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Evaluation of the Gallbladder Wall Thickening as a Non-invasive Predictor of Esophageal Varices in Cirrhotic Patients

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Authors' contributions

This work was carried out in collaboration among all authors. Author NMS conceptualization, methodology, resources, investigation, writing - original draft, formal analysis, writing - review and editing. Author AAA formal analysis, investigation, writing – review and editing. Author MAEM conceptualization, methodology, formal analysis, writing - review and editing. Author YMH conceptualization, methodology, formal analysis, writing - review and editing. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Background: Liver cirrhosis represent the end stage of fibrosis that destroy normal liver parenchyma and leads to serious complication as portal hypertension which result in esophageal varices (EV), EV bleeding leads to high mortality, so repeated upper endoscopy needed to control bleeding which is invasive procedure and of high risk of hazards as infection.
Our Study Aimed: to evaluate the Gallbladder Wall Thickening (GBWT) as a non-invasive predictor of Esophageal Varices (EV) in cirrhotic patients.
Methods: In this cross sectional study, we tested 120 cirrhotic patients at gastroenterology and hepatology unit, internal medicine department, Tanta university hospitals. They were divided into 60 cirrhotic patients with EV and 60 cirrhotic patients without EV. All patients were subjected to history taking, physical examination, investigation (complete blood count, liver function tests, viral

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markers) ultrasound detecting (gall bladder wall thickness, portal vein diameter, portal vein flow velocity, portal cross sectional area and gall bladder fasting volume) upper gastrointestinal endoscopy to detect presence or absence of varices.
Results: Significant correlation was observed between gall bladder wall thickness (GBWT) and portal hypertension, GBWT ranged from 2.5 to 7 mm in group 2 (cirrhotic patients with EV) and from 1.5 to 5 in group 1(cirrhotic patients without EV).
There is significant difference between group 1 and group 2 as regard GBWT with (P value < 0.05), portal vein diameter (PVD) with (P value <0.05) and platelets counts with (P value <0.05).
Conclusions: We recommend thatgall bladder wall thickness can be used as a non-invasive predictor of esophageal varices in cirrhotic patients.

Keywords: Gall bladder wall thickness; esophageal varices and portal hypertension.

1. INTRODUCTION

Liver cirrhosis represents the end stage of progressive fibrosis which destroys normal liver tissue, in which the normal microcirculation, the gross vascular anatomy, and the hepatic architecture have been variably destroyed and altered with fibrous septa surrounding regenerated parenchymal nodules [1,2].

A clinically relevant complication of liver cirrhosis is the development of portal hypertension with all its clinical consequences such as ascites, spontaneous bacterial peritonitis and development of portosystemic collaterals [3].

Portal Hypertension is an increase in the pressure of portal vein that carries blood from the digestive organs to the liver. The increase in pressure is caused by ablockage in the blood flow through the liver. Increase pressure in the portal vein causes varices to develop across the esophagus and stomach. The varices become fragile and can bleed easily [4].

Although the mortality of variceal hemorrhage has declined in the last decades, it is still very high with a six-week-mortality of up to 37% [5], and a high recurrence rate after the first bleeding incident [6].

Although repeated endoscopic controls of patients with an advanced liver cirrhosis are justified, it is an invasive diagnostic procedure with its own risks, and it is not always widely available in countries with lower health care standards. Therefore, non-invasive predictors for portosystemic collaterals are of high interest. Notably, the venous blood is drained from the gall bladder in part via small vessels directly into the liver. An additional venous blood drain flows via small veins towards the cystic duct and then with vessels from the common bile duct terminating in the portal venous system [7].

Therefore, the gall bladder should be directly affected by portal hypertension causing a thickened gall bladder wall due to impaired venous drainage.

Here, we aim to evaluate the gall bladder wall thickening as a non-invasive predictor of esophageal varices in cirrhotic patients.

2. MATERIALS AND METHODS

2.1 Study Design

This is a cross sectional study conducted at Gastroentrology and hepatologyUnit of Tanta university hospitals, Egypt.

The study was conducted in a period Between June, 2019 to May, 2020.

2.2 Subjects

The study included 120 cirrhotic patients who were selected from the Gastroentrology and HepatologyUnit of Tanta university Hospitals, Egypt, according to inclusion and exclusion criteria.
The study population were categorized in two groups:

Group 1: 60cirrhotic patients without esophageal varices (non EV).
Group 2: 60 cirrhotic patients with esophageal varices (EV).

2.3 Inclusion Criteria

1-Patients aged between 18-75 years old.
2-All cirrhotic patients whatever's the cause

2.4 Exclusion Criteria

- Patients who had a cholecystectomy.

- Patients with HCC.
- Pregnant Women.
- Acute cholecystitis.
- Chronic calcularcholecystitis
- Chronic non calcularcholecystitis
- Severe hypoalbuminemia (below 2.2)
- Acute and chronic pancreatitis
- Peritonitis
- Gallbladder carcinoma

2.5 Methods

All patients were subjected to history taking, physical examination, investigation (complete blood count, liver function tests, viral markers) ultrasound detecting (gall bladder wall thickness, portal vein diameter, portal vein flow velocity, portal cross sectional area and gall bladder fasting volume) upper gastrointestinal endoscopy to detect presence or absence of varices.

2.6 Statistical Analysis of the Data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. We used Chi-square test for categorical variables, to compare between different groups, Monte Carlo correction test used for chi-square when more than 20% of the cells have expected count less than 5. We used Student t-test for normally distributed quantitative variables, to compare between two studied groups, ANOVA with repeated measures for normally distributed quantitative variables, to compare between more than twostudied groups. Mann Whitney test for abnormally distributed quantitative variables, to compare between two studied groups, Friedman test for abnormally distributed quantitative variables, to compare between more than two groups. Multivariate regression analysis to detect the most independent affecting factor.

3. RESULTS

Significant correlation was observed between gall bladder wall thickness (GBWT) and portal hypertension, GBWT ranged from 2.5 to 7 mm in group 2 (cirrhotic patients with EV) and from 1.5 to 5 in group 1(cirrhotic patients without EV).

Table 1. Demographic data in both groups

		Group 1			Group 2			Test	p. value
Age	Range	46	–	70	40	–	68	T: 0.006	0.939
	Mean ± S. D	54.45	±	7.04	54.55	±	7.16		
duration of	Range	2	–	8	2	–	10	T: 2.280	0.134
disease	Mean ± S. D	4.45	±	1.42	4.95	±	2.13		
Sex	Male (%)	43 (71.7%)			39 (65%)			X^2: 0.616	0.432
	Female (%)	17 (28.3%)			21 (35%)				

There is no significance difference between both groups as regard age, sex and duration of cirrhosis (P value 0.001)

Table 2. Liver function tests in both groups

		Range			Mean	±	S. D	t. test	p. value
ALT (U/L)	Group 1	15	–	70	34.05	±	13.10	1.482	0.226
	Group 2	12	–	90	37.58	±	18.27		
AST (U/L)	Group 1	13	–	91	42.30	±	17.74	1.614	0.206
	Group 2	19	–	110	46.85	±	21.33		
S. albumin (g/dl)	Group 1	2.9	–	4.1	3.48	±	0.39	1.304	0.256
	Group 2	2.6	–	4	3.39	±	0.45		
S. bilirubin (mg/dl)	Group 1	0.5	–	2.0	1.19	±	0.44	1.909	0.170
	Group 2	0.6	–	2.3	1.30	±	0.45		
PT (sec)	Group 1	13.5	–	17	14.69	±	1.06	47.112	0.001*
	Group 2	15	–	20	17.24	±	1.24		
INR	Group 1	1	–	1.6	1.22	±	0.17	45.474	0.001*
	Group 2	1.12	–	2.6	1.6	±	0.41		
Alkaline phosphatase	Group 1	20	–	71	38.10	±	12.91	2.689	0.104
(Iu/L)	Group 2	20	–	66	34.47	±	11.31		

There is no significance difference between group 1 and 2 as regard ALT , AST , serum albumin , serum total bilirubin and alkaline phosphatase , but, there is a significant difference between two groups as regard PT and INR (P value 0.001)

Table 3. CHILD score in both groups

CHILD score			Group 1	Group 2	Total
A		N	25	18	43
		%	41.7%	30.0%	35.8%
B		N	33	35	68
		%	55.0%	58.3%	56.7%
C		N	2	7	9
		%	3.3%	11.7%	7.5%
Total		N	60	60	120
		%	100.0%	100.0%	100.0%
Chi-square	X^2	3.188			
	P-value	0.203			

There is no significance difference between 2 groups as regard CHILD score as in group 1: They were 25 (41.7%) patients CHILD A, 33 (55%) CHILD B and 2 patients (3.3%) with CHILD C ,in group 2: They were 18 (30.0%) patients CHILD A, 35 (58.3 %) CHILD B and 7 (11.7%) CHILD C , (P value >0.05)

Table 4. Abdominal ultrasound finding in both groups

		Range			Mean	±	S. D	t. test	p. value
PVD	Group 1	8	–	16	11.79	±	1.95	12.262	0.001*
(mm)	Group 2	9	–	19	13.32	±	2.76		
PVFV	Group 1	8	–	18	15.46	±	2.97	3.481	0.065
(cm/sec)	Group 2	10	–	21	16.39	±	2.44		
Portal cross sectional area (mm2)	Group 1	40	–	60	49.13	±	5.87	1.136	0.289
	Group 2	31	–	65	47.73	±	8.23		
GBWT	Group 1	1.5	–	5	2.97	±	0.88	78.096	0.001*
(mm)	Group 2	2.5	–	7	4.56	±	1.08		
GB fasting volume (cc)	Group 1	11	–	130	34.60	±	17.18	1.358	0.246
	Group 2	30	–	50	37.33	±	4.34		
Splenic diameter (cm)	Group1	8	-	17	12.65	±	2.36	46.312	0.001*
	Group 2	13	-	23	16.12	±	3.16		

There is significant difference between two groups as regard Gall bladder wall thickness (GBWT), portal vein diameter (PVD), splenic diameter , but , there is no significant difference between both groups as regard portal vein flow velocity (PVFV), portal cross sectional area and gall bladder fasting volume

Table 5. Correlation between GBWT and other parameters in the studied groups

	GBWT	
	R	P
Hb	0.060	0.650
PLT	-0.706	0.001*
s. albumin	-0.023	0.860
s. bilirubin	-0.074	0.576
INR	0.390	0.002*
CHILD score	0.169	0.254
MELD score	-0.048	0.713
PVD	0.828	0.001*
Grade of EV	0.634	0.001*
s. creatinine	-0.250	0.054
s. sodium	0.208	0.111
Splenic diameter	0.648	0.001*

There were positive significant correlation between GBWT and INR, PVD, grade of esophageal varices and splenic diameter, but, there was negative significant correlation between GBWT and PLT

Table 6. Predictors of esophageal varices in univariate and multivariate logistic regression analysis

	Univariate		Multivariate	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
PLT	4.531 (1.931– 11.632)	0.021*	2.745 (0.365 – 5.241)	0.218
INR	0.524 (0.369 – 0.954)	0.013*	0.687 (0.239 – 5.632)	0.203
GBWT	0.408 (0.264 – 0.854)	0.001*	0.352 (0.068 – 0.604)	0.005*
PVD	0.365 (0.117 – 0.634)	0.011*	0.625 (0.524 – 3.362)	0.228
Splenic diameter	0.528 (0.362 – 0.875)	0.001*	0.394 (0.116 – 4.521)	0.336

Univariate and multivariate logistic regression analysis were performed to investigate the possible predictors of esophageal varices; In univariateanalysis: PLT (P value 0.021), INR (P value 0.013), GBWT was highly significant (P value 0.001), PVD (P value 0.011) and splenic diameter was significant (P value 0.001). They were all correlated with the presence of esophageal varices; In multivariate analysis using model adjusted for previously mentioned predictors GBWT was significant and positive independent predictor of esophageal varices.

Table 7. ROC curve of the GBWT

	Cutoff	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
GBWT	4	82	77	78	81	79

ROC curve analysis was done to pick up the best cutoff value of GBWT to predict the presence of esophageal varices which reveiled that GBWT > 4 mm is a predictor of EV with sensitivity 82 %, specificity 77% and accuracy 79%

4. DISCUSSION

Patients with decompensated liver cirrhosis have high chance to develop esophageal varices (EV) due to development of portal hypertension that means increase pressure in portal venous system which leads to signs and symptoms of cirrhosis as EV, ascites and splenomegaly. Once theses signs noticed in patients , preferred to do upper endoscope to decrease risk of bleeding from EV, however , many patients undergo upper endoscope with negative results [8].

Therefore, more accurate non-invasive parameters for the presence of EV could be a valuable and clinically relevant tool. We based our study on non-invasive, standard diagnostic tests, which are routinely performed in patients with chronic liver disease: abdominal ultrasound, clinical and laboratory results were evaluated in terms of prediction of EV.

This study was concluded to evaluate a gallbladder wall thickening as a non invasive predictor of esophageal varices in cirrhotic patients.

In our study, platelets counts are lower in cirrhotic patients with esophageal varices than cirrhotic without EV (p value 0.001), and this in agreement with [9] due to change in the microcirculation, hypersplenism related to portal hypertension and decreased level of thrombopiotein either due to decreased production or rapid degradation.

Thomopoulos et al, [10] reported that low platelet count could be an independent risk factor for the presence of varices due to pooling and destruction of platelets in the spleen which may be mediated by platelet-associated lgG and portal hypertension, also reduced levels of thrombopoeitin either due to impaired production or rapid degradation may also cause thrombocytopenia.

On the other hand, Berzigotti et al [11], showing no dependant association of platelets counts or splenic diameter with esophageal varices and periodic endoscope should be done for screening cirrhotic patients with esophageal varices.

In our study, there was no significant difference in hemoglobin level between the two groups and this in agreement with A Sarangapani, et al [12] due to dilution, hemolysis, occult blood loss from gastrointestinal tract, hypersplenism

In our study, as regard liver function tests, there was no significant difference between both groups in (ALT, AST, S. bilirubin and S. albumin) ,but there was significant difference between both groups as regard INR and these in agreement with Gill, ML et al [13] who said that INR of cirrhotic patients with esophageal varices is higher than cirrhotic patients without esophageal varices and serum albumin level in patients with varices was 2.64±0.31 and among non-variceal group was 2.80 ±0.10 (no significant difference).

Our current data showed that GBWT is higher in cirrhotic patients with esophageal varices than in cirrhotic patients without esophageal varices (P value <0.05) as (mean gall bladder wall thickness of cirrhotic patients with EV 4.56 ± 1.08 and in cirrhotic patients without EV 2.97 ± 0.88) and these findings are in agreement with SA Begum et al [14] who found that Mean gallbladder wall thickness (GBWT) of cirrhotic patients with esophageal varices (EV) was 5.6±0.2mm compared to 2.7±0.1mm of cirrhotic patients without esophageal varices.

Our study showed GBWT is considered as a predictor of esophageal varices at cutoff value of >4mm and this in agreement with Roberto et al [15] who found that GBWT is a good predictor of EV at cutoff value >4.3 due to portal hypertension .

In our study the portal vein diameter (PVD) is larger in cirrhotic patient with EV (mean 13.32±2.76) than in cirrhotic patients without EV (mean 11.79±1.95) with (p value 0.001) and this in agreement with R Mohanty, et al, [16] who found that average portal vein diameter of patients with esophageal varices was 13.46 ± 0.98 mm and that of patients without varices was 10.91 ± 0.65 mm (p=0.03). Schepis et al, [17] found a portal vein diameter of 13.82 ± 2.1 mm, among patients with oesophagealvarices and 12.33 ± 2.04 mm among patients without esophageal varices. Prihatini et al, [18] concluded in their study that portal vein diameter of 10 -20 mm by ultrasound gives the evidence of presence of esophageal varices. Theses finding due to: Portal hypertension that results from increased resistance to portal blood flow and has the potential complications of variceal bleeding and ascites. The splenoportal veins increase in caliber with worsening portal hypertension, and partially decompress by opening a shunt with systemic circulation, ie, a varix.

As a result of portosystemic shunting, there is a differential decompression across the portal vein and splenic vein (portal vein > splenic vein), with a resultant decrease in the ratio of portal vein diameter to that of splenic vein , so Portal vein to splenic vein diameter ratio and gradient could be valuable tools in predicting the presence of esophageal varices as mentioned by Schepis et al, [17] and Prihatini et al , [18].

Also, Plestina et al [19] recommended that PVD on ultrasound independently associated with esophageal varices by doing study on 99 patients with liver cirrhosis and esophageal varices underwent color Doppler ultrasonography and upper endoscope.

In our study, there was no significant difference between both groups in portal vein flow velocity (PVFV and this in agreement with Salvatore Travali et al [20] who found that no statistical differences in portal diameter and doppler parameters as PVFV were found between cirrhotic patients and normal subjects due to most patients included in her study of CHILD A with no sign of portal hypertension.

Our study showed that , there is no significant difference between the studied groups as regard portal cross sectional area and this not in agreement with MinalShastri et al [21] who found also that hepatic congestion index as ratio between portal cross sectional area and portal vein velocity >0.1in portal hypertension , and Moriyasu F et al., [22] in a study of 72 patients of cirrhosis, showed that a mean cross sectional area of portal vein was 1.49± 0.49 cm2 with p-value of < 0.001 and these finding due to pathophysiological changes that occur in portal hypertension .

As regard MELD score, in our study, there is no significant difference between both groups and this not in agreement with BledarKrata et al [23] who showed that, there is significant association between MELD score and esophageal varices because most patients involved in his study were decompensated liver disease and had high chance to develop bleeding from varices that lead to high mortality.

As regard CHILD score, in our study, there was no significant difference between both groups and this in agrerment with Thabut D et al, [24] who found that Child-Pugh was not significantly associated with the presence of large esophageal varices.

On the other hand, Tafarel et al [25] reported that with increasing size of EV demonstrated by upper endoscopy, the number of patients increased with the advancement in Child score and Nandan Deepak et al [26] found that Child Pugh class B/C, low platelet count and spleen diameter emerged as significant predictors for the presence of large esophageal varices due to the development of portal hypertension in decompensated liver disease.

In our study , in univariate and multivariate logistic regression analysis , we found that combination of multiple predictors as (GBWT , PVD, splenic diameter , PLT and INR) is more significant than one predictors and this in agreement with Wang et al, [27] who found that combination of more than one predictive parameter for esophageal varices as (hemoglobin level , platelets counts and portal vein diameter) were more significant in predicting esophageal varices and portal hypertension than one parameter alone as this improves the predictive accuracy in screening the most at risk patients with potential variceal hemorrhage.

Our current data showed that gall bladder wall thickness is positive and significant independent predictor of presence of esophageal varices by using multivariate analysis and this in agreement with Jaya Pathak et al, [28] who found that increased gall bladder wall thickness > 4 mm on ultrasound in cirrhotic patients without intrinsic gall bladder diseases is independent predictor of presence of esophageal varices and considered as early sign of portal hypertension due to raised hydrostatic pressure of vasculature of gall bladder wall.

5. CONCLUSION

The result of this study showed that:

- Gall bladder wall thickness is higher in cirrhotic patients with esophageal varices than in cirrhotic patients without esophageal varices
- Significant positive correlation between gall bladder wall thickness and portal vein diameter, INR and splenic diameter.
- Negative correlation between gall bladder wall thickness and platelets counts
- Significant positive correlation between gall bladder wall thickness and grade of esophageal varices.
- Gall bladder wall thickness is an independent predictor of esophageal

varices with sensitivity 82% and specificity 77%.

We concluded that gall bladder wall thickness can be considered as a non invasive predictor of esophageal varices in cirrhotic patients.

CONSENT

An informed written consent will be taken from all participants after explaining study design, anticipated benefits and possible risks.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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