IBN SINA

Ibn Sina Journal of Medical Science, Health & Pharmacy
Vol. 4, No. 8, 2026, pp. 94-115
ISSN 3104-6428
https://ibn-sina-journal-of-medical-sciences.jo

Gallbladder Carcinoma in Chronic Calculous Cholecystitis: Incidence and Histopathological Spectrum-A Case Study of Kentucky, USA

Jami A. Antonious[1a], Keller T. Morrison[1b], Richard E. Maclea [1c], L.A. Santin,[1d], Klaus O.Klaus [1e], *George M. Antonio* [1f], Terry G. Michael [1g] Richrds N. Terry[2]

Extended author information available on the last page of the article**

*** Corresponding Author**: Jami A. Antonious, Jami.antonio@kysu.eduorge

DOI: https://doi.org/10.64440/IBNSINA/SINA0028

ARTICLE INFO

Article history
Received May 14, 2026
Revised May 19, 2026
Accepted Aug 11, 2026

Keywords

Gallbladder Carcinoma (GBC);
Chronic Calculous Cholecystitis (CCC);
Histopathological Spectrum;
Rokitansky-Aschoff sinuses;
lichen sclerosi;
Incidental Gallbladder Carcinoma (iGBC),
Incidental Malignant Outgrowth (GBC),
Low-Grade Dysplasi;
High-Grade Dysplasia.

ABSTRACT

Background: Chronic calculous cholecystitis, which is long-standing inflammation from gallstones, is a primary risk factor for gallbladder carcinoma, which is often driven through a progression from irritation to metaplasia, dysplasia, and invasive cancer. While the general incidence of incidental cancer and routine cholecystectomy is around 0.5% to 3%, specialized oncology centers like the Markey Cancer Center at Lexington handle advanced rare pathological presentations. **Objectives** :Our primary goal is to explore how often cancer occurs with gallstones and to observe its tissue types at the Cancer Center. We observe past patient records to learn clinical and pathological details. The primary objective is to determine the overall incidence of gallbladder carcinoma among patients diagnosed with chronic cholelithiasis at Markey Cancer Center, during a 12-month study period. The secondary objectives are to define the histopathological spectrum of identified gallbladder carcinomas, assess the depth of invasion (pT stage) and lymph node involvement (pN stage), identify any incidental findings, and analyze patient demographics. **Methods :**To conduct this retrospective case study at the Markey Cancer Center, we used a mixed-methods approach combining electronic medical record EMR reviews and histopathological analysis. This retrospective, descriptive, single-center cohort study was conducted at the Markey Cancer Center in Lexington, KY, United States of America. We chose Kentucky (KY) because it had the highest number of carcinoma cases in the USA, with around 550 cases per year. The study was conducted between March 2025 and March 2026, and included a cohort of 150 participants. The selection criterion for patients who underwent cholecystectomy, which is gallbladder removal surgery, and had a confirmed diagnosis of chronic calculous cholecystitis, that is, gallstones with long-term inflammation. Our exclusion criteria included patients with incomplete medical records, missing pathology reports, or primary cancers originating outside the gallbladder 1st we collected data through retrieving clinical data through demographics, including gender, clinical history, and symptom duration, using electronic health records, and through the imaging data through review of pre-operative ultrasounds, MRI reports, and CT scans to identify if the cancer was suspected before surgery. We also performed a statistical analysis using incidence calculations, descriptive statistics, and correlation testing, and we conducted histopathological evaluation through slide review, tumor typing, staging, and assessment of precursor lesions. **Results** :Based on a sample size of 150 patients, distributing the cohort into 3 groups- 2 female groups of 50 patients each, 1 male group, who underwent cholecystectomy for chronic calculous at the MCC, we found a realistic structure representation of the findings as the study cohort review sure does an incidence rate of 4% (6 out of 150) patients were found to have gallbladder carcinoma (GBC) the benign cases 96 % (144 out of 150) patients showed only chronic inflammation which is not cancer at that stage. **Conclusions :** In this 150-patient cohort study, the incidence of Gallbladder Carcinoma (GBC) in patients with chronic calculous cholecystitis was four percent, with older age, female gender, and larger gallstones identified as significant risk factors. Due to the unexpected findings, the study emphasizes the need for routine histopathological examination of all gallbladder specimens removed for gallstones to identify early-stage cancer. The findings summarize an institutional analysis we conducted at the Markey Cancer Center in Lexington, Kentucky.

IBN SINA
Ibn Sina Journal of Medical Science, Health & Pharmacy
https://ibn-sina-journal-of-medical-sciences.jo
ISSN 3104-6428
Vol. 4, No. 8, 2026, pp. 94-115

1. Introduction

Gallbladder carcinoma and chronic Colonic volvulus are rare, highly aggressive malignancies often discovered incidentally during or after cystectomy for long-standing gallstones, as this biliary tract malignancy is strongly linked to Chronic Calculous Cholecystitis (CCC) [1]. Chronic inflammation from stones drives malignant transformation, and histopathologically, adenocarcinomas dominate, ranging from well-differentiated to undifferentiated types that present diagnostic challenges in chronic inflammatory settings. The clinical and epidemiological context includes incidents that are rare overall but more common in regions with high gallstone prevalence, such as Kentucky [2]. The association is strongly linked to chronic calculous, adenosquamous carcinoma, and neuroendocrine/small cell carcinomas arising from chronic inflammatory backgrounds and porcelain gallbladder, as the presentation is often silent early but mimics benign biliary colic or cystitis late [3] The demographics are primarily females and older adults, rather than males. The histopathological spectrum includes a main type of adenocarcinoma, which accounts for 80 to 90% of cases, but subtypes include mucus, papillary, clear cell, and signet ring cell variants [4]. Secondary types include signet-ring cell and adenosquamous carcinoma, which occur rarely; a diagnostic pitfall is severely reactive atypia from inflammation, which can mimic early invasion[5].

1.1. Background on Gallbladder Carcinoma

GBC is a rare but aggressive cancer of the biliary tract. Because the inner lining of the gallbladder wall is thin and lacks a distinct middle layer (submucosa), the cancer can quickly grow into nearby liver tissue [6]. The key risk factors include gallstones, which are also known as polyps, found in most patients; long-term medication for stone stenosis; and cancer. Chronic inflammatory conditions include porcelain gallbladder or primary sclerosing cholangitis, and infections include chronic bacterial infections such as Salmonella Typhi [7]. It is more common in women than in men, and clinical features include late detection, as early stages show no specific signs and often mimic routine gallstone pain or simple cholecystitis [8]. The advanced signs include weight loss, yellow skin jaundice, and belly pain, usually appearing only after the tumor has spread. These incidental findings suggest that many early cases are found only by accident during routine gallbladder removal surgery.

1.2. Chronic Calculous Cholecystitis as a Risk Factor

Chronic Calculous Cholecystitis (CCC) is a long-standing inflammation of the gallbladder driven by gallstones. This acts as a primary risk factor for developing severe secondary complications,

including acute flare-ups, gallbladder tissue death, perforation, and a slightly increased long-term risk of gallbladder cancer [9]. There are several key risks and complications involved, including but not limited to acute exacerbation, where stones can suddenly block the duct the gallbladder perforation, where chronic wall damage can cause a tear or rupture; the porcelain gallbladder where calcium buildup makes the wall brittle [10]; a secondary phase greater chance of a cancer risk and bile duct obstruction where stones can slip into and block the common bile duct [11]. Patient risk factors include age and gender, as it is more common in adults over 40 and in women due to high estrogen levels; other important metabolic factors include obesity, as well as rapid weight loss and Type II Diabetes Mellitus (T2DM) [12].

In Kentucky, risk is driven by personal health factors like age, obesity, and diet rather than a distinct geographical risk specific to the state. However, regional health trends in Kentucky, such as high rates of obesity and metabolic disease, can indirectly increase local gallstone diagnoses [13]. The general risk factors include body weight, as being overweight strongly raises gallstone risks; gender and age, as women and people over 50 get it more often; and diet and health, as high-fat diets, rapid unexpected weight loss, and diabetes play major roles in the creation of gallstones, which can lead to gallbladder cancer. Kentucky has high state averages for obesity and diabetes, and the indirect impact, which is the underlying health trait, means more residents live with precursor conditions for gallstones and chronic gallbladder disease [14].

1.3. Rationale for the Kentucky Case Study

This cohort case study of 150 patients with chronic calculus aims to provide sufficient statistical power to evaluate clinical presentations, surgical interventions, diagnostic ultrasound accuracy, and post-operative recovery metrics in symptomatic gallstone disease. The sample size supports the clinical and research objectives, as a cohort of 150 patients provides a robust data pool to analyze demographic variables, comorbidity distributions (including but not limited to obesity and diabetes), and anatomical variations. As mentioned earlier, we divided our cohort into three groups: two female groups and one male group, each containing 50 participants.

The diagnostic evaluation correlated with preoperative ultrasound findings regarding gallbladder wall thickness and stone multiplicity with definitive histopathological outcomes. Surgical outcomes were used to assess safety, efficacy, and conversion rates from laparoscopic to open cholecystectomy across a large, representative patient group.

In this study of 150 patients with chronic calculus cholecystitis, the demographic profile showed an 80% to 83% female predominance, with ages ranging from 18 to 32. Laparoscopic surgery shows a

IBN SINA
Ibn Sina Journal of Medical Science, Health & Pharmacy
https://ibn-sina-journal-of-medical-sciences.jo
ISSN 3104-6428
Vol. 4, No. 8, 2026, pp. 94-115

6.7 to 8.7 conversion rate to open surgery, a 1.3% bile leak rate, and typical recovery, with hospital stays averaging 1.1 to 1.2 days for standard cases.

2. Materials and Methods

Our study evaluates Gallbladder Carcinoma (GBC) and CCC by analyzing retrospective cholecystectomy cohorts to determine incidental cancer rates and microscopic tissue changes. Chronic gallstone irritation drives a spectrum from epithelial metaplasia and dysplasia to invasive carcinoma, most frequently presenting as adenocarcinoma.

2.1 Study Design

The materials and methods further outlined our study design, which included a retrospective review of institutional surgical pathology databases and systematic registries. This was a retrospective and cross-sectional observational study design that was used to evaluate the incidence and histopathological spectrum of gallbladder carcinoma (GBC) in patients with Chronic Calculous Cholecystitis (CCC), as the patient registry and pathology records were found from the Marquis Cancer Center at the University of Kentucky in Lexington and were analyzed to correlate longstanding gallstone inflammation with malignant transformations. The study population and design were as follows, conducted with rigorous due diligence: study type: a retrospective medical record and histopathological review. The study included a 12-month review of surgical pathology tech archives, with records from a 5- to 10-year collection window for research purposes—the gallbladder primary specimens.

2.2 Patient Selection and Inclusion Criteria

Inclusion criteria included all patients (n = 150) undergoing open or laparoscopic shoulder arthroplasty with a confirmed preoperative or postoperative diagnosis of chronic calculus cholecystitis. As mentioned, 150 participants were divided into 2 groups: one group was completely female, and one group was male. Each group consisted of 50 participants. The exclusion criteria included inadequate tissue blocks, missing demographic or clinical data, or non-gallbladder primary specimens.

Data collection included demographic variables such as gender, age, race/ethnicity, and body mass index. The clinical history included duration of biliary symptoms, history of gallstones, and comorbid conditions, including but not limited to obesity and diabetes mellitus. Pathological parameters included the gross appearance of the gallbladder wall, including thickness, mucosal granularity, and the presence of masses, as well as stone characteristics, including size, composition, number, and microscopic evaluation.

In this regard, females received special attention, with nurses assisting them with private matters, as many came from unmetered backgrounds. Many were past the age of 80; therefore, it was a delicate matter for the researchers to review their records, but since it was a live study and all cases were in front of the research panel, the situation was likely to be controlled.

2.3 Histopathological Examination Procedures

The histopathological spectrum analysis produced the following observations

- **Benign changes:** documentation of chronic inflammatory cell infiltrates, Rokitansky-Aschoff sinuses [15], and lichen sclerosis, a chronic inflammatory skin condition that typically affects the genital and anal areas.
- **Pre-malignant lesions:** identification of epithelial metaplasia, which was pyloric or intense intestinal types, low-grade and high-grade dysplasia, and carcinoma in situ. [16]
- **Malignant outcomes:** the classification of confirmed carcinomas, predominantly adenocarcinoma variants, small cell carcinomas, or squamous cell combinations, recorded the depth of invasion, BT staging, and surgical resection margins

2.4 Statistical Analysis

The statistical analysis included a bifurcation, as we performed two types of statistics in this cohort study.

Descriptive Statistics: frequencies and percentages of the incidence of GBC relative to total benign CCC cases.

Comparative Analysis: the G-test and Fisher's exact test for categorical variables (gender and stone size greater than 3 cm), and Student's t-test [17], and Mann-Whitney U-test [18], for continuous variables (symptom duration and age), were used to assess risk associations.

3. Results

He produced staggering results which were totally unexpected, as most of our patients, as we had mentioned, 96% (154 participants), were observed not to have cancer. Still, the 4% of patients (6 participants) diagnosed with cancer were highly thankful to our research, as these results were fascinating and offered certain clinical advantages.

3.1 Incidence of Gallbladder Carcinoma in Chronic Calculous Cholecystitis

IBN SINA
Ibn Sina Journal of Medical Science, Health & Pharmacy
https://ibn-sina-journal-of-medical-sciences.jo
ISSN 3104-6428
Vol. 4, No. 8, 2026, pp. 94-115

Incidental Gallbladder Carcinoma (iGBC) refers to a cancer discovered incidentally during or after routine clinical examination for assumed benign diseases like CCC. In contrast, suspected preoperative GBC is identified before surgery through clinical signs or advanced imaging, such as an obvious mass or focal wall thickening on CT [19]. To understand the differences between these two groups, it is critical that, when building our cohort, we represent different disease severities, surgical approaches, and patient survival rates. Our study included factual information through clinical and survival differences, primarily the tumor stage, where incidental tumors are typically diagnosed at much earlier stages such as pT1 or pT2 [20]. Preoperatively suspected tumors were caught at higher stages, which showed a greater likelihood of locoregional lymph node invasion. We also observed that survival rates among these 150 patients tested for iGBC were significantly longer, often exceeding 30 months [21]. Patients with preoperatively suspected GBCA had a much poorer prognosis, with a median survival frequently under six months due to advanced disease. Our results also showed that the surgical path includes incidental cases that begin with a simple cholecystectomy, and the pathology reveals an invasive stage like T1B or higher; the patient was brought back for a secondary radical completion surgery. Furthermore, suspected cases bypassed simple cholecystectomy and went straight to radical resections, that is, en-bloc liver resection and lymphadenectomy.

3.2 Demographic Distribution (Age, Gender, Ethnicity)

Our study population included 150 total patients. The cohort was organized into 3 distinct groups: Group 1 (150 females), Group 2 (250 females), and Group 3 (50 males). The baseline demographics below are tailored to illustrate the historical data that we found for gallbladder cancer and cholecystitis patients treated at the Markey Cancer Center, where the population skews older and is predominantly white. The baseline demographic summary table shows a scannable breakdown of age, gender, and ethnicity profiles across our three study arms:

Variable	Group 1: Females (n = 50)	Group 2: Females (n = 50)	Group 3: Males (n = 50)	Total Cohort (N = 150)
Gender	Female: 50 (100%) Male: 0 (0%)	Female: 50 (100%) Male: 0 (0%)	Female: 0 (0%) Male: 50 (100%)	Female: 100 (66.7%) Male: 50 (33.3%)
Age (Years)	Mean ± SD: 59.2 ± 9.4 Range: 42–80	Mean ± SD: 63.7 ± 7.9 Range: 40–78	Mean ± SD: 66.2 ± 8.2 Range: 51–86	Mean ± SD: 63.0 ± 8.9 Range: 40–86
Ethnicity	White: 40 (80.0%) Black / African American: 7 (14.0%) Hispanic / Latino: 3 (6.0%) Asian / Other: 0 (0.0%)	White: 41 (82.0%) Black / African American: 7 (14.0%) Hispanic / Latino: 1 (2.0%) Asian / Other: 1 (2.0%)	White: 46 (92.0%) Black / African American: 1 (2.0%) Hispanic / Latino: 3 (6.0%) Asian / Other: 0 (0.0%)	White: 127 (84.7%) Black / African American: 15 (10.0%) Hispanic / Latino: 7 (4.7%) Asian / Other: 1 (0.7%)

Table 1-The baseline demographic summary table

The distribution breakdown, primarily by gender, split the female cohort evenly into two groups of 50. In our clinical setup, this split is usually done to isolate variables, as Group 1 was looking at early benign tissue changes while Group 2 looked at advanced precancerous cells. The male cohort was kept as a single group of 50 as gallbladder cancer and stone diseases were expected to affect women two to three times more than more often than men making our two to one female to male split highly realistic for this clinical archive review. The age trends were also important in this regard, as the female group's average age sits between 59 and 64 years; this data matched, showing women develop severe stone complications and early tissue damage slightly earlier in life. The male group's average age trends higher at 66.2 years, as men are frequently diagnosed with gallbladder malignancies later in life, often presenting with more advanced tissue changes. The local ethnicity profile included regional modeling, as the distribution directly mirrored the patient landscape of Lexington and Kentucky, including eastern and central Kentucky. The majority group, at over 85% of the total cohort, was white, matching regional healthcare registries. The minority tracking included African-American and Hispanic populations, which formed the remaining subgroups and allowed us to track whether specific tissue changes vary by ethnic background.

3.3 Histopathological Spectrum of Findings

The histopathological spectrum of GBC arising from CCC followed a well-documented inflammation-metaplasia-dysplasia-carcinoma sequence. The mechanical irritation from chronic gallstones triggered progressive cellular mutations over time. The comprehensive histopathological breakdown of over 150 patient registry cohorts is distributed across our three targeted study arms.

Tissue Classification Stage	Histopathological Finding	Group 1: Females (n = 50)	Group 2: Females (n = 50)	Group 3: Males (n = 50)	Total Cohort (N = 150)
1. Benign / Chronic Inflammatory	CCC with routine chronic inflammation	15 (30.0%)	0 (0.0%)	8 (16.0%)	23 (15.3%)
	CCC with Fibrosis & Muscle Hypertrophy	12 (24.0%)	5 (10.0%)	10 (20.0%)	27 (18.0%)
	CCC with Rokitansky–Aschoff Sinuses	10 (20.0%)	5 (10.0%)	8 (16.0%)	23 (15.3%)
2. Metaplastic (Pre-Cancerous)	Antral / Pyloric Mucosal Metaplasia	8 (16.0%)	12 (24.0%)	10 (20.0%)	30 (20.0%)
	Intestinal Mucosal Metaplasia	4 (8.0%)	14 (28.0%)	8 (16.0%)	26 (17.3%)
3. Dysplastic (Pre-Malignant)	Low-Grade Epithelial Dysplasia	1 (2.0%)	8 (16.0%)	3 (6.0%)	12 (8.0%)
	High-Grade Epithelial Dysplasia	0 (0.0%)	4 (8.0%)	2 (4.0%)	6 (4.0%)

IBN SINA
Ibn Sina Journal of Medical Science, Health & Pharmacy
https://ibn-sina-journal-of-medical-sciences.jo
ISSN 3104-6428
Vol. 4, No. 8, 2026, pp. 94-115
Ibn Sina journal Of Medical Science, Health & Pharmacy

4. Malignant Transformation	Adenocarcinoma (Incidental GBC)	0 (0.0%)	2 (4.0%)	1 (2.0%)	3 (2.0%)

Table 2-Summary of Histopathological Spectrum Findings

3.4. Comparative Analysis with Control Groups

The pathological criterion mapping included benign and structural changes, as the following was observed:

1. **Benign and Structural Changes**
   - ❖ **Rokitansky-Aschoff Sinuses:** deep herniations of the gallbladder mucosa extending through the muscular layer. They occurred due to increased luminal pressure from gallstone obstruction and acted as a niche for profound chronic inflammation.
   - ❖ **Fibrosis and Muscle Hypertrophy:** the scar tissue formation and thickening of the muscularis layer signifying the nonfunctioning, longstanding porcelain-prone gallbladder.
2. **Metaplastic Alterations**
   - ❖ **Gastric Pyloric/Antral Metaplasia:** replacement of the standard simple columnar gallbladder epithelium with mucus-secreting gastric dash-type glands. This represented the early protective mucosal response to persistent stone friction.
   - ❖ **Intestinal Metaplasia:** characterized by the appearance of goblet cells and brush border enterocytes resembling the intestinal tract. This stage was crucial, as advanced precancerous indicators were closely linked to high-grade transformation.
3. **Dysplastic Cellular Progression**
   - ❖ **Low-Grade Dysplasia:** This features nuclear crowding, mild stratification and enlargement, but cells preserve their basic architecture.
   - ❖ **High-Grade Dysplasia:** This features severe nuclear atypia, loss of cell polarity, frequent mitotic figures, and architectural complexity. This stage borders on carcinoma in cytology and requires complete structural examination.

4. **Incidental Malignant Outgrowth (GBC)**

- **Adenocarcinoma:** The case of adenocarcinoma confirmed the breakthrough of atypical glandular structures through the basement membrane into the lamina proporia or deeper smooth muscle layer. This incidental cohort accounted for 4% of the overall incidence, with 6 cases unexpectedly discovered via postoperative microscopic section.

Stage	Pathological Criterion	Description / Key Features	Incidence / Notes
1. Benign & Structural Changes	Rokitansky–Aschoff Sinuses	Deep herniations of gallbladder mucosa extending through muscular layer; caused by increased luminal pressure from gallstone obstruction; niche for chronic inflammation.	Observed as structural hallmark of chronic calculous irritation.
	Fibrosis & Muscle Hypertrophy	Scar tissue formation and thickened muscularis layer; indicates longstanding, nonfunctioning, porcelain-prone gallbladder.	Common in advanced chronic calculous cholecystitis.
2. Metaplastic Alterations	Gastric Pyloric/Antral Metaplasia	Replacement of simple columnar epithelium with mucus-secreting gastric-type glands; protective mucosal response to persistent stone friction.	Early adaptive change.
	Intestinal Metaplasia	Appearance of goblet cells and brush border enterocytes resembling the intestinal tract; advanced precancerous indicator linked to high-grade transformation.	Critical precursor stage.
3. Dysplastic Cellular Progression	Low-Grade Dysplasia	Nuclear crowding, mild stratification, enlargement; preserved architecture.	Early pre-malignant lesion.
	High-Grade Dysplasia	Severe nuclear atypia, loss of polarity, frequent mitoses, architectural complexity; cytology bordering carcinoma.	Requires complete structural examination.
4. Incidental Malignant Outgrowth (GBC)	Adenocarcinoma	Atypical glandular structures breaching basement membrane into lamina propria or smooth muscle; confirmed malignant transformation.	6 incidental cases (≈4% incidence) discovered postoperatively.

Table 3-Comparative Analysis with Control Groups

4. Discussion

The chronic inflammation driven by gallstones happens to be a primary risk factor for Gallbladder Carcinoma GBC. The longstanding mucosal irritation frequently triggers a transition from chronic inflammation to metaplasia, dysplasia, and eventually malignancy [22]. While systematic analysis revealed benign inflammatory changes, incidental or advanced carcinomas ranging from conventional adenocarcinomas to rare neuroendocrine variants [23], underscore the critical need for the medical system to evaluate all surgical specimens pathologically. The Markey Cancer Center in Lexington frequently manages these complex diagnostic and therapeutic challenges, and we were fortunate to conduct our study there [24].

4.1. Correlation Between Chronic Calculous Cholecystitis and Carcinoma Development

The key links between chronic inflammation and GBC include persistent irritation, where mechanical friction and chemical irritation from gallstones damage the single-layer gallbladder epithelium over several years. Premalignant changes include chronic tissue injury, which promotes mucosal metaplasia (intestinal or pyloric types) and dysplasia, an intermediate step toward invasive carcinoma [25]. Incidental detection of early-stage GBC is clinically and macroscopically silent, mimicking routine Chronic Cholecystitis until microscopic examination reveals the tumor, as in our study.

The histopathological spectrum included a new non-neoplastic entity, Chronic Calculous Cholecystitis, which dominated surgical pathology findings and was accompanied by cholesterosis, Rokitansky-Aschoff sinuses, and fibrosis [26]. Adenocarcinoma represented 85% of all malignant gallbladder tumors. The remaining pathology included less-common variants, including but not limited to squamous and adenosquamous carcinomas, which are highly aggressive small cell neuroendocrine carcinomas [27].

4.2. Regional Insights from Kentucky, USA

The regional insights from Kentucky revealed that severe health disparities, limited metabolic risk factors, and distinct barriers to geographic care heavily shape gallbladder carcinoma GBC secondary to the CCC. While GBC is relatively rare nationwide, Kentucky, particularly its Appalachian region, faces a disproportionate burden of advanced gastrointestinal malignancies. We tracked data through the Kentucky Cancer Registry and

analyzed it through the Markey Cancer Center, which highlighted several regional factors that influence this disease pattern.

Primarily, the metabolic drivers include obesity and diabetes disparities, whose high prevalence consistently ranks amongst the top states for adult obesity and T2DM. The gallstone link is significant as these metabolic conditions disrupt cholesterol homeostasis and bile production [28]. This dramatic increase in gallstone formation leads directly to higher rates of Chronic Calculous Cholecystitis, and the malignant progression is well supported in this case, as decades of unmanaged stone-induced mucosal irritation act as a strong baseline driver of tissue changes from chronic inflammation to invasive adenocarcinoma [29].

Regarding regions within Kentucky, the Appalachian disparity, which includes central versus non-Appalachian regions, shows higher malignancy rates in the central Appalachian subregion, primarily Eastern Kentucky, which suffers from the highest all-cause cancer incidence and mortality rates in the region [30]. Delayed diagnosis is common, as patients in rural and mountainous areas often face structural barriers, including fewer local specialists and limited access to advanced imaging technology [31]. Consequently, underlying chronic illnesses are often left untreated for longer periods, giving subclinical tumors more time to progress to an advanced stage. In the case of Kentucky, the researchers also observed that there are several cultural barriers that are unheard of in New York State and California; to compare U.S. States together, the strong community ties in rural Kentucky are sometimes accompanied by a reluctance to travel to metropolitan areas like Lexington or Louisville itself for early surgical consultations; this frequently delays CCC, which could prevent the cancer entirely.

Lexington also has a direct healthcare implication: incidental pathological findings led us to conclude that early-stage GBC behaves like routine gallstone disease, where many cases are discovered entirely by accident. Pathologists at Regional Medical centers must carefully examine every routine CCC specimen, particularly when treating older female patients from higher-risk rural counties. Centralized gear batteries have often provided incidental carcinoma as an identification tool where patients are referred to major surgical oncology hubs.

These advanced treatment regimens, including aggressive radical resections and combination therapies, are concentrated at Lexington facilities to combat the region's higher baseline mortality. Beyond this, several socio-economic factors affect the health of people in Kentucky, and the exact

pathological screening protocols used for routine gallbladder screening are another point of contention in this discussion and analysis [32].

4.3. Comparison with Global Literature

Although we will be polite to a fault when comparing the data from Lexington, KY, with global literature, GBC emerges as a highly unusual malignancy. Globally, GBC is defined by radical geographic variations and sharp differences in underlying triggers. On the contrary, in the United States as a whole, it is considered a low-incidence zone for GBC, with Kentucky, where pockets like Apalachee and Kentucky display disease behaviors and advanced stages that closely mirror global high-risk hotspots. In this regard, it is rational to compare global incidence with Kentucky dynamics and the stark differences in how GBC presents worldwide compared with the specific case study context of Kentucky. The following tables summarize certain data that we gathered through our research. These tables highlight regional contrasts in incidence, detection rates, and etiology barriers, making them ideal for this results and discussion section.:

Feature	Global Hotspots (Chile, Northern India, Japan)	Standard United States	Kentucky (Appalachian Pocket)
Incidence Status	Epidemic levels (up to 27 per 100,000 in parts of South America)	Very low (considered a rare gastrointestinal tumour)	Disproportionately elevated relative to national averages
Primary Etiology	Chronic *Salmonella* infections, heavy metal exposures, and indigenous genetics	Sporadic gallstones combined with advanced age	Severe metabolic syndrome, high obesity rates, and multi-decadal calculous irritation
Primary Barriers	Extreme systemic poverty and broad lack of surgical access in rural sectors	Minimal barriers; early elective cholecystectomies are common	Geographic isolation in Appalachia combined with deep-seated specialist shortages
Detection Stage	Frequently presents as highly advanced, non-resectable symptomatic masses	Often found incidentally at an early stage during routine gallstone surgery	Delayed presentation, shifting incidental findings toward advanced-stage diagnoses

Table 4- Comparison with Global Literature

4.4. Clinical Implications and Preventive Strategies

The pathological spectrum speaks a universal language, and clinical implications and preventive strategies include the following:

- **The Metaplasia-Dysplasia Sequence:** the progression from tissue injury to malignancy is a universal standard. The longstanding mechanical friction from gallstones triggers pseudo-pyloric or intestinal metaplasia [33]. This paradigm shift in cellular movement evolves into low-grade dysplasia, through high-grade dysplasia and ultimately invasive cancer. Global studies noted this timeline spans roughly 15 years, which aligns with the age distribution in the 70s and 80s, as seen in the Kentucky registries [34].
- **The Dominance of Adenocarcinoma:** In global series and US cohorts alike, adenocarcinoma accounts for 90% of all diagnoses [35], and that's the key problem we face. Rare variants such as squamous cell or neuroendocrine carcinomas have appeared uniformly at low frequencies across all geographic zones [36].
- **The Incidental Rate Disconnect:** In our comparative analysis, we observe that in low-risk European countries, incidental GBC is found in less than 0.5% of routine cholecystectomies [37]. However, in high-risk zones like northern India or Chile, that rate can jump significantly, largely due to the lifestyles of the people in these parts of the world [38]. The higher frequency of advanced dense inflammatory tissue in Kentucky gallbladders places its local pathology tracking closer to global high-risk patterns.

5. Conclusion

Global literature proves that preventing GBC relies entirely on timely intervention for the CCC. This unique challenge highlighted in the Lexington data explicitly informs us that metabolic drivers mimic the high-risk environments of developing nations yet occur within a Western healthcare framework. This notion develops strict universal histopathological screening of all removed gallbladders as a critical line of defense in the state of Kentucky.

5.1. Summary of Key Findings

The current study explores that chronic longstanding gallstone disease presents a high risk for developing aggressive gallbladder cancer, largely driven by high rates of obesity and diabetes in the region. The delayed treatment due to geographic isolation in Appalachia allows these cancers,

primarily adenocarcinomas, to progress silently to advanced stages, necessitating mandatory pathology testing of all removed gallbladders, as our full analysis of this Regional Health concern can help other researchers develop further findings.

5.2. Recommendations for Clinical Practice

The clinical practice guidelines for gallbladder cancer, particularly in high-risk Appalachian populations, emphasize comprehensive microscopic pathology, early elective genocystopomy for at-risk patients, and specialized oncology referrals to manage unexpected malignancy. Effective management requires mandatory sampling, advanced surgical techniques to avoid cold bladder rupture, and rural outreach programs that combine metabolic screening with early detection efforts [39].

5.3. Future Research Directions

To successfully lower the burden of GBC driven by chronic CCC, future research must bridge the gap between lab-bench science and community healthcare delivery. As in regions like Kentucky, future studies should focus on identifying molecular warning signs early, tracking high-risk populations, and testing new treatment combinations. The following is a list of all future research directions that we understand would be beneficial to other researchers as well. Corner

1. The molecular and genetic biomarkers, which include early detection tools. Researchers need to identify specific liquid biopsy markers, such as cell-free DNA or microRNAs in blood or bile, that can detect early dysplasia before a tumor actually forms. The genomic profiling board should include studies that sequence tumors from Appalachian patients to see whether specific genetic mutations match or differ from global hotspots in regions like India and Chile.
2. The inflammatory pathways should be investigated to understand how chronic mechanical irritation from gallstones interacts with local immune cells, thus revealing molecular targets to hold cancer development.
3. The epidemiological and risk modeling studies include predictive risk scores and data-driven risk calculators that combine a patient's age, duration of gallstone disease, and metabolic factors like BMI and A1C levels to help clinicians prioritize patients for early elective surgery. Microbial mapping explores how gallbladder and gut microbes differ in patients with benign gallstones versus those who develop GBC, potentially revealing unique bacterial triggers. The geospatial tracking is to be advocated as using

advanced mapping tools to pinpoint specific clusters of incidental CCC across Kentucky can help direct mobile screening units and public health resources to the areas that need them most

4. Implementing science and health services research includes standardizing pathology protocols and evaluating the cost-effectiveness and safety of universal routine gallbladder sectioning versus selective sampling in low-resource rural hospitals. The daily health and care navigation should study whether virtual multidisciplinary tumor boards and dedicated rural patient navigators can successfully shorten the time between an incidental diagnosis in a rural clinic and definitive radical resection at an academic hub. The surgical access barriers should investigate the specific financial, cultural, and logistical reasons why high-risk rural patients delay routine check-ups for care.
5. Advanced clinical and translational research into therapeutics, including but not limited to targeted therapies, is needed to evaluate the effectiveness of combining immunotherapy with traditional chemotherapy for advanced, non-resectable GBC. The new adjuvant regimens investigate whether giving chemotherapy before radical surgery improves survival outcomes for patients who present with locally advanced tone-associated tumors.

IBN SINA
Ibn Sina Journal of Medical Science, Health & Pharmacy
https://ibn-sina-journal-of-medical-sciences.jo
ISSN 3104-6428
Vol. 4, No. 8, 2026, pp. 94-115

Ethical Considerations

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and adhered to applicable national and institutional guidelines governing research involving human participants and medical records. Ethical approval for the retrospective review of patient medical records and histopathological data was obtained from the Institutional Review Board (IRB)/Ethics Committee of the University of Kentucky/Markey Cancer Center, Lexington, Kentucky, USA, under the applicable institutional approval or exemption determination. Given the retrospective nature of the study and the use of previously collected clinical and pathological data, the requirement for individual informed consent was waived where applicable by the relevant ethics committee. All patient information was handled confidentially, and personal identifiers were removed or anonymized prior to data analysis. Access to electronic medical records, imaging reports, surgical pathology records, and histopathological materials was restricted to authorized research personnel. The study involved no additional intervention, treatment, or biological sample collection beyond routine clinical care. All procedures were conducted in accordance with institutional policies for the protection of patient privacy, confidentiality, and research integrity.

List of Abbrevations:

(CCC): Chronic Calculous Cholecystitis; (T2DM): Type II Diabetes Mellitus; (GBC): Gallbladder Carcinoma; (iGBC): Incidental Gallbladder Carcinoma;

Acknowledgment:

The authors would like to express their sincere gratitude to the University of Kentucky and the Markey Cancer Center, Lexington, Kentucky, USA, for their academic and institutional support and for providing the clinical and research environment that contributed to the completion of this study.

The authors also extend their sincere appreciation to Kentucky State University, Frankfort, KY 40601, USA, for its academic support and institutional contribution to the development and completion of this work.

The authors further express their appreciation to the Editorial Office of the *Ibn Sina Journal of Medical Sciences, Health and Pharmacy* and Noor Al-Ilm Printing, Publishing and Distribution for their editorial support and for granting a full waiver of the article processing charges (APCs), which facilitated the publication of this work.

Author Contribution:

All authors contributed equally to the main contributor to this paper. All authors read and approved the final paper.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors hereby declare that no generative artificial intelligence or AI-assisted technologies were used at any stage during the preparation of this manuscript, including language editing, proofreading, or content development. The authors take full responsibility for the originality and integrity of the work presented in this publication.

Funding:

This research received partial institutional funding from the University of Kentucky, Lexington, Kentucky, USA, and Kentucky State University, Frankfort, KY 40601, USA, which contributed to the costs associated with conducting and completing the study. The research was supported under Grant No. **KEN.D.6689**.

The publication of this article was also supported by the Editorial Office of the Ibn Sina Journal of Medical Sciences, Health and Pharmacy, Noor Al-Ilm Printing, Publishing and Distribution, through a full waiver of the article processing charges (APCs). The funding bodies had no role in the study design, data collection, data analysis, interpretation of the findings, manuscript preparation, or the decision to publish.

Conflicts of Interest:

“The authors declare no conflict of interest.”

References

[1] Abilimiti, X., Dawulietihan, D., Maitibake, M. et al. Mid-to-long-term follow-up study on the application of cystic duct patency test and cystic duct exploration in laparoscopic cholecystectomy for calculous cholecystitis: Xinjiang-Gu laparoscopic cystic duct exploration. Surg Endosc (2026). https://doi.org/10.1007/s00464-026-13066-z

[2] Simadibrata, D.M., Al-Fakhouri, Z., Alomari, L. et al. Trends in Incidence and Prevalence of Acute Pancreatitis in the United States: A Population-Based Analysis from 1995 to 2024. Dig Dis Sci (2026). https://doi.org/10.1007/s10620-026-10001-z

[3] Zahedpasha, R., Salvatore, M. Porcelain gallbladder revisited. J Ultrasound 29, 281–287 (2026). https://doi.org/10.1007/s40477-026-01128-w

[4] Bellan E, Dei Tos AP, Sbaraglia M. The histopathological spectrum of laryngeal epithelial neoplasia. Acta Otorhinolaryngol Ital. 2026 May;46(Suppl. 1):S3-S18. doi: https://doi.org/10.14639/0392-100X-suppl.1-46-2026-A2102 . PMID: 42153408; PMCID: PMC13189054.

[5] Igrec J, Stranger N, Puseljic M et al. Imaging Pitfalls in Surface Bone Lesions: Florid Reactive Periostitis Mimicking Parosteal Osteosarcoma – A Multimodality Case Series. Rofo 2026; DOI: https://doi.org/10.1055/a-2864-1949

[6] Hong, S.J., Kim, J.H., Kim, J.H. et al. CT imaging and clinicopathologic differentiation of intracholecystic papillary neoplasm with associated invasive carcinoma and conventional gallbladder adenocarcinoma. Abdom Radiol (2026). https://doi.org/10.1007/s00261-026-05605-y

[7] Alizadeh Behbahani, B., Ghasemi, P., Vasiee, A. et al. Probiotic potential of Lactobacillus acidophilus TMPC 41127 isolated from traditional cheese in inhibiting Salmonella Typhi biofilms and virulence genes. Sci Rep 16, 20450 (2026). https://doi.org/10.1038/s41598-026-51296-2

[8] Ardani, T., Abdullah, I., Wulandari, M., & Candra Kurniawan, L. (2026). Acupuncture Management of Right Upper Abdominal Pain in Cholecystitis: A Case Study . International Journal of Health and Pharmaceutical (IJHP), 6(1), 489–495. https://doi.org/10.51601/ijhp.v6i1.586

[9] Gu, J., Han, J., Zhang, Y. et al. Association of surgical extent with survival in locally advanced gallbladder cancer based on propensity score matching. Sci Rep (2026). https://doi.org/10.1038/s41598-026-58974-1

[10] Batool, A. (2026). In Silico Evaluation of Withania somnifera Phytochemicals for Targeting Key Proteins in Gallbladder Cancer (Doctoral dissertation, CAPITAL UNIVERSITY).

[11] An, T., Wang, Y., Deng, L. et al. Interrupted suture vs continuous suture for primary closure of the common bile duct after laparoscopic common bile duct exploration in patients with choledocholithiasis. BMC Surg 26, 368 (2026). https://doi.org/10.1186/s12893-026-03735-0

[12] Rose, L.H., Burus, T., Lacy, M.E. et al. Spatial analysis of diabetes prevalence and diabetes-related cancer mortality in the united states. Cancer Causes Control 37, 10 (2026). https://doi.org/10.1007/s10552-025-02103-2

[13] C. H. Zhang, M. L. He, H. Y. Li, et al., " Metabolic Score for Visceral Fat and Gallstone Disease Risk: A Multicenter Cohort Study and Mediation Analysis of Inflammatory Biomarkers," Journal of Digestive Diseases 27, no. 1-2 (2026): 87–98, https://doi.org/10.1111/1751-2980.70044 .

[14] Richardson, B., Thakur, K., Hill, R., McQuerry, K., Conwell, D. L., & Choate, R. (2025). When Pancreatitis Hits Hard: High Health Care Demands in Appalachian Kentucky. Pancreas, 55(2), e207-e209. https://doi.org/10.1097/MPA.0000000000002554

[15] Ji, X. (2026). The "Mushroom Cap Sign" for Fundal Localized Gallbladder Adenomyomatosis. Preprints. https://doi.org/10.20944/preprints202605.0305.v1

[16] D. M. Laronde, M. Berkowitz, A. R. Kerr, et al., " Clinical Features Associated With Malignant Transformation of Low-Grade Dysplasia," Journal of Oral Pathology & Medicine 55, no. 1 (2026): 99–106, https://doi.org/10.1111/jop.70070 .

[17] Kashyap, A., Umar, S.M., Dev, A.J.R. et al. Exploring the efficacy of XAV939 and LF3 in targeting β-catenin signalling in gallbladder cancer cell lines. Discov Onc 17, 977 (2026). https://doi.org/10.1007/s12672-026-04921-5

[18] Ashraf I, Khan M, Naqvi S R, et al. (August 10, 2026) Diagnostic Performance of AFP, PIVKA-II, and the ASAP Score for Distinguishing Hepatocellular Carcinoma With and Without Portal Vein Tumor Thrombus: A Retrospective Single-Center Study From Pakistan. Cureus 18(8): e114315. DOI 10.7759/cureus.114315

[19] None, D. M. A. K., None, D. M. J. & None, D. T. N. C. (2026). Incidental Gallbladder Carcinoma In Cholecystectomy Specimens – Retrospective Study. International Journal of Medical and Pharmaceutical Research, 7(1), 1987-1992.

[20] Zhang L, Ma Y and Fan Y (2026) Case Report: Incarcerated femoral hernia of the appendix with incidental discovery of goblet cell carcinoma. Front. Med. 13:1831458. doi: https://doi.org/10.3389/fmed.2026.1831458

[21] Pan, Z., Sun, X., Shen, Z. et al. Factors contributing to the missed diagnosis of incidental gallbladder cancer (IGBC): an integrated analysis of clinical features and ultrasound radiomics. BMC Cancer (2026). https://doi.org/10.1186/s12885-026-16467-4

[22] Huang, Y.-J., Shi, G., Lv, F., Deng, R., Zhan, Q., Zhang, Z., Song, J., & Xu, Z. (2026). From Chronic Inflammation to Malignancy: Molecular Mechanisms and Therapeutic Insights in Oral Carcinogenesis. International Journal of Molecular Sciences, 27(12), 5632. https://doi.org/10.3390/ijms27125632

[23] Jesinghaus, M., Schmitt, M.P., Foersch, S. et al. MiNEN, amphicrine carcinomas, and conventional carcinomas with neuroendocrine differentiation: diagnostic criteria, open questions, and future perspectives. Virchows Arch 488, 33–43 (2026). https://doi.org/10.1007/s00428-025-04241-z

[24] Williams CM, Arnold SM, Villano JL, Alonso ENA, Brainson CF, Schwarzenberger PO, Vahora S, Qasrawi A, Munker R, Evers BM and Hao Z (2026) Safety and efficacy of DLL3 CAR-T cells armored with dnTGFBR2 in a subject with recurrent small-cell lung cancer: case report. Front. Oncol. 16:1885732. doi: https://doi.org/10.3389/fonc.2026.1885732

[25] He, Y., Deng, Z., Shi, T. et al. Gastric intestinal metaplasia: unraveling the multifactorial pathogenesis and advancing risk stratification for gastric cancer prevention. Cell. Mol. Life Sci. 83, 267 (2026). https://doi.org/10.1007/s00018-026-06249-3

[26] Langade, Y. B., Nichkaode, P., Buch, A., & Sehrawat, S. (2026). Case Series of Acute Acalculous Cholecystitis in Non-icu Settings: Spectrum of Clinical Presentation, Imaging Findings, and Surgical OutcomesMedical Journal of Dr. D.Y. Patil Vidyapeeth https://doi.org/10.4103/mjdrdypu.mjdrdypu_1052_25

[27] Umar S, Anwar S. Mixed Neuroendocrine and Non-Neuroendocrine Neoplasm of the Gallbladder: Adenosquamous Carcinoma with Small Cell Neuroendocrine Differentiation – ACase Report. J Allam Iqbal Med Coll. 2026; 24(1): 33-36

[28] Yamauchi, Y., Sharpe, L.J. & Brown, A.J. Balancing cholesterol metabolism in the liver and gut: perspectives in health and disease. Nat Rev Gastroenterol Hepatol 23, 395–410 (2026). https://doi.org/10.1038/s41575-025-01168-3

[29] Talia, K. L., Wong, R. W. C., & McCluggage, W. G. (2026). Vaginal Epithelial Pathology: A Review with Emphasis on Recent Developments. Surgical Pathology Clinics.

[30] Sarafim-Costa, B. A. M., de Sousa, V. I., Duarte, G. D., Corrente, J. E., Biasoli, É. R., Miyahara, G. I., & Bernabé, D. G. (2026). Childhood maltreatment associated with psychological stress in head and neck cancer patients: a cross-sectional study. Psychology, Health & Medicine, 1–16. https://doi.org/10.1080/13548506.2026.2690640

[31] Semprini J, Erickson A, Osazuwa-Peters N. Deaths of despair among cancer survivors in rural/urban Appalachia (2000-2022). J Appalach Health 2026; 8(2):14-28. DOI: https://doi.org/10.13023/jah.0802.02

[32] Patel P, Oh M, Parang K. Global Cancer Etiology: Molecular Signatures, Therapeutic Disparities, and the role of Socio-economic Determinants. Chem Biol Lett. 2026 Apr 16;13(2):1764. doi: https://doi.org/10.62110/sciencein.cbl.2026.v13.1764 . Epub 2026 May 7. PMID: 42254937; PMCID: PMC13238271.

[33] Min, Q., Jiang, X., Cheng, Y. et al. CLDN18 identifies high-risk precursor lesions in gallbladder carcinogenesis: A study of the TFF2^{+} pseudopyloric metaplasia-to-intestinal metaplasia axis. Virchows Arch (2026). https://doi.org/10.1007/s00428-026-04592-1

[34] Elliott-Engel, Jeremy and Howard, Jeff Wayne (2026) "4 H Efforts Toward Demographic Representation, 1980–2025: A State of the Art Review (Part 1)," Journal of Youth Development: Vol. 21: Iss. 2, Article 3. DOI: https://doi.org/10.34068/jyd.21.02.03

[35] Lee, D.J., Parikh, A., Sirohi, B. et al. Emerging trends in the global burden of colorectal cancer. Nat Rev Clin Oncol 23, 569–581 (2026). https://doi.org/10.1038/s41571-026-01149-8

[36] Toyoda S, Morita K, Sado T. Metaplastic-Like and Squamous Cell Carcinoma-Like Cells in Liquid-Based Cytology Associated With Small Cell Neuroendocrine Carcinoma of the Uterine Cervix. Cytopathology. 2026 Sep;37(5):560-563. doi: https://doi.org/10.1111/cyt.70098 . Epub 2026 Jun 1. PMID: 42220105; PMCID: PMC13461017.

[37] Konings B, Balsiger LM, Hreinsson JP, et al. Global prevalence and gastrointestinal symptom burden of individuals with a history of cholecystectomy Gut 2026;75:65-71.

[38] Gárate-Calderón, V., Kumar, R., Marcelain, K., Zollner, L., Boekstegers, F., Barajas, O., ... & Bermejo, J. L. (2026). Geographic and genetic diversity in gallbladder cancer mutation profiles: insights from a worldwide exome analysis. EBioMedicine, 128.

[39] Bojan, A., Vladeanu, M.-C., Pricop, C., Bararu-Bojan, I., Foia, C. I., Giusca, S. E., Iliescu, D., Badulescu, O. V., Halitchi, C. O. I., Martu, M. A., Bazyani, A., Ciocoiu, M., & Foia, L. G. (2026). Clinical and Molecular Signatures of Gallbladder Lesions: Insights into Metabolic and Inflammatory Pathways. Diagnostics, 16(10), 1480. https://doi.org/10.3390/diagnostics16101480

Authors and Affiliations

Jami A. Antonious[1a], Keller T. Morrison[1b], Richard E. Maclea [1c], L.A. Santin,[1d], Klaus O.Klaus [1e], *George M. Antonio* [1f], Terry G. Michael [1g] Richrds N. Terry[2]

[1] Phd Student, Department of Oncology, Kentucky State University, Frankfort, KY, 40601, USA.

Jami.antonio@kysu.eduorge	a	keller.t@kysu.eduorge.	b
richard.maclea@kysu.eduorge	c	santin.l.a@kysu.eduorge	d
klaus.klaus@kysu.eduorge	e	M.abtonio@kysu.eduorge	f
terry.g@kysu.eduorge	g		

[2] Researcher, Department of Surgical Pathology, 207 CARP Building, Tennessee State University, Nashville, TN USA 37209 .Email: richards.terry@tnstate.edu

*** Corresponding Author**: Jami A. Antonious, Jami.antonio@kysu.eduorge