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Association of Various Factors with Gallbladder Malignancy in Patients Surgically Treated with Malignancy

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ABSTRACT

Introduction: Gallbladder cancer occurs when malignant (cancer) cells grow in your gallbladder. Your gallbladder is a pear-shaped organ in the upper right of your abdomen, just under your liver. 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. 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. ***Methods:*** This prospective cross-sectional and observational study was carried out in the Department of Surgery BSMMU from July 2023 to August 2024. Total of 100 patients were included in the study. Patients who had undergone gallbladder surgery at the hospital were recruited for the study using consecutive sampling. 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. ***Results:*** The present study findings showed that the majority (65%) of the participants were between the age of 50-59 years, with 38% being male and 62% being female. The most common comorbidities were diabetes (63%), hypertension (44%) and anaemia (40%). The most common clinical presentation was abdominal pain (76%) and the most common histopathological diagnosis was chronic calculous cholecystitis (49%), 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 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. 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

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 [1]. 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 [2,3]. 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 [4,5]. 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 [6,7]. Factors such as chronic bacterial infection, primary sclerosing cholangitis, an anomalous junction of the pancreaticobiliary duct, and several types of gallbladder polyps are associated with a higher risk of gallbladder cancer. There is also an interesting correlation between risk factors and the histological type of cancer. However, despite theoretical risk factors, only a third of gallbladder carcinomas are recognized preoperatively. 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.

METHODS

This study was a prospective, cross-sectional and observational study conducted in the Department of Surgery BSMMU from July 2023 to August 2024. Total of 100 patients were included in the study. Patients who had undergone gallbladder surgery at the hospital were recruited for the study using

consecutive sampling. 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.

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.

RESULTS

Table 1: Distribution of participants by basic characteristics (N=100)

Variables	N	%
Age		
40-49	11	11%
50-59	65	65%
≥60	24	24%
Gender		
Male	38	38%
Female	62	62%
Gall Bladder Wall Thickness		
Mild (4-7 mm)	37	37%
Moderate (8-10 mm)	53	53%
Severe (>10 mm)	10	10%
Type of Surgery		
Laparoscopic	86	86%
Open Normal	8	8%
Open Radical en bloc	6	6%

Among the participants, majority (65%) had been between the age of 50-59 years, with 24% being 60 years or older, and 11% being from the youngest age group of 40-49 years. Higher female prevalence was observed, with 62% female and 38% male participants. Gall bladder wall thickness was moderate for over half (53%) of the participants, and 10% had severe wall thickness of over 10 mm. Laparoscopic surgery was the most common method of management, with 86% having undergone laparoscopic surgery, 8% having normal open surgery, and 6% having open radical en bloc [Table 1].

Table 2: Associated co-morbidity and personal history of study patients (N=100)

Comorbidities	n	%
Diabetes	69	63%
Hypertension	44	44%
Anemia	40	40%
Overweight	36	36%
Ischemic Heart Disease	10	10%
Bronchial Asthma	8	8%
Hypothyroidism	3	3%
H/O smoking	14	14%
H/O alcohol consumption	2	2%

Multiple comorbidities were present in many of the participants. Diabetes was the most common comorbidity, observed in 63% of participants, while hypertension was present in 44% of the participants, anemia in 40%, ischemic heart disease in 10%, bronchial asthma in 8%, and 36% were overweight. 14% of the participants had a history of smoking, while 2% had a history of alcohol consumption [Table 2].

Table 3: Clinical presentations among study patients (N=100)

Clinical presentation	N	%
Abdominal pain	76	76%
Anorexia	55	55%
Nausea	59	59%
Weight loss	28	28%
Jaundice	34	34
Asymptomatic	8	8%

Multiple clinical presentations were observed among individual participants. Abdominal pain was a common clinical presentation observed in 76% of cases, while 55% had anorexia, 59% had nausea, 34% had jaundice, 28% had weight loss and 8% had been asymptomatic [Table 3].

Table 4: Histopathological diagnosis of study patients (N=100)

Histopathological diagnosis	N	%
Gall bladder carcinoma	20	20%
Chronic calculous cholecystitis	49	49%
Chronic acalculous cholecystitis	7	7%
Gall bladder cholesterics	6	6%
Gall bladder polyp	6	6%
Empyema gall bladder	4	4%
Acute cholecystitis	3	3%
Gall bladder mucocele	3	3%
Gall bladder adenomyoma	1	1%
Granulomatous inflammation	1	1%

Histopathological diagnosis of the study population revealed that 49% had Chronic calculous cholecystitis, while 7% 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% of the participants [Table 4].

Table 5: Multivariate logistic regression analysis to detect independent predictors of gall bladder carcinoma (N=100)

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 5].

DISCUSSION

In developed countries gallbladder carcinoma (GBC) is an uncommon neoplasm, whose incidence depends on geographic, age-, gender- and ethnicity-related genetics and/or environmental factors (1-3). GBC is highly aggressive, with a low 5-year survival rate, varying between 5% to 32%, and the only effective treatment depends on an early diagnosis (2,4). Half of the patients are detected incidentally during or after a cholecystectomy and fewer that 20% with non-incidental GBC are potential candidates for surgery, as it progresses silently, consequently associated with a worse prognosis (5). As such, the search for new therapeutic new targets is of utmost importance. However, due to the rarity of GBC, solid information about the pathophysiology and the clinical outcomes is limited. GBC is linked to multiple genetic and environmental factors, such as chronic infection, gallstones and gender (10). The present study was conducted to evaluate the possible relations between gallbladder carcinoma with various factors. A total of 100 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%) were between the age of 50-59 years, with a higher female prevalence (62%). 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 (77%) and from the>60 years of age group (46%), 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 (63%), followed by hypertension (44%) 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%), followed by anorexia (55%) and nausea (59%). A similar prevalence of clinical presentations was observed in other studies as well [24]. The most common histopathological diagnosis was chronic calculous cholecystitis (49%), while 20% of participants had gallbladder carcinoma. In this study, 49% of patients were diagnosed with chronic calculous cholecystitis, followed by chronic acalculous cholecystitis (7%), gall bladder polyp (6%), gall bladder cholesterol (6%), empyema gall bladder (4%), gall bladder mucocele (3%), adenomyoma (1%), chronic granulomatous inflammation (1%) 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] 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% of the participants had undergone laparoscopic surgery. 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.

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. 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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