

Original Article

Clinical Profile and Survival of Patients with Carcinoma Gall Bladder: A Retrospective Study of 1002 Patients from Eastern India

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ABSTRACT

Background: Gall bladder cancer (GBC) is one of the most prevalent gastrointestinal cancer in India, seen more in the north and central India. However, the data from eastern India is scanty, especially from state of Odisha, where there is recent surge in numbers of GBC.

Methods: A retrospective study was conducted after reviewing hospital records over a period of 7 years from 2012 to 2018. A total 1002 GBC patients were examined for clinical features, histological grade, and survival as per stage of the disease.

Result: Median age of patients was 55 years and with male: female ratio of 1:2.2. Total number of GBC cases were steadily increasing every year from 2012(80) to 2018 (204). Around 95 % GBC patients were of stage III and stage IV disease. Most common symptom was pain abdomen (85%) followed by jaundice (72%) and pruritus (54%). Cholelithiasis was noted in 387 (39%) patients. Most common radiological finding was mass replacing GB fossa in 645 (64%). Adenocarcinoma was the most common histologic subtype of GBC in 86% cases. Liver was most common site of metastasis (44%) followed by peritoneum (24%), lungs (13%), and bones (3%). Adrenal metastasis, which is a rare finding in GBC, was found in 2% patients. The median survival for stage I, II, III and IV diseases was 44, 38, 26 and 5.3 months respectively.

Conclusion: The incidence of GBC is alarming in the state of Odisha and most patients presented in stage IV disease with median survival of less than 6 months. Adrenal metastasis although rare occurrence in GBC, was found in 2% patients.

KEYWORDS: Carcinoma gall bladder, GBC, Epidemiology, Survival.

Introduction

Gall bladder cancer (GBC) is one of the most common biliary malignancy and the third most prevalent cancer of the gastrointestinal tract with wide geographical variation in its occurrence.^{1,2} The highest incidence of GBC is observed in Chile which approximates the incidence witnessed in northern parts of India, along the banks of river Ganga, Sutlej and Brahmaputra.^{3,4,5} However, other South American Countries like Bolivia and Ecuador and some Asian countries Pakistan, Japan, and South Korea also have higher incidence of GBC.^{3,4} Although the exact etiopathogenesis is unclear, the risk factors of GBC include advanced age, female sex, gall stone disease, typhoid carrier state, chemical carcinogens, dietary factors and genetic susceptibility. The pathogenesis of GBC involves progression from metaplasia to dysplasia to carcinoma in situ, and then to invasive cancer over a period of 5 to 15 years.⁶

GBC is diagnosed either incidentally at the time of cholecystectomy or at an advanced stage with jaundice, hepatomegaly, ascites or duodenal obstruction.⁷ Various studies have shown that at the time of presentation, approximately 60% patients have local infiltration to liver, duodenum or colon. Lymphatic spread is also common with GBC with 45% patients having regional lymph node involvement and 30% with distant metastasis. Due to the advanced stage of presentation, survival of GBC is significantly reduced with a five-year survival rate only of 5%.^{8,9} Although surgery is the only curative treatment for GBC, only 10% of patients are operable at the time of presentation.⁸ With the advancement of extensive resection surgery for GBC, 5-year survival rates of 20-25% could be achieved.¹⁰

As the gallbladder mucosa cannot not be assessed endoscopically, there is no screening program for GBC. The symptoms are nonspecific in the early part of disease, so diagnosis of GBC can be made by radiological imaging such as ultrasonography, CT scan, and MRI of abdomen. So, identification of risk factors and primary prevention become the mainstay in prevention of GBC. Despite being a major health problem in India, only a few studies are available from the eastern part of India on the clinical presentation and natural history of disease. Most of the

studies published from India are from northern part of the country. Hence, this study was conducted to assess the clinical and radiological picture in a large cohort of patients from a tertiary health-care centre and to estimate the survival in different stages of GBC.

Methods

A retrospective cohort study was conducted after reviewing the hospital records of all patients with GBC, who attended the Department of Gastroenterology and hepatobiliary at the designated centre from January 2012 to December 2018. A total of 1002 patients were available for analysis. The diagnosis of GBC was primarily based on the clinical symptoms and contrast enhanced computerized tomography (CECT) findings. The clinical symptoms and signs, routine blood investigations, ultrasonography, and CECT findings obtained from the in-patient departmental records were entered in a pre-designed proforma and was subsequently analysed. The history of gall bladder stones and addiction history were recorded along with stage of the disease. Depending on the stage of disease, the patients were instituted the appropriate treatment options. Simple cholecystectomy or radical resection was undertaken for resectable GBC and endoscopic retrograde cholangiopancreatography with placement of either plastic or metal stents for unresectable disease for palliation of jaundice and pruritus. The patients were followed up every 3 months for the progress of disease till death or lost to follow-up.

Statistical analysis

The data was analysed on the SPSS version 20.0 (SPSS, Inc. Chicago, IL, USA). Continuous variables were presented as mean \pm standard deviation and categorical variables as number of patients and percentages in parenthesis. Continuous data were analysed using independent t test or Mann-Whitney U test, where applicable and categorical variables were analysed with chi square test. The Kaplan Meir survival analysis was carried to calculate the survival according to the stage of GBC. P values below 0.05 were considered significant.

Results

Clinical and Demographic profile:

The clinico-epidemiologic profile GBC patients is depicted in **Table 1**. Out of 1002 patients, 307 (31%) were males and 695 (69%) were females with male: female ratio of 1:2.2. Median age of patients was 55 years with range of 15-96, with more than half patients in age group 40-60 years. There was statistical difference in mean age of males and females (58.35 ± 13.38 vs 54.85 ± 12.17 , $p < 0.001$). Around one third of patients had addiction to tobacco and one fifth had history of smoking, most of these were males. Most of the patients were nonvegetarian (71%), taking red meat and fish. Pain abdomen was most common symptom (85%) followed by jaundice (72%) and pruritus (54%). Lump in abdomen (27%), ascites (23%) and cholangitis (17%) were present in around one fifth of all patients.

Biochemical & Radiological Features of GBC:

Table 2 reveals laboratory and radiological features of GBC patients. The mean Bilirubin was 11.93 ± 8.7 g/dl and mean alkaline phosphatase was 675.55 ± 314.07 IU/ml. Cholelithiasis was present in 387 (39%) patients. Out of 1002 GBC patients, 645 (64%) had mass replacing GB fossa, 326 (32.5%) had asymmetric GB wall thickening and 31 (3.1%) had only polypoidal lesion in GB. A total of 896 (89.4%) patients had liver involvement from GB mass, 451 (45.1%) had direct liver infiltration and 445 (44.4%) had metastasis from GB lesion. Porcelain GB was present in 5 (0.5%) and GB perforation was seen in 10 (1%) patients.

Staging of GBC:

The staging and histologic types of GBC, as shown in **Table 3**, revealed that around 95% of patients had stage III

Table 1: Clinico-epidemiologic parameters of patients of carcinoma gall bladder.

Parameters	Findings in the present study (n=1002)
Age	
Age in years (median, range)	55 (15-96)
≤40 years	137 (13.7%)
40-60 years	544 (54.3%)
>60 years	321 (32 %)
Gender	
Male: Female	307 (31%): 695 (69%)
Age of males /Age of females (mean ±SD)	58.35 ± 13.38 / 54.85 ± 12.17 ($p < 0.001^*$)
Addictions	
Tobacco Users (Total; Male; Females)	330 (33 %); 240 (24%); 90 (9%)
Smoking (Total; Male; Females)	190 (19%); 182 (18%); 8 (1%)
Alcohol (Total; Male; Females)	120 (12%); 120 (12%); 0
Diet	
Vegetarian / Non-vegetarian	290 (29%)/712 (71%)
Clinical features	
Pain	849 (84.7%)
Jaundice	722 (72.1%)
Pruritus	541 (54.0%)
Cholangitis	171 (17.1%)
Ascites	236 (23.6%)
Vomiting	87 (8.7%)
Lump in abdomen	270 (27%)
Haematemesis	12 (1%)

Table 2: Laboratory and radiologic features of patients with carcinoma gall bladder.

Parameters	Findings in the study (n=1002)
Laboratory features	
Hemoglobin in g/dl; Mean ± SD	9.7 ± 1.7
Total Leucocyte count in mm ³ ; Mean ± SD	12.80 ± 2.98
Total bilirubin in mg/dl; Mean ± SD	11.93 ± 8.70
AST in IU/ml; Mean ± SD	214.62 ± 120.26
ALT in IU/ml; Mean ± SD	221.45 ± 1232.58
ALKP in IU/ml; Mean ± SD	675.55 ± 314.07
Total albumin in mg/dl; Mean ± SD	3.22 ± 0.58
Imaging features	
Cholelithiasis	387 (38.6%)
GB Mass	
Mass replacing GB fossa	645 (64.4%)
Asymmetrical wall thickening of GB	326 (32.5%)
GB polypoidal lesion	31 (3.1%)
Liver infiltration	896 (89.4%)
Direct Liver Infiltration	451 (45%)
Metastasis	445 (44.4%)
Porcelain gall bladder	5 (0.5%)
Gall bladder perforation	10 (1%)

AST - Aspartate Aminotransferase; ALT - Alanine Aminotransferase; ALKP - Alkaline Phosphatase.

(12 %) and stage IV (83%) disease. Out of 1002 patients, 723 (72%) had histology report. Adenocarcinoma was the most common histologic subtype of GBC (86%) followed by papillary (7%), mucinous (5%), signet ring carcinoma (1%), and neuroendocrine tumor (1%). Most common location of enlarged lymph nodes was periportal (69%), 55% had enlarged peripancreatic lymph nodes, 46% had paraaortic lymph nodes, and 11.6% had retropancreatic lymph nodes. Among all sites of metastasis from GBC, liver was most common (44%) followed by peritoneum (24%), lungs (13%), and bones (3%) . Adrenal metastasis was seen in 2% patients.

Survival in GBC:

The year size distribution of GBC cases is shown in **Figure 1**. Total number of cases of GBC in the year 2012, 2013, 2014, 2015, 2016, 2017 and 2018 were 80(8%), 90(9%), 118(12%), 151(15%), 169(17%), 190(19%) and 204(20%) respectively. Hence, the number of GBC cases was increasing every year from 2012 to 2018. Kaplan Meir survival analysis for different stages of GBC is shown in **Figure 2**. Due to the retrospective nature of

Table 3: Staging, histological types, lymph node involvement, and different sites of metastasis in carcinoma gall bladder patients.

	Number (n=1002)
Stage of disease	
Stage I	4 (0.3%)
Stage II	47 (4.6%)
Stage III	123 (12.2%)
Stage IV	828 (82.6%)
Histological type	
	(n=723)
Adenocarcinoma	620 (86%)
Papillary	51 (7%)
Mucinous	36 (5%)
Signet ring cell Carcinoma	7 (1%)
Neuroendocrine	9 (1%)
Lymph node involvement	
Periportal	720 (69%)
Peripancreatic	573 (55%)
Para-aortic	483 (46%)
Retroperitoneal	116 (11%)
Metastasis	
Liver metastasis	445 (44.4%)
Peritoneal metastasis	239 (23.9%)
Lung metastasis	126 (12.6%)
Bone metastasis	31 (3.1%)
Adrenal metastasis	20 (2%)

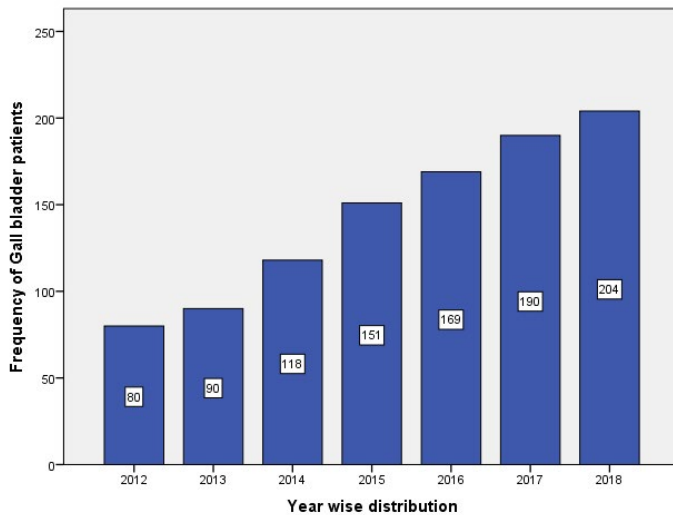


Figure 1: Year wise distribution of Gall bladder cancer patients from 2012 to 2018.

study, only 50 % had complete follow-up data till death. Median survival in months for stage I, II, III and IV diseases were 44 months, 38 months, 26 months and 5.3 months respectively, as shown in **Figure 3**, suggesting significantly lower median survival among stage IV GBC patients ($p < 0.001$).

Discussion

The present study has highlighted the fact that GBC is a disease predominantly affecting middle aged females with pain and jaundice being the common clinical symptoms. The incidence of GBC is increasing every year causing significant health burden to the community. Adrenal metastasis is not as uncommon as it was thought to be in previous studies because 2% of GBC patients were found to have metastasis to adrenals. Around 83% patients presented in stage IV of disease with a median survival of only 5 months, causing significant morbidity and mortality. Cholelithiasis was only present in 38% patients in our study.

The major burden of cancer of gall bladder is predominantly in Gangetic belts of north and central India and part of eastern India, due to pollution of river Ganga with human waste, agricultural waste and industrial waste products causing bacterial proliferation in the downstream which affects the densely populated inhabitants residing in the river bank.¹¹ However, other local environmental

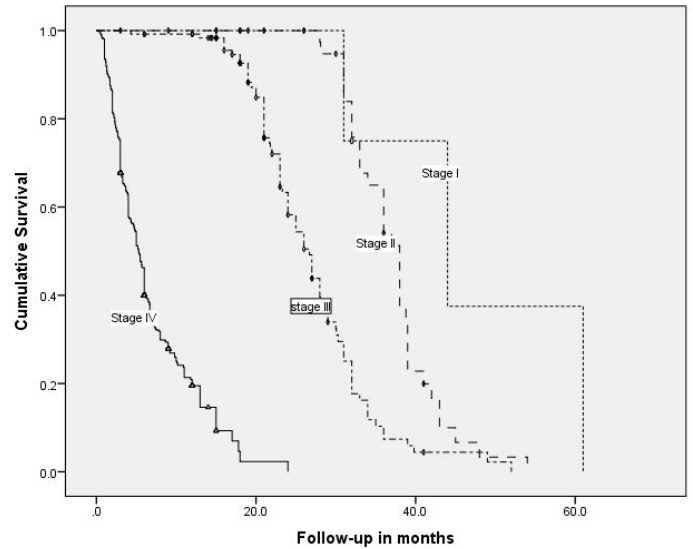


Figure 2: Kaplan Meier curve showing survival of patients with carcinoma gall bladder according to stage of disease.

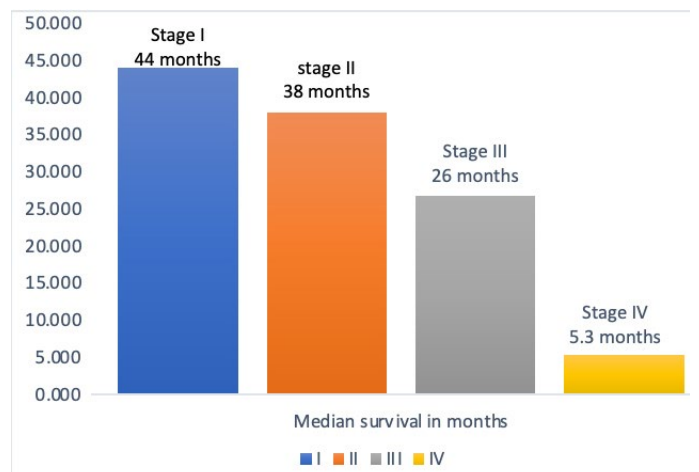


Figure 3: Bar diagram showing median survival according to different stages of Gall bladder carcinoma.

factors also might play a role in causing GBC as river Ganga does not flow through our state. In our study, the incidence of GBC was steadily rising every year from 2012 to 2018, making our state a high-risk region for this deadly cancer. In a systematic analysis of global, regional, and national burden of gallbladder and biliary tract cancer, gall bladder and biliary tract cancers incidence increased by 76%, mortality increased by 65%, and DALYs increased by 52% from 1990 to 2017.¹²

The incidence of GBC among north Indian population is 10 times higher than south Indian, however, there is no data in the available literature regarding the incidence and risk factors of GBC in Odisha.¹³ Mustard oil, a common edible oil used in Odisha for cooking is found to be commonly adulterated with yellow butter, a known carcinogenic, which could be a risk factor of GBC in this region.¹⁴

In our study, GBC was more common in females with male: female ratio of 1:2.2. Although, median age of patients with GBC in the current study was 55 years, females developed GBC at an earlier age as compared to males. Women are more prone to develop GBC as compared to men due to various reasons. The increased occurrence of cholelithiasis and effects of estrogen and progesterone during child bearing age, including pregnancies may risk a female to develop GBC about 2-6 times more than a male.¹⁵ Moreover, the poor nutritional status with substandard immunity along with less access to healthcare facilities makes them more vulnerable to develop GBC.¹⁶ Multiple Indian studies had also found a higher female to male ratio of 2-3 : 1 with younger onset of GBC in females as compared to males, at par with our study.^{1,2,16,17} In the west, the age of onset of GBC was one to two decade later than the Indian population, as multiple risk factors for GBC in Indian females play an additive role in the carcinogenesis of GB.^{18,19,20,21}

The association of gallstones with GBC is a matter of debate despite the constant relationship between both verified in numerous studies. In the current study, gallstone was detected in only 39% of GBC patients and majority had multiple stones. Previous studies had reported gall stones in 70-90% of GBC patients. A retrospective study from China of 2379 carcinoma GB patients found gallstones in 57 %.²² Lower rate of gallstones in our study may be due to high percentage of stage IV GBC patients due to which stones might be embedded in the GB mass, hence, not detected on ultrasound. Hence, surgical series have reported higher percentage of gall stones in GBC patients.²³

Pain abdomen was the commonest symptom of GBC in our study. However, jaundice and pruritus were distressing symptoms, found in 72% and 54% patients, respectively. Jaundice usually develops due to biliary

obstruction due to infiltration of tumor to common bile duct or obstruction by enlarged porta hepatis nodes. Palliative biliary bypass either endoscopic, radiologic or surgical is needed to relieve jaundice and pruritus in advanced GBC patients. Another study from India also found jaundice in 72% and pruritus in 40% patients.⁷ Moreover, the early nonspecific symptom in GBC like pain abdomen results in delay in diagnosis and presentation in more advanced stages of disease.²⁴

The majority (83%) of our patients had stage IV GBC and another 13% had stage III disease, hence, 95% patients presented in advanced stages of disease. The median survival of stage IV disease was only 5.3 months and stage III was 26 months, making GBC one of the most dangerous cancers of gastrointestinal tract. A retrospective study of 634 patients from New Delhi also found similar median survival rates, 6 months for stage IVA and IVB, and 25 months for stage III disease.⁷ The most common histologic subtype of GBC in our study was adenocarcinoma in 86% cases, at par with earlier studies.²⁵ The most common site of metastasis was liver followed by peritoneum and lungs. In a study of 1526 patients with data extracted from the SEER database, it was shown that 788 (51.6%) patients had isolated liver metastases, 45 (2.9%) had isolated lung metastases, 21 (1.4%) had isolated bone metastases, 2 (0.1%) had isolated brain metastases and 590 (38.7%) had multiple metastases.²⁶

Adrenal metastasis is a rare occurrence in GBC patient, only few case reports have been published in the literature.²⁷ We found 20 patients with GBC metastasizing to adrenals. As gallbladder lacks serosa adjacent to the liver and its peri muscular connective tissue is contiguous with hepatic connective tissue, liver invasion and metastasis to other organs is early. Hence, most patients present in advanced stage of disease.¹⁸ So, stage of disease is the main prognostic factor for carcinoma gallbladder patients.²⁸

The retrospective design is the major limitation of our study. Follow-up data was not available in almost 50% patients, likely due to the retrospective design and because of poor prognosis of this devastating cancer. Despite this, current study showed the real time data of large number of GBC patients over a period of 7 years.

The clinical features, histologic types, stage of disease and survival analysis of substantial number of GBC patients add significant strength to this study.

Conclusion

Based on the present study, we conclude that the rise in incidence of gall bladder cancer is alarming in eastern part of India. GBC is a catastrophic disease with advanced stage at presentation in most of the patients. Hence, only palliative therapy is offered to majority of GBC patients to relieve jaundice and pruritus and improve quality of life. The future studies should focus on early detection techniques, possible risk factors in our region and viable methods of mass screening.

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