Non Invasive Indices of Portal Hypertension in Patients of Chronic Liver Disease for Prediction of Variceal Bleed

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ABSTRACT

Introduction: Non Invasive Indices of Portal Hypertension(PH) are well studied to assess Hepatic Fibrosis. There are few studies looking at risk of High Risk Varices using Non Invasive Indices. Therefore we studied the role of Non Invasive Indices of PH to predict High Risk Varices and Risk of Bleed.

Material and methods: Consecutive patients of Chronic Liver Disease were taken. Upper GI endoscopy done and History of Upper GI Bleed was taken. Routine Blood tests such as LFT , CBC ,PT/INR were done and Non Invasive Indices of PH were calculated.

Results: There were total of 57 patients (45 male& 12 females) out of which 28 were bleeders and 29 non bleeders. 31 had high risk varices, rest had low risk varices. Mean value of LSM, LSPS, PSR, APRI and FIB-4 in patients with high risk versus low risk varices were 31.59 vs 17.89(p<0.001), 5.81 vs 1.31(p<0.001), 658.7 vs 1578(p<0.001), 1.89 vs 1.12(p=0.006) and 5.19 vs 2.95(p=0.001). Mean value of LSM, LSPS, PSR, APRI and FIB-4 in patients with bleeders vs non bleeders were 30.44 vs 20.42(p<0.001), 6.07 vs 1.53(p<0.001), 558.25 vs 1569.5 (p<0.001), 1.98 vs 1.12(p=0.001) and 5.51 vs 2.87(p<0.001).

Conclusion: Our study shows that Non Invasive Indices of PH particularly LSPS, PSR are good tools to predict high risk varices or risk of bleeding.

Keywords: Portal Hypertension, Non-invasive Indices, Risk of Bleed

INTRODUCTION

Non-invasive tests for the assessment of the severity of hepatic fibrosis and assessment of variceal status are gaining ever more ground among hepatologists, who are now put in the difficult position of choosing which one to use, taking into account that, at this time more than 20 biochemical tests are available, not to mention elastographic methods.[1] Invasive techniques are considered the ''gold standard'' for assessing liver fibrosis.[2] Liver biopsy (LB) is not a perfect method as there is inequality of fibrosis in the two lobes of liver. LB is also an invasive maneuver, (with a risk of complications, even if it is low) causing discomfort for the patients.[2] Hence, non-invasive methods of assessing the severity of fibrosis may someday completely replace LB and are constantly being searched for.[2]

Among the non-invasive tests, the best results were obtained with liver stiffness measurement (LSM) by means of transient elastography (TE) (FibroScan). This non-invasive method is expensive and require equipment that is not widely available.[2] Universal screening endoscopy benefits only a minority of these patient as it is invasive and places increasing burden on endoscopy units.[3]

Simple, non-invasive, accurate indices are needed to prioritize patients before screening endoscopy for varices (EV).[3] Researchers worldwide have been looking to develop non invasive but accurate tests, first to identify patients with varices (particularly high risk), then to assess the risk of complication such as bleed, so that they can be put on primary prophylaxis, bypassing the need for routine endoscopy thereby reducing the financial costs and burden as well, also reducing the need for unnecessary procedure in low risk patients and reducing complication associated with it.[2]

Study aimed to evaluate the performance of noninvasive indices like platelet to spleen ratio, APRI (AST to platelet index ratio), aspartate aminotransferase (AST)/alanine transaminase (ALT) ratio, liver stiffness (LS), Fibrosis-4 (FIB-4) index, and liver stiffness- spleen diameter-to-platelet ratio score(LSPS) in patients of chronic liver disease and predicting the risk of variceal bleed.

MATERIAL AND METHODS

A total of 57 patients were included in the study. All patients attending OPD and IN PATENTS admitted in Department of gastroenterology over a period of 6 months from January 2018 till june 2018 with chronic liver disease were included in the study.

Exclusion criteria: Patients with age less than 18, pregnant females, severe co-morbid conditions, patients who have had previous surgery for portal hypertension or transjugular intrahepatic portosystemic stent shunt placement, portal vein or splenic vein thrombosis, hepatocelluar carcinoma or presence of severe ascites that might significantly hamper the accurate assessment of LSM were excluded from the study.

The diagnosis of chronic liver disease was based on findings of elastography and ultrasonographic findings. Routine

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biochemical and hematological tests were done including complete blood count, PT/INR, liver function test and renal function test. History of upper GI BLEED in form of frank painless hematemesis or malena was elucidated from the patient at the time of interview. Upper GI endoscopy was done in all patients and the size and risk of esophageal varices was seen. Additionally presence or absence of gastric varices and portal hypertensive gastropathy and duodenopathy was also noted.

Non invasive indices used were calculated using the following formulas:

- LSPS= LSM (kPa) X Spleen size(cm) / platelet count $(10^9/L)$
- Platelet spleen ratio = Platelet count (mm^3) / spleen size (mm)
- APRI = {AST/AST (ULN) X 100} X platelet count $(10^9/L)$
- FIB-4 = Age (yrs) X AST (U/L) / platelets X $\sqrt{(ALT)}$
- AST/ALT ratio = AST/ALT

STATISTICAL ANALYSIS

Continuous variables were expressed as the means ± standard deviation (SD), and categorical data were expressed as numbers (percentages). The nonparametric Mann±Whitney test was used to analyze differences between groups, and the $\chi 2$ test or Fisher's exact test was applied for the comparison of categorical data. A receiver operating characteristic (ROC) analysis was used to assess the diagnostic performance of each noninvasive test and each area under the ROC curve (AUC) was calculated. The diagnostic value of each noninvasive index was calculated based on sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), negative likelihood ratio (-LR) and 95% confidence intervals (CIs). For all analyses, p-values was calculated, and p-values < 0.05 were considered statistically significant.

RESULTS

The present study was carried out with an aim to evaluate the performance of various non-invasive indices of portal hypertension for prediction of high risk varices among patients with compensated chronic liver disease. For this purpose, a total of 57 patients with compensated chronic liver disease were enrolled in the study.

Table 1 shows Age of patients ranged from 25 to 80 years. Mean age of patients was 51.89±12.58 years. Majority of patients were males (78.9%). Sex ratio of study population was 3.75. Alcohol (56.1%) was the most common etiological factor followed by hepatitis (28.1%) and NASH (15.8%) respectively. Child-Turcott-Pugh Grade C was most dominant (66.7%) followed by Grade B (29.8%) and Grade A (3.5%) respectively. On upper GI endoscopy, large varices were revealed in 31 (54.4%) cases. A total of 28 (49.1%) varices showed bleeding. Spleen size of the patients ranged from 8 to 21 cm (mean 13.42±2.82 cm). Platelet count of the study population ranged from 45 to 400x10⁹/L with a mean of 130.86±64.64 x 10⁹/L. Mean AST and ALT values were 60.38±43.50 and 45.11±27.99 U/L respectively. Mean PSR,

SN	Characteristic	Statistic
1.	Mean Age±SD (Range) in years	51.89±12.58 (25-80)
2.	Sex Male Female	 45 (78.9%) 12 (21.1%)
3.	Etiology Alcohol Hepatitis * NASH	 32 (56.1%) 16 (28.1%) 9 (15.8%)
4.	Child-Turcott-Pugh Grade A B C	 2 (3.5%) 17 (29.8%) 38 (66.7%)
5.	UGIE Nil/Early/Small Large/Severe	 26 (45.6%) 31 (54.4%)
6.	Bleeding	28 (49.1%)
7.	Mean spleen size±SD (range) in cm	13.42±2.82 (8-21)
8.	Mean platelet count±SD (range) x 10⁹/L	130.86±64.64 (45-400)
9.	Mean AST±SD (range) U/L	60.38±43.50 (12-223)
10.	Mean ALT±SD (Range) U/L	45.11±27.99 (20-180)
11.	Mean LSM±SD (Range) KPa	25.34±10.70 (8-75)
12.	Mean LSPS±SD (Range)	3.76±2.96 (0.52-12.58
13.	Mean PSR±SD (Range) cm/10⁹/L	1072.75±661.3 (294.12-3636.36)
14.	Mean APRI±SD (Range)	1.54±1.07 (0.00-5.19)
15.	Mean FIB-4±SD (Range)	4.19±2.52 (0.83-10.69)
16.	Mean AST/ALT±SD (Range)	1.35±0.52 (0.50-2.49)
*HCV=5, HBV=10, HCV+NASH=1		
Table-1: General profile and clinical characteristics of patients		

APRI, FIB-4 and AST/ALT values were 1072.75±661.3, 1.54±1.07, 4.19±2.52 and 1.35±0.52 respectively.

(Table 2) On comparing the general and clinical profile of bleeders with that of non-bleeders, no significant difference was observed between two groups with respect to mean age, etiology, CTP grade, Mean AST, Mean ALT and Mean AST/ALT ratio (p>0.05).

However, bleeders as compared to non-bleeders had significantly higher proportion of females and those with large varices. Mean spleen size, liver stiffness measure (LSM), LSPS ratio, APRI and FIB-4 levels were significantly higher in bleeders as compared to non-bleeders (p<0.05) whereas mean platelet count and PSR was significantly lower in bleeders as compared to non-bleeders (p<0.05).

(Table 3) At predefined cut-off values LSPS and PSR were found to have best performance while AST/ALT had the worst performance. LSPS was found to be 89.3% sensitive and 93.1% specific. It had positive and negative predictive values of 92.6% and 90% respectively. On the other hand, PSR was found to be 92.9% sensitive and 93.1% specific. It had positive and negative predictive values of 93.1% and

92.9% respectively. LSPS and PSR had accuracies of 91.2% and 94.7% respectively. FIB-4 was on the next rung with a sensitivity of 89.3% and specificity of 71.4%. The positive and negative predictive values of FIB-4 were 75.8% and 87% respectively. FIB-4 had an accuracy of 80.7%. Both APRI and AST/ALT were least effective. While AST/ALT had a high sensitivity (85.7%) but a low specificity (14.3%), APRI had low sensitivity (39.3%) and high specificity (89.7%). Both these markers thus lacked a balanced sensitivity-specificity scenario. The accuracy of APRI and AST/ALT was 64.9% and 49.1% only.

(Table 4) AST/ALT ratio was excluded from ROC analysis, as it did not show a significant association with bleeding on univariate analysis (Table 2). Thus, the ROC analysis was limited to four ratios, *viz.*, LSPS, PSR, APRI and FIB-4. The area under curve values were maximum for PSR (AUC 0.982±0.014) followed by LSPS (AUC 0.964±0.027), FIB-4 (0.809±0.059) and APRI (AUC 0.802±0.061). The cut-off values derived for LSPS, PSR, APRI and FIB-4 were ≥2.67, <961.50, ≥1.25 and ≥3.76 respectively. At the derived cut-off values, PSR had maximum sensitivity (100%) while

SN	Characteristic	Bleeders (n=28)		Non-bleeders (n=29)		Statistical significance	
		Mean	SD	Mean	SD	't'	'p'
1.	Age	51.79	11.79	52.00	13.50	-0.06	0.949
2.	Sex Male Female	18 (64.3%) 10 (35.7%)		27 (93.1%) 2 (6.9%)		χ^2=7.118; p=0.008	
3.	Etiology Alcohol Hepatitis * NASH	13 (46.4%) 8 (28.6%) 7 (25.0%)		19 (65.5%) 8 (27.6%) 2 (6.9%)		χ^2=3.886; p=0.143	
4.	CTP Grade A B C	0 (0%) 6 (21.4%) 22 (78.6%)		2 (6.9%) 11 (37.9%) 16 (55.2%)		χ^2=4.402; p=0.111	
5.	UGIE Small Large	0 28 (100%)		26 (89.3%) 3 (10.3%)		χ^2=46.16; p<0.001	
6.	Spleen size	15.64	1.90	11.27	1.63	9.33	<0.001
7.	Platelet count	85.82	24.61	174.34	61.54	-7.08	<0.001
8.	AST	56.07	22.16	64.68	57.66	-0.74	0.464
9.	ALT	44.04	16.97	46.18	36.13	-0.28	0.777
10.	LSM	30.44	5.87	20.42	12.03	3.97	<0.001
11.	LSPS	6.07	2.35	1.53	1.35	8.98	<0.001
12.	PSR	558.25	180.61	1569.51	568.22	-8.99	<0.001
13.	APRI	1.98	0.88	1.10	1.08	3.38	0.001
15.	FIB-4	5.51	2.49	2.87	1.78	4.58	<0.001
16.	AST/ALT	1.34	0.49	1.36	0.55	-0.17	0.869
	Table-2: Comparison of General and Clinical Profile of Bleeders and Nonbleeders						

SN	Indicator with Cut-off	TP	FP	FN	TN	Sens	Spec	PPV	NPV	Accuracy
1.	LSPS>3.5	25	2	3	27	89.3	93.1	92.6	90.0	91.2
2.	PSR<884.3	26	2	2	27	92.9	93.1	93.1	92.9	94.7
3.	APRI > 2.0	11	3	17	26	39.3	89.7	78.6	60.5	64.9
4.	FIB-4 > 3.25	25	8	3	20	89.3	71.4	75.8	87.0	80.7
5.	AST/ALT > 0.8	24	24	4	4	85.7	14.3	50.0	50.0	49.1
	Table-3: Evaluation of diagnostic efficacy of different indicators using predefined cut-off for prediction of bleeding									

SN	Indicator	Area Under curve±SE	Projected Cut-off	Projected Sensitivity	Projected Specificity
1.	LSPS	0.964±0.027	≥2.67	96.4	93.1
2.	PSR	0.982±0.014	<961.54	100	92.9
3.	APRI	0.802±0.061	>1.25	78.6	71.4
4.	FIB-4	0.809±0.059	>3.76	82.1	75.0
AST/ALT has been excluded as it did not show a significant association with outcome (Table 2)					
Table-4: Evaluation of Study Specific Cut-off values and their projected sensitivity and specificity based on ROC Analysis for outcome bleeding					

LSPS had maximum specificity (93.1%). Both LSPS and PSR had sensitivity as well as specificity above 90%. APRI had sensitivity of 78.6% and specificity of 71.4% whereas FIB-4 had sensitivity of 82.1% and specificity of 75%.

DISCUSSION

As table 1 shows mean age was 51.89 years. 45 (78.9%) out of 57 patients were males. Most common etiology was alcohol (56.1%), viral hepatitis (28.1%) and NASH (15.8%). 66.7% of the patients had advanced liver disease (CTP C). Large/ High risk varices were present in 54.4% of patients. Upper GI Bleed in the form of malena and hematemesis was present in 49.1% of the size. In the study[4], done in VMMC, average age was 43, males were significantly high (41:10) and alcohol was etiology in 49% of the patients.

Table 2 shows comparison between general profile among bleeders and non-bleeders. Mean age was comparable (51.79 vs 52). Males were common in non-bleeders (93 vs 64%) but it did not reach statistical significance. Alcohol as etiology was common in both groups (65% vs 46%). Again 78% of the bleeders were in advance liver disease.

Tseng et al assessed the use of liver/spleen stiffness in diagnosing and predicting portal hypertension using hepatic vein pressure gradient (HVPG). They found for detecting significant portal hypertension, liver stiffness of 16.0 kPa had an accuracy of 75%, sensitivity of 78%, specificity of 54%, positive predictive value of 92%, negative predictive value of 27% for predicting bleed and high risk varices.[6] Similarly in our study Mean LSM values were higher in bleeders (30.44 vs 20.22, p<0.001) and also for predicting high risk varices mean LSM was higher in patients with large /high risk varices (31.59 vs 17.8, p<0.001). [Table 2].

Liu et al. investigated the clinical value of FibroScan transient elastography for assessing portal hypertension[7] They found that the estimated prevalence of esophageal varices was 97.87% and the optimized cut-off level of liver stiffness was 18.0 kPa. In our study we found non bleeders had significantly low liver stiffness (12 Kpa)[7] [table 2].

Mean spleen size was 15.64 cm vs 11.27 cm (p<0.001) in bleeders vs non bleeders. Similarly platelet count was significantly low in between these two groups (85.82 k vs 174.34 k, p<0.001). Mean PSR ratio was significantly low in bleeders (558.25 vs 1569.51, p<0.001). [table 2] Baig et al studied the value of platelet count to spleen diameter ratio for diagnosing esophageal varices in liver cirrhosis.[8] By applying receiver operating characteristic curves, they found out a platelet count to spleen diameter ratio cut-off value of 1014 gave positive and negative predictive values of 95.4%

and 95.1%, respectively for predicting esophageal varices. In our study non bleeders had significantly high PSR (1569) as compared to bleeders (558.25), p<0.001. In our study the AUROC of PSR to predict was good at 0.938 with projected sensitivity and specificity of 90.3 and 92 respectively.[8] [table 4, fig 4.2]

Values of APRI were significantly high in bleeders (1.98 vs 1.10, p<0.001) in our study. Loaeza-del-Castillo A, et al did an observational, cross-sectional, comparative and retrolective fashion studied 164 pts with cirrhosis.[9] They compared fibrosis and APRI score. They found out that an APRI values of less than or equal to 0.3 and more than 0.5 can be used to rule out significant fibrosis and cirrhosis.[10] Another study from National University of Medical Sciences Rawalpindi Pakistan, 135 patients were involved and APRI was measured for each of these patients keeping 1.3 as the cutoff value. APRI was compared to upper gastrointestinal endoscopy. They found poor PPV, NPV, low specificity and diagnostic accuracy values of APRI when used as screening tool for predicting esophageal varices in cirrhotics.[10] In contrast our study showed that AUROC for APRI to predict bleed is 0.802 with projected sensitivity of 82.1 and specificity of 71.4 [4.1, table 4]. In our study the difference between groups of high risk vs low risk varices was also significant (1.89 vs 1.12, p <0.001) [table 2], which was in contrast to the study by Raza et al.[11]

In a study[5] median APRI score was 1.09. They compared HVPG and APRI score .The negative predictive value (NPV) of 38%, positive predictive value (PPV) of 94% and accuracy of 73% was obtained. APRI also correlated well with CTP, variceal size, bleeding status, ascites but not with
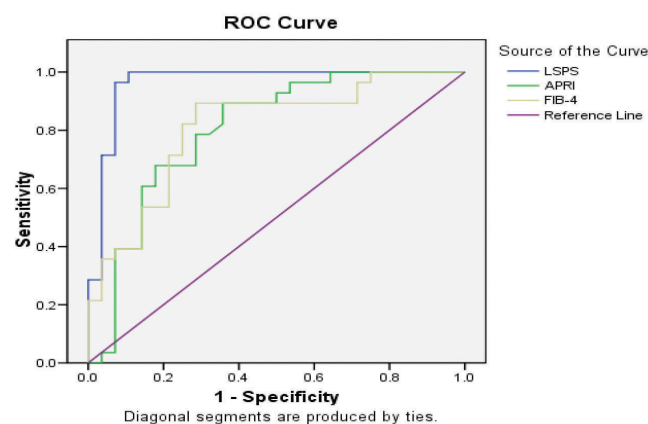
Figure-4.1: Receiver-Operator Characteristic Curves of LSPS, APRI and FIB-4 showing area under curve for prediction of bleeding

MELD. Our study also showed comparable values of APRI as in their study.[5]

Our study showed the FIB 4 values were significantly different in both groups, bleeders vs non bleeders (5.51 vs 2.87, p<0.001). Kraja et al assessed 139 cirrhotic patients. They found out, FIB-4 could strongly predict esophageal varices and was only index showing significant results (multivariable-adjusted OR = 1.57 for one unit increment; 95%CI: 1.15-2.14). Furthermore, they established a cut-off value of 3.23 for FIB-4 to significantly predict esophageal varices and found a sensitivity of 72%, a specificity of 58% and a proportion of area under the curve (AUC) of 66% (*P* = 0.01).[12] We used a cut off of 3.25, many studies have used similar parameters.[12,13] The AUROC in our study was 0.809, to predict bleed which was higher than other studies.[12,13] [fig 4.1]. The projected sensitivity and specificity were 82.1 and 75 respectively [table 4].

The LSPS values were also significantly different in two groups of bleeders vs non bleeders was (6.07 vs 1.53, p<0.001) [table 2], and AUROC for the same was 0.964 with projected sensitivity and specificity of 96.4 and 93.1 respectively at a projected cut off of 2.67[table 4, fig 4.1] .In a cross sectional study done by Berzigotti et al in 117 patients with cirrhosis, without any prior decompensation. The role of following parameters (platelet count, spleen diameter, LS, ratio of platelet count to spleen size, and LSPS) was used to identify patients with CSPH and EV.[14] They found that LSPS to be the best noninvasive variable when used singly for identifying patients with CSPH (area under the ROC, 0.883; 95% CI, 0.824-0.943; P < .0001). They also noted that the area under ROC value increased when LS was combined with other variables like platelet count and spleen size, either as PH risk score (0.935; p< .0001 or LSPS (0.918; p< .0001). Varices risk score and LSPS were found to be superior to all other noninvasive tests in identification of patients with EVs (area under the ROC, 0.909; 95% CI, 0.841-0.954 and 0.882; 95% CI, 0.810-0.935, respectively).[14] These findings were in concordance with our group. Our study showed a significant difference in LSM values in bleeders vs non bleeders (30.44

vs 20.4), p<0.001. [table 2] as also shown in other studies[15,16] which also showed a direct correlation between LS, high risk varices, associated risk of bleed and portal hypertension.

In contrast to above studies Mattos AZ et al. found significant association between PSR and presence of high risk /large varices.[17] Ying et al[18,19] performed a meta-analysis and, concluded that the index PSR could decrease the need for endoscopy in cirrhotic patients.

Drawbacks: It was a cross-sectional study and patients were not followed up for any recurrence of bleed. Also the sample size of the study was small, only 57 patients were included. Liver biopsy was not used as diagnostic criterion for liver cirrhosis.

CONCLUSION

Historically the value of non-invasive indices for assessment of fibrosis as well as portal hypertension is clearly established. In our study we studied various parameters, mainly LSPS, FIB-4, APRI AST/ALT ratio and platelet spleen diameter ratio. AST / ALT ratio failed to reach statistical significance on univariate analysis for predicting bleed but rest of the four parameters did show favorable results as potential screening tools to assess portal hypertension and risk of bleed. For predicting bleed from varices APRI had the poorest sensitivity where as PSR showed highest accuracy. Both LSPS and PSR showed good NPV and PPV with PSR fairing slightly better. The AUROC analysis showed that PSR was best among all other parameters with LSPS following in closely.

Our study shows that both LSPS and PSR are good screening tools when it comes to assess the risk of bleed in cirrhotics. We need to do this study in a larger cohort of patients with various etiologies and hence prove that many compensated cirrhotics, can safely avoid endoscopy, the risks associated with it and also the burden of cost.

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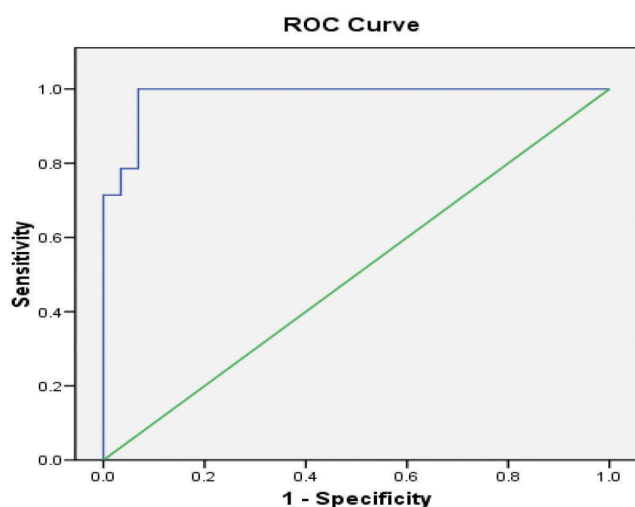
Figure-4.2: Receiver-Operator Characteristic Curves of PSR showing area under curve for prediction of bleeding

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