

Gall bladder carcinoma (GBC): Rising incidences in the Malwa belt region of northern India a hospital based cancer registry

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Abstract

A prospective study conducted in the department of Radiation Oncology at Guru Gobind Singh Medical College and Hospital, Faridkot, including all the gall bladder cancers (GBC) presenting over a 48 months period and analysing how the epidemiological factors were influencing the disease. This data was collected from all over the Malwa region which comprises mainly of three regions, Malwa, Majha and Doaba. The total number of GBC cases registered in this area were 244 over this period. The rural versus urban distribution was 68.6% to 31.5%. Incidence reported were about Four cases per 100,000 populations per year. The peak incidence was observed in the 51 to 60 years age group (32.3%) patients. Female to male ratio was 3.36, as opposed to the male preponderance in other regions. The most common clinical presentation were pain abdomen and loss of appetite. Amongst the various risk factors, fatty diet along with spices in 175-180 (80-83%) patients and gall stones in 154 (71%) patients were found as the most common culprits. Out of all the cases, 29 (11.88%) patients were overweight with BMI between 25 and 29.9 ($p = 0.003$), as against the majority who presented as undernourished which correlated with advanced stages. Adenocarcinoma was the most common histopathology seen in 181(75.5%) patients. Subtle onset of symptoms explains the advanced stage at initial presentation. Almost 49.1% patients presented with T3 and 38.7% with T4 stage at the time of initial presentation. This data highlights high prevalence of gall bladder carcinoma in North-western belt of India. Better hygiene and water supply, prevention of malnutrition, early intervention for cholelithiasis, importance of balanced diet, increase in awareness about risk of tobacco and alcohol consumption all are highlighted as significant modifiable factors.

Key Words: Gallbladder carcinoma, Epidemiology, Cholelithiasis.

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Received Date: 12/04/2018 Revised Date: 19/05/2018 Accepted Date: 03/06/2018

DOI: <https://doi.org/10.26611/1021632>

Access this article online

Quick Response Code:



Website:

www.medpulse.in

Accessed Date:
08 June 2018

INTRODUCTION

GBC is a well recognised malignancy of hepato-biliary tract and is the fifth most common malignancy of gastrointestinal tract in United States.¹ Even after two centuries of its description; the tumour remains characterised by an unfavourable prognosis due to silent

progression of the clinical course and limited knowledge of its etiology and poor scientific capability for epidemiological forecasting. The incidence of GBC varies in different parts of the world.² It is more common in northern India while rarer in southern part of the country. Data on north-western part of the country is highlighted poorly due to immature studies and inadequate data. Gall stones, choledochal cysts, chronic infections of the gallbladder and environmental exposure to specific chemicals such as urea enriched fertilizers are known predisposing factors. There exists an opportunity to identify prevalent factors in any specific geographic area. The use of focused area specific primary prevention can reduce the incidence of this dreaded disease. We took up a prospective study of all the gall bladder cancer presenting in our tertiary care hospital in north-western part of India over a 48 months period. It is a mix of urban,

semi urban and rural population with a catchment area of approximately 21,70,076 million people. We assessed the incidence, presentation, and tried to identify any relevant risk factors.

MATERIALS AND METHODS

All cases presenting over the 48months period were included in this prospective study. All cases were histological proven diagnosis. All histologically proven cases were further subjected to the complete battery of imaging investigations including computerised tomography and PET-Scan for complete stage evaluation. Complete information was recorded in the medical records file for the assessment of various epidemiological factors affecting the temporal profile of the disease.

RESULTS

Table 1: Table comparing epidemiological factors of the study with other studies that have highlighted them before. Out of the total 7000 cases registered in the 48 months, 244 (3.5%) cases were diagnosed as cases of gall bladder carcinoma (GBC).

Age	4th decade	Varies between 5th-7th decade
Gender	1:3.36	1:3.4
Low socioeconomic status	significant (68.6%)	Varies from significant to non-significant
Associated gallstones	Significant (71.4%)	Significant, varies from 69-90%
Diet (Non-veg)	Significant p<0.001	Significant with p<0.05
High BMI	Non-significant	Significant with p value=0.02.

Age Incidence: The peak incidence was in 51-60 years age group, which was a decade earlier than the world data. Seventy-nine patients (32.3%) were in this age group. GBC is significantly higher in older patients reaching its maximum in seventh decade worldwide.

1. Male Female Ratio: Out of 244 GBC cases, 188 were females and 56 were males. Male to female ratio in this study was 1:3.36, significantly higher for females (p = 0.001).
2. Socioeconomic status: out of the 244 GBC cases registered, 167 (68.6%) patients were reportedly from rural background and remaining 77 (31.5%) patients form urban background as recorded on the medical record files.
3. Dietary groups: 236 out of 244 patients (96.62 %) were non-vegetarians. Proportion of gall bladder cancer is significantly higher among non-vegetarians (p = 0.000 001).
4. Personal habits: Out of the 244 patients with GBC, 39 (18%) patients consumed alcohol, and 36 (15%) patients were addicted to opium and tobacco. Chi-square test shows that incidence of

gall bladder carcinoma is significantly higher among tobacco users in males (p = 0.0001) and females (p = 0.04).

5. Body Mass Index (BMI): Out of the 244 cases, majority of patients 166 (68.2%) patients were underweight with BMI of less than 18, at the time of presentation due to severe anorexia. Only 29 (11.88%) patients were overweight suggesting BMI of 25-29.9. Chi Square test shows that there was no significant association between occurrence of gall bladder carcinoma and body weight in the study.
6. Gallstones were present in 154 cases (71%) as per ultrasonography. There was also an interesting finding of increased detection of incidental diabetes mellitus type II in patients of GBC in 6% of patients.
7. Clinical features: Pain abdomen and loss of appetite were the most common complaints at the time of presentation in the patients of GBC.
8. The most common histopathology was adenocarcinoma in (75.5%) patients. The most common stage unfortunately was T3 in (49.1%) patients and T4 in (38.7%) patients, with only (3.2%) patients presenting in T1 stage. The risk of nodal involvement as evidenced by CT Scan was as high as (80%).

DISCUSSION

The present study is an attempt to study the epidemiological parameters in a tertiary care teaching institution in a sub-urban city in north western part of India, with a drainage area and patient referral from both urban and rural areas of adjacent districts and states. After analysing our data, we compared the results with the data of other National and International Institutions.

Incidence: There are wide geographical variations. About 66% of GBC cases occur in less developed countries. The highest incidence of GBC is in South America and Asia, and the lowest incidence is in Africa.(3) SEER estimates revealed an incidence of 1.1 cases per 100,000 populations per year in the United States.(4) In India, carcinoma of gall bladder is much more common in women in north and central part than in the west and south. In Kashmir, it is the third most common cancer in females after cancer cervix and breast cancer. In 1998–2006, incidence rates of gallbladder cancer (age-standardized rate, ASR) were high in Delhi and Kamrup (3.6 and 7.4) and (5.3 and 14.3) per 10⁵ person years in males and females, respectively and lowest in Aurangabad, 0.0 in both genders. The incidence rate revealed an increase in all registries. (5) In our study, the incidence of GBC was found to be 10 cases per 100,000

population per year (calculating the drainage area population of 21,70,000 lakh population approximately and adjusting the data taken over 48 months) which appears remarkably increased as compared to other parts of the Gangetic belt in northern India where the incidence of GBC is high. However, the percentage of this disease, out of the total hospital admissions (0.062%) and among all cancer patients (2.92%) still remains very minimal probably because of the higher percentage of sick population attending in hospital and higher incidence of other forms of malignancies.

Age: The median age was 67 years in a Memorial Sloan-Kettering report of 435 GBC patients. US data from 2010 reveals that age-adjusted incidence rates (per 100,000) in 2010 rose from 0.16/100,000 (for those 20–49 years) to 1.47/100,000 (for those 50–64 years), to 4.91/100,000 (65–74 years), and to 8.69/100,000 for individuals over the age of 75 years (6). In our study, the cases ranged from 28 to 72 years with peak incidence in 51-60 years age group (32.3%), a decade earlier than the reported worldwide data.

Sex Ratio: Male: Female ratio is around 1:3.5 as per published literature⁷. In the study, 56 were male and 188 were female constituting a male to female ratio of 1:3.36 which is consistent with other studies. Socioeconomic, Educational and Occupational Factors Gallstones and lower socio economic status are independent determinants for early onset of gall bladder carcinoma⁸. Lower socio economic status is indirectly a result of illiteracy and poor education standards. This leads to unemployment and decreased livelihood capacity influencing preventive aspects of Gall bladder cancer⁹. In our study (2012-2015), majority of the gall bladder, carcinoma patients (68.5 %) were from rural background consistent with poor socio-economic status as per the scale set by Kuppaswamy. One possible factor is neglect of health care in this strata specially delay in seeking treatment for gallstone disease. Diet, Personal Habits and Body Weight Further indications of a protective role of vegetables and fruits were found in an integrated series of case-control studies conducted in Northern Italy, in which researchers found a weak inverse association with high consumption of fruits and vegetables for GBC.¹⁰ Another study in Japan, reported a positive association between the mortality rate of biliary tract cancer and expenditure for foods like pork¹¹. Tavani *et al*, (2000) demonstrated a positive relationship with consumption of red meat and several neoplasm; but no statistically significant association was found with red meat intake and risk of GBC¹². In a case control study, red meat consumption was found to be associated with increased risk of GBC. Majha and Doaba where GBC is highly prevalent, as our catchment area lies downstream of the rivers Satlej and

Beas, which is the main source of water for drinking and irrigation purposes. It is quite likely that certain environmental pollutants are acting as carcinogens. An inverse relationship for incidence of gall bladder carcinoma exists with fibre, vitamin C and E intake. Lowering of risk associated with vegetable consumption and increase in risk with added sugar in desserts and drinks is seen in gall bladder carcinoma¹⁴. In our study, 236 out of 244 patients (96.62 %) were nonvegetarians, adding on chilli and spices as contributory factors in their staple diet. Combined effects of environmental pollutants and dietary factors could have a role in high incidence of GBC in this region. A prospective cohort study in the USA, found that GBC mortality rates were associated with obesity in women¹⁵. Other studies also revealed that obesity was positive associated with a higher incidence of GBC.¹⁶ Several reports have demonstrated a strong relationship between obesity, gallstones and GBC^{17,18}. In our study, out of the 244 cases of GBC, 29 (11.88%) patients were overweight with BMI ranging between 25-29.9 and none were in the obese category with a BMI of over 30. This was probably due to the fact that two-thirds of the patients presented with locally advanced disease with anorexia already set in. As a result, they had started losing weight due to cancer cachexia. Majority of the patients in our set up were from low socio economic strata and not only the body habitus but overall malnutrition may be contributing to decreased BMI.

Personal Habits: Earlier published data on the relationship of alcohol consumption and chewing tobacco with gall bladder carcinoma remained inconclusive. Some studies suggested an increased risk, while others suggested that longterm alcohol use might play a role by reducing the cholesterol saturation of bile. Recent data however point more in favour of the conclusion that Alcohol intake, smoking (cigarettes per day) and number of tobacco chewing per day are all independent risk factors for gall bladder carcinoma.¹⁹ In the present study, statistical analysis for patients with a history of alcohol consumption was not carried out due to their small numbers. Alcohol did not constitute a risk factor in females. May be the female patients, who were mostly from lower socioeconomic strata in our social setting, rarely consume alcohol.

Cholelithiasis: The association of cholelithiasis with GBC is very strong. The gallstones are the commonest factor leading to GB carcinogenesis. Chronic trauma and inflammation can induce epithelial dysplasia, carcinoma in situ and invasive cancer but a cause and effect relationship is not proven.²⁰ The evidence at the current time indicates that gallstones are a cofactor in the causation of GBC. Absolute proof of their role as a cause for gallbladder cancer is lacking. The recommendation

for prophylactic cholecystectomy in countries reporting a high incidence of GBC and associated gallstones needs to be tailored to the epidemiological profile of the place.²¹ In our study, gallstones were found in 154 out of 244 GBC patients (71%). Consistent with other GBC case series, our study also showed high incidence of cholelithiasis in GBC patients.

Clinical Presentations: GBC has been quite difficult to diagnose preoperatively as the symptoms and signs are vague and non-specific. In most cases, it is discovered quite late, in a stage where cure is difficult, if not impossible. Pain is a presenting feature in nearly all the cases (97 %) followed by weight loss (77 %), hepatomegaly (65 %) and (64%) patients complaining of nausea and vomiting.²² According to cancer.net editorial board 2017 (doctor approved patient information from ASCO) abdominal pain, nausea and vomiting along with jaundice forms the most common presenting complaints of patients with GBC. In our study, pain abdomen was the commonest complaint (86.6%), followed by loss of appetite (80.6%), fever (59.4%), jaundice (50.2%), nausea and vomiting (45.6%), lump abdomen (35%) and ascites (32.1%) which was respectively similar to previous results.

CONCLUSION

This sample data highlights high prevalence of GBC in a tertiary care hospital in northwestern part of India. Factors like better hygiene, water supply and basic education about GBC along with prevention of malnutrition, and early intervention for cholelithiasis are important. Balanced diet, decreasing the red meat and increasing low fat, mineral and antioxidant rich diet, increase awareness about risk of tobacco and alcohol consumption all are highlighted as significant factors which can prevent /decrease incidence of this otherwise dreaded disease. Overall socio economic improvement along with environmental pollution control and education to increase awareness can play important part for prevention. Above all, early detection and screening of vague upper abdominal symptoms while keeping the possibility of GBC should be kept in mind.

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Source of Support: None Declared
Conflict of Interest: None Declared