Noninvasive predictors of large esophageal varices: is there an emerging role of aspartate aminotransferase-to-platelet ratio index in hepatocellular carcinoma?

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Background and aim

Variceal size has been identified to be closely related to variceal bleeding. Repeated endoscopic examinations have a great burden on endoscopic units and cost-implication issues. Our aim was to evaluate the role of AST to platelet ratio index (APRI) in predicting the existence of large esophageal varices (EV) in hepatitis C virus-related liver cirrhotic patients.

Patients and methods

Seventy-four patients with liver cirrhosis were prospectively recruited. Laboratory data, CTP, MELD and APRI, also ultrasonographic and endoscopic findings are performed and investigated whether associated with the size and bleeding of EV.

Results

Patients were divided into two groups; group 1 with small varices and group 2 with large varices. Group 2 had significantly prolonged prothrombin time, splenomegaly, ascites, higher Child score compared to group 1. CTP was associated with variceal bleeding (P = 0.028). While APRI was a poor predictor both for the presence of LVs and bleeding yet it revealed favorable results with bleeding EVs in patients with HCC with AUC (0.61). APRI was a good predictor for the presence of HCC and number of focal lesions with AUC (0.651, 0.61 respectively).

Conclusion

Splenomegaly, CTP, ascites could be used as noninvasive predictors for large EVs. However, at the moment, these tests could not substitute for endoscopy. Although APRI is a poor predictor for the size and bleeding of EV, yet it might have a role in prediction of HCC and number of focal lesions.

Keywords:
aspartate aminotransferase-to-platelet ratio index, esophageal varices, hepatitis C virus-related liver cirrhosis, large varices, noninvasive

Introduction

Variceal hemorrhage is the most dreaded complication in liver cirrhosis and may lead to life-threatening bleeding, particularly in the case of large esophageal varices (LEVs) [1,2]. The standard diagnostic tool for esophageal varices (EV) is endoscopy [3]. Noninvasive predictors of EVs have been assessed in various studies [4–8].

As the aspartate aminotransferase-to-platelet ratio index (APRI) is a predictor of fibrosis, it is reasonable to explore whether it could be considered a noninvasive marker for detecting EV [9].

The aim of this study was to determine the ability of APRI in predicting the existence of LEVs in hepatitis C virus (HCV)-related liver cirrhotic patients.

Exclusion criteria

Patients with previous variceal hemorrhage, prior variceal bleeding prophylaxis or treatment, (including nonselective β-blocker use, nitrates, endoscopic variceal ligation, or sclerotherapy), and those with gastrointestinal (GI) ulcerations were excluded. None was approved by the ethical committee of the Faculty of Medicine, Cairo University. Patients were fully informed about possible complications of the diagnostic procedures, and written informed consent was obtained from the patients or from a responsible family member. Seventy-four patients were included in this prospective study. The included patients were above 18 years of age with HCV-related liver cirrhosis based on clinical, biochemical, and ultrasonographic findings.
of the patients were treated with NSAIDs, antiplatelets, or anticoagulants. Patients with liver cirrhosis due to causes other that HCV and those with renal failure, portal or splenic vein thrombosis, or any associated malignancies other than hepatocellular carcinoma (HCC) were excluded as well.

Physical and clinical characteristics recorded included age, sex, and symptoms and signs of liver cell failure, with special emphasis on presentation with first attack of GI bleeding. Laboratory workup was carried out, which included measurement of hemoglobin, platelet count, alanine aminotransferase and aspartate aminotransferase (AST), prothrombin time, and international normalized ratio (INR), serum bilirubin, albumin, creatinine, and α-fetoprotein. Severity of liver disease was assessed by the Child–Pugh–Turcotte classification (CPT) [10]. Model for end-stage liver disease (MELD) [11] was reviewed.

Ultrasonographic characteristics were recorded, especially splenic size and degree of ascites, which was graded as none, mild (detectable only on ultrasound), moderate (visible as a moderate symmetrical abdominal distension), or severe (marked abdominal distension). For HCC, the size and number of the hepatic focal lesions were determined.

Upper GI endoscopy was performed for all patients using a videoscope (Olympus 240, Tokyo, Japan) to detect the presence and grading of EV. All endoscopies were performed in a single endoscopy unit by an experienced endoscopist. Accordingly, EVs were classified as small (veins minimally elevated above the esophageal mucosal surface), medium (tortuous veins occupying less than one-third of the esophageal lumen), and large (those occupying more than one-third of the esophageal lumen) [12]. Presence of fundal varices and portal hypertensive gastropathy were also recorded. Control of bleeding was done either with injection sclerotherapy or with band ligation. In this study, patients were divided into two groups according to the size of EVs: group 1 included patients with no or small EVs and group 2 included patients with medium-sized or large-sized varices and an APRI score:

\[
\text{APRI} = \frac{(\text{AST} / \text{ULN}) / \text{platelet count (10^9/l)} \times 100}{\text{ULN is the upper limit of normal}}.
\]

The APRI score was calculated as follows [9]:

\[(\text{AST/ULN})/\text{platelet count (10^9/l)}] \times 100,\]

in which ULN is the upper limit of normal.

### Statistical methodology

Data were analyzed on an IBM computer using SPSS (Statistical Program for Social Science, version 12) software. Quantitative variables were presented as mean and SD and qualitative variables as number and percentage. The \(\chi^2\)-test was performed to compare qualitative variables between groups. The unpaired \(t\)-test was used to compare quantitative variables in parametric data (SD <50% mean). One-way analysis of variance was calculated to compare more than two groups as regards quantitative variables. Spearman’s correlation coefficient was used to rank variables versus each other positively or inversely. The receiver operating characteristic (ROC) curve was generated to find the best cutoff value, and the validity of certain variables \((P > 0.05, \text{insignificant}; P < 0.05, \text{significant}; P < 0.01, \text{highly significant})\).

### Results

#### Patient characteristics

Table 1 shows the characteristics of the 74 enrolled patients. Chronic hepatitis C (CHC) was the cause of cirrhosis in all patients. Fifteen patients (20.3%) had no varices, whereas 59 (79.7%) showed different variceal sizes. Congestive gastropathy was detected in 31 (41.8%) patients, and nine (12.2%) patients had fundal varices.

### Comparison between group 1 and group 2

According to the result of the upper GI endoscopy, patients were classified into two groups according to the size of EVs: group 1 included 32 patients with small varices (SVs) and group 2 included 42 patients with large varices. Table 2 shows a comparison between the two groups as regards the studied variables.

LVs were associated with elevated INR and splenomegaly. Patients with LVs were associated

### Table 1 Patient characteristics

| Variables          | Mean ± SD or n |
|--------------------|----------------|
| Age (years)        | 57.4 ± 7.1     |
| Sex (male/female)  | 44/30          |
| Upper GI bleeding  | 38/36          |
| Hepatic encephalopathy (yes/no) | 26/48 |
| PLT (n/mm³)        | 146 520.3      |
| APRI               | 1574.3±5102.1  |
| CPT score (A/B/C)  | 16/27/31       |
| MELD               | 16.2±6.8       |
| APRI               | 2.2±2.6        |
| Splenomegaly       | 62/12          |
| Ascites (present/absent) | 42/32 |
| HCC (present/absent)| 29/45          |
| Size of focal lesions | 9.2 ± 8        |
| Variceal size (small/large) | 32/42 |

Data are expressed as mean ± SD unless otherwise stated; AFP, α-fetoprotein; APRI, aspartate aminotransferase-to-platelet ratio index; CPT, Child–Pugh–Turcotte classification; GI, gastrointestinal tract; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NS, nonsignificant; PLT, platelets; S, significant; \(P = 0.05\).
with elevated INR. Distribution of CPT was evaluated. Frequency of Child A score was significantly higher in group 1 compared with group 2 (40.6 vs. 7.1%, respectively). Similarly, there was a significantly lower frequency of Child B and C scores in group 1 (28.1 and 31.3%, respectively) compared with group 2 (42.9 and 50.0%, respectively) \((P = 0.002)\).

When the ROC curve for CPT and MELD scores was determined, it showed that CPT was superior to MELD in the prediction of large varices. Area under the curve (AUC) was 0.663 for CPT \((P = 0.017)\) compared with 0.615 \((P = 0.092)\) for MELD score. The best threshold for CPT was above 7.5. Sensitivity was 73.8% and specificity was 50% (Fig. 1).

To demonstrate the association between different studied parameters including laboratory, imaging, and endoscopic findings and their relation to both bleeding EV and the presence of HCC, the whole population was reclassified according to the presence of both bleeding EV and HCC.

### Predictors of upper gastrointestinal tract bleeding

The whole population was reclassified according to the presence of gastrointestinal tract (GIT) bleeding into two groups: group A, which presented with GIT bleeding, and group B, which presented without bleeding (Table 3). Comparison between group A and group B in relation to laboratory, imaging, and endoscopic findings was performed. This analysis revealed that 62/74 patients (83.7%) had splenomegaly, 29/62 patients (80.6%) had no bleeding, and 33/62 (86.8%) presented with variceal bleeding \((P = 0.538)\). However, the probability of GIT bleeding was 1.5 times among those with splenomegaly [odds ratio 1.59; 95% confidence interval (CI) 0.456–5.568] (results not shown). CPT score was higher with variceal bleeding, and at a threshold greater than 7.5 points it was significantly associated with LVs \((P = 0.017)\), with a sensitivity of 73.8% and a specificity of 50% (Fig. 1).

| Variable | No or small EVs \((N = 32)\) | Medium or large EVs \((N = 42)\) | \(P\) value |
|----------|----------------|----------------|-------------|
| Age | 57.3 ± 7.3 | 57.4 ± 6.9 | 0.566 |
| Sex \([n (%)]\) | | | |
| Male | 17 (38.6) | 27 (61.4) | 0.351 |
| Female | 15 (50.0) | 15 (50.0) | NS |
| Upper GI bleeding \([n (%)]\) | | | |
| Yes | 11.0 (34.4) | 27.0 (64.3) | 0.018 (S) |
| No | 21.0 (65.6) | 15.0 (35.7) | |
| Hb (g/l) | 9.7 ± 2.1 | 9.6 ± 2.3 | 0.604 |
| PLT \((\text{n/mm}^3)\) | 150.281 ± 111.711 | 143.654 ± 111.553 | 0.823 |
| AFP | 305.2 ± 732.4 | 2541.2 ± 6612.7 | 0.904 |
| CPT \((A/B/C)\) | 8.4 ± 2.9 | 10 ± 2.9 | 0.016 (S) |
| MELD | 14.9 ± 7.1 | 17.3 ± 6.4 | 0.092 (NS) |
| APRI | 2.2 ± 2.9 | 2.1 ± 2.3 | 0.559 |
| Splenomegaly \((\text{present/absent})\) \([n (%)]\) | 7 (11.3)/5 (41.7) | 55 (88.7)/7 (58.3) | 0.021 (S) |
| Ascites \((\text{present/absent})\) \([n (%)]\) | 19 (59.3)/13 (40.6) | 13 (30.9)/29 (69.04) | 0.019 (S) |

Data are expressed as mean ± SD unless otherwise stated; AFP, α-fetoprotein; APRI, aspartate aminotransferase-to-platelet ratio index; CPT, Child–Pugh–Turcotte classification; EV, esophageal varices; GI, gastrointestinal; MELD, model for end-stage liver disease; NS, nonsignificant; PLT, platelet; S, significant; \(P = 0.05\); Bold denotes significant \((P < 0.05)\) and highly significant value \((P < 0.01)\).

| Variable | Bleeding EV | Nonbleeding EV | \(P\) value |
|----------|-------------|----------------|-------------|
| Hb | 8.9 ± 1.9 | 10.4 ± 2.2 | 0.005 |
| PLT | 157 223.7 ± 117 645.9 | 135 222.2 ± 103 761.6 | 0.462 |
| INR | 1.6 ± 0.6 | 1.56 ± 0.8 | 0.540 |
| AFP | 1864.4 ± 5240.5 | 1269.0 ± 5007.4 | 0.073 |
| CPT | 10 ± 2.8 | 8.6 ± 3.0 | 0.028 |
| MELD score | 16.7 ± 5.6 | 15.8 ± 8.0 | 0.265 |
| APRI | 1.7 ± 1.3 | 2.7 ± 3.4 | 0.462 |
| Small size varices \([n (%)]\) | 11.0 (28.9) | 21.0 (58.3) | 0.018 |
| Large size varices \([n (%)]\) | 27.0 (71.1) | 15.0 (41.7%) | |

AFP, α-fetoprotein; APRI, aspartate aminotransferase-to-platelet ratio index; CPT, Child–Pugh–Turcotte classification; EV, esophageal varices; INR, international normalized ratio; MELD, model for end-stage liver disease; PLT, platelet; Bold denotes significant \((P < 0.05)\) and highly significant value \((P < 0.01)\).
Correlation between aspartate aminotransferase-to-platelet ratio index and the studied variables

Table 4 displays a significant correlation between APRI and bilirubin, AST, alanine aminotransferase, albumin, platelet, CPT, and MELD score. A significant positive correlation was detected between APRI and α-fetoproteins ($r = 0.254$, $P = 0.029$).

Association between aspartate aminotransferase-to-platelet ratio index and variceal size and bleeding

APRI had no predictive ability for LEVs or bleeding (Tables 1 and 2). Table 5 summarizes the different cutoff values of APRI to assess its predictive value in LEVs. When the ROC curve was determined, at a cutoff of 1.4, APRI was not associated with variceal size (AUC = 0.540; 95% CI 0.401–0.679) (Fig. 2).

Figure 3 illustrates that APRI was a poor predictor of bleeding EV with AUC 0.51, sensitivity 53%, specificity 46%, positive predictive value (PPV) 55%, and negative predictive value (NPV) 50%. Above a cutoff value of 1.2, sensitivity was 75%, specificity was 52%, PPV was 53%, and NPV was 57%. On performing logistic regression analysis, APRI was insufficient in providing diagnostic accuracy for EV bleeding ($P = 0.248$).

An unexpected finding is that APRI was a good predictor of bleeding EV in patients with HCC only: AUC 0.55, sensitivity 70%, specificity 51%, PPV 49%, and NPV 64%, at a cutoff value of 1.5.

Association between aspartate aminotransferase-to-platelet ratio index and hepatocellular carcinoma

Higher APRI scores were detected in patients with HCC ($3.2 \pm 3.6$) compared with those without ($1.5 \pm 1.2$) ($P = 0.029$) (Table 6 and Fig. 4).

This was further investigated at different cutoff values of APRI. APRI was a good positive marker for prediction of HCC with AUC 0.65. Table 6 and Fig. 4 showed a favorable sensitivity and specificity of APRI in predicting the presence of HCC. At a lower cutoff value sensitivity was high, whereas specificity was low (51.1%).
Validity of APRI in predicting the number of focal lesions was studied. When the ROC curve was ascertained we found that an APRI cutoff of 1.4 was better positive than negative in the prediction of more than three focal lesions if the actual value was greater than the cutoff value and of less than three lesions if the value was less than the cutoff value, at an AUC of 0.61 (Table 6).

Discussion
The mortality rate from variceal bleeding is about 20% when patients are treated optimally in hospital [1]. Prevention of bleeding from EV is crucial and remains at the forefront of long-term management of cirrhotic patients. The standard diagnostic screening tool for EV is endoscopy [3]; however, endoscopy is invasive and costly. Egypt as a developing country with limited resources and a high incidence of liver cirrhosis mainly due to CHC infection has to limit the frequency of unnecessary endoscopic examinations. Whereas there is ample evidence indicating the value of noninvasive variables for the presence or absence of EV [4–8,13–16], there are few data to predict the presence of large varices in decompensated patients [7,17].

In this study, we considered simple, commonly available, reproducible, and inexpensive laboratory and imaging parameters as predictors of variceal size and bleeding. In order not to miss the presence of EV, which can be extremely hazardous to the health of patients, a good NPV of these studied variables is needed.

We included 74 patients with liver cirrhosis due to CHC who were divided into two groups according to the size of varices: group 1 with SVs and group 2 with LVs. The reason for including CHC only is that APRI was first prescribed to predict fibrosis among patients with CHC [9], and thus it could be possible that it would have a better performance in this population. Both groups were comparable with respect to clinical and laboratory findings; however, upper GI bleeding showed a higher frequency in patients with LVs compared with those with SVs, with a statistically significant difference (\(P = 0.018\)). LVs were associated with elevated INR, higher CPT score, and splenomegaly. Patients with LVs were associated with elevated INR, higher CPT score, splenomegaly, and ascites. Also, upper GI bleeding was more frequent in patients with LVs (\(P = 0.018\)).

No association between platelet count and size of varices was detected in our patients, which was similar to some published data [13,18]. This could be partly attributed to the matched platelet count in the two studied groups. Moreover, it is worth noting that portal parameters as predictors of variceal size and bleeding.

![Figure 3](image)

Receiver operating characteristic curves of APRI for prediction of bleeding EVs. APRI, aspartate aminotransferase-to-platelet ratio index; EV, esophageal varices.

![Figure 4](image)

Receiver operating characteristic curves of APRI for prediction of HCC (AUC = 0.651, \(P = 0.029\)). AUC, area under the curve; APRI, aspartate aminotransferase-to-platelet ratio index; HCC, hepatocellular carcinoma.

| Variable                  | Cutoff | AUC  | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---------------------------|--------|------|----------------|-----------------|---------|---------|
| Presence of HCC           | 1.2    | 0.65 | 75             | 53              | 52      | 57      |
| Number of focal lesions   | 1.4    | 0.61 | 83             | 50              | 52      | 78      |

AUC, area under the curve; HCC, hepatocellular carcinoma; NPV, negative predictive value; PPV, positive predictive value.
hypothesis is not the sole factor responsible for thrombocytopenia. Furthermore, different mechanisms have been implicated in thrombocytopenia, including shortened mean life span, thrombopoietin deficiency, myelotoxic effect, and bone marrow suppression [17].

Although previous studies have found that platelet count below 100,000 nearly always predicts the presence of LVs [3,6], there is still no consensus as to the best cutoff point for platelets for predicting EV [19,20].

Prothrombin time and serum albumin are considered markers of hepatocellular dysfunction. Patients with LVs had higher INR compared with patients with SVs. Although serum albumin was lower in patients with LVs than in those with SVs, no statistical difference was found (P = 0.058). However, it was a good marker for variceal bleeding (P = 0.031), which indicated that these biomarkers, consistent with previous studies [14], could have a good diagnostic performance. On the other side, other investigators showed discordant results [15,18].

 Decompensated liver cirrhosis (Child B and C) is deemed to be the appropriate parameter for predicting variceal bleeding [12,18]. Our results demonstrated that CPT score was higher with variceal bleeding, and at a threshold more than 7.5 points it was significantly associated with LVs (P = 0.017). Our data were in accordance with previous results [21–24].

It is notable that inclusion of prothrombin time and albumin within the CPT score gave a favorable association between Child score and these parameters. In contrast, CPT might be a poor predictor of EVs because of the subjectivity of its clinical parameters and limited discriminant ability. In accordance with previous studies [7,25], we detected no correlation between MELD score and the size and bleeding of EV (P = 0.092 and 0.265, respectively).

Evaluation of different sonographic findings revealed that enlarged spleen and presence of ascites were able to discriminate the varical size. The predictive value of splenomegaly in variceal bleeding was poor. However, the detailed analysis of our data demonstrated that the probability of GIT bleeding was 1.5 times among those with splenomegaly (odds ratio 1.59, 95% CI 1.045–6.568). Previous studies showed discordant data in assessing splenomegaly as a predictor of varices [7,17,18,26]. Our results were in general agreement with these studies [7,17,18,25]. Nevertheless, discordant results were reported [14,26]. A possible explanation for these variable results might be the different etiologies of liver cirrhosis, as splenomegaly is more frequently found in posthepatitic cirrhosis than in alcoholic cirrhosis [27].

The divergence of the results between studies could be attributed to the fact that both endoscopy and ultrasonography are operator-dependent techniques with a lack of interobserver agreement [19].

Increasing size of varices is associated with an increase in variceal wall tension to a critical level, at which varices rupture and cause life-threatening bleeding.

SV progress to LV at a rate of 5–10% per year [16]. The current results revealed a strong association between variceal size and bleeding. We found that 71.1% of patients presenting with bleeding EV had LEVs, whereas 58.3% of those with no bleeding had SEVs (P = 0.018). This was supported by the North Italian Endoscopic Club [12].

Wai et al. [9] validated for the first time an index known as the APRI, which establishes the relationship between this score and liver fibrosis.

APRI has good accuracy in predicting fibrosis, the major cause of portal hypertension. This index is feasible and simple as it uses two easily obtained parameters; thus, it can be applied in every cirrhotic patient without a cost burden. An earlier study [28] reported the association of APRI with the presence of EVs; however, they included compensated cirrhotic patients. A possible explanation for that association may be that fibrosis indicates more severe hepatic parenchyma architectural distortion and increased intrahepatic circulatory resistance, resulting in portal hypertension, variceal formation, and finally EV bleeding [22].

In accordance with a good performance of the liver stiffness measurement in assessing both liver fibrosis and EVs [29], further studies may be necessary to evaluate the potential utility of serum liver fibrosis markers. However, it remains unclear whether serum liver fibrosis markers can be useful for screening the presence of EVs [29–31].

Because of the aforementioned reasons, we propose here that APRI may be a potential valuable marker for predicting the presence of LEVs and their risk of bleeding. There are convincing data showing that patients with cirrhosis and HCC are more likely to suffer from variceal hemorrhage [7].

Our data revealed that APRI was insufficient in providing diagnostic accuracy for discrimination between SEVs and LEVs even at different cutoff values. When the ROC curve was determined, we found that at a cutoff of 1.4 APRI was not associated with variceal size [AUC = 0.540 (P = 0.559), 95% CI 0.401–0.679]. Further, the predictive ability of APRI was poor regarding bleeding EV, with an AUC of 0.51.
Different cutoff values for APRI as a predictor of EV were tested in previous research, which showed similar results to ours [31–33].

HCC develops in a multistage process involving chronic liver injury and local inflammation, progressive liver fibrosis and cirrhosis, initiation of neoplastic niches, and malignant transformation. It is well known that advanced fibrosis and cirrhosis are high-risk conditions that prompt intensive surveillance for HCC. It could be hypothesized that APRI might have a role in predicting the progression of advanced fibrosis and cirrhosis into HCC. To investigate this hypothesis, we investigated the association of APRI with HCC at different cutoff values. Higher APRI levels were detected in patients with HCC with statistically significant difference compared with patients without HCC (P = 0.029). At cutoff more than 1.39, APRI was found to be a good positive marker for predicting the presence of HCC. On applying the ROC curve at the same cutoff point, AUC was 0.65. There was significant association between APRI and number of focal lesions, with AUC 0.61. Moreover, significant correlation was found between APRI and α-fetoprotein level.

APRI has been evaluated as a prognostic biomarker in HCC patients secondary to hepatitis B virus after radiofrequency ablation [34]. A recent publication by Hann et al. [35] concluded that APRI might be a marker of HCC in hepatitis B virus patients. Despite the inconsistent results, these studies substantiated the potential usefulness of APRI in the evaluation of liver diseases.

To the best of our knowledge, our study is the first to investigate the role of APRI in the prediction of HCV-related HCC, especially advanced cases, as indicated by the presence of EV and GIT bleeding. Extensive fibrosis indicates more severe hepatic parenchyma architectural distortion and increased intrahepatic circulatory resistance, resulting in portal hypertension, variceal formation, and finally EV bleeding [32]. There are convincing data to show that patients with cirrhosis and HCC are more likely to suffer from variceal hemorrhage [7]. The current results showed that APRI was a good predictor for bleeding EVs in a cohort of patients with HCC with good discriminative value (AUC = 0.55). These data point at the role of APRI in advanced cirrhosis that has progressed to HCC. Additional studies should be conducted to confirm whether or not the condition is cirrhosis dependent.

**Conclusion**

Although we found an association between LEV and CPT, splenomegaly, and ascites, at present these parameters cannot be advocated as a surrogate for endoscopy. In addition, APRI cannot be used as a predictor of LEV.

However, our study highlighted the proposed role of APRI in HCC, its association with the size and number of focal lesions, and its predictive role in variceal bleeding in this cohort of patients. Yet, further studies are warranted to validate the clinical applicability of APRI to predict HCC and its clinicopathological parameters.

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**Conflicts of interest**

There are no conflicts of interest.

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