https://doi.org/10.29309/TPMJ/2024.31.12.8306

The Professional Medical Journal
www.theprofesional.com
2024, Volume, 31 Issue, 12

ORIGINAL ARTICLE

Validation of Gall bladder wall thickness as a non-invasive marker for the prediction of esophageal varices in cirrhotic patients with portal hypertension.

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Article Citation: Kumar A, Mansoor Ul Haq, Kumar D, Sheikh T. Validation of Gall bladder wall thickness as a non-invasive marker for the prediction of esophageal varices in cirrhotic patients with portal hypertension. Professional Med J 2024; 31(12):1705-1711. https://doi.org/10.29309/TPMJ/2024.31.12.8306

ABSTRACT… Objective: To validate the gall bladder wall thickness as a non-invasive marker for the prediction of esophageal varices (EV) in cirrhotic patients with portal hypertension. **Study Design:** Cross-sectional study. **Setting:** Department of Gastroenterology, Liaquat National Hospital, Karachi, Pakistan. **Period:** January 2024 to June 2024. **Methods:** Patients of age 18 years, of any gender diagnosed with cirrhosis and were endoscopy naïve with no previous history of intervention for varices were included. After an overnight fast, the gall bladder (GB) thickness was measured twice at two distinct places, and an average value was determined. **Results:** Total 210 patients were enrolled into the study with mean age of 56.3 ± 11.8 years. Majority were males (57.1%). Patients had comorbidity of hypertension (17.1%) and diabetes (16.2%). Median gall bladder thick was 2.3 (IQR=1.2-2.9) cm. AUC for GB to predict EV was found to be 0.983 (95% CI: 0.96-1, p<0.001) which shows excellent predictive ability of GB thickness. The optimal cut-off value of GB thickness was found to be ≥1.95 cm. On multivariable regression analysis, increasing gall bladder thickness was found to be associated with higher odds of esophageal varices. **Conclusion:** The present demonstrated that GB thickness is a promising parameter with excellent predictive ability for prediction of EV among cirrhotic patients with portal hypertension, which should be included in part of routine evaluation in such cohort of patients for timely detection of EV.

Key words: Cirrhosis, Endoscopy, Esophageal Varices, Gall Bladder, Portal Hypertension.

INTRODUCTION

Portal hypertension (PH) is defined as raised portal venous pressure than the normal range of 5-10mmHg in chronic liver disease.[1] A obstruction in the blood flow through the liver is the cause of this elevated pressure. Varices across the stomach and esophagus arise from increased portal venous pressure. The varices become weak and prone to bleeding. Significant clinical in cirrhotic patients, PH is the primary cause of death due to the development of ascites, splenomegaly, and—most importantly—gastric esophageal varices (GOV).[2]

GOV prevalence in Cirrhotic is patient is around 30 – 60 % depending upon the severity of portal hypertension and liver cirrhosis with 5 to 10 % formation of new cases and 5 – 30 % of growth rate from small to large varices. There is significant 30% mortality from variceal hemorrhage despite of advancement in the treatment options.[3] Hence high risk patients need to be identified early for primary prophylaxis.[4]

The gold standard tests for diagnosing esophageal varices (EV) and PH are hepatic venous pressure gradient through hepatic vein catheterization; however, both procedures are invasive, patients may not always accept them, and difficulties may arise.[5,6]

There are many non-invasive tests for prediction of clinical significant PH, i.e. platelet count, portal vein diameter, splenic diameter etc.[1] Gall Bladder wall thickness is now included in the non-invasive test for predicting GOV.[7,8] Previously there is no such study which could identify the GBWT for prediction of GOV in any prospective

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Article received on: 22/05/2024
Accepted for publication: 26/07/2024

or comparative cohort. On the other hand there are multiple studies for evaluation or non-invasive marker assessment for portal hypertension.[9,10] Thus we planned the current study to validate the Gall Bladder Wall Thickness as a non-invasive marker for the prediction of esophageal varices in cirrhotic patients with PH.

METHODS

This cross-sectional study was performed in Gastroenterology Department at Liaquat National Hospital during January 2024 to June 2024. Patients were enrolled from both outpatient clinics and inpatient department. Patients of age 18 years, of any gender diagnosed with cirrhosis and were endoscopy naïve with no previous history of intervention for varices were included. Patients with bleeding EV, HCC, organ transplant, portal or splenic vein thrombosis, cholecystitis, GB carcinoma, CCF, pancreatitis, biliary or abdominal surgery, SBP or any active infection were excluded. Pregnant and lactating females were also excluded. The study commenced after taking approval from Hospital Ethics Committee (IRB No.744-2022 LNH-ERC).

Patients were enrolled with their written informed consent. Previously conducted similar study, reported an area under the curve of 0.9 to predict esophageal varices.[7] Therefore, to estimate a 90% area under the curve with 95% confidence interval and 5% precision, a sample of 105 disease positive and disease negative is required. Sample size calculation was performed as described by Hajian-Tilaki K.[11]

After an overnight fast, the gall bladder's thickness was measured twice at two distinct places, and an average value was determined. It was noted whether ascites was present or not. In addition, laboratory and clinical parameters were recorded, such as total bilirubin, albumin levels, platelet counts, ALT, AST, and PT/INR. Clinical parameters included HCVAB and HBSAG.

Data was entered into SPSS version 26 to perform statistical analysis. Categorical variables were expressed as frequency and percentage. Numerical variables were expressed as mean ± standard deviation. Predictive ability of gall bladder thickness was identified using receiver operating characteristic curve (ROC) and area under the curve was calculated (AUC). Multivariable logistic regression was applied to determine influence of gall bladder thickness on esophageal varices after controlling the effects of other covariates. Statistical significance was defined when two-tailed p-value was lower than 5% levels of significance.

RESULTS

Total 210 patients were enrolled with mean age of 56.3 ± 11.8 years. Majority were males (57.1%). Patients had comorbidity of hypertension (17.1%) and diabetes (16.2%). Half of the patients had ascites (50.5%). Hepatic encephalopathy was seen in nearly quarter of the patients (23.8%). EV were present in 69% patients. Out of 145 (69%) with EV, 12.4% had small EV, 20.7% had medium EV and 66.9% had large EV. Median levels of hemoglobin, platelets, albumin, total bilirubin, ALT, AST, and PT/INR were 10.1 (IQR=8.9-11.3), 126 (IQR=78.8-168), 2.9 (IQR=2.6-3.3), 1.1 (IQR=0.80-1.4), 41 (IQR=30.1-55.3), 50 (IQR=34.3-63.3) and 1.4 (IQR=1.2-1.5) respectively. Median gall bladder thick was 2.3 (IQR=1.2-2.9) cm. Table-I displays sociodemographic and clinical features of study participants.

Variables	Groups	Count	Percentage
Age	25-39 years	14	6.7
	40-59 years	110	52.4
	≥60 years	86	41
Gender	male	120	57.1
	female	90	42.9
Ascites	yes	106	50.5
	No	104	49.5
Hepatic encephalopathy	yes	50	23.8
	No	160	76.2
Esophageal varices	No	65	31.0
	yes	145	69.0
HCV	Positive	152	72.4
	Negative	58	27.6
HBsAg	Positive	26	12.4
	Negative	184	87.6

Table-I. Description of clinical and socio-demographic characteristics

None of patients' features were found to be significantly different among those with and

without EV except age. The frequency of EV was considerably greater in younger patients compared to older ones (p=0.034) (Table-II).

Variables	Groups	Esophageal Varices		P-Value
		Present Count (%)	Absent Count (%)	
Age	25-39 years	14(100)	0(0)	0.034
	40-59 years	74(32.7)	36(32.7)	
	≥60 years	57(33.7)	29(33.7)	
Gender	male	89(25.8)	31(25.8)	0.064
	female	56(37.8)	34(37.8)	
Ascites	yes	83(21.7)	23(21.7)	0.003
	no	62(40.4)	42(40.4)	
Hepatic encepha-lopathy	yes	37(26)	13(26)	0.385
	no	108(32.5)	52(32.5)	
HCV	Positive	107(29.6)	45(29.6)	0.494
	Negative	38(34.5)	20(34.5)	
HBsAg	Positive	18(30.8)	8(30.8)	0.983
	Negative	127(31)	57(31)	

Table-II. Comparison of patients' features among those having esophageal varices and without esophageal varies

Figure-1 depicts ROC curve predictive ability of GB thickness for prediction of EV. AUC for GB to predict EV was found to be 0.983 (95% CI: 0.96-1, p<0.001) which shows excellent predictive ability of GB thickness. The optimal threshold value of GB thickness was found to be ≥1.95 cm. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) at threshold of ≥1.95 cm was 0.979, 0.908, 0.959 and 0.952 respectively. Overall diagnostic accuracy at this threshold was 0.957.

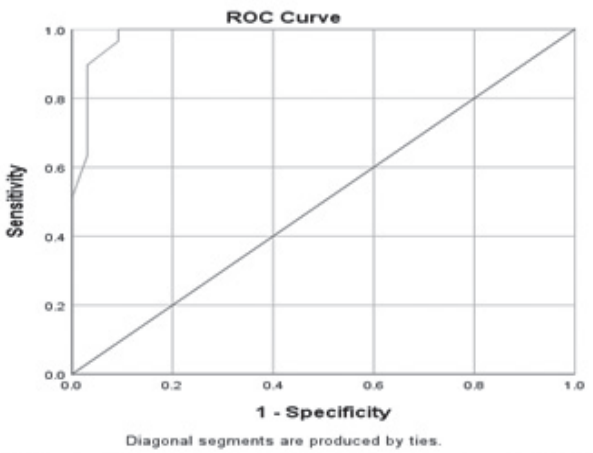

Figure-1. ROC curve depicting predictive ability of GB thickness for prediction of EV

Variables	Adjusted Odds Ratio	Confidence Interval		P-Value
		Lower Limit	Upper Limit	
Gender, male versus female	0.540	0.06	4.76	0.583
Ascities	3.070	0.03	305.59	0.632
Platelet count (10^9/L)	0.990	0.98	1.00	0.075
Albumin level (g/dl)	0.410	0.01	13.35	0.613
Total bilirubin (umol/L)	1.550	0.56	4.32	0.400
ALT (U/L)	0.990	0.90	1.10	0.915
AST (U/L)	1.010	0.93	1.10	0.820
PT/INR (sec)	72.070	0.02	3.00	0.314
CTP A vs CTP C	1.300	0.02	85.75	0.902
CTP B vc CTP C	0.190	0.00	10.06	0.415
Gall bladder thickness (cm)	1160.240	34.11	39461.38	**<0.001

Table-III. Gall bladder thickness as predictor of esophageal varices on multivariable regression analysis

DISCUSSION

Cirrhotic patients with portal hypertension commonly present with bleeding varices, posing a significant risk to life. Various strategies have been implemented to facilitate early diagnosis of EV, in order to avoid grave complications if left undiagnosed. While several non-invasive methods have been widely discussed in the literary works, the utilization of gallbladder wall thickness as a diagnostic marker remains relatively underexplored.[12,13]

Annually, almost 7–8% of cirrhotic patients can be diagnosed with varices. In the current study, 69% exhibited the presence of EV, highlighting its significance as a major event in cirrhotic patients. These findings are corroborated by Diaz Soto et al. and Kamil Ozdil et al., demonstrating that esophageal varices are present in more than half of uncompensated liver patients, ranging from 50% to 66%, respectively, and even more so in patients with decompensated cirrhosis.[14-16]

Esophageal varices (EV) are categorized by size, with varices ≤5 mm termed as small and those >5

mm termed as medium-large.[17] The rate at which tiny varices become large varices is between 10% and 12% per year.[1] In our study, 12.4% of patients had small EV, 20.7% had medium EV, and the majority, 66.9%, had large EV. These findings are consistent with Jensen et al.'s study, indicating that a higher proportion of cirrhotic patients present with large esophageal varices rather than small to medium-sized ones.[18]

The present study underscores a higher prevalence of esophageal varices (EV) in young to middle-aged patients (<60 years old) compared to older individuals, in line with findings published in Cureus in 202.[19] However, there is a notable difference in the mean age reported between the two studies: 45.5 years in their study versus 56.3 years in ours. This slight variation can be attributed to the substantial difference in sample sizes between the two studies. Shrestha et al. recruited nearly 15,657 patients over a span of 6 years, while our study had a more limited sample size and duration.[19] Consequently, although significance was evident in univariate analysis, it did not persist in multivariable analysis.

Mattos and coworkers have identified several non-invasive parameters, such as PH diameter albumin, platelet count, spleen diameter, the Child-Pugh classification, ascites and among others, to detect the presence of esophageal varices.[20] These non-invasive markers are not only cost-effective in identifying EV but also help avoid unnecessary use of endoscopic procedures and their associated complications. Consistent with other studies, our study also investigated above mentioned factors, revealing significant correlation between ascites, platelet count, albumin levels, AST, PT/INR, and Child-Pugh classification with EV on univariate analysis.

The connotation between platelet count and EV has been widely investigated.[21,22] Our findings indicate that increasing platelet count and albumin levels are related to a decreased risk of EV, aligning with current researches that observed an increased chance of detecting EV with decreasing platelet count.[23-25] Additionally, the prevalence of varices upturns with liver disease severity as classified as CTP C were at elevated risk compared to those with CTP A.[12,26] Our results further strengthen findings reported by Chandail and coauthors that elevated AST and PT/INR levels are associated with increased risk for EV.[27] Despite these positive findings, these variables only showed a substantial link in univariate analysis but not in multivariable analysis.

Among various effective alternatives to invasive procedures, the measurement of gallbladder wall thickness has emerged as a promising non-invasive diagnostic marker for EV. Interestingly, diffuse gallbladder wall thickening, even in the absence of gallbladder disease, is frequently detected on imaging in patients with advanced liver disease and PH compared to healthy individuals.[28,29]

Our study identified AUC for gallbladder thickness to predict EV as 0.983 (95% CI: 0.96-1, $p<0.001$). Similar results were also reported in a meta-analysis of 12 papers published in 2023, which revealed that patients with EV had considerably thicker gallbladders than the control group, with an AUC of 86% on the ROC curve.[13] Analogous to this, Tsaknakis and colleagues concluded that gallbladder wall thickness was an independent predictor for EV, with ROC analysis yielding an AUC of 0.864 (CI 0.809–0.919).[8] These findings collectively with other studies demonstrate that gallbladder thickness exhibits excellent predictive ability for EV.[30,31]

Our findings reveal that gallbladder wall thickness at a cutoff level of ≥1.95 cm can envisage the EV presence with a 0.979 sensitivity, 0.908 specificity, 0.959 PPV and 0.952 NPV. Several research have drawn attention to variable cutoff values; generally, GBWT >4 mm is linked to adequate sensitivity up to 90% in numerous investigations.[8,31,32]

Our values differ from those published by Elkerdawy et al.[7], who reported a cutoff value at >3.1 mm. 54.29% sensitivity, 97.14% specificity, 97.4% PPV, and 51.5% negative predictive value at a threshold of >3.1 mm.[7] This discrepancy arises from their inclusive approach, considering

all variceal types (gastric and esophageal), whereas our investigation focused solely on esophageal varices. Tsaknakis et al. indicated a gallbladder wall thickness of ≥4 mm for detecting EV, yielding 46% sensitivity, 89% specificity, 70% PPV, and 73% NPV.[8] Variations in cutoff values across studies occur majorly due to differences in cirrhosis etiology and disease severity among these patients. Elkerdawy et al.[7] exclusively enrolled patients with viral cirrhosis, whereas Tsaknakis et al.[8] included only 20% of such cases. Viral cirrhotic patients exhibit varying degrees of hepatic fibrosis compared to non-viral counterparts, leading to lower GBWT cutoffs in studies focusing on viral etiologies.[32] After adjusting for the effects of other biomarkers in a multivariable model, GB thickness was still associated with EV according to our results, similar to that reported by Shehata et al.[30]

The current study is subjected to few limitations. To reduce time effect of either the GBWT or the varices both investigations, endoscopy and ultrasound should ideally be conducted concurrently. Furthermore, GBWT can be influenced by factors beyond portal hypertension, including the serum-ascites albumin gradient among others.[8,32] Thus introducing potential confounding variables. Additionally, the relationship between GBWT and portal vein parameters (such as diameter and flow velocity) and other relevant parameters was not comprehensively explored in this study. Lastly, the current article did not distinguish between different grades of cirrhosis, which may have implications for the generalizability of the findings.

CONCLUSION

The present demonstrated that GB thickness is a promising parameter with excellent predictive ability for prediction of EV among cirrhotic patients with portal hypertension, which should be included in part of routine evaluation in such cohort of patients for timely detection of EV.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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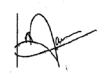
AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Ameet Kumar	Conceptualized the study, Designed the study protocol, Initial manuscript writing, Data collection, Manuscript revision.	
2	Mansoor Ul Haq	Designed the study, Protocol Critical review & revision of initial manuscript draft.	
3	Dheeraj Kumar	Designed the study protocol, Statistical analysis, Initial manuscript writing.	
4	Tauqeer Sheikh	Data collection.