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A Case-Control Study on the Relationship Between Cholecystectomy and Cholangiocarcinoma in China

Donglie Zhu
Xijing Hospital
Hang Fu
Xijing Hospital
Zelong Yang
Xijing Hospital
Mingzuo Jiang
Xijing Hospital
Yanjie Ren
Xijing Hospital
Shi Zheng
Xijing Hospital
Yong Chen (gdwkcy@163.com)
Xijing Hospital

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Abstract

Aims: The present study aimed to explore the correlation between cholecystectomy and cholangiocarcinoma, and to provide preliminary clinical basis for precise cholecystectomy in China.

Methods: We conducted a retrospective analysis of 9744 patients with cholangiocarcinoma, colon cancer, pancreatic cancer, femoral fracture, and hepatic hemangioma diagnosed in Xijing hospital from August 2008 to August 2018. They were divided into three groups: case group (1749 cases of cholangiocarcinoma), positive control group (3137 cases of colon cancer and 1950 cases of pancreatic cancer), negative control group (1794 cases of femoral fracture and 1114 cases of hepatic hemangioma). We collected the general information (gender, age), past medical history, cholecystectomy history from the patients, and these data were analyzed by chi-square test and logistic regression analysis.

Results: The cholecystectomy rate of the case group was significantly higher than that of the positive control group and the negative control group by chi-square test ($p<0.025$). The cholecystectomy rate and the history of cholecystolithiasis were analyzed by logistic multivariate regression analysis. The OR values of cholecystectomy rate were 1.553 (95%CI: 1.311-1.840) and 3.181 (95%CI: 2.561-3.951), respectively, and the difference was statistically significant ($p<0.000$). The OR values of the history of cholecystolithiasis were 2.460 (95%CI: 2.093-2.890) and 5.426 (95%CI: 4.325-6.809), respectively, and the difference was statistically significant ($p<0.000$). In case group, the difference between cholecystectomy and cholecystolithiasis was statistically significant ($p<0.000$) by chi-square test.

Conclusions: In conclusion, cholecystectomy is one of the risk factors of cholangiocarcinoma and the patients who undergo cholecystectomy have a higher risk of cholangiocarcinoma than the control groups. Cholecystectomy should be conducted with caution and the precise surgical treatment of gallbladder diseases is advocated.

Introduction

With the improvement of living conditions and the change of dietary habit of Chinese people, the incidence of cholecystolithiasis in China has reached from 2–7% to 8–10%, which leads to the increasing number of the cholecystectomy year by year. With the development of minimally invasive technology, endoscopic cholecystectomy has become one of the most effective therapies for cholangiocarcinoma[1–3]. And endoscopic cholecystectomy has become one of the most frequent hepatobiliary surgery and general surgery[4–7]. Cholecystectomy can remove gallstones, gallbladder polyps and other lesions, greatly reduce the incidence of gallbladder carcinoma, and can eliminate the pain caused by gallbladder stones or biliary pancreatitis[8–10]. Because of the large amount of cholecystectomy, the complications of it can’t be ignored. The major short term complication is biliary tract injury, which seriously affects the patient’s quality of life, and can cause a secondary operation. When it comes to the irreparable biliary stenosis, it could even threaten the patient's life[11, 12]. Long term complications of cholecystectomy are easy to be ignored, which mainly included dyspepsia and the increased risk of gastrointestinal cancer[13, 14]. It is known that the incidence of gastrointestinal cancer after cholecystectomy increased and the most common malignance is colon cancer[15, 16]. And it has also been reported that the incidence of pancreatic cancer increased after cholecystectomy[17, 18].

Cholangiocarcinoma is the second most common malignancy of the liver, originating from biliary epithelial cells[19, 20]. In recent years, according to the clinical and basic research of cholangiocarcinoma, viral hepatitis plays a crucial role in the development of cholangiocarcinoma. Hepatitis C was thought to be a risk factor of cholangiocarcinoma in USA and Europe[21–23]; studies showed that hepatitis B was a risk factor of cholangiocarcinoma in Asia[24, 25]. Owing to the unconspicuous symptoms at the early stage, cholangiocarcinoma is usually diagnosed at advanced disease stages, leading to poor prognosis[26, 27]. At present, the diagnosis of this disease mainly depends on imaging technology, endoscopy, the examination of tumor markers and pathological biopsy. And surgery is the most effective therapy for cholangiocarcinoma[28, 29].

In this study, for the first time, we conducted a case-control study in China to explore the correlation between cholecystectomy and the incidence of cholangiocarcinoma, so as to provide suggestion for the precise surgical treatment of cholecystolithiasis.

Methods

Study population

The Ethics Committee of Xi Jing Hospital approved this study. We collected patients with cholangiocarcinoma, colon cancer, pancreatic cancer, femoral fracture and hepatic hemangioma who were admitted to Xijing hospital from August 2008 to August 2018 through the Case data collection system of digital center from Xijing hospital. We collected patients' name, gender, age, admission time, discharge time, impatient department, operative name and the first diagnosis after discharge, and then screened them. Patients with cancer and hepatic hemangioma were diagnosed pathologically, and patients with femoral fracture were diagnosed by X-ray, and the cases with ambiguous diagnosis were excluded. After the screening, 1749 cases of cholangiocarcinoma, 3137 cases of colon cancer, 1950 cases of pancreatic cancer, 1794 cases of femoral fracture and 1114 cases of hepatic hemangioma were included, a total of 9744 cases. We collected the general information of all patients (gender, age), past medical history (hypertension, diabetes, coronary disease, cholecystolithiasis) and the history of cholecystectomy, in which cholecystectomy was due to cholecystolithiasis (excluding the patients with cholecystectomy due to gallbladder polyps, gallbladder cancer and other gallbladder-related diseases).

Inclusion And Exclusion Criteria

Patients that met the following criteria could be included: (1) patients with cancer and hepatic hemangioma were diagnosed pathologically, and patients with femoral fracture were diagnosed by X-ray.

(2) the interval between the cholecystectomy and the diagnosis of related diseases after admission was more than 1 year. (3) the general information required in this study, the past medical history, the previous surgical history were complete, and the diagnosis was clear.

The exclusion criteria were based on the following: (1) patients with other malignancies at the same time or the related malignance was metastases of tumors derived from other sites. (2) the interval between the cholecystectomy and the diagnosis of related diseases after admission was less than 1 year (3) cases with cholecystectomy due to surgical treatment for other malignances. (Such as patients with pancreatic cancer underwent pancreaticoduodenectomy, and patients with liver cancer underwent partial hepatectomy) (4) cases of space-occupying lesions were not diagnosed as related malignant tumor. (5) cases of the general information required in this study, the past medical history, the previous surgical history were incomplete or the diagnosis was unclear.

Study Design

According to the above inclusion and exclusion criteria, 9744 cases were included in this study (1749 cases of cholangiocarcinoma, 3137 cases of colon cancer, 1950 cases of pancreatic cancer, 1794 cases of femoral fracture and 1114 cases of hepatic hemangioma). We collected the general information of all patients (gender, age), past medical history (hypertension, diabetes, coronary disease, cholecystolithiasis) and the history of cholecystectomy (operative time and postoperative pathological diagnosis). All the cases were divided into three groups: case group (1749 cases of cholangiocarcinoma), positive control group (3137 cases of colon cancer and 1950 cases of pancreatic cancer), and negative control group (1794 cases of femoral fracture and 1114 cases of hepatic hemangioma). Chi-square test and logistic regression analysis were used to study the factors, including gender, age, past medical history (hypertension, diabetes, coronary disease, cholecystolithiasis) and the history of cholecystectomy, that might affect the pathogenesis of the above diseases. To further determine whether cholecystectomy is one of the risk factors of cholangiocarcinoma and when is the high-risk period of cholangiocarcinoma after cholecystectomy, we explored the differences of the interval between cholecystectomy and the first diagnosis of cholangiocarcinoma after cholecystectomy, and the differences between the cholecystolithiasis and the cholecystectomy in the case group.

Statistical analysis

SPSS 22.0 statistical software was used for data analysis. The enumeration data was described by number and percentage. The normality test of the measurement data was performed by Shapiro-Wilk method. The measurement data conforming to the normal distribution was described by mean ± standard deviation, while the measurement data deviating from the normal distribution was described by means of median and quartile range. The chi-square test was used to compare the rate of cholecystectomy between groups. Logistic regression analysis was used to investigate the risk factors of cholangiocarcinoma and two-tailed $P < 0.05$ was considered statistically significant in this study.

Results

Descriptive analysis

The normal test of the general information in three groups showed that age does not fit the normal distribution (supplementary file1). So we used median and quartile range to describe the concentration and dispersion trend of age. The median of age of the case group was 63, 25 percentiles and 75 percentiles were 55 and 72, respectively. And the corresponding values of negative control group and positive control group were shown in Table 1. Then we used chi square test to compare the factors (gender, age, and past medical history) among the three groups. As shown in Table 2, among the three groups, the proportion of patients with hypertension in case group, negative control group and positive control group were 16.8%, 18.3% and 18.4%, respectively, and the chi square value was 2.391, p value was 0.303, the difference was not statistically significant. In addition, the difference of coronary disease among the three groups was not statistically significant. These evidence indicated that there was no difference in the history of hypertension and coronary disease among the three groups. However, there were significant differences in age, gender and diabetes history among the three groups.

Table 1
Concentration and dispersion trend of age of patients with cholangiocarcinoma and control subjects.

Age(years)			
Group	**Median**	**Percentile(25)**	**Percentile(75)**
Case group	63	55	72
Negative control group	56	43	72
Positive control group	61	53	70

Table 2
Chi square analysis of the factors (gender, age, hypertension, diabetes, coronary disease) among the three groups.

Group	Case group (n = 1749)		Negative control group (n = 2863)		Positive control group (n = 5087)		χ2 p value	
	N	Percentage (%)	N	Percentage (%)	N	Percentage (%)		
Age							240.564	**0.000**
Gender							184.847	**0.000**
Male	1043	59.6%	1317	45.3%	3074	60.4%		
Female	706	40.4%	1591	54.7%	2013	39.6%		
Hypertension							2.391	0.303
Absent	1455	83.2%	2375	81.7%	4149	81.6%		
Present	294	16.8%	533	18.3%	936	18.4%		
Diabetes							12.914	**0.002**
Absent	1607	91.9%	2626	90.3%	4525	89.0%		
Present	142	8.1%	282	9.7%	561	11.0%		
Coronary disease							1.674	0.433
Absent	1692	96.7%	2801	96.3%	4887	96.1%		
Present	57	3.3%	107	3.7%	200	3.9%		

Chi-square Test Of The Rate Of Cholecystectomy

As shown in Table 3, the number of patients with cholecystectomy in the case group was 239, accounting for 13.7%; the number in the negative control group was 164, accounting for 5.6%; the number in the positive control group was 515, accounting for 10.1%. The chi square value was 88.586 and p value was 0.000, the difference of the rate of cholecystectomy among the three groups was statistically significant. The data indicated that effect of cholecystectomy on cholangiocarcinoma is different from that on the other diseases (colon cancer and pancreatic cancer, femoral fracture and hepatic hemangioma). Furthermore, the rate of cholecystectomy was compared in the case group and the positive control group, and compared in the case group and the negative control group separately, and the test level was adjusted with the partitions of X2 method. Comparing the rate of cholecystectomy between the case group and the positive control group, the chi square value was 16.631 and p value was 0.000, which means the difference was statistically significant (Table 4). Similarly, the difference of the rate of cholecystectomy between the case group and the positive control group was statistically significant too (Table 5).

Table 3
Chi square analysis of the rate of cholecystectomy among the three groups.

Group		Cholecystectomy		$\chi2$ p	
		Absent	**Present**	value	
				88.586	0.000
Case group	**N**	1510	239		
	Percentage (%)	86.3%	13.7%		
Negative control group	**N**	2744	164		
	Percentage (%)	94.4%	5.6%		
Positive control group	**N**	4572	515		
	Percentage (%)	89.9%	10.1%		
Sum	**N**	8826	918		
	Percentage (%)	90.6%	9.4%		

Table 4
Chi square analysis of the rate of cholecystectomy between the case group and the positive control group.

Group		Cholecystectomy		χ2 p	
		Absent	**Present**	value	
				16.631	**0.000**
Case group	**N**	1510	239		
	Percentage (%)	86.3%	13.7%		
Positive control group	**N**	4572	515		
	Percentage (%)	89.9%	10.1%		
Sum	**N**	6082	754		
	Percentage (%)	89.0%	11.0%		

Table 5
Chi square analysis of the rate of cholecystectomy between the case group and the negative control group.

Group		Cholecystectomy		χ2 p	
		Absent	**Present**	value	
				88.985	**0.000**
Case group	**N**	1510	239		
	Percentage (%)	86.3%	13.7%		
Negative control group	**N**	2744	164		
	Percentage (%)	94.4%	5.6%		
Sum	**N**	4254	403		
	Percentage (%)	91.3%	8.7%		

Logistic Univariate Regression Analysis

Then we analyzed a series of confounding factors such as gender, age, past medical history (hypertension, diabetes, coronary disease, cholecystolithiasis) and cholecystectomy by logistic univariate regression analysis, from which we screened out the differential factors among the groups for the subsequent logistic multivariate regression analysis. As shown in Table 6, we can conclude that except for coronary disease there were significant differences in gender, age, cholecystectomy, cholecystolithiasis, hypertension and diabetes among the groups. These evidence indicated that all these factors besides coronary disease may affect the incidence of cholangiocarcinoma. So we included all the factors except coronary disease into the logistic multivariate regression analysis to observe which were the risk factors of cholangiocarcinoma actually.

Table 6
Logistic univariate regression analysis.

Group	likelihood ratio test			
	-2 Log likelihood	$\chi 2$	DOF	p
Gender	6244.024	235.361	2	**0.000**
Age	6293.053	284.391	2	**0.000**
Cholecystectomy	6126.656	117.993	2	**0.000**
Cholecystolithiasis	6252.102	243.439	2	**0.000**
Hypertension	6028.325	19.662	2	**0.000**
Diabetes	6026.402	17.739	2	**0.000**
Coronary disease	6014.403	5.741	2	0.057

DOF: degree of freedom

Logistic Multivariate Regression Analysis

Logistic multivariate regression analysis between the case group and the positive control group.

Firstly, we compared the six factors (gender, age, cholecystectomy, cholecystolithiasis, hypertension and diabetes) between the case group and the positive control group by logistic multivariate regression analysis. As shown in Table 7, we find that the OR value of gender was 0.976 (95%CI = 0.871–1.093) and p value was 0.661, the difference was not statistically significant. Because there were more male patients in case group and positive control group, it can be considered that male patients were more likely to suffer from cholangiocarcinoma, colon cancer and pancreatic cancer than female patients. Although the difference in age was statistically significant (0.000), however the OR value was 1.011 (95%CI = 1.007–1.016), basically showing no significant difference. Since the median age in the case group and the positive control group were 63 and 61, respectively, indicating that the risk of cholangiocarcinoma, colon cancer and pancreatic cancer increased with age. Patients with hypertension were more likely to suffer from colorectal cancer and pancreatic cancer than cholangiocarcinoma. The OR value of hypertension was 0.851 (95%CI = 0.730–0.991) and p value was 0.037. That is to say, compared with the incidence of colon cancer and pancreatic cancer, hypertension has less influence on the incidence of cholangiocarcinoma. Next, we compared the diabetes between the case group and the positive control group. The OR value of diabetes was 0.675 (95%CI = 0.553–0.824) and p value was 0.000. The data showed that patients with diabetes have a slightly higher risk of colorectal and pancreatic cancer than those with cholangiocarcinoma. Refer to the difference of cholecystectomy, the risk of cholangiocarcinoma in patients with cholecystectomy was 1.553 times higher than that of colon cancer and pancreatic cancer (OR = 1.553, 95%CI = 1.311–1.840), and the difference was statistically significant. And the risk of cholangiocarcinoma was higher in patients with cholecystolithiasis, which was 2.46 times higher than that of colorectal cancer and pancreatic cancer (OR = 2.460, 95%CI = 2.093–2.890).

Table 7
Logistic multivariate analysis between the case group and the positive group.

							95% CI	
Group	**B**	**SE**	**Wald**	**DOF**	**P**	**OR**	**Lower**	**Upper**
Gender	-0.025	0.058	0.183	1	0.669	0.976	0.871	1.093
Age	0.011	0.002	27.438	1	**0.000**	1.011	1.007	1.016
Cholecystectomy	0.440	0.086	25.917	1	**0.000**	1.553	1.311	1.840
Cholecystolithiasis	0.900	0.082	119.512	1	**0.000**	2.460	2.093	2.890
Hypertension	-0.162	0.078	4.331	1	**0.037**	0.851	0.730	0.991
Diabetes	-0.393	0.101	14.997	1	**0.000**	0.675	0.553	0.824
B: regression coefficient, SE: standard error, DOF: degree of freedom, OR: odds ratio								

Logistic multivariate regression analysis between the case group and the negative control group.

Subsequently, we compared the six factors (gender, age, cholecystectomy, cholecystolithiasis, hypertension and diabetes) between the case group and the negative control group by logistic multivariate regression analysis. As shown in Table 8, we find that the OR value of gender was 0.484 (95%CI = 0.427–0.549) and p value was 0.000, the difference was statistically significant. Which means compared with the incidence of cholangiocarcinoma, women were more likely to suffer from hepatic hemangioma or femoral fracture. Although the difference in age was statistically significant (0.000), however the OR value was 1.037 (95%CI = 1.032–1.042), basically showing no significant difference. Since the median age in the case group and the negative control group were 63 and 56, respectively, indicating that the risk of cholangiocarcinoma, hepatic hemangioma and femoral fracture increased with age. Patients with hypertension were more likely to suffer from hepatic hemangioma or femoral fracture than cholangiocarcinoma. The OR value of hypertension was 0.688 (95%CI = 0.580–0.817) and p value was 0.000. Then we compared the diabetes between the case group and the negative control group. The OR value of diabetes was 0.659 (95%CI = 0.527–0.824) and p value was 0.000. The data showed that patients with diabetes have a higher risk of hepatic hemangioma or femoral fracture than those with cholangiocarcinoma. Refer to the difference of cholecystectomy, the risk of cholangiocarcinoma in patients with cholecystectomy was 3.181 times higher than that of hepatic hemangioma or femoral fracture (OR = 3.181, 95%CI = 2.561–3.951), and the difference was statistically significant. And the risk of cholangiocarcinoma was higher in patients with cholecystolithiasis, which was 5.426 times higher than that of hepatic hemangioma or femoral fracture (OR = 5.426, 95%CI = 4.325–6.809).

Table 8
Logistic multivariate analysis between the case group and the negative group.

							95% CI	
Group	**B**	**SE**	**Wald**	**DOF**	**P**	**OR**	**Lower**	**Upper**
Gender	-0.726	0.064	127.686	1	0.000	0.484	0.427	0.549
Age	-0.036	0.002	224.211	1	**0.000**	1.037	1.032	1.042
Cholecystectomy	1.157	0.111	109.559	1	**0.000**	3.181	2.561	3.951
Cholecystolithiasis	1.691	0.116	213.362	1	**0.000**	5.426	4.325	6.809
Hypertension	-0.374	0.087	18.301	1	**0.000**	0.688	0.580	0.817
Diabetes	-0.417	0.114	13.388	1	**0.000**	0.659	0.527	0.824
B: regression coefficient, SE: standard error, DOF: degree of freedom, OR: odds ratio								

Comparison between cholecystectomy and cholecystolithiasis by Chi-square test in case group

Based on logistic multivariate regression analysis, we found that patients with cholecystolithiasis were more likely to suffer from cholangiocarcinoma than those with cholecystectomy. Therefore, we compared cholecystectomy and cholecystolithiasis by Chi-square test in the case group to determine if there was any difference between them. As shown in Table 9, the number of patients with cholecystolithiasis in the case group was 304, accounting for 17.4%; the number of patients with cholecystectomy in the case group was 239, accounting for 13.7%. The chi square value was 45.063 and p value was 0.000, the difference between cholecystectomy and cholecystolithiasis was statistically significant. These data showed patients with cholecystolithiasis has a higher risk of cholangiocarcinoma than those with cholecystectomy.

Table 9
Comparison between cholecystectomy and cholecystolithiasis by Chi-square test in case group.

Group	Cholecystolithiasis	Cholecystectomy	χ2	p
			45.063	**0.000**
Presence	304(17.4%)	239(13.7%)		
Absence	1445(82.6%)	1510(86.3%)		

Distribution of time interval between cholecystectomy and the diagnosis of cholangiocarcinoma the first time after cholecystectomy

Based on the above evidence, we can conclude that cholecystectomy has a close relationship with the incidence of cholangiocarcinoma. To further elucidate whether the risk of cholangiocarcinoma related to the interval between cholecystectomy and the diagnosis of cholangiocarcinoma the first time after cholecystectomy, we divided the interval into three groups: “one to five years” group, “five to ten years” group, and “more than ten years” group. As shown in Table 10, the number of the patients in the “one to five years group” was 105, accounting for 43.93%; the number of the patients in the “five to ten years group” was 63, accounting for 26.36%; and the number of the patients in the “more than ten years group” was 71, accounting for 29.71%. We compared the “one to five years group” with another two groups separately, and the difference was statistically significant. These data indicated that the incidence of cholangiocarcinoma is the highest within one to five years after cholecystectomy.

Table 10
Distribution of time interval between cholecystectomy and the diagnosis of cholangiocarcinoma the first time after cholecystectomy.

Time interval	Number	Proportion	P
1–5 years	105	43.93%	
5–10 years	63	26.36%	
> 10 years	71	29.71%	
			0.000

Discussion

Many researches about the relationship between cholecystectomy and the incidence of cholangiocarcinoma have been reported in many countries, but the association is controversial and there is none in China. Ekbom,A conducted a cohort study in 1993, which indicated that gallstones are considered as a risk factor of cholangiocarcinoma and a reduced risk of cholangiocarcinoma 10 or more years after cholecystectomy[30]. A population based study was performed in Taiwan with 7938 cholelithiasis cases. They find that patients who underwent cholecystectomy can reduce the incidence of subsequent cholangiocarcinoma while the increased risk of cholangiocarcinoma with the treatment of endoscopic sphincterotomy or endoscopic papillary balloon dilatation[31]. However, a systematic review and meta-analysis was performed including 16 articles comprising 220,376 patients with cholecystectomy, indicating that cholecystectomy was related to a significant 54% increase in the risk of cholangiocarcinoma[32]. And a case-control study was conducted to investigate the risk factors of cholangiocarcinoma, which concluded that cholecystectomy is one of the risk factors of extrahepatic cholangiocarcinoma[33]. Thus, to elucidate the relationship between cholecystectomy and the incidence of cholangiocarcinoma, we conducted this case-control study in China.

In this study, descriptive analysis of the general information of patients by Chi square test among the groups (case group, positive control group and negative control group) showed statistical differences in age, gender and diabetes. Based on logistic multivariate regression analysis, it was concluded that the difference of diabetes history between the case group and the positive control group was statistically significant, possibly because diabetes is one of the risk factors of pancreatic cancer[34, 35]. Based on logistic multivariate regression analysis, we found that the difference of gender and diabetes between the case group and the negative control group was even more statistically significant. Which indicated that female patients are more likely to suffer from hepatic hemangioma and femoral fracture, and some studies supported this conclusion[36, 37]. Furthermore, it has been reported that patients with type 2 diabetes have increased BMD (bone mineral density) but impaired structure and mineral properties, showing a unique bone phenotype that increases the risk of fracture[38], which is consistent with our conclusion.

The rate of cholecystectomy between the case group and the positive control group was analyzed by chi-square test, and it was statistically significant. Then we analyzed the rate of cholecystectomy between the case group and the negative control group the same way, and the difference was statistically significant too. Based on the chi-square analysis of the rate of cholecystectomy, we conducted logistic multivariate analysis between the case group and the positive control group, and the data showed that the OR value of the rate of cholecystectomy was 1.553 (CI95%: 1.311–1.840, $p = 0.000$). The data indicates that patients who underwent cholecystectomy have a higher risk of cholangiocarcinoma comparing with colon cancer and pancreatic cancer. The patients in the negative control group are diagnosed with femoral fracture or hepatic hemangioma. And no research has been reported that these two diseases are related to cholecystectomy. Similarly, logistic multivariate analysis between the case group and the negative control group in this study showed that the OR value of the rate of cholecystectomy was 3.181 (CI95%: 2.561–3.951, $p = 0.000$). We can conclude that cholecystectomy is one of the risk factors of cholangiocarcinoma based on these evidence.

The comparison between cholecystolithiasis and cholecystectomy of patients in the case group showed that the difference was statistically significant. And based on the logistic multivariate analysis, the OR value of cholecystolithiasis between the case group and the positive control group was 2.460 (CI95%: 2.093–2.890, $p = 0.000$), while the OR value of cholecystolithiasis between the case group and the negative control group was 5.426 (CI95%: 4.325–6.809, $p = 0.000$). These evidence indicated that patients with cholecystolithiasis have a higher risk of cholangiocarcinoma comparing with the patients who underwent cholecystectomy. However, the risk of cholangiocarcinoma remained high after cholecystectomy and did not fall to the level of the negative control group. Cholecystolithiasis as one of the risk factors of cholangiocarcinoma can be attributed to the chronic inflammatory stimulation to gallbladder and bile duct by gallstones. Inflammation has become a recognized oncogenic mechanism, and pro-inflammatory cytokines could stimulate the expression of abnormal genes in biliary epithelial cells, which is closely related to the occurrence of cholangiocarcinoma[39–41]. Although cholecystectomy can eliminate the inflammatory stimulation of cholecystolithiasis, it can lead to bile acid metabolism disorder and increase the secretion of secondary bile acids, which has been shown to be involved in carcinogenesis[42–44]. In addition, cholecystectomy can lead to alteration of intestinal flora which is associated with the development of gastrointestinal tumor[45, 46].

Conclusion

In conclusion, cholecystectomy has a close relationship with the incidence of cholangiocarcinoma and the patients who undergo cholecystectomy have a higher risk of cholangiocarcinoma than the control groups. So it is not recommended to perform cholecystectomy blindly. Therefore, we suggest that cholecystectomy should still be performed in patients, whose gallbladder lost the biological function or who have surgical indications, to eliminate the risk of gallstones-induced malignancy. With regard to the patients of cholecystolithiasis whose gallbladder is functional or the surgical indication of choledochotomy is not met, we should perform cholecystectomy with caution or the conservative treatment is practicable.

Declarations

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Not applicable.

Authors’ contributions

DLZ extracted data and analyzed most of the data. HF contributed to data analysis. MZJ performed data interpretation. YC contributed to the funding support, participated in the design of the study. DLZ wrote the manuscript. YJR designed the study. All authors approved the final version of the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the ethics committee of the Xijing Hospital and performed in accordance with their guidelines. Because of the anonymous characteristics of the data, the informed consent was waived.

Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no conflicts of interest.

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