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Original Research Article

Prediction of esophageal varices and risk of bleeding in liver cirrhosis by aspartate aminotransferase to-platelet ratio index and fibrosis-4 index

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ABSTRACT

Background: Liver cirrhosis is the end-stage for chronic liver disease. During the course of cirrhosis repeated endoscopy is recommended. As this intervention is expensive and often poorly accepted by patients who may refuse further follow up, there is a need for non-invasive methods to predicts the progression of portal hypertension as well as the presence and size of esophageal varices. This study was aimed to assess the value of aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and fibrosis-4 index (FIB-4) for predicting esophageal varices in cirrhotic patients. Objectives of the study were: prediction of esophageal varices and risk of bleeding in liver cirrhosis by APRI, and prediction of esophageal varices and risk of bleeding in liver cirrhosis by FIB-4.
Methods: It was a single centre, observational study in 100 patients of chronic liver disease. Patients were included in the study after applying inclusion and exclusion criteria. Complete blood count (CBC), liver function test (LFT), kidney function test (KFT), SE, viral marker, ultrasonography (USG) whole abdomen, and upper gastrointestinal endoscopy (UGIE) was done for all patients. Child-Pugh-Turcotte (CTP) score was calculated for every patient.
Results: The APRI and FIB-4 shows moderate diagnostic accuracy in predicting the presence of esophageal varices and variceal bleed.
Conclusions: In conclusion, the APRI and FIB-4 shows moderate diagnostic accuracy in predicting the presence of esophageal varices and variceal bleed. They help in starting prophylactic therapy earlier to prevent the bleeding and other complications of varices. Although endoscopy remains the primary modality for diagnosis of esophageal varices but these non-invasive parameters can also play an effective role in conjunction with endoscopy in predicting the presence of esophageal varices.

Keywords: Liver cirrhosis, CLD, APRI, FIB-4, CTP, UGIE

INTRODUCTION

Liver cirrhosis is the end-stage for chronic liver disease and is the leading cause of liver-related death globally.[1] Cirrhosis is frequently compensated. The development of complications of portal hypertension and/or liver dysfunction is decompensated cirrhosis. It is defined by the presence of variceal haemorrhage, ascites, encephalopathy, hepatorenal syndrome, jaundice or hepatocellular carcinoma. The transition from a compensated to a decompensated stage occurs at a rate of 5 to 7% per year.[2] Esophageal variceal bleeding is a life-threatening portal hypertension-related complication in liver cirrhosis.[3] Esophageal varices are present at diagnosis in approximately 50% of cirrhotic patients and the rate of development of new varices and increase in grades of varices is 8% per year.[4] The mortality is 3.4% per year in patients with non-bleeding varices. By comparison, the

mortality rises to 57% per year in patients with variceal bleeding.

Endoscopy is the only means to directly visualize varices which are a consequence of portal hypertension.[5] Current practice guidelines recommend endoscopic screening for the presence of esophageal varices in all patients with cirrhosis. If varices are not present, screening endoscopy should be repeated 2-3 years or sooner if there is evidence of hepatic decompensation.

During the course of cirrhosis repeated course of endoscopy is recommended. As this intervention is expensive and often poorly accepted by patients who may refuse further follow up, there is a need for non-invasive methods to predicts the progression of portal hypertension as well as the presence and size of esophageal varices.

Several studies have recently attempted to identify non-invasive predictors of esophageal varices. They are platelet count, AST–to-ALT ratio, AST-to-platelet ratio index (APRI), Platelet count/ spleen diameter ratio, Lok index, Forn index, Fib-4 and fibro index.[6]

This study was aimed to assess the liver stiffness values for predicting esophageal varices in cirrhotic patients and to assess the value of APRI and FIB-4 for predicting esophageal varices in cirrhotic patients.

Aims and objectives

The present study was conducted with following aims and objectives: prediction of esophageal varices and risk of bleeding in liver cirrhosis by APRI, and prediction of esophageal varices and risk of bleeding in liver cirrhosis by FIB-4.

METHODS

Study design

It was a single centre, Observational study carried out in KPS Post Graduate institute of Medicine, G.S.V.M. Medical College, Kanpur from January 2021 to October 2022.

Ethical approval

Ethical approval was taken by ethics committee (for biomedical health and research), GSVM Medical College, Kanpur, Uttar Pradesh.

Patients

100 patients of chronic liver disease were included in the study after applying inclusion and exclusion criteria. CBC, LFT, KFT, SE, viral marker, USG whole abdomen, UGIE was done for all patients. CTP score was calculated for every patient.

Inclusion criteria

Patients willing to give written signed informed consent to participate in the study, >18 to <75 years of age, of either sex (male/female), alcoholics, cirrhotic patients undergoing screening endoscopy at the time of cirrhosis diagnosis, and patients with a known diagnosis of liver cirrhosis but who had never under gone screening endoscopy for esophageal varices (EV) were included.

Exclusion criteria

Patients with active bleeding, previous endoscopic sclerosis for band ligation of EV, previous surgery of portal hypertension or trans – jugular intrahepatic porto-systemic stent shunt, patients not willing to give consent, pregnancy, and psychiatric illness were excluded.

Statistical analysis

Statistical analysis of the obtained data was performed using Jamovi (v2.3.18) software. P value <0.05 was taken as statistically significant.

RESULTS

Our study population consisted of 100 patients of whom 88 were male and 12 were female. Males constituted about 88% of the study population. Incidence of cirrhosis was maximum in the age group 31-50 years (60%). Over all mean age was 43.78±11.78. Youngest patient in our study was 18 years old and oldest was 75 years. In our study 35 were in the age group 31-40 years and also 35 were in the age group 41-50 years. Males predominated in each of the age group studied.

Among 100 patients studied cause of cirrhosis was found to be alcoholism in 83% followed by HBV+ in 7%, cryptogenic in 6% and HCV+ in 4%. Majority of patients belongs to the platelet count below 1 lakh accounting about 64% and 36% of the study population has the platelet count more than 1 lakh. The mean platelet count (lac/mm^3) in our study was 0.97±0.64.

Viral markers were positive in only 11 patients out of which 7 showed positivity to Hep B and 4 showed positivity to Hep C. Among 100 patients studied 95% patients were found to have varices. Based on endoscopic grading, the grading of the varices in the study population was done. Incidence of grade II and grade III are predominated and were similar 38% in each, however the incidence of grade I varices accounting for 19% and varices were absent in 5% of cases. Patients were grouped according to Child Pugh classification of cirrhosis. Majority of the study group patients belonged to Child Pugh class B (49%) also varices of higher grade belonged to Child Pugh class B.

On correlation of the age of the patients with the grade of varices it did not show any statistical significance by

according to a p=0.619. On correlation of grade of varices with gender, there was no statistical significance associated with gender p=0.366. Our study did not show any statistical significance when presence of HE was correlated with grade of varices p=0.669. In our study the area under the ROC curve (AUROC) for APRI for prediction of EVs is 0.699. At a cut off of APRI >0.9, it predicts varices with a sensitivity of 85.3% and specificity of 60% (Figure 1).

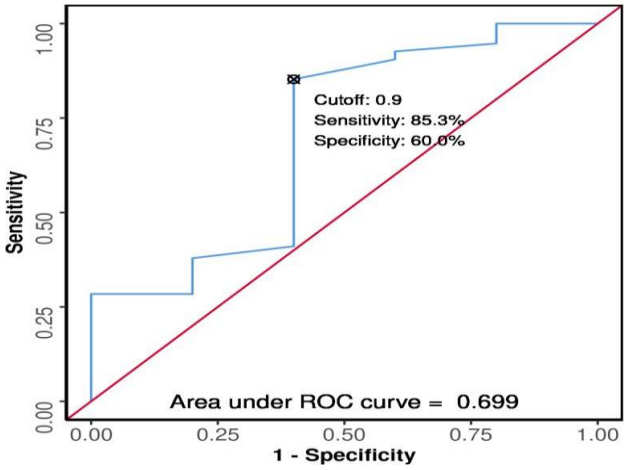

Figure 1: ROC curve analysis showing diagnostic performance of APRI in predicting varices present versus varices absent.

In our study the area under the ROC curve (AUROC) for FIB-4 for prediction of EVs is 0.662 at a cut off of FIB-4 >2.02 it predicts varices with a sensitivity of 92.6% and a specificity of 40% (Figure 2).

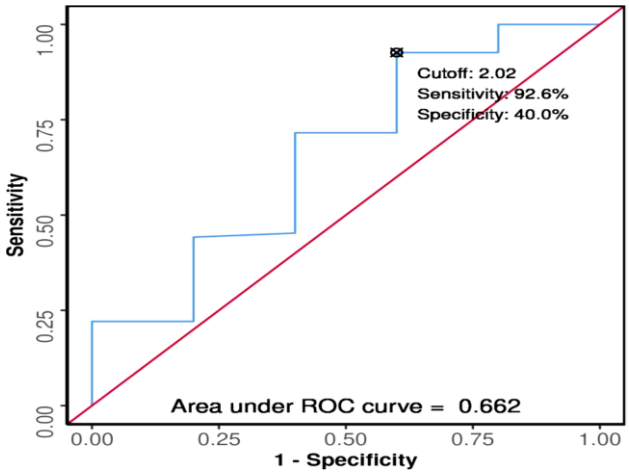

Figure 2: ROC curve analysis showing diagnostic performance of FIB-4 in predicting varices present versus varices absent (n=100).

In our study the area under the ROC curve (AUROC) for APRI for prediction of EV bleed is 0.543. At a cut off of APRI >2.8, it predicts varices with a sensitivity of 42.3% and specificity of 73% (Figure 3).

Table 1: Comparison of the diagnostic performance of various predictors in predicting varices present versus varices absent.

Predictor	AUROC	95%CI	P value	Sn (%)	Sp (%)	PPV (%)	NPV (%)	DA (%)
APRI	0.699	0.403-0.995	0.137	85	60%	98	18	84
FIB-4	0.662	0.371-0.953	0.226	93	40	97	22	90

Table 2: Comparison of the diagnostic performance of various predictors in predicting EV bleed present versus EV bleed absent.

Predictor	AUROC	95%CI	P value	Sn	Sp	PPV	NPV	DA
APRI	0.543	0.405-0.681	0.517	42	73	36	78	65
FIB-4	0.543	0.405-0.681	0.517	42	77	39	79	68

Table 3: Cut-off value of APRI and FIB-4 for prediction of EVs and EV bleed score and AUROC comparing them with other investigators.

Investigators	Cut off value for prediction of EVs	AUROC	Cut off value for prediction of EV bleed	AUROC
APRI				
Our study	>0.9	0.699	>2.8	0.543
Deng et al[7]	>0.87	0.54	>0.85	0.51
Hassan et al[8]	>0.85	0.79	>1.22	0.79
Morishita et al[9]	>1.5	0.68	>1.62	0.67
FIB-4				
Our study	>2.02	0.662	>8.53	0.543
Hassan et al[8]	>2.8	0.8	>3.4	0.81
Sebastiani et al[10]	>3.5	0.64	>4.3	0.63

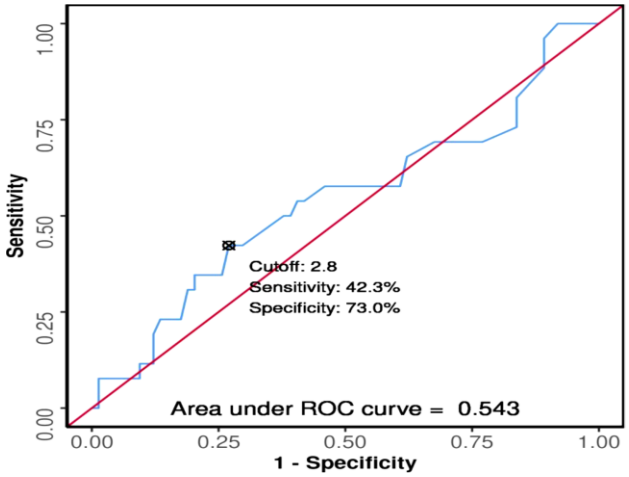

Figure 3: ROC curve analysis showing diagnostic performance of APRI in predicting EV bleed present versus EV bleed absent (n=100).

In our study the area under the ROC curve (AUROC) for FIB-4 for prediction of EV bleed is 0.543 at a cut off of FIB-4 >8.53 it predicts varices with a sensitivity of 42.3% and a specificity of 77% (Figure 4).

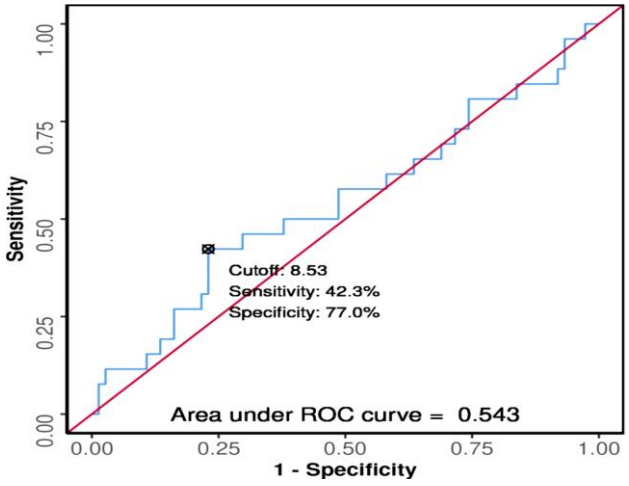

Figure 4: ROC curve analysis showing diagnostic performance of FIB-4 in predicting EV bleed present versus EV bleed absent (n=100).

DISCUSSION

In 2007, the American Association for the Study of Liver Diseases stated that screening esophagogastro-duodenoscopy (EGD) for the diagnosis of esophageal and gastric varices is recommended when the diagnosis of cirrhosis of liver is made according to the AASLD guidelines. Baveno18 IV consensus conference on portal hypertension recommended that all cirrhotic patients should be screened for the presence of esophageal varices when liver cirrhosis is diagnosed (EASL).

Therefore, there is a particular need for a non-invasive predictor for the presence of EVs to ease the medical, social and economic burden of the disease. Many previous studies have documented good predictive value of various non- endoscopic variables for the presence or absence of varices. In our study we considered only simple, commonly available, reproducible parameters.

Our study sample consisted of 100 patients of whom 88 were male and 12 were female. Males constituted about 88% of the study population. Incidence of cirrhosis was maximum in the age group 31-50 years (60%). Over all mean age was 43.78±11.78. However, mean age was 51 (range 20-80) in study by Baig et al, mean age was 42 (range 17-73) in a study by Cherian et al and in study by Sarangapani's et al median age was 45 (range 18-74).[11,12] Youngest patient in our study was 18 years old and oldest was 75 years. In our study 35 were in the age group 31-40 years and also 35 were in the age group 41-50 years. Males predominated in each of the age group studied.

Among 100 patients studied cause of cirrhosis was found to be alcoholism in 83% followed by HBV+ in 7%, cryptogenic in 6% and HCV+ in 4%.

This was also demonstrated by Sarangapani's study in which the prevalence of cirrhosis secondary to alcohol was over 50% and the specificity remained at 83%.[12]

Majority of patients belongs to the platelet count below 1 lac accounting about 64% and 36% of the study population has the platelet count more than 1 lac. The mean platelet count (lac/mm^3) in our study was 0.97±0.64.

Khuram et al (200 patients) found EV in 146 with 121 having thrombocytopenia (94.5%).[13] Zaman et al reported that groups without varices had a higher mean platelet count (mean platelet count 1,28,500) than the group with small varices (mean platelet count, 1,07,800) and platelet count of <90,000 increased the risk of having EV by nearly 2.5-fold.[14] The limitations of the study were retrospective analysis and inclusion of liver transplant patients only.

Viral markers were positive in only 11 patients out of which 7 showed positivity to Hep B and 4 showed positivity to Hep C. Among 100 patients studied 95% patients were found to have varices. Based on endoscopic grading, the grading of the varices in the study population was done. Incidence of grade II and grade III are predominated and were similar 38% in each, however the incidence of grade I varices accounting for 19% and varices were absent in 5% of cases.

Patients were grouped according to Child Pugh classification of cirrhosis. Majority of the study group patients belonged to Child Pugh class B (49%) also varices of higher grade belonged to Child Pugh class B.

On correlation of the age of the patients with the grade of varices it did not show any statistical significance by

according to a p=0.619. On correlation of grade of varices with gender, there was no statistical significance associated with gender p=0.366.

Our study did not show any statistical significance when presence of HE was correlated with grade of varices p=0.669.

Castera proposed the cut off of 1.3 for APRI as a predictor of EV, where they found sensitivity 68%, specificity 64%, PPV 51%, NPP 78% which is dissimilar from out study.[15] That study was only a hepatitis C positive patients and Child Pugh A class were included. In our study all etiologies and all grade including compensated and decompensated cirrhosis were included.

Tafarel studied at a higher cut off point (1.64) and found it is significant.[16] Here in this study at a cut off of APRI >0.9 it predicts varices with a sensitivity of 85% and specificity of 60% with AUROC of 0.699.

Wang proposed lower cut off value 0.77 as the optimal one to predict EVs with a better sensitivity 71% and NPV 79.[17]

Shah et al have shown that a FIB4 cut off 1.3 can identify patients without advanced fibrosis.[18] In our study the area under the ROC curve (AUROC) for FIB 4 predicting EVs was 0.662. At a cut off of FIB4 >2.02 it predicts varices with a sensitivity of 93% and a specificity of 40%.

Limitations

Limitation of our study was single centered with small study population. Further multicentric study with large sample size with prospective cohort studies are needed to validate its efficacy.

CONCLUSION

In conclusion, the APRI and FIB-4 shows moderate diagnostic accuracy in predicting the presence of esophageal varices and variceal bleed. The parameters mentioned above play effective role in predicting esophageal varices non-invasively and would help in starting prophylactic therapy earlier to prevent the bleeding and other complications of varices. Although endoscopy remains the primary modality for diagnosis of esophageal varices.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980- 2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392(10159):1736-88.
2. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006;44(1):217-31.
3. Biecker E. Portal hypertension and gastrointestinal bleeding: diagnosis, prevention and management. World J Gastroenterol. 2013;19(31):5035-50.
4. Groszmann RJ, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med. 2005;353(21):2254-61.
5. Par G, Trosits A, Pakidi F, Szabo I, Czimer J. Transient elastography as a predictor of esophageal varices in patients with liver cirrhosis. J Orv Hetil 2014;155(7):270-6.
6. Tempesta D, Fattovich G, Laurent C, Halfon P. Prediction of esophageal varices in hepatic cirrhosis by simple non-invasive markers: Results of a multicenter, large scale study. J Hepatol. 2010;53:630-8.
7. Deng H, Qi X, Peng Y. Diagnostic Accuracy of APRI, AAR, FIB-4, FI, and King Scores for Diagnosis of Esophageal Varices in Liver Cirrhosis: A Retrospective Study. Med Sci Monit. 2015;21:3961-77.
8. Hassan EA, El-Rehim ASEA, Sayed ZEA, Ashmawy AM, Kholef EFM, Sabry A, et al. Noninvasive Fibrosis Scores as Prognostic Markers for Varices Needing Treatment in Advanced Compensated Liver Cirrhosis. Open J Gastroenterol. 2017;7:230-42.
9. Morishita N, Hiramatsu N, Oze T, Harada N, Yamada R, Miyazaki M, et al. Liver stiffness measurement by acoustic radiation force impulse is useful in predicting the presence of esophageal varices or highrisk esophageal varices among patients with HCV-related cirrhosis. J Gastroenterol. 2014;49(7):1175-82.
10. Sebastiani G, Tempesta D, Fattovich G, Laurent C, Halfon P. Prediction of esophageal varices in hepatic cirrhosis by simple non-invasive markers: Results of a multicenter, large scale study. J Hepatol. 2010 ;53:630-8.
11. Baig, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003;38(2):518-26.
12. Sarangapani A, Shanmugam C, Kalyanasundaram M, Rangachari B, Thangavelu P, Subbarayan JK. Non-invasive prediction of large esophageal varices in chronic liver disease patients. Saudi J Gastroenterol. 2010;16(1):38-42.
13. Khuram M, Stefanescu H, Grigorescu M, Lupsor M. A new and simple algorithm for the noninvasive assessment of esophageal varices in cirrhotic patients using serum fibrosis markers and transient elastography. J Gastrointestin Liver Dis. 2011;20(1):57-64.

14. Zaman A, Flamm SL, Gordon FD, Chopra S. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. Am J Gastroenterol. 1998;93(1):44-8.
15. Castera L, Vergniol J, Fouchar J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of ransientelastography, fibrotest, APRI and liver biopsy for assessment of fibrosis in chronic hepatitis C. Gastroenterology. 2013;128:343-50.
16. Tafarel JR, Tolentino LH, Correa LM, Bonita DR, Matin FS. Prediction of esophageal varices in hepatic cirrhosis by noninvasive markers. Eur J Gastroenterol Hepatol. 2011;23:754-8.
17. Wang JH, Cruah SK, Lu SN, Hung CH, Chen CH. Transient elastography and simple blood markers in the diagnosis of esophageal varices for compensated patients with hepatitis B virus related cirrhosis. J Gastroenterol Hepatol. 2012;27:1213-8.
18. Shah VH, Kamath. Portal hypertension and variceal bleeding. In: Feldman M, Friedman LS & Brandt LJ (eds). Sleisenger and Fordtrans Gastrointestinal and Liver Disease. 10th ed. Philadelpia, Elsevier. 2016.

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