Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

Original Article

Evaluation of patients with carcinoma gall bladder with respect to timing of presentation and compounding risk factors

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Abstract

Background: Gall bladder cancer (GBC) is one of the commonest malignancies of hepatobiliary tract which progresses silently and has a poorer outcome. Thus, we evaluated the time of presentation and compounding risk factors in GBC.

Materials and Methods: This was a single centre, prospective, observational study performed in the Department of General Surgery over a period of 18 months. A total of 100 patients diagnosed with GBC, underwent ultrasonography (USG), Computed Tomography (CT), Magnetic Resonance Cholangiopancreatography (MRCP), biopsy, or fine needle aspiration cytology (FNAC).

Results: The patients were predominantly females (57%), and the mean age of the patients was 55.57 ± 9.3217 years. Most common presenting symptoms were nausea/vomiting (72%) and abdominal pain (63%) with mean duration of diseases as 12.39 ± 8.77 months. GB fossa mass with extension in liver metastasis with multiple calculi within GB (22%), and GB wall thickening suspicious of malignancy (20%) were the commonest findings on USG and CT, respectively. The predominant finding on MRCP was obstructive jaundice with dilated intrahepatic biliary radicals, common bile duct, main pancreatic duct due to common bile duct calculi (25%). Moderately differentiated adenocarcinoma was the most frequent finding on biopsy (67%), and FNAC (50%). Due to inoperable nature of the disease, patients mainly received chemo-radiation (70%), while 10% underwent exploratory laparotomy.

Conclusion: GBC is rare disease with poor prognosis with most of the cases presenting in late stages.

Key Words*: Cholelithiasis, Gallbladder carcinoma, Prognosis*

I. Introduction

Gallbladder cancer (GBC) arises from the epithelial lining of gallbladder (GB) and cystic duct.[1] It contributes to approximately 165,000 deaths annually, accounting for 1.7% of global cancer mortality.[2] The current burden of GBC, as per GLOBOCAN 2020, is 41,062 cases in males and 74,867 cases in females with an overall 115,949 new cases and 84,695 new deaths.[3] In India, it contributes to about 10% of the worldwide GBC burden. The ethnic and geographical variations affect the incidence of GBC. Northeast and Central India accounts for the majority of incidence relative to South and West India.[4] Absence of serosa in GB limits the cancer spread and presents with indeterminate symptoms; thus, the diagnosis of GBC frequently happens at an advanced stage, with deplorable prognosis.[5] GBC has multifactorial risk factors, including gallstones, nutritional

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

status (high fat diet), chronic diseases (diabetes), alcohol, and bacterial infections.[6,7] Despite of these known risks, GBC has poor outcome.[8] Usually, in 5-10 years, metaplasia progresses to dysplasia, carcinoma in-situ, and consequently into invasive GBC.[8,9] This suggests silent yet very rapid invasion and anticipating a desolated outcome. A competent prognosis, therefore, is highly dependent on early diagnosis and resection.[6] Notwithstanding the prospect of cure, hardly 10% cases have resectable tumors at the time of resection, and probably 50% have lymph nodes invasion.[10,11] Thus, early diagnosis with appreciation of risk factors and time of presentation are crucial. Based on these findings, we evaluated the patients with GBC in terms of timing of presentation and compounding risk factors.

II. Material and Methods

This was a prospective, observational study performed over a period of 18 months (January 2017 to August 2018) in the Department of General Surgery of a tertiary case institute. The study was conducted after the approval of protocol by the Institutional Ethics Committee and obtaining written informed consent of all the patients.

Patients of either sex, belonging to the age group of more than 12 years, who presented with radiologically suspected or biopsy proven GBC, and inoperable cases of GBC proven by fine needle aspiration cytology (FNAC) were included in the study. Pregnant and lactating females were excluded from the study.

A total of 100 patients with radiological suspected or biopsy proven GBC were screened. After taking consents, these patients underwent clinical, pathological, and radiological investigations. All patients underwent ultrasonography (USG), and either contrast-enhanced computed tomography (CECT) or magnetic resonance cholangiopancreatography (MRCP). Data related to age, sex, education, residence, pathological investigations (FNAC and biopsy), and radiological investigations (USG, MRCP, and CECT) was recorded. The patients with FNAC proven GBC were referred to the Department of Radiation Oncology for chemoradiotherapy.

Statistical analyses

Descriptive statistics were used. Continuous and categorical variables are represented as mean ± standard deviation (SD) and frequencies (percentages), respectively.

III. Results

Assessment in terms of baseline characteristics demonstrated that majority of the patients were in the age group of 51-60 years (45%). The mean age of the patients was 55.57 ± 9.32 years. Maximum patients were females (57%). Based on the education, primary education was completed in majority (60%) and least patients were graduates (13%). Majority of patients resided in rural areas (84%) (Table 1).

Table 1. Baseline characteristics

Characteristics	N (=100)	%
Age group (years)		
≤ 40	7	7
41-50	24	24
51-60	45	45
61-70	18	18
> 70	6	6
Mean Age (years)	55.57 + 9.32	----
Sex distribution		
Female	57	57
Male	43	43
Education		

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

Primary	60	60
Secondary	27	27
Graduate	13	13
Residence		
Rural	84	84
Urban	16	16

Assessment in terms of clinical profile of patients demonstrated that majority of patients had chief complaints of nausea/vomiting (72%) and abdominal pain (63%). Moreover, nausea/vomiting (77%) and abdominal pain (72%) were the first initial presenting symptoms. The mean duration of diseases was 12.3900 ± 8.7651 months. Majority of patients had history of gall stones (80%), and tobacco smoking (44%) was the most common addiction. Few patients had no history of addiction (21%) (Table 2).

Table 2. Clinical profile

Parameters	**Chief complaints (%)**	**First initial presenting complaint (%)**
Abdominal Pain	63	72
Right hypochondrium lump	25	21
Jaundice	43	31
Weight loss	15	--
Nausea vomiting	72	77
Anorexia	20	28
Patient history	**N**	**%**
Gall stones	80	80
Smoking	44	44
Tobacco chewing	20	20
Alcohol and smoking	9	9
Alcohol	6	6
No addiction	21	21
Duration of disease (months)	12.39 ± 8.77	--

All 100 patients were assessed with USG and CT. On USG, patients predominantly had GB fossa mass with extension in liver metastasis with multiple calculi within GB (22%), while on CT, GB wall thickening suspicious of malignancy (20%) was the commonest finding. A total of 24 patients underwent MRCP, revealing obstructive jaundice with dilated intrahepatic biliary radicals (IHBR), common bile duct (CBD), main pancreatic duct (MPD) due to CBD calculi (25%) as commonest finding. Thirty patients underwent biopsy and 70 underwent FNAC. On biopsy, patients mostly had moderately differentiated adenocarcinoma (67%). Similarly, on FNAC, commonest finding was moderately differentiated adenocarcinoma (50%) (Table 3).

Assessment of treatment history demonstrated that majority patients were inoperable cases due to late presentation of the disease and received chemo-radiation (70%) while least underwent exploratory laparotomy followed by biopsy from GB mass (10%) (Table 4).

IV. Discussion

The principal finding of the present study suggested that abdominal pain and nausea/vomiting were the most common symptoms as well as initial presenting symptoms. Typically, GBC is symptomatic only in advanced disease. When symptoms occur, they are often related to coexisting cholelithiasis.[12] From the above percentage of sign and symptoms, at the initial presentation of the disease, it was found that maximum of the patients were in early stage of the disease. The most common complaints of abdominal pain in majority of patients was revealed in a study by Smithson et al., and nausea/vomiting was one of the least observed complaints in

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

Table 3. Distribution of patients according to investigations and diagnoses

USG findings	**N**	**%**
GB fossa mass with extension in liver metastasis with multiple calculi within GB	22	22
Asymmetrical wall thickening of GB wall with multiple calculi within GB	18	18
GB fossa mass with extension in liver with multiple calculi within GB	15	15
Gross and diffuse GB wall thickening forming mass like lesion with multiple calculi within GB	15	15
Heterogenous polypoid mass in GB lumen, invading porta hepatis with multiple calculi within GB	10	10
GB polyp >10 mm with irregular GB wall thickening	9	9
Hydrops GB	6	6
Irregular GB wall thickening without multiple calculi within GB	5	5
CT scan findings		
GB wall thickening suspicious of malignancy	20	20
GB mass with liver invasion	19	19
GB mass with IHBR dilatation causing GOO	12	12
GB mass with porta hepatis invasion and IHBR dilatation causing GOO and liver metastasis	12	12
GB mass with porta hepatis invasion and IHBR dilatation	11	11
GB mass with porta hepatis invasion	11	11
GB mass with liver metastasis	10	10
Polypoid hypoechoic SOL with no liver invasion	5	5
MRCP findings		
GB mass with porta hepatis invasion and IHBR dilatation	5	20.8
GB mass in neck region of cystic duct till confluence of hepatic ducts	4	16.7
GB mass obstructing CBD and IHBR dilatation	4	16.7
Dilated right and left hepatic ducts with right anterior hepatic duct calculus, contracted thick GB wall, obstruction at confluence of right and left hepatic ducts	5	20.8
Obstructive jaundice with dilated IHBR, CBD, MPD due to CBD calculi	6	25
Biopsy findings		
Moderately differentiated adenocarcinoma	20	67
Poorly differentiated adenocarcinoma	7	23
Well differentiated adenocarcinoma	3	10
FNAC findings		
Moderately differentiated adenocarcinoma	35	50
Poorly differentiated adenocarcinoma	24	34
Well differentiated adenocarcinoma	11	16

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GB - gall bladder, CBD - common bile duct, IHBR - Intra Hepatic Biliary Radicals, MPD - main pancreatic duct, USG - ultrasonography, FNAC - Fine needle aspiration cytology, CT - Computed Tomography, MRCP - Magnetic Resonance Cholangiopancreatography, SOL - space occupying lesions

Table 4. Treatment history

Treatment history	N	%
Radical cholecystectomy	20	20%
Exploratory laparotomy followed by biopsy from GB mass (inoperable during operation)	10	10%
Inoperable cases due to late presentation of the disease and received chemoradiation	70	70%
Total	100	100%

their study.[13] So, these findings were partially in consensus with our study findings regarding presenting complaints. Our study findings are strengthened by Cunningham et al., as the most common presenting symptom was abdominal pain (82.7%) followed by nausea-vomiting (44.8%).[11] In another study, Fong et al. reported pain (64%) and jaundice (37%) as the most common presenting symptom.[14] Furthermore, Kumar et al. estimated the most common complaint in the symptomatic patient with GBC as right upper quadrant pain, which was a contrary finding to the present study.[15] Early diagnosis is at times troublesome as symptoms resemble or the etiology can be co-existing cholecystitis. Hence, screening such presenting symptoms is core need. Symptoms early in this disease often are indeterminate, resulting in delayed diagnosis.

In the present study, majority of patients had history of gall stones (80%), alcohol addiction (9%) alcohol and smoking addiction (44%) smoking (20%), tobacco chewing (21%). Smoking, alcohol, constipation, chronic typhoid infection, chronic cholecystitis, an anomalous junction of pancreaticobiliary duct, and genetic predisposition are various risk factors for GBC.[6,7,16] Even if smoking is known risk factor for GBC, Smithson et al. called for more attention towards non-smokers (58%) in their cohort and chronic cholecystitis in 5% of patients.[13] GBC fetches a poor prognosis, and the only plausibility for cure abides in early detection, and total resection. Vague abdominal symptoms often mask a more worrisome diagnosis.[17] The gap between first symptom and visit to a surgeon was 12.37 ± 8.77 months. Final impact of this delay leading to advancement of disease stage is a poorer prognosis. Delay in presentation and diagnosis is a leading cause of increased morbidity and mortality from GBC. Kumar et al. also reported a case with delay in time of presentation of 6 months.[15]

USG and CT imaging has upgraded preoperative GBC detection in early stages. Regardless of these advancements, only 50% patients with GBC are diagnosed prior to surgery. USG is most commonly preferred initial modality for such patients.[18] The most common USG findings in the present study was GB fossa mass with extension in liver metastasis with multiple calculi. Lobulated heterogenous polypoidal lesion in the GB anterior wall

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

with increased vascularity with mobile calculi was valued by Kumar et al., while Konstantinidis et al. found focal mass with irregular GB wall thickening and direct extension in the pericholecystic space and liver.[15,19] Moreover, 71% of ultrasound revealed cholelithiasis, which was in accordance with the findings of the present study. The CECT findings of the present study are in consensus with Kumar et al., where CECT determined distended GB wall with lobulated soft tissue density mass while biopsy revealed adenocarcinoma of GB body invading the muscular layer with negative margins.[15] Similarly, the present study also appraised GB wall thickening on CT and moderately differentiated adenocarcinoma on biopsy. Additionally, CT is known to have moderate sensitivity in diagnosing pathologies of gastrointestinal, omental, and abdominal wall involvement, but its high positive predictive value to diagnose distant metastasis and lymph node involvement brings it up as an imaging study in GBC. Main interest for CT lies in the establishment of the tumor extension.[20] Goerge et al. used CT and reported IHBR dilatation in majority patients (30%) with commonest site of obstruction at confluence of the left and right main hepatic ducts. On pathology, they also valued majority (49 patients) with adenocarcinoma, while 1 patient with squamous cell carcinoma.[21] Pathological findings were further supported by Fong et al., as moderately well differentiated adenocarcinomas predominated. They also appraised majority patients (n=51) with unresectable condition and unsuitable for surgical exploration supporting the findings of the present study, few patients (n=48) were proven by intraoperative biopsy to have unresectable disease, rest (n=19) were treated with a biliary bypass.[14] On the contrary, cholecystectomies were undertaken in maximum patients (n=26), followed by radical or extended resections (n=5) and chemotherapy in a study by Smithson et al.[13] The median age determined was 72 years with female sex predilection (72.3%) as per Konstantinidis et al.[19] Similar evidences were valued in literature.[11,13,14,22] These findings were in accordance with the present study.

The present study had few limitations. The small sample size was anticipated, considering GBC as a rare malignancy, but it is insufficient to draw a definitive conclusion. No molecular study regarding epidermal growth factor receptor-2 status and its association with GBC was not conducted. Other risk factors like family history, parity, food habits, body mass index, obesity, and comorbidities were not evaluated.

V. Conclusion

It can be concluded that most of the GBC present in an advanced stage with poor prognosis. Time of presentation and diagnosis has an influence on the prognosis of patients. Improvements in imaging and preoperative planning are mandatory. We recommend performing cooperative multicentric efforts to gather ample evidences to ameliorate such patients care within lifetime.

Funding:

None of the authors received funding for this study.

Competing interest:

There is no Competing interest.

Authors contribution:

All authors in our study contributed to the data collection of the patients.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

Acknowledgments:

The authors would like to thank Dr. Vikas S. Sharma (MD), CEO, Maverick Medicorum® (India), for data analyses and medical writing assistance in the preparation of this article.

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