Section: Medicine

Original Research Article

EVALUATION OF THE "PLATELET COUNT AND BIPOLAR SPLEEN DIAMETER RATIO FOR PREDICTION OF PRESENCE OF ESOPHAGEAL VARICES IN PATIENTS WITH CIRRHOSIS OF LIVER

Received : 30/10/2023
Received in revised form : 21/12/2023
Accepted : 06/01/2024

Keywords:
Esophageal varices, non-invasive predictor of varices, platelet spleen ratio, liver cirrhosis.

Corresponding Author:
Dr. Ningthoukhongjam Reema,
Email: thangjamreema@gmail.com.

DOI: 10.47009/jamp.2024.6.1.59

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (1); 304-309

Thingbaijam Shanti Devi[1], Jhutan Chowdhury[2], Thangjam Gautam Singh[3],Ningthoukhongjam Reema[4], Seram Rajeshwor Singh[5], Supongbenla[6]

[1,4]Assistant Professor, Department of Medicine, RIMS, Imphal, Manipur, India.
[2,5,6]Junior Resident, Department of Medicine, RIMS, Imphal, Manipur, India.
[3]Assistant Professor, Department of Radiodiagnosis, Shija Academy of Health Sciences, Imphal, Manipur, India.

Abstract

Background: Esophageal varices (EVs) are a serious consequence of portal hypertension in patients with liver diseases. Several studies have evaluated possible non invasive markers of esophageal varices but no variable alone have enough power to predict the presence of esophageal varices without upper GI endoscopy in patients of liver cirrhosis. Hence this study aims to evaluate the platelet count/spleen diameter ratio as non-invasive predictor of esophageal varices (EV) in patients of liver cirrhosis. **Material & Methods:** This hospital based cross sectional study analyzed 50 patients with liver cirrhosis from October 2014 to September 2016. Complete blood count, liver function, renal function, prothrombin time, and international normalisation ratio, USG and Upper GI endoscopy were done for every patients. Maximum spleen diameter was determined and bipolar spleen diameter was expressed in millimeter (mm). Platelet count/spleen diameter ratio was collected and compared with the presence/ absence of esophageal varices. **Results:** The study showed that presence of esophageal varices had a significant relation ($P<0.05$) with platelets count, bipolar spleen diameter, as well as with platelet count/ bipolar splenic diameter ratio. **Conclusion:** Platelet count/ Splenic diameter ratio can be used as non-invasive predictors of EV in patients with liver cirrhosis.

INTRODUCTION

Chronic liver disease (CLD) of any etiology can occur when liver damage lasts longer than six months. It usually takes 20 to 40 years for cirrhosis to develop from hepatitis. It may cause portal hypertension, which can lead to the significant consequences of esophageal varices (EV) and portal hypertensive gastropathy (PHG). In these individuals, the majority of non-variceal bleeding events are likely caused by severe PHG. PHG hemorrhage is often subtle and chronic, although it can occasionally become severe and even fatal.[1]

Esophageal varices are the porto-systemic collaterals formed as a consequence of an increase in splanchnic blood flow secondary to vasodilation and increased resistance to passage of blood through the cirrhotic liver.[2]Varices usually form when portal pressure exceeds 10 mm Hg and bleed when it exceeds 12 mm Hg.[3] Its prevalence varies from 50 to 60% in patient with cirrhosis of liver.[4] The rate of incidence of esophageal varices was 5% at 1 year and 28% at 3 years. The rate of esophageal varices progression was 12% at 1 year and 31% at 3 years.[5] The risk of initial bleeding from varices is 25-35% within two years with most first bleeding episode occurring within one year of detection of varices.[6] Variceal hemorrhage is a serious life-threatening complication of portal hypertension, with overall mortality rates reported as 30-50%.[7] The larger the esophageal varices, the more dangerous they are, since large esophageal varices may cause a higher tension on variceal walls.[8,9] The rate of yearly increase in size of varices varies from a range of 8% to 31%.[10,11] The mean risk of hemorrhage from larger varices (>5mm) is 30% at 2 years compared to 10% from small varices at 2 years.[6,7] Gastrointestinal bleeding is attributed only 1-2% to causes other than varices, but 5% to small

ISSN (O): 2687-5365; ISSN (P): 2753-6556

esophageal varices, and 15-20% to large esophageal varices.[12]

Patients with large esophageal varices or varices with red wale signs are considered high risk esophageal varices (HREV) and they should begin primary prophylaxis for variceal bleeding,[13] which include the use of non-selective beta-blockers or band ligation thereby reducing the incidence of variceal bleeding in approximately 50%.[14] Thus, identification of large-sized esophageal varices, before their first bleeding, is essential to prevent or minimize this life threatening complication of liver cirrhosis. The presence esophageal varices usually correlate with the severity of liver disease which can be estimated by Child - Pugh classification. The higher the Child-Pugh grade is the most severe CLD and more prone for development of complications. Among them only 40% of Child A patients has varices whereas 85% of Child C patients have varices.[15] The rate of development of new varices is 8% per year and strongest predictor for development of varices is hepatic venous pressure gradient more than 10 mm Hg.[16]

Most of the reported variables are directly or indirectly associated with portal hypertension, such as decreased platelet count, low albumin, splenomegaly and ascites. However in patients with liver cirrhosis, the presence of decreased platelet count can be associated with several factors unrelated with portal hypertension, such as shortened platelet mean half-life, decreased thrombopoietin production and myelotoxic effects of alcohol.[17] On the other hand the presence of splenomegaly in cirrhotic patients is likely the result of vascular disturbance that mainly linked to portal hypertension. Overall, no variable alone have enough power to predict the presence of esophageal varices without upper GI endoscopy study.[18]

The Baveno V consensus,[19] conference on portal hypertension recommended that all cirrhotic patient should be screened for presence of esophageal varices when liver cirrhosis is diagnosed. However, this approach has two major limitations. Endoscopy is an invasive procedure and secondly the cost-effectiveness is questionable as only, 9-36% patients with cirrhosis are found to have varices on screening endoscopy.[20]

Transient elastography (TE) has been applied to the non-invasive diagnosis of portal hypertension and has been used to quantify liver stiffness (LS). When three simple techniques—platelet count, spleen size, and LS—are combined into a single score (LSPS), it has been demonstrated that patients with compensated cirrhosis can accurately identify EVs. Golgi Phosphoprotein 2 (GOLPH2)/Golgi protein 73 (GP73), the aspartate aminotransferase-to-platelet ratio index (APRI), the aspartate-to-alanine aminotransferase ratio (AAR), the fibrosis-4 index (FIB-4), the fibrosis index (FI), King, Lok, Forns, and FibroIndex scores, have all been suggested as minimally- or non-invasive tests (NITs) as alternatives to EGD for EV screening. However, these tests have a low diagnostic accuracy for EVs.[21]

Several attempts have been made to identify the parameters that can non-invasively predict the presence of EVs. Most studies have shown that platelet count and spleen diameter are directly or indirectly linked to the presence of EVs. It may therefore be cost effective to routinely screen patients at high risk for presence of varices to reduce the increasing burden and procedural cost of the endoscopy unit. Identification of non-invasive predictors will enable us to carry out endoscopy in selected patients, thus avoiding unnecessary intervention and at the same time not missing the patient at risk of bleeding. Therefore, there is a particular need for non invasive predictor for the presence of esophageal varices as that might ease the medical, social and economic burden of the disease.

MATERIALS AND METHODS

This hospital based cross-sectional study enrolled 50 liver cirrhosis patients admitted in Medicine ward, RIMS, Imphal for a period of 2 years from October 2014 to September 2016. After written consent was obtained, the participants underwent upper GIT endoscopy in our endoscopy unit, RIMS.

Inclusion criteria: Included patients >18 years age diagnosed as liver cirrhosis by physical, laboratory, and radiological evaluation.

Exclusion Criteria

Included patients having active variceal bleeding, history of previous gastrointestinal bleeding of any origin, use of medication for primary prophylaxis for variceal bleeding, patient who has undergone endoscopic sclerotherapy, band ligation for esophageal varices, history of surgery for portal hypertension, thrombocytopenia due to causes other than hypersplenism and patients not willing for the study.

Study Procedure

At the time of the upper endoscopy, a history was taken and a clinical examination was performed and a careful abdominal examination to diagnose chronic liver disease. After hospital admission, complete blood count (CBC), liver function test (LFT), renal function test (RFT),prothrombin time (PT), and international normalisation ratio (INR) were done for every patients.

Study Tool

1. Platelet counts done by automatic cell counter, HORIBA-ADIVA-60 in the dept. of Pathology, RIMS, Imphal.
2. Ultrasonography was done by a 3.5 MHz transducer attached MEDISON SONOACE X8 USG machine in the dept. of Radiodiagnosis, RIMS, Imphal. Liver architecture, size and nodularity; bipolar spleen diameter (the maximum diameter from upper pole to lower pole of spleen

ISSN (O): 2687-5365; ISSN (P): 2753-6556

in mm) and presence of ascites, collaterals, portal vein diameter, thrombus were recorded.

3. Upper gastrointestinal endoscopy: Patients were evaluated for the presence of esophageal varices, gastropathy, and other findings by. All endoscopies were performed by two gastroenterologists who were blinded to the patient's data. Platelet count/spleen diameter ratio was calculated in all patients as platelet count (N/mm3)/spleen diameter (mm).

Operational Definition

Cirrhosis: A combination of of clinical, biochemical, and ultrasonography data were used to diagnose cirrhosis. The existence of a heterogeneous liver with homogenous nodules, portal vein dilating, and crenellated liver contours were the basis for the ultrasound diagnosis of cirrhosis.

The Child Pugh score was used to determine the severity of cirrhosis. Class A scores were 5–6, class B scores were 7–9, and class C scores were 10–15.

Splenic diameter: Measured in millimeters (mm), the splenic diameter is the biggest diameter measured from the lowest tips to the highest point on the diaphragm, passing via the splenic hilum.[3]

Esophageal Varices: If varices were found during an endoscopic examination, they were categorized as either absent or present, and their grade was determined using the Paris classification system.

- Grade I: varicose veins vanish upon insufflation;
- Grade II: veins persist after insufflation but do not confluence;
- Grade III: veins persist after insufflation and confluence.

Large esophageal varices/high risk varices were classified as grades III, whilst tiny varicose veins were classified as grades I and II.[3]

Statistical Analysis

IBM: SPSS Statistics Version 20 was used for statistical analysis. Qualitative/categorical variables are described as number of cases and percentages while numerical/continuous variables are presented as Mean ± SD (standard deviation) or Median ± Interquartile range. For normality test for continuous data, One-sample Kolmogorov-Smirnov test was conducted. The unpaired t-test was conducted for two means of normally distributed data whereas Mann-Whitney U test was used for non-normally distributed data. And χ^2-test is applied according to the suitability of the test for the categorical data. In order to estimate Sensitivity and Specificity of the tool i.e., PC/SD ratio to predict esophageal varices among the liver cirrhosis patients, Receiver Operating Characteristic (ROC) curve technique is used. All comparisons are two-sided and the P-values of < 0.05, < 0.01 and < 0.001 are taken as the cut off values for significance, highly significance and very highly significance respectively.

Approval of Research Ethics Board and Informed consent: The study was approved by Research Ethics Board Regional Institute of Medical Sciences, Imphal.

RESULTS

The present study enrolled 50 liver cirrhosis patients with median age of 47 years and majority males (45, 90%). The baseline characteristics of the study subjects were given in table 1. Median platelet count was 6550.00 and the mean hemoglobin (Hb) level was 10.22. The most common presentation is ascites (43,86%) which is followed by hepatic encephalopathy (17,34%) and others and the commonest cause for liver cirrhosis was found to be alcohol (40,80%). Child turcotte pugh score(CTP) showed majority subjects in class C (26,52%) followed by class B(24,48%) and no patients in class A and among them 75% of CTP class B and 96.15% of C patients had varices respectively. Esophageal varices was found in 43(86%) patients and had strong relation with ascites (P=0.024) and low albumin (p-value = 0.049). Status of Varices-wise comparison of patients according to ascites was shown in table 2. Status of varices-wise comparison of Mean±SD / Median ± interquartile range of liver function test, PT INR, PC, SD and PC/SD ratio were given in table 3.

The findings of One-sample Kolmogorov-Smirnov test for the distribution of USG spleen diameter (SD) in mm (P=0.043) and PC/SD ratio (P=<0.001) showed that they don't follow normal distribution and therefore comparison is made in terms of median by Mann-Whitney U test. It is observed that the mean PC /µL in lacs for patients with esophageal varices (1.08 lacs / µL) was significantly lower than that of patients without esophageal varices (2.49 lacs / µL) as evident by a very highly significant P value of <0.001. On the contrary, median SD for former group was found to be 160 as against 100 for latter group and the difference was significant statistically as P=0.043. Further, a very highly significant P<0.001 for PC/SD ratio highlights that patients with esophageal varices have lower ratio (1034.48) than the patients without esophageal varices (1888.05).

The Receiver Operating Characteristic (ROC) analysis was performed to determine PC/SD ratio as a predictor of presence of varices. The area under the ROC curve was found to be 0.934 with 95% CI (graphically also shown in fig-1). It indirectly indicates that diagnostic accuracy of PC/SD ratio to detect esophageal varices among the liver cirrhosis is 93.4%. In other words, the test can distinguish between two diagnostic groups viz., presence or absence of varices by 93.4% which is highly significant statistically (P<0.001). The cutoff value of PC/SD ratio i.e., ≤1391.987 is recorded with 86.00% sensitivity and 85.70% specificity respectively. It indicates that the cut off value of PC/SD ratio ≤1391.987 is adequate to predict 86.00% correct results (true positive) out of patients who have varices and wrong diagnosis for 14 % of patients with varices (false negative). On the other hand, 85.70% specificity highlights that 85.70% of

ISSN (O): 2687-5365; ISSN (P): 2753-6556

the non-varices patients will give true negative result, 14.30% of non-varices screened by the test will be wrongly classified as varices when they are not. In the present study positive predictive value and negative predictive value were found to be 53.75% and 96.93% respectively which can be treated very high statistically. Furthermore, the likelihood ratio of a positive test is defined as sensitivity/ (1-specificity) and the likelihood ratio of a negative test value is defined as (1-sensitivity)/ specificity. And the corresponding findings were 6.01 and 0.16.

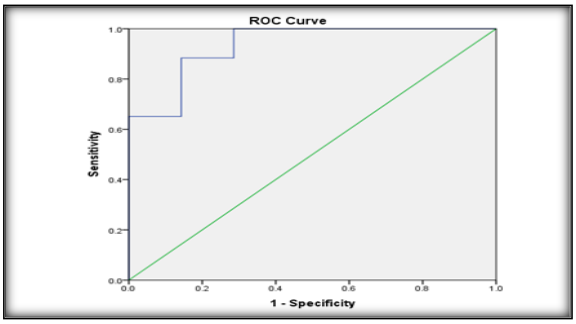

Figure1: Showing ROC curve along with sensitivity and 1-specificity

Table 1: Baseline characteristics of the study subjects (N = 50)

Characteristics	Study patients (N = 50), n (%)	
Sex: Female: Male	5(10) : 45(90)	
Age (year)	47.00 (40.00 - 55.00)	
Hb	10.22 ± 1.38	
TLC	6550.00 (4950.00 - 10372.50)	
Clinical presentation		
Hepatic encephalopathy	17(34%)	
Ascites, jaundice	11(22%)	
Ascites	7(14%)	
Hepatic encephalopathy, ascites, edema	6(12%)	
Ascites,edema, jaundice	5(10%)	
Ascites, HRS-2	2(4%)	
Ascites, pleural effusion, acute kidney injury, edema	1(2%)	
Ascites, SBP, hepatic encephalopathy, edema	1(2%)	
Cirrhosis etiology		
Alcoholic	40(80%)	
Hepatitis-C	4(8%)	
Hepatitis-C with alcohol	2(4%)	
Hepatitis-B with alcohol	2(4%)	
Hepatitis-B	1(2%)	
Cryptogenic	1(2%)	
Child Turcotte Pugh Score		Varices presence
A	0(0%)	0%
B	24(48%)	75%
C	26(52%)	96.15%

Table 2: Status of Varices-wise comparison of patients according to ascites (N=50)

Ascites	Status of Varices			χ^2-value	d.f.	P-value
	Absence (n=7)	Presence (n=43)	Total (n=50)			
No	5(71.4%)	12(27.9%)	17(34.0%)	5.081	1	0.024
Yes	2(28.6%)	31(72.1%)	33(66.0%)			
Total	7(100.0%)	43(100.0%)	50(100.0%)			

n: number of cases; df: degree of freedom, χ^2-test,
P: probability of difference due to chance factors

Table 3: Status of varices-wise comparison of Mean±SD / Median ± interquartile range of liver function test, PT INR, PC, SD and PC/SD ratio (N = 50)

Characteristics	Mean±SD / Median ± interquartile range		t-value/ U-value*	df	p-value
	Absence of EV (n=7)	Presence of EV (n=43)			
Bilirubin	3.56± 3.57	6.31± 7.50	0.946	48	0.349
Albumin	2.60(2.20- 3.00)	2.00(1.80 - 2.20)	0.049*		
AST	138.00(94.00- 239.00)	88.00(56.00 - 156.00)	0.149*		
ALT	59.00(31.00- 77.00)	44.00(35.00 - 68.00)	0.459*		
ALP	203.00(176.00 -260.00)	200.00(136.00 - 256.00)	0.459*		
GGT	57.00(48.00 - 76.00)	74.00(50.00 - 94.00)	0.213*		
PT	15.88± 3.34	20.88± 3.34	3.489	48	0.043
INR	1.40±.38	2.80±.53	7.887	48	0.045
PC /µL	249571.42± 112992.41	108069.76± 36282.88	5.219	48	<0.001
USG spleen diam (mm) (SD)	110.00(100.00 - 120.00)	160.00(140.00 - 180.00)	0.043*		
PC/SD ratio	1888.05(1400.00 - 2800.00)	1034.48(844.44 - 1313.86)	<0.001*		

Normal distribution data: mean ± standard deviation (Mean ± SD),
Non-Normal distribution data: median ± interquartile range,
n: number of cases; df: degree of freedom; independent sample test;

ISSN (O): 2687-5365; ISSN (P): 2753-6556

U:Mann-Whitney U Test, P: probability of difference due to chance factors

DISCUSSION

The present study included 50 liver cirrhosis patients, majority males (45, 90%) mostly belonging to Child Pugh score class C (26,52%). Esophageal varices was detected in 43(86%) patients and the presence of ascites is significantly associated with the presence of esophageal varices (P=0.024) and serve as independant predictor for large esophageal varices which was at par with studies by Thomopoulos KC et al,[22] and Zaman A et al,[23] who reported that advanced Child-Pugh class were more commonly associated with the presence of varices. In the present study also it reveals that low albumin has statistically strong relation with the presence of varices (p-value = 0.049) which is similar to study by Bressler B et al.[24]

In the present study, PT & INR can be an independent predictor for presence of EV with a significant p-value of 0.043 and 0.045 respectively which was also supported by Madhotra et al.[25] Pilette C,[26] et al in his study reported that PT can diagnose large esophageal varices with diagnostic accuracy of 80%.

In this study, the analysis of the non- invasive predictors was based on the maximum spleen diameter (SD), measured in millimeters using abdominal USG and the platelet count (PC). These two parameters were used to calculate the PC/SD ratio. Patients with EV has significantly higher bipolar spleen diameter mean (160 mm) in comparison to patients without EV. Statistical analysis (p-value <0.43) shows that presence of EV can be predicted from higher bipolar spleen diameter which was in agreement with a study by Sharma SK et al.[27]

In the present study mean platelet value in patients with EV is 1.08 lakhs/µL compared to 2.49 lakhs /µL in patients without EV which is statistically very highly significant (p-value < 0.001) which was consistent with the studies by Sharma SK et al 27(p-value of <0.002), Zaman A et al,[28] (p < 0.05). In the study by Chalasani et al,[29] the PC and splenomegaly independently predicted the presence of EV.

Thrombocytopenia can be caused by splenic sequestration or by a decrease in hepatic production of thrombopoietin from cirrhotic liver, bone suppression from alcohol and immunologically antibody mediated platelet destruction. Spleen become enlarged in portal hypertension due to hypersplenism in the present study PC/SD ratio has a significant relation with the presence of EV in cirrhotic patients as revealed from very highly significant p-value (<0.001). A cut-off point of ≤1391.987 produced for prediction of varices, with a sensitivity and specificity of 86.00% and 85.70% respectively. The positive predictive value and negative predictive value of PC/SD ratio are 53.75% and 96.93% respectively. For prediction of EV, PC/SD ratio is significantly better than accuracy of either PC alone or SD alone which is similar to the studies by Freeman et al,[30]Legasto GMA et al,[31] (sensitivity 88.4%, specificity 80.2%)and Giannini et al,[32] (specificity of 67%).These parameters all are easy to obtain, reproducible, and non-invasive. Another advantage is that no additional expense is involved as these studies are performed routinely in patients with liver cirrhosis. So from this study we found that these predictors especially platelet count/ bipolar spleen diameter ratio may predict the existence of EV in cirrhotic patients with high diagnostic accuracy which will be helpful areas where endoscopy facilities are not readily available, to initiate appropriate therapy in these patients.

Limitations

Cirrhosis of liver due to other etiology may not be determined by PC/SD ratio. The diagnosis of cirrhosis was made mainly on clinical, biochemical and USG parameters rather than liver biopsy. The USG abdomen and UGI endoscopy were not routinely done by single consultant, so there may be intra-observer variability in measuring spleen diameter and varices grading. Moreover, size of sample is also small.

CONCLUSION

Large bipolar spleen diameter and thrombocytopenia could be reliable, independent and strong indicators of esophageal varices. Patients with liver cirrhosis can also be accurately predicted to have esophageal varices using the platelet count/bipolar spleen diameter ratio. When endoscopic facilities are unavailable, the platelet count to spleen diameter ratio may be a helpful non-invasive diagnostic technique for EVs in liver cirrhosis, thereby helping the treating physicians to start preventative treatment for EVs as soon as possible.

Funding

No funding sources

Conflict of interest

None declared

Ethical Approval

The study was approved by the Institutional Ethics Committee.

REFERENCES

1. De Franchis R, Primignani M. Natural history of portal hypertension in patients with cirrhosis. Clin Liver Disease 2001; 5: 645-63.
2. Gupta TK, Chen L, Groszmann RJ. Pathophysiology of portal hypertension. Clin Liver Dis 1997; 1:1-12.
3. Gebregziabiher HT, Hailu W, Abay Z, Bizuneh S, Meshesha MD. Accuracy of non-invasive diagnosis of esophageal varices among cirrhotic patients in a low-income setting. Heliyon. 2023 Dec 3;9(12):e23229. doi: 10.1016/j.heliyon.2023.e23229. PMID: 38149190; PMCID: PMC10750066.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

4. Luketic VA, Sanyal AJ. Esophageal varices. I clinical presentation, medical therapy and endoscopic therapy. Gastroenterology Clinics of North America 2000: 29: 337-85.
5. Merli M, Nicolini G, Angeloni S. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol 2003; 38: 266-78.
6. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices A prospective multicenter study. The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. N Engl J Med 1988; 319: 983-90.
7. D'Amico G, Pagliano L, Bosch J. The treatment of portal hypertension, a meta-analysis review. Hepatology 1995; 22: 332-54.
8. Nevens F, Bustami R, Scheys I, Lesa_re E, Fevery J. Variceal pressure is a factor predicting the risk of a first variceal bleeding: a prospective cohort study in cirrhotic patients. Hepatology 1998; 27: 15-19.
9. Merkel C, Zoli M, Siringo S, van Buuren H, Magalotti D, Angeli P, et al. Prognostic indicators of risk for first variceal bleeding in cirrhosis: a multicenter study in 711 patients to validate and improve the North Italian Endoscopic Club (NIEC) index. Am J Gastroenterol 2000; 95: 2915-2920.
10. Merkel C, Marin R, Angeli P, Zanella P, Felder M, Bernardinello E, et al. A placebo-controlled trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. Gastroenterology 2004; 127(2): 476-84.
11. Zoli M, Merkel C, Magalotti C, Gueli C, Grimaldi M, Gatta A, et al. Natural history of cirrhotic patients with small esophageal varices: a prospective study. Am J Gastroenteterol 2000; 95(2): 503-8.
12. D'Amico G, L Pagliaro. The clinical course of portal hypertension in liver cirrhosis. In: Rossi P, ed. Diagnostic Imaging and Imaging Guided therapy. Berlin: Springer-Verlag 2000:15-24.
13. Cales P, Desmorat H, Vinel JP, Caucanas JP, Gerin P, Brouet P, et al. Incidence of large esophageal varices in patients with cirrhosis: application to prophylaxis of first bleeding. Gut 1990; 31: 1298-1302.
14. D' Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension. A meta-analytic review. Hepatology 1995; 22: 332-54.
15. Pagliaro L, D'Amico G, Pasta L, Politi F, Vizzini G, Traina M, et al. Portal hypertension in cirrhosis: Natural history. In: Bosch J, Groszmann RJ, editors. Portal Hypertension. Pathophysiology and Treatment. Oxford: Blackwell Scientific; 1994: 72-92.
16. Merli M, Nicolini G, Angeloni S, Rinaldi V, De Santis A, Merkel C, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol 2003; 38: 266-72.
17. Salerno F, Grebes F, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 2007; 21: 111-23.
18. Wadei HM, Mai ML, Ahsan N, and Gonwa TA. Hepatorenal Syndrome: Pathophysiology and Management. Clin J Am Soc Nephrol 2006; 1: 1066 –1079.
19. De Franchis R. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2010; 53(4): 762-68.
20. Peck Radosavljevic M. Thrombocytopenia in liver disease. Can J Gastroenterol 2000; 14: 60-66.
21. Li S, Huang P, Jeyarajan AJ, Ma C, Zhu K, Zhu C, Jiang N, Li M, Shao T, Han M, Tan L, Lin W. Assessment of Non-invasive Markers for the Prediction of Esophageal Variceal Hemorrhage. Front Med (Lausanne). 2021 Dec 1; 8:770836. doi: 10.3389/fmed.2021.770836. PMID: 34926512; PMCID: PMC8672133.
22. Thomopoulos KC, Labropoulou-Karatza C, Mimidis KP, Katsakoulis EC Iconomou G, Nikolopoulou VN. Non-invasive predictors of the presence of large esophageal varices in patients with cirrhosis. Dig Liver Dis 2003; 35:473-78.
23. 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: 2564-70.
24. Bressler B, Pinto R, El-Ashry D, Heathcote EJ. Which patients with primary biliary cirrhosis or primary sclerosing cholangitis should undergo endoscopic screening for esophageal varices detection. Gut 2005; 54: 407-10.
25. Madhotra R, Mulcahy HEI, Willner L. Prediction of esophageal varices in patients with cirrhosis. J Clin Gastroenterol 2002; 34: 4-5.
26. Pilette C, Oberti F, Aube C, Rousselet MC, Bedossa P, Gallois Y, et al. Non-invasive diagnosis of esophageal varices in chronic liver diseases. J Hepatol 1999; 31(5): 867-73.
27. Sharma SK, Aggarwal R. Prediction of large esophageal varices in patients with cirrhosis of the liver using clinical, laboratory and imaging parameters. J Gastroenterol Hepatol 2007; 22: 1909-15.
28. Zaman A, Hapke R, Flora K. Factors predicting the presence of esophageal or gastric varices in patients with advanced liver disease. Am J Gastroenterol 1999; 94: 3292-96.
29. Chalasani N, Imperiale TF, Ismail A. Predictors of large esophageal varices in patients with cirrhosis. Am J Gastroenterol 1999; 94: 3285-91.
30. Freeman JG, Darlow S, Cole AT. Platelet count as a predictor for the presence of esophageal varices in alcoholic cirrhotic patients. Gastroenterology 1999; 116: A 1211.
31. Legasto GMA, Sevilla J, Balay A, Tan JA, Cham LV, Vitug A, et al. Platelet count/Spleen diameter ratio: A non-invasive parameter to predict the presence of esophageal varices. Phil J Gastroenterol 2006; 2: 33-38.
32. Giannini E, Botta F, Borro P, Risso D, Romangnoli P, Fasoli A, et al. Platelet count/spleen diameter ratio: Proposal and validation of a non-invasive parameter to predict the presence of esophageal varices in patients with liver cirrhosis. Gut 2003; 52: 1200-1205.

ISSN (O): 2687-5365; ISSN (P): 2753-6556