

A PROSPECTIVE STUDY OF CORRELATION BETWEEN GALLSTONE DISEASE WITH CARCINOMA GALLBLADDER

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ABSTRACT

Background: Gallbladder carcinoma is the most common biliary tract malignancy accounting for 80-95% of all biliary tract cancers. Gallbladder cancer shows geographical and racial variations. Gallstones appear to be an important associated factor for development of gallbladder carcinoma. The purpose of this study is, therefore, to find out, any differences in the incidence of gallbladder cancer in patients with and without gallstones, and any correlation between the number, type and size of gallstones with the incidence of gallbladder cancer. **Materials and Methods :** It is a hospital based prospective observational study conducted in Assam Medical College for one year. A detailed history and clinical examination followed by radiological investigations specially Ultrasound whole abdomen was done for all the patients. Follow up of the patients was done. **Results:** The proportion of females was found to be higher (70%) than males. Test of proportion showed that proportion of patients with stone (81.43%) was significantly higher than the patients without stone (18.57%) ($p < 0.0001$). In our study, operative intervention was performed in 30 cases, out of which 11 underwent simple cholecystectomy, 15 underwent extended cholecystectomy and 4 had only laparotomy and biopsy. In our study, 17 of the operated patients (62.96%) had cholesterol stones, 2 patients (7.41%) had pigmented stones and 8 patients (29.63%) had mixed stones. In our study, 59 patients (84.29%) were diagnosed with Biliary Adenocarcinoma NOS. Majority of Adenocarcinoma patients had cholesterol stones (62.50%), followed by mixed stones (29.17%) and pigmented stones (8.33%). **Conclusion:** A high index of suspicion for the disease and health education are warranted for early diagnosis of gallbladder carcinoma in the North Eastern part of our country, especially Assam, where the incidence is the highest, and, the associated risk factors along with gallstones which makes the region a high-risk zone should be studied extensively.

Keywords: Carcinoma gallbladder, Gallstone disease

INTRODUCTION

Gallbladder carcinoma is the most common biliary tract malignancy accounting for 80-95% of all biliary tract cancers¹. Gallbladder cancer shows geographical and racial variations. Gallbladder carcinoma is a frequent diagnosis in our tertiary care centre in Assam. Gallbladder cancer is the most prevalent hepatobiliary cancer in women in North Eastern, Northern, and Central India, which strikes them earlier in life than it does in western countries. Compared to the local populations, even Indian immigrants to foreign nations have a higher risk of developing

gallbladder cancer. Gallstones appear to be an important associated factor for development of gallbladder carcinoma. The purpose of this study is, therefore, to find out, any differences in the incidence of gallbladder cancer in patients with and without gallstones, and any correlation between the number, type and size of gallstones with the incidence of gallbladder cancer.

According to the GLOBOCAN 2018 data regarding India, gallbladder carcinoma was the 14th most common cancer, with the number of new cases being 25,999 and a mortality of 19,676. The incidence of gallbladder carcinoma in India was found considerably high, particularly in the North, Central, Eastern and North-Eastern parts of India, lowest being in Southern and Western states. The actual reason for this North-South difference is still not clear². The river basin of Ganga-Brahmaputra is known as the 'high-risk zone' for carcinoma gallbladder, which is assumed to be due to the heavy metal content in the water as well as the food habits of the people. Its incidence in women of North and Central India is as high as 6.6 and 5.2 respectively, while that in Chennai and Bangalore in Southern India are 0.6 and 0.8 respectively. Epidemiological reviews from Mumbai have reported an incidence of 0.5 and 1.3 per 100,000 populations in men and women, respectively^{3 4,5}.

The incidence of gallbladder cancer parallels the prevalence of gallstone disease^{6,7}; large and long-standing gallstones being associated with a higher risk of gallbladder cancer. Here, patients with gallstones also present for treatment late. These factors result in prolonged exposure of the gallbladder mucosa to stones.

North-eastern states of India have a high incidence of gallbladder cancer especially in the state of Assam, and the majority of patients are female. North-eastern states have a different ethnicity, lifestyles, food-habits and tobacco consumption from rest of the country along with other factors. Hence, gallbladder carcinoma has a serious impact in the North-eastern states and should be considered as an epidemic warranting more epidemiological studies⁸.

Cholelithiasis is found in approximately 80-90% of people with gallbladder cancer in India though most people with gallstones never develop gallbladder cancer. Only 0.5% of the patients having gallstones will develop gallbladder cancer. Gallstones affect 10-15% of the adult population. The association between cholelithiasis and gallbladder cancer ranges from 2.3 to 34.4 in various case-control studies⁹.

Gallstones thus appear to be an important associated factor for development of gallbladder carcinoma. The purpose of this study is, therefore, to find out, any differences in the incidence of gallbladder cancer in patients with and without gallstones, and any correlation between the number, type and size of gallstones with the incidence of gallbladder cancer.

AIMS AND OBJECTIVES

The aim of the study was to analyze the association of gallstone disease with carcinoma Gallbladder. The objective was to study the relationship between gallstone disease and carcinoma

gallbladder in relation to size, type and number of stones in patients with Gallstone disease developing gallbladder cancer.

MATERIALS AND METHODS

PLACE OF STUDY : Patients attending General Surgery OPD/admitted under Department of General Surgery, Assam Medical College & Hospital

STUDY POPULATION : All patients diagnosed with carcinoma gallbladder admitted in all units of Department of General Surgery, Assam Medical College & Hospital

PERIOD OF STUDY : One year

STUDY DESIGN : Hospital based Prospective Observational study.

SAMPLE SIZE : Considering 95% confidence interval with relative error of 10% and considering the proportion of patients with gallstone disease with gallbladder carcinoma to be 86% (Hamdani NH et al)¹⁹, the sample size for the present study is calculated and rounded off to be 70.

INCLUSION CRITERIA

All cases attending study area within the mentioned time line, diagnosed clinically or by imaging, as carcinoma gallbladder.

EXCLUSION CRITERIA

Suspected carcinoma gallbladder patient without histopathological evidence.

Age <12years.

GBC presenting with other concurrent malignancies.

Incidental gallbladder carcinoma post operatively diagnosed on histopathological examination.

Patients who do not give consent for the study.

METHODOLOGY

This study included all the patients admitted in General Surgery Ward of Assam Medical College, Dibrugarh from 01st June, 2021 to 31st May, 2022, with carcinoma gallbladder and underwent surgical or non-surgical management for the same. Information regarding demographic profiles, co-morbidities and prior documented history of gallstones were noted and recorded. Particulars of the patient regarding Name, age, sex, religion, address, MRD numbers were recorded. Detailed History, General Examination, Systemic Examination as per the proforma. Required blood investigations and radiological investigations like Ultrasound abdomen, Contrast CT scan of the abdomen, USG guided FNAC done for diagnosis of carcinoma gallbladder. Management of the patient and the outcome was recorded. Follow up during the limited period.

RESULTS AND OBSERVATIONS

Descriptive statistical analysis was performed to calculate the means with corresponding standard deviations (S.D.). Test of proportion was used to find the Standard Normal Deviate (Z) to compare the difference in proportions and chi-square test and Fisher Exact Test was performed to find the associations. $p < 0.05$ was taken to be statistically significant.

TABLE 1 : GENDER DISTRIBUTION OF THE PATIENTS

Gender	Number (n)	Percentage (%)
Male	21	30.00
Female	49	70.00
TOTAL	70	100.00
<i>Ratio (Male : Female)</i>	1 : 2.33	

The proportion of females was found to be 70% compared to just 30% males. The ratio of male and female was found to be 1.0: 2.33.

TABLE 2 : PRESENCE OR ABSENCE OF STONES OF THE PATIENTS

Stone	Number (n)	Percentage (%)
Present	57	81.43
Absent	13	18.57
TOTAL	70	100.00

Test of proportion showed that proportion of patients with stone (81.43%) was significantly higher than the patients without stone (18.57%) ($Z=10.39$; $p < 0.0001$).

TABLE 3 : MANAGEMENT

Management	Number (n)	Percentage (%)
Operative	30	43
Conservative	40	57
TOTAL	70	100.00

In our study, operative intervention was performed in 30 cases, out of which 11 underwent simple cholecystectomy, 15 underwent extended cholecystectomy and 4 had only laparotomy and biopsy.

TABLE 4 :DISTRIBUTION OF TYPE OF STONE IN OPERATED PATIENTS

Type of Stone	Number (n)	Percentage (%)
Cholesterol Stone	17	62.96
Pigmented Stone	2	7.41
Mixed Stone	8	29.63
TOTAL	27	100.00

In our study, 17 of the operated patients (62.96%) had cholesterol stones, 2 patients (7.41%) had pigmented stones and 8 patients (29.63%) had mixed stones.

TABLE 5: DISTRIBUTION OF HPE

Histopathology	Number (n)	Percentage (%)
Biliary Adenocarcinoma NOS	59	84.29
♦ Well differentiated	10	16.95
♦ Moderately differentiated	31	52.54
♦ Poorly differentiated	18	30.51
Papillary Adenocarcinoma	5	7.14
Mucinous Adenocarcinoma	3	4.28
Adenosquamous carcinoma	2	2.86
Squamous cell carcinoma	1	1.43
TOTAL	70	100.00

In our study, 59 patients (84.29%) were diagnosed with Biliary Adenocarcinoma NOS out of which 10 patients (16.95%) were diagnosed as well differentiated, 31 patients (52.54%) as moderately differentiated, 18 patients (30.51%) as poorly differentiated. 5 patients (7.14%) were diagnosed as Papillary Adenocarcinoma, 3 patients (4.28%) with Mucinous Adenocarcinoma, 2 patients (2.86%) as Adenosquamous Carcinoma and 1 patient (1.43%) as Squamous cell Carcinoma.

TABLE 6: DISTRIBUTION OF PRESENCE OF STONE IN RELATION TO TYPE OF CARCINOMA ACCORDING TO BIOPSY REPORT (HPE)

Stone	HPE Type						TOTAL	p value*
	Adenocarcinoma		Adenosquamous carcinoma		Squamous cell carcinoma			
	n	%	n	%	n	%	n	
Present	54	94.74	2	3.51	1	1.75	57	0.699
Absent	13	100.00	0	0.00	0	0.00	13	
TOTAL	67		2		1		70	

In our study, on comparing the HPE findings with the presence of stones, we found, out of 57 patients with stones, 54 of them (94.74%) were diagnosed as Adenocarcinoma, 2 patients (3.51%) were diagnosed as Adenosquamous Carcinoma and 1 patient (1.75%) was diagnosed as Squamous

Cell Carcinoma. All patients (100%) with adenosquamous and squamous cell carcinomas showed presence of gallstones. However the result was found to be not significant on Fisher Exact Test (p value =0.699).

TABLE 7: DISTRIBUTION OF TYPE OF STONE IN RELATION TO TYPES OF CARCINOMA ACCORDING TO BIOPSY REPORT (HPE)

Type of Stone	HPE Type						TOTAL	<i>p value*</i>
	<i>Adenocarcinoma</i>		<i>Adenosquamous carcinoma</i>		<i>Squamous cell carcinoma</i>			
	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	
Cholesterol Stone	15	62.50	1	50.00	1	100.00	17	0.052
Pigmented Stone	2	8.33	0	0.00	0	0.00	2	
Mixed Stone	7	29.17	1	50.00	0	0.00	8	
TOTAL	24	100.00	2	100.00	1	100.00	27	

In our study, on comparing the HPE findings with the type of stone, we found that out of 17 cases with cholesterol stones, 15 patients (55.5%) belonged to Adenocarcinoma group, and 1 patient (3.7%) each belonged to Adenosquamous carcinoma and Squamous cell carcinoma groups. 2 patients (7.4%) with pigmented stones belonged to Adenocarcinoma group. Out of 8 patients with mixed stones, 7 patients (25.9%) belonged to Adenocarcinoma group and 1 patient (3.7%) belonged to Adenosquamous carcinoma group.

Majority of Adenocarcinoma patients had cholesterol stones (62.50%), followed by mixed stones (29.17%) and pigmented stones (8.33%). Adenosquamous carcinoma was equally distributed between cholesterol and mixed stones. All cases of Squamous cell carcinoma had cholesterol stones.

TABLE 8 : DISTRIBUTION OF HPE TYPE AND SIZE OF STONE

Size of Stone (in cm)	HPE Type						TOTAL	<i>p value*</i>
	<i>Adenocarcinoma</i>		<i>Adenosquamous carcinoma</i>		<i>Squamous cell carcinoma</i>			
	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	
≥3.0	13	86.67	1	6.67	1	6.67	15	0.172
1.5 – <3.0	27	96.43	1	3.57	0	0.00	28	
<1.5	14	100.00	0	0.00	0	0.00	14	
TOTAL	54		2		1		57	

In our study, on comparing HPE findings with the size of stones, we found that a total of 15 patients had stones ≥ 3 cm in size of which 13 patients (86.67%) belonged to Adenocarcinoma group, 1 patient (6.67%) each belonged to Adenosquamous Carcinoma group and Squamous cell carcinoma group. 28 patients had stones in size range of 1.5 - <3.0 cm out of which 27 patients (96.43%) belonged to Adenocarcinoma group and 1 patient (3.57%) belonged to Adenosquamous carcinoma group. 14 patients had stones of size <1.5 cm all belonging to Adenocarcinoma group. The results were not significant as per Fisher Exact Test (p value =0.172).

TABLE 9 : DISTRIBUTION OF TYPE OF GROWTH AND PRESENCE OF STONE

Type of Growth	Stone				Total (n)
	Present		Absent		
	n	%	n	%	
Polypoidal	13	50	13	50	26
Infiltrating	44	100	0	0	44
TOTAL	57		13		70

In our study on comparing the type of growth with the presence of stone we found that, all 44 patients (100%) of Infiltrating mass had stones while 13 patients (50%) of Polypoidal mass had stones and 13 (50%) of them were devoid of stones.

DISCUSSION

This observational non randomised study, conducted over a period of one year, included 70 consecutive patients attending General Surgery OPD or admitted in General Surgery ward in Assam Medical College & Hospital Dibrugarh with the diagnosis of carcinoma gall bladder.

The proportion of females was found to be 70% in our study, which correlates with most of the studies done worldwide which shows a female preponderance for carcinoma of gallbladder. The male:female ratio was found to be 1:2.33. Incidence of gallbladder carcinoma with gall stones was 81.53% in our series while that without stones was 18.47%. The result is in accordance with the data available so far where gall stone disease is known as one of the most important predisposing factors for carcinoma gall bladder. In our study, 17 of the operated patients (62.96%) had cholesterol stones, 2 patients (7.41%) had pigmented stones and 8 patients (29.63%) had mixed stones. In our study, 59 patients (84.29%) were diagnosed with Biliary Adenocarcinoma NOS out of which 10 patients (16.95%) were diagnosed as well differentiated, 31 patients (52.54%) as moderately differentiated, 18 patients (30.51%) as poorly differentiated. 5 patients (7.14%) were diagnosed as Papillary Adenocarcinoma, 3 patients (4.28%) with Mucinous Adenocarcinoma, 2 patients (2.86%) as Adenosquamous Carcinoma and 1 patient (1.43%) as Squamous cell

Carcinoma. In our study, on comparing the HPE findings with the presence of stones, we found, out of 57 patients with stones, 54 of them (94.74%) were diagnosed as Adenocarcinoma, 2 patients (3.51%) were diagnosed as Adenosquamous Carcinoma and 1 patient (1.75%) was diagnosed as Squamous Cell Carcinoma. All patients (100%) with adenosquamous and squamous cell carcinomas showed presence of gallstones. On comparing HPE findings with the size of stones, we found that a total of 15 patients had stones ≥ 3 cm in size of which 13 patients (86.67%) belonged to Adenocarcinoma group, 1 patient (6.67%) each belonged to Adenosquamous Carcinoma group and Squamous cell carcinoma group. 28 patients had stones in size range of 1.5 - <3.0 cm out of which 27 patients (96.43%) belonged to Adenocarcinoma group and 1 patient (3.57%) belonged to Adenosquamous carcinoma group. 14 patients had stones of size <1.5 cm all belonging to Adenocarcinoma group. In our study on comparing the HPE findings with the type of stone, we found that out of 17 cases with cholesterol stones, 15 patients (55.5%) belonged to Adenocarcinoma group, and 1 patient (3.7%) each belonged to Adenosquamous carcinoma and Squamous cell carcinoma groups. 2 patients (7.4%) with pigmented stones belonged to Adenocarcinoma group. Out of 8 patients with mixed stones, 7 patients (25.9%) belonged to Adenocarcinoma group and 1 patient (3.7%) belonged to Adenosquamous carcinoma group. All cases of Squamous cell carcinoma (3.7%) had cholesterol stones.

Conflict of Interest : Nil

CONCLUSION

Elderly women are most commonly affected by gallbladder carcinoma. Our study shows a strong association between gallstone disease and gallbladder carcinoma. Hence, a female who has lately started having constant pain in her right hypochondrium or whose discomfort has altered in nature, especially if she is in her forties or fifties, should undergo a thorough evaluation. Early discovery of gallbladder cancer may allow for curative surgery and provide patients a greater chance of survival, every gallbladder should undergo routine histological investigation after cholecystectomy. A high index of suspicion for the disease and health education are warranted for early diagnosis of gallbladder carcinoma in the North Eastern part of our country, especially Assam, where the incidence is the highest, and, the associated risk factors along with gallstones which makes the region a high-risk zone should be studied extensively.

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