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# Role Of Aspartate Aminotransferase To Platelet Ratio Index As A Non-Invasive Predictor Of Variceal Aetiology

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## Abstract

**Objective:** To determine the diagnostic accuracy of the aspartate aminotransferase to Platelet ratio index as an indicator of upper gastrointestinal bleeding, taking endoscopy as the gold standard.

**Methodology:** A cross-sectional validation study was conducted in the Department of Medicine, Unit I, Benazir Bhutto Hospital, Rawalpindi, from September 25, 2022, to March 24, 2023. A total of 350 patients aged 16-75 years, both genders, diagnosed with cirrhosis were included. Then a blood sample was taken in a 3cc disposable syringe. Reports were assessed, and APRI was calculated. The patient was labelled as positive or negative. Then the patient underwent upper gastrointestinal endoscopy within 24 hours of admission, and the patient was labelled as positive or negative based on endoscopy findings.

**Results:** Aspartate aminotransferase - Platelet Ratio Index overall sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy as a predictor of upper gastrointestinal bleeding requiring endoscopy were 93.24%, 91.60%, 94.15%, 90.34%, and 92.57%, respectively.

**Conclusion:** The Aspartate Aminotransferase Platelet Ratio Index (APRI) has a fairly high diagnostic accuracy for variceal bleeds.

**Keywords:** variceal bleed, Aspartate Aminotransferase, Cirrhosis, portal hypertension.

## Introduction

Cirrhosis is the most common cause of portal hypertension. Typical clinical consequence in people with liver cirrhosis is the progression of oesophageal varices. Oesophageal varices (EV) have a considerable morbidity and death rate of 60 to 80% in cirrhotic patients. Variceal bleed is a haemorrhage which can occur from the upper gastrointestinal tract proximal to the Treitz ligament. Hematemesis is seen in 40–50% of UGIB patients, while melena or hematochezia is present in 90–98% of cases. The second cause of mortality in cirrhosis is variceal bleeding, which is 30% more common in compensated cirrhosis as compared to 60% in decompensated cirrhosis.[2]
Within a year of diagnosis, approximately 30% of these patients will have an episode of variceal haemorrhage.[3] The 6-week mortality rate for a single variceal bleed incident varies from 0–30% in patients with Child Class A and Child Class C illness, respectively.[4] The main method for monitoring, treating, and assessing the risk of bleeding from oesophageal varices is esophagogastroduodenoscopy. Universal oesophageal varices screening by endoscopy for cirrhosis is advised by guidelines for patients with the disease.[2] Several non-invasive scores have been demonstrated to be useful in predicting the expected survival (EV) in cirrhotic patients. Aspartate aminotransferase (AST)-alanine aminotransferase (ALT) ratio (AST/ALT), AST - Platelet ratio index (APRI), fibrosis-4-index (FIB-4), fibrosis index (FI), and King's score are all included in the MELD (model for end-stage liver disease).[3] When determining whether to treat severe oesophageal varices early on, APRI > 1.4 can serve as a reference indicator.[4] According to reports, APRI showed 84.1% sensitivity, 76.8% specificity, 70.7% positive predictive value, and 89.9% negative predictive value when it came to predicting the variceal aetiology of upper gastrointestinal bleeding.[1] According to a different study, the APRI's sensitivity for EV prediction

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H.A, K.N, A.A, M.R.M, K.S, L.M - Conception of study - Experimentation/Study Conduction
H.A, K.N, A.A, M.R.M, K.S, L.M - Analysis/Interpretation/Discussion
H.A, K.N, A.A, M.R.M, K.S, L.M - Manuscript Writing
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in cirrhosis patients was 64.7%, whereas their negative predictive value (NPV) was only 43.2%.[5] While one study reported that APRI demonstrated a diagnostic accuracy of 72 % for variceal bleeding.[6]

APRI's sensitivity, specificity, and accuracy were found to be 78.3%, 32.7%, and 60.7%, respectively. In another investigation,[7] APRI's diagnostic accuracy, positive predictive value, and negative predictive value were 65.0%, 48.5%, and 60.7%. Determining the diagnostic accuracy of APRI as a noninvasive indicator of upper gastrointestinal bleeding was the purpose of this investigation. Recently, the World Health Organisation suggested using non-invasive markers to identify oesophageal varices as a potential source of upper gastrointestinal bleeding. APRI is a reliable and sound marker in various contexts. However, the literature highlights variability in its accuracy rates. Additionally, no prior studies have been conducted in Pakistan to evaluate the use of APRI as a non-invasive tool for detecting oesophageal varices, particularly in cases where endoscopy results are negative. The study was undertaken to generate evidence specific to the local population, aiming to replace invasive diagnostic methods with APRI in suitable cases. The findings of the study will not only help improve clinical practice but also provide a basis for recommending the implementation of this non-invasive test in the local healthcare setting.

**Objectives:** To determine the diagnostic accuracy of the aspartate aminotransferase to Platelet ratio index as an indicator of upper gastrointestinal bleeding

**Operational Definitions**

Aspartate aminotransferase to Platelet Ratio Index (APRI): Aspartate aminotransferase to platelet ratio index (APRI) was calculated as below. Varices: On the APRI scale, it was labelled as positive if APRI ≥1.3 was noted and was labelled as negative when

$$APRI = \frac{\frac{AST\ (IU/L)}{AST(upper\ limit\ of\ normal)}}{Platelet\ count\ (10^9/L)} \times 100$$

**Varices:** On the APRI scale, it was labelled as positive if APRI ≥1.3 was noted and was labelled as negative when APRI <1.3 was noted. On endoscopy, oesophageal varices grade ≥ 1 or gastric varices were labelled as positive, while grade 0 was labelled as negative.

**Oesophageal varices grading**: Grading of varices was done as below, according to adapted Paquet and Palmer, and Brick endoscopic criteria.

| Grade | Endoscopic findings |
|---|---|
| **0** | Absence of oesophageal varices |
| **I** | Micro vessels that sketch varicose veins are located in the esophagogastric transition or the distal oesophagus. |
| **II** | One/two fine-calibre varices (smaller than 3 mm diameter) located in the distal oesophagus |
| **III** | Thick calibre varices, larger than 6 mm in diameter, in any part of the oesophagus |
| **IV** | Medium calibre varices (between 3- or 6-mm diameter) or more than varices up to 3 mm that may reach up to a third of the oesophagus |

**Gastric varices:** Gastric varices were graded according to the Sarin classification

| Grade | Classification |
|---|---|
| **Gastroesophageal varix type 1 (GOV1)** | Extension of oesophageal varices along the lesser curvature |
| **Gastroesophageal varix type** | Extension of oesophageal varices along the greater curvature |
| **Isolated gastric varix type1 (IGV1)** | Isolated Varices in the gastric fundus, and they do not extend into the oesophagus or cardia |
| **Isolated gastric varix type2 (IGV2)** | Ectopic gastric varices that occur in other parts of the stomach |

**True positive:** when the case is positive on both APRI and endoscopy.
**True negative:** when the case is negative on both APRI and endoscopy.
**False positive:** when the case is positive on APRI but negative on endoscopy.
**False negative:** when the case is negative on APRI but positive on endoscopy.
**Sensitivity**: Measures the ability of a test to detect the condition when the condition is present.
**Specificity**: Measures the ability of a test to correctly exclude the condition when the condition is absent.
**Positive Predictive Value**: It is the proportion of positives that corresponds to the presence of the condition.
**Negative Predictive Value**: It is the proportion of negatives that corresponds to the absence of the condition.

## Materials And Methods

The cross-sectional validation study was conducted in the Department of Medicine Unit I, Benazir Bhutto Hospital, Rawalpindi, from 25th September 2022 to 24th March 2023. The technique was Non-probability, consecutive sampling. A total of 350 patients aged 16-75 years, both genders, diagnosed with cirrhosis were included. Patients who have already undergone a previous intervention for portal hypertension, like portosystemic shunts, portal vein thrombosis, intra-abdominal, hepatic, or extrahepatic malignancy, and hepatocellular carcinoma, were excluded. Then, a blood sample was taken in a 3cc disposable syringe. All samples were sent to the laboratory of the hospital for assessment of AST and platelet count. Reports were assessed, and APRI was

calculated. The patient was labelled as positive or negative predictive values. Then the patient underwent upper gastrointestinal endoscopy within 24 hrs. of admission, and the patient was labelled as positive or negative based on endoscopy findings. 350 patients fulfilling the selection criteria were included in this study from the Emergency Department of Medicine, Benazir Bhutto Hospital, Rawalpindi. Informed consent was obtained from each case. Demographic information, including name, age, gender, BMI, diabetes (BSR>200 mg/dl), hypertension (BP≥140/90mmHg), h/o smoking (>5 pack years), hepatitis B/C, duration of cirrhosis, and Child-Pugh grade, was also noted.

All the information was recorded on a pro forma. Data was entered and analysed through SPSS version 23. Quantitative variables like age, BMI, duration of cirrhosis, AST, platelet count, and APRI score were presented as mean and standard deviation. Qualitative variables like gender, diabetes, hypertension, smoking, h/o hepatitis B/C, Child-Pugh grade, liver fibrosis grade, and variceal bleed (on APRI and endoscopy) were presented as frequency and percentage. A 2x2 table was generated to calculate sensitivity, specificity, PPV, NPV and diagnostic accuracy of APRI, taking endoscopy as the gold standard. Data was stratified for age, gender, BMI, diabetes, hypertension, smoking, duration of cirrhosis, hepatitis B/C and Child-Pugh class. Post-stratification, the diagnostic accuracy of APRI was calculated for each group. A sample size of 350 patients is calculated with a 95% confidence level, percentage of oesophageal varices, i.e. 80% [1], sensitivity of APRI, i.e. 84.1%[1,] with a 15% margin of error and specificity of APRI, i.e. 76.8% [1,] with a 10% margin of error.

| | ENDOSCOPY | | ENDOSCOPY | |
|---|---|---|---|---|
| | POSITIVE | NEGATIVE | POSITIVE | NEGATIVE |
| APRI | =1.3 | | True Positive | False positive |
| | <1.3 | | False Negative | True Negative |

## Results

Out of 350 patients, 207(59.14%) were males, as well as 143 (40.86%) were females, with a ratio of 1.4:1, having Age ranges 16-75 years with a mean age of 44.89 ± 9.33 years. The mean duration of cirrhosis was 6.91±1.74 months. Mean BMI was 28.56 ± 3.23 kg/m2. According to the distribution of patients concerning confounding variables, diabetes was observed in 158(45.14%, Hypertension in 113(32.29%), smoking in 85(24.29%), hepatitis B in 150(42.86%), and Hepatitis C in 200(57.14%). As per Child-Pugh classification, 74(21.145) were class-A, 142(42.17%) were class-B and 134(38.29%) were class-C).

**Table 1: Stratification of diagnostic accuracy according to Aspartate aminotransferase to Platelet Ratio Index, Hepatitis B & C serology, Child-Pugh class (n=350).**

| Stratification for hepatitis serology and Child-Pugh class | Positive onendoscopy | Negative onendoscopy | P-value |
|---|---|---|---|
| **Aspartate Aminotransferase to Platelet Ratio Index** | | | |
| • **Positive result onAPRI** | 193 (TP)* | 12 (FP)*** | **0.0001** |
| • **Negative result onAPRI** | 14 (FN)** | 131 (TN)**** | |
| **Sensitivity 93.24%, Specificity 91.6%, PPV 94.15%, NPV 90.34%, Diagnostic Accuracy 92.57%** | | | |
| **Hepatitis B(n=150).** | | | |
| • **Positive result onAPRI** | 89 (TP) | 11 (FP) | **0.001** |
| • **Negative result onAPRI** | 01 (FN) | 49 (TN) | |
| **Sensitivity 98.89%, Specificity 81.67%, PPV 89%, NPV 98.0%, Diagnostic Accuracy 92%** | | | |
| **Hepatitis C(n=200).** | | | |
| • **Positive result onAPRI** | 104 (TP) | 01 (FP) | **0.001** |
| • **Negative result onAPRI** | 13 (FN) | 82 (TN) | |
| **Sensitivity 88.89%, Specificity 98.8%, PPV 99.05%, NPV 86.32%, Diagnostic Accuracy 93%** | | | |
| **Child-Pugh class A (n=74).** | | | |
| • **Positive result onAPRI** | 35 (TP) | 07 (FP) | **0.001** |
| • **Negative result onAPRI** | 00 (FN) | 32 (TN) | |
| **Sensitivity 100%, Specificity 82.05%, PPV 83.33%, NPV 100%, Diagnostic Accuracy 90.54%** | | | |
| **Child-Pugh class B (n=142).** | | | |
| • **Positive result onAPRI** | 72 (TP) | 03 (FP) | **0.001** |
| • **Negative result on APRI** | 12 (FN) | 55 (TN) | |
| **Sensitivity 85.71%, Specificity 94.83%, PPV 96%, NPV 82.09%Diagnostic Accuracy 89.44%** | | | |
| **Child-Pugh class C (n=134).** | 86 (TP) | 02 (FP) | |
| • **Positive result onAPRI** | | | **0.001** |
| • **Negative result onAPRI** | 02 (FN) | 44 (TN) | |
| **Sensitivity 97.73%, Specificity 95.65%, PPV 97.73%, NPV 95.65%, Diagnostic Accuracy: 97%** | | | |

**-TP=True positive **-FN=False negative ***-FP=False positive ****-TN=True negative*

**Table 2: Stratification of diagnostic accuracy according to age, gender and duration of cirrhosis (n=350).**

| Stratification for age, gender and duration of cirrhosis | Positive onendoscopy | Negative on endoscopy | P-value |
|---|---|---|---|
| **Age 16-45 years (n=175)** | | | |
| • **Positive result onAPRI** | 90 (TP) | 10 (FP) | **0.001** |
| • **Negative result onAPRI** | 07 (FN) | 68 (TN) | |
| **Sensitivity 92.78%, Specificity 87.18%, PPV 90.0%, NPV 90.67%, Diagnostic Accuracy: 90.29%** | | | |
| **Age 46-75 years** | | | |
| • **Positive result onAPRI** | 103 (TP) | 02 (FP) | **0.001** |
| • **Negative result onAPRI** | 07 (FN) | 63 (TN) | |
| **Sensitivity 93.64%, Specificity 96.92%, PPV 98.10%, NPV 90%, Diagnostic Accuracy 94.86%** | | | |
| **For Male Gender** | | | |
| • **Positive result onAPRI** | 118 (TP) | 01 (FP) | **0.001** |
| • **Negative result onAPRI** | 06 (FN) | 82 (TN) | |
| **Sensitivity 95.16%, Specificity 98.8%, PPV 99.16%,NPV 93.18%, Diagnostic Accuracy 96.62%** | | | |
| **For Female gender (n=143)** | | | |
| • **Positive result onAPRI** | 75 (TP) | 11 (FP) | **0.001** |
| • **Negative result onAPRI** | 08 (FN) | 49 (TN) | |
| **Sensitivity 90.36%, Specificity 81.67%. PPV 87.21%, NPV 85.96%, Diagnostic Accuracy 86.71%** | | | |
| **Cirrhosis for ≤6 months (n=137).** | | | |
| • **Positive result onAPRI** | 54 (TP) | 03 (FP) | **0.001** |
| • **Negative result onAPRI** | 06 (FN) | 74 (TN) | |
| **Sensitivity 90%, Specificity 96 %, PPV 94.74%, NPV 92.5%, Diagnostic Accuracy: 93.43%** | | | |
| **Cirrhosis for >6 months (n=213).** | | | |
| • **Positive result onAPRI** | 139 (TP) | 09 (FP) | **0.001** |
| • **Negative result onAPRI** | 08 (FN) | 57 (TN) | |
| **Sensitivity 94.56%, Specificity 86.36%, PPV 93.92%, NPV 87.69%, Diagnostic Accuracy 92.02%** | | | |

**Table 3: Stratification of diagnostic accuracy according to BMI, diabetes, hypertension and smoking history (n=350).**

| Stratification for BMI, Diabetes, hypertension and smoking | Positive onendoscopy | Negative onendoscopy | P-value |
|---|---|---|---|
| **BMI ≤30 kg/m$^2$ (n=218).** | | | |
| • **Positive result onAPRI** | 119 (TP) | 06 (FP) | **0.001** |
| • **Negative result onAPRI** | 13 (FN) | 80 (TN) | |
| **Sensitivity 90.15%, Specificity 93.02%, PPV 95.2% NPV 86.02%,Diagnostic Accuracy: 91.28%** | | | |
| **BMI >30 kg/m$^2$ (n=132).** | | | |
| • **Positive result onAPRI** | 74 (TP) | 06 (FP) | **0.001** |
| • **Negative result onAPRI** | 01 (FN) | 51 (TN) | |
| **Sensitivity 98.67%, Specificity 89.47%, PPV 92.50%, NPV 98.08%, Diagnostic Accuracy: 94.7%** | | | |
| **Diabetic (n=158).** | | | |
| • **Positive result onAPRI** | 90 (TP) | 03 (FP) | **0.001** |
| • **Negative result onAPRI** | 06 (FN) | 59 (TN) | |
| **Sensitivity 93.75%, Specificity 95.16%, PPV 96.77%, NPV 90.77%, Diagnostic Accuracy 94.3%** | | | |
| **Non diabetic (n=192)** | | | |
| • **Positive result onAPRI** | 103 (TP) | 09 (FP) | **0.001** |
| • **Negative result onAPRI** | 08 (FN) | 72 (TN) | |
| **Sensitivity 92.79%, Specificity 88.89%, PPV 91.96%, NPV 90%, Diagnostic Accuracy: 91.15%** | | | |
| **Hypertensive (n=113).** | | | |
| • **Positive result onAPRI** | 75 (TP) | 05 (FP) | **0.001** |
| • **Negative result onAPRI** | 00 (FN) | 33 (TN) | |
| **Sensitivity 100%, Specificity 86.84%, PPV 93.75%, NPV 100%,Diagnostic Accuracy 95.57%** | | | |
| **Non-Hypertensive (n=237).** | | | |
| • **Positive result onAPRI** | 118 (TP) | 07 (FP) | **0.001** |
| • **Negative result onAPRI** | 14 (FN) | 98 (TN) | |
| **Sensitivity 89.39%, Specificity 93.33%, PPV 94.4%, NPV 87.5%, Diagnostic Accuracy 91.14%** | | | |
| **Smoking(n=85)** | | | |
| • **Positive result onAPRI** | 46 (TP) | 03 (FP) | **0.001** |
| • **Negative result onAPRI** | 00 (FN) | 36 (TN) | |
| **Sensitivity 100 %, Specificity 92.3%, PPV 93.88%, NPV 100%, Diagnostic Accuracy 96.47%** | | | |
| **No smoking(n=265).** | 147 (TP) | 09 (FP) | |
| • **Positive result onAPRI** | | | **0.001** |
| • **Negative result onAPRI** | 14 (FN) | 95 (TN) | |
| **Sensitivity 91.3%, Specificity 91.35%, PPV 94.23%, NPV 87.16%, Diagnostic Accuracy 91.32%** | | | |

Twelve False Positives and 193 True Positives have been discovered. The 145 APRI negative patients, 14 (False Negative) had variceal bleeding and 131 (True Negative) had no variceal bleeding (p=0.0001). As a predictor of the variceal aetiology of upper gastrointestinal bleeding requiring endoscopy, APRI Index had overall sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of 93.24%, 91.60%, 94.15%, 90.34%, and 92.57%, respectively. ***(Table 1).*** The Stratification of diagnostic accuracy according to BMI, diabetes, hypertension, smoking history, age, gender and duration of cirrhosis are presented in Tables 2 and 3.

## Discussion

Esophageal varices (EV) affect 60–80% of people with cirrhosis.[7,8] The mortality rate from variceal haemorrhage episodes is approximately 10-20%, whereas the approximate life expectancy is 63%.[9] Proton pump inhibitors continue to be the cornerstone of care for bleeding that is not variceal.[10] In contrast, intravenous vasoactive treatment (terlipressin and octreotide), intravenous (IV) antibiotics, and blood product (PLT) transfusions are the mainstays of medical management for variceal haemorrhage.[11] Evidence also favours early endoscopy in cases of variceal haemorrhage, though less in cases of non-variceal haemorrhage.[12] APRI were developed to detect the amount of fibrosis in patients with Hepatitis C. Nevertheless, numerous studies have since shown that APRI is also a reliable predictor of cirrhosis.[13] This investigation used endoscopy as the gold standard to assess the diagnostic accuracy of APRI as an indicator of upper gastrointestinal bleeding. Upper gastrointestinal bleeding requiring endoscopy, APRI had overall sensitivity, specificity, positive and negative predictive value as well as diagnostic accuracy of 93.24%, 91.60%, 94.15%, 90.34%, and 92.57%, respectively. It has been reported that when APRI was ≥ 1.3, having 84.1% sensitivity, 76.8% specificity, 89.9% NPV, and 70.7% PPV, indicating upper gastrointestinal bleed.[1] Another study reported that the APRI in cirrhotic patients demonstrated a sensitivity of 64.7% and NPV of only 43.2% for predicting Esophageal variceal.[14,15] However, according to one study, APRI showed a 72% diagnosis accuracy for variceal bleed. Six APRI's specificity, sensitivity, and accuracy were found to be 78.3%, 32.7%, and 60.7%, respectively. In another investigation,[7] APRI's diagnostic accuracy, positive predictive value, and negative predictive value were 65.0%, 48.5%, and 60.7%.[16,17]

An APRI score of 0.4 was utilised in a study by Civan and his colleagues to direct the early care of an acute upper gastrointestinal bleed.[9] Comparably, a different investigation with a value of ≥1.0 revealed that while imagining EV, the corresponding sensitivity, specificity, PPV, and NPV were 68%,89%,77%, and 83%.[10] The first authors reported the possibility of APRI associated with the appearance of Oesophagal Varices were Sanyal et al.[12] While they looked at 1,016 compensated cirrhotic patients and found a relationship with APRI score and oesophagal varices (p=0.01). Later, Castéra et al. proposed the cutoff point. Shaheen et al. reported that the APRI score of 0.5 in compensated C patients had a 72% NPV, while the APRI score >1.5 had a PPV. Abdel Aziz M et al., showed in a Meta-analysis that an APRI threshold of 0.5 provided an 80% negative predictive value (NPV), was 81% sensitive, and 50% specific in chronic viral hepatitis C (CHC) at a 40% prevalence of severe fibrosis. For cirrhosis and severe fibrosis, the AUCs of the APRI were 0.76 [95% CI: 0.74-0.79] and 0.82 [95% CI: 0.79-0.86], in that order. An NPV of 91% was associated with a 1.0 threshold for cirrhosis, which was 76% specific and 76% sensitive at a 15% prevalence of the disease. The primary benefit of the APRI is its capacity to rule out severe fibrosis caused by HCV.[14]

In addition, Tafarel et al. observed a link (p = 0.02) between the APRI score and oesophageal varices in 300 liver cirrhotic patients.[13] Sanyal et al. studied 1,016 compensated liver cirrhotic patients in 2006 and found a significant (p = 0.01) association between the APRI score and the existence of oesophageal varices. Sebastian et al. found a good connection (APRI = 1.4, sensitivity 54%, specificity 69%) between the APRI score and the existence of oesophageal varices (15–17).[16]

Ucar and colleagues compared other blood indicators; APRI has been shown to have superior diagnostic value in severe fibrotic patients.[18-21] A Study conducted by Dr SK Sareen et al included 74 professed HVPG and APRI showed a significant connection (p¼=0.001; Spearman's rho = 0.365). The area under the curve (ROC) for APRI's performance in predicting high portal pressure (HVPG >12 mmHg) was 0.716 (95% CI 0.574 -0.858). When it came to predicting HVPG >12 mmHg at the cutoff of 1.09, APRI's sensitivity was 66%, specificity was 73%, PPV was 85%, NPV was 47%, and diagnostic accuracy was 68%. Thus, it can serve as a non-invasive, low-cost bedside marker for the identification of elevated portal pressure in cirrhotic patients. [22] APRI is a reliable marker, but its accuracy varies, and no studies in Pakistan have assessed its use for detecting oesophageal varices. This study aims to provide local evidence to replace invasive methods with APRI in appropriate cases, improving future clinical practice.

## Conclusions

Aspartate Aminotransferase Platelet Ratio Index for variceal bleed had quite high diagnostic accuracy. APRI should be used routinely for early recognition and management of variceal bleeding in CLD patients to reduce the morbidity and mortality of these patients.

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