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Uncovering Gallbladder Cancers: A Retrospective Study Approach

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A B S T R A C T

Gall bladder cancers, predominantly adenocarcinomas, are associated with significant malignancy and are more common in women, especially in their seventh decade of life. This study aims to evaluate the prevalence, distribution, and histopathological characteristics of gall bladder tumors, emphasizing the need for early diagnosis and understanding the role of chronic cholecystitis in tumor development. A retrospective analysis was performed on 45740 surgical biopsies, including 3107 cholecystectomies, from 1994 to 2007 at Misurata Medical Center, Libya. Data collected included patient demographics, clinical details, and microscopic diagnoses. Biopsy samples were processed and stained, and histopathological evaluation was performed following standard criteria. The study showed a female predominance in gall bladder tumors with a female: male ratio of 3:1. Most tumors were adenocarcinomas (83.33%), with high and moderate differentiation being the most frequent. Tumor diagnoses were most prevalent in the 51-65 age group. The majority of tumors were diagnosed at advanced stages (3 and 4). Tumor invasion was common, with 75% showing perivascular, intravascular, or perineural involvement. Chronic cholecystitis was observed in more than two-thirds of the tumor cases. Chronic inflammation is closely linked to gallbladder carcinogenesis, with most tumors diagnosed at advanced stages due to vague symptoms and aggressive behavior. Early detection and multidisciplinary approaches are vital to improve outcomes, especially in high-risk groups.

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INTRODUCTION

Gallbladder cancer (GBC) is an aggressive malignancy that constitutes 80% to 95% of biliary tract cancers, despite its relative rarity [1]. Its global incidence ranges from 0.3% to 1.5% [2], and it ranks as the sixth most common gastrointestinal malignancy and the 25th most common cancer worldwide, according to GLOBOCAN 2020 data [3]. GBC is an aggressive malignancy associated with a poor prognosis, primarily due to its nonspecific clinical presentation, which often leads to delayed diagnosis [1-4]. Multiple molecular and genetic mechanisms have been implicated in the pathogenesis of gallbladder cancer (GBC). Two principal hypotheses have been proposed. The predominant and widely accepted theory links GBC to chronic inflammation, typically secondary to recurrent cholecystitis caused by cholelithiasis, which remains the leading etiological factor in most populations.

A less common but notable mechanism involves anomalous pancreatic biliary junctions (APBJs), a congenital anomaly predominantly observed in East Asian populations, particularly in Japan and Korea. Anomalous pancreatic biliary junction (APBJs) is believed to predispose the biliary epithelium to chronic injury and malignant transformation [5]. The etiology of GBC is multifactorial, involving both environmental and genetic components. Epidemiological studies have identified several associated risk factors, including obesity, dietary habits, exposure to industrial chemicals or heavy metals, gallstones, gallbladder polyps, and persistent gallbladder inflammation [6], A history of benign gallbladder disease, a family history of GBC, a chronic salmonella infection, and a helicobacter infection are additional strong risk factors [7]. Age, female gender, congenital biliary tract defects, and genetic susceptibility are significant intrinsic risk factors [1]. Epidemiological studies have revealed substantial geographic and ethnic inequalities, with a particularly high incidence among American Indians, an elevated frequency in Southeast Asia, and relatively low rates in other areas of the Americas and globally [1].

Gallbladder cancer (GBC) shows a distinct female predominance in both incidence and mortality, with prevalence increasing with age, in contrast to the male predominance observed in most solid tumors, except for breast and thyroid cancers [3]. Globally, the female-to-male incidence rate ratio for GBC is approximately 2:1, although regional variations

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exist, ranging from 1:1 in parts of the Far East to as high as 4:1 in Spain [8]. This consistent female predominance suggests a potential role of sex hormones in gallbladder carcinogenesis. Hormonal influences, particularly estrogen, may alter bile composition by increasing cholesterol saturation, thereby promoting gallstone formation—a major risk factor in GBC development [3]. A hypothesis that the gallbladder may be hormonally responsive, and that female sex hormones may contribute to the pathophysiology of GBC [4]. The gallbladder epithelium expresses estrogen and progesterone receptors, and hormonal fluctuations, particularly during pregnancy, have been implicated in gallstone pathogenesis.

Elevated estrogen levels promote hepatic cholesterol secretion, while progesterone reduces bile acid synthesis and delays gallbladder emptying, leading to bile supersaturation and increased risk of gallstone formation [3]. Epidemiological studies indicate that gallbladder cancer (GBC) mortality rates are highest in regions with a high prevalence of gallstones [1]. Gallstones are detected in approximately 70%–80% of GBC cases and are associated with a four- to sevenfold increased risk of gallbladder carcinoma [2]. However, geographic variation exists; for example, in Korea, only about 30% of GBC cases are associated with gallstones [5]. The gall bladder mucosa is typically inflamed by cholelithiasis, which is associated with a number of histological alterations that may be a sign of malignancy; these alterations may be cancer, metaplasia, dysplasia, or chronic cholecystitis [9]. Gallstones are linked to high parity and are frequently the first sign of gallbladder dysplasia. Gallbladder volume rises and bile flow falls during pregnancy. Increased bile cholesterol saturation is a result of elevated estrogen levels during pregnancy. By reducing the biliary tract's smooth muscle contractility, progesterone, which is also increased during pregnancy, contributes to biliary stasis and causes cholesterol gallstones to develop [8].

Adenocarcinoma accounts for over 90% of gallbladder cancers, with varying degrees of differentiation [6]. Less common subtypes include squamous, adenosquamous, mucinous, and papillary adenocarcinomas, the latter associated with a better prognosis [7]. Rare tumors like carcinosarcoma, containing both epithelial and mesenchymal components, comprise less than 1% of cases [10]. Because of some regional differences in the prevalence of inflammatory diseases and cancer of the gall bladder, it is necessary to periodically analyze the frequency and structure of gall bladder neoplastic proliferation. This study aims to investigate the prevalence, histopathological characteristics, and potential risk factors associated with gallbladder malignancies in this population.

Methods

A retrospective analysis was conducted on 45,740 surgical biopsy specimens received at the Department of Surgical Pathology, Misurata Medical Center, Libya, over the years (1994–2007). Among these, 3,107 specimens were from cholecystectomy procedures (Fig. 1), including 2,790 cases of chronic cholecystitis, 275 cases of Phlegmonus exacerbation of cholecystitis, 12 cases of Phlegmonus cholecystitis, and 30 tumor cases. For each biopsy, recorded data included the registration number, patient demographics (name, age, sex, nationality), and clinical and histopathological diagnoses. Following formalin fixation and gross examination, representative tissue sections (ranging from one to five or more blocks) were selected, processed, and embedded in paraffin. Microtome sections of approximately 7 µm thickness were prepared and microscopically evaluated by a team of pathologists using standardized diagnostic criteria. The most frequently diagnosed histopathological changes were chronic fibrous cholecystitis, Phlegmonus exacerbation of chronic cholecystitis, tumors, and Phlegmonus cholecystitis, in descending order of prevalence.

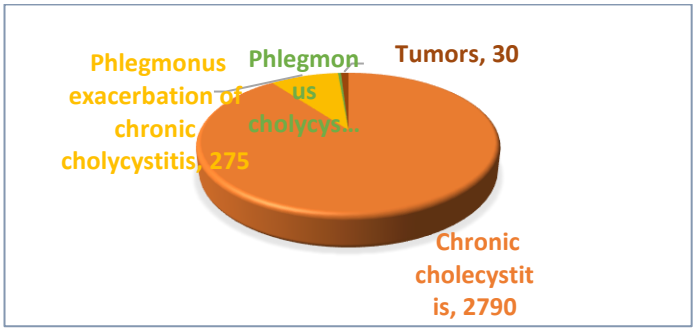

Figure 1. Number of reported gall bladder biopsies

Results

A total of 3,107 cholecystectomy specimens were analyzed. The sex distribution (Figure 2) showed a predominance of female cases, accounting for 87% of all reported gallbladder biopsies, with a female-to-male ratio of 6.6:1. The youngest patient was a 14-year-old female, while the oldest was an 86-year-old female.

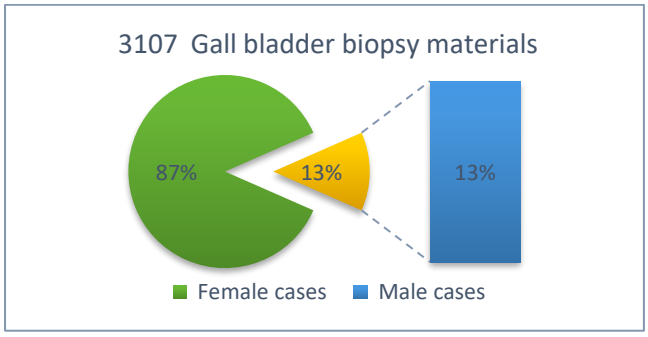

Figure 2. Sex distribution of cholecystectomy patients.

Table 1 presents the demographic distribution of patients diagnosed with chronic fibrous cholecystitis. The highest prevalence was observed in the 56–65-year age group (51.1%), followed by the

46–55-year group (50.3%), indicating a strong association with middle-aged and older individuals. The lowest incidence occurred in the 15–25-year group (1.3%). A pronounced female predominance was noted, with 88.9% of cases in females (n = 2,481) and 11.1% in males (n = 310), yielding a female-to-male ratio of 8:1.

Table 2 summarizes the demographic data of 275 patients with microscopically confirmed phlegmonous exacerbation of chronic cholecystitis. Females accounted for 66.5% (n = 183) and males 33.5% (n = 92), with a female-to-male ratio of approximately 2:1.

The highest incidence occurred in the 56–65-year group (21.8%), followed by 46–55 years (21.1%) and 66–75 years (18.9%), with the lowest in the 15–25-year group (6.2%). A progressive rise in cases was noted from ages 26–35 to 56–65, then a slight decline thereafter.

Female predominance was observed across all age groups, most marked in the 46–65-year range.

Table 3 shows the age and sex distribution of 12 patients with phlegmonous cholecystitis, all of whom were female. Most cases occurred in middle-aged women, with the highest incidence in the 46–55-year group (50%), followed by 36–45 years (33.3%). Single cases were reported in the 26–35 and 56–65-year groups (8.3% each). No cases were identified below 26 or above 65 years, suggesting either true age-related trends or limitations due to small sample size.

Table 4 presents the age and sex distribution of 30 gallbladder tumor cases. Patients ranged from 45 to 80 years, with no cases under 36. The youngest was a 45-year-old female; the oldest, an 80-year-old male. Most cases occurred in individuals aged ≥56. Females were predominantly affected (76.7%, n = 23), with a female-to-male ratio of 3.3:1. The highest incidence in females was in the 56–65 age group (n = 10), while in males it was 46–55 (n = 4). These findings highlight a female predominance and an age-related increase in tumor incidence.

Table 1. Age and Sex Distribution of microscopically diagnosed Chronic fibrous cholecystitis.

Age Group (years	15- 25	26- 35	36-45	46-55	56-65	66- 75	76-85
Female (n=2,481)	14	56	62	666	685	242	18
Male (n=310)	21	72	110	738	741	149	26
Total (n=2,791)	35	128	172	1,404	1,426	391	44

Table 2: Age and sex distribution of patients with Phlegmonus Ex acerbation of chronic cholecystitis.

Age Groups (years)	15- 25	26-35	36-45	46-55	56-65	66-75	76-85	Total
Female (n, %)	12 (6.6%)	35 (19.1%)	30 (16.4%)	41 (22.4%)	37 (20.2%)	28 (15.3%)	0 (%0.0)	183 (%66.5)
Male (n, %)	5 (5.4%)	8 (8.7%)	15 (16.3%)	17 (18.5%)	23 (25.0%)	24 (26.1%)	0 (%0.0)	92 (33.5%)
Total (n, %)	17 (6.2%)	43 (15.6%)	45 (16.4%)	58 (21.1%)	60 (21.8%)	52 (18.9%)	0 (%0.0)	275 (100%)

Table 3. Age and sex distribution of the patients with Phlegmonus cholecystitis.

Age Group (years)	15- 25	26- 35	36-45	46-55	56-65	66- 75	76-85	Total
Female (n)	0	1	4	6	1	0	0	12
Male (n)	0	0	0	0	0	0	0	0
Total (n)	0	1	4	6	1	0	0	12

Table 4: Age and sex distribution of the patients with gall bladder tumors.

Age Group (Years)	15- 25	26- 35	36-45	46-55	56-65	66- 75	76-85	Total
Female	0	0	1	8	10	4	0	23
Male	0	0	0	0	4	2	1	7
Total	0	0	1	8	14	6	1	30

Figure 3 illustrates the annual distribution of gallbladder tumor cases from 1994 to 2007. A fluctuating pattern was observed, with notable peaks in 1997, 2002, and 2003, each recording the highest number of cases (n = 5). The incidence remained relatively elevated between 1996 and 2003, followed by a marked decline in 2004, with minimal or no cases reported in some subsequent years. These data reflect temporal variation in case frequency over the 14 years.

Figure 4 shows the distribution of gallbladder tumors by sex and histological subtype. Adenocarcinoma was the most common (83.3%, 25/29), followed by adenosquamous (n = 2), squamous cell carcinoma (n = 1), and one mixed adenosquamous–small cell carcinoma. A single benign fibrovascular-glandular polyp was also noted. Adenocarcinomas were more frequent in females, underscoring their predominance and the rarity of other variants.

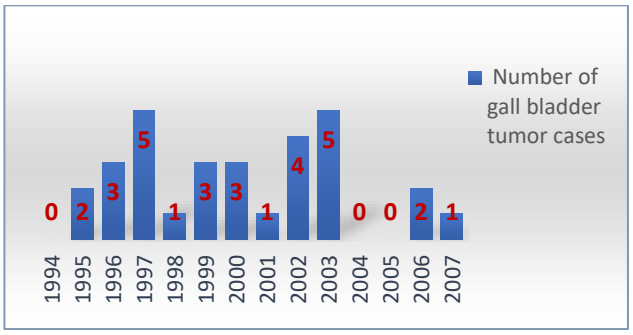

Figure 3. Yearly incidence of gall bladder tumors.

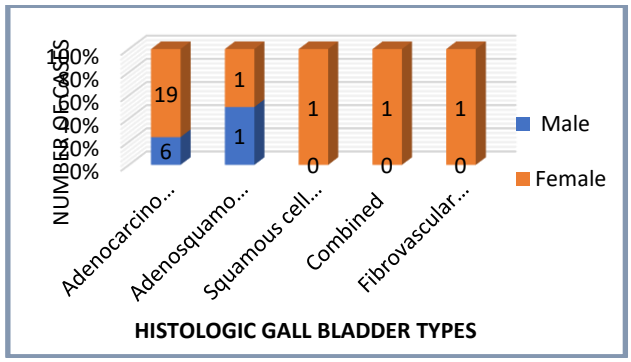

Figure 4. Distribution of gallbladder tumors histological subtypes by sex.

Figure 5 shows that 45% of gallbladder carcinomas were well-differentiated, 31% moderately differentiated, 20% poorly differentiated, and 4% undifferentiated. The predominance of well-differentiated tumors suggests a more favorable prognosis, while 24% of high-grade tumors indicate a more aggressive subset.

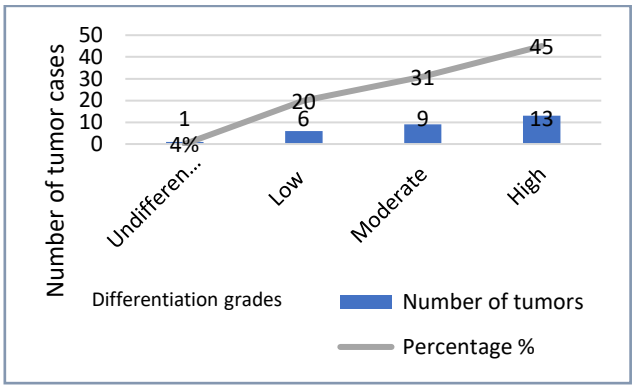

Figure 5. Distribution of Gall bladder carcinomas by the level of differentiation.

Figure 6 depicts the staging distribution of gallbladder carcinoma within the cohort, with all cases presenting at advanced stages. Stage T3 tumors constituted 69% of cases, indicating local extension beyond the gallbladder, potentially amenable to surgical intervention. The remaining 31% were classified as Stage T4, signifying invasion into major vascular structures or adjacent organs, consistent with a poor prognosis and limited treatment options.

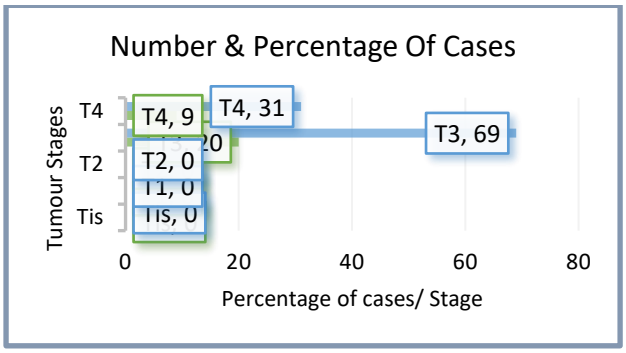

Figure 6. Percentage of gall bladder tumors according to stages.

Figure 7 illustrates the incidence of vascular and neural invasion in gallbladder carcinoma cases. Among the analyzed cases, 75.86% (22 cases) exhibited perivascular, intravascular, and perineural infiltration, with intraneural invasion identified in three cases. These patterns reflect an aggressive tumor phenotype with a high potential for local progression and distant dissemination via hematogenous and perineural pathways.

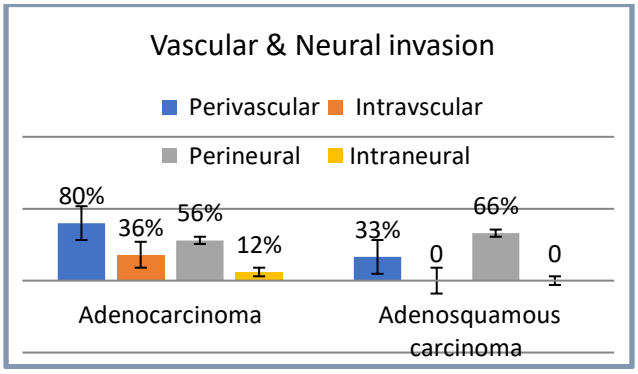

Figure 7. The microscopically found vascular and neural invasion of gall bladder tumors.

Figure 8 shows chronic inflammation in over two-thirds of gallbladder tumor cases, emphasizing its role as a major risk factor for gallbladder carcinoma (GBC). Histopathological changes in the epithelium serve as early indicators of neoplastic transformation. Repeated injury and repair in chronic cholecystitis can lead to metaplasia, dysplasia, and eventual malignancy.

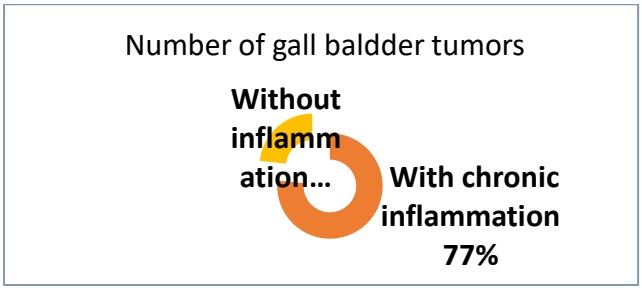

Figure 8. The association of the tumors with chronic inflammation.

Discussion

Incidental gallbladder carcinoma (GBC) remains an uncommon yet significant histopathological finding

in cholecystectomy specimens, with reported rates ranging from 0.2% to 2% worldwide [11]. In our series at the Surgical Pathology Department of Misurata Medical Center, 29 cases of incidental GBC were identified among 3,107 cholecystectomy specimens (0.93%) examined between 1994 and 2007. These procedures were predominantly performed for benign conditions, such as chronic cholecystitis and cholelithiasis. This incidence is consistent with global data, though slightly lower than that reported by Lam et al. (2005), who found a 2.3% incidence among 2,700 ethnic Chinese patients undergoing cholecystectomy for acute cholecystitis in Hong Kong [12]. Such findings highlight the importance of routine histopathological examination (HPE) of all gallbladder specimens, particularly given the often-asymptomatic nature of GBC and the frequent incidental detection of this malignancy. Significant geographic variations in GBC incidence have been well documented. For example, northern India reports the highest rates, reaching 7 to 10 per 100,000, compared to an average of 1.2 per 100,000 in Western countries [13].

A broader analysis by [14] Ramalhosa (2022) supports these disparities, identifying 41 cases of GBC (0.45%) among 9,150 cholecystectomies over 11 years. Our findings are in line with these international trends, suggesting the need for heightened awareness and region-specific considerations when assessing GBC risk. In terms of age, GBC in our cohort predominantly affected older adults, with a mean age of 62.5 years. This aligns with findings by Ramalhosa et al. (2022), who reported a mean patient age of 70.1 years, and U.S. data showing typical diagnosis at age 72, with incidence increasing significantly after 60 and peaking in mortality at 4.9 per 100,000 for individuals over 75 [15]. These age-related trends also appeared in our data, with the highest incidence observed in females aged 56–65 and males aged 46–55. This pattern reflects previous studies, including those by Aesun Shin, Sooyoung Cho, and Sashibhusan Dash [3,16,4], which also reported an increased incidence in older adults. Indian research by Rajni Yadav (2013) further corroborates this, highlighting a peak incidence in the seventh decade of life [17]. Notably, these findings may be influenced by the natural progression of risk factors, such as gallstones and chronic inflammation, which are more prevalent in the aging population. Moreover, the progressive increase in incidence with age, from 0.16 per 100,000 in individuals aged 20–49 to 8.69 per 100,000 in those aged 75 and above in the U.S. (2010), further underscores the importance of age as a key risk factor. [1].

Sex-based differences in GBC incidence are particularly striking. In our study, 76.7% of cases occurred in females, with a female-to-male ratio of 3.3:1, which is consistent with several international reports. For example, Randi et al. (2006) found the highest female incidence rates in Delhi (21.5/100,000), South Karachi (13.8/100,000), and Quito (12.9/100,000), with elevated rates also observed in Korea, Japan, and parts of Central and Eastern Europe [18]. While the global female-to-male incidence ratio typically approximates 3:1, this ratio varies significantly across regions—ranging from near parity in East Asia to over 5:1 in countries such as Spain and Colombia. These regional variations likely reflect differences in risk factors, including genetics, hormonal influences, and environmental exposures [18]. Supporting this, Cook et al. (2009) utilized SEER data (1975–2004) to report that GBC is one of only five cancers more common in women, and it remains the only gastrointestinal malignancy with a consistently higher incidence in females [19].

The role of estrogen in this sex discrepancy is significant. Estrogen increases bile cholesterol saturation, which promotes gallstone formation—a major risk factor for GBC [15]. This hormonal influence is further supported by higher GBC incidence in women with high parity and repeated pregnancies. Additionally, although estrogen and progesterone receptor levels may be similar between sexes, their coexpression is significantly higher in females, potentially suggesting hormonal pathways in tumor development [1]. Furthermore, genetic predispositions, such as TP53 gene mutations and the presence of gallstones, are more strongly associated with early-stage GBC in women [5]. Epidemiological evidence consistently shows that women are affected by GBC two to six times more frequently than men [7, 16]. This disparity is particularly pronounced in countries such as Pakistan, northern India, and among American Indian women [1]. Global data, including those from Okumura Kenji (2021), report approximately 220,000 cases of GBC in 2018, with the disease remaining rare (1.2% of all cancers).

Despite its rarity, its incidence shows considerable regional variation, with the highest rates reported in Southeast Asia (e.g., Thailand) and Latin America (e.g., Bolivia and Peru). GBC also accounts for around 1.7% of all cancer-related deaths, making it the most lethal malignancy of the biliary tract [6]. The consistently higher burden of disease among females across diverse populations further reinforces the hypothesis that reproductive and hormonal factors may play a critical role in GBC development [3].

Acute cholecystitis (AC), primarily triggered by gallstones (~90%), remains the most common surgical pathology of the gallbladder, with Acalculous cases constituting the minority [20, 21]. Although typically benign, AC has been associated with gallbladder carcinoma (GBC), particularly in elderly patients presenting with acute symptoms [20]. Phlegmonous cholecystitis—a severe form of AC marked by transmural inflammation and necrosis—may further increase this risk [21]. Lam et al. reported a 2.3% incidence of GBC among 2,700 cholecystectomy specimens, with a notably higher frequency in acutely presenting ethnic

Chinese patients, suggesting that GBC can mimic or coexist with AC, underscoring the importance of early pathological assessment [12].

In our cohort, all 12 patients diagnosed with phlegmonous cholecystitis were female, predominantly in the 46–55 (50%) and 36–45 (33.3%) age groups. Among the broader group of 275 patients with phlegmonous exacerbation of chronic cholecystitis, females accounted for 66.5% (female-to-male ratio 2:1). The highest incidence was observed between 46 and 65 years, indicating a consistent age and gender distribution across disease severity. These patterns suggest a middle-aged to older female predominance in both acute and chronic inflammatory gallbladder conditions. Chronic inflammation is recognized as a key driver in the metaplasia–dysplasia–carcinoma sequence of GBC pathogenesis, irrespective of gallstone presence [22, 5, 23].

In our study, chronic fibrous cholecystitis was identified in 45.9% of cholecystectomy specimens, aligning with rates reported in similar cohorts [5, 9]. The peak prevalence in patients aged 46–65 supports the established correlation between aging and gallbladder inflammation [1]. A notable finding was the striking female predominance in chronic cholecystitis cases, with a female-to-male ratio of 8:1—exceeding commonly reported ratios of 3:1 to 6:1 [1, 2]. This pronounced gender disparity may reflect hormonal, genetic, or lifestyle-related factors, warranting further investigation. Collectively, these findings underscore the overlapping demographic and pathological features of inflammatory gallbladder diseases and GBC. They highlight the importance of vigilant histopathological evaluation in patients—especially older women—presenting with acute or chronic cholecystitis to facilitate early detection and management of malignancy. Future studies should aim to clarify the mechanisms behind gender susceptibility and explore strategies for early intervention in high-risk populations.

Gallbladder carcinoma (GBC) predominantly affects older adults and shows a clear female predominance. In our study, all cases occurred in individuals aged ≥45 years, with most patients older than 56. This observation aligns with previous studies: Justo et al. reported a mean age of 72 years with 70% female patients, while George Bazoua and Hamza (2007) found a median age of 61 years with a similar gender distribution in a cohort of 2,890 cholecystectomy specimens [24, 25]. SEER data (2015) further confirm a rising incidence and mortality rate with age, particularly beyond 75 years [15]. These findings highlight the importance of clinical vigilance in elderly patients, particularly women undergoing cholecystectomy for chronic gallbladder disease. Histologically, adenocarcinoma was the predominant tumor type, consistent with reports indicating that over 90% of GBCs are adenocarcinomas [6, 1].

In our cohort, 45% of tumors were well-differentiated, while 24% were poorly differentiated or undifferentiated, reflecting the biological heterogeneity of the disease. Rare variants—adenosquamous, squamous, and mixed types—were also identified. Most cases were diagnosed at an advanced stage: 69% at T3 and 31% at T4. Vascular and perineural invasion was present in 75.9% of cases, underscoring the tumor's aggressive nature and the frequent delay in diagnosis due to non-specific early symptoms. These findings are consistent with previous studies that have identified poor differentiation, lymphovascular invasion, and depth of infiltration as key adverse prognostic factors [26, 7]. Treatment is stage-dependent. T1a tumors confined to the lamina propria are typically curable by simple cholecystectomy, whereas T2 and T3 tumors usually require extended resections. Survival outcomes for these stages vary considerably [27, 28]. T4 tumors are generally unresectable and managed palliatively. Notably, only about 25% of GBCs are resectable at diagnosis [29], reinforcing the need for early detection. At the molecular level, hormonal receptor profiling may offer additional prognostic information. Park et al. (2009) reported ERβ expression in 43.3% of GBCs, with an association to tumor differentiation yet paradoxically linked to poorer outcomes, suggesting a complex and possibly dualistic role of hormone signaling in GBC pathogenesis [16].

CONCLUSION

This retrospective study, covering the period from 1994 to 2007, highlights key epidemiological and pathological features of gallbladder carcinoma (GBC) in our region. Although rare, GBC was most often diagnosed incidentally in cholecystectomy specimens, predominantly affecting older adults and females, and frequently associated with chronic cholecystitis. The advanced stage at diagnosis in most cases underscores the importance of routine histopathological examination of all gallbladder specimens, even in the absence of clinical suspicion. Our findings not only align with global trends but also provide essential baseline data for future investigations. This study lays the groundwork for ongoing and prospective research aimed at monitoring GBC incidence, identifying local risk factors, and improving early detection and management strategies in our population.

Conflict of interest. ***Nil.***

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