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Investigating the Relationship between Gallbladder Malignancy and Various Factors in Surgically Treated Gallbladder Disease Patients

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Abstract **Original Research Article**

Introduction: Gallbladder cancer is a rare but aggressive disease with a poor prognosis. Factors that may contribute to the development of gallbladder cancer include chronic inflammation, gallstones, and obesity. This study will examine the prevalence of these factors in patients who have undergone surgery for gallbladder disease, and determine if there is a correlation with the development of gallbladder cancer. This information will be valuable in identifying high-risk individuals and developing strategies for the early detection and prevention of gallbladder cancer. ***Methods:*** This 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. ***Result:*** The present study findings showed that the majority (65.45%) of the participants were between the age of 50-59 years, with 38.18% being male and 61.82% being female. The most common comorbidities were diabetes (62.73%), hypertension (43.64%) and anaemia (40%). The most common clinical presentation was abdominal pain (76.36%) and the most common histopathological diagnosis was chronic calculous cholecystitis (49.09%), while 20% of participants had gallbladder carcinoma. The study found an association between age, gallbladder wall thickness and gallbladder malignancy. Participants who were 60 years or older were 4.865 times more likely to have gallbladder carcinoma and those with severe wall thickness (>10mm) were 13.32 times more likely to have gallbladder carcinoma. ***Conclusion:*** The present study found that the majority of participants were between the age of 50-59 years, with a higher female prevalence. The most common comorbidities were diabetes, hypertension, and anaemia, while the most common clinical presentations were abdominal pain, anorexia, and nausea. 20% of participants had gallbladder carcinoma. The study found an association between age, gallbladder wall thickness and gallbladder malignancy. Elderly females with gall bladder diseases should be evaluated extensively for early diagnosis and management of gall bladder carcinoma. All resected gall bladder specimens should be examined by the histopathological study to confirm the diagnosis.

Keywords: Carcinoma, Gall Bladder, Thickening, Wall Thickening.

INTRODUCTION

Gallbladder malignancy is a rare but aggressive type of cancer that affects the gallbladder, a small organ located under the liver that stores bile and releases it into the small intestine to aid in digestion. The incidence of gallbladder malignancy is relatively low, but it carries a poor prognosis because it is often not diagnosed until it is in an advanced stage [1, 2]. The main reason is that most gallbladder malignancy patients are asymptomatic, and the symptoms are similar to those of benign gallbladder diseases such as

cholecystitis and cholelithiasis. Thus, the diagnosis of malignancy is often delayed and the outcomes of patients with gallbladder malignancy are poor [3, 4]. The surgical treatment of gallbladder malignancy is the only curative option available and it is a complex procedure, involving a radical resection of the gallbladder, regional lymph nodes and sometimes liver resection [5]. The surgical approach and the extent of the resection are determined by the stage of the disease, the location of the tumour, and the patient's overall health [6, 7]. Given the rarity and poor prognosis of gallbladder malignancy, it is important to understand the relationship between the disease and various factors to improve diagnosis, treatment, and outcomes for patients [8]. This can be achieved by investigating the relationship between gallbladder malignancy and various factors in surgically treated gallbladder disease patients. Several factors have been proposed as possible risk factors for the development of gallbladder malignancy, including age, sex, obesity, diabetes, and a history of gallstones [9, 10]. However, the relationship between these factors and gallbladder malignancy remains unclear, and further research is needed to confirm these associations. Additionally, research on the relationship between gallbladder malignancy and other factors, such as genetic predisposition, viral infections, and environmental exposures, is needed to better understand the underlying causes of the disease [10]. Another important aspect of investigating the relationship between gallbladder malignancy and various factors is studying the surgical outcomes of patients with the disease [11, 12] This includes evaluating the success of the surgery in terms of the extent of the resection, the rate of recurrence, and the overall survival of the patients. Additionally, research on the long-term complications and quality of life of patients who have undergone surgery for gallbladder malignancy is also important [13–15]. In conclusion, gallbladder malignancy is a rare but aggressive type of cancer that carries a poor prognosis. The surgical treatment of gallbladder malignancy is the only curative option available, but the outcomes for patients are poor. Therefore, it is crucial to investigate the relationship between gallbladder malignancy and various factors to improve diagnosis, treatment, and outcomes for patients. Such a study will help us understand the underlying causes of the disease, and identify potential risk factors that can aid in early detection and prevention. Additionally, by studying the surgical outcomes, long-term complications and quality of life of patients who have undergone surgery for gallbladder malignancy, we can improve the overall care and management of these patients. In light of this, it is imperative to conduct further research on this topic to improve the outcomes for patients suffering from gallbladder malignancy.

OBJECTIVE

- To observe the association of various factors with gallbladder malignancy in patients surgically treated with malignancy

METHODS

This study was a prospective, cross-sectional and observational study conducted in the Department of General Surgery and Hepato-Biliary-Pancreatic Surgery at BIRDEM General Hospital in Dhaka, Bangladesh. It ran from August 2019 to February 2021. Patients who had undergone gallbladder surgery at the hospital were recruited for the study using consecutive sampling. Due to the COVID pandemic and limited resources, a total of 110 patients were included in the study. Participants were selected based on specific inclusion and exclusion criteria, and data was collected through a structured questionnaire and digital Vernier slide calliper, after obtaining informed written consent. The study was conducted in Bengali and the questionnaire was pre-tested on similar patients. The study collected detailed patient information, including symptoms of biliary colic, previous attacks of colic, jaundice, and pancreatitis, as well as comorbid conditions and previous symptoms. Physical examination, abdominal examination, routine investigations, and biochemical markers were also collected. The thickness of the gallbladder wall was identified through specific investigation using USG of the abdomen, and findings were recorded. Additionally, the findings of imaging studies such as CECT abdomen, MRI, and MRCP were noted when performed. All information was recorded in separate case record forms.

Inclusion Criteria

- Patients who would undergo surgery for gallbladder disease and suggestive of having gallbladder wall >3mm wall (confirmed by pre-operative Ultrasonography).
- Adult patients irrespective of age, sex, comorbidity.
- The patient who gave consent.

Exclusion Criteria

- 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 <3mm.
- Patients who had gall bladder mass.
- Patients who were not undergoing surgery.

Operative Procedure

After obtaining informed consent and completing pre-anaesthesia checkup, patients underwent surgery under general anaesthesia. The procedures included Open and laparoscopic cholecystectomy, Radical en bloc resection, Whipple's

procedure, etc. Intraoperative findings such as gallbladder wall thickness, number of stones, empyema gallbladder, adhesions, Calot's triangle anatomy, cut section appearance, level of difficulty, and duration of surgery were recorded. The thickness of the gallbladder was measured using the fine dissecting method. A longitudinal incision was made using a sharp B-P blade through the peritoneal smooth surface of the gallbladder from the fundus to the neck, and the interior of the gallbladder was cleaned with jets of tap water. Then, the thickness was measured in mm at 3-5 different sites using a digital slide calliper, and the maximum value was used for inclusion in the study. After the operation, dissected specimens were sent to the pathology laboratory at BIRDEM General Hospital for histopathology, and the confirmatory diagnosis was recorded according to the histopathology report.

Data Processing and Analysis

Statistical analysis was performed using SPSS version 26 software. Categorical variables were presented as frequencies and percentages, while continuous variables were presented as means and standard deviations. The association between categorical variables was analyzed using the chi-square test, and the difference between continuous variables was analyzed using the student t-test. The receiver's operating curve (ROC) was done to find out the cut-off value. Diagnostic accuracy was measured by calculating sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. A significance level of 0.05 was used for all tests.

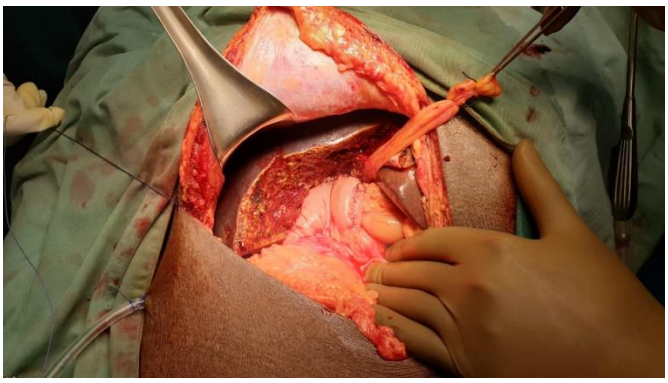


Fig. 1: Gall bladder wall thickness measurement in millimeters with help of a digital Vernier calliper

RESULTS

Table 1: Distribution of participants by basic characteristics (N=110)

Variables	N	%
Age		
40-49	12	10.91%
50-59	72	65.45%
≥60	26	23.64%
Gender		
Male	42	38.18%
Female	68	61.82%
Gall Bladder Wall Thickness		
Mild (4-7 mm)	41	37.27%
Moderate (8-10 mm)	58	52.73%
Severe (>10 mm)	11	10.00%
Type of Surgery		
Laparoscopic	95	86.36%
Open Normal	9	8.18%
Open Radical en bloc	6	5.45%

Among the participants, majority (65.45%) had been between the age of 50-59 years, with 23.64% being 60 years or older, and 10.9% being from the youngest age group of 40-49 years. Higher female prevalence was observed, with 61.82% female and 38.18% male participants. Gall bladder wall thickness was moderate for over half (52.73%) of the participants, and 10% had severe wall thickness of over 10 mm. Laparoscopic surgery was the most common method of management, with 86.36% having undergone laparoscopic surgery, 8.18% having normal open surgery, and 5.45% having open radical en bloc [Table 1].

Table 2: Associated co-morbidity and personal history of study patients (N=110)

Comorbidities	n	%
Diabetes	69	62.73%
Hypertension	48	43.64%
Anemia	44	40.00%
Overweight	40	36.36%
Ischemic Heart Disease	11	10.00%
Bronchial Asthma	9	8.18%
Hypothyroidism	3	2.73%
H/O smoking	16	14.55%
H/O alcohol consumption	2	1.82%

Multiple comorbidities were present in many of the participants. Diabetes was the most common comorbidity, observed in 62.73% of participants, while hypertension was present in 43.64% of the participants, anemia in 40%, ischemic heart disease in 10%, bronchial asthma in 8.18%, and 36.36% were overweight. 14.55% of the participants had a history of smoking, while 1.82% had a history of alcohol consumption [Table 2].

Table 3: Clinical presentations among study patients (N=110)

Clinical presentation	N	%
Abdominal pain	84	76.36%
Anorexia	61	55.45%
Nausea	65	59.09%
Weight loss	31	28.18%
Jaundice	38	34.55%
Asymptomatic	9	8.18%

Multiple clinical presentations were observed among individual participants. Abdominal pain was a common clinical presentation observed in 76.36% of cases, while 55.45% had anorexia, 59.09% had nausea, 34.55% had jaundice, 28.18% had weight loss and 8.18% had been asymptomatic [Table 3].

Table 4: Histopathological diagnosis of study patients (N=110)

Histopathological diagnosis	N	%
Gall bladder carcinoma	22	20.00%
Chronic calculous cholecystitis	54	49.09%
Chronic acalculous cholecystitis	8	7.27%
Gall bladder cholesterics	7	6.36%
Gall bladder polyp	7	6.36%
Empyema gall bladder	4	3.64%
Acute cholecystitis	3	2.73%
Gall bladder mucocele	3	2.73%
Gall bladder adenomyoma	1	0.91%
Granulomatous inflammation	1	0.91%

Histopathological diagnosis of the study population revealed that 49.09% had Chronic calculous cholecystitis, while 7.27% had Chronic acalculous cholecystitis. Other types of diagnosis were also observed among the participants, but 20% had gall bladder carcinoma. Gall bladder cholesterics and gall bladder polyps were each observed in 6.36% of the participants [Table 4].

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

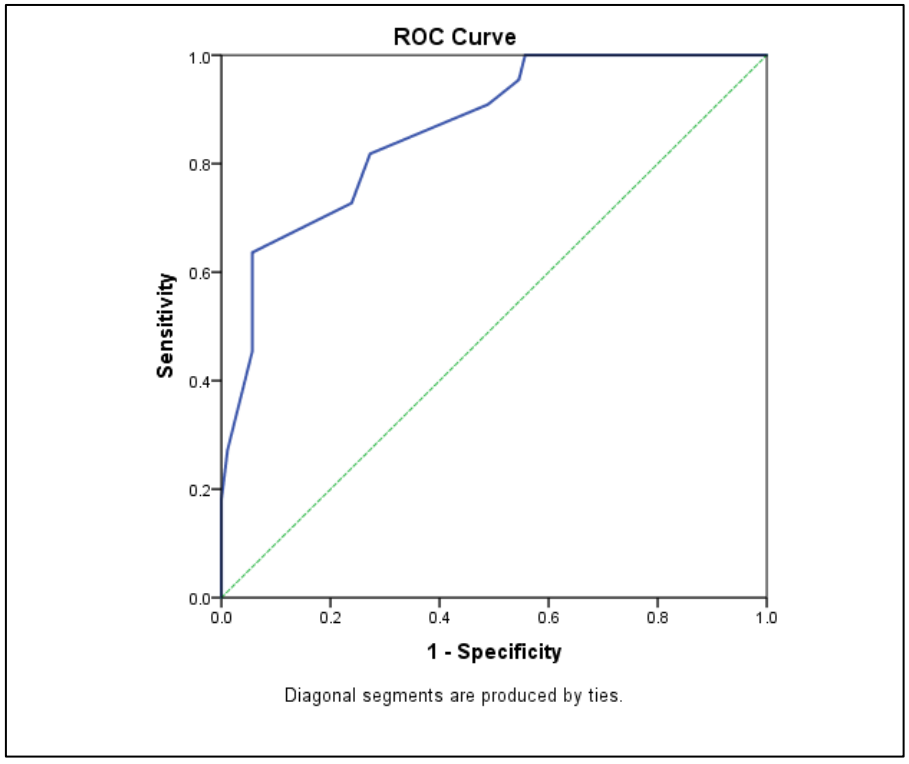
Demographic profile	Gall bladder carcinoma		*p value**
	Present (n=22)	Absent (n=88)	
Age (in years)			
40-49	0 (0)	12 (13.64)	<0.001
50-59	10 (45.45)	62 (70.45)	
≥60	12 (54.55)	14 (15.91)	
Mean±SD	60.50±2.72	54.80±4.96	<0.001
Gender			
Female	13 (59.09)	55 (62.50)	0.768
Male	9 (40.91)	33 (37.50)	

Association of the patient's age and gender with the prevalence of gall bladder carcinoma revealed that none of the youngest age group had carcinoma, while among the 22 patients who had cancer, 54.55% had been from the oldest age group. On the other hand, 70.45% of the 88 who had no cancer belonged to the age group of 50-59 years. This discrepancy was statistically significant. In regards to gender, the distribution of participants among male and female of both groups was similar, and no significant association was observed between gender and gall bladder carcinoma patients [Table 5].

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

Gall bladder wall thickness (in mm)	Gall bladder carcinoma		p value*
	Present (n=22)	Absent (n=88)	
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**

Among the 22 patients with gall bladder carcinoma, only one had mild wall thickness, while 59.09% had moderate and 36.36% had severe gall bladder wall thickness. On the other hand, among the 88 patients who had did not have gall bladder carcinoma, only 3.41% had severe thickness, with 51.54% having moderate levels of thickness and 45.45% had mild gall bladder thickness. This difference was statistically significant. The mean gall bladder wall thickness was 9.80 mm among those who had cancer, and 6.93 among those who did not have cancer. This difference was also statistically significant [Table 6].



	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%	.781	.945	<0.001

Figure 2: Receiver operator curve showing performance of gall bladder wall thickness in predicting gall bladder carcinoma (N=110)

Receiver operator curve (ROC) analysis found highly significant cut-off value for gall bladder wall thickness at 8.25 mm, with 81.8% sensitivity and 72.7% specificity (AUC 0.863, p value <0.001).

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	<0.001
Female gender	3.624	0.798	16.453	0.095
Positive smoking history	2.081	0.37	11.703	0.405
Gall bladder wall thickness ≥8.25 mm	13.32	3.427	51.781	<0.001

The above table shows that patient age of ≥60 years was associated with a 4.865-fold increased risk of the outcome, with a statistically significant (p<0.001) association. Female gender was associated with a 3.624-fold increased risk of the outcome, but this association was not statistically significant (p=0.095) Similarly, positive smoking was also not significantly associated with the outcome. Gall bladder wall thickness of ≥8.25 mm was associated with a 13.32-fold increased risk of the outcome, with a statistically significant (p<0.001) association [Table 7].

DISCUSSION

The present study was conducted to evaluate the possible relations between gallbladder carcinoma with various factors. A total of 110 patients with gall bladder diseases who had undergone cholecystectomy were included in this study irrespective of their age, gender, race and ethnic group after careful history taking, examination and appropriate investigations fulfilling inclusion and exclusion criteria. The study found that the majority of participants (65.45%) were between the age of 50-59 years, with a higher female prevalence (61.82%). Previous studies have also found that most gall bladder carcinomas occur in the 6th decade of life more commonly in females [16-19]. 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 [19]. Therefore, elderly females with gallbladder diseases should be evaluated extensively for early diagnosis and management of gallbladder carcinoma. The most common comorbidity was diabetes (62.73%), followed by hypertension (43.64%) and anaemia (40%). This distribution of comorbidities was not uncommon, as many other studies have also observed similar comorbidities, and some had observed higher incidences of ischemic diseases [20-23]. The most common clinical presentation was abdominal pain (76.36%), followed by anorexia (55.45%) and nausea (59.09%). A similar prevalence of clinical presentations was observed in other studies as well [24]. The most common histopathological diagnosis was chronic calculous cholecystitis (49.09%), while 20% of participants had gallbladder carcinoma. 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 (.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 [25] Therefore, all resected gall bladder specimens should be examined by the histopathological study to confirm the diagnosis. The results of the study also showed an association between age and gallbladder malignancy. Participants who were 60 years or older were more likely to have gallbladder carcinoma compared to those who were younger. This was in line with the findings of other previous studies, where old age had a significant positive relation with gallbladder cancer [26, 27]. Additionally, there was an association between gallbladder wall thickness and gallbladder malignancy, with participants who had severe wall thickness (over 10 mm) more likely to have gallbladder carcinoma [19]. The results also showed that laparoscopic surgery was the most common method of management, with 86.36% of the participants had undergone laparoscopic surgery. However, there was no association found between the type of surgery and gallbladder malignancy. The results found that the average gallbladder wall thickness among all patients was 7.50±2.23 mm (ranging from 4-13 mm). The majority of patients had moderate wall thickness (8-10 mm, 52.7%), followed by mild (4-7 mm, 37.3%), and severe wall thickness (>10 mm, 10%). The study also found that patients with gallbladder carcinoma had significantly thicker gallbladder walls (9.80 vs 6.93 mm) and a higher frequency of severe wall thickness (36.36% vs 3.41%) compared to patients without gallbladder carcinoma. Multivariate logistic regression analysis also revealed that a gallbladder wall thickness of ≥8.25 mm had the highest significant odds ratio in predicting gallbladder carcinoma (OR=13.32, 95% CI= 3.43- 51.78, p-value <0.001) after adjusting for age, gender, and positive smoking history. These findings align with previous studies, which also observed a relationship between thicker gallbladder walls and gallbladder carcinoma [19, 28]. Overall, this study suggests that there is a relationship between gallbladder malignancy and various factors in surgically treated gallbladder disease patients. Age, gallbladder wall thickness, and comorbidities such as diabetes may play a role in the development of gallbladder carcinoma. Further research is needed to confirm these findings and explore potential interventions to reduce the risk of gallbladder malignancy in at-risk patients.

Limitations of the Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community. There was no comparison group.

CONCLUSION

The present study found that the majority of participants were between the age of 50-59 years, with a higher female prevalence, similar to findings in previous studies. The most common comorbidities were diabetes, hypertension, and anaemia, while the most common clinical presentations were abdominal pain, anorexia, and nausea. The most common histopathological diagnosis was chronic calculous cholecystitis, while 20% of participants had gallbladder carcinoma. The study also found an association between age, gallbladder wall thickness, and gallbladder malignancy. Participants who were 60 years or older were more likely to have gallbladder carcinoma and those with severe wall thickness were more likely to have gallbladder carcinoma. However, there was no association found between the type of surgery and gallbladder malignancy. Overall, the study suggests that gallbladder wall thickness may be an important risk factor for gallbladder carcinoma and may aid in the early detection and management of this disease. So, elderly females with gall bladder diseases should be evaluated extensively for early diagnosis and management of gallbladder carcinoma. Therefore, all resected gall bladder specimens should be examined by the histopathological study to confirm the diagnosis.

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Ethical Approval: The study was approved by the Institutional Ethics Committee.

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