



## Original Research Article

# Histopathological spectrum of gall Bladder diseases in cholecystectomy specimens at a Rural tertiary hospital of Purvanchal in North India-Does it differ from South India?

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## ABSTRACT

**Introduction:** Gall Bladder (GB) diseases are one of the most common digestive system diseases, the prevalence of which is variable within India and ranges from 2-29%. Cholelithiasis (gallstones) is the commonest lesion and accounts for more than 95% of GB diseases. Gall bladder carcinoma showed regional differences in India with prevalence ranging from 0.52% in southern India and as high as 9.6% in northern India.

**Aims and Objectives:** 1) To identify the morphological spectrum of diseases affecting the gall bladder. 2) To identify the most common histopathological lesion and its correlation with clinical and demographic data of the patient. 3) To identify the frequency of Gall Bladder Carcinoma (GBC) and its correlation with clinical and demographic data of the patient and pre-existing lesions if any.

**Materials and Methods:** This study was non-participatory descriptive study carried out retrospectively for a period of one year in the Dept. of Pathology, HIMS, from August 2018 to July 2019. All the specimens received in the study period were included in the study. The gross and microscopic findings on H & E slide were included in the study. The descriptive statistics were applied to analysed data.

**Results:** Total 86 cholecystectomy specimens were received in the Department of Pathology during one year study period. Non-neoplastic lesions (97.67%) of gall bladder outnumbered the neoplastic lesions (2.33%). Most common histopathological lesion was chronic cholecystitis (95.34%). Varied histopathological spectrum was seen comprising of chronic calculous cholecystitis (73.26%), chronic acalculous cholecystitis (13.95%), chronic cholecystitis with cholesterosis (13.95%), Xanthogranulomatous cholecystitis (2.33%), Acute calculous cholecystitis (1.16%), acute gangrenous GB (1.16%), GBC (2.33%). In non-neoplastic lesions, female predilection (70.24%) was seen over male (29.76%) accounting for F:M ratio of 2.4:1, two cases of GBC exclusively seen in females associated with gall stones. Non-neoplastic lesions were common between the age group of 26-50 years accounting for 67.45% whereas neoplastic lesions were common in the age group of >60 years.

**Conclusion:** Chronic cholecystitis with pigmented gall stone was the commonest GB disease in the present study. The study also revealed that females have increased preponderance for the development of all the gall bladder diseases including malignancy. Non-neoplastic lesions were more common till 5<sup>th</sup> decade in the present study whereas females in the 5<sup>th</sup> and 6<sup>th</sup> decade of life were prone for malignancy of gall bladder which was associated with gall stones.

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## 1. Introduction

Gall Bladder (GB) diseases are one of the most common digestive system diseases next to Gastro-esophageal Reflux

Disease (GERD).<sup>1</sup> The prevalence of gall bladder diseases is variable within India and ranges from 2-29%.<sup>2</sup> Non-neoplastic (inflammatory) lesions are far more common than neoplastic lesions. Cholelithiasis (gallstones) is the commonest lesion and accounts for more than 95% of GB

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diseases.<sup>1</sup> The prevalence of gall stones is about 20% in the population of developing countries.<sup>3</sup> The most common types of GB stones found are Cholesterol and pigmented stones. The risk factors in the development of cholesterol stones are increasing age, female gender, ethnicity, family history and genetics which are non-modifiable whereas modifiable risk factors which can contribute are obesity, sedentary life-style, metabolic syndromes, sudden weight loss, Oral Contraceptive Use etc.<sup>2</sup> Risk factors for pigmented gall stones due to biliary sludge include pregnancy, drugs, total parenteral nutrition or fasting, cirrhosis, chronic hemolysis and ileal Crohn's disease.<sup>2</sup> The histopathological spectrum seen in non-neoplastic GB diseases includes chronic cholecystitis, cholesterosis, xanthogranulomatous cholecystitis, hyperplastic and metaplastic lesions and most of these lesions are seen accompanying the cholelithiasis. In neoplastic lesions, Gall Bladder Carcinoma (GBC) is said to be a rare disease in India and showed regional differences within India.<sup>4</sup> The cancer data of studies from northern India (Ganges belt) showed GBC accounted for 9.6% of all cancers in females and was the third leading site of cancer whereas studies from eastern India recorded gallbladder cancer between 5.8% to 6.0% of all cancers.<sup>5,6</sup> In contrast, studies from southern India noted low prevalence of GBC accounting for 0.52% amongst men and 0.66% amongst women.<sup>7</sup> Previous Studies showed that almost 80% of individuals with GBC in north India have gallstones.<sup>8</sup>

The present hospital based study was undertaken to evaluate histomorphological spectrum of lesions associated with GB diseases and to correlate with clinical and demographic data of the patient catering the rural population of Purva nchal which belongs to Eastern Uttar Pradesh of North India.

## 2. Aims and Objectives

1. To identify the morphological spectrum of diseases affecting the gall bladder.
2. To identify the most common histopathological lesion and its correlation with clinical and demographic data of the patient.
3. To identify the frequency of Gall Bladder Carcinoma and its correlation with clinical and demographic data of the patient and pre-existing lesions if any.

## 3. Materials and Methods

This study was non-participatory observational study. After obtaining Institute Human ethical committee clearance, this retrospective descriptive study was carried out in the Department of Pathology. The study period was one year i.e from 1/8/2018 to 31/7/2019.

### 3.1. Inclusion criteria

The study included all the cholecystectomy specimens received in the Department of Pathology during the study period of one year.

### 3.2. Exclusion criteria

Nil.

### 3.3. Methodology

The clinical and Demographic data was obtained from Histopathological Requisition forms and MRD of the hospital. Specimens of cholecystectomy were received in 10% buffered formalin. Representative sections were taken and subjected to routine paraffin processing. Haematoxylin & Eosin[H & E] stained slides were prepared and reviewed.

### 3.4. Statistical test

For Simple numerical data, percentage was calculated, and data was depicted in Tabular format, bar diagram, and pie charts to compare and contrast different data. Advanced statistical test was used for data following normal distribution and to compare significant differences in various variables; p value <0.05 was considered significant.

## 4. Results

A total 86 cholecystectomy specimens were received in the Department of Pathology during one year study period i.e from 1/8/2018 to 31/7/2019.

Non-neoplastic lesions of Gall Bladder outnumbered the Neoplastic lesions with former accounting for 97.67% and later 2.33% of the cases. Gall stones disease was the commonest and seen in 67(77.9%) out of 86 cholecystectomy specimens

**Table 1:** Frequency of various Histopathological Lesions seen in cholecystectomy specimen (n=86)

S. No	Histopathological Lesions	Percentage % (n)
1	Chronic Calculous Cholecystitis	73.26% (63)
2	Chronic Acalculous Cholecystitis	13.95%(12)
3	Chronic Cholecystitis with Cholesterosis	5.81%(5)
4	Xanthogranulomatous Cholecystitis	2.33%(2)
5	Acute Calculous Cholecystitis	1.16%(1)
6	Acute Gangrenous GB	1.16%(1)
7	Carcinoma Gall bladder	2.33%(2)
	Total	100% (86)

In non-neoplastic lesions, chronic cholecystitis with cholelithiasis contributed the majority of the cases (75%), followed by chronic acalculous cholecystitis

(14.28%), chronic cholecystitis with cholesterosis (5.95%), xanthogranulomatous cholecystitis (2.38%) and acute gangrenous GB (1.19%) In gall stones, majority were pigmented (71.42%) followed by mixed stones (19%) and remaining were cholesterol stones (9.52%).

In neoplastic lesions, two malignant cases were reported, one being well differentiated adenocarcinoma with associated pigmented gall stones and other was signet ring cell carcinoma without gall stones. In the latter case, Immunohistochemistry (IHC CK7, CK20 & CDX2) was advised to rule out metastatic tumor. Both the cases showed chronic cholecystitis in the background.

#### 4.1. Gender and age correlation

#### 4.2. Gender

Overall, female predominance (71%) was seen over males (29%) in all GB lesions. In non-neoplastic lesions, female predilection (70.24%) was seen over male (29.76%) accounting for F :M ratio of 2.4:1. In neoplastic lesions, two malignant cases were reported and both the cases were seen exclusively in females; one case was well differentiated adenocarcinoma and other was signet ring cell carcinoma. [Figure 1]

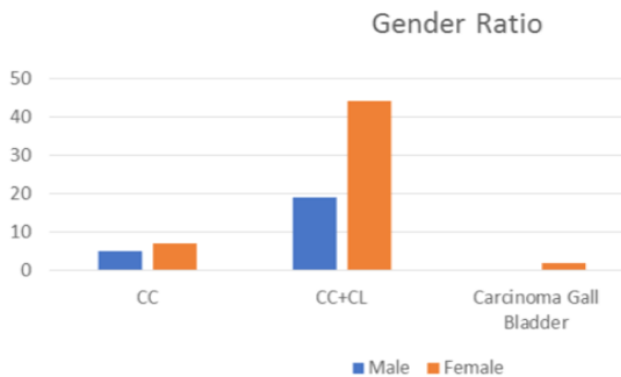


Fig. 1: Gender distribution in common GB diseases.

#### 4.3. Age

Most non-neoplastic lesions of the gall Bladder were common in the age group of 26-50 years accounting for 67.45% of all cases where as neoplastic lesions were common in the age group of >60years with mean age of 60.5 years.

## 5. Discussion

Gall bladder diseases are associated with varied histopathological lesions in cholecystectomy specimens. Non-neoplastic (inflammatory) lesions of GB are far more common than neoplastic lesions.<sup>1</sup>

### 5.1. Non-neoplastic lesions

The present study also showed predominance of non-neoplastic lesions accounting for 97.67% of all the GB lesions received in study period which was comparable with the studies from different parts of India.[Table 2].

Table 2: Frequency of Non -neoplastic lesions in various studies across India

S. No	Study	Non-neoplastic lesions
1.	Present study	97.67%
2.	Khan DM et al (TN) <sup>9</sup>	98.99%
3.	Bansal N (Punjab) <sup>10</sup>	93.6%
4.	Beena Devi etal (Karnataka) <sup>11</sup>	99.5%
5.	Patil M et al (Maharashtra) <sup>12</sup>	98.9%
6.	Srivastav AC et al (UP) <sup>13</sup>	80.0%

Chronic cholecystitis was the commonest histopathological lesion seen (95.34%) in our study, a finding which was seen in the various studies from different geographical regions of India with regional variation in prevalence of chronic cholecystitis.[Table 3]

Table 3: Frequency of chronic chole cystitis in various regions of India

S. No	Study	Chronic cholecystitis %
1	Present study	95.34%
2	Patil M (Maharashtra) <sup>12</sup>	93.1%
3	Gaharwar et al (UP) <sup>14</sup>	92.3%
4	Selvi et al (Tamil Nadu) <sup>15</sup>	85.8%
5	Devi Beena (Karnataka) <sup>11</sup>	82%

Histopathological findings seen in chronic cholecystitis were lymphocytic infiltration and fibrosis with thickening of GB wall; few showed denuded mucosa with atrophy . Other histopathological findings accompanying chronic cholecystitis were cholesterosis , Xanthogranulomatous cholecystitis. Similar findings were noted by various studies.<sup>9,11,12</sup> Chronic cholecystitis accompanied varied lesions; most common being gall stones in the present study (73.26%), a finding noted in other studies.<sup>9,15</sup> Gallstone disease appeared to be increasing in incidence over past couple of decades in India and western world due to increased intake of fatty and high calorie diet and sedentary lifestyle.<sup>16</sup> Cholelithiasis (gallstones) being the commonest lesion and accounts for more than 95% of GB diseases.<sup>1</sup> In non-neoplastic lesions, chronic cholecystitis with cholelithiasis contributed the majority of the cases, (75%) in the present study which was similar to the studies conducted in Chennai, (61.92%), whereas the study from Punjab showed 49.6%.<sup>9,10</sup>

## 5.2. Gall stone disease

Gall stones disease was the commonest lesion and was seen in 77.9% of all cholecystectomy specimens in the present study. Similar findings were noted by Srivastav et al (UP) 78.8%, Beena Devi et al (Karnataka) 65% and Khan et al (Tamil Nadu) 63.95%.<sup>9,11,13</sup> Thus, studies from north India showed comparatively more prevalence of gall stones than south India.

In our study, most common lesion was chronic calculous cholecystitis. Majority of the Gall stones were pigmented (71.42%) which was comparable with Khan et al (76.19%), Devi et al (58.5%), Selvi et al (60.2%) from south India and contrasted with Patil M (Maharashtra) 57%, Sasi et al (Kerala) 57%, and Hemlata 46% (Rajasthan) who noted mixed stones as the most common stone.<sup>9,11,12,15,17,18</sup> Interesting, apart from interstate variation, the type of Gall stones showed intrastate variation viz in contrast with the present study where pigmented stones were common, the study by Srivastav et al from Gorakhpur(UP) (78.69%) and Gaharwar (Kanpur) 89.14%. noted predominantly mixed stones.<sup>13,14</sup> Similar contrasting findings were seen in the studies from south India eg Suresh et al (Karnataka) showed mixed stones (80.7%) whereas Devi et al (Karnataka) showed pigmented stones (58.5%).<sup>11,19</sup> Thus, in general, studies from different parts of India showed high prevalence of pigmented or mixed stones as compared to cholesterol stones, highlighting the contrasting trend seen in western countries where cholesterol stones are more common suggesting that risk factors of pigmented /mixed stones (i.e biliary infections, cirrhosis, multiple pregnancies, chronic hemolysis etc) are more prevalent in the Indian population as against risk factors for cholesterol stones (i.e obesity, hypercholesterolemia, sedentary life-style, metabolic syndromes, sudden weight loss, Oral Contraceptive Use etc).<sup>2</sup>

Apart from cholelithiasis, other lesions accompanying chronic cholecystitis were acalculous cholecystitis (14.28%), cholesterosis (5.93%) and xanthogranulomatous cholecystitis which was comparable with other studies.<sup>9-13</sup>

## 5.3. Gender

Gall bladder diseases are more common in females. It has been postulated that under the influence of female sex hormone, the muscle may relax, biliary passage dilates and duodenal content of pancreatic secretion regurgitates into gallbladder and promote conditions which favour the formation of gallstones which is the commonest lesion of GB diseases.<sup>16</sup> In present study also females were predominantly affected (70.93%) in all GB diseases which was consistent with the studies of Nidhi Bansal et al (75.8%), Srivastav et al (88%), Beena et al 53.5% and Selvi et al (60.25%).<sup>10,11,13,15</sup> Here again, regional variation between north and south could be appreciated in

which females showed more prevalence for GB diseases in northern region as compared to south India.

The incidence of GB malignancy in females is more than that among males worldwide.<sup>20</sup> Similar trend was seen in the present study in which two cases of malignancy were noted and both belonged to females which was comparable with the findings noted by Khan et al.<sup>9</sup> Interestingly, the study from south India showed increasing trend of GBC in males (M:F ratio 1.6:1) in successive decades.<sup>21</sup>

## 5.4. Age

Non-neoplastic lesions were common below 5th decade in our study. Similar findings were noted by other studies.<sup>9,11,13</sup>

Neoplastic lesions (GBC) were common in the age group of >6years which was consistent with the study from North India.<sup>10</sup> In another study from AIIMS Delhi which was based on population based cancer registry data of 5 years showed the median age at diagnosis of GBC was 6.13 years and 57.years in males and females, respectively.<sup>20</sup>

In neoplastic lesions, all cases (2.27%) belonged to malignancy in the present study. No benign tumor or premalignant lesions were noted. This was in contrast with the study by Srivastav et al who noted 10% premalignant and 10% malignant lesions in their study.<sup>13</sup> This variation in both the studies from Purvanchal could be due to availability of two higher referral cancer centres (Tata Cancer Institute) for such cases in our locality.

GBC were reported exclusively in females (2.27%) in our study which was consistent with the study from North India.<sup>4</sup> but the study from South India showed male preponderance.<sup>21</sup>

Most common malignancy of Gall bladder is adenocarcinoma which was noted in various studies.<sup>4</sup> In our study, out of two cases, one was well differentiated adenocarcinoma and other was signet ring cell carcinoma. The primary signet ring carcinoma is rare and is uncommonly reported in literature.<sup>4</sup> Immunohistochemistry (CK7, CK20 & CDX2) was advised in our case to rule out metastatic deposits from other parts of GIT. Devi et al also noted uncommon adenosquamous carcinoma in their study.<sup>11</sup>

Though overall, GBC is said to be a rare disease in India, the incidence varies widely within the country.<sup>21</sup> GBC is more common in North India with frequency of 9.6%, followed by eastern India (6%).<sup>5,6</sup> The GBC showed varied frequency across India ranging from 1.01 % to 10%, lowest in South and highest in North India. [Table 4]

The profile of GBC seen in south India is quite contradictory to reports from northern parts of the country.<sup>8</sup> In north India, almost 80% of individuals with GBC have gallstones.<sup>7</sup> The mean age of presentation of GBC in north India is 5<sup>th</sup> to 7<sup>th</sup> decade with female predominance, while study from south majority of the patients were in the 5th and 6<sup>th</sup> decades with male preponderance of 1.6:1.<sup>21</sup> The

**Table 4:** Distribution of Gall bladder cancer in various regions across India

S. No	Study	Malignancy (%)
1.	Present study	2.33%
2.	Srivastav AC et al (UP) <sup>13</sup>	10.0%
3.	Bansal N (Punjab) <sup>10</sup>	3.5%
4.	Beena Devi etal (Karnataka) <sup>11</sup>	0.5%
5.	Khan DM et al (TN) <sup>9</sup>	1.01%
6.	Patil M et al (Maharashtra) <sup>12</sup>	1.1%

reason/s for the regional differences between North and South India is not clear. It has been hypothesized in literature that environmental carcinogen might play a role in the development of GBC, as excretion of environmental carcinogen (heavy metals like cadmium, chromium and lead) in drinking water may have carcinogenic effect.<sup>2</sup> These heavy metals are found in Ganga and Yamuna River Water which is the main source of drinking water in this belt. Both these rivers are contaminated with several heavy metals mentioned above through industrial waste.<sup>20</sup> In a recent study, high concentration of heavy metals in the water and soil along the Indo-Gangetic plains was considered as a contributing factor to the disease.<sup>22</sup>

## 6. Conclusion

The present study revealed that different spectrum of Histopathological lesions were present in the cholecystectomy specimen. Chronic cholecystitis with pigmented gall stone was the commonest GB disease in the present study. The study also revealed that females have increased preponderance for the development of all the gall bladder diseases including malignancy.

Non-neoplastic lesions were more common till 5<sup>th</sup> decade in the present study whereas females in the 5<sup>th</sup> and 6<sup>th</sup> decade of life were prone for malignancy of gall bladder which was associated with gall stones. Thus, histopathological examination mandates for all cholecystectomy specimens for better understanding of disease process, necessitating further relevant management and better patient outcome.

## 7. Source of funding

None.

## 8. Conflict of interest

None.

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