Journal of the Egyptian Society of Parasitology, Vol.45, No.2, August 2015
J. Egypt. Soc. Parasitol. (JESP), 45(2), 2015: 421 - 428

NON-INVASIVE PREDICTORS FOR THE PRESENCE, GRADE AND RISK OF BLEEDING FROM ESOPHAGEAL VARICES IN PATIENTS WITH POST-HEPATITIC CIRRHOSIS

By
Ahmed El Ray[1], Mohamed Mohamed Azab[2], Ibrahim Mohamed Abd El-Aziz[2], Ahmed Abd El-Aleem[2], Mohamed Darwish El-Talkawy[1], Mohamed Abd El-Hameed Abd El-Badea*, Mahmoud El Ansary[1], Abdelaziz Ali Saleem[1] and Tarek Mahmoud Diab[3].
Department of Hepatogastroenterology[1], and Department of Tropical Medicine[2], Faculty of Medicine, Al-Azhar University, Cairo, Department of Parasitology[3], Theodor Bilharz Research Institute[1,3], Imbaba P. O. Box 30, Giza, Egypt.

Abstract

Variceal bleeding is the last step of a chain of events initiatedby an increase in portal pressure, followed by the development and progressive dilation ofvarices until these finally rupture and bleed. The ideal method to diagnose portal hypertension should be accurate, noninvasive, objective, and reproducible. The study evaluated the predictive value of two non-invasive parameters for the diagnosis of esophageal varices (EV): 1- Right liver lobe diameter/serum albumin ratios (RLLD /S. albumin), and 2- Platelet count/splenic bipolar diameter ratios (Platelets count /SBPD). This study included eighty Egyptian patients with post-hepatitic cirrhosis (45males and 35 females). They underwent laboratory ultrasono-graphic and endoscopic examinations within one week. RLLD/S. albumin and Platelets count/SBPD ratios were calculated. The results showed that EV were not detected by upper digestive endoscopy in 25%, while grade I of EV was found in 17.5%, grade II in 17.5%, grade III in 20%, & grade IV in 20%. RLLD/S. albumin concentration ratio diagnosed the varices at cut off value of 3.43 with 95% sensitivity and 80% specificity. Also, it was positively correlated with grading of E.V, when this ratio increased the grading of E.V increases and vice versa. Besides, it predicted bleeding from E.V. at cut off value of 5.096 with 63% sensitivity and 73% specificity. Platelet count/ SBPD ratio predicted the presence of varices at cut off value 1847 with 95% sensitivity and 93% specificity, and negatively correlated with grading of EV, when this ratio decreased grading of E.V increase and vice versa. It also predicted bleeding from E.V. at cut off value of 4809 with 50% sensitivity and 93% specificity.

Key words: Right liver lobe diameter, esophageal varices, platelet count, splenic bipolardiameter.

Introduction

Variceal bleeding is the last step of a chain of events initiated by an increase in portalpressure, followed by the development and progressive dilation of varices until these finally rupture and bleed. The appearance of varices incompensated patients indicates a change from a clinical stage with a very low risk of death at 1 year (stage 1;1% risk) to an intermediate risk stage (stage 2; 3.4% risk). The occurrence of variceal bleeding isa dreadful event, marking the progression to decompensation of the liver disease and to a very high risk of death stage; stage 4;57% risk (D'Amico, 2006).

Esophagogastroduodenoscopy (EGD), via invasive, remained the gold standard for screening of esophageal varices in cirrhotic patients over many years. EGD directly visualizes esophageal varices and signs of impending rupture (Garcia-Tsao, 2001). The ideal method to diagnose portal hypertension should be accurate, noninvasive, objective and reproducible. Existing methods for diagnosis of portal hypertension includeclinical examination, laboratory tests, imaging studies, HVPG measurement and EGD. Some of those methods are invasive, while others are noninvasive.

Noninvasive biochemical prediction of EV was the subject of several previous studies. Assessed biochemical parameters included hemoglobin, platelet count, leukocyte count, serum albumin, and serum bilirubin and pro-

thrombin time in relation to esophageal varices Giannini *et al.* (2003). Clinical prediction of EV through medical history and thorough clinical examination has been the earliest and cheapest method of diagnosis of portal hypertension and its complications. Ascites, splenomegaly, shrunken liver and hepatic encephalopathy are directly correlated to the presence of esophageal varices (Schepis *et al,* 2001).

Several ratios combining radiological and biochemical parameters have been introduced for prediction of presence of EV. Those ratios included Platelet count/ splenic bipolar diameter (SBPD) ratio and Right liver lobe diameter (RLLD)/ Serum albumin ratio. Sensitivity of Platelet count/ SBPD ratio in predicting the presence of esophageal varices was 100 % and the specificity was 93 %. Sensitivity of RLLD/ Serum albumin concentration ratio in prediction of presence of esophageal varices was 83.1% and the specificity was 73.9% (Alempijevic *et al*, 2007). Routine endoscopic screening of all patients with liver cirrhosis with or without EV has health service cost implications, as 35% to 70% of patients with cirrhosis have EV and up to 30% have large varices. Therefore, it might be cost-effective to identify those patients who would benefit most from routine screening (Giannini *et al,* 2003).

This work aimed to evaluate the predictive value of 2 non-invasive parameters (RLLD/ serum albumin ratios and Platelet count/ SBPD ratios) for the diagnosis of EV; their grading and the prediction of bleeding varices.

Patients, Materials and Methods

This study includes 80 patients treated for post viral liver cirrhosis admitted to the department of Hepatogastroenterology in Theodor Bilharz Research Institute from July 2010 to June 2011. Cirrhosis diagnosis was based on clinical features, laboratory test, imaging diagnostics, and liver histology whenever possible.

The following information was collected for each patient: age, gender, etiology of cirrhosis, biochemical parameters (aspartate aminotransferase, alanine aminotransferase, total bilirubin, serum albumin, prothrombin activity, and platelet count), presence and degree of esophageal varices and degree of liver function Impairment by Child-Pugh classes. Cirrhosis etiology was determined as viral if hepatitis B surface antigen or hepatitis C serum markers were positive. All studied subjects underwent ultrasonographic examination of the upper abdomen. The right lobe diameters (RLLD) in the mid clavicular line, as well as the spleen bipolar diameter (SBPD) were measured for three times and the mean value was recorded.

Using the laboratory and ultrasonographic values, the study calculated two ratios: RLLD/S.albumin and RLLD /S.albumin and Platelets count /SBPD. Varices in the level of mucosa were recognized as grade I, those smaller than 5 mm fulfilling less than 1/3 of the esophageal lumen were recognized as grade Ⅱ, grade Ⅲ were varices larger than 5 mm fulfilling more than 1/3 of the esophageal, while grade Ⅳ varices occupied more than 2/3 of esophageal lumen. Patients with previous variceal bleeding, porto-systemic shunts and those taking beta blockers medications and patients with coexistent illness or infection that could influence the liver and spleen size were excluded.

Child-Pugh score was calculated using five variables (ascites, encephalopathy, bilirubin, albumin, and prothrombin time). Values 1, 2 or 3 were assigned to each of these variables due to increasing abnormality, and the score calculated as sum of the five variables for each patient. A Child-Pugh score less than 7 was considered as class A, from 7 to 9 as class B, while any score greater than 9 was as class C. Laboratory test, ultrasonographic and endoscopic examinations were performed within one week.

The Ethic Committee of Theodor Bilharz Research Institute approved the study (FWA 00010609.) and all patients were given an informed consent prior to inclusion.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS, version 10.0). Basic descriptive statistics included means, standard deviations, ranges and percentages. For correlation analysis, we used Spearman's test. Differences were considered statistically significant if the two-tailed P value was less than 0.05. Sensitivity and specificity, as well as the best cut-off value for the diagnosis of varices were calculated using ROC curves.

Results

According to upper GIT endoscopic findings, the patients were classified into 5 groups: G1: 20 patients with liver cirrhosis but without EV (control). G2: 14 patients with liver cirrhosis and grade I EV. G3: 14 patients with liver cirrhosis and grade II EV: 6 of them presented by first attack of hematemesis and 8 discovered during routine examination. G4: 16 patients with liver cirrhosis and grade III EV: 8 of them presented by first attack of hematemesis and 8 discovered during routine examination and G5: 16 patients with liver cirrhosis and grade IV EV: 8 of them presented by first attack of hematemesis and 8 discovered during routine examination. Details are given in tables (1, 2, 3, 4 & 5) and figures (1, 2, 3 & 4).

Table 1: Demographic features of groups

Items	G1 (n= 20)	G 2 (n= 14)	G3 (n= 14)	G4 (n= 16)	G5 (n= 16)
Age (yrs.)	39-63	34-67	34-67	43-66	45-67
Mean ± SD	46.70±6.53	52.50±8.64	52.43±10.86	54.13±6.78	54.94±6.37
Female/Male	11/9 (55/45%)	8/6 (57.14/42.86%)	6/8 (42.86/57.14%)	4/12 (25/75%)	6/10 (37.5/62.5%)

Table 2: Child's classification in the studied groups

Items	Child A	Child B	Child C
G1 (n= 20)	19 (95%)	1 (5%)	0 (0%)
G2 (n= 14)	7 (50%)	4 (28.6%)	3 (21.4%)
G3 (n= 14)	1 (7.1%)	9 (64.3%)	4 (28.6%)
G4 (n= 16)	1 (6.3%)	5 (31.3%)	10 (62.5%)
G5 (n= 16)	1 (6.3%)	4 (25%)	11 (68.8%)

RLLD/S. albumin ratio, Platelet count/ SBPD ratio, SBPD and S.albumin were significant in differentiation between patients without varices and patients with varices; RLLD showed non-significant in difference between patients with or without varices.

Table 3: Comparison of calculated variables in patients with and without esophageal varices.

Items	No EV (n= 20)	EV (n= 60)	*p*- value
RLLD /S. albumin	3.94±0.88	5.28±1.86	0.003**
Platelets count /SBPD	15054.46±4206.85	6613.56±3468.46	0.001**
S. albumin	3.57±0.47	2.57±0.64	0.001**
RLLD	13.89±2.40	12.71±2.74	0.089
Platelets count	184350.00±47942.15	100298.33±44613.76	0.001**
SBPD	12.56±1.57	15.46±2.13	0.001**

Values = mean ± SD. ** $p< 0.01$= highly significant.

All patients, RLLD/S.albumin ratio showed positive significant correlations with E.V. i.e., any decrease in RLLD/ S.albumin ratio was possibly associated with a decrease in grading of EV and Child's score. Platelets count/SBPD ratio showed significant negative correlation with EV & Child's score i.e., any decrease in that ratio (as in advanced cirrhosis) was associated with increase in grading of EV and Child's score (Tab.4).

Table 4: Correlation of RLLD /S.albumin and Platelets count/SBPD ratios with EV and Child's score

Variable	RLLD /S.albumin ratio		Platelets count /SBPD Ratio	
Correlated	r	*P*	R	*p*
EV	0.305	0.018*	-0.633	0.001**
Child's score	0.316	0.014*	-0.399	0.002**

r= Correlation coefficient * $p< 0.05$= significant. ** $p< 0.01$= highly significant.

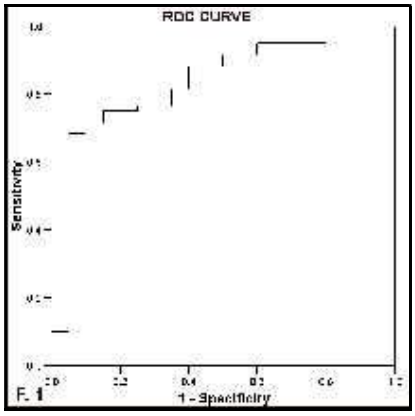

Fig. 1: ROC curve showed cut off value for best sensitivity and specificity of RLLD /S.albumin ratio in difference between patients with and without EV. AUC=0.834 with best cut off value at 3.34 where sensitivity was 95% & specificity 80%.

Test Result Variable(s): RLLD/S.albumin

Area under curve (AUC)	Cut-off	Sensitivity	Specificity
0.834	3.34	0.95	0.80

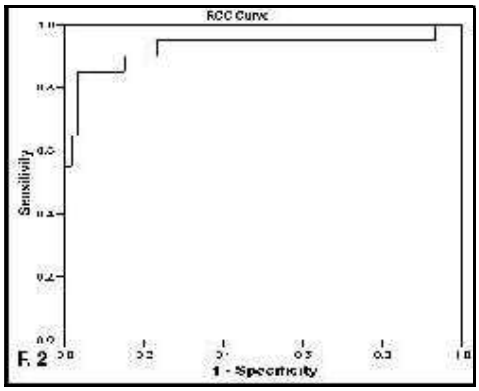

Fig. 2: ROC curve showed cut off value for best sensitivity and specificity of Platelets count /SBPD ratio differentiated between patients with or without varices. Platelet count/SBPD ratio proved highly sensitive and less specific in differentiation between patients with and without esophageal varices with best cut off value at 1847. AUC=0.926 where sensitivity 95 %& specificity 93%.

Area under curve (AUC)	Cut-off	Sensitivity	Specificity
0.926	1847	0.95	0.93

Table 5: Ratios and ultrasonographic findings in groups.

Variables	Control(n=20)	G1 (n= 14)	G2 (n= 14)	G3 (n= 16)	G4 (n= 16)	*p*-value
Platelets count/SBPD Ratio	15054.46± 4206.85	9334.85± 2103.87	8263.31± 3053.18	5688.97± 3335.42	3713.49± 2223.43	0.001**
RLLD/S. albumin ratio	3.94±0.88	4.52±0.91	4.94±1.07	5.53±1.48	6.35±2.42	0.001**
Splenic diameter (cm)	12.56±1.57	13.84±1.33	14.36±0.91	16.09±1.82	17.21±2.23	0.001**
Rt. Lobe diameter (cm)	13.89±2.40	13.89±1.88	13.54±2.26	12.49±1.96	12.15±2.4	0.074 (NS)
PV diameter (cm)	11.39±1.28	12.42±1.53	13.67±1.24	15.06±0.90	15.83±1.74	0.001**

p- value by ANOVA test. ***p*< 0.01= highly significant.

Table 6: Ratios and ultrasonographic findings in control, esophageal varices without bleeding (GA) and bleeding esophageal varices (GB)

Variables	Control (n= 20)	GA (n= 38)	GB (n= 22)	*p*- value
platelets count/SBPD Ratio	15054.46± 4206.84	7606.51±2791.98	5620.61±3826.24	0.001**
RLLD / S.albumin Ratio	3.94±0.88	4.78±1.16	5.78±2.27	0.001**
Splenic diameter	12.56±1.57	14.60±1.51	16.32±2.33	0.001**
Rt. Lobe diameter	13.89±2.40	13.20±1.87	12.21±3.36	0.085
PV diameter	11.39±1.28	13.21±1.57	15.44±1.90	0.001**

. *p*-value by ANOVA test. ***p*< 0.01= highly significant.

Area under curve (AUC)	Cut-off	Sensitivity	Specificity
0.671	5.096	0.63	0.73

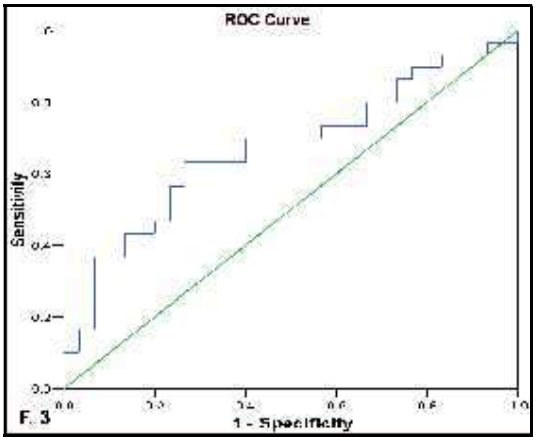

Fig. 3: A ROC curve to determine cut off value for best sensitivity and specificity of RLLD /S.albumin ratio in differentiation between esophageal varices without bleeding and bleeding varices.

RLLD/S. albumin ratio was sensitive and specific to distinguish between esophageal varices in patients with or without bleeding. (AUC=0.671) with best cut off value at 5.096 where sensitivity 63 % & specificity 73 %.

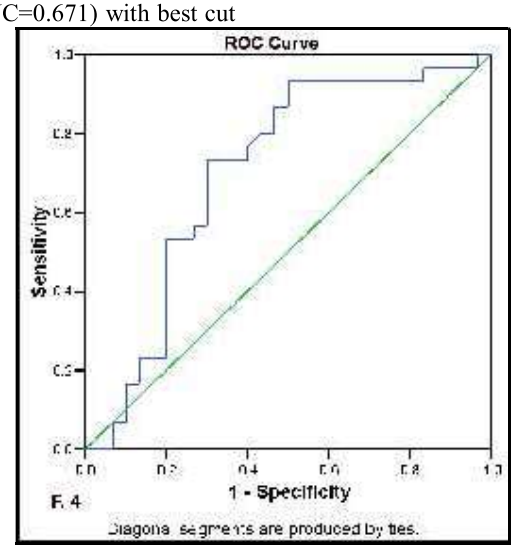

Figure 4: ROC curve to determine cut off value for best sensitivity and specificity of platelet count/SBPD ratio in differentiation between esophageal varices without bleeding and patients with bleeding varices.

Area under curve (AUC)	Cut-off	Sensitivity	Specificity
0.706	4809	0.50	0.93

Platelet count/SBPD ratio less sensitive and highly specific to differentiate between patients with or without varices bleeding (AUC=0.706.) with best cut off value at 4809, sensitivity 50% and specificity 93%.

Discussion

It was estimated that 100 screening endoscopic examinations need to be performed to prevent 1 to 2 cases of variceal bleeding. Therefore, the identification of clinical features and investigations that can accurately predict EV and help identifying patients at greatest risk are important. Predictors of bleeding should help to identify patients with the highest prevalence of esophageal varices and improve the yield and cost-effectiveness of endoscopic screening (Berzigotti *et al,* 2011). Repeated endoscopic examinations are unpleasant for patients, and have cost impact on health care insurance. Therefore, numerous non-invasive parameters have been investigated for assessment of presence of esophageal varices, its grading, and prediction for bleeding (Garcia-Tsao, 2001).

In the present cohort S. albumin showed highly significant differences (P<0.01) in

patients with EV compared to patients without varices. These results agreed with Sharma *et al.* (2007) who found that S. albumin was lowest in patients with large esophageal varices with a mean value = 3.0, range =1.9-4.6, while in patients without esophageal varices, S. albumin was higher with a mean value of = 3.2, range = 1.6-4.5. The present results could be explained by the fact that the rate of albumin synthesis was reduced up to 50% in chronic liver disease and S. albumin was reduced in cirrhosis due to an elevated distribution volume in haemodilution, particularly in association with ascites. Hypoalbuminemia is considered a very important marker of liver dysfunction. However, hypoalbuminemia with chronic liver disease can complicate several associated conditions such as poor nutritional status, immune mediated nephritis associated with viral hepatitis, protein losing enteropathies and any associated inflammatory process. Therefore, hypoalbuminemia may not be the result of liver dysfunction alone. And that is why; it could not stand alone as a single parameter for prediction of presence and risk of bleeding of esophageal varices. However, it has been used in relation to right liver lobe diameter as another marker for liver dysfunction to predict varices (Garcia-Tsao, 2001).

RLLD/ S. albumin ratio shows highly significant differences ($P<0.01$) in patients with bleeding EV compared to non-bleeding EV and patients without varices. This ratio combined an anatomical and a functional parameter of liver disease. With the progress of liver disease, hepatomegaly was observed, and the synthetic function of the liveris more or less normal. Finally, with further progress of liver disease and occurrence of cirrhosis, the liver becomes shrunken and serum albumin decreases. Although S. albumin level can serve as an index of liver synthetic capacity, several factors make albumin concentrations difficult to interpret and thus affect the ratio. Albumin has a plasma half-life of three weeks; therefore, serum albumin concentrations change slowly in response to alterations in synthesis. Also, because two thirds of the amount of body albumin is located in the extravascular and extracellular space; changes in distribution can alter the serum concentration. Combination of one or more of those factors may alter S. albumin and therefore alter the sensitivity and specificity ratio (Kuntz and Kuntz, 2006).

Statistically, in the present study, RLLD/ S. Albumin ratio proved to be sensitive and specific in differentiation between patients without varices and patients with varices (AUC=0.834) with the best cut off value at 3.43 where sensitivity was 95 % and specificity was 80%. This agreed with Alempijevic *et al.* (2007) who found that RLLD/ S.albumin ratio shows overall 83.1% sensitivity and 73.9% specificity in the diagnosis of EV at a cut off value of 4.45. Predictive values, likelihood ratios and accuracy of ratio were not calculated (Garcia-Tsao, 2001).

Platelets count was highest in patients without EV compared to patients with EV. Platelet count may decrease for several reasons in chronic liver disease: thrombocytopenia may be secondary to hypersplenism, impaired platelet production, increased fibrinolytic activity, or decreased thrombopoietin production by the diseased liver (Agha *et al*, 2008). Thus, the use of platelet count alone as a non-invasive predictor of EV can be misleading and cannot be solely attributed to portal hypertension (Zaman, 2003).

The SBPD was highest in patients with bleeding EV compared to non-bleeding EV and patients without EV. The results agreed with Giannini *et al.* (2003) who found that splenic diameter of patients without EV had a mean value of 110mm (range = 90-190) while the splenic diameter of patients with EV had a mean value of 155mm (range = 90-210). Whereas, Agha *et al*. (2008) found that splenic diameter of patients without EV had a mean value of 123mm (range = 98-157) and splenic diameter of patients with EV had a mean value of 141mm (range = 102-181). The present results could be explained by higher portal pressure in patients

with bleeding varices than that of the other two studies. Splenomegaly in chronic liver disease is usually congestive splenomegaly due to portal hypertension (Kuntz and Kuntz, 2006).

Others found no correlation between the splenic size and EV (Pillette *et al*, 1999; Schepis *et al*, 2001; Zaman *et al*, 2001). These differences with the studies that recommend splenic size for the prediction of EV were attributed to differences in the etiology and the stage of liver cirrhosis of the studied population. Thus, using the platelets count/ SBPD ratio in the present study as parameter linking thrombocytopenia to splenic size was taken into consideration the decrease in platelet count which most likely depends on hypersplenism caused by portal hypertension. Platelet count/ SBPD ratio bypasses the possible drawback as it "normalizes" platelet count to splenic sequestration, most likely representing aliquot of thrombocytopenia caused by portal hypertension (Zaman, 2003).

In the present study, platelets count /SBPD ratio was higher in patients without varices, compared to those with non-bleeding or bleeding EV with the best cut off value at 1847 with sensitivity 95% and specificity 93%. Giannini *et al*. (2003) found that platelet count/spleen diameter ratio was 100% sensitivity, 71% specificity, 96% positive predictive value & 100% negative predictive value in diagnosis of EV at a cut off value 909. Giannini *et al.* (2005) found platelet count/ SBPD ratio 100% sensitivity, 73% specificity, 71% positive predictive value, 100% negative predictive value and 93.5% accuracy in diagnosis of EV at a cut off value 909. Agha *et al.* (2008) found that platelet count/ spleen diameter gave 100% sensitivity, 97.6% specificity, 93.8% positive predictive value, 100% negative predictive value, 0.01 negative likelihood ratio and 42 positive likelihood ratio for the EV diagnosis in patients with compensated cirrhosis. In decompensated cirrhosis, the ratio showed 100% sensitivity, 95.9% specificity, 100% negative predictive value, 97.6% positive predictive value, 0.01 negative likelihood ratio and 24.3 positive likelihood ratio for diagnosis of EV at a cut off value of 909.

To use these parameters for detection of different grades of EV, the present study found that RLLD had no role in this issue. However, S. albumin concentration, SBPD, RLLD/s. albumin concentration ratio & platelets count/SBPD ratio gave highly significant values. Serum albumin concentration was lower in patients with higher grade of varices than those with lower grade whatever the history of bleeding or not and RLLD/ serum albumin concentration ratio was significantly increasing in patients with higher grades of varices than those with lower grades. SBPD was higher in patients with higher grade of varices than those with lower grade whatever there a history of bleeding or not and platelets count/SBPD ratio was significantly decreasing in patients with higher grades of varices than those with lower grades. This agreed with Alempijevic *et al*. (2007) who identified the risk of development of esophageal varices and the parameters grading. Also, to use the previous parameters for prediction of bleeding from EV the present study found RLLD/ S. albumin ratio can predict bleeding at cut off value of 5.096 with 63% sensitivity and 73% specificity. Platelets count /SBPD ratio predicted bleeding EV at cut off value of 4809 with 50% sensitivity and 93% specificity. Platelet count/SBPD and RLLD/S. albumin ratios gave good predictors for EV (Alempijevic *et al,* 2007). In the present study, there was also positive significant correlation of RLLD/S. albumin ratio and negative significant correlation of platelets count /SBPD ratio with the presence of EV. This correlation supports the studies indicated that newly introduced ratio was predictive for EV. Those ratios were less likely to be used to exclude patients from initial endoscopic screening; but it might decrease unnecessary follow up endoscopies and help to identify patients at higher risks for EV development.

Transient elastography (TE) is a novel non-invasive technology measuring liver stiffness that has gained popularity over the past few years. Although TE has been initially proposed to assess liver fibrosis, a good correlation was reported between liver stiffness values and HVPG as well as presence of EV, suggested that it could be a good tool for noninvasive portal hypertension evaluation (Castera and Bosch, 2012). When HVPG values exceed 10 to 12mm Hg, threshold for clinically significant portal hypertension and for the development of varices, portal pressure became largely independent from stiffness/ fibrosis (De Franchis and Dell'Era, 2014). More sophisticated imaging methods were under evaluation as MR Elastography and acoustic radiation force imaging (Berzigotti *et al*, 2011).

Conclusion

Combination of different noninvasive tests might provide complementary information, resulting in increased diagnostic value.

The RLLD/S. albumin and platelet count/ SBPD ratios proved as two useful noninvasive parameters. They provided accurate information pertinent to the presence of esophageal varices, their grading and for prediction of bleeding in patients with post-hepatic cirrhosis. The platelet count/spleen diameter ratio might be used for better rationalization of medical resources and use of endoscopy.

References

Agha, A, Anwar, E, Bashir, K, Savarino, V, Giannini, EG, 2008: External validation of the platelet count/spleen diameter ratio for the diagnosis of esophageal varices in hepatitis C virus-related cirrhosis. Dig. Dis. Sci. 54, 3:654-60.

Alempijevic, T, Bulat, V, Djuranovic, S, Kovacevic, N, Jesic, R, *et al*, 2007: Right liver lobe /albumin ratio: Contribution to non-invasive assessment of portal hypertension. World J. Gastroenterol. 13, 40:5331-5.

Berzigotti, A, Ashkenazi, E, Reverter, E, Abraldes, JG, Bosch, J, 2011: Non-invasive diagnostic and prognostic evaluation of liver cirrhosis and portal hypertension. Dis. Markers 31, 3: 129-38.

Castera, L, Pinzani, M, Bosch, J, 2012: Non-invasive evaluation of portal hypertension by transient elastography. J. Hepatol. 56, 3:696-703.

D'Amico, G, Garcia-Tsao, G, Pagliaro, L, 2006: Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J. Hepatol. 44:217-31.

De Franchis, R, Dell'Era, A, 2014: Invasive and noninvasive methods to diagnose portal hypertension and esophageal varices. Clin. Liver Dis. 18:293-302.

Garcia-Tsao, G, 2001: Current management of the complications of cirrhosis and portal hypertension: Variceal hemorrhage, ascites and spontaneous bacterial peritonitis. Gastroenterol. 120, 3:726-48.

Giannini, E, Botta, F, Borro, P, Risso, D, Romagnoli, P, *et al*, 2003: Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict presence of esophageal varices in patients with liver cirrhosis. Gut 52:1200-5.

Giannini, EG, Botta, F, Borro, P, Dulbecco, P, Testa, E, *et al*, 2005: Application of the platelet count/spleen diameter ratio to rule out the presence of esophageal varices in patients with cirrhosis: a validation study based on follow-up. Dig. Liver Dis. 37, 10:779-85.

Kuntz, E, Kuntz, HD, 2006: Hepatology Principles and Practice, 2nd English Ed., Springer Publications, Germany.

Peck-Radosavljevic, M, 2000: Thrombocytopenia in liver disease. Canad. J. Gastroenterol. 14:D60-6.

Pillette, C, Oberti, F, Aubé, C, Rousselet, M, Bedossa, P, *et al*, 1999: Non-invasive diagnosis of esophageal varices in chronic liver diseases. J. Hepatol. 31, 5:867-73.

Schepis, F, Cammà, C, Niceforo, D, 2001: Which patients should undergo endoscopic screening for esophageal varices detection? Hepatol. 33:333-8.

Sharma, SK, Aggarwal, R, 2007: Prediction of large esophageal varices in patients with cirrhosis of the liver using clinical, laboratory and imaging parameters. J. Gastroenterol. Hepatol. 22, 11:1909-15.

Zaman, A, 2003: Current management of esophageal varices. Gastroenterol. 6:499-507.

Zaman, A, Decker, T, Lapidus, J, 2001: Risk factors for the presence of varcies in cirrhotic patients without a history of variceal hemorrhage. Arch. Int. Med. 161:2564-70.