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Potential Role of Gall Bladder Wall Thickness as a Non-Invasive Screening Parameter for Detecting Esophageal Varices

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ABSTRACT
Background: Liver cirrhosis is defined by fibrosis and inflammation. It may occur because of portal hypertension, prolonged alcohol consumption, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), chronic hepatitis B and C (HBV and HCV), and many autoimmune disorders.
Objectives: This study aimed to investigate whether non-inflammatory gallbladder wall thickness predicts esophageal varices (EV), both independently and in conjunction with other non-invasive clinical and laboratory indicators
Subjects and methods: This case-control study included a total of 90 adult cirrhotic patients, attending the Department of Hepatology and Gastroenterology, Ain Shams University Hospitals. This study was conducted over one year between January 2022 to January 2023. **Result:** Subjects with esophageal varices had a statistically significant greater incidence of clinical signs, whether gastrointestinal or systemic, compared to those without varices. 37.78% of individuals with cirrhosis lacking esophageal varices exhibit a normal clinical examination.
Conclusion: It could be concluded that assessing the thickness of the gallbladder wall is an effective method for detecting EV in individuals with liver cirrhosis. We identified a significant correlation between the two in individuals with hepatic cirrhosis who also presented with esophageal varices. Gallbladder wall thickening (GBWT) enhances the non-invasive evaluation of liver disease patients to determine the risk of esophageal varices (EV) existence.
Keywords: GBWT, Non-Invasive Screening Parameter, Esophageal Varices.

INTRODUCTION

Approximately two million individuals succumb annually to liver-related ailments, with fifty percent of these fatalities attributed to cirrhosis (LC) and its repercussions. Cirrhosis constitutes 1.6% of the global illness burden and ranks tenth in mortality frequency, as per the 2010 Global Burden of illness study [(1)].

The esophageal varices, or dilated submucosal distal esophageal veins, link the portal and systemic circulations. Portal hypertension, prevalent in cirrhosis, enhances venous blood influx through the portal vein, while simultaneously increasing resistance to portal blood flow, resulting in this condition. Cirrhosis leads to the most prevalent and lethal consequence, variceal rupture, which increases the risk of haemorrhage as the illness progresses within the liver [(2)]. The most perilous outcome of an EV is haemorrhage, which correlates with a significant fatality rate. Early identification of EV is essential, and primary prophylaxis should be administered with a non-selective beta-blocker, for instance. Esophagogastroduodenoscopy (EGD) and hepatic vein catheterization are the most effective methods for identifying esophageal varices and clinically significant portal hypertension, as they assess the hepatic venous pressure gradient. However, both are invasive, may cause harm to patients, and are not consistently well-accepted [(3)].

A variety of non-invasive markers indicative of the presence of gallbladder ovarian tumour (GOV) were examined, including platelet count, splenic diameter, and portal vein diameter, among others. The assessment of noninflammatory gallbladder wall thickening (GBWT) has recently surfaced as a possible marker for GOV [(4)].

A segment of the gallbladder's venous blood is conveyed directly to the liver by a network of minor veins and arteries. The portal venous system receives blood from the common bile duct, the cystic duct, and several smaller veins. Consequently, portal hypertension should promptly affect the gallbladder, resulting in a thickened gallbladder wall due to inadequate venous drainage [(5)]. To diagnose portal hypertension, a beneficial and non-invasive technique is to evaluate the portal vein diameter with ultrasonography. In patients with chronic liver disease, gallbladder wall thickening seen via ultrasonography can serve as a predictor for esophageal varices [(6)]. The major purpose of the major purpose of this study was to investigate the potential prognostic relevance of non-inflammatory gallbladder wall thickness for esophageal varices.

PATIENT AND METHODS

This case-control study included a total of 90 adult cirrhotic patients with a body mass index (BMI) less than 30 kg/m2, attending the Department of Hepatology and Gastroenterology, Ain Shams University Hospitals. This study was conducted over one year between January 2022 to January 2023.

The included subjects were categorized into two groups according to the existence of EVs; **Group A** consisted of 45 cirrhotic patients with esophageal varices (EV), while **Group B** consisted of the other 45 cirrhotic patients without EV.

The data collection tools specified in the evaluation document comprise the following components:

1. **The patient history,** including personal history, current complaint, analysis of each complaint, cause of

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cirrhosis, other GIT complaints, Current medical comorbidities: cardiac problems, hypertension, chest diseases, renal diseases, liver diseases, blood diseases or bleeding tendency, current medications, and previous surgical operations.

2. **Clinical examination,** including general examination, vital signs (blood pressure, temperature, heart rate, respiratory rate, signs of pallor, cytosis, jaundice, lymph node enlargement, and body mass index (BMI)): Calculated by dividing weight in kg by height in meters squared.

3. **Laboratory investigations,** including complete blood count (CBC), liver function tests (albumin, bilirubin, liver transaminases, prothrombin time, and INR), renal function tests (creatinine and urea), random plasma sugar, haemoglobin A1C (HbA1c), and virological markers including HCVAb, HBsAg, HIV Ab.

4. **Pelviabdominal ultrasound** using Mindray. It was ordered for all cases, and transabdominal ultrasound.

5. **Upper gastrointestinal endoscopy** (diagnostic upper endoscopy was performed in all cases to assess the presence of esophageal varices or not and the grade of these Ovs).

6**. Predicting scores (Child Turcotte Pugh score (CTP))** were evaluated for all cases on admission to assess the severity of liver disease. Child Pugh Turcotte (CTP) Score (made by Charles Gardner Child).

Ethical approval:

This study was ethically approved by Faculty of Medicine, Ain Shams University's Research Ethics Committee. Before the participants' admission to this study, the study's goal, nature, and risk-benefit assessment were elucidated, and informed consent was acquired in accordance with the approved norms of the Ain Shams University committee. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical analysis

Use version 26.0 of the SPSS statistics analysis software. Frequencies and relative percentages were used to display the qualitative data. We used mean± SD to represent the descriptive data. The mean± SD of two sets of statistically regularly distributed data were compared using a Student t-test, and the relationship between qualitative variables was assessed using a Chi-square test. Additionally, the P-value was used to identify the significant differences. The cutoff value with the best sensitivity and specificity was found using the ROC curve. When a P-value is less than 0.05, it is deemed statistically significant.

RESULTS

There were no statistically significant differences between both groups as regard age, sex, associated comorbidities, and the underlying cause of cirrhosis, as demonstrated in **table 1**.

Table (1): General Characteristics of participating cases.

	Cirrhotic with EV N=45	**Cirrhotic without EV** N=45	**Independent Student-t test / X^2-test**	
	Mean ± SD		**t**	**P-value**
Age (year)	52.51 ± 11.35	49.67 ± 14.79	1.023	0.309
Sex	**N (%)**		**X^2**	**P-value**
Male	28 (62.20%)	16 (35.60%)	6.403	0.011
Female	17 (37.80%)	29 (64.40%)		
Associated comorbidities	**N (%)**		**X^2**	**P-value**
NO	18 (40%)	20 (44.4%)	9.915	0.271
HTN	8 (17.8%)	3 (6.7%)		
DM	11 (24.50%)	4 (8.9%)		
RA	3 (6.7%)	5 (11.1%)		
SLE	1 (2.2%)	4 (8.9%)		
COPD	1 (2.2%)	0 (0%)		
IHD	3 (6.7%)	3 (6.7%)		
Autoimmune thyroid	0 (0%)	1 (2.2%)		
Vitiligo	2 (2.2%)	1 (2.2%)		
Causes of cirrhosis	**N (%)**		**X^2**	**P-value**
Post HCV	23 (51.10%)	26 (57.80%)	5.850	0.557
HBV	6 (13.30%)	6 (13.30%)		
PBC	2 (4.40%)	4 (8.90%)		
BCS	3 (6.70%)	0 (0.00%)		
PSC	3 (6.70%)	3 (6.70%)		
AIH	6 (13.30%)	6 (13.30%)		
Hemochromatosis	1 (2.20%)	0 (0.00%)		
Wilson	1 (2.20%)	0 (0.00%)		

Table 2 illustrates the laboratory investigations for all cases, and the results showed a statistically significant lower Hb level, platelet count, lower albumin level, higher urea, creatinine, higher bilirubin, and prolonged PT in subjects with and without esophageal varices.

Table (2): Laboratory investigations of participating subjects

	Cirrhotic with EV N=45	**Cirrhotic without EV** N=45	**Independent Student-t test / X^2-test**	
	Mean ± SD		**t**	P-value
HB (g/dl)	8.99 ± 1.30	11.05 ± 1.93	5.910	0.000
Plt (th/mm^3)	64.29 ± 13.99	206.49 ± 50.88	16.958	0.000
WBCs (th/mm^3)	9.09 ± 1.88	8.42 ± 1.92	1.663	0.100
AST (IU/L)	55.89 ± 13.15	52.16 ± 12.86	0.546	0.587
ALT (IU/L)	50.93 ± 12.41	45.07 ± 11.11	1.086	0.280
Urea (mg/dl)	41.02 ± 10.11	27.27 ± 6.41	4.472	0.000
Creatinine (mg/dl)	1.76 ± 0.42	0.94 ± 0.23	6.880	0.000
PT sec	17.16 ± 1.45	11.80 ± 1.27	18.659	0.000
INR	1.66 ± 0.13	1.29 ± 0.13	13.253	0.000
Albumin (g /dl)	2.74 ± 0.19	3.72 ± 0.15	27.167	0.000
Bilirubin (mg/dl)	2.74 ± 0.65	1.49 ± 0.35	2.860	0.005
Random plasma glucose (mg/dl)	103.33 ± 11.66	100.60 ± 17.17	0.883	0.379
HBA1c (%)	5.42 ± 0.77	5.16 ± 0.57	1.823	0.072
	N (%)		**X^2**	**p-value**
HCV (positive)	24 (53.3%)	24 (53.3%)	0.0000	1.000
HBV (positive)	5 (11.1%)	5 (11.1%)	0.0000	1.000

Table 3 illustrates ultrasound findings for all participating cases, and the results showed statistically significant higher GB wall thickness in subjects with than without esophageal varices (9.89±0.71 vs. 6.98±0.84). While, there was no statistically significant difference regarding cirrhosis (100% vs. 100%).

Table (3): Ultrasonography of participating cases.

	Cirrhotic with EV N=45	**Cirrhotic without EV N=45**	**Independent Student-t test / X^2-test**	
	Mean ± SD		**t**	P-value
GB wall thickness (mm)	9.89 ± 0.71	6.98 ± 0.84	17.723	<0.0001*
Abnormalities	**N (%)**		**X^2**	p-value
Cirrhosis	45 (100%)	45 (100%)	0	1

According to endoscopy findings, among subjects with cirrhotic EV, most of the subjects' esophageal varices were large in 80% and medium in 20%. And most of the subject's esophageal varices were grade 3 in 78.7% and grade 2 in 21.3% (**Table 4).**

Table (4): Endoscopy of participating subjects

Abnormalities	**Cirrhotic with EV** N=45	**Cirrhotic without EV** N=45
Esophageal varices	N (%)	
Medium sized	9 (20%)	---
Large sized	36 (80%)	---
Esophageal varices grades		
Grade 1	0 (0%)	
Grade 2	10 (21.7%)	
Grade 3	36 (78.3%)	

According to CTP grades, among our studied population, all subjects with CTP grade A had cirrhosis without EV, and none of them had EV, while 46.7% of subjects with EV were CTP grade and 53.3% were CTP grade C. None of the subjects with cirrhosis without EV were in CTP grades B and C (**Table 5).**

Table (5): CTP of participating subjects

CTP	Cirrhotic with EV N=45	Cirrhotic without EV N=45	chi square test	
	N (%)		X^2	p-value
A	0 (0%)	45 (100%)	90.000	<0.001*
B	21 (46.7%)	0		
C	24 (53.3%)	0		

Table (6) and Figure (1) illustrate the results of the ROC analysis. At a cutoff point >8.5 mm, GB wall thickness has 95.6% sensitivity and 89% specificity for the prediction of EV in subjects with liver cirrhosis.

Table (6): sensitivity and specificity of GB wall thickness for prediction of EV in subjects with liver cirrhosis

	Cut off value	Sensitivity %	Specificity %	95% CI interval	
				Lower bound	Upper bound
GB wall thickness	8.5 mm	95.6%	89%	0.840	0.980

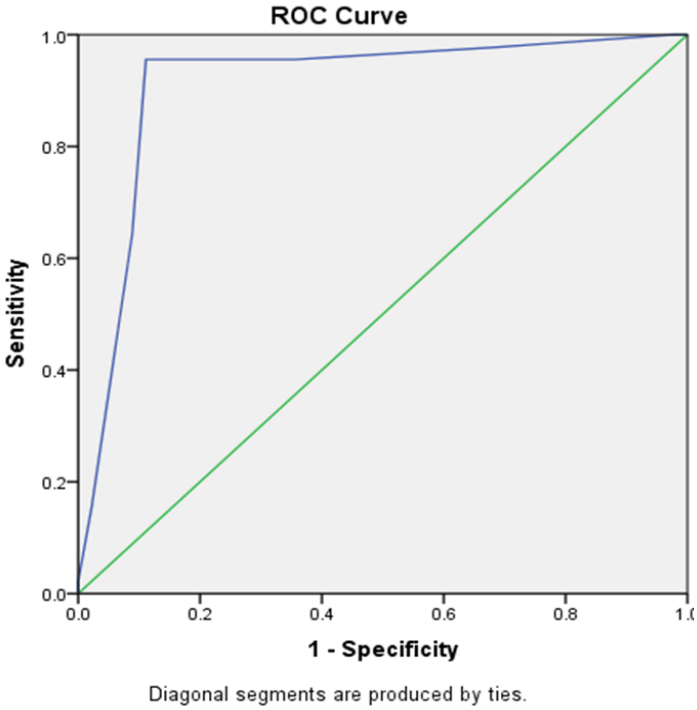

Figure (1): ROC curve of GB wall thickness for prediction of EV in subjects with liver cirrhosis.

DISCUSSION

This study aimed to evaluate the potential of non-inflammatory gallbladder wall thickness as a predictor of esophageal varices. The study found no significant difference in age, sex, or associated comorbidities between patients with liver cirrhosis and non-esophageal varices (OV). This finding was consistent with previous studies by **Afifi *et al.*** [1], **Elkerdawy *et al.*** [4], **Khan *et al.*** [6] and **Tsaknakis *et al.*** [7]. The study also found no statistically significant difference in the presence of OV between groups of cirrhotic patients. The findings align with earlier research by **Afifi *et al.*** [1], **Elkerdawy *et al.*** [4], who also found no significant differences in age or sex between groups of cirrhotic patients. Overall, the study supports the use of non-inflammatory GBPWT as a non-invasive predictor for OV presence.

The study by **Giuffrè *et al.*** [8], found no significant difference in splenic stiffness (SS) in predicting end-stage hepatitis (EVs) in compensated cirrhosis patients without chronic risk factors. The researchers also evaluated splenic stiffness in relation to other non-invasive techniques.

The results are like those of **Petzold *et al.*** [9], who investigated the link between EV and LSM in ACLD patients and found that there was no significant difference in the causes of cirrhosis between the two groups. This suggests that non-invasive predictions could be better.

Tsaknakis *et al.* [7] found no statistically significant difference in the underlying causes of cirrhosis between the two groups, which is consistent with our findings.

We also found the same thing as **Duah *et al.*** [10] who were trying to find out how common OV is and what the clinical signs are in people with cirrhosis. The researchers split the 149 people who had liver cirrhosis into two groups based on whether they had OV. In Group I, there were 14 people with cirrhosis who did not have OV. There was no statistically significant difference between the two groups with respect to the underlying cause of cirrhosis in Group II, which consisted of 135 OV cirrhotic individuals.

In addition, **Sharma *et al.*** [11] sought to determine imaging, biochemical, and clinical variables that could indicate the existence of large esophageal varices (LEVx) and aid in the selection of patients for upper gastrointestinal endoscopy (UGIE). There was no statistically significant difference between the two groups for the underlying cause of cirrhosis, according to this prospective study that included 101 patients.

The findings of **Kraja *et al.*** [12], who sought to identify non-invasive indicators of esophageal varices (EV) and variceal hemorrhage in Albanian patients with liver cirrhosis, are at odds with our own. This analysis included 139 patients with newly diagnosed cirrhosis who did not experience variceal bleeding. The researchers discovered that the etiology of cirrhosis due to alcohol and/or viruses was much more common

among patients with esophageal varices compared to those without.

Esophageal varices were linked to a markedly elevated incidence of gastrointestinal and extra-gastrointestinal issues in our study relative to individuals without varices. Sixty percent of cirrhosis patients devoid of esophageal varices were referred for chronic liver disease tests.

Duah *et al.* [10] also discovered that those with esophageal varices had a significantly greater rate of gastrointestinal and extra-gastrointestinal complaints compared to those without varices. Our results are in line with their findings. Concerning problems with weight loss, anorexia, jaundice, hematemesis, and melena in the stool.

In addition, our findings agreed with those of **Duah *et al.*** [10], who sought to evaluate the non-invasive tests' predictive values for OV detection. Out of the 135 patients studied, 90.60 percent had OV, while 9.40 percent did not. Observers observed symptoms such as jaundice, hematemesis, melena stools, weight loss, and anorexia when OV was present. There was no statistically significant relationship between any of these clinical features and the outcome of the multivariate analysis.

Elkerdawy *et al.* [4] came to the opposite conclusion of jaundice, finding no statistically significant difference between the two groups.

Our analysis demonstrated that participants with esophageal varices exhibited a markedly higher incidence of gastrointestinal or systemic clinical problems compared to those without varices. Clinical investigations indicate that 37.78% of individuals with cirrhosis lacking esophageal varices have no abnormalities.

Our results are consistent with those of **Tsaknakis *et al.*** [7], who detected a statistically significant difference between the two groups with respect to ascites, the prevalence of which was greater in those diagnosed with esophageal varices. Furthermore, our findings are in line with those of **Afifi *et al.*** [1], who also discovered that there was a statistically significant difference between the two groups with respect to ascites, with the former having a significantly lower percentage at 8% and the latter at 50%. This difference was particularly pronounced among subjects with esophageal varices.

The results indicated that those with esophageal varices exhibited significantly lower levels of haemoglobin, platelets, albumin, urea, creatinine, bilirubin, and PT compared to those without esophageal varices.

Afifi *et al.* [1] confirmed our findings by showing that the platelet count was lower in the OV group (136.7±53.7) as compared to the non-OV group (195.2±49.8). The INR was 1.5±0.5 in the OV group and 1.1±0.3 in the non-OV group. In comparison to the non-OV group, the OV group had a lower albumin level (3.2 ± 0.3).

Furthermore, our findings align with those of **Tsaknakis *et al.*** [7], who reported that the EV group exhibited a significantly reduced platelet count compared to the non-EV group (128,000/µl for the EV group versus 227,000/µl for the non-EV group; p-value < 0.001). The average INR value significantly differed between the two groups, with the non-EV group at 1.09 ± 0.38 and the EV group at 1.39 ± 0.46 (p-value < 0.0001).

According to our results, **Giuffrè *et al.*** [8] observed that patients with esophageal varices exhibited elevated platelet counts, creatinine levels, bilirubin levels, and INR in comparison to healthy controls.

Elkerdawy *et al.* [4] conducted a similar investigation, revealing that people with esophageal varices exhibited a markedly reduced platelet count and elevated total bilirubin levels compared to those without. Notwithstanding our findings, they found no statistically significant difference between the two groups on albumin level, hemoglobin, and INR.

In addition, **Abdelwahab *et al.*** [5] aimed to assess the viability of non-invasively screening cirrhotic patients for esophageal varices using the measurement of gallbladder wall thickness. Upon categorizing 150 patients into two cohorts according to the existence of ascites and varices, the researchers found that the platelet levels in the EV group were statistically significant, exhibiting a mean of 109 and an interquartile range of 79 to 146. The non-EV cohort comprised 75 patients with chronic liver disease, with no ascites identified with sonography. This group also includes cirrhotic patients with esophageal varices. The non-EV group had an interquartile range (IQR) of 178–234, with a median value of 19Our analysis shown that individuals with esophageal varices exhibited a markedly thicker gallbladder wall compared to those without (9.89±0.71 vs. 6.98±0.84). Subjects with esophageal varices exhibited a higher prevalence of cirrhosis (95.8% vs. 89%), splenomegaly (57.8% vs. 8.9%), and ascites (97.8%; with 60% classified as moderate and 37.8% as large vs. 0%) compared to those without varices, whereas hepatomegaly was more prevalent in the former group (8.9% vs. 0.5%) than in the latter.

The results of **Tsaknakis *et al.*** [7] supported our findings, indicating that GBWT was significantly higher in EV patients compared to the non-EV group (mean: 4.4 mm vs. 2.8 mm, p < 0.0001). Additional ultrasonography characteristics, such as splenic dimensions, may indicate portal hypertension. Our data revealed that the EV group exhibited a significantly longer average spleen compared to the non-EV group (138 mm vs. 113 mm; p < 0.001). 63% (n = 22) of the EV cohort exhibited cirrhosis, in contrast to 19% (n = 13) of the non-EV cohort.

Consistent with **Khan *et al.*** [6], we observed that patients with esophageal varices exhibited a much thicker gallbladder wall (4.96 ± 0.85 mm) in contrast to those without (2.54 ± 0.76 mm). A substantial difference existed between the two groups, with a P value of less than 0.0001, as 65 patients (81.25%) in group A and 8 patients (10%) in group B exhibited GBWT > 4 mm.

A study by **Elkerdawy *et al.*** [4] revealed a strong association between GBWT and the prevalence of esophageal varices. The measurements for the non-esophageal varices cohort were 2.3±0.5mm and 3.2±0.6mm, respectively (P>0.001). The length of the spleen and the diameter of the portal vein exhibited significant variation between the two groups of individuals.

The study also showed a substantial difference in GBWT between the cirrhotic group with OV (group II) and that without OV (group I), according to **Afifi *et al.*** [1]. Compared to patients without OV, those with hepatic cirrhosis with OV had a mean GBWT of 4.2 mm.

The average GBWT of patients with EV was 3.88 (±1.47) mm, while that of individuals without varices was 2.94 (±1.44) mm, according to **Petzold *et al.*** [9]. There was a statistically significant distinction between those categories (p <.01).

In our cohort of cirrhotic patients with esophageal varices, we found that 33.3% exhibited moderate portal hypertensive gastropathy, 4.4% had intermediate severity, and 60% presented with severe gastropathy. In 80% of the participants, esophageal varices were large, whereas in 20%, they were moderate.

In accordance with our findings, **Afifi *et al.*** [1] found that the non-OV group had a significantly lower prevalence of portal hypertensive gastropathy (12%) compared to the OV group (70%). Group IIa had 22 patients with small-sized ovarian tumours, whereas Group IIb included 28 patients with large-sized ovarian tumours; both groups exhibited ovarian tumours.

Duah *et al.* [10] showed that upper endoscopy screening identified esophageal varices in 135 (90.60%) individuals, whereas 14 (9.40%) patients were without varices. Our findings are analogous to theirs. Among the 111 individuals with varices, 82.22 percent had large varices, whereas 17.78 percent presented with small varices. Furthermore, **Tsaknakis *et al.*** [7] found that the EV group had a significantly elevated prevalence of hypertensive gastropathy.

Additionally, based on the severity of the esophageal varices, **Elkerdawy *et al.*** [4] categorized Group I patients into two subgroups: Group A comprised people exhibiting one or two minor varices in the distal oesophagus, classified as non-advanced. Conversely, Group B comprised patients with more advanced varices. Type III encompasses medium-sized variants (any quantity). Twenty patients classified as grade IV, encompassing grades III and IV, exhibit severe varices in any region of the oesophagus.

In our study, all participants with Cirrhosis without esophageal varices (EV) classified as CTP grade A did not exhibit EV, whereas 46.7% of subjects with EV were classified as CTP grade B and 53.3% as CTP grade C. Conversely, all classes lacking EV received CTP grades of B and C.

Our findings are in line with those of **Duah *et al.*** [10], who also discovered that, in relation to the child Pugh score, 89.06% of subjects with EV had CTP grade B and that all subjects with CTP grade A had Cirrhotic without EV.

Our results are consistent with those of **Tsaknakis *et al.*** [7], who discovered that 92% of non-EV cases had Child-Pugh-Classification A, 3% of non-EV cases had Child-Pugh-Classification B, and 26% of EV cases had Child-Pugh-Classification C.

Another study by **Afifi *et al.*** [1] indicated that CTP grade A was present in 90% of non-EV cases, CTP grade B in 6% of non-EV cases and 36% of EV cases, and CTP grade C in 4% of non-EV cases and 24% of EV cases.

Our study revealed that GB wall thickness has a sensitivity of 95.6% and a specificity of 89% for predicting EV in people with liver cirrhosis when the cutoff threshold is greater than 8.5 mm.

According to **Afifi *et al.*** [1], our findings are in line with theirs; they discovered that GBWT had a sensitivity of 95.6% and a specificity of 89% at a cut-off level of 3.950. In addition, **Elkerdawy *et al.*** [4] discovered that GBWT > 3.5 correctly predicts esophageal varices 54.29% of the time and 97.14% of the time. **Tsaknakis *et al.*** [7] also discovered that GBWT exhibited a sensitivity of 46% and a specificity of 89% when predicting EV, but with a higher cut-off of 4 mm or more.

CONCLUSION

It could be concluded that assessing gallbladder wall thickness is highly effective for detecting EV in cirrhotic patients, as a strong connection exists between gallbladder wall thickness and the presence of EV in individuals with liver cirrhosis. GBWT enhances the non-invasive evaluation of liver disease patients to determine the risk of EV existence.

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