급성 비결석성 담낭염의 근치적 치료로서의 경피적 담낭조루술:

임상적 결과와 재발성 담낭염의 위험 인자

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서울대학교 대학원

임상의과학과

도 윤 아

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임상적 결과와 재발성 담낭염의 위험 인자

지도교수 윤 창 진

이 논문을 의학석사 학위논문으로 제출함
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서울대학교 대학원
임상의과학과
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도윤아의 석사 학위논문을 인준함
2023년 1월

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국문초록

목적: 급성 비결석성 담낭염의 근치적 치료로서 경피적 담낭조루술의 임상적 결과를 확인하고, 담낭조루술 후 재발성 담낭염 발생의 위험 인자를 알아보는 것에 목표를 두고 있다.

대상 및 방법: 2010년 1월부터 2017년 12월까지 중등증 및 중증의 급성 비결석성 담낭염의 근치적 치료로서 경피적 담낭조루술을 시행 받은 124명의 환자를 대상으로, 초기 치료 성공률과 합병증, 도관 제거 후 재발성 담낭염의 발생여부를 후향적으로 평가하였으며, 재발성 담낭염의 위험 인자를 알아보기 위하여 21개의 변수들을 분석하였다.

결과: 경피적 담낭조루술 후 107명 (86.3%)이 3일 이내에, 모든 환자 (100%)들이 5일 이내에 임상적 효과를 보였다. 6례에서 도관의 위치 이동 (3례), 도관 막힘 (3례)과 같은 등급 2의 부작용이 있어 도관을 교체하였다. 123명 (99.2%)의 환자에서 경피적 담낭조루술 도관을 제거하였고, 도관 거치 기간의 중앙값은 18일 (범위 5 - 116일)이었다. 추적 검사 기간 (중앙값, 1624일; 범위, 40 - 4945일) 동안, 5명 (4.1%)의 환자에서 재발성 담낭염이 발생하였고, 6개월, 1년, 5년의 누적발생률은 각각 3.3%, 4.1%, 4.1%였다. 다변량 분석에서, 나이를 보정한 Charlson 동반질환지수가 7점 이상일 때 재발성 담낭염과 양의 상관관계를 보였다. (교차비, 1.97; 95% 신뢰구간, 1.07 - 3.64; p=0.029).

결론: 경피적 담낭조루술은 급성 비결석성 담낭염 환자에서 안전하고 효과적인 치료이며 대부분의 환자에서 담낭조루술 도관을 안전하게 제거할 수 있다. 나이를 보정한 Charlson 동반질환지수가 7점 이상인 경우, 도관 제거 후 담낭염 재발의 위험인자가 된다.

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Introduction

Acute acalculous cholecystitis (AAC) is defined as acute gallbladder (GB) inflammation without biliary calculi or sludge. It accounts for 5 – 10% of acute cholecystitis cases and often occurs in critically ill patients after major surgery, trauma, burn, cerebral infarction, or terminal malignancy [1]. Early recognition and treatment are mandatory to avoid fulminant progression and complications, such as gangrene or perforation, which have a high mortality rate of up to 30% [2].

Percutaneous cholecystostomy (PC) has been widely used as a bridge treatment followed by interval cholecystectomy or as a definitive treatment for acute cholecystitis in patients who are unfit for surgery. PC can play a key role in the treatment of AAC, in which emergency surgery is more frequently ineligible due to severe medical comorbidities. Several studies have demonstrated that PC can be a definitive treatment for AAC that does not require subsequent cholecystectomy [3-7]. However, a major concern regarding definitive PC is the possibility of recurrent cholecystitis after catheter removal. Although recurrent cholecystitis after PC in AAC is less common than acute calculous cholecystitis (ACC) [3], it has been reported in up to 14% of cases [4]. Therefore, the prediction of recurrent cholecystitis after PC would be greatly helpful for patient selection and treatment planning for AAC. This study aimed to investigate the outcomes of PC as a definitive treatment for AAC and to identify the risk factors for cholecystitis recurrence after catheter removal.

Materials and Methods

This single-institution retrospective study was approved by our institutional review board, which waived the requirement for informed consent.

Patient selection

A computerized keyword-based search of electronic medical record using "acute cholecystitis" and "percutaneous cholecystostomy" identified 1338 patients who underwent percutaneous cholecystostomy (PC) for acute cholecystitis from January 2010 to December 2017. The diagnosis of acute cholecystitis was based on clinical symptoms and signs (fever, abdominal pain, positive sonographic Murphy's sign, or elevated inflammatory markers such as white blood cells) and radiologic studies of abdominal US, MRCP, and/or CT. The diagnostic criteria and severity grading of acute cholecystitis were based on the Tokyo Guidelines (TG) 18 [8]. The exclusion criteria were i) gallstones (including sludge) identified by imaging and/or surgical specimens (n=1075), ii) concurrent common bile duct stones (n=42), iii) PC as a bridge treatment for interval cholecystectomy (n=37), iv) biliary obstruction by malignancy (n=24), v) mild cholecystitis (grade 1) based on the TG18 (n=12), vi) concurrent pancreatitis (n=8), and vii) loss to follow-up within 12 months after PC removal (n=16). Finally, 124 patients (mean age, 71.9 years; range, 26‑94 years; men, n=74) who had undergone definitive PC for moderate or severe acute acalculous cholecystitis (AAC) were included in this study.

Percutaneous cholecystostomy

All patients with acute cholecystitis were initially treated with intravenous fluids, electrolyte correction, and broad-spectrum antibiotics. The eligibility for surgery was evaluated by hepatobiliary surgeons and anesthesiologists. When considered unsuitable for emergency surgery, patients were referred to interventional radiologists for PC. When patients had an international normalized ratio (INR) > 1.5 and/or platelet count < 50,000/mm^3, transfusions were performed before PC, with the exception of patients with uncorrectable coagulopathy or sepsis.

All PC procedures were performed under ultrasound and fluoroscopic guidance by one of three board-certified interventional radiologists (5, 5 and 10 years of experience, respectively). The procedures were performed under conscious sedation using intravenous fentanyl (50‒100 μg) and midazolam (1‒3 mg). The gallbladder (GB) was percutaneously punctured using a 21-gauge needle (Cook, Bloomington, USA) under US guidance. A 5-F introducer (Cook) was advanced into the GB over a 0.018-inch guidewire (Cook) and an 8.5-F drainage catheter (Cook) was inserted over a 0.035-inch guidewire (Terumo, Tokyo, Japan). The procedures were performed using a transhepatic approach, when technically feasible.

When the clinical symptoms and laboratory findings improved, the catheter was clamped and left in place for 1‒7 days before removal. The decision to perform interval cholecystectomy was made

by hepatobiliary surgeons on an individual basis for each patient.

Definitions and statistical analysis

The following data were extracted by reviewing the electronic medical records retrospectively: patient demographic data, the last laboratory examination before PC, maximum body temperature within 3 days before PC, laboratory examination 3‑5 days after PC (the highest value was selected when there were multiple results), maximum body temperature 3‑5 days after PC, resolution of abdominal pain, length of antibiotic treatment before PC, postprocedural complications, length of intensive care unit (ICU) stay and admission, and duration of PC indwelling. Baseline comorbidities were evaluated using the age-adjusted Charlson comorbidity index. The evaluation of PC outcomes included clinical effectiveness, complications, catheter removal, and cholecystitis recurrence. Clinical effectiveness was defined as the resolution of abdominal pain, normalized white blood cell count, and temperature within 5 days after PC and no recurrence within at least 30 days. Adverse events were classified according to the Common Terminology Criteria for Adverse Events, version 5.0.

The paired-sample t-test was used to compare pre- and post-PC laboratory findings. The independent samples t-test was used to compare pairs of independent continuous variables between groups. Fisher's exact test was used to compare categorical variables between the groups. The rate of recurrent cholecystitis after PC

removal was calculated using Kaplan-Meier estimation. Data were considered censored for analysis if no biliary event was observed to the point of death or loss to follow-up. Twenty-one relevant variables were included in the logistic regression analyses to identify risk factors for recurrent cholecystitis. Variables with a $p < 0.10$ on univariate analyses were included in the multivariate analysis. All statistical analyses were performed using the SPSS software (version 14.0. SPSS, Chicago, IL, USA). Statistical significance was set at $p < 0.05$.

Results

Patient characteristics

The demographic and clinical characteristics of the patients are summarized in Table 1. There were 74 men and 50 women with a mean age of 71.9 years. There were 57 (46.0%) moderate and 67 (54.0%) severe acute acalculous cholecystitis (AAC) cases. Organ dysfunction included cardiovascular (n=44), neurological (n=23), respiratory (n=25), and renal (n=14). AAC was complicated by gangrenous (n=15), perforated (n=21), and emphysematous (n=3) lesions on pre-procedural CT. The mean age-adjusted Charlson comorbidity index (aCCI) was 6.0 (range 1 – 13). The most common comorbidities were cerebrovascular disease (n=45), followed by malignancy (n=34), and diabetes (n=33). Sixty-five patients with AAC were diagnosed at admission and 59 developed AAC during hospitalization. The 59 were hospitalized for cerebrovascular disease (n=25), respiratory failure (n=12), major surgery (n=12), malignancy (n=7), and renal failure (n=3).

Clinical effectiveness

Percutaneous cholecystostomy (PC) was technically successful in all patients. All procedures were performed using the transhepatic approach. Clinical effectiveness was achieved in 107 patients (86.3%) at 3 days and in all patients (100%) at 5 days after PC placement. The mean white blood cell (WBC) count was $13,600 \pm 7,200/mm^3$

before PC and 8,700 ± 3,200/mm^3 5 days after PC (p<0.001). The mean value of C-reactive protein decreased from 15.7 ± 9.2 mg/dL before PC to 5.1 ± 3.8 mg/dL 5 days after PC (p<0.001). The median length of admission was 16.0 days (range 5‐128), and the median post-PC length of admission was 14.5 days (range 5‐113). Twenty-three patients required ICU management with a median stay of 5 days (range 1‐28 days). The PC catheter was removed in 123 patients with a median indwelling duration of 18 days (range, 5‐116 days). In one patient with hypoxic encephalopathy, AAC-related symptoms and abnormal laboratory test results resolved, but the catheter was retained in situ until death (55 days after placement). Six grade 2 adverse events occurred, including catheter dislodgement (n=3) and clogging (n=3), which required catheter exchange.

Recurrent cholecystitis

The median follow-up duration was 1624 days (range 40‐4945 days) after PC. Five patients experienced cholecystitis recurrence at 26, 117, 127, 139, and 349 days after catheter removal (4.1%, 5/123). Patients were treated with cholecystectomy (n=2) or repeat PC (n=3). During follow-up, 29 patients died 40‐3908 days (median, 641 days) after PC placement. The causes of death were malignancy (n=14; gastric cancer [n=5], lung cancer [n=3], biliary cancer [n=2], leukemia [n=2], hepatocellular carcinoma [n=1], and angiosarcoma [n=1]), pneumonia (n=7), congestive heart failure (n=3), ischemic colitis (n=1), trauma (n=1), urosepsis (n=1), hypoxic encephalopathy

(n=1), and unknown (n=1). Forty-six patients were lost to follow-up (median 980 days, range 366-4481) and 49 patients were still alive.

The results of univariate and multivariate analyses of the risk factors for recurrent cholecystitis are shown in Table 2. Four factors (aCCI, diabetes, cerebrovascular disease, and complicated cholecystitis) were associated with recurrence in univariate analysis. However, in multivariate analysis aCCI ≥7 was the only risk factor positively associated with recurrence (odds ratio [OR], 1.97; 95% Confidence interval, 1.07 - 3.64; p=0.029).

Discussion

Percutaneous cholecystostomy (PC) has been used as an alternative treatment for cholecystectomy in patients with high perioperative risk [9]. Many studies have demonstrated that PC is a safe and effective as a bride treatment for interval cholecystectomy or even a definitive treatment in patients with severe sepsis, shock, or multiple comorbidities [10-13]. However, the majority of these studies included acute calculous cholecystitis (ACC) and acute acalculous cholecystitis (AAC) and did not distinguish between them in their analyses. The primary pathogenesis of AAC is bile stasis and ischemic change in the gallbladder (GB), which is different from that of ACC with GB inflammation caused by cystic duct obstruction [1]. Furthermore, the recurrence rates of acute cholecystitis differ between AAC and ACC groups. Gu et al. [14] reported that the recurrence rate of acute cholecystitis after nonsurgical treatment was significantly lower in the AAC group than in the ACC group (2.7 vs. 23.2%, p = 0.005, OR = 2.389). Bhatt et al. [15] reported that calculous cholecystitis are independent predictors of acute cholecystitis recurrence. Therefore, the role of PC may need to be defined differently in AAC and ACC. However, studies on PC in patients with AAC are limited [3-7], and no consensus guidelines or recommendations advocate definitive PC for patients with AAC.

This study demonstrated that PC can be a rescue treatment for AAC in patients who are unfit for emergency surgery. Clinical effectiveness was achieved in 86.3% of the patients at 3 days and

100% at 5 days after PC placement. This result is comparable to previously published data [4, 5]. In a recent retrospective study [5], symptomatic and laboratory improvements were achieved in 235 of 271 patients with AAC (86.7%) within 4 days after PC. The reported 30-day mortality was 8.5% - 10.7% [3-7], whereas no early mortality occurred in this study. This discrepancy may be explained by the exclusion criteria used for the study population. In previous studies, terminal malignancy was the major cause of death [5, 7]. In contrast, cholecystitis caused by malignant biliary obstruction was excluded from this study because its pathophysiology and prognosis are completely different from those of benign primary AAC, which is the main disease of interest in this study. Other exclusions, including common bile duct stones, grade 1 cholecystitis, and pancreatitis, were similar to those reported in previous studies [3-7].

A major concern regarding PC is the management of the drainage catheter. Long-term or permanent indwelling of the catheter inevitably causes catheter-related complications and discomfort. Therefore, the drainage catheter should be removed, whenever possible. However, controversy remains regarding the removal of PC catheters. In a meta-analysis [16], there was no correlation was found between PC indwelling duration and clinical outcomes. Currently, PC catheter removal is generally recommended after at least 2 weeks of indwelling for tract maturation using a transhepatic approach; but the optimal timing of catheter removal remains unclear. In this study, the drainage catheter was successfully removed in all

patients, except one (99.2%), following a successful trial of catheter clamping.

The recurrence of cholecystitis is a major drawback of PC compared with cholecystectomy. In this study, there were five patients who experienced recurrent cholecystitis, and all recurrences occurred within 1 year after PC removal (4.1%, 5/123). With the exception of one study [7] with a relatively high recurrence rate (17.4%), most previous studies reported recurrence rates of less than 10% (2.3%-9.1%) [3-5, 17]. According to current guidelines, cholecystectomy is recommended whenever possible regardless of ACC or AAC [9]. Therefore, once patients stabilize after PC, interval cholecystectomy should be considered. However, recurrence rates lower than 10% raise the question of whether interval cholecystectomy is necessary. A recent study revealed that AAC patients had a lower likelihood of interval cholecystectomy than ACC patients did (adjusted hazard ratio, 2.35). To our knowledge, no study has compared the outcomes of definitive PC and interval cholecystitis in patients with AAC. Further studies comparing the clinical outcomes and cost-effectiveness between the two groups are needed.

Identification of risk factors would be helpful determining management options after stabilization with PC (interval cholecystectomy, removal of drainage catheter, or permanent PC indwelling). Chen et al. [4] investigated the risk factors for recurrence in AAC, in which a multivariate analysis showed that coronary heart disease or congestive heart failure was positively correlated with

recurrence (odds ratio, 26.50). In this study, potential risk factors similar to those in Chen's study were tested, and age-adjusted Charlson comorbidity index (aCCI) ≥ 7 was a risk factor for cholecystitis recurrence. Although the risk factors found in these two studies were not identical, underlying comorbidities seemed to have a greater effect than those of the other factors (demographic, severity of cholecystitis, and laboratory tests). If patients are ineligible for surgery even after recovery from AAC, the removal of the drainage catheter should be more cautious or a permanent PC indwelling should be considered.

This study had several major limitations. First, retrospective data collection from a single institution might have resulted in selection bias in the patient cohort. Although the study population (n=124) might have been insufficient in size, this is currently one of the largest studies dealing with definitive PC in AAC patients. Second, many patients were lost to follow-up (n=46, 37.1%). This was mainly because patients are frequently transferred to regional hospitals for terminal care. This may have underestimated the rate of cholecystitis recurrence. However, patients were lost after at least 1 year of follow-up, whereas most recurrences occurred within 1 year in previous studies [3-5]. Third, the number of patients with recurrent cholecystitis in this study was small (n=5, 4.1%). This may limit the statistical power of multivariate analysis for risk factors.

In conclusion, definitive PC is a safe and effective treatment option for patients with AAC. The PC catheter can be safely

removed after recovery from AAC in most patients. An aCCI ≥ 7 was a risk factor for cholecystitis recurrence after catheter removal.

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Table 1. Demographic and clinical characteristics of the patients

Variable	AAC patients receiving PC (n=124)
Sex (M:F)	74:50
Age (mean, range)	71.9 years (26-94)
Duration of admission (mean, range)	16.0 days (3-128)
ICU stay	27 (21.8%)
Sepsis	44 (35.5%)
TG13/18 grade II/III	57 (46.0%) / 67 (54.0%)
Cardiovascular dysfunction	44 (35.5%)
Neurological dysfunction	23 (18.5%)
Respiratory dysfunction	25 (20.2%)
Renal dysfunction	14 (11.3%)
Hepatic dysfunction	5 (4.0%)
Hematological dysfunction	18 (14.5%)
Complicated cholecystitis*	39 (31.5%)
aCCI (mean, range)	6.0 (1-13)
Prior myocardial infarction or CHF	45 (36.3%)
Cerebrovascular disease	45 (36.3%)
Malignancy	34 (27.4%)
Diabetes	33 (26.6%)
Chronic pulmonary disease	21 (16.9%)
Moderate or severe renal disease	17 (13.7%)
Initial laboratory tests (mean±SD)	
WBC (×10/L)	13.6 ± 7.2
Platelet (×10/L)	222.4 ± 138.3
ALT (U/L)	61.7 ± 87.7
Total bilirubin (μmol/L)	2.4 ± 2.4
Creatinine (μmol/L)	1.5 ± 2.7
INR (μmol/L)	1.3 ± 0.7
CRP (mg/dl)	15.7 ± 9.2
PC Indwelling duration (median, range)	18.0 days (3-116)

AAC, acute acalculous cholecystitis; PC, percutaneous cholecystitis; ICU, intensive care unit; TG, Tokyo guidelines; aCCI, age-adjusted Charlson comorbidity index; CHF, congestive heart failure; SD, standard deviation; WBC, white blood cells; ALT, alanine aminotransferase; INR, international normalized ratio; CRP, C-reactive protein

* based on CT features of gangrenous, perforated, or emphysematous cholecystitis
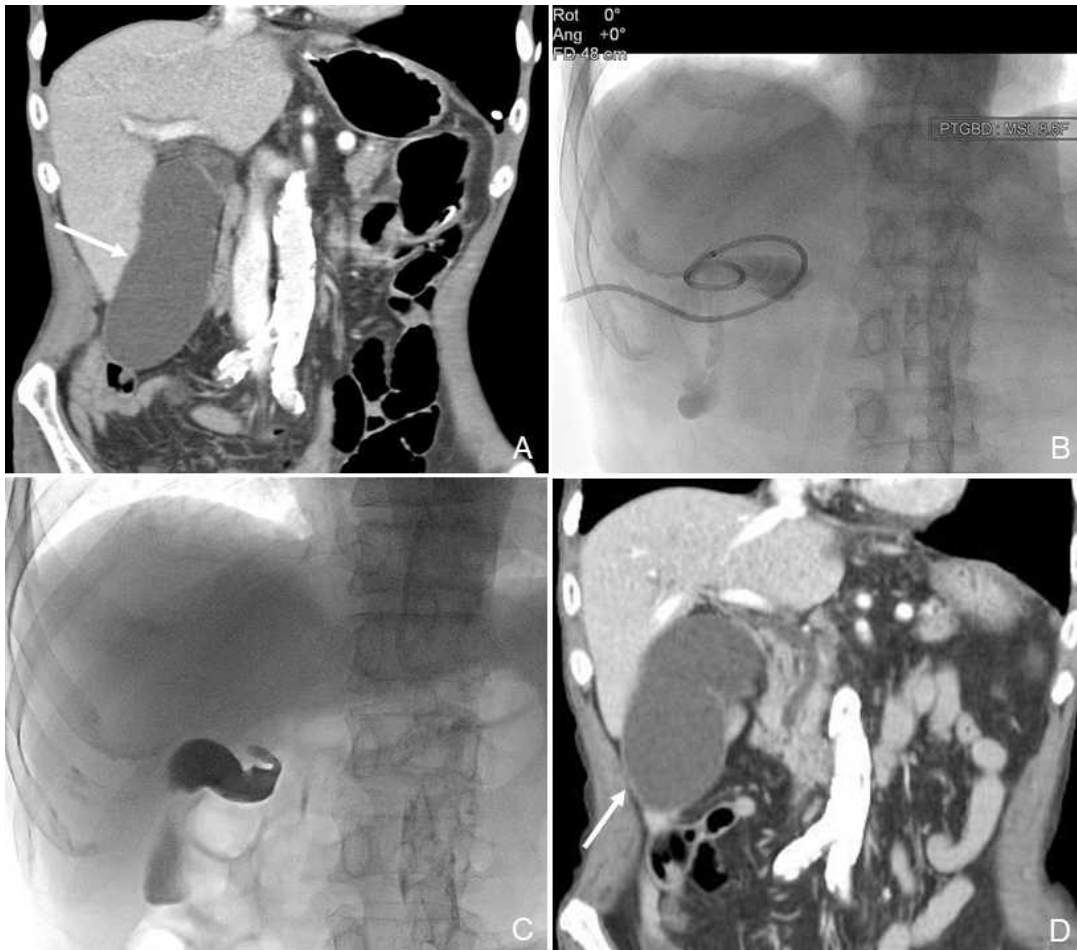
Table 2. Comparison of the nonrecurrent and recurrent patient groups

Variable	No recurrence (n=119)	Recurrence (n=5)	Univariate p-value	Multivariate OR (95% CI), p-value
Sex [male (%)]	60 (50.4%)	4 (80%)	0.647	
Age (≥72 years)	57 (47.9%)	3 (60%)	0.979	
Duration of admission (≥16 days)	15.0 ± 30.7	13.0 ± 18.3	0.875	
TG18 grade (III)	65 (54.6%)	2 (40%)	0.660	
aCCI (≥7)	41 (34.4%)	4 (80%)	0.037	1.97 (1.07–3.64), 0.029
Sepsis	43 (36.1%)	1 (20%)	0.655	
Initial laboratory values				
White blood cells (×10/L)	13.6 ± 7.2	14.9 ± 7.3	0.398	
Platelets (×10/L)	225.2 ± 139.9	154.6 ± 70.6	0.204	
ALT (U/L)	61.9 ± 92.6	51.3 ± 32.1	0.388	
Total bilirubin (μmol/L)	2.5 ± 2.5	1.7 ± 0.8	0.210	
Creatinine (μmol/L)	1.5 ± 2.8	1.7 ± 2.2	0.255	
INR (μmol/L)	1.3 ± 0.3	2.6 ± 3.1	0.269	
CRP (mg/dl)	15.6 ± 9.2	19.2 ± 9.4	0.180	
Prior myocardial infarction or CHF	43 (36.1%)	2 (40%)	0.231	
Cerebrovascular disease	41 (34.5%)	4 (80%)	0.058	5.66 (0.19–164.47), 0.313
Malignancy	33 (27.7%)	1 (20%)	1.00	
Diabetes	30 (25.2%)	3 (60%)	0.117	0.74 (0.05–10.54), 0.825
Chronic pulmonary disease	20 (16.8%)	1 (20%)	1.00	
Moderate or severe renal disease	16 (13.4%)	1 (20%)	0.528	

Complicated cholecystitis	36 (30.3)	3 (60%)	0.179
PC indwelling duration (≥18 days)	49 (41.2%)	3 (60%)	0.649

OR, odds ratio; TG, Tokyo guidelines; aCCI, age-adjusted Charlson comorbidity index; ALT, alanine aminotransferase; INR, international normalized ratio; CRP, C-reactive protein; CHF, congestive heart failure; PC, percutaneous cholecystostomy

Figure 1. A case of recurrent cholecystitis after percutaneous cholecystostomy catheter removal

A. 82-year-old male presented with RUQ pain. Coronal contrast-enhanced CT scan shows acute acalculous cholecystitis. His age-adjusted Charlson comorbidity index was 12 due to hypertension, diabetes mellitus, end stage renal disease, ischemic stroke, peripheral vascular disease, and heart failure.

B. Percutaneous cholecystostomy was performed.

C. After 2 days, catheter was removed without complication.

D. 4 months after catheter removal, the patient complained of fever. Coronal contrast-enhanced CT scan shows recurrent cholecystitis.

Abstract

Percutaneous cholecystostomy as a definitive treatment for acute acalculous cholecystitis:
clinical outcomes and risk factors for

recurrent cholecystitis

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Purpose: To investigate the outcomes of percutaneous cholecystostomy (PC) as a definitive treatment for acute acalculous cholecystitis (AAC) and to identify the risk factors for cholecystitis recurrence after catheter removal.

Materials and methods: Between January 2010 and December 2017, 124 patients who had undergone PC as definitive treatment for moderate or severe AAC. The initial clinical success, complications,

and recurrent cholecystitis after PC removal were retrospectively assessed. Twenty-one relevant variables were analyzed to identify risk factors for recurrent cholecystitis.

Results: Clinical effectiveness was achieved in 107 patients (86.3%) at 3 days and in all patients (100%) at 5 days after PC placement. Six grade 2 adverse events occurred, including catheter dislodgement (n=3) and clogging (n=3), which required catheter exchange. The PC catheter was removed in 123 patients (99.2%), with a median indwelling duration of 18 days (range 5‑116 days). During the follow-up period (median, 1624 days; range, 40‑4945 days), five patients experienced recurrent cholecystitis (4.1%). The cumulative recurrence rates were 3.3%, 4.1%, and 4.1% at 6-months, 1 year, and 5 years, respectively. Multivariate analysis revealed that an age-adjusted Charlson comorbidity index (aCCI) ≥ 7 positively correlated with recurrence (odds ratio, 1.97; 95% Confidence interval, 1.07‑3.64; p=0.029).

Conclusion: Definitive PC is a safe and effective treatment option for patients with AAC. The PC catheters can be safely removed in most patients. An aCCI ≥ 7 was a risk factor for cholecystitis recurrence after catheter removal.

Keywords: Acalculous cholecystitis; Catheters; Cholecystostomy; Comorbidity; Risk factors

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