

RESEARCH ARTICLE

RISK FACTOR ASSOCIATED WITH GALLBLADDER MALIGNANCY IN NORTH INDIA: A PROSPECTIVE STUDY

¹Arpit Bansal, ^{2*}Ashwani Kumar Bansal, ³Vandana Bansal and ⁴Ajay Kumar

¹Department of Surgery, Gujrat Cancer Institute, Ahmadabad

²Department of Surgery, Jeevan Jyoti Hospital, Allahabad, U.P. India

³Guru Gobind Singh Memorial Vandana Women's Hospital, Allahabad, U.P. India

⁴Jeevan Jyoti Institute of Medical Sciences, Allahabad, U.P. India

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ABSTRACT

Introduction: Carcinoma of the gallbladder is the most common malignancy of the biliary tract and the third most common gastrointestinal malignancy in and around the Northern region of India. Owing to its nonspecific symptoms, gallbladder carcinoma is generally diagnosed late in the disease course, but if a patient with gallstones experiences a sudden change of symptoms, then a cancer diagnosis should be considered. There are several factors which is associated with gallbladder malignancy such as gallstone, porcelain gallbladder, obesity, gallbladder polyps, gender, family history of gallbladder cancer and several carcinogens (chemicals).

Objective: Objective of the study was to evaluate the different risk factor associated with gallbladder malignancy. It is an important to assess the risk factor for gall bladder malignancy take into account the confounding effect of gallstone.

Materials and Methods: This prospective study carried out on 115 patients having evidence of gallbladder malignancy. The diagnosis was made accordance of sign and symptom, abdominal ultrasonography (USG) and a computed tomography (CT) scan of the abdomen, and was confirmed by histology.

Results: Gallstone (83.5%) was the major risk factor for malignancy followed by Choledochal cysts (73%), use of tobacco (71.3%), Primary sclerosing cholangitis (36.5%), porcelain gallbladder (29.6%), obesity (24.3%), family history (23.5%), alcohol (20.9%), Gallbladder polyps (13.9%), bile duct abnormality (7.8%) and infection with typhoid (4.3%). The female were more susceptible to gallbladder cancer the male female ratio was (1:2.7).

Key Words: Gall bladder malignancy, Risk factor, Gallstone.

INTRODUCTION

The gallbladder is a pear-shaped organ that lies just under the liver in the upper abdomen. The gallbladder stores bile, a fluid made by the liver to digest fat. When food is being broken down in the stomach and intestines, bile is released from the gallbladder through a tube called the common bile duct, which connects the gallbladder and liver to the first part of the small intestine. The wall of the gallbladder has 3 main layers of tissue. Mucosal (innermost) layer, muscularis (middle, muscle) layer and serosal (outer) layer. Between these layers is supporting connective tissue. Primary gallbladder cancer starts in the innermost layer and spreads through the outer layers as it grows. The poor prognosis associated with GBC is thought to be related to advanced stage at diagnosis, which is due both to the anatomic position of the gallbladder, and the vagueness and non specificity of symptoms. Globally, there is a prominent geographic variability in GBC incidence that correlates with the prevalence of cholelithiasis. High rates of GBC are seen in South American countries, particularly Chile, Bolivia, and Ecuador, as well as some areas of India, Pakistan, Japan and

Korea (Hamrick *et al.*, 1982). In the United States, GBC is the most common cancer arising in the biliary tract (Randi *et al.*, 2006). GBC is the most common malignancy in both Southwestern Native Americans and in Mexican Americans (Lazcano-Ponce *et al.*, 2001). The incidence of GBC is high in many parts of the world including Chile, Peru, Bolivia, Korea, Japan, Czech Republic, Slovakia, Spain and India (Randi *et al.*, 2006). The incidence of GBC among women in northern India is one of the highest in the world, and the incidence of GBC is steadily increasing from 10.1/100,000 population in women in 1993 to 19.6/100,000 population in 2006 (Raina *et al.*, 2010). The incidence of gall bladder disease is high among people living near the Ganga and its tributaries, says the largest-ever study of the local population over six years in this region the prevalence. Recent study shows the high rate of gall bladder in the Bihar, located near the river Gandak. About 20,000 and 30,000 people develop gall bladder disease each year because of the environmental factors in Uttar Pradesh and Bihar. In addition to geography, there are also age, race, and gender-related differences in the incidence of GBC. Incidence steadily increases with age, women are affected two to six times more often than men (Wistuba *et al.*, 1999). Gallstones are the most common risk factor for gallbladder cancer because of these are

*Corresponding author: Ashwani Kumar Bansal

Department of Surgery, Jeevan Jyoti Hospital, Allahabad, U.P. India

so hard, rock-like formations of cholesterol and other substances that form in the gallbladder and can cause chronic inflammation ultimately developed the growth of undefined cells. Approximately, 3 out of 4 people with gallbladder cancer have gallstones but this is quite rare. Another second condition is Porcelain gallbladder in which the wall of the gallbladder becomes covered with calcium deposits. It sometimes occurs after long-term inflammation of the gallbladder and this has high possibility to developing gallbladder cancer (Duffy *et al.*, 2008). Gallstones and gallbladder inflammation are the 2 important risk factors for gallbladder cancer and are also much more common in women than men. Gallbladder cancer can occur in younger people, but it's seen mainly in older people. The average age of people when they are diagnosed is 73. Almost 3 out of 4 people with gallbladder cancer are older than age 65 when it is found. Studies also suggested the Obesity or overweight or obese than people without this disease a risk factor for gallstones, and link to cancer (Lew *et al.*, 1979).

Most important risk factor is, Choledochal cysts are bile filled sacs that are connected to the tube that carries bile from the liver and gallbladder to the small intestine. The cysts can grow over time and may contain as much as 1 to 2 quarts of bile. The cells lining the sac often have areas of pre-cancerous changes, which increase a person's risk for developing gallbladder cancer (Konstantinidis *et al.*, 2009). Other studies have been emphasized parity (Lambe *et al.*, 1993), family history (Andersson *et al.*, 1992), history of typhoid infection (Strom *et al.*, 1995) and exposure to environmental chemical (Fernandez *et al.*, 1994) are recently suggested as risk factor for gallbladder malignancy. The etiopathogenesis of GBC is not well understood. The study of the risk factors for GBC is important not only for understanding the etiopathogenesis but also for preventive strategies. The putative risk factors for GBC include female sex, gallstones, chronic Salmonella typhi carrier status, dietary factors and environmental exposure to specific chemicals. (Engeland *et al.*, 2005, Dutta, 2012). The current knowledge about the risk factors for GBC is limited, and there is inconsistency about the role of risk factors in various studies from different centers. The present study was conducted in northern India, a high-incidence area for GBC, with the objective to find out various risk factors related to gallstones, biliary bile acids, biliary infection, occupational factors, etc., that might be associated with GBC.

METHODS

This was a prospective study conducted in the Department of Surgery & Department of Radiology of Jeevan Jyoti Hospital, Allahabad, U.P. India, and Department of Radiology of Guru Gobind Singh Memorial Vandana Women's Hospital, Allahabad, U.P. India from 20 January 2012 to 01 January 2015.

Cases

All patients having evidence of gallbladder malignancy were included in the study. They were enrolled from out-patient Department of Surgery & gastroenterology of Jeevan Jyoti Hospital, and patients from Guru Gobind Singh Memorial Vandana Women's Hospital, Allahabad, U.P. India.

Diagnosis of gallbladder malignancy

The diagnosis of gallbladder cancer (GBC) was made on the basis of imaging studies included an abdominal ultrasonography (USG) and a computed tomography (CT) scan of the abdomen, and was confirmed by histology. For the confirmation of the diagnosis, either a fine-needle aspiration cytology or percutaneous biopsy or histopathology of the surgically respected specimen was performed.

Criteria of inclusion

Patients having gallbladder malignancy/ gallbladder cancer (GBC) who was in sufficiently good physical and mental health to give reliable answers to the questionnaire were included in the study.

Criteria of exclusion

Patients having GBC with any other major illness and on refusal to participate in the study were excluded from the study.

RESULTS

In our study total 115 patients were enrolled in which 31 (27%) were male and 84 (73%) were female. The mean age of male patients was 68 \pm 5.23 year and 61 \pm 4.54 year of female patients.

Sign and Symptoms

Gallbladder malignancy is generally asymptomatic in the early stage. It does not show defined and specific sign and symptoms. Patients had symptoms for an average duration of 4.2 months prior to presentation of malignancy. The most common presenting symptom was pain in the abdomen (94.8%), followed by fever (93%) Nausea/Vomiting (91.3%), lumps in the belly (90.4%), loss of appetite (78.3%), weight loss (65.2%), jaundice (49.6%), dark urine (13.9%), itchy skin (12.2%) and light colored & greasy stool (7.8%). The sign of gallbladder malignancy was appeared in following order as abdominal mass (74.8%), Icterus (53.9%), Ascites (34.8%) and cachexia (15.7%) (Table 1).

Table 1. Sign and symptoms of gallbladder malignancy

Symptom	No. of patients	Percentage
Abdominal (belly) pain	109	94.8%
Nausea and/or vomiting	105	91.3%
Jaundice	57	49.6%
Lumps in the belly	104	90.4%
Loss of appetite	90	78.3%
Weight loss	75	65.2%
Fever	107	93.0%
Itchy skin	14	12.2%
Dark urine	16	13.9%
Light-colored or greasy stools	9	07.8%
Sign		
Abdominal mass	86	74.8%
Icterus	62	53.9%
Ascites	40	34.8%
Cachexia	18	15.7%

Laboratory investigations revealed the mean hemoglobin concentration of 8.7 g% (range, 4.5–13.8 g%). Anemia (hemoglobin <10 g/dl) was present in 98 (85.2%) patients; of these, 45 (45.9%) patients had hemoglobin level below 8 g%. Leukocytosis (counts>10,000) was present in 31.3%, hyperbilirubinemia (serum bilirubin >2 mg/dl) in 37.4%, and elevated levels of alkaline phosphatase (>100 IU/ml) in 64.5% of the patients.

Factor Responsible for gallbladder malignancy

In our study we have found that female are predominantly found in association with gallbladder malignancy 84 (73%) than the male gender 31 (27%). In our study the major and minor risk factor which was evaluated by us are gall stone (83.5%), choledochal cysts (73%), tobacco (71.3%), primary sclerosing cholangitis (36.5%), porcelain gallbladder (29.6%), obesity (24.3%), family history (23.5%), alcohol (20.9%), gallbladder polyps (13.9%), abnormalities of the bile ducts (7.8%), and typhoid (4.3%) (Table 2).

Table 2. Risk factors of gallbladder malignancy

Factor	No. of patients	Percentage
Male gender	31	27%
Female gender	84	73%
Gall stone	96	83.5%
Porcelain gallbladder	34	29.6%
Obesity	28	24.3%
Choledochal cysts	84	73.0%
Abnormalities of the bile ducts	9	07.8%
Gallbladder polyps	16	13.9%
Primary sclerosing cholangitis	42	36.5%
Typhoid	5	04.3%
Tobacco	62	71.3%
Alcohol	24	20.9%
Family history	27	23.5%

DISCUSSION

Gallbladder malignancy is a highly fatal disease with poor and late prognosis. It is the fifth most common among malignant neoplasms of the digestive tract. To decrease mortality from GBC, we need to implement the preventive and surveillance strategies. Identifying the significant risk factors is an important step towards this. In present study we investigate different risk factor associated with gallbladder malignancy.

Our study showed Abdominal (belly) pain was major symptom followed by fever Nausea/Vomiting, lumps in the belly, loss of appetite, weight loss, jaundice, dark urine, itchy skin and light colored & greasy stool respectively. The sign of gallbladder malignancy was appeared in following order as abdominal mass, Icterus, Ascites and cachexia. Gupta SK reported that the most of patients were asymptomatic while a few present with clinical feature suggestive of benign disease such as right upper abdomen pain with occasional attack of nausea and vomiting. Jaundice, presence of lump and feature of malignant cachexia such as anorexia and weight loss was the feature of extensive disease (Gupta *et al.*, 2007). In our study female are more susceptible to gall bladder malignancy than the male (2.7:1) and about 91% are older age i.e. more than 55 year. Sanjeev Misra *et al* reported more than 90% are older than 50, the peak incidence was 70-75 year and most patients was woman with a

female to male ratio (3:1) (Sanjeev Misra *et al.*, 2003). GBC is more common in woman than in men, have a rising incidence with increasing age (Kapoor *et al.*, 2003). Our study suggested that about 83.5% cases of gallbladder malignancy was associated with gallstone. Also estimated gallstones in 65-90% cases of GBC (Misra *et al.*, 1995). Hsing AW reported 69% of patients of GBC had gallstone (Hsing *et al.*, 2007). Kajal Jain *et al* stated that gallstone is the primary factor of gallbladder malignancy (Kajal Jain *et al.*, 2013). Gall stone disease occurs at a younger age in Indians than in western populations; the median age of patients with gall stone disease in India (Kumar *et al.*, 1996). Porcelain gallbladder, the pathological finding of a brittle gallbladder with bluish discoloration resulting from extensive calcification of the organ wall, has also been associated with carcinoma in 12.5 – 62% of patients (Towfigh *et al.*, 2001). While in our study it was estimated that 29.6% of patients of GBC were associated with Porcelain gallbladder the region was not known. We have also estimated that Choledochal cysts (73%), Primary sclerosing cholangitis (36.5%), Gallbladder polyps (13.9%) also plays an important role in development of gallbladder malignancy. Hsing AW reported that 34.3% patients were alone responsible for gallbladder malignancy in China (Hsing *et al.*, 2007). A study carried out in Japan by Seiki Tashiro *et al* reported 63.3% patients of GBC have choledochal cysts (Seiki Tashiro *et al.*, 2003).

In our study we have evaluated that about 36.5% patients have primary sclerosing cholangitis, while Lewis *et al.* stated that primary sclerosing cholangitis was responsible for 10-20% of gallbladder malignancy (Lewis *et al.*, 2007). It was an estimated that abnormalities in the bile ducts was also associated with gallbladder malignancy this was find about 7.8% cases with abnormal biliary duct in our study. Seen abnormal biliary duct in 17% case of gallbladder malignancy (Henson *et al.*, 1992). In our study we have found that tobacco and alcohol was also risk factor for developing GBC about 71.3% patients uses tobacco and 20.9% was alcoholic. In other study carried out by Hsing Aw reported in 20.7% of patients was alcoholic having gallbladder malignancy (Hsing *et al.*, 2007). In our study we have found that 4.3% patients of gallbladder malignancy were suffered from typhoid while a study carried out by Gupta SK *et al* reported 10.7% patients of GBC were suffered from typhoid (Gupta *et al.*, 2007). The family history of gallstone disease was found to be a significant risk factor and might suggest a genetic predisposition to develop gallbladder disease including gallstone and GBC (Hsing *et al.*, 2007).

Conclusion

Our study concluded that female gender was more vulnerable group for GBC. The important risk factors were gallstone, porcelain gallbladder, gallbladder polyp, use of tobacco & alcohol and family history. We also not ignore the infection of typhoid for development of gallbladder malignancy.

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