ORIGINAL RESEARCH PAPER

General Medicine

PLATELET COUNT/SPLEEN DIAMETER RATIO AND AST/ALT RATIO AS NON INVASIVE PARAMETERS FOR THE DETECTION OF ESOPHAGEAL VARICES IN PATIENTS WITH LIVER CIRRHOSIS

KEY WORDS: Esophageal varices, Endoscopy, Cirrhosis, Platelet count, spleen diameter, AST, ALT.

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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.

Aim: To assess the value of Platelet count/spleen diameter(PLC/BPD) ratio and Aspartate transaminase/Alanine transaminase (AST/ALT) ratio as a non invasive marker for esophageal varices in patient with cirrhosis.

MATERIALS AND METHODS: It is a Diagnostic test evaluation study of 18 months duration conducted in 140 cirrhotic patients admitted in medicine ward of maharajah's institute of medical sciences,nellimarla. 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

I. 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]. 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[0 7] 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[05, 18-22]. In patients with chronic liver disease, thrombocytopenia is due primarily to portal hypertension[2] , thrombocytopenia can depend on other factors, such as shortened mean platelet lifetime, decreased thrombopoetin 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[2] [redacted]/S[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.

II. AIMS AND OBJECTIVES

1. 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.

III. MATERIALS AND METHODS

140 patients All liver cirrhosis patients admitted in Medicine and Gastroenterology wards, Maharajah's Institute of Medical Sciences, Nellimarla, Vizianagaram from December 2016 to June 2018. This study is a Diagnostic test evaluation of patients having cirrhosis with portal hypertension, done over a period of 24 months with 140 patients who attended the hospital on admission and 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.

3.1INCLUSION CRITERIA

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

3.2 EXCLUSION CRITERIA

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

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.

3.3 INVESTIGATIONS USED

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 impedence 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.

IV. OBSERVATION AND RESULTS

Table No. 1: Total number of cases and age distribution

Age	Frequency	Percent
<40	27	19.3
40-49	53	37.9
50-59	45	32.1
>60	15	10.7
Total	140	100.0

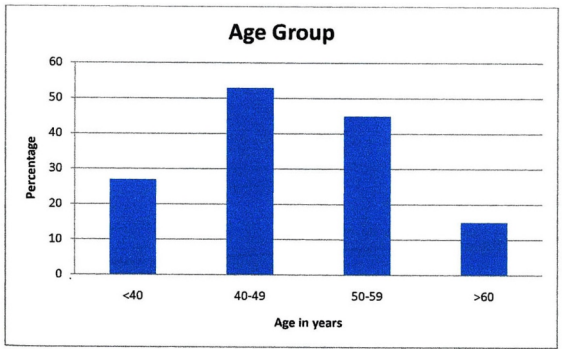


Table No. 2: Sex distribution.

Gender	Frequency	Percent
Male	126	90.0
Female	14	10.0
Total	140	100.0

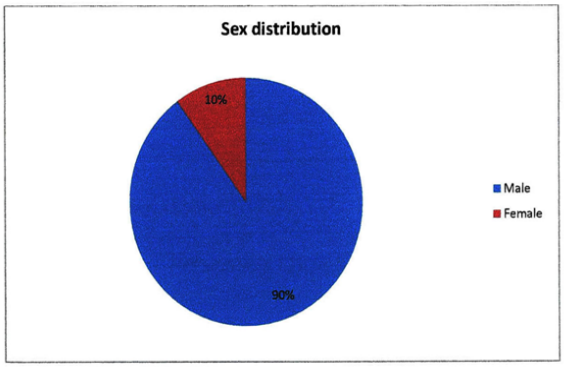


Table No. 3: .Presenting Complaints

Presenting complaints	Frequency	Percent
UGI Bleed	83	59.3
Abdominal distension	9	6.4
Abdominal Pain	4	2.9
Hepatic Encephalopathy (HE)	13	9.3
Jaundice	4	2.9
UGI Bleed+Abdominal distention	7	5.0
HE+UGI Bleed	14	10.0
HE+ Abdominal distension	6	4.3
Total	140	100.0

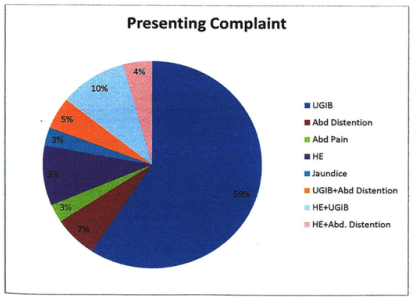


Table no. 4: Presence of upper GI bleed

Presenting complaints	Frequency	Percent
UGI Bleed	110	78.6
Non bleed	30	21.4
Total	140	100.0

Table No. 5: Comorbidities

Comorbidities	Frequency	Percent
Nil	103	73.6
Diabetes Mellitus (DM)	25	17.9
Hypertension (HTN)	12	8.6
Total	140	100.0

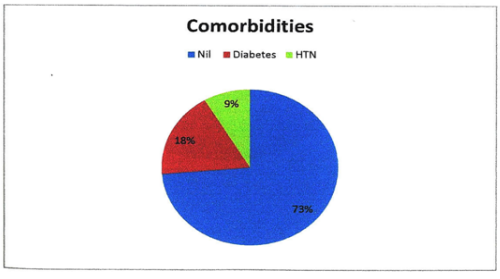


Table no. 6: Etiology

Etiology	Frequency	Percent
Alcohol	112	80.0
HCV	9	6.4
HBV	17	12.1
Others	2	1.4
Total	140	100.0

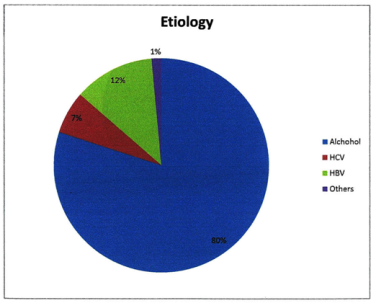


Table no.7: Portal hypertensive gastropathy

PHG	Frequency	Percent
Yes	122	87.1
No	18	12.9
Total	140	100.0

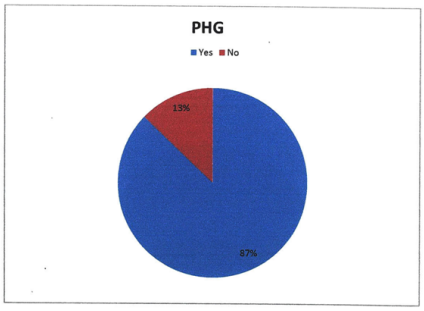


Table no. 8. Esophgeal variceal grade

Vx Grade	Frequency	Percent
0	17	12.9
1	47	33.6
2	53	37.1
3	23	16.4
Total	140	100.0

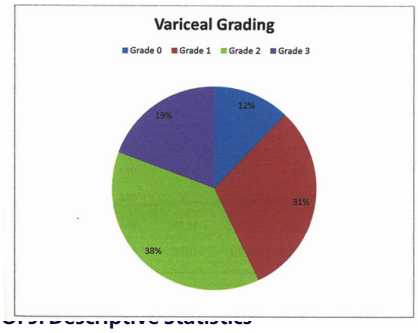
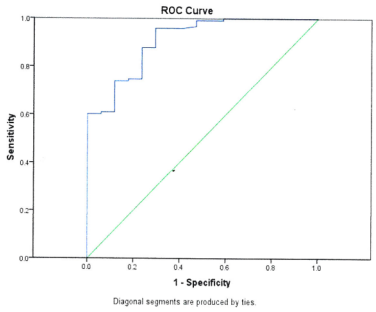


TABLE N

	N	Minimum	Maximum	Mean	Std. Deviation
Hb	140	5.4000	14.0000	10.290714	1.7879652
TC	140	3900	14600	7873.57	2631.891
Platelet Count	140	24000	220000	106497.14	44411.512
Direct Bilirubin	140	.3000	4.0000	1.345143	.7707881
Indirect Bilirubin	140	.3000	4.9000	1.199286	.8468729
SGOT	140	29	220	87.79	38.998
SGPT	140	17	195	65.58	35.024
Total Protein	140	4.0000	7.1000	5.178571	.7301114

Albumin	140	1.8	4.3	2.961	.6642
INR	140	.9000	2.2300	1.455143	.3150939
BPD Spleen	140	90	180	133.04	24.661
Liver Span	140	9	16	12.54	1.660
PV	140	8.0	16.0	12.044	1.6747
SV	140	4	14	9.24	2.398
PLC/BPD	140	141.18	2130.00	838.6170	420.36666
SGOT/SGPT	140	.9510	1.9744	1.414783	.2289502

Fig no. 17: Receiver operating characteristics curve showing PLC/ BPD ratio



Diagonal segments are produced by ties.

Table N

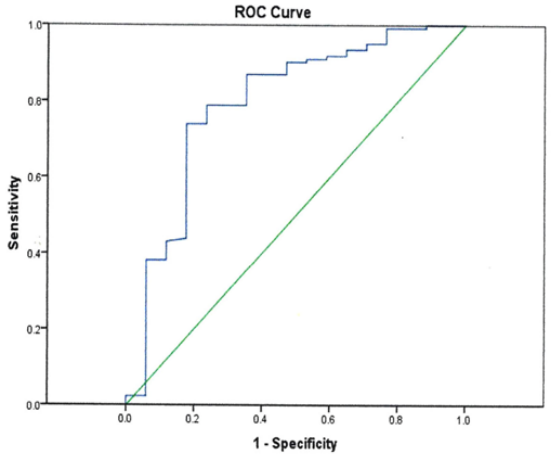
	Test Result Variable(s):PLC/BPD			
Area	Std. Error[3]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.908	.036	.000	.839	.978

	Test Statistics[8]
	PLC/BPD
Mann-Whitney U	191.500
Wilcoxon W	7817.500
Z	-5.448
Asymp. Sig. (2-tailed)	.000

Test Result Variable(s):PLC/BPD

Positive if Less Than or Equal To[a]	Sensitivity	1- Specificity
140.1765	.000	.000
151.8382	.008	.000
178.0242	.016	.000
193.8330	.024	.000
200.0000	.033	.000
222.9412	.041	.000
257.5.000	.049	.000
354.1872	.114	.000
376.3070	.122	.000
388.5484	.130	.000
391.1538	.146	.000
392.9280	.154	.000
400.9409	.163	.000
410.8333	.171	.000
416.1905	.179	.000
422.0238	.187	.000
503.3333	.220	.000
507.8788	.228	.000
513.3690	.236	.000
521.3235	.244	.000
527.5000	.252	.000
604.1667	.309	.000
611.8590	.317	.000
617.2161	.325	.000
624.2297	.333	.000
633.9366	.341	.000
684.2365	.415	.000
692.8572	.423	.000
742.0168	.504	.000
748.3516	.512	.000
772.8111	.545	.000
783.7634	.553	.000
801.2121	.561	.000
843.3000	.602	.059
844.9500	.610	.059
849.5456	.610	.118
854.4706	.618	.118
856.1250	.626	.118
892.1393	.659	.118
893.4839	.667	.118
902.9412	.699	.118
908.8235	.707	.118
912.4024	.715	.118
914.8534	.724	.118
917.4234	.732	.118
919.0900	.740	.118
921.5350	.740	.176
924.4950	.748	.176
925.9229	.748	.235
926.1180	.756	.235
926.4884	.764	.235
932.8984	.772	.235
940.3950	.780	.235
942.2586	.797	.235
944.5035	.805	.235
948.0750	.813	.235
951.0000	.821	.235
953,7778	.829	.235
957.1895	.837	.235
962.0168	.846	.235
967.6050	.854	.235
974.2857	.862	.235
979.2857	.870	.235
986.4250	.878	.235
1014.6465	.886	.294
1094.3182	.911	.294
1165.1515	.919	.294
1239.1609	.935	.294
1302.7971	.943	.294
1390.4762	.959	.353
1450.0000	.959	.412
1550.0000	.967	.471
1630.0000	.992	.471
1654.1667	.992	.529
1740.9091	1.000	.588
1824.0909	1.000	.647
1865.0000	1.000	.706
1950.0000	1.000	.765
2055.5555	1.000	.882
2120.5555	1.000	.941
2131.0000	1.000	1.000

Receiver operating characteristics curve showing AST/ALT ratio



Diagonal segments are produced by ties.

	Test Result Variables):AST/ALT			
Area	Std. Error3	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
794	066	000	665	923

	Test Statistics[8]
	AST/ALT
Mann-Whitney U	430.500
Wilcoxon W	583.500
Z	-3.924
Asymp. Sig. (2-tailed)	.000

Test Result Variable(s): AST/ALT		
Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
-.049020	1.000	1.000
.962990	1.000	.941
.981250	1.000	.882
1.011607	.992	.882
1.046703	.992	.765
1.065883	.984	.765
1.094166	.951	.765
1.106593	.951	.706
1.114835	.943	.706
1.120192	.935	.706
1.126603	.935	.647
1.129320	.927	.647
1.131884	.919	.647
1.134463	.919	.588
1.136604	.911	.588
1.145730	.911	.529
1.160256	.902	.529
1.169540	.902	.471
1.173286	.886	.471
1.175686	.878	.471
1.177893	,870	.471
1.189286	.870	.412
1.204938	.870	.353
1.218272	.862	.353
1.232736	.837	.353
1.239403	.829	.353
1.247449	.797	.353
1.253571	.789	.353
1.257437	.789	.294
1.283053	.764	.235
1.290070	.756	.235
1.296036	.748	.235
1.300800-	.740	.235
1.305162	.740	.176
1.309402	.715	.176
1.314006	.707	.176
1.316987	.699	.176
1.318111	.691	.176
1.324897	.683	.176
1.331989	.675	.176
1.368160	.618	.176
1.369398	.610	.176
1.373972	.602	.176
1.379189	.577	.176
1.382593	.569	.176
1.387905	.553	.176
1.391741	.545	.176
1.396429	.537	.176
1.403704	.520	.176
1.407785	.512	.176
1.413265	.504	.176
1.421827	.488	.176
1.428330	.472	.176
1.460277	.439	.176
1.463092	.431	.118
1.468810	.423	.118
1.478153	.415	.118
1.486111	.407	.118
1.489899	.398	.118
1.495455	.390	.118
1.504237	.382	.118
1.510648	.382	.059
1.517604	.374	.059
1.526819	.350	.059
1.534856	.333	.059
1.540064	.325	.059
1.545343	.317	.059
1.642034	.154	.059
1.655367	.146	.059
1.669540	.122	.059
1.677670	.114	.059
1.694405	.106	.059
1.710084	.098	.059
1.746032	.089	.059
1.834918	.057	.059
1.855208	.049	.059
1.880702	.033	.059
1.922978	.024	.059
1.953871	.024	.000
1.965440	.008	.000
2.074359	.000	.000

V. DISCUSSION

In this study conducted in Maharajah's Institute of Medical Sciences, Vizainagaram a total of 140 patients were included those who have satisfied the inclusion criteria.

5.1 AGE AND GENDER DISTRIBUTION:

These patients were grouped into different age groups (<40,40-49,50-59,>60).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. Certain studies have shown that estrogen may have a protective role against fibrosis in viral hepatitis by inhibiting stellate cells, which are responsible for fibrogenesis in the liver[90]

5.2 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%[91].

5.3DISTRIBUTION OF COMORBITIES:

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

5.4 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 alchohol is only a second cause[\ The cause of cirrhosis in female in the study is mainly viral etiology.

5.5 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.

5.6 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.

5.7 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. A study by Giannini et al, a platelet count/spleen diameter ratio cut off value of 909 had 91.5% sensitivity and 67.0% specificity for detecting esophagealvarices (EV) and p value was .018 (15). 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 ROCcurves 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%[93].

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[94], 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 Castera 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[95]. 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).

5.8 LIMITATIONS OF THE PRESENT STUDY:

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.

VI. Conclusion

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 ratiohave 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 esophagealvarices 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.

REFERENCES

[1]. Schiedermaier P. Splanchnic hemodynamics: cirrhotic versus non-cirrhotic portal hypertension. J Gastroenterol Hepatol 2004;19(s7):S150-S4.
[2]. Hong WD, Zhu QH, Huang ZM, Chen XR, Jiang ZC, Xu SH, et. Predictors of esophageal varices in patients with HBV-related cirrhosis: a retrospective study. BMC Gastroenterol. 2009;9:11.
[3]. Jensen DM. Endoscopic screening for varices in cirrhosis: findings, implications, and outcomes. Gastroenterology 2002; 122(6).T620-30.
[4]. Garceau AJ, Chalmers TC. The Boston Inter-Hospital Liver Group. The natural history of cirrhosis: I. Survival with oesophageal varices NEJM 1963;268:469-73
[5]. Graham D, Smith JL. The course of patients after variceal hemorrhage. Gastroenterology 1981;80;800-9.
[6]. Rigo GP, Merighi A, Chalen JN, et al. A prospective study of the ability of three endoscopic classifications to predict hemorrhage from esophagealvarices. GastrointestEndosc 1992;38:425-9.
[7]. Jensen DM. Endoscopic screening for varices in cirrhosis: findings, implications, and outcomes. Gastroenterology 2002;122:1620-30.
[8]. Grace ND, Groszmann RJ, Garcia-Tsao G, et al. Portal hypertension andvariceal bleeding: an AASLD single topic symposium. Hepatology 1998;28:868-80.
[9]. D'Amico G, Garcia-Tsao G, Cales P, et al. Diagnosis of portal hypertension: how and when. In: De Franchis R, ed. Proceedings of the Third Baveno International Consensus Workshop on Definitions, Methodology and Therapeutic Strategies. Oxford: Blackwell Science 2001;36-63.
[10]. Cales P, Desmorat H, Vinel JP, et al. Incidence of large oesophageal varices in patients with cirrhosis: application to prophylaxis of first bleeding. Gut 1990;31:1298-302
[11]. de Franchis R. Updating consensus in portal hypertension: report of the Baveno III Consensus Workshop on definitions, methodology and therapeutic strategies in portal hypertension. J Hepatol. 2000;33(5):846-52.
[12]. de Franchis R. Evolving consensus in portal hypertension.Report of the BavenoIV consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol.2005;43(l):167-76.
[13]. Gorka W, al Mulla A, al Sebayel M, Altraif I, Gorka Qualitative hepatic venous Doppler sonography versus portal flowmetry in predicting the severity of esophagealvarices in hepatitis C cirrhosis.AJR Am J Roentgenol. 1997;169(2):511-5.
[14]. Lavergne J, Molina E, Reddy KR, Jeffers L, Leon R, Nader AK, et al.Ascites predicts the presence of high grade varices by screening gastroscopy. GastrointestEndosc. 1997;45(4):AB187.
[15]. Pilette C, Oberti F, Aube C, Rousselet MC, Bedossa P, GalloisY, et al. Non invasive diagnosis of esophagealvarices in chronic liver diseases. J Hepatol. 1999;31(5):867-73.
[16]. Madhotra R, Mulcahy HE, Willner I, Reuben A. Prediction of esophagealvarices in patients with cirrhosis.jClinGastroenterol. 2002;34(l):81-5
[17]. McCormick PA. The spleen, hypersplenism, and other relationships between the liver and spleen. In: Bircher J, Benhamou J-P, Mclntyre N, eds. Oxford Textbook of Clinical Hepatology. Oxford: Oxford University Press, 1999:787-95.
[18]. Schepis F, Camma C, Niceforo D, Magnano A, Pallio S, Cinquegrani M, et al. Which patients with cirrhosis should undergo endoscopic screening for esophagealvarices detection? Hepatology.2001;33(2):333-8.
[19]. Chalasani N, Imperiale TF, Ismail A, Sood G, Carey M, Wilcox CM, et al. Predictors of large esophagealvarices in patients with cirrhosis. Am J Gastroenterol. 1999;94(11):3285-91.
[20]. Ng FH, Wong SY, Loo CK, Lam KM, Lai CW, Cheng CS. Prediction Of esophagogastric varices in patients with liver cirrhosis. J Gastroenterol Hepatol. 1999;14(8):785-90.
[21]. Zaman A, Hapke R, Flora K, Rosen HR, Benner K. Factors predicting the presence of esophageal or gastric varices in patients with advanced liver disease. Am J Gastroenterol. 1999;94(11):3292-6.
[22]. Zaman A, Becker T, Lapidus J, Benner K. Risk factors for the presence of varices in cirrhotic patients without a history of variceal hemorrhage. Arch Intern Med. 2001;161(21):2564-70.
[23]. Giannini E, Botta F, Borro P, Risso D, Romagnoli P, Fasoli A, et al. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. Gut. 2003;52(8):1200-5.
[24]. Peck-Radosavljevic M. Thrombocytopenia in liver disease. Can J Gastroenterol. 2000;14(SupplD):60D-6D.
[25]. de Franchis R. Noninvasive diagnosis of esophagealvarices: is it feasible? Am J Gastroenterol. 2006;101(11):2520-2.
[26]. Kumar S, Sarr MG, Kamath PS: Mesenteric venous thrombosis. NEJM 2001;345:1683
[27]. Douglas BE, Baggenstoss AH, Hollingshead WN: The anatomy of the portal vein and its tributaries. SurgGynecolObst 1950; 91:562
[28]. Sarin S, Groszmann R, Mosca P, et al: Propranolol ameliorates the development of portal-systemic shunting in a chronic murine schistosomiasis model of portal hypertension.. J ClinInvest 1991; 87:1032
[29]. Gupta T, Toruner M, Chung M, Groszmann R: Endothelial dysfunction and decreased production of nitric oxide in the intrahepatic microcirculation of cirrhotic rats. Hepatology 1998; 28:926
[30]. Rockey DC, Chung JJ: Reduced nitric oxide production by endothelial cells in cirrhotic rat liver: Endothelial dysfunction in portal hypertension.Gastroenterology 1998; 114:344
[31]. Shah V, Toruner M, Haddad F, et al: Impaired endothelial nitric oxide, synthase activity associated with enhanced caveolin binding in experimental liver cirrhosis. Gastroenterology 1999; 117:1222
[32]. Sarela A, Mihaimeed F, Batten J, et al: Hepatic and splanchnic nitric oxide activity in patients with cirrhosis. Gut 1999; 44:749.
[33]. Chatila R, Theise N, Shah V, et al: Caveolin-1 in normal and human cirrhotic liver. Gastroenterology 2000; 118:A979
[34]. Failli P, DeFranco R, Caligiuri A, et al: Nitrovasodilators inhibit platelet derived growth factor-induced proliferation and migration of activated human hepatic stellate cells. Gastroenterology 2000; 119:479.
[35]. Bellis L, Berzigotti A, Abraldes J, et al: Low doses of isosorbide mononitrate attenuate the postprandial increase in portal pressure in patients with cirrhosis. Hepatology 2003; 37:378.
[36]. Fiorucci S, Antonelli E, Morelli O, et al: NCX-1000, a NO-releasing derivative of ursodeoxycholic acid, selectively delivers NO to the liver and protects against development of portal hypertension. ProcNatl AcadSci U S A 2001; 98:8897 .
[37]. Loureiro-Silva M, Cadelina G, Iwakiri Y, Groszmann R: A liverspecific nitric oxide donor improves the intra-hepatic vascular response to both portal blood flow increase and methoxamine in cirrhotic rats. J Hepatol 2003; 39:940 .
[38]. Dudenhoefer A, Loureiro-Silva M, Cadelina G, et al: Bioactivation of nitroglycerin and vasomotor response to nitric oxide are impaired in cirrhotic rat livers. Hepatology 2002; 36:381
[39]. Rockey DC, Weisiger RA: Endothelin induced contractility of stellate cells from normal and cirrhotic rat liver: Implications for regulation of portal pressure and resistance. Hepatology 1996; 24:233.
[40]. Pinzani M, Milani S, De Franco R, et al: Endothelin 1 is overexpressed in human

cirrhotic liver and exerts multiple effects on activated hepatic stellate cells. Gastroenterology 1996; 110:534.
[41]. Kamath P, Tyce G, Miller V, et al: Endothelin-1 modulates intrahepatic resistance in a rat model of noncirrhotic portal hypertension. Hepatology 1999; 30:401.
[42]. Rockey D, Fouassier L, Chung J, et al: Cellular localization of endothelin-1 and increased production in liver injury in the rat: Potential forautocrine and paracrine effects on stellate cells. Hepatology 1998; 27:472 .
[43]. Alam I, Bass NM, Bacchetti P, et al: Hepatic tissue endothelin-1 levels in chronic liver disease correlate with disease severity and ascites. Am J Gastroenterol 2000; 95:199
[44]. Salo J, Francitorra A, Folio A, et al: Increased plasma endothelin in cirrhosis. Relationship with systemic endotoxemia and response to changes in effective blood volume. J Hepatol 1995; 22:389.
[45]. Douggrell S: The therapeutic potential of endothelin-1 receptor antagonists and endothelin-converting enzyme inhibitors on the cardiovascular system. Expert OpinInvestigDrugs 2002; 11:1537.
[46]. Reynaert H, Vaeyens F, Qin H, et al: Somatostatin suppresses endothelin-1 induced rat hepatic stellate cell contraction via somatostatin receptor subtype 1. Gastroenterology 2001; 121:915.
[47]. Graupera M, Garcia-Pagan J, Titos E, et al: 5-Lipoxygenase inhibition reduces intrahepatic vascular resistance of cirrhotic rat livers: A possible role of cysteinyl-leukotrienes .Gastroenterology 122:387.
[48]. Yokoyama M, Xu H, Kresge N, et al: Role of thromboxane A2 in early BDL-induced portal hypertension. Am J Physiol 2003; 284:G453
[49]. Blendis L, Wong F: Does losartan work after all?. Am J Gastroenterol 2003; 98:1222
[50]. Sikuler E, Groszmann RJ: Hemodynamic studies in long- and short-term portal hypertensive rats: The relation to systemic glucagon levels. Hepatology 1986; 6:414.
[51]. Atucha N, Shah V, Garcia-Cardena G, et al: Role of endothelium in the abnormal response of mesenteric vessels in rats with portal hypertension and liver cirrhosis. Gastroenterology 1996; 111:1627.
[52]. Sieber CC, Groszmann RJ: Nitric oxide mediates hyporeactivity to vasopressors in mesenteric vessels of portal hypertensive rats. Gastroenterology 1992; 103:235.
[53]. Sieber CC, Groszmann RJ: In vitro hyporeactivity to methoxamine in portal hypertensive rats: Reversal by nitric oxide blockade. Am J Physiol 1992; 262:G996.
[54]. Sieber C, Lopez-Talavera JC, Groszmann RJ: Role of nitric oxide in the in vitro splanchnic vascular hyporeactivity in ascitic cirrhotic rats. Gastroenterology 1993; 104:1750.
[55]. Niederberger M, Gines P, Martin P, et al: Comparison of vascular nitric oxide production and systemic hemodynamics in cirrhosis versus prehepatic portal hypertension in rats. Hepatology 1996; 24:947.
[56]. Cahill P, Foster C, Redmond E, et al: Enhanced nitric oxide synthase activity in portal hypertensive rabbits. Hepatology 1995; 22:598.
[57]. Cahill P, Redmond E, Hodges R, et al: Increased endothelial nitric oxide synthase activity in the hyperemic vessels of portal hypertensive rats. J Hepatol 1996; 25:370.
[58]. Garcia-Pagan J, Fernandez M, Bernadich C, et al: Effects of continued NO inhibition on portal hypertensive syndrome after portal vein stenosis in rat. Am J Physiol 1994;267:G984.
[59]. Sogni P, Sabry S, Moreau R, et al: Hyporeactivity of mesenteric resistance arteries in portal hypertensive rats. J Hepatol 1996; 24:487.
[60]. Wiest R, Das S, Cadelina G, et al: Bacterial translocation in cirrhotic rats stimulates eNOS-derived NO production and impairs mesenteric vascular contractility. JClinInvest 1999; 104:1223.
[61]. Shah V, Wiest R, Garcia-Cardena G, et al: Hsp90 regulation of endothelial nitric oxide synthase contributes to vascular control in portal hypertension. Am J Physiol 1999;277:G463.
[62]. Morales-Ruiz M, Jimenez W, Perez-Sala D, et al: Increased nitric oxide synthase expression in arterial vessels of cirrhotic rats with ascites. Hepatology 1996; 24:1481.
[63]. Tazi K, Barriere E, Moreau R, et al: Role of shear stress in aortic eNOS up-regulation in rats with biliary cirrhosis. Gastroenterology 2002; 122:1869.
[64]. Pateron D, Tazi K, Sogni P, et al: Role of aortic nitric oxide synthase 3 (eNOS) in the systemic vasodilation of portal hypertension. Gastroenterology 2000; 119:196.
[65]. Iwakiri Y, Tsai M, McCabe T, et al: Phosphorylation of eNOS initiates excessive NO production in early phases of portal hypertension. Am J Physiol 2002; 282:H2084.
[66]. Vianna A, Hayes PC, Moscoso G: Normal venous circulation of the gastroesophageal junction. A route to understanding varices.Gastroenterology 1987; 93:876.
[67]. Watanabe K, Kimura K, Matsutani S, et al: Portal hemodynamics in patients with gastric varices. A study in 230 patients with esophageal and/or gastric varices using portal vein catheterization.Gastroenterology 1988; 95:434.
[68]. Dilawari JB, Chawla YK: Spontaneous (natural) splenoadrenorenal shunts in extrahepatic portal venous obstruction: A series of 20 cases. Gut 1987; 28:198.
[69]. Sumanovski L, Battegay E, Stumm M, et al: Increased angiogenesis in portal hypertensive rats: Role of nitric oxide. Hepatology 1999; 29:1044.
[70]. Fernandez-Varo G, Ros J, Morales-Ruiz M, et al: Nitric oxide synthase 3-dependent vascular remodeling and circulatory dysfunction in cirrhosis. Am J Pathol 2003; 162:1985.
[71]. Myers JD, Taylor WJ: An estimation of portal venous pressure by occlusive catheterization of a hepatic venule. J ClinInvest 1951; 30:662.
[72]. Groszmann R, Glickman M, Blei AT, et al: Wedged and free hepatic venous pressure measured with a balloon catheter. Gastroenterology 1979; 76:253.
[73]. Boyer T, Triger D, Horisawa M, et al: Direct transhepatic measurement of portal vein pressure using a thin needle. Comparison with wedged hepatic vein pressure.Gastroenterology 1977; 72:584.
[74]. Thalheimer U, Mela M, Patch D, Burroughs AK: Targeting portal pressure measurements: A critical reappraisal. Hepatology 2004; 39:286.
[75]. Menon KV, Shah VH, Kamath PS: The Budd-Chiari syndrome. N Engl J Med 2004; 350:578.
[76]. Grace ND, Groszmann RJ, Garcia-Tsao G, et al: Portal hypertension and variceal bleeding: An AASLD single topic symposium. Hepatology 1998; 28:868.
[77]. D'Amico G, Garcia-Tsao G, Cales P, et al: Diagnosis of portal hypertension: How and when?. In: de Franchis R, ed. Portal Hypertension III. Proceedings of the Third Baveno International Consensus Workshop on Definitions, Methodology and Therapeutic Strategies, Oxford: Blackwell Science; 2001:36.
[78]. Zein CO, Lindor KD, Angula P: Prevalence and predictors of esophagealvarices in patients with primary sclerosing cholangitis. Hepatology 2004; 39:203.
[79]. D'Amico G, Morabito A: Non-invasive markers of esophagealvarices: Another round, not the last. Hepatology 2004; 39:30.
[80]. Beppu K, Inoquachi K, Koyanagi N, et al: Prediction of varicealhemorrhage by esophageal endoscopy. GastrointestEndosc 1981; 27:213.
[81]. Bissell DM. Sex and hepatic fibrosis.Hepatology. 1999;29(3):988~989.
[82]. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: a population-based study. Longstreth GF Am J Gastroenterol. 1995;90(2):206.
[83]. Cirrhosis and chronic liver failure: part I. Diagnosis and evaluation. Heidelbaugh JJ, Bruderly M Am Fam Physician. 2006;74(5):756.
[84]. Khaled El-Mola, HeshamAlshabrawy, Mohamed Salah, and Al sayedM.Rashed. Platelet Count/Spleen Diameter Ratio, as a Non-Invasive Diagnosis of EsophagealVarices in Egyptian Patients with Liver Cirrhosis. J Am Sci
[85]. Nyblom H, Bjornsson E, Simren M, Aldenborg F, Aimer S, Olsson R. The AST/ALT ratio as an indicator of cirrhosis in patients with PBC.Liver International. 2006;26(7):840-845.
[86]. Castera L, Bail BL, Roudot-Thoraval F, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. Journal of Hepatology. 2009;50(l):59-68.