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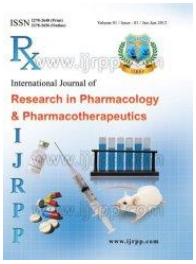

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Study of non-invasive predictors of oesophageal varices in chronic liver disease

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ABSTRACT

Esophageal varices (EVs) are a serious consequence of portal hypertension in patients with liver diseases. Several studies have evaluated possible noninvasive markers of EVs to reduce the number of unnecessary endoscopies in patients with cirrhosis but without varices. This prospective study was conducted to evaluate noninvasive predictors of large varices (LV). The study analyzed 100 patients with liver diseases from February 2014 and July 2015. Relevant clinical parameters assessed included Child-Pugh class, ascites etc. Laboratory parameters like hemoglobin level, platelet count, prothrombin time, serum bilirubin, albumin and ultrasonographic characteristics like splenic size, portal vein diameter were assessed. Univariate and multivariate analysis was done on the data for predictors of large EVs. The incidence of large varices were seen in 44. 46%. On multivariate analysis, independent predictors of the presence of LV were palpable spleen, low platelet count, spleen diameter >154 mm, portal vein >13 mm, splenic vein >11.5 mm. Platelet count /spleen diameter <815 had a sensitivity. The presence and higher grades of varices can be predicted by a low platelet count, Child-Pugh class B/C and spleen diameter. These may be considered as non-endoscopic predictors for the diagnosis and management of large grade varices.

Keywords: Esophageal varices, non-invasive predictors, platelet spleen ratio and portal hypertension.

INTRODUCTION

Chronic liver disease is a process of progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis[1]. Portal hypertension is the significant complicating feature of decompensate cirrhosis and is responsible for the development of ascites and esophageal varices, results in the development of collaterals to bypass the increased resistance to flow within the portal vein to return blood to systemic circulation[2]. Portal hypertension is defined by a pathological increase in portal pressure, in which the pressure gradient between the portal vein and inferior vena cava (the portal pressure gradient [PPG] is increased above the upper normal limit of 5 mm Hg. Portal hypertension becomes clinically significant when the PPG increases above the threshold value of 10 mm Hg

(e.g., formation of varices) or 12 mm Hg (e.g., variceal bleeding, ascites). PPG values between 6 and 10 mm Hg represent subclinical portal hypertension[3, 4]. Bleeding from ruptured esophageal or gastric varices is the main complication of portal hypertension and a major cause of death. Most cirrhotic patients develop esophageal varices, with a lifetime incidence as high as 90%[5]. As per existing guidelines in a case of cirrhosis of the liver was screening with upper gastrointestinal endoscopy to look for any esophagogastric varices present or not and grade the severity of varices and then started the prophylactic measures like propranolol to prevent the first bleed. Doubts are expressed regarding the cost-effectiveness of universal screening with upper gastrointestinal endoscopy. A study done based on the Brennan H. Spiegel et al published in journal 'Hepatology [6]. "Empiric β blocker therapy for the primary prophylaxis of variceal hemorrhage is a cost-effective measure as the use of screening endoscopy to guide the therapy adds significant cost with only a marginal increase in effectiveness."In this setting that can predict the severity of portal hypertension by a low cost and non-invasive method, then uses the upper gastrointestinal endoscopy for only high risk patients. Although the occurrence of esophageal varices and the time of gastrointestinal bleeding in portal hypertension can't be exactly predicted, there are some endoscopic, ultrasonographic, laboratory parameters and clinical signs associated with high risk of bleeding. Some studies have shown good correlation between ultrasonographic findings and platelet count and severity of esophagogastric varices. This study describes an attempt to predict the esophageal varices based on ultrasonographic findings, platelet count and platelet count spleen diameter ratio and its correlation with upper GI endoscopy.

MATERIALS AND METHODS

The study comprised of 100 portals hypertensive patients who were admitted in Mahatma Gandhi Memorial Hospital between February 2014 and July 2015. A detailed clinical history was recorded regarding age, sex, duration of symptoms like jaundice, distension of abdomen, hematemesis and malena. All patients underwent complete clinical examination, including, detailed examination of the gastrointestinal system. Routine biochemical investigations, liver function tests were done in every patient. Every recruited patient underwent Ultrasonography and Fiber Optic upper gastrointestinal endoscopy. Platelet count spleen diameter ratio was calculated.

Exclusion criteria

1. Cases of portal hypertension who are on β blockers,
2. Cases of portal hypertension who underwent EST or EVL,
3. Cases of portal hypertension who underwent TIPS or shunt surgery.
4. Hepatocellular carcinoma,
5. Primary hematological disorders,
6. Active gastrointestinal bleeding on admission,
7. Previously known gastrointestinal bleeding and
8. Unstable medical condition.

Inclusion Criteria

Cases of portal hypertension admitted in Department of General Medicine and Gastroenterology in Mahatma Gandi Memorial Hospital, Warangal, India.

Study Proforma

Laboratory testing, Ultrasonography and Fiber Optic upper gastrointestinal endoscopy is done in every recruited patient.

Laboratory testing

Hematological and biochemical work-up included measurement of hemoglobin, total leukocyte count, platelet count, prothrombin time and serum concentrations of bilirubin (total and conjugated), serum albumin, alanine aminotransferase and aspartate aminotransferase. For each patient, a modified Child-Pugh score was calculated.[7] All patients were tested for HBsAg and antibodies to hepatitis C virus to determine the cause of liver cirrhosis. Tests for other causes of cirrhosis (serum ceruloplasmin and slit lamp examination of Wilson's disease, tests for autoantibodies for autoimmune liver disease, iron studies for hemochromatosis) were carried out only if there was a suggestive clinical clue.

ULTRASONOGRAPHY

Measurement of liver size

Liver size is measured using the sagittal approach in the midclavicular line. It is measured from the diaphragm to the inferior border on b –mode image [8].

Measurement of splenic size

Spleen size was measured by placing the patient in supine position, using 2-5 MHz curvilinear transducer in the coronal plane of section, posteriorly in one of the lower left intercostals spaces. The patient was examined in various degrees of inspiration to maximize the window to the spleen. The spleen parenchyma is extremely homogenous and it has a uniform mid to low echogenicity. When the spleen enlarges it can be more echogenic. A maximum cephalocaudal measurement exceeding 13 cm indicates enlargement with a high degree of reliability [9].

Measurement of portal vein diameter

The portal venous supply to the left lobe of the liver can be visualized using an oblique, cranially angled sub xiphoid view (recurrent subcostal oblique projection). The main and right portal veins are best seen in the sagittal or oblique sagittal plane. It is measured in supine position, during quiet respiration where the portal vein crosses anterior to the IVC [9].

Presence of collaterals

5 major sites of portosystemic venous collaterals are

1. i. Gastroesophageal junction between coronary and short gastric veins and systemic esophageal veins.
2. ii. Paraumbilical vein-connects left portal vein to the systemic epigastric veins near the umbilicus.
3. iii. Splenorenal and gastrorenal.
4. iv. Intestines – regions in which GIT becomes retroperitoneal collaterals form (eg: ascending, descending colon, duodenum and liver).
5. v. Hemorrhoidal- where superior rectal veins anastomose with systemic middle and inferior rectal veins.

Duplex Doppler provides additional information. An increase of less than 20% in the diameter of the portal vein with deep inspiration indicates portal hypertension with 81% sensitivity and 100% specificity. Ultrasonography is the preferred initial investigation because of its low cost and high acuaracy[10-12].

Endoscopy

Endoscopy is important to assess semi quantitatively the number, appearance and size of any esophageal varices.

Esophageal Varices

Grade I

Small Varices without luminal prolapsed.

Grade II

Moderate sized varices with luminal prolapsed with minimal obscuring of Gastroesophageal Junction.

Grade III

Large varices showing luminal prolapsed substantially obscuring of Gastroesophageal Junction.

Grade IV

Very large varies completely obscuring GE junction**.** Grade **1 & 2** are considered as small varices and grade 3 & 4 as large varices [13].

Gastric Varices

These are classified as a continuation of esophageal varices along the lesser curve of the stomach (GOV-1) or in the fundus (GOV-2); more rarely 'Isolated gastric varices' may be found in the fundus (IGV-1) or in the rest of the stomach (IGV-2). The prevalence of gastric varices in portal hypertension is about 20%[14]. They cause 5% to 10% of all episodes of upper gastrointestinal bleeding in portal hypertension.

Portal Hypertensive Gastropathy (PHG)

Two types of Gastric mucosal changes are seen in portal hypertensive gastropathy. Mosaic pattern of gastric mucosa indicates mild PHG and cherry red spots in gastric mucosa reflect severe PHG.

Statistical analysis

This is an observational study where 100 patients were included, of which 50 are cases (with esophageal varices) and 50 are controls (without esophageal varices). The cases were again divided into large and small varices based on endoscopic findings. Detailed history taking and clinical

examination was done. Descriptive statistics of normally distributed variables are reported as mean and SD and that of Non-normally distributed variables were subjected to the Mann Whitney test and median with range was calculated and p-value of <0.05 is taken as significant[15]. All variables which were found to be significant on univariate analyses were included as candidate variables for logistic regression analysis to identify independent predictors of the presence of esophageal varices and their size. Sensitivity, Specificity, Positive predictive value and Negative predictive values were calculated for this parameters[16].

RESULTS

Age distribution

Median age with range among 50 cases was 43.18 (range 24-86) and among 50 controls was 42.16 (range 22-68) for large varices it is 44.46 (range 29-86) and for small varices is 41.79 (range 24-65) and the results were shown in both table and figure number 1.

Table 1 Age distribution among cases and controls

Age	Cases	Controls	Large varices	Small varices
20-30	6	10	3	3
31-40	24	15	12	12
41-50	12	14	6	6
51-60	4	7	3	1
61-70	3	4	1	2
>70	1	0	1	0
total	50	50	26	24

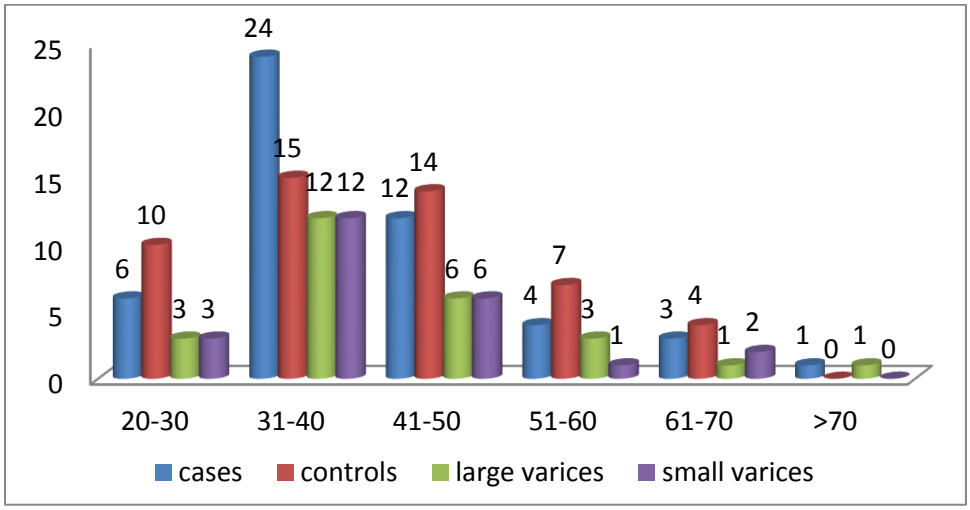

Figure 1 Bar diagram showing age distribution among cases and controls

Sex distribution

Out of 100 patients, 81 were males and 19 were females. Among cases, 39 were males and 11 were females (no. of males/females in Large varices is 20/6 and Small Varices is 19/5) and in controls, 42 were males and 8 were females and results were shown in both table and figure number 2.

Table 2 Sex distribution among cases and controls.

S.No	Females	%	Males	%	Total	%
Cases	11	22	39	78	50	100
Controls	8	16	42	84	50	100
Large varices	6	23	20	77	26	52
Small varices	5	21	19	79	24	48

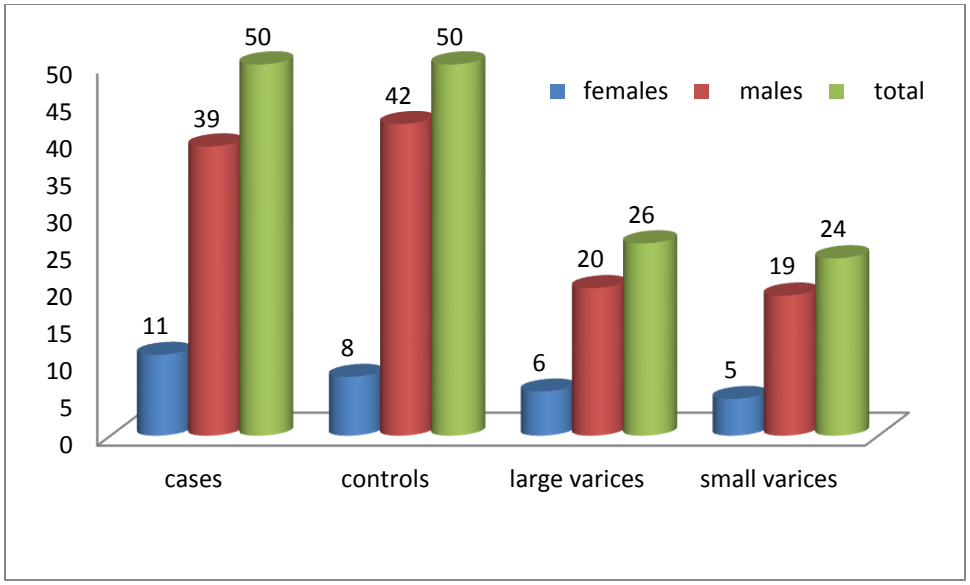

Figure 2 Bar diagram showing sex distribution among cases and controls

Distribution of patients based on etiology

Alcoholic liver disease is the most common etiology in this study corresponding to 62 % of cases followed by hepatitis B with 10% and observations is shown in both table and figure number 3.

Table 3 Distribution of various etiologies among cases and controls

Etiology	Patients
Alcoholic liver disease	62
Hepatitis B	10
Hepatitis C	2
Non Alcoholic Fatty Liver	6
Wilsons Disease	1
Cause Remained Unknown	19

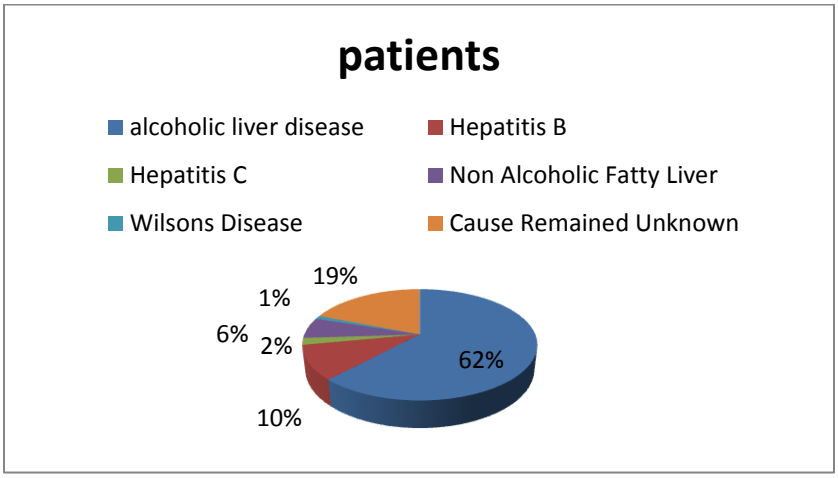

Figure 3 Pie diagram showing various etiologies among cases and controls

Relationship of cases and controls based on child pugh score

The Child pugh score was calculated for all the patients, with most of the patients with varices fall in group C and without varices in group B and the results were shown in both table and figure number 4.

Table 4 Distribution of cases and controls according Child pugh score

COLUMN1	CLASS A	CLASS B	CLASS C	TOTAL
Cases	4	18	28	50
Controls	7	23	20	50
Large	3	10	13	26
Small	1	8	15	24

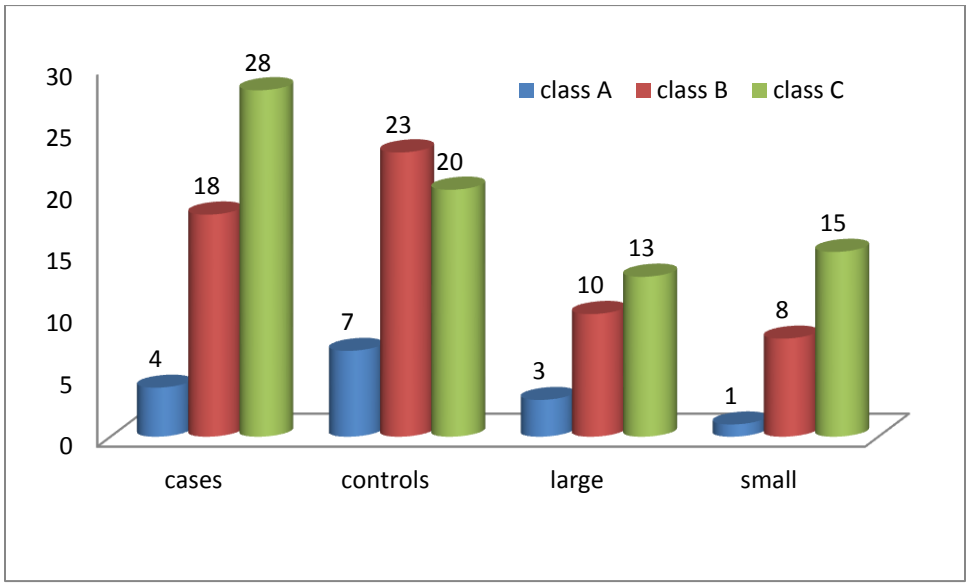

Figure 4 Bar diagram showing distribution of cases and controls according to Child pugh score

Statistical analysis of various parameters

On univariate analysis portal vein diameter, spleen diameter, platelet count and platelet count and spleen diameter ratio were found to be significantly associated with the presence of varices. On multivariate analysis the presence of esophageal varices was significantly associated with platelet count < 102,000/ µl (OR 6.65; 95% CI, 2.51-17.6), spleen diameter > 154 mm (OR 5.78; 95% CI, 2.4-13.94), portal vein diameter > 13 mm (OR 2.49;95% CI, 1.1-5.62) and platelet count /spleen diameter <815 (OR 10.92 ;95% CI 4.07-29.26). On multivariate analysis the presence of large esophageal varices was significantly associated with platelet count < 93500/ µl (OR 4.8; 95% CI, 1.42-16.18), spleen diameter > 162 mm (OR 1.94; 95% CI 0.62-6.02), portal vein diameter > 14.4mm (OR 3.5 ;95% CI 1.05-11.66) and platelet count /spleen diameter <548 (OR 9.4;95% CI 2.46-36.19). As the grade of esophageal varices increases platelet count decreases, with controls (without varices) show a highest median platelet count of 169000/µl and smallest median for large varices of 80500/µl and all results and observations were shown in both figure and table number 5-8.

Table 5 Relationship of various parameters with the presence or absence of esophageal varices on univariate analysis

Variables	Cases	Controls	P-Value
sex (M/F)	39/11	42/8	0.4444
Ascites	47(51.6%)	44(48.4%)	0.7532

Hepatic encephaolpathy	6(66.7%)	3(33.3%)	0.3173
Total bilirubin(mg/dl)	2.9(0.4-25.1)	2.3(0.3-26.9)	0.6027
Serum albumin(gm/dl)	2.7(1.4-4.5)	2.8(1.6-4.2)	0.0692
Prothrombin time(sec)	17.7(11.6-38.5)	15.2(10.6-30)	0.0187
Child pugh score class A	4(36.4%)	7(63.6%)	0.2541
Child pugh score class B	18(43.9%)	23(56.10%)	-
Child pugh score class C	28(58.33%)	20(41.67%)	-
Platelet count(/µl)	98000(45000-380000)	169000(78000-266000)	<0.0001
liver size(cm)	12.3(6.8-18)	12.5(8.9-18)	0.6391
Portal vein diameter(mm)	13.9(8.0-18.0)	12.1(7.8-16)	0.0322
Spleen diameter(cm)	16.0(8.0-26)	13.8(9.0-19.6)	<0.0001
Platelet count /Spleen diameter	608(264-2750)	1277(632-2611)	<0.0001

Table 6 Multivariate logistic regression analysis for the presence of varices

Parameters	**P-Value**	**Odds ratio**	**95% Confidence interval**	
			Lower limit	**Upper limit**
Platelet count (<102000/µl)	0.002	6.65	2.51	17.6
Splenic Diameter(>154mm)	0.018	5.78	2.4	13.94
Portal vein Diameter(>13.0mm)	0.026	2.49	1.1	5.62
Platelet count /Splenic Diameter(<815)	0.001	10.92	4.07	29.26

Table 7 Relationship of various parameters with the presence or absence of esophageal varices on univariate analysis

Variables	**Large Varices**	**Small Varices**	**P-Value**
Sex (M/F)	20/6	19/5	0.8728
Ascites	25(53.2%)	22(46.8%)	0.6617
Hepatic encephalopathy	3(50%)	3(50%)	1
total bilirubin(mg/dl)	2.5(0.4-25.1)	5.3(0.5-21.1)	0.1932
serum albumin(gm/dl)	2.6(1.4-3.6)	2.9(1.8-4.5)	0.1111
prothrombin time(sec)	16.1(11.6-32)	19.2(12-38.5)	0.1065
Child pugh score class A	3(75%)	1(25%)	0.6348
Child pugh score class B	10(55.5%)	8(44.5%)	-
Child pugh score class C	13(46.5%)	15(53.5%)	-
Platelet count(/µl)	80500(45000-380000)	130500(46000-253000)	0.0021
Liver size(cm)	12.7(6.8-18)	11.4(7.5-16.2)	0.1132
Portal vein diameter(mm)	14.7(8.5-16.8)	12.4(8-18)	0.0201
Spleen diameter(cm)	17.2(8-26)	14.3(8-22)	0.0021
Platelet count /spleen diameter	445(279-1727)	910(264-2750)	0.0003

Table 8 Multivariate logistic regression analysis for the presence of large varices

Parameters	**P-Value**	**Odds ratio**	**95% Confidence interval**	
			Lower limit	**Upper limit**
Platelet count (<93500/µl)	0.003	4.8	1.42	16.18
Spleenic Diameter(>162mm)	0.021	1.94	0.62	6.02
Portal vein Diameter(>14.4mm)	0.042	3.5	1.05	11.66
Platelet count /Spleenic Diameter(<548)	0.001	9.4	2.46	36.19

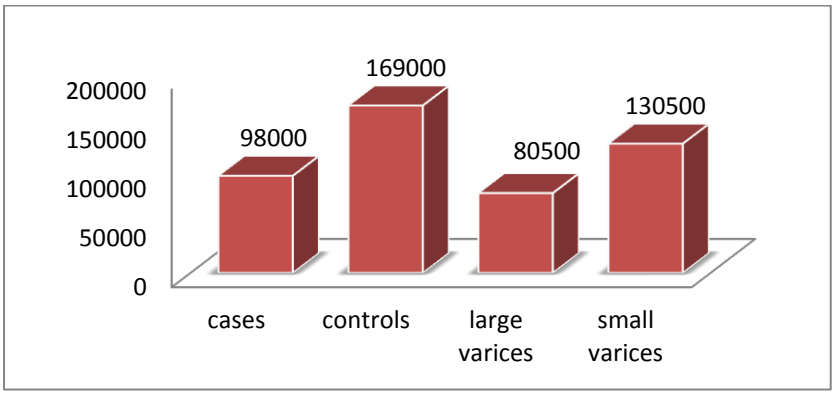

Figure 5 Bar diagram showing platelet count distribution among patients

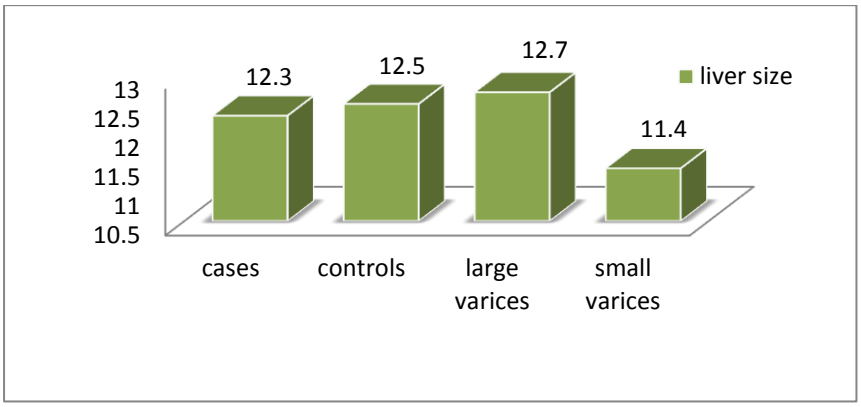

Figure 6 Bar diagram showing liver size distribution among patients

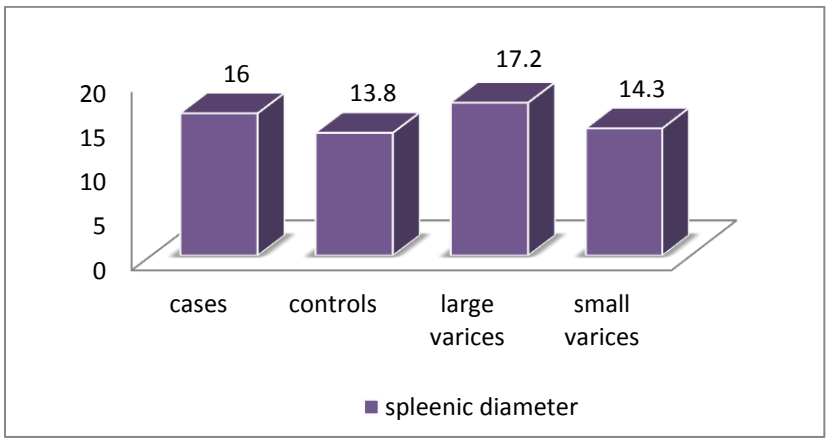

Figure 7 Bar diagram showing Spleenic diameter among patients

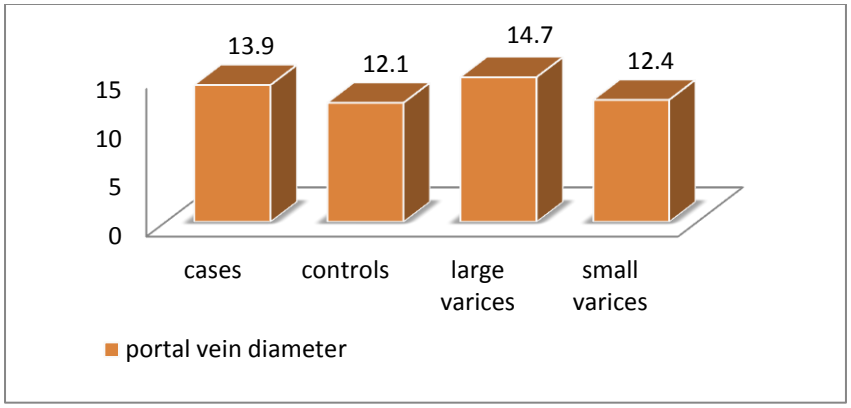

Figure 8 Bar diagram showing portal vein diameter among patients

Relationship of esophageal varices with platelet count

There is no difference between the cases, controls, large and small varices regarding liver size as shown in table number 5 and 7.

Relationship of various ultrasonographic parameters

As the grade of varices increases splenic diameter increases with the lowest median for patients without esophageal varices (controls) of 13.8 cm and highest value for large varices of 17.2 cm. As the grade of varices increases portal vein diameter increases with lowest value seen in patients without esophageal varices (controls) of 12.1 mm and highest with large varices of 14.7 mm. As the grade of varices increases platelet count /splenic diameter decreases with highest value in patients without oesophageal varices of 1277 and lowest with large varices of 445.Platelet count shows highest sensitivity for the detection of esophageal varices with 82.69% followed by platelet count/splenic diameter of 80.77%. Specificity is highest for splenic diameter and platelet count/splenic diameter. Platelet count/splenic diameter show a high sensitivity of 88% and specificity is highest for splenic diameter with 69.23% for detection of large varices and the results were shown in table number 9-10 and figure number 9.

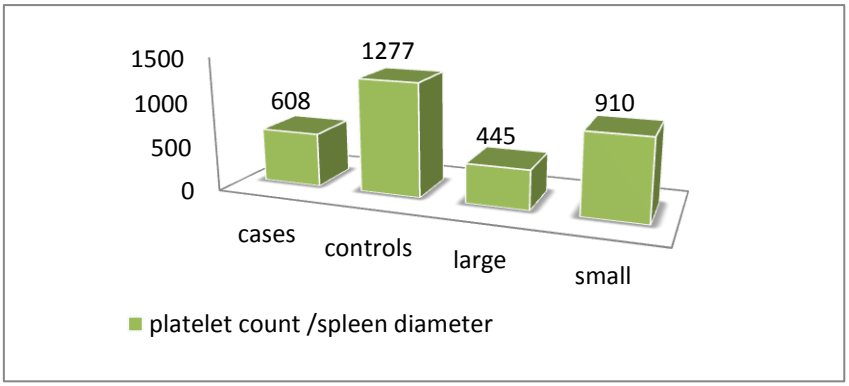

Figure 9 Bar diagram showing platelet count and splenic diameter ratio among patients

Table 9 Sensitivity, Specificity, Positive and Negative predictive values for significant parameters for presence of varices.

Parameters	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Portal vein diameter(>13.05mm)	65%	54%	55.58%	45.26%
Spleen diameter(>15.4cm)	78.80%	64%	56.06%	44.63%

Platelet count(<102000)	82.69%	58%	59.68%	41.03%
Platelet count /splenic diameter(<815)	80.77%	64%	56.67%	44.01%

Table 10 Sensitivity, specifity, positive and negative predictive values for the significant parameters for the presence of large varices

Parameters	**Sensitivity**	**Specificity**	**Positive predictive value**	**Negative predictive value**
Portal vein diameter(>13.05mm)	79.17%	53.85%	60.43%	40.32%
Spleen diameter(>15.4cm)	75%	69.23%	52.84%	47.85%
Platelet count(<102000)	75%	65.38%	54.29%	46.42%
Platelet count /splenic diameter(<815)	88%	65%	58.36%	42.28%

DISCUSSION

Cirrhosis is the most advanced form of liver disease and variceal hemorrhage is one of its lethal complications. Over half of the patients with cirrhosis will develop varices. The risk of bleeding once OV formed is 20% to 35% within 2 years [16]. The reported mortality rate from the first episode of variceal bleeding is 17% to 57% of those who survive the initial episode of bleeding and who do not receive active treatment, the risk of recurrent bleeding is approximately 66% and usually occurs within 6 months of the initial bleeding episode[17,21]. Because cirrhotic patients with large esophageal varices are at a high risk for bleeding, preventive efforts have concentrated on identifying cirrhotic patients with large varices [18].In the present study found that 50% of the cirrhotic patients had an EV diagnosed by endoscopy. This result is similar to the range of 24% to 80% showed in literature[14] and reminds us that a significant part of cirrhotic patients are unnecessarily submitted to this procedure [22].

Relationship of esophageal varices with clinical and laboratory parameters

Ascites and Hepatic encephalopathy

The study done by Fook-Hong NG et al showed that Low platelet count and presence of ascites were the significant independent predictors for high-grade EGV[23]. In the present study ascitis and hepatic encephalopathy was not significantly associated with the presence of varices as compared with Jijo V Cherian et al in predicting oesophageal varices.

Serum Albumin, Total bilirubin, Prothrombin activity

In this study no significance for serum albumin and prothrombin activity in the prediction of esophageal varices as compared with Jijo V Cherian et al and there is no statistical significance in the prediction of esophageal varices based on total bilirubin levels [24].

Child pugh score

In this study child pugh score was not significantly associated with presence of esophageal varices but most of the cases belong to class C and controls (no esophageal varices) belong to class B and compared with Jijo et al study, results shows significance and has a highest sensitivity of 95% for child pugh class B and C in predicting oesophageal varices and postulated an algorithm where patients with child pugh class B and C were given primary prophylaxis and for class A they have seen platelet count and spleen diameter and then initiated prophylaxis accordingly[13].

Platelet count

Pathogenesis of thrombocytopenia includes productive, consumptive or distributional mechanisms[61]. It is commonly believed to be due to pooling and destruction of platelets in the spleen, which may be mediated by platelet-associated IgG. Reduced levels of thrombopoeitin either due to impaired production or rapid degradation may also add to thrombocytopenia. In this study the platelet count is <10200/mm is 82.69 % sensitive and 58 % specific predictor of OV with positive predictive value of 59.63 % and negative predictive value of 41.03 % in predicting presence of varices and a platelet count of 93500/mm is 75% sensitive, 65.38% specific with 54.29 and 46.42 positive and negative predictive values respectively in predicting large varices and compared with standard studies like Jijo .V.Cherian et al with platelet count of 90000/mm^3 with 59.3% sensitivity, 64.2 % specificity and 47.5

PPV and 74.2 is NPV, Chalasani *et al*.[25] platelet count < 88,000 and an independent risk factor for the presence of large varices. Filippo Schepis *et al*.[26] platelet count of <100,000 as predictor of OV.

Relations of esophageal varices with ultrasonographic parameters

Upper GI endoscopy of the study population revealed that a total of 50 patients had developed gastro-oesophageal varices. Ultrasonography showed that the median portal vein diameter (PVD) of the patients with gastro-esophageal varices (GEV) was 13.9 mm with range of 8-18 mm and without gastroesophageal varices (GEV-0) was 12.1 mm with range of 7.8-16mm. This difference was statistically significant ($p < 0.0322$). Radiologically, median spleen diameter of the patients with OV was 16 cm with a range of 8-26 cm and spleen size in the no varices group was 13.8 cm with range of 9-19 cm, and the difference was highly significant ($p < 0.001$) and the results were more or less similar to other studies like .Prihatini *et al* [27], Jijo V Cherian et al[13] ,Thomopoulos *et al*[28],Schepis *et al*[27] and Sharma and Aggarwal[30] .

Relationship of esophageal varices with platelet count and splenic diameter

In this study, on univariate analysis, a platelet count-spleen diameter ratio of 608 was significantly associated with the presence of esophageal varices and it was found significant even in multivariate analysis with odds of 10.92 (CI-4.07-29.26) and compared with standard study like Jijo et al, but there is no evidence the significance in multivariate analysis. Among the noninvasive parameters studied, the platelet count to spleen diameter ratio had the highest accuracy for diagnosing EVs with a sensitivity of 80.77% and specificity of 64%, it did not show the same negative or positive predictive values, nor accuracy published before[29-32]. At present, the available data do not support the substitution of another method for upper gastrointestinal endoscopy when identifying esophageal varices, but the PC/SD ratio may be helpful for stratifying patients with cirrhosis into different risk categories. This may be especially relevant to those whose general health conditions do not permit the use of an invasive study, but whose history suggests the possibility of esophageal varices, thus reducing the number of endoscopies.

CONCLUSION

Ultrasonography of the abdomen is a simple, convenient and non-invasive method for assessing the severity of portal hypertension in patients and to predict the severity of esophagogastric varices indirectly. Patients having portal vein diameter >13.9mm, spleen size >16cm, platelet count of<98000/micro L, platelet count and spleen diameter ratio < 608 were found to have varices which were indirect evidences of severity of portal hypertension. The above said parameters tend to predict varices when they occur in combination than they occur individually.These predictors may be of help to the physicians practicing in rural areas where endoscopy facilities are not readily available, in helping them to initiate appropriate primary pharmacological prophylaxis in these patients.In an urban setting where the endoscopy workload is high, a non invasive predictor, as in this study, can help one to initiate drug therapy while waiting for the endoscopy procedure.

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