

## Original Research Article

# A retrospective single centre study on histopathological analysis of cholecystectomy specimens in a tertiary care centre in India

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## ABSTRACT

**Background:** Gall bladder carcinoma is the 5<sup>th</sup> most common gastrointestinal malignancy which has a poor 5-year survival rate, carrying dismal prognosis. Diagnosing chronic cholecystitis from gall bladder cancer is challenging. Early detection of gall bladder carcinoma allows for the possibility of radical resection surgery, which has been shown to increase patient survival.

**Methods:** A retrospective histopathological analysis was conducted at a tertiary care centre to evaluate the incidence of gall bladder carcinoma. A total of 1728 cholecystectomy samples were evaluated from all age groups for a period of 6 years.

**Results:** Chronic cholecystitis was the most common impression on histopathological analysis, showing females have high predominance of developing gall bladder disease including malignancy. The incidence of gall bladder carcinoma was found to be 0.46 % with 8 cases of adenocarcinoma diagnosed, which were not diagnosed preoperatively.

**Conclusions:** If missed, gall bladder cancer can progress rapidly and has a significant fatality risk if it is not detected in time. We conclude that all histopathology specimens be sent for routine analysis, to rule out gall bladder cancer, which if resected early can improve the survival of the patients.

**Keywords:** Gall bladder carcinoma, Cholecystectomy, Histopathology

## INTRODUCTION

The gall bladder is a small hollow organ located in the right upper quadrant of the abdomen. It is an important part of the biliary system in our body. The liver produces bile, which is stored in the gall bladder and later released in the intestine.<sup>1</sup> Any obstruction to this flow of bile causes a backup of bile in the gall bladder, causing its inflammation, known as cholecystitis.

The gall bladder is composed of three layers named mucosa, muscularis, and adventitia. It is lined by a single layer of columnar epithelial cells surrounded by mucus, thus separating the mucosal cells from the bile.<sup>2</sup> The bile

is then excreted into the intestine and is important for the absorption of dietary fats.

The gall bladder is afflicted with various types of ailments, ranging from inflammatory to congenital to neoplastic in nature. Among them, gallstones are the most common pathological disease of the gall bladder. The prevalence of gallstones in the Western world is 10%, whereas in India it is 4%, with the highest prevalence in Central India.<sup>3</sup>

Many risk factors for gallstones are non-modifiable, like ethnicity, genetics, female gender, and age above forty, but some risk factors can be modified, like obesity, metabolic syndrome, diabetes mellitus, rapid weight loss, total

parenteral nutrition, as well as associated diseases like cirrhosis and Crohn's disease.<sup>4</sup>

Cholecystectomy, either open or laparoscopic, is the mainstay treatment for symptomatic gall stones. Such multiple mucosal insults to the gall bladder overwhelm the tissue repair mechanism, giving way to metaplastic changes that lead to gall bladder cancer. The incidence of gall bladder in India is high in Northern, Northeastern, and Central India, thus causing India to contribute to 10% of the global gall bladder cancer burden. In India, gall bladder cancer affects patients at a younger age, in their fifties, as compared to their western counterparts in developed nations.<sup>5</sup>

The patients remain asymptomatic for many years before showing any symptoms of gall bladder carcinoma. Often gall bladder cancer is found incidentally during the histopathological examination of the cholecystectomy specimen of the gallstone disease and thus carries a dismal prognosis if diagnosed too late in the disease course. Hence, it is a mandatory practice amongst few developing countries to perform routine histopathological analysis of the cholecystectomy specimens to rule out gall bladder cancer. By using histological analysis to detect gall bladder cancer early, the prognosis and survival chances of the patient might be improved.<sup>6</sup>

Hence, the objective of this retrospective single centre study is to perform the histopathological analysis of the cholecystectomy specimens over a time period of 6 year-duration to rule out the incidence of gall bladder carcinoma in the patients.

## METHODS

The present study is a retrospective cross-sectional study of 6-year duration that was conducted at Bhaktivedanta Hospital and Medical Research Institute, Mira Road, Thane. The study was conducted from 2017 to 2023 after obtaining approval from the Institutional Ethics Committee at Bhaktivedanta Hospital and Research Institute. A total of 1728 cholecystectomy biopsy samples

from patients of all age groups were studied. The study included histopathological samples of all gall bladder biopsies obtained in the cholecystectomy operations done over the period of 6 years. The exclusion criteria included patients who were diagnosed with gall bladder carcinoma prior to the cholecystectomy operation based on clinical or radiological basis of ultrasound or CT scan. The biopsy specimens are stored in a container with 10% neutral buffered formalin and sent to the histopathology lab to be processed under routine techniques. Tissue processing and grossing of the sample is done. The samples then undergo hematoxylin and eosin staining and are examined microscopically to provide the diagnosis. The histopathological data is obtained from the histopathology registers at the pathology lab of Bhaktivedanta Hospital and Research Institute. Relevant clinical data, such as demographic data, year of biopsy, and diagnosis of gall bladder biopsies, was also retrieved from the registers of the histopathology lab. A statistical analysis of the histopathological data was done.

## RESULTS

A total of 1728 gall bladder specimens were analysed in the study over a period of 6 years, from 2017 to 2023. There was a female predominance, with 1186 (68.63%) females seen in the study, whereas there were only 542 males (31.37%). The male-to-female ratio was 1:2.1 (Figure 1).

The age group of the patients ranged from 3 to 89 years, with the maximum number of patients with gall bladder disease seen in the age group of 31 to 40 years (23.84%). The mean age of presentation was 46.90 years. The age-wise distribution is shown in Table 1.

A total of 1223 patients, which contributes to 70.78% of the total patients in the study, presented with the most common histopathological impression of chronic cholecystitis. This was followed by 480 patients (27.78%) presenting with acute cholecystitis, 14 patients (0.81%) with cholesterolosis (Table 2).

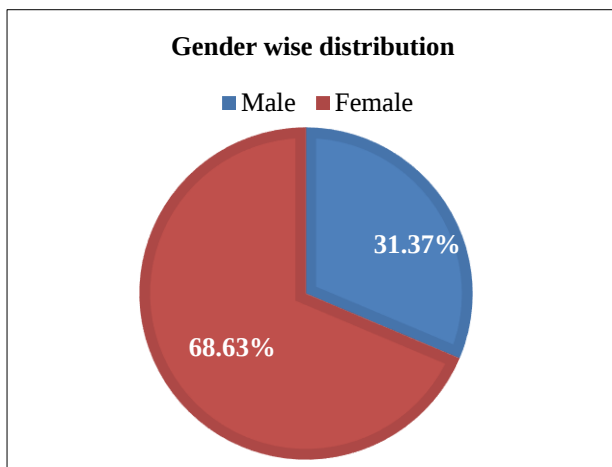
**Table 1: Age wise distribution (mean age=46.90).**

| Impression                        | Age (in years) |       |       |       |       |       |       |       |      |
|-----------------------------------|----------------|-------|-------|-------|-------|-------|-------|-------|------|
|                                   | ≤10            | 11-20 | 21-30 | 31-40 | 4-50  | 51-60 | 61-70 | 71-80 | >80  |
| Chronic cholecystitis             | 2              | 23    | 165   | 283   | 272   | 244   | 165   | 57    | 12   |
| Acute cholecystitis               | 1              | 8     | 42    | 122   | 107   | 82    | 85    | 31    | 2    |
| Cholesterolosis                   | 0              | 0     | 2     | 5     | 3     | 3     | 1     | 0     | 0    |
| Adenocarcinoma                    | 0              | 0     | 1     | 1     | 0     | 3     | 1     | 2     | 0    |
| Porcelain gall bladder            | 0              | 0     | 0     | 0     | 0     | 0     | 1     | 0     | 0    |
| Xanthogranulomatous cholecystitis | 0              | 0     | 0     | 0     | 0     | 0     | 0     | 1     | 0    |
| Tubular adenoma without dysplasia | 0              | 0     | 0     | 1     | 0     | 0     | 0     | 0     | 0    |
| Total                             | 3              | 31    | 210   | 412   | 382   | 332   | 253   | 91    | 14   |
| Total in percentage               | 0.17           | 1.79  | 12.15 | 23.84 | 22.11 | 19.21 | 14.64 | 5.27  | 0.81 |

**Table 2: Spectrum of histopathological findings.**

| Impression                        | Male       | Female      | Total       | (%)   |
|-----------------------------------|------------|-------------|-------------|-------|
| Chronic cholecystitis             | 340        | 883         | 1223        | 70.78 |
| Acute cholecystitis               | 199        | 281         | 480         | 27.78 |
| Cholesterolosis                   | 2          | 12          | 14          | 0.81  |
| Adenocarcinoma                    | 0          | 8           | 8           | 0.46  |
| Porcelain gall bladder            | 0          | 1           | 1           | 0.06  |
| Xanthogranulomatous cholecystitis | 0          | 1           | 1           | 0.06  |
| Tubular adenoma without dysplasia | 1          | 0           | 1           | 0.06  |
| <b>Total</b>                      | <b>542</b> | <b>1186</b> | <b>1728</b> |       |

Only 1 female patient specimen revealed xanthogranulomatous cholecystitis; 1 female patient revealed a porcelain gall bladder; and 1 male patient was histopathologically diagnosed with tubular adenoma without dysplasia. None of the patients were preoperatively diagnosed with malignancy. However, out of a total of 1728 total specimens, 8 specimens (0.46%) were diagnosed with adenocarcinoma of the gall bladder. The incidence of gall bladder cancer was found to be 0.46%.



**Figure 1: Gender wise distribution.**

## DISCUSSION

Cholelithiasis remains the most common disease seen in our health care system, which frequently necessitates cholecystectomy and presents as right upper quadrant stomach pain. The prevalence of gallstones in India is increasing, and since ultrasonography is now widely used, diagnosing gallstones is quick, simple, and affordable.<sup>2,7</sup> However, chronic inflammation of the gall bladder mucosa can cause metastatic changes in gall bladder.<sup>8</sup> Gall bladder carcinoma can be seen as gall bladder wall thickening on ultrasonography or CT scan by the radiologist, or it can be diagnosed directly by inspection of the gross anatomy

intraoperatively by the surgeon. However, all cases of gall bladder carcinoma do not present with obvious lesions. Also, the outcome of gall bladder carcinoma is poor with 5-year survival rate being less than 5%.<sup>9</sup> Hence, it is routine practice in a few developing countries to perform histopathological analysis of all cholecystectomy gall bladder specimens to rule out gall bladder carcinoma that would have been missed otherwise.<sup>8</sup>

Out of the 1728 cholecystectomy specimens analysed for the current investigation, 542 were male and 1186 were female (Table 1). As a result, it was concluded that women were more likely than males to have gall bladder lesions (68.63%) than men (31.37%). The male to female ratio was 1: 2.1, which is comparable to research by Patil et al that showed a male to female ratio of 1:3.2, indicating female preponderance.<sup>6</sup> Gall stones are thought to be more likely to form in women because estrogen triggers the release of biliary cholesterol, which makes bile more hypersaturated with cholesterol and increases the risk of cholelithiasis.<sup>3,10</sup>

The patients ranged in age from 3 to 89 years old. Gall bladder lesions were more frequently found in patients who were between the ages of 31 and 40 (4th decade) (Table 2). Similar research was done by Kulkarni et al and Patil et al.<sup>6,11</sup> However, Kothastane et al indicated that the age range of 41 to 50 years had the greatest number of patients.<sup>12</sup> In Kothastane et al's study, the neoplastic diagnosis was made in patients older than 60 years of age, however in the current investigation, 3 out of 8 adenocarcinomas were discovered in patients between the ages of 51 and 60, followed by 71 to 80.<sup>12</sup>

On histological investigation, chronic cholecystitis, which affected 70.78% of our patient population, was the most frequent finding in our study. This result is consistent with those of other studies.<sup>6,11,12</sup> Chronic cholecystitis, which encompasses conditions like gangrenous cholecystitis, follicular cholecystitis, and suppurative cholecystitis, is characterised by thickening of the GB wall as well as calcifications caused by cholelithiasis as the primary etiology. 27.78% of patients had acute cholecystitis. The findings of Patil et al and Kothastane et al, who found lower incidences of acute cholecystitis of 2.9% and 1.16%, respectively, stand in contrast to this conclusion (Table 3).<sup>6,12</sup>

In our study, 0.81% of the patient population had cholesterolosis. This is in contrast to a study done in Pakistan, which found a greater percentage of 32.8% of people had this condition.<sup>13</sup> The histopathology revealed lipid laden macrophages along with villous hypertrophy causing yellowish streaks.

Xanthogranulomatous cholecystitis was only found in 0.06 percent of the patient group. Xanthogranulomatous cholecystitis is frequently observed in elderly patients in their fifth and sixth decades, which is supported by our study because it manifested in the 71–80-year age range.

In terms of radiological mimicry as well as intraoperative pericholecystic inflammation, hepatic involvement, and lymphadenopathy, xanthogranulomatous cholecystitis resembles gall bladder malignancy. Hence, it is important

to note this mimicry as patients can undergo radical cholecystectomy instead of simple cholecystectomy for a benign process.<sup>14</sup>

**Table 3: Comparison with other studies.**

| Impression                               | Present study (%) | Patil et al study (2019) (%) | Savanur et al study (2022) (%) | Kulkarni et al (2022) (%) | Kothasthane et al (2020) (%) | Almas et al study (2020) (%) |
|------------------------------------------|-------------------|------------------------------|--------------------------------|---------------------------|------------------------------|------------------------------|
| <b>Chronic cholecystitis</b>             | (70.78)           | 98                           | 59.4                           | 57.76                     | 73.26                        | 78.79                        |
| <b>Acute cholecystitis</b>               | (27.78)           | 2.9                          | 0.4                            | 4.96                      | 1.16                         | 2.5                          |
| <b>Cholesterosis</b>                     | (0.81)            | 0.45                         | -                              | -                         | 5.81                         | 32.8                         |
| <b>Adenocarcinoma</b>                    | (0.46)            | 1.1                          | 0.2                            | 0.62                      | 2.33                         | 0.2                          |
| <b>Porcelain gall bladder</b>            | (0.06)            | -                            | -                              | -                         | -                            | -                            |
| <b>Xanthogranulomatous cholecystitis</b> | (0.06)            | 1.1                          | 0.6                            | 1.24                      | 2.33                         | 1.1                          |
| <b>Tubular adenoma without dysplasia</b> | (0.06)            | 0.27                         | 0.4                            | -                         | -                            | -                            |

In a female between the ages of 61 and 70, there was just one instance (0.06%) of porcelain gall bladder. Gall bladder wall calcification brought on by chronic cholecystitis might manifest as "porcelain gall bladder". The gall bladder's fragile wall is caused by calcium deposits. The earlier study found a link between porcelain gall bladder and a higher risk of gall bladder cancer.<sup>15</sup> However, a new study contends that the likelihood of malignancy has decreased. A recent study found that not all individuals with porcelain gall bladders require preventive cholecystectomy.<sup>16</sup>

In the current investigation, 8 incidences of adenocarcinoma were discovered, accounting for 0.46 percent of patients. All 8 occurrences involved female patients, the majority of whom were in the 51–60 age range. Other investigations have verified that adenocarcinoma is the most prevalent kind of gall bladder carcinoma, but Kothasthane et al also showed the prevalence of 1 signet ring type gall bladder cancer.<sup>12</sup>

The most prevalent biliary system cancer is gall bladder cancer, which has a high incidence in Chile, Japan, and northern India.<sup>17</sup> In India, there has been a startling geographic variation in cases of gall bladder cancer. When compared to the southern states of India, it is more prevalent in the northern states, particularly in the Ganges Delta.<sup>18,19</sup> There is a rising tendency of gall bladder cancer in metro areas, which may be brought on by migratory patterns, changes in lifestyle variables such obesity and fatty food consumption, and high parity among females.<sup>19</sup> The incidence of gall stone is parallel to the prevalence of gall stones. Chronic irritation by gall stones can cause metaplasia causing gall bladder cancer.<sup>20</sup>

The reasons for missing the early diagnosis of gall bladder cancer includes lack of specific signs and symptoms, lack of suspicion on preoperative diagnosis. Early identification is helpful to achieve R0 resection as surgery

is often the preferred treatment for gall bladder cancer. Simple cholecystectomy is advisable upto PT2a stage after which radical cholecystectomy is preferred. The operative surgeon should open and examine each gallbladder specimen extracted during laparoscopic cholecystectomy, as well as collect paraffin sections from any worrisome areas. If cancer is detected, open surgery should be conducted, including wedge resection of the liver and regional lymphadenectomy, as well as the removal of the port sites.<sup>20</sup> Hence, it is crucial to analyse the gall bladder specimens sent for histopathology to rule of gall bladder carcinoma.

However, this study also has few noteworthy limitations. Since, it is a retrospective study, the accuracy of the data can be limited, due to lack of standardization of the macroscopic evaluation of the gall bladder. Also, the study was conducted in a small population of a specific region of India, which cannot reflect the demographic of other regions. Hence, a prospective, multicentre study is required for further analysis and development of guidelines.

## CONCLUSION

Our study showed various spectrum of lesions found on histopathological analysis of the cholecystectomy specimens. Chronic cholecystitis was the most common impression on histopathological analysis, showing females have high predominance of developing gall bladder disease including malignancy. The maximum number of patients with gall bladder disease were seen in the age group of 31 to 40 years. The incidence of gall bladder cancer was found to be 0.46% in our study. All 8 occurrences involved female patients, the majority of whom were in the 51–60 age range. In order to avoid missing any gall bladder carcinoma that could be treated with radical resection, we conclude that routine histological investigation of the gall bladder specimens is essential. The approach of routine histopathological

analysis especially in areas of high incidence of gall bladder carcinoma, will help to rule out gall bladder cancer and thus increase the chances of survival of the patients.

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