

Can Incidental Gallbladder Cancer Be Predicted Before Cholecystectomies?

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ABSTRACT

Objective: Gallbladder cancer is a rare disease with a high mortality rate. The gold standard of treatment is based on early diagnosis and eradication of the disease with effective surgery. Almost 70% of cases are detected incidentally in the final pathology report of routine cholecystectomies. Our study aims to predict incidental gallbladder cancer in patients scheduled for surgery for benign reasons.

Methods: Biological characteristics, medical history, family history of hepatobiliary disease, radiological imaging, and laboratory parameters were analyzed in 2852 patients operated on for benign reasons in the general surgery department over 63 months. Patients with incidental gallbladder cancer were compared with patients with cholecystitis. The effects of independent variables in predicting cancer between the two groups were analyzed.

Results: Of 2852 patients who underwent cholecystectomy, 13 (0.45%) had incidental gallbladder cancer. The cancer incidence rate was 0.28% (2/700) in men and 0.51% (11/2139) in women. This difference was not statistically significant (p: 0.34). Among the biological characteristics, history of acute cholecystitis (p: 0.001), and laboratory findings, neutrophil-to-lymphocyte ratio (NLR) (p: 0.001) were the most striking variables. When variables with proven statistical value were tested by logistic regression analysis, NLR (p: 0.001), biliary polyps (p: 0.001), and gallstones (p: 0.038) were ranked as the most valuable cancer predictors, respectively.

Conclusions: In older patients with a history of acute cholecystitis, especially if there are large stones, polyps, and wall thickening on imaging, the possibility of cancer should be considered considering the NLR value, and surgery should be performed under optimal conditions by informing the patient and relatives.

Keywords: Acute Cholecystitis, Cholecystectomy, Gallbladder Neoplasms, Gallstones, Polyps

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INTRODUCTION

Gallbladder cancer is a very rare disease with devastating consequences. Early diagnosis is essential due to the failure of treatments other than surgery. It is known that the incidence

rate in male patients, especially in Western societies, is less than 1 per 100,000 population, whereas it can be as high as 1.4 in women. In Eastern European communities, including our country, the incidence can be up to 5 times higher [1]. The

most important predisposing factors are gallstones (especially porcelain bladder), chronic cholecystitis, bile polyps, advanced age, female gender, and bile duct anomalies [2]. It is difficult to detect before it becomes symptomatic. Therefore, almost 70% of cases are detected incidentally after surgery [3]. It is known that incidental cancer is detected in 0.2-2.9% of cholecystectomies performed for benign gallbladder diseases [4]. When reviewing the final pathology report, this unpleasant surprise can leave inexperienced clinicians in a quandary. Simple cholecystectomy may be sufficient only for invasion of the gallbladder mucosa and lamina propria (T1a). In cancers invading the muscular layer (T1b and other T stages), management between surgery, systemic therapy, or palliative options is possible in better-equipped centers and with experienced clinicians [5]. Despite all these treatments, it is known that the 5-year survival rate of patients who cannot be detected at an early stage does not exceed 5% [6]. The gold standard in the surgical treatment of benign gallbladder diseases worldwide is laparoscopic cholecystectomy. Cholecystectomy operations constitute the majority of laparoscopic operations performed in the general surgery department. It is thought that predicting incidental cancer cases in the preoperative period may provide significant advantages in treatment management. The aim of this study is to contribute to the prediction of early-stage gallbladder cancers and improve treatment management.

MATERIALS AND METHODS

The study was conducted using the data of patients who underwent surgery for benign gallbladder diseases at Şehit Prof. Dr. İlhan Varank Sancaktepe Training and Research Hospital.

Main Points

- Gallbladder cancer is a disease with a very high mortality rate when not detected early.
- It is known that the incidence of incidental gallbladder cancer can be as high as 1.4% in Western societies and even higher in Eastern societies.
- Prediction of incidental cancer requires additional preparations correlated with the extent of the surgical intervention.
- A history of cholecystitis, thickening of the gallbladder wall, large gallstones and polyps, and a high neutrophil-to-lymphocyte ratio in blood tests should warrant a careful approach to these patients.

Cholecystectomy operations performed in the 63 months between June 2018 and September 2023 were analyzed. Consent was obtained from patients to use medical records, and an official approval report for the study was prepared by the ethics committee within the hospital. Demographic information and detailed anamnesis were obtained by interviewing the patients or their companions. In addition to information about hepatobiliary pathologies, comorbidities, smoking, environmental exposure, and gallbladder pathologies of first-degree relatives were also questioned. Imaging findings, laboratory results, preoperative ASA scores (American Society of Anesthesiologists Classification), and operation reports were carefully analyzed using the hospital information management system. Patients operated on with a diagnosis of primary gallbladder tumor, cholecystectomies performed during surgical intervention for a different reason, patients who were currently being treated and actively followed up for malignancy, patients under 18 years of age, and pregnant women were excluded from the study.

Statistical Analysis

All analyses were performed using SPSS version 22 for Windows software. Numerical data were analyzed for normality using the Shapiro-Wilk test. Patients were divided into two groups: malignant pathology and normal cholecystitis. Pearson's chi-square test was used to analyze categorical variables, and Fisher's exact test was used in small groups. A comparison of numerical variables was performed using the Students T-test or Mann-Whitney U test. Logistic regression analysis was used to measure the predictive values of statistically significant variables. ROC (receiver operating characteristic curve) analysis was preferred for the cut-off value.

RESULTS

The mean age of the 2852 patients included in the study was 47 (18-87) years. The difference with the neoplasm group (mean 55) was statistically significant ($p:0.02$). 75.4% (2150) of the participants were women. Contrary to the literature, there was no difference in malignancy rates according to gender [7, 8]. The number of patients with life-threatening severe comorbidities was 364 (12.8%). Body mass index (BMI), comorbidities, and ASA scores increased with age ($p:0.01$). However, unlike age, the different distribution of these parameters between the two groups was not statistically significant. Patients with a history of hospitalization for at least one acute cholecystitis were almost 14%.

In contrast, those with a history of multiple episodes of cholecystitis were significantly higher in the neoplasm group (p:0.001). The cholecystectomy rate for benign gallbladder diseases in first-degree relatives was also higher in the neoplasm group (p:0.03). Demographic and biological data of the participants are summarized in Table 1.

When the participants' imaging, laboratory parameters, and operative findings were compared, it was found that the high neutrophil-to-lymphocyte ratio (NLR) was significantly characteristic of the neoplasm group (p:0.001). A cut-off value of 2.9 was also calculated for NLR (Figure 1). When the presence

and size of polyps were evaluated categorically, it was the second most valuable parameter in terms of neoplasm (p:0.002). The other significant findings were gallstones and increased wall thickness (p:0.03, p:0.04, respectively). All these variables are summarized in Table 2.

When statistically significant variables were evaluated by logistic regression analysis, the presence of NLR and biliary polyp were the two most valuable predictive values (p:0.001), followed by the presence of large gallstones (especially porcelain gallbladder) (Table 3).

Table 1. Demographic and biological data of the participants

Variables	Neoplasm (n:13)	Cholecystitis (n:2839)	P value
Age (mean)	55 (39-67)	47 (18-86)	0.02
Sex(male/female)	2/11 (15.4% / 84.6%)	700/2139 (24.7% / 75.3%)	0.34
ASA Score (median)	2	2	0.93
Comorbidity	3 (23.1%)	361 (12.7%)	0.22
BMI (mean)	26.4 (22-31)	25.6 (18-42)	0.33
Smoking	5 (38.5%)	713 (25.1%)	0.21
HoC (1/1<)	1/2 (7.7% / 15.4%)	394/34 (13.9% / 1.2%)	0.001
HoF	2 (15.4%)	67 (2.4%)	0.03
DoS*	19.3 (2-60)	10.8 (1-60)	0.12

Chi-Square, Student's t-test, *Mann Whitney-U, ASA: American Society of Anesthesiologists; BMI: body mass index; HoC: history of acute cholecystitis; HoF: family history of cholecystectomy; Dos: duration of symptoms

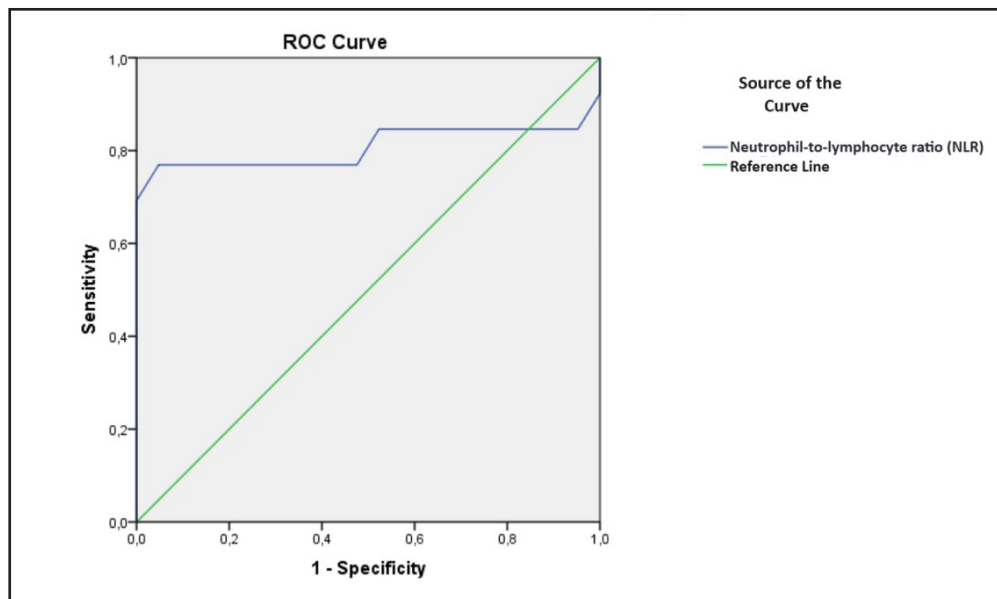


Figure 1. ROC analysis of neutrophil-to-lymphocyte ratio (NLR) in the prediction of gallbladder cancer.

Table 2. Clinical and laboratory differences between groups

Variables		Neoplasm (n:13)	Cholecystitis (n:2839)	P value
Wall thickening		5 (38,5%)	444(15,6%)	0.04
Gallstones	none	3	330	0.03
	<1cm	5	2182	
	1-2 cm	2	218	
	>2cm	2	81	
	porcelain	1	28	
Polyps	none	9	2575	0.002
	<5mm	1	215	
	5-10mm	1	43	
	>10mm	2	6	
HGB (g/dL)		13.24	13.89	0.14
WBC ($\times 10^9/L$)		9.16	8.75	0.55
Lymphocyte ($\times 10^9/L$)		2.02	2.09	0.71
Neutrophil ($\times 10^9/L$)		6.47	5.86	0.23
Platelet* ($\times 1000/\mu L$)		190	202	0.72
NLR*		3,2	2,8	0.001
PLR*		95.5	97	0.07
Operation type(laparoscopic)		12 (92.3%)	2643 (93.1%)	0.6
Difficult cholecystectomy		3 (23.1%)	120 (4.2%)	0.016

Chi-Square , Student's t-test, *Mann Whitney-U, HGB: hemoglobin; WBC: white blood cell; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio

Table 3. Predictive values of independent variables for incidental gallbladder neoplasm

Variables	Exp(B)	95% C.I. for Exp(B)		P value
		Lower	Upper	
Age	1.029	0.973	1.090	0.31
HoC	2.697	0.760	9.575	0.12
HoF	1.410	0.063	31.692	0.82
Wall thickening	3.232	0.735	14.210	0.12
Gallstones	2.086	1.041	4.179	0.038
Polyps	4.813	2.285	10.137	0.001
NLR	164593.042	617.362	43881640.26	0.001
Difficult cholecystectomy	4.097	0.573	29.290	0.16

Binary logistic regression-enter method (Nagelkerke R Square : 0,45)

HoC: history of acute cholecystitis; HoF: family history of cholecystectomy; NLR: neutrophil-to-lymphocyte ratio

DISCUSSION

Patients with a mass detected on imaging are generally in the locally advanced or metastatic stage, constituting approximately 30% of the cases. In the treatment of these patients, a multidisciplinary approach is needed in more advanced centers. According to the literature, survival between 3 and 22 months indicates failure of systemic treatment [9, 10]. All these data make early-stage surgery very important. This study aims to focus on cancers that may be detected incidentally in patients scheduled for cholecystectomy for benign reasons. Preoperative informed consent, preparation of the intensive care unit, reservation of the necessary blood products, and an experienced team are not always possible for routine cholecystectomies. In addition, frozen pathological examination may be required in cases where perioperative clues regarding cancer are insufficient, and an appropriate surgery time should be arranged during the day.

In stages more advanced than T1a, liver segment 4B and segment five resection and regional lymph node dissection must be added to cholecystectomy to save the patient from a second surgery. Extended hepatic resection and bile duct excision may sometimes be required to achieve negative surgical margins [5, 11]. Articles stating that residual disease is seen in up to 59% of cases where a second surgery is performed justify extensive resections [12].

Instead of providing this complex management, transferring the patient to an experienced hepatobiliary surgery center can solve many problems simultaneously. It has been observed that recent prediction models emphasize the importance of patient age along with female gender. It has also been stated that acute cholecystitis with jaundice and previous cholecystitis increase the risk [13]. Unlike other studies, Goussous et al. emphasized the importance of wall thickening seen on imaging without pericholecystic fluid [14]. Promising results have also been obtained from recent biomarker studies. In 2016, it was emphasized that circulating serum-free DNA levels were significantly higher in early-stage gallbladder tumors [15]. Kinugasa and his colleagues drew attention to circulating tumor DNA [16]. More prospective studies are needed for the reliability of this type of biomarkers, and there are concerns about accessibility and routine applicability. Although carbohydrate antigen CA 19-9, which is significant for other hepato-pancreaticobiliary cancers, is not significant for gallbladder cancer, there are articles claiming that both high specificity and a 100% positive predictive value are achieved thanks to its combination with CA

125 and CA 242 [17]. These markers, which can be measured in serum, may become even more critical in predictive ability when evaluated with other biological features. The correlation between high NLR levels and poor prognosis as stated in some articles, was found to be a predictor of incidental cancer in our study [18].

Limitations

Contrary to the literature, the lack of predictive value of the female gender may be related to the low number of malignant patients. Prospective studies by routinely measuring serum biomarkers in patients in the preoperative period may provide a more meaningful prediction model with existing data. When ultrasonography reports were examined, no case was found in which only wall thickness was noted without pericholecystic fluid. However, although increased wall thickness is an indicator of cholecystitis, it may be an indirect predictor of cancer. Although some ultrasonography reports could not distinguish between impacted bile sludge and polyp, these cases were accepted as bile polyps.

CONCLUSION

As a result, biomarkers can be studied in serum for patients with high NLR levels accompanying large gallstones or bile polyps. Genetic counseling may be considered for those with a family history of cancer. Depending on the situation, these patients' operations may be performed in the daytime by more experienced teams, or their transfer to more advanced centers may be considered.

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