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Original Research Article

Wall thickness is an important predictor of gallbladder malignancy in patients surgically treated for gallbladder disease

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ABSTRACT

Background: Gallbladder wall thickening is relatively common on imaging. GB thickening is a frequent finding caused by a spectrum of conditions. It is observed in many intracholecystic as well as intrinsic GB conditions. The study aimed to determine the relationship between the wall thickness of gallbladder malignancy in patients with gallbladder diseases.
Methods: The Prospective cross-sectional and observational study was carried out in the department of general surgery and hepato-biliary-pancreatic surgery, BIRDEM general hospital, Dhaka from August 2019 to February 2021. Patients admitted to the general surgery and hepato-biliary-pancreatic surgery department of BIRDEM hospital who underwent gallbladder surgery were recruited for this study. Consecutive sampling was done in this study.
Results: 86% of patients underwent laparoscopic cholecystectomy, while 14% had open cholecystectomy, of which 9 were simple and 6 were radical en block. The average wall thickness of the gallbladder was 7.5mm, with 52.7% moderate thickness, 37.3% mild, and 10% severe. 20% of patients with gallbladder disease had carcinoma, and the most common diagnosis was chronic calculous cholecystitis. A cut-off value of 8.25mm for gallbladder wall thickness had 81.8% sensitivity and 72.7% specificity in predicting carcinoma, and gallbladder wall thickness ≥8.25 mm had the highest significant odds ratio in predicting gallbladder carcinoma after adjusting for age, gender, and smoking history.
Conclusions: GB carcinoma patients had significantly thicker gall bladder walls (9.80 vs 6.93 mm) and a higher frequency of severe GB wall thickness (36.36 vs. 3.41%) compared to patients without GB carcinoma. Gall bladder wall thickness is an important variable requiring consideration for the proper evaluation to exclude malignancy for undertaking proper surgical management, thus improving the long-term outcome.

Keywords: Gall bladder, Gall bladder malignancy, Gall bladder wall thickening

INTRODUCTION

Gallbladder carcinoma (GBC) represents approximately 165,000 cancer deaths each year, representing 1.7% of all deaths of cancer worldwide. Incidence has been reported to increase over the years. The greatest prevalence has been registered in Asia, South America, and Europe.[1] Accurate worldwide incidences of gallbladder cancer are difficult to diagnose, particularly in low-resource settings where specialized abdominal imaging is not available. The asymptomatic nature of the initial development of gallbladder cancer and its propensity for early and rapid

metastasis results in the majority of gallbladder cancer being diagnosed late. This has led to poor prognosis and early death.[2] Due to the gloomy outcome, early-stage GBC (1a, 1b, 11, selective 111) needs detection because open radical cholecystectomy is the only option that can give patients the benefit of survival.[3] Gallbladder wall thickening is a common yet non-specific finding that can occur in a wide range of gallbladder diseases and even in some *intracholecystic* conditions.[4] Focal or diffuse destructive inflammatory process followed by fibrosis along with infiltration of chronic inflammatory cells with or without malignant change can be useful in making the diagnosis of gall bladder cancer.[5] GBC is usually suspected in cases of diffuse or localized irregular thickening of the gallbladder wall in which irregularities in the mucous membrane are observed along with a loss of uniformity in the inner hypoechoic layer.[6] Diffuse gallbladder wall thickening is a frequently detected finding in cross-sectional imaging in clinical practice. These findings would result from a broad spectrum of pathologic conditions. Among these conditions, are acute cholecystitis, gallbladder malignancy and adenomyomatosis which cause diffuse or focal gallbladder wall thickening.[7] Regarding gall bladder cancer, most are of diffusely infiltrating lesions (6%) whereas the remaining (32%) are of intraluminal polypoid growth type. Moreover, gallbladder cancer manifests as wall thickening, it is challenging to diagnose because it mimics the appearance of more common conditions of the gallbladder.[8] Misinterpretation of diffuse gallbladder wall thickening in imaging studies can lead to unnecessary cholecystectomy in patients without intrinsic gallbladder disease. Perhaps, misdiagnosis in patients who do require cholecystectomy would result in delayed treatment with increased morbidity.[9] The study aimed to determine the relationship between the wall thickness of the gall bladder with gall bladder malignancy in patients with gallbladder diseases.

Objectives

Objectives of current study was to determine the relationship between the wall thickness of gallbladder malignancy in patients with gallbladder diseases.

METHODS

The prospective cross-sectional and observational study was carried out in the department of general surgery and hepato-biliary-pancreatic surgery, BIRDEM General Hospital, Dhaka from August 2019 to February 2021. Patients admitted to the general surgery and hepato-biliary-pancreatic surgery department of BIRDEM hospital who underwent gallbladder surgery were recruited for this study. Consecutive sampling was done in this study. Due to the COVID pandemic and resource constraints, 110 patients (n=110) fulfilled the selection criteria of the study within the stipulated time. As a result, the final sample size was 110. A data sheet and a consent form were prepared, the sample was selected purposively based on inclusion and exclusion criteria and a questionnaire was filled out after taking informed written consent. Research equipments were a structured data collection sheet and digital Vernier slide calliper. A checklist was prepared for each case. The interview schedule was made in Bengali. The questionnaire was pretested in the same categories of admitted patients. A detailed history of the patient with special emphasis on symptoms of biliary colic, history of previous attacks of colic, jaundice, history suggestive of pancreatitis etc. was recorded. History of comorbid conditions including DM, HTN, hypothyroidism, significant illnesses and previous symptoms were collected. General physical examination, abdominal examination routine investigation, biochemical marker. A thick wall was identified by specific investigation of USG of the abdomen and their findings were recorded. Findings on certain imaging studies like contrast-enhanced computed tomography (CECT) abdomen or magnetic resonance imaging (MRI)/ magnetic resonance cholangio pancreatography (MRCP) was noted whenever performed. All information was recorded in separate case record forms.

Inclusion criteria

Inclusion criteria for current study were; patients who would undergo surgery for gallbladder disease and suggestive of having gallbladder wall >3 mm wall (confirmed by pre-operative Ultrasonography), adult patients irrespective of age, sex, comorbidity and the patient who gave consent.

Exclusion criteria

Exclusion criteria for current study were; The patients who were not available to communicate through their residential permanent addresses mentioned in the hospital records, refusal of patient or the attending surgeon at any stage, gallbladder wall thickness <3 mm, patients who had gall bladder mass and patients who were not undergoing surgery.

Operative procedure

After taking informed consent and pre-anaesthesia checkup, patients underwent surgery under general anaesthesia as an allied procedure like Open and laparoscopic cholecystectomy, Radical en bloc resection, Whipple's procedure etc. Intraoperative findings including gall bladder wall thickness, number of stones, empyema gall bladder, adhesions, Calot's triangle anatomy, cut section appearance, level of difficulty, duration of surgery etc. were recorded. The thickness of the gall bladder was measured by the fine dissecting method. A longitudinal incision was made by the sharp B-P blade through the peritoneal smooth surface of the gall bladder from the fundus to the neck and the interior of the gall bladder was cleaned with jets of tap water. Then the thickness was measured in mm with the help of the digital slide calliper at 3-5 different sites and the maximum value was accepted

for inclusion in the study.[9] After the operation, dissected specimens were sent to the pathology Laboratory of BIRDEM General Hospital for histopathology and the confirmatory diagnosis was recorded according to the histopathology report.

Data processing and analysis

Statistical analysis was done using statistical software SPSS version 26. The categorical variables were presented as frequency and percentage. The continuous variables were presented as mean and standard deviation. The association between categorical variables was determined using the chi-square test. The difference between continuous variables was determined using the student t-test. The receiver's operating curve was done to find out the cut-off value. Diagnostic accuracy was determined by measuring sensitivity, specificity, positive predictive value, negative predictive value and accuracy. The significance level of 0.05 was considered for all tests.

RESULTS

The mean age of all patients was 55.94±5.13 years (40-65 years) with the majority belonging to 50-59 years of age (65.5%) (Figure 2).

Figure 1: Gall bladder wall thickness measurement in millimetres with help of a digital Vernier calliper.

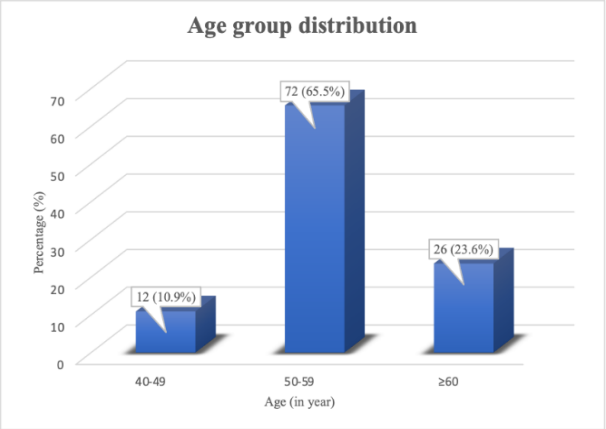


Figure 2: Age distribution of study patients (n=110).

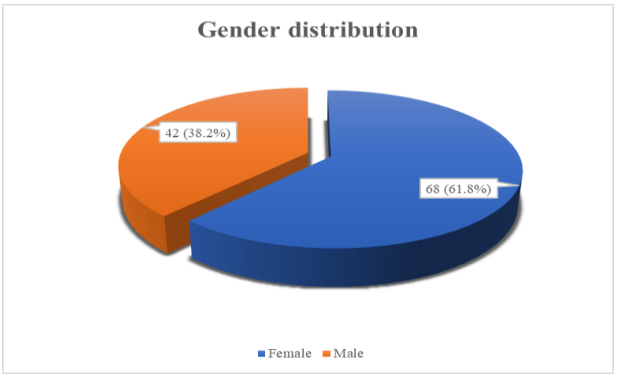


Figure 3: Gender distribution of study patients (n=110).

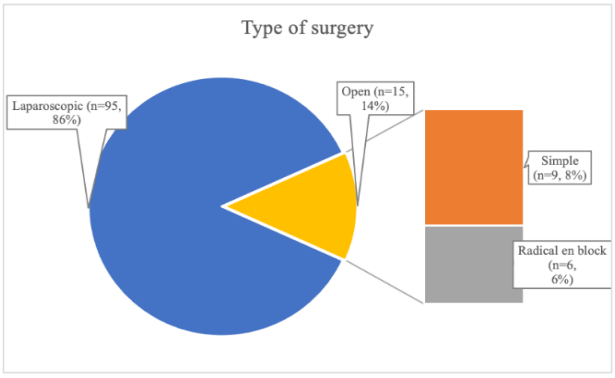


Figure 4: Type of surgery among study patients (n=110).

The major part of the patients was female (61.8%) with a female: male ratio of 1.62:1 (Figure 3). The most common co-morbidity among study patients was DM (62.7%) followed by HTN (43.6%), anaemia (40%) overweight (36.4%), IHD (10%), BA (8.2%), hypothyroidism (2.73%). Positive smoking history was found in 14.5% of patients and only 2 patients (1.82%) gave the history of alcohol consumption (Table 1).

Table 1: Associated co-morbidity and personal history of study patients (n=110).

Variables	N	%
DM	69	62.7
HTN	48	43.6
Anemia	44	40
Overweight	40	36.4
IHD	11	10
BA	9	8.2
Hypothyroidism	3	2.73
H/o smoking	16	14.5
H/o alcohol consumption	2	1.82

*Multiple responses, DM= Diabetes mellitus, HTN= Hypertension, Overweight= BMI ≥25 kg/m^2, IHD= Ischemic heart diseases, BA= Bronchial asthma, H/o= History of.

Majority patients had complained about non-specific or right upper abdominal pain (76.4%) followed by nausea

(59.1%), anorexia (55.5%), jaundice (34.5%) and weight loss (28.2%) (Table 2).

Table 2: Clinical presentations among study patients (n=110).

Clinical presentation*	N	%
Abdominal pain	84	76.4
Anorexia	61	55.5
Nausea	65	59.1
Weight loss	31	28.2
Jaundice	38	34.5
Asymptomatic	9	8.2

*Multiple responses

Table 3: Histopathological diagnosis of study patients (n=110).

Histopathological diagnosis	N	%
Gall bladder carcinoma	22	20.0
Chronic calculous cholecystitis	54	49.1
Chronic acalculous cholecystitis	8	7.3
Gall bladder cholesterosis	7	6.3
Gall bladder polyp	7	6.3
Empyema gall bladder	4	3.6
Acute cholecystitis	3	2.7
Gall bladder mucocele	3	2.7
Gall bladder adenomyoma	1	0.9
Granulomatous inflammation	1	0.9

Table 4: Histopathological features of gall bladder carcinoma patients (n=22).

Histopathological diagnosis	N	%
Adenocarcinoma	21	95.5
Well-differentiated	13	59.09
Moderately differentiated	4	18.2
Poorly differentiated	4	18.2
Adenosquamous carcinoma	1	4.5
Invasion		
pT1	13	59.1
pT2	05	22.7
pT3	04	18.2

The majority of patients had undergone laparoscopic cholecystectomy (86%) whereas only 15 patients (14%) had undergone open cholecystectomy. Among 15 open cholecystectomies, 9 were simple and 6 were radical en block type (Figure 4). Of all patients, the average wall thickness of the gall bladder was 7.50±2.23 mm (4-13 mm). Maximum patients had a moderate wall thickness of gall bladder (8-10 mm, 52.7%) followed by mild (4-7 mm, 37.3%) and severe wall thickness (>10 mm, 10%) (Figure 5). Gallbladder carcinoma was found in 20% of patients with gallbladder diseases. Maximum patients were diagnosed with chronic calculous cholecystitis (49.1%) followed in decreasing order gall bladder polyp (6.3%), chronic acalculous cholecystitis (7.3%), gall bladder cholesterol (6.4%), empyema gall bladder (3.6%), gall bladder mucocele (2.7%) and acute cholecystitis (2.7%), gall bladder adenomyoma (0.9%), granulomatous inflammation of gall bladder (0.9%) (Table 3).

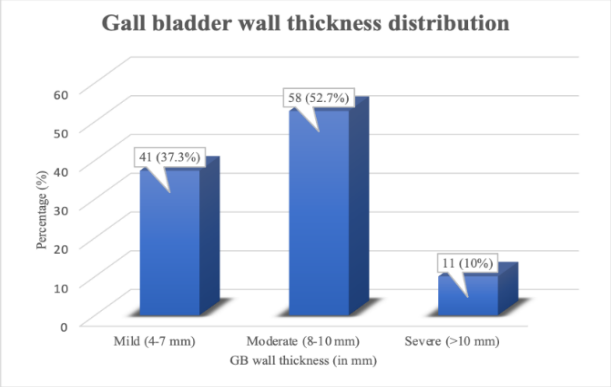
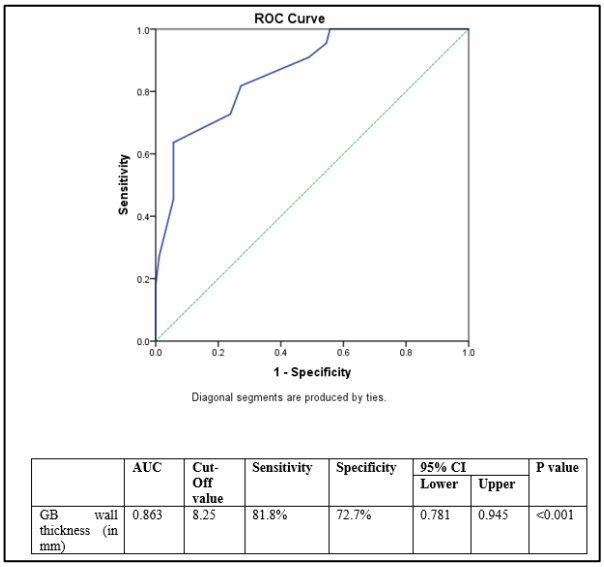


Figure 5: Gall bladder wall thickness among study patients (n=110).



	AUC	Cut-Off value	Sensitivity	Specificity	95% CI		P value
					Lower	Upper	
GB wall thickness (in mm)	0.863	8.25	81.8%	72.7%	0.781	0.945	<0.001

Figure 6: Receiver operator curve showing performance of gall bladder wall thickness in predicting gall bladder carcinoma (n=110).

Among gall bladder carcinoma, adenocarcinoma was the most frequent (N=21, 95.5%), where 13 patients had well differentiation of tumour, 4 had moderate differentiation and another 4 had poor tissue differentiation (Table 4). Out of 22 gall bladder carcinoma cases, the maximum number of patients were female (59.09%) and aged ≥60 years (54.55%) with a significantly higher mean age compared to patients without GB carcinoma (60.50 vs 54.80 years, p value <0.001) (Table 5). GB carcinoma patients had significantly thicker gall bladder walls compared to patients without GB carcinoma (9.80 vs. 6.93 mm, p value <0.001). GB carcinoma patients had also significantly more frequency of severe GB wall thickness compared to patients without GB carcinoma (36.36 vs. 3.41%, <0.001) (Table 6).

Table 5: Association of age and gender distribution with gall bladder carcinoma among study population (n=110).

Demographic profile	Gall bladder carcinoma		P value
	Present (N=22) Frequency (%)	Absent (N=88) Frequency (%)	
Age (years)			
40-49	0 (0)	12 (13.64)	<0.001
50-59	10 (45.45)	62 (70.45)	
≥60	12 (54.55)	14 (15.91)	
Mean±SD	60.50±2.72	54.80±4.96	<0.001
Gender			
Female	13 (59.09)	55 (62.50)	0.768
Male	9 (40.91)	33 (37.50)	

*P value was determined by Chi-square test

Table 6: Association between gall bladder carcinoma and gall bladder wall thickness among study population (n=110).

Gall bladder wall thickness (mm)	Gall bladder carcinoma		P value
	Present (N=22) Frequency (%)	Present (N=22) Frequency (%)	
Mild (4-7 mm)	1 (4.55)	40 (45.45)	<0.001*
Moderate(8-10mm)	13 (59.09)	45 (51.14)	
Severe (>10 mm)	8 (36.36)	3 (3.41)	
Mean±SD	9.80±1.60	6.93±1.98	<0.001**

P value was determined by *Chi-square testand **student t-test

Table 7: Multivariate logistic regression analysis to detect independent predictors of gall bladder carcinoma (n=110).

Predictor	OR	95% CI		P value
		Lower	Upper	
Age ≥60 years	4.865	1.505	15.722	0.008
Female gender	3.624	0.798	16.453	0.095
Positive smoking history	2.081	0.370	11.703	0.405
Gall bladder wall thickness ≥8.25 mm	13.320	3.427	51.781	<0.001

Receiver operator curve analysis found a highly significant cut-off value for gall bladder wall thickness (8.25 mm) with 81.8% sensitivity and 72.7% specificity (AUC 0.863, p value <0.001) (Figure 6). Multivariate logistic regression analysis was conducted to determine the independent predictors of gall bladder carcinoma showed that gall bladder wall thickness ≥8.25 mm had the highest significant odds ratio in predicting gall bladder carcinoma (OR=13.32, 95% CI= 3.43- 51.78, p value <0.001) after adjusting for age, gender and positive smoking history. In addition, patients with age ≥60 years had also a significant odds ratio (OR=4.87, 95% CI= 1.51- 15.72, p value 0.008) for predicting gall bladder carcinoma among gall bladder diseases (Table 7).

DISCUSSION

In the current study, the maximum number of patients with gall bladder carcinoma were female (59.09%) and aged ≥60 years (54.55%) with a significantly higher mean age compared to patients without GB carcinoma (60.50 vs. 54.80 years, p value <0.001). In addition, multivariate logistic regression analysis found that patients with age ≥60 years had a significant odds ratio (OR=4.87, 95% CI=1.51- 15.72, p value 0.008) for predicting gall bladder carcinoma among gall bladder diseases. Previous studies also found that most gall bladder carcinomas occur in the 6th decades of life more commonly in females.[11-13]

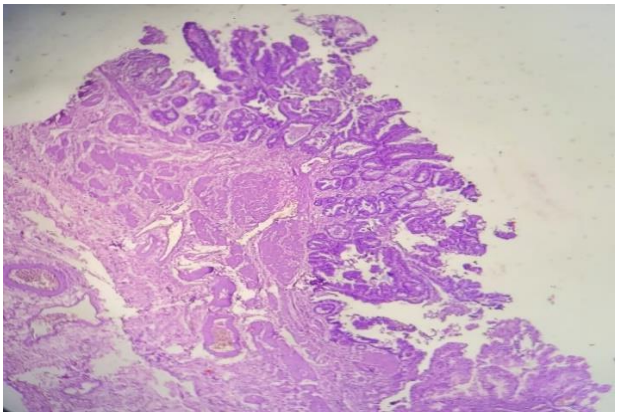


Figure 7: Photomicrograph showing histopathological features of Gall balder Adenocarcinoma (Thickened wall).

A Bangladeshi study by Hasan et al also found that the majority of patients with gall bladder carcinoma were female (76.92%) and from the>60 years of age group (46.15%), irrespective of wall thickness similar to the current study.[13] Therefore, elderly females with gallbladder diseases should be evaluated extensively for early diagnosis and management of gallbladder carcinoma. The major part of the patients was female (61.8%) with a female: male ratio of 1.62:1. The age and gender distribution of our study patients are similar to previous studies on gall bladder diseases.[9,13,15] In this study, gall bladder carcinoma was found in 22 patients (20%) with gall bladder diseases.

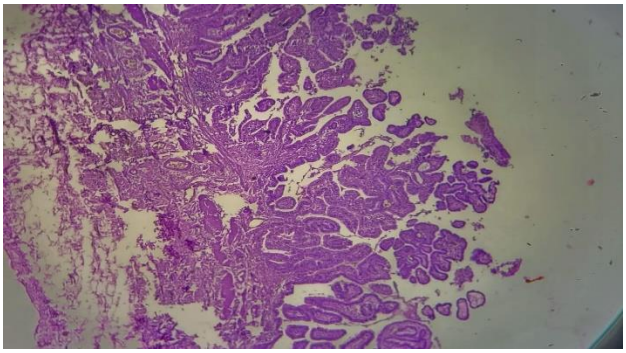


Figure 8: Photomicrograph showing histopathological features of Gall balder Adenocarcinoma (Thickened wall).

Figure 9: Intraoperative photograph of the malignant gall bladder.

The finding in our study is in the upper range of the reported ranges (0.3 to 12%).[13-17] In the present study, the average gall bladder wall thickness of all patients was 7.50±2.23 mm (4-13 mm). Maximum patients had a moderate wall thickness of gall bladder (8-10 mm, 52.7%) followed by mild (4-7 mm, 37.3%) and severe wall thickness (>10 mm, 10%). GB carcinoma patients had significantly thicker gall bladder walls (9.80 vs 6.93 mm) and a higher frequency of severe GB wall thickness (36.36 vs. 3.41%) compared to patients without GB carcinoma. Multivariate logistic regression analysis also found that gall bladder wall thickness ≥8.25 mm had the highest significant odds ratio in predicting gall bladder carcinoma (OR=13.32, 95% CI= 3.43- 51.78, p value <0.001) after adjusting for age, gender and positive smoking history. The relationship between the thicker gall bladder wall and gall bladder carcinoma was also noticed in previous studies.[9,16,17] Hasan et al have found an 84.62% prevalence of gall bladder malignancy in patients with thick-walled GB.[18] The current study revealed 20% cases of gallbladder carcinoma in thick-walled gall bladder which is higher than the previous study mentioned. In this study, the majority of GBC was adenocarcinoma (95%) is higher than in the previous study where adenocarcinoma was 80%.[19] In this study, 49.1% of patients were diagnosed with chronic calculous cholecystitis, followed by chronic acalculous cholecystitis (7.3%), gall bladder polyp (6.3%), gall bladder cholesterol (6.4%), empyema gall bladder (3.6%), gall bladder mucocele (2.7%), adenomyoma (0.9%), chronic granulomatous inflammation (.9%) in decreasing order. Hence, when gall bladder carcinoma manifests as wall thickening, it is challenging to diagnose as it mimics the appearance of more common acute and chronic inflammatory conditions of the GB.[20] Therefore, all resected gall bladder specimens should be examined by the histopathological study to confirm the diagnosis. The analysis of the study population showed the most common presenting complaint to be non-specific or right upper abdominal pain (76.4%), followed by nausea (59.1%), anorexia (55.5%), jaundice (34.5%) and weight loss (28.2%). Our findings are in concordance with the published study.[9,12] However, these signs and symptoms were not specific to carcinoma Gallbladder, hence small early lesions can easily be missed if careful evaluation is not done. The incidence of carcinoma Gall Bladder shows widely variable geographic patterns. In comparison to western countries, incidences of carcinoma Gall Bladder are higher in Asia continent.[14] The per-operative frozen section in suspected gall bladder malignancy and routine histopathology of all Gall Bladder seems to be the only reliable, cost-effective and readily available option in our setup for accurate diagnosis and management of the disease to come with a better survival rate. However, the patient should not be kept waiting for a long duration and the surgeon should counsel the patient regarding every step of treatment planning and adverse complication.

CONCLUSION

GBC was observed in one-fifth of the total study population (22 out of 110 patients). The gallbladder wall was comparatively thicker in patients with GBC with statistical significance. Maximum patients had a moderate wall thickness of gall bladder (8-10 mm, 52.7%) followed by mild (4-7 mm, 37.3%) and severe wall thickness (>10 mm, 10%). GBC patients had significantly thicker gall bladder walls (9.80 vs. 6.93 mm) and a higher frequency of severe GB wall thickness (36.36 vs. 3.41%) compared to patients without GBC. Gallbladder wall thickness is an important variable requiring consideration for the proper evaluation to exclude malignancy for undertaking proper surgical management, thus improving the long-term outcome. The study was conducted in a selected institute, so the study population might not represent the whole community**.** The sample size was not representative of the

whole population**.** Moreover, there was no comparison group.

Recommendations

Further studies with larger sample sizes are recommended. The gallbladder wall can be considered a screening tool for GBC. All surgically removed gallbladders must be carefully examined macroscopically before the histopathological examination. Moderate to severe thick-walled gallbladder patients require intraoperative frozen section facility for the surgeon to consider margin-free resection. Increasing the sample size would have provided further evidence regarding predisposing factors for gallbladder carcinoma and further study is still recommended to validate these findings.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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