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Long-term Outcomes of Symptomatic Gallbladder Sludge

유증상 담낭 담즙앙금의 장기간 추적 임상결과

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이 윤 석

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The Department of Clinical Medical Sciences,
Seoul National University
College of Medicine
Yoon Suk Lee

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지도교수 황 진 혁

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임상의과학과 임상의과학전공
이 윤 석

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Long–term Outcomes of Symptomatic Gallbladder Sludge

by

Yoon Suk Lee

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Professor ____________________ Chairman

Professor ____________________ Vice chairman

Professor ____________________

학위논문 원문제공 서비스에 대한 동의서

본인의 학위논문에 대하여 서울대학교가 아래와 같이 학위논문 제공하는 것에 동의합니다.

1. 동의사항

① 본인의 논문을 보존이나 인터넷 등을 통한 온라인 서비스 목적으로 복제할 경우 저작물의 내용을 변경하지 않는 범위 내에서의 복제를 허용합니다.

② 본인의 논문을 디지털화하여 인터넷 등 정보통신망을 통한 논문의 일부 또는 전부의 복제.배포 및 전송 시 무료로 제공하는 것에 동의합니다.

2. 개인(저작자)의 의무

본 논문의 저작권을 타인에게 양도하거나 또는 출판을 허락하는 등 동의 내용을 변경하고자 할 때는 소속대학(원)에 공개의 유보 또는 해지를 즉시 통보하겠습니다.

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① 서울대학교는 본 논문을 외부에 제공할 경우 저작권 보호장치(DRM)를 사용하여야 합니다.

② 서울대학교는 본 논문에 대한 공개의 유보나 해지 신청 시 즉시 처리해야 합니다.

논문 제목: Long-term Outcomes of Symptomatic Gallbladder Sludge

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학 과: 임상의과학과
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서울대학교총장 귀하

ABSTRACT

Long-term Outcomes of Symptomatic Gallbladder Sludge

Yoon Suk Lee
Department of Clinical Medical Sciences
The Graduate School
Seoul National University

Introduction: Long-term outcomes of symptomatic gallbladder (GB) sludge are not fully established. This study aimed to determine whether patients with symptomatic GB sludge could experience subsequent biliary events.

Methods: This study investigated consecutive patients who presented with typical biliary pain and underwent abdominal ultrasonography from March 2003 to December 2012. A prospectively maintained database of these patients, excluding those with gallstones, was reviewed retrospectively. The development of biliary events such as acute cholecystitis, acute cholangitis, and acute pancreatitis was compared between both GB sludge and non-GB sludge cohorts.

Results: In all, 58 and 70 patients were diagnosed with and without GB sludge, respectively. The 5-year cumulative biliary event rate was significantly higher in the GB sludge (33.9% vs. 15.8%, P = 0.021) and the HR of subsequent biliary events was 2.573 (95% CI, 1.124–5.889; P = 0.025) in patients with GB sludge. The 5-year cumulative rate of each biliary event was higher in the GB sludge cohort (15.6% vs. 5.3 in acute cholecystitis, 15.5% vs. 5.3% in acute cholangitis, 18.4% vs. 11.1% in acute pancreatitis, respectively), although it was not statistically significant. Among the GB sludge cohort, subsequent biliary events were less frequent in patients who underwent cholecystectomy compared to those who did not (2/16, 12.5% vs. 17/42, 40.4%; P = 0.067).

Conclusions: GB sludge accompanying typical biliary pain can cause subsequent biliary events and cholecystectomy may prevent subsequent biliary events. Therefore, GB sludge would be considered as a culprit of biliary events.

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Keywords: gallbladder sludge, gallstone, biliary event, cholecystectomy

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INTRODUCTION

Gallbladder (GB) sludge is defined as a suspension of cholesterol monohydrate crystals or calcium bilirubinate granules mixed with mucin and proteins.[1] GB sludge was first detected in the 1970s with the advent of ultrasonography (US). Thereafter, it has been more frequently identified as US resolution has improved, and routine check-ups that now regularly include abdominal US. GB sludge shares somewhat with gallstone in specific clinical situations, such as pregnancy, rapid weight loss, total parenteral nutrition, octreotide treatment, bone marrow transplantation, and ceftriaxone treatment.[2-7] However, the clinical significance of GB sludge has not been fully established, although a few reports suggest that it may be associated with acalculous cholecystitis,[8] acute cholangitis,[9] and biliary pancreatitis.[10,11] Furthermore, the clinical outcomes of GB sludge accompanying biliary pain remain elusive. Therefore, the aim of this study was to evaluate whether patients with symptomatic GB sludge could experience subsequent biliary events, such as acute cholecystitis, acute cholangitis, or acute pancreatitis.

MATERIALS AND METHODS

1. Patients

Among the patients who visited the outpatient department of prof. Jin-Hyeok Hwang at Seoul National University Bundang Hospital from March 2003 to December 2012, those who presented with typical biliary pain and taken abdominal US were investigated retrospectively. According to the results of abdominal US, the patients were categorized into two separate cohorts (a GB sludge and a non-GB sludge cohort). The presumed diagnosis of those without GB sludge was functional gallbladder disorder based on the Rome III criteria. Exclusion criteria included: (1) GB stones or polyps; (2) common bile duct stones; (3) pregnancy; (4) malignancies; (5) patients with suspected causes of abdominal pain besides GB sludge; and (6) patients who had undergone a previous cholecystectomy or endoscopic sphincterotomy. If both sludge and stones were detected, the patient was excluded from the study (Fig.1). The medical records of eligible patients were then reviewed for development of any biliary events, such as acute cholecystitis, acute cholangitis, and acute pancreatitis. Subsequent biliary events after cholecystectomy were also evaluated in patients with GB sludge. Standardised telephone interviews were performed if the follow-up duration did not reach 12 months at the time of index study period. This study was approved by the human subjects committee of the Seoul National University Bundang Hospital, and it followed the ethical guidelines of the 1975 Declaration of Helsinki.

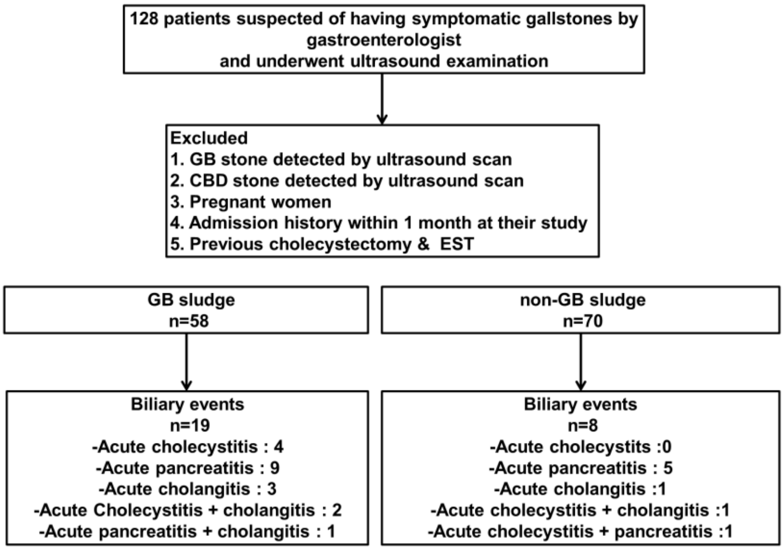

Figure 1. Patient disposition and the overall outcomes in the two cohorts CBD indicates common bile duct; EST, endoscopic sphincterotomy; GB, gallbladder.

2. Definition of gallbladder sludge and biliary events

GB sludge was defined on US as the presence of low-level echoes that shift with position changes and had no post-acoustic shadowing.[12] Patients with hyperechoic foci without associated acoustic shadowing were also defined as having GB sludge for the purposes of this study. All the abdominal US were performed by radiologists who specialize in performing gallbladder US with a standard imaging protocol, using a 3.5- to 7.0-MHz rotatory sector scanning transducer.

Typical biliary pain was defined when all the following were noted: (i) severe, steady pain located in the epigastrium or the right upper quadrant; (ii) episodes lasting ≥30; and (iii) symptoms occurring on one or more occasions in the previous 12 months.[13,14] A biliary event was defined as the occurrence of one of the following: acute cholecystitis, acute cholangitis, or acute pancreatitis. Acute cholecystitis and acute cholangitis was diagnosed according to the revised Tokyo guidelines.[15,16] Acute pancreatitis was diagnosed according to the revised Atlanta classification.[17]

3. Statistical analyses

The baseline characteristics were compared by using an independent t-test or Mann-Whitney U test for the continuous variables, and Chi-square test or Fisher's exact test was used for the categorical variables. After that, the cumulative rate from each type of biliary events was calculated during follow-up by using Kaplan-Meier analysis, and the rates were compared by using a log-rank test. All potential prognostic factors with a probability value <0.05 on univariate analyses were entered into the multivariable Cox regression models, by which the hazard ratio (HR) and 95% confidence interval (CI) were calculated. A two-sided P-value < 0.05 was considered statistically significant in all of the analyses. All the statistical analyses were performed with SPSS software (version 20.0 for Windows).

RESULTS

1. Baseline clinical characteristics

The characteristics of the patients in the GB sludge and non-GB sludge cohorts are summarized in Table 1. The following characteristics were observed for GB sludge vs. non-GB sludge cohorts: age (54.6 vs. 44.9, $P < 0.001$); male sex (44.8% vs. 24.3%, $P = 0.014$); body mass index (BMI) (23.6 vs. 22.9, $P = 0.374$); prevalence of diabetes (15.5% vs. 5.7%, $P = 0.068$); prevalence of hypertension (31.0% vs. 11.6%, $P = 0.007$); current smoking status (8.6% vs. 11.6%, $P = 0.582$); and alcohol use (20.7% vs. 15.9%, $P = 0.489$).

Characteristics	GB sludge (n = 58)	non-GB sludge (n = 70)	p Value
Age, yr – mean (SD)	54.6 (14.4)	44.9 (14.1)	**0.001**
Sex, male - no. (%)	26 (44.8)	17 (24.3)	**0.014**
BMI, kg/m^2 - mean (SD)	23.6 (3.0)	22.9 (2.7)	**0.374**
Diabetes mellitus – no. (%)	9 (15.5)	4 (5.7)	**0.068**
Hypertension – no. (%)	18 (31.0)	8 (11.6)	**0.007**
Current smoker – no. (%)	5 (8.6)	8 (11.6)	**0.582**
Alcohol user – no. (%)	12 (20.7)	11 (15.9)	**0.489**

SD, standard deviation; BMI, body mass index.

Obesity was defined as BMI >25

Table 1 Baseline characteristics of the patients between GB sludge and non-GB sludge cohort

2. Cumulative biliary event rates between GB sludge and non-GB sludge cohort.

The 58 patients with GB sludge were followed up for a mean of 35.4 months and 70 patients with no GB sludge for a mean of 31.5 months. During the follow-up, biliary events occurred in 19 patients (32.7%) in the GB sludge cohort and 8 patients (11.4%) in the non-GB sludge cohort. The 2-year and 5-year cumulative rates of biliary events were 30.7% and 33.9% in the GB sludge cohort and 12.9% and 15.8% in the non-GB sludge cohort, respectively (P = 0.021) (Fig. 2A). Acute cholecystitis, acute cholangitis, and acute pancreatitis occurred in 6 (10.3%), 6 (10.3%), and 10 (17.2%) patients in the GB sludge cohort and 2 (2.8%), 2 (2.8%), and 6 (8.5%) patients in the non-GB sludge cohort, respectively, during the follow-up. The 2- and 5-year cumulative rates of acute cholecystitis, acute cholangitis, and acute pancreatitis were 10.7% and 15.6%, 11.5% and 15.5%, and 18.4% and 18.4%, respectively in the GB sludge cohort and 2.0% and 5.3%, 2.0% and 5.3%, and 11.1% and 11.1%, respectively in the non-GB sludge cohort (Fig. 2C, B, D).

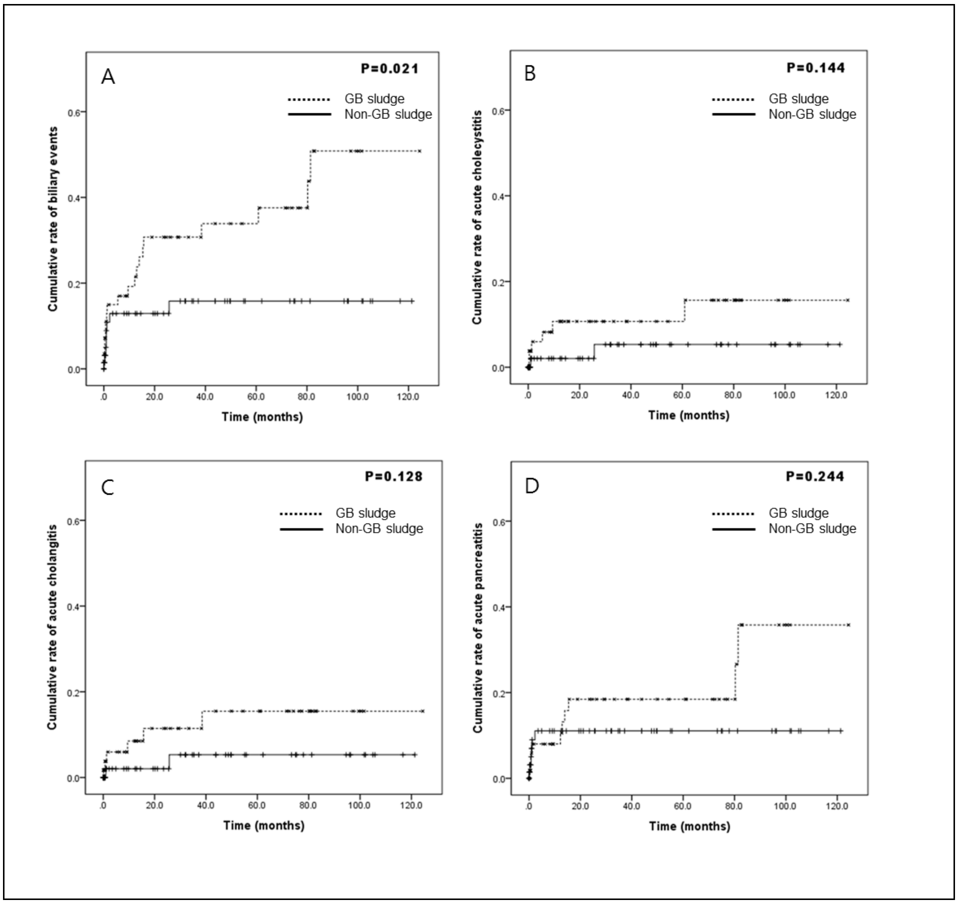

Figure 2. (A) Cumulative rate of biliary events, (B) Cumulative rate of acute cholecystitis, (C) Cumulative rate of acute cholangitis, (D) Cumulative rate of acute pancreatitis between GB sludge and non-GB sludge cohort.

3. Cox regression analysis for biliary events

The Cox model showed that the hazard ratio (HR) for subsequent biliary events was 2.415 (95% CI, 1.133-5.148; P = 0.022) in patients >60 years old; 2.441 (95% CI, 1.146-5.198; P = 0.021) in female patients; 3.007 (95% CI, 1.205-7.505; P = 0.018) in current smokers; 3.190 (95% CI, 1.476-6.895; P =

0.003) in alcohol users; and 2.546 (95% CI, 1.114-5.817; *P* = 0.027) in patients with GB sludge. Adjusted for age, sex, current smoker status, and alcohol use, GB sludge and alcohol use were statistically significant factors with HR 2.819 (95% CI, 1.078-7.376; *P* = 0.035) and HR 3.214 (95% CI, 1.488-6.940; *P* = 0.003), respectively (Table 2).

Variable	**Crude Hazard Ratio on Univariate Analysis (95% CI)**	**p Value**	***Adjusted Hazard Ratio on Multivariate Analysis (95% CI)**	**p Value**
Age(>60yr)	2.415(1.133-5.148)	0.022	1.756(0.776-3.972)	0.177
Female	2.441(1.146-5.198)	0.021	1.366(0.564-3.308)	0.490
BMI	1.073(0.918-1.255)	0.377		
DM	1.732(0.654-4.582)	0.269		
HTN	1.713(0.781-3.757)	0.179		
Smoker	3.007(1.205-7.505)	0.018	1.926(0.624-5.940)	0.254
Alcohol user	3.190(1.476-6.895)	0.003	3.214(1.488-6.940)	0.003
GB sludge	2.546(1.114-5.817)	0.027	2.573(1.124-5.889)	0.025

*Adjusted for age, sex, current smoker, alcohol user, and GB sludge

BMI indicates body mass index; CI, confidence interval; DM, diabetes mellitus; GB, gallbladder; HTN, hypertension.

Table 2 Factors associated with biliary events

4. Biliary events in patients with GB sludge after cholecystectomy

The patients in the GB sludge cohort were further evaluated for biliary events after cholecystectomy. Patients who underwent cholecystectomy experienced less biliary events than those who retained their gallbladders (2/16, 12.5% vs.

17/42, 40.4%, respectively), although it did not reach statistical significance (*P* = 0.067) (Table 3).

Serial abdominal US examinations were performed in 13 of the 58 patients with GB sludge and 14 of the 70 patients without GB sludge. Among the patients with GB sludge, the sludge disappeared in 3 patients (23.1%) and persisted in 5 (38.5%) and gallstones developed in 5 patients (38.5%). Gallstones developed in 4 patients (28.5%) in the cohort without GB sludge.

Factor	with cholecystectomy (n=16)	without cholecystectomy (n=42)	p Value
Biliary events	2	17*	0.067
acute cholecystitis	.	6	
acute pancreatitis	2	8	
acute cholangitis	0	6	

*Three patients with acute cholangitis were accompanied with two of acute cholecystitis & one of biliary pancreatitis.

Table 3 Biliary events in patients with GB sludge according to cholecystectomy for recurrent pain

DISCUSSION

The natural course of GB sludge is diverse and remains unclear. Sometimes, GB sludge disappears spontaneously on removing the predisposing factors. Otherwise, gallstones develop in some patients during follow-up.[8,10] However, the clinical outcome of GB sludge accompanying typical biliary pain has never been reported. This study showed that biliary events occurred more frequently in symptomatic patients with GB sludge, compared to patients without GB sludge and cholecystectomy in symptomatic GB sludge patients reduced subsequent biliary events. Therefore, it is suggested that GB sludge is an independent risk factor for subsequent biliary events in patients with typical biliary pain. To the best of my knowledge, this is the first study to demonstrate that GB sludge is an important risk factor for subsequent biliary events in patients with typical biliary pain.

The 6% annual rate of biliary events in the GB sludge cohort might seem a little higher than expected. This may be explained by the fact that almost half of biliary events were acute pancreatitis, which is usually caused by small stones or sludge migrating to the distal common bile duct.[11,18,19] Moreover, considering gallstones were observed in about 38% in GB sludge cohort using serial US examination, GB sludge may physiologically function as small gallstones, which can cause acute pancreatitis.

In patients without GB sludge, the 5-year cumulative rate of biliary events was 15.8% in our study. Patients with microlithiasis may have been included in the study because abdominal US has a low sensitivity for microlithiasis or sludge, especially stones of < 3 mm diameter or stones located in the GB infundibulum.[11,20,21] Furthermore, even in cases of normal abdominal US finding, GB sludge can be detected through microscopic examination of the duodenal bile.[21] Therefore, in this study, both undetected microlithiasis and sludge might have considerable effect on the development of biliary events.

Abdominal US is the gold standard for the diagnosis of cholecystolithiasis with sensitivity ranging between 92% and 96%.[22] However, it is unlikely to detect biliary events when stones are located in the infundibulum or if stones <3-mm diameter or GB sludge are present.[23] Besides, there are some obstacles to getting clear US images, such as obesity or intestinal loops and gas interposition. Recent studies have shown that the sensitivity of endoscopic US for GB sludge is up to 96%.[21] Therefore, if classical biliary pain without abnormal gallbladder is found on abdominal US, further investigations such as endoscopic US should be considered to identify the culprit because even in patients without GB sludge, subsequent biliary events were as high as 15.8% and 28.5% of the patients eventually developed gallstones on serial abdominal US.

Although cholecystectomy is the treatment of choice in patients with symptomatic gallstones, the role of cholecystectomy for GB sludge has not been well evaluated. Lee et al. emphasized that GB sludge should be treated as gallstones when it is accompanied by biliary pain or recurrent attacks of acute pancreatitis.[11,24] However, there are few reports supporting cholecystectomy having a prophylactic role for subsequent biliary events in symptomatic GB sludge. Cholecystectomy in symptomatic GB sludge patients reduced subsequent biliary events in our data. Moreover, gallstones were observed in one third of patients with symptomatic GB sludge during the follow-up. Therefore, it is suggested that cholecystectomy is a definite treatment in symptomatic GB sludge patients and early cholecystectomy within 2 years after detection of GB sludge is preferable because fewer biliary events developed later than the first 2 years.

This data had certain limitations. First, this was a retrospective study, whereas the data was collected prospectively. Second, the diagnosis of GB sludge was made exclusively on abdominal US, which has a low sensitivity for detecting GB sludge and microlithiasis, so false negatives may have occurred in the non-GB sludge cohort. Finally, functional gallbladder and sphincter of Oddi disorders were not evaluated, which may be accompanied by features of biliary complications.[25] Since the prevalence of functional gallbladder disorder among patients with biliary type pain and a normal abdominal US occurs up to 8% in men and 21% in women,[26,27] it might be a confounder.

In spite of the limitations, this study provides evidence that GB sludge with typical biliary pain can cause subsequent biliary events frequently, and cholecystectomy may prevent subsequent biliary events.

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국문 초록

서론: 담성통증(biliary pain)을 동반한 담낭 담즙앙금(gallbladder sludge)에 대해서 장기간 관찰한 임상연구는 거의 없는 실정이다. 본 연구는 유증상 담낭 담즙앙금이 담도질환을 야기하는지 알아보고자 하였다.

방법: 이 연구는 2003 년 3 월부터 2012 년 12 월까지 담성통증을 주소로 내원하여 복부초음파 검사를 시행한 일련의 환자를 대상으로 하였다. 담석이 발견된 경우는 제외하였고, 전향적으로 수집되는 자료를 연구시점에서 후향적으로 분석하였다. 담도질환은 급성 담낭염, 급성 담관염 그리고 급성 췌장염으로 정의하였고, 이러한 담도질환의 발생률을 '담낭 담즙앙금(GB sludge)군'과 '비담낭 담즙앙금(non-GB sludge)군'으로 나누어서 비교하였다.

결과: '담낭 담즙앙금군'에 58 명, '비담낭 담즙앙금군'에 70 명이 확인되었다. 5 년 누적 담도질환 발생률은 '담낭 담즙앙금군'에서 유의하게 높았고 (33.9% vs. 15.8%, P = 0.021), 담도질환 발생에 대한 HR 는 2.573 (95% CI, 1.124–5.889; P = 0.025)로 확인되었다. 담도질환을 3 개의 세부질환으로 나누어서 비교를 하였을 때도 '담낭 담즙앙금군' 에서 5 년 누적 발생률이 더 높은 경향성이 확인되었다 (급성 담낭염, 15.6% vs. 5.3; 급성 담관염, 15.5% vs. 5.3%; 급성

췌장염, 8.4% vs. 11.1%). 비록 통계적으로 유의하지는 않았지만, ‘담낭 담즙앙금군’ 에서 담낭 절제술을 시행하였을 때 담도질환의 발생이 적게 발생하는 경향이 확인되었다 (2/16, 12.5% vs. 17/42, 40.4%; $P = 0.067$).

결론: 담성통증이 동반된 담낭 담즙앙금은 추후 담도질환의 발생을 야기할 수 있으며, 그것의 예방을 위해서 담낭절제술이 도움이 될 수 있을 것으로 생각된다. 따라서, 담낭 담즙앙금이 담도질환의 유발인자임을 고려해야 하겠다.

주요어 : 담낭 담즙앙금, 담석, 담도질환, 담낭 절제술

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