A novel non-invasive Ratio for oesophageal varices prediction in HCV- liver cirrhosis Egyptian patients.

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Abstract: Background/Aims: A growing need for endoscopic screening of cirrhotic patients has emerged aiming at prevention of bleeding before its occurrence. The increased flow of patients on endoscopy units might not meet demands of cost effectiveness for patients and hospitals particularly in developing nations. This study was conducted to evaluate the value of right liver lobe diameter/prothrombin time ratio for predicting the presence of esophageal varices and the risk of variceal bleeding in patients with chronic liver disease .METHODS: one hundred twenty cases with HCV- liver cirrhosis were studied. Sixty patients with chronic liver disease and no esophageal varices, thirty patients with chronic liver disease and non-bleeding esophageal varices and thirty patients with chronic liver disease and bleeding esophageal varices were tested. A complete biochemical workup, upper gastrointestinal endoscopy and ultrasonographic examination were performed to all patients. Right liver lobe diameter/prothrombin time, Right liver lobe diameter/ serum albumin and platelet count/ splenic bipolar diameter ratios were calculated. Comparison between the three studied groups regarding the calculated ratios was evaluated. RESULTS: RLLD/PT ratio was able to differentiate between patients with no esophageal varices and patients with non-bleeding esophageal varices with sensitivity of 90 % and specificity of 60% at a cut-off value of 9.0033. RLLD/PT was also able to differentiate between patients with no esophageal varices and patients with bleeding esophageal varices with sensitivity of 90% and specificity of 80% at a cut-off value of 8.9637.CONCLUSION: The right liver lobe diameter/prothrombin time ratio may be suggested as a novel noninvasive parameter predicting presence of esophageal varices in patients with chronic liver disease.
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Key words: portal hypertension; esophageal varices; liver cirrhosis; noninvasive markers; right liver lobe diameter.

1. Introduction

Bleeding esophageal varices are one of the most common causes of mortality among patients with chronic liver disease. The incidence of varices in cirrhotic patients is approximately 60-80 percent. The risk of bleeding may reach 25-35 percent of all cases within the first year of variceal detection. The mortality from each episode of variceal bleeding is 17-57 percent [1]. Within the first two years of detection of varices, the incidence of the first attack of bleeding ranges from 20 to 40 percent of all cases, whereas the incidence of recurrent bleeding is 30-40 percent within the following 2 to 3 days and 60 percent within one week. This makes the prevention of esophageal variceal bleeding the cornerstone of long-term management of patients with liver cirrhosis [2] .A growing need for endoscopic screening of cirrhotic patients has emerged aiming at prevention of bleeding before its occurrence [3] . The incidence of bleeding can be reduced with beta-blockers [4]. Also, prophylactic endoscopic variceal ligation can decrease the incidence of variceal bleeding and mortality in patients with liver cirrhosis who have large varices [5]. That is why, annual endoscopic screening is highly recommended for patients with small esophageal varices while the screening is Indicated every two years for patients with liver cirrhosis without diagnosed varices. The increased flow of patients on endoscopy units might not meet demands of cost effectiveness for patients and hospitals [6] .Some studies have evaluated possible non-invasive markers of esophageal varices in cirrhotic patients. The studies concluded that by selecting patients for endoscopic screening based on a few laboratory and/or ultrasonographic variables, the number of unnecessary endoscopies will be reduced, while the rate of undiagnosed varices at risk of bleeding remains acceptably low[7,8] .

2. Subjects and Methods

This study was conducted on 120 patients with liver cirrhosis in the Department of Gastroenterology and Hepatology, Ain Shams University Hospitals. The patients were divided into two main groups according to the results of their assessment. Group 1[G1] included 60 patients with chronic liver disease and with no esophageal varices. Group 2[G2] included 60 patients; age and sex matched to group 1 patients and were further subdivided into two subgroups. Subgroup 2A[G2A] included 30 patients with chronic liver disease and non-bleeding esophageal varices[NBV]. Subgroup

2B [G2B] included 30 patients with chronic liver disease presenting with bleeding esophageal varices [BV].

All patients were subjected to full medical history taking, thoroughclinical examination, laboratory investigations including, Liver Function Tests: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and direct serum bilirubin[S.bil.], total protein and serum albumin, alkaline phosphatase by standard laboratory tests, Renal Function Tests: Serum sodium, serum potassium, serum creatinine and blood urea nitrogen (BUN), Urine analysis and protein creatinine ratio, Coagulation Profile: Prothrombin time (PT), partial thromboplastin time (PTT) and international normalized ratio (INR) by standard lab. tests and Complete Blood Count with platelet count. Abdominal Ultrasonography was performed with measurement of the right liver lobe diameter in mid-clavicular line as well as bipolar splenic diameter. It was performed by a single sonographer. Esophago-gastroscopy was done for detection and grading of esophageal varices using endoscopy. Calculation of the right liver lobe diameter [RLLD]/serum albumin concentration [S.Alb.], platelet count [PC]/spleen bipolar diameter [SPBD] and right liver lobe diameter/prothrombin time [PT] ratios was done with statistical analysis of results. All cases were HCV-antibody positive and PCR confirmed HCV-RNA positivity.

Exclusion criteria: We excluded patients on previous treatment with beta blockers, blood disease, renal disease, acute illness other than bleeding varices, chronic infectious, inflammatory diseases or malignancy, other than chronic liver disease, patients with bilharzias is and causes of liver cirrhosis other than HCV.

The study was approved by our ethical committee and all patients signed a written informed consent prior to inclusion into this study. All collected data were analyzed and correlated. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS). Basic descriptive statistics included means and standard deviations were performed. For correlation analysis, we used ANOVA test, Post-Hoc test and Pearson's correlation coefficient. 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 prediction of varices were calculated using ROC curve.

3. RESULTS

RLLD was non-significantly different on comparing the three groups, despite being higher in patients without varices [G1] than in patients with non-bleeding or bleeding varices [G2]. Splenic bipolar diameter[SBPD], platelet count[PC], serum albumin[S.alb.], prothromine time[PT] ,International normalized ratio[INR], hemoglobin[Hb], blood urea nitrogen[BUN], aspartateaminotransferase[AST], total bilirubin[T.bil.], RLLD/s.alb. Ratio, PC/SBPD ratio, and RLLD/PT ratio were statistically significantly different between the three groups. [Table 1].

Table 1. Comparison between the three groups regarding all parameters by ANOVA test:

Compared Variable	Control [G1] n = 60 (Mean±SD)	NBV [G2A] n = 30 (Mean±SD)	BV [G2B] n = 30 (Mean±SD)	P value
Age (Years)	49.77±13.64	54.27±9.84	53.53±8.08	0.386
RLLD (mm)	137.87±39.69	131±23.99	118.13±32.17	0.199
SBPD (mm)	126.68±31.77	153.33±33.69	165.93±39.76	0.001
PC (10^3/mm3)	187.26±62.40	100.06±46.13	111.47±69.18	0.000
S.Alb. (g/dL)	3.90±0.41	3.22±0.45	3.10±0.37	0.000
PT (second)	12.62±2.17	17.30±5.06	16.57±3.03	0.000
RLLD/S.Alb	33.84±6.31	42.69±10.56	38.84±12.67	0.012
PC/SBPD	1.78±1.52	0.68±0.37	0.67±0.34	0.001
RLLD/PT	10.73±2.50	8.51±3.11	7.13±1.54	0.000
WBC[x10^3/mm^3]	6.36±2.03	6.75±3.25	6.46±3.03	0.896
Hb [g/Dl]	12.72±2.88	9.92±2.34	10.46±2.10	0.001
Na [meq/L]	137.37±3.69	136.80±6.23	133.60±8.82	0.136
K [meq/L]	4.31±0.44	4.37±0.54	4.27±0.55	0.855
Cr.[mg/dl]	0.94±0.24	1.01±0.23	1.00±0.25	0.522
BUN [mg/dl]	16.4±7.01	20.33±7.52	24.4±9.32	0.007
ALT [U/l]	38.83±29.15	43.40±38.67	52.67±31.66	0.406
AST[U/l]	41.97±37.75	53.87±32.58	97.60±107.84	0.022
T.Bil[mg/dl]	1.16±1.03	1.33±0.86	3.01±4.17	0.032
INR	1.14±0.23	1.52±0.52	1.42±0.27	0.001

RLLD; right liver lobe diameter in millimeters.SBPD; splenic bipolar diameter in millimeters. PC; platelet count. S. Alb.; serum albumin.PT; prothrombin time in seconds.cr., serum creatinine. T. Bil.; total bilirubin.

RLLD/Serum albumin ratio was statistically significantly lower in patients with no varices [G 1] than in patients with non-bleeding varices [G 2A] [33.8411 ± 6.31315 VS. 42.6933 ± 10.55811 and Mean difference by Post Hoc test = 8.852, p value =0.004]. [Table 2].

Platelet count/SBPD ratio was statistically significant in differentiation between patients with no varices [G1] and patients with non-bleeding varices [G 2A] [1.7825 ± 1.51889 VS. 0.6848 ± 0.36598, and

Mean difference by Post Hoc test = 1.098, p value = 0.003]. [Table 2]

RLLD/PT ratio was statistically significant in differentiation between patients with no varices [G 1] and patients with non-bleeding varices [G 2A] [Mean = 10.7314 ± 2.50390 VS. 8.5105 ± 3.1120, and Mean difference by Post Hoc test = 2.22, p value = 0.006. [Table 2] .

Table 2. Comparison between Group 1 and Group 2A regarding RLLD/S.Alb, PC/SBPD and RLLD/PT ratios using Post Hoc test:

Ratio	Control [G1] N = 60 (Mean±SD)	NBV [G2A] N = 30 (Mean±SD)	Mean Diff.	Stand. error	P value
RLLD/S.Alb	33.84±6.31	42.69±10.56	-8.85*	2.05	0.004
PC/SBPD	1.78±1.52	0.68±0.37	1.09*	0.35	0.003
RLLD/PT	10.73±2.50	8.51±3.11	2.22*	0.78	0.006

NBV; Non Bleeding Varices, RLLD/S.Alb; Right liver lobe diameter/serum albumin ratio, PC/SBPD; platelet count/splenic bipolar diameter, RLLD/PT; Right liver lobe diameter/Prothrombin time.

RLLD/S.Alb ratio was not statistically significant in differentiation between patients with no varices [G 1] and patients with bleeding varices [G 2B] [33.8411 ± 6.31315 VS. 38.8361 ± 12.6658, and Mean difference by Post Hoc test = 4.99, p value =0.096]. [Table 3]

PC/SBPD ratio was statistically significant in differentiation between patients with no varices [G 1] and patients with bleeding varices [G 2B] [1.7825 ± 1.51889 VS. 0.6712 ± 0.34491, and Mean difference by Post Hoc test = 1.111, p value = 0.003]. [Table 3]

RLLD/PT ratio was statistically highly significant in differentiation between patients with no varices [G 1] and patients with bleeding varices [G 2B] [10.7314 ± 2.50390 VS. 7.1335 ± 1.5375, Mean difference by Post Hoc test = 3.598, p value = 0.000]. [Table 3].

Table 3. Comparison between Group 1 and Group 2B regarding RLLD/S.Alb, PC/SBPD and RLLD/PT ratiosusingPostHoctest.

Ratio	Control [G1] N = 60 (Mean±SD)	BV [G2B] N = 30 (Mean±SD)	Mean Diff.	Stand error	P value
RLLD/S.Alb	33.84±6.31	38.84±12.67	-4.99	2.05	0.096
PC/SBPD	1.78±1.52	0.67±0.34	1.11*	0.35	0.003
RLLD/PT	10.73±2.50	7.13±1.54	3.59*	0.78	0.000

NBV; Non Bleeding Varices, RLLD/S.Alb; Right liver lobe diameter/serum albumin ratio, PC/SBPD; platelet count/splenic bipolar diameter, RLLD/PT; Right liver lobe diameter/Prothrombin time.

RLLD/S.Alb ratio was not statistically significant in differentiation between patients with non-bleeding varices [G 2A] and patients with bleeding varices [G 2B] (42.6933 ± 10.55811 vs. 38.8361 ± 12.6658, and Mean difference by Post Hoc test = 3.857, p value =0.262]. [Table 4]

PC/SBPD ratio was not statistically significant in differentiation between patients with non-bleeding varices [G2A] and patients with bleeding varices [G 2B] [0.6848 ± 0.36598 vs. 0.6712 ± 0.34491, and Mean difference by Post Hoc test = 0.0136, p value = 0.973]. [Table 4]

RLLD/PT ratio was not statistically significant in differentiation between patients with non-bleeding varices [G 2A] and patients with bleeding varices [G 2B] [Mean = 8.5105 ± 3.1120 vs. 7.1335 ± 1.5375, and Mean difference by Post Hoc test = 1.377, p value = 0.134]. [Table 4].

Table 4. Comparison between Group 2A and Group 2B regarding RLLD/S.Alb, PC/SBPD and RLLD/PT ratiosusingPostHoctest.

Ratio	NBV[G2A] N = 30 (Mean±SD)	BV [G2B] N = 30 (Mean±SD)	Mean Diff.	Stand.error	P value
RLLD/S.Alb	42.69±10.56	38.84±12.67	3.86	3.41	0.262
MPC/SBPD	0.68±0.37	0.67±0.34	0.01	0.40	0.973
RLLD/PT	8.51±3.11	7.13±1.54	1.38	0.90	0.134

NBV; Non Bleeding Varices, RLLD/S.Alb; Right liver lobe diameter/serum albumin ratio, PC/SBPD; platelet count/splenic bipolar diameter, RLLD/PT; Right liver lobe diameter/Prothrombin time.

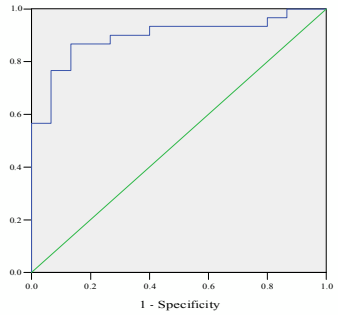
RLLD/PT ratio showed a significant positive correlation withRLLd/S.Alb. Ratio, PC/SPBD ratio, PC, and S.Alb. [Table 5].

Table 5. Correlation between RLLD/PT ratio and other parameters by Pearson's correlation test:

ratio		RLLD/S.Alb.	PC/SPBD	PC	S.Alb.	SBPD
RLLD/PT	r	0.291	0.324	0.433	0.682	-0.233
	p	0.024	0.012	0.001	0.000	0.074

Platelet count/SBPD ratio proved to be highly sensitive and less specific in differentiation between patients with no varices [Group 1] and patients with bleeding varices [Group 2B] (AUC=0.896) with the best cut off value at 0.8357 where sensitivity was 90 % and specificity was 73.3 %. The positive predictive value of the test was 62.76 %, while the negative predictive value of the test was 93.61 %. The positive likelihood ratio of the test was 3.37. The negative likelihood ratio of the test was 0.136. The accuracy of the test was 78.87 %. (Figure 1).

Figure 1. shows a ROC curve to determine the cut off value for the best sensitivity and specificity of platelet count/SBPD ratio in differentiation between patients with no varices [Group 1] and patients with bleeding varices [Group 2B].

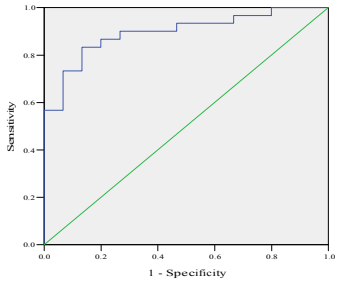


AUC	COV	Sens.	Spec.	PPV	NPV	LR+	LR-	Accuracy
0.896	0.8357	90%	73.3%	62.7%	93.6%	3.37	0.136	78.87 %

AUC; Area under the curve, COV; Cut-off value, Sens.: Sensitivity, Spec.; Specificity, PPV; Positive predictive value, NPV; Negative predictive value, LR+; Positive likelihood ratio, LR-; Negative likelihood ratio.

Platelet count/SBPD ratio proved to be both sensitive and specific in differentiation between patients with no varices [Group 1] and patients with non-bleeding varices [Group 2A] (AUC=0.896) with the best cut off value at 0.8979 where sensitivity was 90 % and specificity was 73.3 %. The positive predictive value of the test was 62.76 %, while the negative predictive value of the test was 93.61 %. The positive likelihood ratio of the test was 3.37. The negative likelihood ratio of the test was 0.136. The accuracy of the test was 78.87 %. (Figure 2).

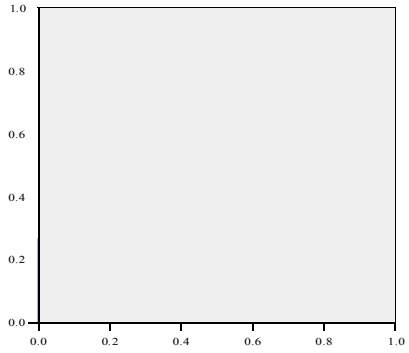
Figure 2. shows a ROC curve to determine the cut off value for the best sensitivity and specificity platelet count/SBPD ratio in differentiation between patients with no varices [Group 1] and patients with non-bleeding varices [Group 2A].



AUC	COV	Sens.	Spec.	PPV	NPV	LR+	LR-	Accuracy
0.896	0.8979	90%	73.3%	62.76%	93.61%	3.37	0.136	78.87 %

The RLLD/Serum Albumin ratio proved to be sensitive and specific in differentiation between patients with no varices [Group 1] and patients with non-bleeding varices [Group 2A] (AUC=0.777) with the best cut off value at 35.4248 where sensitivity was 80 % and specificity was 70 %. The positive predictive value of the test was 57.14 %, while the negative predictive value of the test was 87.5 %. The positive likelihood ratio of the test was 2.6. The negative likelihood ratio of the test was 0.286. The accuracy of the test was 73.33 %. (Figure 3).

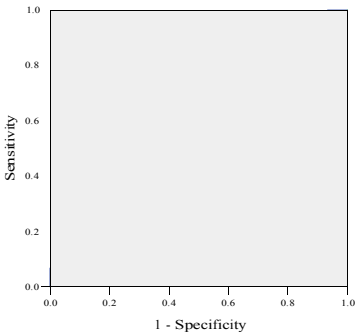
Figure 3. shows a ROC curve to determine the cut off value for the best sensitivity and specificity of RLLD/Serum Albumin ratio in differentiation between patients with no varices [Group 1] and patients with non-bleeding varices [Group 2A].



AUC	COV	Sens.	Spec.	PPV	NPV	LR+	LR-	Accuracy
0.777	35.4248	80 %	70 %	57.14%	87.5%	2.6	0.286	73.33 %

RLLD/ PT ratio proved to be highly sensitive but less specific in differentiation between patients with no varices [Group 1] and patients with non-bleeding varices [Group 2A] (AUC=0.723) with the best cut off value at 9.0033 where sensitivity was 90 % and specificity was 60 %. The positive predictive value of the test was 52.94 %, while the negative predictive value of the test was 92.31 %. The positive likelihood ratio of the test was 2.25. The negative likelihood ratio of the test was 0.167. The accuracy of the test was 70 %. (Figure 4).

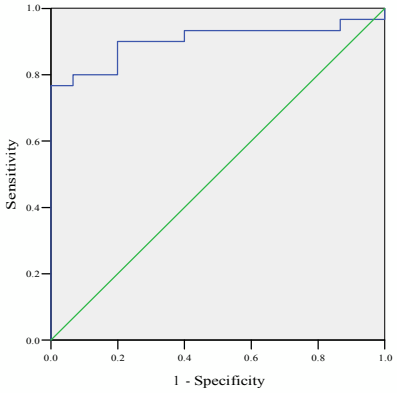
Figure 4. shows a ROC curve to determine the cut off value for the best sensitivity and specificity of RLLD/ PT ratio in differentiation between patients with no varices [Group 1] and patients with non-bleeding varices [Group 2A].



AUC	COV	Sens.	Spec.	PPV	NPV	LR+	LR-	Accuracy
0.723	9.003	90%	60%	52.9%	92.3%	2.25	0.167	70 %

RLLD/PT ratio proved to be highly sensitive and more specific in differentiation between patients with no varices [Group 1] and patients with bleeding varices [Group 2B] (AUC=0.902) with the best cut off value at 8.9637 where sensitivity was 90 % and specificity was 80 %. The positive predictive value of the test was 69.23 %, while the negative predictive value of the test was 94.11 %. The positive likelihood ratio of the test was 4.5. The negative likelihood ratio of the test was 0.125. The accuracy of the test was 83.33 %. (Figure 5)

Figure 5. shows a ROC curve to determine the cut off value for the best sensitivity and specificity of RLLD/ PT ratio in differentiation between patients with no varices [Group 1] and patients with bleeding varices [Group 2B].



AUC	COV	Sens.	Spec.	PPV	NPV	LR+	LR-	Accuracy
0.902	8.9637	90 %	80 %	69.23%	94.11%	4.5	0.125	83.33 %

The three ratios proved to be non-significant in differentiation between patients with non-bleeding varices [Group 2A] and patients with bleeding varices [Group 2B]. RLLD/ S.Alb. Ratio was also non-significant in differentiation between patients with no esophageal varices [Group 1] and patients with bleeding varices [Group 2B].

4. DISCUSSION

Portal hypertension is an important element of survival in patients with liver cirrhosis[9]. However, the formation of esophageal varices with subsequent bleeding is an important cause of morbidity and mortality in that patients. Therefore, early detection of esophageal varices and timely introduction of beta-blockers and band ligation for primary prevention of bleeding, decrease the morbidity and may improve quality of life in liver cirrhosis patients. Endoscopy is the standard method of detection and risk stratification of esophageal varices, but it is unpleasant to some patients, invasive and costly. In addition, prevalence of varices is variable and screening all patients with cirrhosis by endoscopy implies unnecessary endoscopies. For that reasons non-invasive prediction of esophageal varices is of great help in developing countries, in particular those with huge number of patients with chronic liver disease.

In this study we contributed to the non-invasive predictors of the presence of esophageal varices in chronic liver disease patients a new simple test combining the RLLD as determined by ultrasound and a simple laboratory test PT. The RLLD/PT ratio being significantly different on comparing patients with liver cirrhosis and without esophageal varices and patients with liver cirrhosis and non-bleeding and/or bleeding esophageal varices [Table 1,2,3], significantly positively correlated with RLLD/Albumin ratio, platelet/spleen diameter ratio and platelet count[Table 5], is suggested as a simple test for esophageal varices prediction. RLLD/PT ratio at a cutoff value of 9 give a sensitivity of 90% and specificity of 60% in differentiating patients without varices from patients with varices suggesting that cutoff value a critical threshold at or below it screening endoscopy is reasonably indicated with positive predictive value of 52.9% and a value above 9 to make screening endoscopy not indicated with a negative predictive value of 92.31%[figure4]. At a cutoff value of 8.96 the ratio give a sensitivity of 90% ,specificity of 80% ,positive predictive value of 69% and negative predictive value of 94% in differentiation between patients without varices and patients with bleeding varices[figure5], is this finding make a cutoff value below 9 a risk factor for variceal bleeding? A question to be answered by further studies correlating that ratio with other risk factors for variceal bleeding as the ratio was non-significantly different between patients with non-bleeding varices and patients with bleeding varices [Table 4].

RLLD/PT ratio at a cutoff value of 9.0 showed a higher sensitivity and lower specificity in

differentiating patients with liver cirrhosis and without varices from patients with cirrhosis and portal hypertension with varices compared to RLLD/Albumin ratio at a cutoff value of 35.42 [90% and 60% vs. 80% and 70%, respectively] [figure 3 and 4]. But, it showed equal sensitivity and lower specificity compared to platelet/spleen ratio at a cutoff value of 0.897 [90% and 60% vs. 90% and 73%, respectively] [figure 2 and 4], suggesting the new ratio a comparable test to other studied ratios for varices prediction. Further studies may clarify the value of combining all the three ratio in varices diagnosis.

Our results can be explained by the fact that portal hypertension development is related both to increased vascular resistance and increased portal blood flow and collaterals develop when pressure gradient between portal vein and hepatic vein rises above a certain threshold. Increased resistance is due to disturbed architecture and nodularity of cirrhosis, endothelial dysfunction[10], collagen deposition in the space of Disse[11], and contractile properties of stellate cells [12], factors that may be indirectly, roughly and superficially represented by RLLD. While increased portal flow is related to splanchnic vasodilatation and increased cardiac output , both of which is related to the severity of liver cell failure[13], represented in this ratio by the PT, one of the parameters in the Child score. Therefore, the ratio may represent the pathophysiological mechanisms of portal hypertension and varices development.

In a previous study, a cutoff value of 4.4 for RLLD/Albumin ratio was suggested for varices diagnosis in cirrhotic patients with 83% sensitivity and 74% specificity [14], compared to 3.5 with comparable sensitivity and specificity ie 80% and 70%, respectively, after correction for the unit of serum albumin measurement in our study. This suggestes the need for further multicenter studies including a large number of patients with different ethnic background for determining the best cutoff value for that ratio.

Platelet/spleen diameter ratio in our study at a cutoff value of 898 give a comparable sensitivity and specificity[90% and 73% ,respectively] for varices prediction in another study[15], which suggested 909 as best cutoff value with 91.5% sensitivity and 67% specificity , making the best cutoff value still in question to apply to all populations .

The limitations of this study are the small number of patients, including only HCV patients, studying only the Egyptian patients, not correlating the new ratio to red signs and variceal size, or to Child [CTP] score. Further prospective validation studies are needed.

5. CONCLUSION

Right liver lobe diameter/ prothrombin time ratio, at a cut off value of 9.0033 serves as a noninvasive predictor of presence of esophageal varices with adequate sensitivity, specificity and accuracy.

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