

A Retrospective Single Centre Study on Histopathological Analysis of Cholecystectomy Specimens in a Pakistani Tertiary Care Centre. Is the Spectrum Changing?

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Abstract

Objective: To study the histopathological spectrum of gallbladder diseases and compare the occurrence of gallbladder carcinoma in relation to age, gender and weight of the patient.

Methodology: This Cross-sectional study, retrospective study was conducted at Histopathology department of HBS General Hospital and Pakistan Institute of Medical Sciences (PIMS). Study was conducted over a period of 6 months from October 2021 to March 2022. Cholecystectomy specimens from either gender irrespective of their age received at the Histopathology Department of HBS General Hospital and Pakistan Institute of Medical Sciences (PIMS), over a period of 6 months were included in the study. The specimens were fixed in 10% formalin for 24 to 48 hours before sectioning. Then every specimen was macroscopically evaluated followed by cutting of the tissue into three representative sections, one each from the fundus, body and neck of the gallbladder along with the lymph nodes if provided. Hematoxylin & eosin staining was done & specimen. The clinical data from pathology reports and slides were retrieved from the archives and were microscopically examined by the histopathologists and the results were recorded.

Results: Mean age of the patients was 54.58 ± 18.04 years. Females were more than the male patients. There were 315 (77.4%) female patients as compared to 92 (22.6%) male patients. The mean weight of the patients was 60.18 ± 5.11 kg. The most common finding was chronic cholecystitis in 303 out of 407 total cases (85%) followed by acute cholecystitis in 27 cases (9.8%). There were 16 cases (3.9%) of incidental carcinoma and three cases (0.7%) of dysplasia.

Conclusion: A spectrum of histopathological diagnosis is observed in cholecystectomy specimen. The inflammatory gallbladder lesions are the most common pathology and the commonest diagnosis is chronic cholecystitis but the doctors cannot rely on the clinical or radiological diagnosis of gallbladder diseases. Histopathological analysis of all gallbladder specimens is necessary for the detection of carcinoma as the frequency of gallbladder cancer appears to be on the rise in our population which is significantly more common in females.

Keywords: Carcinoma, Gallbladder, Cholecystectomy specimens

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Introduction

Gall bladder diseases are frequently seen in clinical practice. Patients may be asymptomatic or manifest symptoms including acute biliary colic, fever, and jaundice. The most common malignant tumor of the biliary system and the sixth most common cancer of the

gastrointestinal tract are gallbladder cancers. Globally, the incidence of gall bladder carcinoma varies significantly by area, and this variation is correlated with the prevalence of cholelithiasis.¹

Globally gallstones affect 10% to 15% of the adult population and constitute a major health problem. The healthcare burden of gallbladder disease has steadily

increased by 20% in the last three decades.² The prevalence of cholelithiasis in Asian population is 3-4%. In China it is reported as 3%, 6% in Northern India and 5% in Taiwan. Data from Pakistan showed that in the Southern Sindh region of Pakistan, the prevalence rate is 4 percent among men and 14.2 percent among women. This study conducted in Hyderabad, Sindh showed the frequency of gallbladder carcinoma in cholecystectomy specimens to be 4%.³ Another local study from Armed force Institute of Pathology (AFIP), Rawalpindi showed a frequency of gallbladder cancer as 1.55% in 10,549 cholecystectomy specimens.⁴

Gallbladder carcinoma also presents with symptoms of chronic cholecystitis. Gallbladder carcinoma is a common malignancy in the extra-hepatic biliary tract, with females being the most common patients. The disease has a specific ethnic group predisposition, with more cases reported in native Americans, Bolivians, and northern Indian populations.² The most common age group involved is 50-70 years old. Risk factors for gallbladder carcinoma include gallstones, cholecysto-enteric fistula, porcelain gallbladder, ulcerative colitis, adeno-myomatosis, polyposis coli, gartner syndrome, and anomalous connections between the common bile duct and pancreatic duct. Histopathological evaluation of every cholecystectomy specimen is recommended to diagnose gallbladder carcinoma, which can be treatable in early stages but has a poor prognosis when advanced disease is present.⁵

The rationale of this investigation was to find out the frequency of different gallbladder diseases and to find out the incidental finding of gallbladder carcinoma when it is not clinically suspected. This stresses the need for histopathological examination of all routine cholecystectomy specimens so as to guide treatment planning.

Methodology

This Cross-sectional study, retrospective study was conducted at Histopathology department of HBS General Hospital and Pakistan Institute of Medical Sciences (PIMS). Study was conducted over a period of 6 months from October 2021 to March 2022. Nonprobability Consecutive Sampling technique was used. The calculated sample size is 407 for a population proportion of 3.64%⁶ for gallbladder carcinoma, keeping the confidence interval at 95% & margin of error at 1.82%. Sample size was calculated by the WHO calculator.

Inclusion Criteria:

1. All elective cholecystectomy specimens of either gender.

2. All age groups undergoing cholecystectomy.

Exclusion Criteria:

1. Diagnosed as tumour on Ultrasound or CT scan.
2. Grossly autolyzed tissue specimen which could not be processed technically.

Cholecystectomy specimens in 10% buffered formaldehyde were received in the histopathology department. Hematoxylin & eosin staining was done after routine processing. Cases with complete clinical data from pathology reports; mentioning age, gender and benign ultrasound diagnosis were included in the study. Slides were retrieved from the archives and were microscopically examined by the histopathologists and the results were recorded.

The data was analyzed with the help of SPSS version 21. The descriptive statistics like mean & standard deviation was calculated for age. For categorical variables like gender & carcinoma of the gallbladder frequency was calculated. The data was stratified according to age, gender & weight. Post stratification chi-square test was applied to investigate the effect of these factors with various independent variables. Results are represented as tables and graphs. P value < 0.05 was taken as significant.

Results

There were 407 cases of cholecystectomy included in the study. Females were more than the male patients. There were 315 (77.4%) female patients as compared to 92 (22.6%) male patients. The mean age of the patients included in the study was 54.58 ±18.04 years, with 62.4% of them being over 50 year. The mean weight of the patients was 60.18 ±5.11 kg, with 56.8% having a weight below 60 kg. There were 274 (67.5%) cases of laparoscopic cholecystectomy, 40 cases (10%) open cholecystectomies and in 91 cases (22.5%) laparoscopic procedure was changed to open cholecystectomy.

Histopathological examination of gall bladder specimens showed a variety of microscopic diagnosis as shown in Figure 1 and microscopic features of some cases are shown in figures 2, 3, 4.

Table I show the distribution of gallbladder carcinoma in relation to age, gender and weight of the patient. A significant p-value > 0.05 was identified when gender was compared with the occurrence of gallbladder cancer. All cases of cancer occurred in females and none in the males.

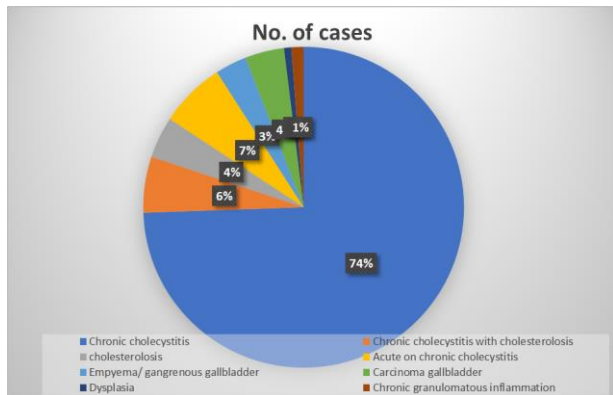


Figure 1. Frequency of different histopathological diagnosis in 407 cholecystectomy specimen. (n=407)

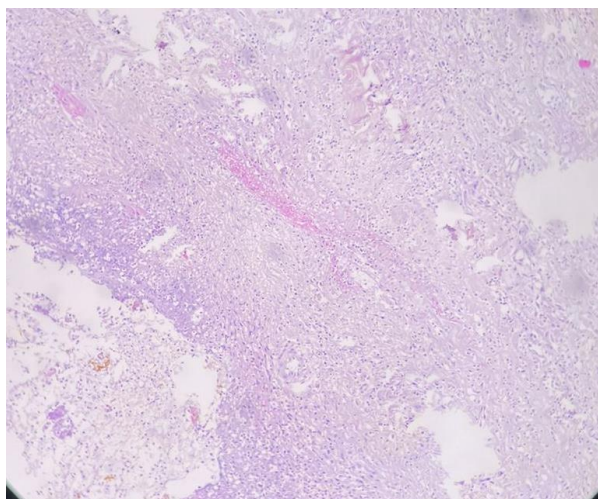


Figure 2. H&E (100x) Acute on chronic cholecystitis showing neutrophils with lymphocytes and plasma cells throughout the wall of gallbladder with mucosal necrosis

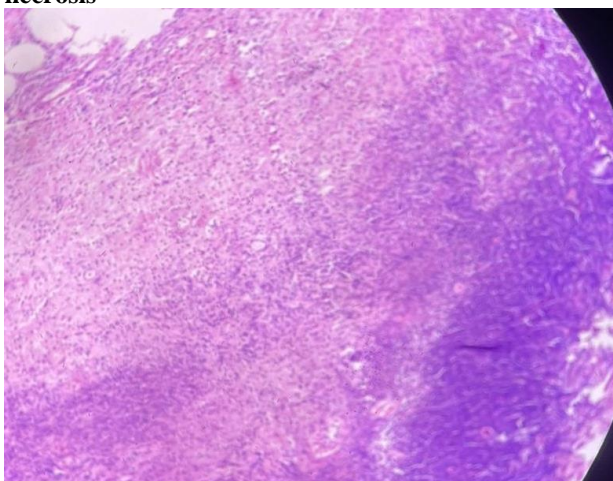


Figure 3. H&E (100x) Empyema gallbladder showing sheets of neutrophils with necrosis in the wall and sloughing of mucosa. This case was associated with pus in the gallbladder lumen.

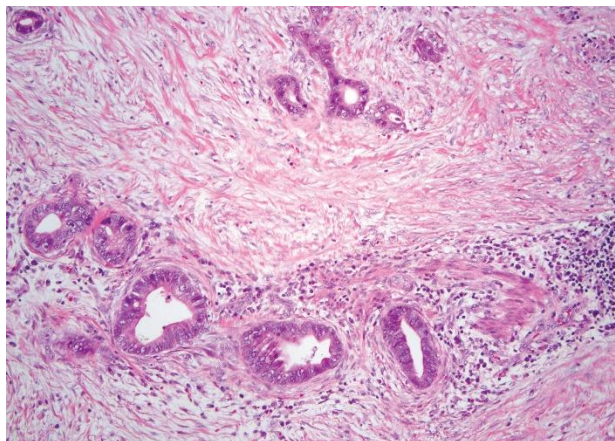


Figure 4. H&E (100x) Carcinoma gallbladder showing glands with open lumina and subtle atypia associated with desmoplasia and invasion.

Table I: Comparison of gall bladder carcinoma with the age, gender, weight of the patient (n=407)

Age (in years)	Carcinoma of gall bladder			P-value
	Present	Absent	Total	
≤50	5 (3.3)	148 (96.7)	153 (100)	0.593
>50	11 (4.3)	243 (95.7)	254 (100)	
Total	16 (3.9)	391 (96.1)	407 (100)	
Carcinoma of gall bladder (Gender)				
Male	0 (0)	92 (100)	92 (100)	0.027
Female	16 (5.1)	299 (94.9)	315 (100)	
Total	16 (3.9)	391 (96.1)	407 (100)	
Carcinoma of gall bladder (weight)				
≤60	8 (3.5)	223 (96.5)	231 (100)	0.578
>60	8 (4.5)	168 (95.5)	176 (100)	
Total	16 (3.9)	391 (96.1)	407 (100)	

Discussion

One of the most commonly encountered cases in general surgery are the diseases of the gall bladder.⁵ The most frequent of these illnesses is cholecystitis, which is mostly caused by cholelithiasis, or the formation of gallstones.⁶ Age, female gender, metabolic syndrome, and obesity are all risk factors for the diseases of the gallbladder.⁷

In our study females were 315 and made up 77.4% of the examined cases. Several studies have documented this female predominance. No studies have been reported to our knowledge to show male predominance.⁸

The mean age of the cholecystitis patients in the current study is 54.58 ±18.04 years, ranging from 28 to 69 years. This is comparable to that reported by Gavriilidis P et al. in 2022, in which the median age was 64 years and the affected age range was 33 to 87 years.⁹

In 74.4% (n=303) of the patients, the diagnosis was chronic cholecystitis, whereas in the 6.6% (n=27) cases it was acute cholecystitis.⁵ Park Se et al reports acute

cholecystitis and acute on chronic cholecystitis in 14-30% of cholecystectomy specimens.¹⁰

Postoperative histopathological evaluation of the excised GB specimens reveals a vast spectrum of underlying pathologies. With the changing lifestyles and other environmental factors this spectrum seems to be evolving. Almas T et al in 2020 have published a study at Maroof hospital, Islamabad. In their study the most common diagnosis was chronic cholecystitis (78.7%) while acute and acute on chronic cholecystitis was 18.7% cases. This is comparable to our study but they have reported 32.8% cases of cholesterols which is much higher than that of our study (10.7% cases). The carcinoma was reported in 0.2% cases in their study which is much less than that of our study (3.9% cases).¹¹ In international and local studies chronic cholecystitis is the most common pathology of gallbladder and every type of gallbladder disease is more common in middle age females.^{9,10,11} The number of cases of acute on chronic cholecystitis is also comparable with that reported in literature. But our study shows less number of cases of cholestrololosis than most other studies.^{11, 12, 13}

Due to significant pathology that may be present even in a specimen that seems to be normal, the Royal College of Pathologists advises sending all removed gallbladder specimens for histopathology. The incidence of gallbladder cancer is low but it carries high mortality and morbidity.¹⁴ This dreary prognosis of the gall bladder carcinoma is caused by the great biological aggressiveness of this carcinoma, the lack of accurate biomarkers, the scarcity of screening methods, as well as the late appearance of symptoms, even at an advanced stage. Also, the gallbladder cancer may not always produce a mass and is often not identified on routine ultrasound. Patient may also have only symptoms of cholecystitis.¹⁵ The gallbladder cancer incidence in Asia's is high (8.1 per 100 000) compared to that in the western nations (0.7 per 100 000). The variations in genetic predisposition, environmental exposure to certain chemicals, and regional intrinsic risk of carcinogenic agents are likely to be responsible for these geographic variances in tumor occurrence.¹⁶

Gall bladder carcinoma is largely asymptomatic until it metastasizes or reaches a late stage.¹⁷ In the current study, sixteen cases (3.9%) gall bladder carcinoma were unintentionally found over the course of study. Several other studies have reported incidental carcinomas in gallbladder samples that are routinely evaluated. Alabi A et al. in 2021 reported incidental gallbladder cancer as a rare entity, with an incidence ranging between 0.19 and 5.5% of all the cholecystectomies.¹⁸ Pyo JS has published a meta-analysis of incidental gallbladder carcinoma in

2020 and has reported incidence rate as 0.6%. Their findings were based on data from 51 related studies.¹⁹

The distribution of gallbladder carcinoma in relation to age, gender and weight of the patient was also done in the present study. It was noted that all cases of cancer occurred in females and none in the males ($p=0.029$). Nascimento JHFD et al has reported that all types of gallbladder pathologies are significantly more common in females.²⁰ Halaseh SA et al reports incidental gallbladder carcinoma to be present in 0.3 to 3% of routine cholecystectomies and the cancer risk is 2-6 times higher in females than males. The T1a stage of cancer carries a significantly better prognosis than stage T1b and T2. They also stress the need of histopathological analysis of all cholecystectomy specimen as clinical and ultrasound diagnosis may not be totally reliable.²¹

A study from Lahore by Iqbal S. et al in 2022 showed that out of 214 simple or laparoscopic cholecystectomy specimens, there were three (1.4%) cases of incidental gallbladder carcinoma exclusively found in females.²²

A large-scale study from Rawalpindi Armed Force Institute of Pathology in 2023 showed the frequency of incidental gallbladder to be 0.9% in 995 cholecystectomy cases. The cancer was mostly found in females and the age group involved was 51 to 60 years. They also stressed the need of histological examination of all cholecystectomy cases.²³

The local studies report the frequency of gallbladder cancer as 1.4%, 0.9%, 1.5% with high incidence in females. These studies were conducted in Punjab.^{4,19,20} Gallbladder cancer in a study from Sindh is reported as 4%.³ The present study is conducted in a tertiary care hospital of Islamabad suburbs with patients from Punjab and Khayber Pakhtunkhuwah. The frequency of incidental gallbladder cancer was 3.9% which is higher than that reported in other studies from Punjab. This points out an increasing trend of gallbladder cancer in our population and stresses the need for histopathological analysis of all cholecystectomy specimen.

Conclusion

A spectrum of histopathological diagnosis is observed in cholecystectomy specimen. The inflammatory gallbladder lesions are the most common pathology and the commonest diagnosis is chronic cholecystitis but the doctors cannot rely on the clinical or radiological diagnosis of gallbladder diseases. Histopathological analysis of all gallbladder specimens is necessary for the detection of carcinoma as the frequency of gallbladder

cancer appears to be on the rise in our population which is significantly more common in females.

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Authors Contribution:

- 1,6 Substantial contributions to the conception or design of the work;
- 2,3,4 The acquisition, analysis, or interpretation of data for the work;
- 1,6 Final approval of the version to be published;
- 1,5,6 Drafting the work or revising it critically for important intellectual content.