Original Article

Clinical Factors Predictive of GB Adenoma/Carcinoma in Patients with GB Polyps

Piti Ungarreevittaya MD[1], Jureerat Thammaroj MD[2], Kriengsak Jenwitheesuk MD[3]

[1] Department of Pathology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[2] Department of Radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[3] Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Objective: To evaluate clinical risk factors of gallbladder adenoma or adenocarcinoma in Thai patients with gallbladder polyps.

Materials and Methods: The present study was conducted as a cross-sectional analytical study at the Department of Surgery, Faculty of Medicine, Khon Kaen University, Thailand. The inclusion criteria were adult patients that underwent laparoscopic cholecystectomy, diagnosed as gallbladder polyps by any of the radiographical modalities, with available pathological results. Factors associated with gallbladder adenoma/carcinoma were analyzed by using multivariate logistic regression analysis.

Results: Eighty-five eligible patients were included in the present study. Of those, 19 patients (22.4%) had adenoma polyp, while 66 patients (77.7%) were in cholesterol polyp group. Five patients were gallbladder carcinoma (5.9%). After adjusted, there were two independent factors associated with adenoma polyp including imaging size and pain or biliary colic symptom. Neutrophil lymphocyte ratio [NLR] and imaging polyp size were significant predictors for gallbladder carcinoma with adjusted odds ratio of 4.28 (95% CI 1.01 to 17.57) and 1.31 (95% CI 1.01 to 1.72), respectively.

Conclusion: Clinical factors are important predictors for gallbladder adenoma/carcinoma. Imaging gallbladder polyp size and biliary colic pain are indicators for gallbladder adenoma, while NLR and the imaging gallbladder polyp size are suggestive for gallbladder adenocarcinoma.

Keywords: Biliary colic, Neutrophil lymphocyte ratio, Sensitivity, Specificity

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Gallbladder polyps are defined as projections into the gallbladder lumen[1]. It can cause symptoms similarly to gall stones or can be asymptomatic. Those asymptomatic patients with gallbladder polyps can be accidentally found by several radiographic modalities, most commonly ultrasonography[2]. The main clinical consideration for gallbladder polyps is judgment in nature or pathology of the polyps[2].

Even though adenocarcinoma of gallbladder is relatively rare with an incidence of 1.5/100,000 population[3], it may be reasonable to be aware of it in case of presence of gallbladder polyp. The recent guideline recommends differentiating between cholesterol and adenoma polyp[2]. The latter one is at higher risk for gallbladder cancer. A long-term follow-up study from Taiwan found that size of polyps over 10 mm may be an indication for cholecystectomy[4]. Similarly, several studies focused on risk of gallbladder cancer and polyp sizes that varied from 6 to 14 mm[5-7]. Some studies used ultrasound technique or other radiological modalities to identify gallbladder cancer risk such as high-resolution ultrasound or magnetic resonance imaging [MRI][8,9]. Few studies evaluated clinical factors. Additionally, high-resolution ultrasound or MRI may not be widely available. The present study aimed to evaluate clinical risk factors of gallbladder adenoma or adenocarcinoma.

Correspondence to:

Jenwitheesuk K. Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
Phone: +66-43-363133
Email: surgerykkh@gmail.com

Materials and Methods

The present study was conducted as a cross-sectional analytical study at the Department of Surgery, Faculty of Medicine, Khon Kaen University, Thailand. The study period was between January and December 2017. The inclusion criteria were adult patients that underwent laparoscopic cholecystectomy, diagnosed as gallbladder polyps by any of the radiographical modalities, and available pathological results. Medical records of all eligible patients were retrospectively reviewed. Clinical data were collected including demographic baseline characteristics, symptoms of

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gallbladder polyps, risk factors for gallbladder polyps, laboratory results, and pathological results.

Patients were categorized into two groups by pathological results, cholesterol polyps, and adenoma polyps. The cholesterol polyp group included patients with cholesterol polyp and/or benign/chronic inflammation by pathological results, while the adenoma polyp group were those with adenoma polyps, adenocarcinoma, papilloma, or xanthomatous polyp.

Statistical analysis

Descriptive statistics were used to compare studied variables between both groups. A logistic regression analysis was used to predict adenoma polyp. A goodness of fit of the final predictive model was tested by Hosmer-Lemeshow method. Independent numerical predictive factors were executed for various appropriate cutoff points. Sensitivities and specificities were calculated for each cutoff point. An area under a receiver operating characteristic [ROC] curve was also reported. A subgroup analysis within the adenoma polyp group was performed to find independent factors for carcinomatous polyps by using multivariate logistic regression analysis. Finally, predictors for carcinomatous polyps in all study population were computed by the same procedures for prediction of adenomatous polyp. Results were shown as unadjusted/adjusted odds ratio with 95% confidence interval, sensitivity, specificity, and the area under the ROC curve. All statistical analyses were performed by Stata software, version 10.1 (College Station, Texas, USA).

Results

There were 85 eligible patients in the present study. Of those, 19 patients (22.4%) had adenoma polyps, while 66 patients (77.7%) were in cholesterol polyp group. Five patients were gallbladder carcinoma (5.9%). Among studied clinical variables, only one factor was significantly different between both groups. A proportion of patient presenting with pain was significantly higher in adenoma group than cholesterol group (57.9% versus 30.3%; *p*-value 0.034) as shown in Table 1.

After adjusted, there were two independent factors

Table 1. Clinical factors of patients with gallbladder polyps categorized by types of pathological diagnosis

Factors	Cholesterol polyp (n = 66)	Adenoma polyp (n = 19)	*p*-value
Age (years)	52 (45 to 59)	52 (43 to 60)	0.996
Male, n (%)	33 (50.0)	5 (26.3)	0.115
Married, n (%)	62 (93.9)	15 (79.0)	0.070
BMI (kg/m^2)	25.0 (22.6 to 27.5)	24.6 (22.1 to 29.4)	0.954
Diabetes, n (%)	35 (53.0)	10 (52.6)	0.999
Numbers of sons/daughters	5 (5 to 5)	5 (5 to 5)	0.050
Family history of cancer, n (%)	1 (1.5)	1 (5.3)	0.399
Presenting symptom, n (%)			
Asymptomatic	24 (36.4)	3 (15.8)	0.103
Pain	20 (30.3)	11 (57.9)	0.034
Discomfort	18 (27.3)	5 (26.3)	0.999
Burning	2 (3.0)	0 (0.0)	0.999
Hematocrit (%)	39.1 (36.4 to 41.7)	37.1 (34.8 to 42.0)	0.235
White blood cell ($x10^3/mm^3$)	7.1 (6.4 to 8.3)	7.6 (6.7 to 8.2)	0.719
Platelet ($x10^6$)	2.6 (2.11 to 3.00)	2.6 (2.3 to 3.4)	0.256
PMN (%)	55.1 (48.8 to 62.8)	60.1 (51.2 to 65.6)	0.119
NLR	1.6 (1.3 to 2.3)	2.0 (1.6 to 2.5)	0.094
Serum creatinine (mg/dL)	0.8 (0.7 to 1.0)	0.9 (0.7 to 1.0)	0.716
Serum albumin (g/dL)	4.3 (4.0 to 4.6)	4.3 (4.0 to 4.6)	0.827
Serum ALT (U/L)	24 (17 to 39)	20 (13 to 30)	0.077
Serum AST (U/L)	24 (19 to 32)	23 (16 to 28)	0.308
Imaging size (mm)	5.1 (4.0 to 7.0)	7.0 (5.0 to 13.0)	0.084
Pathological size (mm)	3.0 (2.0 to 5.0)	5.0 (3.0 to 10.0)	0.068

BMI = body mass index; PMN = polymorphonuclear neutrophil; NLR = neutrophil lymphocyte ratio; ALT = alanine aminotransferase; AST = aspartate aminotransferase

Data presented as median (1^{st} to 3^{rd} quartile range), unless indicated otherwise

associated with adenoma polyp including imaging size and pain symptom. Both factors had adjusted odds ratios of 1.28 and 11.58, respectively (Table 2). The predictive final model for having adenoma polyp had Hosmer-Lemeshow chi square of 9.28 (*p*-value 0.319). The radiographic imaging size of gallbladder polyp on having adenoma polyp had the AUC of 0.6713. The sensitivities and specificities of 5 cm and 7 cm of polyp were 90.91%, 35.90% and 54.55%, 69.23%, respectively.

The subgroup analysis within adenoma group showed that two factors were perfectly associated with carcinomatous polyps including pathological size of over 10 mm and presence of family history of gallbladder cancer. No other significant factor was related with carcinomatous polyps.

There were two independent factors related with carcinomatous polyps in the overall analysis. Neutrophil lymphocyte ratio [NLR] had higher adjusted odds ratio than imaging size (4.28 versus 1.31) as shown in Table 3. The Hosmer-Lemeshow Chi-square of the final model for prediction of carcinomatous polyp was 1.17 (*p*-value 0.996). Table 4 shows the sensitivity and specificity of various cutoff points of imaging sizes and NLR on having carcinomatous polyp. The imaging size of 10 mm provided specificity of 82.61% and the NLR of 1.28 gave the sensitivity of 83.33%.

Discussion

A previous study from China[10] found that predictors for cholesterol polyps were serum lipid abnormalities and multiple polyps. The present study added that patients with gallbladder polyps increased risk of having gallbladder adenoma by 11 times if biliary colic was present. Another predictor for adenoma in the present study was gallbladder polyp size. If the gallbladder polyp size increased by one mm, the risk of adenoma increased by 27%. These results were different from the previous study from China that found that polyp size was not a risk factor for having cholesterol polyps. Note that polyp size used in that study was a categorical type with a size of larger than 15 mm. However, in the present study, polyp size was a numerical type.

Table 2. Factors associated with adenoma polyp by multivariate logistic regression analysis in all patients (n = 85)

	Unadjusted odds ratio (95% confidence interval); *p*-value	Adjusted odds ratio (95% confidence interval); *p*-value
Age (years)	0.90 (0.95 to 1.03); 0.613	0.96 (0.89 to 1.02); 0.195
BMI (kg/m^2)	1.03 (0.90 to 1.19); 0.632	1.21 (0.93 to 1.58); 0.146
Imaging size (mm)	1.12 (0.98 to 1.29); 0.103	1.28 (1.05 to 1.55); 0.012
Pain (%)	3.16 (1.11 to 9.05); 0.032	11.58 (1.98 to 67.69); 0.006

BMI = body mass index

Table 3. Factors associated with carcinomatous polyp by multivariate logistic regression analysis in all patients (n = 85)

Factors	Unadjusted odds ratio (95% confidence interval); *p*-value	Adjusted odds ratio (95% confidence interval); *p*-value
Imaging size (mm)	1.25 (1.04 to 1.51); 0.011	1.31 (1.01 to 1.72); 0.008
NLR	1.45 (0.99 to 2.27); 0.764	4.28 (1.04 to 17.57); 0.042

NLR = neutrophil lymphocyte ratio

Table 4. Sensitivity and specificity of various cutoff points on carcinomatous polyp predictions in patients with gallbladder polyps

Factors/cutoff points	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)
Imaging size (mm)*		
5	75.00 (30.80 to 98.90)	30.43 (26.90 to 31.20)
8	75.00 (30.80 to 98.90)	76.09 (73.20 to 77.40)
10	75.00 (30.80 to 98.90)	82.61 (79.40 to 83.70)
13	75.00 (30.80 to 98.90)	93.48 (90.80 to 94.90)
NLR		
1.05	100 (68.40 to 100.00)	2.53 (0.50 to 2.50)
1.28	83.33 (30.70 to 98.90)	20.25 (16.90 to 21.20)
1.53	83.33 (30.70 to 98.90)	40.51 (36.90 to 41.20)

NLR = neutrophil lymphocyte ratio

The area under a receiver operating characteristic [ROC] curve equal 0.7609* and 0.5717**

As previous reported, symptomatic gallbladder polyps increased risk of gallbladder cancer[11]. Biliary colic increased risk of gallbladder cancer by 11 times. Note that the analysis was a subgroup analysis in those with adenoma polyp. For all patients, the imaging size of polyps and NLR[12] were related to risk of gallbladder cancer. The authors found similar findings as previous studies regarding of polyp sizes from 10 to 14 mm[5,10]. Regardless of age or symptoms, polyp sizes over 10 and 13 mm increased risk of gallbladder cancer with sensitivity of 75% and specificity 82.61% to 93.48%. For NLR, ratio of 1.2 to 1.53 had sensitivity of gallbladder cancer 83.33%, but specificity was low (20.25% to 40.51%) as shown in Table 4. The authors recommend using both factors (imaging size and NLR) in combination to evaluate risk of gallbladder cancer. The NLR has been known as a marker of high inflammation related to progression of cancers and poor prognosis in solid tumors[13].

The present study had some limitations. First, this was a single site study conducted in a university hospital with a small sample. However, the models had a goodness of fit by Hosmer-Lemeshow method. Second, most patients had their gallbladder polyps diagnosed mainly by ultrasonography. Finally, all patients are Thai, so the results may not be generalized to other populations.

In conclusion, clinical factors are important predictors for gallbladder adenoma/carcinoma. Imaging gallbladder polyp size and biliary colic pain are indicators for gallbladder adenoma, while NLR and the imaging gallbladder polyp size are suggestive for gallbladder adenocarcinoma.

What is already known on this topic?

Most studies found that gallbladder polyp size is a predictor for gallbladder carcinoma.

What this study adds?

Clinical factors such as biliary colic or NLR are related with gallbladder carcinoma in patients with gallbladder polyps.

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Potential conflicts of interest

The authors declare no conflict of interest.

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