Section: Medicine

Original Research Article

# PREDICTIVE MARKERS OF ESOPHAGEAL VARICES IN CHRONIC LIVER DISEASE PATIENTS

**K.S. Dakshinamoorthy[1], B. Sivasubramanian[2], I. Balaji[3]**

[1]Senior Assistant Professor, Department of Medicine, Tirunelveli Government Medical College, Tamilnadu, India.
[2]Senior Assistant Professor, Department of Medicine, Tirunelveli Government Medical College, Tamilnadu, India.
[3]Assistant Surgeon, Department of Medicine, Government Head Quarters Hospital, Cuddalore, Tamilnadu, India.

*Received* : 04/05/2023
*Received in revised form* : 14/06/2023
*Accepted* : 29/06/2023

*Keywords:*
*PC/SD, Spleen diameter and serum ammonia are noninvasive markers that positively correlate with OGDscopy, an invasive procedure that can lead to adverse effects. Multicentric studies were conducted to validate the results.*

Corresponding Author:
**Dr. I. Balaji,**
Email: dr.bala92@gmail.com

DOI: 10.47009/jamp.2023.5.4.78

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

*Int J Acad Med Pharm*
2023; 5 (4); 384-388

## Abstract

**Background:** Endoscopy is the gold standard, but it is an invasive procedure and cost-effective. Noninvasive markers are needed to reduce endoscopy screenings and mirror the presence of esophageal varices. The study aimed to determine the noninvasive parameters for identifying the presence of esophageal varices and compared the predictive accuracy of these parameters in the development of esophageal varices. **Materials and Methods:** This case-control study was conducted at the Department of General Medicine, Tirunelveli Medical College Hospital, Tirunelveli, on 70 patients. The focus parameters, fasting blood Ammonia level, INR, spleen diameter, PC/SD and SGOT/SGPT, were recorded for patient analysis. All the patients in the study groups were subjected to a detailed history, a general examination, and all laboratory investigations were recorded. **Results:** No significant difference in gender and age between groups. Among the markers investigated, venous ammonia level, spleen diameter, and portal collateral/spontaneous descending (PC/SD) were statistically significant indicators of varices. Elevated ammonia levels and an increased spleen diameter were associated with varices, while abnormal PC/SD findings showed a strong correlation. A significant difference in mean Ammonia, PT, INR, Spleen diameter, Lymphocyte, Platelet, ALP, and PC/SD between groups. Markers such as prothrombin time, international normalized ratio (INR), and several blood cell counts (WBC, neutrophil, lymphocyte, and platelet) were not found to be reliable predictors of varices. **Conclusion:** PC/SD, Spleen diameter and serum ammonia are noninvasive markers that positively correlate with OGDscopy, an invasive procedure that can lead to adverse effects. Multicentric studies were conducted to validate the results.

## INTRODUCTION

The liver is the largest organ in the body and is strategically located to receive nutrient-enriched blood supply from the portal system. The portal vein (PV) is the main vessel of the PVS, resulting from the confluence of the splenic and superior mesenteric veins, and drains directly into the liver. Once in the liver, PV ramifies and reaches the sinusoids, with downstream blood being directed to the central vein at the hepatic lobule level, then to the hepatic veins and inferior vena cava (IVC). On normal anatomy, the splenic vein (SV) joins the superior mesenteric vein (SMV) anteriorly to the IVC and posteriorly to the pancreatic neck to form the PV, which ascends within the hepatoduodenal ligament, posteriorly to the hepatic artery and common bile duct, toward the hepatic hilum, where it divides into right and left.[1,2]

Esophageal varices, formed due to portal hypertension, have a great clinical impact due to their severe complications. Cirrhotic patients should be screened for esophageal varices when portal hypertension is diagnosed. Upper gastrointestinal (GI) endoscopy is the gold standard in diagnosing esophageal varices. It had been suggested that endoscopy be repeated at 2-3 years intervals in patients without varices and at 1-2 years intervals in patients with small varices to evaluate the development or progression of esophageal varices.[3-5] The standard approach has some limitations, as endoscopy is an invasive procedure, and the cost-effectiveness is questionable. The possibility of noninvasive means for identifying cirrhotic patients with esophageal varices or collateral presence is a


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

value add. It could decrease the necessity of endoscopic screening with reduced healthcare costs.[6,7] This study has realised the need for noninvasive markers to reduce the number of endoscopy screenings and mirror the presence of esophageal varices. The study aimed to determine the noninvasive parameters for identifying the presence of esophageal varices and compared the predictive accuracy of these parameters in the development of esophageal varices.

## MATERIALS AND METHODS

This case-control study was conducted at the Department of General Medicine, Tirunelveli Medical College Hospital, Tirunelveli, on 70 patients. Written informed consent was obtained from the patients, and ethics clearance was obtained from the institutional Ethics Committee.

**Inclusion Criteria**

Patients aged 18 years and above admitted with a diagnosis of Liver Cirrhosis from both genders were included.

**Exclusion Criteria**

Patients who received Endoscopic Variceal Ligation (EVL) or Sclerotherapy, hepatic encephalopathy, and renal insufficiency evidenced by serum creatinine of > 1.3 mg per dl were excluded.

The focus parameters, fasting blood Ammonia level, INR, spleen diameter, PC/SD and SGOT/SGPT, were recorded for patient analysis. Upper gastrointestinal endoscopy was done in Cirrhotic patients to note the profile of the size of oesophageal varices. All the patients of the study groups were subjected to a detailed history, a general examination including manifestations of chronic liver disease and liver cell failure, an abdominal examination of liver size, consistency, splenomegaly, ascites and dilated veins on the abdominal wall, laboratory investigations including complete blood count with manual count for platelet, liver profile including ALT, AST and Alkaline phosphatase, total and direct bilirubin, serum albumin, prothrombin time, INR, and renal parameters.

Spleen Longitudinal Diameter (SLD) was performed by postero-lateral scanning with the probe footprint aligned along an intercostal space to provide a longitudinal view of the spleen. The same Sonographer conducted abdominal Ultra Sonography to avoid variances due to inter-observer bias. The patients were requested to breathe slowly, taking long breaths, as varying degrees of inspiration and expiration are needed to optimise splenic visualisation and to roll on the right side to some extent to aid visualisation. The maximum length was recorded, i.e., the optically greatest overall longitudinal dimension obtained from one of the two poles. Liver size, echogenicity, presence of focal lesions, portal vein diameter, and patency were also measured. An advanced video endoscope the upper gastrointestinal endoscopy for use in the upper gastrointestinal tract.

Patients were given a standard protein diet, and the factors that may increase blood ammonia, such as muscular exercise, alcohol, barbiturates, narcotics, and diuretics, were avoided. The factors that may decrease blood ammonia, such as broad-spectrum antibiotics, levodopa, lactobacillus and potassium salts, were avoided. 0.5 ml of venous blood sample was taken in the morning and at complete rest from fasting patients. Blood samples were collected in tubes containing Ethylene Diamine-Tetra Acetic acid (EDTA) and analysed within 30 min of collection. Blood ammonia level was estimated by enzymatic UV method using the glutamate dehydrogenase reaction (GLDH-UV).

**Statistical Analysis**

Based on observation of the results on the four important variables, namely, spleen size, INR, PC/SD and Ammonia in earlier publications and considering 95% statistical confidence level and 80% power, the maximum sample size for the study was 21 patients. A maximum of 30 cases in each group had been added, giving more than 90% power and >99% confidence level for ammonia and spleen size and INR correlation study.

For the comparison of categorical variables, significance testing was done by Pearson chi-square test and 2-sided Fisher's exact test as appropriate. An unconditional logistic regression model estimated Associations between selected factors by computing odds ratios (ORs) and their 95% confidence intervals (CIs). The criterion for significance was set at $P<0.05$ based on a two-sided test.

## RESULTS

Of those 50 cases, 45 were males, and 5 were females, and the maximum number of cases was seen in the age group above 50. The lowest age was 32, and the highest age was 83 years. There is no significant difference in gender and age between groups (Table 1).

**Table 1: Gender and age between groups**

| | | GROUP | | P value |
|---|---|---|---|---|
| | | CASE | CONTROL | |
| Gender | M | 45 | 15 | 0.105 |
| | F | 5 | 5 | |
| Age | < 40 | 2 | 1 | 0.919 |
| | 41-50 | 9 | 5 | |


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

| | | | | |
|---|---|---|---|---|
| | 51-60 | 19 | 8 | |
| | 61-70 | 15 | 5 | |
| | > 71 | 5 | 1 | |

Venous ammonia level was abnormally elevated in 44 patients compared with 11 out of 20 patients in the control group, which is statistically significant (p=0.002). Prothrombin time was elevated in 44 out of 50 patients in the study group and 11 out of 20 in the control group. INR was abnormal in 45 out of 50 patients in the study group and 16 out of 20 in the control group. Analysis of Prothrombin time and INR as a noninvasive marker for oesophagal varices prediction indicates which is not suitable as an effective marker.

Spleen size was abnormal in 22 out of 50 patients in the study group and 12 out of 20 in the control group, which is statistically insignificant. Spleen diameter was increased in 42 patients compared with 9 out of 20 patients in the control group, which is statistically significant (p<0.0001). Spleen diameter was found to be most significantly associated with varices.

Absolute lymphocyte count was abnormal only in 7 out of 50 patients in the study group and 4 out of 20 in the control group. Platelet count was abnormally low in 45 patients compared with 20 out of 20 patients in the control group. The Neutrophil lymphocyte ratio was abnormal in 31 out of 50 patients in the study group and 10 out of 20 in the control group.

**Table 2: Comparison of biochemical parameters between groups**

| | | GROUP | | P value |
|---|---|---|---|---|
| | | CASE | CONTROL | |
| Ammonia | Normal | 6 | 9 | 0.002 |
| | Abnormal | 44 | 11 | |
| PT | Normal | 6 | 9 | 0.39 |
| | Abnormal | 44 | 11 | |
| INR | Normal | 5 | 4 | 0.259 |
| | Abnormal | 45 | 16 | |
| Spleen size | Normal | 28 | 8 | 0.226 |
| | Abnormal | 22 | 12 | |
| Spleen diameter | Normal | 8 | 11 | <0.0001 |
| | Abnormal | 42 | 9 | |
| WBC | Normal | 37 | 13 | 0.451 |
| | Abnormal | 13 | 7 | |
| Neutrophil | Normal | 36 | 10 | 0.08 |
| | Abnormal | 14 | 10 | |
| Lymphocyte | Normal | 43 | 16 | 0.533 |
| | Abnormal | 7 | 4 | |
| Platelet | Normal | 5 | 0 | 0.142 |
| | Abnormal | 45 | 20 | |
| NLR | Normal | 19 | 10 | 0.357 |
| | Abnormal | 31 | 10 | |
| Total protein | Normal | 35 | 17 | 0.195 |
| | Abnormal | 15 | 3 | |
| Albumin | Normal | 6 | 6 | 0.071 |
| | Abnormal | 44 | 14 | |
| Globulin | Normal | 15 | 8 | 0.421 |
| | Abnormal | 35 | 12 | |
| ALT | Normal | 37 | 13 | 0.451 |
| | Abnormal | 13 | 7 | |
| AST | Normal | 16 | 2 | 0.057 |
| | Abnormal | 34 | 18 | |
| AST/ALT | Normal | 4 | 4 | 0.154 |
| | Abnormal | 46 | 16 | |
| PC/SD | Normal | 8 | 11 | <0.0001 |
| | Varices | 42 | 9 | |

No significant difference in WBC, Neutrophil, Lymphocyte, Platelet, NLR, Total protein, Albumin, Globulin, ALT, AST, and AST/ALT between groups. So, those cannot be taken as reliable markers for noninvasive assessment of esophageal varices. PC/SD was abnormal in 42 patients compared with 9 out of 20 patients in the control group, which is statistically significant (p<0.0001) (Table 2).

**Table 3: Mean biochemical parameters between groups**

| GROUP | | Mean | Std. Deviation | P value |
|---|---|---|---|---|
| Age | CASE | 57.84 | 10.32 | 0.446 |
| | CONTROL | 55.75 | 10.25 | |
| Ammonia | CASE | 89.29 | 53.1 | 0.005 |
| | CONTROL | 50.25 | 43.79 | |


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

| | | | | |
|---|---|---|---|---|
| PT | CASE | 22 | 7.91 | 0.024 |
| | CONTROL | 17.55 | 5.29 | |
| INR | CASE | 1.82 | 0.76 | 0.037 |
| | CONTROL | 1.45 | 0.36 | |
| Spleen diameter | CASE | 156.9 | 18.34 | <0.0001 |
| | CONTROL | 128.6 | 34.98 | |
| Spleen size | CASE | 11.88 | 3.81 | 0.582 |
| | CONTROL | 11.39 | 1.83 | |
| WBC | CASE | 7.93 | 3.9 | 0.698 |
| | CONTROL | 7.51 | 4.43 | |
| Neutrophil | CASE | 67.84 | 12.94 | 0.147 |
| | CONTROL | 75.05 | 28.29 | |
| Lymphocyte | CASE | 19.09 | 9.77 | 0.02 |
| | CONTROL | 25.85 | 12.78 | |
| Platelet | CASE | 103.74 | 64.97 | 0.006 |
| | CONTROL | 155.75 | 81.42 | |
| MPV | CASE | 14.16 | 16.75 | 0.53 |
| | CONTROL | 11.76 | 4.28 | |
| NLR | CASE | 6.58 | 12.7 | 0.388 |
| | CONTROL | 4.07 | 3 | |
| PLR | CASE | 8.26 | 9.4 | 0.867 |
| | CONTROL | 7.86 | 7.6 | |
| Total protein | CASE | 6.19 | 1.41 | 0.96 |
| | CONTROL | 6.21 | 1.68 | |
| Albumin | CASE | 3.38 | 3.46 | 0.689 |
| | CONTROL | 3.07 | 0.74 | |
| Globulin | CASE | 3.47 | 1.14 | 0.197 |
| | CONTROL | 4 | 2.24 | |
| AST | CASE | 60.11 | 46.43 | 0.459 |
| | CONTROL | 69.88 | 56.77 | |
| ALT | CASE | 35.65 | 33.95 | 0.312 |
| | CONTROL | 47.65 | 64.28 | |
| ALP | CASE | 114.66 | 50.21 | 0.014 |
| | CONTROL | 175.9 | 153.11 | |
| AST/ALT | CASE | 1.92 | 0.85 | 0.597 |
| | CONTROL | 2.05 | 1.14 | |
| PC/SD | CASE | 671.77 | 426.03 | <0.0001 |
| | CONTROL | 1298.03 | 838.12 | |

No significant difference in mean age between groups, but a significant difference in mean Ammonia, PT, INR, and Spleen diameter between groups.

No significant difference in mean Spleen size, WBC, Neutrophil, MPV, NLR, PLR, Total protein, Albumin, Globulin, AST, ALT, and AST/ALT between groups. A significant association in mean Lymphocyte, Platelet, ALP, and PC/SD between groups (Table 3).

## DISCUSSION

In predicting oesophageal varices in CLD patients in India, PC/SD and splenic diameter as noninvasive markers are used, and it are one of the very few studies that focused on it. By analysing the utility of ammonia levels as noninvasive markers of oesophageal varices, we have extended the scope of this study. In age groups of 51 years to 60 years, oesophageal varices were more commonly found. A study by Peng M et al. reported that liver cirrhosis was commonly found in the age group of 50-59, which follows other studies.[8-10] Many studies have shown that biochemical, clinical and ultra-sonographic parameters alone or together have good predictive power for non-invasively assessing the presence of EV.[11,12]

In predicting oesophageal varices in CLD patients, we used PC/SD, spleen diameter and Serum ammonia levels as noninvasive markers in our study. Indicating its usage as a biomarker for oesophageal varices, analysis of the results of our study demonstrated a strong correlation between PC/SD, splenic diameter and serum ammonia and oesophageal varices. A Khadka D et al. study showed that PC/SD had been significantly associated with varices with a p-value of $< 0.05$. The platelet count/SD ratio with a cut-off value of $\leq 909$ has 93% sensitivity and 100% specificity.[13]

A study conducted by Barrera et al. among 67 patients showed that the platelet count/SD ratio with a cut-off value of less than 830 has 76.9% sensitivity and 74.2% specificity, which follows our study. Contrary to our study, this study shows that PC/SD is not an independent marker for esophageal varices. But this study also shows an association between high-risk esophageal varices and PC/SD ratio.[14] A study was conducted among 91 patients, which showed that the platelet count/SD ratio with a cut-off value of $\leq 884$ has 84% sensitivity and 70% specificity, which supports our study.[15] Meanwhile, the correlation between venous ammonia levels and oesophageal varices is found in a study by Khondaker MF et al.[16] Concurring with our study, and it showed serum ammonia levels of 72 µmol/L


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

in small varices and serum ammonia levels of 97 µmol/L in large varices. Montasser MF et al. demonstrated that moderate to large oesophageal varices had a mean venous ammonia level of 148.2µM/L, slightly higher than that from our inference.[7]

Following our results, Tarantino G et al. found that venous ammonia levels correlated with the severity of CLD, where ammonia levels were 45 µM/L in the mild group and 108 µM/L in the severe group. There is concordance between the grade of oesophageal varices and venous ammonia levels (rho 0.43, p<0.001). Under the curve with 0.78, ammonia concentrations gave the best area.[17] In addition to the above parameters, our study found a significant association between Spleen diameter and oesophageal varices, which is statistically significant (p<0.0001). INR analysis showed no differential indication for identifying oesophageal varices or Liver cirrhosis. A study conducted by Kraja B et al. showed that INR could be correlated as noninvasive in predictive oesophageal varices (p-value<0.001).[18] Manohar TP et al. found the INR value indicated to be used as a marker of predicting oesophageal varices with a p-value of 0.015 and on ROC analysis of 75.5%, a significant association between INR values and the size of varices which is contradictory to our study.[19]

We have analysed other parameters of the liver function test, such as serum protein, albumin, globulin, AST, ALT, ALP, and other parameters of CBC, such as total counts, neutrophils, lymphocytes and platelet in our study. Regarding Liver Cirrhosis and the prediction of Oesophageal varices, our study has not found any correlation between these parameters. At the same time, Sarangapani et al. demonstrated that the individual liver function test parameters did not show any significance as a noninvasive marker for oesophageal varices. Similar to our study, this study included a large sample size of 106 CLD patients.[11] In indicating that the liver function and CBC parameters did not have sufficient statistical significance and potential as noninvasive markers of oesophageal varices, our study results reiterate the above-referred studies.

## CONCLUSION

The study concluded that PC/SD, Spleen diameter and serum ammonia are noninvasive markers that positively correlate with OGDscopy. OGDscopy is an invasive procedure requiring mild sedation, which can lead to adverse effects such as bleeding, perforation, and sedation complications. Patients with trismus, short neck, deranged coagulation profile, and severe cardiac co-morbidities cannot undergo OGDscopy, and deaths have occurred during and post-OGDscopy. PC/SD, spleen diameter and serum ammonia biomarkers for screening patients with oesophageal varices have been suggested for disease management due to the lack of endoscopy facilities and experts in primary health centres and rural hospitals. These markers effectively predict oesophageal varices and monitor the patient for oesophageal varices stage progression. The study's results positively indicated using PC/SD, Spleen diameter and serum ammonia as biomarkers. Multicentric studies with a larger sample size were conducted to validate the results across larger populations.

## REFERENCES


1. Oldham KT, Colombani PM, Foglia RP, Skinner MA. Liver Physiology and Pathophysiology. 2005.
2. Carneiro C, Brito J, Bilreiro C, Barros M, Bahia C, Santiago I, et al. All about portal vein: a pictorial display to anatomy, variants and physiopathology. Insights Imaging 2019;10:38.
3. De Franchis R, Baveno V Faculty. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2010;53:762–8.
4. LaBrecque D, Khan AG, Sarin SK, Le Mair AW. Esophageal varices. World Gastroenterol Organ Glob Guidel. 2014;2014:1-4.
5. 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.
6. Souche R, Herrero A, Bourel G, Chauvat J, Pirlet I, Guillon F, et al. Robotic versus laparoscopic distal pancreatectomy: a French prospective single-centre experience and cost-effectiveness analysis. Surg Endosc 2018;32:3562–9.
7. Montasser MF, Abdella HM, Samy AH. Evaluation of venous ammonia level, splenic longitudinal diameter, portal vein and splenic vein diameters as noninvasive indicators for the presence of portosystemic collaterals in Egyptian cirrhotic patients. Open J Gastroenterol 2014;04:265–74.
8. Peng M, Li Y, Zhang M, Jiang Y, Xu Y, Tian Y, et al. Clinical features in different age groups of patients with autoimmune hepatitis. Exp Ther Med 2014;7:145–8.
9. Umar A, Qazi FA, Sattar RA, Umar B. Noninvasive parameters for the detection of variceal bleed in patients of liver cirrhosis, an experience of a tertiary care hospital in Pakistan. Asian J Med Sci 2014;6:61–6.
10. Hoshida Y, Ikeda K, Kobayashi M, Suzuki Y, Tsubota A, Saitoh S, et al. Chronic liver disease in the extremely elderly of 80 years or more: clinical characteristics, prognosis and patient survival analysis. J Hepatol 1999;31:860–6.
11. Sarangapani A, Shanmugam C, Kalyanasundaram M, Rangachari B, Thangavelu P, Subbarayan JK. Noninvasive prediction of large esophageal varices in chronic liver disease patients. Saudi J Gastroenterol 2010;16:38–42.
12. Kim MY, Jeong WK, Baik SK. Invasive and noninvasive diagnosis of cirrhosis and portal hypertension. World J Gastroenterol 2014;20:4300–15.
13. Khadka D, Kc S, Khadka S, Regmi K, Kc P. Platelet count/spleen diameter ratio as a predictor of esophageal varices in patients with liver cirrhosis. J Nepalgunj Med Coll 2017;15:37–40.
14. Barrera F, Riquelme A, Soza A, Contreras A, Barrios G, Padilla O, et al. Platelet count/spleen diameter ratio for noninvasive prediction of high-risk esophageal varices in cirrhotic patients. Ann Hepatol 2009;8:325–30.
15. González-Ojeda A, Cervantes-Guevara G, Chávez-Sánchez M, Dávalos-Cobián C, Ornelas-Cázares S, Macías-Amezcua MD, et al. Platelet count/spleen diameter ratio to predict esophageal varices in Mexican patients with hepatic cirrhosis. World J Gastroenterol 2014;20:2079–84.
16. Khondaker MF, Ahmad N, Al-Mahtab M, Sumi SA. Correlation between blood ammonia level and esophageal varices in patients with cirrhosis of the liver. Euroasian J Hepatogastroenterol 2013; 3: 10. 2013;14.
17. Tarantino G, Citro V, Esposito P, Giaquinto S, de Leone A, Milan G, et al. Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins. BMC Gastroenterol 2009;9:21.
18. Kraja B, Mone I, Akshija I, Koçollari A, Prifti S, Burazeri G. Predictors of oesophagal varices and first variceal bleeding in liver cirrhosis patients. World J Gastroenterol 2017;23:4806–14.
19. Manohar TP, Patil V, Salkar HR. Combination of non-endoscopic parameters as predictors of large esophageal varices. Trop Gastroenterol 2014;35:173–9.




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