



## Gallbladder Carcinoma: Epidemiology, Risk Factors and Modes of Presentation in Eastern Part of India

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### Abstract

**Introduction:** Gallbladder cancer is the most common malignant tumour of the biliary tract worldwide and also the most aggressive cancer of the biliary tract with the shortest median survival from the time of diagnosis.

**Materials and Methods:** A descriptive observational study was carried out at R.G. Kar Medical College, Kolkata over a period of one and half years (January 2012 to June 2013). Fifty one diagnosed cases of carcinoma gall bladder (proven either on preoperative/peroperative biopsy or computed tomography or ultrasound-guided fine needle aspiration cytology) were included as study subjects. Interview of the study subjects for eliciting socio-demographic, reproductive and other risk factors was done. Information on clinical and histological staging was ascertained by review of relevant records/reports as well as clinical examination as and when applicable.

**Results:** Our study revealed that gallbladder cancer has a prominent peak in the 5<sup>th</sup> decade of life with the mean age of presentation being 58.2 years. Male:female ratio of gallbladder cancer is 1:2.93. Only four patients had a suggestive family history. Most of the patients are from rural Bengal and of poor socioeconomic status. The most prevalent addiction in the affected patients was addiction to tobacco and pan (beetle leaf). Most of the patients were having body mass index below 24, which is in sharp contrast to the available literatures. Significant association between gallstone disease and chronic typhoid infection was found. In female significant association is found with reproductive characteristics. Increased exposure to reproductive hormones by means of increased level of estrogen and progesterone in body as in OCP intake, early age at menarche, late age of first pregnancy, late menopause etc, postmenopausal status are found in majority of female patients. Pain is the most common symptom followed by constitutional symptoms, and most common clinical finding was jaundice followed by lump abdomen. Majority of patients presented at later stage of the disease i.e. in stage IV and stage III with initial raised CA19-9 level.

**Conclusion:** Gall bladder cancer is a very deadly disease with very poor prognosis with most of the cases presenting in advanced stages.

**Keywords:** Gall bladder cancer; Gall stone; Advanced stage; Poor prognosis

### Introduction

Carcinoma of the gallbladder is highly malignant with a poor survival rate. Although First described in 1777 by M deStoll, it still continues to be challenge for the physician and surgeons because of its uncertain aetiology, late presentation and poor prognosis [1,2]. There is a striking difference in incidence with regard to age, gender, race, genetic influence and geographical distribution. It is a highly aggressive malignancy that affects women 2 to 6 times more frequently than men. Older age group (>60 years) are most often affected and coexisting gall stone and chronic cholecystitis are present in majority of cases (68% to 98%) [1,3].

High incidence among females suggests a role of female hormones in the aetiology of the disease. Early age at menarche, younger age at first pregnancy, multiple pregnancies and prolonged fertility may increase the risk because of elevated levels of oestrogen and progesterone. Positive association between the number of live-births and carcinoma of the gallbladder has been found. A significant association of early menarche and prolonged reproductive period has also been reported [3,4].

Postmenopausal state as a risk factor was associated with development of carcinoma of the

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gallbladder. Oral contraceptive use is however not associated with a higher incidence. A chronic typhoid carrier state may be a predisposing factor for carcinoma of the gallbladder [5]. Higher incidence of this carcinoma is reported in relation to poor socioeconomic condition, low level of education and lifestyle factors like smoking, tobacco chewing and alcohol consumption. A few studies have also emphasized the role of dietary factors in the aetiology of carcinoma of the gallbladder [6-9].

The clinical presentation of gallbladder carcinoma is nonspecific. It is often recognized late with the diagnosis established during advanced stage of disease. A vast amount of work has been done on gall bladder carcinoma in the western world but in India it has been little studied though the numbers of cases are pretty higher than Europe. So, this study is aimed to analyze the risk factors, mode of clinical presentation and stage at presentation of gall bladder carcinoma in this part of our country.

### Methods

A descriptive observational study was carried out at R.G. Kar Medical College, Kolkata over a period of one and half years (January 2012 to June 2013). All diagnosed cases of carcinoma gall bladder (proven either on preoperative/peroperative biopsy or computed tomography or ultrasound-guided fine needle aspiration cytology) patients attending various departments of R.G. Kar Medical College & Hospital during the data collection period of the study was included as study subjects. Number of study population was 51 patients. A pre-designed, pre-tested schedule was used for data collection. Interview of the study subjects for eliciting socio-demographic, reproductive and other risk factors was done. Information on clinical and histological staging was ascertained by review of relevant records/reports as well as clinical examination as and when applicable. Before data collection, informed consent was obtained from each and every study subjects.

### Result

Our study revealed that gallbladder cancer has a prominent peak in the 5<sup>th</sup> decade of life, in addition to an expected peak in the 6<sup>th</sup> decade of life and onwards. Youngest patient registered in this study was of 32 years of age. The mean age of presentation was 58.23 years, in our patients (Table 1). Genetic predisposition to gallbladder cancer was not found in younger age group patients in our study. Only four patients had a suggestive family history. This calls for a detailed research into the genomic basis of gallbladder cancer so that specific bio molecular markers for early detection of gallbladder cancer and aimed at a screening in the younger age group. Regarding sex predilection in the present study male:female ratio of gallbladder cancer is 1:2.93 (Table 1). Regarding distribution amongst various religious groups Hindu predilection was seen though the catchment area of R.G. Kar. Medical College Hospital, which is predominantly occupied by the Hindu community (Table 2). Most of the patients are from rural Bengal and of poor socioeconomic status. The occurrence of gallbladder cancer in these groups of people clearly shows scope of further studies regarding their lifestyle factors, dietary habits and environmental exposures (Table 3). From the present study it is very difficult to conclude the relationship between addiction and gallbladder cancer, though the most prevalent addiction in the affected patients were addiction to tobacco and pan (beetle leaf) (Table 4). Regarding comorbidities most of the patients were having age related comorbidities, most prevalent being hypertension followed by

**Table 1:** Sex distribution.

Age	Male	Female	Total
30-40	1	5	6
41-50	1	6	7
51-60	7	12	19
61-70	3	13	16
71-80	1	2	3
Total	13	38	51

**Table 2:** Religious distribution.

	Hindu	Muslim	Total
Male	5	8	13
Female	27	11	38
Total	32	19	51

**Table 3:** Distribution based on socioeconomic status.

Region	Number	Percentage
Urban	6	11.76%
Rural	34	66.67%
Semi urban	11	21.57%
Total	51	100%
Socioeconomic status	Number	Percentage
Lower	32	62.74%
Lower-Middle	14	27.45%
Middle	5	9.81%
Total	51	100%

**Table 4:** Addictive Factors.

Addiction	Number	Percentage
Smoking	14	27.45%
Tobacco	5	9.80%
Pan	16	31.37%
Alcohol	9	17.64%

**Table 5:** Association with comorbidity.

Co-morbidity	Number	Percentage
DM	12	23.52%
Hypertension	17	33.33%
IHD	2	3.92%
COPD	6	11.76%
Pul. TB	0	0%

diabetes (Table 5). Most of the patients were having body mass index below 24, which is in sharp contrast to the available literatures where obesity is marked as a predisposing factor of gallbladder carcinoma (Table 6). We have found significant association between gallstone disease and coexistent gallbladder carcinoma. Association was also found between chronic typhoid infection and gallbladder carcinoma (Table 7). In female significant association is found with reproductive characteristics. Increased exposure to reproductive hormones by means of increased level of estrogen and progesterone in body as in OCP intake, early age at menarche, late age of first pregnancy, late menopause etc, post menopausal status are found in majority of female patients. Pain is the most common symptom followed by

**Table 6:** BMI and GB Cancer.

BMI	Male	Female	Total	% age
<18	4	19	23	45.09%
18-24	6	11	17	33.34%
25-30	2	7	9	17.64%
31-40	1	1	2	3.93%
>40	0	0	0	0%
<b>Total</b>	13	38	51	100%

**Table 7:** Etiological factors.

Risk Factors	Number	% age
Cholelithiasis	34	66.67%
Typhoid inf.	3	5.88%
Family hist	4	7.84%
Hormonal exposure	23	45.09%

**Table 8:** Clinical Presentation.

Presentation	Number	Percentage
Pain	44	86.27%
Anorexia	31	60.78%
Jaundice	27	52.94%
Weight Loss	23	45.09%
Lump	21	41.17%
Nausea/ Vomiting	33	64.70%
Abdominal distension	2	3.90%
Findings	Number	Percentage
Pallor	21	41.17%
Edema	24	47.05%
Jaundice	40	78.48%
Lump	29	56.86%
Hepato-megaly	18	35.29%
Ascites	28	54.90%

constitutional symptoms, and most common clinical finding was jaundice followed by lump abdomen (Table 8). Majority of patients presented at later stage of the disease i.e. in stage IV and stage III with initial elevated CA19.9 level which denotes indolent but highly aggressive nature of the disease. Prognosis is therefore generally poor among those patients (Table 9).

## Discussion

Gallbladder cancer incidence is gradually increasing in India and is projected as a major cause of mortality and morbidity in the Indian population. Despite this, only a few studies have been done so far. The prevalent epidemiologic factors like age and sex distribution, rural and urban distribution, socioeconomic stratification, religion, comorbidities and addiction are thoroughly studied. Quite prominently, the age of presentation is a little early in our country in comparison to the western world. From our study we found that gallbladder carcinoma has a prominent peak in the 5<sup>th</sup> decade of life in both males and females. This is in contrast to a study by Piehler and Crichlow [9] where the mean age of patient with carcinoma gallbladder was reported to be 65 years and the highest incidence occurred in seventh and eighth decade of life. But our results match

**Table 9:** CA19.9 and Gall bladder cancer and Stages of presentation.

a)

CA19.9 (Unit/ml)	Number
0-37	4
38-100	9
100-1000	19
>1000	7

b)

Stage	Number	Percentage
I	3	5.88%
II	2	3.92%
III	7	13.72%
IV	39	76.48%
<b>Total</b>	51	100%

with a study by Shukla et al. [1] where the mean age of presentation was found to be 50 years. In our study disease occurred mainly in females with the male:female ratio being 1:2.93 and in every age group female almost invariably out represents male. Shukla et al. [1] in their series of 315 patients found a female to male ratio of 2.5:1. The F/M ratio of GC incidence rates also varied greatly: It exceeded 5 in several high-risk areas (e.g. Pakistan, Colombia and Spain) as well as in low-risk areas (e.g. Denmark), but was typically between 2 and 3. F/M ratio was close to unity in Korea, Japan and some parts of China [10-14].

In India no data has been published to detect increase incidence of gallbladder cancer in a particular religion. In our study Hindu patients do share a majority over Muslim patients with a ratio of 1.6:1, probably owing to the fact that the predominant community the medical college caters to is Hindus. Although majority of patients are from rural Bengal (66.67% of the patient population) and its surrounding towns (21.57% of the patient population), a few numbers of patients are from city of Kolkata, accounting 11.76% of our patients. It is noteworthy that life style and dietary habits of rural Bengal do vary considerably from those in the city or its surroundings. The national level data reflects that incidence of gallbladder cancer is predominant in rural population with lower income and education, who are either unaware of the extreme consequences or are too poor to afford the cost of diagnosis and treatment and hence, continue to suffer. Our study also supports this. Majority of patients were hypertensive i.e. 33.33% of patients having co-morbidities, followed by diabetes mellitus, in 23.52% of patients with co-morbidities. This association is possibly due to older age related morbidities at presentation and further studies will be required to find out any causal relationship between these two most prevalent co-morbidities in the recent population worldwide and the association of gallbladder carcinoma. 37.25% patients were addicted to tobacco in the form of smoking and tobacco chewing. A significant percentage (31.37%) of patients was addicted to pan (betel leaf). It would really be required to find as to whether consumption of pan has any significant association with the causation of gallbladder cancer and which ingredient of pan is the actual detrimental factor. In the existing literature higher incidence of this carcinoma is reported in relation to lifestyle factors like smoking, tobacco chewing and alcohol consumption. The risk of cancer was more than twice in patients who used to chew tobacco [1]. Existing literatures suggest that increased body mass index and obesity is a

causative factor for development of carcinoma gallbladder. A positive association of high fat intake with Gall bladder cancer risk was found in a case control study by. [9,16] we found a very few patients are in obese group (3.93%). Major groups of patients (45.09%) were malnourished probably due to late presentation and emaciation due to the disease process. Most common symptom to be presented with is pain (86.27%) in right upper abdomen. Shukla et al. [1] and Silk et al. [3] also reported pain to be the most frequent symptom in their respected studies. Pain is due to acute cholecystitis due to presence of gallstone or due to stretching of capsule of the gall bladder or due to malignant infiltration of surrounding visceral structures. Constitutional symptoms like nausea and vomiting are present in 64.70% of patients. Most of the symptoms are associated with anorexia and weight loss. 52.94% patient presented with obstructive jaundice. 41.17% patients presented with lump per abdomen at the time of presentation due to palpable gallbladder or hepatomegaly. Among clinical findings jaundice is most commonly present and it is mostly obstructive in nature found in 78.43% of patients. Derangement of hepatocellular function can occur due to liver metastasis in patients presenting at later stage of the disease. Almost half of the patients i.e. 56.86% were having palpable lump in the right upper quadrant of abdomen. Significant percentage of patients (41.17%) was having associated pallor and edema mostly in pedal and pitting type. This is most commonly due to associated hypoproteinemia and compression of the mass over inferior vena cava. Hepatomegaly present in 35.29% of patients. It is most commonly due to liver metastasis. Ascites present in 54.9% of patients. It occurs due to dissemination process and also due to hypoproteinemia. Most patients, (66.67%) have their initial CA19.9 levels above 100. This could be attributed to the presentation of the patients in their later stage. CA19.9 has a prognostic importance and elevated preoperative serum CA19-9 level is associated with poor prognosis in gallbladder cancer. We have studied the association between known risk factors and gallbladder cancer. We found Gallbladder carcinoma is associated with cholelithiasis in 66.67% of patients which is a known risk factor. 5.88% of patients were having chronic typhoid infections. Positive family histories of related malignancies are present in 7.84% of patients. Increased hormonal exposure by means of increased level of estrogen and progesterone in body as in OCP intake, early age at menarche, late age of first pregnancy, late menopause etc, postmenopausal status is present in 45.09% of patients. Existing literatures also support our findings [17-22]. Regarding stage at presentation we have found that majority of the patients (76.48%) presented at later stage i.e. stage IV disease that means there was extra hepatic organ invasion (two or more) and spread to major vascular structures like portal vein and hepatic artery. 13.72% patients presented with stage III disease i.e. disease spread to the adjacent structures perforating the visceral peritoneum. Only 9.8% of patients presented early at stage I and II i.e. tumor limited within serous. Presentation at later stage contributes to its indolent coarse and highly aggressive nature [23-29].

## Conclusion

Most of the gall bladder cancers present in an advanced stage with poor prognosis. Surgery is the most curative and definitive mode of treatment.

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