AST/ALT Ratio for detection and severity classification of Esophageal Varices in Child A HCV Liver cirrhosis Egyptian Patients

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Abstract: Background: Variceal bleeding is a dramatic and common complication of cirrhosis. The development of esophageal varices depends on the progression of liver fibrosis. **Aim:** to assess the relation of three established markers of fibrosis, including AST-to-ALT ratios (AAR), FIB-4 and AST-to-platelet ratio (APRI), to the presence and severity of esophageal varices in HCV cirrhotic patients with Child-Pugh class A status. **Patients and Methods:** 100 consecutive patients with HCV-related liver cirrhosis (Child-Pugh Class A) were enrolled in the study. All patients underwent esophagogastroduodenoscopy (EGD) for detection and grading of esophageal varices (OV). The values of established biomarkers of fibrosis (AAR, FIB-4 and APRI) were calculated in all patients, and the relationships between these markers and OV were investigated. **Results:** Values of AAR, FIB-4 and APRI in patients with OV were significantly higher than those in patients with no varices (p<0.05). The values of AAR in the patients with varices with a high risk of hemorrhage were significantly higher than those in the patients with non risky varices (p = 0.001), whereas the values of FIB-4 and APRI were not found to be different between both groups. In addition, the values of AAR increased in line with increasing variceal severity. In detecting esophageal varices, AAR showed a sensitivity of 58.3%, specificity of 75 %, positive predictive value (PPV) 77.8% and negative predictive value (NPV) 54.5% at cut off value ≥1.3. As regards the presence of high risk varices, AAR showed a sensitivity of 77.78%, specificity of 81.82%, positive predictive value of 77.8% and negative predictive value of 81.8% at cut off value ≥1.37. **Conclusion:** higher values of AAR, FIB-4 and APRI are related to the presence of OV in class A Child-Pugh HCV cirrhotic patients. Moreover, AAR is associated with the increasing variceal severity and the risk of variceal bleeding.

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1. Introduction:

The development of esophageal varices due to portal hypertension is a major complication of liver cirrhosis, and variceal hemorrhage is a life-threatening event that carries a significant risk of mortality. The risk of bleeding is related to variceal size, the presence of red signs on varices and advanced liver disease (Child-Pugh class B or C) [(1)].

Although several biochemical parameters, such as low platelet counts, advanced Child-Pugh class, hypoalbuminemia and low prothrombin activity, have been reported to be associated with the presence of varices , esophagogastroduodenoscopy (EGD) is the most reliable method of evaluating variceal size and the presence of red signs[(2)].

If it were possible to predict esophageal varices by noninvasive means, this would restrict testing to the population deemed to be at most risk and reduce the number of endoscopies required. Such a screening test should be simple, quick, reproducible, and cost effective [(3)].

Based on the concept that the development of portal hypertension is caused by the progression of liver fibrosis, non-invasive biomarkers of liver fibrosis have been used to predict presence of varices in cirrhotic patients [(4)]. However, it has not yet been sufficiently clarified whether biomarkers of liver fibrosis can be used to predict the presence of varices in cirrhotic patients with a well-maintained liver function (Child-Pugh class A).

We performed this study to examine the values of three established markers of fibrosis, including AST-to-ALT ratios (AAR) [(5)], FIB-4 indices [(6)] and AST-to-platelet ratio indices (APRI) [(7)], in predicting presence and severity of esophageal varices in HCV cirrhotic patients with Child-Pugh class A status.

2. Patients and methods:

A total of hundred consecutive patients with Child-Pugh Class A HCV-related liver cirrhosis attending the Endoscopy unit of Ain Shams University hospital were enrolled in the present study. The study was performed in the period between August 2014 and January 2015 according to the ethical standards for human experimentation approved by the human research committee of our

institution. An informed consent was obtained from each patient.

Patients with causes of liver cirrhosis other than HCV, with recent acute variceal bleeding (within 2 weeks), with hepatic malignancy, patients on beta blockers or underwent endoscopic treatment (band ligation or sclerotherapy) were excluded from the study.

Baseline assessment included a thorough medical history and full clinical examination. A complete panel of laboratory studies, including complete blood count, liver and renal functions were performed for all patients. An abdominal ultrasound (Toshiba real-time scanner instrument with a 3.5 MHz convex transducer) was also done. The diagnosis of liver cirrhosis was based on clinical, biochemical and radiological findings. HCV antibodies were detected in all patients using Micro particle Enzyme Immunoassay (AxSYM, third generation assay, Abbott Laboratories, IL, USA).

Upper GI endoscopy (UGIE) was performed for all patients (Pentax EG-3440 videoscope) to assess the presence of esophageal varices (OV). With regard to patients with esophageal varices, variceal size was graded from I-IV based on the Paquet grading system [10], and the presence of red signs on the varices was evaluated. Patients with large varices (grade III-IV) or small varices with red signs were categorized to be patients with high-risk varices.

In the present study, the values of 3 useful biomarkers (AAR, FIB-4 and APRI) of the progression of liver fibrosis were calculated and correlated with the presence of OV and detection of high risk OV. The value of AAR was simply calculated as the AST/ALT ratio [7]. The FIB-4 and APRI values were calculated based on formulas proposed by Vallet-Pichard *et al.* [8] and Wai *et al.* [9], respectively: FIB-4 = Age [years] × AST [U/L] / (platelets [10^9/ L] × (√ ALT [U/L]), in which the age of the patient is the age at the time of endoscopic treatment; APRI = 100× (AST level/upper limit of normal)/platelets [10^9/ L].

Statistical analysis:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Quantitative variables are expressed as mean± standard deviation. Qualitative variables are expressed as frequencies and percents. Student T Test was used to compare a continuous variable between two study groups. ANOVA test was used to compare a continuous variable between more than two study groups. Chi square test and Fisher's exact test were used to examine the relationship between Categorical variables. Correlation analysis using spearman's method was used to assess the strength of association between two quantitative variables. The ROC Curve (receiver operating characteristic) provides a useful way to evaluate the sensitivity and specificity for quantitative diagnostic measures (AAR) that categorize cases into one of two groups. P-value< 0.05 was considered statistically significant.

3. Results:

A total of hundred adult patients with established Child-Pugh Class A HCV-related liver cirrhosis referred to the endoscopy unit at Ain Shams university hospital, were enrolled in the present study. They were 79 males (79%) and 21 females (21%); with their age ranged from 37 to 70 years (mean age 55.6 ± 7.1 years). On doing upper GI endoscopy, OV was found in 60 patients (60%). Prevalence of high risk esophageal varices was 27% (27 patients) (Table 1).

There was no statistical significant difference between patients with risky OV (n=27) and those with non risky OV (n=33) as regards age, sex and laboratory data (P>0.05) (Table 2).

Comparing the patients with OV and those with no OV regarding the three non invasive indices in the study, the values of AAR, FIB-4 and APRI in patients with OV were significantly higher than those in patients with no varices (p <0.05) (Table 3). However, on comparing the patients with high risk OV and those with non risky OV regarding the same non invasive indices in the study, there was a significant difference between the two groups as regards the values of AAR only (p = 0.001) (Table 4). Furthermore, significant correlation was found between AAR and grading of OV (p = 0.0001) (Table 5).

Area under the ROC curve (AUROC) for AAR in predicting the presence of esophageal varices of any degree was 0.659 (95% CI 0.557 - 0.750, p= 0.003). It showed sensitivity of 58.3 %, specificity of 75%, positive predictive value (PPV) 77.8%, negative predictive value (NPV) 54.5%, at cut off value ≥1.3 (Table 6, Figure1).

Area under the ROC curve (AUROC) for AAR in predicting the presence of high risk esophageal varices was 0.865 (95% CI 0.752 - 0.939, p= 0.001). It showed sensitivity of 77.78 %, specificity of 81.82%, positive predictive value 77.8%, negative predictive value 81.8%, at cut off value ≥1.37 (Table 6, Figure2).

Table (1): Study population characteristics

Parameter	Characteristics	
Age (years)	55.6 ± 7.1 years	(37-70 years)
Gender	Male 79 (79%) Female 21 (21%)	
Esophageal varices	Present 60 (60%) Absent 40 (40%)	
Grading of varices	No varices 40 (40%)	
	Grade I 19 (19%)	
	Grade II 20 (20%)	
	Grade III 11 (11%)	
	Grade IV 10 (10%)	
High risk esophageal varices	High risk 27 (27%) Non risky 33 (33%)	
ALT (IU/L)	58.02 ± 23.9	(21-138)
AST (IU/L)	71.06 ± 28.00	(31-171)
Hemoglobin (gm/dl)	13.07 ± 1.18	(10-15)
WBCs (x 10^3/mm³)	5.33 ± 1.85	(2.50-11)
Platelets (x 10^3/mm³)	123.96 ± 56.02	(48-290)
INR	1.20 ± 0.12	(1.0-1.43)
Total bilirubin (mg/dl)	0.99 ± 0.30	(0.40-1.70)
Serum albumin (gm/dl)	3.61 ± 0.41	(2.90-4.5)

Table (2): Comparison between patients with risky OV and those with non risky OV.

		Patients with risky OV (N=27)	Patients with non risky OV (N=33)	*P*	Sig
Age (years)		53.15 ± 7.44	56.41 ± 7.50	>0.05	NS
Gender	**Male n (%)**	21 (77.8%)	26 (78.8%)	>0.05	NS
	Female n (%)	6 (22.2%)	7 (21.2%)		
Hemoglobin (gm/dl)		12.90 ±1.43	12.85±1.06	>0.05	NS
WBCs (x 10^3/mm³)		5.01 ±1.46	5.02 ±1.64	>0.05	NS
Platelets (x 10^3/mm³)		119.85 ± 49.00	105.52 ± 45.04	>0.05	NS
ALT(IU/L)		50.15 ±17.79	57.45 ± 20.83	>0.05	NS
AST(IU/L)		74.41 ± 20.26	65.00 ± 23.58	>0.05	NS
Serum albumin (gm/dl)		3.63 ± 0.39	3.52 ± 0.35	>0.05	NS
Total bilirubin (mg/dl)		0.97 ± 0.23	1.02 ± 0.35	>0.05	NS
INR		1.19 ± 0.12	1.22 ± 0.12	>0.05	NS

Table (3): Comparison between patients with OV and those without OV as regards AAR, FIB-4 and AAR

	Patients with OV (N=60)	Patients without OV (N=40)	*p*	Sig
AAR	1.31 ± 0.30	1.16 ± 0.21	0.007	S
FIB-4	5.39 ± 2.43	4.18 ± 1.92	0.009	S
APRI	1.85 ± 0.92	1.47 ± 0.77	0.031	S

Table (4): Comparison between patients with risky OV and those with non risky OV as regards AAR, FIB-4 and AAR

	Patients with risky OV (N=27)	Patients with non risky OV (N=33)	*p*	Sig
AAR	1.51 ± 0.20	1.14 ± 0.25	0.001	S
FIB-4	5.62 ± 2.70	5.21 ± 2.21	0.523	NS
APRI	2.01 ± 1.05	1.72 ± 0.79	0.231	NS

Table (5): Correlation between grades of OV and each of AAR, APRI and FIB-4

		AAR	APRI	FIB-4
Grade of O.V	**R**	0.588	0.208	0.163
	P	0.0001	0.111	0.214
	Sig.	S	NS	NS

Table (6):-Performance of AAR in detection of esophageal varices presence and the high risk esophageal varices.

Parameter	Esophageal varices presence	High risk esophageal varices
AUROC	0.659 (95% CI 0.557 - 0.750)	0.865 (95% CI 0.752 - 0.939)
***P* value**	0.003	0.001
Cutoff point	≥1.3	≥1.37
Sensitivity	58.3%	77.78 %
Specificity	75%	81.82 %
PPV	77.8	77.8
NPV	54.5	81.8

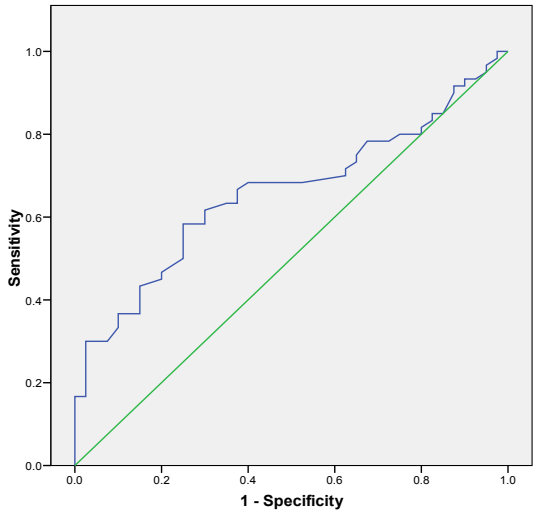

Figure (1): ROC curve for AAR in predicting esophageal varices of any degree

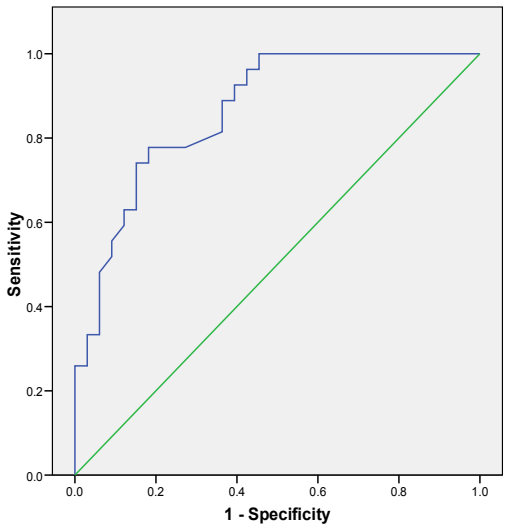

Figure (2): ROC curve for AAR in predicting high risk esophageal varices

4. Discussion:

EGD is the gold standard method of determining whether a cirrhotic patient should receive treatment for varices [2, 9]. According to the Baveno IV Consensus Conference on portal hypertension, EGD should be performed at 2-3 year intervals in patients without varices and at 1-2 year intervals in patients with small varices [10]. However, repeating EGD is invasive, expensive and sometimes hardly accepted by patients. Therefore, many non-invasive or minimally invasive methods to assess the presence/size of varices have been researched. For example, low platelet counts have been reported to be associated with the presence of varices or large varices in several reports [2, 11]. However, none of the available tools completely fulfill the criteria of an ideal (accurate, simple, inexpensive and easily reproducible) diagnostic tool [12].

Despite the fact that the risk of variceal hemorrhage is associated with variceal size, the presence of red signs on varices and advanced liver disease (Child-Pugh class B or C), it has not been sufficiently clarified which biomarker reflects the presence of high risk varices in patients with a well-maintained liver function (Child-Pugh class A status).

In the present study, we examined various biomarkers of liver fibrosis in HCV-positive cirrhotic patients with a Child-Pugh class A status based on the concept that portal hypertension depends on the progression of liver fibrosis. We found that the values

of AAR, FIB-4 and APRI in patients with OV were significantly higher than those in patients without varices ($p < 0.05$). These findings are consistent with Nyblom, *et al.*[13] and Iwata, *et al.* [14] who found significantly higher AAR in patients with varices compared to those without ($p < 0.0001$ and $p < 0.05$ respectively).

The current study revealed that values of AAR were significantly higher in patients with high risk OV (1.51 ± 0.20) than those with non risky OV (1.14 ± 0.25) ($p = 0.001$). Moreover, significant positive correlation was found between AAR values and grading of OV ($p = 0.0001$). Interestingly, the values of FIB-4 and APRI were not significantly different between the two groups nor correlated to the grade of OV, indicating that FIB4 and APRI, excellent markers of liver fibrosis, are not related to the presence of risky varices in cirrhotic patients with Child-Pugh class A status. Similarly, the recent study of Iwata, *et al.* [14] showed that the values of AAR were significantly higher in patients with risky OV than those with non risky varices ($p =0.02$) and it significantly correlated with the grade of OV ($p < 0.05$). Iwata, *et al.* [14] demonstrated that there is significant difference in FIB-4 values between risky OV group and non risky OV group ($p >0.05$) and this doesn't coincide with our study. This is due to less number of patients included in their study.

The sensitivity and specificity of AAR has been shown to vary with the different cutoff values used. The sensitivity and specificity of AAR to detect the presence of OV were 58.3 % and 75% respectively, at a cut off value of ≥1.3 with positive predictive value 77.8%, negative predictive value 54.5%, and an AUROC of 0.659. Furthermore, AAR showed a sensitivity of 77.78 %, specificity of 81.82%, positive predictive value 77.8%, negative predictive value 81.8%, and an AUROC of 0.865 at cut off value ≥1.37 in detecting high risk varices. Cast´era, *et al.* [15] performed his study on 298 consecutive chronic hepatitis c patients, of which 70 had liver cirrhosis. They reported that for the detection of varices, using an AAR cut-off ≥1.0 showing sensitivity of 68%, specificity of 89%, PPV 77%, NPV 83%, with an AUROC 0.83. While, for the prediction of large oesophageal varices, this gave a sensitivity 68%, specificity 77%, PPV 41%, NPV 92%, and AUROC 0.79. Another study by Treeprasertsuk, *et al.* [16], performed on 150 patients with primary biliary cirrhosis revealed that at cut off value of AAR >1.12 significantly associated with the presence of varices at initial endoscopy. This cutoff gave a sensitivity of 47.8%, specificity of 87%, PPV 42.3%, NPV 89.2%, and an AUROC of 0.69.

In conclusion, some fibrosis markers, such as AAR, FIB-4 and APRI, could be useful for predicting the presence of varices in HCV-positive cirrhotic patients with Child-Pugh class A status. Moreover, AAR is associated with more variceal severity and can be used as a cheap, bedside reliable non invasive tool for predicting the presence of risky OV in the same cirrhotic population. However, it will be necessary to confirm our findings in both larger and different populations.

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