

Study of Incidental Carcinoma Gallbladder in Operated Cases of Gallstone Disease at Tertiary Care Hospital in Eastern Uttar Pradesh

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ABSTRACT

Background and objectives: Due to the late detection of primary carcinoma of gallbladder (CaGB), the overall prognosis has remained poor with a 5-year survival of 5–10%. In practice, after elective cholecystectomy for presumably benign gallbladder disease, primary CaGB is an unexpected histopathological finding in resected specimens. Current study aims to determine the incidence of incidental CaGB and to determine factors predictive of CaGB in patients operated for chronic cholecystitis.

Materials and methods: In this single center, prospective observational study, analysis of incidence and various biological characteristics of 200 consecutive patients with chronic cholecystitis was done who underwent cholecystectomy and were subsequently histologically diagnosed as incidental CaGB. Results of the study were compiled, tabulated, and analyzed using statistical methods, and inference was drawn.

Results: In the study, five patients were diagnosed with incidental CaGB histologically after cholecystectomy for chronic cholecystitis, and the incidence of incidental CaGB was 2.5%. Sociodemographic parameters and pathophysiological observations are additionally drawn to determine factors predictive of primary CaGB.

Conclusions: In view of the study findings, it may be inferred that chronic cholecystitis is a significant surgical disease in our population. This is significant because laparoscopic cholecystectomy is being more commonly used for the treatment of chronic cholecystitis in which there are considerable chances of perioperative spillage of biliary contents because of which there are possibilities for the very early gallbladder carcinoma becoming a disseminated disease. The operating surgeon should have high index of suspicion regarding this incidental but fatal gastrointestinal malignancy.

Keywords: Carcinoma, Cholecystectomy, Gallbladder, Incidental, Laparoscopic.

World Journal of Laparoscopic Surgery (2021): 10.5005/jp-journals-10033-1475

INTRODUCTION

Gallbladder cancer is the most common malignant tumor of the biliary tract worldwide and the fifth most common cancer involving the gastrointestinal (GI) tract.^{1,2} Primary carcinoma of gallbladder (CaGB) clinically resembles benign disease because of which it is detected late in its course. In practice, after elective cholecystectomy for presumably benign gallbladder disease, primary CaGB is an unexpected histopathological finding in 1–3% resected specimens. It is prevalent mainly in sixth and seventh decades of life. The overall prognosis has remained poor because of the late detection of the disease with a 5-year survival of 5–10%. Before the era of computed tomography (CT) scan and ultrasonography (USG), the rate of correct preoperative diagnosis was only 8.6%, which has improved considerably with the use of newer imaging techniques. Still a preoperative diagnosis of early gallbladder carcinoma (EGBC) is rarely made, where the 5-year survival is 91–100%. Most of the available literature is reported from developed countries, which have a different socioeconomic culture and health setup from that of a developing country such as India.^{1,2}

The purpose of undertaking this study was that a reasonably high number of CaGB patients have been noted in the Gangetic planes of Uttar Pradesh, which forms the area of our study. We have undertaken a study of the incidence of CaGB in operated cases of gallstone disease, which included all cases who underwent cholecystectomy (laparoscopic/open) at Department of Surgery in a tertiary care referral hospital in eastern Uttar Pradesh, India, on consecutive 200 patients. The study involves the analysis of

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How to cite this article: Jain V, Mishra RY, Gupta M, et al. Study of Incidental Carcinoma Gallbladder in Operated Cases of Gallstone Disease at Tertiary Care Hospital in Eastern Uttar Pradesh. *World J Lap Surg* 2021;14(3):177–182.

Source of support: Nil

Conflict of interest: None

incidence and various biological characteristics of patients of gallstone disease who underwent cholecystectomy and were subsequently histologically diagnosed as incidental CaGB.

MATERIALS AND METHODS

The study comprised a single center, prospective observational study. This study was conducted at Department of Surgery in

a tertiary care referral hospital in eastern Uttar Pradesh, India, on 200 consecutive patients who underwent cholecystectomy (laparoscopic/open) for chronic cholecystitis between October 2014 and May 2016. An informed written consent was taken.

Inclusion Criteria

All patients who underwent cholecystectomy (laparoscopic/open) for chronic cholecystitis.

Exclusion Criteria

- Diagnosed or suspected case of CaGB.
- Patients not fit for surgery.

Parameters Studied

- Detailed history and clinical examination.
- Baseline investigative work up.
- Special investigations like prothrombin time (PT), USG whole abdomen, CT scan abdomen, magnetic resonance cholangiopancreatography—where indicated, endoscopic retrograde cholangiopancreatography (ERCP)—where indicated.
- Histopathology.

Statistical Analysis

SPSS statistical software was used for analysis. One-way analysis of variance test was used to compare between two groups. To test the association between variables, Fisher’s exact test was used. The *P*-value less than 0.05 was considered as significant. Results of the study were compiled, tabulated, and analyzed using statistical methods, and inference was drawn. All information recorded in the proforma was verified. The results were compared with data obtained from different geographical regions. A total of 200 consecutive chronic cholecystitis patients who satisfied the study criteria were incorporated as the study group. This study was ethically conducted in accordance with Declaration of Helsinki.

RESULTS

Results and findings observed in studied sample are presented in the subsequent sections.

Intraoperative Findings

Intraoperative findings are depicted in Table 1 and Figure 1. In most of the patients, gallbladder (GB) was distended, adhesion was minimal, and GB contained multiple or single stones.

Histopathology Findings

Different biopsy findings are mentioned in Table 2 and Figure 2. According to the biopsy report, five cases were diagnosed as CaGB, usually infiltrating up to lamina propria. Most of these were adenocarcinoma. Rest were frank chronic cholecystitis.

Final Diagnosis

Among 200 patients, 195 had chronic cholecystitis, and 5 cases were diagnosed as CaGB in the postoperative settings from their biopsy report (Table 3; Figure 3). These cases are incidental CaGB.

Comparative Results between Chronic Cholecystitis and Incidental CaGB

Demographic Profile

Age

- Among the incidental CaGB patients, mean age: 45.4 years; median age: 36 years; standard deviation: 18.64; mode: 30; minimum age: 30 years; maximum age: 76 years (Tables 4 and 5).

Table 1: Intraoperative findings of our study group (N = 200)

Operative finding	Frequency	%	Valid %	Cumulative %
Valid				
GB distended, adhesion-minimal	165	82.5	82.5	82.5
GB contracted, adhesion+	21	10.5	10.5	93
GB contracted, adhesion-	9	4.5	4.5	97.5
GB distended, adhesion+	5	2.5	2.5	100
Total	200	100.0	100.0	

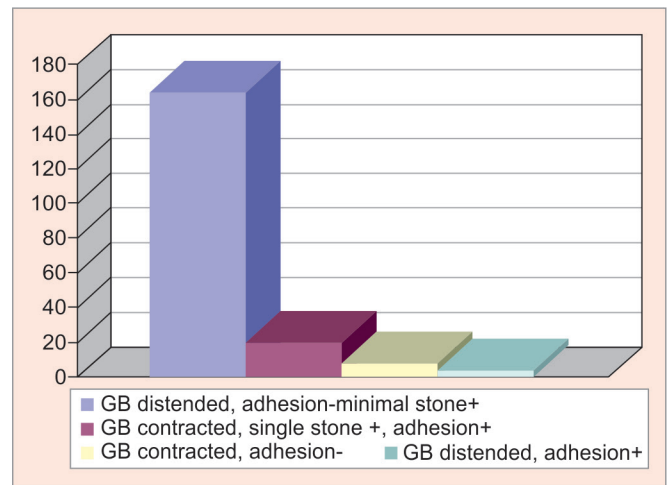


Fig. 1: Bar graph showing intraoperative findings of our study group (N = 200)

Table 2: Histopathology examination findings of our study group (N = 200)

Histopathological examination (HPE)	Frequency	%	Valid %	Cumulative %
Valid				
Chronic cholecystitis	195	97.5	97.5	97.5
Dysplasia bordering to adeno Ca <i>in situ</i>	1	0.5	0.5	98
Well-differentiated adeno CaGB (pT3NxMx)	1	0.5	0.5	98.5
Moderately differentiated adeno CaGB (pT3NxMx)	1	0.5	0.5	99
Poorly differentiated adeno CaGB (pT2NxMx)	1	0.5	0.5	99.5
Poorly differentiated adeno CaGB (pT3NxMx)	1	0.5	0.5	100
Total	200	100.0	100.0	

- Among chronic cholecystitis patients, mean age: 44.15 years, median: 44; mode: 45; standard deviation: 14.67; minimum age: 6 years; maximum age: 78 years (Tables 4 and 5).
- *p* = 0.85 (unpaired *t*-test)—not significant.



Other Demographic Profiles

- Among incidental CaGB patients, 40% were male and 60% were female; 29.74% of chronic cholecystitis patients were male and 70.1% were female (Table 6).
- Regarding incidental CaGB patients, 40% were doing desk job, 60% were housewives.
- Among chronic cholecystitis patients, 19.48% were doing desk job, 9.2% were retired persons, and 66.66% were housewives (Table 6).
- In total, 40% of incidental CaGB patients lived in rural area and 60% in urban area; 69.23% of chronic cholecystitis patients lived in rural area and 30.77% in urban area (Table 6).
- Table 7 shows statistical tests for demographic profiles in CaGB vs chronic cholecystitis patients.

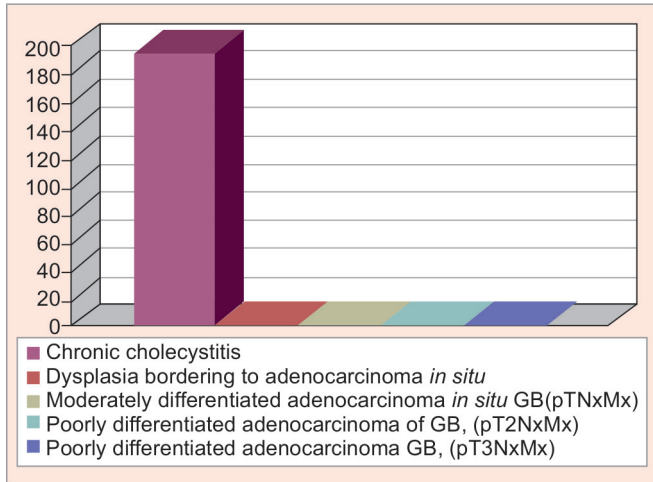


Fig. 2: Bar graph showing histopathology examination findings of our study group (N = 200)

Table 3: Frequency of CaGB patients in study group (N = 200)

	Frequency	%	Valid %	Cumulative %
Valid				
CaGB	5	2.5	2.5	2.5
Chronic cholecystitis	195	97.5	97.5	100.0
Total	200	100.0	100.0	

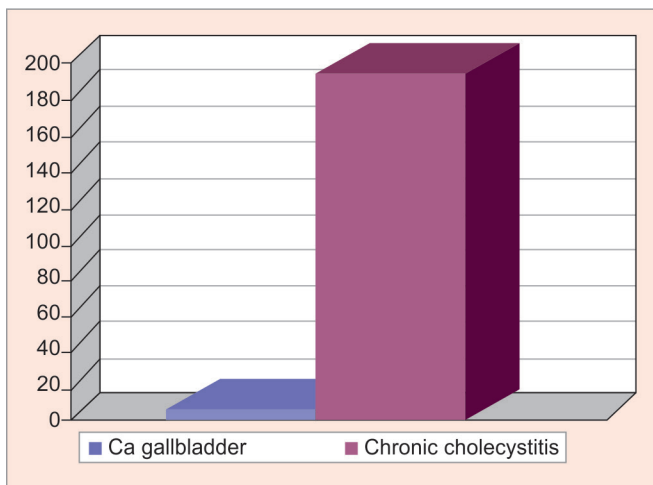


Fig. 3: Bar graph showing frequency of CaGB patients in study group (N = 200)

Table 4: Age comparison in CaGB vs chronic cholecystitis patients (N = 200)

Diagnosis	Cases					
	Valid		Missing		Total	
	N	%	N	%	N	%
Age CaGB	5	100.0	0	0.0	5	100.0
Chronic cholecystitis	195	100.0	0	0.0	195	100.0

Table 5: Age distribution in CaGB vs chronic cholecystitis patients (N = 200)

Age	CaGB (N = 5)	Chronic cholecystitis (N = 195)
Minimum age	30	6
Maximum age	76	78
Median age	36	44

Table 6: Demographic profiles in CaGB vs chronic cholecystitis patients (N = 200)

Case profile	Incidental CaGB (n = 5)		Chronic cholecystitis (n = 195)		Total (n = 200)	
	No.	%	No.	%	No.	%
Sex: male	2	40	58	29.74	60	30
Sex: female	3	60	137	70.16	140	70
Occupation: desk job	2	40	38	19.48	40	20
Occupation: retired person	0	0	18	9.2	18	9
Occupation: housewife	3	60	130	69.23	133	66.5
Rural	2	40	135	69.23	137	68.5
Urban	3	60	60	30.77	63	31.5

Table 7: Statistical tests for demographic profiles in CaGB vs chronic cholecystitis patients

Parameter	p value	Test	Comment
Sex: male/female	0.63	#Fisher's Exact test	*Not significant
Occupation housewife—others	0.98	Do	Do
Rural/urban	0.37	Do	Do

#Fisher exact test used. *p <0.05 significant

Patient's History

After cross-tabulation, the following results were obtained. Table 8 shows symptom comparison in CaGB vs chronic cholecystitis patients as mentioned as follows:

- Among five CaGB patients, four (80%) had upper abdominal pain and one (20%) had no pain. Among 195 chronic cholecystitis patients, 149 (76.02%) patients had upper abdominal pain.
- Forty percent of incidental CaGB patients had nausea and 60% had no nausea.
- Among chronic cholecystitis patients, 38.46% had nausea.
- Among incidental CaGB patients, 20% had vomiting, 80% had no vomiting. Among chronic cholecystitis patients, 17.43% had vomiting.

Table 8: Symptoms comparison in CaGB vs chronic cholecystitis patients (N = 200)

Chief complaints	Incidental CaGB (n = 5)		Chronic cholecystitis (n = 195)		Total (n = 200)	
	No.	%	No.	%	No.	%
Upper abdominal pain	4	80	149	76.02	153	76.5
Nausea	2	40	75	38.46	79	39.5
Vomiting	1	20	34	17.43	36	18
Fever	1	20	6	3	8	4
Upper abdominal mass	0	0	0	0	0	0
Weight loss	0	0	8	4	8	4
Anorexia	2	40	17	8.7	19	9.5
Jaundice	1	20	4	2	5	2.5

Table 9: Statistical tests for symptoms in CaGB vs chronic cholecystitis patients

Parameter	p value	Test	Comment
Upper abdominal pain	0.72	Chi-square with Yate's correction	Not significant
Nausea	0.69	Do	Do
Vomiting	0.65	Do	Do
Fever	0.42	Do	Do
Anorexia	0.11	Do	Do
Jaundice	0.27	Do	Do

- Among incidental CaGB patients, 20% had fever. Among chronic cholecystitis patients, 3% had fever.
- Among incidental CaGB patients, 0% had mass, 100% had no mass. Among chronic cholecystitis patients, 0% had mass and 100% had no mass.
- Among incidental CaGB patients, 0% had weight loss, 100% had no weight loss, and 4% of chronic cholecystitis patients had weight loss, 96% had no weight loss.
- Forty percent of incidental CaGB patients had anorexia, 8.7% of chronic cholecystitis patients had anorexia.
- Among incidental CaGB patients, 20% had jaundice. Among chronic cholecystitis patients, 2% had jaundice and 98% were normal.
- Rest of the clinical features, investigations and intraoperative findings also resemble with chronic cholecystitis.
- It was also noted that among the incidental CaGB patients, four patients had laparoscopic cholecystectomy in which there are more chances of biliary spillage. Thus, possibility of the very early disease becoming a disseminated disease.
- Table 9 shows statistical tests for symptoms in CaGB vs chronic cholecystitis patients.

Follow-up

- One-hundred and ninety-five patients with histopathological examination (HPE) report symptoms of chronic cholecystitis were followed up for a period of 1 week postcholecystectomy.
- Two patients with poorly differentiated adeno CaGB (pT3NxMx) and poorly differentiated adeno CaGB (pT2NxMx) lost to follow up.
- Two patients with well-differentiated adeno CaGB (pT3NxMx) and moderately differentiated adeno CaGB (pT3NxMx) underwent radical cholecystectomy and followed up subsequently for

1 month in surgery outpatient department (OPD) and later in oncology OPD.

One patient with dysplasia bordering to adeno CaGB *in situ* was followed up after 1 month for 3 months and then 3 monthly. Subsequent radiological studies were normal.

DISCUSSION

Inapparent (also called occult or incidental) GBC is defined as GBC unrecognized before or at operation and detected for the first time on HPE of the gallbladder, which has been removed for presumed gallstone disease.³

In our study, among the Incidental CaGB patients, minimum age was 6 years; maximum age was 78 years, and mean age was 43.46 years. This finding is in accordance with previous studies. Shukla et al.¹ reported mean age of the CaGB patients to be 50 years (range 40–60 years.), the mean age of 1,728 patients from 29 series, reported upon since 1960, was 65.2 years with incidence of CaGB of 0.1, 1.5, 8.9, 19.6, 37.0, and 32.0% in third, fourth, fifth, sixth, seventh, and eighth decades, respectively.⁴

Among 200 chronic cholecystitis patients, 30% are male and 70% are female. This could be because of the fact that cholecystitis is most common in female. Thus, in a hospital-based study, women patients form a majority.

Piehler and Crichlow⁴ showed that “Carcinoma of the gallbladder is predominantly a disease of elderly females of 2,998 patients from 51 series reported over last 20 years, there were 2,292 females (75%) and 706 males (25%), a female to male ratio of 3.2:1.⁴ In the study by IARC under SEARCH program, gallbladder cancer was found to be commonest among women (56%) with cancer of the ampulla of the Vater coming second with 30%”.

According to our study, CaGB is common in female population because chronic cholecystitis is common in female population.

Among 200 patients, 66.5% patients were housewives, 20% were doing desk job. This could be explained by the Indian socioeconomic status and literacy rate.

Among 200 patients, 68.5% are from rural area and 31.5% are from urban area indicating geographical distribution of cases in population.

Shukla et al.¹ reported an incidence of 4.4% of all malignancies and 0.03% of total hospital admissions from Varanasi, India. Chao and Greager¹⁹ reported an incidence of 2.5/100,000 population and found CaGB in 1–3% of cholecystectomy specimens. In our study, the incidence of incidental CaGB is 2.5%. Table 10 depicting comparison of incidence rate of incidental CaGB by various authors.

Clinical features of patients in this study were as follows.

Among 200 patients, 76.5% patients have upper abdominal pain. In this population, 39.5% had nausea, 18% patient had vomiting, fever was present in only 4% of patients, 0% patient had abdominal mass, 4% patients had weight loss, 9.5% had anorexia, and 2.5% patients had clinical jaundice. In comparison, data regarding the presentation of CaGB are presented in Table 11 depicting comparison of clinical symptoms of GBC by various authors.

Pain was present in 47–97% of patients. This is comparable to the data (76.5%) in our study. Similarly, anorexia, weight loss, nausea, and vomiting were comparable in this study, and jaundice is a feature of advanced CaGB. This shows that there are no clinical features that would be suggestive of CaGB in a patient who presents with symptoms of chronic cholecystitis (Table 11).



Table 10: Comparison of incidence rate of incidental CaGB by various authors

Studies	Number of incidental CaGB	Total cholecystectomy	Incidence rate (%)
Daphna ⁵ et al.	6	1697	0.3
Tantia ⁶ et al.	19	3205	0.6
Mittal ⁷ et al.	13	1305	0.9
Morera ⁸ et al.	4	372	1.1
Amanullah ⁹ et al.	8	428	1.9
Shigeki ¹⁰ et al.	4	84	4.7
Present study	5	200	2.5

Table 11: Comparison of clinical symptoms of GBC by various authors

Series	Pain	Anorexia	Jaundice	Weight loss	Nausea/vomiting
Piehler and Crichlow	76%	34%	38%	39%	32%
Shieh et al. ¹¹	60.4%	43.7%	35.4%	33.3%	35.4%
Al-Hadeedi et al. ¹²	47.3%	39.4%	36.4%	39.4%	10.5%
Shukla et al.	85%	40%	60.3%	14.9%	24.7%
Klamer and Max ¹³	70%	—	40%	40%	30%
Silk et al. ¹⁴	78.5%	35.6%	28.5%	45.7%	35.6%
Perpetuo et al. ¹⁵	97%	—	44%	77%	64%
Kelly and Chamberlain ¹⁶	74%	—	32%	48%	51%
Chao et al. ¹⁷	81.1%	4.1%	32.4%	1.4%	16.2%
White et al. ¹⁸	83%	—	47%	70%	—
Chao and Greager ¹⁹	54.1%	18.9%	45%	28.4%	18.9%

No suggestive parameter of incidental CaGB could obtain from this comparison. Other parameters were also compared, but no result obtained. Only intraoperative findings are suggestive of CaGB in a few cases. These findings include adhesions, thickening, irregularity of GB wall, and disappearance of shiny appearance of gallbladder.

The following parameters of incidental CaGB were compared with chronic cholecystitis patients: Among incidental CaGB patients, mean age was 49.11 years, median age was 47 years, minimum age was 30 years, and maximum age was 76 years. Among incidental CaGB cases ($n = 5$), male patients were 40% and female patients were 60%. Among incidental CaGB patients, 40% were doing desk job, and 60% were housewives. Among incidental CaGB patients, 40% were living in urban area and 60% were living in rural area. Among incidental CaGB patients, 80% had pain abdomen and 20% had no pain. Among incidental CaGB patients, 40% had nausea and 20% had vomiting. Among incidental CaGB patients, 0% had weight loss. Among incidental CaGB patients, 100% had no jaundice. USG was normal (i.e.: only suggestive of chronic cholecystitis) in 100% of incidental CaGB cases.

No clinical, biochemical, or radiological parameters were found as preoperative predictor of CaGB in patients who underwent cholecystectomy for chronic cholecystitis.

There are no characteristic clinical features of EGBC. Unfortunately, it becomes clinically apparent only when it is locally advanced; the symptoms being due to invasion of neighboring organs. In two series, both from areas with a high incidence of GBC, where the index of suspicion was high, none of the EGBC was diagnosed clinically

and almost half of these were first diagnosed on HPE of resected specimen, thereby highlighting the elusive nature of EGBC.^{20,21}

All patients diagnosed with incidental CaGB were subsequently underwent staging work up with contrast enhanced CT abdomen and tumor markers. They were discussed among a team of surgical oncologist, GI surgeon, pathologist, radiologist, and radiation oncologist. They were managed as per consensus, which could be a second operation like completion cholecystectomy, or chemotherapy, chemoradiotherapy, palliative biliary drainage by ERCP, PTBD, or best supportive care at home.

It was also noted that among the incidental CaGB patients, four patients had laparoscopic cholecystectomy in which there are more chances of biliary spillage. Thus, possibility of the very early disease becoming a disseminated disease.

CONCLUSION

- In our study, the incidence of incidental CaGB was 2.5%.
- Unfortunately, no clinical, biochemical, or radiological parameters were suggestive or predictive of CaGB in patients who underwent cholecystectomy for gallstone disease.
- Further analysis revealed incidental CaGB was predominantly a disease of elderly female patients. The mean age was 45.4 years and 60% of incidental CaGB cases were female.
- In view of the findings from this study, it may be concluded that chronic cholecystitis remains a significant surgical entity in our population. However, the suspicion of incidental CaGB should be borne in mind.
- This is important as laparoscopic cholecystectomy is being increasingly used for the treatment of chronic cholecystitis. Also, if there is perioperative spillage of biliary contents, there is a possibility of the very early disease becoming a disseminated disease. The operating surgeon should have high index of suspicion regarding this not so uncommon and uniformly fatal GI malignancy.

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