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Association of Gall Bladder Carcinoma with Gall Stones; A Single Centre Study in a Tertiary Care Hospital

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ABSTRACT

Objective: To evaluate the occurrence of gall bladder carcinoma and its association with gall stones in patients undergoing cholecystectomies.

Study Design: Cross sectional study.

Place and Duration of Study: Army Liver Transplant Unit, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Feb 2020 to Jun 2022.

Methodology: We enrolled 500 patients, between the ages of 18 to 80 years, presenting to outpatient department of a tertiary care hospital, with complaints of gall stone disease, and planned for cholecystectomy. Detailed history was obtained, along with laboratory investigations and abdominal ultrasonography. Gall bladder samples were sent to Armed Forces Institute Pathology for reporting by a consultant pathologist.

Results: Out of 500 patients enrolled for the study, 330(66%) were females and 170(34%) were males, with the mean age of 45.00±8.87 years. Histopathological findings revealed 455(91%) cases of inflammation, 27(5.4%) cases of dysplasia and 18(3.6%) cases of carcinoma. A significant association was observed between age and gall bladder carcinoma (*p*-value <0.001). Number of stones had no significant association, but size of stone had strong association with gall bladder carcinoma (*p*-value=0.001).

Conclusion: Gall stones have a strong link to the malignancy of gall bladder, more specifically in old age and among females having larger sized gall stones. Early cholecystectomies are recommended, especially with larger (>3cm) stones.

Keywords: Cholecystectomy, Cholelithiasis, Gall bladder cancer.

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INTRODUCTION

Gallbladder cancer (GBC) is by far the most prevalent and severe biliary cancer, with the shortest median survival rate of all biliary tract tumors, responsible for around 85,000 deaths each year worldwide with studies reporting that gall stones lead to dysplasia of gall bladder mucosa causing GBC.[1,2] GBC has multiple risk factors with many studies having confirmed the link between cholelithiasis and GBC.[2] Gallstones tend to be more common in women over the age of 65 years, who have a lengthy history of gallstones.[3] While malignancies of the gastrointestinal tract are prevalent in all regions of the world, in the past, gall bladder cancers were not recorded as frequently as other tumors in this region but the occurrence of GBC in any community differs widely, ranging from 1 to 23 per 100,000 in diverse geographical locations and ethnic groupings mostly in low- and middle-income countries,[4] with only 1 % of cholecystectomies containing occult gall bladder carcinoma.[5] It is, therefore, of great clinical importance to determine the causal effect of gall stones to GBC, which could lead to direct intervention in highly prevalent areas. As cholecystectomy is amongst the most routinely conducted abdominal surgeries in the world, multiple approaches have been adopted in the past, with laparoscopic cholecystectomy emerging as the preferred one, particularly for benign disorders of the gall bladder or adjacent tissues, however, cancers of the tract can also necessitate this procedure. Early diagnosis and medication have been linked to a better outcome and prolonged survival among these patients in previous studies.[6] Thus, we planned to conduct this study to evaluate the relationship of gall stones and gall bladder carcinoma in patients undergoing cholecystectomy for cholelithiasis.

METHODOLOGY

This cross-sectional study was conducted in Army Liver Transplant Unit, Pak Emirates Military

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Hospital (PEMH), Rawalpindi, Pakistan, for 16 months from February 2020 to June 2022. The study began after taking ethical approval from the Ethics Committee of the hospital (ltr no. A/28/1840) and informed consent of individuals was taken. We used WHO calculator to calculate the sample size, taking frequency of gall stones as 60% from a local study.[7] Using non-probability convenience sampling, we recruited 500 patients in the study.

Inclusion Criteria: All patients between the ages of 18 to 80 years of either gender, presenting with complaints of symptomatic cholelithiasis and planned for cholecystectomy, were included.

Exclusion Criteria: All patients with diagnosed biliary cancer or any other malignancy in the body were excluded. Patients with porcelain GB, GB polyps, primary sclerosing cholangitis, uncontrolled diabetes or hypertension were also excluded.

Detailed history was obtained along with laboratory investigations and abdominal ultrasonography. All patients were given their routine medications according to hospital protocols. Post-operatively, gall bladder specimens were sent to Armed Forces Institute of Pathology (AFIP) for histopathology. Histological findings were based on Formalin Fixed and Paraffin Embedded (FFPE) tissue specimens examined by two consultants as per College of American Pathologist (CAP) protocol (version 3.1.0.2). Immunohistochemistry (IHC) help was sought in difficult cases and Leica Microsystems®, USA Cytokeratin (CK) 7 and 20 were employed where CK-7 positivity while CK-20 negatively confirmed GBC.[7] GBC diagnosed cases were discussed in multidisciplinary team (MDT) meetings comprising operating surgeon, histo-pathologist, gastroenterologist and oncologist. All the data was analyzed using Statistical Package for Social Sciences (SPSS) version 27, Mean±SD was used for quantitative data while frequencies and percentages were calculated for qualitative data. We applied t-test and chi-square test for numerical and categorical variables respectively while a *p*-value of ≤0.05 was taken as significant.

RESULTS

A total of 500 patients were included in the analysis, among whom 330(66%) were females and 170(34%) were males, with 2:1 ratio between both. The age range was between 18 to 80 years, with a mean age of 45.00±8.87 years, mean BMI of 26.74±11.41 kg/m^2 as 147(29.4%) patients had diabetes. Additionally, 356(71.2%) patients had hypertension and 66(13.2%) were smokers. Histopathological findings revealed 455(91%) cases of inflammation, 27(5.4%) dysplasia and 18(3.6%) of carcinoma. As dysplasia is a pre-malignant condition, it was included in the malignant category for the purpose of result interpretation. A significant association was observed between age and GBC (*p*-value <0.001), which demonstrated that probability of carcinoma increased with increase in age.

Out of 45 cases of gallbladder carcinoma, 18(40.0%) were males and 27(60.0%) were females with male to female ratio of 1:1.5. There were 22(48.9%) patients who belonged to age group of 46-60 years. In our sample, most patients belonged to middle class income (28, 68.2%). Another significant association was observed between education and GBC with patients having higher education had lower percentage of GBC and significantly more patients of diabetes mellitus (21, 46.7%) had GBC while hypertension (33, 73.3%) was also linked to GBC in our sample. We found that the association between low CRP (C-reactive Protein) and GBC was also significant (*p*-value=0.029) as 25(55.6%) patients with CRP <100 had GBC. Majority (32, 71.1%) of GBC patients were non-smokers with no habit of exercise (40, 88.9%). Among carcinoma patients, only 11(24%) had single stone while 34(76%) patients had multiple stones and while number of stones and GBC had no significant association, but size of the stone was significantly larger in GBC patients and had strong association with GBC (*p*-value=0.001). These findings are listed in detail in Table.

DISCUSSION

Although most illnesses affecting the gall bladder are mild and patients recover after its resection, malignancy concerns are increasing. We found the mean age of patients in this study to be 45 years, with the peak age of incidence to be fourth decade of life, similar to other studies in which the mean age came out to be 44.9 and 46.1 years with peak age of incidence to be in the third decade of life.[9,10] However, in studies carried out in Eastern India and Nepal, the mean age was 55 years.[11,12] Gall bladder carcinoma is associated with more than 70 years of age, but in our study the peak age of malignancy was in the range of 45-60 years of age, however, this decreasing trend may be linked to reduced average life expectancy in our area. Majority of the patients who presented with gallbladder stones were females which

Table: Demographic Characteristics and Association Between Patient Characteristics and Gall Bladder Carcinoma (n=500)

Characteristics	Gall Bladder Carcinoma		*p*-value
	Yes	No	
Male	18(40.0)	152(33.4)	0.373
Female	27(60.0)	303(66.6)	
Age Groups (years)			
15-30	2(4.4)	31(6.8)	<.001
31-45	16(35.6)	229(50.3)	
46-60	22(48.9)	187(41.1)	
61-75	1(2.2)	8(1.8)	
76 and above	4(8.9)	0(0.0)	
Socio-Economic Status			
Lower	10(22.2)	101(22.2)	0.815
Middle	28(68.2)	298(65.5)	
Higher	7(15.6)	56(12.3)	
Education			
Elementary	15(33.3)	83(18.2)	0.052
Secondary	23(51.1)	284(62.4)	
Higher	7(15.6)	88(19.3)	
Smoking Habit			
No	32(71.1)	374(82.2)	0.191
Yes	9(20.0)	57(12.5)	
Ex-Smoker	4(8.9)	24(5.3)	
Exercise			
No	40(88.9)	386(84.8)	0.581
Moderate	3(6.7)	53(11.6)	
Vigorous	2(4.4)	16(3.5)	
Concomitant Diseases			
Diabetes Mellitus			
Non-Diabetic	20(44.4)	282(62.0)	0.028
Pre- Diabetic	4(8.9)	47(10.3)	
Diabetic	21(46.7)	126(27.7)	
Hypertension			
Yes	33(73.3)	323(71.0)	0.740
No	12(26.7)	132(29.0)	
Hepatitis-B Virus			
Yes	28(62.2)	303(66.6)	0.554
No	17(37.8)	152(33.4)	
Hepatitis-C Virus			
Yes	35(77.8)	321(70.5)	0.307
No	10(22.2)	134(29.5)	
C-Reactive Protein			
<100	25(55.6)	302(66.4)	0.029
>100	10(22.2)	110(24.2)	
>200	10(22.2)	43(9.5)	
Duration of symptoms			
1 Episode	1(2.2)	29(6.4)	0.186
2 Episodes	16(35.6)	203(44.6)	
3 Episodes	28(62.2)	223(49.0)	
Surgical Anatomy			
Single Stone	11(24.4)	155(34.1)	0.191
Multiple Stone	34(75.6)	300(65.9)	
Size of the Stone			
Less than 1cm	29(64.4)	373(82.0)	0.001
Greater Than 1cm	12(26.7)	75(16.5)	
Greater than 3cm	4(8.9)	7(1.5)	

was consistent with the findings of other studies.[11,13] Our study showed a positive association of GBC with female gender which was in concordance with other studies,[3,14-16] but one study did report that there is no difference in incidence of GBC in either gender.[17] While the association of smoking with gall bladder disease has not yet been established, as there are few studies predicting the role of smoking in developing gallbladder disease,[11,18,19] which was similar to our findings. In our study, illiteracy was found to be significantly associated with GBC, most likely due to less access to health care system and less awareness about healthy nutritional practices as reported by a study from Pakistan,[20] and Argentina.[16]

Hypertension, Diabetes, Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) are commonly associated comorbidities,[21] but our data showed that majority of the cases were negative for HBV, HCV, hypertension, and diabetes but our findings did show that diabetes mellitus is significantly associated with GBC. As literature is scarce on this association it may simply be due to more prevalent diabetes in the region. Many studies have shown greater risk of GBC with increased duration of gall stones, causing chronic inflammation, which can develop into dysplasia and eventually invasive carcinoma,[14,22,23] but in our study, symptoms were recorded in number of acute episodes before cholecystectomy, which demonstrated that incidence of GBC was higher in those who had multiple episodes of acute symptoms for a longer duration but it was not significantly associated to GBC. In majority of patients, C-Reactive Protein was <100 and with no significant association to GBC.[24] However, one study reported that there was a significant association of increased CRP to GBC in Europeans.[4] Ultrasonography results revealed that the size of stones (>3 cm) was significantly associated with GBC, similar to previous studies.[16,25]

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LIMITATIONS OF STUDY

As this study was a single center study, patients had not been followed before the incidence of gall stone in a prospective cohort fashion, which, if conducted in future studies, will lead to better understanding of this association.

CONCLUSION

We found gall stones to have a strong association with GBC, and keeping in view the aggressive nature of the GBC, early cholecystectomies for gall stones are recommended especially with larger sized stones (>3cm).

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Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MSN & NMW: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MN & NS: Conception, data analysis, drafting the manuscript, approval of the final version to be published.

AHM & MUN: Data acquisition, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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