



Original Article

Prevalence of gallbladder cancer in cholecystectomized patients in Sulaymaniyah city



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Abstract



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Gallbladder cancers (GBC) are rare, and they are one of lethal neoplasms of biliary system. The diagnosis is either incidentally during histopathological examinations after cholecystectomy or due to complications of local or systemic spread of the malignancy. The incidence differs ethnically and geographically. The aim was to identify increase risk of cancer in the Kurdistan region by searching for the number of GBC cases among cholecystectomy patients in Sulaymaniyah governorate. This study is laboratory-based retrospective study, including data obtained from 8315 cholecystectomized patients in Sulaymaniyah governorate from 2017- 2021. The information within the questionnaire included: age, sex, clinical notes and histopathological findings; including GBC. The total of 8315 cases; were 2149 males (25.8%) and 6166 females (74.2%). The mean age was (44.67+/-15.18) years. Forty-five cases have been reported as adenocarcinoma of GB and one case of Carcinosarcoma. Among the patients, 875 cases (10.50%) had acute cholecystitis. A significant relationship was found between the findings and the age and gender of the patients. GBC is not common and is mainly diagnosed incidentally after routine post-operative histopathological examination, and mainly affects old ages.

Keywords: Gallbladder cancer, Cholecystectomy, Incidental diagnosis.

1. Introduction

Gallbladder (GB) diseases are the core of major internal studies nowadays as it's common [1], but GB malignancies are rare though it is one of lethal neoplasms of the biliary system worldwide [2]. Gallbladder cancer (GBC) develops from mucosal lining of cystic duct and neck, body, or fundic part of GB. At the initial stages of the development of GBC, most of the patients don't have any symptoms or just have nausea, and abdominal pain, which are very similar to signs and symptoms of benign GB disease [3], and busy anatomical site for carcinogenesis and significant delay of diagnosis are the major concerns in the lethality of this malignancy [4, 5]. GBC is either detected incidentally during histopathological examinations after cholecystectomy in approximately 50 % to 70% of cases [6, 7] or due to complications of local or systemic spread of the malignancy [8]. Due to these unapproachable choices managing GBC is difficult [9]. Early detection and surgery are still the best choices for management and survival among other choices as chemotherapy, radiotherapy and immunotherapy which are not particularly curative [10, 11].

The incidence of GBC differs ethnically and geographically [12], the risk factors of GBC is gallstone which's the most common one, obesity, *Salmonella Typhus* and *Helicobacter pylori* infections, biliary cysts and exposure to radiologic contrast, especially if large amount of contrast used for procedures [13–15].

TNM staging is a common system used to describe the extent or severity of cancer based on three key pieces of information [12-15]:

T (Tumor): This component describes the size and extent of the primary tumor. T categories typically range from TX (tumor cannot be assessed) to T4 (tumor of any size with direct extension to adjacent organs or structures).

N (Node): This component indicates whether cancer has spread to nearby lymph nodes. N categories range from NX (regional lymph nodes cannot be assessed) to N3 (cancer has spread to nearby lymph nodes, often indicating more advanced disease).

M (Metastasis): This component indicates whether cancer has spread to distant parts of the body. M categories range from MX (presence of distant metastasis cannot be assessed) to M1 (cancer has spread to distant organs or

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tissues).

Each of these components is assigned a specific stage based on the T, N, and M categories. The combination of these stages provides an overall stage of cancer, which helps guide treatment decisions and prognosis. The stage may also include additional factors, such as tumor grade and biomarker status, depending on the specific cancer type.

Tis (Carcinoma in situ): This stage indicates that cancerous cells are present but have not invaded nearby tissues or structures.

T1a: This stage indicates a small tumor that has invaded only a minimal amount of tissue. The exact definition may vary depending on the specific type of cancer.

T1b: Similar to T1a, T1b indicates a small tumor but with slightly greater invasion of nearby tissues compared to T1a.

T2: This stage indicates a larger tumor that may have invaded nearby tissues more extensively than T1 tumors.

T2a: T2a indicates a specific size and extent of tumor invasion, usually falling within the range specified for T2 tumors.

T2b: Similar to T2a, T2b indicates a specific size and extent of tumor invasion but may involve different nearby structures or tissues.

T3: This stage indicates further tumor growth and invasion into nearby tissues or structures beyond what is classified as T2.

"N" stage refers to the extent of regional lymph node involvement, while the "M" stage indicates the presence or absence of distant metastasis.

N Stage including:

N0: No regional lymph node metastasis. Cancer cells have not spread to nearby lymph nodes.

N1: Cancer has spread to nearby lymph nodes, but only to a limited extent.

N2: Cancer has spread to nearby lymph nodes to a greater extent than in N1, but still limited.

N3: Cancer has spread to nearby lymph nodes extensively, often indicating more advanced disease.

M Stage including:

M0: No distant metastasis. Cancer cells have not spread to distant organs or tissues.

M1: Distant metastasis is present. Cancer cells have spread to distant organs or tissues, indicating more advanced disease.

In Kurdistan region, in the North of Iraq, no research has been undertaken to identify the prevalence of GBC and to highlight the increased risk of malignancy in this region [16].

This study aimed to provide the 1st report about cancer incidence in the Kurdistan region and to identify the increased risk of cancer in this region by searching for the number of GBC cases among cholecystectomy patients in Sulaymaniyah governorate from 2017 to 2021. Sulaymaniyah is the largest governorate located in North East of Iraq, in the Kurdistan region, and it is the ninth largest governorate in Iraq with population of more than 2,250,000 people.

2. Materials and Methods

This study was a retrospective study, including data obtained from 8315-cholecystectomized patients in Sulaymaniyah governorate from 2017- 2021. All cholecys-

tectomies GB were sent either to governorate or private histopathological laboratories for analysis of the restricted organ. The 8315 cases of this study have been brought from database reports of histopathological labs of Shar and Teaching hospitals, Shorsh General Hospital, Kurdistan Hepatology and Gastroenterology Hospital, Ali Kamal Hospital, and 9 private laboratories. The information within the questionnaire of this study includes age, sex, clinical notes and histopathological findings; Acute cholecystitis (AC), Non-acute cholecystitis (NAC) which include cases of biliary colic, chronic cholecystitis (CC), biliary pancreatitis which were treated conservatively, and GB polyps, in addition to GBC, and cancer staging. The recorded data have been summarized on Excel sheets and the statistical analysis was done using SPSS software version 22. A descriptive statistic was performed to explore the number, frequency, mean and standard deviation. Analytical analysis was performed to find the significance of the variables, including Chi-squared test for the proportion and independent t-test for the difference among the mean of 2 independent variables. P value <0.05 was considered significant.

3. Results

A total of 8315 patients who had cholecystectomy have been enrolled, from January 2017 to December 2021; 2149 males (25.8%) and 6166 females (74.2%). The mean age was (44.67±15.18) years. Female to male ratio was about 3:1 (Table 1).

Among those patients, 875 cases diagnosed as AC, the cases were increasing continuously from 2017 (11.4%) to 2021 (32.2%), and 7394 cases of NAC were included, the highest record was in 2021 (28.4%), while the lowest found in 2020 (15.7%) (Table 2) (Fig. 1). AC found more in older patients (48.68±15.65) (Table 2).

The percentage of AC was higher in male patients

Table 1. Gender and age.

Gender	Mean age/St. deviation	Total
Male	47.09±15.77	44.67±15.18
Female	43.83±14.87	
F/M* ratio	2.9/1(3/1)	

*F/M=Female/Male.

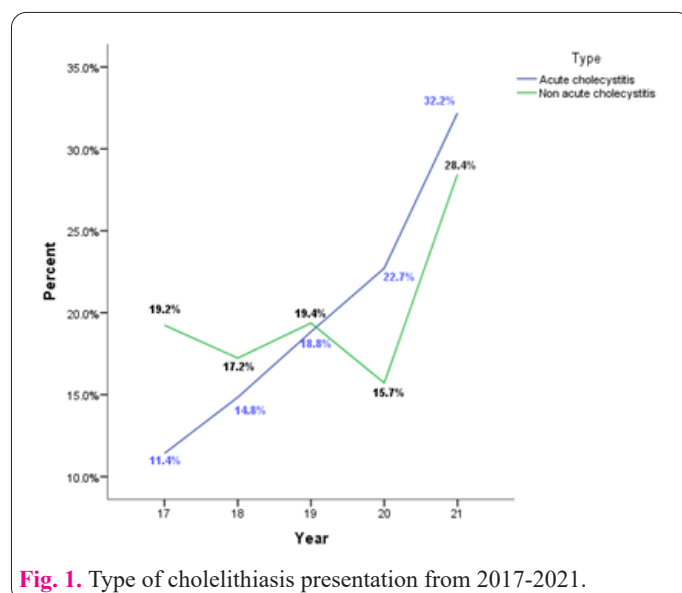


Fig. 1. Type of cholelithiasis presentation from 2017-2021.

Table 2. Relation between age and the types of cholelithiasis presentation.

Diagnosis	No. of Cases	%	Age (Years) Mean +/- std. deviation	P Value*
AC	875	10.50%	48.68+/-15.65	<0.001
NAC	7394	88.90%	44.19+/-15.05	
Total	8269	99.40%		

*P Value calculated using Independent T-test.

Table 3. The association between gender and types of cholelithiasis presentation.

Sex	AC	NAC	P Value*
Male	391	1741	<0.001)
	4.70%	20.90%	
Female	484	5653	
	5.80%	67.98%	
Total	875	7394	
	100.00%	100.00%	

*P Value calculated using Chi-square test.

(4.7%), in comparison with NAC (20.9%), while in female patients (5.8%) had AC, and (67.98%) had NAC. (Table 3).

The GBC was found in 46 patients (0.55%) of all cholecystectomies patients, only 5 of them were diagnosed preoperatively and had radical cholecystectomy, while 3 had completed surgery.

GBC was found more in the age above 60 years; the mean age was (64.11+/-11.98). Among the GBC patients, the highest percentage was found to be in 2021 (32.6%), while the lowest percentage was recorded in 2019 (10.9%) (Fig. 2). Majority of GBC; 16 (35.55%) was found to be grown right through the GB wall (T3 staging of TNM staging), while the least have shown metastasis (2.22%), and 5 cases were recorded with no reported stage. (Table 4). GBC nearly was equal in both genders (Table 5).

The most clinical presentation of GBC was NAC (82.61%) (Table 6).

4. Discussion

GBC is uncommon cancer of alimentary tract, but it carries high mortality rate [4], while it is the most common malignant tumour of the biliary tract worldwide [17], its incidence is differed according to geographical differ-

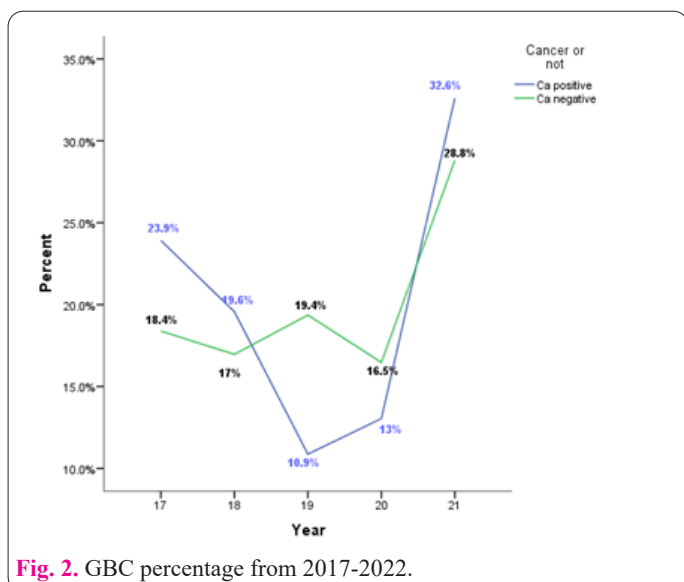


Fig. 2. GBC percentage from 2017-2022.

Table 4. TNM staging of Cancers.

T Stage*	NO. of Cases
Tis	4(8.88%)
T1a	1(2.22%)
T1b	5(11.11%)
T2	6(13.33%)
T2a	3(6.66%)
T2b	5(11.11%)
T3	16(35.55%)
N Stage	
N0	
N1	8(17.77%)
N2	1(2.22%)
M Stage	
M0	
M1	1(2.22%)

*5 Cases without reported stage. Where, Tis: (Carcinoma in situ): This stage indicates that cancerous cells are present but have not invaded nearby tissues or structures; T1a: This stage indicates a small tumor that has invaded only a minimal amount of tissue. The exact definition may vary depending on the specific type of cancer; T1b: Similar to T1a, T1b indicates a small tumor but with slightly greater invasion of nearby tissues compared to T1a; T2: This stage indicates a larger tumor that may have invaded nearby tissues more extensively than T1 tumors; T2a: T2a indicates a specific size and extent of tumor invasion, usually falling within the range specified for T2 tumors; T2b: Similar to T2a, T2b indicates a specific size and extent of tumor invasion but may involve different nearby structures or tissues; T3: This stage indicates further tumor growth and invasion into nearby tissues or structures beyond what is classified as T2; "N" stage refers to the extent of regional lymph node involvement, while the "M" stage indicates the presence or absence of distant metastasis.

ences, its incidence may reach 22/ 100000 population, like in India and Latin American [18], and it is 0.4–0.8 in men and 0.6–1.4 in women per 100000 in western countries [19].

Diagnosis of GBC is usually delayed and most cases are diagnosed after routine postoperative histopathological examination of GB [20], and incidental GBC is found to be

Table 5. The association between gender and GBC.

Gender	GBC positive	GBC negative	P value*
Male	16 0.19%	2133 25.70%	0.165
Female	30 0.36%	6136 73.80%	
Total	46 0.55%	8269 99.45%	

*P value calculated using Chi-square test.

Table 6. The association between type of cholelithiasis presentation and GBC.

Cancer	AC	NAC	Total	P Value*
Male	4 8.69%	12 26.08%	16 34.78%	0.064
Female	4 8.69%	26 56.50%	30 65.21%	
Total	8 17.39%	38 82.61%	46 100.00%	

0.1-3.3% in the literatures [21]. So after database reports of histopathological labs were rechecked in Sulaymaniyah governorate, the incidence of GBC among cholecystectomized patients was found to be 0.55%, 65.21% of cases were female, and the incidence in the females was 0.48% (30 of 6166), while it was 0.74% in males (16 of 2149). Our results of GBC were less than a study done in Turkey; 2.05% [21] and in Poland; 0.87%⁽²²⁾, and nearly same as one done in Sweden; 0.59%⁽²³⁾.

In our study GBC was found mainly in those who were above 60 years (mean age: 64.11+/-11.98), which was also found in other studies; 67.71 years [21], 67.1 years [22], and it was 70 ± 11 years in Sweden [23].

In this study, although GBC was found mainly in women (65.21%), GBC nearly was equal in both genders (P-value: 0.165(>0.05), GBC was 78% in Poland [22], 80% in Sweden [23], and 85.71% in Turkey [21].

Forty-five cases of GBC had GS which the common risk factor of GBC [1, 21, 24], and only one patient had GB polyp. Most histopathological results of GBC were T3, then T2, while it was mainly T2 in that study done in Turkey; T2 was 4:7 cases [21].

In addition, we found that the commonest reason for cholecystectomy was NAC (88.9%), which included those patients who had history of attacks of biliary colic and/or cholecystitis, CC, pancreatitis due to presence of GS, and AC was (10.50%), and in both conditions, the incidences were more in females; (55.31%: 44.68%) for AC, and (76.45%: 23.54%) for NAC, while in a study in Korea, the incidence of CC was only about twice of AC; 65.7%: 34.29%, and AC were more in male patients and CC more in females [25]. In another study done in Iran on 2017, there were nearly equal; 52.4% for CC, and 47.6% for AC, and both were found more in females [26], the reason may be due to the policy of timing of cholecystectomy in cases of AC, as the timing of operation is related to the onset and magnitude of symptoms [27]. We noted that the percentage of AC operated was (11.4%) in 2017, and became (32.2%) in 2021, which indicates improvement in operative skill.

5. Conclusion

GBC is not common and is mainly diagnosed incidentally after routine post-operative histopathological examination of removed GB, and most cases are T2-3. Risk factors include old age and GS.

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Conflict of interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were used in the present research.

Informed consent

The authors declare not to use any patients in this research.

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References

1. Stinton LM, Shaffer EA (2012) Epidemiology of gallbladder disease: Cholelithiasis and cancer. *Gut Liver* 6 (2): 172–187. doi: 10.5009/gnl.2012.6.2.172.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.

- CA Cancer J Clin 68 (6): 394–424. doi: 10.3322/caac.21492.
3. Serra I, Calvo A, Sharp A, Goñi I (1987) Carcinoma de la vesícula biliar. *Rev Med Chil* 115 (7): 706–708.
 4. Kanthan R, Senger JL, Ahmed S, Kanthan SC (2015) Gallbladder cancer in the 21st century. *J Oncol*. doi: 10.1155/2015/967472
 5. Mullen JT, Crane CH, Vauthey JN (2007) Benign and malignant gallbladder tumors. In: *Dis. Gall. Bile Ducts Diagnosis Treat.* pp 252–262.
 6. Choi KS, Choi SB, Park P, Kim WB, Choi SY (2015) Clinical characteristics of incidental or unsuspected gallbladder cancers diagnosed during or after cholecystectomy: A systematic review and meta-analysis. *World J Gastroenterol* 21 (4): 1315–1323. doi: 10.3748/wjg.v21.i4.1315.
 7. Pawlik TM, Gleisner AL, Vigano L, Kooby DA, Bauer TW, Frilling A, et al (2007) Incidence of finding residual disease for incidental gallbladder carcinoma: Implications for Re-resection. *J Gastrointest Surg* 11 (11): 1478–1487. doi: 10.1007/s11605-007-0309-6.
 8. Hundal R, Shaffer EA (2014) Gallbladder cancer: epidemiology and outcome. *Clin Epidemiol* 6 99.
 9. Krell RW, Wei AC (2019) Gallbladder cancer: surgical management. *Chinese Clin Oncol* 8 (4): 36.
 10. Cai ZQ, Guo P, Si S Bin, Geng ZM, Chen C, Cong LL (2017) Analysis of prognostic factors for survival after surgery for gallbladder cancer based on a Bayesian network. *Sci Rep* 7 (1): 1–10. doi: 10.1038/s41598-017-00491-3.
 11. Sirohi B, Mitra A, Jagannath P, Singh A, Ramadvar M, Kulkarni S, et al (2015) Neoadjuvant chemotherapy in patients with locally advanced gallbladder cancer. *Futur Oncol* 11 (10): 1501–1509. doi: 10.2217/fon.14.308.
 12. Rawla P, Sunkara T, Barsouk A (2019) Epidemiology of colorectal cancer: Incidence, mortality, survival, and risk factors. *Prz Gastroenterol* 14 (2): 89–103. doi: 10.5114/pg.2018.81072.
 13. International Agency for Research on Cancer. (2001) Ionizing radiation. Part 2, Some internally deposited radionuclides. International Agency for Research on Cancer.
 14. IARC (2012) Radiation Lyon. Lyon.
 15. Travis LB, Hauptmann M, Gaul LK, Storm HH, Goldman MB, Nyberg U, et al (2003) Site-Specific Cancer Incidence and Mortality after Cerebral Angiography with Radioactive Thorotrast. *Radiat Res* 160 (6): 691–706. doi: 10.1667/RR3095.
 16. Khoshnaw N, Mohammed HA, Abdullah DA (2016) Patterns of cancer in Kurdistan - Results of eight years cancer registration in Sulaymaniyah Province-Kurdistan-Iraq. *Asian Pacific J Cancer Prev* 16 (18): 8525–8531. doi: 10.7314/APJCP.2015.16.18.8525.
 17. Lai CHE, Lau WY (2008) Gallbladder cancer—a comprehensive review. *Surg* 6 (2): 101–110.
 18. Dutta U, Bush N, Kalsi D, Popli P, Kapoor VK (2019) Epidemiology of gallbladder cancer in India. *Chinese Clin Oncol* 8 (4): 33. doi: 10.21037/cco.2019.08.03.
 19. Vijayakumar A, Vijayakumar A, Patil V, Mallikarjuna MN, Shivaswamy BS (2013) Early Diagnosis of Gallbladder Carcinoma: An Algorithm Approach. *ISRN Radiol* 2013 1–6. doi: 10.5402/2013/239424.
 20. Ethun CG, Le N, Lopez-Aguilar AG, Pawlik TM, Poultides G, Tran T, et al (2017) Pathologic and prognostic implications of incidental versus nonincidental gallbladder cancer: A 10-institution study from the United States extrahepatic biliary malignancy consortium. *Am Surg* 83 (7): 679–686. doi: 10.1177/000313481708300721.
 21. Tatli F, Ozgönül A, Yucel Y, Yalçın HC, Çiftçi R, Gümer M, et al (2017) Incidental gallbladder cancer at cholecystectomy. *Ann Ital Chir* 88 (5): 399–402. doi: 10.1097/sla.0000000000000485.
 22. Dorobisz T, Dorobisz K, Chabowski M, Pawłowski W, Janczak D, Patrzalek D, et al (2016) Incidental gallbladder cancer after cholecystectomy: 1990 to 2014. *Onco Targets Ther* 9 4913–4916. doi: 10.2147/OTT.S106580.
 23. Muszynska C, Lundgren L, Lindell G, Andersson R, Nilsson J, Sandström P, et al (2017) Predictors of incidental gallbladder cancer in patients undergoing cholecystectomy for benign gallbladder disease: Results from a population-based gallstone surgery registry. *Surg (United States)* 162 (2): 256–263. doi: 10.1016/j.surg.2017.02.009.
 24. Ghimire P, Yogi N, Shrestha BB (2011) Incidence of incidental carcinoma gall bladder in cases of routine cholecystectomy. *Kathmandu Univ Med J* 9 (34): 3–6. doi: 10.3126/kumj.v9i2.6278.
 25. Yeo DM, Jung SE (2018) Differentiation of acute cholecystitis from chronic cholecystitis: Determination of useful multidetector computed tomography findings. *Med (United States)*. doi: 10.1097/MD.00000000000011851
 26. Malekzadegan A, Rezaie Ghazik H, Sargazi A, Sargazi M (2017) Investigation of Relationship between Gender, Age and Living Place with Outbreak of Acute and Chronic Cholecystectomy and Gall Bladder Carcinoma in Amiralmomentin Hospital of Zabol in 1394. *Iran J Surg* 25 (1): 55.
 27. Mou D, Tesfasilassie T, Hirji S, Ashley SW (2019) Advances in the management of acute cholecystitis. *Ann Gastroenterol Surg* 3 (3): 247–253. doi: 10.1002/ags3.12240.