

# Clinicopathological Evaluation of Gallbladder Lesions in Cholecystectomy Specimens with Special Emphasis on Incidentally Detected Cases of Gallbladder Carcinoma: An Immunohistochemical Study of Cytokeratin 7 and Cytokeratin 20

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## Abstract

**Background and objective:** Cholecystectomy specimens exhibit a wide clinicopathological spectrum, ranging from common non-neoplastic diseases to rare neoplastic lesions. Histopathological examination remains the gold standard for definitive diagnosis. Gallbladder cancers (GBCs) are rare, accounting for 0.5% to 1.09% of all gallbladder lesions. These cancers are either clinically suspected or incidentally diagnosed following cholecystectomy. **Materials and Methods:** This hospital-based cross-sectional study included all cases diagnosed clinically and radiologically as cholecystitis and subsequently subjected to cholecystectomy. Histopathological diagnosis of gallbladder lesions, age and sex distribution across different gallbladder pathologies, association with gallstones, pathological pT staging of malignant cases, and CK7 and CK20 immunohistochemical findings in malignant cases were observed in this study. **Results:** A total of 340 gallbladder specimens were examined histopathologically, revealing 12 cases of gallbladder carcinoma. The most common histopathological diagnosis was chronic cholecystitis (79.4%), followed by chronic cholecystitis with cholesterosis (7.6%) and adenocarcinoma (3.5%). The most common age group for gallbladder lesions was the fourth decade (26.2%). The age range was 9-85 years, with a mean age of 39.4 years. Overall, females (83%) were more commonly affected than males (17%), with a male:female ratio of 1:4.96. Gallstones were present in 89.1% of all cases, including 83.3% of malignant cases. Incidentally detected gallbladder carcinoma represented 1.17% of the cases, with adenocarcinoma NOS being the most common histopathological type. Pathological pT staging was limited to pT1 and pT2, indicating early-stage disease. CK7 positivity was observed in 91.6% of cases, while CK20 positivity was found in 16.7% of cases. Both CK7 and CK20 were positive in 16.7% of cases, while both were negative in one case (8.33%). **Conclusion:** While chronic cholecystitis remains the most common histopathological diagnosis in gallbladder specimens, the possibility of incidental malignancy should be ruled out by mandatory routine histopathological examination of all cholecystectomy specimens.

**Keywords:** Histopathology- Cholecystitis- Gallbladder carcinoma- Immunohistochemistry- CK7- CK20

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## Introduction

Gallbladder is the organ where bile is stored and concentrated, which helps in digestion of fat [1]. Cholecystectomy is one of the most frequently performed abdominal operation and the gallstones are one of the major causes of morbidity and mortality all over

the world affecting 10% of adult population [2]. In India, gallstone disease is seven times more common in the north as compared to the south. Northern and Northeastern states of Uttar Pradesh, Bihar, West Bengal, Orissa, and Assam show the high prevalence of the gall bladder

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disease. This significant difference was attributed to the environmental factors, diet and lifestyle [3,4].

Cholelithiasis is one of the major gastrointestinal disorders, which is formed due to metabolic problems of hepatobiliary system. It is a major cause of morbidity and mortality throughout the world [5]. The estimated prevalence of gall stone disease in India is 2-29% with 7 times more common in North India than in South India [5,6]. Cholelithiasis cause various changes in gallbladder mucosa ranging from acute cholecystitis, chronic cholecystitis, polyp, empyema, eosinophilic cholecystitis, metaplasia, hyperplasia, dysplasia to carcinoma [7].

Gall Bladder Cancers (GBCs) are rare and account for 0.5% to 1.09% of all gall bladder lesions. It is either clinically suspected or incidentally diagnosed following cholecystectomy for gall stone disease [8].

Cytokeratins are well-described intermediate filament proteins of both normal epithelia and epithelial tumors. Antibodies to several different subtypes of cytokeratin have been available, including cytokeratin 7 (CK7) and cytokeratin 20 (CK20). In normal tissues, CK7 is typically found in simple epithelia from the gastrointestinal tract (including the gallbladder, hepatic ducts and pancreatic ducts), female genital tract (the endometrium and fallopian tube), breast, urinary tract (bladder), and respiratory tract (lung). In contrast, CK20 is found in more complex epithelia from the gastrointestinal tract (such as the gastric and intestinal mucosa), genitourinary tract (urothelium), squamous epithelia from any site, and Merkel cells. Because these cytokeratins usually retain their tissue specificity in their neoplastic counterparts, coordinate expression of these 2 cytokeratins has recently been proposed to help identify the site of origin of various metastatic carcinomas [9].

Studies on various carcinomas suggest that the combined use of Cytokeratin 7 and Cytokeratin 20 may provide helpful information for the discrimination of the origin of metastatic tumours of unknown primary location [10-12]. Again, comparison of the expression pattern of Cytokeratin 7 and Cytokeratin 20 in cases of chronic cholecystitis with lithiasis and in gall bladder carcinoma may highlight possible alterations linking inflammatory and metaplastic changes and carcinoma [13-16].

#### *Aims and Objectives*

The aims & objectives of the present study were -

- a) To study the histopathological features of different gall bladder lesion with special reference to malignancy.
- b) To investigate the co-ordinated expression of Cytokeratin 7 and Cytokeratin 20 in histologically confirmed gall bladder carcinoma.

#### **Materials and Methods**

It was a Hospital based cross-sectional Study and included 340 cholecystectomy cases received at the Department of Pathology; Fakhruddin Ali Ahmed Medical College and Hospital during the period of 1 year. Histopathological examination of the gallbladder specimens was done following standard protocols.

The specimens those fulfilled the inclusion criteria were included in the study and rest were excluded.

#### *Inclusion criteria*

- Formalin fixed cholecystectomy specimens excised for clinically or radiologically diagnosed gall bladder diseases with or without gall stones, polyp or porcelain gallbladder and received in Pathology Department.

#### *Exclusion criteria*

- Specimens received in a poorly preserved or autolysed state and improperly labelled were excluded from the study.

The study was conducted after getting permitted by the Institutional Ethical Committee under the IEC no. 10552. All the relevant clinical findings were noted and properly formalin fixed specimens were grossed with three sections each from fundus, body and neck region of the gall bladder. Extra sections were also taken from the tumour or any thickened area of wall in clinically suspicious cases of gallbladder cancer.

Sections were processed and were further subjected to Haematoxylin and Eosin (H&E) stain. H&E stain was done using Harris haematoxyline with a regressive staining method. Sections were examined microscopically and histomorphological evaluation for a wide spectrum of gall bladder lesions was done. The neoplastic lesions were further classified according to the latest

2019 WHO Classification of Digestive System Tumours that includes BillIN, ICPN and Carcinoma [17]. Immunohistochemical examination of malignant cases was done using CK7 & CK20 IHC markers following standard protocols.

#### **Results**

Detailed analysis of 340 cholecystectomy specimens was performed under parameters including age, sex, presence of gall stones, histopathological diagnosis, basic pathology of cases, classification of malignant cases with Pathological pT staging, presence of Perineural invasion (PNI) and Lymphovascular invasion (LVI) and CK7 & CK20 immunohistochemical staining status of malignant cases.

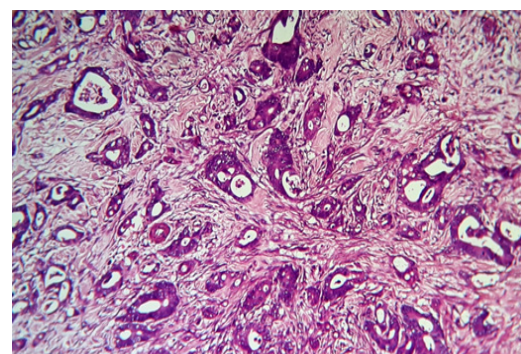


Figure 1. Microphotograph of Moderately Differentiated Adenocarcinoma of Gallbladder Showing Malignant Glands Infiltrating the Perimuscular Connective Tissue (40X)

Table 1. Showing Distribution of Cholecystectomy Specimens According to Histopathological Diagnosis

Serial No	Histopathological diagnosis	No of cases	Percentage %
1	Acute Cholecystitis	4	1.2
2	Acute on Chronic Cholecystitis	2	0.6
3	Chronic cholecystitis	270	79.4
4	Eosinophilic Cholecystitis	1	0.3
5	Xanthogranulomatous Cholecystitis	5	1.5
6	Chronic Cholecystitis with foreign body giant cell reaction	3	0.9
7	Chronic Cholecystitis with epithelial hyperplasia	4	1.2
8	Chronic Cholecystitis with adenomatous hyperplasia	4	1.2
9	Chronic Cholecystitis with antral metaplasia	2	0.6
10	Chronic Cholecystitis with epithelial dysplasia	7	2
11	Chronic Cholecystitis with cholesterosis	26	7.6
12	Adenocarcinoma	12	3.5
	Total	340	100

Table 2. Showing WHO Classification of the Malignant Gallbladder Cases

WHO Type	ICD-O code	No of cases
Adenocarcinoma NOS	8140/3	8
Intracystic papillary neoplasm with associated invasive carcinoma	8503/3	3
Mucinous adenocarcinoma	8480/3	1
Total		12

#### A. Histopathological Distribution of the Cases

There were 12 different types of histopathological diagnosis and the most common histopathological diagnosis was chronic cholecystitis (79.4%) followed by chronic cholecystitis with cholesterosis (7.6%) and adenocarcinoma (3.5%). Incidentally detected gallbladder carcinoma (IGBC) is 1.17%. Details were shown in the Table 1.

Among the 340 cases, 311 cases (91.4%) were inflammatory lesion, 08 cases (2.3%) cases were hyperplasia, 02 cases (0.6%) were metaplasia, 07 cases (2%) cases were dysplasia and 12 cases (3.5%) were carcinoma.

#### B. Age Distribution

Age distribution in the present study was from 09

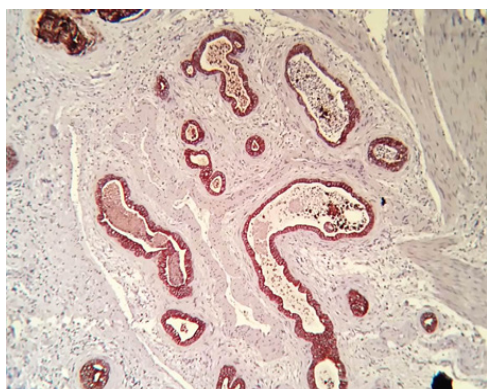


Figure 2. Microphotograph of Adenocarcinoma of Gallbladder Showing IHC Marker - CK7 positivity (10X)

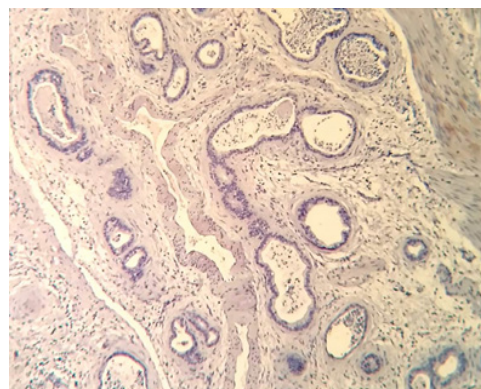


Figure 3. Microphotograph of Above Adenocarcinoma of Gallbladder Showing IHC Marker – CK20 Negative (10X)

years to 85 years with a mean age of 39.4 years. Again; age distribution in benign lesions of gallbladder cases was from 09 years to 85 years with a mean age of 38.9 years. Overall, the most common age group was 4<sup>th</sup> decade (26.2%) followed by 3<sup>rd</sup> decade (24.4%) and 5<sup>th</sup> decade (23.5%).

#### C. Sex Distribution

Overall females (83%) were more commonly affected than males (17%) and male: female ratio was 1:4.96. In cholesterosis cases; females (73%) were more commonly affected than male (27%). Again; in both benign and malignant lesions of gallbladder cases; females (83%) were more commonly affected than male (17%). All incidentally detected gallbladder carcinoma (IGBC) cases were observed in females (100%).



Table 3. Showing Pathological pT Staging of the Malignant Gallbladder Cases

Pathological staging	No of malignant cases
pT1	6
· pT1a	· 01
· pT1b	· 05
pT2	5
· pT2a	· 04
· pT2b	· 01
pT3	1
pT4	0
Total	12

#### D. Association of gallstones in the cholecystectomy cases

Out of total 340 gallbladder specimens; gallstones were found in 303 cases i.e. 89%. Again; out of 303 cases; number of male cases were 52 and females were 251 i.e. 82.8%. Out of 12 malignant cases; gallstones were associated with 10 cases i.e. 83%. Gallstones were present in all 07 gallbladder associated with dysplasia (100%).

#### E. WHO classification of the malignant cases

There were total 12 number of malignant cases and they were categorized in Table 2.

#### F. Differentiation of adenocarcinoma NOS cases

There were total 08 number of adenocarcinoma NOS cases and they were classified against their differentiation as:- 06 cases as well differentiated adenocarcinoma and 02 cases as moderately differentiated.

#### G. Pathological pT staging of the malignant cases

According to their pathological pT staging; the malignant cases were categorized in Table 3.

#### H. Perineural invasion (PNI) & Lymphovascular invasion (LVI) status in malignant case

Out of total 12 malignant cases; PNI was observed in 02 cases and both are diagnosed as moderately differentiated adenocarcinoma and pathological pT staging of the cases were pT2a & pT2b. LVI was not seen in any malignant cases.

#### I. Incidentally detected gallbladder carcinoma cases (IGBC)

In this study; 04 cases were detected incidentally with incidence rate of 1.17% (04/340) and all cases were female. Age distribution was 25 years to 60 years with a mean age of 46.25 years. The gallbladder wall thickness was  $\geq 8$  mm in all four cases; which may be one gross finding for gallbladder cancer. Out of total 04 cases; three cases were diagnosed as adenocarcinoma NOS and one case was diagnosed as Intracystic papillary neoplasm with associated invasive carcinoma. Regarding differentiation; 02 cases were diagnosed as well differentiated adenocarcinoma and 01 case as moderately differentiated adenocarcinoma (Figure 1). Pathological pT

staging of IGBC cases: 02 cases – pT1 and 02 cases – pT2. Details were shown in Table 4.

#### J. Immunohistochemistry for CK7 & CK20 findings

Out of 12 GBC cases; CK7 was positive in 91.6% (11/12) cases and CK20 was positive in 16.7% (2/12) cases. CK20 positive cases were diagnosed as adenocarcinoma NOS with pathological pT staging of pT1. Total number of CK7 & CK20 positive cases were 02, CK7 positive (Figure 2) & CK20 negative (Figure 3) cases were 09 and both negative cases was 01. Both CK7 & CK20 negative case was diagnosed as mucinous adenocarcinoma (Figure 4 and 5) with pathological staging pT2. Details were shown in Table 5.

## Discussion

In the present study; the most common histopathological diagnosis was chronic cholecystitis (79.4%) which is correlated with other studies like Devi B et al [18] (82%), Mondal B et al [19] (79.8%).

The mean age group of the cholecystectomy cases was 39.4 years which is comparable to Gupta K et al [20] (41.69 years). 4<sup>th</sup> decade was the commonest age group in the present study; which is similar in the studies by Gupta K et al [20] and Islam Mj et al [21]. The age ranged from 25 years to 65 years in malignant gallbladder cases; which is comparable to Shah B et al [22], Bhattacharjee

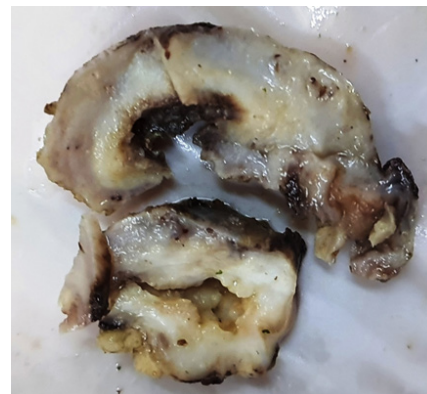


Figure 4. Showing Specimen of Gallbladder Having Thickened Gallbladder Wall (case of mucinous adenocarcinoma of gallbladder).

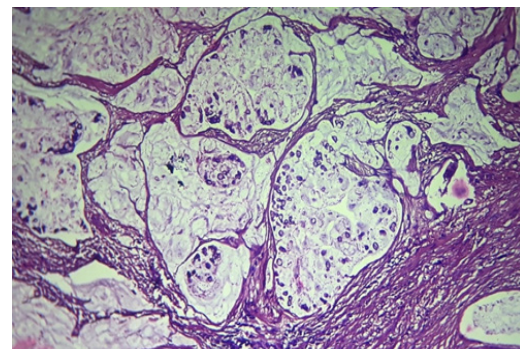


Figure 5. Microphotograph of Mucinous Adenocarcinoma of Gallbladder Showing Pools of Extracellular Mucin (40X)

Table 4. Showing the Detailed Parameters of the Incidentally Detected Gallbladder Carcinoma Cases

Serial No	Age Yrs	Sex	GB wall thickness in millimeter	Histopathological type	Pathological pT staging
1	45	F	08 mm	Well differentiated adenocarcinoma	pT1b
2	55	F	08 mm	Intracystic papillary neoplasm with associated invasive carcinoma	pT1a
3	25	F	15 mm	Moderately differentiated adenocarcinoma	pT2b
4	60	F	08 mm	Well differentiated adenocarcinoma	pT2a

Table 5. Showing the Co-ordinate Expression Status of CK7 and CK20 in Gall Bladder Carcinoma Cases

IHC markers	No of positive cases	Percentage (%)
CK7+/CK20+	02/12	16.70
CK7+/CK20-	09/12	75
CK7-/CK20+	00/12	0
CK7-/CK20-	01/12	8.33

K P et al [23]. In the present study; the upper limit of age is lower than most of the other studies like Dutta U et al [24], Harikleia K et al [25], Hussain N H et al [26], Geramizadeh B et al [27] etc. The mean age in malignant cases was 49.8 years; which is comparable to other studies like Dutta U et al [24], Hussain N H et al [26], Shah B et al [22], Bhattacharjee K P et al [23].

In the present study; the male:female ratio among the cholecystectomy cases was 1:4.96; which is comparable to the studies - Mondal B et al [19] where male:female ratio was 1:4.2, Kumbhakar D et al [28] (1:4.71), Tiwari A et al [29] (1:4) and Gupta K et al [20] (1:3.9). All incidentally detected gallbladder carcinoma cases were found in females. Gall bladder disease is more common in females attributable to female sex hormones and sedentary lifestyle as the risk factors.

Gall stones cause obstruction that leads to development of chronic cholecystitis which, in turn, chronically predisposes to carcinoma of the gallbladder. Around 83.3% cases of gallbladder carcinoma are associated with gall stones in the present study; which is comparable to Kumar H et al [30] (80%) and Tiwari A et al [29] (80%). The incidence of incidentally detected gallbladder carcinoma was 1.17% which is comparable to the studies like Tiwari A et al [29] (1.25%), Yadav R et al [31] (1.26%). This observation is higher than the other studies like Jetley S et al [32] (0.96%) & Kumbhakar D et al [28] (0.75%).

In the present study, the most common type of carcinoma was adenocarcinoma NOS (66.7%) followed by Intracystic papillary neoplasm with associated invasive carcinoma and this observation is comparable to Giang T H et al [33] (60%), Hussain N H et al [26] (57.6%), Shah B et al [22] (71.4%) and Manuela S et al [34] (65.6%). There were 06 cases of well differentiated adenocarcinoma (75%) followed by 02 cases of moderately differentiated adenocarcinoma and 00 cases of poorly differentiated adenocarcinoma. This observation is comparable to other studies like Dutta U et al [24] (71.4% - Well differentiated adenocarcinoma) and Manuela S et al [34] (52.3% - Well differentiated adenocarcinoma). Perineural

invasion (PNI) is noted in 02 cases and no case had shown Lymphovascular invasion (LVI). Both are taken as prognostic parameter for gallbladder carcinoma.

For pathological staging, there were 06 cases in stage pT1 (50%) followed by 05 cases in stage pT2 and one case in stage pT3. This observation is comparable to Siddiqui et al [35] (50% - pT1), Geramizadeh B et al [27] (55.5% - pT1) and Servet K et al [36] (61% - pT1).

Regarding immunohistochemistry findings, out of total 12 cases; 11 cases (91.6%) had shown CK7 positivity; which is higher than other studies like Duval J V. et al [9] (82%), Harikleia K et al [25] (69.05%) and Dursun N et al [37] (57%). Again; 02 cases had shown CK20 positivity (02/12, 16.7%) which is lower than other studies like Duval J V. et al [9] (27%), Harikleia K et al [25] (28.57%) and Dursun N et al [37] (27%).

In conclusion, although the most common gall bladder histopathology diagnosis is chronic cholecystitis, the possibility of any incidental malignancy needs to be ruled out by mandatory routine histopathological examination of all cholecystectomy specimens. Secondly; most of the gallbladder carcinoma cases express CK7 by immunohistochemical examination.

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## Conflict of Interest

The authors declare no conflict of interest.

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