Clinicopathological Presentation and Survival Outcomes of Gallbladder Cancer in a Low-Middle-Income Country (LMIC)

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ABSTRACT

Background

Gallbladder cancer (GBC) remains a highly fatal malignancy with poor prognosis in LMIC. This study evaluated the clinicopathological presentation and survival outcomes of GBC patients in LMIC.

Methodology

A review of medical records was conducted for patients with GBC referred to the center from May 2019 to June 2024. Descriptive statistics alongside Kaplan-Meier survival analysis were employed to evaluate survival data through SPSS v27.

Results

Forty-four cases were identified, and 38 were analyzed after excluding 6 due to incomplete data. The mean age at diagnosis was 61.85 ± 10.70 years, and more than (73.7%) of patients were female. Presenting symptoms were abdominal pain (63.2%), weight loss (31.6%), jaundice (21.1%), loss of appetite (18.4%), and fatigue (15.8%). Alcohol history in 9 patients (23.7%) and smoking history in 2 patients (5.3%). Comorbidities were present in 24 patients (63.2%), and a family history of cancer was reported in 5 patients (13.2%). The most common metastatic site was lung (68.4%). GBC diagnosis was confirmed by histology in 42.1% cases, while 57.9% were diagnosed based on CT imaging, with 89.5% cases presenting at stage IV. Treatment modalities included surgery (15.8%), chemotherapy (100%), and radiotherapy (7.9%). The mean survival time for VC patients was 5.60 ± 1.80 months and a median survival time of 1.95 ± 0.23 months. The overall 1-year survival rate was 15%.

Conclusion

Gallbladder cancer in this cohort was marked by late-stage presentation, limited surgical treatment, and poor survival outcomes. The 1-year survival rate of 15% highlights the urgent need for earlier diagnosis and improved cancer care in LMICs.

Keywords: Gallbladder cancer (GBC), Clinical and Histopathological Presentation, Survival Outcome, Low-Middle-Income Country (LMIC)

INTRODUCTION

Gallbladder cancer (GBC) is the predominant cancer of the biliary system, accounting for 80–95% of biliary malignancies and positioned as the sixth most prevalent gastrointestinal tumor worldwide (1). According to GLOBOCAN 2018 estimates, there are around 116,000 new cases and 84,700 fatalities each year. There exists significant geographic variation in the incidence of gallbladder carcinoma. Elevated rates of GBC are observed in South American nations, particularly in Chile, Bolivia, and Ecuador, along with certain regions of India, Pakistan, Japan, Korea, and specific African countries (2). In Chile, the mortality rates due to GBC are the highest globally, making it the most prevalent cancer among women and the leading cause of cancer-related deaths in women (2). Conversely, the United Kingdom, Denmark, and Norway report the lowest incidence rates internationally (3).

GBC predominantly affects older adults, with a median age of 60–70 years, and exhibits a higher incidence in females (female-to-male ratio 2:1). Established risk factors include gallstones, gender, age, obesity, reproductive factors, race, primary sclerosis, cholangitis, gallbladder polyps, congenital biliary cysts, typhoid, *Helicobacter pylori* infection, alcohol intake, smoking, fatty liver disease, unhealthy diet, and environmental exposure to specific chemicals (4). GBC often presents with nonspecific symptoms such as right upper quadrant pain, weight loss, jaundice, and fatigue, resulting in delayed diagnosis, frequently at advanced stages (III-IV), and less than 10% of cases are surgically resectable at presentation. Adenocarcinoma (AC) is the most common histologic type in GBC, representing approximately 76% to 90% of cases. Papillary carcinoma (PC) constitutes 5% to 6%, while squamous cell carcinoma (SCC) and adenosquamous carcinoma (ASC) combined constitute 2% to 10% (5).

Evidence has shown that radical cholecystectomy with regional lymphadenectomy and partial hepatectomy is the only potentially curative option, yet most patients present too late for resection (6). Late presentation may be due to a lack of specific symptoms associated with the early disease, aggressiveness of the tumor, or possibly due to the rich lymphatic supply of the gallbladder, which can result in early spread of the disease (7). Surveillance, Epidemiology, and End Results Program (SEER) Database documented 67% (localized), 29% (regional), and 4% (distant-stage disease) survival rates for patients diagnosed with GBC between 2015 and 2021 (8). Results from India indicated a 5-month median survival time for GBC patients between 2019 and 2021 for 1-year (24.4%), 2-year (8.5%), and 3-year (4.5%) (4).

In LMICs, including many SSA countries, survival outcomes remain among the poorest globally due to late presentation, limited diagnostic infrastructure, and inadequate access to specialized care. Pathology services are often under-resourced, further delaying definitive diagnosis and staging (9). This study aims to evaluate the clinicopathological presentation and survival outcomes of GBC in an LMIC.

METHODOLOGY

Study Area

The study area is the MEDSERVE – Lagos University Teaching Hospital (MEDSERVE-LUTH) Cancer Centre, which was established in 2019. MEDSERVE-LUTH Cancer Centre is a specialized cancer treatment centre that offers cutting-edge therapies and a modern approach to cancer care in Africa. Situated within the site of Lagos University Teaching Hospital, it possesses the largest and most experienced oncology team in Nigeria. The treatment centre is equipped with high-quality modern technology, such as linear accelerators, brachytherapy machines, and treatment planning systems. Several treatments are also available at the cancer centre, which include internal and external beam radiation therapy, chemotherapy, and pharmacy treatments.

Study design and data collection

This is a retrospective study using data from the physical and electronic medical record of the MEDSERVE-LUTH Cancer Centre between May 2019 and June 2024. Patient records diagnosed with gallbladder cancer from May 2019 to June 2024 were reviewed. Records were excluded if medical records were incomplete. Among the 44 gall bladder cancer patients identified during the study period, 38 had complete Electronic Medical Record, and 6 cases with inconclusive diagnoses or missing results were omitted from the study. The information collated included age at presentation, sex, presenting symptoms, comorbidities, family history of

cancer, alcohol history, smoking history, histology, stage, metastases, treatment modalities, and outcomes. Patients who had not been seen in the clinic in >3months were contacted to ascertain their status. Survival was determined and calculated as the difference between the date at presentation and the date of death.

Statistical Analysis

Descriptive statistics was used to analyze the clinicopathological features of all patients. Kaplan-Meier survival analysis was used to estimate survival probabilities over time for different variables. The software SPSS Statistics version 27.0 was used for statistical analysis and p-values less than 0.05 was considered statistically significant.

RESULTS

Table 4.1 demonstrates the demographic characteristics of the patients. The mean at which diagnosis occurred was 61.85 ± 10.70 (range from 35 to 82), and most of the population (28, 73.7%) were female. Of the 38 patients, 52.6% fall within the age group of 66 or older, while 36 to 45 years accounted for 3 patients (7.9%). More than half of the patients (25, 65.8%) identified as Christians, and a significant proportion (28, 73.7%) were married. Most patients (22, 57.9%) were identified as Yoruba.

Table 4.1 Demographic Characteristics of Gall Bladder Cancer Patients

Variables	Frequency	Percentage
Age (years)		
36 – 45	3	7.9
46 – 55	9	23.7
56 – 65	6	15.8
66 and above	20.	52.6
Mean ± SD	61.85 ± 10.70	
Sex		
Male	10	26.3
Female	28	73.7
Religion		
Christianity	25	65.8
Islam	6	15.8
Marital Status		
Single	1	2.6
Married	28	73.7
Widowed	4	10.5
Ethnicity		
Yoruba	22	57.9
Igbo	6	15.8
Edo/Delta	7	18.5
Others	3	7.9

Table 4.2 shows the Clinicopathological presentation of the patients. Presenting symptoms observed were abdominal pain (24, 63.2%), jaundice (8, 21.1%), loss of appetite (7, 18.4%), fatigue (6, 15.8%), and weight loss (12, 31.6%). More than half of the patients (24, 63.2%) had pre-existing comorbidities, including hypertension (15, 39.5%), diabetes (8, 21.1%), peptic ulcer disease (5, 13.2%), hypertension & diabetes (6, 15.8%), and hypertension & PUD (1, 2.6%). A history of alcohol consumption was noted in 9 patients (23.7%), 2 patients (5.3%) reported having a smoking history, and 5 patients (13.2%) reported a family history of cancer. Adenocarcinoma was confirmed by histology in 42.1% of cases, while 57.9% were diagnosed based on CT imaging. More than half of the patients (34, 89.5%) were diagnosed at an advanced stage (stage IV), and 2 patients each were stage III (5.3%) and II (5.3%). Metastases were observed in 29 patients (76.3%), the most common site being the liver (26, 68.4%). Other metastatic sites included the lung (9, 23.7%), lung and liver (6, 15.8%), bone (2, 5.3%), and bone and liver (2, 5.3%).

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Table 4.2 Clinicopathological Presentation of Gall Bladder Cancer Patients

Variables	Frequency	Percentage
Abdominal Pain	24	63.2
Jaundice	8	21.1
Loss of Appetite	7	18.4
Fatigue	6	15.8
Weight Loss	12	31.6
Comorbidities	24	63.2
Hypertension	15	39.5
Diabetes	8	21.1
Peptic Ulcer Disease (PUD)	5	13.2
Hypertension & Diabetes	6	15.8
Hypertension & PUD	1	2.6
Smoking History	2	5.3
Alcohol History	9	23.7
Family history of Cancer	5	13.2
Histology		
Adenocarcinoma	16	42.1
Stage		
Stage II	2	5.3
Stage III	2	5.3
Stage IV	34	89.5
Metastatic Site	29	76.3
Liver	26	68.4
Lung	9	23.7
Lung and Liver	6	15.8
Bone	2	5.3
Bone and Liver	2	5.3

Table 4.3 presents the treatment modalities of the patients. Only 6 patients (15.8%) underwent surgery, and 4 (10.5%) underwent cholecystectomy. All patients (38, 100%) received chemotherapy, and 3 (7.9%) received radiotherapy.

Table 4.3 Treatment Modalities of Gall Bladder Cancer Patients

Variables	Frequency	Percentage
Surgery	6	15.8
Cholecystectomy	4	10.5
Chemotherapy	38	100
Radiotherapy	3	7.9

Table 4.4 shows the Kaplan-Meier survival function with a mean survival time of 5.60 ± 1.80 months and a median survival time of 1.95 ± 0.23 months.

Table 4.4 Means and Median for Survival Time

Mean				**Median**			
Estimate	Std. Error	**95% Confidence Interval**		Estimate	Std. Error	**95% Confidence Interval**	
		Lower Bound	Upper Bound			Lower Bound	Upper Bound
5.601	1.802	2.068	9.134	1.950	.232	1.495	2.405

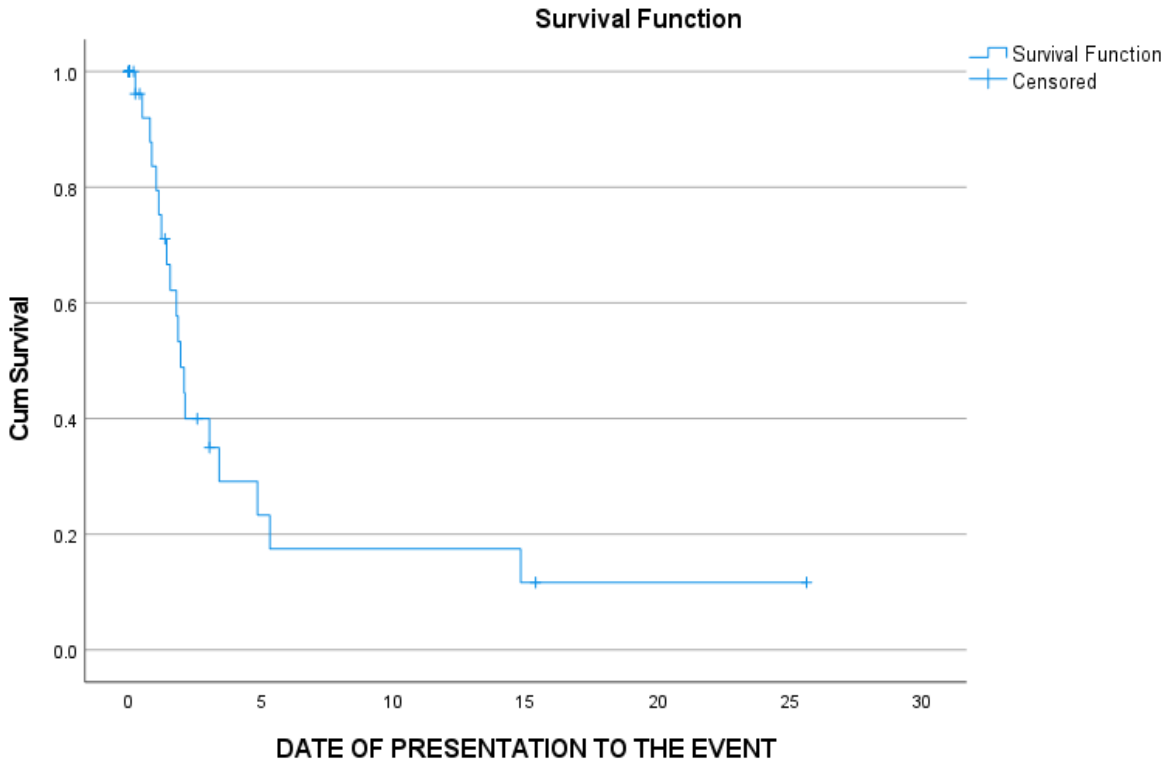

Figure 4.1 Kaplan-Meier survival curve for patients diagnosed with gall bladder cancer

DISCUSSION

This study's mean age at diagnosis was 61.85 ± 10.70, with most of patients (52.6%) above 66 years of age and a few proportions (7.9%) within 36 – 45 years. The mean age for GBC patients was 55 years in Nigeria (10), 51 ± 11 years in India (11), 71.2 ± 12.5 years in the USA (12), and 69 ± 11.5 in Netherlands (13). Previous studies have reported that GBC is common after the age of 60 years (14). GBC rates become more common with age, likely because the disease takes decades to develop (14). Most patients (73.7%) in this study with GBC cases was detected in females. This is consistent with other studies report. Similar findings were also observed in Netherlands (73.2%) (13), Eastern India (75.5%) (15), USA (63%) (16), Nigeria (87.1%) (17), and Nepal (66.7%) (18). Evidence of GBC increases with age, and women are two to six times more at risk than men. Previous studies have reported GBC in the eighteenth and seventeenth years of life as a disease in elderly women with an increased incidence. Women are at increased risk due to fertility, pregnancy, and hormonal factors (19). Research conducted in India showed that GBC predominantly affects women in their forties, and later appears due to a shorter life expectancy (19). The earlier age onset of GBC in Indian women may be due to a genetic factor in their population (19).

Presenting symptoms were mostly abdominal pain, weight loss, jaundice, loss of appetite, and fatigue. This is similar to the results of Alatise *et al.* who observed that most GBC patients complained of abdominal pain, weight loss, and jaundice (17). Another research found that abdominal pain and jaundice were the most frequent complaints of patients (20). Paudyal *et al.* found that abdominal pain, weight loss, and jaundice were the frequent signs and symptoms (18). Another study documented abdominal pain, weight loss, anorexia, nausea, and anemia as the most presenting signs and symptoms (21).

63.2% of patients in this study had pre-existing or newly diagnosed comorbidities, the most of which were hypertension (39.5%) diabetes (21.1%), PUD (13.2%), hypertension and diabetes (15.8%), and hypertension and PUD (2.6%) co-existing. Alatise *et al.* reported 19.4% of comorbid conditions present in patients with GBC in Nigeria and Alkhayyat *et al.* (16) documented a 31.5% rate of diabetes among GBC patients in the USA. Evidence has reported that both hypertension and diabetes are chronic conditions frequently found in cancer patients (22). However, both conditions are not usually life-threatening in the short term, but their co-existence with a malignancy alters the prognosis and suggests the need for more specialized care (22).

The prevalence of alcohol use and smoking in this study population was 23.7% and 5.3%, respectively. This is similar to the results of other studies (16). Cigarette smoking is associated with increased chances of gallbladder cancer (23). Current finding supports a positive relationship between cigarette smoking and the risk of gallbladder cancer, but this relationship needs more investigation (24). Evidence documented that alcohol dose was linearly associated with the risk of gallbladder cancer, but there was no clear association between alcohol consumption and the risk (19). Bagarndi *et al.* found that heavy drinking (<50 γ of alcohol per day) was associated with a RR of 2.64 for GBC (25).

This study documented 13.2% prevalence rate of family history of cancer present in GBC. Findings from this study was lower than the data obtained by Alkhayya *et al* (16) reported a family history of cancer present in 5% of patients in the USA. A family history of gallbladder cancer can increase a person's risk of developing gallbladder cancer (14). Evidence regarding the familial risk of gallbladder cancer has been contradictory. Familial clustering of gallbladder cancer has been noted in some studies (14). Research conducted in Sweden showed that the standardized incidence ratio (SIR) for gallbladder cancer in offspring of parents diagnosed with gallbladder cancer was 2.47 (26). However, results from the Biliary Tract Cancers Pooling Project did not show any association between family history of cancer and gallbladder cancer (27). Multiple genetic mutations have been implicated among gallbladder cancer cases, including *KRAS, P16, c-erb-B2,* and *TP53*. Most are common oncogenes or tumor suppressor genes implicated in many cancers, but it is not clear which are driving mutations unique to gallbladder cancer (14).

In this study, adenocarcinoma was confirmed by histology diagnosis, comprising 42.1%. Similar finding was observed in Nigeria, where Alatise *et al.* documented predominance (100%) of adenocarcinoma. Saha *et al.* found that adenocarcinoma is the predominant (81.3%) histological subtype in India (21). Another study documented a high prevalence rate (73.33%) of adenocarcinoma in Nepal (18). Adenocarcinoma is the most common histological subtype of gallbladder malignancy, contributing 90-95% of all cases (21).

Most patients had locally advanced GBC with Stage IV (89.5%) and Stage III (5.3%) at the time of diagnosis. Stage II (5.3) and Stage I (0%) were less than a quarter of the patient population. Saha *et al.* reported that 45.4%, 25%, and 15.6% were stage IV, III, and II, respectively among GBC patients in India (21) and Alatise *et al.* documented 36.4%, 36.4%, and 27.2% were stage IV, stage III, and stage II, respectively among GBC patients in Ile-Ife, Nigeria (17). Gupta *et al.* found a high rate (71.4%) of stage IV GBC (20).

The treatment pattern in this cohort reflects the advanced stage at diagnosis and the limited availability of curative options in this setting. Only 6 patients (15.8%) underwent surgery, and even fewer (4 patients, 10.5%) had a simple cholecystectomy. This extremely low surgical intervention rate correlates with the high proportion of Stage IV disease (89.5%), where curative surgery is typically not feasible due to unresectability, distant metastasis, or poor performance status (4). In Nigeria, Alatise *et al.* reported a higher surgical resection rate due to late presentation. In comparison, studies from India and China have reported higher rates of surgical management, with 24.4-87.5% of patients undergoing curative resection (4,28). All patients (100%) received chemotherapy, which suggests that systemic therapy comprised the majority of treatment. Nevertheless, chemotherapy in developing countries is largely palliative and not curative, and treatment regimens like gemcitabine-cisplatin offer slight survival benefits of only 3–6 months extension in advanced GBC (1). Lack of surgical candidates also attests to the palliative intent of therapy among this population of patients. Radiotherapy was not commonly used (3 patients, 7.9%), which is consistent with its limited role in the management of GBC, reserved usually for adjuvant treatment after surgery or symptom palliation of local symptomatology such as pain or biliary obstruction (1).

The survival analysis showed a mean survival time of 5.60 ± 1.80 months and a median survival time of 1.95 ± 0.23 months. The overall survival rate (1-year) was 15%. This overall 1-year survival rate was lower than results obtained from Nigeria among GBC patients with overall 1- and 5-year survival rates were 32% and 10% (17), overall 1-, 2- and 3-year survival rates were 69.6%, 55.4%, and 48.8%, respectively in China (29), and 3- and 5-year survival rates were 43.2% and 39.6% in Portugal (30). Findings from India indicated that the median survival duration for GBC patients was 5 months between 2019 and 2021, with a 1-year survival rate of 24.4%, a 2-year rate of 8.5%, and a 3-year rate of 4.5% (4). The low survival rate observed could be due to a combination of delayed diagnosis, aggressive disease biology, limited curative treatment access, and systemic healthcare challenges, which were encountered in this study (1).

CONCLUSION

This study reported that most patients presented with advanced-stage disease and adenocarcinoma. Most presenting symptoms were abdominal pain, weight loss, jaundice, loss of appetite, and fatigue. Moreover, findings also demonstrated predominance of comorbidities, such as hypertension, diabetes, and PUD among GBC patients. The estimated survival time was 15%, due to late-stage diagnosis in many cases. This study indicates the need for earlier diagnosis, better treatment strategies, and supportive care infrastructure to improve outcomes.

List of Abbreviations

LMIC - Low-Middle-Income Country

GBC - Gallbladder Cancer

AC – Adenocarcinoma

PC - Papillary Carcinoma

SCC - Squamous Cell Carcinoma

ASC - Adenosquamous Carcinoma

SEER - Surveillance, Epidemiology, and End Results Program

SSA – Sub-Saharan Africa

PUD – Peptic Ulcer Disease

Statements and Declarations

This research is a unique piece of work resulting from the contributions of multiple researchers in different roles.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Authors Contribution

All authors were involved in the conception and design of the study. Eben A. Aje, Samson Ezekiel, and Toyosi Akerele were responsible for preparing materials, collecting data, and conducting analysis. Aje drafted the initial version of the manuscript, while the other authors provided feedback on earlier drafts. All authors reviewed and endorsed the final version of the manuscript.

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