



Research Article

NON-INVASIVE METHODS OF PREDICTING ESOPHAGEAL VARICES IN PATIENTS WITH INTRAHEPATIC PORTAL HYPERTENSION

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ABSTRACT

Background: Esophageal variceal bleeding is a severe complication of portal hypertension. The standard diagnostic screening test and therapeutic procedure to confirm esophageal varices is endoscopy. However because esophagogastroduodenoscopy is invasive, we studied the effectiveness of various noninvasive parameters in predicting the presence of esophageal varices.

Methods: The patients studied were either newly diagnosed as liver cirrhosis or were previously diagnosed with liver cirrhosis and were on follow up. The Non-invasive parameters that were used either in retrospective or prospective way for prediction of esophageal varices in our study were:AST, ALT Ratio (AST/ALT),Platelet count,APRI score, Splenic size (AP Diameter),Portal vein diameter,FIB -4 Score,LOK Score and Platelet/Splenic(AP)Diameter.

Results: A total of 144 patients were enrolled prospectively as well as retrospectively for a period of 2 years. Majority of our patients were males in age group of 40- 60 yrs and the most familiar etiology was Nonalcoholic fatty liver. Among the noninvasive predictors, the sensitive predictors to foretell the presence esophageal varices were platelet count, portal vein diameter, splenomegaly, High APRI, FIB4, and LOK Scores with sensitivity and specificity of around 85% and 80%.

Conclusion: Platelet count, Platelet/ Splenic ratio, and various fibrosis scores can be helpful in identifying cirrhotic patients with high risk of esophageal varices and higher chances of bleeding vis-a-vis higher mortality.

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INTRODUCTION

Portal hypertension is a progressive complication of liver cirrhosis and it is the cause of high morbidity and mortality. Esophageal varices develop because of high portal pressures and are seen in approximately 50% of patients with cirrhosis. Development of esophageal varices and variceal bleeding have a direct relationship with severity of portal hypertension for example varices are found in 40% of Child A patients, and can be present in up to 85% of Child C patients [1]. Cirrhotic patients develop varices at a rate of 8% per year and the strongest predictor for their development in those who have no varices at the time of initial endoscopic screening is a portal-hepatic venous pressure gradient (HVPG) more than 10 mmHg [2] [3]. Variceal hemorrhage occurs at a yearly rate of 5% - 15%, and its most important predictor is the size of varices, with the highest risk of first hemorrhage occurring in patients with large varices [4].

The gold standard for the diagnosis of varices is esophagogastroduodenoscopy (EGD). It is recommended that patients with cirrhosis undergo endoscopic screening for varices at the time of diagnosis [5] [6].

Since the point prevalence of medium/large varices is approximately 15% - 25% [1], the majority of subjects undergoing screening EGD either do not have varices or have varices that do not require prophylactic therapy. Thus, several models have been proposed to predict the presence of high risk varices by non- endoscopic methods and have excited considerable interest among researchers. Multiple studies have evaluated possible noninvasive markers of esophageal varices in patients with cirrhosis such as: the platelet count, Fibrotest, spleen size, portal vein diameter, and transient elastography [7] [8]. To address this research question, we assessed sensitivity, specificity, positive predictive value and negative predictive value of noninvasive parameters to foretell presence of esophageal varices.

METHODS

We conducted this study in the Department of Gastroenterology, SKIMS Soura, Jammu and Kashmir, India. This was an observational study with both retrospective and prospective limbs. After acquiring ethical clearance from the Institutional Ethical Committee, we included 144 patients with liver cirrhosis in our study. The patients were either newly

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diagnosed as liver cirrhosis or were previously diagnosed with liver cirrhosis and were on out-patient follow up.

Diagnosis of cirrhosis was based on standard clinical, biochemical, radiological, and pathological data wherever available. Every patient was evaluated for presence or absence of esophageal varices by standard oesophagogastroduodenoscopy (OGD).

The following non-invasive parameters were assessed for their ability to predict esophageal varices in our patients:

1. AAR ratio(AST/ALT)
2. PLT count
3. APRI score
4. Splenic size(AP Diameter)
5. Portal vein diameter
6. FIB -4 SCORE
7. LOK SCORE
8. PLATELET/SPLENIC(AP) Diameter ratio

The patients with liver cirrhosis who met the following criteria were excluded from the study:

1. Patients suffering from Grade III and grade IV hepatic encephalopathy
2. Patients with previous history of upper GI bleed secondary to portal hypertension.
3. Patients who are currently or were previously on treatment with Beta blockers, Diuretics or other vasoactive drugs.
4. Patients with previous history of Sclerotherapy or banding for esophageal varices.
5. Patients with HIV, hepatocellular carcinoma, or metastatic lesions of the liver.
6. Patients receiving drugs which are strongly associated with Thrombocytopenia.
7. Patients with recent h/o fever (15 days) or with h/o fever associated with thrombocytopenia in the past.
8. Other cases with portal hypertension, i.e., non-cirrhotic portal fibrosis, Budd-Chiari syndrome, and extra- hepatic portal venous obstruction.
9. Patients with any hematological malignancies, connective tissue disorders, h/o splenectomy, and splenomegaly secondary to causes other than portal hypertension.

Statistical methods

Measures of central tendency like mean, standard deviation, sensitivity, specificity and calculation of p values were done by using simple statistics. We also applied logistic regression for calculation of other parameters and a receiver operator characteristic curve was constructed, and the area under the curve was assessed.

Statistical analysis was performed using SPSS Software.

RESULTS

We conducted study in Department of Medical Gastroenterology for a period of two years to find the predictive power of non-invasive parameters for detection of esophageal varices in patients of liver cirrhosis. Cases were either previously diagnosed or newly diagnosed Cirrhotic attending outdoor and admitted indoor. A total of 144 patients are enrolled during a period of 2 years and the results are obtained as under:

In our study males slightly outnumbered the females (54:46) (table 1) and patients in the age group of 40-60 years formed the majority (66%). The patients between 20 and 40 years of age and those above 60 years constituted 16% and 13% respectively. Only 5% of our patients were below 20 years of age. (Table 2)

Table 1 Age distribution

Age group	Number	Percentage
Less than 20 years	7	5%
20 -40years	23	16%
40-60 years	95	66%
Greater than 60 years	19	13%

Table 2 Gender distribution

Gender	Number	percentage
Male	78	54%
Female	60	46%

Table 3 Etiology of liver cirrhosis

Etiology	number	Percentage
Cryptogenic	41	28.5%
Hepatitis B	21	14.6%
Hepatitis C	17	11.8%
Alcoholic	5	3.5%
NAFLD	46	31.9%
Others	14	9.7%

Table 4 Comparison between patients with esophageal varices and patients without varices regarding non-invasive markers

Parameter	Patients With OV		Patients Without OV		P-value
	Mean	SD	Mean	SD	
Portal Vein Diameter	14.70	1.52	13.05	1.57	<0.001*
Splenic Long Diameter	14.68	1.72	12.79	1.64	<0.001*
AST/ALT Ratio	1.40	0.251	1.23	0.312	0.002*
PLT Count	86.95	28.98	132.81	41.52	<0.001*
PLT/Splenic Diameter	660.46	189.79	1112.72	345.75	<0.001*

Table 5 Comparison between patients with esophageal varices and patients without regarding serum fibrosis scores

Parameter	Patients With OV		Patients Without OV		P-value
	Mean	SD	Mean	SD	
APRI	2.56	2.59	1.31	2.25	0.004*
FIB-4	5.72	2.19	3.18	1.40	<0.001*
LOK Score	0.89	0.096	0.78	0.169	<0.001*

Table 6 Showing diagnostic accuracy at optimum cut-off values of non-invasive parameters in predicting esophageal varices

Parameter	Cut-off	Sens	Spec	PPV	NPV	Accuracy
Portal Vein Diameter	>13.6	79.2	76.7	88.9	61.1	78.5
Splenic Long Diameter	>14	54.5	90.7	93.2	45.9	65.3
AST/ALT Ratio	>1.2	71.3	74.4	86.7	52.5	72.2
PLT Count	≤92	86.1	81.4	91.6	71.4	84.7
PLT/Splenic Diameter	≤825	86.2	86.0	93.6	72.6	86.1

Table 7 Showing diagnostic accuracy at optimum cut-off values of serum fibrosis scores in predicting oesophageal varices

Parameter	Cut-off	Sens	Spec	PPV	NPV	Accuracy
APRI	>1.3	90.1	72.1	88.4	75.6	84.7
FIB-4	>4.18	78.2	83.7	91.8	62.1	79.9
LOK Score	>0.78	89.1	44.2	78.9	63.3	75.7

Fig 1 ROC curves of different noninvasive parameters in predicting esophageal varices.

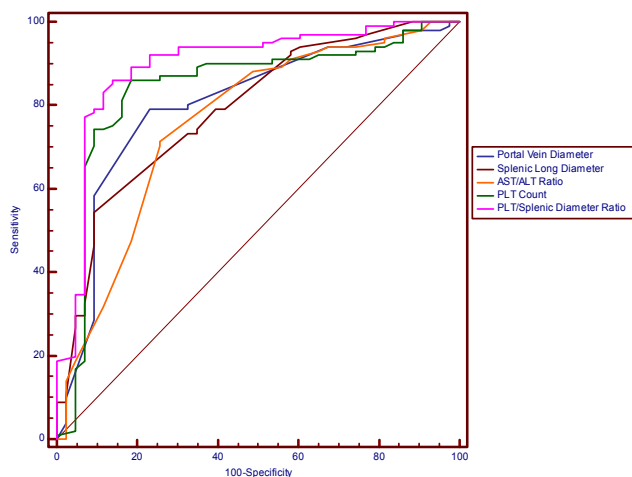


Fig 1 ROC curves of different parameters and their comparison with each other in predicting esophageal varices.

Table 8 various Parameters and their AUC, SE and 95% CI.

Parameter	AUC	SE	95% CI
Portal Vein Diameter	0.802	0.0418	0.727- 0.864
Splenic diameter	0.789	0.0407	0.714 -0.853
AST/ALT Ratio	0.759	0.0460	0.681 -0.826
PLT Count	0.841	0.0408	0.770 -0.896
PLT/Splenic Diameter	0.895	0.0328	0.832 -0.940

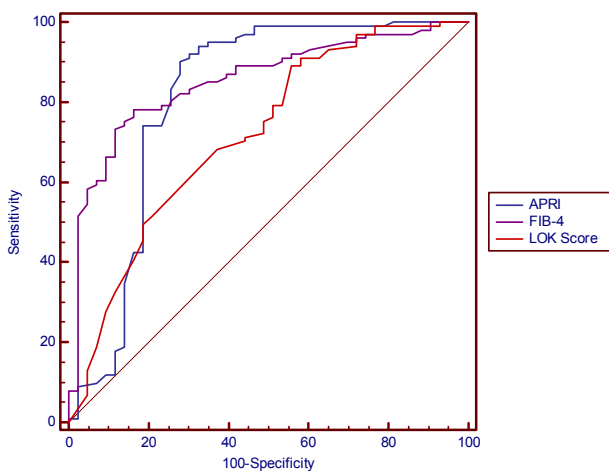


Table 9 showing AUC, SE, 95% CI of various Fibrosis Parameters.

Fibrosis parameter	AUC	SE	95% CI
APRI	0.813	0.0499	0.739 – 0.873
FIB-4	0.853	0.0337	0.785-0.907
LOK Score	0.717	0.0484	0.636-0.789

DISCUSSION

This study was carried out in a tertiary care institute of North India to assess the utility of non-invasive parameters in detection of esophageal varices in patients of liver cirrhosis by measuring their predictive values. Among the total of 144 patients enrolled, 78 (54.2%) were males while the rest 60(45.8%) were females. The mean age of our study population was 51 ± 14.13 years. The majority of our patients belonged to the age group of 40-60 years (66%). These results were consistent with those found by Prihartini *et al* (9), where 62% of their patients were males and 38% were females. The mean age in their study was 56±12.3 years. The skewed gender distribution in study by Prihartini *et al*. could be explained due to their small sample size. Similar results were obtained by

Mattos *et al* [10] who enrolled one hundred and sixty four patients.

Most of the studied patients had liver cirrhosis related to NAFLD, n=42 (31.9%) followed by cryptogenic causes n=41 (28.5%). Alcohol was cause of liver cirrhosis in only 5 (3.5%of our patients and autoimmune hepatitis was found in 6 patients. Thirty eight (38) of our patients had liver cirrhosis related to Hep B (n=21) and Hep C (n= 17).Most of our patients had T2DM as underlying comorbidity. According to a study by Mattos *et al* [10] cirrhosis was caused by viral hepatitis (hepatitis B virus-HBV or hepatitis C virus- HCV) in 72 patients (43.9%). Alcohol intake was its cause in 48 cases (29.3%). Viral hepatitis in association with alcohol intake was implicated in 17 cases (10.4%). Other causes of liver disease accounted for 27 cases (16.5%).Our findings vary because majority of our patients have fatty liver as component of metabolic syndrome explaining the skewness in our data.

The main aim of our study was to assess multiple noninvasive parameters portal vein diameter, splenic longitudinal diameter, AST/ALT ratio, platelet count and platelet/splenic longitudinal diameter between patients with esophageal varices and patients without varices. Noninvasive parameters:-Portal vein diameter, splenic longitudinal diameter and AST/ALT ratio, have higher mean in patients with esophageal varices than patients without esophageal varices with statistically significant p value for all the three parameters. Mean value of platelet count and platelet/splenic diameter is less for patients with esophageal varices than without varices and p value was statistically significant.

In studies by Hussein *et al*[11], Mandal *et al*[12], Hussein *et al* [11] and Sudha *et al*[13] all found that patients with esophageal varices are having higher mean for portal vein diameter, splenic longitudinal diameter and AST/ALT ratio than in patients without esophageal varices with p value for all the three parameters statistically significant. But platelet count and platelet/splenic diameter mean value is less for patients with esophageal varices than without varices and p value was statistically significant. However according to study by Berzigotti *et al* 62 in patients with Clinically Significant Portal hypertension with esophageal varices are having higher mean for portal vein diameter and, splenic longitudinal diameter but p value is statically significant for splenic longitudinal diameter. However Platelet count and platelet/splenic diameter mean value is less for patients with esophageal varices than without varices and p value was statically insignificant for both. This may be because of their small sample size and they enrolled only those patients where cirrhosis is related to viral hepatitis.

Second main aim was to compare non-invasive fibrosis scores APRI, FIB-4 and LOK between patients with esophageal varices and patients without varices. We found mean value of all the three fibrosis scores is higher in patients with esophageal varices than patients without esophageal varices with p value for all the three parameters statically significant. Our results match the studies done by Berzigotti *et al* [14] and Hussein *et al* [11]

Based on statistical significance of these non-invasive parameters we obtained cutoff points for these variables for prediction of esophageal varices using receiver operator characteristic curves .We also calculated NPV, PPV and accuracy.

In our study cut off point were:

1. Portal vein diameter > 13.6 cm with sensitivity 79.2% , specificity 76.7%, PPV 88.9, NPV 61.1, accuracy 78.5 and AUC 0.802 95% CI 0.727 to 0.864
2. Splenic longitudinal diameter > 14cm with sensitivity 54.5%, specificity 90.7%, PPV 93.2, NPV 45.9, accuracy 65.3 and AUC 0.789 95% CI 0.714 to 0.853
3. AST/ALT RATIO > 1.2 with sensitivity 71.3%, specificity 74.4%, PPV 86.7, NPV 52.5, accuracy 72.2 and AUC 0.759 95% CI 0.681 to 0.826
4. Platelet count < 92 with sensitivity 86.1%, specificity 81.4%, PPV 91.6, NPV 71.4, accuracy 84.7 and AUC 0.841 95% CI 0.770 to 0.896
5. Platelet count/Splenic diameter ratio < 825 with sensitivity 86.2%, specificity 86.0%, PPV 93.6, NPV 72.6, accuracy 86.1 and AUC 0.895 95% CI 0.832 to 0.940
6. APRI > 1.3 with sensitivity 90.1%, specificity 72.1%, PPV 88.4, NPV 75.6, accuracy 84.7 and AUC 0.813 95% CI 0.739 to 0.873
7. FIB-4 > 4.18 with sensitivity 78.2%, specificity 83.7%, PPV 91.8, NPV 62.1, accuracy 79.9 and AUC 0.853 95% CI 0.785 to 0.907
8. LOK > 0.78 with sensitivity 89.1% , specificity 44.2%, PPV 78.9, NPV 63.3, accuracy 75.7 and AUC 0.717 95% CI 0.636 to 0.789

Results were consistent with Johana Prihartini *et al*(9) Nashaat *et al*[15] , Wang *et al*[16], Gennani *et al*(17) Amin *et al* (18), Stefanescu *et al*(19), Cast'era, *et al.* (20) and Treeprasertsuk, *et al.* (21) .

CONCLUSION

From this study, we conclude that despite upper endoscopy being the gold standard for detection of esophageal varices, noninvasive parameters could be used to screen liver cirrhotics and to identify patients who should be considered for endoscopy at earliest.

This study does not replace Endoscopy as a screening tool for esophageal varices, but probably will help in our patients to plan an urgent Endoscopy in high risk patients to prevent variceal bleed and thus decreasing morbidity as well as mortality.

Conflict of interest: NONE

References

1. Pagliaro, L., D'Amico, G., Pasta, L., Politi, F., Vizzini, G., Traina, M., *et al.* (1994) Portal Hypertension in Cirrhosis: Natural History. In: Bosch, J. and Groszmann, R.J., Eds., Portal Hypertension. Pathophysiology and Treatment, Blackwell Scientific, Oxford, 72-92.
2. Groszmann, R.J., Garcia-Tsao, G., Bosch, J., Grace, N.D., Burroughs, A.K., Planas, R., *et al.*, The Portal Hypertension Collaborative Group (2005) Beta-blockers to Prevent Gastroesophageal Varices in Patients with Cirrhosis. *New Engl and Journal of Medicine*, 353, 2254- 2261. <http://dx.doi.org/10.1056/NEJMoa044456>
3. Merli, M., Nicolini, G., Angeloni, S., Rinaldi, V., De Santis, A., Merkel, C., *et al.* (2003) Incidence and Natural History of Small Esophageal Varices in

- Cirrhotic Patients. *Journal of Hepatology*, 38, 266-272. [http://dx.doi.org/10.1016/S0168-8278\(02\)00420-8](http://dx.doi.org/10.1016/S0168-8278(02)00420-8)
4. The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices (1988) Prediction of the First Variceal Hemorrhage in Patients with Cirrhosis of the Liver and Esophageal Varices. A Prospective Multicenter Study. *New Engl and Journal of Medicine*, 319, 983-989. <http://dx.doi.org/10.1056/NEJM198810133191505>
5. Grace, N.D., Groszmann, R.J., Garcia-Tsao, G., Burroughs, A.K., Pagliaro, L., Makuch, R.W., *et al.* (1998) Portal Hypertension and Variceal Bleeding: An AASLD Single Topic Symposium. *Hepatology*, 28, 868-880. <http://dx.doi.org/10.1002/hep.510280339>
6. D'Amico, G., Garcia-Tsao, G., Cales, P., Escorsell, A., Nevens, F., Cestari, R., *et al.* (2001) 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, Blackwell Science, Oxford, 36-64.
7. D'Amico, G. and Morabito, A. (2004) Noninvasive Markers of Esophageal Varices: Another Round, Not the Last. *Hepatology*, 39, 30-34. <http://dx.doi.org/10.1002/hep.20018>
8. Garcia-Tsao, G., D'Amico, G., Abraldes, J.G., Schepis, F., Merli, M., Kim, W.R., *et al.* (2006) Predictive Models in Portal Hypertension. In: de Franchis, R., Ed., Portal Hypertension IV. Proceedings of the Fourth Baveno International Consensus Workshop on Methodology of Diagnosis and Treatment.
9. Detection of Esophageal Varices in Liver Cirrhosis Using Non-invasive Parameters by Johana Prihartini*, LA Lesmana**, Chudahman Manan***, Rino A Gani**
10. Ângelo Zambam de MATTOS1, 2, Angelo Alves de MATTOS1, 2, Fernanda Farias VIANNA1, 2, Maiara Isabel MUSSKOPF1, 2, Júlio Carlos PEREIRA-LIMA1, 2 and Antônio Carlos Maciel2platelet Count/Spleen Diameter Ratio: analysis of its capacity as a predictor of the existence of esophageal varices
11. Hany Aly Hussein, Wael Mahmoud Tamer and Mohamed Salaheldin Khalaf (AST/ALT Ratio for detection and severity classification of Esophageal Varices in Child A HCV Liver cirrhosis Egyptian Patients)Internal Medicine Department, Ain Shams University- Cairo, Egypt.
12. Lopamudra Mandal*, Sanjay Kumar Mandal**, Dipanjan Bandyopadhyay**, Saumik Datta** (Correlation of portal vein diameter and splenic size with gastro-oesophageal varices in cirrhosis of liver)
13. Dr. K.V.L. Sudha Rani, Dr. B. Sudarsi, Dr. R. Siddeswar, Dr. S. Manohar, [Correlation of Portal Vein Size with Esophageal Varices Severity in Patients with Cirrhosis of Liver with Portal Hypertension].
14. Annalisa Berzigotti, M.D., 1, 2, 3 Rosa Gilabert, M.D., 2 Juan G. Abraldes, M.D., 1 Carlos Nicolau, M.D., 2 Concepcio'n Bru, M.D., 2 Jaime Bosch, M.D., 1 and Juan C. Garcia-Pagan, M.D.1 [Noninvasive Prediction of Clinically Significant Portal Hypertension and Esophageal Varices in Patients With Compensated Liver Cirrhosis

15. Ehab H. Nashaat, Hossam Abd-Elaziz, Manal Sabry&Ahmed Aly Ibrahim Non-Endoscopic Predictors of Esophageal Varices and Portal Hypertensive Gastropathy Internal Medicine Departement,Ain Shams University
16. Lijing Wang, MM1 JunWei Hu, MM1 Shuang Dong, MM1 Yi Cheng Jian, MM1 Lijuan Hu, MM1 Genmei Yang, MB2 Jinjun Wang, MB2 Wujun Xiong, MD1(Noninvasive prediction of large esophageal varices in liver cirrhosis patients)Department of gastroenterology, Shanghai East Hospital affiliated with Tongji University
17. E Giannini, F Botta, P Borro, D Risso, P Romagnoli, A Fasoli, M R Mele, E Testa, C Mansi, V Savarino, R Testa Platelet count/spleen diameter ratio: proposal and validation of a noninvasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis
18. Mona A. Amin, Ahmed E. El-Badry, May M. Fawzi1, Dalia A. Muhammed, Shorouk M. Moussa Internal Medicine, Cairo University, Cairo, Egypt 2Community Medicine, Cairo University , Cairo, Egypt New Non-Invasive Index for Detecting Esophageal Varices in Patients with Liver Cirrhosis
19. Horia Stefanescu1,2, Mircea Grigorescu1, Monica Lupsor2, Anca Maniu2, Dana Crisan1, Bogdan Procopet1, Diana Feier2, Radu Badea2 1) Hepatology Department; 2) Medical Imaging Department, 3rd Medical Clinic, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania (A New and simple Algorithm for the Noninvasive Assessment of Esophageal Varices in Cirrhotic Patients using serum Fibrosis Markers)
20. Caste'ra 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
21. Treeprasertsuk S, Kowdley KV, Luketic VAC, *et al.*: The predictors of the presence of varices in patients with primary sclerosing cholangitis. *Hepatology* 2010; 51, 4: 1302-1310

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