Original Article

Correlation between Platelet Count vs Spleen Bipolar Diameter Ratio and Esophageal Varices in Liver Cirrhosis

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Abstract

Background: *Esophageal variceal bleeding is a potentially fatal complication in patients with liver cirrhosis and portal hypertension. In cirrhotic patients, endoscopic screening for esophageal varices (EV)is currently recommended at the time of diagnosis. The present study intends to find out correlation between platelet count-spleen bipolar diameter ratio and esophageal varices in liver cirrhosis and prospectively validate its use for the noninvasive diagnosis of EV.*

Methods: *This observational study was done at theDepartment of Gastrointestinal Hepatobiliary and Pancreatic Disorder, BIRDEM General Hospital, Dhaka, during the period of November, 2013 to October, 2014. A total 64 patients with cirrhosis of liver were included. Complete blood count, liver function tests, ultrasonographyof whole abdomenand endoscopy of upper gastro-intestinal tract (GIT)were done in all patients. Statistical analysis was done with SPSS version 16.*

Results: *Among 64 study population EV were detected in 54 patients (84.4%). The platelet count/ spleen bipolar diameter ratio was significantly higher without EV compared with those with EV(1570 ± 493) and (688 ± 227), respective-ly; ($p<0.001$).Patients with EV had lower platelet counts (86799.84 ±27389.99/mm^3, $p<0.001$), higher bipolar spleen diameters (127.94±15.14 mm, $p<0.001$) and lower platelet count/ spleen bipolar diameter ratios (688.79 ±227.13, $p<0.001$). In this analysis, by applying (ROC)curve the platelet count-spleen bipolar diameter ratio at a cut-of 908.5 maintained high sensitivity (100 %), Robust negative predictive value NPV (100%),specificity (55.6%) and PPV (85.4%), with an overall diagnostic accuracy of 87.50% for the prediction of EV.With advancing Child-Pugh (C-P) class the percentage of patients with varices increased, 33.3% in C-P class A, 85.7% in C-P class B and 91.6% in C-P class C. The presence of EVcorrelated signifi-cantly with the severity of liver cirrhosis ($p = 0.03$) as measured by Child-Pugh score.*

Conclusion: *The identification of non-endoscopic, noninvasive methods that can accurately predict esophageal varicesin cirrhosis of liver has been addressed in several recent studies. This study was yet another attempt to achieve this goal. Predicting the presence of EV by noninvasive means would restrict the performance of endoscopy and reducing the number of unpleasant screening endoscopies.*

Key wards: *Liver Cirrhosis, Platelet Count / Spleen Bipolar Diameter Ratio, Esophageal Varices.*

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Introduction

Cirrhosis of liver is the end stage of chronic liver disease resulting in formation of fibrous tissue, disorganization of liver architecture and nodule formation which interferes with liver function and lead to development of portal hypertension. Portal hypertension is associated withdevelopment of a hyperdynamic circulation and complications such as ascites, hepatic encephalopathy and oesophago-gastric varices.[1] Esophageal variceal bleeding is a potentially fatal complication in patients with liver cirrhosis and portal hypertension. Most cirrhotic patients develop esophageal varices (EV) with a lifetime incidence as high as 90%. Approximately one

third of cirrhotic patients with EV develops an episode of esophageal hemorrhage and subsequently has high morbidity and mortality.[2] Therefore early detection of EV in cirrhotic patients are crucial to reduce complications. An endoscopic examination is currently considered to be the gold standard.

American College of Gastroenterology recommends screening of all cirrhotic patients for the presence of esophageal varices.[3] Other investigators recommend that screening should be performed every 2 years for cirrhotic patients without varices and those patients with known small varices undergo endoscopy every year.[4]These recommendations imply a large workload on endoscopic units and significant cost burden on patients with liver cirrhosis. Thus, there is a need for noninvasive means to detect or guess the presence of esophageal varices to ease the medical and social burden of the disease. Platelet count, white blood cell (WBC) count, splenomegaly, platelet count/spleen diameter ratio (PC/SD), advanced Child-Pugh class, serum albumin and high portal vein diameter may be useful noninvasive predictors of esophageal varices in patients with cirrhosis.[5, 6]

Splenomegaly detected on clinical examination was an independent risk factor for the presence of large varices.[7]It was demonstrated that cirrhotic patients in Child-Pugh classes B or C were almost 3 times as likely to have esophageal varices or large varices as compared to patients in Child-Pugh class A.[8]In a recent analysis of homogenous patients with compensated Child-Pugh class A/B cirrhosis, 84% were found to have cytopenia and 32%of these patients had a combination of cytopenia. The pathogenesis of abnormal hematological indices in cirrhosis is multifactorial and includes portal hypertension induced sequestration, alterations in bone marrow stimulating factors, viral and toxin induced bone marrow suppression and consumption or loss.[9]

Schepis et al. reported screening by gastroscopy when platelet count <100,000/mm^3 resulted in a significant yield of esophageal varices.[10]Another studiesof cirrhotic patients without history of variceal bleeding who underwent gastroscopy as part of a liver transplant evaluation, found platelet count of <88,000/mm^3 associated with the presence of large varices.[4,5]The discriminating thresold for the presence of varices varied widely, ranging between 68,000 and 160,000/mm^3.[11]

The sensitivities for thrombocytopenia fluctuate from 62% to 100% and the specificities range from 18% to 77%.[12] Thrombocytopenia and leucopenia can be used to stratify risk for occurrence of EV in cirrhotic patient and gastroscopy will have a high yield for varices when platelet count is d" 130,000/mm3 or WBC count is d" 3,500/mm3.[13] This variation of platelet count may be due to retrospective pattern of the majority of studies, heterogeneous cohorts of patients results both selection and spectrum bias. Different studies found no definite level of platelet count that accurately predicted the presence of esophageal varices (AUROC curve 0.63) and they, therefore, concluded that platelet count is an inadequate noninvasive marker for prediction of the presence of esophageal varices. In an attempt to improve the predictive value of the platelet count, it has been combined with other variables.[14]

Platelet count/Spleen diameter ratio is calculated easily dividing the platelet number/mm3 by the maximum spleen bipolar diameter in mm as estimated by abdominal ultrasound. Different studies are done for assessing this parameter as a predictor of oesophagealvarices.Giannini et al. 2003, reported the platelet count/spleen diameter ratio to be the only independent variable associated with presence of EV on multivariate analysis and identified a cut-off value of 909, giving a PPV of 96% and NPV of 100%. The second part of the study confirmed the reproducibility of this cut-off level with a PPV of 74% and NPV of 100% in compensated cirrhotic patients. The same group then followed up 68 patients without EV with repeat endoscopy and calculation of the platelet/spleen diameter ratio. At follow-up patients with a platelet count/spleen diameter ratio <909 had 100% NPV and 84% PPV and they concluded that the platelet count spleen diameter ratio was effective in ruling out the presence of EV when cirrhotic patients were followed longitudinally.[15] Subsequently, a multicentre international validation study using the 909 ratio was performed among 218 patients which found the similar findings.[6]This study is aimed to evaluate the relationship between platelet count/spleen diameter ratio and esophageal varices among the patients of cirrhosis of liver, which is a noninvasive parameter to determine the presence of esophageal varices.

Methods

This observational cross sectional study was carried out at the GHPD department, BIRDEM General Hospital, Dhaka from November 2013 to October 2014. Non probability sampling (Purposive sampling) technique was applied. Adult patients age>18 years who are suffering from CLD on the basis of clinical, biochemical and USG or fibroscan of liver irrespective of cause, had no history of variceal band ligation or sclerotherapy and who wants to take active participation to this study were included in this study. Patients having active gastrointestinal bleeding at the time of admission, with severe cardiac, pulmonary, renal or cerebrovascular disease, H/O portosystemic shunt operation, known hematological malignancy ,solid organ malignancy & splenomegaly due to other Infectious disease were excluded from the study.

Informed written consent was taken from each patient before enrollment. To detect etiology of cirrhosis of liver HBsAg, AntiHCV were done in all cases. Demographic data like age, sex, clinical data like presence of jaundice, ascites, hepatomegaly, splenomegaly, features of hepatic encephalopathy, anaemia, active bleeding were recorded. Laboratory data like haemoglobin, white cell count, platelet count, peripheral blood film, serum bilirubin, serum albumin, AST, ALT, prothrombin time were recorded.In case of requirement of transfusion, blood sample were collected before the first transfusion. Endoscopy of upper GIT were done by Olympus GIF-Q 160 video endoscopy in endoscopy room in presence and under direct supervision of the thesis guide or co-guide. Varices were classified into small, medium & large by W. G. O. practice guideline, June, 2013, grading system. All the information was properly noted in the preformed data sheet. Relationship between platelet count/spleen diameter ratios and different sizes of esophageal varices were evaluated later.

Statistical analyses were carried out by using the Statistical Package for Social Sciences version 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean, standard deviation, and categorical variables as frequencies and percentages. The differences between groups were analyzed by unpaired t-test, chi-square (X^2) test, and ANOVA test. Correlation between variables was measured by PearsonCs correlation coefficient test. Receiver operating characteristic (ROC) curves were generated. A p-value <0.05 was considered as significant.

Ethical clearance

It was taken from ethical committee of Bangladesh Diabetic Samity. Informed written consent had been taken from every patient prior to data collection.

Operational definitions

Cirrhosis of liver

Imaging and/or histopathological evidence of cirrhosis of liver with clinical features suggestive of cirrhosis of liver.

Table I. Child Pugh Score[16]

Assessment criteria	Points scored for abnormality		
	1	2	3
Encephalopathy grade	None	Mild	Marked
Ascites	None	Mild	Marked
Bilirubin (µmol/L)	<34	34-50	>50
Albumin (g/L	>35	28-35	<28
Prothrombin time(second prolonged)	<4	4-6	>6

Individual scores should be added

Score <7= Childs A

7—9 Childs B

>9 Childs C

Table II. Grading of esophageal varices[17]
Progression of gastrointestinal varices can be determined on the basis of the size classification at the time of esophagogastroduodenoscopy (EGD).

Size of varix	Two-size classification	Three-size classification
Small	< 5 mm	Minimally elevated veins above the esophageal mucosal surface.
Medium	-	Tortuous veins occupying less than one-third of the esophageal lumen
Large	> 5 mm	Occupying more than one-third of the esophageal lumen.

Cytopenia
Defined as a platelet count of less than or equal to 150,000/mm³, WBC count of less than or equal to 4000/mm³ or hemoglobin level less than or equal to 13.5 g/dL for men and 11.5 g/dL for women.

Results
Out of 110 patients, 64 were included in this study after exclusion. The mean age was 53±6 years (range 30–74 years).Cirrhosis was predominantly found in fifth decade (n=31). 48(75%) were male & 16(25%) were female. EVs were detected in 54 patients (84.4%). The platelet count/ spleen bipolar diameter ratio was significantly higher without EVs compared with those with EVs (1570 ± 493) and (688 ± 227), respective-ly; (p<0.001).Patients with EVs had lower platelet counts (86799.84 ±27389.99/mm^3, p<0.001), higher bipolar spleen diameters (127.94±15.14 mm, p<0.001) &lower platelet count/ spleen bipolar diameter ratios (688.79 ±227.13, p<0.001). In this analysis, by applying ROC curve the platelet count/spleen bipolar diameter ratio at a cut-of 908.5 maintained high sensitivity (100 %), Robust negative predictive value NPV (100%), specificity (55.6%) and PPV (85.4%), with an overall diagnostic accuracy of 87.50% for the prediction of esophageal varices.With advancing Child-Pugh (C-P) class the percentage of patients with varicesincreased, 33.3% in C-P class A. 85.7% in C-P class B and 91.6% in C-P class C. The presence of EVs correlated signifi-cantly with the severity of liver cirrhosis (p = 0.03) as measured by Child-Pugh score.

Table III. Demographic and laboratory characteristics of cirrhotic with and without esophageal varices (N=64)

Variables	Cirrhotic without EV(n=10) (Mean ±SD)	Cirrhotic with EV(n=54) (Mean ±SD)	p value*
Sex (male /female)	7/3	41/13	0.70
Age (in years)	54.10±8.31	57.62±9.18	0.26
Albumin (gm/L)	34.0±3.68	29.96±4.71	0.01
Prothrombin time (sec)	11.67±0.55	14.72±2.29	<0.001
Platelet count (n/mm^3)	170080±47226	86799±27389	<0.001
Spleen diameter (mm)	110.3±13.2	127.94±15.14	0.001
Platelet count/spleen ratio	1570 ±494	688±227	<0.001

* p value were obtained by “t” test

Table IV. Endoscopic finding among the study population (N=64)

Endoscopic finding	Frequency	Percent
No EVs	10	15.6
EVs		
• Small(grade-I)	26	40.6
• Medium(gr-II)	13	20.4
• Large(gr-III)	15	23.4
Total 64	100.0	

EV=Esphagealvarices.

Table III shows total 54 (84.4%) patients had EVs. Among them 40.6% had small varices, 20.3% had medium varices and 23.4% had large varices. Only 10 (15.6%) patients had no esophageal varices.

Table V. Distribution of patients with and without esophageal varices by Child-Pugh score (N=64)

Variables	Patients without EVs(n=10)	Patients with EVs(n=54)	Total (%)	p value
Child-Pugh A	02 (20%)	01(1.8%)	03 (4.6)	Not done
Child -Pugh B	07 (70%)	42 (77.8%)	49(76.5)	0.03
Child -Pugh C	01 (10%)	11 (20.4%)	12(18.7)	Not done

EVs = esophageal varices. Data are expressed as numbers and percentages and compared by chi-square test

Table VI. Best-fittinglogistic regression predictors of esophageal varices.

Predictor	Regression coefficient	Odds ratio	99% CI	p-value
Platelet count/bipolar spleen diameter ratio	0.756	2.37	2.247-2.511	<0.001

Table VII. Predictive accuracy of the best cutoff value of platelet count/ bipolar spleen diameter ratio in the diagnosis of esophageal varices

Cut off value	Sensitivity	Specificity	PPV	NPV	Accuracy
908.5	100%	55.56%	85.19%	100%	87.50%

NPV = negative predictive value
PPV = positive predictive value

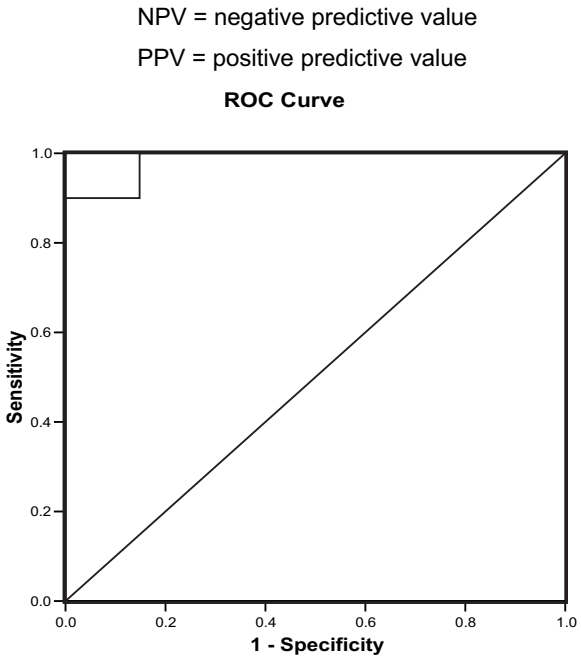

Figure 1. *Receiver operating characteristic (ROC) curve of platelet count/ bi-polar spleen diameter ratio. The area under the ROC curve for the platelet count/ bipolar spleen diameter ra-tio was 0.98 (± 0.02) which represents the overall diagnostic accuracy (87.5%) in prediction of esophageal varices. AUC = area under the curve, AUC for ratio = 0.98 ± 0.02*

Discussion

Cirrhosis of liver is not uncommon problem in Bangladesh. For all cirrhotic patients, regular periodic evaluation with endoscopy is required.[1]But Endoscopy unit is not available in all hospitals of Bangladesh, particularly in rural areas, so it is necessary to find other easier modalities for the diagnosis and monitor-ing of portal hypertension. Thus, a method of predicting the presence of EVs noninvasively, is in great demand to avoid unpleasant endoscopy and improve the management. In this study the mean age of study population was found 53(±6) years. Similarly, Said et al. and Gue et al. also found cirrhosis in older age group.[13, 18]It was observed that among 64 patients 54 (84.4%) had esophageal varices,40.6% patients had small esophageal varices, 20.3% had medium, 23.4% had large esophageal varices and 15.7% had no varices which is similar to endoscopic findings of other studies.[4, 10, 15, 19]In this current series showed more patient of advanced cirrhosis according to Child Pough score, had oesophagealvarices.[20]Varices eventually develop in all patients with liver cirrhosis and they tend to increase in size with time. The prevalence of varices is higher in decompensated than in compensated cirrhosis, and that large varices have a higher propensity to bleed than small varices.[11]

In this study it was found that cirrhotic patient with splenomegaly,thrombocytopenia and increase spleen bipolar diameter measured by USG had more possibility to have OV. Different studies in recent years also found similar findings. [1,5,6]Splenomegaly is recognized as one of the diagnostic signs of cirrhosis and portal hypertension. Several studies have reported that splenomegaly could be a good predictor of LEV for cirrhotic patients.[5, 21, 22] Spleen width measured by ultrasonography was an independent predictor for the presence of EV.[23]Platelet count/Spleen bipolar diameter ratio have been recently found as a good indirect parameters for prediction of presence of EV in cirrhotic patients.[6, 15]But available data are limited in our country regarding this factor. The possible relationships between splenomegaly and portal hypertension have been analysed in patients with cirrhosis. Splenomegaly is not only caused by portal congestion, but it is mainly due to tissue hyperplasia and fibrosis. The increase in spleen size is followed by an increase in splenic blood flow, which participates in portal hypertension actively and congesting the portal system.[24]Thrombocytopenia is the most common hematological abnormality encountered in patients with chronic liver disease (CLD). In addition to being an indicator of advanced disease and poor prognosis, it frequently prevents crucial interventions. Multiple factors contribute to the development of thrombocytopenia and these can broadly be divided into those that cause decreased production, splenic sequestration, and increased destruction. Depressed thrombopoietin levels in CLD, together with direct bone marrow suppression, result in a reduced rate of platelet production. Thrombopoietin regulates both platelet production and maturation and is impaired in CLD. Bone marrow suppression can be caused by viruses, alcohol, iron overload, and medications. Splenic sequestration results from hypersplenism. The increased rate of platelet destruction in cirrhosis also occurs through a number of pathways: increased shear stress, increased fibrinolysis, bacterial translocation, and infection result in an increased rate of platelet

aggregation, while autoimmune disease and raised titers of antiplatelet immunoglobulin result in the immunologic destruction of platelets.[25]Historically, thrombocytopenia in cirrhosis was attributed to increased pooling of platelets in an enlarged spleen.[26] The term hypersplenism was first used in 1909 to describe the presence of splenomegaly in patients with hemolytic anemia. The concept subsequently evolved to describe a distinct clinical syndrome of splenic hyperactivity associated with splenomegaly, a reduction in one or more peripheral cell types, an appropriately proliferative bone marrow response, and potential for reversal with splenectomy.[27] Congestive splenomegaly develops as a result of portal hypertension and is characterized by a redistribution of blood flow and platelets from the circulating pool to the splenic pool.[28] As a result, splenomegaly leads to thrombocytopenia by sequestration, and there is an inverse relationship between spleen size and platelet count.[29] Because the sequestrated platelets are still capable of removing TPO from the circulation, they further contribute to the development of thrombocytopenia by lowering TPO levels.[30]The limitation was study population was selected from single centre, short period of time, small sample size, **g**rading of varices may be subject to inter-observer variability and **w**hen the grade of varices was showed as a range, the upper grade was taken.

Conclusion

The identification of non-endoscopic, noninvasive methods that can accurately predict EVs in cirrhosis of liver has been addressed in several recent studies. This study was yet another attempt to achieve this goal which showed thrombocytopenia, higher bipolar spleen diameter as well as, significant positive correlation between platelet count/spleen bipolar diameter ratio with esophageal varices as noninvasive parameter. Predicting the presence of EVs by noninvasive means would restrict the performance of endoscopy and reducing the number of unnecessary screening endoscopies.

Recommendation: However, the evidence for the noninvasive diagnosis is not yet sufficient to replace endoscopy as a diagnostic tool for EVs in all cirrhotic patients. Further study with large sample size and prospective cohort studies are needed to validate its efficacy.

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Conflict of interest: Nothing to diclare.

References

1. Garcia-Tsao G, Sanyal AJ, Grace ND, and Carey W. Prevention and management of Gastro-oesophagealvarices and varicealhaemorrhage in cirrhosis. AASLD Practice Guideline, Hepatology 2007; 46(3): 922–38.
2. Chang YW. Indication of treatment for esophageal varices: who and when? Digestive Endoscopy 2006;18(1): 10-15.
3. Grace N. Diagnosis and treatment of gastrointestinal bleeding secondary to portal hypertension. American college of gastroenterology practice parameter committee. Am J gastroentol 1997;92:1081-91.
4. Zaman A, Becker T, Lapidus J, Benner K.. Risk factors for the presence of varices in cirrhotis patients without a history of variceal haemoorhage. Arch Intern Med 2001; 161: 2564-70.
5. Chalasani N, Imperiale TF, Ismail A, Sood G, Carey M, Wilcox CM. Predictors of large esophageal varices in patients with cirrhosis. Am J Gastroenterol 1999; 94: 3285-91.
6. Giannini E, Zaman A, Kreil A, Floreani A, Dulbecco P, Testa E, et al. Platelet count/spleen diameter ratio for the noninvasive diagnosis of esophageal varices: Results of a multicenter, prospective, validation study. Am J Gastroenterol 2006; 101: 2511-19.
7. Zaman A, Hapke R, Flora K, Rosen HR, Benner K. 1999. Factors predicting the presence of esophageal or gastric varices with advanced liver disease. Am J Gastroenterol 1999;94: 3292-96.
8. Barrera F, Riquelme A, Soza A, Contreras A, Barrios G, Padilla O. Platelet count/spleen diameter ratio for non-invasive prediction of high risk esophageal varices in cirrhotic patients.' Ann Hepatol 2009;8(4):pp 325-30.
9. Qamar AA, Grace ND, Groszmann RJ, Garcia-Tsao G, Bosch J, Burroughs AK. et al. Incidence, prevalence, and clinical significance of abnormal hematologic indices in compensated cirrhosis. Clin Gastroenterol Hepatol 2009;7(6): 689-95.
10. Schepis F, Camma C, Niceforo D, Magnano A, Pallio S, Cinquegrani M. et al. Which patients with cirrhosis should undergo endoscopic screening for esophageal varices detection? Hepatology 2001; 33(2): 333-8.
11. De Franchis, R. Noninvasive diagnosis of esophageclvarices. is it feasible? Am J Gastroenterol 2006;101(11): 2520-22.
12. D'Amico G, Morabito A.. Noninvasive markers of esophageal varices. Another round not the last. Hepatology 2004;39(1): 30-34.
13. Said HEE, Elsayed EY, Ameen A, Elal HA.. Cytopenia as A Predictor Of OesophagealVarices In Patients with Liver Cirrhosis. Report and Opinion 2010;2(7): 17-23.

14. Qamar AA, Grace ND, Groszmann RJ, Garcia-Tsao G, Bosch J, Burroughs AK, et al., "Platelet count is not a predictor of the presence or development of gastroesophagealvarices in cirrhosis," Hepatology 2008; 47(1): 153–59.

15. Giannini E, Botta F, Borro P, Risso D, Romagnoli P, Fasoli A, Mele MR, et al. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophagealvarices in patients with liver cirrhosis, *Gut* 2003; 52: 1200–1205.

16. Anstee QM, Jones DEJ, Liver and billiary tract disease. In: Walker RB, Colledge NR, Ralston SH, Penman ID. Davidson's Principles & Practice of Medicine, 22nd Edition. 2014. Edinburgh: Elselvier. 2014.

17. WGO. 2013. Practice guideline, Esophagealvarices; World Gastroenterology Organisation.

18. Gue CS, Yap CK, Ng HS. The correlation between cytopenia and esophageal varices in patients with liver cirrhosis. Med J Malaysia; 2004; 59(5): 604-608.

19. Masjedizadeh AR, Hajiani E, Nejad PA, Hashemi J, Shayesteh AA, Yasin Z. Efficacy Platelet/Spleen Diameter Ratio for Detection of Esophageal Varices in Cirrhotic Patients. Journal of Gastroenterology and Hepatology Research, 2013; 2(5): 590-92.

20. Sumon SM, Sutradhar SR, Chowdhury M, Khan NA., Uddin MZ, Hasan MI. et al. Relation of different grades of esophageal varices with Child-Pugh classes in cirrhosis of liver. Mymensingh Med J, 2013; 22(1): 37-41.

21. 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.

22. Madhotra R, Mulcahy HE, Willner I, Reuben A. Prediction of esophageal varices in patients with cirrhosis. J Clin Gastroenterol 2002;34:81-5.

23. Hong WD, Zhu QH, Huang ZM, Chen XR, Jiang ZC, Xu SH, et al. Predictors of esophageal varices in patients with HBV-related cirrhosis: a retrospective study. BMC Gastroenterol 2009;9:11.

24. Bolognesi M, Merkel C, Sacerdoti D, Nava V, Gatta A. Role of spleen enlargement in cirrhosis with portal hypertension. Dig Liver Dis 2002;34(2):144-50.

25. Oscar M, David M F, Marla D, Samuel H S. The pathophysiology of thrombocytopenia in chronic liver disease. Hept. Med 2016; 8: 39–50.

26. Aster RH. Pooling of platelets in the spleen: role in the pathogenesis of "hypersplenic" thrombocytopenia. J Clin Invest. 1966;45:645–57.

27. Jandl JH, Aster RH. Increased splenic pooling and the pathogenesis of hypersplenism. Am J Med Sci. 1967;253: 383–98.

28. Morris PW, Patton TB, Balint JA, et al. Portal hypertension, congestive splenomegaly, and portacaval shunt. Gastroenterology 1962;42:555–59.

29. Kawasaki T, Takeshita A, Souda K. Serum thrombopoietin levels in patients with chronic hepatitis and liver cirrhosis. Am J Gastroenterol 1999;94:1918-22.

30. Rios R, Sangro B, Herrero I. The role of thrombopoietin in the thrombocytopenia of patients with liver cirrhosis. Am J Gastroenterol 2005;100:1311-16.