

A STUDY ON NONINVASIVE PARAMETERS AS PREDICTORS OF OESOPHAGEAL VARICES IN CIRRHOTIC PATIENTS

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ABSTRACT

BACKGROUND

Varices can be seen anywhere in the gastrointestinal tract. Distal end of oesophagus is one of the commonest sites. About 50% of cirrhotic patients develop oesophageal varices of which only 5-35% is gastric varices. Rest 70% are oesophageal varices.

The aim of this study is to identify non-endoscopic parameters that could predict the presence and grade of oesophageal varices and to assess platelet count:splenic size ratio as a predictor of high-grade oesophageal varices.

MATERIALS AND METHODS

After obtaining institutional approval, 300 consenting patients satisfying the inclusion criteria were enrolled in this study. Demographic, clinical, biochemical and ultrasonographic parameters were recorded by structured questionnaire. Oesophageal varices were classified as low grade and high grade at endoscopy data analysis was done using SPSS software. Tests of significance, ROC curves and bivariate logistic regression analysis were done to find out any relation with presence of high-grade varices and these noninvasive parameters.

RESULTS

Platelet count, spleen size, portal vein diameter and platelet count:spleen size ratio were the variables that showed significant difference between the two groups. Area under curve is significant for platelet count (0.823) and platelet count:spleen size ratio (0.845), spleen size (0.753) and portal vein diameter (0.623). The cutoff values were set and platelet count <90500, (sensitivity of 70.71% and specificity of 83.12%), portal vein diameter >12.05 mm (sensitivity - 67.86% and specificity - 51.25%), spleen size >12.45 cm (sensitivity - 80.71% and specificity - 64.38%) and platelet count:spleen size ratio less than 728.2 (sensitivity of 71.43% and specificity - 87.50%) could predict presence of high-grade varices.

CONCLUSION

Platelet count, splenic size, portal vein diameter and platelet count:spleen size ratio can be used in predicting the presence of high-grade oesophageal varices in patients with liver cirrhosis.

KEYWORDS

Noninvasive Parameters, Oesophageal Varices, Platelet Count, Splenic Size, Portal Vein Diameter and Platelet Count, Spleen Size Ratio.

HOW TO CITE THIS ARTICLE: Sreenath S, Saraswathy ST, Anoop VS. A study on noninvasive parameters as predictors of oesophageal varices in cirrhotic patients. J. Evid. Based Med. Healthc. 2017; 4(49), 2985-2991. DOI: 10.18410/jebmh/2017/591

BACKGROUND

The importance of gastroesophageal varices lies in the fact that variceal bleeding accounts for 10-30% of upper gastrointestinal bleeds¹ and variceal haemorrhage is the most common lethal complication of cirrhosis of liver. Oesophageal varices develop in patients with cirrhosis at an annual rate of 5-8%, but only in 1-2% of cases. The varices are large enough so that they pose a risk of bleeding. 30% of cirrhotic patients have oesophageal varices at the time of

diagnosis. In the next 10 years, it reaches up to 90%. Oesophageal varices develop at an annual rate of 5-8% in cirrhotic patients, but only 1-2% has substantially large varices to pose a higher risk of bleeding. Each year, the risk of bleeding increases as 4-30% of patients with small varices develop larger ones. Even though, most of the oesophageal variceal bleeding ceases spontaneously (40%), there is at least 20% mortality at 6 weeks.¹

As already mentioned, development of varices closely correlates with development of portal hypertension. As portal pressure increases, small varices starts developing. The progressive hyperdynamic circulation resulting in increased blood flow raises the wall tension in varices and they start enlarging. When the expanding force exceeds, the maximum wall tension varices rupture. If the wall tension remains unmodified, the risk of recurrence goes on increasing.

Financial or Other, Competing Interest: None.

Submission 15-05-2017, Peer Review 18-05-2017,

Acceptance 02-06-2017, Published 16-06-2017.

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DOI: 10.18410/jebmh/2017/591



By placing a catheter in the hepatic vein and wedging it into a small branch or by inflating a balloon and occluding a larger branch of the hepatic vein, we can measure Wedged Hepatic Venous Pressure (WHVP). This has shown to correlate very closely with portal pressure both in those having alcoholic as well as nonalcoholic cirrhosis. From this, the Hepatic Venous Pressure Gradient (HVPG) can be calculated. This is by subtracting the Free Hepatic Vein Pressure (FHVP) or the intraabdominal inferior vena cava pressure.

The normal HVPG is 3-5 mmHg. The hepatic venous pressure gradient and changes in HVPG that occur over time have predictive value for the development of oesophagogastric varices^{2,3} and the risk of variceal haemorrhage.^{4,5,6} They also have a good predictive value in the development of non-variceal complications of portal hypertension^{6,7,8} and death.^{4,7,8,9} Single measurements are useful in the prognosis of decompensated as well as compensated cirrhosis. Repeat measurements are found to be useful to monitor response to pharmacological therapy and progression of liver disease. The lack of local expertise and poor adherence to guidelines that ensures reliability and reproducibility in the measurements as well as the invasive nature makes the use of HVPG measurement practically impossible.

Nonselective β -blockers are found to be useful in preventing bleeding in more than half of patients with medium or large varices. Therefore, it is recommended that at the time of diagnosis, all patients having cirrhosis should undergo endoscopic screening for varices.^{10,11} Since the point prevalence of medium and large varices is approximately 15%-25%, when upper gastrointestinal screening is performed, most of the patients have varices that do not require any prophylactic therapy or no varices at all, here comes the role of models in predicting the presence of high-risk varices by non-endoscopic and noninvasive methods. The possible noninvasive markers of oesophageal varices such as the platelet count, spleen size, portal vein diameter, Child-Pugh score, MELD score and several others including routine liver function tests are being evaluated worldwide. Lack of evidence stands in way of these noninvasive parameters to be recommended as positive or negative predictors of oesophageal varices.

This study is an attempt to bring about possible new predictors and interrogating the reliability of existing noninvasive parameters in predicting oesophageal varices.

OBJECTIVES

1. To identify non-endoscopic parameters that could predict the presence and grade of oesophageal varices.
2. To assess platelet count:splenic size ratio as a predictor of high-grade oesophageal varices.

MATERIALS AND METHODS

It was a hospital-based prospective observational study conducted in medical OP and wards of Department of Medicine, Medical College Hospital, Trivandrum, for a period

of one year from 2015 to 2016, after getting an approval from the ethical committee clearance.

Study Population

Patients diagnosed with chronic liver disease with no previous history of variceal bleed.

Inclusion Criteria

Patients diagnosed with chronic liver diseases by ultrasonogram attending medical outpatients and inpatients in medical wards of medical college, Thiruvananthapuram.

Exclusion Criteria

Those with a past history of bleed and who had undergone sclerosis or band ligation of oesophageal varices, portal vein thrombosis, hepatoma or on current or past treatment with beta-adrenergic receptor blockers will be excluded from the study.

Sample Size

$$n = \frac{Z^2 \cdot 1 - \alpha \cdot 2P_0(1-P_0) + Z1 - \beta \cdot P_1(1-P_1) + P_2(1-P_2)}{(P_1 - P_2)^2}$$

$$P_0 = P_1 + P_2$$

$$2$$

P_1 = Sensitivity (Gold standard).

P_2 = Sensitivity (new test).

α = Type 1 error fixed at 5% level.

$1 - \beta$ = Power fixed at 80% level.

First calculation with sensitivity yielded 160 diseased persons to be screened and second one with specificity yielded 140 non-diseased persons, sample size = 300.

Data Collection and Analysis

Data analysis will be done using SPSS software. Tests of significance will be done and those with significant association will be identified. ROC curves will be drawn to assess the significant area under the curve.

OBSERVATIONS AND RESULTS

Age	Disease				Total	
	Present		Absent			
	N	%	N	%	N	%
<50	83	59.3	71	44.4	154	51.3
>50	57	40.7	89	55.6	146	48.7
Total	140	100	160	100	300	100
Table 1. Age Distribution of Population						

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$\chi^2 = 6.645$	$P = 0.010$
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The age distribution in both diseased (varices present) and non-diseased (absent) groups showed no significant difference.

Sex	Disease				Total	
	Present		Absent			
	N	%	N	%	N	%
Male	129	92.1	147	91.9	276	92
Female	11	7.9	13	8.1	24	8
Total	140	100	160	100	300	100
Table 2. Distribution of Varices Among Males and Females						

$\chi^2 = 0.007$	P = 0.932
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	Varices				t	p
	Present (N=140)		Absent (N=160)			
	Mean	SD	Mean	SD		
Age	49.1	10.1	52.2	9.1	-2.738	0.007
Haemoglobin	10.4	2.2	10.5	1.9	-0.490	0.624
TC	8768.4	10890.9	8952.9	4088.4	-0.199	0.842
ESR	44.9	27.4	49.5	29.4	-1.388	0.166
Platelet count	85921.4	32854.8	151565.0	77724.3	-9.292	0.000
PCV	31.2	5.2	31.5	5.7	-0.354	0.723
Total bilirubin	4.2	3.1	5.1	4.4	-2.018	0.044
SGOT	108.4	56.4	114.5	58.4	-0.925	0.356
SGPT	64.8	35.5	64.1	33.5	0.180	0.857
ALP	195.4	103.7	213.4	107.5	-1.472	0.142
Total protein	6.7	0.8	6.6	0.9	0.450	0.653
Albumin	2.9	0.6	5.6	33.8	-0.963	0.337
PT	19.9	4.5	20.5	7.6	-0.821	0.412
INR	1.7	0.5	1.7	0.6	-0.352	0.725
RBS	131.6	52.3	123.4	50.3	1.380	0.169
Urea	28.6	16.0	27.1	14.2	0.862	0.389
Creatinine	1.0	1.0	0.9	0.9	0.761	0.447
Sodium	134.4	5.0	134.3	5.1	0.204	0.838
Potassium	4.0	0.8	4.1	0.9	-0.823	0.411
Liver size	13.7	1.9	13.6	2.1	0.281	0.779
Portal vein diameter	12.6	1.2	12.0	1.3	3.910	0.000
Spleen size	13.5	1.6	12.1	1.6	7.549	0.000
Platelet count:spleen size ratio	6544.6	2807.0	12906.7	7841.3	-9.102	0.000
Table 3. Mean Values of Variables						

Age, platelet count, portal vein diameter, spleen size and platelet count/spleen size ratio were the only variables in the study population that showed significant difference in the two groups studied.

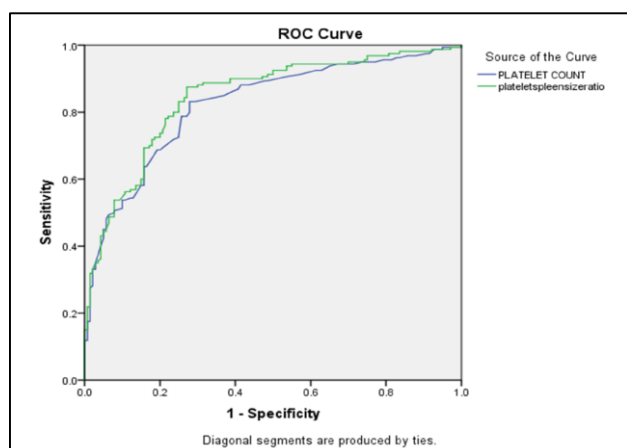


Figure 1. ROC Curve for Platelet Count and Platelet Count-Spleen Size Ratio

Area under curve is significant for both. Platelet count and platelet count:spleen size ratio.

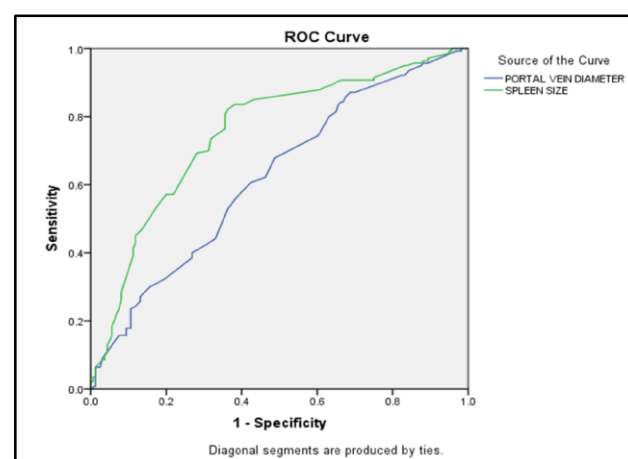


Figure 2. ROC Curve for Spleen Size and Portal Vein Diameter

The area under curve was significant for both spleen size and portal vein diameter.

The area was less for portal vein diameter; hence, its less significant.

Platelet Count	Varices				Total		x²	p	OR	95% CI for OR	
	Present		Absent							Lower	Upper
	N	%	N	%	N	%					
<90500	99	70.7	27	16.9	126	42	88.85	<0.001	11.89	6.855	20.64
>90500	41	29.3	13.3	83.1	174	58					
Total	140	100	160	100	300	100					
Table 4. Cutoff Values for Platelet Count											

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The cutoff values for platelet count was set at 90,500. With that, a cirrhotic patient with platelet count less than 90,500 can be predicted with high-grade varices with-

Sensitivity - 70.71%.

Negative predictive value - 76.44%.

Specificity - 83.12%.

Positive likelihood ratio - 4.19.

Positive predictive value - 78.57%.

Negative likelihood ratio - 0.35.

	Varices				Total		x²	p	OR	95% CI for OR	
	Present		Absent							Lower	Upper
	N	%	N	%	N	%					
>12.45	113	80.7	57	35.6	170	56.7	61.82	<0.001	7.563	4.451	12.85
<12.45	27	19.3	103	64.4	130	43.3					
Total	140	100	160	100	300	100					
Table 5. Cutoff Values for Spleen Size											

Table 5. Cutoff Values for Spleen Size

The cutoff values for spleen size was set at 12.45 cm. With that a cirrhotic patient with spleen size more than 12.45 cm can be predicted with high-grade varices with-

Sensitivity - 80.71%.

Negative predictive value - 79.23%.

Specificity - 64.38%.

Positive likelihood ratio - 2.27.

Positive predictive value - 66.47%.

Negative likelihood ratio - 0.30.

Portal Vein	Varices				Total		x ²	p	OR	95% CI for OR	
	Present		Absent							Lower	Upper
	N	%	N	%	N	%					
>12.05	95	67.9	78	48.8	173	57.7	11.17	0.001	2.219	1.386	3.555
<12.05	45	32.1	82	51.2	127	42.3					
Total	140	100	160	100	300	100					
Table 6. Cutoff Values for Portal Vein Diameter											

Table 6. Cutoff Values for Portal Vein Diameter

The cutoff values for portal vein diameter was set at 12.05 mm. With that a cirrhotic patient with portal vein diameter more than 12.05 mm can be predicted with high-grade varices with-

Sensitivity - 67.86%.

Negative predictive value - 64.57%.

Specificity - 51.25%.

Positive likelihood ratio - 1.39.

Positive predictive value - 54.91%.

Negative likelihood ratio - 0.63.

Platelet Count Spleen size Ratio	Varices				Total		x ²	p	OR	95% CI for OR	
	Present		Absent							Lower	Upper
	N	%	N	%	N	%					
<728.2	100	71.4	20	12.5	120	40	108	<0.001	17.5	9.653	31.73
>728.2	40	28.6	140	87.5	180	60					
Total	140	100	160	100	300	100					

Table 7. Cutoff Values for Platelet Count:Spleen Size

Table 7. Cutoff Values for Platelet Count:Spleen Size

The cutoff values for platelet count:spleen size was set at 728.2. With that a cirrhotic patient with platelet count:spleen size less than 728.2 can be predicted with high-grade varices with-

Sensitivity - 71.43%.

Negative predictive value - 77.78%.

Specificity - 87.50%.

Positive likelihood ratio - 5.71.

Positive predictive value - 83.33%.

Negative likelihood ratio - 0.33.

	B	S.E.	p	OR	95% C.I. for OR	
					Lower	Upper
Age	-0.127	0.313	0.685	0.881	0.477	1.626
Portal vein diameter	0.149	0.321	0.643	1.161	0.618	2.178
Spleen size	1.376	0.35	<0.001	3.96	1.996	7.857
Platelet:spleen size ratio	1.238	0.504	0.014	3.447	1.284	9.251
Platelet count	1.397	0.473	0.003	4.043	1.598	10.22
Constant	-6.039	0.814	<0.001	0.002		

Table 8. Binary Logistic Regression Analysis

Binary logistic regression analysis reveals that spleen size, platelet count and spleen size:platelet count ratio is the three significant predictors of varices.

DISCUSSION

This is a hospital-based observational study. 300 patients with cirrhosis were studied, of which 140 patients were diseased, i.e. they had high-grade varices. Rest 160 patients were having low grade or no varices and were classified into diseased and non-diseased group. In both groups, males were predominant with 92.1% in the diseased group and 91.9% in the non-diseased group. Females constituted only 7.9% in diseased group, while in non-diseased group, it was 8.1%. So, both groups were similar in gender distribution. When age was compared, the groups showed some difference as the mean age in diseased group was 49.1 years, and in non-diseased group, it was 52.2 years, which was found to be statistically significant with p value of 0.007.

The general examination findings showed no statistically significant difference in distribution in two groups. When patients with pallor were considered, it was equally present in the diseased and non-diseased group with 45% of patients in diseased group had pallor, 44.4% in the non-diseased group also had pallor. Similar was the case of icterus, clubbing, lymphadenopathy and oedema. In both groups, the distribution was similar. In case of icterus, 56.4% of patients in the diseased group and 63.7% in non-diseased group had icterus. In case of clubbing, only 10.7% of patients in the diseased group and 5% in non-diseased group had clubbing. About 97.9% and 98.1% had no lymphadenopathy in the diseased and non-diseased group respectively and was statistically insignificant with p value of 0.869. 53.6% of the diseased and 61.9% of the non-diseased group had oedema, which was also statistically insignificant with a p value of 0.146.

Now, if we consider the aetiology of cirrhosis in the study population, alcohol-related cirrhosis was the predominant one with 87.1% in diseased and 80% in non-diseased group. Hepatitis B related infection was the cause of cirrhosis in 4.3% of diseased and 8.8% in the non-diseased. Hepatitis C virus infection was the cause of cirrhosis in 1.4% and 1.3% in diseased and non-diseased groups, respectively. Others which included NASH-related Wilson's disease, unknown and multiple aetiologies constituted 7.1% in diseased and 10% in non-diseased group. The presence of high-grade varices could not be attributed to any of the known aetiology of cirrhosis in our study population.

The mean values of variables were also separately studied. In the case of haemoglobin, mean for the high-

grade varices was 10.4 mg% and that of low grade or no varices was 10.5 mg%, which was not statistically significant for the presence of high-grade varices (p value 0.624). For total WBC count, mean for high-grade varices was 8768.4 and that of low grade or no varices was 8952.9 with p value of 0.842, it was statistically insignificant. Mean ESR for the population of high-grade varices was 44.9 mm and that of low-grade varices was 49.5 mm (p value 0.196), statistically not significant.

When platelet count was studied, mean for the high-grade varices was 85921.4 and that of low grade or no varices was 151565.0. This was found to be statistically significant with p value <0.0001. For PCV, mean for the diseased was 31.2 and that of non-diseased was 31.5 (p value - 0.723), which was not significant. The mean for total serum bilirubin for the population of high-grade varices was 4.2 mg% and that of low grade or no varices was 5.1 mg%. This was also statistically significant with a p value of 0.044. In the case of serum SGOT, mean for the population of high-grade varices was 108.4 and that of low grade or no varices was 114.5. It also failed to show any statistically significant difference in the two groups (p value - 0.356). Mean serum SGPT for the population of high-grade varices was 64.8 and that of low grade or no varices was 64.1. No statistically significant association could be made out with increase or decrease in serum SGPT also (p value - 0.857). Mean serum ALP value for the population of high-grade varices was 195.4 and that of low grade or no varices was 213.4, (p value - 0.142) statistically insignificant. Mean serum total protein for the population of high-grade varices was 6.7 mg% and that of low grade or no varices was 6.6 mg%. Mean serum albumin for the population of high-grade varices was 2.9 mg% and that of low grade or no varices was 5.6 mg%. Both could not show any statistically significant difference in the two groups with p value of 0.663 and 0.337, respectively. Mean PT for the population of high-grade varices was 19.9 secs and that of low grade or no varices was 20.5 secs, while mean INR for the population of high-grade varices was 1.7 and that of low grade or no varices was 1.7. Both were statistically insignificant (P values- 0.412 and 0.725). Mean serum RBS for the population of high-grade varices was 131.6 mg% and that of low grade or no varices was 123.4 mg%. Mean serum urea for the population of high-grade varices was 28.6 mg% and that of low grade or no varices was 27.1 mg%. Mean serum creatinine value for the population of high-grade varices was 1.0 and that of low grade or no varices was 0.9. Mean serum sodium for the population of high-grade varices was 134.4 mEq/dL and that of low grade or no varices was

134.3 mEq/dL. Mean serum potassium for the population of high-grade varices was 4.0 mEq/dL and that of low grade or no varices was 4 mEq/dL. The serum RBS, urea, creatine, sodium and potassium values did not show any statistically significant difference in the two groups (p values- 0.169, 0.389, 0.447, 0.838, 0.411, respectively). Mean liver size based on ultrasonography for the population of high-grade varices was 13.7 cm and that of low grade or no varices was 13.6 cm, which was also statistically insignificant (p value - 0.779). Mean portal vein diameter for the population of high-grade varices was 12.6 mm and that of low grade or no varices was 12.0 mm. This showed statistically significant difference with p value <0.0001. Mean spleen size for the population of high-grade varices was 13.5 cm and that of low grade or no varices was 12.1 cm, which was also statistically significant (p value <0.0001). Mean platelet count:spleen size ratio for the population of high-grade varices was 654.46 and that of low grade or no varices was 1290.67. It also showed statistically significant difference in two groups with p value <0.0001.

Thus, it was clear that platelet count, spleen size, portal vein diameter and platelet count:spleen size ratio was the variables that showed significant difference between the two groups and were marked as predictors of high-grade oesophageal varices.

ROC curves were drawn for all the four variables and cutoff values were ascertained with acceptable sensitivity and specificity. Area under curve is significant for both platelet count (0.823) and platelet count:spleen size ratio (0.845). The area under curve was significant for both spleen size (0.753) and portal vein diameter also (0.623). The area was less for portal vein diameter; hence, it is considered less significant when compared with the other three variables.

The cutoff values for platelet count in predicting presence of high-grade varices was set at 90,500 by which we can predict the presence of high-grade oesophageal varices in patients with a platelet count of less than 90,500 with a sensitivity of 70.71%, specificity of 83.12%, positive predictive value of 78.57%, negative predictive value of 76.44%, positive likelihood ratio - 4.19 and negative likelihood ratio - 0.35. Similar studies by Jijo V Cherian et al in 2009,¹² Zaman A et al,¹³ Chalasani et al¹⁴ also showed similar results stating that platelet count was significant in the demonstration of oesophageal varices.

Portal vein diameter based on ultrasound abdomen was the next parameter that was found significant. With a cutoff value of 12.05 mm, portal vein diameter >12.05 mm could predict presence of high-grade varices with a sensitivity - 67.86%, specificity - 51.25%, positive predictive value - 54.91%, negative predictive value - 64.57%, positive likelihood ratio - 1.39 and negative likelihood ratio - 0.63. No studies demonstrate portal vein diameter as a direct indicator of oesophageal varices. But, hepatic venous pressure gradient has been proposed as a predictor of oesophageal varices in many studies.^{15,16}

Spleen size also showed statistical significant difference and cutoff was set at 12.5 cm. With this, those cirrhotic patients having spleen size more than 12.45 cm can be predicted with high-grade varices with sensitivity - 80.71%, specificity - 64.38%, positive predictive value - 66.47%, negative predictive value - 79.23%, positive likelihood ratio - 2.27 and negative likelihood ratio - 0.30. Most of the studies of noninvasive predictors of oesophageal varices also recognise spleen size as a very good predictor.^{13,14,17,18,19}

Platelet Count- Spleen size ratio was the last significant variable studied. The cutoff was set at 728.2, so that in cirrhotic patients, the presence of high-grade oesophageal varices can be predicted if the ratio is less than 728.2 with a sensitivity of 71.43%, specificity - 87.50%, positive predictive value - 83.33%, negative predictive value - 77.78%, positive likelihood ratio - 5.71 and negative likelihood ratio - 0.33.

Most of the studies recommend a cutoff value of 909 as significant.

Finally, binary logistic regression analysis was done, which showed an odds ratio of 0.881 for age, 3.96 for splenic size, 4.043 for platelet count, 1.161 for portal vein diameter and 3.447 for platelet count:spleen size ratio. Based on this platelet count, spleen size and platelet count:spleen size ratio were found to be significant noninvasive parameters in the prediction of oesophageal varices.

CONCLUSION

The following conclusions were made from this study-

- Platelet count, splenic size and portal vein diameter can be used effectively in predicting the presence of oesophageal varices in patients with liver cirrhosis.
- These noninvasive parameters are better in predicting the presence of high-grade varices.
- Platelet count and splenic size are the best noninvasive predictors among the three.
- Platelet count:spleen size ratio was also found to be a significant predictor of high-grade oesophageal varices.

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