



Demographic and clinicopathological Profile of Gall Bladder Cancer Patients: Study from a tertiary care center of the Sub-Himalayan region in Indo-Gangetic Belt

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Abstract:

INTRODUCTION: Gall bladder cancer (GBC) accounts for 80%-95% of biliary tract malignancies in the world. There is however striking variability in the global incidence of gallbladder cancer, reaching epidemic levels for some regions and ethnicities. The aim of this study was to evaluate the demographic and clinicopathological profile of the gallbladder cancer patients.

MATERIALS AND METHODS: All patients of carcinoma gall bladder presenting to department of surgery in hepatopancreaticobiliary unit from July 2017 to November 2020 were included in this study. A proforma containing all the relevant details including history, examination, blood, radiology, and pathological investigations was filled.

RESULTS: A total of 326 patients of GBC were analyzed. The majority (75%) were found to be females with a mean age of 55 years. Pain abdomen was the most common presenting symptom in 81% of patients. The most common stage of presentation was stage IV and only 6 were in stage I. Two hundred and thirty three (71.4%) patients had metastatic disease at presentation. Liver infiltration at the time of diagnosis was present in 89% of patients. The most common site of metastasis was found in the liver (23.3%). GBC was more common in patients with A blood group. Baseline serum albumin levels were found to be significantly associated with the staging of GBC.

CONCLUSIONS: Due to the non specific symptoms patients of GBC present at very advanced stages, high index of suspicion and health education seems to play an important role in early detection and improvement of survival.

Keywords:

Cholelithiasis, gallbladder cancer, incidence, metastasis

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Introduction

GBC accounts for 80%-95% of biliary tract malignancies in the world.^[1] There is however striking variability in the global incidence of gallbladder cancer, reaching epidemic levels for some regions and ethnicities. There is a variation of these risk

factors geographically and among different ethnic groups. The highest incidence of GBC is found in Chile, followed by Bolivia and South Korea. The majority of GBC (65%) occurs in developing countries.^[2] The median age according to indexed literature is 67 years^[3] GBC is found more in females worldwide, and females are affected two to six times more often than males.^[4] The

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association with the female gender is strengthened by the fact that GBC is associated with high parity and a greater number of pregnancies. However, estrogen and progesterone receptor expression in GBC is not significantly different between males and females but co-expression of both estrogen and progesterone receptors is increased in females with GBC as compared with males, suggesting a potential target for treatment.^[5] The main etiology in GBC is gall stone disease, porcelain gall bladder, gall bladder polyps, primary sclerosing cholangitis, chronic salmonella infection, *Helicobacter pylori* infection, congenital biliary cyst with anomalous pancreaticoduodenal junction, exposure to carcinogens such as aflatoxin, mycotoxin, and obesity.

Most often, GBC develops over 5 to 15 years when metaplasia progresses to dysplasia, carcinoma in situ, and then, invasive cancer.^[1] The majority of this disease presents in advanced stages and <10% of patients of GBC are resectable, while more than 50% have lymph node metastases at the time of presentation.^[6] The dismal prognosis is related to the advanced stage at diagnosis, mainly due to the anatomic position of the gallbladder, and the vagueness and non-specificity of symptoms.^[7] At present, the diagnosis of GBC depends mainly on non-invasive auxiliary imaging and invasive tests such as laparoscopy and biopsy. Furthermore, there is no ideal single tumor marker available presently for the diagnosis and prognosis of GBC.^[8] Patients suffering from early GBC are most often asymptomatic. Among symptomatic patients, pain is the most common complaint, followed by anorexia, nausea, or vomiting. Advanced GBC often presents with biliary colic and features of advanced malignancy such as malaise or weight loss, and obstructive jaundice which can occur from direct invasion of the biliary tree or due to compression of bile ducts by enlarged lymph nodes at porta or from metastatic disease to the region of hepatoduodenal ligament.^[9] The aim of the present study is to evaluate the demographic and clinicopathological profile of GBC patients at a tertiary care center of North India.

Materials and Methods

This retrospective study was conducted in the Department of Surgery in Hepatopancreaticobiliary Unit at our institute. The data were collected on the basis of hospital records. The diagnosed patients of GBC were included from July 2017 to November 2020. Institutional ethical committee approval was taken to conduct the study (AIIMS/IEC/20/678). A detailed proforma was prepared which encompassed relevant history, physical examination findings, and relevant blood investigations including tumor markers (CA19-9, CEA, and CA-125), with radiology investigations including ultrasound abdomen, and contrast enhanced

computed tomography (CECT) of the chest and abdomen, and FNAC/Biopsy reports were included in the study. Parameters assessed are as follows:

1. Age, gender, and clinical features: including jaundice, fever, lump, and pain abdomen.
2. Presence of cholelithiasis
3. ABO blood group
4. Serum albumin levels
5. Morphology of gall bladder mass in CECT scan
6. Biopsy/FNAC findings
7. TNM staging (patients were staged according to the 8th edition AJCC)
8. Treatment received by patients

This data were transferred to an Excel sheet and statistical analysis was performed using IBM SPSS version 25.0 statistical software (SPSS Inc., Chicago, IL, United States).

Statistical analysis included descriptive analysis by mean, median, and percentage. Standard deviation was used in cases of normal distribution and interquartile range for non normal distributed data. Correlation between gall stones, morphology of gall bladder lesion and stage of disease and between obstructive jaundice and tumor markers was assessed by Pearson's correlation coefficient. Association of serum albumin with the various stages of GBC was assessed using One-way Anova test. $P < 0.05$ was considered statistically significant.

Results

A total of 326 patients of GBC were analyzed. The age of patients ranged from 32-73 (mean-55) years. Females were 243 (75%) whereas 83 (25%) were males.

Pain abdomen was the most common symptom found in GBC experienced by 264 (81%) GBC patients, while jaundice was found to be present in 162 (50%) patients. Fever was presenting symptom in 88 (27%) patients and a palpable abdominal lump on examination was present in 120 (36%) patients of GBC.

History of smoking and alcohol consumption was present in 124 and 77 patients respectively. A family history of malignancies was present in 23 (8%) patients. Incidental GBC was found in 4 patients, who had undergone cholecystectomy for gall stone disease. Two hundred and thirty three (71.4%) patients had metastatic disease at presentation. Morphology of gall bladder lesion in CECT abdomen was mass in 168 followed by increased wall thickness in 118 patients. Clinicopathological and radiological profile is mentioned in Table 1.

Serum tumor markers CEA, CA 19-9 and CA125 were done and the values (range and IQR are mentioned in Table 2.

Table 1: Clinicopathological profile of patients of gallbladder cancer

| Variables | Options | Frequency, n (%) |
|--------------------------------------|-----------------------------------|------------------|
| Age (years) | 32-73 (55.04±1.20) | |
| Gender | Male | 83 (25) |
| | Female | 243 (75) |
| Smoking | No | 202 (62) |
| | Yes | 124 (38) |
| Alcohol | No | 249 (77) |
| | Yes | 77 (23) |
| Family history of any cancer | No | 303 (92) |
| | Yes | 23 (8) |
| History of any treatment/drug intake | No treatment | 263 (80) |
| | OHA | 15 (4) |
| | Antihypertensive | 21 (6) |
| | OHA+antihypertensive | 2 (0.5) |
| | Thyroxin | 5 (2) |
| | Insulin | 7 (3) |
| | Insulin+antihypertensive | 10 (3) |
| | Aspirin | 1 (0.5) |
| | Chemotherapy | 1 (0.5) |
| | Inhalers | 1 (0.5) |
| Obstructive Jaundice | No | 164 (50) |
| | Yes | 162 (50) |
| Pain abdomen | No | 62 (19) |
| | Yes | 264 (81) |
| Fever | No | 238 (73) |
| | Yes | 88 (27) |
| Lump | No | 206 (64) |
| | Yes | 120 (36) |
| Radiological presentation of GB | Polypoidal growth | 36 (12) |
| | Mass | 168 (51) |
| | Wall thickening | 118 (36.2) |
| | Incidental diagnosed carcinoma GB | 4 (1) |
| GB stone | No | 184 (56) |
| | Yes | 142 (44) |
| Liver infiltration | No | 36 (11) |
| | Yes | 290 (89) |
| Presence of regional lymph-nodes | No | 56 (17) |
| | Yes | 270 (83) |
| Metastases | No | 93 (28.5) |
| | Omental metastases | 5 (1) |
| | Liver metastases | 76 (23.3) |
| | Paraaortic lymph node metastases | 75 (23) |
| | Bone metastases | 1 (0.003) |
| | Malignant ascites | 75 (23) |
| | Lung metastases | 3 (1) |
| Stage of cancer | Stage I | 6 (2) |
| | Stage II | 14 (4) |
| | Stage III | 73 (21.7) |
| | Stage IV | 233 (71.4) |
| Resectability of cancer | No | 282 (86.5) |
| | Yes | 44 (13.5) |
| Histopathology | Adenocarcinoma | 149 (45) |
| | Malignant | 163 (50) |
| | Atypical cells | 7 (2) |
| | Poorly differentiated carcinoma | 6 (2) |
| | Adenosquamous carcinoma | 1 (1) |

OHA: Oral Hypoglycaemic Agents, GB: Gallbladder

Correlation was done between gall-stone and stages of disease, but it showed a negative correlation ($r=-0.112$). Furthermore, there was negative correlation of morphology of gall bladder lesion on radiology with stages of disease. This is shown in Table 3.

Correlation was assessed between levels of tumor markers CEA, CA 19-9, and CA 125 and obstructive jaundice to ascertain whether these markers increase with rise in bilirubin levels but there was no significant correlation; $P = 0.169, 0.218$, and 0.182 respectively [Table 4].

On the evaluation of blood groups in these patients, A positive was the most common blood group in 132 (40.4%) patients. Association of serum albumin with the various stages of GBC was assessed using a One-way Anova test, which showed a statistically significant difference in various groups ($P=0.003$) [Table 5].

Forty-four patients of gall bladder cancer patients were resectable at the time of presentation. Staging laparoscopy was done in these patients and intraoperative cystic duct margin and paraaortic lymph node sampling were done and sent for frozen section. Cystic duct margin was positive on frozen section in three patients, and bile duct excision and Roux en y hepaticojejunostomy were performed as part of surgery. They underwent radical cholecystectomy [Figure 1]. Three patients were resectable as per radiology findings but intraoperatively were unresectable due to the presence of omental metastases. Adenocarcinoma was the most common histopathology diagnosis. Patients who had locally advanced disease were referred for neoadjuvant

chemotherapy. One patient had partial response but was not resectable so considered for definite radiotherapy but post radiation therapy had stable disease.

Patients with metastatic disease with good performance status (ECOG 1-2) were considered for palliative chemotherapy (gemcitabine and cisplatin based) and those with poor performance status were referred for palliative care which included pain management and for obstructive jaundice. One hundred and thirteen patients had obstructive jaundice range 6.95-39.2 and (mean 17.77) for which they were considered for percutaneous biliary drainage and internal stenting. Patients with internal stenting had a better quality of life. In patients with percutaneous biliary drainage and internal stenting, 14 had normalization of bilirubin levels and were considered for palliative chemotherapy. Pain control was required in 117 patients and the WHO analgesic ladder pattern was followed. Seven patients were referred for the celiac block as the pain was not controlled on oral, intravenous, or transdermal patch. Three patients were considered for palliative gastrojejunostomy in view of duodenal obstruction due to the mass lesion. Two patients were considered for palliative radiotherapy for bone metastases and one for brain metastases.

Discussion

GBC is the most common biliary tract malignancy in the world and the high incidence is observed in northern part of India. It is found in the older age group average being 67 years.^[3] It is more commonly found in females with the ratio being 2-6:1. The most common symptom of GBC is the pain abdomen.

Table 2: Frequency and interquartile range of carcinoembryonic antigen, cancer antigen 19-9, and cancer antigen 125

| Variables | Options | Frequency, n (%) | Interquartile value | |
|----------------|--------------|------------------|---------------------|-------|
| | | | Q1 | Q3 |
| CEA (ng/ml) | Normal 0-2.5 | 16 (5) | 1.82 | 20.10 |
| | High>2.5 | 310 (95) | | |
| CA 19.9 (U/ml) | Normal 0-39 | 79 (24) | 34.70 | 1.12 |
| | High>39 | 247 (76) | | |
| CA 125 (U/ml) | Normal 0-35 | 100 (30) | 30.02 | 2.21 |
| | High>35 | 226 (70) | | |

CEA: Carcinoembryonic antigen, CA: Cancer antigen

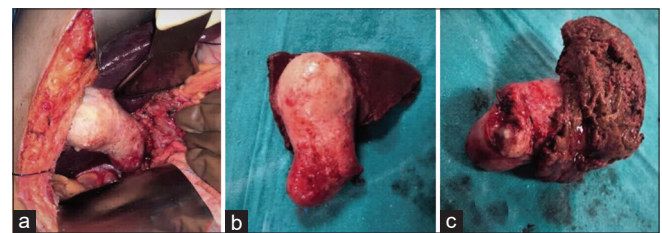


Figure 1: (a) Intraoperative photograph of radical cholecystectomy for carcinoma of gallbladder with (b) resected specimen showing gallbladder with (c) segment IVb and V of the liver

Table 3: Pearson correlation (r) coefficient of stage of cancer with gallbladder stone and morphology (n=326)

| Variables | Options | Stage | | | | "r" P |
|---------------------------------|-----------------------------------|-------|----|-----|----|--------|
| | | I | II | III | IV | |
| GB stone | No | 3 | 5 | 82 | 94 | -0.112 |
| | Yes | 3 | 9 | 72 | 58 | |
| Radiological presentation of GB | Polypoidal growth | 1 | 1 | 16 | 18 | -0.100 |
| | Mass | 4 | 4 | 74 | 86 | |
| | Wall thickening | 1 | 7 | 63 | 47 | |
| | Incidental diagnosed carcinoma GB | 2 | 2 | 0 | 0 | |

GB: Gallbladder

Table 4: Pearson correlation (r) coefficient of obstructive jaundice with tumor makers (n=326)

| Variables | Options | Obstructive jaundice | | P |
|-----------|---------|----------------------|-----|-------|
| | | No | Yes | |
| CEA | Normal | 14 | 02 | 0.169 |
| | High | 150 | 160 | |
| CA 19.9 | Normal | 55 | 24 | 0.218 |
| | High | 109 | 138 | |
| CA 125 | Normal | 64 | 36 | 0.182 |
| | High | 100 | 126 | |

CEA: Carcinoembryonic antigen, CA: Cancer antigen

Table 5: Association of serum albumin with gallbladder cancer stages

| Stage | Mean±SD | P |
|-------------|-----------|-------|
| I (n=2) | 4.29±0.22 | 0.003 |
| II (n=7) | 4.05±0.46 | |
| IIIA (n=34) | 3.23±0.75 | |
| IIIB (n=41) | 3.10±0.75 | |
| IV (n=79) | 3.11±0.69 | |

SD: Standard deviation

Risk factors associated with Gall Bladder cancer are gall stone disease,^[10] porcelain gall bladder^[11], gallbladder polyps^[12], Helicobacter infection^[13], abnormal pancreaticobiliary duct junction^[14], drug history (methyl dopa, isoniazid and oral contraceptive pills have been implicated in biliary carcinogenesis)^[15-17] Chronic salmonella infection^[18], and carcinogens: occupational risk factors include persons in oil, paper, chemical, shoe, textile, and cellulose acetate fiber manufacturing industries and minors exposed to radon.^[19] Pathogenesis of GBC is hypothesized to be due to chronic irritation of gall bladder mucosa with due to stones or in case of ABPJ characterized by KRAS mutations. Other mechanisms postulated include mutations in catenin beta 1 (CTNNB1).^[20-21] Usual presentation of the disease is non-specific symptoms. Advanced cases present with jaundice and a palpable abdominal lump.^[22]

Diagnosis is usually multimodal, initially detected with radiological imaging including USG abdomen and CECT Abdomen. For gallbladder neck tumors endoscopic ultrasound is better, owing to the proximity to the bile duct allowing for excellent imaging quality with the option of FNAC from the lesion^[23]. Tumor markers are used as an adjunct in diagnosis and prognosis in the treatment of the disease. Response to treatment is the most common use of tumor markers. Operable diseases undergo radical cholecystectomy whereas advanced malignancy patients are given palliative chemotherapy after tissue diagnosis.

The incidence of GBC increases with age, and the mean age at diagnosis was 55.04 years in the present study. In the previous studies, the mean age of GBC at the diagnosis is 64–69.4 years.^[24,25] The median age of

presentation was 67 years in a Memorial Sloan–Kettering report of 435 GBC patients.^[26] Dubey *et al.*^[27] in 2018 in India reported in their study average age of 51.8 years, suggesting occurrence of GBC in younger population in India. They found gall bladder carcinoma occurring mainly in females of 77.9%, close to 75% of females in our study.

Distribution of blood group in GBC patients was studied which showed the highest incidence with A positive blood group (40%) followed by O positive (28%). This is similar to various studies suggesting a higher incidence of Cancers like that of stomach and ovarian Cancers in A blood group than others.^[28] It has been postulated that forssman antigen is expressed in malignancies such as gastric cancer, which is structurally similar to A blood group antigen. Antibodies that may develop in A blood group may cross-react with forssman antigen, leading to the development of malignancy is the long run. A higher incidence of A blood Group in gall bladder carcinoma could be due to a similar mechanism. However, further studies are required on a molecular level to diagnose the same.^[29]

The incidence of GBC is more in females (2–6 times) in comparison to males worldwide, especially in the northern part of India, and in American-Indian females, and furthermore, in the present study the female to male ratio was 2.92:1. Regarding the clinical presentation of the disease, the pain abdomen was the most common symptom found in 81% of our patients, comparable to study done in 2008 by Lai and Lau^[30] showed pain as the most common symptom in 54%-83% of patients. Jaundice was found in 10-46% of patients in their study, while it was found to be in 35.8% of patients of GBC in the present study. Palpable mass at the time of presentation was found in 3%-8% of patients in the Lai review compared to 36% in patients in the present study. This could be attributed to the presentation of the disease in advanced stages in our country. Dubey *et al.* in 2018 conducted a similar study in India with 68 patients of GBC, they concluded that pain was found in all patients of GBC in their study (81% in our study), while obstructive jaundice at the time of presentation was found in 51% of individuals (35.8% in our study). Cholelithiasis was found in 61.6% of patients in their study compared to 44% of patients in our study. Furthermore, these patients had multiple stones and size more than 1 cm in 80% of patients.

Association of serum albumin levels with various stages of GBC was assessed which showed statistically significant differences in albumin levels among various groups. It was noted that as the stage of the disease increased, the serum albumin level of the patients reduced. However, no studies were available comparing staging with albumin

levels in patients of GBC. On studying the staging and pattern of metastasis Dubey *et al.* found 72% of their patients presenting in Stage IV disease similar to 71.4% in our study. Liver metastasis was found in 57% of their patients compared to 23.3% of gall bladder patients in our study. Malignant ascites was found in 72% of their patients compared to 23% in our study. Non-regional lymph nodes involvement and omental deposits occurred in 54% and 20% of patients respectively in the Dubey *et al.* study, compared to 23% and 1% in our study.

Conclusions

Due to the non specific symptoms, patients of GBC present at very advanced stages, and therefore, a high index of suspicion and health education seems to play an important role in early detection and improvement of survival. Since, most of the cases of GBC presents in advanced stages of the disease, palliative care services need to be strengthened to provide better quality of life care for such patients. Mass screening programs are needed for early detection of GBC. Public awareness about the disease need to be enhanced by various methods such as classes, advertisement and presentations. There is a minimal role of surgery in advanced diseases, even the results of radiation and or chemotherapy in such patients are dismal so far. Hence, new targeted therapies need to be identified.

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Conflicts of interest

There are no conflicts of interest.

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