

# Long-term outcomes of acute acalculous cholecystitis treated by non-surgical management

Sung Bum Kim, MD, PhD, Min Geun Gu, MD, Kook Hyun Kim, MD, Tae Nyeun Kim, MD, PhD\*

## Abstract

Although cholecystectomy is generally recommended for acute acalculous cholecystitis (AAC) treatment, non-surgical management can be considered in patients at a high risk for surgery. This study compared outcomes of surgical and non-surgical management and analyzed the long-term outcomes of AAC patients managed non-surgically.

We retrospectively analyzed 89 patients diagnosed with AAC between January 1, 2007 and April 30, 2014. These patients were divided into 2 groups: non-surgical (n=41) and surgical (n=48). Non-surgical management methods were percutaneous cholecystostomy (PC, n=14) and antibiotics only (n=27). The non-surgical group was followed up for >3 years after treatment.

The mean age was slightly higher in the non-surgical group than in the surgical group without significant difference. The prevalence of cerebrovascular accident in the non-surgical group was significantly higher than that in the surgical group (26.8% vs 8.3%,  $P=.020$ ). Mean hospital stay was not statistically different between two groups. The surgical group had a significantly higher incidence of posttreatment complications than the non-surgical group (18.8% vs 2.4%,  $P=.015$ ). During the mean follow-up of 5.7 years, AAC recurred in 4 (9.8%) patients in the non-surgical group. Three patients underwent cholecystectomy, 1 was treated with antibiotics, and no recurrence-related death occurred. The recurrence rate of AAC was not different between PC and antibiotics only groups (14.3% vs 7.4%,  $P=.596$ ).

Recurrence was observed in 9.8% of AAC patients treated non-surgically and the outcome in the non-surgical group was not inferior to that in the surgical group.

**Abbreviations:** AAC = acute acalculous cholecystitis, ALT = alanine aminotransferase, AST = aspartate aminotransferase, PC = percutaneous cholecystostomy.

**Keywords:** acalculous cholecystitis, antibiotics, cholecystectomy, percutaneous cholecystostomy

## 1. Introduction

Acute acalculous cholecystitis (AAC) is a necro-inflammatory state of the gallbladder, without obstruction of the cystic duct by a gallstone, occurring commonly in injured, surgical, or critically ill patients.<sup>[1]</sup> AAC can also occur in young and middle aged healthy individuals without critical illness<sup>[2]</sup> and comprises 10% of all acute cholecystitis cases. AAC is often complicated with gangrene and perforation of the gallbladder, and the mortality

rate associated with AAC is 30%.<sup>[3]</sup> If diagnosis and treatment of AAC are delayed, mortality can increase to 75%.<sup>[4]</sup> Primary pathogenesis of AAC is bile stasis and ischemic change of the gallbladder,<sup>[5]</sup> different from that of acute calculous cholecystitis, which involves inflammation of the gallbladder due to cystic duct obstruction caused by a gallstone.<sup>[6]</sup>

Cholecystectomy is the standard treatment for AAC. Some critical ill patients are unfit for cholecystectomy, and percutaneous cholecystostomy (PC) is performed as a minimally invasive alternative to surgery.<sup>[7]</sup> In PC procedure, a drainage catheter is placed within the gallbladder lumen to decompress the gallbladder and relieve inflammation.<sup>[8]</sup> PC alone is reported to control up to 90% of AAC<sup>[7,8]</sup> and has been used as a bridge therapy to cholecystectomy. Although recent studies suggest PC to be the definitive treatment method for AAC,<sup>[9]</sup> its role as the definitive treatment option for AAC is controversial. Antibiotics are also used to control secondary infection of the gallbladder caused by bile stasis in AAC. It would be important to compare outcomes between surgical treatment and non-surgical treatment approaches for AAC to clarify the role of non-surgical management including PC and/or antibiotics in AAC.

Recurrence of acute cholecystitis after non-surgical treatment is an important issue. Recurrence rate after PC in both acute calculous and acalculous cholecystitis is reported to range from 2.7% to 22%. A study including 145 acute cholecystitis patients treated with PC reported calculous cholecystitis and purulence in the gallbladder as 2 risk factors associated with recurrence of acute cholecystitis.<sup>[10]</sup> As recurrence of acute cholecystitis is lower in AAC than in acute calculous cholecystitis, identifying

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Division of Gastroenterology and Hepatology, Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Republic of Korea.

\* Correspondence: Tae Nyeun Kim, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Yeungnam University College of Medicine, 42415, 170, Hyeonchung-ro, Nam-gu, Daegu, Republic of Korea (e-mail: tnkim@yu.ac.kr).

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clinical outcomes of non-surgical management is important in treatment of AAC.

The aims of this study were to compare clinical outcomes between surgical and non-surgical methods and to analyze long-term outcomes of non-surgical management in patients with AAC.

## 2. Methods

Patients diagnosed with AAC in Yeungnam University hospital between January 2007 and April 2014 were included in this study, and their medical records were collected and reviewed retrospectively. Diagnosis of AAC was made if radiologic examinations including abdominal ultrasound or abdominal computed tomography scan showed thickness of gallbladder wall  $\geq 3$  mm, suggesting cholecystitis, and no evidence of gallstones or sludge within the gallbladder. Patients with hepato-biliary malignancies and AAC complicated with perforation were excluded from this study. Among patients who underwent non-surgical management of AAC, patients with a follow up duration of  $<3$  years were also excluded from this study.

Patients were divided into 2 groups: the non-surgical group and surgical group. Patients who underwent open or laparoscopic cholecystectomy for treatment of AAC at initial occurrence of AAC were classified under the surgical group, and those who received PC and/or intravenous antibiotics were classified under the non-surgical group, which was divided further into a PC group and antibiotics only group. PC was performed using either the transhepatic or the trans-peritoneal approach based on radiologists' decision.

The following parameters were recorded for this study: age; sex; body mass index; comorbidities including diabetes mellitus, hypertension, cerebrovascular accidents, ischemic heart disease, chronic liver disease, and chronic kidney disease; presence of systemic inflammatory response syndrome and sepsis; laboratory tests including white blood cell count, C-reactive protein, total bilirubin, aspartate aminotransferase (AST), alanine aminotrans-

ferase (ALT), and creatinine; length of hospital stay; complications related to surgical and non-surgical methods; recurrence of acute cholecystitis; and outcomes related to recurrence of acute cholecystitis. Results of blood and/or bile culture were reviewed. Institutional review board approval was obtained for this study.

### 2.1. Statistical analysis

Statistical analysis was performed using SPSS (version 23.0, SPSS, Inc., Chicago, IL), and  $P$  values of  $<.05$  were considered statistically significant. Continuous variables were compared using the student  $t$  test or the Mann-Whitney  $U$  test. Categorical variables were analyzed using Fisher exact test.

## 3. Results

Among the 89 patients with AAC, 48 patients received cholecystectomy for treatment of AAC at initial occurrence. Non-surgical treatments were used in 41 patients; 27 patients were treated with antibiotics only, and 14 patients underwent percutaneous cholecystostomy. The trans-hepatic approach for PC was used in 11 patients and the trans-peritoneal approach in 3 patients.

Mean age was slightly higher in the non-surgical group than in the surgical group, without statistically significant difference ( $70.1 \pm 11.0$  vs  $65.9 \pm 11.1$  years,  $P=.077$ ). The male to female ratio was not significantly different between the non-surgical and surgical groups. Among comorbidities, cerebrovascular accident was significantly more frequent in non-surgical group than surgical group (26.8% vs 8.3%,  $P=.020$ ). The prevalence of systemic inflammatory response syndrome and sepsis was not significantly different between 2 groups. Among laboratory tests, median level of AST was significantly higher in the non-surgical group than in the surgical group ( $85.7 \pm 126.2$  vs  $42.9 \pm 43.0$  U/L,  $P=.043$ ) (Table 1).

Mean duration of hospital stay was not significantly different between the non-surgical and surgical groups ( $9.8 \pm 5.6$  vs  $9.4 \pm$

**Table 1**  
Baseline characteristics of patients with AAC according to treatment methods.

	Non-surgical group (n=41)	Surgical group (n=48)	P-value
Sex (male:female)	27:14	30:18	.742
Age, y (mean $\pm$ SD)	70.1 $\pm$ 11.0	65.9 $\pm$ 11.1	.077
BMI (mean $\pm$ SD)	23.0 $\pm$ 3.4	23.9 $\pm$ 2.9	.151
Comorbidities			
Diabetes mellitus (%)	9 (22.0)	12 (25.0)	.736
Hypertension (%)	15 (36.6)	20 (41.7)	.625
CVA (%)	11 (26.8)	4 (8.3)	.020
Ischemic heart disease (%)	8 (19.5)	5 (10.4)	.226
Chronic liver disease (%)	1 (2.4)	2 (4.2)	1.000
CKD (%)	2 (4.9)	2 (4.2)	1.000
SIRS	8 (16.7)	12 (29.3)	.156
Sepsis	3 (7.3)	1 (2.1)	.331
Laboratory tests			
WBC	13419.8 $\pm$ 7607.3	11601.3 $\pm$ 742.1	.199
CRP	9.5 $\pm$ 10.3	12.9 $\pm$ 11.0	.238
Total bilirubin	1.8 $\pm$ 1.7	1.3 $\pm$ 1.2	.174
AST	85.7 $\pm$ 126.2	42.9 $\pm$ 43.0	.043
ALT	58.6 $\pm$ 77.1	40.3 $\pm$ 51.1	.198
Creatinine	1.2 $\pm$ 1.0	1.1 $\pm$ 0.7	.517

AAC=acute acalculous cholecystitis, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BMI=body mass index, CKD=chronic kidney disease, CRP=C-reactive protein, CVA=cerebral vascular accident, SD=standard deviation, SIRS=systemic inflammatory response syndrome, WBC=white blood cell.

**Table 2**  
**Comparison of clinical outcomes according to treatment methods.**

	Non-surgical group (n=41)	Surgical group (n=48)	P-value
Mean hospital stay, d	9.8±5.6	9.4±14.9	.865
Treatment-related complications (%)	1 (2.4)*	9 (18.8)†	.015

\* Catheter insertion site infection.

† Remnant cystic duct leakage (n=3), bleeding (n=1), acute kidney injury (n=3), paralytic ileus (n=1), and ventral hernia (n=1).

14.6 days,  $P=.865$ ). Prevalence of complications related to treatment method was significantly higher in the surgical group than in the non-surgical group (18.8% vs 2.4%,  $P=.015$ ). In the non-surgical group, 1 patient developed PC catheter insertion site infection. In the surgical group, leakage from remnant cystic duct and acute kidney injury were observed in 3 patients and postoperative bleeding, paralytic ileus, and ventral hernia developed in 1 patient (Table 2). Most commonly cultured bacteria from blood and bile were *Escherichia coli*, followed by *Enterococcus* species and *Klebsiella pneumoniae*.

### 3.1. Clinical outcomes in the non-surgical group

Mean duration of catheter placement was 23.5 days in patients with AAC who underwent PC. During a mean follow up period of 5.7 years for the non-surgical group, recurrence of AAC was noted in 4 (9.8%) patients. Mean duration between the initial occurrence of AAC and recurrence was 23 months. Three of them underwent cholecystectomy and 1 of them was treated with antibiotics, and there was no recurrence-related death. There was no difference in the recurrence rate between the PC and antibiotics only groups (14.3% vs 7.4%,  $P=.596$ ). Mean interval from the initial occurrence to recurrence of AAC was 26.5 months in the antibiotics only group and 19.5 months in the PC group, without any statistically significant difference. Two patients with recurrence in the antibiotics only group underwent cholecystectomy and 2 patients in the PC group were treated with antibiotics and cholecystectomy. There was no mortality related to recurrence in both groups (Table 3). In surgical group, no patient developed biliary complication.

## 4. Discussion

AAC is known to occur mostly in patients with debilitating conditions, and most studies have reported the development of AAC in advanced age groups, as well as a male predominance

compared with that in patients with acute calculous cholecystitis. A previous study of 156 patients with acute cholecystitis showed that patients with AAC were older and predominantly of male sex than patients with calculous cholecystitis.<sup>[11]</sup> Mean age and male to female ratio of AAC patients in the present study were  $67.8 \pm 11.2$  years and 1.8:1, respectively, and the results were comparable with a previous study of AAC.<sup>[11]</sup> Although mean age and sex proportion were not significantly different between the surgical and non-surgical groups in the present study, patients in the non-surgical group had a significantly higher rate of cerebrovascular accident and ischemic heart disease than those in the surgical group. Due to poor clinical conditions and/or use of anti-platelet agents or anti-coagulants in AAC patients with these comorbidities, use of non-surgical managements might have been more frequent than surgery.

Cholecystectomy is the suggested treatment of choice for AAC, especially in cases of perforation or gangrenous cholecystitis. In some recent studies, nonsurgical treatments such as PC can be a lifesaving alternative in patients with comorbidities.<sup>[7,8,10,13,14]</sup> In the present study, 48 (53.9%) patients underwent cholecystectomy while 41 (46.1%) patients were treated with non-surgical methods including PC or antibiotics only. In the present study, both surgical and non-surgical methods were successful in managing AAC, and overall therapeutic outcomes related to non-surgical group in patients with AAC were not inferior to those in the surgical group. It is interesting that in the present study, 27 (30.3%) AAC patients were treated successfully with antibiotics only. The recurrence rate in those treated with antibiotics only was lower than that in patients treated with PC. Further studies are needed to identify the patients who can benefit from the use of antibiotics only without performing PC in AAC.

Duration of hospital stay was not significantly different between the non-surgical and surgical groups in this study. This might be due to higher prevalence of complications in the surgical group than in the non-surgical group. Although there were no major complications or mortality in both groups, the incidence of complications was significantly higher in the surgical group than in the non-surgical group. Rate of complications was 7.4% in patients treated with PC, with the results being comparable to previous reports of 3% to 11%. PC is speculated to be a safe procedure to control inflammation of the gallbladder in patients with AAC. A previous study of 127 patients who underwent diagnostic puncture and PC reported that complications related to PC were catheter dislodgement, bile peritonitis, hemorrhage, hypotension secondary to procedure related bacteremia.<sup>[12]</sup> In this study, only 1 patient developed a complication in the non-surgical group, namely catheter insertion site infection. In patients who underwent PC, the transhepatic approach was

**Table 3**  
**Long-term outcomes of AAC treated with non-surgical methods.**

	Antibiotics only (n=27)	PC (n=14)	Total (n=41)	P-value
Follow-up duration, median (range), yr	5.7 (3–10)	5.6 (3–9)	5.7	.332
Recurrence of acute cholecystitis (%)	2 (7.4)	2 (14.3)	4 (9.8)	.596
Mean recurrence interval, mo	26.5±29.0	19.5±17.7	23.0±20.0	1.000
Treatment of recurrent AAC				
Antibiotics only	0	1	1	
PC	0	0	0	
Cholecystectomy	2	1	3	
Mortality related to recurrence	0	0	0	1.000

AAC=acute acalculous cholecystitis, mo=month, PC=percutaneous cholecystostomy, yr=year.

more frequently performed than the transperitoneal approach in concordance with previous report.<sup>[13]</sup> As the transhepatic approach for PC is considered safer than the transperitoneal approach in patients without severe liver disease or coagulopathy, higher performance of PC through the transhepatic approach might have contributed to a lower rate of complications related to PC.

The recurrence rate of acute cholecystitis after recovery from initial occurrence of AAC in the non-surgical group was 9.8%. A study of 271 patients with AAC treated with PC reported a recurrence rate of 2.3% after PC, and our study showed a higher rate of recurrence than the previous study. All patients with recurrence of AAC after non-surgical management were treated well, without any mortality. In the non-surgical group, the recurrence rate of AAC was higher in the PC group than in the antibiotics only group, without statistical significance. Mean interval between the initial occurrence and recurrence of AAC was longer in patients treated with antibiotics only than in those treated with PC, without statistical significance. Patients who recovered from AAC without PC are speculated to have higher chances of normalization of gallbladder function as inflammation of the gallbladder improved without draining it with PC, which might have affected the recurrence of AAC. Further studies with large number of patients are needed to compare the recurrence rates of AAC between patients treated with antibiotics only and PC.

Culture results from blood and/or bile were not significantly different from those in previous reports. On the whole, 12 patients had bacterial infection in blood or bile. The most common bacterial species associated with AAC was *E coli*, in concordance with the previous report. Other bacteria cultured from blood and/or bile in this study were *Enterococcus* species and *K pneumoniae*.<sup>[14]</sup>

There are several limitations in this study. As this is a retrospective study, patients were assigned to the surgical and non-surgical groups based on their “status and physician’s” decision. This could have affected outcomes related to treatment methods. As we included AAC patients treated by non-surgical methods with >3 years of follow up duration, critically ill AAC patients were less likely to be included in this study. Diagnosis of AAC could have been missed in patients with critical illness.

In conclusion, recurrence occurred in 9.8% of patients with AAC treated with non-surgical management, and the treatment

outcomes of non-surgical group were not inferior to those of the surgical group. Further studies are needed to clarify role of non-surgical management in patients with AAC.

### Author contributions

Tae Nyeun Kim, Kook Hyun Kim, and Min Geun Gu designed study. Sung Bum Kim and Min Geun Gu analyzed the data and wrote the paper; Tae Nyeun Kim and Sung Bum Kim revised the paper. Tae Nyeun Kim supervised the report.

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