

# Frequency, Risk Factors, and Outcome of Gallbladder Polyps in Patients With Primary Sclerosing Cholangitis: A Case-Control Study

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The prevalence of gallbladder polyps (GBPs) in the general population has been estimated to be approximately 5%, with up to 10% of these being dysplastic or malignant. Previous studies have suggested that patients with primary sclerosing cholangitis (PSC) have increased frequency of GBPs. However, data on the prevalence, risk factors, and outcome of GBPs in these patients are sparse. This case-control study investigates the frequency, risk factors, and outcome of GBPs in patients with PSC. In this study, 363 patients with an established diagnosis of PSC based on magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), or liver biopsy were identified. Patients with at least one abdominal imaging and no history of cholecystectomy before the first available abdominal imaging were included. The presence of GBPs was confirmed by abdominal computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound. Patients with GBPs were compared to those without GBPs. Furthermore, patients with malignant/premalignant polyps were compared to those with benign polyps. The frequency of GBPs in patients with PSC was 10.6%. There was no significant difference in the frequency of inflammatory bowel disease (IBD) between the two groups. Of the 16 patients with GBPs who underwent cholecystectomy, 10 had malignant/premalignant lesions, of whom 6 had adenocarcinoma, and 4 had high-grade dysplasia. Of the 6 patients with adenocarcinoma, 4 had lesions >10 mm, 1 had a lesion as small as 4 mm, and 1 had a 7-mm lesion. **Conclusion:** GBPs may be frequently seen in patients with PSC. These lesions seem to occur independent of IBD. In patients with PSC, even small GBPs appear to have a risk of malignancy. These findings suggest that patients with PSC and GBPs may benefit from cholecystectomy, regardless of the size of the polyp. (*Hepatology Communications* 2018;2:1440-1445).

PSC is a chronic progressive disorder of the biliary system characterized by cholestasis secondary to ongoing inflammation, demolition, and fibrosis of both intrahepatic and extrahepatic bile ducts.<sup>(1-4)</sup> PSC is associated with an increased risk of gastrointestinal cancers, including cholangiocarcinoma, gallbladder carcinoma (GBC), and hepatocellular carcinoma as well as colorectal carcinoma.<sup>(5-9)</sup> Elevated risk for gallbladder malignancy in patients with PSC can be secondary to chronic inflammation precipitated by PSC, gallstone formation, and recurrent bacterial cholecystitis, potentially resulting in dysplasia and eventually carcinoma.<sup>(9)</sup>

*Abbreviations:* BMI, body mass index; CD, Crohn disease; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; GBC, gallbladder carcinoma; GBP, gallbladder polyp; IBD, inflammatory bowel disease; ICD-9/10, International Classification of Diseases, Ninth/Tenth Revision; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

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GBP is the outgrowth of the inner gallbladder wall, protruding into its lumen.<sup>(10)</sup> The prevalence of GBPs in the general population has been estimated to be approximately 5%, with up to 10% of these being dysplastic or malignant. Patients with PSC have increased frequency of GBPs.<sup>(5,11-14)</sup> There are sparse data on the prevalence, risk factors, and outcome of GBPs in these patients. However, available data suggest gallbladder lesions found in patients with PSC have a higher risk of malignancy.<sup>(5,11,12,14)</sup> Therefore, GBPs are of significant importance in patients with PSC. This case-control study was designed to investigate the prevalence, associated risk factors, and outcome of GBPs in patients with PSC.

## Patients and Methods

### DATA SOURCE

A comprehensive chart review was performed on 487 consecutive patients with a diagnosis of PSC based on the International Classification of Diseases, Ninth Revision (ICD-9), and ICD-10 codes. These patients had received part of their care at Cleveland Clinic, Cleveland, OH. The diagnosis of PSC was confirmed in 363 patients based on the findings of previously obtained MRCP, ERCP, or liver biopsy. At the Cleveland Clinic, routine surveillance for cholangiocarcinoma and GBC in patients with PSC consisted of annual imaging with abdominal ultrasound, CT, or MRI. These previously obtained studies were reviewed to determine the presence of GBPs.

### INCLUSION AND EXCLUSION CRITERIA

Of the 363 patients with an established diagnosis of PSC, 5 were excluded due to lack of available

abdominal CT, MRI, or ultrasound in their records. Of the 358 remaining patients, 112 were excluded due to a history of cholecystectomy before the first available abdominal imaging. Eventually, 236 patients who met the above criteria were enrolled and considered for further review (Fig. 1).

### CLINICAL VARIABLES

Initially, data regarding the following variables were extracted: age at time of study, age at time of PSC diagnosis, sex, ethnicity, body mass index (BMI), history of tobacco use, presence of GBPs, IBD, ulcerative colitis (UC), Crohn disease (CD), indeterminate colitis, cirrhosis, and colon polyps. In addition to the above variables, in patients with GBPs, data regarding age at time of diagnosis of GBPs, number of polyps, size of the largest polyp, cholecystectomy after the diagnosis of polyps, and if applicable, the pathology of polyps were collected and analyzed. Subsequently, patients with a diagnosis of PSC who also had GBPs were considered the case group and those without GBPs were considered the control group. Furthermore, in patients with GBPs who underwent cholecystectomy, those with dysplastic or malignant lesions were compared to patients with benign lesions.

### STATISTICAL ANALYSIS

Statistical analysis was performed using JMP Pro 12 (Statistical Analysis System Institute, Cary, NC). The chi-square test was used to compare nominal variables, and the *t* test was used to compare numeric variables. All tests were 2-tailed with a significance level of alpha = 0.05. Multiple linear regression was calculated to predict the presence of GBP based on age, sex, ethnicity, BMI, history of tobacco use, presence of IBD, cirrhosis, and colon polyps.

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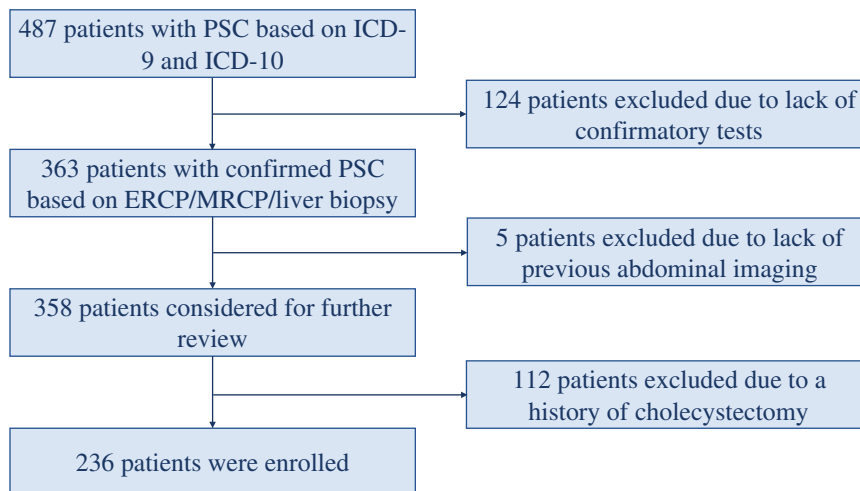


FIG. 1. Selection of study subjects. All patients received at least part of their care at Cleveland Clinic, Cleveland, OH.

## Results

### FREQUENCY OF GBPs IN PATIENTS WITH PSC

Of the 236 patients with PSC, 25 had GBPs (10.6%). The mean age at time of diagnosis of GBPs was  $53 \pm 3$  years (range, 27–53 years). Of the 25 patients who were found to have GBPs, 11 had a single polyp, 7 had two polyps, and 7 had three or more polyps. The mean size of the largest polyp was  $8 \pm 1.5$  mm (range, 2–27 mm). In 4 patients, the diagnosis of GBPs preceded the diagnosis of PSC. In 3 patients, GBPs were found at the time of the diagnosis of PSC, and in the remaining patients, GBPs were found up to 17 years after the diagnosis of PSC (mean,  $10 \pm 5$  years).

### RISK FACTORS FOR GBPs IN PATIENTS WITH PSC

There was no statistically significant difference in the age of patients with GBPs compared to the age of those without GBPs ( $57 \pm 3$  versus  $52 \pm 1$  years, respectively;  $P = 0.1$ ). The majority of the study subjects were either Caucasian or African American. Due to the insufficient number of patients of other ethnicities, only the above ethnicities were considered for comparison, and no statistically significant difference was identified. Compared to patients without GBPs,

there were no significant differences in sex, ethnicity, BMI, history of tobacco use, presence of cirrhosis, or colon polyps in patients with GBPs. Additionally, there was no significant difference between the frequency of IBD, UC, or CD in these two groups (Table 1). Overall, no significant regression equation was found based on multivariate analysis.

TABLE 1. CHARACTERISTICS OF PATIENTS WITH PSC WITH GBPs COMPARED TO THOSE WITHOUT GBPs

	Patients With GBPs	Patients Without GBPs	P Value
Number of patients	25	211	
Age at time of study (year)*	$57 \pm 3$	$52 \pm 1$	0.10
Age at time of diagnosis of PSC (year)*	$45 \pm 3$	$41 \pm 1$	0.13
Female (%)	9 (36.0)	60 (28.4)	0.43
BMI ( $\text{kg}/\text{m}^2$ ) <sup>†</sup>	$26.1 \pm 3.9$	$27.4 \pm 8.4$	0.21
Ethnicity, C/AA (%)	23/2 (92.0)	180/25 (87.8)	0.54
IBD (%)	22 (88.0)	161 (76.3)	0.19
UC (%)	19 (76.0)	119 (56.4)	0.06
CD (%)	2 (8.0)	41 (19.4)	0.16
Smoker (%)	3 (12.0)	52 (24.6)	0.16
Cirrhosis (%)	14 (56.0)	130 (61.6)	0.59
Colon polyp (%) <sup>‡</sup>	14/10 (58.3)	72/103 (41.1)	0.11

\*Mean  $\pm$  SEM; <sup>†</sup>mean  $\pm$  SD; <sup>‡</sup>N = 199.

Abbreviations: AA, African American; C, Caucasian.

## OUTCOME OF GBPs IN PATIENTS WITH PSC

Out of the 25 patients with GBPs, 16 underwent cholecystectomy in our center. Review of pathology reports revealed 6 patients had adenocarcinoma and 4 had high-grade dysplasia. The other 6 patients had benign lesions: 3 had cholelithiasis and 3 had acute/chronic inflammation. Of the 9 remaining patients, 3 were undergoing further assessment for cholecystectomy at the time of study, 2 had polyps  $\leq 2$  mm and decided to be followed expectantly with interval surveillance, 2 were lost to follow-up, 1 was not a candidate for cholecystectomy due to multiple comorbidities, and 1 underwent cholecystectomy at another center. Those with malignant or premalignant lesions (adenocarcinoma or high-grade dysplasia, respectively) were compared to those with benign lesions. The mean age at the time of study, the diagnosis of PSC, and the diagnosis of GBPs were greater in patients within the malignant/premalignant group; however, this difference was not statistically significant. There were no significant differences in age at the time of study, age at the time of diagnosis of PSC, sex, ethnicity, BMI, history of tobacco use, presence of IBD (UC, CD), cirrhosis, or colon polyps between patients with benign lesions and patients with malignant/premalignant lesions (Table 2). Of the 6 patients with adenocarcinoma, 4 had lesions  $>10$  mm, 1 had a lesion as small as 4 mm, and 1 had a 7-mm lesion. Of the 4 patients with premalignant lesions, 1 had a 7-mm

lesion and 2 had lesions that grew from 3 mm and 4 mm to 13 mm and 23 mm, respectively. Of note, 5 out of 6 patients with benign GBPs had lesions  $\leq 6$  mm and 1 had a 27-mm lesion.

## Discussion

Patients with PSC tend to have an increased frequency of gastrointestinal cancers, including GBC.<sup>(5-9)</sup> The development of cancer strongly affects the prognosis in patients with PSC and is responsible for more than 40% of the mortality in these patients.<sup>(15,16)</sup> In fact, deaths caused by end-stage liver disease and other nonmalignant complications of PSC are far below cancer-related deaths.<sup>(6,7,17)</sup> A favorable prognosis is embedded in early stage detection and treatment of PSC-associated malignancies. Gallbladder adenocarcinoma can present as a GBP.<sup>(18)</sup> On the other hand, GBPs can be malignant or harbor malignant potential.<sup>(18)</sup> Although it is not clear how many GBCs are preceded by a GBP, generally it takes more than 5 to 15 years for a metaplastic polyp to progress to invasive cancer.<sup>(19)</sup>

In this study, 10.6% of patients with PSC had GBPs. There was no significant difference between the frequency of IBD, UC, or CD in patients with GBPs and patients without GBPs. The prevalence of GBPs in the general population has been estimated to be approximately 5%.<sup>(18,20,21)</sup> Some studies have reported a higher prevalence of gallbladder cancer in

**TABLE 2. CHARACTERISTICS OF PATIENTS WITH MALIGNANT/DYSPLASTIC GBPs COMPARED WITH THOSE WITH BENIGN GBPs**

	Patients With Dysplastic or Malignant GBPs	Patients With Benign GBPs	P Value
Number of patients	10	6	
Age at time of study (year)*	58 $\pm$ 4	54 $\pm$ 6	0.25
Age at time of diagnosis of PSC (year)*	46 $\pm$ 5	43 $\pm$ 5	0.37
Age at time of diagnosis of GBP (year)*	54 $\pm$ 4	50 $\pm$ 6	0.29
Female (%)	3 (30.0)	3 (50.0)	0.42
BMI (kg/m <sup>2</sup> ) <sup>†</sup>	24.9 $\pm$ 3.3	25.5 $\pm$ 2.9	0.36
Size of largest GBP (mm) <sup>†</sup>	11 $\pm$ 2	8 $\pm$ 4	0.24
IBD (%)	10 (100)	6 (100)	
UC (%)	10 (100)	6 (100)	
CD (%)	0 (0)	0 (0)	
Smoker (%)	0/10 (0)	1/5 (16.7)	0.18
Cirrhosis (%)	8/2 (80.0)	3 (50.0)	0.21
Colon polyp (%) <sup>‡</sup>	5/3 (62.5)	4/3 (57.1)	0.83

\*Mean  $\pm$  SEM; <sup>†</sup>mean  $\pm$  SD; <sup>‡</sup>N = 15.



patients with UC and to some extent patients with CD.<sup>(22,23)</sup> However, available data suggest this association is most likely secondary to concomitant PSC and not to IBD independently.<sup>(7)</sup> The findings of this study also suggest that GBPs in patients with PSC occur independent of the underlying IBD.

In the study population, there was no statistically significant difference in the mean age of patients with GBPs compared to the age of those without GBPs. Additionally, sex distribution, ethnicity, BMI, tobacco use, the presence of cirrhosis, and colon polyps were not found to be associated with the presence of GBPs. As with most studies,<sup>(18,24)</sup> this study failed to identify any particular risk factors for GBPs.

Although the majority of GBPs in the general population are benign,<sup>(18,25,26)</sup> available data suggest GBPs in patients with PSC have an increased risk of malignancy.<sup>(5,11)</sup> In this study, 6 patients (2.5%) were found to have GBC, which is comparable to data from a cohort of 830 patients with PSC, with 6 patients (0.7%) developing GBC.<sup>(27)</sup> Predictors for the presence of malignancy in GBPs with underlying PSC are yet to be described.<sup>(15)</sup> In the general population, the size of the GBPs seems to be an important factor,<sup>(11,28)</sup> with malignancy significantly more frequent in polyps >10 mm; however, it can also be present in smaller polyps.<sup>(10,29)</sup> Another important risk factor for the presence of GBC within GBPs is increased age at time of identification of the lesion.<sup>(28,30,31)</sup> These risk factors may also apply to patients with PSC. In this study, of the 16 patients who underwent cholecystectomy, 6 (37.5%) had malignant polyps, 4 (25%) had premalignant lesions, and 6 (37.5%) had benign polyps. The mean age of patients with malignant or premalignant lesions was greater than those with benign lesions. However, this was not statistically significant; neither was the difference in the size of the polyps. There was also no statistically significant association between malignant/premalignant lesions and sex, ethnicity, BMI, presence of IBD, cirrhosis, or colon polyps. The results of this study suggest that in patients with PSC, GBPs may have an increased risk of harboring malignancy regardless of the size of the polyp, the age of the patient, the presence of cirrhosis, or underlying IBD.

GBPs are generally asymptomatic and usually identified incidentally. Given the increased risk of malignancy in GBPs in patients with PSC, current guidelines recommend an annual abdominal

ultrasound to increase the chance of early detection of these lesions and subsequently improve survival.<sup>(32,33)</sup>

Despite these guidelines, there is no unanimous agreement on the management of GBPs. Some experts recommend cholecystectomy, regardless of the polyp size.<sup>(33,34)</sup> However, because patients with PSC might be at increased risk of perioperative complications, others argue lesions <8 mm can be managed expectantly with serial follow-up.<sup>(14)</sup> In the study subjects, 1 patient had adenocarcinoma within a polyp as small as 4 mm and 1 patient had adenocarcinoma in a 7-mm polyp. These findings suggest that patients with PSC and GBPs may benefit from cholecystectomy, regardless of the size of the polyp.

There are limitations to the current study. The scope of this study is limited by the small number of patients with GBPs. As a retrospective chart review case-control study, the generalizability of the results is limited. To minimize the risk of recall bias, only objective data were studied. Furthermore, this study did not investigate the potential impact of medical management of PSC on GBPs and GBC.

In conclusion, GBPs may be frequently seen in patients with PSC. These lesions seem to occur independent of IBD. In patients with PSC, even small GBPs appear to have an elevated risk of malignancy. Therefore, the results of this study suggest that patients with PSC and GBPs may benefit from cholecystectomy, regardless of the size of the polyps. Larger studies are required to further investigate the risks and benefits of cholecystectomy in these patients.

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