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AN OBSERVATIONAL STUDY ABOUT THE ROLE OF FIBROSIS–4 INDEX FOR THE DIAGNOSIS OF ESOPHAGEAL VARICES

General Medicine

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ABSTRACT

Background: The prevalence of cirrhosis and esophageal varices has increased in the last decade. But endoscopic screening of every cirrhotic patient is not possible in a developing country like India, where resources are limited. We aim to find the role of the non-invasive marker Fibrosis-4 (Fib-4) index in diagnosing esophageal varices. **Methods:** A total of 80 chronic liver disease patients were enrolled in this cross-sectional observational study conducted at a tertiary care center between September 2023 and June 2024. Ultrasound/ elastography was used to establish the diagnosis of chronic liver disease. Fib-4 index was calculated, and patients underwent upper gastrointestinal endoscopy. Receiver operating characteristic curve (ROC) analysis was performed to evaluate the predictive value of fib-4 index. **Results:** Among 80 patients, 75% (n = 60) had esophageal varices on endoscopy. The highest proportion of patients (37.5%) was in the age group of 30-39 years. Alcohol consumption was found to be the cause of chronic liver disease in most patients (57.5%). Aspartate aminotransferase (AST) levels were significantly higher, while hemoglobin and platelet count were significantly lower in patients with esophageal varices. Fib-4 index was significantly higher in patients with esophageal varices, with a mean of 7.05±2.58, compared to a mean of 2.05±0.81 in those without varices. **Conclusion:** Our study concluded that Fib-4 index is a reliable predictor of esophageal varices in patients with chronic liver disease.

KEYWORDS

Cirrhosis, Esophageal varices, Endoscopic screening, Fib-4, observational study

INTRODUCTION

Cirrhosis is characterized by the replacement of healthy liver tissue with regenerative liver nodules. It is the end stage of chronic liver disease (CLD), which can be caused by hepatotropic viruses, alcohol consumption, non-alcoholic fatty liver disease (NAFLD), and autoimmune hepatitis [1-3]. The prevalence of cirrhosis has increased in recent years, with 5.2 million cases of CLD occurring in 2017 [4]. Cirrhosis can lead to portal hypertension and esophageal varices, which cannot be felt unless they start bleeding [5]. Therefore, endoscopic screening is required for the diagnosis of esophageal varices [6]. Numerous non-invasive tests that can detect the presence of esophageal varices have been developed in recent years, like fibrosis-4 (FIB-4) index, aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio, AST to platelet ratio index (APRI), and King's score [6,7]. The World Health Organization's (WHO) guidelines for measuring hepatic fibrosis recommend and validate the use of FIB-4 and APRI [8]. FIB-4 index was originally described in 2006 for the diagnosis of liver cirrhosis in patients with HIV/ Hepatitis C coinfection [9]. FIB-4 index can be used to determine the severity of liver fibrosis in chronic liver disease due to various causes [10]. The formula [age x AST (IU/L)]÷[platelets (x 10^9) x √ALT(IU/L)] is used to determine FIB-4 from hematologic testing [11].

In this study, we will try to establish the role of FIB-4 index in determining esophageal varices by comparing FIB-4 index values with the findings of esophagogastroduodenoscopy.

MATERIAL AND METHODS

Study Design: cross-sectional observational study

Setting: The study was conducted at the wards and OPD of a tertiary care center between 1st September 2023 and 30th June 2024 after approval by the research and ethical committee of SMS Hospital, Jaipur, wide letter no. 04MC/EC/2023 in its meeting held on 05/08/2023.

Selection of Participants

Patients with an aged ≥18 years whose abdominal imaging (USG/ Fibroscan) findings were consistent with chronic liver disease and who had given informed consent were included in the study. Patients who received beta-blockers or nitrate therapy, had a history of hepatitis B or C treatment, had previous porto-systemic shunt surgery, had a history of gastrointestinal malignancies, including hepatocellular carcinoma (HCC), or a history of lymphoproliferative diseases, or had infections or diseases affecting liver or spleen size, were excluded.

Esophagogastroduodenoscopy was done for all the study participants for the confirmation of esophageal varices, and varices having a large coil shape, occupying more than one-third of the lumen, or red color signs were considered high-risk varices.

Sample Size

A sample size of 70 patients was calculated with 80% study power and an alpha error of 0.05 with an allowable error of 5% assuming a standard deviation of +7.3 as FIB-4 for diagnostic accuracy of oesophageal varices as per seed article (Ishida K. et al.). Further, a rounded sample size of 80 patients was adequate with a 10% attrition [10].

Study Parameter

FIB-4 index = [Age x AST (IU/L)] ÷ [Platelets (x 10^9) x √ALT(IU/L)]

Statistical Methods Used

The FIB-4 index was calculated using the formula [Age x AST (IU/L)] ÷ [Platelets (x 10^9) x √ALT(IU/L)]. Categorical variables are reported as counts and percentages, while normally distributed data is presented as means with standard deviations. For data with a skewed distribution, medians along with minimum and maximum values are used. To compare two independent groups with normally distributed data, an independent sample t-test was employed, whereas the Mann-Whitney U test was used for non-normally distributed data. For comparing categorical variables between independent groups, either Pearson's chi-square test or Fisher's exact test was used, depending on the data. Receiver Operating Characteristic (ROC) curve analysis was conducted to evaluate the predictive value of the FIB-4 index. The results included AUC values, cut-off points, sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV). A p-value of less than 0.05 was deemed statistically significant.

RESULTS

A total of 80 patients were included in the study. The mean age of the patients was 45.92 years. The highest proportion of patients, 37.5%, was in the 30-39 age group, 80% were male and 20% were female.

The cause of cirrhosis was alcohol consumption in 57.5% of cases, cryptogenic in 25%, and NASH in 17.5%. Among 80 patients, 25% (n = 20) do not have oesophageal varices, while 75% (n = 60) have oesophageal varices, of which 11.25% (n = 9) patients have high-risk oesophageal varices. The various laboratory parameters tested for the patients with chronic liver disease are shown in Table 1.

Table 1: Clinical Characteristics and Laboratory Data in Patients with Liver Cirrhosis

Variables	Mean ± SD	Reference Range
AST (U/L)	78.15 ± 58.61	0 – 35 U/L
ALT (U/L)	44.52 ± 54.34	0 – 40 U/L
Bilirubin (mg/dl)	4.2 ± .93	0.2 - 1.1 mg/dl
INR	2.17 ± .54	< 1.1
Creat. (mg/dl)	1.35 ± .40	Male: 0.6 – 1.5 mg/dl Female: 0.6 – 1.4 mg/dl
Hb (g/dl)	11.04 ± 1.91	Male: 13 – 17 mg/dl Female: 12 – 15 mg/dl
WBC x109/L	10.95 ± 1.42	4.0 – 11.0 x109/L
PLAT x103/µL	120.50 ± 70.37	150 – 400 x103/µL
FIB-4 index	5.80 ± 3.14	*Low Risk < 1.30 Intermediate Risk 1.31-2.67 High Risk >2.68

AST- Aspartate aminotransferase, ALT- Alanine aminotransferase, INR- International Normalised Ratio, Creat.- Creatinine, Hb- Haemoglobin, WBC- White blood cells, PLAT- platelets.*[12]

There was no significant difference in age and sex among the study subjects. AST levels were significantly higher in patients with oesophageal varices compared to those without varices, with $p < 0.05$. Additionally, hemoglobin levels and platelet counts were significantly lower in patients with oesophageal varices. The Fib-4 index was significantly higher in patients with oesophageal varices, with a mean of 7.05 ± 2.58, compared to a mean of 2.05 ± 0.81 in those without varices (Table 2).

Table 2: Laboratory Analysis and Scores in Relation to the Presence of Oesophageal Varices.

Variables	With Varices (n=60) Mean ± SD	Without Varices (n=20) Mean ± SD	P- value
Age	46.35±11.74	44.65±16.32	.614
Sex (M: F)	49:11	10:9	.052
AST (U/L)	88.23 ± 63.11	47.90±25.11	.007
ALT (U/L)	48.80 ± 61.25	31.70 ±19.96	.225
Bilirubin (mg/dl)	4.38 ± .89	3.88±.99	.057
INR	2.20 ± .55	2.06±.48	.318
Creat. (mg/dl)	1.35 ± .40	1.35 ± .402	.951
Hb (g/dl)	10.30±2.43	11.29 ± 1.65	.04
WBC x109/L	11 ± 1.42	10.7±1.42	.537
PLAT x103/µL	95.31 ± 50.25	196.05 ±68.83	.000
FIB-4 index	7.05 ± 2.58	2.05±.81	.000

AST- Aspartate aminotransferase, ALT- Alanine aminotransferase, INR- International Normalised Ratio, Creat.- Creatinine, Hb- Haemoglobin, WBC- White blood cells, PLAT- platelets.

The Fib-4 index was significantly higher in patients with high-risk oesophageal varices, with a mean of 10.88 ± 2.34, compared to a mean of 5.12 ± 0.60 in those without high-risk varices. AST and ALT levels were significantly higher in patients with high-risk varices compared to those without high-risk varices ($p < 0.05$). Platelet counts were also lower in patients with high-risk varices (Table 3).

Table 3: Laboratory Analysis and Scores in Relation to the Presence of High-risk Oesophageal Varices

Variables	With high-risk Varices (n=9) Mean ± SD	Without high-risk Varices (n=51) Mean ± SD	P- value
Age	50.77±13.17	45.30± 12.88	.235
Sex (M: F)	6:3	54:17	.21
AST (U/L)	134.2 ± 109	71.04± 45.28	.002
ALT (U/L)	89.6 ± 106	38.80± 41.78	.007
Bilirubin (mg/dl)	4.8 ± .87	4.18 ± .92	.06
INR	2.17 ± .50	2.17± .54	.949
Creat. (mg/dl)	1.16 ± .31	1.3 ±.41	.122
Hb (g/dl)	10.9 ± 1.9	11.06 ±1.91	.836
WBC x109/L	10.7 ± 1.61	10.97 ±1.40	.664
PLAT x103/µL	70.55 ± 28.53	126.83 ±71.65	.023
FIB-4 index	10.88 ± 2.34	5.1 2± .60	.000

AST- Aspartate aminotransferase, ALT- Alanine aminotransferase, INR- International Normalised Ratio, Creat.- Creatinine, Hb- Haemoglobin, WBC- White blood cells, PLAT- platelets

Among 80 study subjects, the sensitivity, specificity, PPV, and NPV were 96.6%, 75%, 92.06%, and 88.24%, respectively, for the recommended FIB-4 cutoff 3.3 to predict varices (Table 4). The cutoff for Fib-4 index was taken to be 3.3 for diagnosing oesophageal varices, as this cutoff value shows the highest diagnostic accuracy calculated from the AUC (AUC = 0.987 for the 95% confidence interval) of the ROC curve plotted (Figure 1).

Table 4: Performance of Fibrosis-4-index For Prediction of Oesophageal Varices

Characteristics	AUC (95% of CI)	Cutt of	Sensi-tivity	Specifi-city	PPV	NPV
Oesophageal varices (n=60)	.987 (.969-1.000)	3.3	96.6 %	75%	92.06 %	88.24 %

AUC- Area under the curve, CI- Confidence interval, PPV- Positive predictive value, NPV- Negative predictive value

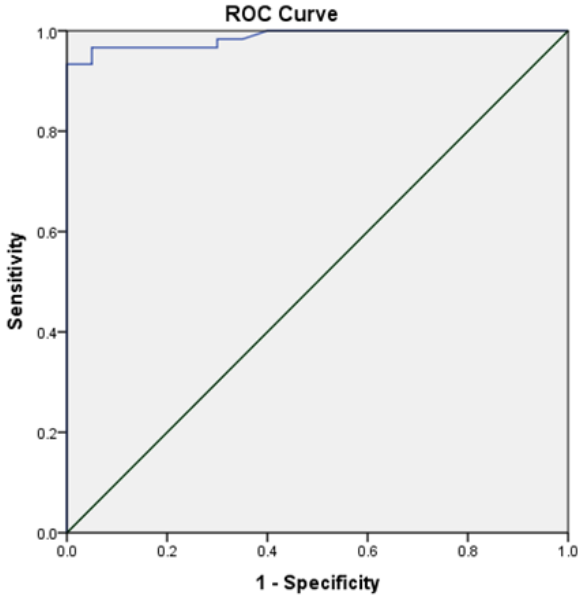

Figure 1 - Diagnostic Accuracy of FIB-4 Index in the Prediction of Oesophageal Varices

DISCUSSION

A total of 80 patients were included in this observational cross-sectional study, comprising 64 males and 16 females with chronic liver diseases, recruited from the OPD and IPD of SMS Medical College, Jaipur. The mean age of the patients was 45.92 years. The highest proportion of patients (37.5%) fell within the 30-39 age group, with a predominance of males. Similar findings were reported by Parate T et al. [13], where the mean age was 49.44 ± 7.67 years and 95.18% of the patients were males. Rajesh et al. [14] reported a mean age of 54.05 ± 11.58 years, with 70 males and 30 females among the patients. The predominance of males is consistent with the existing literature [15].

In our study population, the primary cause of cirrhosis was alcohol consumption, which accounted for 57.5% of cases. Alcohol is a significant contributor to liver cirrhosis [16,17]. This high prevalence of alcohol-related cirrhosis significantly contributes to the development of oesophageal varices, as chronic alcohol intake can lead to severe liver damage and portal hypertension.

Among the 80 patients studied, 75% had oesophageal varices, with 11.25% of these being high-risk cases. The younger mean age in our study, compared to others, likely reflects earlier onset of liver damage due to high alcohol consumption rates. The male predominance seen in our study and others may be due to higher alcohol consumption and risky behaviors traditionally more common in men. This early presentation of oesophageal varices highlights the urgent need for early detection and intervention strategies in younger populations to manage and mitigate the progression of liver disease and its complications.

Liver function parameters revealed that AST levels were significantly higher in patients with oesophageal varices compared to those without, with a p-value > 0.05. Additionally, patients with oesophageal varices

had significantly lower levels of hemoglobin and platelet counts. This is consistent with the previous studies where thrombocytopenia had been linked to portal hypertension due to liver cirrhosis [18,19].

Our results aligned with the study conducted by Rajesh et al. [14], which also found no significant differences in age and sex between the two groups. Unlike our study, their research did not reveal differences in AST levels.

We found that the Fibrosis-4 index was notably higher in patients with oesophageal varices, with a mean of 7.05 ± 2.58, compared to 2.05 ± 0.81 in those without varices. Our results align with those of Rajesh et al.[14], who reported a Fib-4 of 9.22 in patients with varices compared to 4.68 in those without. Similarly, Sami Cifci et al. [8] found a higher Fib-4 index in patients with varices (8.74 vs. 6.29). We also observed that the Fib-4 index was significantly higher in patients with high-risk oesophageal varices, with a mean of 10.88 ± 2.34, compared to a mean of 5.12 ± 0.60 in those without high-risk varices.

In our study, the sensitivity, specificity, PPV, and NPV for the recommended FIB-4 cutoff of 3.3 to predict varices were 96%, 75%, 86.96%, and 88.24%, respectively. Previous studies investigating FIB-4 as a predictor of EV in liver cirrhosis patients have shown similar results (Table 5).

Table 5: Comparison of Our Study With Previous Studies

Author	Cutoff	AUC	Sensitivity	Specificity	NPV
Stefanescu H et al. [20]	3.98	0.62	0.76	0.66	-
Hassan EM et al. [21]	2.8	0.78	0.80	0.54	-
Sebastiani et al. [22]	3.5	0.64	-	-	-
Bleder et al. [23]	3.23	0.66	0.72	0.58	-
Koji et al. [10]	2.78	0.69	0.91	0.39	0.74
Our study	3.3	0.98	0.96	0.75	0.88

AUC- Area under the curve, NPV- Negative predictive value

Limitations

The findings of the study cannot be generalized because of the cross-sectional study design and relatively small sample size. Also, the FIB-4 index is influenced by age and gender, as older patients tend to have higher scores, and it may not be as accurate for females due to differences in liver fibrosis progression. Further research is needed to overcome these shortcomings.

CONCLUSION

In conclusion, our study concluded that the FIB-4 index is a highly reliable predictor of oesophageal varices in patients with liver cirrhosis. Due to its high sensitivity and specificity, the FIB-4 index serves as an effective non-invasive screening tool, particularly valuable in resource-limited settings where access to endoscopy is restricted.

Conflict of Interest

The authors declare that they have no conflict of interest.

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