ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

A study of non-invasive predictors of esophageal varices in patients with cirrhosis of liver – A cross-sectional study

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Submission: 14-05-2024 Revision: 03-06-2024 Publication: 01-08-2024

ABSTRACT

Background: Current guidelines advise that patients diagnosed with liver cirrhosis undergo screening through upper gastrointestinal endoscopy to detect esophageal varices (EV). Prophylactic measures should be taken for those with large varices on diagnosis and during follow-up. However, this poses a dual challenge, both social and medical, as the number of cirrhotic patients rises while the availability of endoscopy units remains limited. **Aims and Objectives:** In this study, we aim to evaluate the diagnostic accuracy of the non-invasive predictors such as spleen size, platelet count (PC), and PC/spleen diameter (PC/SD) ratio for the diagnosis of EV. **Materials and Methods**: This hospital-based prospective observational study was done in the SDM College of Medical Sciences and Hospital, Dharwad, among 50 patients with cirrhosis of liver. **Results:** Among the 50 patients studied males pre-dominated the study with 80%. Out of the study population, 70% of the patients had varices. For a cutoff point of PC/SD ratio 916, the sensitivity was 71.42% and specificity was 93.3%. For a cutoff value of PC of 1.32 lakhs, the sensitivity was 71.42%, and the specificity was 73.3%. For a cutoff value of the longest SD of 12.40 cm, the sensitivity was 94.30%, and specificity was 33.3%. **Conclusion:** These non-invasive predictors can be useful screening tools for the diagnosis of EV. These can be effective for the initiation of prophylactic treatment when the endoscopy facility is not available.

Key words: Esophageal varices; Thrombocytopenia; Hepatic cirrhosis; Gastrointestinal endoscopy

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v15i8.65502

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Cirrhosis is an important cause of morbidity and mortality among patients with chronic liver disease (CLD) which can lead to hepatocellular carcinoma and hepatic decompensation, including ascites, hepatic encephalopathy, and variceal bleeding.[1] Associated with 2.4% of global deaths in 2019. Globally, cirrhosis currently causes 1.16 million deaths, and liver cancer causes 788,000 deaths, making them the 11th and 16th most common causes of death, respectively.[2] The contribution of cirrhosis and its complications, collectively CLDs, as causes of mortality in India have been increasing progressively since 1980.[3]

The liver develops fibrosis and nodules due to persistent damage that changes the liver's natural lobular organization, a condition known as cirrhosis. CLD usually progresses to cirrhosis. The common causes are viral, alcohol-induced, and nonalcoholic steatohepatitis. Other causes are autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency, Budd-Chiari syndrome, drug-induced liver cirrhosis, and chronic right-sided heart failure.[4] It can be symptomatic or asymptomatic, depending on whether the condition is clinically compensated or decompensated. One of the main effects of cirrhosis is portal hypertension (PHT), which is characterized by a portal pressure gradient >5–10 mmHg. It can cause ascites,

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hepatosplenomegaly, and prominence of the periumbilical abdominal veins, which can cause caput medusa.

Esophageal varices (EV) is another serious complication that leads to increased blood flow in the collateral circulation and accounts for 20% of the mortality rate within 6 weeks after the bleeding episode.[5] At the time of diagnosis of cirrhosis, EVs are present in about 40% of patients with compensated disease and in 60% of those with decompensated disease and ascites.[6] It has been shown that the risk of variceal bleeding is related to the size of varices with large EV being at a greater risk; this is possibly due to a higher variceal wall tension in large EV.[7,8] It is possible that stopping this kind of bleeding will increase these patients' chances of survival. It has been demonstrated that giving beta-adrenergic receptor antagonists for an extended period can lower the risk of initial variceal bleeding in patients with EV.

To screen for EV, upper gastrointestinal endoscopy is the recommended approach.[9,10] The main disadvantage of endoscopy is invasive, so it can increase the risk of bleeding and infection. Not all health centers, mainly in rural regions, have facilities for this procedure. Consequently, there is a huge need for a non-invasive technique to detect EVs to reduce the need for needless endoscopy and increase management's cost effectiveness. Perhaps it would be more economical to have only high-risk patients undergo this procedure for the diagnosis of EV hence reducing the inconvenience of patients. Several studies have evaluated possible non-invasive markers of large EV and found that low platelets, splenomegaly, advanced Child status, serum albumin, and high portal vein diameter at ultrasonography (USG) are useful parameters for identifying high-risk individuals.[11,12] A platelet count-spleen diameter ratio (PC/SD), PC, and long SD have been proposed as useful non-invasive monitoring tools for EV, as they are less expensive and easy to access.

Therefore, this study was conducted to assess these parameters to forecast whether EV will develop in patients with PHT or not.

Aims and objectives

- The objectives of the study are as follows: To analyze the association between PC, spleen size, and their ratio with the presence of varices
- To evaluate these measures' potential as non-invasive tools to predict the presence of EV.

MATERIALS AND METHODS

It is a hospital-based cross-sectional study conducted in the SDM College of Medical Sciences and Hospital, Dharwad, India. Totally 50 subjects, aged >18 years, diagnosed with cirrhosis were included in the study. This study was done for 1 year during 2015–2016. Exclusion criteria included subjects with a history of portal hypertensive bleeding, hepatocellular carcinoma, portal vein thrombosis, patients on β-blockers, diuretics, or other vasoactive drugs in the past or present, Budd Chiari Syndrome, and with other causes of noncirrhotic PHT.

Totally 50 subjects with liver cirrhosis based on the inclusion and exclusion criteria were recruited. Abdominal examination was done for all patients and subjects were undergoing diagnostic endoscopy, USG abdomen, complete hemogram, renal function test, liver function tests, and viral markers. Table 1 is Child-Turcotte-Pugh class (CTP). The cutoff values are determined by the receiver operating characteristic curve. The cutoff value for the longest SD, PC, and PC/SD was calculated to be ≤12.4 cm, <1.32 lakhs, and ≤916, respectively, and its diagnostic accuracy was calculated.

Ethics

The study protocol was approved by the Institutional Ethics Committee (SDMIEC/0380/2015). Each research subject gave their verbal and written agreement, and information was only collected after a thorough description of the study's objectives was explained. Confidentiality of the participant's information was assured.

Statistical analysis

Data were entered into the Excel sheet and the Statistical Package for the Social Sciences version 28.0 statistical was used at analyze the data. The Chi-square test and t-test were used to assess the association between variables.

RESULTS

Table 2 shows the distribution of the study subjects. Out of 50 participants 35 had EV, the prevalence was 70%. The mean age in the study was 53.12±11.70. Most of the study participants were in the age group of 51–60 years (34%) followed by 41–50 years (28%). The prevalence of EV among the 41–50 years age group was 92.85%, among

Table 1: Child-Turcotte-Pugh class (CTP)

Factor	1 point	2 points	3 points
Total bilirubin (μmol/L)	<34	34-50	>50
Serum albumin (g/l)	>35	28-35	<28
INR	<1.7	1.71-2.30	>2.30
Ascites	none	mild	Moderate – severe
Hepatic encephalopathy	none	Grade I-II	Grade III-IV
	Class A	**Class B**	**Class C**
Total points	5-6	7-9	10-15

the 60+ age group it was 66.67%. The prevalence was 58.82% among 51–60 years patients. 80% of the study participants were male. The prevalence in both sexes was found to be 70%. The mean CTP score among subjects with varices was 9.60±1.17, among non-EV subjects it was 9.87±2.13. 24 patients were Child-Pugh Class B among them 16(66.67%) had EV, 26 were in Class C among them 19(73.07%) had EV. The presence of EVs correlated significantly with (P<0.05), with the severity of cirrhosis is categorized by Child-Pugh Score. A significant correlation (P<0.05) was observed for the variables such as age and CTP score.

Table 3 shows the mean comparison of the presence or absence of EV to various non-invasive parameters.

In our study, (Table 4)the cutoff SD value was 12.40 cm. Thirty-three out of 43 participants with enlarged spleen were diagnosed with EV. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to be 94.2%, 33.33%, 76.74%, and 71.4%, respectively. The mean SD among subjects with EV was 14.5±2.10 cm, without varices, it was 12.52±1.88. The mean PC among EV group was 1.04±0.42, among non-EV subjects, it was 1.80±1.77 lakhs. The cutoff platelet was kept at 1.32 lakhs. 25 out of 29 with low platelet subjects had varices; in the other group, 11 out of 21 had varices. Sensitivity, specificity, PPV, and NPV for low platelets were found to be 71.4%, 73.3%, 86.2%, and 52.8%, respectively. The mean PC/SD ratio among subjects with varices was 736.80±318.18, and in non-EV subjects, it was 1467.67±661.92. PC/SD cutoff was 916. About 96% of the subjects with PC/SD <916 had varices, and 14 out of 24 with ≥916 PC/SD had varices. It reports 71.42% sensitivity, 93.3 % specificity, 96.15% PPV, and 58.33% NPV.

DISCUSSION

In this study, a total of 50 subjects with liver cirrhosis were included in the study. The prevalence of EV was 70%. In the study done by Madhotra et al., among 184 subjects 94 had varices.[11] Among 206 participants, 176 were diagnosed

Table 2: Distribution of study subjects

Variable	Group	No EV	With EV	Total (%)	P-value
Age distribution	31–40	3	4	7 (14)	0.0164*
	41–50	1	13	14 (28)	
	51–60	7	10	17 (34)	
	61+	4	8	12 (24)	
Sex distribution	Male	12	28	40 (80)	1.0000
	Female	3	7	10 (20)	
Ascites	Present	15	32	47 (94)	0.6034
	Absent	0	3	3 (6)	
Encephalopathy	Present	4	3	7 (14)	0.2134
	Absent	11	32	43 (86)	
Viral markers	HBSAG	4	2	6 (12)	
	HCV	1	1	2 (4)	0.0651
	HBSAG+HCV	0	1	1 (2)	
	Negative	10	31	41 (82)	
CTP	5–6 (class A)	0	0	0	0.047*
	7–9 (class B)	8	16	24 (48)	
	10–15 (class C)	7	19	26 (52)	

EV: Esophageal varices, CTP: Child-Turcotte-Pugh class, HBSAG: Hepatitis B surface antigen, HCV: Hepatitis C virus, *p- value <o.5 indicate statistical significance. Correlation was observed for age and CTP with occurance of EV.

Table 3: Comparison of patients with EV and No EV with respect to various non-endoscopic parameters

Variables	With EV		No EV		T-value	P-value
	Mean	SD	Mean	SD		
Hb	9.25	1.81	9.32	1.54	-0.1282	0.8985
Albumin	2.17	0.47	1.99	0.47	1.2433	0.2198
Platelets	1.04	0.42	1.80	0.77	-4.4941	0.0001*
Total bilirubin	3.95	3.23	5.71	6.82	-1.2421	0.2202
Direct bilirubin	2.39	2.35	4.19	5.51	-1.6311	0.1094
ALP	138.40	40.59	169.27	85.87	-1.7364	0.0889
SGOT	93.09	49.67	118.27	107.55	-1.1402	0.2599
SGPT	50.34	29.86	75.20	108.37	-1.2646	0.2121

EV: Esophageal varices, SD: Standard deviation, Hb: Hemoglobin, ALP: Alkaline phosphatase, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase

Table 4: Diagnostic accuracy of non- invasive parameters

Parameter	Cutoff value	EV	No EV	Total	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	P-value
Longest splenic diameter (cm)	>12.40	33	10	43	94.28	33.33	76.74	71.4	0.0330*
	≤12.40	2	5	7					
Platelet count (in lakhs)	≤1.32	25	4	29	71.42	73.33	86.20	52.38	0.0040*
	>1.32	10	11	21					
PC/SD ratio	≤916	25	1	26	71.42	93.33	96.15	58.33	0.0001*
	>916	10	14	24					

EV: Esophageal varices, PPV: Positive predictive value, NPV: Negative predictive value, PC/SD: platelet count (PC), and spleen diameter

with varices in another study.[13] The prevalence of EV was 54.1% (118 out of 218) in Giannini et al., study report.[14]

The prevalence was the same in both genders. Distribution of varices was studied in various age groups, in the age group 41–50 years in which there were 13 patients had EV out of 14 (92.85%) followed by age more than 61 years, which accounted for 66.67% and the significant correlation was found according to the P-value.

In our study, linear association was observed for the prevalence of EV and severity of cirrhosis, higher in Class C subjects (73.07%) compared to Class B (66.67%). Similar reports were noticed in another study.[15] Another Indian study reports, that CTP class B/C is a significant predictor (odd's ratio – 3.3) for the diagnosis of EV.[16] In Cherian et al., report incidence of varices among Class A, B, and C subjects was 59%, 78%, and 96.6%, respectively.[16]

Our study kept the cutoff platelet value of 1.32 lakhs (Table 4). The sensitivity was 71.42%, specificity was 73.33%, PPV was 86.20% and NPV was 52.38%. For the platelet cutoff of 1.38 lakhs, the diagnostic sensitivity was 92.6% and the specificity was 66.9% in the Yu et al., study report.[15] In another investigation for the cutoff PC of ≤121,000 had a sensitivity of 87.5% and a specificity of 73.3%. Using a cutoff point of 1.4 lakhs, this prediction rate is similar to data from Italy where the sensitivity was in the range of 63–77% and the specificity was 69–88%.[17] However, compared a study from Tanzania, where a PC cutoff value kept at 98,000, reports the sensitivity and specificity of 59.1% and 54.8%, respectively, which is comparatively lower than our study.

In our study (Table 4), we kept the cutoff of SD at 12.40 cm, which yielded 94.28% sensitivity, 33.3% specificity, 76.74% PPV, and 71.4% NPV. Cutoff for SD was 14.8 in the Yu et al., study. They found sensitivity, specificity, PPV, and NPV were 58%, 84.7%, 72.3%, and 74.6%, respectively.[15] Enlarged spleen also has a strong estimation capacity at 14.5 cm in the study by Haile Tesfaye et al., with a sensitivity of 93.2% and a specificity of 63.3%.[13] A Tanzanian study using a 152 mm threshold showed a sensitivity of 65.9% and a specificity of 65.2%.[18] In the report of Ivory Coast, an SD cutoff value of >102 mm produced a sensitivity of 86% and a specificity of 75%.[19]

In our study (Table 4), the cutoff value for PC/SD was ≤916 which revealed a sensitivity, specificity, PPV, and NPV were reported to be 71.42%, 93.33%, 96.15%, and 58.33%, respectively. Giannini et al., used the cutoff of ≤909, they reported a comparable outcome of 91.5 % sensitivity and 67.0 % specificity.[14] The same cutoff number was utilized in another study conducted in China, which produced a PPV of 73% and an NPV of 88%.[15] Haile Tesfaye et al., used the cutoff of ≤818, and the sensitivity and specificity were found to be 92.05%, and 60%, respectively.[13] An Italian study that used a cutoff of <736 produced results for varices prediction that were less accurate than our study's results, with 38% sensitivity and 40% specificity. According to the reports from Egypt, a cutoff of 939.7 yields 100% sensitivity, 95.6% specificity, 95.6% PPV, and 100% NPV which has higher diagnostic accuracy than ours.[20] PC/SD was first proposed in 2003. Due to efficient EV prediction, it has become a vital assessment tool to date.

Limitations of the study

In our study, the diagnosis of cirrhosis was not made up with the histopathologic discoveries, which is the gold standard. Another limitation is the small sample size. The chance of selection bias is there.

CONCLUSION

Diagnostic accuracy of PC, longest SD CTP class B/C, and PC/SD were analyzed in this study. High sensitivity was shown for enlarged spleen and high specificity was observed for PC/SD. Better diagnostic performance was noticed in all parameters especially PC/SD with 71% sensitivity and 93% specificity. Combining these non-invasive parameters in patients with chronic CLD can increase the reliability of predicting the occurrence of EV. Their application in the detection and monitoring of EVs may significantly lower medical expenses, alleviate patient suffering, and lighten the workload for endoscopic units. Also, these predictors can be useful to start prophylaxis treatment when the endoscopy facility is not there.

ACKNOWLEDGMENT

We express our gratitude to all participants for their invaluable support to this study, and to our seniors for their guiding wisdom.

REFERENCES

1. Ginès P, Krag A, Abraldes JG, Solà E, Fabrellas N and Kamath PS. Liver cirrhosis. Lancet. 2021;398(10308):1359-1376.
   https://doi.org/10.1016/s0140-6736(21)01374-x
2. Asrani SK, Devarbhavi H, Eaton J and Kamath PS. Burden of liver diseases in the world. J Hepatol. 2019;70(1):151-1571.
   https://doi.org/10.1016/j.jhep.2018.09.014
3. Mokdad AA, Lopez AD, Shahraz S, Lozano R, Mokdad AH, Stanaway J, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: A systematic analysis. BMC Med. 2014;12:145.
   https://doi.org/10.1186/s12916-014-0145-y
4. Naveau S, Perlemuter G and Balian A. Epidemiology and natural history of cirrhosis. Rev Prat. 2005;55(14):1527-1532.
5. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W, Practice Guidelines Committee of the American Association for the Study of Liver Diseases and Practice Parameters Committee of the American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007;46(3):922-938.
   https://doi.org/10.1002/hep.21907
6. De Franchis R. Non-invasive (and minimally invasive) diagnosis of oesophageal varices. J Hepatol. 2008;49(4):520-527.
   https://doi.org/10.1016/j.jhep.2008.07.009
7. Nevens F, Bustami R, Scheys I, Lesaffre E and Fevery J. Variceal pressure is a factor predicting the risk of a first variceal bleeding: A prospective cohort study in cirrhotic patients. Hepatology. 1998;27(1):15-159.
   https://doi.org/10.1002/hep.510270104
8. Merkel C, Zoli M, Siringo S, Van Buuren H, Magalotti D, Angeli P, et al. Prognostic indicators of risk for first variceal bleeding in cirrhosis: A multicenter study in 711 patients to validate and improve the North Italian Endoscopic Club (NIEC) index. Am J Gastroenterol. 2000;95(10):2915-2920.
   https://doi.org/10.1111/j.1572-0241.2000.03204.x
9. Grace ND, Groszmann RJ, Garcia-Tsao G, Burroughs AK, Pagliaro L, Makuch RW, et al. Portal hypertension and variceal bleeding: An AASLD single topic symposium. Hepatology. 1998;28(3):868-880.
10. Poynard T, Calès P, Pasta L, Ideo G, Pascal JP, Pagliaro L, et al. Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. An analysis of data and prognostic factors in 589 patients from four randomized clinical trials. Franco-Italian multicenter study group. N Engl J Med. 1991;324(22):1532-1538.
    https://doi.org/10.1056/nejm199105303242202
11. Madhotra R, Mulcahy HE, Willner I and Reuben A. Prediction of esophageal varices in patients with cirrhosis. J Clin Gastroenterol. 2002;34(1):81-85.
    https://doi.org/10.1097/00004836-200201000-00016
12. Zaman A, Becker T, Lapidus J and Benner K. Risk factors for the presence of varices in cirrhotic patients without a history of variceal hemorrhage. Arch Intern Med. 2001;161(21):2564-2570.
    https://doi.org/10.1001/archinte.161.21.2564
13. Gebregziabiher HT, Hailu W, Abay Z, Bizuneh S and Meshesha MD. Accuracy of non-invasive diagnosis of esophageal varices among cirrhotic patients in a low-income setting. Heliyon. 2023;9(12):e23229.
    https://doi.org/10.1016%2Fj.heliyon.2023.e23229
14. Giannini EG, 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(11):2511-2519.
    https://doi.org/10.1111/j.1572-0241.2006.00874.x
15. Yu S, Chen W and Jiang Z. Platelet count/spleen volume ratio has a good predictive value for esophageal varices in patients with hepatitis B liver cirrhosis. PLoS One. 2021;16(12):e0260774.
    https://doi.org/10.1371/journal.pone.0260774
16. Cherian JV, Deepak N, Ponnusamy RP, Somasundaram A and Jayanthi V. Non-invasive predictors of esophageal varices. Saudi J Gastroenterol. 2011;17(1):64-68.
    https://doi.org/10.4103/1319-3767.74470
17. Colli A, Gana JC, Yap J, Adams-Webber T, Rashkovan N, Ling SC, et al. Platelet count, spleen length, and platelet count-to-spleen length ratio for the diagnosis of oesophageal varices in people with chronic liver disease or portal vein thrombosis. Cochrane Database Syst Rev. 2017;4(4):CD008759.
    https://doi.org/10.1002/14651858.cd008759.pub2
18. Gunda DW, Kilonzo SB, Mamballah Z, Manyiri PM, Majinge DC, Jaka H, et al. The magnitude and correlates of esophageal Varices among newly diagnosed cirrhotic patients undergoing screening fibre optic endoscope before incident bleeding in North-Western Tanzania; a cross-sectional study. BMC Gastroenterol. 2019;19(1):203.
    https://doi.org/10.1186/s12876-019-1123-9
19. Mahassadi AK, Bathaix FY, Assi C, Bangoura AD, Allah-Kouadio E, Kissi HY, et al. Usefulness of noninvasive predictors of oesophageal varices in black African cirrhotic patients in Côte d'Ivoire (West Africa). Gastroenterol Res Pract. 2012;2012:216390.
    https://doi.org/10.1155/2012/216390
20. Abu MA, Makarem E, Shatat ME, Shaker Y, Aleem AA, El Sherif AM, et al. Platelet count/bipolar spleen diameter ratio for the prediction of esopha-geal varices: The special Egyptian situation. Noninvasive prediction of esophageal varices. Hepat Mon. 2011;11(4):278-284.

Authors' Contributions:
NM- Definition of intellectual content, literature survey, prepared the first draft of the manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation, and submission of article; **KA-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **DM-** Design of study, statistical analysis and interpretation, review manuscript; review manuscript, literature survey and preparation of figures; coordination, and manuscript revision

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Source of Support: Nil, **Conflicts of Interest:** None declared.