Assessment of Right Liver Lobe Size / Serum Albumin Ratio as a New Non-Invasive Predictor for the Presence of Oesophageal Varices in Egyptian Patients with HCV Related Liver Cirrhosis

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ABSTRACT

Background: Oesophageal varices are the most critical porto-systemic shunts that develop secondary to portal hypertension, which is considered the main complication of liver cirrhosis. Many studies recommend the screening of all cirrhotic patients by endoscopy, but repeated endoscopic examinations are unpleasant for patients and have a high-cost impact and burden on endoscopic units. **Objective:** This study aimed to evaluate the accuracy of using the right liver lobe size/serum albumin ratio as a non-invasive predictor of esophageal varices in patients with HCV-related liver cirrhosis.
Patients Methods: This prospective study included 30 patients with liver cirrhosis and 30 patients who underwent upper gastrointestinal endoscopy for any causes other than liver cirrhosis. All studied subjects underwent a detailed history and clinical examination, biochemical workup, upper gastrointestinal endoscopy, and abdominal ultrasound. The right liver lobe/serum albumin ratio was calculated for all patients.
Results: There was a statistically significant difference between the control and the study subgroups as regards the Right lobe of the Liver/Albumin ratio (p-value 0.007). The diagnostic accuracy of the Right lobe of the Liver/Albumin ratio was assessed using the ROC curve which revealed a sensitivity of 86.67% and specificity of 73.33% at cut-off value >3.88, with an acceptable discriminative accuracy of 79.9%.
Conclusion: The use of Right liver lobe/serum albumin ratio can help physicians by restricting the use of endoscopic screening only to patients presenting a high probability of esophageal varices. This is especially useful in clinical settings where resources are limited, and endoscopic facilities are not present in all areas.
Keywords: Non-invasive diagnosis of oesophageal varices, Right liver lobe size/serum albumin ratio, Oesophageal varices, HCV.

INTRODUCTION

Esophageal varices are submucosal, expanding esophageal veins connecting the portal and systemic circuits [1]. This is caused by portal hypertension most commonly due to cirrhosis, resistance to portal blood flow, and increased inward portal venous blood flow [2]. The most common fatal complication of cirrhosis is the rupture of varicose veins. The severity of the liver disease is associated with the presence of varicose veins and the risk of bleeding [3, 4]. Variceal bleeding occurs in 20-40% of cirrhotic patients with esophageal varices and is associated with high morbidity and mortality [5]. Mortality associated with each episode of varicose veins ranges from 17% to 57% [6].

Gastroesophageal endoscopy (EGD) is the gold standard procedure used in the diagnosis of esophageal varices (GOVs). Based on the endoscopic evaluation, GOVs are classified into small (<5 mm) and large (> 5 mm) varicose veins for clinical management. The disadvantages of endoscopy include the risks of anesthesia, high cost, bleeding, and risk of aspiration (7). Endoscopic ultrasound (EUS) has also been evaluated as a diagnostic tool in the evaluation of GOVs. Endoscopic ultrasound imaging is better than EGD at detecting gastric varices (GVs), and its ability to evaluate the anatomy of the

lateral and perforate veins makes it an excellent choice in monitoring treatment response to endoscopic varicose ligation (EVL) and predicting their recurrence [8, 9]. Currently, EUS is not considered a primary diagnostic method due to the Limited availability of local expertise. A recent meta-analysis reviewed the use of capsule endoscopy for the diagnosis and classification of esophageal varices and noted a diagnostic accuracy of 90% with a combined sensitivity and specificity of 83% and 85%, respectively [10].

The inability of capsule endoscopy to detect GVs is a major drawback. Although capsule endoscopy is relatively less invasive and does not require anesthesia, diagnostic sensitivity is not enough to call for index monitoring. There may be a consideration for a select subset of high-risk patients who do not wish to undergo further conventional endoscopic evaluation [11, 12]. For these reasons, several studies have examined how to identify patients with varicose veins using non-invasive or minimally invasive methods to avoid endoscopy in patients with low risk of varicose veins. However, it is not accurate enough to diagnose or exclude clinically significant portal hypertension (CSPH) (HVPG> 12 mm Hg). Specifically, transient

elastography, platelet count, spleen volume, magnetic resonance imaging, and splenosclerosis are among the most frequently used predictors of CSPH and varicose veins in patients with cirrhosis. The presence of jihadist portal collaterals on ultrasound, computed tomography, or magnetic resonance imaging is indicative of CSPH and requires an endoscopic examination [7].

Measurement of liver stiffness using transient elastography combined with a platelet count can rule out the presence of high-risk varicose veins [13]. Hepatic stiffness <20 kPa and platelet count> 150,000 / μl indicates a less than 5% chance of developing high-risk varicose veins, and endoscopic examination can be safely postponed if continuous clinical monitoring can be assured [14]. The use of endoscopic prophylactic tape ligation and non-selective beta-blockers can reduce the risk of esophageal bleeding by 50% [15]. Therefore, the guidelines recommend that all patients with cirrhosis be screened by endoscopy to identify those at risk of bleeding so that they can be administered prophylactic [14]. Practice guidelines issued by the American College of Gastroenterology (ACG) and the American Association for the Study of Liver Diseases (AASLD) for esophageal varices indicate that all cirrhotic patients should be screened for varicose veins at least every two years [16].

In this study, we aim to investigate non-invasive predictors of esophageal varices in patients with liver cirrhosis using the right liver lobe/serum albumin ratio as a non-invasive predictor of esophageal varices in cirrhotic patients, for restricting the performance of screening endoscopy.

PATIENTS AND METHODS

This cross-sectional study was conducted on sixty patients who were selected from Internal Medicine and Hepatology outpatient clinics and inpatient wards at Ain shams University Hospitals. After eligibility was confirmed, written informed consent was obtained from all patients participating in the study. Patients were divided into 2 groups:

Group 1 (cases): which included 30 age and sex-matched cirrhotic patients due to HCV infection with or without liver cell failure. The diagnosis was based on physical findings, laboratory investigations, and ultrasonographic findings.

Group 2 (control): This included 30 subjects attending the endoscopy unit for conditions other than cirrhosis.

Patients with previous variceal bleeding, previous endoscopic sclerotherapy or band ligation of oesophageal varices, previous surgery for portal hypertension or trans jugular, intrahepatic, portosystemic shunt (TIPS), patients those taking Beta-blocker (e.g, propanolol or carvedilol) medications, patients with other causes of liver cirrhosis, patients with portal vein thrombosis or

HCC, other conditions that may affect serum albumin level, serum platelet, liver or spleen size (e.g. diabetes mellitus, renal disease, cancer, malnutrition, malabsorption syndrome, infections, patients on regular albumin therapy and patients with hematological diseases), also other causes of hepatomegaly as fatty liver, congested liver or infiltration of the liver (by e.g, lymphoma or sarcoidosis) were excluded from the study.

All participants were subjected to:
- **Full history taking and clinical examination.**
- **Laboratory investigations included:**
  o Complete Blood Count (CBC).
  o Liver function tests: Alanine Transaminase (ALT), Aspartate Transaminase (AST), Serum Bilirubin (total, direct & indirect), Serum Albumin, and Prothrombin Time (PT) and activity, alfa fetoprotein.
  o Hepatitis viral markers e.g. Hepatitis B surface Antigen (HBsAg), Hepatitis C Virus antibody (HCV Ab).
  o Renal function tests including serum creatinine, urea, and urine analysis.
  o Random blood sugar.
- **Abdominal Ultrasound:** patients were prepared for abdominal ultrasound by Hitachi, EUB-5500 after fasting for eight hours. One investigator performed all measurements to reduce the inter-observer errors in assessing the diameters. Abdominal ultrasound included:

(A) Diagnosis of liver cirrhosis or normal liver.

(B) Excluding other diseases of the liver rather than cirrhosis and any disease of other organs in the abdomen.

(C) Ultrasound measurement of the right liver lobe diameter(cm):

While the patient is in the supine position a curvilinear probe of a high-resolution real-time scanner was placed sub-costally in the right mid-clavicular line in a sagittal plane showing a good liver window. The craniocaudal right lobe diameter at the mid-clavicular line was measured from the diaphragm to the liver edge. Measurements were taken during deep inspiration to reduce masking by the lung, with the right hand under the head to raise the lower costal margin.

(D) Ultrasound measurement of the spleen diameter (cm):

While the patient is in the right lateral decubitus position with the left arm raised away from the abdomen, the transducer was placed between the ribs at the level of the ninth intercostal space, and then the patient was asked to take a deep breath and hold it. The transducer was manipulated in the coronal plane or the coronal oblique plane until a suitable longitudinal view of the spleen is obtained, then the length of the spleen was measured between the

superior and the inferior borders of the spleen. Gel was applied to the upper abdomen before scanning for better resolution.

o Right liver lobe size /serum Albumin ratio was calculated.
o Platelet count/spleen diameter ratio was calculated.
o Upper GI endoscopy to assess the presence of esophageal varices.

Statistical analysis

Data were collected, coded, translated to English to facilitate data manipulation and double entered Microsoft Access, and data analysis was performed using SPSS software version 18 under windows 10.

RESULTS

This cross-sectional study involved 60 patients made of two groups, HCV cirrhotic patients (study group) and non-cirrhotic patients who came for endoscopy for any other causes than liver cirrhosis (control group) each comprising 30 patients.

As regards the epidemiological features of our patients their ages were ranged as follows: Control group ranged from 33 – 69 years with a mean of 48 ± 10.51 (Males represent 50% and females represent 50% also), while the Study group ranged from 45 – 61 years with a mean of 53 ± 4.60 (Males represents 46.67% and females represent 53.33 %).

Table (1): Comparison between control & study groups as regard to laboratory investigations.

	Groups						T-Test	
	Control N=30			Study N=30			T	P-value
AST (U/L)	26	±	8.54	58.5	±	10.16	-2.183	<0.001*
ALT (U/l)	25.5	±	8.76	56	±	9.12	-2.211	<0.001*
Total Bilirubin (mg/dl)	0.9	±	0.20	3.1	±	0.56	-3.468	<0.001*
Direct Bilirubin (mg/dl)	0.2	±	0.01	1.4	±	0.24	-4.217	<0.001*
Indirect Bilirubin (mg/dl)	0.75	±	0.24	1.7	±	0.04	-3.125	<0.001*
Serum Albumin (g/dl)	3.53	±	0.42	2.66	±	0.07	5.326	<0.001*
Prothrombin time "PT" (sec)	12.17	±	1.54	15.91	±	3.00	-4.775	<0.001*
INR	1.01	±	0.02	1.5	±	0.08	-6.661	<0.001*
Urea (mg/dl)	13.5	±	2.89	15	±	2.30	-3.505	<0.005
Creatinine(mg/dl)	0.8	±	0.14	1	±	0.14	-0.470	0.640
White blood cells "WBCs" (x10³ /ml³)	6.95	±	1.78	6.22	±	1.04	-3.574	0.624
Red blood cells "RBCs" (x10³ /ml³)	4.11	±	0.87	3.85	±	0.50	3.250	0.051
Haemoglobin "Hb" (g/dl)	10.8	±	1.94	10.25	±	0.58	1.985	0.052
Alpha fetoprotein (ng/mL)	5.5	±	2.51	75.23	±	17.54	-21.778	<0.001*
Platelet (x10³ /ml³)	238.10	±	8.16	109.47	±	19.82	7.882	<0.001*
Right liver lobe (cm)	13.240	±	1.257	15.357	±	0.837	-4.050	<0.005
Spleen diameter (cm)	12.910	±	1.744	16.543	±	1.793	-7.955	<0.001*
Platelet count /spleen diameter ratio	18.44	±	7.50	6.62	±	1.04	8.570	<0.001*
Right liver lobe size / Serum Albumin ratio	3.750	±	0.295	5.773	±	0.809	-3.728	<0.005

This table showed that there were highly statistically significant difference between the cirrhotic liver group (study group) and the non-cirrhotic group (control group) as regard AST, ALT, Total bilirubin, direct bilirubin, indirect bilirubin, serum albumin, PT, INR, Alpha-fetoprotein (p-value0.001), also there were highly statistically significant difference between the two groups as regard spleen diameter, platelet count (p-value0.001). But there were highly statistically significant differences between both groups as regard Right liver lobe size/Serum Albumin ratio and Right Liver Lobe (p-value <0.005).

Table (2): Grades of OV in the study group

Study groups	Number	%
Grade I varices (Group I)	6	10.00
Grade II varices (Group II)	8	13.33
Grade III varices (Group III)	9	15.55
Grade IV varices (Group IV)	7	11.67
Total	30	100.00

Table 2 showed the grading of oesophageal varices in the study group.

Table (3): Comparison of right liver lobe size between the control group and subgroups of the study group

Groups	Right lobe of Liver			ANOVA	
	Mean	±	SD	F	P-value
Control N=30	13.240	±	1.257	3.971	0.007*
Group I N=6	14.870	±	0.925		
Group II N=8	14.938	±	0.780		
Group III N=9	14.922	±	0.743		
Group IV N=7	14.886	±	1.085		
TUKEY'S Test					
	Control	Group I	Group II	Group III	
Group I	0.089				
Group II	0.163	0.992			
Group III	0.047	1.000	0.997		
Group IV	0.168	0.997	1.000	0.999	

There was a statistically significant difference between subgroups of the study group as regard Rt liver lobe and the grade of O.V.

Table (4): Comparison between the control group and study subgroups as regard serum albumin

Groups	Serum Albumin			ANOVA	
	Mean	±	SD	F	P-value
Control N=30	3.440	±	0.561	5.985	<0.001*
Group I N=6	3.150	±	0.339		
Group II N=8	2.913	±	0.264		
Group III N=9	2.789	±	0.298		
Group IV N=7	2.714	±	0.530		
TUKEY'S Test					
	Control	Group I	Group II	Group III	
Group I N=6	0.658				
Group II N=8	0.056	0.888			
Group III N=9	0.006	0.609	0.984		
Group IV N=7	0.006	0.480	0.929	0.998	

This table showed a highly statistically significant difference between the control group and the study subgroups according to O.V grades as regard serum albumin level (p-value 0.001)

Table (5): Comparison between the control group and study subgroups as regard platelet count

Groups	Platelet count			ANOVA	
	Mean	**±**	**SD**	**F**	**P-value**
Control N=30	238.100	±	8.162	15.717	<0.001*
Group I N=6	135.667	±	19.086		
Group II N=8	113.125	±	7.376		
Group III N=9	106.000	±	12.062		
Group IV N=7	87.286	±	6.473		
TUKEY'S Test					
	Control	**Group I**	**Group II**	**Group III**	
Group I N=6	0.006*				
Group II N=8	<0.001*	0.965			
Group III N=9	<0.001*	0.902	0.999		
Group IV N=7	<0.001*	0.654	0.935	0.977	

This table showed that there was a highly statistically significant difference between the control group and study subgroups as regard platelet count (p-value<0.001).

Table (6): Comparison between the control group and study subgroups as regard spleen diameter

Groups	Spleen diameter			ANOVA	
	Mean	**±**	**SD**	**F**	**P-value**
Control N=30	12.910	±	1.744	36.722	<0.001*
Group I N=6	14.433	±	1.250		
Group II N=8	15.788	±	0.530		
Group III N=9	16.611	±	0.426		
Group IV N=7	19.129	±	0.808		
TUKEY'S Test					
	Control	**Group I**	**Group II**	**Group III**	
Group I N=6	0.109				
Group II N=8	<0.001*	0.368			
Group III N=9	<0.001*	0.031*	0.730		
Group IV N=7	<0.001*	<0.001*	<0.001*	0.005*	

There was a highly statistically significant difference between the control group and study subgroups as regard the spleen diameter (p-value <0.001)

Table (7): Comparison between the control group and study subgroups as regard Right lobe of Liver/Albumin ratio

Groups	Right lobe of Liver/Albumin ratio			ANOVA	
	Mean	**±**	**SD**	**F**	**P-value**
Control N=30	4.048	±	1.295	3.927	0.007*
Group I N=6	4.657	±	0.637		
Group II N=8	4.930	±	0.600		
Group III N=9	5.230	±	0.664		
Group IV N=7	5.451	±	1.189		
TUKEY'S Test					
	Control	**Group I**	**Group II**	**Group III**	
Group I N=6	0.722				
Group II N=8	0.263	0.990			
Group III N=9	0.046	0.855	0.979		
Group IV N=7	0.026	0.685	0.886	0.994	

Table 7 showed that there was a statistically significant difference between the control and the study subgroups as regards the Right lobe of Liver/Albumin ratio (p-value 0.007).

Table (8): Comparison between the control group and study subgroups as regard Platelet count/Spleen diameter ratio

Groups	Platelet count/Spleen diameter ratio			ANOVA	
	Mean	**±**	**SD**	**F**	**P-value**
Control N=30	18.981	±	7.505	18.975	<0.001*
Group I N=6	9.575	±	2.447		
Group II N=8	7.180	±	0.612		
Group III N=9	6.387	±	0.734		
Group IV N=7	4.563	±	0.295		
TUKEY'S Test					
	Control	**Group I**	**Group II**	**Group III**	
Group I N=6	0.003*				
Group II N=8	<0.001*	0.928			
Group III N=9	<0.001*	0.807	0.998		
Group IV N=7	<0.001*	0.482	0.889	0.965	

There was a highly statistically significant difference between the control group and the study subgroups as regard Platelet count/Spleen diameter ratio (p-value <0.001)

Table (9): Statistical analysis of Right lobe of Liver/Albumin ratio and Platelet count/Spleen diameter ratio between Study and Control groups for ROC curve

Statistical Indices						
	Cutoff	Sens.	Spec.	PPV	NPV	Accuracy
Right lobe of Liver/Albumin ratio	>3.88	86.67	73.33	76.5	84.6	79.9%
Platelet count/Spleen diameter ratio	≤1415	96.67	83.33	85.3	96.2	93.4%

The diagnostic accuracy of **the Right lobe of Liver/Albumin ratio** was assessed using the ROC curve which revealed a sensitivity of 86.67% and specificity of 73.33% at cut-off value >3.88, with an acceptable discriminative accuracy of 79.9%, also the diagnostic accuracy of **Platelet count/Spleen diameter ratio** was assessed using ROC curve which revealed a sensitivity 96.67% and specificity of 83.33% at cut-off value ≤1415, with an acceptable discriminative accuracy of 93.4%.
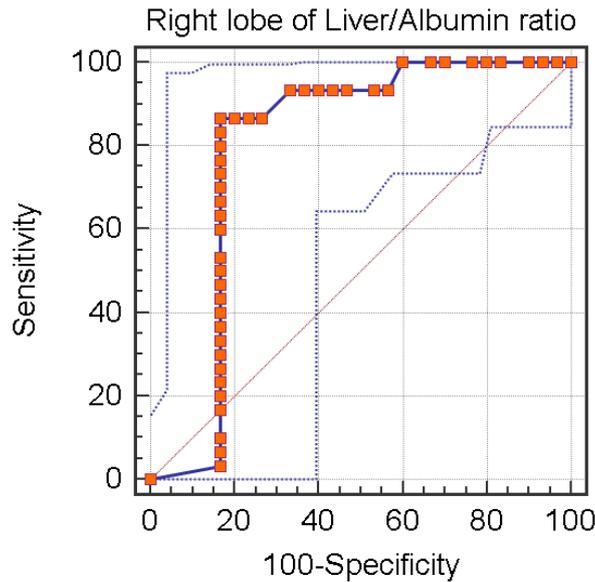
**Figure (1)** ROC curve between Study and Control regarding right liver lobe/Albumin ratio
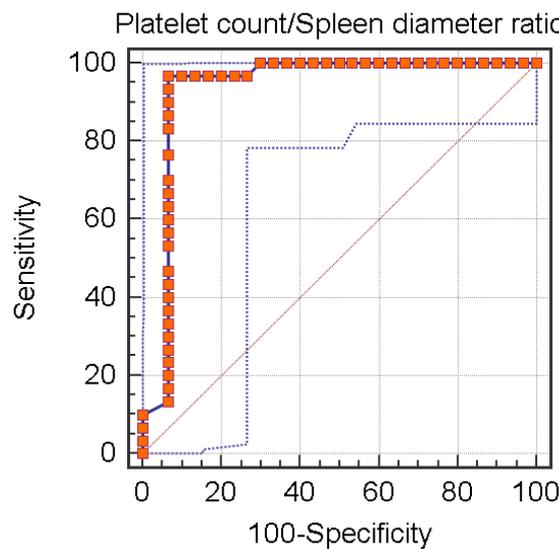
Figure (1): ROC curve between Study and Control regarding Platelet count/spleen diameter ratio.

Table (10): Correlation between Right lobe of Liver/Albumin ratio and Platelet count/Spleen diameter ratio

| Correlations		
	Right lobe of Liver/Albumin ratio	
	R	P-value
Platelet count/Spleen diameter ratio	-0.404	0.027*
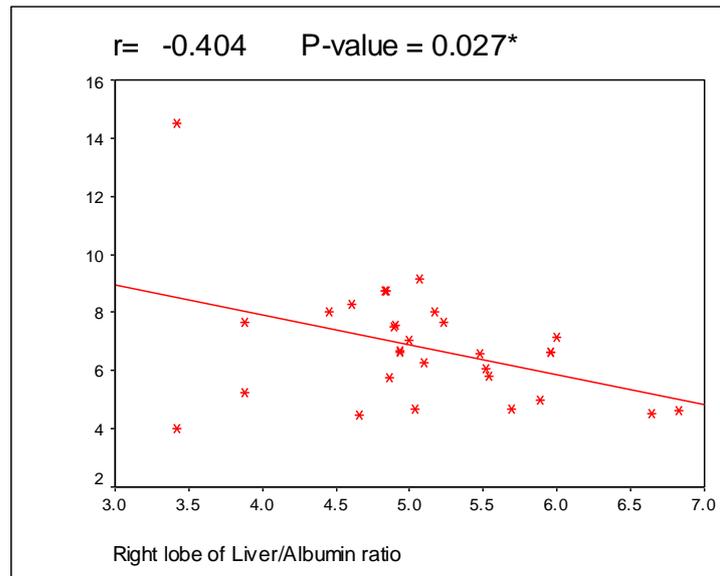
Figure (32): Correlation between Right lobe of Liver/Albumin ratio and Platelet count/Spleen diameter ratio. Table 10 and figure 3 showed that there was a significant negative correlation between the Right lobe of Liver/Albumin ratio and Platelet count/Spleen diameter ratio (p-value=0.027).

DISCUSSION

Oesophageal varices are the most critical porto-systemic shunts that develop secondary to portal hypertension, which is considered the main complication of liver cirrhosis [5].

This study was conducted on 60 cases (divided into 30 cases as control group & 30 patients with HCV-related liver cirrhosis as study group) to evaluate the possibility of using Right liver lobe/serum albumin ratio as a non-invasive predictor of esophageal varices in cirrhotic patients due to HCV, for restriction of performance of screening endoscopy.

Regarding the presence of Oesophageal varices (OV) in the study group, we found that 6 patients have grade I OV, 8 patients have grade II, 9 patients have grade III while 7 patients have grade IV OV.

In this study liver enzymes (AST & ALT), Serum Bilirubin (Total, Direct& indirect), Prothrombin time, INR, and AFP were higher in the study group than in the control group with highly statistically significant difference ($p = <0.001$).

But the serum albumin level was lower in the study group than in the control group with a highly statistically significant difference ($p = <0.001$). Also, we found that serum albumin is decreased as the grade of varices increased.

These results were similar to the results of some researchers [17, 18] which can be explained by the fact that the rate of albumin synthesis is reduced up to 50% in chronic liver disease. Also, serum albumin is reduced in cirrhosis due to an elevated distribution volume in haemodilution, particularly in association with ascites [19].

In this study, WBCs, RBCs, and hemoglobin levels showed a non-significant difference between the control and study groups.

But the platelet count was highly statistically significantly decreased in the study group than in the control group ($p = <0.001$). Also, the platelet count is decreased as the grade of varices increased with a highly significant value ($p = <0.001$). This goes in line with what has been reported in a study by **Gana et al.** [20] that showed that platelet count is significantly decreased in cirrhotic patients with OV.

Also in our study Spleen diameter (SD) increased in the study group than in the control group with a highly statistically significant difference (p= <0.001), and the spleen diameter increased with the increase of the grade of varices with a high statistically significant difference (p= <0.001). This comes in agreement with another study by **Esmat et al.** [21] that reported a high statistically significant correlation between the presence and grade of oesophageal varices with the splenic diameter.

The right liver lobe diameter/serum albumin (RLLD/Alb) ratio was significantly increased in the study group than in the control group (P= <0.005). But there was no statistically significant difference between both groups as regard grades of varices.

In this study, the sensitivity & specificity of the RLLD/Alb ratio was 86.67% & 73.33% respectively and the accuracy of the test was 79.9%, positive predictive value 76.5, negative predictive value 84.6 with the best cut off point value at >3.88.

In comparison to the other similar studies, **Alempijevic and his colleagues** [19] found that RLLD/albumin ratio can be used for the determination of the presence of OV with a sensitivity of 83.1% and

the specificity of 73.9% with a cut-off value of 4.425 which is nearly similar to our study.

Also, our results go in line with the results by **Sanjay and Chandrashekar**[22] who found that the sensitivity of the RLLD/Alb ratio was 83.3 % and the specificity was 29.5% with the best cut off point value 4.42.

Sheta et al. [23] also supported our results with his colleagues who found that RLLD/albumin at a cut-off value of ≥4.92 significantly predicted the presence of EV with 63.61% sensitivity, 97.67% specificity, PPV of 97.3%, and an NPV of 66.7%. The same as in results by **Charan et al.** [24] who found that the sensitivity of RLLD/Alb ratio was 74.4, specificity 94.4, cut-off value 4.27, PPV was 98.4%, NPV was 44.7% and accuracy was 78%.

As regard platelet count/spleen diameter (PC/SD) ratio we found that it was decreased in cirrhotic patients with OV than in the control group with a highly statistically significant difference ($p = <0.001$) (Table 2, Fig. 19). Also, the PC/SD ratio was decreasing as grades of varices was increasing with a highly significant value ($p = <0.001$) (table 9, fig. 25). The sensitivity of PC/SD ratio was 96.67%, specificity was 83.33% and the accuracy of the test was 93.4%, positive predictive value was 85.3, negative predictive value was 96.2 with best cutoff ≤1415 as in (table 10, fig. 27).

This comes in agreement with a study by **Charan et al.** [24] found that the sensitivity of PC/SD ratio was 90.2%, specificity was 88.9%, PPV was 97.4%, NPV was 66.7% and accuracy was 90%, with the best cut-off value at 1167.2 (AUC 0.965).

Finally, a comparison between RLLD/Alb ratio and PC/SD ratio in predicting the presence of OV, showed that the PC/SD ratio had more sensitivity, specificity, and accuracy than did RLLD/Alb ratio, and the correlation between the RLLD/Alb ratio and PC/SD ratio, showed a significant negative correlation between them ($r = -0.404$, $P = 0.027$).

CONCLUSION

The use of Right liver lobe size/serum albumin ratio (with or without using platelet count/spleen diameter ratio) can help physicians as a non-invasive predictor of esophageal varices to restrict the use of endoscopic screening only to patients presenting a high probability of esophageal varices. This is especially useful in clinical settings where resources are limited and endoscopic facilities are not present in all areas.

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