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Editorial Board Member of *World Journal of Hepatology*, Heng M El Tayebi, PhD, Associate Professor, Pharmacist, Senior Scientist, Clinical Pharmacology and Pharmacogenomics Research Group, Department of Pharmacology and Toxicology, Faculty of Pharmacy and Biotechnology, German University in Cairo, Cairo 11835, Egypt.
hend.saber@guc.edu.eg

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WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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Sonographic gallbladder wall thickness measurement and the prediction of esophageal varices among cirrhotics

Mohamed H Emara, Mariam Zaghloul, Ibrahim F Amer, Aya M Mahros, Mohammed Hussien Ahmed, Mahmoud A Elkerdawy, Eslam Elshenawy, Abdelrahman M Ahmed Rasheda, Tarik I Zaher, Mona Talaat Haseeb, Emad Hassan Emara, Hassan Elbatae

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Mohamed H Emara, Mariam Zaghloul, Ibrahim F Amer, Aya M Mahros, Mohammed Hussien Ahmed, Mahmoud A Elkerdawy, Eslam Elshenawy, Hassan Elbatae, Department of Hepatology, Gastroenterology and Infectious Diseases, Kafrelsheikh University, Kafr-Elshikh 33516, Egypt

Abdelrahman M Ahmed Rasheda, Department of Internal Medicine, Gastroenterology Unit, Security Forces Hospital, Riyadh 11481, Saudi Arabia

Tarik I Zaher, Tropical Medicine, Zagazig University, Zagazig 44519, Egypt

Mona Talaat Haseeb, Emad Hassan Emara, Department of Diagnostic and Interventional Radiology, Kafrelsheikh University, Kafr-Elshikh 33516, Egypt

Corresponding author: Mohamed H Emara, MD, MSc, Professor, Department of Hepatology, Gastroenterology and Infectious Diseases, Kafrelsheikh University, Algeish Street, Kafr-Elshikh 33516, Egypt. emara_20007@yahoo.com

Abstract

Acute variceal bleeding in patients with liver cirrhosis and portal hypertension (PHT) is the most serious emergency complication among those patients and could have catastrophic outcomes if not timely managed. Early screening by esophago-gastro-duodenoscopy (EGD) for the presence of esophageal varices (EVs) is currently recommended by the practice guidelines for all cirrhotic patients. Meanwhile, EGD is not readily accepted or preferred by many patients. The literature is rich in studies to investigate and validate non-invasive markers of EVs prediction aiming at reducing the unneeded endoscopic procedures. Gallbladder (GB) wall thickness (GBWT) measurement has been found promising in many published research articles. We aim to highlight the validity of sonographic GBWT measurement in the prediction of EVs based on the available evidence. We searched databases including Cochrane library, PubMed, Web of Science and many others for relevant articles. GBWT is associated with the presence of EVs in cirrhotic patients with PHT of different etiologies. The cut-off of GBWT that can predict the presence of EVs varied in the literature and ranges from 3.1 mm to 4.35 mm with variable sensitivities of 46%-90.9% and lower cut-offs in viral cirrhosis compared to non-viral, however GBWT > 4 mm in many studies is associated with acceptable sensitivity up to 90%. Furthermore, a relation was also noticed with the degree of varices and portal hypertensive gastropathy.

Among cirrhotics, GBWT > 3.5 mm predicts the presence of advanced (grade III-IV) EVs with a sensitivity of 45%, the sensitivity increased to 92% when a cut-off ≥ 3.95 mm was used in another cohort. Analysis of these results should carefully be revised in the context of ascites, hypoalbuminemia and other intrinsic GB diseases among cirrhotic patients. The sensitivity for prediction of EVs improved upon combining GBWT measurement with other non-invasive predictors, *e.g.*, platelets/GBWT.

Key Words: Sonographic; Gallbladder wall thickness; Prediction; Esophageal varices; Portal hypertension; Esophago-gastro-duodenoscopy

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Core Tip: Ruptured varices is a medical emergency and is associated with high mortality. Hence, it was recommended by the current practice guidelines to screen cirrhotic patients with portal hypertension for the presence of varices and eradicate the risky varices early. However, many issues exist with this policy. This directed the clinicians to search for non-invasive assessment tools aiming to refer only indicated cases for endoscopic examination. Among the promising tools is sonographic measurement of gallbladder wall thickness that was found related not only with the presence of esophageal varices but also with the degree of varices and portal hypertensive gastropathy.

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INTRODUCTION

Acute bleeding from ruptured gastro-esophageal varices (EVs) is a serious and potentially fatal outcome of portal hypertension (PHT) particularly among cirrhotic patients. Although the management of PHT has evolved dramatically, ruptured EVs still represents a major medical emergency with high morbidity and mortality rates[1]. Therefore, the current practice guidelines recommend screening of all cirrhotics by esophago-gastro-duodenoscopy (EGD) for the presence of EVs and to deliver management if large risky varices were detected[2,3].

Over the last few decades, non-invasive prediction has become the focus of interest for many researchers and clinicians. Many composite scores were proposed for early prediction of liver cirrhosis and its complications, particularly PHT. These predictors ranged from very simple tests such as the platelet count or prothrombin index that are readily available, affordable, and routinely used as part of cirrhotic patients' regular care to much more specific, costly, and not-readily available ones such as hyaluronic acid or type IV collagen assay. Many of these were correlated with the presence of EVs of various degrees, but their accuracy in diagnosis were not consistent[4-6].

To increase the diagnostic accuracy of these non-invasive predictors for EVs detection, combinations of markers were investigated, tested and some of them were proved useful, such as aspartate transaminase (AST) to alanine transaminase ratio[7], AST to platelet ratio index (APRI)[8], or platelet count to spleen diameter ratio[7].

Among the studied predictors, gallbladder (GB) wall thickness (GBWT) measurement by ultrasonography has been found promising in many of the published research articles. The relation of GBWT to PHT and EVs have been spotted late in the last century[9,10].

The aim of this review is to evaluate the validity of the sonographic GBWT measurement in the prediction of EVs based on the available evidence.

LITERATURE SEARCH

We searched databases including Cochrane library, Web of Science, Ovid, Science Direct, Scopus, Directory of Open Access Journals, EBSCO HOST, ProQuest, Institute for Scientific Information, EBESCO, MEDLINE /PubMed, Egyptian knowledge bank, Google scholar, *Reference Citation Analysis* (<https://www.referencecitationanalysis.com/>) and the Research Gate for relevant articles. We retrieved a number of studies focusing on sonographic GBWT measurement and PHT or EVs. The articles were

analyzed for delineating the relationship to PHT, EVs or portal hypertensive gastropathy (PHG). In our search strategy, we used the relevant keywords of "gallbladder wall thickness" and "gastro-esophageal varices", "gastric varices", "esophageal varices", "portal hypertensive gastropathy", "PHT", and "cirrhosis".

WHY NOT ENDOSCOPY?

EGD is the gold standard procedure in the management of EVs due to the possibility of both diagnostic and therapeutic potentials[11]. However, the application of EGD screening among cirrhotic patients-as advised by many of the current guidelines-carries the burden of performing large numbers of unnecessary endoscopies. Moreover, it is of an invasive nature with possible procedure associated adverse events, unavailable in the remote areas, requires special skills and experience with a formal training program. Furthermore, endoscopy is refused by a reasonable number of patients[3]. Hence, several trials to investigate and validate non-invasive predictors for detection of EVs were tried[3,12] with the aim to pick up appropriate candidates for the screening endoscopy.

RATIONALE FOR GBWT MEASUREMENT (PATHOPHYSIOLOGY)

The question that pops up here is, why GBWT measurement is used to predict the presence of EVs although its main function is bile storage. The answer is inferred from our knowledge of four points. First, ultrasonography either the grey scale or the color Doppler mode is a non-invasive imaging technique used to evaluate cirrhotic patients. Furthermore, it is part of the hepatologists' and gastroenterologists' day-to-day practice. Second, there is growing evidence documenting validity of GBWT measurement in predicting the presence of varices[7,12-15]. Third, measuring GB wall could easily be calculated in the out-patient clinic, it is non-invasive, and is reproducible. Fourth, the GB is drained through veins of the portal circulation. This means that, it will be affected by the conditions influencing the portal venous pressure. The possible explanation for the increased GBWT in patients with EVs, is the impairment reported in the portal venous blood out flow that could precede the significant changes in the portal vein velocity[16], and it was concluded in a study by Li *et al*[13], that the degree of PHT among patients with liver cirrhosis could be predicted through the measurement of GB wall.

GB venous blood is drained through 2 pathways. First, through small veins directly into the liver. Second, through small veins toward the veins of the cystic duct and then with vessels from the common bile duct, terminating in the portal venous system. Consequently, in cases of PHT the venous drainage is impaired, and congestion of the GB wall do occur and hence the wall thickness is increased and that is why it is referred to as congestive cholecystopathy[17] in some studies.

Indirect evidence supporting this assumption is that cirrhotic patients treated with propranolol developed a significant reduction in portal pressure that subsequently was associated with a decrease in GBWT measurements[18].

OPTIMIZATION OF GBWT MEASUREMENT

The increase in GBWT may be a focal increase due to intrinsic GB diseases or diffuse[15,16,18,19]. The diffuse thickness may be related to intrinsic GB disease or diseases not related to the GB. Among the intrinsic gall bladder diseases are acute cholecystitis, chronic cholecystitis, and GB tumors. However, extrinsic diseases that may also affect the GBWT include hypoalbuminemia, sepsis, AIDS, right sided heart failure, and chronic kidney diseases[20]. Determination of GBWT measurement at different locations could differentiate focal from diffuse thickening, while revising the clinical, laboratory as well as sonographic data would differentiate intrinsic from extrinsic GB affection. In fact, among patients with liver cirrhosis, the diffuse non-inflammatory thickening of the GB wall is multifactorial and is related to PHT[9], hypoalbuminemia and the presence of ascites[21,22].

For perfect evaluation of the GBWT, sonographic assessment should be done in the fasting state. The fasting may be for 6-8 h[23], or sometimes evaluation can be done on the same day of endoscopy but before it following an overnight fasting[24,25]. In case of diffuse GBWT increase, measurements in more than one area of the GB wall are advised and the average is then taken. The position of the patient during examination was also focused on in the studies[26,27]. It would be beneficial to shift the patient from the classic supine position to the left lateral position. This position displaces the GB below the ribs and minimizes the gas interference from the colon[26,27]. The issue of gaseous interference was focused in some studies[24,25] where overnight simethicone was given to the patients prior to examination in an attempt to adsorb gases.

GBWT MEASUREMENT CAN PREDICT THE PRESENCE OF VARICES

The prediction of PHT and EVs through the GBWT measurement got attention of hepatologists around the globe over the last decades (Table 1). Li *et al*[13] figured out an inverse relationship between wall thickness of the GB and both portal vein blood flow and its mean velocity. The authors recommended that the degree of PHT in patients with liver cirrhosis could be predicted *via* measuring the GB wall.

De Alcantara *et al*[15] noticed a correlation between the increased wall thickness of the GB and the presence of GB varices as well as extra-hepatic portal vein obstruction that was favorable to correlations reported for cirrhotic patients with PHT. Meanwhile, Tsaknakis *et al*[12] found that the increase in the GBWT has occurred more significantly among cirrhotic patients with EVs despite its low sensitivity.

Elkerdawy *et al*[24] evaluated the diagnostic accuracy of GBWT measurement in comparison to several readily available and easily calculated indices (*e.g.*, platelet count and platelet count/splenic diameter ratio index) and they found GBWT measurement to have a comparable diagnostic accuracy to many of these parameters.

Khan *et al*[28] found that patients with EVs had significantly increased GBWT of 4.96 ± 0.85 mm compared to 2.54 ± 0.76 mm among patients without EVs. Among the cirrhotic group with varices, 81.25% of patients had GBWT > 4 mm compared to 10% among cirrhotic non-variceal patients ($P < 0.0001$). The authors concluded that measuring GBWT is very useful for the detection of EVs in cirrhotic patients.

Shehata *et al*[29] found a significant correlation between GBWT and PHT and they recommended GBWT to be used as a non-invasive predictor of EVs in cirrhotic patients. They reported GBWT as an independent predictor for varices in both univariate (GBWT OR: 0.408, CI: 0.264–0.854, $P < 0.001$) and multivariate logistic regression analysis (OR: 0.352, CI: 0.068–0.604, $P < 0.005$).

Recently in 2022, Afifi *et al*[14], focused GBWT measurement in comparison with platelet/splenic diameter ratio in predicting the presence of varices among cirrhotic patients of different Child classes. They reported GBWT at a cut-off value ≥ 3.350 to predict the presence of EVs. However, GBWT at a cut-off value ≥ 3.350 was less sensitive and less specific than platelet count to spleen diameter ratio at cut-off level ≤ 1391.00 for detection of EVs, while GBWT at cut-off level ≥ 3.950 was a predictor for the presence of large varices with a 92% sensitivity and furthermore GBWT at cut-off level ≥ 3.950 was more specific and more sensitive than platelet count to spleen diameter ratio at the same cut-off level.

GBWT AND THE DEGREE OF VARICES

The relationship of the GBWT to the endoscopic grade of varices was described in a few studies as shown in Table 2. Shehata *et al*[29] reported positive correlation (OR: 0.634, $P = 0.001$) between GBWT and the grade of EVs among cirrhotic patients. Elkerdawy *et al*[24] in their study grouped the varices as advanced (grades III and IV) and non-advanced (grades I and II). The authors reported the ability of the GBWT measurement to predict the presence of advanced varices ($P \leq 0.001$). GBWT predicted advanced EVs at a cut-off level of > 3.5 mm, with 45%, 90%, and 77.1% sensitivity, specificity, and accuracy, respectively. In the same study both platelet count and spleen length were also independent predictors for advanced EVs. Platelet count predicted advanced EVs at a cut-off level of < 115 , with 80%, 76%, and 74.3% sensitivity, specificity, and accuracy, respectively. Spleen length was a valuable predictor of advanced EVs at a cut-off level of > 15 cm, with 90% sensitivity, although it had a 60% and 71.4% specificity and accuracy, respectively.

Begum *et al*[26] observed that the mean GBWT was significantly increased ($P < 0.05$) in chronic liver disease (CLD) with grade III and IV varices (6.1 ± 0.8 mm) than in grade I and II varices (3.9 ± 0.7 mm).

One study published in 2011 by Yousaf *et al*[23], surprisingly reported that GBWT was most profound in patients with smaller (F1) and moderate (F2) EVs. Most of the patients with no varices in that study had normal GBWT and the authors concluded that the evolving nature of PHT causing gradual congestion of the GB stands behind this[23]. However, this study recruited patients with Child B and C cirrhosis in whom hypoalbuminemia and ascites were seen, making these conclusions unsafe.

More recently, GBWT at a cut-off level ≥ 3.95 mm was a predictor for the presence of large varices with a 92% sensitivity, 95% specificity, 86.7% positive predictive value (PPV), and 97.1% negative predictive value (NPV), with area under the curve (AUC) = 0.986. It was more superior than (more sensitive 92% *vs* 80% and more specific 75% *vs* 70%) platelet count to spleen diameter ratio at the same cut-off level ≤ 1391.00 [14].

It seems that the GB wall diameter increases with evolving stages of liver diseases and its associated EVs grades. In patients with CLD with advanced varices the GBWT was 6.1 ± 0.8 mm, in compensated cirrhotics it was ≥ 3.5 mm while in advanced cirrhosis GBWT was ≥ 3.95 mm. The variability in these measurements may be related to the underlying etiologies of liver diseases.

Table 1 Studies focusing gallbladder wall thickness measurement in the prediction of varices

Ref.	Target patients	Number of patients	GBWT cut-off	Reported sensitivity	Conclusions
Li <i>et al</i> [13]	Cirrhotic	152			GBWT is closely related to hemodynamic parameters. It is feasible to predict the degree of portal hypertension through the observation of GBWT
Begum <i>et al</i> [26]	CLDs	61			GBWT among CLD patients with EVs was 5.6 ± 0.2 mm compared to 2.7 ± 0.1 mm in non-variceal group ($P < 0.05$). GBWT may be considered as an important marker for the presence of esophageal varices in CLD patients
de Alcantara <i>et al</i> [15]	Children and adolescents younger than 20 years with CLD and extrahepatic portal venous obstruction (EHPVO)	53	≥ 4.35 mm	For group I ($n = 35$; patients with CLD): 60%. For group II ($n = 18$; patients with EHPVO): 90.9%	The presence of SS and greater LOT were indicative of EVs in patients with CLD. The presence of gallbladder varices and greater GBWT indicated the presence of EVs in patients with EHPVO. The presence of an SS and a greater LOT indicated the presence of PHG in patients with CLD
Pathak <i>et al</i> [21]	Alcoholic Cirrhosis	60	> 4 mm		Thus, the presence of increased GBWT on ultrasonography in patients of cirrhosis without intrinsic gallbladder disease should be considered as an early sign of portal hypertension
Tsaknakis <i>et al</i> [12]	Chronic hepatic diseases of variable etiologies	194	≥ 4 mm	46%	GBWT occurs significantly more often in patients with EVs. However, because of the low sensitivity, combination with other non-invasive parameters such as platelet count is recommended
Elkerdawy <i>et al</i> [24]	Post-viral cirrhosis with portal hypertension	105	≥ 3.1 mm	54.29%	GBWT was associated not only with the presence of EVs, but also with advanced EVs. Although, the reported sensitivity of GBWT in prediction of EVs was low, its diagnostic accuracy was comparable and even superior to some simple non-invasive predictors
Khan <i>et al</i> [28]	Liver cirrhosis of Child-Pugh class A (80% were due to HCV)	160	> 4 mm	Not calculated	Patients with esophageal varices had significantly increased gallbladder wall thickness 4.96 ± 0.85 mm as compared to patients without esophageal varices 2.54 ± 0.76 mm. In group A, 65 (81.25%) patients had GBWT > 4 mm while in group B, 8 (10%) patients had GBWT > 4 mm and significant difference was observed between both groups with P value < 0.0001
Shehata <i>et al</i> [29]	Cirrhosis (multiple etiologies; causes not mentioned)	120	4	82%	Significant correlation was observed between GBWT and portal hypertension, they recommend that GBWT can be used as a non-invasive predictor of esophageal varices in cirrhotic patients
Amer <i>et al</i> [25]	Liver cirrhosis	100	> 3.5 mm	64%	Sensitivity and specificity of GBWT in prediction of PHG were 64% and 68%
Afifi <i>et al</i> [14]	Cirrhosis (causes not mentioned)	100	3.35 mm	68%	GBWT was significantly higher in EVs patients compared to the non-EVs group (mean: 4.2 mm <i>vs</i> 2.7 mm, $P < 0.001$)

CLD: Chronic liver diseases; EHPVO: Extra-hepatic venous obstruction; EVs: Esophageal varices; GBWT: Gallbladder wall thickness; HCV: Hepatitis C virus LOT: Lesser omental thickness; PHG: Portal hypertensive gastropathy; SS: Splenorenal shunt.

GBWT MEASUREMENT CAN PREDICT PORTAL HYPERTENSIVE GASTROPATHY

The relation of the GBWT measurement to the PHG was investigated in only one study. Amer *et al*[25] reported that GBWT was significantly higher in the PHG group than non-PHG ($P < 0.001$) and this difference exists irrespective of the prevalence of varices in both groups. The significant difference ($P < 0.001$) was still seen when the ratio of Platelets/GBWT was compared between both groups which was lower in the PHG group. Furthermore, Platelets/GBWT was significantly decreased in the severe grade of PHG than in the mild group ($P < 0.001$). Similarly, GBWT was significantly higher ($P = 0.003$) with severe PHG than with mild PHG.

CUT-OFFS OF GBWT MEASUREMENTS

The cut-off in GBWT measurement varied in the published literature and this had an impact on the reported indices of diagnostic accuracy. In the study of Shehata *et al*[29], GBWT ranged from 2.5 mm to 7 mm in cirrhotic patients with EVs while in cirrhotic patients without EVs, it ranged from 1.5 mm to 5 mm. Mean GBWT of cirrhotic patients with EVs was 4.56 ± 1.08 and in cirrhotic patients without EV was 2.97 ± 0.88 . They reported a cut-off value of 4 mm, hence GBWT > 4 mm is a predictor of EVs with a

Table 2 Studies focusing gallbladder wall thickness measurement and the degree of esophageal varices

Ref.	Target patients	Number of patients	GBWT cut-off	Reported sensitivity	Conclusions
Yousaf <i>et al</i> [23]	Child B and C cirrhosis	103	4 mm	Not reported	GBWT most profound in the patients with smaller (F1) and moderate (f2) esophageal varices. Most of the patients with no varices had normal gall bladder wall
Begum <i>et al</i> [26]	CLDs	61			The mean GBWT was significantly ($P < 0.05$) higher in CLD patients with grade III and IV varices (6.1 ± 0.8 mm) compared to grade I and II (3.9 ± 0.7 mm).
Elkerdawy <i>et al</i> [24]	Post-hepatitis cirrhosis with portal hypertension	105	≥ 3.1 mm	54.29%	GBWT was associated not only with the presence of EVs, but also with advanced EVs. Although, the reported sensitivity of GBWT in prediction of EVs was low, its diagnostic accuracy was comparable and even superior to some simple non-invasive predictors
Afifi <i>et al</i> [14]	Cirrhosis (Child A, B and C)	100	≥ 3.950	92%	GBWT at cut-off level ≥ 3.950 had 92% sensitivity, 95% specificity, 86.7% PPV, and 97.1% NPV for detection of large-sized EVs, with AUC = 0.986

AUC: Area under the curve; CLD: Chronic liver disease; EVs: Esophageal varices; GBWT: Gallbladder wall thickness; NPV: Negative predictive value; PPV: Positive predictive value.

sensitivity of 82%, specificity of 77%, PPV of 78%, NPV of 81% and accuracy of 79%. In the study of Khan *et al* [28], the cut-off value that discriminated variceal from non-variceal group was 4 mm. Another study by Elkerdawy *et al* [24] used 3.1 mm as a cut-off to predict the presence of EVs among cirrhotic patients of viral etiology with 54.29%, 97.14%, 97.4%, 51.5%, and 68.5% sensitivity, specificity, PPV, NPV, and diagnostic accuracy, respectively. One study focusing on adult cirrhotic patients found that GBWT had 46%, 89%, 70%, 73% sensitivity, specificity, PPV, and NPV, respectively in the prediction of EVs [12] but with higher cut-off of ≥ 4 mm. Among children and adolescents with cirrhosis at a cut-off of ≥ 4.35 mm, GBWT had a sensitivity, specificity, PPV, and NPV of 60%, 90%, 85.7%, and 69.2%, respectively, while its diagnostic accuracy was 67.5% [15]. One recent study by Afifi *et al* [14] reported GBWT at a cut-off of ≥ 3.350 mm and ≥ 3.950 mm to predict the presence of varices and to a large degree varices with reasonable sensitivities, respectively (Tables 1 and 2).

For PHG, Amer *et al* [25] showed that GBWT, with a cut-off > 3.5 mm predict PHG, with a sensitivity of 64%, specificity of 68%, PPV of 66.7%, NPV of 65.4%, AUC was 0.736, and P value was < 0.001 . Amer *et al* [25] found that both GBWT and Platelets/GBWT were significantly associated with PHG in the univariate logistic regression analysis however both were non-significant in the multivariate analysis.

The differences of the GBWT cut-offs and the subsequent reported indices may be related to the underlying causes of cirrhosis. All cirrhotic patients in Elkerdawy *et al* [24] were of viral etiology, while only 20% of patients in Tsaknakis *et al* [12] study were of viral etiology, and none of the patients in de Alcantara *et al* [15] study were cirrhotics of viral causes. While Shehata *et al* [29] and Khan *et al* [28] did not report the underlying causes of cirrhosis, despite the high prevalence of viral hepatitis in the Egyptian and Pakistani community, respectively.

Patients in Tsaknakis *et al* [12] and the de Alcantara *et al* [15] studies were predominantly alcoholics and those with autoimmune hepatitis, respectively, while the study carried out by Pathak *et al* [21] recruited only patients with alcoholic cirrhosis. The degrees of associated hepatic fibrosis are different from those of viral hepatitis and this probably justified the lower cut-offs of the GBWT which emerged out of the viral cirrhosis studies.

GBWT in comparison to other non-invasive predictors

In many studies, GBWT measurement was compared to many non-invasive predictors of EVs. Elkerdawy *et al* [24] reported in multivariate logistic regression analysis GBWT ($P \leq 0.001$) and APRI ($P \leq 0.046$) as the independent predictors for the presence of EVs. They also reported Platelet count/Splenic diameter ratio at a cut-off level of ≤ 8.64 and predicts the presence of EVs with 61.4%, 80%, 86%, 50.9%, and 67.6% sensitivity, specificity, PPV, NPV, and the accuracy, respectively. These findings match those of Tsaknakis *et al* [12] who reported GBWT ($P < 0.04$) and platelet count ($P < 0.001$) as the independent predictors for EVs.

Other simple and easily calculated parameters for prediction of EVs, with sensitivities ranging from 60%-70% were evaluated in an Egyptian study [24] including the splenic length (cut-off 14.9 cm), PV diameter (cut-off 14.6 mm), and APRI score (cut-off 0.9). However, when these parameters were compared to GBWT, it was obvious that the GBWT measurement had the highest area under ROC curve (0.09) with the highest diagnostic accuracy (68.5%). These simple parameters were shown in different studies to predict the presence of EVs with variable sensitivities [3].

GBWT COMBINATION WITH OTHER PARAMETERS

Many authors reported improved sensitivity in prediction of varices upon combining GBWT with other non-invasive parameters. Tsaknakis *et al*[12] reported that the platelet count/GBWT ratio (cut-off > 46.2) achieves a sensitivity of 78%, a specificity of 86%, 76% PPV, 87% NPV and an AUC of 0.864 in predicting EVs. In that study, ROC analysis showed that the platelet count/GBWT ratio performed at a comparable level to the platelet count/spleen (cut-off > 909) diameter ratio.

Amer *et al*[25] reported that platelets/GBWT ratio, using a cut-off of < 40 predict PHG, with a sensitivity of 68%, specificity of 78%, PPV of 75.6%, NPV of 70.9%, AUC was 0.861 and *P* value was < 0.001, although it was significant in the univariate logistic regression analysis but was non-significant in the multivariate analysis.

LIMITATIONS

Despite the favorable results of the current studies, there are many considerations that should not be overlooked. First, the inter-observer variability. The subjective nature of sonographic assessment of GBWT can be reduced by rendering specialized experienced sonographer/radiologist/physicians rather than hepatologists who should examine the patients as demonstrated in some studies[21,24]. Optimal examination of the GB requires the patient to come fasting. This was considered in the individual studies. Fasting for 8 h was advised by Begum *et al*[26], while overnight fasting was advised by others [24,25]. Following the initial scan in the supine position, patients were turned onto the left decubitus position, as this position allows the liver and GB to medially fall away from the ribs, unfolding the GB and moving the overlying bowel away from the region of interest. GBWT was measured in its thickest portion preferably at the anterior wall[26]. In addition, some sonographic features (*e.g.*, GB wall varices) may be detected during examination in those patients especially with pre-hepatic PHT.

Secondly, the time interval. In an attempt to reduce the time effect on either the GBWT or the varices both sonography and endoscopy should be performed in the same period of time and this was considered in some studies[24,25].

Thirdly, many confounding factors may affect the GBWT, *e.g.*, ascites and hypoalbuminemia. It was clear in some studies (*e.g.*, Shehata *et al*[29]) that cases with severe hypoalbuminemia of 2.2 gm/dL were excluded. In the study of Pathak *et al*[21] cirrhotic patients with ascites and hypoalbuminemia were not excluded and as expected a correlation between GBWT, both serum albumin and ascites was observed and hence the relationship between GBWT and both PHT and EVs is questionable.

Fourthly, the relationship between GBWT and portal vein parameters (*e.g.*, diameter and flow velocity out) and the remaining parameters were not thoroughly investigated.

Lastly, liver cirrhosis is a heterogeneous group and in the current review we did not differentiate between different etiologies and grades of cirrhosis. This should trigger future studies focusing specific types of liver cirrhosis with different stages of functional decompensation.

CONCLUSION

Among cirrhotic patients with PHT of different etiologies, GBWT is associated with the presence of EVs. The cut-off of GBWT that can predict the presence of EVs varied in the literatures and ranges from 3.1 mm to 4.35 mm with variable sensitivities of 46%-90.9% with lower cut-offs in viral cirrhosis compared to non-viral. However, GBWT > 4 mm in many studies is associated with an acceptable sensitivity up to 90%. Furthermore, a relationship was also noticed with the degree of varices and PHG. Among cirrhotics, GBWT > 3.5 mm predicts the presence of advanced (grade III-IV) EVs with a sensitivity of 45%; the sensitivity increased to 92% when a cut-off ≥ 3.95 mm was used in another cohort. Analysis of these results should be carefully revised in the context of ascites, hypoalbuminemia and other intrinsic GB diseases before those cirrhotic patients are referred to endoscopy. The sensitivity for prediction of EVs improved upon combining GBWT measurement with other non-invasive predictors, *e.g.*, platelets/GBWT. Consequently, there is a need to standardize the criteria for GBWT measurement and its utility among those patients.

FOOTNOTES

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Country/Territory of origin: Egypt

ORCID number: Mohamed H Emara 0000-0002-1504-7851; Mariam Zaghloul 0000-0002-4244-5396; Aya M Mahros 0000-0002-6849-4065; Mohammed Hussien Ahmed 0000-0003-1761-3527; Tarik I Zaher 0000-0002-3846-0032; Emad Hassan Emara 0000-0003-4952-3366; Hassan Elbatae 0000-0001-7804-8424.

Corresponding Author's Membership in Professional Societies: Egyptian Association for Research and Training in Hepatogastroenterology.

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