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Pak J Med Res
Vol. 63, No. 4, 2024

Original Article

Gallbladder Wall Thickness as a Non-Invasive Tool for Prediction of Esophageal Varices in Patients with Hepatitis C Related Chronic Liver Disease

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Abstract

Background: The early identification of esophageal varices in patients with chronic liver disease (CLD) is important in order to mitigate the risk of variceal hemorrhage and mortality. Many noninvasive predictors have been studied for esophageal varices (EVs).
Objective: This study investigated the relationship of gallbladder wall thickness (GBWT) with the presence of EVs in patients with HCV-related CLD.
Study type, settings & duration: This cross-sectional study was conducted at the Department of Gastroenterology, Shifa International Hospital Ltd., Islamabad, Pakistan from February to August 2024.
Methodology: In this study 145 patients were considered and were categorized into Variceal (Group 1) and non-variceal groups (Group II). Group I is further divided into Group 1a (non-advanced /low-risk varices: Grade-I EVs) and Group 1b (Advanced/High-risk varices: Grade II/III EVs). After detailed history, examination laboratory investigations, EGD and ultrasound abdomen were performed.
Results: The median age of patients was 54±10.13 years. 89 patients were male (61.4%), and 56 were female (38.6%). 86.9% of patients had EVs Group 1) and 27.6% had no EVs (Group II). GBWT at a cutoff value of 3 mm predicted EVs in patients with HCV-CLD with a sensitivity of 79.37%, specificity of 89.47%, PPV of 98.04%, NPV of 39.53%, diagnostic accuracy of 80.67% with AUC of 0.882. GBWT at 3.7mm predicted advanced/high-risk varices with a sensitivity of 80.65%, specificity of 75.76%, PPV of 90.36%, NPV of 58.15%, and diagnostic accuracy of 79.37% with AUC of 0.813.
Conclusion: GBWT demonstrated a significant association with the presence of EVs and advanced grades of EVs.
Key words: Gallbladder wall thickness (GBWT), hepatitis-C (HCV), chronic liver disease (CLD), esophageal varices (EVs), CSPH.

Introduction

Esophageal varices (EVs) are one of the most serious complications of liver cirrhosis which are likely to develop in patients with clinically significant portal hypertension (CSPH) which is defined as hepatic venous pressure gradient (HVPG) ≥10mmHg.[1,2] Acute variceal bleeding significantly increase the rates of morbidity and mortality.[3] Moreover the uncontrolled variceal hemorrhage is significantly associated with development of acute on chronic liver failure (ACLF), one of the major determinants of mortality in cirrhotic patients.[4] Therefore, early identification of EVs is an important measure to improve outcomes in this subgroup of patients.

The best method to diagnose EVs and CSPH is esophagogastroduodenoscopy (EGD) or measurement of HVPG,[2] however, these tools are invasive and have financial implications. Therefore, many non-invasive tests have been put into use to

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Received: 09 October 2024, **Accepted:** 13 January 2025
Published: 11 Feburary 2025

Authors Contribution

MA & MA** conceptualized the project and did the literature search. MA**, SR, MS & RN did the data collection. MA* performed the Statistical analysis. Drafting, revision & writing of manuscript were done by MA & MA**.

detect EVs at an early stage. These include splenic stiffness measurement (SSM),[2] liver stiffness measurement (LSM),[2] platelet count to spleen diameter ratio (PLT/SD),[5] albumin, platelet count, and Platelet-Prothrombin time ratio (PLT/PT ratio).[6,7] However these predictors are still not widely employed for predicting EVs.

Small veins drain blood from gallbladder (GB) into the portal circulation. Therefore, portal hypertension can affect the thickness of the gallbladder wall (GBWT). Various studies have shown a significant association of GBWT with portal hypertension and hence the presence of EVs.[8,9] Egyptian research by Elkerdawy et al showed that GBWT at ≥ 3.1 predicted EVs with a sensitivity of 97.14% and specificity of 54.29%. EVs prevalence in this study was 66.7%.[10] Similar observations were made by Tsaknakis et al, demonstrating that GBWT at >4mm predicted EVs with a sensitivity and specificity of 46% and 89% respectively.[10,11] Hence a variability has been found in its cut-off values in terms of accuracy, sensitivity, and specificity. Therefore, it was important to establish a unanimous cut-off value for predicting EVs among HCV-related cirrhotic patients, especially in our population. This could potentially be introduced as an upcoming noninvasive assessment tool in our patient population, with financial constraints.

With this background, we sought to investigate the relationship of GBWT measurement with the presence of EVs among HCV-related chronic liver disease (HCV-CLD) as the primary objective. The secondary objective was to find the association of GBWT with the severity or advanced grades of EVs.

Methodology

This study was performed at the Department of Gastroenterology, Shifa International Hospital Ltd. Islamabad Pakistan. This cross-sectional study was conducted from February to August 2024. Non-probability consecutive sampling was used for patient recruitment. Based on the previous estimate of sensitivity of 54.29% and specificity of 97.14% at GBWT ≥3.1mm respectively and a 95% confidence level, a sample size of 145 patients was calculated for this study.[10]

After approval of the study protocol patients presenting to the Department of Gastroenterology and Hepatology, Shifa International Hospital Ltd. Islamabad Pakistan, were taken into the study. The inclusion criteria encompassed patients with HCV-CLD, aged ≥18 years. Exclusion criteria included those with a history of previous interventions for EVs (endoscopic band ligation, and sclerotherapy), GB-related recent (<3 months) surgical or radiological intervention (e.g. cholecystectomy, partial cholecystectomy), presence of any disease of GB (cholecystitis, GB polyps, GB carcinoma), factors affecting portal pressure (use of beta blockers, portal or splenic vein thrombosis, history of shunt surgery or trans jugular intrahepatic portosystemic shunts, presence of hepatocellular cancer) and ascitic fluid due to causes other than liver cirrhosis (e.g. congestive heart failure and Tuberculosis).

Written informed consent was taken after explaining all the risks and benefits. Demographic data (age, gender, and ethnicity) and laboratory parameters including liver function test (LFT), serum albumin, complete blood count (CBC), creatinine, international normalized ratio (INR), and prothrombin time (PT) were recorded. Screening EGD for varices and abdominal ultrasound were performed on the same day after 12 hours of fasting. Ultrasound was performed by an experienced sonologist, and findings as per operational definition were measured. Both the sonologist and endoscopist were kept blinded to the findings. All data was entered in a predesigned performa by the investigators.

Based on the presence and absence of EVs the patients in the study were allocated into two groups.

Group 1 included HCV-CLD patients with EVs. They were subsequently categorized into two subgroups. Group 1a comprised individuals with non-advanced or low-risk varices (varices without red signs or bleeding stigmata; whereas Group 1b included those with grade 2/3 or high-risk varices (varices with red wheal signs and high risk for bleeding). Group 2: included patients with no EVs as a control group.

EGD was performed under sedation after explaining the nature of the endoscopic intervention and overnight 12 hours of fasting. Patients were assessed for EVs as per operational definition (presence of abnormally enlarged, tortuous dilated veins in the esophagus). Varices seen on endoscopy were classified according to modified endoscopic Paquet classification.[12]

Ultrasound abdomen was performed by expert sonologists after 12 hours of fasting. All parameters including liver, portal vein, ascites, spleen, and GB wall thickness were assessed thoroughly. A diagnosis of liver cirrhosis was based on 3 or more of the following findings (altered liver echotexture, irregular hepatic margins, spleen size >12 cm, portal vein diameter >12 mm, and presence of free abdominal peritoneal fluid. The thickness of GB wall was measured at two distinct locations, and

then the average value of these measurements was calculated.[10]

Data was entered and analyzed utilizing IBM SPSS Statistics for Windows, Version 26.0. (IBM, NY, USA). The qualitative data were displayed using numbers and percentages. Median ± standard deviation was utilized for quantitative variables. The Chi-square test was used for the comparison of qualitative data between two groups, whereas the Mann–Whitney U test was employed to assess differences in non-normally distributed data between the two groups. The multivariate logistic regression analysis using the forward Wald technique to get adjusted odds ratios with a 95% confidence interval was applied. A *p*-value of 0.05 or lower is regarded as statistically significant.

The ethical approval was obtained from the Instructional Review Board & Ethics Committee of Shifa International Hospital Ltd., Islamabad vide letter no. 0357-22.

Results

A total of 145 patients with HCV-CLD were included. The median age of the patients was 54±10.13 years (25 to 86 years). 89 patients were male (61.4%), and 56 were female (38.6%) They were segregated into two groups (Variceal and non-variceal) based upon the presence or absence of EVs as observed during EGD (Figure A & B).

Table 1: Demographic, laboratory, sonographic and endoscopic findings of patients.

		Group 1. (Esophageal Varices) n=126	*Group 2. (Non-Esophageal Varices) n=19*	
Variable		*n (%) Median ± SD*		*p-value*
Age		55±9.8	51±12.1	0.833
Gender	Male	81 (64.3)	8 (42)	0.079
	Female	45 (35.7)	11 (57.9)	
Esophageal varices	Grade 1	33 (26.2)	0	
	Grade 2	43 (34.1)	0	0.000*
	Grade 3	50 (39.7)	0	
	None	0	19 (100)	
LFTs	Total Bilirubin	1.30±1.69	0.79±0.75	0.002*
	Aspartate transaminase	47.0±41.6	37.0±42.0	0.092
	Alanine transaminases	32.5±53.0	25.0±19.9	0.367
	Albumin	3.00±0.55	4.00±0.39	0.000*
CBC	Hemoglobin	10.20±2.35	12.80±2.10	0.001*
	Total leukocyte count	5430.0±8948.5	5600.0±1823.6	0.874
	Neutrophils	68.5±11.8	69.0±9.4	0.751
	Lymphocytes	17.5±9.8	20.0±9.5	0.504
	Platelets	101000.0±49137.5	155000.0±95607.7	0.000*
Coagulation profile	Prothrombin Time	13.00±2.34	10.50±2.54	0.000*
	INR	1.25±.26	1.09±2.05	0.000*
RFTs	Creatinine	93±0.56	0.72±0.72	0.045*
	Sodium	135.5±5.2	136.0±5.0	0.266
	Blood urea nitrogen	15.00±12.87	15.00±17.97	0.585
Ultrasound Abdomen	GBWT	4.5±2.0	2.5±0.8	0.000*
	PV Diameter	11.95±2.20	10.00±1.19	0.143
	Spleen Size	14.00±12.19	13.00±2.06	0.001*
Ascites	Mild	46 (36.5)	1 (5.3)	0.007*
	Moderate	15 (11.9)	1 (5.3)	
	Gross	6 (4.8)	0	
	No Ascites	59 (46.8)	17 (89.5)	
CTP class	Class A	46 (36.5)	16 (84.2)	0.000*
	Class B	65 (51.6)	3 (15.7)	
	Class C	15 (11.9)	0	
Others	MELD Sodium	13.0±6.2	10.0±5.0	0.001*
	PLT/SD ratio	7115.73±4688.98	12500.0±5831.97	0.000*
	Fibrosis-4	4.91±4.80	2.40±6.66	0.001*
	APRI	1.10±1.21	0.60±1.50	0.008*

Table 2. Non-advanced/Low risk Vs. advanced/ high risk variceal subgroups.

Variable		Group A Non-advanced/Low risk (Grade I) n=33	Group B advanced/High risk Varices (Grade II & III) n=93	p-value
		n (%) Median ± SD		
Age		54.0±10.2	55.0±9.6	0.177
Gender	Male	21 (63.6)	60 (64.5)	1.000
	Female	12 (36.4)	33 (35.5)	
LFTs	Total Bilirubin	1.30±1.07	1.29±1.86	0.337
	Aspartate transaminase	42.0±33.2	47.0±44.2	0.162
	Alanine transaminases	32.0±31.6	34.0±58.8	0.465
	Albumin	3.30±0.45	3.00±0.57	0.004*
CBC	Hemoglobin	11.0±2.40	10.0±2.31	0.089
	Total leukocyte count	5200.0±11231.8	5500.0±8031.4	0.527
	Neutrophils	67.0±9.6	69.0±12.5	0.413
	Lymphocytes	20.0±9.6	17.0±9.8	0.346
	Platelets	135000.0±58177.4	97000.0±43145.3	0.006*
Coagulation profile	Prothrombin Time	11.90±2.0	13.30±2.37	0.001*
	INR	1.12±0.20	1.27±0.27	0.001*
RFTs	Creatinine	0.96±0.42	0.91±0.61	0.543
	Sodium	134.0±4.3	137.0±5.5	0.019*
	Blood urea nitrogen	15.0±9.97	17.0±13.60	0.032*
Ultrasound Abdomen	GBWT	3.1±1.1	5.0±2.0	0.000*
	PV Diameter	10.20±1.71	12.0±2.33	0.073
	Spleen Size	13.50±23.53	14.20±2.61	0.091
Ascites	Mild	8 (24.2)	38 (40.9)	
	Moderate	3 (9.1)	12 (12.9)	0.045*
	Gross	0	6 (6.5)	
	No Ascites	22 (66.7)	37 (39.8)	
CTP class	Class A	22(66.7)	24 (25.8)	0.000*
	Class B	9(27.3)	56 (60.2)	
	Class C	2 (6.1)	13 (14.0)	
Others	MELD Sodium	11.0±5.5	14.0±6.3	0.030*
	PLT/SD ratio	9806.45±6011.04	6548.66±3950.74	0.013*
	Fibrosis-4	3.30±4.35	5.27±4.85	0.002*
	APRI	0.80±1.10	1.20±1.23	0.006*

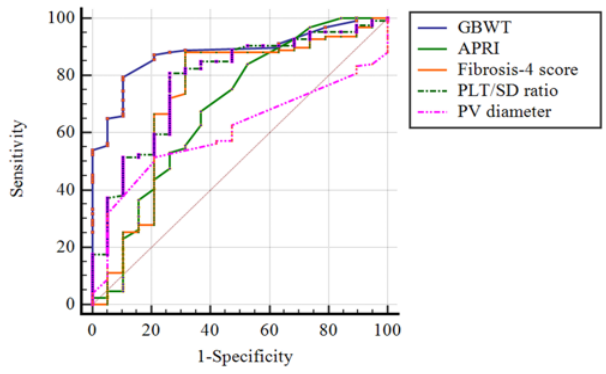

Figure A: ROC curve for presence and absence of varices

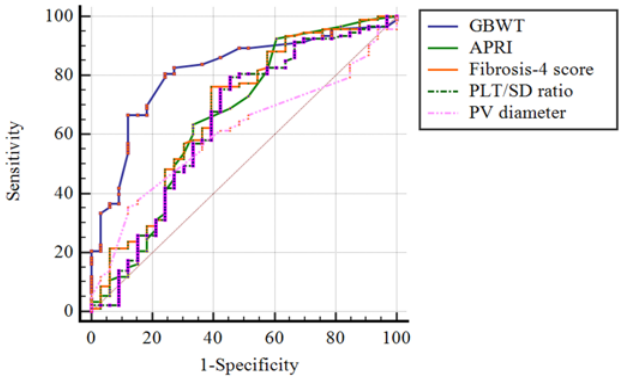

Figure B: ROC curve for Advanced grades/high risk varices

126/145 (86.9%) patients had esophageal varices (Group I).19/145 (27.6%) patients did not have any visible varices (Group II). Patients in group 1 had significantly prolonged PT, INR and increased total bilirubin, while lower hemoglobin level, albumin, and platelets counts (p <0.05) (Table 1).

The MELD-Na (Model for End-Stage Liver Disease-Sodium) Score (p <0.01), CTP (Child-Turcotte-Pugh Score) (p <0.01), APRI (AST to Platelet Ratio Index) (p =0.008), FIB-4 (Fibrosis-4) (p <0.01), and PLT/SD ratio (p <0.001) showed statistically significant differences between the two groups (Table-1).

Table 3: Diagnostic values of significant factors associated with E.varices (EVs) and advanced varices.

Parameters	*Cutoff Value*	*AUC*	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*Accuracy*
Esophageal varices (Presence & Absence)							
GBWT	>3	0.882	79.37	89.47	98.04	39.53	80.67
PV Diameter	>11	0.603	51.59	78.95	94.21	19.73	55.17
Fibrosis-4 score	>2.5	0.731	88.10	68.42	94.87	46.43	85.52
APRI	>0.5	0.689	84.13	47.37	91.38	31.03	79.31
PLT/SD ratio	≤10714	0.783	80.95	73.68	95.33	36.83	79.99
Advanced grades/high risk Varices							
GBWT	>3.7	0.813	80.65	75.76	90.36	58.15	79.37
PV Diameter	>12.5	0.604	35.48	87.88	89.19	35.58	49.20
Fibrosis-4 score	>3.39	0.679	76.34	60.61	84.52	47.62	72.22
APRI	>0.5	0.661	92.47	39.39	81.13	64.99	78.57
PLT/SD ratio	≤9618.32	0.645	79.57	54.55	83.15	48.65	73.02

Table 4. Multivariate logistic regression analysis of independent predictors of esophageal varices.

Parameters	*β*	*AOR (95% CI)*	*p-value*
GBWT	-1.270	0.281 (0.147-0537)	<0.001*
Platelet/splenic ratio	.000	1.0 (1.0-1.0)	0.047*
Constant		1.08	
% correctly predicted		86.9%	
Model χ^2, p-value		39.8, <0.001	
Predictors of advanced varices			
GBWT	0.907	2.478 (1.647-3.727)	<0.001*
Platelets	0.00	1.0 (1.0-1.0)	0.004*
Constant		-0.924	
% correctly predicted		81%	
Model χ^2, p-value		39.54, <0.001	

β: regression coefficient; AOR, adjusted odds ratio; CI, confidence interval.

GBWT was significantly greater in Group 1 patients (4.5 +/-2.0 mm vs. 2.5 +/-0.8 mm; *p* <0.01) (Table-1)

Group 1a (n=33, 26%) included those patients who had grade I EVs (non-advanced/low-risk EVs). Group 1b (n=93, 73.9%) encompassed patients with grade II-III EVs (advanced/high-risk varices). The platelet count and albumin levels appeared to be lower in group 1b patients compared to those in group 1a (*p* <0.05 for both) (Table-2).

MELD-Na score (*p* =0.030), FIB-4 score (*p* =0.002), APRI (*p* =0.006), and PLT/SD ratio (*p* =0.013) were significantly different between both subgroups (Table-2).

The GBWT measurement in Group 1b significantly surpassed that in Group 1a (5.0 +/- 2.0 vs. 3.1 /- 1.1 mm; *p*: 0.000) (Table-2).

Among the total studied population, only 18 patients (12.41%) had fundal varices. The majority of these patients had Child-Pugh Class-B (n=13, 72.2%), mild ascites (n=8, 44.4%) with significantly increased APRI (*p* =0.028), and GBWT (*p* <0.01).
The overall diagnostic accuracy of GBWT for identification of EV was 80.67% with an AUC of 0.882 (Table-3). Overall diagnostic accuracy of GBWT for the identification of advanced varices was 79.377% with an AUC of 0.813. (Table-3)

GBWT and the PLT/SD ratio emerged as independent predictors in the multivariate logistic regression analysis, for the presence of EVs (*p* <0.001 and 0.047, respectively). Additionally, GBWT and platelet count have been discovered as independent prognostic indicators for the existence of high-risk or advanced varices. (*p* <0.001 and 0.004, respectively), as detailed in (Table-4).

Discussion

Presently GBWT at 3 mm predicted esophageal varices in patients with HCV-CLD and portal hypertension with a sensitivity of 79.37%, specificity of 89.47%, PPV of 98.04%, NPV of 39.53%, diagnostic accuracy of 80.67% with AUC of 0.882. Likewise, GBWT at 3.7mm predicted advanced/high-risk varices with a sensitivity of 80.65%, specificity of 75.76%, PPV of 90.36%, NPV of 58.15%, and diagnostic accuracy of 79.37% with AUC of 0.813.

Although the Fibrosis-4 score was found to have the highest sensitivity and diagnostic accuracy among the studied variables for the detection of esophageal varices (88.1% and 85.52% respectively), GBWT >3mm had the highest specificity (89.47%) and PPV (98.04%). Moreover, GBWT had the highest an overall diagnostic

accuracy (79.37%) and PPV (90.36%), for the detection of advanced grades of EVs or high-risk varices while the sensitivity (80.65%) and specificity (75.76%) falls second after APRI (92.47% sensitivity) and portal vein diameter (specificity; 87.88%) respectively.

The established cut-off values of GB wall thickness for predicting the presence of esophageal varices (EVs) is reported in the literature to vary between 3.1 mm and 4.35 mm, with associated sensitivities ranging from 46% to 90.9%.[13] These cut-off values are comparable to present results.[13]

Besides, a relationship was also observed between the degree of varices and the presence of portal hypertensive gastropathy (PHG). In cirrhotic patients, GBWT exceeding 3.5 mm predicted the presence of advanced varices with a sensitivity of 45% in one cohort and the sensitivity rose to almost 92% when a different cut-off value was used in another cohort i.e. >3.9mm.[13] Similarly in another comparable study, a GBWT of 6.1 mm was significantly associated with advanced grades of EVs in individuals with chronic liver disease.[14] Recently, a meta-analysis showed increased gallbladder wall thickness in patients with chronic liver disease to predict EVs with a sensitivity of 73% and specificity of 86%, almost similar to our results in terms of sensitivity and specificity.[15]

Although. It has been postulated that the evolving nature of portal hypertension causes graded congestion of the GB which might be a surrogate marker of advancement of disease. However, the presence of hypoalbuminemia and ascites in patients with advanced disease might confound this hypothesis.[16] Nevertheless, GB wall thickness seems to be reflective of the multiple factors in parallel to the advanced disease process in these patients. This concept has been previously documented in a study in which the authors concluded that GBWT is associated with advanced chronic liver disease, irrespective of serum albumin levels.[17]

Reviewing the cost and invasive nature of EGD with potential complications Boveno VII introduced some non-invasive tests such as LSM, SSM, and a combined model with platelet count to stratify the stage of liver disease process, identify clinically CSPH, risk of decompensation, and development of esophageal varices and prioritize treatment protocol. Patients with CLD and LSM more than 25Kpa or Value between 20Kpa to 25Kpa along with a platelet count of <150 x 10^9/L were found to have about 60% risk of CSPH and development of EVs and comparable outcomes were found between EGD and beta blockers.[2,18] This reflects to avoidance of unnecessary EGD in cirrhotic patients. Similarly in a retrospective analysis, the combined approach of SSM with Boveno-VI guideline identified a number of patients with CLD that can safely avoid unnecessary EGD.[19]

GBWT thickness is easy to measure on ultrasound which is widely available modality with almost negligible complications. However, still, no data exists to find the correlation between the liver stiffness index and GBWT. Therefore, we believe that further studies should look at the association of GBWT and LSM with the hope that we can incorporate GBWT into the evolving algorithm for the evaluation of portal hypertension. The main limitations of this study include this being a single-center, cross-sectional study. In conclusion GBWT in HCV-CLD patients has a significant association with the presence of EVs and the advanced grades of EVs.

Acknowledgement

We would like to thank Dr Sadaf Yousuf for her support in conducting this study.

Conflict of interest: None declared.

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