



Platelet Count/Spleen Diameter Ratio and AST/ALT Ratio as Non-invasive Parameters for the Detection of Esophageal Varices in Patients with Cirrhosis

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ABSTRACT

Esophageal varices in liver cirrhosis is a major complication increasing its morbidity and mortality. Prevalence of esophageal varices in liver cirrhosis range from 60-80 %. Patients with cirrhosis should be screened for varices with esophageal endoscopy. Endoscopy is an invasive procedure and also may not be affordable for ordinary people in developing countries. This study aims to find out diagnostic efficacy of non invasive marker for detecting esophageal varices.

Materials and Methods: *It is a Diagnostic test evaluation study of 1 year duration conducted in 140 cirrhotic patients admitted on Medicine and Gastroenterology ward in a tertiary care centre. Data collected and analysed using SPSS. ROC curve was drawn with different cut offs for Platelet count/Spleen thickness and AST/ALT ratio.*

Result: *PLC/ BPD ratio have sensitivity 74 % and specificity 88% which is statistically significant with a p value <.001. This ratio have a cut off value 919 with area under ROC curve 0.908 which denotes a good test. AST/ALT ratio have sensitivity 74% specificity 82 % which is statistically significant with a p value <.001 and the ratio have a cut off value 1.30 with area under ROC curve 0.794*

Conclusion: *Platelet count/spleen diameter ratio and AST/ALT ratio may be used as non invasive marker for esophageal varices in cirrhotic patients*

Keywords: *Esophageal varices, Endoscopy, Cirrhosis, Platelet count, spleen diameter, AST, ALT.*

INTRODUCTION

Liver Cirrhosis contributes significantly to global health burden. Liver Cirrhosis is a major cause for morbidity and mortality in underdeveloped countries, owing to unawareness, inadequate facilities and financial implication related to the disease. The latest WHO data published in May 2014 indicate that liver disease deaths in India accounts for 2.44% of total deaths. Portal

hypertension and esophageal varices (EVs) are common major complications of liver cirrhosis, occurring in approximately 24% to 80% of cases, with an extremely high mortality rate^[1-3]. Others are ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, portal hypertensive gastropathy, infection, hepato renal syndrome, hepatocellular carcinoma.

The prevalence of esophageal varices in patients with liver cirrhosis may range from 60% to 80%, and the reported mortality from variceal bleeding ranges from 17% to 57%^[4-7]. Therefore, the prevention of variceal bleeding is an important goal in management patients with liver cirrhosis.

The 1996 the American Association for the Study of Liver Disease (AASLD) single topic symposium recommended that cirrhotic patients should be screened for the presence of EV when portal hypertension is diagnosed^[8]. Similarly, the Baveno III Consensus Conference on portal hypertension recommended that all cirrhotic patients should be screened for the presence of EV when liver cirrhosis is diagnosed^[9]. Other groups suggest follow up endoscopy at 2–3 year intervals in patients without varices and at 1–2 year intervals in patients with small varices so as to evaluate the development or progression of this feature^[10]. Primary prophylaxis with universal endoscopic screening of for EVs is recommended in conjunction with in patients who are at high-risk of variceal bleeding^[11,12]. This screening is invasive, and many patients may not have varices, rendering this method cost-ineffective. Thus, noninvasive diagnosis of portal hypertension may be useful^[2]. Recently, several studies have attempted to identify the variables that can noninvasively predict the presence of EVs (including large ones), examining various biochemical, clinical, and ultrasonographic parameters alone or in combination, with promising results^[13-16]. Overall, the most common result of these studies was that parameters directly or indirectly linked to portal hypertension, such as splenomegaly and decreased platelet count, were predictors of the presence of EV. On the other hand, the presence of splenomegaly in cirrhotic patients is likely the result of vascular disturbances that are mainly related to portal hypertension^[17] and the decrease in platelet count which most likely depends on hypersplenism caused by portal hypertension.

Most such variables, however, have several limitations, which has hindered the wide

application of these results. Early studies were retrospective and were performed in a specific subgroup of patients—eg. patients on a wait list for liver transplantation^[15,18-22].

In patients with chronic liver disease, thrombocytopenia is due primarily to portal Hypertension^[23], thrombocytopenia can depend on other factors, such as shortened mean platelet lifetime, decreased thrombopoietin production, and the myelotoxic effects of alcohol or hepatitis viruses^[24].

Moreover, in previous studies, there has been a lack in uniformity in the classification and diagnosis of EVs^[15,18-22], in which EVs were not categorized by a single endoscopist or in the same endoscopy unit. Moreover, their focus on patients with large EVs might have led to the omission of an important subset of patients with less severe disease who required medical counseling. Thus, the analysis of the presence or absence of EVs might prevent data from being misinterpreted and allow results to be generalized^[23]. The platelet count: spleen diameter ratio, proposed by Giannini *et al.*^[23], appears to be one of the best noninvasive predictors of EVs that have emerged^[25]. There have been attempts to associate various biochemical markers to assess the presence of esophageal varices. Levels of Aspartate Transaminase (AST) and Alanine Transaminase (ALT) being the more commonly used. With progression of chronic liver disease (CLD), there is derangement of liver enzyme values, with a rise in AST and ALT, with AST>ALT.

If non-invasive tests can predict the presence of esophageal varices, then the use of endoscopy can be limited to patients identified to be at risk of varices. With this in mind, in this study we used the platelet count/spleen diameter ratio and AST/ALT as a parameter for detecting EV.

All the patients who have undergone EVL should be periodically monitored with Hepatic Venous Pressure Gradient (HVPG). But in our resource limited set up HVPG monitoring which is an invasive procedure is not feasible. So, this study aims to find out whether the platelet count/spleen

diameter and AST/ALT ratio can be used as a non invasive parameter to assess esophageal variceal grade and further to look whether it can predict the need for EVL or the patient has high risk of re-bleeding.

Aim of the study to identify clinical, biochemical and radiological parameters which might non-invasively predict the presence of esophageal varices and risk of bleeding in patients with liver cirrhosis.

RELEVANCE

Esophageal variceal bleed is one of the major complication in liver cirrhosis increasing its morbidity and mortality. Esophageal endoscopy is mandatory for all cirrhotic patients both for therapeutic and prophylactic purpose. It is an invasive method, requiring expert hands and not cost effective. This study is an attempt to identify the clinical, biochemical, and ultrasonographic parameters associated with the presence of Esophageal Varices, mainly Platelet count/Spleen diameter ratio and AST/ALT ratio, which is cost effective and simple.

MATERIALS AND METHODS

This study is a Diagnostic test evaluation of patients having cirrhosis with portal hypertension. Patients are selected according to inclusion & exclusion criteria who are admitted in Medicine and Gastroenterology wards. The diagnosis of cirrhosis is by clinical history, physical examination (jaundice, signs of CLD), laboratory investigations (LFT abnormalities), imaging with USG (nodular liver and coarse echotexture). Liver biopsy is not necessary. The diagnosis of portal hypertension is by ascites, splenomegaly, USG abdomen showing collaterals around gastro-esophageal junction & splenic hilum, splenomegaly, dilated portal vein >12mm, dilated splenic vein >10mm and demonstration of esophageal varices by Esophageal endoscopy. The CBC which includes platelet count is done in our clinical pathology lab by means of the Automated cell counter (SYSMEX KX21 3 part

hematological autoanalyser.). EDTA blood sample is placed in the cell counter and blood is passed through aperture tube along with a diluting electrolyte fluid. This is passed through an electrical field and the cell count and volumes are measured using impedance measurement principle. USG abdomen will be done in Radiodiagnosis department using GE Logiq Pro machine with 3.5 megaHz curvilinear probe. The maximum bipolar diameter (in mm) of spleen will be assessed using this probe. The grade of varices will be assessed with Esophageal endoscopy using Olympus flexible video endoscope. This was done in the Gastroenterology department. The classification of esophageal varices is based on the endoscopic appearance. The classification system is given below

GRADE ENDOSCOPIC APPEARANCE

- 0 Absent
- 1 Small straight varices not disappearing on insufflation
- 2 Medium varices occupying less than one third of the lumen
- 3 Large varices occupying more than one third of the lumen

Liver function tests were done using Transasia XL 300 Clinical Chemistry analyzer. Bilirubin was measured by the Diazo reaction. AST and ALT by ultra-violet kinetic method, ALP by PNPP kinetic method and Total Protein and Serum Albumin by Biuret and BCG methods respectively. All these investigations are done free of cost in this institution. Platelet count/spleen diameter ratio is calculated by dividing the platelet number/mm³ by the maximum spleen bipolar diameter in millimeter as estimated by abdominal ultrasound. AST/ALT ratio is also calculated. With further statistical analysis the usefulness of these ratios as predictive score for Esophageal varices will be estimated.

The study design is a diagnostic test evaluation. A detailed history was taken, physical examination performed and baseline investigations noted using a structured proforma. Laboratory investigations

as done routinely during the evaluation of the patient were noted.

The data were analyzed using appropriate statistical methods to determine the presence of any correlation of the Platelet count with Spleen size in the various etiological groups.

Study design: Diagnostic test evaluation

Study Period: 1/11/2015 to 31/10/2016

Sample size: 140 cases.

Inclusion Criteria

All diagnosed cases of cirrhosis with portal hypertension admitted in medical and gastroenterology wards during the study period. The etiologies of cirrhosis includes alcoholic cirrhosis ,HBV, HCV, Others (Wilson's disease, hemochromatosis, Alpha1 antitrypsin deficiency, Autoimmune hepatitis, and Non-alcoholic steatohepatitis, Biliary cirrhosis, Cardiac cirrhosis& Cryptogenic cirrhosis.)

Exclusion Criteria:

1. All patients with other quantitative platelet abnormalities & disorders like ITP, Leptospirosis, Dengue fever, Hematological malignancies.
2. Other causes of splenomegaly-myelofibrosis, lymphoma, IMN, malaria and EHPVO.
3. Patients<12 yrs 40
4. Patients suffering from acute liver failure
5. Non-cirrhotic portal hypertension
6. Hemodynamically compromised patients
7. Patients who had previously undergone sclerosis or band ligation of EV, transjugular intrahepatic portosystemic stent shunt
8. Patients taking drugs for primary prophylaxis of variceal bleeding
9. Those who do not consent to the study.

RESULTS

Total 140 patients were included in the study. The following were the observations.

Fig No.1: Sex distribution

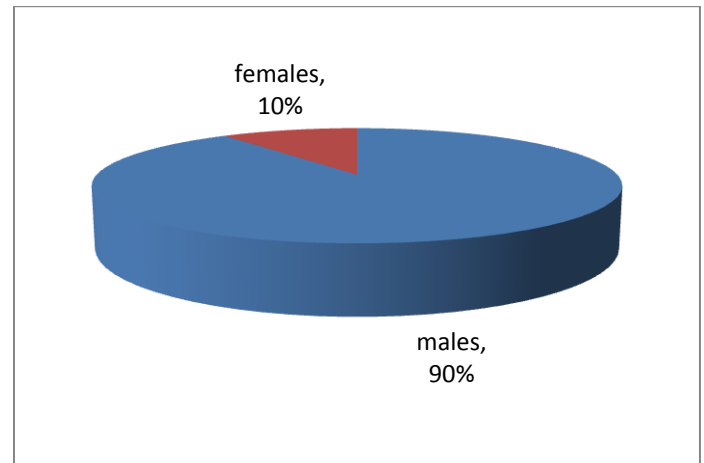


Fig No.2: Age group

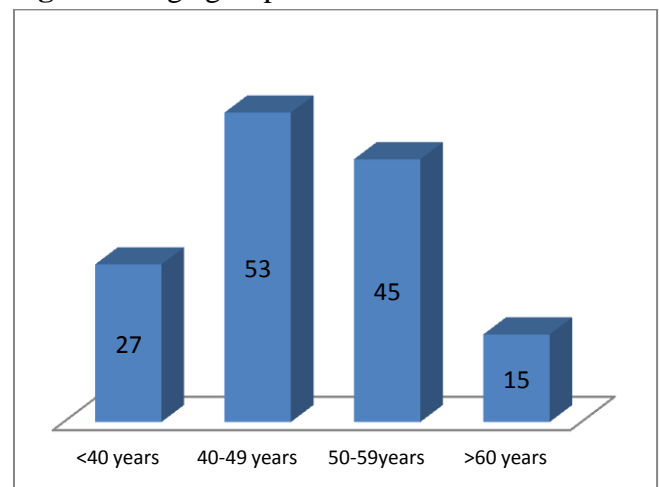


Fig No.3: Presenting complaint

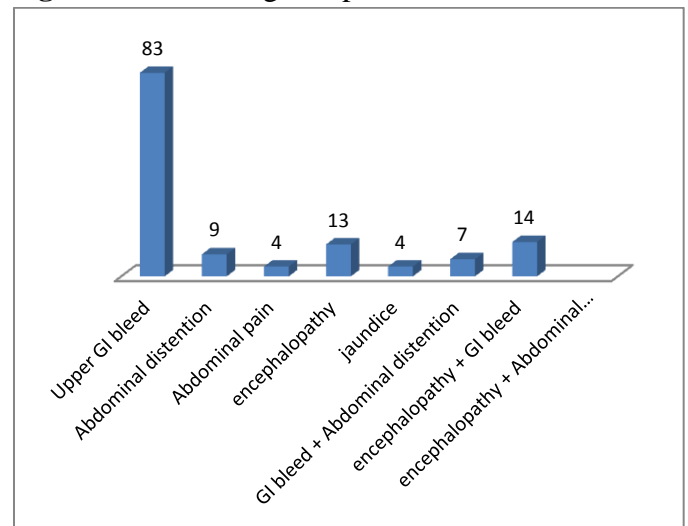


Fig no. 4: Presence of upper GI bleed

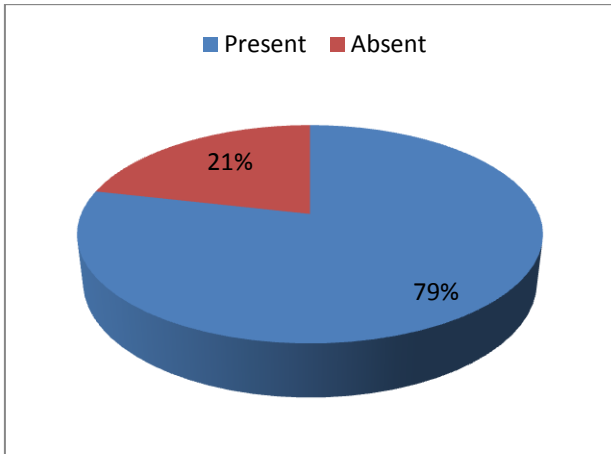


Fig No.7: Prevalence of Portal hypertensive gastropathy (PHG)

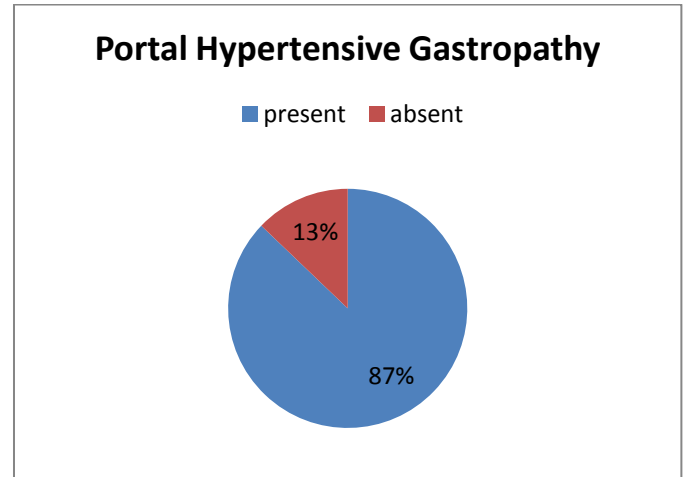


Fig No.5: Comorbidities

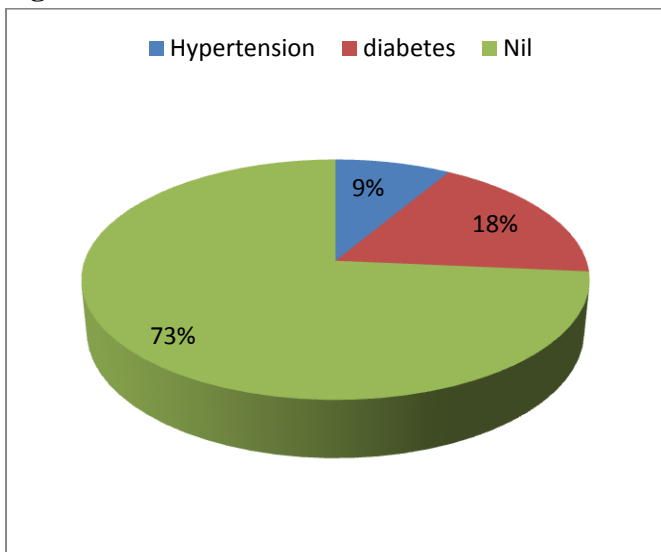


Fig No. 8: Variceal grading

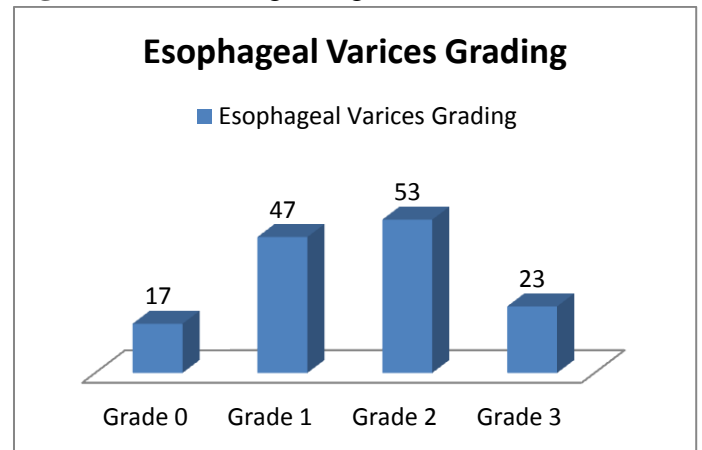


Fig No.6: Etiology of Chronic liver disease

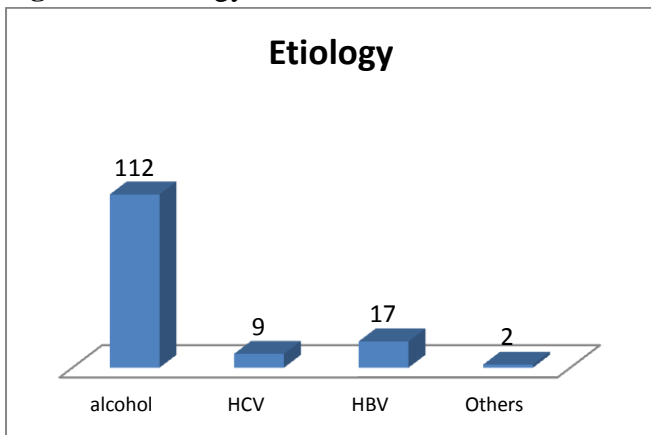
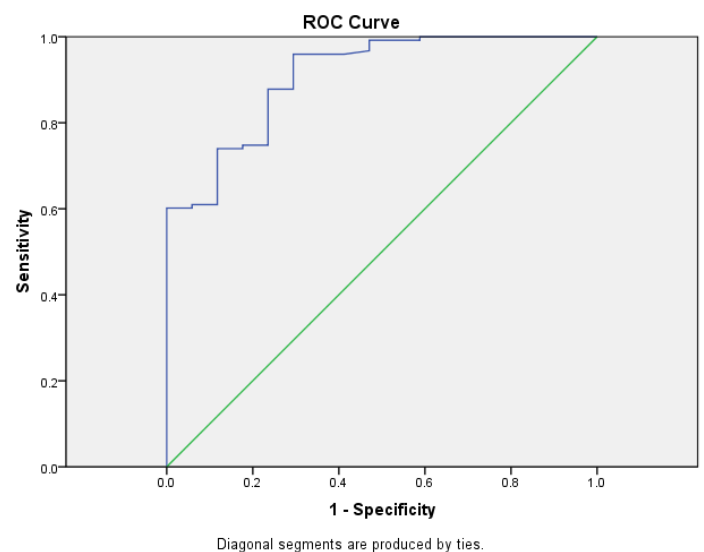


Fig no. 9: Receiver operating characteristics curve showing PLC/ BPD ratio

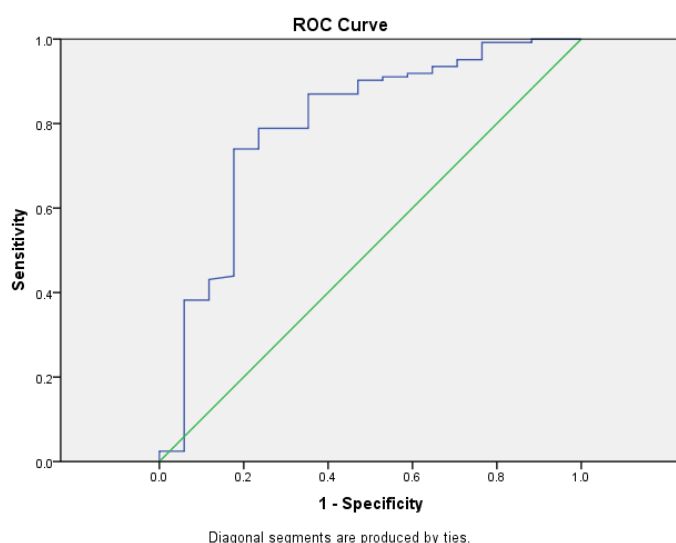


ROC curve showing PLC/ BPD ratio with area under curve 0.908 cut off value 919 with sensitivity 74 % specificity 88 %

Variable : PLC/BPD			Test	Result
Area	Std. Error ^a	Asymptotic Sig ^b	Asymptotic 95% Confidence Interval	
			Lower bound	Upper bound
.908	.036	.000	.839	.978

TEST	
STATISTICS	PLC/BPD
Mann – whitney U	191.500
Wilcoxon W	7817.500
Z	-5.448
Asym. Sig (2-tailed)	.000

Fig No.10: Receiver operating characteristics curve showing AST/ALT ratio



ROC curve showing AST/AST ratio with area under curve 0.794 cut off value 1.30 with sensitivity 74% specificity 82 %

Test Result Variable : AST/ALT				
Area	Std. Error ^a	Asymptotic Sig ^b	Asymptotic 95% Confidence Interval	
			Lower bound	Upper bound
.794	.066	.000	.665	.923

TEST	
STATISTICS	PST/ALT
Mann – whitney U	430.500
Wilcoxon W	583.500
Z	-3.924
Asym. Sig (2-tailed)	.000

DISCUSSION

In this study conducted, a total of 140 patients were included those who have satisfied the inclusion criteria.

AGE AND GENDER DISTRIBUTION

These patients were grouped into different age groups .Of these 37.9% of the patients were in the 40-49 age group and 32.1% of patients were in the 50-59 age group. Majority of study population was between 40-59 years of age group (70%). 90% of patients were males and the rest females constituting only a minor fraction.

PRESENTING COMPLAINT

The major presenting complaint was upper gastrointestinal bleed (78.6%) with or without other complaints. Remaining 22.4% patients presented with abdominal distention, abdominal pain, hepatic encephalopathy, jaundice. Upper gastrointestinal bleed was the only complaint in about 59.3%. In a population based study endoscopy was performed in 241 patients who presented with upper GI bleed and diagnoses were: peptic ulcer 61.6%, mucosal erosive disease 14.3%, varices 6.2%, miscellaneous 9.7%, and unknown 8.1%.

DISTRIBUTION OF COMORBIDITIES

There were no comorbidities in 103 individuals, 25 had diabetes mellitus and 12 had hypertension.

ETIOLOGY

On analyzing the etiology the major etiological factor was alcohol which was present in 80% of the patients. 12.1% had HBV infection and 6.4% had HCV infection as their causative factor for their chronic liver disease. Remaining 1.4% constituted other cause like NASH and Cryptogenic liver cirrhosis. In developed countries major cause for cirrhosis is viral hepatitis and alcohol is only a second cause. The cause of cirrhosis in female in the study is mainly viral etiology.

DISTRIBUTION OF VARICEAL GRADE

In the present study 37.1% had Grade 2 varices, 33.6% had Grade 1 varices and 16.4% had Grade 3 varices. 12.9 % had no varices. 87.1 % had portal hypertensive gastropathy.

STATISTICAL ANALYSIS

The ratios namely platelet count/bipolar diameter of spleen (PLC/BPD), AST/ALT ratio were analysed using receiver operating characteristics (ROC) curves and its statistical significance was calculated using test like Mann-Whitney U and p value was calculated.

RESULT

In this study ROC curve showing PLC/ BPD ratio with area under curve 0.908 which denotes a good test and cut off value 919 with sensitivity 74 %, specificity 88% which is statistically significant with a p value < .001.. According to Khaled El-Molaet al, the PLC/BPD ratio in patients with EVs was significantly lower than in patients without EVs. In an analysis of ROC curves test had a good diagnostic accuracy [AUC= 0.99] the best cutoff value was 976.0 with sensitivity of 99.3% and specificity of 97.4%.

ROC curve showing AST/ALT ratio was also plotted in the present study with area under curve 0.794 cut off value 1.30 with sensitivity 74% specificity 82 % which is statistically significant with a p value < .001. In a retrospective study, significantly higher AST/ALT ratios were seen in patients with varices compared to those without (ratio: 1.8 versus 1.0, P < 0.0001). A study by Castéra L et al, using a different cut-off of ≥ 1.0 demonstrated a sensitivity of 68%, specificity of 89%, PPV 77%, and NPV 83%, with an AUROC 0.83 (0.72–0.94) for predicting the presence of oesophageal varices. For the prediction of large oesophageal varices, this gave a sensitivity 68%, specificity 77%, PPV 41%, and NPV 92%, and AUROC 0.79 (0.64–0.94).

SUMMARY AND CONCLUSION

This is a Descriptive study in order to find out the diagnostic efficacy of platelet count/spleen diameter ratio and AST/ALT as a non-invasive marker for esophageal varices in liver cirrhosis.

140 patients with features of chronic liver disease were taken up for the study.

Clinical, biochemical, radiological assessment and endoscopy was done and appropriate analysis was done.

Results are as follows:

- Majority of patients with cirrhosis and portal hypertension were males (90%) and the age group 40-59(69%).
- The most common presenting complaint was upper gastrointestinal bleed present in 78.6% of the patients.
- Most common etiology for cirrhosis is chronic alcoholism.
- 87.1% had portal hypertensive gastropathy at the time of presentation.
- 37.1% had Grade 2, 33.6% had Grade 1, 16.4% had Grade 3 and 12.9 % had absent varices on endoscopy.
- PLC/ BPD ratio have sensitivity 74 % and specificity 88% which is statistically significant with a p value < .001. This ratio has a cut off value 919 with area under ROC curve 0.908 which denotes a good test.
- AST/ALT ratio have sensitivity 74% specificity 82 % which is statistically significant with a p value < .001 and the ratio have a cut off value 1.30 with area under ROC curve 0.794.

From this study I conclude that two non-endoscopic parameters: platelet count/splenic diameter ratio and AST/ALT ratio may be used to predict the presence of esophageal varices and use as surrogate markers for the presence of esophageal varices where endoscopic facilities not available. However endoscopy may still be required for diagnosing the esophageal and gastric varices and for therapeutic interventions. As such

these patients can be put on prophylactic treatment to prevent variceal bleeding.

LIMITATIONS

1. As this study has small sample size the observations cannot be generalized to the general population.
2. Larger studies should be carried out to confirm the findings of this study.

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ABBREVIATIONS

- ALT Alanine Transaminase
 AST Aspartate Transaminase
 AUROC Area Under ROC
 CLD Chronic Liver Disease
 CTP Child-Turcotte-Pugh
 cGMP cyclic Guanosine monophosphate
 DM Diabetes Mellitus
 eNOS Endothelial NO synthase
 ET-1 Endothelin-1
 FHVP Free Hepatic Vein pressure
 GABA Gamma-aminobutyric acid
 HE Hepatic Encephalopathy
 HSC Hepatic Stellate Cell
 HTN Hypertension
 HVPG Hepatic Vein Pressure Gradient
 NO Nitric Oxide
 ROC Receiver operating characteristics
 TGF- β Transforming Growth Factor- β
 TIPS Transjugular Intrahepatic Porto-systemic Shunt
 WHVP Wedged Hepatic Venous Pressure