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Original Research Article

The Role of Aspartate Aminotransferase to Platelet Ratio Index as a Non-Invasive Predictor of Variceal Etiology of Upper Gastrointestinal Bleeding

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ABSTRACT:

Introduction: Non-invasive strategies to predict variceal from non-variceal bleeding will be highly beneficial for preemptive management of Upper Gastrointestinal Bleeding (UGIB). This study aimed to assess the role of aspartate aminotransferase (AST) to platelet ratio index (APRI) as a non-invasive predictor of variceal etiology of UGIB. **Methods:** This was a retrospective descriptive study conducted at Endoscopy Department of Dhulikhel Hospital between January 2017 and December 2019 in patients presenting with acute UGIB. We assessed the diagnostic utility of the APRI score relative to other objective measures by Area Under the Receiver Operating Characteristic (AUROC) curve analysis. **Results:** A total of 158 patients with history of UGIB were included in the study. There were total 123 males (77.8%) and the mean age of the patients was 50.3±16.1 years. The APRI score performed well in predicting a variceal etiology of acute UGIB, with AUROC 0.9. When APRI was used at cut-off of 1.3, it had a sensitivity of 84.1% and specificity of 76.8%, a positive predictive value of 70.7% and a negative predictive value of 89.9% while predicting variceal etiology of UGIB at presentation. The relative risk of varices at an APRI cut-off of 1.3 is 17.5 with a p-value of <0.0001. **Conclusion:** The present study highlighted that APRI score can be used as an objective metric that helps to predict a variceal etiology of acute UGIB.

Keywords: Aspartate aminotransferase, Gastrointestinal bleeding, Platelets, Variceal bleeding

INTRODUCTION:

Cirrhosis is characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.[1] The prevalence of esophageal varices (EV) in cirrhotics is between 60 and 80%.[2] Mortality rate due to variceal bleeding episode is about 10-20% and the life expectancy is around 63%.[3,4]

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Till date proton pump inhibitor remains the mainstay of treatment for non-variceal bleeding.[5] In contrast, for variceal hemorrhage, medical management mainly involves intravenous vasoactive therapy (octreotide and terlipressin), intravenous antibiotics (third generation cephalosporins) and guarded blood transfusion.[6] Evidence also supports benefits of early endoscopy for variceal bleed but not as much for non-variceal bleed.[7,8]

Aspartate aminotransferase to Platelet Ratio Index (APRI), was initially introduced as a measure to quantify fibrosis of the liver in patients with Hepatitis C, however today it has been established

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as a marker of cirrhosis and portal hypertension in many studies.[9,10] APRI can hence also act as a good non-invasive method for the screening of variceal bleeding in acute setting of Upper Gastrointestinal Bleeding (UGIB) and direct us towards early management before definite diagnosis is established with endoscopy.

METHODS:

This was a hospital based retrospective descriptive study conducted from January 2017 to December 2019. All patients presenting with features suggestive of UGIB in the out-patient and emergency department (ED) were included in the study. The patients with no documented complaints of overt gastrointestinal (GI) bleeding, in whom endoscopy was not performed during admission, and with incomplete medical records were excluded from the study. Questionnaire included variables such as age, gender, ethnicity, history of malena, hematemesis, hematochezia, cirrhosis / portal hypertension, endoscopic diagnosis, biochemical levels of aspartate aminotransferase (AST) , alanine aminotransferase (ALT) and platelet count. Patients who presented with repeated UGIB due to the same underlying etiology were included only once. Prior ethical approval was taken from Institutional Review Committee (IRC) of Dhulikhel Hospital, Kathmandu University hospital (IRB: 291/19). APRI was calculated using first available ED data as following: [9]

APRI = [AST level / AST-upper limit X platelet count (10^9/L)] X 100

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS™) 20.0 software for windows. We used Area Under the Receiver Operating Characteristics Curve (AUROC) as the measure of relative diagnostic accuracy in comparing tests. Deviations from the null hypothesis with a probability of $p<0.05$ were considered significant.

RESULTS:

There were 283 presentations with UGIB out of which 158 cases met the inclusion criteria and were included in the study. The mean age of the study population was 50.3±16.1 years, with a range of 4-86 years. The age group 40-60 years included 76 (47.8%) patients. There was a male predominance with 123 (77.8%) patients. The predominant ethnic groups included Tamang (n=44, 27.4%), Newar (n=42, 26.6%) and Brahmin/Chettri (n=37, 23.4%).

Table 1. Clinical Variables of the Study Population (N=158).

Clinical variables	Category	Frequency (%)
Malena	Absent	50 (31.6)
	Present	108 (68.4)
Hematemesis	Present	133 (84.2)
	Absent	25 (15.8)
Hematochezia	Absent	151 (95.6)
	Present	7 (4.4)
History of Cirrhosis / Portal Hypertension	Absent	108 (68.4)
	Present	50 (31.6)
Endoscopic diagnosis	Variceal	63 (39.9)
	Non-variceal	95 (60.1)
ALT (IU/L)	≤56	101 (63.9)
	>56	57 (36.1)
AST (IU/L)	≤40	55 (34.8)
	>40	103 (65.2)
Platelets / cumm	≤150000	68 (43)
	150000-450000	88 (55.7)
	>4500000	2 (1.3)

Table 2. Causes of Non Variceal Bleeding (N=95).

Causes	Frequency (%)
Gastric Ulcer	22 (23.2)
Duodenal Ulcer	21 (21.1)
Gastroduodenitis	19 (20)
Malory Weiss Tear	13 (13.7)
Esophagitis/esophageal Ulcer	8 (8.4)
Gastric Carcinoma	4 (4.2)
GAVE (Gastric Antral Vascular Ectasia)	3 (3.2)
Polyp bleed	3 (3.2)
Deulafoy's Lesion	2 (2.1)
Total	95 (100)

Table 1 represents the clinical variables among the study population. Upon review of all available data including endoscopy reports, we classified 63 (39.9%) cases as variceal UGIB and 95 (60.1%) as non-variceal UGIB. Of the patients with clinical features of chronic liver disease (CLD), 40 (80%) had variceal bleeding, nine (18%) had non-variceal bleeding, and one (2%) had unknown source of bleed. In contrast, among patients without clinical features of CLD 23 (21.3%) had variceal bleeding, 79 (73.1%) had non-variceal bleeding, and six (5.6%) had unknown source of bleed. Table 2 represents the causes of non-variceal bleeding.

We plotted sensitivity versus specificity over a range of possible cut-off values for each score to generate a receiver operating characteristic (ROC) curves comparing the performance of APRI score (Table 3). When APRI was used at cut-off of 1.3, it had a sensitivity of 84.1% and specificity of 76.8%, a positive predictive value (PPV) of 70.7% and a negative predictive value (NPV) of 89.9% while predicting variceal etiology of UGIB at presentation. The relative risk of varices at an APRI cut-off of 1.3 is 17.5 with a p-value of <0.0001 (Table 4).

Table 4. Relative risk at APRI score of 1.3.

Cut-off	Endoscopic findings		RR	p value
	Variceal	Non-variceal		
>1.2	53	22	17.5	<0.0001
<=1.2	10	73		

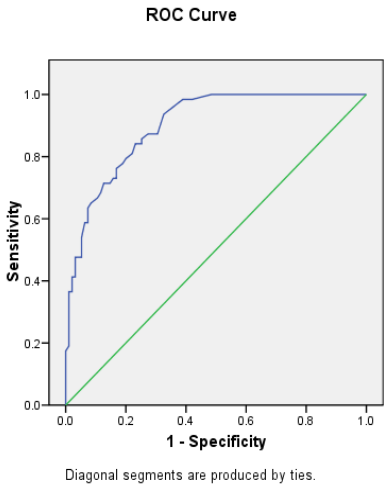

Figure 1. ROC curve (AUC=0.90).

Other cutoff points were also tested, but none of them could reach a significantly better positive and negative predictive value. Considering all patients presenting with apparent UGIB, we found that APRI had good performance in discriminating between variceal versus non-variceal UGIB with AUROC of 0.9 (Figure 1). An ideal test is associated with AUROC of 1.0 and with an AUROC of 0.9 the APRI score would be considered to have very good to excellent performance.[11]

DISCUSSION:

Variceal bleeding is one of the most dramatic and fatal complications of cirrhosis. The prevalence of esophageal varices (EV) in cirrhotics is highly

Table 3. Sensitivity, Specificity, PPV and NPV of APRI Score At Different Cut Offs Levels (FN = False Negative; TN = True Negative; TP = True Positive; FP = False Positive).*

APRI cut-off levels	Endoscopic finding		Sensitivity	Specificity	PPV	NPV
	Variceal	Non-variceal				
<=0.5	1(FN)	55 (TN)	98.5	57	60.7	98.2
>0.5	62 (TP)	40 (FP)				
<=1	9	71	85.70%	74.7	69.2	88.8
>1	54	24				
<=1.1	10	71	84.1	74.7	68.8	87.7
>1.1	53	24				
<=1.2	10	73	84.1	76.8	70.7	89.9
>1.2	53	22				
<=1.3	12	74	80.9	77.9	70.8	86.0
>1.3	51	21				

variable.[2] Even in known cirrhotic patients presenting with UGIB, non variceal etiology of bleeding has to be ruled out because of difference in their management. For variceal bleeding evidence suggests early endoscopy along with intravenous vasoactive drugs, antibiotics and guarded blood transfusion.[6,7,8] Whereas proton pump inhibitors remain the mainstay of treatment for non-variceal bleeding.[5] Hence, the prediction of variceal bleeding in the Emergency Department (ED) will help in the management of patients with UGIB before the definite diagnostic and therapeutic endoscopy is performed.

The APRI score is easily calculated from routinely collected laboratory data available early in the ED setting. Shaheen et. al. reported that in patients with chronic hepatitis C, APRI score < 0.5 had a negative predictive value (NPV) of 72%, while the APRI score >1.5 had a positive predictive value (PPV) of 87% for prediction of fibrosis.[12]Wai CT et al. in their study had a conclusion that APRI score can predict accurately significant fibrosis and cirrhosis in 51% and 81% respectively, potentially avoiding the need for liver biopsies in patients.[9] The first authors to raise the hypothesis that APRI could be related to the presence of EV were Sanyal et al.[13] They examined 1,016 patients with compensated liver cirrhosis and reported a correlation between APRI score and the presence of esophageal varices (p=0.01). Later Castéra, et al. proposed the cutoff of 1.3 for APRI as a predictor of EV.[14]

While plotting the sensitivity, specificity, PPV and NPV of APRI score at different cut off levels, we also found that cut-off at 1.3 had a very good NPV. (Table 3) For a non-invasive test like APRI to be considered helpful in the studied context, it should have a great negative predictive value, as misdiagnosing variceal bleeding as not having EV is a risk for major complication. The mortality of variceal bleeding in different studies is around 15%.[15] Clinical signs and symptoms of cirrhosis prompting suspicion for a variceal etiology can be unreliable.[16] In this study, we found that the APRI score performed well as measured by ROC analysis with an AUROC of 0.9 in predicting a variceal etiology of acute UGIB. Thus, the APRI score represents an objective measure that could be used to guide early management decisions for UGIB patients while awaiting endoscopy.

A study by Civan et al., concluded that a clinical decision rule based on APRI improves adherence to published guidelines on the management of acute variceal bleeding using the prophylactic antibiotics and somatostatin analogues.[17] The APRI cutoff value of 0.4 was used in their clinical decision rule which is lower than the cutoffs reported in other studies. The reason for low cut-off value of APRI used in this study according to the authors was their reflection of their prioritization of sensitivity over specificity, and led them to design a clinical decision rule with a positive predictive value of 0.33 and negative predictive value of 0.98.

In this study, at APRI cut-off of 0.4 we had PPV of 0.61 and NPV of 0.98 that is an increased NPV compared to APRI cut-off at 1.3. Low PPV will increase the number of patients without varices receiving antibiotics and somatostatin analogues. Octreotide is very well tolerated and a brief course in patients without varices will not cause increased morbidity.[18] Unnecessary courses of antibiotics however might cause an increase in *Clostridium difficile* infection. Both these factors also will increase the cost of treatment which has to be taken into account especially in developing country like ours. At APRI cut-off of 1.3 however there is a good sensitivity and specificity without significantly compromising either of the PPV and NPV values (Table 3).

CONCLUSION:

The present study found that the APRI score could serve as a useful objective measure to identify variceal etiology of bleeding in UGIB patients. Patients presenting with apparent acute UGIB with APRI score of more than or equal to 1.3 can be managed in the line of variceal bleed before definite endoscopic diagnosis.

Conflict of Interest:

The authors declare that no competing interests exist.

Financial disclosure:

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