

## Non-Endoscopic Parameters for Prediction of Esophageal Varices

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### ABSTRACT

**Introduction:** Non invasive assessment of esophageal varices may improve the management and lower the medical and financial burden related to the screening. In this study, Our aim was to validate the prediction of varices using platelet count/spleen diameter ratio and Alanine transaminase/platelet ratio index (APRI).

**Methods:** Fifty patients with newly diagnosed and treatment naive cirrhosis underwent screening endoscopy along with hematological and ultrasonographic studies. Platelet count/spleen diameter ratio and APRI index were assessed and their diagnostic accuracy calculated. Based on previous studies , a cutoff of 909 was applied for platelet count/spleen diameter ratio and cutoff of > 1.3 for APRI. The diagnostic accuracy of both the indices were further evaluated for severity and size of varices.

**Results:** Prevalence of varices was 36% out of which 24% were large varices. Platelet count/spleen size diameter, portal vein diameter and APRI index had significant association for prediction of presence of varices and strongly correlated with size of varices. Platelet count/spleen size diameter of 909 had diagnostic accuracy of 80.5% for prediction of varices with diagnostic accuracy being 95.8 for predicting large varices. APRI index of more than 1.3 had accuracy of 75% for predicting varices and 87.5% for accurately predicting them as large varices.

**Conclusions:** In a resource limited country like ours, where access to specialized and tertiary care hospitals and availability of endoscopy facilities in rural areas is an issue, these non invasive parameters platelet count/spleen diameter and APRI can be taken as a safe and reliable predictor for esophageal varices.

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### Keywords

Non-endoscopic parameter; esophageal varices; platelet count/spleen diameter ratio; APRI

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### INTRODUCTION

Cirrhosis is the end stage for chronic liver disease and results in portal hypertension. Portal hypertension is associated with hyper dynamic circulation resulting in increased gradient and redirection of blood to areas with low venous pressure and finally forms esophageal, gastric, rectal varices. Gastro-esophageal varices are the most relevant porto-systemic collaterals because their rupture results in variceal hemorrhage,

the most common and lethal complication of cirrhosis. Esophageal varices are dilated sub-mucosal veins mostly in the lower third of the esophagus. Esophageal varices are present at diagnosis in approximately 50% of cirrhotic patients, being more common in Child-Pugh class C patients compared to

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Child-Pugh class A patients (85% versus 40%).<sup>1</sup> The rate of development of new varices and increase in grades of varices is 8% per year; the former is largely predicted by a hepatic venous pressure gradient (HVPG) exceeding 10 mm Hg.<sup>2</sup> De novo formation of varices occurs at a rate of 5% per year, with a higher incidence in patients continuing to consume alcohol or with worsening liver function.<sup>3</sup> Once varices form, they enlarge from small to large at a rate of 5–12% per year and bleed at a rate of 5–15% per year.<sup>3</sup> Patients with small varices develop large varices at the rate of 8% per year. Early diagnosis of varices before the first bleed is essential as studies of primary prophylaxis clearly show that the risk of variceal hemorrhage can be reduced by 50% to about 15% for large esophageal varices.<sup>4</sup> Upper GI endoscopy remains the gold standard for screening, but this test has its own limitations. It is an invasive procedure with significant cost and burden to the patients and endoscopy units. It necessitates patients having repeated unpleasant procedures even when up to 50% may still not have developed esophageal varices 10 years after the initial diagnosis.<sup>5</sup> There is, therefore, considerable interest in developing models to predict the presence of high-risk varices by non-endoscopic methods. It may be more cost effective to screen these patients routinely at risk for presence of varices. If patients at low or high risk of having esophageal varices (EV) could be identified from easily obtainable clinical variables, a more affordable approach for screening would be possible. It would be very much helpful in a country like Nepal where availability and affordability of endoscopy is a thriving issue. Certain biochemical, clinical and ultrasonography parameters alone and in combination are found to have predictive value for assessing the presence of varices.<sup>6</sup>

## AIMS AND OBJECTIVES

To identify the relationship and diagnostic accuracy and predictive value of non-endoscopic parameters like platelet count, spleen size, portal vein diameter and platelet count / splenic ratio, Aspartate aminotransferase/ platelet count ratio index (APRI) for the presence of esophageal varices. Also to determine the correlation between these parameters and size of varices along with the state of liver disease.

### Risk factors for variceal bleeding

Variceal hemorrhage occurs at a yearly rate of 5%-15%, and the most important predictor of hemorrhage is the size of varices, with the highest risk of first hemorrhage (15% per year) occurring in patients with large varices. Other predictors of hemorrhage are decompensated cirrhosis (Child B/C) and

the endoscopic presence of red wale marks and cherry red spots. Their presence correlates with the severity of liver disease while only 40% of Child A patients have varices, they are present in 85% of Child C patients.<sup>7</sup> Patients without varices develop them at a rate of 8% per year and the strongest predictor for development of varices in those with cirrhosis who have no varices at the time of initial endoscopic screening is an HVPG >10mmHg. Patients with tense ascites are also at increased risk for bleeding from varices. Although bleeding from esophageal varices ceases spontaneously in up to 40% of patients, and despite improvements in therapy over the last decade, it is associated with a mortality of at least 20% at 6 weeks.<sup>8,9</sup> Intra abdominal pressure clearly influences several hemodynamic variables in portal hypertension, but there is no concluding evidence that tense ascites increases the risk of variceal bleeding.<sup>10</sup>

Before the widespread use of current therapies for acute variceal hemorrhage, the mortality rate of a single variceal hemorrhage was 30 percent, and only one-third of patients survived for one year.<sup>11,12</sup> Although survival has improved with modern techniques for controlling variceal hemorrhage, mortality rates remain high.

In a study by Carbonell et al., who showed that between 1980–2000, the in hospital mortality from variceal bleeding decreased from 42.6% to 14.5% and was associated with decreased re-bleeding.<sup>13</sup> Although mortality from a bleeding episode has decreased with improved endoscopic and radiological techniques together with new pharmacologic therapies, 20 – 30% mortality means that bleeding from esophageal varices remains of significant clinical importance.<sup>14</sup> Early diagnosis of varices before the first bleed is essential as studies of primary prophylaxis clearly show that the risk of variceal hemorrhage can be reduced by 50% to about 15% for large esophageal varices.<sup>15</sup>

### Non-endoscopic predictors:

Current guidelines recommend that all cirrhotic patients should undergo screening endoscopy at diagnosis to identify patients with varices at high risk of bleeding who will benefit from primary prophylaxis. This approach places a heavy burden upon endoscopy units and the repeated testing over time may have a detrimental effect on patient compliance. Noninvasive identification of patients at highest risk for esophageal varices would limit investigation to those most likely to benefit. Several studies have examined the usefulness of different clinical and laboratory parameters as predictors of the presence or size of esophageal varices.

## MATERIALS AND METHODS

This cross-sectional analytical study was carried out at the Department of Internal Medicine, Tribhuvan University Teaching Hospital, Maharajgunj, Kathmandu, Nepal. Targeted sample sizes of 50 cirrhotic patients admitted to the hospital during the period from March 2012 to May 2014 were studied. Written informed consent was taken from each patient or their relatives prior to enrollment in study.

## METHODS

All patients included in the study were evaluated for clinical, hematological, biochemical and ultra-sonographic parameters. Uniformity was maintained by repeating scans by the same radiologist to avoid inter observer variation. All patients underwent UGI endoscopy to evaluate for the presence and degree of esophageal varices using an Olympus video Endoscope GIF type V<sub>2</sub>.UGI endoscopies were carried out mostly by the single gastroenterologist during the study period to avoid inter-observer disagreement. The degree of esophageal varices was classified according to Paquet Grading system of varices.<sup>42</sup> and further classified into small and large varices based on AASLD and Baveno IV recommendations.<sup>6,43</sup>

### Etiology of Cirrhosis of liver

Alcoholic liver disease was the most common cause of cirrhosis. It comprised of 43 patients (86%). Chronic viral hepatitis B accounted for 5 cases (10%) and Hepatitis C for 1 case (2%). 1 case (2%) had NASH as its cause for cirrhosis.

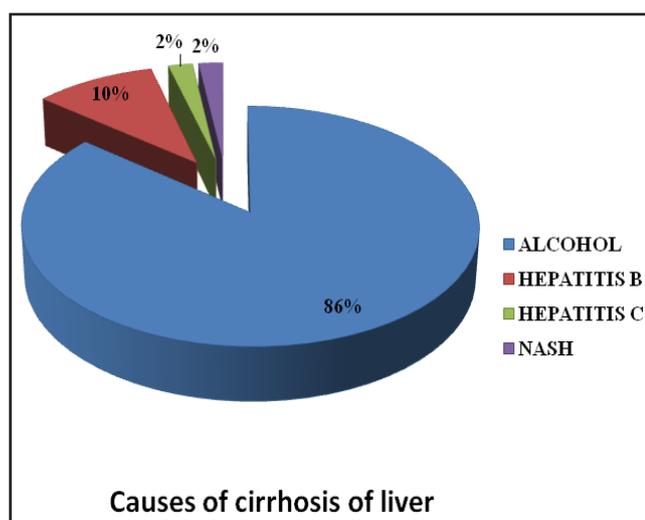


FIG 1: Etiological cause of Cirrhosis of Liver

**Table 1: Clinical, biochemical and ultrasonography parameters: comparison between patients with and without esophageal varices.**

Variables	Patients with varices (n = 36)	Patients without varices (n = 14)	P value
Age (years)	48.47 ± 9.6	46.79 ± 10	0.585
Sex (M/F)	26 (72.2%)/ 10(27.8%)	12(85.7%)/ 2 (14.3%)	0.468
Ascites	34 (94.4%)	11 (5.6%)	0.126
Hepatic encephalopathy	8 (22.2%)	3 (21 %)	0.114
Bilirubin (μmol/l)	117.75 ± 85	154.21 ± 136	0.26
Albumin (g/L)	28.1± 3.2	28.2 ± 3.4	0.985
Prothrombin time(sec)	23.56 ± 7.6	24 ± 10	0.869
Platelet count (N/mm <sup>3</sup> )	110777 ± 38605	165571 ±47842	0.0001
Spleen size (mm)	128.28 ± 11.3	121.9 ± 13.26	0.096
Portal vein size (mm)	13.1 ± 0.78	12.07 ± 1.24	0.0001
Platelet/spleen ratio [N/mm <sup>3</sup> ]/mm]	882.69 ± 407.7	1383 ± 464	0.0001
APRI [(IU/L)/N/mm <sup>3</sup> ]	1.54 ± 0.61	1.18 ± 0.63	0.071

Data expressed as Mean ±SD, statistical analysis by  $\chi^2$  and student t test.

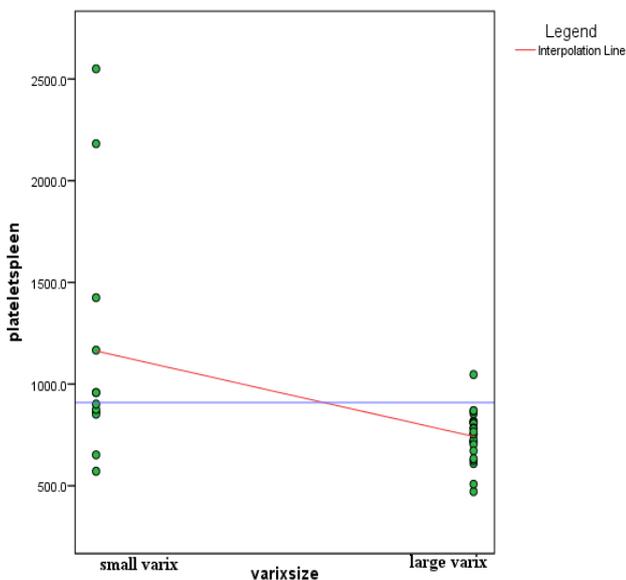
The above table 1 shows that age and gender wise differences in cirrhotic population were not statistically significant for the presence of esophageal varices. Among the 50 cirrhotic patients studied, 36 patients (72%) had endoscopic evidence of esophageal varices. Laboratory values of prothrombin time, serum albumin and bilirubin levels did not have significant differences among the groups with varices and without varices. Platelet count values among the cirrhotic with varices were significantly lower, 110777(± 38605) as compared to 165571 (±47842) among those without varices with significant p value. Size of spleen as measured by ultrasonography of abdomen showed that larger spleen size were associated with the presence of esophageal varices, 128.28 (± 11.3) in group with varices as compared to 121.9 (± 13.26) in group without varices, however the association was statistically not significant. Moreover the platelet count and spleen diameter ratio had a significant association for presence of varices with mean value of 882.69 (± 407.7) in cirrhotic with varices as compared to 1383 (± 464) in cirrhotic without varices and the association was statistically significant.

Portal vein diameter with mean value of 13.1 mm was also

associated with presence of esophageal varices as compared to mean value of 12.07 mm in those without varices with a significant p value. APRI, aspartate aminotransferase to platelet ratio index showed mean value of 1.58 in cirrhotic with varices against 1.18 in those without varices, though the association was statistically not significant.

**Association of platelet count/ spleen diameter ratio and esophageal varices**

The ratio of platelet count and spleen diameter had strongest correlation among all the predictors studied. It had a highest correlation coefficient of 0.52 and 0.47 for the presence of varices and presence of large varices respectively. The platelet count/ spleen diameter ratio mean values were significantly lower in those with varices, mean value of 882.69 (± 407.7) in cirrhotic with varices as compared to 1383 (± 464) in cirrhotic without varices with a significant p value. Similarly the ratio had a strong correlation with presence of large varices evidenced by values of 742.588± 121 for large varices as compared with 1162± 607 for small varices with a significant p value < 0.05.



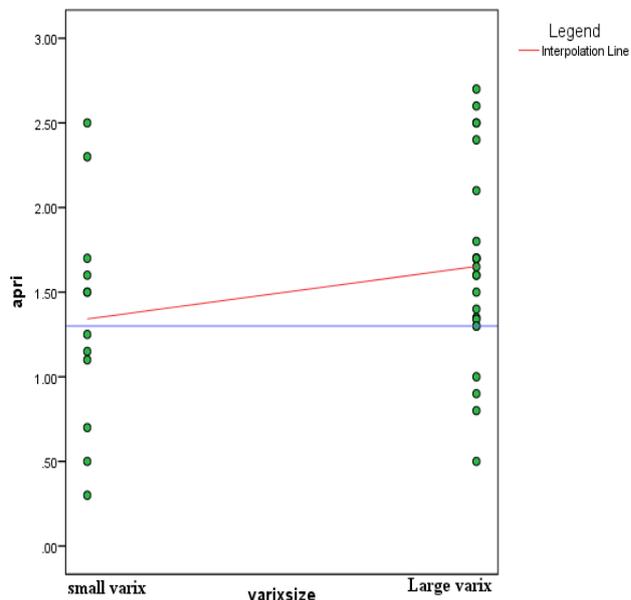
**Figure 2: Scatter diagram showing association between platelet count/ spleen diameter ratio and size of varix.**

Using the cut-off of platelet count/ spleen diameter ratio of 909 showed strong correlation and association for presence of varices as well as for further predicting large sized varices.

**Association of APRI and esophageal varices**

APRI values did show differences among the patients with varices compared to those without varices with mean value of 1.58 in cirrhotic with varices against 1.18 in those without varices, though the association was statistically not significant.

Same was the case for patients with large varices where APRI value of 1.65± 0.58 was present as compared to 1.34± 0.66 for patients with small varices and yet again the association was not significant statistically.



**Figure 3: Scatter diagram and interpolation line showing association between APRI and size of varices.**

**Table 2: Non-endoscopic parameters and their correlation with presence of esophageal varices using the study cut-off values.**

Parameters	With varices n= 36	Without varices n=14	P value	cor- relation coeffi- cient
Platelet count (cutoff of <100000/mm3)	14 (38.88%)	2 (14.2%)	0.175	0.23
Spleen size (cut-off of > 130 mm)	17 (47.2%)	5 (35.7%)	0.537	0.104
Portal vein size ( cut off of > 13 mm)	22 (61.11%)	3 (21.42%)	<b>0.025</b>	0.336
Platelet count/ spleen size ratio ( cut-off of <909)	29 (80.5%)	2 (14%)	<b>0.0001</b>	<b>0.523</b>
APRI index (cutoff >1.3)	27 (75%)	5 (35.7%)	<b>0.019</b>	0.345

**Table 3: Non-endoscopic parameters and their correlation with size of esophageal varices using the study cut-off values.**

Parameters	Small varices n= 12	Large varices n= 24	P value	Correlation coefficient
Platelet count (cutoff of <100000/ mm3)	2 (16.67%)	12 (50%)	0.076	0.307
Spleen size (cutoff of >130 mm)	3 (21.4%)	14 (58.3%)	0.083	0.3
Portal vein size ( cut off of >13 mm)	4 (33.33%)	18 (75%)	<b>0.029</b>	0.374
Platelet count/ spleen size ratio (cutoff of <909)	6 (50%)	23 (95.83%)	<b>0.003</b>	<b>0.479</b>
APRI index (cutoff >1.3)	6 (50%)	21 (87.5%)	<b>0.036</b>	0.378

**Table 4: Diagnostic features of Non-endoscopic predictors for the presence of esophageal varices**

Predictors	Sensi- tivity	Speci- ficity	PPV	NPV	PLR	NLR	Corre- lation coef- ficient
Platelet count (cutoff of <100000/ mm3)	38.39%	85.71%	87.5%	35.29%	2.72	0.71	0.23
Spleen size (cutoff of >130 mm)	47.22%	64.29%	77.27%	32.14%	1.32	0.82	0.104
Portal vein size ( cut off of >13 mm)	61.11%	78.57%	88%	44%	2.85	0.49	0.336
Plateletcount/ spleen size ratio (cutoff of <909)	80.56%	85.71%	93.55%	63.16%	5.64	0.23	<b>0.523</b>
APRI index (cutoff >1.3)	75%	64.35%	84.38%	50%	2.1	0.39	0.345

PPV- positive predictive value, NPV – negative predictive value,  
PLR- positive likelihood ratio, NLR- negative likelihood ratio

**Table 5: Diagnostic features of Non-endoscopic predictors for the presence of large varices**

Predictors	Sensi- tivity	Speci- ficity	PPV	NPV	PLR	NLR	Corre- lation coef- ficient
Platelet count (cutoff of <100000/ mm3)	50%	83.33%	85.71%	45.45%	3	0.6	0.307
Spleen size (cutoff of >130 mm)	58.3%	75%	82.35%	47.3%	2.33	0.56	0.3
Portal vein size ( cut off of >13 mm)	75%	66.67%	81.82%	57.14%	2.25	0.38	0.374
Plateletcount/ spleen size ratio (cutoff of <909)	95.83%	50%	79.31%	85.71%	1.92	0.08	<b>0.479</b>
APRI index (cutoff >1.3)	87.5%	50%	77.78%	66.67%	1.75	0.25	0.378

PPV- positive predictive value, NPV – negative predictive value,  
PLR- positive likelihood ratio, NLR- negative likelihood ratio

**DISCUSSION**

Severe upper gastrointestinal bleeding as a complication of portal hypertension develops in about 30-40% of patients with cirrhosis. Due to the increasing prevalence of chronic liver diseases, variceal hemorrhage is associated with significant morbidity, mortality, and health care costs. Numerous studies have demonstrated the efficacy of pharmacotherapy for primary prevention of variceal bleeding in patients with high-risk varices indicating the importance of screening for the presence of esophageal varices.

Although this study had a small sample population, based on the inferred results, the use of Platelet count/Spleen diameter ratio and Portal vein size showed a good result and high yield in predicting esophageal varices and thereby presence of large varices in cirrhosis patients. The use of this strategy of non-endoscopic parameters would necessarily lower the cost of management of cirrhotic patients since no additional expense would be entailed with the use of ultrasonography and routine hematological and biochemical tests. As the yearly incidence of esophageal varices in patients with cirrhosis is approximately 5%, it is felt that the use of non-invasive non endoscopic diagnostic modality would provide an affordable alternative to detection of esophageal varices.

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