



# Pathologic results of laparoscopic cholecystectomy specimens with 8148 patients in a single center

Hikmet Pehlevan Özel<sup>1</sup>, Tolga Dinç<sup>2</sup>

<sup>1</sup>Clinic of General Surgery, Mamak State Hospital, Ankara, Türkiye

<sup>2</sup>Department of General Surgery, University of Health Sciences Türkiye, Ankara Bilkent City Hospital, Ankara, Türkiye

## ABSTRACT

**Objective:** The aim of this study was to investigate the frequency of incidental pathologies detected in the surgical specimens of patients who underwent laparoscopic cholecystectomy in high-volume referral center, which accepts patients from different regions of our country, and to contribute to epidemiological studies.

**Material and Methods:** Male and female patients over 18 years of age who underwent laparoscopic cholecystectomy between July 2010 and May 2019 were included in the study. All surgical specimens were taken for pathologic examination. The pathology results were classified into three categories: Benign pathologies (including cholecystitis, non-neoplastic lesions and benign tumors), premalignant pathologies and malignant pathologies.

**Results:** The study included a total of 8148 patients. The mean age was  $49.74 \pm 14.51$  years (minimum 18, maximum 94) and 72.2% of the patients were female. Benign pathologies included cholecystitis in 1742 (21.4%), non-neoplastic lesions in 6203 (76.1%) and benign tumors in 12 (0.1%), premalignant pathologies in 173 (2.1%) and malignant pathologies in 18 (0.2%). Although no statistically significant gender difference was observed between benign, premalignant and malignant pathologies, the incidence of premalignant and malignant pathologies increased with age ( $p=0.273$ ,  $p<0.001$ , respectively).

**Conclusion:** In this study of 8148 patients, incidental premalignant and malignant pathologies were identified in 2.1% and 0.2% of cases, respectively, which is consistent with the findings of literature. These results may be instructive for epidemiologic studies.

**Keywords:** Gallbladder, histopathology, cancer, dysplasia

## INTRODUCTION

Gallbladder surgeries are one of the most common procedures performed by general surgery clinics in daily practice. Cholecystectomy, together with inguinal hernia surgery, appendectomy, and hemorrhoidectomy, constitutes approximately 25% of daily practice (1). Gallbladder surgery may be indicated for a number of conditions, including cholecystitis, symptomatic cholelithiasis, biliary dysfunction, gallstone pancreatitis, polyps, and gallbladder masses. In cases where no pathological findings are present before or during surgery and the macroscopic characteristics appear benign, further management and follow-up may be required due to the presence of underlying pathologies. While the guidelines recommend routine pathological examination, there is still a debate surrounding the necessity of performing this examination on all cholecystectomy specimens, as it is a labor-intensive and costly process (2-5). Gallbladder cancers are rare and have a poor prognosis. The diagnosis of gallbladder cancer is made preoperatively in symptomatic patients, intraoperatively with macroscopic findings, or incidentally during routine pathologic examination after surgery (6). Gallbladder pathologies can be classified as benign, premalignant and malignant. In the 5<sup>th</sup> edition of the World Health Organization's (WHO) classification of tumors of the digestive system, three types of premalignant pathology of the gallbladder were defined: pyloric gland adenoma (PGA), biliary intraepithelial neoplasm (BillIN) and intracholecystic papillary neoplasm (ICPN) (7). Gallbladder cancer is responsible for 7% of cancer-related deaths, only 20% of which are early diagnoses. Furthermore, the incidental diagnosis of gallbladder cancer is increasing worldwide as more laparoscopic cholecystectomies for symptomatic gallbladder disease are safely performed (8). The aim of this study was to analyze the prevalence of incidental gallbladder pathologies in patients with no suspicion of malignancy in the preoperative or intraoperative period, at a surgical center that

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### Corresponding Author

Hikmet Pehlevan Özel

E-mail: hikmet.pehlevan@gmail.com

ORCID ID: [orcid.org/0000-0002-9146-3742](https://orcid.org/0000-0002-9146-3742)

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performs as a high-volume referral center and accepts patients from different regions of our country. Additionally, this study aimed to contribute to epidemiological studies.

## MATERIAL and METHODS

The study was approved by the Institutional Review Board University of Health Sciences Türkiye, Ankara Bilkent City Hospital (date: 04.04.2024 and number: 2-24-131) and conducted in accordance with the Declaration of Helsinki. The study included cholecystectomies performed between 2010 and 2019 in the hospital, which is a high-volume referral center and accepts patients from different regions of our country. A total of 9.259 patients who underwent cholecystectomy for gallbladder disease (cholecystitis, stones, polyps, etc.) were analyzed for the study. 8.148 patients were eligible for the study.

**Inclusion Criteria:** Male and female patients over 18 years of age were included in the study, and only those who underwent standard laparoscopic cholecystectomy for benign causes were investigated.

**Exclusion Criteria:** Those who did not undergo laparoscopic surgery, those who underwent cholecystectomy simultaneously while having surgery for another reason, those with suspected malignancy in the gallbladder and patients already diagnosed with any type of cancer.

## Pathological Classification

Patients were divided into three groups: Benign pathologies, premalignant pathologies, and malignant pathologies. The benign pathologies were categorized into three main groups: Cholecystitis, non-neoplastic lesions, and benign tumors, and then these three groups were divided into subgroups. Cholecystitis was classified as acute, chronic, erosion, follicular, eosinophilic, gangrenous, xanthogranulomatous, and porcelain gallbladder. Non-neoplastic lesions were classified as cholelithiasis, cholesterolosis, cholesterol polyp, adenomyoma, and metaplasia (gastric antral metaplasia, pyloric metaplasia, intestinal metaplasia, osseous metaplasia). Benign tumors were classified as biliary adenoma, tubulovillous adenoma, hyperplastic polyp, papillomatosis, fibroepithelial polyp, and mucinous cystadenoma. Premalign pathologies were classified as PGA, ICPN, and BillIN. BillIN was divided into grade 1, 2, and 3. Malignant pathologies were classified as neuroendocrine tumors and adenocarcinomas.

## Statistical Analysis

IBM Statistical Package for the Social Sciences (SPSS) version 21 software (SPSS Inc., Chicago, IL, USA) was used for the study. Frequency (n) and percentage values were used in the evaluation of categorical variables, and mean, standard deviation, and minimum-maximum values were used in the evaluation of numerical variables. The chi-square test was used for categorical

variables, while the t-test and the ANOVA test were used for numerical variables. Receiver operating characteristic (ROC) curve was generated to determine the relationship between malignancy and age. The whole study was evaluated with a 95% confidence interval (CI).

## RESULTS

A total of 8.148 patients were included in the study. 5.885 (72.2%) were female and 2263 (27.8%) were male. The mean age of the patients was  $49.74 \pm 14.51$  years with a minimum age of 18 years and a maximum age of 94 years. The mean age was  $49.10 \pm 14.52$  years in women and  $51.42 \pm 14.34$  years in men ( $p < 0.001$ ).

7957 (97.7%) of the patients had benign pathologies, 173 (2.1%) patients had premalignant pathologies and 18 (0.02%) had malignant pathologies (Table 1). When male and female genders were compared, there was no statistically significant difference between benign, premalignant and malignant pathologies ( $p = 0.249$ ) (Table 1).

The mean age was  $49.63 \pm 14.50$  years for benign patients,  $52.86 \pm 13.48$  years for premalignant patients and  $69.55 \pm 9.82$  years (minimum 51 years old and maximum 86 years old) for malignant patients (Table 2, Figure 1). When the ROC curve was constructed for the age of malignant patients, the cut-off age was 50 years [area under the curve 0.868, sensitivity 100%, specificity 51.1%, 95% CI (0.806-0.930)]. In this patient group, all patients with a malignant diagnosis were over 50 years of age, and the frequency of patients with premalignant conditions also increased over 50 years of age (Table 3).

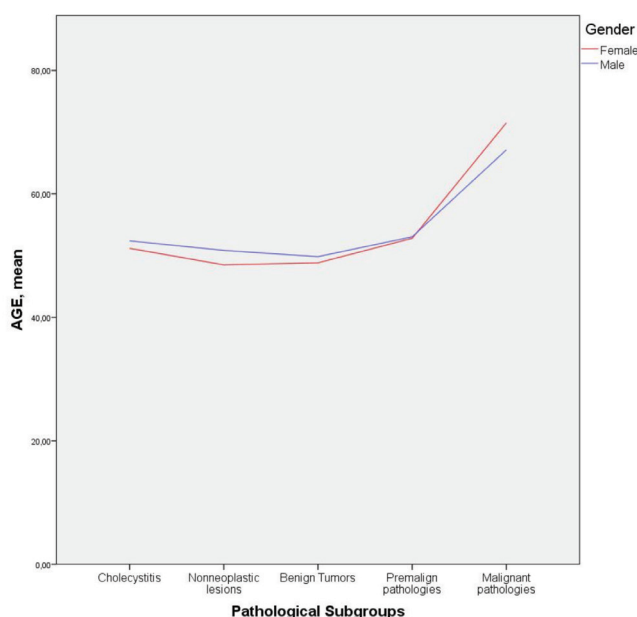


Figure 1. Age distribution according to pathologies.

**Table 1.** The incidence of gallbladder pathologies according to gender

Pathology	Female, n (%)	Male, n (%)	Total, n (%)	p-value
	5.748	2.209	7.957 (97.7%)	0.273
<b>Cholecystitis</b>	<b>1.040 (59.7%)</b>	<b>702 (40.3%)</b>	<b>1.742 (21.4%)</b>	
Acute	273 (49.6%)	277 (50.4%)	550 (6.8%)	
Chronic	618 (61.1%)	289 (31.9%)	907 (11.1%)	
Follicular	34 (58.6%)	24 (41.4%)	58 (0.7%)	
Erosyone	52 (56.5%)	40 (43.5%)	92 (1.1%)	
Eosinophilic	2	0	2	
Gangrenous	38 (48.7%)	40 (51.3%)	78 (1.0%)	
Xanthogranulomatous	22 (40.7%)	32 (59.3%)	54 (0.7%)	
Porcelain gallbladder	1	0	1	
<b>Non-neoplastic lesions</b>	<b>4.702 (75.8%)</b>	<b>1.501 (42.2%)</b>	<b>6.203 (76.1%)</b>	
Adenomyoma	52 (61.1%)	33 (38.8%)	85 (1%)	
Cholelithiasis	2.958 (74%)	1.040 (26%)	3.998 (49.1%)	
Choleterol polyp	154 (70%)	66 (30%)	220 (2.7%)	
Cholesterellosis	1.367 (81.2%)	316 (18.8%)	1.683 (2.7%)	
<b>Metaplasia</b>				
Gastric antral metaplasia	6	0	6	
Pyloric metaplasia	61 (78.2%)	17 (21.8%)	78 (1.6%)	
Intestinal metaplasia	104 (78.8%)	28 (21.2%)	132 (1.6%)	
Osseous metaplasia	1	2	3	
<b>Benign tumors</b>	<b>6 (0.1%)</b>	<b>6 (0.3%)</b>	<b>12 (0.1%)</b>	
Biliary adenoma	2	1	3	
Tubulovillous adenoma	0	1	1	
Hyperplastic polyp	1	2	3	
Papillomatosis	2	1	3	
Fibroepithelial polyp	0	1	1	
Mucinous cystadenoma	1	0	1	
	<b>127</b>	<b>46</b>	<b>173 (2.1%)</b>	
<b>Premalign pathologies</b>				
Pyloric gland adenoma	4	2	6	
Intracholecystic papillary neoplasm	1	1	2	
<b>BiIN</b>	<b>122 (73.9%)</b>	<b>43 (26.1%)</b>	<b>165 (2.0%)</b>	
BiIN 1	105 (75.0%)	35 (25.0%)	140	
BiIN 2	10 (62.5%)	6 (37.5%)	16	
BiIN 3	7 (77.8%)	2 (22.2%)	9	
	<b>10</b>	<b>8</b>	<b>18 (0.2%)</b>	
<b>Malignant pathologies</b>				
NET Grade 1	2	0	2	
<b>Adenocancer</b>	<b>8</b>	<b>8</b>	<b>16 (0.2%)</b>	
Poorly differentiated	1	2	3	
Moderately differentiated	5	3	8	
Good differentiated	1	2	3	
Musinous	1	1	2	
<b>Total</b>	<b>5.885 (72.2%)</b>	<b>2.263 (27.8%)</b>	<b>8.148</b>	

BiIN: Biliary intraepithelial neoplasia, NET: Neuroendocrine tumor

## DISCUSSION

Gallbladder surgeries are common procedures in general surgery practice. It is a generally accepted approach to operate laparoscopic surgery primarily. The growing number of laparoscopic cholecystectomy procedures has led to an increased prevalence of incidental pathologies. This study

analyzed cholecystectomies performed over a nine-year period in a high-volume referral center that accepts patients from diverse regions within the country. The objective was to investigate the frequency of incidental pathologies encountered during these procedures.

The development of premalignant lesions of the gallbladder is typically attributed to a sequence of injury, inflammation,

**Table 2.** Distribution of pathologies by age

	Age average	p-value	Female age average	p-value	Male age average	p-value
<b>Benign pathologies</b>	49.63±14.51	<0.001	48.98±14.52	<0.001	51.33±14.33	0.006
<b>Premalign pathologies</b>	52.86±13.48		52.79±13.27		53.04±14.21	
<b>Malignant pathologies</b>	69.55±9.82		71.50±9.31		67.12±10.53	

**Table 3.** Pathology results are classified as over and under 50 years of age

		Pathologies			p-value
		Benign pathologies	Premalign pathologies	Malignant pathologies	
Female	<50 years old	2.877 (98.5%) <sup>a</sup>	44 (1.5%) <sup>b</sup>	0 <sup>b</sup>	<0.001
	≥50 years old	2.871 (96.9%) <sup>a</sup>	83 (2.8%) <sup>b</sup>	10 (0.3%) <sup>b</sup>	
Male	<50 years old	1.006 (98.2%) <sup>a</sup>	18 (1.8%) <sup>a,b</sup>	0 <sup>b</sup>	0.016
	≥50 years old	1.203 (98.2%) <sup>a</sup>	28 (2.3%) <sup>a,b</sup>	8 (0.6%) <sup>b</sup>	
Totally	<50 years old	3.883 (97.6%) <sup>a</sup>	62 (1.6%) <sup>b</sup>	0 <sup>c</sup>	<0.001
	≥50 years old	4.074 (96.9%) <sup>a</sup>	111 (2.6%) <sup>b</sup>	18 (0.4%) <sup>c</sup>	

<sup>a,b,c</sup>: Each superscript letter denotes a subset of pathology categories whose column ratios are not significantly different from each other at the 0.05 level

regeneration, and neoplastic transformation (9). One hundred seventy-three patients had premalignant pathology, of which 6 were PGA, 2 were ICPN, and 165 (2%) were BillN. There was no statistical difference between male and female patients; however, the incidence of these pathologies increased with increasing age ( $p=0.273$ ,  $p<0.01$ , respectively).

BillN is a microscopic, non-invasive, micropapillary premalignant lesion with atypical features similar to those seen in cancer but confined to the bile duct. As such, requiring examination of the entire tissue to differentiate it from cancer (10). In countries where BillN gallbladder cancer is endemic, Grade 1-2 disease is seen in 15% and Grade 3 disease in 1-3.5%, whereas in North America, Grade 1-2 disease is seen in <5% and <0.1% (11). In this patient group, the number of patients with BillN was 165 (2%) and only 9 (0.005%) patients were diagnosed with grade 3, which is consistent with the literature.

PGA is a polypoid non-invasive epithelial lesion of the gallbladder classified as a premalignant lesion by WHO as of 2019 (12). PGA is a pathology found in 0.2-0.5% of patients operated for chronic cholecystitis or cholelithiasis, and is mostly seen in women and adults (11). In this study, the condition was observed in 6 patients (<0.01%), and 4 of them were women.

ICPN is a preinvasive neoplasm of the gallbladder, and studies have reported that ICPN is found in 4% of cholecystectomies and is associated with approximately 6% of gallbladder carcinomas (12). In this study, ICPN was found in two patients only.

Gallbladder cancer is the fifth most common cancer among cancers of the gastrointestinal tract. Less than 10% of patients are resectable; half of these patients have lymph node metastases. Five-year survival is less than 5% (13). It is commonly found in women, increases in frequency in older ages, and is common

in Chile, Japan, and India (13). Incidental gallbladder cancer is identified in 0.2% to 2.9% of all cholecystectomies performed for gallstone disease surgery (8,14). While cholecystectomy is sufficient in patients diagnosed with stage Tis and T1a cancer in gallbladder examinations, stage T1b and above require further surgical treatment (6). In this study, the incidental gallbladder cancer rate was found to be 0.2%, consistent with the literature. Unlike the literature, there was no difference between genders; however, the incidence increased with age in accordance with the literature ( $p=0.273$ ,  $p<0.001$ , respectively).

## CONCLUSION

Although most gallbladder specimens obtained after cholecystectomy are benign, a small number are incidentally detected as malignant or potentially malignant. This study examined the occurrence of incidental gallbladder pathologies in our country, confirming the presence of such unexpected lesions in accordance with the literature. The findings underscore the importance of routine pathological examination to ensure timely intervention and improve patient outcomes.

## Ethics

**Ethics Committee Approval:** The study was approved by the Institutional Review Board University of Health Sciences Türkiye, Ankara Bilkent City Hospital (date: 04.04.2024 and number: 2-24-131) and conducted in accordance with the Declaration of Helsinki.

**Informed Consent:** Informed consent was obtained from all patients before treatment.

## Footnotes

### Author Contributions

Concept - H.P.Ö., T.D.; Design - H.P.Ö.; Supervision - T.D.; Data Collection or Processing - H.P.Ö.; Analysis or Interpretation - H.P.Ö.; Literature Search - H.P.Ö.; Critical Review - T.D.; Writing - H.P.Ö.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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