

## Original Research Article

**Histopathological Spectrum of Gall Bladder Diseases: A Three-Year Retrospective Study in a Rural Tertiary Care Hospital in Haryana, North India****Nisha Sharma<sup>1</sup>, Sandhya Panjeta Gulia<sup>2</sup>, Manika Kundra<sup>3</sup>, Samriddhi Sood\*, Raj Kumar<sup>4</sup>**<sup>1,3</sup>*Assistant Professor, Department of Pathology, Adesh Medical College, Shahabad(M), Kurukshetra, Haryana, India*<sup>2</sup>*Professor and Head, Department of Pathology, Adesh Medical College, Shahabad(M), Kurukshetra, Haryana, India*<sup>4</sup>*Associate Professor, Department of Surgery, Adesh Medical College, Shahabad(M), Kurukshetra Haryana, India***Received: 10-06-2021 / Revised: 24-11-2021 / Accepted: 16-12-2021****Abstract**

**Background:** Gallstones is the most common condition leading to cholecystectomy with a prevalence within India ranging from 2% to 29%. Long standing cases can induce mucosal changes in gall bladder mucosa ranging from chronic cholecystitis, metaplasia, dysplasia and finally carcinoma gall bladder. Although malignancy is the most important condition to be ruled out on histopathology, it is important to understand the intermediate pathologies leading to this. **Aim:** 1) To study the histomorphological spectrum of diseases affecting gall bladder in rural population of Haryana. 2) To identify the frequency of gall bladder carcinoma in this region of Haryana and its demographic correlation with other studies. **Material methods:** This was a 3 year retrospective study conducted in Department of pathology, Adesh medical college, Shahabad(M), Kurukshetra from a period of December 2016 to December 2019. Results were compiled into non neoplastic, pre-neoplastic and neoplastic category to study the spectrum of lesions in gall bladder specimens. Data collected was analyzed using (SPSS) v. 20.0 software. **Results:** Most of the histopathological changes were found in female gender with associated multiple mixed stones. Overall and among non-neoplastic category chronic cholecystitis was the commonest pathology. Incidence of carcinoma was low (0.4%) as compared to studies from different regions of country. **Conclusion:** Present study provides an insight into the incidence, clinical profile and association of gall bladder conditions with gall stones in a tertiary care center serving the rural population of Haryana, North India.

**Keywords:** pathology, cholecystectomy, cholecystitis, gallstones, carcinoma

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**Introduction**

Cholecystectomy is performed electively or as emergency procedure in gall bladder diseases with cholelithiasis as most common indication.[1]

Prevalence of gall stone disease in India is reported to be 2-29%.[2] It is seven times higher in North India in comparison with South India.[3] Gall stones can irritate the tall columnar epithelial lining of gall bladder leading to various non-neoplastic and neoplastic conditions. These include chronic cholecystitis, acute cholecystitis, cholesterosis, empyema, pre-neoplastic conditions like adenomatous hyperplasia, metaplasia and dysplasia which may finally lead to carcinoma.[4] Carcinoma of the gall bladder is the most common malignancy of biliary tract, incidentally found in 0.3 – 1.5% of cholecystectomy specimens with associated gall stones present in 40-100% cases.[5,6,7] Incidence of gall bladder disease can vary depending on age and sex distribution and also on ethnicity of population studied. [8] The various changes in lifestyle of individuals, even in rural India, like intake of fatty food, obesity, lack of adequate exercise and sedentary habits have attracted attention to diseases of gall bladder.[9] It is important to analyse the histopathological changes associated with the gall bladder disorders in order to ascertain the incidence, distribution as well as the histomorphological features common in rural population of Haryana, North India.

**Aims and Objectives**

Present study is aimed

1. To study the histomorphological spectrum of diseases affecting gall bladder in rural population of Haryana.
2. To identify the frequency of gall bladder carcinoma in this region of Haryana and its demographic correlation with other studies.

**Materials and methods**

This was a 3 year retrospective study. After obtaining Institute Ethical Committee (IEC) clearance, data was collected from archives of Pathology department and all the Hematoxylin & Eosin stained slides of cholecystectomy specimens sent for routine histopathology were reviewed for morphological changes from a period of December 2016 to December 2019. Results were compiled into non neoplastic, pre-neoplastic and neoplastic category to study the spectrum of lesions seen in gall bladder specimens. Data collected was analysed using (SPSS) v. 20.0 software.

**Inclusion criteria**

Study included all cholecystectomy specimens received in 10% buffered formalin.

**Exclusion criteria**

Specimens not received in 10% buffered formalin or were autolyzed were excluded from the study.

**Results**

During the above mentioned study period a total of 228 cases of cholecystectomy were received of which only 226 cases were included in this study as two cases were not received in 10% buffered formalin and showed autolytic changes. Among these patients, majority were females 177 (78.3%) and only 49 (21.7 %) were males with a Female: Male ratio of 3.6: 1. The age of the patients ranged

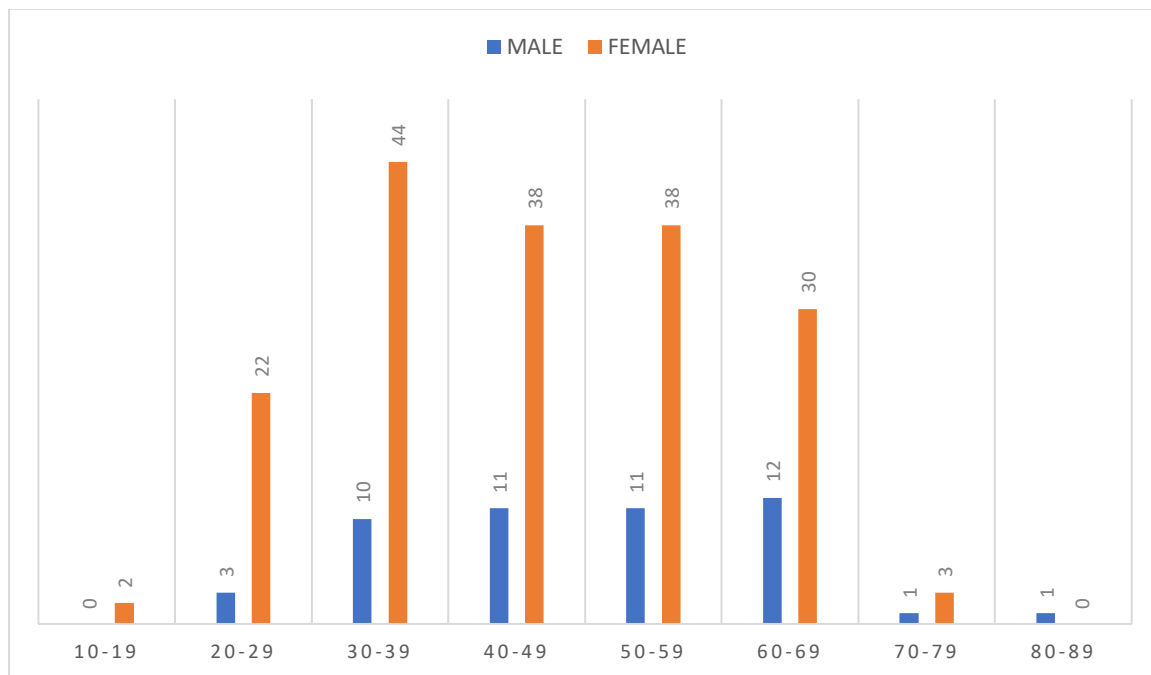
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from 17 years to 80 years. Maximum number of patients were females and in 4<sup>th</sup> decade. Fig. 1 summarizes the age and gender-wise distribution of total cases.



**Fig. 1: Age and Gender Distribution of cases**

Overall calculus lesions 147(64.1%) were more common as compared to acalculus ones 79(34.9%) and females (115 and 62 cases of calculus and acalculus pathology respectively) outnumbered males (32 and 17 cases of calculus and acalculus pathology respectively) in both the types of lesions. Most of the calculi associated disease was due to mixed stones seen in 102 (69.4%) of 147 cases followed by cholesterol 40(27.2%) and pigment stones 05(3.4%). Number of stones varied from single calculus in 49 (33.3%) cases, two calculi in 5 (3.4 %) cases to a maximum number of multiple calculi in 93 (63.3%) cases of total 147 cases of cases with gall stone disease. Hence, majority of stones were multiple, mixed stones.

Of all the lesions, chronic cholecystitis 127(56.2%) was the commonest followed by cholesterosis 47(20.1%), metaplasia 21(9.3%), acute on chronic cholecystitis 16(7.1%), Xanthogranulomatous cholecystitis 5(2.2%), Hyperplasia 4(1.8%), dysplasia and empyema gall bladder 2(0.9% each) and hyalinising chronic cholecystitis 01(0.4%). Among all the cholecystectomy specimens, carcinoma of gall bladder contributed to 01(0.4%) of all cases. Table 1 shows the histopathological spectrum noted and also association of individual pathology with gall stones.

**Table 1: Distribution of histopathological cases among all cholecystectomy specimens**

HISTOLOGICAL DIAGNOSIS	CALCULUS	ACALCULUS	TOTAL
Chronic Cholecystitis	95	32	127 (56.2%)
Acute on Chronic Cholecystitis	9	7	16 (7.1 %)
Cholesterosis	25	22	47 (20.1 %)
Metaplasia	10	11	21 (8.4 %)
Xanthogranulomatous Cholecystitis	1	4	5 (2.2%)
Hyalinising Chronic Cholecystitis	-	1	1 (0.4%)
Empyema GB	1	1	2 (0.9%)
Hyperplasia	4	-	4 (1.8%)
Dysplasia	1	1	2 (0.9%)
Adenocarcinoma	1	-	1 (0.4%)
<b>Total No. Of Cases</b>	<b>147</b>	<b>79</b>	<b>226 (100%)</b>

When grouped into non-neoplastic, pre-neoplastic and neoplastic categories, non-neoplastic lesions were in majority seen in 198 (87.6%) of 226 cases in comparison with 28(12.4%) cases of pre-neoplastic and neoplastic pathology. Among non-neoplastic lesions, chronic cholecystitis was the commonest with 127(56.2%) cases while among pre-neoplastic and neoplastic category, metaplasia was the commonest with 21(9.3%) cases.

Age-wise distribution of gall bladder histopathological lesions revealed non-neoplastic lesions being commonest in 30-39 years age group (4<sup>th</sup> decade) and pre-neoplastic and neoplastic pathology commonest in 40-49 year age group (5<sup>th</sup> decade) as shown in Tables 2 & 3. In present study, female preponderance was noted in all lesions except hyalinising chronic cholecystitis and empyema gall bladder with female patients

constituting 97(76.3%) of cases of Chronic cholecystitis, 9 (56.3%) cases of acute on chronic cholecystitis, 41(87.2%) cases of Cholesterolosis, 80% cases of Xanthogranulomatous cholecystitis, 3(75%) cases of Hyperplasia and 19 (90.4%) cases of Metaplasia. Two cases of dysplasia and one case of adenocarcinoma gall bladder was reported in females only.

**Table 2: Age-Wise Distribution of Gall Bladder Lesions with special reference to non-neoplastic types**

Age (in yrs)	C C	Acute a on chronic cholecystitis	Cholesterolosis	GC	Emphyema GB	Hyalinizing CC	Total
0-19	2	-	-	-	-	-	2 (1%)
0-29	11	-	10	-	-	-	11 (10.6%)
0-39	30	6	12	1	-	-	30 (24.7%)
0-49	28	1	11	1	-	1	28 (21.2%)
0-59	31	4	6	2	-	-	31 (21.7%)
0-69	24	4	8	1	1	-	24 (19.2%)
0-79	-	-	-	-	1	-	1 (1.0%)
0-89	-	-	-	-	-	-	0 (0.5%)
<b>Total</b>	<b>27</b>	<b>16</b>	<b>47</b>	<b>5</b>	<b>2</b>	<b>1</b>	<b>8 (100%)</b>

**Table 3: Age-Wise Distribution of Gall Bladder Lesions with special reference to pre-neoplastic (hyperplasia, metaplasia and dysplasia) and neoplastic types**

AGE (in yrs)	Hyperplasia	Metaplasia	Dysplasia	Carcinoma	Total
20-29	-	4	-	-	4 (14.3%)
30-39	1	4	-	-	5 (17.8%)
40-49	1	5	1	-	7 (25%)
50-59	2	4	-	-	6 (21.4%)
60-69	-	2	1	1	4 (14.3%)
70-79	-	2	-	-	2 (7.1%)
<b>Total</b>	<b>4</b>	<b>21</b>	<b>2</b>	<b>1</b>	<b>28 (100%)</b>

## Discussion

Wide variation in incidence of gall bladder (GB) diseases have been reported in different studies which maybe partly due to differences in age and gender distribution in different population groups. [10]

### Gender distribution

In present study, females (78.3%) outnumbered males (21.7%) with female: male ratio of 3.6:1. The results are similar to other studies showing female preponderance by Thukral S et al (75.8%), Srivastav AC et al (88%), Beena D et al (53.5%) and Selvi et al (60.25%). [11,12,13,14] A favoured female sex ratio was also noted in a comparative study between South India and North India by Kumar H et al where sex ratio in South India was 1.3:1 and in North India was 4.8:1. [3] Present study is in concordance with above findings where North Indian population shows a greater female to male sex ratio. It has been proposed that due to effect of female sex hormones, gall bladder is more susceptible to formation of gall stones which is commonly associated with GB disease. Hence, greater representation in cholecystectomy specimens.

### Age distribution

Age of patients in this study ranged from 17 years to 80 years. Maximum number of patients were seen in 30-39 year age group i.e. 4<sup>th</sup> decade. Siddiqui et al (27.8%), Narendra et al (37%) and Sangwan et al (23.77%) also found maximum number of patients within age range of 31-40 years which is like our study.[15,16,6] This was a decade early as compared to studies by Beena et al (26%), Awasthi et al (27.2%), and Nigam et al (41.92%) where highest number of patients presented in 41-50 years age group i.e. 5<sup>th</sup> decade. [13,17,18]

### Calculus pathology

Gall stones are a major cause of mortality and morbidity throughout the world causing significant histopathological changes in gall

bladder mucosa some even leading to carcinoma.[4] In our study, gall stone disease was common with calculus lesions seen in 64.1% cases. Present study from Haryana showed mixed stones in majority observed in 69.2% cases with calculus lesions (n=147). This was in concordance with a study by Mathur SK et al conducted in a medical college in Rohtak, Haryana where 330 cases were studied of which 194 (59%) were mixed stones, 84 (25%) combined stones, 30 (9%) pigment and 22 (7%) cholesterol stones.[19] Studies from other regions of India which had similar findings were by Navyashree N, Karnataka (64.04%), Patil M et al, Maharashtra (60.2%), Parambil SM et al, Kerala (57%), Sharma H et al, Rajasthan (46%), Srivastav AC et al, Uttar Pradesh (78.69%), Gaharwar A et al, Uttar Pradesh (89.1%). [ 8,2,20,21,12,22] These findings can be contrasted from studies by Thukral S et al, Punjab (75.7%), Kotasthane VD et al, Uttar Pradesh (71.42%) and also studies from South India by Khan DM et al (76.1%) and Devi B et al (58.5%) which showed high prevalence of pigment stones.[11,23,24,13] Hence, studies from different regions of India show variability based on type of gall bladder stones. Table 4. represents a comparative analysis among studies from regions across India for better correlation. A higher number of mixed/pigment stones are noted in Indian population in comparison with cholesterol stones. This may be due to high prevalence of predisposing risk factors for e.g. biliary infection, liver disease, multiple pregnancies, etc in Indian population. Also, female patients 115 (78.2%) had a higher incidence of calculus pathology as compared to male patients 32(21.8%) in our study. Patil M et al also reported that gall stones were common in females (66%) than males (34%). [2] The above findings can be attributed to sedentary lifestyle and increased predisposition of female hormones to formation of gall stones.

**Table 4: Commonest gall stones in studies from different regions of India**

S. No.	Study	Predominant Stone Type (%)
1.	Present study	Mixed (69.2%)
2.	Mathur SK et al (Rohtak, Haryana)	Mixed (59%)
3.	Srivastav AC et al (Uttar Pradesh)	Mixed (78.69%)

4.	Gaharwar A et al (Uttar Pradesh)	Mixed (89.1%)
5.	Sharma H et al (Rajasthan)	Mixed (46%)
6.	Patil M et al (Maharashtra)	Mixed (60.2%)
7.	Parambil SM et al (Kerala)	Mixed (57%)
8.	Navyashree N et al (Karnataka)	Mixed (64.04%)
9.	Thukral S et al (Punjab)	Pigment (75.7%)
10.	Kotasthane VD (Uttar Pradesh)	Pigment (71.42%)
11.	Khan DM et al (Tamil Nadu)	Pigment (76.1%)
12.	Devi B et al (Karnataka)	Pigment (58.5%)

Based on number of stones, multiple stones 93 (63.2%) were commonly associated with gall stone disease. SK Mathur and associates in their study of 330 cases also found multiple stones in 170 (51.6%) cases, single calculi in 131 (39.6%) cases and double stones in 29 (8.8%) cases.[19] However, in their study the association between number of stones and mucosal response was not statistically significant ( $p=0.256$ ).

#### *Histopathological findings*

Gall bladder diseases are marked by varied histopathological lesions in cholecystectomy specimens.[8] The specimens received were evaluated for histopathological lesions. A predominance of non-neoplastic lesions was observed in our study constituting 198 (87.6%) cases. These findings are comparable with studies across India by Thukral S et al, Punjab (93.6%), Khan DM et al, Tamil Nadu (97.76%), Patil M et al (Maharashtra) (98.9%) and Srivastav AC et al, Uttar Pradesh (80.0%).[11,24,2,12] Most of the non-neoplastic lesions were seen in 30-39 year age group or 4<sup>th</sup> decade and females which is analogous to results of previous studies which also found females in 4<sup>th</sup> decade to be a common presentation. Pre-neoplastic and neoplastic lesions had maximum no. of patients, 7 out of 28 i.e.25%, in 40-49 year age group or 5<sup>th</sup> decade which is similar to study by Mondal B et al where 25 of 75 patients i.e. 33.3% had presentation in 40-49 year age group.[25]

Among non-neoplastic lesions, chronic cholecystitis had highest frequency with 127 out of 198 i.e. 56.2% cases. Most of the patients were females (76.4%) associated with calculus pathology (95 of 127 or 74.8%). A higher frequency of chronic cholecystitis has also been reported in studies from other regions of Haryana by Sangwan MK et al, Sonapat (69.8%) and Mathur SK et al, Rohtak (45%). [6,19] Analogous findings were observed by studies from other states by Thukral S et al, Punjab (81.5%), Mondal B et al, West Bengal (79.8%), Kotasthane VD et al, Uttar Pradesh (73.26%) and Selvi et al, Tamil Nadu (85.8%). [11,25,23,14] Hence, despite some regional variation, chronic cholecystitis remains the major presentation resulting in cholecystectomy.

Cholesterosis was the second highest histopathological finding reported in 47 (20.1%) cases of total. Similar results were also reported by Thukral S et al (22.69%) and Rao et al (13.4%) in their studies.[11,26] Also a female dominance was noted in our study in such cases (87.2%). Rao et al in their study also reported female predominance. [26] Patients with cholesterosis are usually asymptomatic clinically and found on histopathology incidentally. It is characterized by deposition of lipid containing foamy macrophages in the lamina propria of gall bladder. Presence of cholesterosis negatively correlates with gall bladder carcinoma.[6]

Xanthogranulomatous cholecystitis (XGC) is an entity commonly misdiagnosed as carcinoma on radioimaging studies and warrants histopathological analysis of cholecystectomy specimens.[6,11] A positive correlation has been found between XGC and gall bladder carcinoma varying from 0.2%-15% in different studies.[27,28,29] Frequency of such cases was 5 (2.2%) in present study. Similar findings were reported by Sangwan MK et al (2.64%), Goyal S et al (2.5%), Arathi N et al (1.8%) and Mondal B et al (1.7%).[6,30,31,25] However, Thukral S et al (0.71%) reported a lower frequency of these cases.[11] A meta-analysis of 1399 cases by Hale et al reported percentage of XGC cases varying from 1.3% - 1.9%.[27]

Emphyema GB is sometimes difficult to differentiate from uncomplicated acute cholecystitis. In this study, 2 (0.9%) cases were diagnosed with empyema GB. Devi B et al (0.5%) and Thukral S et al (0.71%) also reported similar findings.[13,11] However, these were in contrast with findings by Memon W et al (31.5%).[32]

Among the pre-neoplastic diseases, metaplasia (pyloric and intestinal) was the commonest reported with a total number of 21 cases of 226 i.e. 9.3%. Mathur SK et al, Kaushik R et al and Yaylak F et al also found metaplasia in 18%, 18.6% and 7.9% cases in their respective studies.[19,33,34] Thukral S et al (3.54%) and Mittal et al (0.8%), however, reported lower incidence of cases of metaplasia.[11,35] Metaplasia is the first step in sequelae of metaplasia-dysplasia - carcinoma. Frequency of dysplastic lesions is high with concurrent metaplasia.[36] Metaplasia of intestinal type is also associated with a high risk of gall bladder carcinoma.[37]

In our study, 2 (0.9%) cases were diagnosed with low grade dysplasia, an incidental finding in gall bladder specimens. Mondal et al also reported 2.2% cases as dysplasia.[25] Epithelial dysplasia if encountered in cholecystectomy specimen, raises the need for additional sectioning of specimen to rule out carcinoma. Rais R in a study on significance of incidental gall bladder dysplasia and adenocarcinoma documented almost no risk of hidden invasive carcinoma in cholecystectomy specimens without any gross abnormality. However, in same study, 18.9% of cases with incidental carcinoma had associated carcinoma of pancreatobiliary system, a finding in support of multifocal neoplastic potential in pancreatobiliary tree known as 'field effect'. Radioimaging studies should be done to rule out the same.[38]

Most important aspect in histopathological examination of gall bladder specimens is to detect malignancy. Malignancy of gall bladder has one of the worst cancer mortality. Gall bladder carcinoma poses a diagnostic difficulty in early stages due to non-specific clinical presentation and non-obvious lesions on radiology in some cases. In present study conducted in Haryana, there was 1 case of moderately differentiated adenocarcinoma of gall bladder with an incidence of 0.4%. It was reported in a female patient in 7<sup>th</sup> decade of life with associated multiple mixed gall stones. Also noted in same patient were the spectrum of Intestinal metaplasia and high grade dysplasia which further correlate with metaplasia-dysplasia-carcinoma sequence. It has been predicted by scientists Wistuba and Gazdar that long standing gall stone disease can induce changes in normal gall bladder mucosa from cholecystitis-hyperplasia-metaplasia-dysplasia to carcinoma. This was based on hypothesis of "Multistep pathogenesis of gall bladder cancer from gallstones".[39] The risk of developing cancer among patients of untreated cholelithiasis has been estimated to be 0.2-0.5% over a 20 year time period.[40] Commonest type of gall bladder carcinoma encountered is adenocarcinoma which is seen in present study also. Various studies across the country and in same state have reported different incidence of gall bladder carcinoma. Studies by Devi B et al, Karnataka (0.5%) and Mondal B et al, West Bengal (0.6%) reported similar incidence of gall bladder carcinoma.[13,25] In comparison, a study conducted in Rohtak, Haryana by SK Mathur and colleagues, carcinoma was noted in 2% patients while MK Sangwan in their study from Sonapat, Haryana reported carcinoma in 1.9% patients.[19,6] Studies from other states reporting higher cases of carcinoma gall bladder are also present with incidence of 3.5% by Thukral S et al, Punjab, 2.33% by

Kotasthane VD and colleague, Uttar Pradesh to even as high as 10% in a study by Srivastav AC et al, Uttar Pradesh.[11,23,12] Sangwan et al and Mathur et al also reported and increased association of gall bladder carcinoma with female gender, multiple mixed stones with highest number of cases in their 7<sup>th</sup> decade.[6,19] All these findings are analogous with present study.

#### Conclusion

Gallstones are associated with a series of changes leading to various histopathological conditions. Our study concluded that most of the histopathological changes were found in female gender with associated multiple mixed stones. Majority of lesions were non-neoplastic of which chronic cholecystitis was the commonest. Incidence of carcinoma was relatively low (0.4%) as compared to other studies from different regions of country. An increase in age interval of chronic cholecystitis, metaplasia, dysplasia and carcinoma was noted with highest frequency of patients in respective age groups being in 30-39 yrs, 40-49 yrs, 40-49 yrs and 60-69 yrs. A high index of suspicion combined with careful assessment of cholecystectomy specimen is a must to rule out gall bladder carcinoma. Present study provides an impetus for further research to find factors leading to histomorphological changes in cholecystectomy specimens and the importance of this common yet underrated specimen in histopathology.

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