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Incidence and Predictors of Incidental Gallbladder Carcinoma After Cholecystectomy: A Prospective Algerian Multicenter Cohort Study

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ABSTRACT

Introduction: Incidental gallbladder carcinoma (IGBC) is an unexpected diagnosis after cholecystectomy for presumed benign disease. Prospective multicenter data from Africa remain limited. We aimed to determine the incidence of IGBC and identify associated factors.

Methods: This predefined secondary analysis used data from the Algerian Cholecystectomy Outcomes and Determinants Study, a prospective multicenter cohort study conducted across 32 surgical centers in Algeria. Consecutive adult patients undergoing cholecystectomy for presumed benign gallbladder disease between January 1 and June 30, 2025, were included. All gallbladder specimens underwent systematic histopathological examination. The primary outcome was the incidence of IGBC. Associations were explored using univariable logistic regression and age-adjusted Firth penalized likelihood logistic regression to address sparse-data bias.

Results: Among 813 patients, IGBC was identified in eight cases, corresponding to an incidence of 0.98%. Patients with IGBC were significantly older than those without IGBC (mean age 67.4 *versus* 48.9 y). In the primary age-adjusted model, age was independently associated with IGBC (adjusted odds ratio 1.08 per year, 95% confidence interval 1.01-1.14). Diabetes and conversion to open surgery showed positive but imprecise associations in exploratory analyses.

Conclusions: In this prospective multicenter North African cohort, 0.98% of cholecystectomies for presumed benign disease revealed IGBC, supporting routine histopathological examination of all cholecystectomy specimens.

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Introduction

Cholecystectomy is one of the most frequently performed abdominal surgical procedures worldwide and represents the definitive treatment for symptomatic gallstone disease and its complications. The widespread adoption of laparoscopic cholecystectomy has led to substantial improvements in postoperative recovery and perioperative outcomes.[1] As a consequence, gallbladders removed for presumed benign disease are routinely subjected to systematic histopathological examination.[2]

A clinically important finding following cholecystectomy is incidental gallbladder carcinoma (IGBC), defined as gallbladder cancer unexpectedly diagnosed on intraoperative assessment or postoperative histopathological examination in patients operated on for benign indications. IGBC is of particular clinical relevance because its prognosis is highly stage dependent.[3] Early-stage disease may benefit from timely reresection and specialized hepatobiliary management, whereas delayed diagnosis is frequently associated with advanced disease and poor oncological outcomes. Consequently, accurate estimation of IGBC incidence and identification of associated risk factors are essential to optimize surgical strategies, pathological assessment policies, and postoperative referral pathways.[4,5]

The reported incidence of IGBC varies widely across geographic regions, reflecting differences in gallbladder cancer epidemiology, patient demographics, surgical indications, preoperative imaging practices, and the systematic use of histopathological examination of cholecystectomy specimens. Higher incidences have been reported in regions with endemic gallbladder cancer, while lower rates are observed in Western countries. These variations underscore the importance of region-specific data to inform clinical decision-making and healthcare planning.[6,7]

Despite the high volume of cholecystectomies performed annually in Algeria, published national data on the incidence and determinants of IGBC remain scarce. Existing evidence is largely limited to single-center retrospective series or academic theses, characterized by heterogeneous methodologies and limited external validity. Moreover, there are no prospective multicenter studies providing nationally representative estimates of IGBC incidence and its associated clinical and operative factors. This represents a significant gap in the understanding of gallbladder cancer epidemiology in Algeria and, more broadly, in North Africa.[8]

To address this gap, the Algerian Cholecystectomy Outcomes and Determinants Study (AL-CODS) was designed as a prospective, multicenter observational cohort including patients undergoing cholecystectomy for presumed benign disease across diverse health care settings in Algeria. Beyond its primary objectives, AL-CODS provides a unique opportunity to assess the incidence of IGBC and to explore factors associated with its occurrence in a large, nationally representative population.

The present study is a predefined secondary analysis of the AL-CODS cohort. Its objectives are to determine the incidence of IGBC following cholecystectomy for presumed benign disease in Algeria and to identify independent predictors associated with IGBC.[9]

Beyond its national relevance, this study addresses a critical evidence gap in North Africa and other African settings where cholecystectomy volumes are increasing but region-specific data on IGBC remain limited. Understanding the burden and predictors of IGBC in such contexts is essential to inform pathology policies, referral pathways, and resource allocation across African health systems.

Methods

Study design and setting

This study is a predefined secondary analysis of the Algerian Cholecystectomy Outcomes and Determinants Study (AL-CODS), a prospective, multicenter, observational cohort study conducted in Algeria. While the primary AL-CODS study was designed to evaluate postoperative outcomes following cholecystectomy, the present analysis focuses exclusively on the incidence and predictors of IGBC.

The study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

AL-CODS was conducted across 32 public and private surgical centers distributed throughout Algeria, including university hospitals, regional hospitals, and private clinics.

Patient enrollment occurred between January 1 and June 30, 2025. This 6-month inclusion period was predefined in the AL-CODS protocol and was selected to facilitate close data monitoring, ensure data completeness, and maintain investigator adherence to prospective reporting during the initial nationwide implementation of the collaborative registry.

All consecutive adult patients undergoing cholecystectomy during the study period were screened for eligibility.

Study population

All consecutive adult patients undergoing cholecystectomy during the study period were screened for eligibility.

Patients were eligible for inclusion if they were aged $\geq$18 y and underwent cholecystectomy for presumed benign gallbladder disease, either in an elective or emergency setting, using a minimally invasive or open surgical approach. Postoperative histopathological examination of the gallbladder specimen was mandatory in accordance with the AL-CODS protocol.

Patients with preoperative imaging findings suspicious for gallbladder malignancy, including infiltrative gallbladder lesions or gallbladder polyps larger than 10 mm, were excluded from the study.

Patients were excluded if cholecystectomy was performed as part of a major associated abdominal procedure (including hepatectomy, bariatric surgery, pancreatic resection, or complex biliary reconstruction), or if the patient was aged $<$18 y. Patients with missing or incomplete data were also excluded from the present analysis.

Definition of IGBC

IGBC was defined as gallbladder carcinoma diagnosed on final histopathological examination following cholecystectomy performed for presumed benign disease, with no preoperative suspicion of malignancy. All histological types and stages were included.

Data collection

Data were collected prospectively using a secure, password-protected electronic case report form developed for the AL-CODS study. Participating surgeons registered on the study platform and consecutively included all eligible patients during the inclusion period.

For each patient, demographic variables, clinical presentation, and indication for cholecystectomy were recorded. Operative data included surgical approach and intraoperative findings as documented by the operating surgeon. Histopathological reports were centrally reviewed to identify cases of IGBC, and tumor staging was recorded.

Data entry was performed by registered investigators with access restricted to their own cases. Data completeness and internal consistency were verified before analysis, and only fully completed records were included in the final dataset.

Study outcomes and statistical analysis

The primary outcome of this study was the incidence of IGBC, defined as the proportion of histologically confirmed gallbladder carcinomas diagnosed unexpectedly after cholecystectomy performed for presumed benign disease. The secondary outcome was the identification of clinical, biological, and operative factors associated with the occurrence of IGBC.

Statistical analyses were performed using IBM SPSS Statistics software (version 26.0; IBM Corp., Armonk, NY, USA). Firth regression analysis was carried out using the R extension integrated within SPSS. Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate, and categorical variables are presented as frequencies and percentages.

Univariable logistic regression was used to assess associations between candidate predictors and IGBC. Given the low number of events ($n = 8$), standard multivariable logistic regression was considered to carry a high risk of small-sample bias and separation. Owing to the limited number of events, Firth penalized logistic regression was used to reduce small-sample bias in the estimation of odds ratios.

To minimize overfitting, adjusted models were restricted a priori to age plus one additional covariate per model. The primary adjusted model included age and gallbladder polyp status. Additional covariates (American Society of Anesthesiologists [ASA] status ≥3, anemia, diabetes mellitus, and conversion to open surgery) were evaluated in separate age-adjusted models as exploratory analyses.

Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) are reported. Statistical significance was assessed using penalized likelihood ratio tests, with a two-sided P value < 0.05 considered statistically significant[9]

Ethical approval and trial registration

The AL-CODS study protocol was approved by the Ethics Committee of the University Hospital Establishment of Oran in November 2024. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants, and data were anonymized before analysis.

The AL-CODS study was prospectively registered in a public clinical trial registry: Clinical trial registration number: NCT06481007.[10]

Results

A total of 813 patients undergoing cholecystectomy for presumed benign gallbladder disease were included in the analysis. The study population was predominantly female (77.5%, $n = 630$), with a mean age of 49.0 ± 15.9 y and a mean body mass index of 27.8 ± 4.8 kg/m^2. Most patients were classified as ASA status I-II (96.4%).

According to the World Health Organization performance status scale, the majority of patients had good functional status, with performance status 0 in 77.5% and performance status 1 in 17.0%; only a small proportion had a performance status ≥2.

Most cholecystectomies were performed electively (91.8%), while 8.2% were conducted in an emergency setting. The main indication for surgery was symptomatic cholelithiasis (67.2%), followed by acute cholecystitis (22.5%). The most frequent comorbidities were hypertension (27.1%) and diabetes mellitus (17.8%). Preoperative imaging demonstrated a dilated common bile duct (>8 mm) in 6.6% of patients and perivesicular fluid collection in 3.8%. Gallbladder polyps measuring <10 mm were identified preoperatively in 10 patients (1.2%).

Cholecystectomy was performed predominantly via a laparoscopic approach (82.4%, $n = 670$), with conversion to open surgery required in 4.1% of cases. A primary open approach was used in 13.5% of patients. The mean operative duration was 61.8 ± 33.4 min. Total cholecystectomy was achieved in 96.6% of cases, whereas partial cholecystectomy was performed in 3.3%. Intraoperative cholangiography was used in 3.4% of patients. Abdominal drainage was placed in 33.9% of procedures, and a specimen extraction device was used in 46.9%.

Intraoperative bile spillage occurred in 23.5% of cases and gallstone spillage in 7.4%. Ambulatory cholecystectomy was performed in 25.1% of patients. The mean postoperative hospital stay was 1.87 ± 3.86 d, and 4.1% of patients required postoperative admission to the intensive care unit.

IGBC was identified in eight patients, corresponding to an overall incidence of 0.98% among cholecystectomies performed for presumed benign gallbladder disease. All cases were diagnosed on final histopathological examination of the gallbladder specimen. All patients were referred to specialized hepatopancreatobiliary centers for further oncologic management.

Table 1 – Clinicopathological characteristics of patients with IGBC (n = 08).

Case	Age (sex)	Histologic type	Tumor differentiation	Pathological TNM stage	Bile spillage
1	69 (female)	Adenocarcinoma	Well differentiated	pT2a Nx M0	No
2	68 (male)	Squamous (epidermoid) carcinoma	Well differentiated	pT3 Nx M1	Yes
3	66 (female)	Adenocarcinoma	Well differentiated	pT1a Nx M0	No
4	63 (female)	Adenocarcinoma	Moderately differentiated	pT2a Nx M0	Yes
5	62 (male)	Adenocarcinoma	Well differentiated	pT2a Nx M0	No
6	61 (female)	Adenocarcinoma	Well differentiated	pT2a Nx M0	Yes
7	64 (female)	Adenocarcinoma	Well differentiated	pT3 Nx M1	Yes
8	83 (female)	Adenocarcinoma	Well differentiated	pT2 Nx M0	No

Tumor nodes metastasis staging according to the American Joint Committee on Cancer classification. Nx indicates that regional lymph nodes were not assessed.

Among the eight patients, two presented with stage IV disease and died within 60 d postoperatively. The remaining patients were referred to specialized hepatopancreatobiliary centers and underwent completion radical surgery, consisting of hepatic resection of segments IVb and V with regional lymphadenectomy.

Detailed clinicopathological characteristics of the eight patients with IGBC are summarized in Table 1. The mean age of patients with IGBC was 67.4 y (range 61-83), and six patients were female. Histologically, seven tumors were adenocarcinomas, and one was an epidermoid carcinoma. Regarding tumor stage, one patient had T1a disease, five had T2/T2a tumors, and two presented with T3 disease. Two patients had metastatic disease (M1) at diagnosis. Tumors were predominantly well differentiated, with one moderately differentiated carcinoma.

In univariable logistic regression analyses, patients with IGBC were significantly older and more frequently aged ≥65 y compared with patients without IGBC. Several clinical, biological, and gallbladder-related variables were associated with IGBC, including acute and chronic cholecystitis, gallbladder polyps, higher ASA status, diabetes mellitus, hypertension, lower hemoglobin levels, impaired renal function, longer operative duration, and intraoperative conversion to open surgery. Preoperative hemoglobin levels were significantly lower in patients with IGBC, and anemia was more frequent among patients with IGBC (50.0% *versus* 18.6%, $P = 0.039$). These associations were considered exploratory (Table 2).

Given the very low number of IGBC events, standard multivariable logistic regression was deemed unreliable due to sparse-data bias and potential separation. Therefore, Firth's penalized likelihood logistic regression was applied. To minimize overfitting, the primary adjusted model was restricted a priori to age and gallbladder polyp status. Additional variables (ASA status ≥3, anemia, diabetes mellitus, and intraoperative conversion to open surgery) were evaluated in separate age-adjusted Firth models as exploratory analyses.

In the primary Firth model, age was independently associated with IGBC (aOR 1.08 per year; 95% CI 1.01-1.14; penalized likelihood ratio test [PLRT] $P < 10^{-5}$). Gallbladder polyp status reached statistical significance (aOR 14.69; 95% CI 1.38-88.73; PLRT $P = 0.030$; Table 3).

In age-adjusted exploratory models, ASA status ≥3 (aOR 13.42; PLRT $P = 0.001$) and anemia (aOR 4.19; PLRT $P = 0.043$) were positively associated with IGBC, while diabetes mellitus showed a weaker association (aOR 3.55; PLRT $P = 0.068$). Intraoperative conversion to open surgery was associated with increased odds of IGBC (aOR 5.77), although the estimate was imprecise and of borderline statistical significance (95% CI 0.99-24.4; PLRT $P = 0.051$). These secondary findings should be interpreted cautiously in light of the limited number of events.

Discussion

This secondary analysis of the AL-CODS cohort provides the first prospective, multicenter estimate of IGBC in Algeria. Among 813 consecutive cholecystectomies, IGBC was identified in 0.98% of cases, suggesting an intermediate-risk profile: higher than rates reported in Western populations but lower than endemic regions. These findings offer the first nationally representative data from North Africa and provide a benchmark for clinical and pathological practices in similar settings (Fig.).[7,11-16]

The IGBC incidence of 0.98% is higher than reported in Western registries (0.2-0.3%),[12,13] but lower than in endemic regions of South America and Asia,[7,14,16] supporting an intermediate-risk profile for Algeria. The prospective, multicenter design and mandatory histopathology strengthen the reliability of this estimate. By excluding patients with a preoperative suspicion of malignancy (e.g., polyps ≥10 mm or irregular wall thickening), our study reflects truly incidental cases, reinforcing the value of routine histopathological examination for all cholecystectomy specimens.

In our cohort, age showed the clearest and most consistent association with IGBC. In univariable analysis, age behaved as a strong risk marker, suggesting a progressive increase in IGBC probability with advancing age.

Because IGBC events were rare (n = 8), we used Firth's penalized likelihood logistic regression to limit sparse-data bias. In the primary adjusted model, age remained independently associated with IGBC, confirming that age is a robust predictor in our setting.

This finding is highly concordant with the international literature. In a large Swedish population-based gallstone surgery registry study, older age was among the main predictors

Table 2 – Baseline characteristics and univariable associations with IGBC in patients undergoing cholecystectomy for presumed benign disease ($n = 813$).

Variables	Total population ($n = 813$)	No IGBC group ($n = 805$)	IGBC group ($n = 8$)	P-value	OR	95% CI
Age (y)	49.04 ± 15.89	48.86 ± 15.85	67.38 ± 6.95	0.003	1.081	1.028-1.138
Age ≥65 y	154 (18.9%)	149 (18.5%)	5 (62.5%)	0.007	7.338	1.734-31.044
Female sex	630 (77.5%)	624 (77.5%)	6 (75%)	0.865	0.870	0.174-4.348
BMI (kg/m^2)	27.75 ± 4.76	27.78 ± 4.77	25.30 ± 3.32	0.132	0.865	0.717-1.044
BMI ≥30 (kg/m^2)	221 (27.2%)	220 (27.3%)	1 (12.5%)	0.367	0.380*	0.046-3.105
WHO ≥2	45 (5.5%)	44 (5.5%)	1 (12.5%)	0.387	2.471*	0.297-20.527
Modality of admission						
Elective	746 (91.8%)	741 (91.9%)	5 (75%)		-	-
Emergency	67 (8.2%)	65 (8.1%)	2 (25%)	0.107	3.795	0.751-19.181
Previous admissions						
≤1	750 (92.3%)	744 (92.4%)	6 (75%)		-	-
≥2	63 (7.7%)	61 (7.6%)	2 (25%)	0.090	4.066	0.803-20.574
Acute cholecystitis	201 (24.7%)	196 (24.3%)	5 (50%)	0.025	5.179	1.226-21.865
Gallbladder polyp	10 (1.2%)	9 (1.1%)	1 (12.5%)	0.024	12.635*	1.406-113.562
Biliary colic	546 (67.2%)	545 (67.7%)	1 (12.5%)	0.012	0.068*	0.008-0.557
Biliary pancreatitis	19 (2.3%)	19 (2.4%)	0 (0%)	0.999	NE	NE
Choledocholithiasis	20 (2.5%)	20 (2.5%)	0 (0%)	0.999	NE	NE
Chronic cholecystitis	4 (0.5%)	3 (0.4%)	1 (12.5%)	0.003	38.190*	3.526-413.609
Other	4 (0.5%)	4 (0.5%)	0 (0%)	0.999	NE	NE
ASA ≥3	30 (3.7%)	26 (3.2%)	4 (50%)	0.000	29.962	7.099-126.450
Diabetes	145 (17.8%)	140 (17.4%)	5 (62.5%)	0.005	7.917	1.870-33.511
Hypertension	220 (27.1%)	214 (26.6%)	6 (75%)	0.010	8.285	1.660-41.363
Smoking	94 (11.6%)	93 (11.6%)	1 (12.5%)	0.796	1.239*	0.245-6.265
Asthma	21 (2.6%)	21 (2.6%)	0 (0%)	0.998	NE	NE
COPD	1 (0.1%)	1 (0.1%)	0 (0%)	1.000	NE	NE
Myocardial infarction	5 (0.6%)	4 (0.5%)	1 (12.5%)	0.005	28.607*	2.828-289.406
Heart failure	2 (0.2%)	2 (0.2%)	0 (0%)	1.000	NE	NE
Chronic corticosteroid use	8 (1%)	8 (1%)	0 (0%)	0.999	NE	NE
Chemotherapy	5 (0.6%)	5 (0.6%)	0 (0%)	0.999	NE	NE
Dysthyroidism	54 (6.6%)	52 (6.5%)	2 (25%)	0.058	4.827	0.951-24.508
Stroke	8 (1%)	8 (1%)	0 (0%)	0.999	NE	NE
CKD	2 (0.2%)	2 (0.2%)	0 (0%)	1.000	NE	NE
Cirrhosis	3 (0.4%)	2 (0.2%)	1 (12.5%)	0.002	57.357*	4.647-707.978
Anticoagulant therapy	12 (1.5%)	12 (1.5%)	0 (0%)	0.999	NE	NE
Hemoglobin (g/dL)	12.71 ± 1.42	12.72 ± 1.41	11.67 ± 1.76	0.038	0.579	0.346-0.790
Hemoglobin ≤11.6 g/dL	154 (18.9%)	150 (18.6%)	4 (50%)	0.039	4.367	1.080-17.658
Creatinine level (mg/L)	9.19 ± 4.98	9.14 ± 4.95	13.31 ± 6.87	0.070	1.043	0.997-1.092
Creatinine ≥15 mg/L	34 (4.2%)	32 (4%)	2 (25%)	0.013	8.052	1.564-41.464
Duration of surgery (min)	61.82 ± 33.40	61.58 ± 33	85.63 ± 33.32	0.043	1.015	1.002-1.031
Surgical approach						
Open surgery	110 (13.5%)	108 (13.4%)	2 (25%)		-	-
Laparoscopic surgery	703 (86.5%)	697 (86.6%)	6 (75%)	0.352	0.465	0.093-2.333
Converted surgery	33 (4.1%)	31 (3.9%)	2 (25%)	0.011	8.323	1.614-42.908
Hemorrhage	43 (5.3%)	42 (5.2%)	1 (12.5%)	0.378	2.595*	0.312-21.582

(*continued*)

Table 2 – (*continued*)

Variables	Total population ($n = 813$)	No IGBC group ($n = 805$)	IGBC group ($n = 8$)	*P*-value	OR	95% CI
Bile duct injury	8 (1%)	8 (1%)	0 (0%)	0.999	NE	NE
Digestive injury	3 (0.4%)	3 (0.4%)	0 (0%)	0.999	NE	NE
Same-day surgery	203 (25.2%)	202 (25.1%)	1 (12.5%)	0.423	0.424*	0.052-3.464

BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; NE = not estimable; WHO = World Health Organization.
* ORs for variables with very low event counts should be interpreted with caution due to sparse data.

of incidental gallbladder cancer, with an effect size very close to ours (OR around 1.08 per year).[6] Similarly, a Korean series evaluating IGBC after routine cholecystectomy reported that age >65 y was the only identified risk factor for IGBC in their analysis, reinforcing the clinical usefulness of an age threshold for heightened suspicion and systematic pathology.[7] Evidence syntheses also support this pattern: systematic reviews/meta-analyses of incidental/unsuspected gallbladder cancer consistently describe a higher occurrence in older patients, although the magnitude varies by region and baseline gallbladder cancer incidence.[17]

From a mechanistic perspective, the association with age is biologically plausible. Increasing age likely reflects cumulative exposure to chronic gallbladder inflammation and repeated epithelial injury, favoring progressive dysplastic and neoplastic transformation. As early malignant changes may escape preoperative detection, advanced age as risk marker may help identify patients who warrant more thorough preoperative evaluation, including careful radiological and biological assessment, as well as heightened intraoperative vigilance. In selected high-risk cases, intraoperative frozen-section analysis may be considered to guide surgical strategy and allow timely adjustment of the extent of resection,[2] particularly in centers with hepatobiliary surgical expertise.

In the present study, gallbladder polyps were associated with IGBC in univariable analysis, and this association remained statistically significant after age adjustment. This finding should be interpreted in light of the study

Table 3 – Age-adjusted exploratory Firth penalized logistic regression models for predictors of incidental gallbladder carcinoma.

Predictor	Adjusted OR	95% CI (Wald, penalized)	*P*-value Penalized likelihood ratio test
Model 1: Age + polyp			
Age (per 1 y)	1.08	1.01-1.14	$<10^{-3}$
Polyp	14.69	1.38-88.73	0.030
Predictor	Adjusted OR	95% CI (Wald, penalized)	*P*-value Penalized likelihood ratio test
Model 2: Age + ASA≥3			
Age (per 1 y)	1.05	1.01-1.11	0.048
ASA ≥3	13.42	2.92-62.95	0.001
Predictor	Adjusted OR	95% CI (Wald, penalized)	*P*-value Penalized likelihood ratio test
Model 3: Age + anemia (≤11.6 g/dL)			
Age (per 1 y)	1.07	1.03-1.12	$<10^{-3}$
Anemia (≤11.6 g/dL))	4.19	1.05-16.68	0.043
Predictor	Adjusted OR	95% CI (Wald, penalized)	*P*-value Penalized likelihood ratio test
Model 4: Age + diabetes			
Age (per 1 y)	1.07	1.02-1.13	0.010
Diabetes	3.55	0.92-15.83	0.068
Predictor	Adjusted OR	95% CI (Wald, penalized)	*P*-value Penalized likelihood ratio test
Model 5: Age + conversion			
Age (per 1 y)	1.07	1.03-1.13	0.003
Conversion	5.77	0.99-24.4	0.051

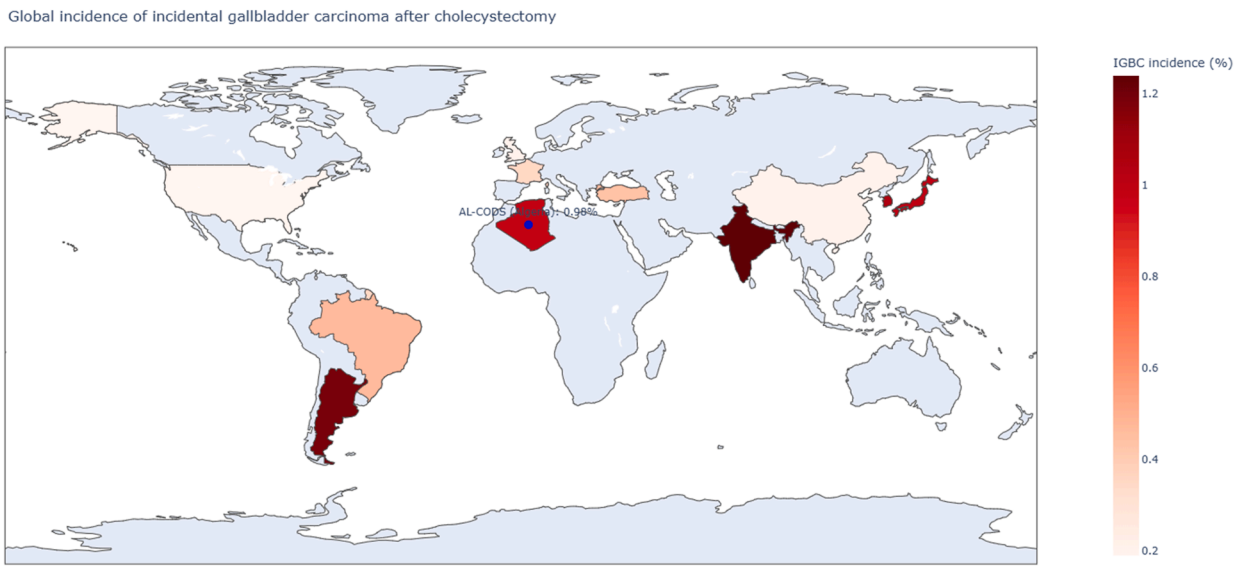

Fig – Reported incidence of IGBC after cholecystectomy for presumed benign disease in selected regions worldwide. The incidence observed in Algeria is derived from the AL-CODS prospective cohort. Incidence estimates for other countries are based on previously published population-based or large institutional studies and are shown for contextual comparison only. Differences in study design, inclusion criteria, histopathological policies, and health care systems preclude direct comparison between regions.

design, as patients with gallbladder polyps larger than 10 mm were excluded a priori, being considered potentially suspicious for malignancy and therefore not eligible for inclusion. Consequently, only small polyps were analyzed, and exposure sparsity was substantial, with a single IGBC case occurring among polyp-positive patients. Despite this limitation, the large magnitude of the adjusted effect estimate suggests a clinically relevant association that could not be robustly quantified due to the very low number of events.

These results are consistent with the existing literature, which identifies gallbladder polyps as a heterogeneous entity with variable malignant potential depending on size, morphology, and patient-related factors, particularly age. Multiple studies have shown that the risk of gallbladder carcinoma increases significantly for polyps ≥10 mm, which justifies their classification as potentially malignant lesions and their exclusion from the definition of incidental disease.[18] However, even smaller polyps have been reported in association with incidental carcinoma, especially in older patients. A large population-based cohort study demonstrated that while gallbladder cancer remains rare in patients with small polyps, cases do occur, suggesting that polyp presence may act as a contextual risk marker rather than a direct causal factor.[19] In this context, the presence of statistical independence after adjustment in our study should not be interpreted as evidence against a true association.

In the present study, a higher ASA status (ASA ≥3) was strongly associated with IGBC in univariable analysis and remained independently associated with IGBC in age-adjusted Firth regression. This finding suggests that IGBC tends to occur in patients with a greater burden of systemic disease even when cholecystectomy is performed for presumed benign indications.

The observed association between higher ASA status and IGBC is consistent with previous reports, which indicate that IGBC is more frequently identified in older and comorbid patients. Large clinical series and population-based studies have shown that patients with IGBC often have a greater burden of comorbid conditions, as reflected by higher ASA classes or comparable comorbidity indices, compared with patients undergoing cholecystectomy for benign disease.[6] Similar findings have been described in other clinical studies, where frailty and comorbidity burden were associated with an unexpected diagnosis of gallbladder carcinoma.[7] Rather than representing a direct oncogenic mechanism, ASA status likely acts as a global surrogate marker of patient vulnerability, encompassing cumulative exposure to chronic inflammatory, age-related, and metabolic conditions, as well as potential delays in disease recognition.

In the present study, preoperative anemia was significantly more frequent among patients with IGBC and remained independently associated with IGBC in age-adjusted Firth regression. This finding suggests that anemia may represent an additional marker of biological vulnerability in patients harboring occult gallbladder malignancy. Anemia in this context may reflect chronic inflammation, nutritional deficiencies, or occult disease activity, reinforcing its role as a nonspecific but clinically relevant warning signal rather than a direct causal factor.

The association between anemia and IGBC has been reported in previous studies. Population-based and clinical series have shown that patients with IGBC often present with lower hemoglobin levels compared with those undergoing

cholecystectomy for benign disease, even in the absence of overt clinical signs of malignancy. Similar observations have been described in Asian cohorts, where anemia was more prevalent among patients with IGBC.[7,20] In a case-control study in which patients with IGBC were matched 1:4 with patients undergoing cholecystectomy for benign disease, anemia was identified as an independent factor associated with IGBC.[20]

In the present study, diabetes mellitus was more frequent among patients with IGBC and showed an imprecise association in age-adjusted Firth regression, although the effect estimate was weaker and less precise than that observed for age, ASA status, or anemia. This finding suggests that diabetes may contribute to an increased background risk of IGBC, while acknowledging the limitations imposed by the small number of events.

These findings are consistent with previous epidemiological and clinical studies reporting an increased risk of gallbladder cancer among patients with diabetes mellitus. Population-based analyses have shown that diabetes is associated with a higher risk of gallbladder cancer, independent of major confounders, with part of the effect mediated by gallstone disease.[21] This association is also supported by meta-analytic evidence showing increased gallbladder cancer risk in individuals with diabetes.[22] In the specific context of cholecystectomy populations, registry-based data have identified diabetes as a factor associated with incidental gallbladder cancer in univariable analyses, although this association did not remain statistically significant after multivariable adjustment.[20] Our findings are further supported by recent large-scale population-based evidence. In a nationwide cohort study including more than 1.7 million matched individuals, diabetes was independently associated with a higher overall cancer risk, with a moderately increased risk of gallbladder cancer among affected patients (hazard ratio 1.34, 99% CI 1.20-1.50) compared with nondiabetic controls. Notably, this risk was even higher in patients with diabetic microvascular complications, supporting the concept that metabolic and inflammatory disease severity may contribute to gallbladder carcinogenesis.[23]

In the present study, operative complexity markers, including longer operative duration and conversion from laparoscopic to open surgery, were significantly associated with IGBC in univariable analysis. Conversion to open surgery remained borderline associated with IGBC after age adjustment, although the estimate was imprecise, reflecting the limited number of cancer events.

These findings are consistent with previous reports indicating that unexpected gallbladder carcinoma is frequently encountered in technically difficult cholecystectomies. Registry-based and clinical studies have shown that patients ultimately diagnosed with IGBC more often experience intraoperative difficulties, including dense adhesions, severe inflammation, distorted anatomy, or unclear Calot's triangle, all of which may prompt prolonged operative time or conversion.[6,24,25]

In this context, intraoperative difficulty, particularly when occurring in older or comorbid patients, should heighten suspicion for occult malignancy. Careful inspection of the gallbladder specimen, avoidance of bile spillage, and systematic histopathological examination are essential.

Several limitations should be acknowledged. The most important is the low number of IGBC events, which reflects the rarity of the disease but limits statistical power and precludes the construction of fully adjusted multivariable models. As a result, associations beyond age should be interpreted as exploratory and hypothesis-generating rather than definitive.

Second, although data collection was prospective, the present analysis represents a secondary analysis of the ALCODS cohort, and the study was not specifically powered to investigate oncological predictors. Residual confounding cannot be excluded, particularly for factors related to intraoperative findings. In addition, some clinically relevant variables, such as polyp morphology or detailed inflammatory grading, were not systematically captured and could not be analyzed.

This study included 813 cholecystectomies over 6 month across 32 hospitals. As cholecystectomy volumes per center in Algeria are lower than in large tertiary centers in high-income countries. As a result, the relatively small number of IGBC events may introduce imprecision in the incidence estimate, which should be interpreted with caution.

From a clinical standpoint, these findings strongly support the continued policy of routine histopathological examination of all cholecystectomy specimens in Algeria. Selective histology strategies would likely miss a substantial proportion of IGBC cases, particularly among older and comorbid patients. Early identification of IGBC is critical, as timely referral for staging and potential reresection can substantially improve outcomes in early-stage disease.

Conclusions

In this prospective multicenter Algerian cohort, IGBC was identified in approximately 1% of cholecystectomies performed for presumed benign disease. Advanced age was the strongest independent predictor, while comorbidity burden, anemia, diabetes, gallbladder polyps, and operative complexity appeared to be associated factors. These findings support the routine histopathological examination of all cholecystectomy specimens, particularly in older and comorbid patients, and provide the first nationally representative estimate of IGBC incidence in Algeria. From a regional perspective, this study offers actionable evidence for African health systems facing similar epidemiological transitions, where selective histopathology strategies may fail to detect early-stage disease.

Supplementary Materials

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jss.2026.04.003

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Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGPT in order to improve language and readability of this manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplementary Data

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CRediT authorship contribution statement

Anisse Tidjane: Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mohammed Tidjane:** Validation, Supervision, Software, Project administration, Formal analysis. **Benali Tabeti:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization **AL-CODS Collaborative Group:** Investigation; Data curation.

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