fibrosis and/or cirrhosis in patients of chronic HCV Genotype 3 at our center.

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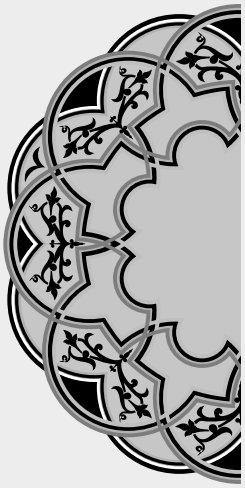

"You cannot push anyone up the ladder unless he is willing to climb."

Andrew Carnegie

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