

## NON-INVASIVE MARKERS AS PREDICTORS OF ESOPHAGEAL VARICES IN CIRRHOSIS

### Gastroenterology

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### ABSTRACT

This study aims to assess the utility of non-invasive markers like aspartate and platelet ratio index (APRI), aspartate amino transferase- alanine amino transferase ratio (AAR) and FIB-4 in predicting presence of esophageal varices in cirrhosis. This was an observational cross sectional study conducted in Kilpauk Medical College over a period of 1 year. A total of 65 patients were included and divided into two groups as with or without esophageal varices. Of the 65 patients, 48 had esophageal varices and 17 had no varices. APRI and FIB4 were comparatively more in the varices group, but the difference was not statistically significant (p value: 0.064 and 0.084 respectively). In the ROC curve of esophageal varices, the AUC values of APRI, AAR and FIB-4 were 0.719, 0.409 and 0.683 respectively. APRI and FIB-4 were found to have low to moderate diagnostic accuracy in predicting esophageal varices.

### KEYWORDS

Cirrhosis, Esophageal varices, Non-invasive markers

### INTRODUCTION

Cirrhosis is the final pathway of various chronic liver diseases. It is characterized histologically by development of diffuse hepatic fibrosis with replacement of the normal liver architecture by nodules. It leads to portal hypertension and end stage liver disease.<sup>1</sup>

One of the fatal complications of portal hypertension is the development of esophageal varices and variceal bleeding due to the rupture of varices.<sup>2</sup> Earlier, the mortality rate due to esophageal variceal bleeding was 50%.<sup>3</sup> Now with advances in medical science, mortality has come down. But the 6 week mortality rate is still as high as 20%.<sup>4</sup>

Upper gastrointestinal endoscopy is the gold standard diagnostic and screening tool for esophageal varices.<sup>5</sup> But, it is a semi-invasive investigation requiring expertise and has its own risk. As a result, non invasive predictors of esophageal varices has gained attention and became a research focus to reduce the pain and economical burden of patients to some extent.

World Health Organisation has recommended APRI and FIB-4 for evaluating hepatic fibrosis.<sup>6</sup> Very few researchers have applied it in prediction of cirrhosis and esophageal varices.<sup>2</sup> Hence, we decided to conduct a study to know the predictive value of Aspartate amino transferase to platelet ratio index (APRI), Aspartate aminotransferase to Alanine aminotransferase ratio (AAR) and Fibrosis-4 index (FIB-4) in esophageal varices.

### METHODS:

An observational cross sectional study was conducted in Department of Digestive Health and Disease, attached to Kilpauk Medical College over a period of 1 year from January 2019 to December 2019.

#### Inclusion criteria

Total 65 patients above the age of 18 years with diagnosis of cirrhosis of any etiology were included

#### Exclusion criteria

Patients who had undergone endoscopic banding or sclerotherapy  
Patients who were on beta blockers

Liver cirrhosis was diagnosed based on clinical data, laboratory test and liver imaging. All the patients were subjected to clinical examination, biochemical investigations, ultrasound abdomen and upper Gastrointestinal endoscopy. Informed written consent was taken from all the participants included in the study. Study population was divided into two groups as with or without esophageal varices. Laboratory data included hemoglobin, platelet count, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels,

serum albumin, total serum bilirubin, prothrombin time with international normalized ratio (INR) and serum creatinine. All patients were classified according to the Child-Turcotte-Pugh (CTP) class. Model for end-stage liver disease (MELD), aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (AAR), AST to platelet ratio index (APRI), fibrosis-4-index (FIB-4) were measured for all participants.

### STATISTICAL ANALYSIS

The collected data was entered in MS Excel and analysed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & standard deviation were used for continuous variables. To find the significant difference between the bivariate samples in independent groups the Unpaired sample t-test was used. For the multivariate analysis the one way ANOVA with Tukey's Post-Hoc test was used. Chi square or Fischer exact test was applied for finding significance in qualitative data. The Receiver Operating Curve [ROC] was used to assess the efficacy of the tools with sensitivity and Specificity. In all the cases, the probability value < 0.05 was considered as statistically significant.

### RESULTS

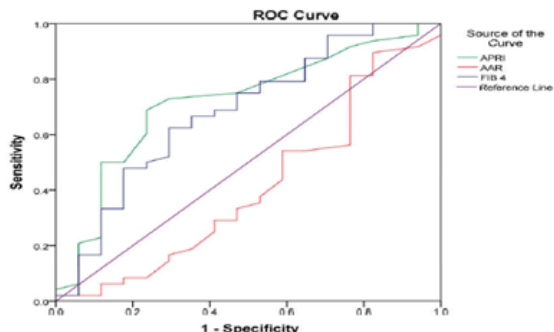
Total of 65 patients were included in the study of which 56 were males (86.2%) and 9 (13.8%) were females. The mean age was 49.76 ± 9.95 years in patients without varices and 51.94 ± 9.04 years in patients with varices. Out of 65 patients of cirrhosis included in the study, 48 patients were detected to have esophageal varices on upper GI endoscopy. Sixteen (33.3%) of these patients had grade III varices, 13 (27.1%) had grade II varices and 19 (39.6%) had grade I varices.

**Table 1: Comparison of non-invasive parameters in study population**

| Variable        | Without varices (N=17) (Mean±SD) | With varices (N=48) (Mean±SD) | P value |
|-----------------|----------------------------------|-------------------------------|---------|
| Platelet count  | 2.35 ± 0.84                      | 1.52 ± 0.62                   | 0.001   |
| PT/INR          | 1.31 ± 0.36                      | 1.57 ± 0.36                   | 0.014   |
| AST             | 78.35 ± 39.71                    | 91.83 ± 51.69                 | 0.333   |
| ALT             | 34.59 ± 20.17                    | 45.58 ± 24.97                 | 0.107   |
| Total bilirubin | 6.6 ± 6.73                       | 5.9 ± 5.73                    | 0.681   |
| Albumin         | 2.43 ± 0.64                      | 3.01 ± 0.51                   | 0.001   |
| MELD score      | 18.52 ± 6.68                     | 19.14 ± 5.89                  | 0.722   |
| FIB 4 score     | 4.07 ± 2.85                      | 5.38 ± 2.57                   | 0.084   |
| APRI            | 1.07 ± 0.7                       | 1.77 ± 1.46                   | 0.064   |
| AAR             | 2.64 ± 1.25                      | 2.25 ± 1.02                   | 0.209   |

The mean platelet count among the patients without varices was 2,35,000/mm<sup>3</sup> and it was 1,52,000/mm<sup>3</sup> among the patients with

varices with statistically significant difference among the 2 groups in platelet count (p value 0.05). There was also no statistically significant difference found in PT/INR, AST and ALT among the patients with and without varices (Table 1). Even though, APRI and FIB4 were comparatively more in the varices group, difference was not statistically significant (p value: 0.064 and 0.084 respectively). AAR was found to be less in varices group and the difference was statistically insignificant. In the ROC curve of esophageal varices, the AUC values of APRI, AAR and FIB-4 were 0.719, 0.409 and 0.683 respectively. At an optimal cut off of 1.05, APRI had a sensitivity of 72.9% and specificity of 70.6%. At an optimal cut off of 4.44, FIB-4 had a sensitivity of 64.4% and specificity of 64.7%.



**Figure 1: ROC curve of APRI, FIB-4 and AAR in predicting esophageal varices**

## DISCUSSION

Since variceal bleeding is a lethal complication of cirrhosis, many studies are going on to find out “ideal” noninvasive predictors for esophageal varices.<sup>7</sup> Ideal non-invasive predictors means the investigation should be economical, easier to obtain, highly sensitive and specific. Hence, clinicians can bring down the number of screening endoscopy and avoid the risks of an invasive procedure. Such non-invasive predictors are especially necessary in developing countries due to shortage of endoscopy and limited resources. Therefore, we conducted a study to know whether APRI, AAR and FIB-4 can foretell the presence of esophageal varices in cirrhotic patients.

In the present study, mean age of population with varices was  $51.94 \pm 9$  and without varices was  $49.77 \pm 9$ . Of the 65 patients, 48 had esophageal varices and 17 had no varices. There was significant difference in platelet count between two groups (p value 0.005). Even though, APRI and FIB4 were comparatively more in the varices group, difference was not statistically significant (p value: 0.064 and 0.084 respectively). AAR was found to be less in varices group and the difference was statistically insignificant. In the ROC curve of esophageal varices, the AUC values of APRI, AAR and FIB-4 were 0.719, 0.409 and 0.683 respectively. At an optimal cut off of 1.05, APRI had a sensitivity of 72.9% and specificity of 70.6%. At an optimal cut off of 4.44, FIB-4 had a sensitivity of 64.4% and specificity of 64.7%.

In the study done by Kraja B et al, there was noteworthy association between esophageal varices and FIB-4 score (OR = 1.18 for one unit increment; 95%CI: 1.01-1.38). But there was no statistically noteworthy relation with the other non-invasive markers (APRI, AAR).<sup>7</sup>

The systematic review and meta analysis done by Han D et al showed that APRI, AAR and FIB-4 has low to moderate diagnostic accuracy in predicting esophageal varices and among them FIB-4 has better diagnostic accuracy.<sup>8</sup>

A study done by Akshatha S et al revealed that the non-invasive markers such as platelet count, portal vein diameter, FIB 4 score, APRI and AST/ALT ratio have poor predictive value for esophageal varices.<sup>9</sup>

In the present study, APRI and FIB-4 were found to be reasonably good predictors of esophageal varices. AAR had poor predictive value for esophageal varices. Among the three, APRI was found to have highest predictive value for esophageal varices.

The limitation of present study is small sample size. This study needs to be done on a larger group of patients for further confirming the results.

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## CONCLUSION

APRI and FIB-4 has low to moderate diagnostic accuracy in predicting the presence of varices. Among them, APRI has better diagnostic accuracy. Since the diagnostic accuracy is low to moderate, they cannot act as substitute for upper gastrointestinal endoscopy as screening and diagnostic tool in esophageal varices. Further studies with huge sample size are required to establish these findings and to look into the predictive value of non-invasive biomarkers.

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