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ACCURACY OF MELD-NA SCORE AND OTHER NON-INVASIVE PREDICTORS OF ESOPHAGEAL VARICES STATUS IN EGYPTIAN PATIENTS WITH LIVER CIRRHOSIS

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Abstract

Esophageal varices (OV) are a serious and common complication of portal hypertension associated with liver cirrhosis. Hemorrhage from OV rupture is a life-threatening complication with high mortality. The model for end stage liver disease (MELD), MELD-Na+ scores are predictors of non-transplant surgical mortality among patients with cirrhosis and has been a useful tool predicting the mortality in patients awaiting liver transplantation. As well, they have been suggested in many studies as useful predictors of OV presence and severity.

This study evaluated accurate cut-off values of MELD-Na and aspartate aminotransferase to platelet count ratio index (APRI), AST/ALT (AAR), creatinine (ASR/Cr) as well as AST/ Bilirubin (AST/Bil.) ratios as new non-invasive predictors for liver cirrhosis patients.

Keywords: Patients, esophageal varices, MELD score, APRI, AAR, Non-invasive predictors, platelet count

Introduction

Generally, liver fibrosis is the major consequence of chronic hepatitis C (CHC) and representing a major global health problem (Friedman, 2000). Hepatitis C virus (HCV) was a worldwide health problem and a leading cause of chronic liver disease (Ghany *et al,* 2009). It was estimated that, hepatitis C virus genotype 4 (HCV-4) was the cause of approximately 20% of 180 million cases of chronic hepatitis C in the world. HCV-4 infection was common in the Middle East and Africa, highest in Egypt at >10% of the general population and China has the most people with HCV, 29.8 million (Abd El Razek *et al,* 2014).

The largest HCV epidemic was found in Egypt, with an estimated national prevalence reported to be 14.7% (Cuadros *et al,* 2014). End stage of chronic HCV infection is cirrhosis, ultimately complicated by portal hypertension, an established contributing factor in evolution of a variety of cirrhosis complications as ascites, hepatic encephalopathy, and esophageal varices (Elalfy, *et al,* 2016). Patients, who survived the first episode of esophageal hemorrhage, had a risk of recurrent bleeding up to 60% with a mortality rate up to 33% (Bari and Garcia-Tsao, 2012). Non-invasive predictors were recommended as a useful way to screen for the presence and severity OV (Herwanto *et al,* 2018).

This study aimed to evaluate the MELD-Na accurate cut-off values & other non-invasive predictors as aspartate aminotransferase to platelet count ratio index (APRI), AST/ALT (AAR), AST/ Creatinine (ASR/Cr) and AST/Bilirubin(AST/Bil.) ratios as a new non-invasive predictor for presence of OV and degree in liver cirrhosis patients

Subjects and Methods

The study included 60 patients with liver cirrhosis of variable etiology admitted to Ain-Shams University Hospitals, Hepatology and Gastroenterology unit in the period from February 2019 to October 2019. All were dealt with according to the ethical guidelines of Ain-Shams University Hospitals and after having a written consent from all. Patients were divided into 2 groups: GI: 40 patients with liver cirrhosis & esophageal varices diagnosed by upper GIT endoscopy as (patients) which were subdivided into 4 groups of 10 patients each according to the esophageal varices, grade (SG1,SG2, SG3 &

SG4). GII: 20 patients with liver cirrhosis without esophageal varices (G-0) endoscopy evident as (control group).

Both groups were subjected to the following: 1- Full history taking & clinical examination. 2- Laboratory investigations including: 1- CBC. 2- Liver function tests: ALT, AST, total bilirubin, direct bilirubin, Prothrombin time (PT) & international normalization ratio (INR). 3- Renal function tests: serum urea, serum creatinine, serum sodium & potassium.

4- Abdominal ultrasound. 5- Upper GIT endoscopy under Propofol® IV to diagnose esophageal varices presence & its grade acco rding to: Grade I: Small straight cords of varices confined to the lower third of esophagus, Grade 2: Moderate sized clubbed varices, with well- defined areas of normal mucosa between them, forming several distinct variceal cords and confined to lower half of the esophagus, Grade 3: Gross varices extended into the proximal half of esophagus, normal mucosa might not be visible in-between them unless esophagus was fully distended with air and Grade 4: Varices like grade 3 but with dilated capillaries on top or in-between them (Dagradi *et al,* 1966).

6- MELD score evaluation according to the following formula: MELD= 3.78[Ln serum bilirubin (mg/dL)] +11.2[Ln INR]+ 9.57[Ln serum creatinine (mg/dL)]+ 6.43 (Kamath and Kim, 2007). If the initial MELD scores were 12 or more, the score was adjusted by incorporating the serum sodium value according to The United Network for Organ Sharing (White *et al*, 2019). 7- MELD-Na equation= MELD +1.32x (137-Na)- [0.033 x MELDx (137-Na)]. After Kalra *et al.* (2016) the MELD was utilized log scale calculations with a value less than 1 was given a lower limit value of 1 to prevent generating a negative score. The lower limit of serum sodium (Na) was capped at 125mmol/l, and the upper limit was capped at 137mmol/l. The upper limit of serum creatinine was capped at 4; in addition, if the patient had dialysis at least twice in the past week, the value for serum creatinine would be adjusted to 4.0, with maximum MELD score of 40. 8-APRI Score (De Fr-anchis, 2010): APRI = AST (IU/L)/AST upper normal limit (IU/L) x100/Platelet count (10^9/L) or [(AST/ULN AST x 100)/ Platelets (10^9/L)].

9- Calculation of other suggested non-invasive predictors: AST/ALT Ratio (AAR), AST/Creatinine Ratio (AST/Cr) and AST/ Bilirubin (AST/Bil.) ratio.

Statistical analysis: Data were analyzed using SPSS ver. 18 IBM® incorporation. Numerical data were tested for normality with D'Agostino-Pearson test (Willemsen *et al,* 2019), presented as mean ± SD. Categorical data were presented as number and percent of total. Comparative analysis of numerical data was done with ANOVA with post hoc Bonferroni test. Comparative analysis of categorical data was done with Chi-square (X^2), or Fisher-exact test due to distributed frequencies. Correlations were tested using Spearman rank correlation and interpreted as in table. Receiver-operating characteristic curve analysis examined predictive value of APRI, AAR, MELD-Na+, AST/ creatinine or AST/bilirubin, Area under ROC curve (AUC) was interpreted as in table.

Correlation coefficient (Spearman rho)	Strength of correlation
<0.2	Very weak
0.2 – 0.39	Weak
0.4 – 0.59	Moderate
0.6 – 0.79	Strong
0.8 – 1.0	Very strong

Area under ROC curve (AUC)	Predictive value
0.9 – 1.0	Excellent
0.8 – 0.89	Good
0.7 –0.79	Fair
0.6 – 0.69	Poor
<0.6	Fail

P-value <0.05 was considered significant; data were tabulated and graphically illustrated, and probability (P-value) less than 0.05 was considered significant and less than 0.01 was as highly significant and more than 0.05 was considered nonsignificant.

Results

The results were shown in tables (1, 2 & 3) and figures (1, 2, 3, 4, 5, 6 & 7)

Table 1: Comparison between patient & control groups as regard demographic data

Variants	OV Grade I (10)		OV Grade II (10)		OV Grade III (10)		OV Grade IV (10)		Control (20)		P value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age (year5)	48.10a	6.59	52.80a	6.58	50.70a	4.11	48.70a	7.44	48.95a	5.38	0.384
Male	8 (80%)		6 (60%)		7 (70%)		10 (100%)		12 (60%)		0.148
Female	2 (20%)		4 (40%)		3 (30%)		0		8 (40%)		

There was a significant positive correlation between OV grade and each of APRI, AAR, MELD-NA and AST creatinine, but without significant correlation between OV grade and AST/Bilirubin (Figs.1, 2, 3, 4 & 5).

As to diagnostic performance of non-invasive predictors in discrimination between patients with and without esophageal varices using APRI, AAR, MELD-Na^+, AST/ Creatinine ratio or AST/Bilirubin ratio was shown (Tab. 2 & Fig. 6).

Table 2: ROC curve analysis for discrimination between patients with or without OV by using predictors.

Case to Control	Predictor				
ROC metric	APRI	AAR	MELD-Na^+	AST/Creatinine	AST/Bilirubin
AUC	0.953	0.722	0.826	0.726	0.537
P-value*	<0.0001	0.0024	<0.0001	0.0004	0.6192
Cut-off criterion	>0.42	>1.087	>10.8	>40.0	>35.8
Sensitivity, %	85.0	80.0	92.5	52.5	37.5
Specificity, %	95.0	65.0	65.0	90.0	100.0
+PV, %	97.1	82.1	84.1	91.3	100.0
-PV, %	76.0	61.9	81.3	48.6	44.4

AUC = area under the ROC curve, +PV = positive predictive value, -PV = negative predictive value,*DeLong method.

Table 3: ROC curve analysis between OV-G0-2 and G3-4 by using predictors.

G0-2 / G3-4	Predictor				
ROC metric	APRI	AAR	MELD-Na^+	AST/Creatinine	AST/Bilirubin
AUC	0.946	0.744	0.805	0.829	0.534
P-value*	<0.0001	0.0002	<0.0001	<0.0001	0.7279
Cut-off criterion	>1.24	>1.455	>15.7	>40.0	≤12.5
Sensitivity, %	80.0	70.0	55.0	80.0	30.0
Specificity, %	100.0	75.0	92.5	82.5	97.5
+PV, %	100.0	58.3	78.6	69.6	85.7
-PV, %	90.9	83.3	80.4	89.2	73.6

Discussion

Esophageal varices (OV) being one of the commonest complications of liver cirrhosis responsible for a high mortality rate, while initiation of non- cardio- selective β- blockers enabled a 50% reduction in the incidence of the first hemorrhage. Therefore, endoscopic screening for OV at time of diagnosis is strongly recommended by all clinical guidelines (Lin *et al,* 2011).

As an invasive technique endoscopy is not easily accepted by many patients raising the need for non- invasive approaches for OV prediction and identified patients who could benefit from non-selective beta-blockers therapy or start endoscopic prophylaxis (Zaman *et al,* 2001*).* The Child-Pugh and MELD scores had similar capability for predicting in-hospital overall mortality in patients with chronic liver disease. Besides, MELD was significantly better than Child-Pugh score for predicting hospital mortality due to variceal bleeding (Flores-Rendón *et al,* 2008).

The present study assessed different laboratory, parameters as a non-invasive methods for diagnosis and grading of esophageal varices in (60) patients with liver cirrhosis, without significant difference between their

age & sex.

In the current study, MELD-Na score presented a good predictor of OV presence (AUC: 0.82) with sensitivity of 92.5 % and specificity of 65% at cut off value> 10.8, which agreed with a previous study that found MELD-Na at cut-off value of 11.5 had highest sensitivity (93.3%) and specificity of 76% and it confirmed a positive correlation of MELD-Na with varices' grade (Ashraf and El-Sayed, 2018). The present study however showed MELD-Na score could discriminate bet-ween OV G0-2 & G3-4 (AUC:0.80) with sensitivity of 55% & specificity of 92.5% at cut-off value >15.7. APRI score in this study was an excellent predictor of OV presence (AUC: 0.95) with sensitivity of 85% and specificity of 95% at cut off value >0.42. It had a positive correlation with esophageal varices grade with sensitivity80 % and specificity 100%, at cut-off value>1.24. However, APRI at cutoff value showed 0.908 of 87.3% sensitivity and 71.4% specificity (Mandal *et al,* 2019). Thus, AAR and AST/Cr ratios were fair predictors of OV presence with AUC:0.7 for each with sensitivity of 80% & 52.5% and specificity of 65% & 90% at cut off value >1.087, >40.0 respectively and both discriminated between OV Grades

In the present study, in the G0-2a & G3-4, AAR was fair predictor for discrimination (AUC:0.72) with sensitivity of 70% and specificity of 75% at cut of values >1.45 and AST/Cr ratio a good predictor (AUC:0.85) with sensitivity of 80% and specificity of 82.5% at cut of values >40, these results goes partially with a study done in 2015 which concluded that APRI, AAR had modest diagnostic accuracy for varices in liver cirrhosis (Deng *et al,* 2015). However, in our study APRI score was excellent predictor, the difference in cut off values and sensitivity of predictors between the present study and the other studies may be due to racial and genetic differences. As for the knowledge, AST/Cr ratio as a predictor was not studied or suggested before.

Conclusion

Non-invasive predictors specially the APRI score among others (MELD Na score, and AAR as well as AST/Cr ratio) could be used as a non-invasive low cost screening of the esophageal varices presence and might even predict its grade as a trial to avoid unnecessary costly upper endoscopy in liver cirrhosis patients.

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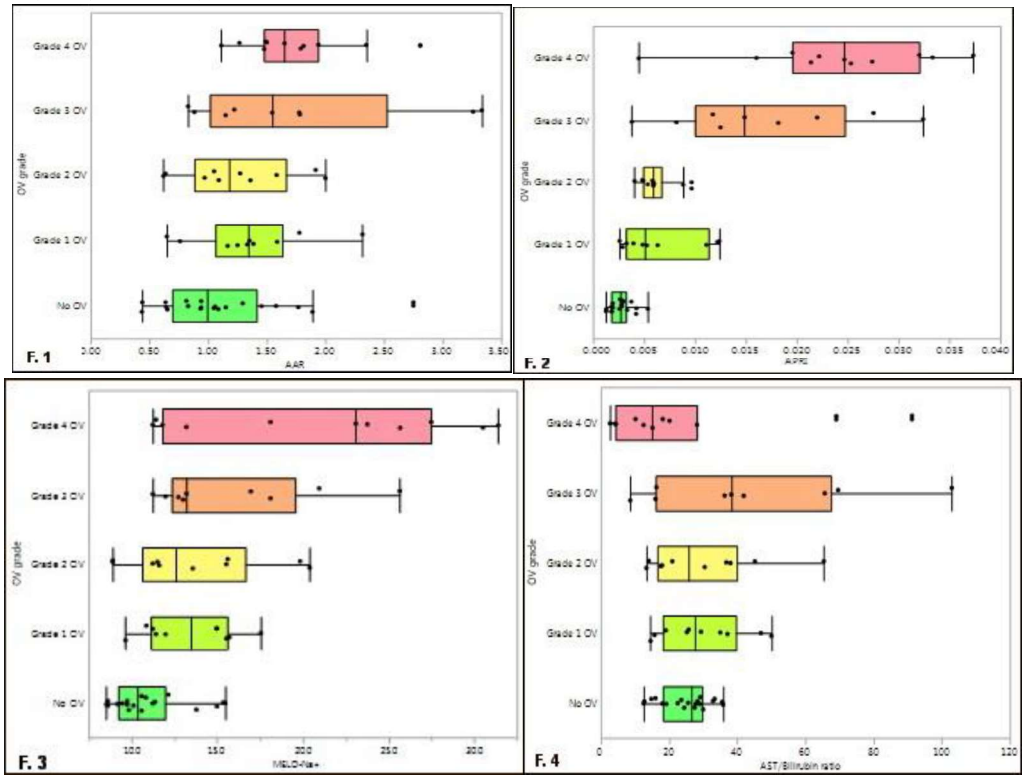
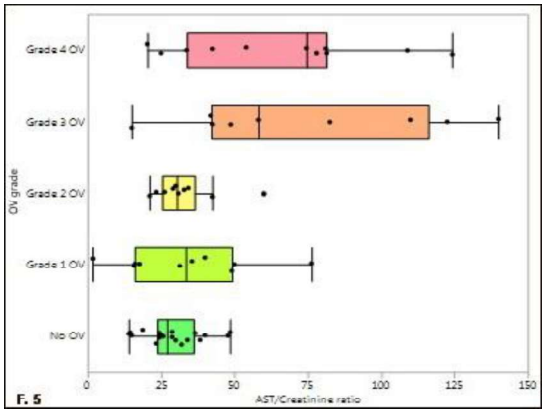
Explanation of figures

Figs.1- 5: Box plot illustrating the correlation between OV grade and APRI score (Fig. 1), AAR (Fig. 2), MELD-Na^{+} (Fig. 3), AST/creatinine ratio (Fig. 4), AST/bilirubin ratio (Fig. 5). Box represents the interquartile range. Line inside box represented median. Whiskers represent minimum and maximum values. Dots represent individual observation)

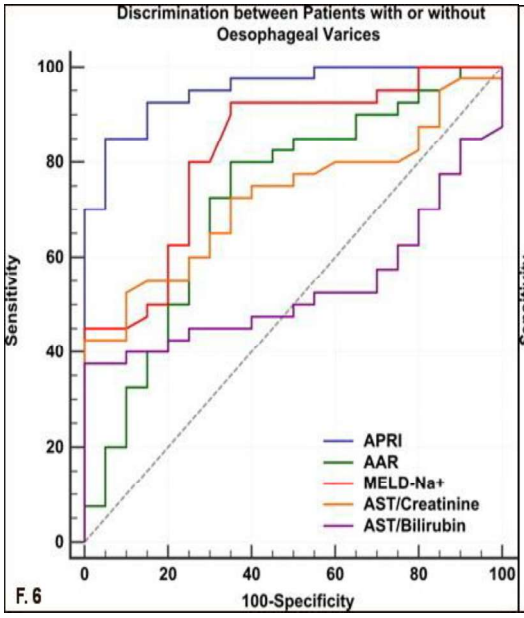
Fig.6: Receiver-operating characteristic (ROC) curves for discrimination between patients with or without esophageal varices using APRI, AAR, MELD-Na+, AST/creatinine ratio or AST/bilirubin ratio.

Fig.7: Receiver-operating characteristic (ROC) curves for discrimination between patients with grade 3-4 or grade 0-2 esophageal varices using APRI, AAR, MELD-Na+, AST/creatinine or AST/bilirubin.

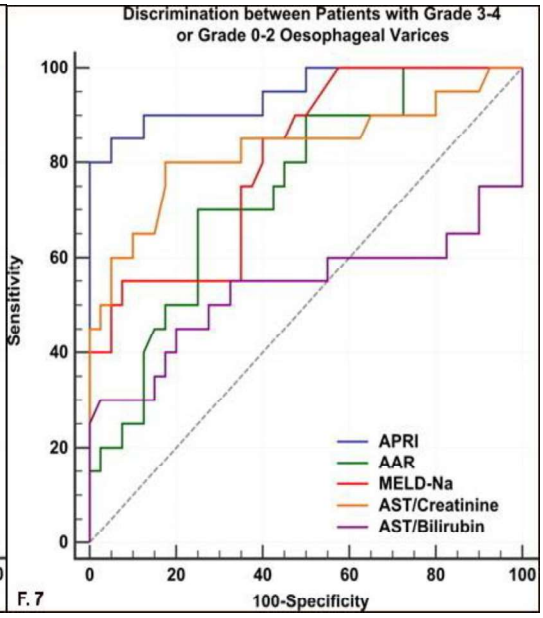



Grade 4 OV
Grade 3 OV
Grade 2 OV
Grade 1 OV
No OV
OV grade
0
25
50
75
100
125
150
AST/Creatinine ratio

F. 5


Discrimination between Patients with or without Oesophageal Varices
Sensitivity
100-Specificity
APRI
AAR
MELD-Na+
AST/Creatinine
AST/Bilirubin
0
20
40
60
80
100

F. 6


Discrimination between Patients with Grade 3-4 or Grade 0-2 Oesophageal Varices
Sensitivity
100-Specificity
APRI
AAR
MELD-Na
AST/Creatinine
AST/Bilirubin
0
20
40
60
80
100

F. 7