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ORIGINAL ARTICLE

Clinical presentation and management modalities of gallbladder cancer in Sudan: A single-center study

Khatab M. Adam,* Elfatih Yousif Abdelrahim,* Wael Mohialddin Doush*,† and Muataz S. Abdelaziz†

*Department of Gastroenterological Surgery, Ibn Sina Specialized Hospital and †Department of Surgery, Faculty of Medicine and Health Sciences, Omdurman Islamic University, Khartoum, Sudan

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Correspondence
Dr. Wael Mohialddin Doush, MD, MRCSEd, Assistant Professor of General Surgery, Consultant Surgeon, Faculty of Medicine and Health Sciences, Omdurman Islamic University, Department of Gastroenterological Surgery, Ibn Sina Specialized Hospital, P.O.Box 7597, Khartoum 11123, Sudan.
Email: dr.wael.doush@gmail.com

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Abstract

Background and Aim: Gallbladder cancer (GBC) is a rare and highly aggressive malignancy characterized by late presentation of nonspecific symptoms, poor curability, and high mortality. The gold standard for effective treatment depends on early detection and surgical excision. Hence, the aim of this study was to determine the patterns of clinical presentation and management modalities to reach excellent practice.
Methods: A retrospective study was conducted during the period from May 2021 to April 2022 at Ibn Sina specialized hospital, Khartoum, Sudan, on 50 patients with GBC who underwent a preoperative clinical and radiological evaluation to enable the use of appropriate surgical and oncological approaches.
Results: GBC was more prevalent in females in this series where all had GBC (68%), in the ratio 2:1. Distribution of patients according to age ranged between 61 and 75 years, representing 44% of patients. Abdominal pain, nausea, and vomiting were present in 40% of patients. Fifty-six percent of patients resided in urban areas. Transabdominal ultrasound (TUS) with CT scan diagnosed GBC in 54% of patients. GBC was metastatic (stage IV) in 52% of patients. Based on preoperative decision by a multidisciplinary team (MDT), 62% of patients had palliative nonsurgical oncological treatment. Histopathological analysis of the resected GBC showed adenocarcinoma in 74% of cases. The inoperable patients (42%) were treated palliatively with endoscopic retrograde cholangiopancreatography/systemic chemotherapy. Finally, the overall mortality rate was 56%.
Conclusions: Accurate early clinical diagnosis and advanced radiological modalities with curative surgical approaches including clear surgical resection margins and systemic oncological therapies will potentially help in improving GBC survival outcomes.

Introduction

Gallbladder cancer (GBC) is a rare and highly aggressive malignancy (1.2%) characterized by either diffuse thickening of wall or mass arising from any part of the gallbladder. Its incidence worldwide is 2/100,000 individuals, and it accounts for 1.7% of all mortalities due to cancer. It is found mainly in south-east Asia (particularly Thailand) and in Latin America (particularly in Peru and Bolivia).[1,2] Moreover, in the United States, the overall GBC incidence is estimated to be 1.5/100,000 residents.[3] It represents the fifth common cancer of the gastrointestinal tract and the most common cancer of the biliary tract (80%–90%).[4] Most reported incidences occur after the seventh decade of life, and it is more common in the White Caucasian population. The incidence is 2–3 times more in females than males due to prolonged hormonal influences and recurrent pregnancies, which raise bile cholesterol to develop gallstones. Also, in native American females with gallstones, the incidence of GBC is 7.1/100,000 cases.[3,5–8] The associated risk factors for GBC are symptomatic nontreated cholelithiasis for 20 years (70%–94%), chronic gallbladder infections (e.g., salmonella), gallbladder polyps, porcelain gallbladder, obesity, radiation, special chemicals (vinyl chloride), heavy metals, drugs (isoniazid, oral contraceptives), tobacco, alcohol consumption, and genetic alterations (including *KRAS*, *TP53*, and *c-ERB-B2* mutations). The latter are associated with poor prognosis.[5,8–12]

Over 90% of GBC are adenocarcinomas in histopathological analysis. GBC location is found to be 60% in the fundus, 30% in the body, and 10% in the neck of the gallbladder.[2,4] Furthermore, GBC is mostly diagnosed incidentally at the advanced disease stage because of late presentation of nonspecific symptoms. Although proper imaging modalities and professional multidisciplinary team (MDT) help are available, the disciplinary referral and management protocols have not been established in most areas of Sudan.

The aim of this study was to determine the patterns of clinical presentation and management modalities of GBC in Sudanese patients to reach excellent practice at Sudanese national surgical centers.

Clinical presentation of gallbladder cancer. The clinical presentation of the GBC is often vague and nonspecific, which is related to the pathologic progression and dismal prognosis at the time of diagnosis. Moreover, Pitt *et al*. found four strong factors associated with incidental GBC at cholecystectomy: female gender, age ≥65 years, Asian or African American ethnic group, and increased serum alkaline phosphatase.[13] Pain in the right hypochondriac region is the most common symptom presented in 72%–77% of cases. Frequently, this pain is characterized by intense paroxysmal attacks radiating to the right shoulder tip, with respiratory inhibition.[14] Nausea and vomiting are found in 20%–49% of cases. Clinical examination is variable: normal at the early stages, cancerous gallbladder mass in 15%–50% of cases, and right hypochondrial tenderness in 50%–80% of cases.[15] Moreover, jaundice was observed in 58% of cases secondary to tumor invasion, extrinsic compression of the bile ducts by lymphadenopathy, and liver metastases.[16] Weight loss, anorexia, and jaundice were considered signs of advanced disease. Furthermore, Hawkins *et al*. reported that localized GBC with jaundice will worsen the outcome.[17]

Preoperative diagnostic evaluation that assists in the detection of gallbladder cancer

Relevant laboratory tests.

- Liver function tests: Elevated alkaline phosphatase and bilirubin levels were found to be more prevalent with advanced disease.
- Renal function tests, serum electrolytes, and urinalysis: Kidney function is assessed prior to performing a contrast-enhanced CT scan.
- Complete blood count for anemia detection: It gives an indication of more advanced disease.
- Tumor markers are weak screening predictors for GBC. Carcinoembryonic antigen (CEA) lacks sensitivity (50%) when used as a screening test for GBC. Cancer antigen 19-9 (CA 19-9) >20 U/ml is sensitive and specific up to 75%. Moreover, serum CEA and CA 19-9 levels are considered weak screening predictors for GBC in the literature. They are useful in patient follow-up and earlier detection of recurrence. Hence, new, promising biomarkers with higher sensitivity and specificity need to be found.[18,19]

Radiological imaging studies. Transabdominal ultrasonography (TUS) is the first modality of choice for GBC imaging but its overall accuracy for staging is limited. Ultrasonography findings include protruding mass in the gallbladder lumen, loss of interface between the gallbladder and the liver, direct liver infiltration, gallbladder polyps ≥10 mm, and calcification and abnormal thickening the gallbladder wall.[20] Additional imaging necessary to complete GBC staging work-up is abdominopelvic CT scan, which is the most accurate radiological test. It can determine surgical resectability with sensitivity 37%–73% and specificity 75%–91% and has an overall accuracy of 87%. This modality evaluates peritoneal implants and the extent of cancer invasion into liver parenchyma, hepatic artery invasion, portal vein invasion, and regional lymph involvement.[21,22] Moreover, magnetic resonance cholangiopancreatography (MRCP) has a reported sensitivity of 91% and specificity of 87% for detection of direct GBC extension into the liver and biliary obstruction by giving anatomical details of the biliary tree.[23,24] Endoscopic ultrasonography (EUS) has a reported sensitivity of 73% for the GBC diagnosis and it is more accurate than TUS in providing high-resolution images of the gallbladder layers and staging of the GBC extension.[25] Positron emission tomography (PET) scan is still useful for distant metastasis in spite of low sensitivity (73%) in imaging peritoneal carcinomatosis.[26] Currently, the TNM staging system of the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) is the standard classification for the staging of GBC (Table 1).[27]

Table 1 Staging system information of the GBC.

Stage no.	Stage information
Stage I	GBC limited to the lamina propria.
Stage II	GBC invading the muscular tissues without extension beyond the serosa or into the liver.
Stage III	GBC extending beyond the serosa with invasion of the liver and other adjacent organs (intraperitoneal metastasis).
Stage IV	GBC invading the major blood vessels with lymph nodes along it or two or more organs outside the liver.

Treatment modalities of GBC

Patterns of surgical interventions. GBC needs accurate multimodal treatment approaches. Therefore, surgical resection remains the only gold standard option to reach optimal curative point depending on the cancer extent, tumor location, and procedure type that lead to radical excision without residual disease. Surgical options are classified into curative and palliative.

Curative surgical procedures for GBC. Because of its rare incidence, GBC is often discovered incidentally, with a majority of cases discovered postoperatively on pathological analysis rather than intraoperative diagnosis which is estimated at 0.28%.[28] Hence, re-operative radical resection is recommended for stage T-1b and above. In addition, if carried out within 4–8 weeks after initial cholecystectomy, it will give the best survival rate.[29] For cases with stage T-b1 tumors, wedge resection of 2–3 cm margin is required. For T2 and T3 tumors, segment IV-b and V resection with lymphadenectomy around the hepatoduodenal ligament is recommended.[30] Furthermore, re-operation still has very poor prognosis.[31] Stage I GBC is when

cancer is limited to the lamina propria. It is usually identified incidentally after cholecystectomy for gallstone. This approach of simple cholecystectomy is the best treatment option giving 85.9% 5-year survival rate when the muscular layer is not invaded.[32,33] Stage II GBC is defined as malignant tumor invading the muscular tissues without extension beyond the serosa or into the liver. Then, radical cholecystectomy is recommended, extending from liver margin at the GB fossa to involve the right hepatic lobe including segment IV-b/V and lymphadenectomy for six lymph nodes at least (Fig. 1). This surgical technique results in 56% 5-year survival rate.[32,34] Stage III GBC extending beyond the serosa with invasion of the liver and other adjacent organs is considered as intraperitoneal metastasis. Then the surgical plan consists of complete cancerous radical excision including extended right hepatectomy with the possibility of caudate lobectomy, lymphadenectomy, and resection of the involved organs. For patients who can tolerate this extensive surgical approach, 5-year survival rates can reach up to 19.2%.[3,32]

Palliative treatments. When GBC invades the major blood vessels with lymph nodes along it or two or more organs outside the liver, then this is described as typical unresectable stage IV GBC and requires palliative procedures such as bilio-digestive anastomosis to bypass biliary and intestinal obstruction.[28] Surgical biliary drainage usually allows prolonged palliation and results in 5-year survival rates of up to 14.1%. The median survival for cases with unresected distant metastasis is between 1 and 3 months. Most commonly, death occurs as a result of biliary sepsis or liver failure.[3,5]

Chemoradiotherapy treatments of GBC. This oncological therapy option has had a very low therapeutic impact because the majority of the GBC patients are diagnosed at an unresectable stage with loco-regional or distant recurrence in 75% of cases.[35] Moreover, the recurrence rates are variable as follows: distant in 52.6%–79.8%, loco-regional in 33.9%–79.2%, and both in 18.9%–50% of cases.[36] Hence, neoadjuvant or adjuvant therapy in MDT protocols is valuable.[37] Chemotherapeutic regimens for GBC in the neoadjuvant setting include gemcitabine/cisplatin, gemcitabine/oxaliplatin, and capecitabine/oxaliplatin, and combinations of gemcitabine, capecitabine, and 5-fluorouracil can inhibit cell proliferation and promote apoptosis. The American Hepato-Pancreato-Biliary Association supports the use of neoadjuvant therapy for GBC with clinical T3/T4/N1 stages. On the other hand, other international studies have analyzed 474 patients and found insufficient data to support routine neoadjuvant therapy for advanced GBC.[28,38] Furthermore, there are randomized controlled trials (RCTs) in the literature that adopted the use of gemcitabine- and fluropyrimidine-based adjuvant chemotherapy.[39] Another recent phase III BILCAP RCT found adjuvant capecitabine as a reference regimen in resectable GBC.[40] A more recent study has reported the safe and effective outcome of combined oxaliplatin and gemcitabine adjuvant regimen in the improvement of 3-year disease-free survival, hepatic metastases-free survival, and overall GBC survival post recurrence after curative intent for second and third GBC stages.[41]

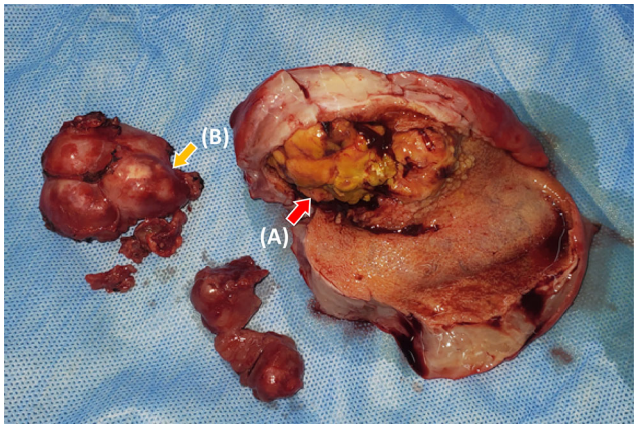

Figure 1 Postoperative photo of (a) radical open cholecystectomy for GBC (stage II) with (b) lymphadenectomy.

Immunotherapy for GBC. Unresectable metastatic GBC needs preoperative evaluation and biopsy for diagnostic confirmation. Advanced GBC has molecular alterations that need immunotherapy interference.[28,42] Pembrolizumab is a monoclonal antibody against PD-L1. In several advanced cancers, it has shown long-lasting antitumor activity and low toxicity. A recent study reported better response of pembrolizumab when there is high PD-L1 expression.[43]

Methods

This is a retrospective, observational, analytic, cross-sectional, hospital-based study conducted during the period May 2021 to April 2022. The study received no funding and was conducted in the gastroenterological surgical department of Ibn Sina Specialized Hospital, Khartoum, Sudan. Before the study commenced, ethical approval was obtained from the local research ethics committee of the Faculty of Medicine and Health Sciences, Omdurman Islamic University, at the committee meeting 179 held on March 15, 2021. A written consent was taken from the participants. Data in this study, including demographic characteristics, clinical presentation, provisional diagnosis, modalities of investigation, indications for surgical approaches, risk factors of GBC, and postoperative complications, were collected through a questionnaire. Inclusion criteria were the following: Sudanese patients aged 15–75 years or more of either sex who were clinically diagnosed as having GBC as confirmed by TUS and MRCP. Then, variable stages of GBC were found, as revealed by an abdominopelvic CT scan with IV and water-soluble contrasts. These patients underwent various surgical modalities ranging from simple open cholecystectomy to extensive surgical resections. Exclusion criteria included the following: laparoscopic cholecystectomy, biliary trauma, bilio-enteric fistula, and other hepatobiliary cancers; also excluded were patients with incomplete records, those who were admitted outside the time duration of the study, and those with any other co-morbidity that precluded general anesthesia (GA). The clinical details of all patients included in this study were entered into a spread sheet (Excel 2016 for Windows software). This data was statistically analyzed by the authors using the program Statistical Package for Social Sciences (SPSS) version 26. The results were considered

Table 2 Age distribution of GBC patients.

Age (Years)	Frequency	Percentage	*P*-value
16–30	2	4%	<0.05
31–45	5	10%	<0.05
46–60	18	36%	<0.05
61–75	22	44%	<0.05
>75	3	6%	<0.05
Total	50	100%	

Table 3 Clinical presentation patterns of GBC.

Clinical presentation of GBC	Frequency	Percentage	*P*-value
Abdominal pain, nausea, and vomiting	20	40%	<0.05
Scleral icterus and weight loss	17	34%	<0.05
Abdominal pain with right hypochondrial mass	13	26%	<0.05
Symptoms of distal metastasis	0	0	
Total	50	100%	

significant when the *P*-value was <0.05 using Chi-square statistical tests.

Results

GBC is a rare and highly aggressive malignancy. Therefore, only 50 patients were included in this study. These patients were diagnosed with GBC, some of them having undergone elective open surgical resection. Thirty-four patients were females (68%) and 16 were males (32%) with the ratio 2:1 (*P*-value <0.05). The distribution of patients according to age ranged from 61 to 75 years (elderly age), representing 22 (44%) patients (*P*-value <0.05) (Table 2). Abdominal pain, nausea, and vomiting were present in 20 patients (40%). Scleral icterus with highly dark colored urine, weight loss, and itching were found in 17 patients (34%). Abdominal pain associated with right hypochondrial mass was found in 13 patients (26%). There was no clinical distant metastatic presentation in any case in this study (*P*-value <0.05). No patient with GBC (100%) in this study had a previous family history of the disease (Table 3). Twenty-eight patients (56%) resided in urban areas, while 22 patients (44%) resided in rural areas. TUS, abdominopelvic CT scan, and MRCP were done in all patients as preoperative diagnostic tests. TUS with CT scan diagnosed GBC in 27 patients (54%), while TUS, CT scan, and MRCP were carried out in 13 patients (26%). Ten patients (20%) had CT scan with MRCP (*P*-value <0.05) (Table 4). Based on the tests, GBC in this study group was staged as follows: metastatic stage (IV) in 26 patients (52%); locally advanced stage in 15 patients (30%); and local stage in 9 patients (18%) (*P*-value <0.05) (Table 5). On the basis of preoperative MDT decision, 31 patients (62%) had palliative nonsurgical oncological treatment. Radical open cholecystectomy was performed in eight patients (16%), while seven patients (14%) had simple open cholecystectomy. Intraoperatively, four patients (8%) were discovered to have unresectable disease (*P*-value <0.05) (Table 6).

Table 4 Gallbladder cancer diagnostic imaging tools.

Diagnostic imaging tools	Frequency	Percentage	*P*-value
TUS/CT scan	27	54%	<0.05
TUS/CT scan/MRCP	13	26%	<0.05
Abdominopelvic CT scan/MRCP	10	20%	<0.05
Total	50	100%	

Table 5 Gallbladder cancer staging categories.

Staging type	Frequency	Percentage	*P*-value
Metastatic (stage IV)	26	52%	<0.05
Locally advanced (stage III)	15	30%	<0.05
Local (stage I & II)	9	18%	<0.05
Total	50	100%	

Table 6 Surgical choices to GBC patients for survival rate improvement.

Diagnostic imaging tools	Frequency	Percentage	*P*-value
Preoperative MDT decision for palliative treatment for GBC (stage IV)	31	62%	<0.05
Radical open cholecystectomy with lymphadenectomy for GBC (stage III)	8	16%	<0.05
Simple cholecystectomy for GBC (stage I & II)	7	14%	<0.05
GBC unrespectable intraoperatively (stage IV)	4	8%	<0.05
Total	50	100%	

Histopathological analysis of the resected GB tumors showed adenocarcinoma in 37 cases (74%) and cholangiocarcinoma in 13 cases (26%). Our patients had variable postoperative prognoses. Inoperable patients with GBC in this study were treated palliativelly with ERCP/systemic chemotherapy (21 patients, 42%), systemic chemotherapy sessions (17 patients, 34%), and percutaneous transhepatic biliary drainage (PTBD)/systemic chemotherapy (12 patients, 24%) (*P*-value <0.05). Finally, the overall mortality rate was 28 (56%). All of them with metastatic inoperable GBC (stage IV) died within 5 months of regular follow-up after diagnostic confirmation.

Discussion

GBC is an aggressive, highly lethal, silent cancer characterized by late presentation of nonspecific symptoms. This related to low quality of health services with deficient diagnostic tools, resulting in significant delay of GBC diagnosis. Curative surgery is not always feasible and palliative therapy is sometimes the only option. Hence, the aim of this study was to describe the clinical presentation, accurate diagnostic tests, and appropriate treatments of GBC. Our study showed that GBC was more common in female patients (68%). The female-to-male ratio is 2:1. This is

consistent with the literature, where GBC had a marked predominance in women by 2–3 times over men worldwide, especially in Thailand, Peru, Bolivia, and native America.[1–3] This is related to the long-term influences of estrogen and progesterone sex hormones during recurrent pregnancies, which raises the bile cholesterol level to develop gallstones.[5–8] The mean age of GBC, as noticed in our study, was between 61 and 75 years, representing 44% of cases. This is in agreement with other studies, which proposed an advanced age (>60 years) raising the risk of GBC related to elderly patients who have a long history of gallbladder stones with recurrence of inflammatory attacks progressing into invasive cancerous changes.[5,6] The most common presenting complaint in our patients was right hypocondrial pain with nausea and vomiting (40%), followed by jaundice (34%) and right hypochondrial palpable mass (26%). These findings are in agreement with the literature, which has reported the most common complaints to be right hypocondrial pain in 20%–49% and right hypochondrial mass in 15%–50% of the cases.[14,15] These symptoms and signs explain advanced stages of GBC at presentation due to delayed attendance of patients in referral clinics to diagnose suspicious GBC. Our study showed that most of the GBC patients were from urban areas (56% of cases). This was in agreement with other studies which revealed that the incidence is higher in urban areas, such as native America, related to increased gallstone incidence.[3] TUS, abdominopelvic CT scan, and MRCP were carried out in all patients to detect preoperative diagnostic patterns of GBC to help plan curative treatment. In this study, TUS and abdominopelvic CT scan could successfully detect GBC in 54% of patients. These findings are in agreement with the literature stating that TUS is the initial modality of choice for the detection of GBC; but its overall accuracy for GBC staging is limited. These ultrasonographic findings included protruding mass in the GB lumen, loss of interface between GB and the liver, direct liver infiltration, gallbladder polyps ≥10 mm, and calcification and abnormal thickening of the GB wall.[20] Preoperative abdominopelvic CT scan is considered a necessary additional imaging modality to complete GBC staging work-up and to determine GBC resectability through the identification of involved liver bed, vascular branches, lymph nodes, or distant metastases.[21,22] Furthermore, another study showed that abdominopelvic CT scan had moderate sensitivity and poor specificity in differentiating GBC from acute cholecystitis.[23] Therefore, the addition of MRCP in the radiological diagnosis of GBC will assist in differentiating benign from malignant gallbladder lesions with a sensitivity of 91% and specificity of 87%. Also, MRCP allows planning for preoperative surgical resectability through the detection of extra-GBC extension into the surrounding viscera such as the liver, blood vessels, and bile ducts, which is associated with malignant biliary obstruction.[23,24] The most common stage of GBC in our study was metastatic (stage IV) in 52% of cases after radiological diagnosis and MDT evaluation. Our results are consistent with those in the literature where the metastatic stage of the GBC was reported in 56.2% of the cases.[3,36] This is related to the silent nature of GBC, which progresses into a metastatic stage with delayed patient presentation to referral clinics. Our patients who were diagnosed with GBC had several surgical choices. Preoperative MDT meeting decided palliative nonsurgical treatment in metastatic (stage IV) nonoperable patients (62%). Sixteen percent of the patients were planned for open radical cholecystectomy with lymphadenectomy for locally advanced GBC (stage III). Simple cholecystectomy was performed in 14% of cases where suspicious cancerous mass in the gallbladder was accidently discovered intraoperatively (stages I & II). Moreover, 8% of cases were unresectable intraoperatively (stage IV) because of vascular encasements and ascites for which biopsy was taken for histopathological analysis. Therefore, our results are similar to those of studies which reported that in patients who could tolerate these extensive radical surgeries for locally advanced GBC, it was technically feasible to obtain tumor-free resection margins.[3,32] In our study, adenocarcinoma was the most detected postoperative histopathological subtype in 74% of cases, followed by cholangiocarcinoma subtype (in 26% of cases). This is consistent with the literature, which reported that adenocarcinoma is the most GBC subtype (90%).[2,4] Furthermore, 42% of cases in our study had palliative treatment in the form of ERCP/adjuvant chemotherapy because of inoperability and progressive metastatic extrahepatic biliary obstruction (stage IV). ERCP with biliary drainage allows adequate patient palliation. Some international studies that analyzed 474 patients have revealed insufficient data to support routine neoadjuvant therapy for advanced GBC.[28] Hence, our results go with the literature, which show the safe use of adjuvant chemotherapy regimens in cases with metastatic GBC for palliative purpose.[36,41] The overall mortality rate was 56%. All of them with metastatic, inoperable GBC (stage IV) died within 5 months of follow-up after diagnostic confirmation because of delayed presentation and hepatic failure related to malignant obstructive jaundice. These results were in agreement with a few studies in the literature that reported the mortality rate of GBC was high and accounted for 3830 deaths in the United States.[3,44–46] The main strength of our study is the applicability of the updated patterns of clinical presentation and management modalities of GBC in Sudanese patients to reach excellent practice at Sudanese national surgical centers in spite of significant delay in the diagnosis of advanced GBC. The small number of patients is a limitation of our study that needs to be addressed. Future studies are recommended to compare the findings of this study with larger sample sizes in the long term.

Conclusions

Accurate and early clinical diagnosis of GBC patients as well as advanced radiological modalities with curative surgical approaches including clear surgical resection margins and systemic oncological therapies will potentially help in improving GBC survival outcomes.

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Ethics statement

Our research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was

obtained from the local Research Ethics Committee of Faculty of Medicine and Health Sciences, Omdurman Islamic University, at the committee meeting number 179 of March 15, 2021, which permitted the use the Sudanese patients after they had provided written and signed consent to publish this original article for the purpose of research and collect medical data from the international medical websites and medical literature. No clinical trials were involved in this study. Written informed consent was obtained from all patients to participate in the study.

Data availability statement. Datasets are not allowed to be made available publicly by the local Research Ethics Committee because of ethical grounds. However, the data might be available from the corresponding author upon reasonable requests.

References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 2018; **68**: 394–424.

2 Shaffer EA. Gallbladder cancer: the basics. *Gastroenterol Hepatol (NY)*. 2008; **4**: 737–41.

3 Haisley K, Hunter J. Gallbladder and the extrahepatic biliary system. In: Brunicardi F (ed.). *Principles of Surgery*, 11th edn. New York: McGraw Hill, 2019; 1421–2.

4 Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. *Clin. Epidemiol.* 2014; **6**: 99–109.

5 Mahdavifar N, Mohammadian M, Salehiniya H. Gallbladder cancer in the world: epidemiology, incidence, mortality and risk factors. *World cancer research journal.* 2018; **5**: 7.

6 Duffy A, Capanu M, Abou-Alfa GK *et al*. Gallbladder cancer (GBC): 10-year experience at Memorial Sloan Kettering Cancer Centre (MSKCC). *J. Surg. Oncol.* 2008; **98**: 485–9.

7 Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. *Int. J. Cancer*. 2006; **118**: 1591–602.

8 Barreto SG, Haga H, Shukla PJ. Hormones and gallbladder cancer in women. *Indian J. Gastroenterol.* 2009; **28**: 126–30.

9 Iqbal S, Ahmad S, Saeed U, Al-Dabbagh M. Porcelain gallbladder: often an overlooked entity. *The surgery journal.* 2017; **3**: e145–7.

10 Gupta S, Kori C, Kumar V, Misra S, Akhtar N. Epidemiological study of gallbladder cancer patients from North Indian gangetic planes—a high-volume centre's experience. *J. Gastrointest. Cancer.* 2016; **47**: 27–35.

11 Sharma A, Sharma KL, Gupta A, Yadav A, Kumar A. Gallbladder cancer epidemiology, pathogenesis and molecular genetics: Recent update. *World J. Gastroenterol.* 2017; **23**: 3978–98.

12 Jain K, Sreenivas V, Velpandian T, Kapil U, Garg PK. Risk factors for gallbladder cancer: a casecontrol study. *Int. J. Cancer*. 2013; **132**: 1660–6.

13 Pitt SC, Jin LX, Hall BL, Strasberg SM, Pitt HA. Incidental gallbladder cancer at cholecystectomy: when should the surgeon be suspicious? *Ann. Surg.* 2014; **260**: 128–33.

14 Dutta U. Gallbladder cancer: can newer insights improve the outcome? *J. Gastroenterol. Hepatol.* 2012; **27**: 642–53.

15 Furlan A, Ferris JV, Hosseinzadeh K, Borhani AA. Gallbladder carcinoma update: multimodality imaging evaluation, staging, and treatment options. *Am. J. Roentgenol.* 2008; **191**: 1440–7.

16 Von Meyenfeldt EM, Mantel SF, Gouma DJ, van Gulik TM. Tumors in the gallbladder: A possible differentiation between malignant and benign tumours. *Ned. Tijdschr. Geneeskd.* 2007; **151**: 1049–54.

17 Hawkins WG, De matteo RP, Jarnagin WR, Ben-Porat L, Blumgart LH, Fong Y. Jaundice predicts advanced disease and early mortality in patients with gallbladder cancer. *Ann. Surg. Oncol.* 2004; **11**: 310–15.

18 Ritts RE Jr, Nagorney DM, Jacobsen DJ, Talbot RW, Zurawski VR Jr. Comparison of preoperative serum CA19-9 levels with results of diagnostic imaging modalities in patients undergoing laparotomy for suspected pancreatic or gallbladder disease. *Pancreas.* 1994; **9**: 707–16.

19 Kang JS, Hong SY, Han Y *et al*. Limits of serum carcinoembryonic antigen and carbohydrate antigen 19-9 as the diagnosis of gallbladder cancer. *Annals of surgical treatment and research.* 2021; **101**: 266–73.

20 Pandey M, Sood BP, Shukla RC, Aryya NC, Singh S, Shukla VK. Carcinoma of the gallbladder: role of sonography in diagnosis and staging. *J. Clin. Ultrasound*. 2000; **28**: 227–32.

21 Sakamoto K, Takai A, Ueno Y, Inoue H, Ogawa K, Takada Y. Scoring system to predict pT2 in gallbladder cancer based on carcinoembryonic antigen and tumor diameter. *Scand. J. Surg.* 2019; **109**: 301–8.

22 Li B, Xu XX, Du Y *et al*. Computed tomography for assessing resectability of gallbladder carcinoma: A systematic review and meta-analysis. *Clin. Imaging*. 2013; **37**: 327–33.

23 Abraham S, Rivero HG, Erlikh IV, Griffith LF, Kondamudi VK. Surgical and nonsurgical management of gallstones. *Am. Fam. Physician*. 2014; **89**: 795–802.

24 Kaza RK, Gulati M, Wig JD, Chawla YK. Evaluation of gall bladder carcinoma with dynamic magnetic resonance imaging and magnetic resonance cholangiopancreatography. *Australas. Radiol.* 2006; **50**: 212–17.

25 Sadamoto Y, Kubo H, Harada N, Tanaka M, Eguchi T, Nawata H. Preoperative diagnosis and staging of gallbladder carcinoma by EUS. *Gastrointest. Endosc.* 2003; **58**: 536–41.

26 Anderson CD, Rice MH, Pinson CW, Chapman WC, Chari RS, Delbeke D. Fluorodeoxyglucose PET imaging in the evaluation of gallbladder carcinoma and cholangiocarcinoma. *J. Gastrointest. Surg.* 2004; **8**: 90–7.

27 Amin MB, Edge SB, Greene FL *et al*. *AJCC Cancer Staging Manual*, 8th edn. New York: Springer, 2017; 1032.

28 Benson AB, D'Angelica MI, Abbott DE *et al*. Hepatobiliary cancers, version 2.2019 featured updates to the NCCN guidelines. *J. Natl. Compr. Canc. Netw.* 2019; **17**: 302–10.

29 Ethun CG, Postlewait LM, Le N *et al*. Association of optimal time Interval to reresection for incidental gallbladder cancer with overall survival: A multi-Institution analysis from the US extrahepatic biliary malignancy consortium. *JAMA Surg.* 2017; **152**: 143–9.

30 Goetze TO, Paolucci V. Adequate extent in radical re-resection of incidental gallbladder carcinoma: analysis of the German registry. *Surg. Endosc.* 2010; **24**: 2156–64.

31 Foster JM, Hoshi H, Gibbs JF *et al*. Gallbladder cancer: Defining the indications for primary radical resection and radical re-resection. *Ann. Surg. Oncol.* 2007; **14**: 833–40.

32 Miyakawa S, Ishihara S, Horiguchi A, Takada T, Miyazaki M, Nagakawa T. Biliary tract cancer treatment: 5,584 results from the biliary tract cancer statistics registry from 1998 to 2004 in Japan. *J. Hepatobiliary Pancreat. Surg.* 2009; **16**: 1–7.

33 Lee SE, Jang JY, Lim CS, Kang MJ, Kim SW. Systematic review on the surgical treatment for T1 gallbladder cancer. *World J. Gastroenterol.* 2011; **17**: 174–80.

34 Ito H, Ito K, D'Angelica M *et al*. Accurate staging for gallbladder cancer: implications for surgical therapy and pathological assessment. *Ann. Surg.* 2011; **254**: 320–5.

35 Goetze TO. Gallbladder carcinoma: Prognostic factors and therapeutic options. *World J. Gastroenterol.* 2015; **21**: 12211–17.
36 Hakeem AR, Papoulas M, Menon KV. The role of neoadjuvant chemotherapy or chemoradiotherapy for advanced gallbladder cancer: A systematic review. *Eur. J. Surg. Oncol.* 2019; **45**: 83–91.
37 Chaudhari VA, Ostwal V, Patkar S *et al*. Outcome of neoadjuvant chemotherapy in locally advanced/borderline resectable gallbladder cancer: The need to define indications. *HPB (Oxford)*. 2018; **20**: 841–7.
38 Aloia TA, Jarufe N, Javle M *et al*. Gallbladder cancer: expert consensus statement. *HPB (Oxford)*. 2015; **17**: 681–90.
39 Valle J, Wasan H, Palmer DH *et al*. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N. Engl. J. Med.* 2010; **362**: 1273–81.
40 Primrose JN, Fox RP, Palmer DH *et al*. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): A randomized controlled multicenter phase 3 study. *Lancet Oncol.* 2019; **20**: 663–73.
41 Margonis GA, Gani F, Buettner S *et al*. Rates and patterns of recurrence after curative intent resection for gallbladder cancer: A multi-institution analysis from the US extra-hepatic biliary malignancy consortium. *HPB (Oxford)*. 2016; **18**: 872–8.
42 Verlingue L, Malka D, Allorant A *et al*. Precision medicine for patients with advanced biliary tract cancers: An effective strategy within the prospective MOSCATO-01 trial. *Eur. J. Cancer*. 2017; **87**: 122–30.
43 Ahn S, Lee JC, Shin DW, Kim J, Hwang JH. High PD-L1 expression is associated with therapeutic response to pembrolizumab in patients with advanced biliary tract cancer. *Sci. Rep.* 2020; **10**: 12348.
44 Justo I, Marcacuzco A, Nutu OA *et al*. A retrospective analysis of patients with gallbladder cancer: Surgical treatment and survival according to tumor stage. *Rev. Esp. Enferm. Dig.* 2018; **110**: 485–92.
45 Abdelrahim WE, Elsiddig KE, Akoad ME, Abbas M, Khalil EA. Gallbladder cancer in Sudan: A two-centre study. *Global journal of surgery.* 2017; **5**: 17–19.
46 Henley SJ, Weir HK, Jim MA, Watson M, Richardson LC. Gallbladder cancer incidence and mortality, United States 1999-2011. *Cancer Epidemiol. Biomarkers Prev.* 2015; **24**: 1319–26.