

# Spectrum of Clinico-pathological Presentations of Gall Bladder Diseases in Eastern UP

A. C. Srivastav<sup>1</sup>, Manglesh Srivastava<sup>2</sup>, Rajesh Paswan<sup>3</sup>

<sup>1</sup>Senior Consultant Surgeon OPEC Hospital, Kaily, Basti, U.P, <sup>2</sup>Consultant Pathologist, Tilak Pathology, Gorakhpur, UP,

<sup>3</sup>Consultant Radiologist, OPEC Hospital, Kailey, Basti, UP, India

**Corresponding author:** Dr Abhay Chand Srivastava, Senior Consultant Surgeon, OPEC Hospital, Basti – 272001 (UP), India

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## A B S T R A C T

**Introduction:** Gallstone disease is a major public health problem worldwide, particularly in adult population. Incidence of gallstone disease shows considerable geographical and regional variations. Gallbladder cancer is the most common malignancy of the biliary tract. So the study was undertaken with the aim of estimating the clinico-pathological spectrum of gall bladder disease.

**Material and Methods:** A total of 800 resected cholecystectomy specimens received during the period of 3 years were included. Clinical details and other relevant information were collected from the records. Statistical correlation was calculated using chi-square test and p-value was. Value of  $p < 0.05$  was considered statistically significant.

**Results:** Of the total of 800 cholecystectomy specimens it included 95 males and 705 females. Most of the cases were of age group 31-40 years. Majority of the malignant cases occurred in the 8<sup>th</sup> decade. Most common diagnosis was chronic cholecystitis and more common in females. Multigravida females were more prone to develop gall bladder diseases. The commonest presenting complaints were right hypochondrial pain in 460 (92%), followed by nausea in 15 (3%), epigastric pain in 13 (2.6%), vomiting in 10 (2%), jaundice in 2(0.4%).

**Conclusion:** Study of the clinico-pathological spectrum of gallstone diseases in this region would help in understanding the disease and its complications. Gall bladder diseases are more common in females. Multiparity and mixed diet are important risk factors. Majority of the cases are benign lesions. It is also recommended that each and every specimen of gallbladder be subjected to histopathological examination.

**Keywords:** Gall Bladder, Stones, Histopathology, Pain

## INTRODUCTION

Gallstone disease is a major public health problem worldwide, particularly in adult population. Incidence of gallstone disease shows considerable geographical and regional variations. Its occurrence has been found to be at least 6% in the adult population of North India.

The rate of gall bladder diseases are more common among females than males. Gall bladder disease are more common in the Northern and Northeastern states of Uttar Pradesh, Bihar, Orissa, West Bengal and Assam.<sup>1</sup> Risk factors for gall bladder disease include diet, obesity, multiparity and chronic infections including Salmonella typhi and paratyphi and Helicobacter pylori.<sup>2</sup>

Gall stones (cholelithiasis) has increasingly become a major cause of abdominal pain and discomfort in the developing world. The prevalence of gall stones is has increased in the recent years. The types of gall stones include - Mixed stones, combined stones, Pigment stones and, Cholesterol stones.

Gallbladder cancer (GBC) is the most common malignancy of the biliary tract, accounting for 80%–95% of biliary tract cancers.<sup>8</sup> Gall bladder cancer is more common among north

Indian cities and two times higher in women.<sup>2</sup> The incidence of gall bladder carcinoma has great geographic and ethnic variation.<sup>4</sup>

In India, gall bladder cancer is rare (1%). Majority of the incidence of gall bladder cancer are from northern (The Gangetic belt) and central parts of the country.<sup>5</sup> Screening of pre-malignant lesions of gall bladder is mandatory for early detection of disease and presence of suspicious lesion. An appropriate early measure is important for curative treatment and long-term survival of patients. Screening examinations are necessary to reduce mortality and morbidity among high-risk patients.

### Aims and objectives

The study was undertaken with the aim of estimating the clinico-pathological spectrum of gall bladder disease and, to study the frequency of various lesions of gall bladder and their association with age, sex and other probable risk factors.

## MATERIAL AND METHODS

A total of 800 resected specimens of gallbladder received during the period of 3 years from January 2015 to December

2017 were included. The place of study was in a 150 bedded hospital set-up. Specimens which were not sent in proper fixative and where morphological details were not discernible were excluded out. Clinical details and other relevant information were collected from the records including gross examination findings-size of gallbladder, serosa, wall thickness, mucosa, presence/absence of stones, their number, and type was noted along with any mass lesions. At least three representative sections were taken, one each from fundus, body and neck. Additional sections were taken whenever any grossly visible abnormal area was present. One section was taken from the attached lymph

node, if present. Microscopic examination was performed on paraffin embedded blocks. Haematoxylin and eosin stained tissue sections were examined and the following features were assessed-inflammation, cholesterosis, granulomas, metaplasia, calcification, dysplasia, benign and malignant neoplasms. Ethical clearance was obtained from Institutional Ethical Committee.

### STATISTICAL ANALYSIS

Statistical correlation was calculated using chi-square test and p-value was. Value of  $p < 0.05$  was considered statistically significant.

### RESULTS

In the present series a total of 800 cholecystectomy specimens were subjected to histopathologic evaluation. This included 95 males and 705 females. Most of the cases were of age group 31-40 years and only two cases (both malignant) occurred in the age group of 81-90 years. Majority of malignant cases occurred in the eighth decade. Most common diagnosis rendered was chronic cholecystitis and was relatively more common in females. Majority of the lesions were more common in females except for the porcelain gallbladder. Peak incidence of gallstone diseases in the present study was 31 – 40 years. Females have outnumbered the males in the present study by ratio of 7.42%. Majority of patients were females (441) accounting for 88.2% whereas males were only 59 (11.8%). (Table I)

Multigravida females were 425 (96.38%) and are more prone to develop gall bladder diseases, than nullipara which were 16 (3.63%). (Table II).

Stone characteristics and its association with various benign and malignant cases are shown in [Table VI]. Most common type of stone was mixed, present in 496 cases. No stones were present in 170 cases. All these acalculous cases showed features of chronic cholecystitis. A total of 136 and cases

Gender	No. of cases	%
Females	705	88.13
Males	95	11.87
Total	800	100

**Table-1:** Gender wise incidence of gallbladder lesion

Symptoms	Frequency	%
Right hypochondrial pain	736	92.00
Nausea	24	3.00
Epigastric pain	21	2.60
Vomiting	16	2.00
Jaundice	3	0.38
TOTAL	800	100

**Table-2:** Distribution of cases accordind to the presenting symptoms

Category of lesions	No. of cases	%
Calculous lesions	630	78.75
Acalculous Lesion	170	21.25
Total	800	100

**Table-3:** Distribution of lesion in relation to stones

Age (In years)	Non-neoplastic				Pre-malignant				Malignant			
	Male	%	Female	%	Male	%	Female	%	Male	%	Female	%
0-10	1		3	0.6								
11-20	6	8.7	26	4.5	2	25						
21-30	11	15.2	157	27.7			14	19.6				
31-40	22	30.4	176	31.1			27	37.0	2	10	17	27.5
41-50	8	10.9	118	20.9	5	75	11	15.2	5	30	22	35
51-60	10	13.0	64	11.3			13	17.4	5	30	21	32.5
61-70	8	10.9	22	4.0			8	10.9	3	20	3	5.0
71-80	8	10.9							2	10		
TOTAL	74	11.56	566	88.44	7	8.75	73	91.25	17	21.25	63	78.75
	* $\chi^2$ -38.17, p=0.000 (Highly Significant)				* $\chi^2$ -20.9, p=0.000 (Highly Significant)				* $\chi^2$ -1.14, p=0.887 (Not Significant)			

**Table-4:** Age and sex wise distribution of gall bladder lesion.

Diet	Non neoplastic	%	Premalig nant	%	Malignant	%
Veg	240	37.5	24	30	13	16.25
Mixed	400	62.5	56	70	67	83.75
Total	640	100	80	100	80	100

\* $\chi^2$ -9.599, p=0.008 (Highly Significant)

**Table-5:** Distributions of cases of gall bladder lesions according to the diet

Type of lesions	Mixed	%	Combined	%	Pigment	%	Cholesterol	%
Non neoplastic	434	87.5	38	82.61	43	79.63	23	67.65
Pre-Malignant	24	4.84	5	10.87	8	14.81	5	14.71
Malignant	38	7.66	3	6.52	3	5.56	6	17.65
Total	496	100	46	100	54	100	34	100
*X <sup>2</sup> -7.356, p=0.289 (Not Significant)								
<b>Table-6: Relation of type of stones with gall bladder lesions</b>								

had single stone and 13 malignant cases had multiple stones. All the cases of granulomatous cholecystitis and empyema had multiple stones. A statistically significant relation was found between presence of stones and carcinoma (p=0.01). However, no significant correlation was found between presence of stones and benign lesions (p=0.416).

The most common presenting complaints among patients suffering from gall bladder diseases were right hypochondrial pain in 460 (92%), followed by nausea in 15 (3%), epigastric pain in 13 (2.6%), vomiting in 10 (2%), jaundice in 2(0.4%). (Table III)

The highest number of cases of gall bladder lesions were associated with calculi in 394 (78.8%) and no stones in 106 (21.2%). (Table IV)

Maximum number of cases of gall bladder lesions are associated with multiple gallstones in 277 (70.31%), followed by single calculous in 85 (21.58%), double calculi in 32 (8.13%). Mixed stones were more commonly found in 310 (78.69%), followed by pigment in 34 (8.63%), combined in 29 (7.37%), cholesterol in 21(5.33%). (Table V)

Among total cases, 400 (80%) turned out to be benign, 50 (10%) were pre-malignant and 50 (10%) were malignant.

It was observed that among the non-neoplastic lesions maximum cases were in the age group of 31-40 yrs for both males and females. In the pre-malignant category majority of the male patients belong to the 41-50 yrs, whereas in females the 31-40 yrs had the maximum cases 17 (37.7%). Amongst males, both the age group of 41-50 and 51-60 years were affected in the malignant category, but for females 41-50 years had the maximum cases. (Table IV)

When the lesions were divided as per the dietary intake majority of the patients 327 (65.4%), were observed to consume mixed diet in all the cases. In the malignant category mixed diet consumption was the maximum with 42 patients (84%) affected (Table V). Distribution of the type of lesions as per the type of stone is depicted in Table VI.

## DISCUSSION

Male to female ratio observed was 1:4 as also reported by Schirmer et al (2005). The results of the present study exhibit female preponderance thus holding true the saying that 'a fatty, fertile, flatulent, female of forty is the classical sufferer from symptomatic gallstones.'

In the present study, the most commonly involved age group for cholelithiasis was found to be 31-40 years while Pradhan et al<sup>6</sup> reported maximum 32.5% cases belongs to age group 30-39 years with M:F of 1:3.2, similar observations were reported by Idris et al<sup>7</sup> and Aslam t al<sup>8</sup>, who observed majority of cases from age group 31-50 years.

In the present study, most of the cases of cholelithiasis presented with pain in the right hypochondrium, nausea

was present in 24 cases and only 19.14% had vomiting. Jaundice was observed only in 3 cases. Similar observations were reported by Pradhan et al<sup>6</sup>, in their study they observed maximum 75% cases presented with pain Right Hypochondrium followed by epigastric pain (57.5%).

The commonest physical sign in the present study was gallbladder lump followed by right hypochondrial tenderness. However, in majority of the cases, there was no major clinical sign suggestive of acute biliary disease at the time of presentation. This being a tertiary care referral centre, the patients are usually referred here by local practitioners from remote areas after giving them symptomatic relief. In this study, maximum percentage of cases had mixed type of gallstones followed in decreasing frequency by cholesterol combined and pigment type gallstones in only cases. The findings are similar with the finding in the study done by Pradhan et al.<sup>6</sup> In contrast Idris et al<sup>7</sup> reported in their study in Sudan, maximum 51.1% cases had pigment stone.

Non-vegetarians were found to be more commonly involved with cholelithiasis than vegetarians. The ratio of incidence of cholelithiasis in non-vegetarian – vegetarian was found to be the exact cause can not be stated however it could be due to the consumption of high protein and fat. The findings were similar with the findings in a study done by. Whereas Pradhan et al<sup>11</sup>, reported non- vegetarian and vegetarian ratio of 9:1 When the lesions were divided as per the dietary intake majority of the patients 327 (65.4%), were observed to consume mixed diet in all the cases. In the malignant category mixed diet consumption was the maximum with 42 patients (84%) affected. Among 310 cases of mixed gallstones, maximum 271 (87.41%) mixed gall stones were present in non-neoplastic category, 24(7.74%) mixed gall stones were present with malignant lesions, mixed stones were seen in pre-malignant condition.

Khanna et al<sup>9</sup> conducted a histopathological study of 140 consecutive gallbladders in which, epithelial hyperplasia was observed in 83(69%), antral metaplasia in 53(16.5%), intestinal metaplasia in 22(15.5%), dysplasia in 12(8.5%) and carcinoma in situ in 1 specimen (0.7%). Cholelithiasis and even silent gallstones, which were asymptomatic, produced a series of epithelial pathological changes in the gallbladder mucosa, which could be precursor lesion of carcinoma gallbladder. These changes include hyperplasia, metaplasia and dysplasia.<sup>22</sup> The incidence of gallbladder cancer is approximately 7 times more common in the presence of cholelithiasis and chronic cholecystitis than in people without gallstones. In addition, the risk of developing gallbladder cancer is higher in patients with symptomatic gallstones than in patients with asymptomatic gallstones as reported by Ahrendt and Pitt.<sup>10,11</sup>

Prophylactic cholecystectomy has been recommended in many

high risk populations, such as in Chile. Since the incidence and mortality rates of gallbladder cancer in Northern Indian women is one of the highest in the world, Mohandas and Patil<sup>12,13</sup> suggest that preventive cholecystectomy be offered to all young healthy women in Northern India when they are diagnosed to have asymptomatic gallstones.

Khanna et al<sup>9</sup> also support the contention that cholecystectomy should be offered to all asymptomatic gallstone patients, especially if they are less than 60 years of age and are living in a high-incidence area. Eastern U.P. and Indo-Gangetic belt have amongst the highest incidence of gallbladder carcinoma in the world.

Gall bladder diseases constitute a significant health problem in developed societies, affecting 10% to 15% of the adult population.<sup>14</sup> The 5 F's that are implicated include - Fair, Fatty, Female, Fertile, Forty. Gall stones are one of the major causes of morbidity and mortality all over the world affecting 10% of adult population.<sup>15</sup> Age incidence for gall stone diseases is 31-40 yrs of age group. Females were predominantly affected with a M:F ratio of 1:6. Risk factors for gall stone diseases are non-vegetarians (93.93%), multiparous woman (90.82%), obesity, sedentary life style.<sup>15</sup> Most common presenting complaints of gall bladder diseases were found to be abdominal pain (100%). Four types of gall stones are found- mixed, combined, pigment, cholesterol. Maximum percentage of cases of mixed type (66.41%) of gall stones are reported.<sup>16</sup>

The most common malignancy of biliary tract reported is gallbladder cancer (GBC) which is the third most common cancer in gastrointestinal tract.<sup>17</sup> Gall bladder cancer is most common in the Northern and Northeastern States of India. (75). The highest incidence of Carcinoma gallbladder in India has been seen along the Ganges delta.<sup>18</sup> A significantly higher incidence of carcinoma gall bladder has been observed in patient with gallstones for longer duration which progress from various epithelial lesions.<sup>19</sup> Prolonged irritation by gall stones or chronic inflammation causes metaplastic changes in the gall bladder mucosa which leads to development of carcinoma.<sup>20</sup> Various epithelial pathological changes in the gall bladder mucosa are ruled out with the help of clinico-radiological examination and extensive histological evaluation to prevent cancer related morbidity and mortality.

In the present study the commonest presenting complaint among patients suffering from gall bladder disease was right hypochondrial pain 460 (92%) cases. This observation was consistent with the findings of Agrawal et al.<sup>13</sup> In the present study the maximum number of cases of gall bladder lesions were associated with gall stones in 630 (78.8%) and acalculous gall bladder were in 170 (21.2%) patients. This was consistent with the findings of Goyal S et al<sup>21</sup> who showed 313 cases (90%) associated with gall stones and the rest 33 cases (10%) were without stones. Mazlum M et al<sup>22</sup> studied specimen of gall bladder in which rate of cholelithiasis was 89.9%. Vrbica SM et al<sup>23</sup> studied gall bladder specimens and found 80% were calculous lesions. Observation made by Dattal DS et al<sup>24</sup> was similar to our study as he found, 1259 (91.8%) cases had gall stones and 112 (8.2%) cases were not associated with gall stones.

In present study, out of total 394 cases, 277 (70.30%) cases

were having multiple gallstones. This was consistent with the findings of Mathur SK et al<sup>25</sup> who studied gall bladder specimens and found multiple gallstones in 170 (51.6%) cases. Similar to the present study Goyal S et al<sup>21</sup> found maximum cases (218) are associated with multiple gall stones. Observation made by Singh AK et al<sup>26</sup>, (58%) were similar to that of our study.

In the present study, among all cases, majority were benign, followed by pre-malignant and malignant sessions. This was sharp in contrast to the concept given by Sharma I et al<sup>27</sup>, Singh G et al<sup>19</sup> who reported maximum number of cases of non-neoplastic lesions of gall bladder. Kumbhakar D<sup>28</sup> found 395 (98.75%) specimens of gall bladder showing non-neoplastic pathology and 5 (1.25%) specimens showed neoplastic pathology which was similar to our study. Yadav A et al<sup>16</sup> performed study on 106 cholecystectomy specimen in which he found 99 (93.3%) cases of inflammatory lesions, 05 (4.7%) cases of malignancy which was similar to our study.

In present study it was observed that among the non-neoplastic lesions maximum number of cases were in the age group of 31-40 yrs for both males and females. In the pre-malignant category majority of the male patients belong to the 41-50 yrs, whereas in females the 31-40 yrs had the maximum cases 17 (37.7%). Amongst males, both the age group of 41-50 and 51-60 years were affected in the malignant category, but for females 41-50 years had the maximum cases. This was in sharp contrast to the concept given by Siddiqui FG et al<sup>28</sup>, Kapoor S<sup>29</sup> Goyal S et al<sup>21</sup>, Kumbhakar D et al<sup>28</sup>, Singh G et al (52) and found that maximum number of patients was in the age group of 30-40 years. Gulwani HV et al<sup>30</sup> found age of patients at diagnosis ranged from 32 to 80 years. Gopalakrishnan M et al<sup>31</sup> found gallstones were more common in the 40-49 age group. Naiding M et al<sup>32</sup> out of 22 cholecystectomies, in both the sexes the most common age group of presentation was 50-59 years. But study by Gupta P et al<sup>33</sup> found age of patients ranged from 30 to 70 years. 54% of patients were aged below 40 years of age, age of patients in neoplastic group ranged from 30 to 70 years. The proportion of patients aged above 50 years was 72%. In Non-neoplastic group, age of patients ranged from 31 to 63 years. The proportion of patients aged above 50 years was 20%.

## CONCLUSION

The conclusions were drawn from this study included - gall bladder diseases are more common in females. Multiparity and mixed diet are important risk factors. Majority of the cases are benign lesions. Maximum number of gall stones are mixed followed by pigment, combined, cholesterol. In non-neoplastic lesions of gall bladder, 259 cases of chronic cholecystitis with cholelithiasis are found in which maximum number of cases were 75, seen in age group of 30-39 yrs. Maximum number of cases with multiple gallstones are found in chronic cholecystitis with cholelithiasis, chronic cholecystitis with cholelithiasis and dysplasia, well differentiated adenocarcinoma with cholelithiasis and intestinal metaplasia. Gall stones mainly injure the mucosal columnar epithelium and thus causes changes like metaplasia, dysplasia and neoplasia.

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