Section: Gastroenterology

Original Research Article

ROLE OF NON-INVASIVE MARKERS IN PREDICTION OF ESOPHAGEAL VARICES IN PATIENTS WITH CIRRHOSIS OF LIVER: A CROSS-SECTIONAL OBSERVATIONAL STUDY

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Abstract

Background: Cirrhosis of the liver causes portal hypertension, which progresses to esophagogastric varices. The gold standard for the diagnostis is upper GI endoscopy. The presence of varices is determined by the degree of underlying portal hypertension, which can be almost precisely graded by using the hepatic venous pressure gradient (HVPG). However, HVPG and endoscopy are invasive procedures that are not widely available in all centres and may not be acceptable to patients. Non-invasive markers are based on clinical, laboratory and ultrasonographic parameters to predict the development of esophageal varices. **Materials and Methods:** This cross-sectional observational study was done on patients with liver cirrhosis. The patient's detailed history, relevant laboratory parameters, physical examination, and portal venous doppler examination were made on all enrolled patients. In addition, upper GI endoscopy was done on all of them to detect esophageal varices. **Result:** There was a statistically significant correlation between the presence of esophageal varices and platelet count ($p<0.0001$), total bilirubin ($p=0.024$), CTP and MELDNa score ($p<0.0001$ & $p=0.002$ respectively), platelet count and splenic diameter ratio ($p<0.0001$), portal vein congestion index ($p<0.0001$), portal vein diameter and velocity ($p<0.0001$). On the application of the ROC curve, splenic diameter ratio and platelet count, portal vein congestion index, portal vein velocity, portal vein diameter, and platelet count all appear significant in predicting esophageal varices. **Conclusion:** Non-invasive markers such as platelet count and splenic diameter ratio, portal vein diameter, portal vein congestion index, and velocity all have a significant association with esophageal varices.

INTRODUCTION

In individuals with chronic liver disease, esophageal varices develop due to portal hypertension (PHT).[1] In cirrhotic individuals, new esophageal varices occur at around 5% yearly. Current recommendations advise, all cirrhotic people to get endoscopic varices screening. Upper GI endoscopy is still the gold standard for finding esophageal varices.[2] The most exact method of assessing portal pressure is to measure the hepatic vein pressure gradient (HVPG), that is the difference between wedged hepatic venous pressure (WHVP) and free hepatic vein pressure (FHVP).[3] HVPG had a favourable correlation with the endoscopy grading of esophageal varices.[4] When the hepatic venous pressure gradient (HVPG) is increased to more than 10 mm Hg, there is increased chance of development of oesophagal varices.[5] The main disadvantages of HVPG are that it is invasive, necessitates technical skill and often found in tertiary medical centres (not available at many centres).[6] Endoscopy is invasive and requires the patient's proper preparation and technical expertise. Though the overall procedure is safe, there is still a chance of procedure-related complications (perforation, bleeding, infection). It may be cumbersome for the patient to follow the

instructions before and during the procedure. It is expensive and may not be available at all centers.[2,7] Therefore, using non-invasive methods to identify oesophagal varices will likely prevent some complications associated with endoscopy and are readily acceptable by the patients. Several investigations have found that non-invasive indicators such as blood and radiological parameters were closely linked to esophageal varices in cirrhotic individuals.[8]

Aims of the Study

To evaluate the non-invasive biomarkers based on clinical, laboratory, and doppler characteristics for predicting esophageal varices.

MATERIALS AND METHODS

This is observational cross-sectional research. The trial lasted six months, from October 1, 2021, to March 31, 2022. There were 140 people in all (the Cochran formula was used to calculate the sample size), all of who attended the Medical Gastroenterology outpatient department and were admitted to the Medical Gastroenterology ward, Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai, Tamil Nadu.

The study protocol was under ethical principles. Accordingly, the study protocol was approved by the institutional ethical committee reg no. ECR/270/Inst./TN/2013/RR-20.

Inclusion Criteria

1. (18-75) year old aged patients
2. Cirrhosis of liver due to various etiologies
3. Patients given consent for the study.

Exclusion Criteria

1. History of previous Gastroenterol intestinal surgery including splenectomy and portosystemic shunt surgery,
2. Clinically unstable
3. Liver metastasis and hepatocellular carcinoma, extrahepatic malignancy
4. No history of endoscopic intervention or beta-blocker therapy
5. Portal vein, hepatic vein and splenic vein thrombosis
6. Acute or chronic liver failure/ fulminant hepatic failure
7. Spleen in chronic myeloid leukemia, myeloproliferative neoplasm, affection of the liver, tropical splenomegaly due to chronic malaria.

Detail history was taken & clinical examination was done for all patients. A detailed laboratory assessment including biochemical and haematological parameters including haemoglobin, platelet count, prothrombin time, total leukocyte count, serum levels of bilirubin, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, and serum creatinine were done for all enrolled patients. Doppler ultrasonography abdomen was done to assess portal vein diameter, velocity, splenic bipolar diameter and portal vein collaterals. All enrolled patients were classifiedon the basis of Child-Turcotte-Pugh (CTP) score and MELD-Na score with the help of clinical and laboratory parameters. MDCalc online calculator was used to calculate MELD Na & CTP scores. Platelet count and splenic bipolar diameter ratio were calculated for all patients. The portal venous congestion index was derived by dividing the cross-sectional area of portal vein (cm2) by the portal vein velocity (cm/sec). Endoscopy was performed on all recruited patients to determine the existence and degree of varices , and further therapy was provided as needed.

Statistical Analysis

IBM-SPSS version 21.0 was used to analyse the data (IBM-SPSS Science Inc., Chicago, IL). The student t-test was used to compare continuous variables that were provided as mean and standard deviation. The Pearson chi-square test was used to assess the correlation between categorical variables. The ROC curve was used to generate cut-off values for sensitivity and specificity. A two-tailed test determined significance as P values less than 0.05.

RESULTS

The study involved 140 patients in total. There were 106 men and 34 women among them. The participant's mean age was 55.63+/- 5.83. 82 patients were alcoholics and 58 patients were with other etiologies. On endoscopy total of 104 patients were diagnosed with having esophageal varices & 36 patients had no varices. A total of 36 patients had portal vein collaterals in portal vein doppler. Pair-wise comparisons of AUROCs show that There was a significant relationship between esophageal varices appearance and platelet count ($p<.0001$), total bilirubin ($p< .024$), CTP and MELD-Na score ($p<.0001$ & $p<.002$ respectively), platelet count and splenic diameter ratio ($p<.0001$), portal vein congestion index ($p<.0001$), portal vein diameter and velocity ($p <.0001$). There was no significant relation between esophageal varices and age, gender, alcohol, liver enzymes (AST, ALT), splenic vein diameter, total protein, albumin, creatinine and PT/INR. Cut off value of CTP score was 6.5 with sensitivity 85.60% & specificity 52.80% with PPV 83.96% (OR 6.63). Cut off, the value of MELD-Na was 18.5 with sensitivity and specificity of 79.80% & 47.20%, respectively, with PPV 81.37% (OR 3.54). PV velocity cut off value was 14.8 cm/sec with sensitivity and specificity was 83% & 83.7% respectively. PPV of PV velocity was 93.55%. Cut off the value of platelet count and splenic diameter ratio was 880.94 with sensitivity was 81.70% & specificity was 91.67% with PPV was 96.59%. PV diameter cut-off value was 13.35 mm, with sensitivity and specificity was 82.70% & 63.90%, respectively. PPV was 86.27%. Cut off value of the PV congestion index was .0935, with sensitivity and

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specificity was 86.50% & 80.60%. PPV was 92.78%. Cut off, and the platelet count value was 1,14,510 with sensitivity and specificity of 88.90% & 83.70%. PPV was 96.59%.

Table 1:

Alcoholic		**Frequency**	**Percent**
Valid	No	58	41.4
	Yes	82	58.6
	Total	140	100.0
Gender		**Frequency**	**Percent**
Valid	Male	106	75.7
	Female	34	24.3
	Total	140	100.0
PV collateral		**Frequency**	**Percent**
Valid	No	104	74.3
	Yes	36	25.7
	Total	140	100.0
Varices		**Frequency**	**Percent**
Valid	No	36	25.7
	small varices	31	22.1
	large varices	61	43.6
	large varices with red spot	12	8.6
	Total	140	100.0
Varices		**Frequency**	**Percent**
Valid	No	36	25.7
	Yes	104	74.3
	Total	140	100.0

Table 2:

Descriptive Statistics	**N**	**Mean**	**Std. Deviation**
Age	140	55.63	5.83
TLC	140	6118.94	2413.35
PLT	140	96532.64	33566.36
AST	140	33.94	8.63
ALT	140	32.91	22.06
T protein	140	6.59	0.58
ALB	140	2.51	0.41
T bilirubin	140	2.28	0.88
Cr	140	0.94	0.28
INR/PT	140	1.20	0.15
SD (cm)	140	13.38	1.33
CTP	140	8.29	2.00
MELDna	140	20.22	2.62
PC/SD	140	728.59	262.91
PV Congestion index	140	0.11	0.02
PV diameter (mm)	140	13.85	0.87
PV velocity (cm/sec)	140	13.92	1.34

Table 3:

	Varices				**P-value**
	No		**Yes**		
	Mean	**Standard Deviation**	**Mean**	**Standard Deviation**	
Age	56.61	5.78	55.29	5.83	0.242
TLC	6610.64	2407.39	5948.74	2403.50	0.157
PLT	132572.22	16756.83	84057.40	28530.23	<0.0001
AST	31.53	9.32	34.78	8.26	0.051
ALT	36.86	40.13	31.54	10.09	0.213
T protein	6.55	0.53	6.61	0.60	0.609
ALB	2.46	0.41	2.52	0.41	0.422
T bilirubin	1.99	0.91	2.38	0.86	0.024
Cr	0.86	0.24	0.96	0.29	0.051
INR/PT	1.17	0.14	1.21	0.16	0.16
SD (cm)	13.45	1.23	13.35	1.37	0.699
CTP	6.56	1.27	8.89	1.85	<0.0001
MELDna	19.06	2.45	20.63	2.57	0.002
PC/SD	994.17	161.32	636.66	226.39	<0.0001
PV Congestion index	0.09	0.01	0.12	0.02	<0.0001
PV diameter (mm)	13.24	0.55	14.06	0.86	<0.0001
PV velocity (cm/sec)	15.30	0.67	13.44	1.18	<0.0001

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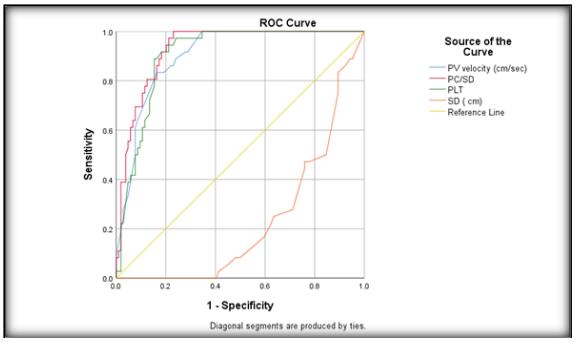
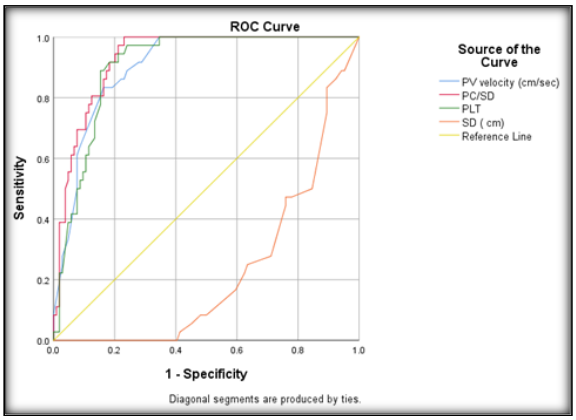
Area Under the Curve												
Test Result Variable(s)	AUC	Std. Error[a]	P value	Asymptotic 95% Confidence Interval		Sensitivity	Spesificity	Cut off value	PPV	NPV	DA	OR
				Lower Bound	Upper Bound							
CTP	0.833	0.033	<0.0001	0.767	0.898	85.60%	52.80%	6.5	83.96%	55.88%	77.14%	6.63
MELDna	0.669	0.052	0.003	0.566	0.771	79.80%	47.20%	18.5	81.37%	44.74%	71.43%	3.54
/ velocity (cm/sec)	0.903	0.025	<0.0001	0.854	0.925	83%	83.70%	14.8	93.55%	63.83%	83.57%	25.59
PC/SD	0.929	0.021	<0.0001	0.888	0.969	81.70%	91.67%	880.94	96.59%	63.46%	84.29%	49.21
V diameter (mm)	0.795	0.040	<0.0001	0.718	0.873	82.70%	63.90%	13.35	86.87%	56.10%	77.86%	8.45
/ Congestion index	0.917	0.024	<0.0001	0.871	0.963	86.50%	80.60%	0.0935	92.78%	67.44%	85.00%	26.63
PLT	0.905	0.025	<0.0001	0.856	0.953	88.90%	83.70%	114510	96.59%	63.46%	84.29%	49.21
SD	0.230	0.040	<0.0001	0.152	0.308	83.30%	10.60%	11.7	75.61%	35.29%	70.71%	1.69





DISCUSSION

Out of 140 participants in our research, 106 were male, and 36 were female. Eighty-two participants were alcoholics, with the remainder suffering from non-alcoholic causes. Gender and alcoholic etiologies did not affect the occurrence of esophageal varices. Sutton R et al. discovered a link between esophageal varices in alcoholic patients with cirrhosis and hypertension.[9] The mean age of the patients in this research was 55.635.83 years, which was not associated with the occurrence of esophageal varices. Duah A et al,[8] also showed similar findings. In our study, laboratory parameters like platelet count (thrombocytopenia) & raised total bilirubin are significantly associated with esophageal varices. Similarly study conducted by Mahmood K et al. showed a strong link between total bilirubin and esophageal varices.[15] In our study liver enzymes are not associated with esophageal varices. A study by Duah A et al,[8] also showed the same. A study by Afsar A et al,[10] Ozdil K et al,[11] & Nouh MA et al,[12] showed platelet count (thrombocytopenia) is statistically significant with esophageal varices. But on contrary, study done by Qamar AA et al,[13] failed to show platelet count as a change in HVPG or surrogate marker for HVPG. Portal vein doppler indices like portal vein velocity, portal vein diameter, and portal vein congestion index are significantly associated with esophageal varices, but portal vein collaterals and splenic bipolar diameter are not significantly associated with it in our study.

Suraj Uppalapati S,[14] discovered that portal vein size/dilatation identified via ultrasonography could predict the existence of esophageal varices. In our research, we found platelet count and splenic diameter ratio are statistically significant with esophageal varices. A study by Khadka D et al,[2] González-Ojeda A et al,[16] & Baig WW et al,[17] also showed a statistically significant association between platelet count and splenic diameter ratio & esophageal varices. Though few studies warrant further large-scale evaluation, like a study conducted by Mattos AZ et al,[23] showed that the Platelet count and splenic diameter ratio is inadequate to predict esophageal varices in cirrhotic patients. Elkenawy YN et al,[18] Shastri M et al,[19] & Zironi G et al,[20] showed portal vein velocity with high sensitivity and specificity to predict esophageal varices, and it was statistically significant. The study by Nouh MA et al,[21] & Tarzamni MK et al,[22] suggested that the portal vein congestion index is useful as a non-invasive predictor of esophageal varices. All these studies support our findings. Though in our study, portal vein diameter & splenomegaly were not found to be significantly associated with esophageal varices but study conducted by Kumar P et al,[1] showed splenomegaly was significantly related to large esophageal varices in their study. In our study high CTP and MELD-Na scores are associated with esophageal varices. Shrestha A et al,[24] Thapa PB et al,[26] & Gomaa AA et al,[27] showed similar outcomes that cirrhotic patients with CTP classes B and C have large varices. On the other hand, Tafarel JR et al,[25] showed MELD and Child-Pugh scores are not useful as non-endoscopic predictors of EV. Another study conducted by Kraja B et al,[28] showed neither hepatic enzymes ratio nor MELD score could be used as predictors of esophageal varices. In our study esophageal varices did not show any association with total protein, albumin,

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serum creatinine & PT/INR (International Normalized Ratio). Study by Hsieh et al also showed no association between esophageal varices and INR, but in the other hand study conducted by Arulselvan V,[30] revealed an association between PT/INR and esophageal varices.

CONCLUSION

Non-invasive markers such as low platelet count, portal vein congestion index, portal vein diameter, platelet count and splenic diameter ratio and velocity are significantly associated with esophageal varices.

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