Pathological gallbladder wall thickening is associated with advanced chronic liver disease and independent of serum albumin

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Abstract

Purpose: Increased gallbladder wall thickness (GBWT) is a common finding. Reported causes include advanced chronic liver disease (ACLD), ascites and hypalbuminemia. GBWT is a marker for the prediction of esophageal varices. It remains unclear which of these factors is the decisive driver of GBWT. We aim to investigate whether there is a predominant factor associated with the GBWT.

Methods: We enrolled 258 patients with ascites, hypalbuminemia and/or ACLD and 98 healthy volunteers that underwent abdominal ultrasound. Differences of mean GBWT in subgroups of patients with ACLD, ascites, and/or hypalbuminemia were analyzed. Correlation between various parameters and GBWT were calculated using multiple regression analysis.

Results: GBWT in patients with ACLD + ascites + hypalbuminemia (n = 59; 5.70 ± 2.05 mm) was pathologically increased compared to patients with hypalbuminemia + ascites without ACLD (n = 36; 2.14 ± 0.66 mm; p < .001) and to patients with only hypalbuminemia (n = 76; 2.02 ± 0.80 mm; p < .001). GBWT of patients with ACLD + hypalbuminemia (n = 30; 3.42 ± 1.52 mm) and with ACLD and normal albumin level were not different (n = 46; 3.10 ± 1.62 mm; p > .999). Significant correlation was seen between GBWT and ACLD (r = .53; p < .001) and ascites (r = .51; p < .001) but not albumin level (r = .04; p = .510).

Conclusion: We demonstrate that ACLD is predominantly associated with GBWT. In contrast to the current literature, serum albumin level appears not to be associated with pathological GBWT.

KEYWORDS
advanced chronic liver disease, gallbladder, hypalbuminemia, liver cirrhosis, ultrasonography
1 | INTRODUCTION

Diffuse gallbladder wall thickening in the absence of gallbladder disease is a common finding on imaging. Reported causes include advanced chronic liver disease (ACLD), portal hypertension, ascites, and hypalbuminemia, which were postulated in various studies as independent driver. Diffuse gallbladder wall thickening must be distinguished from focal or irregular wall thickenings, which can be associated with gallbladder carcinoma, polyps, or chronic cholecystitis.

Recently, we showed a positive correlation between the gallbladder wall thickness (GBWT) and the presence of esophageal varices (EV) in patients with chronic liver disease. These findings were recently confirmed by Elkardawy et al. EV are a common complication of patients with ACLD. About 50% of patients with liver cirrhosis suffer from EV. The most severe complication of EV is hemorrhage due to its high mortality. The early detection of EV and primary prophylaxis with, for example, non-selective beta-blocker is important. The gold standard for the detection of EV is gastroscopy that has rare but potentially severe complications, for example, injuries and consecutive hemorrhage of EV. Gastroscopy is a semi-invasive procedure and most of the patients need sedation during the procedure. In addition, endoscopic examinations are not worldwide available and affordable. Recently, we were able to show that combining GBWT with non-invasive parameters, especially liver stiffness, improved the diagnostic accuracy for predicting EV in patients with ACLD.

Concurrence of various factors such as ACLD, hypalbuminemia, and ascites can frequently be observed in patients with EV. Nevertheless, it is unclear which of these factors has the decisive influence on the GBWT. Pathophysiologically, GBWT in patients with portal hypertension can be explained by the blood supply of the gallbladder: branches of the hepatic artery provide the arterial supply; the venous drainage returns blood directly into the portal vein. In portal hypertension, venous drainage is malfunctioning, leading to edematous GBWT. Few previous studies demonstrated this correlation between GBWT and portal hypertension. The pathophysiological mechanism of ascites or hypalbuminemia in GBWT is unclear. It could be hypothesized that hypalbuminemia might lead to increased GBWT because of decreased oncotic pressure and resulting edema. Nevertheless, both findings can occur in patients with ACLD and portal hypertension, but also independent of an underlying liver disease.

The aim of our study was to systematically analyze the impact of the parameters ACLD, ascites and hypalbuminemia and other factors on GBWT both in patients suffering from ACLD and patients without advanced liver disease. We hypothesized that ACLD is the main driver of GBWT and ascites and hypalbuminemia might only be a secondary phenomenon in these patients while ascites and hypalbuminemia do not affect GBWT without underlying advanced liver disease.

2 | METHODS

In this study, we included adult patients of the University Medical Center Goettingen who underwent routine abdominal ultrasound between January and December 2019 and had evidence of ACLD, ascites or hypalbuminemia. ACLD was defined as histological evidence of liver cirrhosis, clinically significant portal hypertension (CSPH, defined as hepatic vein pressure gradient ≥10 mm Hg or existence of esophageal or gastric varices), or significant sonography findings (nodular liver surface and irregular parenchyma) in combination with typical pathological blood values as signs of chronic liver damage. Hypalbuminemia was defined as serum albumin less than 3.5 g/dl. All included patients were examined in pre-prandial state, defined as no food intake for at least 3 h before examination.

For first analysis, all included patients were assigned to at least one group depending on the presence of ACLD, ascites, or hypalbuminemia.

Seven subgroups were pre-defined: (I) patients with only ACLD, (II) patients with ACLD and ascites, (III) patients with ACLD, ascites, and hypalbuminemia, (IV) patients with ACLD and hypalbuminemia, (V) patients with hypalbuminemia and ascites, (VI) Patients with only hypalbuminemia, and (VII) patients with only ascites (Figure 1).

We documented current blood test results (within 2 days before or after ultrasound examination) of the included patients. Patients who had hepatic malignancies, cholecystectomy, positive Murphy’s sign, upper abdominal pain or other clinical or biochemical signs of acute or chronic cholecystitis, missing blood analyzes, missing consent for data use, serum alanine aminotransferase >10 × ULN or signs of focal or irregular gallbladder wall thickening were excluded.

Abnormal GBWT was defined as GBWT of more than 4 mm.

As control for normal GBWT we used a group of healthy volunteers that were recruited by targeted addressing. For this group, a standardized questionnaire was used to identify possible exclusion criteria. Exclusion criteria were acute or chronic diseases (according to the medical history), recent medication (with the exception of oral contraceptives), alcohol abuse (defined as >30 g of alcohol daily for men and >20 g for women) or drug abuse (except for tobacco), and morphologic abnormalities in the baseline sonography examination of the liver (e.g., tumor, nodular liver surface, caudate lobe hypertrophy, inhomogeneous parenchyma, ascites), abnormal liver stiffness (defined as ≥7 kPa measured by 2D-shearwave elastography) or signs of hepatic steatosis (increased echogenicity). All participants underwent preprandial ultrasound of the gall bladder. After this procedure the probands ingested a standardized liquid meal with 800 kcal within 10 min (2 Fresubin Drinks á 200 ml; per ml: 2 kcal, 0.1 g protein, 0.078 g fat, 0.225 g carbohydrates). Then all participants underwent a second sonography of the gall bladder 30–40 min after ingestion.

2.1 | Ethics

Patient data collection did not influence the diagnostic or therapeutic management of the patients. The study was approved by the ethic committee of the University Medical Center Goettingen (August 18, 2019 and July 5, 2017). The study also conformed to the Helsinki Declaration (2013) and local legislation. Written informed consent was obtained from all participants.
2.2 Ultrasound

Ultrasound was performed by different investigators with individual experience of more than 500 examinations with GE Logiq E9 devices (GE Medical Systems, Wauwatosa, United States, software R1.0.6) using a convex transducer (4.0 MHz). GBWT was measured at two different locations in longitudinal scan at the level of anterior wall and mean value was calculated. Ultrasound images of representative gall bladder wall measurements are provided in Figure 2. Spleen diameter was measured as maximum bipolar diameter. The ultrasound procedures were performed by different examiners, but all GBWT measurements were confirmed by one experienced examiner based on the digital image documentation.

2.3 Statistical analysis

Statistical analyzes were performed with GraphPad Prism version 9.1.2, Graphpad Software, San Diego, California, United States and with IBM SPSS Statistics version 26.0.0.0. Data are given as mean including SD, unless otherwise stated. Normality test was performed with Shapiro-Wilk test. Differences between two groups were performed with 2-tailed Mann-Whitney test or two-sided Chi-square test, respectively. Kruskal-Wallis test followed by Dunn’s multiple comparisons test was used to analyze differences of GBWT between the subgroups and the control.
We used the bivariate Pearson correlation to analyze correlation between various parameters and GBWT. All variables with a p value < .1 in the univariable analysis were included in the multiple regression analysis model to evaluate independent relation. Statistically significance was defined as p < .05.

3 | RESULTS

3.1 | Study population

Of all patients screened, 258 fulfilled the inclusion criteria in the absence of exclusion criteria. One hundred and forty-five of the patients suffered from ACLD, whereas 113 patients had ascites or hypalbuminemia without evidence of ACLD. The patient characteristics are shown in Table 1. Additionally, 98 healthy volunteers were included in this study (Figure 1).

3.2 | Overall analysis

For first analysis, we grouped all included patients depending on the presence of ACLD, ascites, or hypalbuminemia. In order to get an impression of the extent to which the GBWT is increased in contrast to healthy subjects, we compared these groups with 98 healthy probands in preprandial and postprandial state, respectively. All patients were examined in fasting state. The mean GBWT of healthy volunteers was 1.51 ± 0.34 mm in fasting state and increased significantly to 2.31 ± 0.48 mm after food intake (p < .01), but did not reach abnormal levels.

Of the 258 patients included, 145 suffered from ACLD, 106 had ascites and 181 presented hypalbuminemia, respectively. Consistent with postulated expectations, mean GBWT of patients with ACLD (4.36 ± 2.39 mm, p < .01, n = 145), ascites (4.4 ± 2.39 mm, p < .01, n = 106) or hypalbuminemia (3.42 ± 2.23 mm, p < .01, n = 181) were significantly increased compared to fasting healthy volunteers (Figure 3).

3.3 | Subgroup analysis

In order to be able to analyze combinations of the examined factors more precisely, we included each observed patient in one of seven subgroups. Regarding the defined subgroups, we included 46 patients which suffered only from ACLD (Group I), 10 patients with combination of ACLD and ascites (Group II), 59 patients with ACLD, ascites and hypalbuminemia (Group III) and 30 patients with ACLD and hypalbuminemia (Group IV). In the subgroups without patients with evidence of ACLD, we enrolled 36 patients with ascites and hypalbuminemia (Group V), 76 patients that presented only hypalbuminemia (Group VI), and one patient that presented ascites without ACLD or hypalbuminemia (Group VII). The patient characteristics of the subgroups are listed in the Table S1.

**TABLE 1 Patient characteristics**

| Characteristic                  | Healthy volunteers (n = 98) | ACLD patients (n = 145) | Other patients (n = 113) | p   |
|--------------------------------|-----------------------------|-------------------------|--------------------------|-----|
| Age mean (SD) (years)          | 25.2 (4.55)                 | 57.66 (11.7)            | 58.38 (17.9)             | .204|
| Sex female (no. (%))           | 51 (52.04)                  | 52 (35.9)               | 50 (44.2)                | .172|
| INR (mean ± SD)                | N/A                         | 1.47 (0.71)             | 1.22 (0.42)              | .001|
| Serum albumin (mean ± SD) (g/dl)| N/A                         | 3.07 (0.80)             | 2.38 (0.63)              | <.001|
| Bilirubin (mean ± SD) (mg/dl)  | N/A                         | 3.01 (4.41)             | 1.29 (3.39)              | <.001|
| Spleen length (mean ± SD) (cm) | N/A                         | 137.2 (31.97)           | 119.3 (31.87)            | <.001|
| CTP points (mean ± SD)         | x                           | 7.7 (2.18)              | x                        | x   |
| labMELD (mean ± SD)            | x                           | 13.79 (7.15)            | x                        | x   |

Note: Significant differences are printed in bold. Abbreviations: ACLD, advanced chronic liver disease; CTP, Child–Turcotte–Pugh–score; labMELD, laboratory model for end-stage liver disease; N/A, not available.
Mean GBWT of the seven subgroups

Subgroup analysis. All included patients were grouped according to the presence or absence of advanced chronic liver disease (ACLD), ascites, hypalbuminemia or combinations. Only patients with ACLD in combination with ascites had mean gallbladder wall thickness (GBWT) above 4 mm. Isolated or combined hypalbuminemia or ascites were not associated with increased GBWT. ±: mean, dashed line: 4 mm mark

Interestingly, GBWT reached pathological mean levels in all groups with included ACLD ± ascites while the absence of ACLD was not associated with GBWT mean levels above 4 mm (Table 2, Figure 4). The highest mean GBWT of 5.7 ± 2.05 mm was seen in patients with combination of ACLD, ascites, and hypalbuminemia (group III) followed by patients with ACLD and ascites (Group II, 5.18 ± 2.17 mm). The lowest mean GBWT was observed in patients which presented only ascites (1 mm, n = 1), only hypalbuminemia (2.02 ± 0.8 mm) and in healthy subjects (1.51 ± 0.34 mm), respectively.

Performing Kruskal-Wallis test and Dunn’s multiple comparisons test, differences of mean GBWT were calculated between all groups (Table 3). Strikingly, patients which presented only hypalbuminemia (2.02 ± 0.8 mm) and in healthy subjects (1.51 ± 0.34 mm), respectively. GBWT in patients with hypalbuminemia compared to healthy volunteers, the GBWT was not pathologically increased and the patients suffered from several morbidities. The latter fact is in contrast to different studies which described a significant correlation between hypalbuminemia and pathologically increased GBWT.3,9,17 However, most of the patients in these studies also had advanced cirrhosis, so that ACLD appears to be the main factor here and hypalbuminemia is to be seen as a bystanding phenomenon. This assumption is supported by the studies of Colli et al. and Kaftori et al. who were able to show that there is no gallbladder wall thickening in patients with ascites and hypalbuminemia in the absence of ACLD.16,21

TABLE 2 Mean GBWT of the seven subgroups

| Group (n) | Characteristics                  | Mean GBWT (±SD) |
|-----------|----------------------------------|-----------------|
| I (n = 46) | ACLD                             | 3.10 (±1.62)    |
| II (n = 10) | ACLD + ascites                   | 5.18 (±2.17)    |
| III (n = 59) | ACLD + ascites + hypalbuminemia | 5.70 (±2.05)    |
| IV (n = 30) | ACLD + hypalbuminemia           | 3.42 (±1.52)    |
| V (n = 36)   | Ascites + hypalbuminemia         | 2.14 (±0.66)    |
| VI (n = 76)  | Hypalbuminemia                  | 2.02 (±0.80)    |
| VII (n = 1)  | Ascites                         | 1.00 (N/A)      |
| Control     | Preprandial healthy              | 1.51 (±0.34)    |

Abbreviations: ACLD, advanced chronic liver disease; GBWT, gallbladder wall thickness; N/A, not available.

3.4 Correlation analysis

We performed the bivariate Pearson Correlation to analyze correlation between various parameters and GBWT. Significant correlation was observed between GBWT and the parameters ACLD (r = .53; p < .001), ascites (r = .51; p < .001), bilirubin (r = .20; p = .001), INR (r = .16; p = .013), and spleen length (r = .14; p = .027). No significant correlation was observed between GBWT and the parameters albumin (r = .04; p = .510), age (r = −.03; p = .637), and sex (r = −.09; p = .143).

All variables with a p value < 1 in the bivariate analysis were included in the multiple regression analysis model to evaluate independent relation. Only the correlation between GBWT and the parameters ACLD and ascites remained significant (Table 4).

4 DISCUSSION

Diffuse gallbladder wall thickening in the absence of gallbladder disease is a common finding on imaging. Reported causes of GBWT include ACLD with portal hypertension, ascites and hypalbuminemia. The aim of our study was to analyze the impact of the mentioned parameters and other factors on GBWT detected by high-end ultrasound.

Our data showed that presence of ACLD had the strongest impact on GBWT. Presence of ascites was also independently associated with GBWT, but interestingly albumin level did not influence GBWT in the multivariate analysis. Although our analysis revealed significant higher GBWT in patients with hypalbuminemia compared to healthy volunteers, the GBWT was not pathologically increased and the patients suffered from several morbidities. The latter fact is in contrast to different studies which described a significant correlation between hypalbuminemia and pathologically increased GBWT.3,9,17 However, in our dataset, the highest mean GBWT was seen in patients with ACLD in combination with ascites and hypalbuminemia. This constellation reflects patients with pronounced CSPH that have high risk of EV and variceal hemorrhage. Interestingly, GBWT in these patients was not significantly increased in comparison to patients with ACLD, ascites and normal albumin levels.
Patients with hypalbuminemia and without ACLD had normal GBWT, independently of the additional presence of ascites. Mohammadi et al. examined patients with ascites and compared patients with cirrhosis associated ascites with those who suffered from peritoneal carcinomatosis. Mean GBWT above 3 mm was seen only in patients with liver cirrhosis associated ascites. This is in accordance to data of Brogna et al. and Marti-Bonmati et al. who found increased GBWT significantly more frequent in patients with cirrhotic ascites than in patients with non-cirrhotic ascites. The authors concluded that GBWT is a suitable parameter to differentiate between cirrhotic and non-cirrhotic ascites. Nevertheless, our study identified ascites as an independent parameter associated with increased GBWT, but with lower impact on GBWT than in combination with ACLD.

In healthy subjects, GBWT was within the normal range and after food intake there was a significant increase of GBWT but below the

### TABLE 3

| Group                              | I (ACLD) | II (ACLD + ascites) | III (ACLD + ascites + hypalbuminemia) | IV (ACLD + hypalbuminemia) | V (ascites + hypalbuminemia) | VI (hypalbuminemia) | VII (ascites) | Healthy (preprandial) |
|------------------------------------|----------|---------------------|--------------------------------------|---------------------------|-----------------------------|--------------------|----------------|----------------------|
| I (ACLD)                           | x        | .699                | <.001                                 | >.999                     | .580                        | .005               | >.999          | <.001                |
| II (ACLD + ascites)                | .699     | x                   | >.999                                 | >.999                     | .008                        | <.001              | .237            | <.001                |
| III (ACLD + ascites + hypalbuminemia) | <.001    | >.999               | x                                    | .054                      | <.001                       | <.001              | .119            | <.001                |
| IV (ACLD + hypalbuminemia)         | >.999    | >.999               | .054                                 | x                         | .097                        | <.001              | .878            | <.001                |
| V (ascites + hypalbuminemia)       | .580     | .008                | <.001                                 | .097                      | x                           | >.999              | >.999           | .002                 |
| VI (hypalbuminemia)                | .005     | <.001               | <.001                                 | <.001                     | >.999                       | x                  | >.999           | .003                 |
| VII (ascites)                      | >.999    | .237                 | .119                                 | .878                      | >.999                       | >.999              | x               | >.999                |
| Healthy (preprandial)              | <.001    | <.001               | <.001                                 | <.001                     | .002                        | .003               | >.999           | x                    |

Note: Significant differences are printed in bold.

Abbreviations: ACLD, advanced chronic liver disease; GBWT, gallbladder wall thickness.

### TABLE 4

| Characteristic     | Regression coefficient b | Standardized beta coefficient | 95% CI         | p Value |
|--------------------|--------------------------|-------------------------------|---------------|---------|
| ACLD               | 1.888                    | .442                          | 1.431–3.345   | .000    |
| Ascites            | 1.028                    | .387                          | 0.745–1.311   | .000    |
| Bilirubin          | 0.008                    | .016                          | 0.046–0.061   | .775    |
| INR                | 0.041                    | .012                          | 0.305–0.386   | .817    |
| Spleen length      | –0.002                   | –.025                         | –0.008–0.005  | .637    |

Note: Significant differences are printed in bold.

Abbreviations: ACLD, advanced chronic liver disease; CI, confidence interval.

FIGURE 5  Representative images of a gallbladder wall using different ultrasound transducers. (A) Representative image of the gallbladder of a healthy subject with normal wall thickness using a convex transducer (4.0 MHz). Only a single hyperechoic layer of the gallbladder wall is visible (white arrow). (B) Image of the gallbladder of the same healthy subject using a linear transducer (9.0 MHz). Two layers of the gallbladder wall are visible: An inner hypoechoic layer (gray arrow) and an outer hyperechoic layer (white arrow)
4 mm limit. These findings are in line with another study that examined the GBWT in patients with histologically proven hepatic steatosis. Nevertheless, the impact of food intake in patients with ACLD is unclear and should be investigated in future studies. The parameters INR, sex, age, spleen length, and bilirubin were not independently associated with GBWT.

Focal or irregular gallbladder wall thickening must be distinguished from diffuse gallbladder wall thickening. In our study, patients with focal or irregular gallbladder wall were excluded. Focal wall thickening and inner or outer layer discontinuity are associated with malignancy. Linear probe using high-frequency transducers can better visualize the gallbladder wall layers (Figure 5). Furthermore, the application of contrast enhanced ultrasound (CEUS) is helpful to distinguish benign and malignant wall thickening, in particular by using the parameters enhancement homogeneity and time to hypo-enhancement.

Our study has potential limitations. First, not all patients had histological confirmation of their ACLD, but at least clinical and laboratory evidence. Second, the observed cohort size is limited. Third, no blood tests were available in the healthy group. Further studies including confirmation of portal hypertension are needed to obtain further insight into the crucial role of portal hypertension in gallbladder wall thickening. Since no high frequency transducer or CEUS was used in this study, a malignancy as the cause of GBWT cannot be ruled out with certainty in individual cases.

In summary, we were able to show that ACLD is independently associated with gallbladder wall thickening, while serum albumin level appears not to be significantly associated with pathologically increased GBWT. Further analyzes of the GBWT with regard to hepatic venous pressure gradient measurement are recommended in order to gain further insight into the pathophysiology of GBWT.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**SUPPORTING INFORMATION**

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