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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 (OV) are discovered in 24% and up to 80% of cirrhotic liver cirrhotic patient and the severity of varices differs from patient to another, oesophageal endoscopy is the best method for evaluating OV.
Objective: As a non-invasive indicator of OV in cirrhotic patients, we hypothesize that we can use the right liver lobe diameter/serum albumin ratio. This will allow us to limit the usage of screening endoscopy.
Patients and Methods: Sixty individuals with cirrhotic liver were included in this cross-sectional analysis. Two equal groups of patients (N=30) were formed: Group (1), which included patients with cirrhosis due to HCV infection with or without LCF and Group (2), which included patients with matching ages and sexes who were visiting an endoscopic unit for problems other than cirrhosis.
Results: Oesophageal varices was statistically correlated with Rt liver lobe diameter/serum albumin ratio (RLLD/Alb). The sensitivity and specificity were 95.7 % and 93.3% respectively and the cutoff point value was >3.98. Plt count/spleen diameter ratio (P/S) demonstrated a statistical correlation with incidence of esophageal varices. The sensitivity was 90.4% and specificity was 98.2% with best cutoff point value≤16.3.
Conclusions: Physicians can benefit from using RLLD/Alb (with or without P/S) as a non-invasive OV predictor.
Keywords: RLLD/Alb, Non-Invasive Predictor, OV, HCV.

INTRODUCTION

Oesophageal varices (OV) are hepatic-systemic shunts in the lower oesophagus that occur as a consequence of liver cirrhosis with consequence of rupture and bleeding, this is why OV puts patients in a critical situation [1]. OV transforms liver cirrhosis patients from asymptomatic mild case to another clinical stage with associated mortality up to 57% [2, 3].

The American College of Gastroenterology and the American Association for the Study of Liver Disease have also agreed that all patients with liver cirrhosis should have upper GIT endoscopy for varices assessment, which should be repeated annually depending on clinical status. [4-6].

Due to variability of occurrence of (OV) among liver cirrhotic patients with wide range from 24% to 80% we thought that screening all patients in developing countries will be costly and puts large burdens on the health care [7-8]. Much research was done to test non-invasive maneuvers for screening for (OV) including CT scanning and video capsule endoscopy [8, 9].

Our study aims at evaluating the accuracy of the RLLD/Ab as a non-invasive predictor of (OV) in patients with liver cirrhosis in order to limit the use of screening endoscopy.

PATIENTS AND METHODS

Our analytic study included 60 cirrhotic cases selected from Hepatology outpatient clinics and inpatient wards at Al-Azhar Assiut University Hospital.

Two equally sized groups of patients were formed (N=30): Patients in groups 1 and 2 were matched for age and sex and as for the second group, patients were undergoing endoscopies for conditions other than cirrhosis. Group 1 included patients who were cirrhotic due to HCV infection with or without LCF.

Inclusion Criteria: HCV-related liver cirrhotic patients.

Exclusion criteria:

1- Patients did not have cirrhotic liver.
2- Subjects with portal vein thrombosis.
3- Subjects with hepatic focal lesions or hepatocellular carcinoma.
4- Those decline sharing in the research.

Investigations done to all cases:

1. **History taking.**
2. **Full physical examination.**
3. **Laboratory investigations** which included:
   - CBC, ALT, AST, direct, total, and indirect serum bilirubin, serum albumin, and (PT), as well as alfa fetoprotein, which are tests for liver function.
   - Viral indicators for hepatitis, such as HBsAg and HCV Ab.
   - Renal function tests, including urea, urethane, and serum cr measurements.
   - Unexpected blood sugar.

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4. **Abdominal US:**
   a) Diagnose live (normal or cirrhotic).
   b) Ruling out any other liver illnesses than cirrhosis.
   c) **Right liver lobe estimation (cm):** In the supine position, the ultrasound probe was put in the RT MCL below costal margin and the patient was asked to take deep breathes.
   d) **Spleen diameter estimation (centimeter):** With the patient in the rt lateral decubitus position, the probe was placed in the lt MAL at the ninth intercostal gap. The patient was instructed to breathe deeply as this procedure is performed.
   e) RLLD/Alb was calculated.
   f) **P/S was calculated.**

Ethical approval:

Al-Azhar Medical Ethics Committee of the Al-Azhar University, Assiut gave its approval to this study. All participants gave written consent after receiving all information. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

The SPSS Version 22 for Windows® was used. To ascertain whether the data distribution was normal, the Shapiro Wilk test was employed. To represent qualitative data, frequencies and relative percentages were used. The chi square test (X^2) was used to determine differences between 2 sets of qualitative variables. Quantitative data were expressed as mean, standard deviation (SD), median, and range. The independent samples t-test was used to compare 2 independent groups of normally distributed variables (parametric data). Significant P values were defined as those below 0.05.

RESULT

Eighty and five patients were assessed for eligibility, twenty-five of them did not meet the selection criteria, and sixty patients (thirty in study group and thirty in control group) remained for the analysis. The CONSORT flowchart of the patients is shown in **Figure (1.**

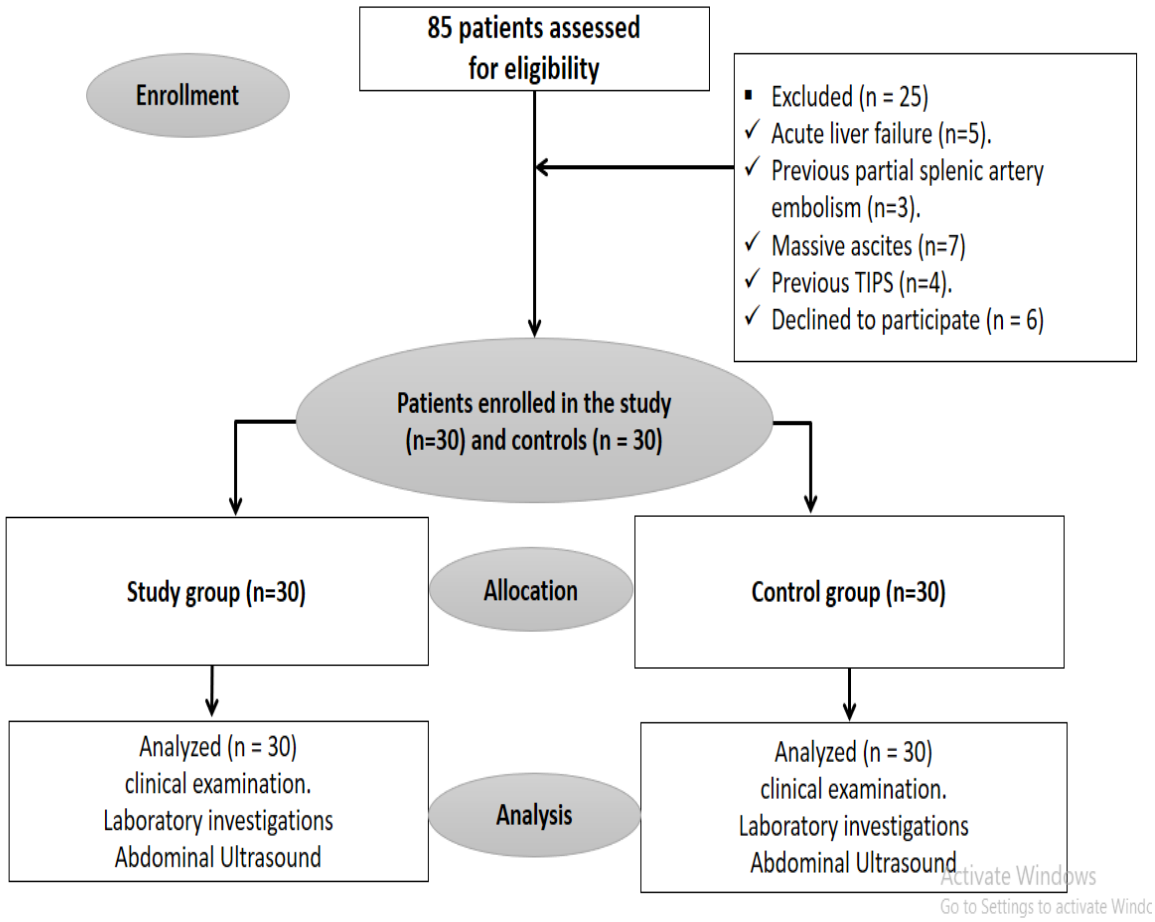

Figure (1): The CONSORT flow chart of the patients through the study

Demographic data in study groups showed that there was non-significant difference between study and control groups regarding to age and sex (**Table (**1**).**

Table (1): Demographic information for the two groups

		Group				p value
		Group A (cases) (N=30)		**Group B (control) (N=30)**		
Age		53.63 ±5.07		49.43 ±9.51		0.037
		N	%	n	%	
Gender	male	22	73.3%	24	80.0%	0.542
	female	8	26.7%	6	20.0%	
Grade of Varices	I	6	20.0%	0	0.0%	---
	II	8	26.7%	0	0.0%	
	III	9	30.0%	0	0.0%	
	IV	7	23.3%	0	0.0%	

Between the two groups, there was no statistically significant different in WBCs, Hb%, and RBCs. However, there was a significant difference between platelet count and INR. There was a statistically significant difference between the two groups in the following measurements: AST, ALT, total Bilirubin, direct bilirubin, indirect bilirubin, and P.T. There was a highly statistically significant difference between groups regarding urea and creatinine (**Table (2**).

Table (2): Laboratory investigations of the studied groups

	Group				**P value**
	Group A (cases) (N=30)		**Group B (control) (N=30)**		
	Mean	SD	Mean	SD	
CBC					
WBC'S (mcL)	6.14	0.65	6.52	0.93	0.103#
RBC'S (mcL)	3.69	0.30	4.02	0.49	0.657#
Hb% (g/dL)	11.07	0.65	11.89	0.90	0.789#
Platelet Count (mcL)	103.2	14.2	300.7	33.7	**<0.001**
Liver function tests					
AST(U/L)	59.37	7.83	28.73	5.83	**<0.001**
ALT (U/L)	54.47	6.97	24.83	5.06	**<0.001**
Total Bilirubin (µmol/L)	2.94	0.42	0.93	0.12	**<0.001**
Direct Bilirubin (µmol/L)	1.36	0.15	0.30	0.08	**<0.001**
Indirect Bilirubin (µmol/L)	1.58	0.30	0.64	0.08	**<0.001**
INR	1.46	0.06	0.98	0.05	**<0.001**
PT	15.37	1.37	12.35	0.84	**<0.001**
Kidney function tests					
Urea (mg/dl)	15.67	1.44	13.20	1.12	**<0.001**
Creatinine (mg/dl)	1.19	0.74	0.91	0.10	**<0.001**

A highly significant difference existed between the 2 groups for spleen diameter, P/S ratio, serum albumin, Rt liver lobe diameter, and RLLD/Alb ratio (**Error! Reference source not found.**).

Table (3): Ultrasonography findings and ratio in the two studied groups

	Group				**P value**
	Group A (cases) (N=30)		**Group B (control) (N=30)**		
	Mean	SD	Mean	SD	
Spleen Diameter	16.13	1.29	13.11	0.65	**<0.001**
Platelet Count/Spleen Diameter	6.48	1.32	23.06	2.88	**<0.001**
S. Albumin	2.77	0.29	3.59	0.34	**<0.001**
Rt Liver lobe diameter	15.36	0.70	13.49	0.49	**<0.001**
Rt Liver lobe diameter/Albumin Ratio	5.61	0.68	3.79	0.41	**<0.001**

There was a statistical significant difference in the Rt hepatic lobe and the grade of OV between the subgroups of the patients group. A substantial difference in blood albumin levels was found between the study subgroups and the control group, as measured by OV grading **(Table 4)**.

Table (4): Right liver lobe diameter and serum Albumin between the control group and subgroups of the study group

	Group										**P value**
	Control		**Group I**		**Group II**		**Group III**		**Group IV**		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Rt Liver lobe diameter	13.49	0.49	14.8	0.23	15.2	0.36	15.28	0.46	16.21	0.80	**<0.001**
P value 1			**<0.001**		**<0.001**		**<0.001**		**<0.001**		
P value 2					0.514		0.272		**<0.001**		
P value 3							0993		**0.002**		
P value 4									**0.004**		
Serum Albumin	3.59	0.34	3.15	0.19	2.70	0.22	2.77	0.21	2.53	0.19	**<0.001**
P value 1			**0.038**		**<0.001**		**<0.001**		**<0.001**		
P value 2					0.338		0.108		0.345		
P value 3							0989		0.718		
P value 4									0.466		

P value 1: compared to control group; P value 2: compared to group I
P value 3: compared to group II; P value 4: compared to group III

There was a substantial statistical difference between the study subgroups and the control group in terms of platelet count. There was a large statistical significant discrepancy in the spleen diameter between the study subgroups and the control group **(Table (5).**

Table (5): Comparison between the control group and study subgroups as regard Spleen Diameter

	Group										**P value**
	Control		**Group I**		**Group II**		**Group III**		**Group IV**		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Platelet Count	300.7	33.7	124.3	7.8	110.7	5.2	92.0	1.87	91.07	1.92	**<0.001**
P value 1			**<0.001**		**<0.001**		**<0.001**		**<0.001**		
P value 2					0.845		0.109		0.125		
P value 3							0.527		0.542		
P value 4									0.989		
Spleen Diameter	13.11	0.65	15.1	0.22	15.06	0.65	16.24	0.42	18.10	0.38	**<0.001**
P value 1			**<0.001**		**<0.001**		**<0.001**		**<0.001**		
P value 2					0.989		**0.003**		**0.004**		
P value 3							**<0.001**		**0.001**		
P value 4									**<0.001**		

P value 1: compared to control group; P value 2: compared to group I
P value 3: compared to group II; P value 4: compared to group III

Platelet count/spleen diameter ratio diagnostic accuracy was assessed using the ROC curve, which demonstrated 90.4% as sensitivity and 98.2% as specificity at cutoff value 16.3 and rt lobe of liver/Alb ratio diagnostic accuracy of 95.7% and 93.3% at cutoff value of >3.98 **(Figure (**2**)**.

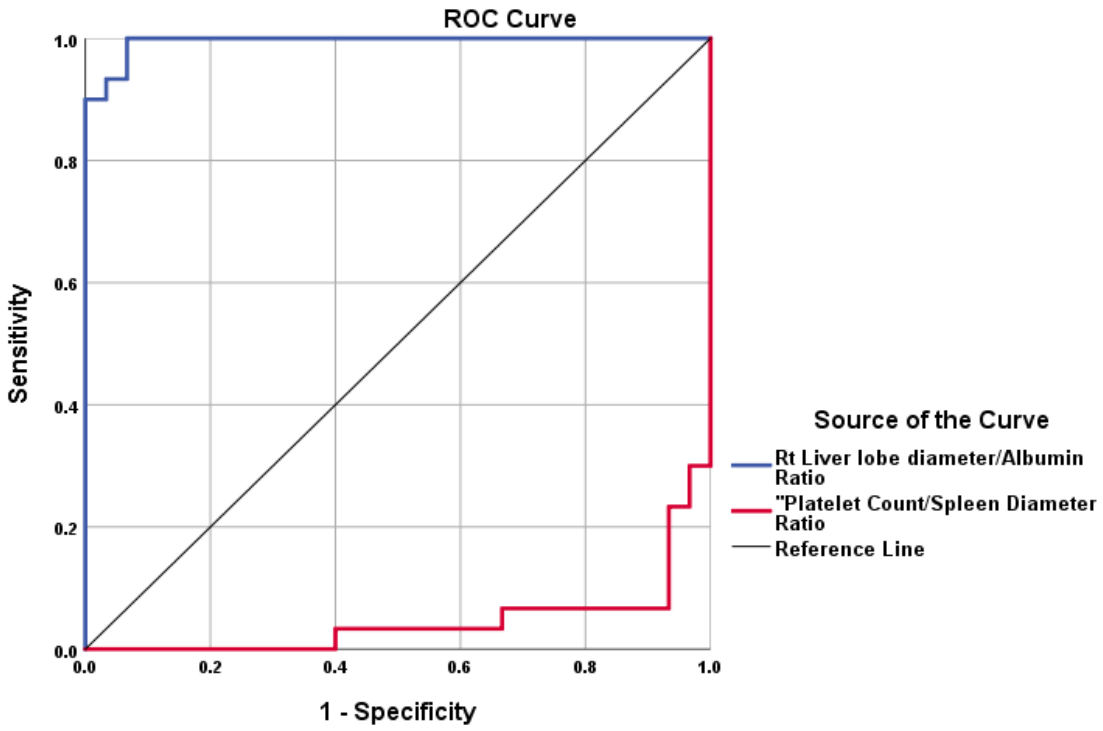

Figure (2): ROC curve between cases and control regarding right liver lobe/Albumin ratio and platelet count/spleen diameter ratio.

A negative correlation with high significance existed between the Rt lobe of Liver/Albumin ratio and the Plt count/spleen diameter ratio (r = -0.784, p 0.001) (

Figure (3**).**

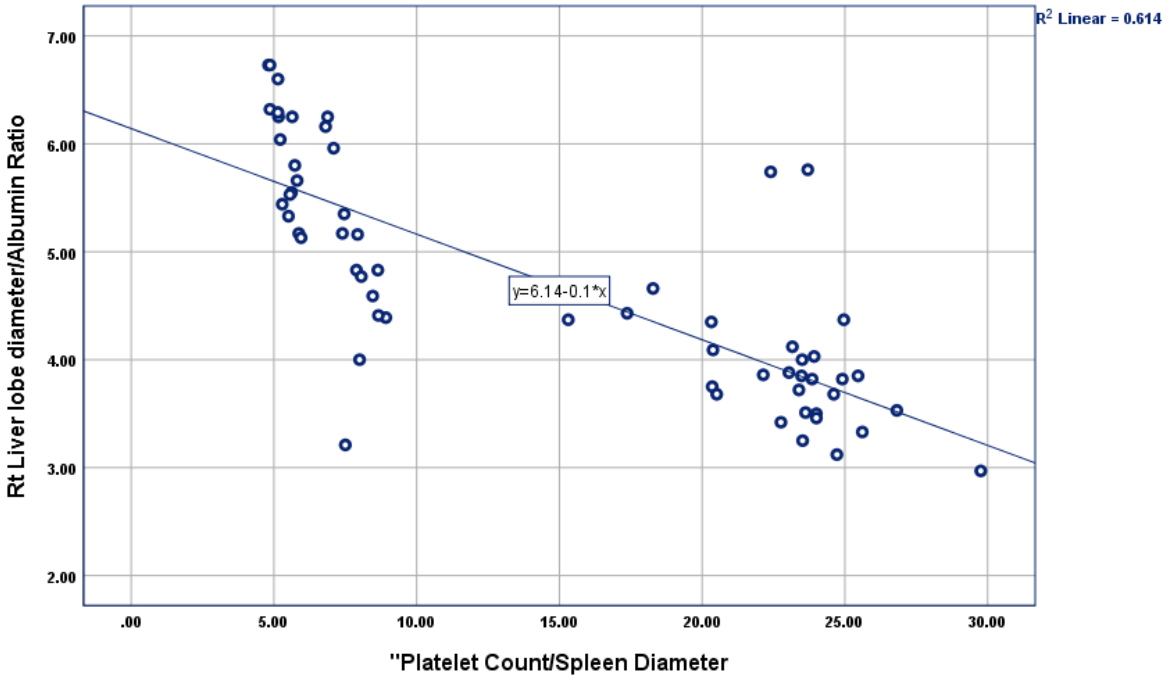

Figure (3): Correlation between Right lobe of Liver/Albumin ratio and Platelet count/Spleen diameter ratio.

DISCUSSION

Currently, EGD is the gold standard test for the examination of varices. However, it is expensive and necessitates the patient being sedated throughout [10]. These drawbacks necessitate the development of innovative, quick, and easy methods for detecting and monitoring esophageal varices. According to new recommendations, patients with liver cirrhosis who have stiffness less than 20 kPa and a normal plt count, as mentioned in Baveno VI, do not require a varices screen. [11].

Non-invasive methods can have a distinct role in defining high risk group to develop portal hypertension [12]. Regarding platelet count, multiple studies noticed that lower platelet count is associated with larger OV as in **Afsar *et al.*** [13] and **Sheta *et al.*** [14]. Accordingly, platelet count can identify large varices and patients who need upper GIT endoscopy [13].

We describe the results of spleen diameter, in group A its estimated mean ± SD was 16.13 ±1.29 and in group B its estimated mean ± SD was 13.11 ±0.65. Spleen diameter has significant increase in patients with esophageal varices grades I, II, III and IV (mean ± SD; 15.1 ±0.22, 15.06 ±0.65, 16.24 ±0.42 and 18.10 ±0.38, respectively) than in those without esophageal varices (13.11 ±0.65). This supports the findings of a different study by **Awad *et al.*** [15] that found a strong statistically significant association between the presence and grade of OV and the splenic diameter. Splenomegaly and portal vein width were also mentioned by **Mohanty *et al.*** [16] as valid indicators of variceal haemorrhage.

In our study, mean ± SD of P/S ratio in group A was of 6.48 ±1.32 and in group B was 23.06 ± 2.88. This is consistent with a research by **Awad *et al.*** [15], where individuals with cirrhosis who also had OV had a lower (P/S) ratio. **González-Ojeda *et al.*** [17] demonstrated that the grade of varices has no impact on the P/S ratio used to detect esophageal varices.

In the current study, there was a highly statistically significant difference between the serum albumin levels of the groups A and B ($p< 0.001$). Additionally, we discovered that serum albumin levels dropped as the quality of the varices rose. Concerning the mean ± SD of serum albumin, we reported that; in group A it was 2.77 ±0.29 and in group B it was 3.59 ±0.34. Patients with grades I, II, III, and IV esophageal varices had considerably decreased serum albumin (mean ± SD; 3.15 ±0.19, 2.70 ±0.22, 2.77 ±0.21and 2.53 ±0.19, respectively) than in those without esophageal varices (3.59 ±0.34).

Interestingly, serum albumin was significantly lower in OV cases than those without OV (2.7 ± 0.49 for patients with OV vs. 3.93 ± 0.66 for patients without OV) [18]. **Hossain *et al.*** [19] in a study that was carried out on one hundred patients with liver cirrhosis concluded that hypoalbuminemia alone is a good indicator for OV, this was also proposed by **Said *et al.*** [20] and **Husová *et al.*** [21].

In the current study group A had a larger Rt liver lobe diameter than group B (p 0.001). Additionally, we discovered that the diameter of the Rt liver lobe grew as the degree of varices rose. Rt liver lobe diameter, was evaluated to be 13.49 ±0.49 cm in group B and 15.36 ±0.70 cm in group A on average. Patients with grades I, II, III, and IV esophageal varices had considerably increased Rt liver lobe diameter (mean ± SD; 14.75 ±0.23, 15.17 ±0.36, 15.28 ±0.46 and 16.21 ±0.80 cm, respectively) than in those without esophageal varices (13.49 ±0.49).

Furthermore, RLLD/Alb findings showed that in group A, its estimated mean ± SD was 5.61±0.68 and in group B, its calculated mean ± SD was 3.79±0.41. The RLLD/Alb ratio's sensitivity and specificity were 95.7% and 93.3%, respectively, in this investigation, with >3.98 being the optimum cutoff point value.

The use of the RLLD/Alb ratio as an OV predictor was first proposed by **Alempijevic and Kovacevic** [22]**.** They discovered that the RLLD/Alb ratio was connected to the existence of OV. The sensitivity was 83.1% and the specificity was 73.9% at a cutoff value of 4.425. According to **Awad *et al.*** [15]**,** the RLLD/Alb ratio had a sensitivity of 83.3 percent and a specificity of 29.5 percent with a cutoff point value of 4.42.

Sheta *et al.* [14] also supported our results with his colleagues who found that RLLD/Alb at a cutoff value of ≥4.92 detected OV 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.*** [23] 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%.

Other investigations, such as **Adel and George** [24] (sensitivity of 80% and specificity of 70 percent at a cutoff value of 3.5), also corroborated these findings.

Sanjay and Chandrashekar [25] (sensitivity of 83.3% and specificity of 29.5 percent at a cutoff value of 4.42) and **Nouh *et al.*** [18] (sensitivity of 93 percent, specificity of 95 percent, and accuracy of 96.5 percent at a cutoff value of 4.683) also support our results.

The difference between this study and the other studies can be explained by many factors, such as different etiology of cirrhosis, for example, in the **Alempijevic *et al.*** study[26], the patients had mixed etiology (alcoholic 43%, infective 19%, and autoimmune 17%, others 15%) as well as the different ethnic backgrounds of the patients in those studies.

Additionally, the best cutoff was 16.3 for the P/S ratio, with sensitivity of 90.4 percent, and specificity was 98.2%. This is consistent with **Charan *et al.* study** [23], which found that the ideal cutoff value of P/S ratio was >6.9 (AUC 0.965), the accuracy was ninety percent, sensitivity was 90 percent, specificity was 88.9 percent, PPV was 97.3 percent, and NPV was 66.7 percent.

Giannini *et al.* [27] developed the first method to predict OV using the P/S ratio. When a cutoff value of 909 was used in that experiment, the 100 percent sensitivity and was 93 percent as specificity. With a cutoff value of 608 and a sensitivity and specificity of 80.77% and 64%, respectively, **Shekar *et al.*** [28] study revealed a mean P/S ratio of 1277 in patients without OV and 445 in patients with OV. **Sheta *et al.*** [14] cutoff value of less than 570 had 77.1 percent as a sensitivity, 93.02 percent as specificity, 93.6 percent as PPV, and 75 percent AS NPV.

CONCLUSIONS

Physicians can use the RLLD/Alb ratio (with or without utilizing the P/S ratio) as a non-invasive predictor of the high-risk group of patients with esophageal varices who require upper GI. Particularly in areas with low resources, this is necessary.

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