ORIGINAL ARTICLE

A Tertiary Care Center's Experience with Clinicopathological Characteristics of Gallbladder Carcinoma in Our Population

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Abstract

Introduction: Gallbladder cancer (GBC) is the most common malignant biliary tract tumor with the shortest survival from the time of diagnosis. This poor prognosis is due to the destructive biologic behavior of GBC, lack of sensitive screening tests for early detection, and vague nature of first presentation. Here in this study, we will evaluate the baseline characteristics of the patients presenting with gallbladder carcinoma in our population.

Materials and methods: This retrospective study was conducted in the Department of Gastroenterology at Sindh Institute of Urology and Transplantation (SIUT), Karachi. Patient data were compiled and composed from the in-patient health records, radiology, and operational records. Those patients with suspicion of GBC, but negative at histology, or patients having inconclusive radiologic findings, were excluded. Baseline characteristics were recorded. Results were presented as means ± SD for quantitative data or as numbers with percentages for qualitative data. Continuous variables were analyzed using the Student's *t*-test, while categorical variables were analyzed using the Chi-square test. A *p*-value of <0.05 was considered statistically significant.

Results: A total of 162 patients were included in our study. Among them, 101 (62.3%) were females. Hypertension was the most common comorbid illness noted in 29 (17.9%) patients while 91 (56.2%) patients had no concurrent comorbidities. Most common risk factor for carcinoma of gallbladder was gallstones seen in 106 (65.1%) patients. The most common presenting complaint was combination of obstructive jaundice, weight loss with right hypochondrial pain seen in 66 (40.7%) patients. On CT abdomen, direct liver infiltration without lymphovascular invasion was noted in 77 (47.5%) patients followed by liver infiltration along with lymphovascular invasion in 26 (16%) patients and distant metastasis in 24 (14.8%) patients. On gallbladder (GB) mass biopsy, 58 (35.8%) patients had well-differentiated, 46 (28.4%) had moderately differentiated, while 33 (20.4%) had poorly differentiated adenocarcinoma. Of 162 patients, 103 (63.6%) patients underwent endoscopic retrograde cholangiopancreatography (ERCP). The most common finding on ERCP was proximal common bile duct (CBD) stricture with intrahepatic biliary system dilatation which was noted in 95 (58.6%) patients. Percutaneous transhepatic cholangiography (PTC) was performed only in 9 (5.6%) patients. Seventeen (10.5%) patients were managed by simple cholecystectomy, 39 (24.1%) patients underwent extended cholecystectomy, 14 (8.6%) patients underwent chemotherapy, while 102 (56.8%) patients were given palliative management. When followed for 1 year, 101 (62.3%) patients died within 6 months.

Conclusion: The baseline characteristics, biopsy findings, modes of treatment, and rates of 1 year mortality were studied in patients with gallbladder carcinoma in our population. Advanced age, high white blood cell counts, and serum bilirubin at presentation with low lymphocyte count and presence of comorbid illnesses were the factors independently associated with increased mortality in patients with gallbladder carcinoma. However, further studies with large sample size and stratification with respect to age, gender, and different variables can be done in terms of mortality in patients with gallbladder carcinoma.

Keywords: Demographics, Gallbladder, Gallbladder cancer.

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Introduction

Gallbladder cancer is the most common malignant tumor of the biliary tract worldwide.[1] It is also the most violent biliary tract cancer with the shortest moderate survival from the time of diagnosis.[2–4] The incidence of GBC shows wide geographical and racial variations[5,6] and the incidence varies widely within countries.[7] Incidence increases consistently with age, with more than two-thirds of patients being above age 65 years.[8] The most common presentations of GBC are right upper quadrant or epigastric pain, jaundice, nausea, vomiting, anorexia, weight loss and only a few having a palpable mass.[3] Those presenting symptomatically typically have advanced disease with 75% being unresectable and carrying very poor prognosis.[9] Approximately 1% of patients undergoing cholecystectomy will have an incidental tumor discovered on pathology review.[10,11] The 5-year survival of early (stage II) and advanced disease (stage IVb) is as low as 29% and 2%, respectively.[12] This poor prognosis is due to the

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aggressive biological behavior of GBC, lack of sensitive screening tests for early detection,[13] and vague nature of first presentation. Among those suitable for resection, the mortality rate is high due to the anatomical complexity, surgical complications associated with liver resection, and risks of extent of disease due to tumor handling.[14] Additionally, among those that do undertake surgical resection, relapse rates remain high.[2]

Gallbladder cancer is considered as a disease more prevalent in elderly population with a dismal prognosis. However, with time, there has been a robust increase in the cases observed in young individuals that differ in certain characteristics such as the gross appearance of the tumor, the stage at presentation, and the histological characteristics along with better survival but it comes with aggressive tumor behavior.[15,16]

Although significant research work has been done to study the various aspects related to GBC including clinical presentation, histology, and outcome, very little work is available from our part of the world in this regard. An understanding of the baseline characteristics of these patients may help the concerned physician to devise better diagnostic and therapeutic strategies in managing these patients. The purpose of this study was therefore to study the demographic features, clinical manifestations, and stage of presentation of patients with GBC.

Aim

The aim of this study was to evaluate the demographic characteristics, clinical manifestations, and stage of presentation of patients with GBC in our population.

Materials and Methods

This was a retrospective cohort study which was carried out at the Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation, included all the patients with the diagnosis of CGB on the basis of imaging and or histopathology for a period of 5 years from January 2015 to December 2021. Those patients (who were evaluated with suspected CGB but there was no evidence based on either imaging or histopathology) with suspicious GBC but negative at histology or imaging (were excluded).

The demographic characteristics of the patients including age of presentation, gender, comorbid illness, clinical presentation, treatment, histopathological findings and outcome were obtained.

All the data were entered and analyzed using SPSS Version 22. Continuous variables were presented as mean ± (SD) while categorical variables were stated as frequency and percentages. Continuous variables were compared using student-*t*-test while categorical variables were compared using Chi-square test. A *p*-value of <0.05 was considered significant.

Results

A total of 162 patients were included in our study. Among them, 101 (62.3%) were females. Mean age was 52 ± 12 years (Table 1). Hypertension was the most common comorbid illness noted in 29 (17.9%) patients while 91 (56.2%) patients had no concurrent comorbidities. Most common risk factor for carcinoma of gallbladder was gallstones seen in 106 (65.1%) patients. Mostly, patients were presented with a combination of symptoms of obstructive jaundice and weight loss with or without right hypochondrial pain seen in 43 (26.5%) patients. On CT abdomen, direct liver infiltration without lymphovascular invasion was noted in 77 (47.5%) patients followed by liver infiltration along with lymphovascular invasion in 26 (16%) patients and distant metastasis in 24 (14.8%) patients. On GB mass biopsy, 58 (35.8%) patients had well-differentiated, 46 (28.4%) had moderately differentiated, while 33 (20.4%) had poorly differentiated adenocarcinoma. Of 162 patients, 103 (63.6%) patients underwent ERCP. The most common finding on ERCP was proximal CBD stricture with intrahepatic biliary system dilatation which was noted in 95 (58.6%) patients. Percutaneous transhepatic cholangiography was performed only in 9 (5.6%) patients. Seventeen (10.5%) patients were managed by simple cholecystectomy, 39 (24.1%) patients underwent extended cholecystectomy, 14 (8.6%) patients underwent chemotherapy while 102 (56.8%) patients were given palliative management. When followed for 1 year, 101 (62.3%) patients died within 6 months (Table 2). The mortality was higher in patients with advanced age, female gender, poor Eastern Cooperative Oncology Group (ECOG) status, presence of comorbidities, decreased hemoglobin and lymphocyte count, increased total leukocyte count and neutrophils, deranged liver enzymes, and coagulopathy at the time of admission (Tables 3 and 4). On multivariate analysis, female gender, increased total leukocyte count and serum bilirubin, decreased absolute lymphocyte count, and presence of comorbid illnesses were the factors associated with increased risk of mortality in patients with GBC in our population (Table 5).

Table 1: Baseline parameters of study population (*n* = 162)

Variables	*Mean ± Std. deviation*
Age (years)	52 ± 12
Hemoglobin (gm/dL)	10.8 ± 2.0
TLC (10^9/L)	13.7 ± 6.9
Platelets (10^9/L)	319 ± 153
Total bilirubin (mg/dL)	10.1 ± 9.5
Direct bilirubin (mg/dL)	1.01 ± 0.79
Alkaline phosphatase (U/L)	533 ± 548
Aspartate transaminase (AST) (U/L)	87 ± 76
Alanine transaminase (ALT) (U/L)	72 ± 79
Gamma glutamyl transferase (GGT) (U/L)	316 ± 412
BMI (kg/m^2)	32.4 ± 14.1

Discussion

Gallbladder cancer is the most common malignant biliary tract tumor with the shortest survival from time of diagnosis. This dismal prognosis related to this tumor is likely due to the destructive biologic behavior of GBC.[1–4] Lack of the sensitive screening tests can result in delay of early detection of this deadly tumor. There is geographical variation observed with this tumor, having different demographics in different parts of the world.[5–7] Here in this study, we have evaluated the clinical and pathological characteristics of the patients presented with gallbladder carcinoma in our population.

Worldwide, the incidence of gallbladder carcinoma is higher in women pointing toward an important role of female hormones, i.e., estrogen and progesterone, in causing GBC.[17] One of the studies done by Pandey et al. also revealed that multiple pregnancies significantly increased the risk of gallbladder cancer, which is associated with the higher levels of progesterone and endogenous estrogen during pregnancy.[18] These findings can

Table 2: Frequency of categorical variables of the patients enrolled in the study

Variable	*Frequency (%)*
Gender	
Male	61 (37.7)
Female	102 (62.3)
Presenting complaint	
Jaundice, weight loss, and abdominal pain	66 (40.7)
Abdominal pain only	37 (22.8)
Jaundice only	33 (20.4)
Etiology	
Gallstones	106 (65.4)
Carcinogens	48 (29.7)
Others	8 (4.9)
Comorbid illness	
Hypertension	29 (17.9)
Diabetes	15 (9.3)
Kidney disease	3 (1.9)
None	90 (55.6)
TNM classification	
Stage I	10 (6.2)
Stage II	50 (30.9)
Stage III	57 (35.2)
Stage IV	45 (27.8)
Biopsy	
Well-differentiated	58
Moderately differentiated	46
Poorly differentiated	33
Squamous cell carcinoma	2
Not done	23
ERCP	
Yes	103 (63.6)
No	59 (34.4)
CBD stricture on ERCP	
Present	95 (58.6)
Absent	68 (42.4)
PTC	
Yes	9 (5.6)
No	153 (94.4)
Treatment	
Simple cholecystectomy	17 (10.5)
Extended cholecystectomy	39 (24.1)
Chemotherapy	14 (8.6)
Palliative care	92 (56.2)
Six month mortality	
Present	101 (62.3)
Absent	61 (37.7)

be correlated to our population as most of the patients affected with GBC were females comprising more than 50% of the affected patients.

In comparison with the regional data, there was no major difference between the age of presentation in GBC in our study and the other studies done on north Indian and Chinese population

Table 3: The baseline characteristics in mortality vs nonmortality group for continuous variables

Variable	*Alive (n = 61) Mean ± SD*	*Dead (n = 101) Mean ± SD*	*p-value*
Age	51.3 ± 11.6	62 ± 12.4	**0.04**
Hemoglobin (gm/dL)	11.5 ± 1.88	10.3 ± 2.01	**≤0.001**
TLC (10^9/L)	11.26 ± 6.0	15.2 ± 7.01	**≤0.001**
Neutrophils (%)	68 ± 13	75 ± 13	**≤0.001**
Lymphocytes (%)	23 ± 15	15 ± 9	≤0.001
Platelets (10^9/L)	297 ± 137	333 ± 161	0.148
INR	1.2 ± 0.8	1.8 ± 1.67	**0.01**
Urea (mg/dL)	35 ± 34	32 ± 25	0.627
Serum creatinine (mg/dL)	0.9 ± 0.6	1.1 ± 1.3	0.574
Total bilirubin (mg/dL)	4.6 ± 7.4	13.4 ± 9.1	**≤0.001**
Alkaline phosphatase (U/L)	336 ± 451	652 ± 570	**≤0.001**
Gamma glutamyl transferase (U/L)	231 ± 454	367 ± 378	**0.042**
Aspartate transaminase (U/L)	71 ± 77	97 ± 75	**0.034**
Alanine transaminase (U/L)	60 ± 82	78 ± 77	**0.160**

Bold values state that *p*-values are significant (≤0.001); CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography

Table 4: Comparison of baseline categorical variables in terms of mortality

Variable	*Alive (n = 61) n (%)*	*Dead (n = 101) n (%)*	*p-value*
Gender			
Male	34 (55.7)	27 (26.7)	**≤0.001**
Female	27 (54.3)	74 (73.3)	
Jaundice on presentation			
Yes	15 (24.5)	48 (47.5)	**0.04**
No	46 (75.5)	53 (52.5)	
Stage of the tumor			
Early (I, II)	27 (44.3)	33 (32.6)	0.139
Advanced (III, IV)	34 (55.7)	68 (67.8)	
ECOG			
Good	45 (73.7)	37 (36.6)	**≤0.001**
Poor	16 (26.3)	64 (63.4)	
Comorbidities			
Present	36 (59)	37 (36.6)	**0.01**
Absent	26 (41)	64 (63.4)	

Bold values state that *p*-values are significant (≤0.001); ECOG, Eastern Cooperative Oncology Group

where the mean age of presentation of GBC was in 5th to 6th decade,[5–8] while majority of our population effected were in the 7th decade of their life.

Among the 162 patients with gallbladder carcinoma, 106 (65.1%) had gallstones. Gallstones are considered as an important risk factor for gallbladder cancer. Globally, the incidence rates of GBC were directly proportional to the presence of gallstones. This is likely due to the obstruction of gallbladder by stones causing mechanical damage and bile stasis resulting in the repetitive inflammation and proliferation of mucous membrane of gallbladder resulting in malignancy.[19]

Table 5: Multivariate analysis of variables in predicting mortality in patients with gallbladder carcinoma

			CI (95%)	
Variables	*p-value*	*Odds ratio*	*Lower limit*	*Upper limit*
Age	0.388	0.983	0.946	1.022
Female gender	**0.001**	0.145	0.054	0.388
Presence of jaundice	0.897	1.073	0.370	3.1
Hemoglobin	0.916	1.013	0.794	1.3
TLC	**0.031**	0.905	0.82	0.991
Neutrophils	0.498	1.018	0.96	1.072
Leukocytes	**0.046**	1.051	1.001	1.015
INR	0.176	0.639	0.335	1.222
Total bilirubin	**0.002**	0.893	0.832	0.959
Alanine transaminase	0.317	1.003	0.997	1.01
Alkaline phosphatase	0.418	1.001	0.998	1.001
Gamma glutamyl transferase	0.194	0.999	1.000	1.002
ECOG status	0.12	0.455	0.167	1.238
Presence of comorbid illnesses	**0.04**	0.360	0.136	0.956

Bold values state that *p*-values are significant (≤0.001); ECOG, Eastern Cooperative Oncology Group

No specific clinical symptoms of early gallbladder carcinoma were noted in the present study. Although the common presenting complaint in our population was a combination of obstructive jaundice, weight loss with or without right hypochondrial pain was noted in 43 (26.5%) patients. On imaging, direct liver infiltration without lymphovascular invasion was noted in 77 (47.5%) patients followed by liver infiltration along with lymphovascular invasion in 26 (16%) patients and distant metastasis in 24 (14.8%) patients.

Among the 162 analyzed patients, 139 (53.6%) underwent gallbladder mass biopsy and established a type A diagnosis (histopathological findings) and 23 (46.4%) received a type B diagnosis (imaging and clinical examination), as they presented at a late or advanced stage of the disease. Pathological examination showed that almost all patients 137/139 (98.5%) had adenocarcinoma, out of which 58 (35.8%) patients had well-differentiated, 46 (28.4%) had moderately differentiated, while 33 (20.4%) had poorly differentiated adenocarcinoma while only two had squamous cell carcinoma. Kang et al. suggested that simple cholecystectomy is sufficient for stage I or II gallbladder carcinoma.[20] In addition, a study showed that this operation could result in a 5-year survival rate up to 100%. According to the TNM staging classification, in our study 24 of 162 (14.8%) patients were classified as having stage IV cancer. We found that most patients with progressive malignancy and invasion were at an advanced stage when they were presented to the hospital. Therefore, it is very essential to improve the gallbladder cancer detection rate for early diagnosis and prompt intervention.

Among all 162 patients with gallbladder carcinoma, 56 of 162 patients (34.5%) received surgical treatment. The surgical treatment included simple cholecystectomy, extended cholecystectomy, and palliative surgery and palliative care including percutaneous transhepatic cholangiography (PTC)-guided drainage and ERCP with stenting. A total of 14 (14/139, 8.6%) patients underwent postoperative chemotherapy, mainly the oxaliplatin, fluorouracil, and leucovorin (FOL/FOX) regimen. The rate of metastasis in this study was high, leading to a low resection rate and high death rate of 62% within 6 months. This poor prognosis of the GBC can be attributed to its aggressive behavior and an advanced stage at presentation.[2–4]

Lastly, based on our present observation, we believe that GBC is common in Pakistan and is commonly associated with gallstone disease.

There were certain limitations to our study. First and foremost was the retrospective nature of the study. Secondly, it was a single-centered study and lastly no all patients underwent GB biopsy because of advanced disease at presentation. On the other hand, the strength of the study was the data of a large cohort of patients affected with GBC from single center who were managed with the standard protocol, with homogeneity to the diagnosis and the pathological evaluation of the observations.

Conclusion

The baseline characteristics, biopsy findings, modes of treatment, and mortality rates were studied in patients with gallbladder carcinoma in our population. Advanced age, high white blood cell counts, and serum bilirubin at presentation with low lymphocyte count and presence of comorbid illnesses were the factors independently associated with increased mortality in patients with gallbladder carcinoma. However, further studies with large sample size and stratification with respect to age, gender, and different variables can be done in terms of mortality in patients with gallbladder carcinoma.

This study also emphasizes that early cholecystectomy, identification of risk factors causative of GBC, and focused research are required to prevent the development of this lethal malignancy.

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