

**STUDY OF GALLBLADDER CANCER & IDENTIFICATION OF ITS RISK FACTORS
AMONG THE PATIENTS WITH CHOLELITHIASIS-A MULTICENTRE STUDY IN
NORTH BENGAL**

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ABSTRACT

Background: The etiology of cholesterol gallstones is multifactorial, with interactions of genes and the environment. Risk factors for gallbladder cancer (GBC) except gallstones are not well known. Gallbladder cancer is usually associated with gallstone disease, late diagnosis, unsatisfactory treatment, and poor prognosis. **Objective:** The study is aimed at finding out the prevalence of gallbladder cancer & identification of its risk factors among patients with cholelithiasis admitted in tertiary level hospitals of North Bengal. **Methods:** This was descriptive type of cross-sectional study. This study was carried out in the department of surgery of Rajshahi Medical College Hospital, Rajshahi from January 2013 to June 2013. The patients with inclusion criteria admitted in tertiary level hospitals of North Bengal. Data was collected from the patients with inclusion criteria of different tertiary Level Hospitals in North Bengal. Different doctors were selected as a data collector for the different hospitals. At first principal investigator was explained the procedure of data collection to data collectors. Then the data collectors were arranged all the information of the patients to fulfill the objectives of the study through a structured questionnaire by face to face formal interview and from patient's record sheets. The principle investigator was monitored the procedure of data collection of the study. **Result:** The mean age was found 45.3±15.0 years with range from 9 to 85 years. Majority (74.0%) patients were female and 286(95.3%) were married. Abdominal pain, nausea, vomiting and abdominal discomfort were more common (58.0%) complaints of the patients. More than one fourth 80(26.7%) patients had over weight and 70(23.3%) were obese. Majority (93.3%) patients were found in normal temperature, 9(3.0%) jaundice and 6(2.0%) patients had lymphadenopathy. During abdominal examination 174(58.0%) had tenderness, 4(1.3%) abdominal lump/ palpable mass, 78(26.0%) Murphy's sign, 3(1.0%) ascites and 8(2.7%) underwent digital rectal examination. Almost all (99.7%) patients were operated and more common indication was chronic calculus cholecystitis 215(71.7%) and 299(99.7%) biopsy send for histopathological examination. Malignancy found in 8(2.7%) of the study patients, among them half (50.0%) of the patients belonged to age >60 years followed by 5(62.5%) patients were female. Almost two third 5(62.5%) patients had obesity, 2(25.0%) patients had salmonella infection of GB, 5(62.5%) chronic inflammation of GB, 1(12.5%) polyp within GB and 2(25.0%) immunized. All patients had adenocarcinoma in histopathology. In malignant cases, 5(62.5%) patients were found in tumour stage 1, 2(25.0%) stage 2 and 1(12.5%) stage 0. One third 6(75.0%) patients were found in tumour grade 1 and 2(25%) in grade 2. Regarding the association between risk factor with malignant and without malignant group Obesity, infection of GB, inflammation of GB, suspicious pathology within GB, immunization status, fertility, under hormonal contraceptives and ≥ 5 number of pregnancy were significantly (p<0.05) higher in malignant group. **Conclusion:** There is a statistical or indirect association between the risk factors and development of GBC among the patients with cholelithiasis.

KEYWORDS: Gallbladder Cancer, cholelithiasis, surveillance.

INTRODUCTION

Gallbladder cancer was first described in 1777.^[1] For more than two centuries, late diagnosis and absence of effective treatment for many patients remain as typical features of this disease. Gallbladder cancer (GBC) is an uncommon but highly fatal malignancy; fewer than 5000 new cases are diagnosed each year in the United States.

Worldwide, there is a prominent geographic variability in gallbladder cancer (GBC) incidence that correlates with the prevalence of cholelithiasis. High rates of gallbladder cancer (GBC) are seen in South American countries, particularly Chile, Bolivia, and Ecuador, as well as some areas of India, Pakistan, Japan and Korea.^[3,4,5] In Chile, mortality rates from gallbladder cancer (GBC) are the highest in the world. These populations share a high prevalence of gallstones and/or salmonella infection, both are recognize risk factors for gallbladder cancer (GBC)^[6,7] Both genetic factors and socioeconomic issues that delay or prevent access to cholecystectomy for gallstones are thought to be contributory.^[8] North America is considered a low incidence area. In the United States, gallbladder cancer (GBC) is the most common cancer arising in the biliary tract. Estimates from the SEER (Surveillance, Epidemiology and End Results) database reveal an Incidence of 1 to 2 cases per 100,000 population in the US. In contrast to the general population, gallbladder cancer (GBC) is the most common GI malignancy in both Southwestern Native Americans and in Mexican Americans.^[5]

In addition to geography, there are also age, race, and gender-related differences in the incidence of gallbladder cancer (GBC). Incidence steadily increases with age, women are affected two to six times more often than men, and gallbladder cancer (GBC) is more common in Caucasians than in blacks.^[9] Gallbladder cancer affects most commonly elderly above 65 years.^[10]

No known etiologic factor is found but associated risk factors identified so far include cholelithiasis (especially untreated chronic symptomatic gall stones), obesity, reproductive factors, chronic infections of the gallbladder and environmental exposure to specific chemicals eg, radon. These suspected factors likely represent promoters of carcinogenesis.

OBJECTIVE

General Objective

The study is aimed at finding out the prevalence of gallbladder cancer & identification of its risk factors among patients with cholelithiasis admitted in tertiary level hospitals of North Bengal.

Specific Objective

- To calculate the prevalence of gallbladder cancer in relation to selective sociodemographic variables of the patients (age, gender, socioeconomic condition, occupation)

- To identify the risk factors of gallbladder cancer among patients with cholelithiasis.

MATERIAL AND METHODS

Study design: Descriptive type of cross sectional study.

Place of study: Department of surgery of Rajshahi Medical College Hospital, Rajshahi.

Study period: January 2013 to June 2013.

Study population: The patients with inclusion criteria admitted in tertiary level hospitals of North Bengal.

Sampling method: Purposive Sampling Method

Sample size

Total three hundred (300) cases. On basis of $N = \frac{z^2 pq}{d^2}$ formula. (N= Required Sample size, z=1.96 at 95% CI, p= Prevalence, q= 1-P, d= Error Limit= 5%=.05)

Inclusion and exclusion criteria

Inclusion criteria

- Patients of all age & both gender will be included.
- Patients with acute or chronic calculus cholecystitis, as well as incidental cholelithiasis.
- Patients admitted with diagnosed gall bladder cancer with cholelithiasis.

Exclusion criteria

- Patients who refuse to include in the study.
- Patients with cholelithiasis who will not admit in tertiary level hospitals of North Bengal

Procedures of collecting data

Data were collected from the patients with inclusion criteria of different Tertiary Level Hospitals in North Bengal. Different doctors were selected as a data collector for the different hospitals. At first principal investigator were explained the procedure of data collection to data collectors. Then the data collectors were arranged all the information of the patients to fulfill the objectives of the study through a structured questionnaire by face to face formal interview and from patient's record sheets. The principle investigator was monitored the procedure of data collection of the study.

Procedure of data analysis

Statistical analysis was done by using statistical package for social science (SPSS) software. The invariant analysis was tested using by appropriate statistical test or methods (the Chi-square/Z-test/T test etc.)

Quality assurance strategy: Not applicable.

Ethical implications

Follow the guidelines from the appropriate Ethical Review committee(s)- of the concerned institution(s) and/or BCPS and attach necessary documents accordingly. The aims and objectives along with procedure, methods, risks and benefits of the study were explained to the patient in an easily understandable local

language. Clearance from ethical committee of concerned institution were taken prior to study.

RESULTS

Table 1: Particulars of the patient (n=300).

Particulars of the patient	Number of patients	Percentage
Age group (in years)		
≤30	48	16.0
31-40	77	25.7
41-50	100	33.3
51-60	38	12.7
>60	37	12.3
Mean±SD	45.3	±15.0
Range (min, max)	9	, 85
Gender		
Male	78	26.0
Female	222	74.0
Religion		
Islam	282	94.0
Hindu	18	6.0
Occupation status		
House wife	201	67.0
Service	45	15.0
Business	27	9.0
Student	9	3.0
Farmer	18	6.0
Socioeconomic condition		
Low class	49	16.3
Middle class	72	24.0
Low middle class	125	41.7
High class	54	18.0
Marital status		
Married	286	95.3
Unmarried	14	4.7

Table 1 shows particulars of the patient, it was observed that more than one third (33.3%) patients belonged to age 41-50 years. The mean age was found 45.3±15.0 years with range from 9 to 85 years. Majority (74.0%) patients were female and 78(26.0%) were male. Majority

(94.0%) were Muslims and 18(6.0%) were Hindu. Majority (67.0%) patients were housewives. Majority (41.7%) of the patients came from lower middle class family and 286(95.3%) were married.

Table 2: Distribution of the patients by complaints (n=300).

Complaints	Number of patients	Percentage
Abdominal pain	174	58.0
Nausea, vomiting & abdominal discomfort	45	15.0
Silent Gall Stone (Diagnosed during USG for other resion)	30	10.0
Jaundice & loss of appetite	9	3.0
Others	42	14.0

Table 2 shows complaints of the study patient, it was observed that 174(58.0%) patients had abdominal pain, 45(15.0%) had nausea, vomiting & abdominal discomfort, 30(10.0%) patients had silent Gall Stone (Diagnosed during USG), 9(3.0%) had Jaundice & loss of appetite and 42(14%) had other complaints.

Table 3: Distribution of the patients by weight, height and BMI (n=300).

Character	Mean±SD	Range (min, max)
Weight (kg)	63.2±8.7	28, 85
Height (cm)	157.7±8.4	110,170
BMI (kg/m ²)		
Below normal	10	3.3
Normal	140	46.7
Over weight	80	26.7
Obese	70	23.3
BMI (kg/m ²)	24.9±3.8	18.4, 31.0

Mean weight was found 63.2±8.7 kg with range from 28 to 85 kg. The mean height was found 157.7±8.4 cm with range from 110 to 170 cm. Almost half (46.7%) patients had normal BMI. The mean BMI was found 24.9±3.8 kg/m² with range from 18.4 to 31.0 kg/m².

Table 4: Distribution of the patients by risk factors (n=300).

Risk factors	Number of patients	Percentage
Infection of Gallbladder- Detected by bile culture		
Salmonella	27	9.0
E. Coli	39	13.0
Enterococci	4	1.3
Other	16	5.3
Absent	214	71.3
Inflammation of Gallbladder (detected by USG)		
Acute inflammation	65	21.7
Chronic inflammation	94	31.3
No	141	47.0
Exposure to X-ray frequency		
1	20	6.7
2	22	7.3
3	16	5.3
4	9	3.0
5	8	2.7
No	225	75.0
Suspicious pathology within gallbladder		
Polyp	3	1.0
Diverticulum's	2	0.7
Absent	295	98.3
Immunization status		
Non immunized	85	28.3
Partially immunized	66	22.0
Immunized	149	49.7
Fertility (n=222)		
Fertile	175	78.8
Infertile	47	21.2
Hormonal contraceptives (n=222)		
OCP	48	21.6
Injectable	3	1.4
Norplant	4	1.8
No	167	75.2
Number of pregnancy (n=222)		
<5	133	59.9
≥5	42	18.9
No	47	21.2

Table 4 shows risk factors of the patient, it was observed that 27(9.0%) patients had salmonella infection of gallbladder followed by 65(21.7%) acute inflammation of gallbladder, 22(7.3%) exposure to X-ray 2 frequency, 2(0.7%) diverticulum's suspicious pathology within gallbladder and 149(49.7%) immunized.

In female, 47 (21.2%) patients were infertile, 48 (21.6%) patients were found in hormonal contraceptives of OCP and 133(59.9%) had <5 number of pregnancy.

Table 5: Distribution of the malignant patients by risk factor (n=8).

Risk factor	Number of patients	Percentage
BMI (kg/m ²)		
Normal	1	12.5
Over weight	2	25.0
Obese	5	62.5
Infection of GB		
Salmonella	2	25.0
E.coli	2	25.0
Enterococci	1	12.5
Absent	3	37.5
Inflammation of GB		
Acute inflammation	2	25.0
Chronic inflammation	5	62.5
No	1	12.5
Suspicious pathology within GB		
Diverticulum's	1	12.5
Polyp	1	12.5
Absent	6	75.0
Immunization status		
Non Immunized	5	62.5
Partially immunized	1	12.5
Immunized	2	25.0
Fertility	(n=5)	
Fertile	4	80.0
Infertile	1	20.0
Hormonal contraceptives	(n=5)	
Under hormonal contraceptives	4	80.0
Not under hormonal contraceptives	1	20.0
Number of pregnancy	(n=5)	
< 5	1	20.0
≥ 5	3	60.0
No	1	20.0

In malignant cases, almost two third (62.5%) patients had obesity, 2(25.0%) patients had salmonella infection of GB, 5(62.5%) chronic inflammation of GB, 1(12.5%) polyp within GB, 2(25.0%) immunized, 4(80.0%) female

were fertile, 4(80.0%) female were found under hormonal contraceptives and 3(60.0%) female had ≥5 number of pregnancy.

Table 6: Distribution of the malignant patients by histopathological variant (n=8).

Histopathological variant	Number of patients	Percentage
Adenocarcinoma	8	100.0
Squamous carcinoma	0	0.0

In malignant cases, all (100.0%) patients had adenocarcinoma.

Table 7: Association between risk factor with malignant and without malignant (n=300).

Risk factor	Malignant (n=8)		Without malignant (n=292)		P value
	n	%	n	%	
BMI (kg/m ²)					
Obese	5	62.5	65	22.3	0.019 ^s
Non obese	3	37.5	227	77.7	
Infection of GB					
Yes	5	62.5	81	27.7	0.046 ^s
No	3	37.5	211	72.3	
Inflammation of GB					
Yes	7	87.5	152	52.1	0.048 ^s
No	1	12.5	140	47.9	
Suspicious pathology within GB					

Yes	2	25.0	3	1.0	0.006 ^s
No	6	75.0	289	99.0	
Immunization status					
Immunized/ partially immunized	3	37.5	212	72.6	0.044 ^s
Non Immunized	5	62.5	80	27.4	
Fertility		(n=5)		(n=217)	
Infertile	1	20.0	174	80.2	0.008 ^s
Fertile	4	80.0	43	19.8	
Hormonal contraceptives		(n=5)		(n=217)	
Under hormonal contraceptives	4	80.0	51	23.5	0.014 ^s
Not under hormonal contraceptives	1	20.0	166	76.5	
Number of pregnancy		(n=5)		(n=217)	
≥ 5	3	60.0	39	18.0	0.048 ^s
< 5/ no	2	40.0	178	82.0	

s= significant

P value reached from chi square test

5 (62.5%) patients were obese in malignant group and 65(22.3%) in without malignant group. 5 (62.5%) patients were found with infection of GB in malignant group and 81(27.7%) in without malignant group. 7 (87.5%) patients were found with inflammation of GB in malignant group and 152(52.1%) in without malignant group. 2 (25.0%) patients were found with suspicious pathology within GB in malignant group and 3(1.0%) in without malignant group. 3 (37.5%) patients were found immunized/ partially immunized in malignant group and 212(72.6%) in without malignant group. Four (80.0%) female were found fertile in malignant group and 67(30.9%) in without malignant group. 4 (80.0%) female were found under hormonal contraceptives in malignant group and 51(23.5%) in without malignant group. 3 (60.0%) female had ≥ 5 number of pregnancy in malignant group and 39(18.0%) in without malignant group. The difference were statistically significant ($p < 0.05$) between two group.

DISCUSSION

The frequency of Gallbladder Cancer increases with age, escalating markedly after age 40 to become 4 to 10 times more likely in older individuals.^[11,12] Similarly, in this present study it was observed that more than one third (33.3%) patients belonged to age 41-50 years. The mean age was found 45.3±15.0 years with range from 9 to 85 years.

Duffy et al. (2008) found the median age 67 years with ranged from 28–100 years, which is higher to the current study.^[9] The age and age ranged obtained by the above authors maybe due to geographical variations, racial, ethnic differences and genetic causes may have significant influences on Gallbladder Cancer.

The highest frequency of the disease is found among females over the age of 65 years.^[10] There is a marked regional and ethnic variation in the incidence of gallbladder cancer. These conditions are positively correlated with age, female sex, genetic factors, obesity, multiple pregnancies, a family history of gallstones, and low levels of physical activity (89 et al to 101 et al).

Similarly, in this present study it was observed that majority (74.0%) patients were female and 26.0% were male and female male ratio was almost 3:1.

In this current study it was observed that majority (94.0%) patients were Muslims, female patients mostly (67.0%) housewives, 41.7% patients came from lower middle class family and 95.3% were married.

Since most gallstones are asymptomatic, it is essential to define exactly which symptoms are caused by gallstones: true biliary pain and/or complications, versus nonspecific abdominal complaints including dyspepsia (Jorgensen et al. 1989, Traverso et al. 1993, Fenster et al. 1995).^[13,14,15] Gallstone-associated pain seems to follow a certain pattern in most patients (Festi et al. 1999 and Berhane et al. 2006).^[16,17]

Similarly, in this current study it was observed that 58.0% patients presented with abdominal pain, 15.0% nausea, vomiting with abdominal discomfort, 10.0% silent Gall Stone (Diagnosed during USG), 3.0% had Jaundice with loss of appetite and 14.0% had other complaints.

Patients with gallbladder cancer are more often overweight or obese than people without this disease. Obesity is also a risk factor for gallstones, which might help explain this link. In this study it was observed that mean weight was found 63.2±8.7 kg with range from 28 to 85 kg. The mean height was found 157.7±8.4 cm with range from 110 to 170 cm. More than one fourth (26.7%) patients were over weight and 23.3% obese and the mean BMI was found 24.9±3.8 kg/m² with range from 18.4 to 31.0 kg/m².

In this present study it was observed that E. Coli was more common, which was 13.0% of the patients followed by salmonella 9.0%, Entero cocci 1.3% and 5.3% others. Chronic inflammation was found 31.3% evaluated by USG, 7.3% exposure to X-ray 2 frequency. Polyp and diverticulum's were found 1.0% and 0.7% respectively and 49.7% patients were immunized.

On the other hand in malignant 8 cases, almost two third (62.5%) patients had obesity, 2(25.0%) patients had salmonella infection of GB, 5(62.5%) chronic inflammation of GB, 1(12.5%) polyp within GB and 2(25.0%) immunized.

The reproductive factors, the number of live births and a younger age at marriage were found to be important risk factors of GBC on comparison to the patients with healthy controls (females)^[18] Similar findings were also obtained by [Shukla et al. (Shukla 2008)], the authors showed that a younger age at menarche (<13 years), higher number of child births (>4), higher number of pregnancies (>4) and a higher age at last childbirth (>25 years) were factors responsible for a relatively increased risk of GBC, which are comparable with the current study.^[19]

The underlying mechanism is female sex hormones; parity, oral contraceptive use and estrogen replacement therapy are established risk factors for cholesterol gallstone formation.^[20] In this study it was observed in female patients 21.2% patients were infertile, 48(21.6%) patients were found in hormonal contraceptives of OCP and 133(59.9%) had <5 number of pregnancy.

In this study it was observed that mean pulse was found 75.6±4.4 bpm with ranged from 70 to 86 bpm. The mean systolic BP was found 126.1±18.9 mmHg with ranged from 100 to 180 mmHg. The mean diastolic BP was found 78.7±4.9 mmHg with ranged from 70 to 90 mmHg.

In this series it was observed that majority (93.3%) patients had normal temperature, 9.7% ill looking, 56.7% average body build, 71.0% average nutritional status, 4.7% anaemia, 3.0% jaundice, 1.0% oedema, 3.0% dehydration and 2.0% patients had lymphadenopathy present.

In this study it was observed that 62.5% patients had obese in malignant group and 22.3% in without malignant group. 5 (62.5%) patients were found infection of GB in malignant group and 27.7% in without malignant group. 7 (87.5%) patients were found inflammation of GB in malignant group and 52.1% in without malignant group. 2 (25.0%) patients were found suspicious pathology within GB in malignant group and 1.0% in without malignant group. 3 (37.5%) patients were found immunized/ partially immunized in malignant group and 72.6% in without malignant group. 4 (80.0%) female were found fertile in malignant group and 30.9% in without malignant group. 4 (80.0%) female were found under hormonal contraceptives in malignant group and 23.5% in without malignant group. 3 (60.0%) female had ≥ 5 number of pregnancy in malignant group and 18.0% in without malignant group. Obese, infection of GB, inflammation of GB, suspicious pathology within GB, immunization status, fertility, under hormonal

contraceptives and ≥ 5 number of pregnancy were significantly (p<0.05) higher in malignant cases.

CONCLUSION

This study was undertaken to find out the prevalence of gallbladder cancer & identification of its risk factors among patients with cholelithiasis admitted in tertiary level hospitals of North Bengal. Most of the patients were in 5th decade and the total prevalence of was greater in women. Abdominal pains, Nausea, vomiting with abdominal discomfort were more common presenting complaints and most of the patients were Over weight/ Obese. *E. Coli* and *Salmonella* were more common. Genetic influence, multiparity and previous surgeries were significant risk factors in women. Preventable risk factors in male, who normally work in fields, were drinking unprotected water and consumption of excess chickpeas. Obese, infection of GB, inflammation of GB, suspicious pathology within GB, immunization status, fertility, under hormonal contraceptives and ≥ 5 number of pregnancy were significantly higher in malignant cases.

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