

Risk Factors and Clinical Profile in Patients of Gall Bladder Cancer in Sub Himalayan Region: A Retrospective Study

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Received: September 2020

Accepted: September 2020

ABSTRACT

Background: Gallbladder cancer is the most common malignant tumour of the biliary tract. It is also the most aggressive tumour and ranks 6th among gastrointestinal tumours in the world. Various risk factors for its causation have been described in literature. **Methods:** A retrospective study was carried out at Dr Rajendera Prasad Government Medical College, Kangra at Tanda in Himachal Pradesh over a period of one year (from 1st January 2019 to 31st December 2019). Thirty cases were diagnosed as a case of carcinoma gallbladder which were proven either on preoperative biopsy or computed tomography or ultrasound guided fine needle aspiration cytology. The case records of 30 patients were thoroughly studied which met the inclusion criteria. The main parameters which were included in study were age, sex, religion, socioeconomic status, addictive factors, comorbidities, body mass index, aetiological factors, family history, clinical presentation, clinical findings, nutritional status, various biochemical findings, CA19-9 levels and stage of disease at the time of presentation. **Results:** Our study revealed that the peak age of the disease was 7th decade of life. The mean age of presentation in all the patients was 64.3 years. Male to female ratio in gallbladder cancer was 1:9. Ninety percent of patients belonged to rural background. Three patient's had history of either smoking or alcohol. Out of 30 patients, 3 patients had comorbidities like diabetes mellitus or hypertension. Most of the patients had BMI in range from 18-24. Cholelithiasis as main etiological factor was present in 80% of cases. Pain was main clinical presentations followed by nausea/ vomiting and anorexia. Pallor, jaundice and abdominal lump were chief clinical findings on examination. In most of the patients CA19-9 levels were in the range group from 0 to 37. Majority of the patients presented in the late stage of the disease ie, stage IV. **Conclusion:** Gallbladder cancer is a disease associated with various risk factors as described in literature with presentation in late stages thus increasing mortality and prognosis.

Keywords: Gallbladder Cancer, Risk Factors, Cholelithiasis, Morbidity, Jaundice, Stage.

INTRODUCTION

Gallbladder cancer is the most common malignancy of the biliary tract, representing 80-90% of biliary tract cancers worldwide, according to autopsy studies.^[1] It is also the most aggressive cancer of the biliary tract with the shortest median survival from the time of diagnosis.^[2] This poor prognosis is due, in part to, an aggressive biological behaviour and a lack of sensitive screening tests for early detection resulting in delayed diagnosis at advanced stage.^[3] It ranks sixth among gastrointestinal cancers. However, the global rates for gallbladder cancer exhibit striking variability, reaching epidemic levels for some regions and ethnicities. The basis for this variance likely resides in differences in environmental exposure and intrinsic genetic predisposition to carcinogenesis. These risk factors vary geographically and among the ethnic groups.

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 with coexisting gallstone and chronic cholecystitis present in majority of the cases.^[4,5]

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 gallbladder has been found. A significant association of early menarche and prolonged reproductive period has also been reported.^[5,6]

Postmenopausal state as a risk factor was associated with development of carcinoma of the 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.^[7] Higher incidence of carcinoma

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gallbladder is also related to poor socioeconomic and education status and certain lifestyle factors including smoking, alcohol consumption and tobacco chewing. There are certain studies which have emphasized the role of dietary factors responsible in causation of gallbladder cancer.^[8-10]

In most of the cases, the clinical presentation of gallbladder cancer is highly nonspecific. It may be an incidental finding while patient is investigated for some other disease where the symptoms do not correlate directly with the disease. It is often recognized late, with the diagnosis established during advanced stage of the disease. Pain, anorexia, jaundice, weight loss, abdominal lump and abdominal distension are few symptoms with which patient presents to the clinician. A vast amount of work has been done in western world and rest of Asian region but there are limited reports from India where the burden of disease is more as compared to other countries. So, this retrospective study was aimed to analyze the risk factors, mode of clinical presentation and stage at presentation of gall bladder cancer in Sub Himalayan region.

MATERIALS AND METHODS

A retrospective study was carried out at Dr Rajendera Prasad Government Medical College, Kangra at Tanda in Himachal Pradesh over a period of one year (from 1st January 2019 to 31st December 2019). Thirty cases were diagnosed as a case of carcinoma gallbladder which were proven either on preoperative biopsy or computed tomography or ultrasound guided fine needle aspiration cytology. These patients attended various units in Department of Surgery in the above mentioned period. We included only those patients which were proved pathologically, and cases which presented as carcinoma gallbladder but due to some reason could not be diagnosed, were excluded. The case records of all these 30 patients were thoroughly studied. The main parameters which were included in the study were age, sex, religion, socioeconomic status, addictive factors, comorbidities, body mass index, aetiological factors, family history, clinical presentation, clinical findings, nutritional status, various biochemical findings, CA19-9 levels and stage at the time of presentation. The findings were recorded in excel sheet and the data was interpreted using various methods.

RESULTS

Our study revealed that the gallbladder cancer peaks in the 7th decade of life which is followed by a surge in 6th decade. Youngest patient who was diagnosed having carcinoma was a female aged 39 years and oldest patient was again a female aged 90 years. The mean age of presentation was 64.3 years in all 30 patients. The mean age in male patients was 69.3

years whereas in female patients, it was 63.4 years. Regarding sex distribution, out of total 30 patients, 27 (90%) were female while only 3 (10%) were male patients [Table 1]. All the patients belonged to Hindu community. As far as socioeconomic status is concerned, 27 (90%) patients were from rural population and only 3 (10%) patients from semi urban population [Table 2]. In the present study, it is very difficult to conclude the relationship between addiction and gallbladder cancer, as only 1 (3.33%) was smoker, who was a male patient and 3 (10%) consumed alcohol, again all male patients [Table 3].

Table 1: Age and sex distribution

Age group (Years)	Male	Female	Total
<41	0	1	1
41-50	0	5	5
51-60	1	5	6
61-70	1	7	8
71-80	0	4	4
81 and above	1	5	6
Total	3	27	30

Table 2: Distribution based on socioeconomic status

Region	Number	Percentage
Urban	0	0%
Semi urban	3	10%
Rural	27	90%
Total	30	100%

Table 3: Addictive factors

Addiction	Number	Percentage
Smoking	1	3.33%
Alcohol	3	10%

Regarding comorbidities, most of the patients had age related comorbidities. Both hypertension and diabetes mellitus were seen in 3 (10%) patients each, followed by hypothyroidism and pulmonary tuberculosis in 1 (3.33%) patient each. Two (6.67%) patients were suffering from both hypertension and diabetes mellitus [Table 4]. Sixteen (53.33%) patients were having body mass index ranging from 18-24.9, followed by 7 (23.33%) patients each in group less than 18 and in another group ranging from 25-30. There was no patient with body mass index above 30 [Table 5].

Table 4: Association with comorbidities

Co-morbidity	Number	Percentage
DM	3	10%
Hypertension	3	10%
IHD	0	0%
Hypothyroidism	1	3.33%
COPD	0	0%
Pulmonary TB	1	3.33%

Table 5: BMI and Gallbladder cancer

BMI	Male	Female	Total	Percentage
<18	0	7	7	23.33%
18-24.9	0	16	16	53.33%
25-30.9	3	4	7	23.33%
31-40.9	0	0	0	0%
>41	0	0	0	0%
Total	3	27	30	100%

We found significant relationship between cholelithiasis and gall bladder cancer, as 24 (80%) patients suffered from gallstone disease. Family history of gallbladder cancer was present in 4 (13.33%) patients, where in 3 (10%) patients, mother died of some cancer associated with jaundice. One (3.33%) patient took oral contraceptive pills long ago for about 6 years [Table 6]. Regarding nutritional status, 18 (60%) patients were in average status group, 9 (30%) patients had good nutritional status followed by 3 (10%) having poor status [Table 7].

Table 6: Etiological factors

Risk factors	Number	Percentage
Cholelithiasis	24	80%
Typhoid	0	0%
Family history	4	13.33%
Hormonal exposure	1	3.33%
Drugs	0	0%

Table 7: Nutritional status

Status	Number	Percentage
Good	9	30%
Average	18	60%
Poor	3	10%
Total	30	100%

As far as clinical presentation is concerned, the most consistent symptom was pain which was present in 26 (86.67%) cases, followed by nausea/ vomiting in 22(73.33%) cases, anorexia in 21(79%) cases, jaundice in 9(30%), weight loss in 8(26.67%), abdominal distension in 6(20%) and abdominal lump in 1(3.33%) case [Table 8]. On clinical examination, pallor was present in 13(43.33%) cases followed by icterus and abdominal lump in 12(40%) cases each. Ascites, hepatomegaly and oedema was present in 5(16.66%), 4(13.33%) and 2(6.67%) cases respectively [Table 9].

Table 8: Clinical presentation

Presentation	Number	Percentage
Pain	26	86.67%
Anorexia	21	70%
Jaundice	9	30%
Weight loss	8	26.67%
Abdominal lump	1	3.33%
Nausea/ Vomiting	22	73.33%
Abdominal distension	6	20%

Table 9: Clinical examination

Findings	Number	Percentage
Pallor	13	43.33%
Oedema	2	6.67%
Jaundice/Icterus	12	40%
Abdominal lump	12	40%
Hepatomegaly	4	13.33%
Ascites	5	16.66%

Regarding CA19-9 levels, most of the patients were in range group from 0-37units/ml (63.33%), followed by 6 (20%) patients in range group from

100-1000 units/ml, 4(13.33%) in 38-100 units/ml group. Only 1(3.33%) had CA19-9 levels more than 1000(2292units/ml) [Table 11]. Majority of the patients presented in the later stage of the disease i.e. Stage IV and stage III (86.67%), followed by 3(10%) in stage II and 1(3.33%) patient presented in stage I [Table 12].

Table 11: CA19-9 levels and Gallbladder cancer

CA19-9 levels (Units/ml)	Number	Percentage
0-37	19	63.33%
38-100	4	13.33%
100-1000	6	20%
>1000	1	3.33%

Table 12: Stage at presentation

Stage	Number	Percentage
I	1	3.3%
II	3	10%
III	6	20%
IV	20	66.67%
Total	30	100%

DISCUSSION

Gallbladder cancer is the most common malignant tumour of the biliary tract worldwide.^[11] Its incidence is gradually increasing in India and is projected as the major cause of morbidity and mortality in Indian population. Despite this, only few studies have been done so far. A striking geographical variability is observed in the prevalence of carcinoma gallbladder worldwide. Regions reporting high incidence of gallbladder cancer include India, Bolivia, Pakistan and Ecuador.^[11] High rates are also reported from Chile, Poland, Japan and Israel.^[12] The prevalent epidemiological factors like age and sex distribution, rural and urban distribution, socioeconomic stratification, religion, comorbidities and addiction have been thoroughly studied.

Gallbladder cancer rates become more common with advancing age, likely because the malignancy takes decades to develop. It is common after the age of 60 years.^[13] The mean age of presentation in our study was 64.3 years, which is comparable to a study by Piehler and Crichlow,^[14] where the mean age of presentation was reported to be 65 years and the highest incidence occurred in seventh and eighth decades of life. It is higher as compared to a study by Shukla et al,^[4] where the mean age of presentation was 50 years.

This disease is more common in females than males.^[15] Women are 2 to 6 times more commonly affected than men.^[16] The female hormone estrogen is known to increase the saturation of cholesterol in bile, thus increasing the risk of gallstone formation and subsequent development of cancer.^[17] In our study, disease occurred mainly in female patients, with male to female ratio being 1:9 and in every age group female patients invariably out represents male. It was very high as compared to a study by Halder A

et al,^[18] where male to female ratio was 1:3 and in a study by Shukla et al^[14], it was 1:2.5.

All the patients who presented with gallbladder cancer were Hindus, which may be attributable to the fact that in this part of country, about 98% of population that this medical college caters to, is Hindu. About distribution based on socioeconomic status, most of the patients belonged to rural population (90%) and 10% were from semi urban background. No patient presented from urban area again due to the fact that here, the burden of urban population is very small as compared to rural and semi urban population. It is noteworthy that the lifestyle and dietary habits of rural population do vary considerably from those in the cities. The national data reflects that the incidence of gallbladder cancer predominates in population with low income and education, who are unaware of extreme consequences or are too poor to afford the cost of diagnosis and treatment and hence, continue to suffer from the disease.

In our study, 3(10%) patients were smoker and only 1(3.33%) patient had history of alcohol intake. It would really be required to find out whether there is any link between smoking and development of gallbladder cancer. In the existing literature, there is higher incidence of cancer in relation to smoking, tobacco chewing and alcohol consumption.^[4] Three (10%) patients each were suffering from hypertension and diabetes mellitus. This association is possibly due to higher incidence of comorbidities in older age group but, any causal relationship of these comorbidities with gallbladder cancer needs further studies.

Obesity is a well recognised risk factor for the development of gallbladder cancer. For each 5 point increase in BMI, the relative risk of developing gallbladder cancer increases by 1.59 for women and 1.09 for men.^[19,20] A positive association of high fat intake with gallbladder cancer risk was found in a case control study by Chijiwa K et al.^[21] In our study, most of the patients (53.33%) had BMI in the range from 18-24.9 with average nutritional status and very few in the obese group. This may be due to late presentation and emaciation secondary to the disease process.

The most important risk factor for the development of gallbladder cancer is cholelithiasis with an average 8 times higher risk than general population.^[22] Among patients with gallbladder cancer 70-90% have a history of cholelithiasis.^[23,24] Larger stones pose a higher risk, with stones more than 3 centimetres carry 9.2 to 10.1 time higher risk, than stones less than 1 centimetre in size. This increased risk is most likely attributable to greater local epithelial irritation. In our study, 24 (80%) patients had cholelithiasis which is comparable to the existing data. Moreover, majority of the patients had a stone size in the range from 2 to 3 centimetres. Family history of gall bladder cancer can increase a

person's risk of developing gallbladder cancer.^[25,26] In our study, 4 (13.33%) patients had family history for this disease. A Swedish study showed that the standardized incidence ratio (SIR) for gallbladder cancer in offspring of parents diagnosed with this disease was 2.47.^[27]

The most common symptom with which the patient presented to our hospital having gallbladder cancer was pain in right upper abdomen (86.67%). This was comparable to the study by Halder et al,^[18] where pain was present in 86.27% cases. Shukla et al,^[4] also reported pain to be most common presenting complaint in such patients. It may be due to acute cholecystitis secondary to gallstones or due to stretching of gallbladder capsule by malignant infiltration of surrounding structures. Constitutional symptoms like anorexia, nausea and vomiting were present in about 70% patients. Other symptoms include jaundice, weight loss, abdominal distension and awareness of abdominal lump. In such patients, jaundice is usually due to extrahepatic biliary obstruction and abdominal distension is mostly seen in advanced cases with ascites, secondary to peritoneal metastasis.

Among clinical findings, pallor, jaundice and abdominal lump were consistent findings seen in 43.33%, 40% and 40% cases respectively. Pallor in this part of the country is mostly due to nutritional anaemia but may be attributable to disease process. Derangement of hepatocellular function may occur due to liver metastasis in these patients, presenting at later stage of the disease. Lesser number of the patients presented with ascites, hepatomegaly and oedema. Ascites occurs due to dissemination process and hypoproteinemia. Hepatomegaly is attributed to liver metastasis later in the disease process. Oedema is pedal and pitting type which is due to hypoproteinemia and compression by mass over inferior vena cava.

Most of the patients (63.33%) had their initial CA19-9 levels in the range from 0 to 37 units per ml (millilitre). Ten (33.33%) patients had CA19-9 levels ranging from 38 to 1000 units per ml. Only 1 patient had levels more than 1000. CA19-9 levels have prognostic importance and elevated levels are associated with poor prognosis in gallbladder cancer. However, we could not find any positive relation between elevated CA19-9 levels and prognosis, including stage at presentation.

Regarding stage at presentation, 20(66.67%) patients presented in stage IV disease, which means there was extrahepatic organ invasion (two or more) and spread to major vascular structures like portal vein and hepatic artery. It was followed by 6(20%) patients in stage III disease ie. disease spread to adjacent structures perforating the visceral peritoneum. Only 4(13.33%) patients presented early at Stage I and II ie. tumour limited to layers of gall bladder wall. It may be due to the fact that in this part of the country patients presented late after

taking some symptomatic treatment at local centers. Also the late presentation may contribute to its indolent course and highly aggressive nature.

CONCLUSION

In most of the patients, risk factors, clinical presentation and findings supports the previous literatures on carcinoma gallbladder as seen in rest of the world. However, most of the gallbladder cancer patients present in late stage of the disease. Thereby surgery, which is most curative and definite mode of treatment, could not be done in such patients.

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How to cite this article: Sharma R, Chaudhary A, Thakur R, Kumar GR, Shashikant. To Study Risk Factors and Clinical Profile in Patients Presenting with Gall Bladder Cancer in Sub Himalayan Region: A Retrospective Study. *Ann. Int. Med. Den. Res*. 2020; 6(6):SG23-SG27.

Source of Support: Nil, **Conflict of Interest:** None declared