

FREQUENCY AND HISTOPATHOLOGICAL TYPES OF GALL BLADDER CARCINOMA AND ITS ASSOCIATION WITH DEMOGRAPHIC FACTORS AND COMORBIDITIES IN PATIENTS UNDERGOING SURGERY FOR CHOLELITHIASIS AT A TERTIARY CARE HOSPITAL

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ABSTRACT

BACKGROUND: Gall bladder carcinoma (GBC) is an aggressive malignancy with a poor prognosis, commonly identified at an advanced stage. Cholelithiasis is identified as a key risk factor for the development of gall bladder cancer in regions with a high prevalence of gallstones. Several cases of gall bladder carcinoma are incidentally detected during or following the surgery for presumed benign gallstone disease. Early diagnosis in patients undergoing cholecystectomy could improve the outcomes.

OBJECTIVE: To determine the frequency, histopathological types of gallbladder carcinoma, and association of demographic factors (age, gender, BMI) and comorbidities (diabetes mellitus, hypertension) with GBC among patients undergoing surgery for cholelithiasis at a tertiary care hospital.

METHODOLOGY: This cross-sectional study was conducted on 189 patients undergoing surgery for cholelithiasis in the age range of 18 to 65 years, with either gender at the General Surgery department of Ayub Teaching Hospital MTI, Abbottabad, from 24 May 2024 to 24 November 2024. All the patients underwent gross examination, where characteristic features such as a firm /tan-white to yellow-gray cut surface and the presence of exophytic or polypoid friable mucosal lesions were noted, and confirmation was made with histopathological assessment for the diagnosis of carcinoma. The collected data were then analyzed with SPSS 27

RESULTS: The mean age in our study was 40.03 ± 11.86 years. Gender distribution showed that 102 (54.0%) were females and 87 (46.0%) were males. Gallbladder carcinoma was observed in 7 (3.7%) patients. A significant association was found between gallbladder carcinoma and diabetes ($p=0.009$) and age ($p=0.05$). No significant associations were observed with gender, BMI, and hypertension ($p > 0.05$ for all). The recorded mean age in gallbladder carcinoma patients was 52.43 ± 13.697 years ($p=0.005$). The recorded mean duration of symptoms was 15.43 ± 1.90 months ($p<0.001$).

CONCLUSION: The frequency of gall bladder carcinoma among patients undergoing surgery for cholelithiasis was 3.7%. Diabetes, older age, and prolonged duration of symptoms were associated with GBC.

KEYWORDS: Gallbladder Neoplasm, cholelithiasis, cholecystectomy, diabetes mellitus

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INTRODUCTION

Gallstones constitute a prevalent etiology of digestive dysfunction globally.^{1,2} Gallstones can result in severe pain as well as intermittent discomfort. They can also induce acute conditions that impact the pancreatic, hepatic, and gastrointestinal systems.^{3,4} While nearly all of individuals with gallstones stay asymptomatic, roughly 10% may exhibit signs within 5 years, as well as 20% within twenty years of identification. The likelihood of gallstones rises with older age. More than 25% of women over the age of 60 are impacted by gallstones.⁵ The rate of gallstones rises with age, leading to an elevated need for treatments related to gallstones in elderly people.⁶ Cholesterol gallstones are on the rise around the globe, especially and are estimated to influence 20% of European population. In developing countries, bilirubin-produced stones are more frequent and are linked to hematologic disorders of the biliary tree.⁷

Gallbladder carcinoma (GBC) represents most frequently

occurring biliary tumor, even though being a relatively uncommon cancer overall.^{8,9} The rate of GBC rises with advancing age, noted to be more prevalent in females. The incidence of GBC is elevated in certain populations, attributed to a significant number of gallstones along with chronic gallbladder infections.¹⁰ Incidental GBC occurred in 3.04% of patients after cholecystectomy.¹¹ The successful treatment of patients with GBC necessitates an extensive strategy. The relationship between gallstones and GBC has been thoroughly documented, suggesting that chronic inflammation triggered by gallstones could significantly lead to malignant change in gallbladder mucosa.¹²⁻¹⁴

The challenges posed by GBC extend beyond its ambiguous nature and diagnostic intricacy. The late stage at which gallbladder cancer is often diagnosed limits treatment options and negatively impacts overall patient outcomes. This study aims to assess the prevalence of gallbladder carcinoma in patients undergoing surgery for cholelithiasis at our hospital, addressing the limited local literature on this topic. This study's results will

aid health professionals in understanding risk factors and diagnostic methods, emphasizing the urgent need for a fundamental change in addressing cholelithiasis.

This study aimed to determine the frequency of gallbladder carcinoma (GBC) in patients undergoing surgery for cholelithiasis at a tertiary care hospital, and to evaluate its association with demographic factors and comorbid conditions such as diabetes mellitus and hypertension.

METHODOLOGY:

This cross-sectional study was conducted in the department of general surgery (24-May-2024 to 24-November-2024), Ayub Teaching Hospital, Abbottabad, after securing ethical approval from the institute. We used a consecutive non-probability sampling technique to enroll 189 participants. The sample size was calculated using the WHO sample size calculator software, based on a previous frequency of gallbladder carcinoma of 4.15%, a 95% confidence level, and an absolute precision of 2.8%.¹⁵

Patient having age 18 to 65 years, regardless of gender, who presented with cholelithiasis were selected for this research. The diagnosis of cholelithiasis included symptoms such as vomiting, nausea, and pain in the right upper area of the abdomen with a Visual Analogue Scale (VAS) score greater than 6; these patients were experiencing these symptoms from minimum of five months. Patients having a bleeding disorder, a previous history of any malignancy, or who were pregnant were not included in the research.

Each participant provided written consent. A pre-designed, structured proforma was used to record demographic details such as age, gender, body mass index (BMI), educational status, profession, socioeconomic status, and place of residence. Diabetes mellitus and hypertension were also recorded.

All enrolled patients who underwent surgery for cholelithiasis were subjected to gallbladder carcinoma evaluation. This involved gross examination and histopathology assessment. Gross examination revealed characteristic features such as a firm/tan-white to yellow-gray cut surface and the presence of exophytic or polypoid friable mucosal lesions. Each specimen was then sent for histopathological assessment for microscopic confirmation and classification according to histological subtype (adenocarcinoma, papillary carcinoma). Tumors were staged

according to the TNM system based on depth of invasion: T1a (mucosa), T1b (muscularis propria), T2 (perimuscular connective tissue), and T3 (serosa or beyond). The whole assessment was performed under the supervision of a consultant with at least five years of experience.

For data analysis, we used SPSS 27. Age, height, weight, and BMI were evaluated using mean and standard deviation. Gender and other categorical demographic variables, along with diabetes, gallbladder carcinoma, and hypertension, were presented using frequencies with percentages. Age, BMI, diabetes, gender, and hypertension were stratified with gallbladder carcinoma using Chi Square test, where we kept the P value significant at ≤ 0.05 .

The ethical approval for this study was obtained from the ethical committee of Ayub Teaching Hospital, with approval code RC-EA-2024/052 on 21/02/2024.

RESULTS

The study included 189 patients with a mean age of 40.03 ± 11.86 years and a mean BMI of 25.15 ± 1.55 kg/m². Regarding the gender distribution, our study consisted of 102 (54.0%) female and 87 (46.0%) male patients. Diabetics were 36 (19.0%), and hypertension was observed in 54 (28.6%) cases (Table 1). The majority of the cholecystectomies performed were laparoscopic (Figure 1). Gallbladder carcinoma was present in 7 (3.7%) patients. Out of the 7 cases of GBC, four (57.1%) were adenocarcinoma, and 3 (42.9%) were papillary carcinoma (Table 2). Table 3 presents the staging of gall bladder carcinoma.

Analysis of factors associated with gallbladder carcinoma revealed that a majority of carcinoma patients were in the 51–65 years age group 4 (57.1%). However, no statistically significant association was found between age and carcinoma presence ($p = 0.33$). Similarly, a higher proportion of carcinoma cases were found in females 5 (71.4%), gender was not associated with the presence of carcinoma ($p = 0.34$). BMI categorization also showed no difference ($p = 0.77$).

Diabetes showed a statistically significant association with gallbladder carcinoma; around 4 (57.1%) of carcinoma patients had diabetes ($p = 0.009$). Hypertension was not significantly associated with 42.9% of carcinoma patients having hypertension compared to 28.0% in those without carcinoma ($p = 0.39$) (Table 1).

Table 1- Baseline characteristics & comorbidities

Baseline characteristics & comorbidities		Statistics
Gender	Male	87 (46.0%)
	Female	102 (54.0%)
Education status	Educated	91 (48.1%)
	Uneducated	98 (51.9%)
Profession	Office worker	52 (27.5%)
	Business	53 (28.0%)
	Retired	27 (14.3%)
	Other	57 (30.2%)
Residence	Urban	85 (45.0%)
	Rural	104 (55.0%)
Socioeconomic status	Poor	55 (29.1%)
	Middle class	78 (41.3%)
	Rich	56 (29.6%)
Diabetes	Yes	36 (19.0%)
	No	153 (81.0%)
Hypertension	Yes	54 (28.6%)
	No	135 (71.4%)

The majority of patients underwent laparoscopic cholecystectomy, while a smaller proportion underwent open surgery. The distribution of surgical techniques is illustrated in Figure 1.

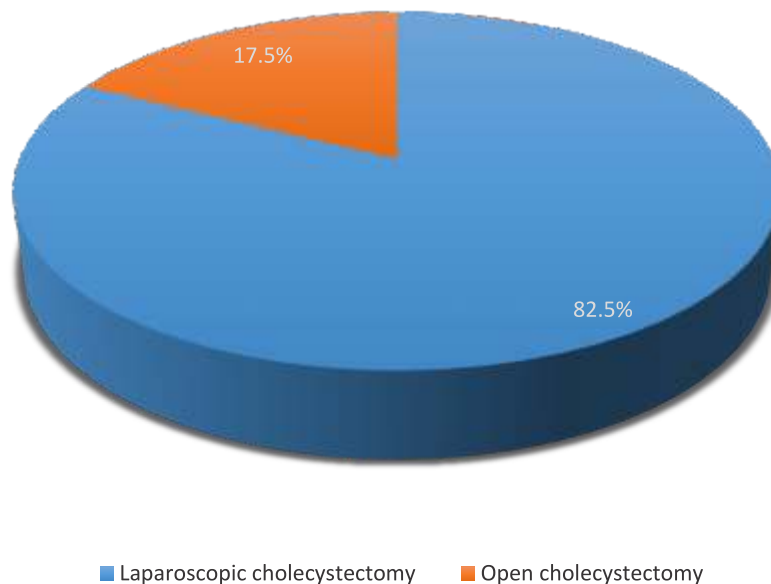


Figure 1- The distribution of surgical techniques

Gallbladder carcinoma was identified in 7 out of 189 patients, giving a frequency of 3.7%. Among the confirmed carcinoma cases, adenocarcinoma was the most common histopathological subtype (57.1%), followed by papillary carcinoma (42.9%). The detailed histopathological findings are shown in Table 2.

Table 2- Histopathological typing of GBC

Histopathological Type	Frequency
Adenocarcinoma	4 (57.1%)
Papillary carcinoma	3 (42.9%)

Tumor staging revealed that the majority of cases were detected at early stages. T1b (muscle invasion) was the most frequent stage (42.9%), followed by T1a (mucosal involvement only) and T2/T3 stages (28.6% each). The staging distribution is summarized in Table 3.

Table 3- Staging of GBC

Carcinoma Stages	Frequency
T1a (mucosal only)	2 (28.6%)
T1b (muscle invasion)	3 (42.9%)
T2/T3 (deeper invasion)	2 (28.6%)

Stratification analysis demonstrated that although a higher proportion of carcinoma cases were observed in females (71.4%) and in patients aged 51–65 years, these associations were not statistically significant ($p > 0.05$). BMI and hypertension also showed no significant association with carcinoma.

However, diabetes mellitus showed a statistically significant association with gallbladder carcinoma ($p = 0.009$). Among carcinoma patients, 57.1% were diabetic compared to 17.6% in

the non-carcinoma group.

Furthermore, the mean age of patients with carcinoma (52.43 ± 13.697 years) was significantly higher than that of those without carcinoma (39.55 ± 11.566 years) ($p = 0.005$). Similarly, the mean duration of symptoms was significantly longer in carcinoma patients (15.43 ± 1.90 months) compared to non-carcinoma patients (8.02 ± 2.18 months) ($p < 0.001$) (Table 4).

Table 4- Stratification of gallbladder carcinoma with demographics and comorbidities

Demographics & comorbidities		Gallbladder carcinoma				P-value
		Yes		No		
		Frequency	Percentage	Frequency	Percentage	
Gender	Male	2	28.6%	85	46.7%	0.34
	Female	5	71.4%	97	53.3%	
Diabetes	Yes	4	57.1%	32	17.6%	0.009
	No	3	42.9%	150	82.4%	
Hypertension	Yes	3	42.9%	51	28.0%	0.39
	No	4	57.1%	131	72.0%	
		Mean	SD	Mean	SD	P-value
Age (Years)		52.4	13.6	39.5	11.5	0.005
Duration of symptoms (Months)		15.4	1.9	8.0	2.1	< 0.001

SD = Standard deviation, a = Fischer's exact test applied, b = Independent T test applied

DISCUSSION

In the present study, we found that gallbladder carcinoma (GBC) was observed in 3.7% patients undergoing cholecystectomy. The findings are similar to a local study conducted by Alam et al., who reported a frequency of 3.04% GBC in their cohort.¹¹ Khan et al. found a 4% incidence of GBC in their study.¹⁶ However, it stands in contrast to studies reporting lower figures, such as Sufyan et al. at 0.4% and Ullah et al. at 0.9%.^{17,18} These difference in prevalence underscores the nature of gallbladder carcinoma in specific regions, particularly parts of South Asia, including Pakistan and Northern India, where genetic tendencies, dietary factors, and a high prevalence of gallstone disease may contribute to a greater disease burden.^{19,20} The proportion observed in this study highlights the concept that gallbladder carcinoma, while globally rare, represents a significant and not uncommon pathological finding in cholecystectomy specimens within high-incidence zones.

The present study found that the most common histopathological finding of GBC was adenocarcinoma, while T1a and T1b were the most common stages. Similar findings have been reported by Alam et al. in their study; they identified adenocarcinoma as the most common histopathological finding and reported T1a and T1b in the majority of the GBC patients.

The demographic profile of the cohort, with a mean age of 40.03 ± 11.86 years and a female majority (54.0%) aligns with the characteristics commonly associated with gallstone disease itself. This profile is similar to Sufyan et al. (2023), who reported 81.8% females, and Baseer et al. whose cohort had a mean age of 42 years and was 65% female.^{17,21} When examining the subset of patients with carcinoma, it was observed that the mean age of the patients with GBC was significantly higher than those without the condition, this pattern is supported by Alam et al. who found a significant association reporting that patients with incidental carcinoma were older with a mean age of 49.2 years and 40.2 years in those without cancer ($p=0.002$).¹¹ These findings suggest that increasing age is a notable risk factor for malignancy in chronic cholecystitis and lithiasis. Similarly, it was observed that the mean duration of cholelithiasis symptoms was also higher in the patients with GBC. This finding aligns with the aforementioned study by Alam et al. They argued that a delay in the presentation can lead to GBC, as its symptoms are silent and similar to benign biliary diseases in their early duration.¹¹

A similar trend was noted concerning gender, as we observed 71.4% of carcinoma patients were female compared to 53.3% in the non-carcinoma group, though this difference was not significant ($p=0.34$). This female majority presentation in GBC is reported by Sufyan et al., as they documented 85.71% females with GBC in their study.¹⁷ The hormonal influence on gallstone formation, the role of estrogen in promoting cholesterol saturation in bile, is often cited as a major reason for the higher prevalence of gallstones in women.²²

One of the most important findings of our research was the

significant association between diabetes mellitus and gallbladder carcinoma ($p=0.009$). Among patients with GBC, 57.1% had diabetes compared to only 17.6% in the non-carcinoma group. This finding aligns with a study conducted by Park et al., who documented that hyperglycemia was notably associated with the increased risk of GBC.²³ A systematic review analyzed eight studies, and it documented that diabetes had a direct link with mortality in GBC patients when compared to non-diabetics.²⁴

The mean BMI of the entire cohort was 25.16 ± 1.55 kg/m², placing it at the upper limit of the normal weight category and bordering on overweight. While obesity is a known risk factor for gallstone formation, its direct link to gallbladder cancer shall be assessed in future literature. The absence of a significant association in this study may be due to the uniform BMI distribution across the patients.

It is suggested that histopathological examination of all cholecystectomy specimens should be a practice in all hospitals that manage surgical interventions of gallstones. Furthermore, as is evident from our analysis, diabetes can expose patients to the risk of the development of GBC; we suggest that proper glycemic control strategies must be applied to high-risk diabetic patients before surgery.

The limitations of the study included small sample size, a probable selection bias and the study based in a single centre.

CONCLUSION

In conclusion, the frequency of gall bladder carcinoma among patients undergoing surgery for cholelithiasis in our study was 3.7%, while a statistical association was observed between diabetes and GBC. GBC was more common in elderly patients and those with prolonged duration of symptoms.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this publication

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 - B. Acquisition, Analysis, or Interpretation of Data
 - C. Manuscript writing
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- All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved



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