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Comparative Study for the Prediction of Large Oesophagheal Varices by Ultrasound Doppler and Serum Markers in Portal Hypertension due to Liver Cirrhosis

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Abstract

Introduction: Number of non-invasive tests of fibrosis has shown favorable results in identifying patients with portal hypertension and large varices. On the other hand, the performance of non-invasive tests is suboptimal and often unclear. **Aims & Objectives:** Authors aimed to compare serum marker based indices and portal vein diameter assessed by ultrasound in portal hypertension due to chronic liver diseases for prediction of large oesophageal varices graded on endoscopy. **Methods & Study Design:** In this case control study, 30 patients with large varices were compared with 27 controls with suggestion of either portal hypertension or fatty liver disease. Ultrasound was the sole modality to measure portal vein diameter and assess blood flow in the splenic and portal veins to rule out thrombosis. Liver was evaluated as normal, fatty liver and cirrhosis based on sonography features. Serum markers were used to derive indices APRI, FiB4, Forn's Index, and Lok Score. Data analysis was done by using SPSS software for computation of Area under Receiver Operative Curve values. **Results:** The mean portal vein size did not suggest portal hypertension in control group (criteria>13mm). The mean portal vein diameter of large varices was (13.03±2.03) mm. Area under Curve plotted for all non-invasive parameters of portal hypertension with 95% CI revealed that portal vein was significantly better than serum-based markers.(*p=<0.0001*). **Conclusion:** Forns index, APRI, FIB-4 and APRI, LOK were less accurate non-invasive markers to predict large oesophageal varices as compared to portal vein diameter.

Keywords: Oesophageal varices, Portal vein diameter, Serum markers, Ultrasound doppler.

INTRODUCTION

Currently, upper gastrointestinal endoscopy is the gold standard for screening and is recommended to be performed every 2 years in patients without varices and yearly in those with small varices [1]. However, this procedure is invasive, not comfortable under topical anesthesia as well as not cost effective, especially in a resource limited set up or inability to perform endoscopy for other reasons. In portal hypertension, half of these patients will not develop varices in 10 years and therefore may undergo screening, unnecessarily. Hence, search for prediction varices by non-invasive methods is continuously goes on in patients with cirrhosis [2].

Portal hypertension is defined by an increased pressure gradient between the portal vein and inferior vena cava (N < 5 mmHg). The most reliable and gold standard method to evaluate the presence and severity of portal hypertension is hepatic venous portal pressure gradient. (HVPG) [3].

A normal HVPG is between 1 and 5 mmHg [4,5]. Portal hypertension is present if the HVPG is ≥6 mmHg. Portal hypertension is clinically significant when the HVPG is ≥10 mmHg, when varices may develop. Portal pressure exceeding 10 mmHg is considered as clinically significant portal hypertension (CSPH). Once the HVPG is ≥12 mmHg, patients are at risk for variceal bleeding and the development of ascites [6].

However, the need for appropriate equipment, reliable expertise and their ready availability in addition to the costs, have restricted its use outside Liver Units specifically devoted to the clinical management of portal hypertension. These factors result in its diminished applicability [7]. The procedure is not without pitfalls due to errors in measurement and interpretation. The procedure usually needs repetition to monitor treatment response [8].

In recent years, a number of non-invasive tests of fibrosis have been studied in identifying patients with

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portal hypertension and large varices. The latest Baveno VI consensus guidelines (2017) support the use of such tests as initial evaluation to select patients for varices screening. On the other hand, the performance of non-invasive tests in assessing the response to non-selective beta-blockers is suboptimal and often unclear [9].

Due to the less accuracy of individual markers, scores or indices combining array of markers are being used due to "sufficient" diagnostic accuracy. APRI score is based on AST and platelet count. FIB-4 score combines the platelet count, ALT, AST and age. Forns index is based on 4 parameters: age, platelet count, cholesterol and γ-glutamyl-transferase (γ-GT)]. Lok index is an extrapolation of the APRI combining platelet count, INR and AST/ ALT ratio [10].

On the other hand, simple and single non-invasive method of assessing the portal vein size and flow characteristics also has been tested for this purpose [11].

AST-to-platelet ratio was introduced (2003) by Wai *et al* to identify chronic liver disease patients with significant fibrosis and cirrhosis; with a high accuracy rate [12]. A recent large meta-analysis study published by Lin ZH *et al* (2011) concluded that APRI can identify hepatitis C-related fibrosis with a moderate degree of accuracy [13].

Fibro Test is a composite of five serum markers (alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, γ-glutamyl transpeptidase {GGT}, and bilirubin) associated with hepatic fibrosis, which was developed by Poynard *et al* [14].

Many researchers have validated this test in several liver diseases, including chronic hepatitis [14-16].

Aims and Objectives

Authors aimed study and compare the performance and utility of serum marker based indices and portal vein diameter assessed by ultrasound in patients of portal hypertension due to chronic liver diseases in prediction of large oesophageal varices; graded on endoscopy.

MATERIAL AND METHODS

Written and informed consent was taken from each patient enrolled in this study after approval from institutional ethics committee.

The study was undertaken at tertiary referral hospital affiliated to medical college in Pune India. It was a prospective case control study undertaken during January 2017 to September 2017 after ethics committee approval. Thirty patients having signs of portal hypertension with chronic liver disease and presence of large oesophageal varices on endoscopy were included. Twenty-seven age and sex matched controls that were endoscoped after clinical and ultrasound assessment suggested either fatty liver or portal hypertension. Out of 27 controls, only 8 patients had early varices.

All the patients underwent detailed clinical evaluation which included details of alcoholism, jaundice, ascites, pedal edema and gastrointestinal bleed. Icterus, ascites, splenomegaly and hepatic encephalopathy were noted if present. Appropriate investigations, ultrasound abdomen and gastroscopy performed on all patients. Portal hypertension was diagnosed primarily on clinical, laboratory and ultrasound finding. Hemoglobin, platelet count, prothrombin time, blood urea, serum creatinine, serum cholesterol, liver function tests including serum bilirubin, albumin and transaminases were estimated. Child Turcotte Pugh class was noted. Serology for hepatitis B and C was done. At ultrasonography; the portal vein diameter was noted. Blood flow in portal and splenic veins was assessed and liver architecture was noted to categorise it as normal, fatty liver and cirrhosis. Oesophageal varices were detected on endoscopy and graded as large according to AASLD classification [17].

Those presenting with variceal bleed, or history of sclerotherapy or band ligation, portal vein thrombosis, gastrooesophageal varices, and patients on current or past treatment with beta-adrenergic receptor blockers, hepatocellular carcinoma were excluded from the study. Pregnant and lactating women were also excluded.

Serum markers were used to derive indices APRI- (Aspartate aminotransferase to platelet ratio index), FiB4- (Fibrosis 4 score.), Forn's Index, Lok Score.

1) APRI- [(AST/ULN) *100]/ platelet count 10^9/L]

(ULN= upper limit of normal)

2) FiB4 = [age(years)*AST (IU/L)]/ platelet count (10^9/L) *ALT (IU/L)1/2]

3) Forn's Index= 7.811 -3.131 *In [platelet count (10^9/L)] +0.781* In [GGT(IU/l)] +3.467* In[age(years))]-0.014[cholesterol (mg/dl)]

4) Lok Score- log odds = -5.556 -0.0089* platelet count (10^3/mm3) + 1.26 * (AST/ALT) +5.27* INR;

Lok= [exp (log odds)]/ [1+exp (log odds)]

Fujinon EG-201 FP video gastroscope was used for endoscopy after taking informed written consent from each patient for the procedure under topical anaesthesia of oropharynx.

Statistical Analysis

Data analysis was done by using SPSS (statistical Package for the Social Science) software version 17. SPSS showed the values for Area under Receiver Operative Curve (AUROC/AUC). The demographic variables for sensitivity and specificity were calculated as the percentage.

OBSERVATIONS AND RESULTS

The results and observations were tabulated with mean and standard deviations, p values as indicated for analysis. The demographic data and laboratory parameters of all patients are depicted in table-1. The mean age was 44.63 years and all of them had mean values for indicative of liver dysfunction with thrombocytopenia; however, means of PT/INR, GGT, and Cholesterol values were not affected. The mean portal vein size in control group did not suggest portal hypertension (criteria>13mm) [6].

Clinical data on all patients with large oesophageal varices and comparison of demographics and various laboratory parameters between large varices and control group were tabulated as in table-1.

The comparison between large oesophageal varices and control group showed that except portal vein size, all other parameters were not significantly different. The mean portal vein diameter in control group (9.87 ±2.46) was significantly lower than varices group (*p=<0.0001*) in comparison with large varices having mean variceal size larger (13.03±2.03) mm.

The serum markers based indices were compared between large oesophageal varices and control group. There was no statistically significant difference *(p<0.05). The* Forn's index, which is based on platelets, GGT and cholesterol values; was found to be better than the other thee indices *(p=0.57).* APRI was next better *(p=0.78)*.

Table 1: Demographic parameters between large oesophageal varices and control group

Parameter	Large varices (n=30)		Control (n=27)		P Value
	Mean	SD	Mean	SD	
Age (Yrs)	45.7	14.13	43.44	9.83	0.49
SEX (M: F)	26/4		24/3		0.48
Alcohol abuse	19		12		0.13
HBsAg +ve	5		2		0.6
Total bil. (mg/dl)	1.77	1.35	1.18	1.07	0.3
ALT (IU/L)	41.36	19.14	40.6	21.31	0.89
AST (IU/L)	87.73	40.88	79.59	31.31	0.85
ALP (IU/L)	109.41	49.43	121.79	75.59	0.46
Platelet(10^9/L)	97.7	35.82	211.74	46.42	0.2
PT/INR (IU/L)	1.42	0.43	1.34	0.33	0.44
GGT (IU/L)	72.33	35.05	82.3	26.16	0.23
Serum albumin	3.85	0.61	3.06	0.78	0.61
Cholesterol	115.07	33.69	118.74	35.93	0.69
PV size (mm)	13.03	2.03	9.87	2.46	*<0.0001*

Table 2: Comparison of Serum markers for detection of large oesophageal varices

Parameter	Large varices (n=30)		Control (n=27)		MW test	P Value
	Mean	SD	Mean	SD	Z Value	
APRI score	3.04	1.99	2.84	1.82	0.28	0.78
FiB4 score	6.49	4.34	6.09	4.22	0.17	0.87
Forn's score	8.35	1.22	8.07	1.84	0.57	0.57
LoK score	0.89	0.14	0.87	0.18	0.11	0.91

MW- Mann Whitney Test

Area under Curve plotted for all non-invasive parameters of portal hypertension with 95% CI revealed that portal vein was significantly better than serum-based markers. (*(p=<0.0001)*

Forn's index scored better than other three serum markers (*p=0.57)*.

The predictive role of non-invasive markers is shown in table-3; which indicated than portal vein diameter was better in positive and negative prediction of oesophageal varices as compared to serum markers. Similarly, portal vein diameter had better sensitivity and specificity in detection of oesophageal varices than serum markers.

Table 3: Comparison of Non-Invasive Markers for their value in detection of large varices

Parameters	cut off point	AUC	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
PV diameter (mm)	≥ 10.5	0.84	74.3	81.8	86.7	76.7
APRI score	≥ 1.845	0.6	56.7	51.9	58.7	53.9
FIB-4 score	≥ 4.865	0.54	54.4	50.2	53.5	50.2
FORN score	≥ 7.905	0.64	65.5	60.7	65.3	62.8
LOK score	≥ 0.945	0.51	51.6	46.2	53.3	44.4

The AUC for portal vein diameter (0.84) shown in figure 1 is reflecting the significance of *p=<0.0001*.

DISCUSSION

In the present times, endoscopy has been the gold standard modality in identifying oesophageal varices [18]. However; many studies have identified noninvasive markers predicting the presence and grades of oesophageal varices [19-26].

Oesophageal varix (OEV) is the result of spontaneous formation of collateral vessels between oesophageal veins and portal vein via the left/short gastric veins. Thus, presence/absence of OEV may depend on existence of portal hypertension [21,22].

Cherian *et al* (2011) studied this subject on 229 subjects and concluded that the presence and higher grades of varices can be predicted by a low platelet count, Child-Pugh class B/C and spleen diameter [23].

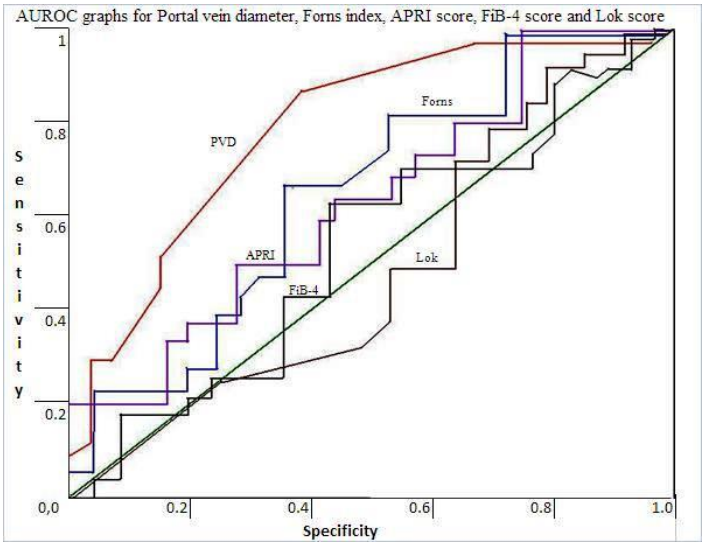

Figure 1: AUC for portal vein

Sharma *et al*; in their prospective study (2007) found that platelet count and splenomegaly were independent predictors for presence of large oesophageal varices [24].

Number of studies have revealed that multiple factors can be used in prediction of the presence of oesophageal varices like splenomegaly, [24] Child Turcotte Pugh grading system[25] platelet count[25, 26] portal vein diameter,[27, 28] prothrombin time [28,29]; platelet count: spleen diameter ratio [20, 20].

Schepis *et al* (2001) reported their study on 143 consecutive compensated cirrhotic patients who underwent upper gastrointestinal endoscopy. Clinical, biochemical, ultrasonographic parameters were recorded. They concluded that compensated cirrhotic patients should be screened by upper gastrointestinal endoscopy when prothrombin activity less than 70%, platelet count less than 100 x 10(9)/L, and ultrasonographic portal vein diameter greater than 13 mm are observed, whereas those without any of these predictors should not undergo endoscopy. The contribution provided by portal doppler study with ultrasonographic parameters does not appear of practical utility [28]. Ying L *et al* published (2012) meta-analysis study on significant role of platelet count/spleen diameter ratio for diagnosis of oesophageal varices in cirrhosis [29].

Mandal L *et al* (2011) found good correlation of portal vein diameter and splenic size with gastro-oesophageal varices in cirrhosis of liver [30].

Zardi *et al* (2007) failed to confirm value of PVD in prediction of avarices when the cut-off was taken to be 13 mm in prevalently HCV-related cirrhotic patients [31]. Manohar *et al* (2014) in their study of 143 patients; ultrasound showing PVD > 13 mm was one of the independent criteria for presence of EV [32].

In our study, in univariate analysis size of PVD was correlated with the presence of large oesophageal varices.

In most recent study reported by Chandail *et al* (2017), portal vein size was found to useful predictor of large varices [33]. Our study shows the similar results.

In a study reported by Sudha Rani *et al* (2015) measurement of PVD (> 13 mm) and ultrasound findings were independent non-invasive predictors for presence of oesophageal varices in patients with chronic liver disease with portal hypertension [34]. We found that portal vein diameter >13.03 mm±2.03 was independent marker for prediction of large oesophageal varices.

Sirli R *et al* (2008) studied several non-invasive markers to assess the extent of fibrosis in chronic hepatitis C virus (HCV) infection. The serum markers (platelet count, APRI score, Forn's score, Lok score, FIB-4, Transient Elastography [TE]) were compared with percutaneous liver biopsy (LB) to predict the extent of disease. All the evaluated tests had outstanding predictive value (AUROCs 0.839-0.979) [35].

In our study, liver biopsy and elastography were not taken as variables, but portal vein size; and serum based indices were compared as an indirect evidence of portal hypertension due to liver fibrosis based on ultrasonographic evaluation.

The reliability in variceal prediction for APRI, FIB-4, Lok, and Forn's scores where all had low to moderate diagnostic accuracy in predicting presence or absence of varices in liver cirrhosis according meta-analysis study was reported (2005) by Han Deng *et al* [36].

However, a recent survey done by Qi X *et al* (2015) suggests that noninvasive diagnostic tests for varices in chronic liver diseases were rarely used in clinical practice [37].

In another study conducted by Xiao G *et al* (2016) studied two markers i.e. APRI and FIB-4 on 2176 patients to correlate with liver fibrosis. However, these two models had very low accuracy in predicting HBV-related liver fibrosis in HCC patients suggesting that liver fibrosis alone may not be the sole factor to influence the markers [38].

In our study, we did not study this variate of HCC presence of which could have potential influence on these markers.

Either large varices or small varices or both with the red signs are globally known as Varices Needing Treatment (VNT). There have been widespread researches regarding the use of non-invasive methods in diagnosing CSPH, leading to development of varices and VNT [38] and a study done on varices; by Velazquez *et al* (2017) has shown that sensitivity, specificity, PPV, NPV and AUC are nearly similar values, for serum based non-invasive markers and differences were not significant [39].

Limitations of the study

The present study has some limitations. The sample size is modest 57. The non- invasive markers are linked to biochemical tests which can be affected by factors not related to liver fibrosis and portal hypertension. However, the strength of our study was marked by wider exclusion criteria and single observer imaging assessment of portal vein and liver architecture and endoscopies in assessing grades of varices, thus avoiding observer error.

CONCLUSION

In conclusion, the Forns index, APRI, FIB-4 and APRI, LOK were less accurate non-invasive markers to predict the large oesophageal varices in our patients as compared to portal vein diameter. The endoscopy remained the gold standard for detection of oesophageal varices.

Conflict of Interest

No conflicts of interest.

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