

# Evaluation of non-invasive marker of esophageal varices in cirrhosis of liver

Pardeep Kumar<sup>1</sup>, Kuldeep Singh<sup>1</sup>, Arun Joshi<sup>2</sup>, Priyanka Thakur<sup>3</sup>,  
Subodh Kumar Mahto<sup>1</sup>, Brijesh Kumar<sup>4</sup>, Nitasha Pasricha<sup>4</sup>,  
Biswa Ranjan Patra<sup>5</sup>, Brinder M. S. Lamba<sup>1</sup>

<sup>1</sup>Department of Medicine, PGIMER, DR. RML HOSPITAL, New Delhi, <sup>2</sup>Department of Nephrology, Army Research and Referral Hospital, New Delhi, <sup>3</sup>Department of Medicine, Topiwala National Medical College, Mumbai, <sup>4</sup>Department of Medicine, Smt. Sucheta Kriplani Hospital and LHMC, New Delhi, <sup>5</sup>Department of Gastroenterology, Seth GS Medical College KEM and Hospital, Mumbai, India

## ABSTRACT

**Introduction:** Esophageal varices develop as a consequence of portal hypertension (PHT) in patients with chronic liver disease. Hence, screening of all cirrhotic patients with upper gastrointestinal endoscopy to detect the presence of significant esophageal varices implies a number of unnecessary endoscopies and has its limitation where such facilities are not available, especially in the rural part of country. **Method:** Patients with either sex, aged between 18 and 60 years with diagnosis of cirrhosis were studied. Detailed history, physical examination along with relevant investigations were recorded and upper gastrointestinal endoscopy was done within 2–3 days of investigation. Esophageal varices were graded as I-IV, using the Paquet grading system and patients were classified dichotomously either as having large esophageal varices (LEV) group A (Grade III-IV) and no varices group B (grade I-II). **Result:** A total of 50 patients with cirrhosis of liver were recruited in the study. Among hematological markers, only low platelet count was significantly associated with the presence of LEV ( $P$  value  $<0.05$ ). None of the biochemical markers were found to be significantly associated with LEV. All the ultrasonographic parameters, i.e. spleen size, splenic vein size, portal vein size, and the presence of portosystemic collaterals were found to be significantly associated with the presence of LEV ( $P$  value  $<0.05$ ). **Conclusion:** Though upper gastrointestinal endoscopy remains the gold standard for the diagnosis of esophageal varices in cirrhotic patients, those patients at high risk of having LEV can be screened by using clinical, hematological, biochemical, and radiological markers.

**Keywords:** Chronic liver disease, clinical, hematological markers, esophageal varices, radiological markers

## Introduction

Esophageal variceal bleeding is one of the most dreaded complications of cirrhosis because it is a leading cause of morbidity and mortality in cirrhosis. The prevalence of varices in patients with cirrhosis is approximately 60–80% and the risk of bleeding is 25–35%.<sup>[1]</sup> Increasing the size of varices is associated with an

increase in variceal-wall tension to a critical level at which varices rupture and cause life-threatening bleeding. The mortality rate from variceal bleeding is about 20% when patients are treated optimally in hospital.<sup>[2]</sup> Intravariceal pressure is less important than size and appearance of varices although a portal pressure of 10 mmHg is required for varices to form and 12 mmHg for them to subsequently bleed.<sup>[3]</sup> After a variceal bleed, the risk of rebleeding is particularly high, approximately 60% to 70% over a 24-month period. However, the risk of rebleeding is greatest within hours or days after an acute bleed.<sup>[4]</sup> The American Association for the Study of Liver Disease and the Baveno IV Consensus Conference on

**Address for correspondence:** Dr. Subodh K. Mahto,  
Anandi Prakash Hospital, Hospital Road, Sitamarhi, Bihar, India.  
E-mail: drsubodhkr05@gmail.com

Received: 10-03-2019

Revised: 08-01-2020

Accepted: 21-01-2020

Published: 28-02-2020

### Access this article online

#### Quick Response Code:



Website:  
www.jfmipc.com

DOI:  
10.4103/jfmipc.jfmipc\_854\_19

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

**How to cite this article:** Kumar P, Singh K, Joshi A, Thakur P, Mahto SK, Kumar B, *et al.* Evaluation of non-invasive marker of esophageal varices in cirrhosis of liver. *J Family Med Prim Care* 2020;9:992-6.

portal hypertension (PHT) recommended that all cirrhotic patients should be screened for the presence of esophageal varices (OV) when liver cirrhosis is diagnosed.<sup>[5]</sup>

## Method

It was a cross-sectional observational study conducted in department of medicine at PGIMER, Dr. Ram Manohar Lohia Hospital, New Delhi, over period of 1-year span. Numbr-01-32/13/2011/IEC/Thesis/PGIMER-RMLH/9324.

The diagnosis of cirrhosis was based on clinical feature (signs and symptoms of liver cell failure), biochemical parameters (raised bilirubin, Serum Glutamic-Oxaloacetic Transaminase (SGOT), Serum Glutamate Pyruvate Transaminase (SGPT), low albumin), and radiological parameters (absence of thin hyperechoic capsular line, paucity of peripheral hepatic vessels, accentuated echogenic walls of the portal vein, nodular liver cirrhosis, contracted liver, sign of portal hypertension). Patients fulfilling the above-mentioned criteria for diagnosis of cirrhosis of liver, age group of 18–60 years, were included in the study.

Patients with the previous treatment with beta-blockers, nitrates, diuretics, spironolactone with active or previous episode of upper gastrointestinal bleeding, who have received endoscopic or surgical intervention for portal hypertension, with portal vein thrombosis were excluded from the study.

Relevant history with careful attention to occupation, family history, blood transfusion, history of sexual contacts, recreational drug use, alcohol consumption, and medication was taken. Physical examination including signs of liver cell failure, liver span, splenomegaly, and abdominal vein collaterals and ascites was recorded. Hepatic encephalopathy was graded from 0 to IV, as per Conn's grading.<sup>[3]</sup> Hematological and biochemical workup include measurement of hemoglobin, total leucocyte count, platelet count, prothrombin time, and serum concentration of bilirubin (total and conjugated), serum albumin, SGOT, and SGPT. For each patient, a modified child-Pugh score was calculated.<sup>[4]</sup> All patient was tested for HBsAg and antibodies to hepatitis C virus to determine the cause of liver cirrhosis. Test for other causes of cirrhosis (serum ceruloplasmin and slit lamp examination for Wilson's disease, test for autoantibodies for autoimmune liver disease, and iron studies for hemochromatosis) was carried out only if there is a suggestive clinical clue.

A blood sample was collected and hematological and biochemical tests were performed. Hemoglobin, total leucocytes, and platelet counts were done by Medonic CA 620/530 auto analyzer based on electronic impedence principle. PT: done by using lyophilized calcified thromboplastin reagent. Serum bilirubin level is calculated by calorimetric assay by Roche/Hitachi 911 analyzer: ACN 269. SGOT/SGPT was measured according to IFCC/with pyridoxal activation by Roche/Hitachi 904 analyzer: ACN 111 and 912 analyzer: ACN 098.

Serum albumin level was measured by Bromocresol green method. Other routine tests including kidney function test, fasting plasma glucose, ECG, urine examination, and chest X-ray were performed. All patients underwent ultrasonography after overnight fasting and the following details were recorded: maximum vertical span of the liver, spleen size (length of its longest axis), diameter of the portal and splenic veins, presence of portal-systemic collaterals, and presence of ascites.

All patients underwent upper gastrointestinal endoscopy for assessment of esophageal and gastric varices within 2–3 days of admission or on OPD basis. Esophageal varices were graded as I-IV, using the Paquet grading system.<sup>[6]</sup>

- Grade 0: No varices.
- Grade I: Varices, disappearing with insufflations.
- Grade II: Larger, clearly visible, usually straight varices, not disappearing with insufflations.
- Grade III: More prominent varices, locally coil-shaped and partly occupying the lumen.
- Grade IV: Tortuous, sometimes grape-like varices occupying the esophageal lumen.

Further, patients were classified dichotomously either as having large esophageal varices (LEV) group A (Grade III-IV) and group B (no varices, grade I and II).

## Statistical analysis

Categorical variables were presented in numbers and percentage (%) and continuous variables were presented as mean  $\pm$  SD and median. Normality of data was tested by Kolmogorov–Smirnov test. If the normality was rejected, then nonparametric test was used.

Statistical tests were applied as follows:

1. Quantitative variables were compared using Independent *t*-test/Mann–Whitney Test (when the data sets were not normally distributed) between the two groups.
2. Qualitative variables were correlated using Chi-Square test/ Fisher's Exact test.

A *P* value of  $<0.05$  was considered statistically significant.

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

## Result

A total of 50 patients with cirrhosis of liver were recruited in the study. Both males and females were included in the study and their mean age of presentation was  $53.40 \pm 6.2$  years. Esophageal varices were graded as I-IV, using the Paquet grading system. Patients were dichotomously divided into group A (grade III and IV) and group B (no varices, grade I and II).

Out of 50 patients, 12 were female (24%) and 38 patients were male (76%). Alcohol was the cause of cirrhosis in 32 patients (64%). Nine patients (18%) were HBsAg positive and HCV was the cause in 5 patients (10%). Autoimmune etiology and Wilson's disease were the cause in one patient each and two patients were diagnosed as cryptogenic cirrhosis after ruling out all the causes. Eight percent of patients (4 patients) belong to child-Pugh class A (score 5–6), 46% patients (23 patients) belong to child-Pugh class B (score 7–9), and 46% patients (23 patients) belong to child-Pugh class C (score 10–15). Fifty-six percent of patients of child-Pugh class C were having LEV (Group A), while only 39.1% patients of child-Pugh class B were having LEV (Group A). The higher the child-Pugh class, the more the risk of LEV.

Clinically detectable ascites was present in 35 patients (70%), and 15 patients (30%) had clinically undetectable ascites. Eighteen (78.26%) of patients who were having ascites had LEV (Group A). There was no significant association was found between ascites and LEV (Group A) ( $P < 0.239$ ). Out of 50 patients, spleen was palpable clinically in 26 patients (52%), and 24 patients (48%) had clinically nonpalpable spleen. Seventeen (73.91%) patients of clinically palpable spleen were having LEV. A significant association was found between splenomegaly and LEV (Group A) ( $P < 0.004$ ) [Table 1].

Mean hemoglobin was  $10.2 \pm 2.2$  gm/dl. Mean hemoglobin levels were  $10.79 \pm 1.98$  gm/dl and  $9.75 \pm 2.28$  gm/dl of group A and group B, respectively. Mean leukocyte count was  $8795.65 \pm 5554.15 \times 10^9/L$  and  $9625.93 \pm 3808.65 \times 10^9/L$  of group A and group B, respectively, while platelet counts in group A and groups B were  $113608.7 \pm 34849.9 \times 10^9/L$  and  $167037.04 \pm 55538.26 \times 10^9/L$ , respectively. Among hematological markers, only low platelet count was significantly associated with the presence of LEV group A ( $P$ -value  $< 0.0002$ ) [Table 2].

Among biochemical markers, mean serum bilirubin levels among Group A and groups B were  $5.44 \pm 6.69$  mg/dl and  $4.95 \pm 6.59$  mg/dl, respectively. Group A was found to have lower mean of SGOT and SGPT level, i.e.  $104.87 \pm 66.28$  U/L and  $75.09 \pm 55.94$  U/L, in comparison to group B, i.e.  $130.04 \pm 142.8$  U/L and  $112.85 \pm 149.21$  U/L. Similarly, Group A was having lower mean serum albumin level ( $2.87 \pm 0.79$  gm/dL) in comparison to group B ( $3.26 \pm 0.69$  gm/dL). Mean value of prothrombin time in group A and group B was  $22.08 \pm 6.2$  s and  $19.56 \pm 6.6$  s.

Among all, biochemical markers were not significantly associated with the presence of LEV (group A) [Table 3].

Mean value of prothrombin time in group A and group B was  $22.08 \pm 6.2$  s and  $19.56 \pm 6.6$  s. Mean value of INR between Group A and group B was  $1.81 \pm 0.5$  and  $1.52 \pm 0.5$ , respectively. Prothrombin time was also not significantly associated with the presence of LEV group A ( $P$ -value  $< 0.108$ ) [Table 4].

Out of 50 patients, 40 patients (80%) had ascites detected by ultrasound and 10 (20%) patients had no free fluid was detected in peritoneal cavity by ultrasound. Fifty percent of patients who were having ascites had LEV. Portosystemic collaterals were detected by ultrasonography and were present in 62% patients (31 patients) and absent in 38% patients (19 patients); 74.2% patients with portosystemic collaterals were having LEV. The group A had lower mean value of liver span and higher mean value of spleen size, splenic vein size, and portal vein size in comparison to group B. All the ultrasonography parameters, i.e. liver size, spleen size, splenic vein size, portal vein size, and the presence of Portosystemic collaterals were found to be significantly associated with the presence of LEV ( $P$ -value  $< 0.05$ ) [Table 5].

## Discussion

For all patients, modified child-Pugh score was calculated and according to their score, they are divided into Class A, Class B, and Class C; 8% patients belonged to Class A and 46% patients belonged to Class B and Class C in each. 56.5% patients of child class C were having LEV, while only 39.1% patients of child class B belonged to this group (LEV). The prevalence of all varices in patients with advanced child-Pugh class was higher than that in patients with child-Pugh class A. A Similar result found in the study conducted by Hong *et al.*<sup>[7]</sup> Cherian *et al.*<sup>[8]</sup> also found that child-Pugh class B/C emerged as significant predictors for the presence of LEV.

Splenomegaly is recognized as one of the diagnostic signs of cirrhosis and portal hypertension. In our study, clinically detectable ascites was present in 70% patients and splenomegaly was present in 52% patients; 78.26% patients with ascites were having LEV (group A), while 73.91% patients with clinically palpable spleen were having LEV. Only splenomegaly was found to be significantly associated with LEV. Chalasani *et al.*<sup>[9]</sup>

**Table 1: Significant association between ascites and splenomegaly and the presence of large esophageal varices**

Clinical findings	esophageal varices		Total	P
	Group A (grade III and IV)	Group B (no varices, grade I and II)		
Ascites	Absent	5 (21.74%)	10 (37.04%)	0.239
	Present	18 (78.26%)	17 (62.96%)	
Total		23	27	50
Palpable spleen	Absent	6 (26.09%)	18 (66.67%)	0.004
	present	17 (73.91%)	9 (33.33%)	
Total		23	27	50

**Table 2: Association between hematological markers with large esophageal varices**

Hematological markers	Mean±SD of Group A	Mean±SD of Group B	P <sup>x</sup>
Sample size	23	27	
Hemoglobin (gm%)	10.79±1.99	9.75±2.28	0.096
Leucocyte count	8795.65±5554.15	9625.93±3808.65	0.167
Platelet count	113608.7±34849.99	167037.04±55538.26	0.0002

x- Independent t-test

**Table 3: Association between biochemical markers with large esophageal varices**

Biochemical markers	Mean±SD of Group A	Mean±SD of Group B	P <sup>x</sup>
Sample size	23	27	
Total bilirubin level (in mg/dL)	5.44±6.69	4.95±6.59	0.453
Serum albumin level (in gm/dL)	2.87±0.79	3.26±0.7	0.073
SGOT (in U/L)	104.87±66.28	130.04±142.81	0.690
SGPT (in U/L)	75.09±55.95	112.85±149.22	0.748

x- Mann-Whitney test

**Table 4: Association between Prothrombin time with large esophageal varices**

Biochemical markers	Mean±SD of Group A	Mean±SD of Group B	P <sup>x</sup>
Sample size	23	27	
Prothrombin time (in sec)	22.08±6.28	19.56±6.64	0.108
INR	1.81±0.57	1.52±0.59	0.086

x- Mann-Whitney test

**Table 5: Association between all ultrasonographic parameters (spleen size, splenic vein size, portal vein size, and the presence of portosystemic collaterals) with the presence of large esophageal varices**

Ultrasonography parameters	Mean±SD of Group A	Mean±SD of Group B	P <sup>x</sup>
Sample size	23	27	
Liver span (in cm)	12.61±1.62	13.57±1.28	0.022
spleen size (in cm)	17.7±1.76	14.81±2.74	0.0002
splenic vein size (in mm)	10.12±1.44	8.09±1.27	<.0001
portal vein size (mm)	14.71±1.01	13.04±1.2	<.0001

x- Independent t-test

found in their study that ascites was not significantly associated with LEV. Nonendoscopic assessment for the presence and grades of varices from India is few. Few studies have reported that splenomegaly could be a good predictor of LEV for cirrhotic patients.<sup>[10,11]</sup> Amarapurkar *et al.*<sup>[12]</sup> was also reported that splenomegaly alone was a significant predictor for the development of LEV.

In our study, we found that only platelet, among hematological markers, was statistically significant with LEV. Thrombocytopenia in patients with cirrhosis has historically been attributed to hypersplenism due to portal hypertension. This is in accordance

with various studies<sup>[13,14]</sup> where statistically significant relationship of with esophageal varices and platelet could be proved. Sharma *et al.*,<sup>[10]</sup> in a prospective study, observed that splenomegaly and platelet count were the independent predictors for the presence of large varices.

Similarly, statistical significant correlation of prothrombin time and esophageal varices was elucidated which turned out to be not statically significant. Prothrombin time is considered a marker of hepatocellular dysfunction. As PHT is a consequence, in part, of the generalized vasodilation and the hyperdynamic splanchnic and systemic circulatory state, the degree of hepatic function likely affects the development of PHT via humoral factors and, therefore, the development of varices. Moreover, the degree of liver fibrosis is related to liver function and fibrosis can directly affect portal hypertension. It has been reported that serum fibrosis markers can detect LEV with high accuracy<sup>[15]</sup> though in the study conducted by Madhotra *et al.* showed prothrombin time was associated with LEV on univariate analysis.<sup>[11]</sup> Most studies suggested that it was not a predictor for EV.<sup>[7,8]</sup> Serum bilirubin, S. albumin, SGOT, and SGPT were not significantly associated with LEV. It was also reported in a study by Sharma *et al.*<sup>[10]</sup> in which serum bilirubin, S. albumin, SGOT, and SGPT were not significantly associated with LEV.

By ultrasonography, ascites was detected in 80% patients and 62% patients had portosystemic collaterals. 74.2% patients with portosystemic collaterals were found to have esophageal varices, while none of the patients without portosystemic collaterals were found to have varices. Among radiologically, 50% patients with ascites were found to have LEV. The measurement of the spleen bipolar diameter using ultrasonography is easily obtainable, reproducible, and non-invasive and is routinely performed on patients with cirrhosis. All the ultrasonography parameters, i.e. liver size, spleen size, splenic vein size, portal vein size, and the presence of Portosystemic collaterals were found to be significantly associated with the presence of LEV. This is in well accordance with other studies. Cherian *et al.*<sup>[8]</sup> found that thrombocytopenia and spleen diameter >160 mm were found to be independent predictors of esophageal varices, while Hong *et al.*<sup>[7]</sup> in their study found out that platelet count, spleen width, and portal vein diameter were significantly associated with LEV. Chandail *et al.*<sup>[16]</sup> also found that variables independently linked to the presence of esophageal varices were spleen diameter [odds ratio (OR): 1.137, 95% confidence interval: 1.033–1.255;  $P = 0.009$ ] and portal vein size [odds ratio (OR): 41.531, 95% confidence interval: 1.858–928.304;  $P = 0.019$ ].

## Conclusion

Upper gastrointestinal endoscopy remains the gold standard for the diagnosis of esophageal varices in cirrhotic patients. However, its limitations include being invasive and poor availability in peripheral parts of the country. Patients at high risk

of having LEV can be screened by using clinical, hematological, biochemical, and radiological markers. Clinically palpable spleen, thrombocytopenia, portal vein size, splenic vein size, spleen size, and the presence of portosystemic collaterals have a significant association with the presence of LEV.

### Acknowledgements

Nil.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### References

1. Amico GD, Morabito A. Noninvasive markers of esophageal varices: Another round, not the last. *Hepatology* 2004;39:30-4.
2. D'Amico G, De Franchis R. Upper digestive bleeding in cirrhosis: Post-therapeutic outcome and prognostic indicators. *Hepatology* 2003;38:599-612.
3. Merli M, Nicolini G, Angeloni S, Rinaldi V, Incidence and natural history of small esophageal varices in cirrhotic patients. *J Hepatol* 2003;38:266-72.
4. Grace ND. Diagnosis and treatment of gastro-intestinal bleeding secondary to portal hypertension. American College of Gastroenterology Practice Parameter Committee. *Am J Gastroenterol Group* 1997;92:1081-91.
5. Thomopoulos KC, Mimidis KP, Katsakonlis EC. Non-invasive predictors of the presence of large esophageal varices in patients with cirrhosis. *Dig Liver Dis* 2003;35:473-8.
6. Paquet KJ. Prophylactic endoscopic sclerosing treatment of esophageal wall in varices: A prospective controlled trial. *Endoscopy* 1982;14:4-5.
7. Hong WD, Zhu QH, Huang ZM. Predictors of esophageal varices in patients with HBV related cirrhosis: A retrospective study. *BMC Gastroenterol* 2009;9:11.
8. Cherian JV, Deepak N, Ponnusamy RP, Somasundaram A, Jayanthi V. Non-invasive predictors of oesophageal varices. *Saudi J Gastroenterol* 2011;17:648.
9. Chalasani N, Imperiale TF, Ismail A. Predictors of large varices in patients with cirrhosis. *Am J Gastroenterol* 1999;94:3285-91.
10. 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.
11. Madhotra R, Mulcahy HE, Willner I, Reuben A. Prediction of esophageal varices in patients with cirrhosis. *J Clin Gastroenterol* 2002;34:81-5.
12. Amarapurkar DN, Parikh SS, Shankaran K, Chopra K, Dhawan P, Kalro RH, *et al.* Correlation between splenomegaly and oesophageal varices in patients with liver cirrhosis. *Endoscopy* 1994;26:563.
13. Schepis F, Camma C, Niceforo D, Which patients with cirrhosis should undergo endoscopic screening for esophageal varices detection. *Hepatology* 2011;33:333-8.
14. Sarwar S, Khan AA, Butt AK, Shafqat F, Malik K, Ahmad I, *et al.* Non-endoscopic prediction of esophageal varices in cirrhosis. *J Coll Physicians Surg Pak* 2005;15:528-31.
15. Vanbiervliet G, Barjoan-Marine E, Anty R, Piche T, Hastier P, Rakotoarisoa C, *et al.* Serum fibrosis markers can detect large oesophageal varices with a high accuracy. *Eur J Gastroenterol Hepatol* 2005;17:333-8.
16. Chandail VS, Kotwal SK, Koul S, Gupta R, Mahajan A. Non-invasive markers for prediction of varices in patients with portal hypertension. *Int J Res Med Sci* 2017;5:1007-10.