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PATTERN OF CLINICOPATHOLOGIC PRESENTATION OF GALL BLADDER CANCER PATIENTS AT TIKUR ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA: A RETROSPECTIVE CROSS-SECTIONAL STUDY

BY: ANDUALEM DAGNE (GENERAL SURGEON, HPB FELLOW)

A THESIS SUBMITTED TO THE DEPARTMENT OF SURGERY, SCHOOL OF MEDICINE, COLLEGE OF HEALTH SCIENCES, ADDIS ABABA UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE SUB SPECIALITY CERTIFICATE IN HPB SURGERY

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ADDIS ABABA

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The full title of the research project	The pattern of clinicopathologic presentation of gall bladder cancer patients managed at Tikur Anbessa specialized hospital from April 1, 2018, to March 31, 2023, Addis Ababa, Ethiopia: a retrospective cross-sectional study.
Study period	From April 1, 2023 – June 30, 2023.
Study area	Tikur Anbessa Specialized Hospital(TASH)
Budget	71,434 birr

Declaration

This is to certify that the thesis paper entitled “Retrospective cross-sectional study on pattern of clinicopathologic presentation of gall bladder cancer patients managed at Tikur Anbessa Specialized Hospital from April 1, 2018, to March 31, 2023, Addis Ababa, Ethiopia”, is submitted in partial fulfillment for the subspecialty certificate in Hepatopancreatobiliary surgery in Department of Surgery, Addis Ababa University. It is a record of original work carried out by me and has never been submitted to this or any other institution to get any other degree or certificate. The assistance and help I received during the course of this thesis development is duly acknowledged.

Dr. Andualem Dagne	_____	_____
Name of the candidate	Signature	Date

Approval of the advisor

I hereby certify that I have supervised, read, and evaluated this thesis paper titled “Retrospective cross-sectional study on pattern of clinicopathologic presentation of gall bladder cancer patients managed at Tikur Anbessa Specialized Hospital from April 1, 2018, to March 31, 2023, Addis Ababa, Ethiopia” by Dr. Andualem Dagne prepared under my guidance. I approve this thesis to be submitted for oral defense.

1. Dr Shimelis N (Consultant General and HPB surgeon) _____ _____

   Advisor’s name Signature Date

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Abbreviations and Acronym

ASA	American Society of Anesthesiology
CA 19-9	Carbonic anhydrase 19-9
CEA	Carcinoembryonic antigen
ECOG	Eastern Cooperative Oncology Group
GLOBOCAN	Window-based software ---worldwide database of cancer incidence and mortality
HPB	Hepatopancreatobiliary
SPSS	Statistical Product and Service Solutions
TASH	Tikur Anbessa Specialized Hospital
GBC	Gallbladder Cancer
TNM	Tumor size, Nodal status, and Metastasis
PE	Physical examination
HX	History

Abstract

Background: Gallbladder cancer (GBC) is a rare tumor with a very poor prognosis. It is often incidentally found during routine cholecystectomy for gall stone or diagnosed at the advanced clinical stage at the time of presentation. In Ethiopia, no published data assessed the clinicopathologic presentation and the management approach of patients with gall bladder cancer.

Objective: The main objective of this study was to assess the pattern of clinicopathologic presentation of gallbladder cancer patients managed at Tikur Anbessa Specialized Hospital from April 1, 2018, to March 31, 2023, in Addis Ababa, Ethiopia.

Methods: Facility based retrospective cross-sectional study was conducted on the pattern of clinicopathologic presentation of gallbladder cancer patients managed at Tikur Anbessa Specialized Hospital from April 1, 2018, to March 31, 2023, in Addis Ababa, Ethiopia. Secondary data were extracted from patients' clinical charts and recorded to a pre-tested checklist. Data was entered into epidata version 3.1 and exported to SPSS version 26 for descriptive analysis using frequency tables, mean, median and standard deviations.

Result: During the study period a total 70 gallbladder cancer cases were studied. The mean age at presentation was 56.5 ± 12.2 years and most of the patients were females with a 1.9:1 F: M ratio. The Most (82.9%) common presenting feature was abdominal pain with a median duration of symptoms of 3months (IQR 5.7 months). About 12.8% of patients were found incidentally. Close to half (47.2%) of the patients were having metastasis, with liver involvement accounting for 63.6% and non-regional nodes for 30.3% of metastasis. The remaining 31.4% were resectable and 21.4% of patients were locally unresectable. GB mass lesion is the most frequent imaging feature while gallstones were detected in 50% of cases. Surgical exploration was performed in 35.7% of patients, the rest majority were managed with supportive care (35.7%) and palliative chemotherapy (18.6%). Adenocarcinoma was the commonest histologic type identified (94.4%).

Conclusion: - The prevalence of concomitant gallstones in this study was low compared to other studies. Most of the patients were having either locally advanced or metastatic gall bladder cancer. It requires a high index of suspicion and appropriate imaging in middle age individuals and above who presented with persistent abdominal pain to diagnose gall bladder cancer at the early curative stage

Keywords: Clinicopathologic presentation, Risk factors, Gallbladder Cancer

1. Introduction

1.1 Background

Worldwide, according to GLOBOCAN 2018 data, gall bladder cancer constitutes 1.2% of all cancer diagnoses and 1.7% of cancer-related deaths making it the 22nd most incident (age-standardized incidence rate for women is 2.4 / 100,000, for men 2.2 /100,000) but 17th deadliest cancer. The highest incidence, in descending order, is reported in Bolivia, Thailand, the Republic of Korea, Chile, and Nepal[1,2]. In the USA the incidence is decreasing with the highest rate among American Indians and Native Alaska peoples (3.2/100,000) and it is lower than the global figure (1.4 per 100,000 among women and 0.8 among men). The incidence has marked geographic variation and it affects women three times more than men with a peak age of 60 years[2,3].

The most constantly mentioned risk factor in the pathogenesis of gallbladder cancer is cholelithiasis and chronic inflammation. The majority (75 to 90%) of patients have a history of or coexisting chronic cholecystitis or cholelithiasis. On the contrary, it is only 0.3 to 3% percent of patients with gall stone will have gallbladder cancer [4–6]. The risk of gall bladder cancer increase with stone volume and stone size, the relative risk of developing gall bladder cancer with a stone size more than 3 cm is 10.1 times[7]. Other risk factors mentioned in the literature include obesity, chronic salmonella typhi infection, gall bladder polyp, porcelain gall bladder, anomalous pancreaticobiliary junction, biliary cyst, chemical carcinogens, and smoking[8–11].

Gallbladder cancer tends to be asymptomatic at an early stage. Depending on the facility, as high as 10-47% of patients are diagnosed incidentally after routine cholecystectomy[4,12]. But in most reviews, the majority of patients will present with locally advanced or metastatic disease and only 20-25 % of patients will be diagnosed at the surgically resectable stage. The main clinical feature of the presentation is constant abdominal pain, anorexia, jaundice, and abdominal mass[4,12–14]. Although advanced cases can be diagnosed on ultrasonography or computed tomography (CT) scans, there are no specific laboratory or imaging tests available to make an early diagnosis. Histologically the commonest type is adenocarcinoma[15].

Curative surgical resection remains the only effective approach to the treatment of GBC and systemic chemotherapy plays a role in adjuvant therapy or palliative for unresectable or metastatic disease[16]. Treatment outcome is best when managed at an early stage; with T1 tumor 85-100% and T2 tumor 60-100% 5-year survival respectively. The prognosis is dismal if diagnosed at an advanced stage with a median survival of close to 9 months even with

chemotherapy[17,18]. In Ethiopia, to the best of the researcher`s knowledge, there is no published data that assess the clinicopathologic presentation and the treatment outcome of patients with gall bladder malignancies.

1.2 Statement of the problem

Despite advances in diagnostic evaluation, surgical and oncologic management, and perioperative care, gall bladder cancer remains to have a very poor prognosis. The main reason is the disease is asymptomatic at the early curable stage and the majority (80%) of patients present at advanced stage[19]. Only 1 in 5 gallbladder cancers in the US are diagnosed in the early stages[2]. In Asia where the disease is relatively prevalent, resectability is still low; in India (19.8-30%) and in Pakistan(25%)[4,14,20].

Moreover, there is no effective diagnostic or screening modality available to date that can detect GBC at a curable stage. In search of this, the tumor markers known that are of any potential value are carcinoembryonic antigen (CEA) and carbonic anhydrase 19-9 (CA19-9). CEA is less sensitive (50%) and CA19-9 has 75% sensitivity and specificity at a value greater than 20 IU/ml, thus in the clinical decision it has a limited value[21]. Although advanced cases can be diagnosed on ultrasonography or computed tomography (CT) scans, there are no specific tests available to make an early diagnosis despite recent advances in imaging[4,14].

To recent modern medicine, unless GBC is detected early and managed surgically there is no effective chemotherapy or target therapy. For advanced, untreated gallbladder cancer, the median survival is generally 2 to 5 months and long-term survival is exceedingly rare. However, the overall 5-year survival is 20% with a median survival of just 16 months for patients with resectable disease. The main factor affecting survival in most reviews is the stage at presentation[22].

In sub-Saharan Africa, the limited healthcare resources still pose great challenges to surgeons, especially concerning the ability to successfully diagnose and then treat these patients[23]. Moreover, there is no data assessing the clinicopathologic presentation and treatment outcome. This retrospective cross-sectional study has assessed the clinicopathologic presentation of patients with gall bladder malignancy managed at TASH, Addis Ababa, Ethiopia.

1.3 Significance of the Study

This study has identified sociodemographic patient characteristics, common risk factors, clinicopathologic features at presentation, and the type of management intervention of patients with gall bladder malignancies. Identifying the magnitude of morbidity and mortality of gall bladder mass has paramount importance. Knowing this will aid in better preoperative patient selection and optimization of the associated factors before surgery and provide essential input for both the physician and patient during clinical decision-making.

The finding of this study will be an input in developing evidence-based treatment guidelines in resource-poor settings like our country. It will also influence policymakers and program implementers at national as well as regional levels to set up policy guidelines aiming to improve the management outcome of gallbladder malignancies. Moreover, it can also be used as input for further research and contribute to the expansion of knowledge in the field of HPB surgery.

2. Literature review

2.1 Overview and common risk factors

In 2020, about 115,949 people were estimated to have been diagnosed with gallbladder cancer. This constitutes 0.6 % of all cancer diagnoses making GBC the 25th most commonly diagnosed cancer this year. The estimated incidence was 41,062 for men with an age-standardized incidence rate of 0.9 (per 100,000) and 74,887 for women with an age-standardized incidence rate of 1.4 (per 100,000). Countries with the top five highest age-standardized incidence rates per 100,000 for (males, and females) in 2018 are Bolivia (12.8, 15.1), Thailand (9.0, -the), Republic of Korea (8.4, -), Chile (6.6, 11.1), Nepal (6.0,7.3), Bangladesh(-, 7.3) and Peru(-, 6)[1,24]. In the USA, the incidence is lower than that around the world, with a rate of 1.4 per 100,000 among women and 0.8 among men[1].

Gallbladder cancer is among the few cancers that have a greater proportion of cancer mortality than incidence. While the incidence accounts for 0.6 % of all cancer diagnoses, gallbladder cancer mortality accounts for 0.9 % of all cancer deaths making it the 21st most fatal cancer worldwide in estimated by 2020. Estimated age-standardized mortality rates are 1.4 (per 100,000) in females and 0.7 (per 100,000) in males. The cumulative risk of dying from gallbladder cancer stands at 0.16% for women and 0.07% for men. Overall, over the last 4 decades, both the incidence and mortality rate of gallbladder cancer is deacreasing[1,24].

The most constantly mentioned risk factor in the pathogenesis of gallbladder cancer is cholelithiasis and chronic inflammation. The majority (75 to 90%) of patients have a history of or coexisting chronic cholecystitis or cholelithiasis. On the contrary, it is only 0.3 to 3% percent of patients with gall stone will have gallbladder cancer [4–6]. The risk of gallbladder cancer increase with stone volume and stone size, the relative risk of developing gallbladder with a stone size more than 3 cm is 10.1 times[7]. Other risk factors mentioned in the literature include obesity, chronic salmonella typhi infection, gallbladder polyp, porcelain gallbladder, anomalous pancreaticobiliary junction, biliary cyst, chemical carcinogens, and smoking[8–11]

2.2 Clinicopathologic presentation of GBC

GBC is often asymptomatic at its early stage. In clinical practice, gall bladder cancer will come to clinical attention in one of common three scenarios: (1) diagnosis after pathology confirmation following a routine cholecystectomy for other indication; (2) intraoperative discovery; and (3) diagnosis preoperatively with symptomatology and imaging[25]. As high as 10-20% in developing countries and up to 47% of patients in the West are diagnosed incidentally after routine cholecystectomy[4,12]. But in most reviews worldwide, the majority of patients will present with locally advanced or metastatic disease and only 20-25 % of patients will be diagnosed at surgically resectable stage[12–14].

The main clinical feature of the presentation is constant abdominal pain, anorexia, jaundice, and abdominal mass[4,12–14]. Clinically, the diagnosis of GBC should be considered in an elderly patient with constant right upper quadrant abdominal pain with weight loss or anorexia. The presence of significant weight loss, anorexia, and particularly jaundice and palpable abdominal mass suggests an advanced disease[12,25]. GBC can also have an acute presentation as much as 1% of patients operated on for acute cholecystitis have gallbladder carcinoma[19].

Although advanced cases can be diagnosed on ultrasonography or computed tomography (CT) scans, there are no specific laboratory or imaging tests available to make an early diagnosis. The two clinically available tumor makers for GBC are carcinoembryonic antigen (CEA) and carbonic anhydrase 19- 9 (CA 19-9). But an elevated CEA has 90% specificity but only 50% sensitivity whereas CA 19-9 level > 20 U/mL has up to 75% sensitivities and specificities[25]. Although U/S is the first modality of diagnosis in patients suspected of gall Bladder cancer, CT is better at detecting mass lesions or thickening of the GB wall. CT has a low sensitivity for detecting lymph node metastasis, although its positive predictive value is more than 90%. CT also has low sensitivity for detecting local gastrointestinal and omental infiltration and peritoneal deposits[14]. Histologically the commonest type is adenocarcinoma[15].

In India, a combined retrospective (Jan 2004-March 2010) and prospective study (April 2010-Dec 2011) over a period of eight years, 198 patients of gallbladder carcinoma were studied. In this study, the male-to-female ratio is 1:3 (50 males and 148 females) and the age of the patients ranged from 28-82 years (mean 55 years). The most common presenting features were pain in the right hypochondrium and epigastrium (88.9%) and abdominal mass (76.3%). The symptoms were present for an average duration of 4.8 months before presentation. Ultrasonography revealed gallstones in 86% of patients. Surgical exploration was performed in 130, with gallbladder resection in 60 (including 7 incidental GBC). Adenocarcinoma (87.7%) was the commonest histological type. The study indicates that GBC is common in our scenario. It is a disease of elderly females, and has a strong association with gallstones and every cholecystectomy specimen should be examined histopathologically[14].

In another prospective study in Pakistan that asses clinicopathological features and management of gallbladder cancer between November 1, 1990 and December 31, 1998, prospective data were collected for 233 patients with histologically proven diagnoses. Most patients were women (77%). The mean age was 55 years (±11 years). The majority (69%) had a history of symptomatic gallbladder disease. The commonest presenting symptom was pain (89%), followed by nausea and vomiting (52%), weight loss (42%), and jaundice (33%). One-quarter of patients had a palpable abdominal mass. Most had abnormal hepatic function tests and 58% had elevated carcinoma embryonic antigen levels. Stage ($P < 0.001$), jaundice ($P = 0.01$), and palpable mass ($P = 0.02$) were statistically significant variables. However, on multivariate analysis, the tumor node metastases (TNM) stage was the only factor influencing survival. The median survival of the patients was 44 months for patients with stage I disease, 23 months for stage II, 17 months for stage III, and 6 months for stage IV[4].

2.3 Management Approach and treatment outcome

GBC is one of the malignancies which requires a multimodal approach to its management. Surgery remains the gold standard for curative intent management for tumors presented at the early resectable stage. Several factors need to be taken into account when choosing surgical management in patients with GBC: overall performance status of the patient, the extent of surgical intervention needed to attain tumor negative margin, and post-operative outcomes anticipated[25].

In the early stages of GBC (T1a or less), a simple cholecystectomy, regardless of whether the approach is open or minimally invasive (laparoscopic or robotic), is sufficient with close to 100% 5-year survival rate[26]. In GBC with the T stage of T1b or higher, more radical procedures

are required which depends on tumor extent and adjacent organs involved by the tumor. The extent of radical cholecystectomy may vary from extended cholecystectomy, when the liver margin at the gallbladder fossa is resected, to right hepatectomy or multi-visceral resection[27]. In the phase III randomized trial in Japan, the actual 5-year survival is superior in patients taking adjuvant therapy. Overall, it is reasonable to consider patients with high-risk lesions (i.e., T4 tumors, node-positive, R1 resection) for both neoadjuvant and adjuvant therapy and to offer consultation with a medical oncologist[28].

Unfortunately, the majority of patients present with unresectable or metastatic disease when palliative treatment is the only option. Palliative treatment mainly focuses on addressing common pain, jaundice, and bowel obstruction. Chemotherapy has been used to palliate unresectable diseases and often offers little benefit. However, the emergence of targeted therapies is rapidly changing the treatment paradigm for biliary tract cancer[25].
For advanced, untreated gallbladder cancer, the median survival is generally 2 to 5 months and long-term survival is exceedingly rare. However, the overall 5-year survival is 20% with a median survival of just 16 months for patients with resectable disease. The main factor affecting survival in most review is the stage at presentation, resection margin status, and histologic subtype[22].

2.6 Conceptual framework

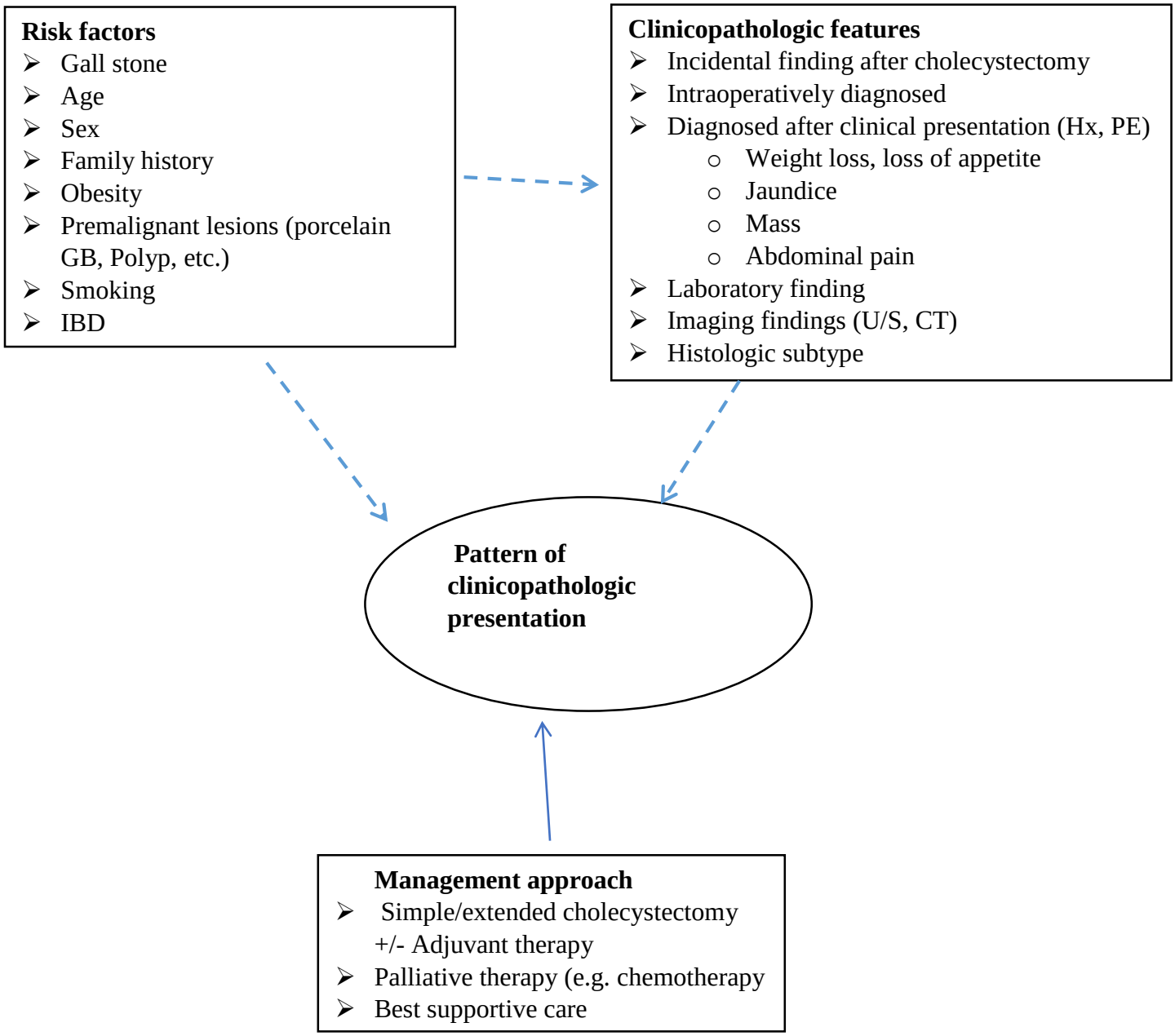

Figure 1: - Conceptual framework for the retrospective cross-sectional study on the pattern of clinicopathologic presentation of gallbladder cancer patients managed at Tikur Anbessa Specialized Hospital from April 1, 2018, to March 31, 2023, Addis Ababa, Ethiopia.

3. Objective

3.1 General Objective

- The main objective of the study was to assess the pattern of clinicopathologic presentation of gallbladder cancer patients managed at Tikur Anbessa Specialized Hospital from April 1, 2018, to March 31, 2023, Addis Ababa, Ethiopia.

3.2 Specific Objectives

- ✓ To describe sociodemographic characteristics and common risk factors of gallbladder malignancies in our setting.
- ✓ To assess the clinicopathologic features of gallbladder malignancies at presentation.
- ✓ To assess the type of management intervention utilized in our setup.

4. Methods and materials

4.1 Study Area and Period

The study was conducted from April 1, 2023 – June 30, 2023. in TASH. It is located in Addis Ababa City, with a projected population size of more than 5.2 million in the Ethiopian Demographic and Health Survey 2016. It is the country's biggest tertiary hospital with around 700 hospital bed capacity. It has specialized care for hepatobiliary malignancies and serves as a referral center from all over the country.

4.2 Study Design

Facility based retrospective cross-sectional study was conducted.

4.3 Population

4.3.1 Source population

All patients with clinically diagnosed gallbladder cancer are managed at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

4.3.2 Study population

All patients with clinically diagnosed gallbladder cancer based on Triphasic CT scan and senior oncologist or HPB evaluation, who were managed at Tikur Anbessa Specialized Hospital from April 1, 2018, to March 31, 2023, Addis Ababa, Ethiopia.

4.4 Sample size determination and sampling procedure

All patients with clinically diagnosed gallbladder cancer based on Triphasic CT scan and senior oncologist or HPB evaluation, who were managed at Tikur Anbessa Specialized Hospital from April 1, 2018, to March 31, 2023, were included in this study. From the registration log book at the surgical and oncologic referral there were ninety-four patients with the diagnosis of gallbladder cancer during the study period, of this seventy patients fulfilled the eligibility criteria and were included in this study.

4.5 Inclusion and exclusion criteria

4.5.1 Inclusion criteria

All patients with clinically diagnosed gallbladder cancer based on Triphasic CT scan and senior oncologist or HPB evaluation, who were managed either surgically or medically at Tikur Anbessa Specialized Hospital from April 1, 2018, to March 31, 2023, Addis Ababa, Ethiopia.

4.5.2 Exclusion criteria

Patients with incomplete documentation, if no CT scan/biopsy confirmation were excluded. Patients with known previous malignancies were also excluded.

4.6 Variables of the Study

4.6.1 Dependent variables

- Pattern of presentation (early at the resectable stage, advanced)

4.6.2 Independent variables

- Socio-demographic characteristics
  - ✓ Sex
  - ✓ Age
- Clinical-related characteristics
  - Incidental finding after cholecystectomy
  - Symptoms and Duration of illness
  - Physical findings at the presentation
    - Jaundice
    - Palpable mass
  - Laboratory investigation
  - Image findings
  - Stage at presentation
  - Histologic type
  - Histologic grade

4.7 Operational Definition and Term Definitions

Gall bladder Cancer: the diagnosis of GBC is made based on contrast-enhanced CT scan conclusion, evaluation of senior oncologist or HPB surgeon +/- biopsy

Resectable GBC: GBC confined to GB, adjacent structures, and regional lymph nodes which is amenable to resection with extended cholecystectomy with or without adjacent visceral resection

Unresectable GBC: GBC involving hilar vascular structures or multiple extrahepatic structures which is not amenable to surgical resection

Extended cholecystectomy: Extended cholecystectomy with resection of segments IVB and V with en bloc regional lymph node dissection. Bile duct resection if the bile duct margin positive

Palliative treatment: any kind of treatment intervention/supportive care for unresectable/ inoperable GBC patents

4.8 Data collection tools and Methods

Retrospective data were collected from the patient's chart and I- care address using a structured pre-tested checklist prepared in the English language. The checklist contains; socio-demographic and clinical characteristics and management approaches prepared from different pieces of literature[4,14,29]. The data was collected by trained Nurses and residents and supervised by the principal investigator.

4.9 Data quality control

Before the actual data collection, data collectors were trained for two days on the general purpose of the study and the procedures to be followed during data collection. The checklist was pre-tested in TASH and was modified and edited based on the findings. During data collection, the principal investigator was checking the data for its completeness and missed information at each point. Furthermore, data were checked during entry and compilation before analysis.

4.10 Data Processing and Analysis

Data was entered into epidata version 3.1 with the necessary precautions and exported to SPSS version 26 for descriptive analysis. Categorical variables were described with frequency tables whereas, continuous variables were described using mean, median, and standard deviation.

4.11 Ethical Consideration

Ethical clearance was obtained from the Institutional Review Board (IRB) of the College of health sciences, Addis Ababa University. The official letters were sought and obtained from the office of Department of Surgery. Confidentiality was secured by avoiding writing the patient's name and making sure that data remained anonymous during analysis and final reporting.

5. Result and Discussion

5.1 Result

5.1.1 Demographic profile of patients

A total of 70 patients were included during the 5-year study period. The mean age was 56.50 ± 12.2 years (Mean ± SD) with a range of 36-90 years, and the most commonly affected patients were 40-60 years 37(52.8%). The Majority of the patients (91.4%) were more than 40 years of age. About 46 (65.7%) of patients were females and 24(34.3) were males with female to male ratio of 1.9 to 1(Table 1).

Table 1: - Demographic characteristics of patients with gallbladder cancer managed at TASH from April 1, 2018, to March 31, 2023, Addis Ababa, Ethiopia

Item			Frequency (%)
Study population			70
Age	Mean age		56.5 ±12.2yr.
	Range		36-90 yr.
	Age distribution	<40yrs.	6(8.6)
		40-60yrs.	37(52.8)
		>60 yrs.	27(38.6)
Sex	Female		46(65.7)
	Male		24(34.3)
	F: M ratio		1.9:1

5.1.2 Clinical Profile of Patients

The majority of the patients (55.7%) present with good performance status (ECOG 0 or 1) which can be a candidate for either surgery or palliative chemotherapy. A significant portion of these patients have a performance status of either ECOG 3 or 4(21.4%). On comorbidity evaluation 28(40%) of patients have known medical comorbidity. DM and hypertension are the two most common comorbidity found in 20% and 17.1% of patients respectively, whereas 10% of these patients had HIV/AIDS. As stated in the table below (Table 2), 38(54.3%) patients had documented risk factors with gall stones found in 35(50%), porcelain gall bladder in 3(0.4%), smoking in 2(0.3%) and IBD and obesity found each in 1 patient.

Table 2: - Clinical profile of patients with gallbladder cancer managed at TASH from April 1, 2018, to March 31, 2023, Addis Ababa, Ethiopia (N=70).

		Frequency	Percent
Performance Status	ECOG 0	11	15.7
	ECOG 1	28	40.0
	ECOG 2	16	22.9
	ECOG 3	12	17.1
	ECOG 4	3	4.3
	Total	70	100.0
Comorbidity	Yes	28	40.0
	DM	14	20.0
	Hypertension	12	17.1
	HIV/AIDS	7	10.0
	COPD/Asthma	2	0.3
	Cardiac disease	2	0.3
Documented risk factors	Yes	38	54.3
	Gall stone	35	50.0
	Porcelain gall bladder	3	0.4
	Smoking	2	0.3
	Others	2	0.3

The clinicopathologic presentation is depicted in the tables below (Table 3-5). The majority of patients in the study (82.9%) were diagnosed with gall bladder malignancy after clinical presentation with symptoms, with a median duration of 3±5.7months (mean 4.27month) before presentation. However, 9(12.8%) were diagnosed incidentally after or during cholecystectomy. The most common presenting clinical symptoms were upper abdominal pain in 58 patients (82.9%), weight loss in 34 patients (48.6%), and loss of appetite in 39 patients (55.7%). Physical findings were present in 39 patients (55.7%), with mild tenderness in 27.1%, abdominal mass in 21.4%, and jaundice in 25.7% of patients. Laboratory investigations revealed elevated bilirubin >1.2 mg/dl (N=49) in 36.7% of the cases, elevated ALP > 270 IU/l (N=56) in 51.8%, and anemia Hg<11g/dl in 15.3% of patients.

Table 3: - Clinical pathologic presentation of patients with gallbladder cancer managed at TASH from April 1, 2018, to March 31, 2023, Addis Ababa, Ethiopia (N=70).

Clinical Characteristics		Frequency	Percent
Incidental after cholecystectomy		8	11.4
Intraoperatively diagnosed		1	1.4
The patient found after extended cholecystectomy		3	4.3
Diagnosed after clinical presentation		58	82.9
Duration of symptoms		Median=3month with IQR of 5.7 months	
Symptoms	Abdominal pain	58	82.9%
	Loss of appetite	39	55.7
	Weight loss	34	48.6
	Nausea and vomiting	24	34.3
	Yellowish discoloration of the eye	18	25.7
	Easy fatigability	11	15.7
	Pruritus	3	4.3
Signs	Any physical finding	39	55.7
	Tenderness	19	27.1
	Abdominal mass	15	21.4
	Jaundice	18	25.7
	Ascites	5	7.1
	Hepatomegaly	11	15.7
Preoperative laboratory	Has documented lab tests	62	88.6
	Bilirubin >1.2 mg/dl (N=49)	18	36.7
	Albumin <3.5 g/dl (N=34)	6	17.6
	Creatinine >1.2 mg/d (N=58)	4	6.9
	Hemoglobin< 10 g/dl (N=59)	9	15.3
	ALP > 270 IU/l (N=56)	29	51.8
	CA 19-9 >35 (N=15)	5	30

Table 4: - Imaging characteristics of patients with gallbladder cancer managed at TASH from April 1, 2018, to March 31, 2023, Addis Ababa, Ethiopia (N=70).

Imaging Characteristics		Frequency	Percent
Appearance	GB mass lesion	49	70.0
	Body	22	31.4
	Fundus	3	4.3
	Infundibulum and neck	8	11.4
	Whole GB	16	22.9
	GB thickening	9	12.9
Resectability status	Locally resectable	22	31.4
	Locally unresectable	15	21.4
	Metastasis	33	47.2
	Liver	21	30.0
	Distant node	10	14.3
	Peritoneum	5	7.1
	Lung	4	5.7
Adjacent organ invasion	No local invasion	3	4.3
	Liver only	48	68.6
	Liver and hilar invasion	18	25.7
	Liver and Colon	1	1.4
Stage	stage I	2	2.9
	stage II	4	5.7
	stage III	16	22.9
	stage IVA	15	21.4
	stage IVB	33	47.1

As stated in the table above (Table 4), among clinically presented patients who had preoperative CT scan (58), 49 patients (84.5%) have gallbladder mass lesions and 9 patients (15.5%) had gall bladder thickening only. The commonest sites of mass lesion were body in 22 patients (37.9%) and the mass involving the entire gall bladder in 16 patients (27.6%). Almost half of the patients (33) were having metastasis (47.2%) with liver and non-regional nodes being the commonest site of metastasis in 63.6% and 30.3% of cases respectively. On preoperative CT scan and pathologic review, the tumor was confined to GB only in 4.3% of the cases, with liver involved in 95.7% of the patients. The tumor has involved the liver hilum in 25.7% of patients. On resectability assessment, in 22 patients (31.4%) the tumor was resectable of these 4 patients were unfit for surgery because of poor performance status and patient comorbidity. Staging of the patients was done according to AJCC TNM 8th edition. Stage I in 2 patients (2.9%), stage II in 4 patients (5.7%), stage III in 16 patients (22.9%), and stage IV in 48 patients (68.5%).

Surgical exploration was performed in 25 patients (37.7%) (including incidentally found gall bladder cancer patients). Eleven patients (15.7%) were managed with extended cholecystectomy with or without adjuvant therapy whereas only biopsy was taken in 4 patients (5.7%) because the disease was found advanced. In those patients who were diagnosed after or during cholecystectomy, 7 patients (10.0%)were having metastasis or hilar invasion and were managed with palliative chemotherapy, and in 1 patient simple cholecystectomy had sufficed. Percutaneous biliary drainage followed by palliative chemotherapy was offered in 2 patients. The rest majority were managed with supportive care (35.7%) and palliative chemotherapy (18.6%) (Table 5). In about 10% of the cases, admission was decided but either the patient lost an appointment or died waiting for surgery.

Half of the patients were having a histologic assessment. Of these, adenocarcinoma was found in 33 patients (94.4%), squamous cell carcinoma in 1 patient (2.8%), and neuroendocrine tumor in 1 patient (2.8%) (Table 5).

Table 5: - Management and their histopathology of patients with gallbladder cancer managed at TASH from April 1, 2018, to March 31, 2023, Addis Ababa, Ethiopia (N=70).

Item	Type of management	Frequency	Percent
After cholecystectomy/ Intra-op diagnosis	Simple cholecystectomy lone	1	1.4
	Simple cholecystectomy followed by palliative chemotherapy	7	10.0
	SC followed by Extended cholecystectomy	1	1.4
After EC	EC + adjuvant therapy	3	4.3
Clinically diagnosed	Exploration and biopsy	4	5.7
	Extended cholecystectomy and adjuvant therapy	7	10.0
	Palliative chemotherapy	13	18.6
	Biliary drainage and palliative	2	2.8
	Best supportive care	25	35.7
	Admitted but not operated(1 for bypass and 6 for EC)	7	10.0
Histologic type			
Histopathology	Not done or documented	35	50.0
	Adenocarcinoma	33	47.1
	Squamous cell carcinoma	1	1.4
	Neuroendocrine tumor	1	1.4
	Total	70	100.0

5.2 Discussion

Gallbladder cancer is among the few cancers that have a greater proportion of cancer mortality (0.9 % of all cancer deaths) than incidence (0.6 % of all cancer diagnoses) with both showing decrement, in 2020 worldwide estimate[1,24]. It has marked geographic variation with the highest incidence in Bolivia and the lowest reported in USA[1,24]. This study is a 5-year review which evaluates the demographic and clinicopathologic profile of gallbladder cancer cases from April 1, 2018, to March 31, 2023, who are managed at our institution located in the capital and is a referral center for the entire country.

Gallbladder cancer is a disease of the elderly, its incidence increases with age which plateaus at 60 years. In this study, the mean age of presentation was 56.5±12.2 years and most of the patients (52.8%) were in the age range of 40-60yr and 38.6% of patients were above the age of

60 years. This is comparable with studies in developing countries but younger than in Western data whose median age is 67 years[4,12,14,29]. Worldwide, gall bladder cancer is 2-6 times more common in females than males[4,12,14,29]. This is also true that in this particular study, the female to male ratio is 1.9 to 1 which is comparable to other studies in developing nations (Hamdani et al, 2012; Dubey et al, 2018; Malik et al, 2002) where it was reported to be 1:3, 1:3.5 and 1: 3.4 respectively.

The most constantly mentioned risk factor mentioned in literature in the pathogenesis of gallbladder cancer is cholelithiasis and chronic inflammation (70-90%). In our study, gall stones were identified in 50% of patients which is quite low compared to other studies. Other studies from India reported the presence of gallstones in 86% (Hamdani et al, 2012) and 62% (Dubey et al, 2018). Another study from Pakistan also reported presence of a gallstone in 69% whereas from USA reported gallstone rate of 88%[4,14,29,30]. The low prevalence of stone disease in this study may be due to poor documentation or another unidentified risk factor in the pathogenesis, moreover, 20% of patients in this study had diabetes which is higher than other studies[29], and 10% of patients were a known HIV/AIDs patient[31].

Often gall bladder cancer is asymptomatic at presentation or presents with very non-specific symptoms. As high as 10-20% in developing countries and up to 47% of patients in the West are diagnosed incidentally after routine cholecystectomy[4,12]. In this study, 12.8% of the patients were diagnosed after or during cholecystectomy which is consistent with other studies in developing countries[4,12]. Most (82.9%) of patients in our study present with signs and symptoms with a median duration of 3 months (with IQR of 5.7) (mean 4.27 months). Upper abdominal pain (82.9%), weight loss (48.6%) and loss of appetite (55.7%) were the most common presenting features. Physical findings were present in 39 patients (55.7%), with mild tenderness in 27.1%, abdominal mass in 21.4%, and jaundice in 25.7% of patients. Consistent results were reported in other studies in India, Pakistan and USA where symptoms and signs were comparable to this study. In an Indian study(Hamdani et al, 2012), most of them(89%) were symptomatic at presentation with abdominal pain being the commonest symptom and jaundice in 1/3rd of the patient and the average duration of symptoms was 4.7 month[4,12,14,30]. But, the incidence of jaundice is higher in previous studies which reach to 51.5%[14,29].

The laboratory workup in this study revealed anemia (hemoglobin, < 10 g/dl) in (9/59)15.4%; elevated levels of alkaline phosphatase (> 270 IU/ ml) in (29/56) 51.8% of the patients and hypoalbuminemia in (6/34)17.6% of the patients. The prevalence of anemia is low whereas the

elevated ALP and hypoalbuminemia rates were comparable with another study(Hamdani et al, 2012)[4,14].

But in most reviews worldwide, the majority of patients will present with locally advanced or metastatic disease and only 20-25 % of patients will be diagnosed at surgically resectable stage[12–14]. The data in our study, on preoperative CT scan and pathologic review, showed that 47.2% of the patients were having metastasis, with liver involvement accounting for 63.6% and non-regional node 30.3% of metastasis. 31.4% were resectable and 21.4% patients were locally unresectable. This is true also in other studies[4,12,14]. The resectability rate was 27.94% and 30.3% in Dubey et al, 2018 and Hamdani et al, 2012 respectively and the respective metastasis rate was 72% and 57.1% with liver and distant nodes being the commonest site of metastasis [14,29]. In another study in Pakistan, more than half of the patients (56.2%) have distant metastasis[4].

In previous Indian studies, 16.18% and 5% of the patient had an early stage disease (Stage 1 and 2), and the rest 83.8% and 95% of the patients had locally advanced/metastatic disease which is comparable with what we found in our study, 8.6% were early stage and the rest were locally advanced or metastatic[29,32]. Moreover, in our study, the tumor was confined to GB only in 4.3% of the cases, with liver involved in 95.7% of the patients.

Among clinically presented patients who had preoperative CT scan (58), gallbladder mass lesion was the most common imaging feature in 84.5% of the cases followed by gallbladder thickening in 15.5% of the cases. GB body is the commonest site of the mass lesion (37.9%). A Similar rate was observed in another study in India, where GB mass lesion is the commonest imaging feature found in 80% of the cases, with GB body being the comments site, followed by GB thickening found in 13.3% of the cases[14]. However, a study in the West showed asymmetric wall thickening in 45% of patients, a mass replacing the gallbladder in 35%, and an intraluminal mass in 20%[33].

In the present study, surgical exploration was performed in 25 patients (35.7%) (including incidentally found gallbladder cancer patients). Of this, in 4 out of 11 patients (36.4%) patients, the disease was advanced, and exploration and biopsy were done. In the previous study in India by Hamdani et al, 2012, surgical exploration was done in 65.6% of the patients, and of this number, the majority of the patients (53.8%) had undergone only biopsy with or without biliary drainage[14]. The accuracy of CT in predicting resectability in this study is lower than to studies[33]. The rest majority were managed with either supportive care (35.7%) or palliative

chemotherapy (18.6%) which is consistent with other studies[12,14]. In about 10% of the cases, admission was decided but either the patient lost an appointment or died waiting for surgery.

Adenocarcinomas are the most frequent histological subtype of malignant gallbladder neoplasms, representing approximately 90-95% of all cases. In this study, histopathology revealed adenocarcinoma in 94.4% of the cases, squamous cell carcinoma in 1 patient (2.8%) and neuroendocrine tumor in 1 patient (2.8%) which is comparable with the result of other studies[12,14].

Limitations of the study

This study was institutionally based retrospective cross-sectional in nature and is based on I care and chart review, it lacks very important variables including investigations and outcomes. Survival analysis was difficult to do.

6. Conclusion and Recommendation

6.1 Conclusion

Although gallbladder cancer is relatively a rare disease, a high index of suspicion is vital for the diagnosis at an early curable stage. In this study, most of the patients were females and in age range between 40- 60 years. The prevalence of concomitant gallstone in this study was low and we have found that the rate of diabetes and HIV/AIDS was high. The median duration of symptoms was 3 months (IQR 5.7 month) and upper abdominal constant abdominal pain was the most frequent symptom. Most of the patients were having either locally advanced or metastatic gallbladder cancer, liver, and distant nodes were the most common site of metastasis. However, 1/3rd of the patients were having resectable tumor. GB mass lesion is the most frequent imaging feature on CT scan with an accuracy of CT scan in predicting resectability was 63.6%. The most common histologic type was adenocarcinoma.

6.2 Recommendation

It requires a high index of suspicion and appropriate imaging in middle age individuals and above who presented with persistent abdominal pain to diagnose gallbladder cancer at the early curative stage. It is also essential practice to routinely evaluate cholecystectomy specimens and subject it to histopathology when necessary to detect incidental cancers. Since this is a retrospective study, we recommend a prospective study to evaluate the outcome of GBC management in the country. At the ministry level cancer registry is important to study the burden and trend of GBC in particular and the entire cancers in general.

7. Reference

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Annex I: English Version Checklist

S/N	Items	Response	Remark
PREOPERATIVE PATIENT STATUS			
1.	Sex	1. Male 2. Female	
2.	Age(in years)	_____ years	
3.	Performance status	1. ECOG……	
4.	Comorbidity	A. No B. Yes 1. Hypertension 2. Cardiac disease a. Ischemic heart disease/cardiomyopathy b. Dysrhythmia c. Valve disease 3. Diabetes mellitus 4. COPD/asthma 5. Peripheral vascular disease 6. Preoperative chemotherapy 7. Other	
5.	Risk factor assessment	8. No documented risk factor identified 9. Gallstone 10. Age 11. Sex 12. Family history 13. Obesity 14. Premalignant lesions (porcelain GB, Polyp, etc.) 15. Smoking 16. IBD 17. Others (specify)	
6.	Method of presentation	1. Incidental finding after cholecystectomy 2. Intraoperatively diagnosed 3. Diagnosed after clinical presentation	

7.	Duration of symptoms at presentation	1. Days……. 2. Weeks……... 3. Months…….	
8.	Symptoms	1. Asymptomatic (incidental finding) 2. Abdominal pain 3. Anorexia 4. Dyspepsia 5. Weight loss 6. Jaundice 7. Nausea and vomiting 8. Malaise 9. Pruritus 10. Other(specify)	
9.	Signs	1. No finding 2. Abdominal mass 3. Tenderness 4. Icterus 5. Ascites 6. Cachexia 7. Fever	
10.	Preoperative tests	Bilirubin___ Albumin _____ Creatinine _____ Serum ALP _____ Hemoglobin ……. CEA…… Ca19-9……..	NB it binomial data
11.	Imaging finding	1. Site and appearance of lesion a. GB mass lesion i. Body	

		ii. Fundus iii. Infundibulum/Neck iv. Whole GB b. GB Wall Thickening only c. Area couldn't be specified 2. Sign of unresectability a. Distance Mets (liver, lung, peritoneum) b. Adjacent organ invasion(specify) 3. US evidence of stone	
12.	Resectability status	1) Resectable 2) Unresectable 3) Inoperable	
13.	Type of management intervention	1. Simple cholecystectomy 2. Extended cholecystectomy 3. Biliary drainage (percutaneous, Endoscopic) 4. Adjuvant chemotherapy 5. Palliative chemotherapy 6. Best supportive care	Single patient can have multiple management
14.	Biopsy finding	1. Adenocarcinoma a. Moderately differentiated b. Poorly differentiated c. Well differentiated 2. Papillary adenocarcinoma 3. Mucinous adenocarcinoma 4. Squamous cell carcinoma 5. Adenosquamous carcinoma 6. Other(specify)	
15.	AJCC stage(TNM) if patient has biopsy	1. …….	8th edition