RESEARCH

INCIDENCE AND PREVALENCE OF GALL BLADDER CARCINOMA IN NORTH INDIAN POPULATION

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Abstract

Background: India is a high incidence region for gallbladder carcinoma accounts for 9-11% burden of gall bladder carcinoma worldwide. The incidence is high in North India, North-East, Central and Eastern India, and least common in West and South India. However, the incidence is equally rise in both genders. North Indian population shows female predominance for gall bladder carcinoma. The advanced disease present with symptoms of right upper quadrant pain and having poor prognosis. Gall bladder carcinoma in India 50-60 years population is more prone as compared to the western population. In Indian population gallstones are present in 70-80% and increases risk of chronic mucosal injury, atrophy, metaplasia, dysplasia and carcinoma of gall bladder. Other risk factors are elder patient, low socio-economic background, infection of Salmonella enterica (S. Typhi), adulterated of mustard oil, exposure to pollutants, chemicals, heavy metals and pancreatobiliary maljunction. Lifestyle modification of the urban population and better accessibility to healthcare centre to manage gall stones appropriately. **Material and method**: In a setup of case control study of 18 months. All the newly diagnosed patients of gall bladder lesions in Era's Lucknow Medical College & Hospital & King George Medical University, Lucknow were included for histopathological examination with observational findings. **Result:** A total of 56 cases of gall bladder lesions were enrolled in the study, based on histological diagnosis 28 cases of cholelithiasis were classified as benign lesions (50.0%) and rest of the cases were classified as Malignant lesions (50.0%). Demographic information of all the subjects was obtained and laboratory investigations were done which were recorded on a separate. **Conclusion**: Early diagnosis of gall bladder lesion or polyp by radiological and histopathological investigation will help to reduced gall bladder carcinoma related mortality.

INTRODUCTION

Gallbladder carcinoma is highly aggressive and less curable disease.[1] Gallbladder carcinoma originates from the lining epithelial of the gallbladder and the cystic duct.[2] The biliary tract malignancies are the most common globally and present as either mass or diffuse thickening of the gallbladder wall arising from the fundus (60%), body (30%) and neck (10%). In developed countries gallbladder carcinoma is rare but frequent in developing countries in some specific geographical areas.[1] In Chile and India showing highest incidence of gall bladder carcinoma.[2] Marked geographical and ethnic variations are found in gallbladder carcinoma. Central India, North and East are among the high incidence areas for gallbladder in contrast to West and South India. In North India the incidence is 10–22% per 1 Lakh population. In North Indian population, gallbladder carcinoma is the 3rd most common malignancy in female having 5-year survival rate of <5%. Gallbladder lesion comprises of acute and chronic cholecystitis, polyps, gall stone disease and gallbladder carcinoma.[3]

More than 80% gall stones are present in gall bladder carcinoma, having major risk factor. Other risk factors are elder patient, low socio-economic background, infection of Salmonella enterica (S. typhi), adulterated of mustard oil, exposure to

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pollutants, chemicals, heavy metals, pancreatobiliary maljunction, Aflatoxin B1 present in improperly stored food consumed by rural population and rare cases with familial cancer such as Familial adenomatous polyposis and Lynch syndrome. In the gallbladder carcinogenesis chronic inflammation is the main factor.[4,5] Pathogenesis of gallbladder carcinoma follows sequence of inflammation, atrophy, metaplasia, dysplasia and carcinoma that may take decades. Incomplete Porcelain gallbladder (Hyalinising cholecystitis) is distinct type of gallbladder injury has close association to carcinoma of gallbladder.[6]

Gallbladder carcinoma having multiple genetic alteration, >50% of gallbladder carcinoma harbour TP53 alteration. Other common mutation includes alteration in CDKN2A or CDKN2B (19%), ARID1A (13%), CTNNB1 (10%), PIK3CA (10%), and amplification of ERBB2 (16%). A higher KRAS mutation related lesion in pancreatobiliary maljunction.[7]

60% gallbladder carcinoma arises in the fundus, 30% body and 10% in neck. Grossly tumours are flat, firm, white, gritty, granular, poorly defined and grow diffusely. According to 5th edition of WHO 2019 classification gallbladder carcinomas are classified as Adenocarcinoma, Squamous cell carcinoma, Adenosquamous carcinoma, Cholangiocarcinoma and neuroendocrine carcinoma. The most common type is Adenocarcinoma and further classified as Clear cell type, Mucinous cystic neoplasm, Mucinous adenocarcinoma, intestinal type, poorly cohesive, Intracystic papillary neoplasm. The sign and symptoms are non-specific and may be caused by gallstones. Pain in right upper quadrant is the commonest symptom. More than 50% cases are diagnosed at a advanced stage.[8,9]

Gallbladder carcinoma progresses silently with late stage so that an early diagnosis is needed. After simple cholecystectomy for assume only cholelithiasis the percentage is 0.5-1.5% of patients who have diagnosed gallbladder carcinoma. Environmental, epidemiologic and genetic factors play an interpretative role in developing carcinoma in gallbladder, best illustrated by gall stones and chronic inflammation.[10] There is unavailability of screening program because it is difficult to early detection of tumour of the gallbladder by direct endoscopic inspection in comparison to other luminal organs. The USG of the gallbladder measures wall thickness but it is non-specific because it may also see in chronic cholecystitis.[11]

The non-specific clinical presentation may result in significantly diagnostic delay. The incidental finding during cholecystectomy due to local spread of the carcinoma in adjacent organ or after routine histological examination of cholelithiasis cholecystectomy.[9] Increasing incidence, diagnosis at advance stage, lack of recent advances in diagnostic modalities, elicit very poor prognosis in gallbladder carcinoma patients.[2,3] No adjuvant chemotherapy is widely accepted due to the drug toxicity, resistance and limited effectiveness and therefore followed only curative surgical approach.[1] Various studies are done over last 2 decades to understand the pathogenesis and fatality of this untreatable disease. Several immunohistochemistry markers like CD97, CD55, CCK and gastrin may help the diagnosis of type of gallbladder carcinoma and prognosis.[5,6,7,8]

Aim

Incidence of gall bladder carcinoma in North Indian population.

Objective

- Age wise distribution of gall bladder carcinoma.
- Gender wise distribution of gall bladder carcinoma.

MATERIALS AND METHODS

Study Area

Era's Lucknow Medical College & Hospital, is a charitable tertiary care facility that caters to patients with almost all the demographic profiles. It has state of the art infrastructure and healthcare facilities with modern diagnostic tools.

Clinical Subjects

All the newly diagnosed patients of gall bladder lesions in Era's Lucknow Medical College & Hospital & King George Medical University.

Study Design: Case-control study.

Study Period: Eighteen months.

Data Collection Technique and Tools

A total of 56 cases of gall bladder lesions were enrolled in the study, based on histological diagnosis 28 cases of cholelithiasis were classified as Benign lesions (50.0%) and rest of the cases were classified as Malignant lesions (50.0%). Demographic information of all the subjects was obtained and laboratory investigations were done which were recorded on a separate Patient Record Form for each subject (Appendix).

Inclusion criteria

All the diagnosed and histologically confirmed cases of non-neoplastic and neoplastic gall bladder lesions.

Exclusion criteria

Any patient with double malignancy, immunodeficiency diseases or any other associated chronic debilitating disorder which was likely to interfere with detection of marker was excluded.

Methodology

Clinical material

Surgically resected gall bladder specimen operated in Era's Lucknow Medical College & Hospital and Department of Surgical Gastroenterology, King George Medical University.

Sample size

Neoplastic gall bladder lesions: 28 cases.

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Non- neoplastic gall bladder lesions: 28 controls.
Tissue was subjected for routine histopathological processing.

Method for H&E stain

- Section was poured to distilled water.
- Alum haematoxylin-stained Nuclei.
- Washed in running tap water.
- Differentiated with 0.3% acid alcohol.
- Washed in running tap water.
- Washed in Scott's tap water substitute.
- Washed in tap water.
- Stained with eosin 2 mins.
- Dehydrate clear and mount.
- Histopathological diagnosis & grading of malignant cases was done on H&E-stained section into well, moderate and poorly differentiated tumour.

RESULTS

The present study was conducted in the Department of Pathology, Era's Lucknow Medical College & Hospital on newly diagnosed patients of gall bladder lesions to correlate the non-neoplastic and neoplastic lesions of gall bladder carcinoma. A total of 56 cases of gall bladder lesions fulfilling the inclusion criteria of the study were enrolled in the study.
[Table 1] shows the histopathological diagnosis of study population.

Table 1: Histopathological Diagnosis of Study Population

Diagnosis	No. of cases	Percentage
Cholelithiasis	28	50.00
Adenocarcinoma	20	35.71
Mucinous adenocarcinoma	5	8.93
Papillary adenocarcinoma	3	5.36

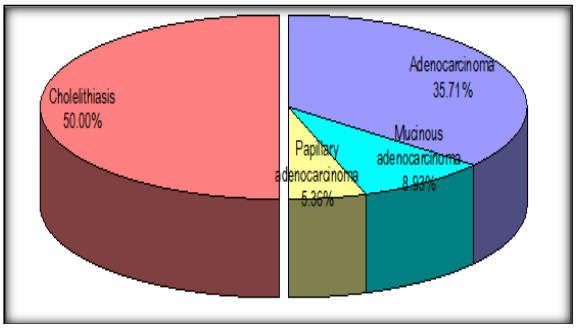

Figure 1: Histopathological Diagnosis of Study Population

Table 2: Age Wise Distribution of Study Population (n=56)

Age Group (years)	Benign (n=28)		Malignant (n=28)		Total (N=56)	
	No.	%	No.	%	No.	%
21-30 yrs	18	64.28	0	0.00	18	32.14
31-40 yrs	10	35.72	0	0.00	10	17.86
41-50 yrs	0	0.00	10	35.72	10	17.86
51-60 yrs	0	0.00	12	42.86	12	21.43
61-70 yrs	0	0.00	6	21.42	6	10.71
	χ^2=56.000 (df=4); p<0.001					
Min-Max (Median)	21-39 (29.50)		45-70 (55.00)		21-70 (42.0)	
Mean±SD	29.46±5.23		55.43±7.41		42.45+14.56	

Out of 56 cases of gall bladder lesions, histopathological diagnosis of 28 (50.0%) was Cholelithiasis, only 3 (5.36%) patients were diagnosed as Papillary adenocarcinoma, 5 (8.93%) as mucinous adenocarcinoma and rest 20 (35.71%) as adenocarcinoma.
All the cases of cholelithiasis were classified as Benign lesions (50.0%) and rest of the cases were classified as Malignant lesions (50.0%).
Demographic details of cases enrolled in the study is given in [Table 2 and 3].

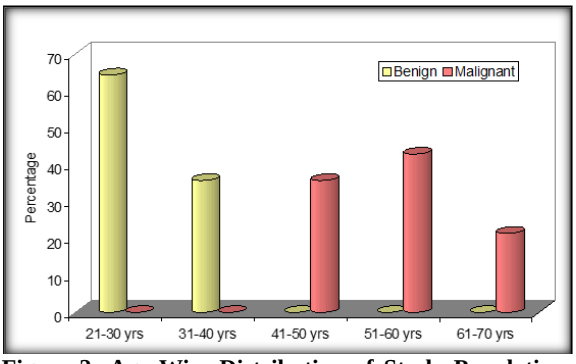

Figure 2: Age Wise Distribution of Study Population (n=56)

In the present study age ranged of the patients was between 21 to 70 years, median age of patients was 42 years and mean age of patients was 42.45±14.56 years. In the present study age of 50.0% patients was up to 40 years and of rest 50.0% were aged above 40 years. Most common age group was 21-30 years (32.14%) followed by 51-60 years (21.43%) while least common age group was 61-70 years (10.71%) followed by 31-40 years and 41-50 years (17.86% each).
All the patients with benign lesions were lower aged. 21-30 years (64.28%) and 31-40 years (35.72%) while all the patients with malignant lesions were aged above 41 years. Difference in patients age with benign lesions and malignant lesions was found to be statistically significant (p<0.001).

Table 3: Gender wise Distribution of Study Population (n=56)

Gender	Benign (n=28)		Malignant (n=28)		Total (N=56)	
	No.	%	No.	%	No.	%
Females	22	78.57	25	89.29	47	83.93
Males	6	21.43	3	10.71	9	16.07

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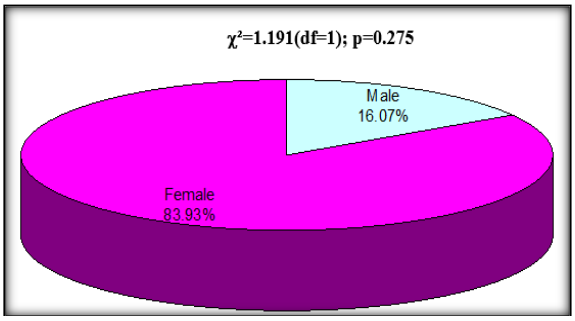

Figure 3: Gender wise Distribution of Study Population (n=56)

Out of 56 cases of gall bladder lesions, 47 (83.93%) were females and rest 9 (16.07%) were males. Male to female ratio in the present study was 0.19.

Though proportion of males was higher among benign (21.43%) as compared to malignant (10.71%) but this difference was not significant.

Table 4: Incidence of Cholelithiasis among Study Population

Cholelithiasis	Benign (n=28)		Malignant (n=28)		Total (N=56)	
	No	%	No	%	No	%
Present	28	100	18	64.28	46	82.14
Absent	0	0	10	35.72	10	17.86

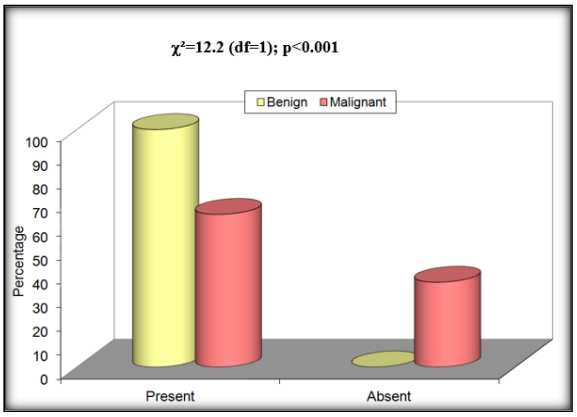

Figure 4: Incidence of Cholelithiasis among Study Population

All the patients of gall bladder lesions were subjected to USG investigation, Cholelithiasis was seen in majority of the patients (n=46; 82.14%) cases.

All the benign cases had cholelithiasis whereas a total of 10 out of 28 (35.72%) cases with malignancy did not have cholelithiasis. Statistically, this difference was significant (p<0.001).

DISCUSSION

Gall bladder carcinoma is a dreadful disease associated with a high rate of mortality. One of the reasons for poor outcome related with gall bladder carcinoma is the fact that it is diagnosed at an advanced stage. The commonly performed histopathological evaluation is a cumbersome task and has a limited prognostic value.[12,13] A study was carried out in which a total of 56 cases (28 cholelithiasis and 28 gall bladder carcinoma) were enrolled.[14] The sampling was done using a purposive sampling design as incidence of gall bladder carcinoma is quite low ranging from 0.5-1.5% cases undergoing cholecystectomy, and hence it was difficult get the adequate number of gall bladder carcinoma cases in a cross-sectional or prospective evaluation. In present study, all the cases of gall bladder carcinoma were adenocarcinoma.[15,16]

These findings are in consonance type of gall bladder cancer found in nearly 75-85% of total gall bladder cancer cases,[2] Among different subtypes of adenocarcinoma non-papillary adenocarcinoma is most common, in present study to 20/28 (71.4%) of cases were non-papillary adenocarcinoma while 5/28 (17.9%) were mucinous adenocarcinoma and 3/28 (10.7%) were papillary adenocarcinoma.

In present study, mean age of benign cases (cholelithiasis cases) was significantly lower (29.46±5.23 years) as compared to that of gall bladder carcinoma cases (55.43±7.41 years). Similar to present study, Rai et al,[17] WHO also conducted a case-control study, reported the mean age of benign gall stone disease cases to be significantly lower than that of gall bladder cancer patients. Similar observations were also made by Faridi et al,[18] who also showed the mean age of gall bladder carcinoma patients to be above 50 years whereas that of cholelithiasis patients was 37.42 years. Meng et al,[19] reported the mean age of patients to be 58 years. However, Kazmi et al,[18] in their study reported the mean age of patients to be only 43.87 years. However, gall bladder carcinoma at younger age is relatively less common. Epidemiological studies in larger set-ups have reported the median age of patients to be more than 60 years.[12] However, in an endemic region like North India, onset at younger age cannot be ruled out.

The study sample was predominantly female dominated (83.93%). There were no gender differences with respect to cholelithiasis and gall bladder cancer. Sex differences showing a predominance of women than men have been reported to be commonly reported worldwide.[13,14] Epidemiological studies from India also show a dominance of females over males in both gall stone disease as well as gall bladder cancer.[2,3] The findings of present study endorse the same.

In present study, majority of cases had cholelithiasis (53.57%), although this proportion was higher in benign (71.43%) as compared to malignant cases (35.72%) and this difference was significant

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statistically too. These findings are in accordance with the classical reports that state that gallstones appear to carry the highest risk for gallbladder cancer with 69% to 100% gall bladder cancer patients having cholelithiasis.[15,16]

CONCLUSION

The present study was conducted on newly diagnosed patients of gall bladder lesions in non-neoplastic and neoplastic lesions of gall bladder cancer. A total of 56 cases of gall bladder lesions fulfilling the inclusion criteria of the study were enrolled in the study. Out of 56 cases, 28 (50.0%) were diagnosed as cholelithiasis, 20 (35.71%) as adenocarcinoma, 5 (8.93%) as mucinous adenocarcinoma and rest 3 (5.36%) as papillary adenocarcinoma. All the cases diagnosed as cholelithiasis were classified as Benign lesions (n=28; 50.0%) and rest of cases diagnosed as adenocarcinoma were classified as Malignant (n=28; 50.0%).

All the cases diagnosed as benign were below 40 years of age (21-39, mean age 29.46±5.23 years) while those diagnosed as were above 40 years of age (45-70; mean 55.43±7.41 years). Difference in age of benign and malignant cases was found to be statistically significant.

Majority of cases enrolled in the study were females (83.93%), only 16.07% of cases were males. Though proportion of males was higher among benign (21.43%) as compared to malignant (10.71%) but this difference was not significant.

Cholelithiasis was present in majority of malignant cases (64.28%) and tall the benign cases, this difference was significant statistically.

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