RESEARCH ARTICLE

Long-Term Outcomes of Patients with Acute Cholecystitis after Successful Percutaneous Cholecystostomy Treatment and the Risk Factors for Recurrence: A Decade Experience at a Single Center

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Abstract

Background

Percutaneous cholecystostomy tube (PCT) has been effectively used for the treatment of acute cholecystitis (AC) for patients unsuitable for early cholecystectomy. This retrospective study investigated the recurrence rate after successful PCT treatment and factors associated with recurrence.

Methods

We reviewed patients treated with PCT for AC from October 2004 through December 2013. Patients with successful PCT treatment were those who were free from persistent PCT drainage. We used multivariable logistic regression analysis sequentially to identify factors associated with each outcome.

Results

The study included 184 patients (mean age: 70.1 years). The average duration for parenteral antibiotics was 14.4 days and 20.0 days for PCT drainage. The one-year recurrence rate was 9.2% (17/184) with most recurrences occurring within two months (6.5%, 12/184) of the procedure. Complicated cholecystitis (odds ratio [OR]: 4.67; 95% confidence interval [CI]: 1.44–15.70; P = 0.01) and PCT drainage duration >32 days (OR: 4.92; 95% CI: 1.03–23.53; P = 0.05) positively correlated with one-year recurrence; parenteral antibiotics...
Conclusion
The recurrence rate was low for patients after successful PCT treatment. Predictors for recurrence included the severity of initial AC and subsequently provided treatments.

Methods
Study Setting and Patient Identification
We conducted a retrospective cohort study in a tertiary medical center, National Taiwan University Hospital (NTUH). Before data collection, the Institutional Review Board of the NTUH approved this study (reference number: 201401100RIN) and waived the requirement for informed consent because the current study was retrospective in design. NTUH is a 2 600-bed urban medical center providing all levels of care. Patients with AC were identified using the International Classification of Diseases, 9th Revision, clinical modification codes 574.0, 574.3, 574.6, 574.8, 575.0, 575.12, and 575.4. Acute cholecystitis was diagnosed through a combination of patient history, physical examination, and laboratory analysis, as suggested by the Tokyo guidelines [12]. The diagnosis must be confirmed by characteristic imaging findings on ultrasonography (US) or computed tomography (CT) [12].

Patient Management
Patients diagnosed with AC were kept nil per os (NPO), given sufficient infusion and electrolyte correction, and received antibiotics and analgesics. Consulting surgeons discussed risk-
benefit profiles of early surgery, either laparoscopic or open cholecystectomy, with patients and/or their family members to achieve consensus regarding the final management strategy. Indications for PCT were based on surgeon discretion, which might include patient preference, failure of response to initial medical management, impending rupture of a severely distended gallbladder, and/or severe sepsis/septic shock.

Placement of PCTs was accomplished under local anesthesia using US or CT guidance at the discretion of the interventional radiologist. Fluoroscopy was used to confirm guidewire placement and the Seldinger technique was used to place 6 to 8 French pigtail catheters. A US-guided transhepatic approach through the right lobe was used to access the gallbladder.

After the resolution of AC, the PCT was removed if biliary symptoms did not recur after the PCT was temporarily clamped or if the cystic duct was patent on a formal cholangiography [13]. In contrast, if the risk of recurrence was expected to be high through the above assessments, the PCT might be left in situ until removed during cholecystectomy.

Patient Selection and Data Collection

We used the following inclusion criteria: (1) adult AC patients admitted through the emergency department from October 1, 2004 through December 30, 2013; (2) absence of cholecdocholithiasis, hepatobiliary malignancy, or concurrent pancreatitis when AC was diagnosed; (3) patients receiving successful PCT treatment, which denoted patients surviving without the need for persistent PCT drainage.

The basic demographics, presenting vital signs, chief symptoms (fever or abdominal pain), physical findings (including right upper quadrant tenderness and Murphy’s sign), laboratory data (including white blood cell [WBC] count, C-reactive protein, and bilirubin levels), imaging findings (including gall bladder wall thickening, the presence of gallstones, distention of the gall bladder, and surrounding fluid accumulation) on US/CT, and the timing of PCT placement/removal were recorded. The severity of AC was graded according to the Tokyo guidelines [12]. Comorbidities were recorded according to the Charlson comorbidity index [14]. Gangrenous cholecystitis, emphysematous cholecystitis, gall bladder perforation, empyema, and pericholecystic abscess were categorized as complicated cholecystitis [12].

The primary outcome measure was recurrence of AC within one year and two months [15] after successful PCT treatment. The secondary outcome measure was IC within one year and two months [2, 9] after successful PCT treatment. Medical records of all patients were reviewed until December 2014.

Statistical Analysis

We used R 2.15.3 software (R Foundation for Statistical Computing, Vienna, Austria) for data analysis. Categorical data were expressed as counts and proportions; continuous data were expressed as means and standard deviations. Categorical variables were compared by the Fisher’s exact test, and continuous variables were examined by the Wilcoxon rank-sum test. A two-tailed P-value of ≤0.05 was considered statistically significant.

We selected the odds ratio (OR) as the outcome measure. We conducted multivariable logistic regression analyses sequentially to examine the association between independent variables and outcomes, in the order of death, IC and then recurrence. Patients with the former outcome were excluded during the analysis of the next outcome. All available variables were considered in the regression model, regardless of whether they were significant by univariate analysis. The stepwise variable selection procedure (with iterations between the forward and backward steps) was applied to obtain the final regression model. Significance levels for entry and for stay were set at 0.15 to avoid exclusion of potential candidate variables. The final regression model
was identified by excluding individual variables with a P-value >0.05, until all regression coefficients were statistically significant.

We used generalized additive models to examine the nonlinear effects of continuous variables and, if necessary, to identify the appropriate cut-off point(s) for dichotomizing a continuous variable during the variable selection procedure. We assessed the goodness-of-fit of the fitted regression model using C-statistics, adjusted generalized R², and the Hosmer-Lemeshow test.

**Results**

As shown in Fig 1, a total of 1154 patients with AC were admitted through the emergency department from October 2004 through December 2013. Of these, 82 patients with cholecystolithiasis, hepatobiliary malignancy, or concurrent pancreatitis were excluded. Of the remaining 1072 patients, 450 underwent cholecystectomy, 343 received antibiotic treatment and 279 patients received PCT placement during the index hospitalization. Of these 279 patients, 9 (3.2%) patients died despite PCT placement; 86 patients (30.8%) had PCT left in situ and removed during cholecystectomy; the remaining 184 patients (65.9%) who completed successful PCT treatment and were free of persistent PCT drainage, were further assessed in the current analysis.

Table 1 summarizes the clinical characteristics and outcomes of the patients included in the study. There were 114 male patients (62%) and the mean age was 70.1 years. There were 73 patients (39.7%) who presented at the emergency department after symptom onset ≥3 days and 74 patients (40.2%) who presented with sepsis. Most of the patients (169/184, 91.8%) underwent CT imaging. A total of 138 (75.0%) patients had gallstones or sludge detected by US or CT and 41 patients (22.3%) suffered from complicated cholecystitis. There were 77 patients (41.8%) categorized as severity grade II per the Tokyo guidelines and 14 patients (7.6%) categorized as AC of severity grade III [12].

Of the 184 patients, 77 (41.8%) were considered unsuitable for early cholecystectomy after surgical consultation; 53 patients (28.8%) rejected an offer of early cholecystectomy after discussion with surgeons; for the remaining patients, there was no explicit documentation. The average duration was 14.4 days for parenteral antibiotics and 20.0 days for PCT drainage. The one-year recurrence rate was 9.2% (17/184) with most recurrences within two months (6.5%, 12/184) after successful PCT treatment.
Table 1. Clinical Characteristics and Outcomes of Enrolled Patients.

| Characteristics                                      | All patients (n = 184) |
|------------------------------------------------------|------------------------|
| Age, years (SD)                                      | 70.1 (12.5)            |
| Male, n (%)                                          | 114 (62.0)             |
| Comorbidity, n (%)                                   |                        |
| Diabetes mellitus                                    | 70 (38.0)              |
| Cerebral vascular disease                            | 36 (19.8)              |
| Myocardial infarction                                | 7 (3.8)                |
| Congestive heart failure                             | 8 (4.3)                |
| Cirrhosis                                            | 8 (4.3)                |
| Malignancy                                           | 23 (12.5)              |
| Charlson comorbidity index (SD)                      | 1.4 (1.6)              |
| Bedridden status, n (%)                              | 9 (4.9)                |
| Previous abdominal surgery, n (%)                    | 43 (23.4)              |
| Clinical symptoms and signs on presentation at ED    |                        |
| Abdominal pain, n (%)                                | 138 (75.0)             |
| Onset of symptoms before presentation, days (SD)     | 2.5 (2.9)              |
| Body temperature °C (SD)                             | 37.3 (1.0)             |
| Body temperature ≥38°C, n (%)                        | 46 (25.0)              |
| Mean arterial pressure, mm Hg (SD)                   | 99.1 (20.0)            |
| Mean arterial pressure ≤60 mmHg, n (%)               | 6 (3.3)                |
| White blood cell count, 10³/µL (SD)                  | 12.9 (5.5)             |
| White blood cell count ≥18 000/µL, n (%)             | 26 (14.1)              |
| Sepsis, n (%)                                        | 74 (40.2)              |
| Diagnostic tools, n (%)                              |                        |
| Ultrasonography                                      | 77 (41.8)              |
| Computed tomography                                  | 169 (91.8)             |
| Findings on ultrasound or computed tomography, n (%) |                        |
| Gall bladder stones or sludge                        | 138 (75.0)             |
| Complicated cholecystitis                            | 41 (22.3)              |
| Severity grade by Tokyo guidelines, n (%)            |                        |
| Grade I                                              | 93 (50.5)              |
| Grade II                                             | 77 (41.8)              |
| Grade III                                            | 14 (7.6)               |
| Early operation not suggested by surgeons, n (%)      | 105 (57.1)             |
| Early operation rejected by patients, n (%)          | 53 (28.8)              |
| Duration after presentation at ED, days (SD)         |                        |
| Parenteral antibiotics                               | 14.4 (8.9)             |
| Fever                                                | 1.8 (2.0)              |
| Parenteral analgesic use                             | 1.2 (1.4)              |
| Nil per os (NPO)                                     | 3.3 (2.3)              |
| Hospital stay (D)                                    | 17.5 (10.2)            |
| PCTT drainage                                        | 20.0 (25.7)            |
| Outcomes, n (%)                                      |                        |
| Events occurring within two months of PCT removal    |                        |
| Two-month recurrence                                 | 12 (6.5)               |
| Two-month cholecystectomy                            | 40 (21.7)              |
| Two-month death                                      | 1 (0.5)                |

(Continued)
Because the number of deaths was small, these patients were excluded from comparison and further regression analysis. Table 2 presents the comparison between patients of one-year cholecystectomy with the rest of patients who did not experience death or IC. After exclusion of patients of one-year cholecystectomy, Table 3 presents the difference between patients with one-year recurrence and the remaining patients who did not experience death, IC, or recurrence. As shown in Table 4, age <70 years (OR: 4.00; 95% CI: 2.02–8.22; P < 0.001) and cerebral vascular disease (OR: 0.25; 95% CI: 0.07–0.72; P = 0.02) were positively and inversely associated with one-year cholecystectomy, respectively. For the primary outcome, complicated cholecystitis (OR: 4.67; 95% CI: 1.44–15.70; P = 0.01) and PCT drainage duration >32 days (OR: 4.92; 95% CI: 1.03–23.53; P = 0.05) positively correlated with one-year recurrence; parental antibiotics duration >10 days (OR: 0.21; 95% CI: 0.05–0.68; p = 0.01) was inversely associated with one-year recurrence.

The comparisons of two-month outcomes are presented in S1 Table and S2 Table. As shown in Table 5, the factors associated with two-month outcomes were similar to those associated with one-year outcomes.

### Discussion

In this retrospective observational study, the results of a decade of experience showed that the recurrence rate after successful PCT treatment was low: 6.5% (12/184) occurring within 2 months and 9.2% (17/184) occurring within one year after treatment. The analysis also indicated that the risk factors associated with increased recurrence were the severity of AC per se, including complicated cholecystitis and WBC counts >18 000/μL, and offered treatments, including duration of antibiotics and PCT treatment.

The PCT technique was introduced by Radder [16] in 1980, and has been established as a cost-effective and reliable procedure for high-risk patients [17]. The procedure-related mortality rate was <3% [17, 18]. Studies have indicated that >80% of patients experienced rapid relief from the clinical symptoms of AC within 3 days after PCT placement [18–21]. After resolution of AC, it was reported to be desirable to perform IC to prevent recurrence [22]. Nevertheless, an increasing number of studies have indicated that PCT might not only serve as a bridge to IC but could probably be a definitive treatment for AC, especially for patients with high operative risk [23–25].

For patients with less comorbidity, the necessity of subsequent IC remained more contentious. It has been reported that while PCT was often performed with the intent of IC, less than half of patients actually underwent surgery after PCT [26]. Elucidating the trajectory after successful PCT treatment might help patients and clinicians in the formulation of optimal management strategy. However, there is a lack of a clear definition for "successful PCT treatment.” Whether patients with resolution of AC but with PCT left in situ until removed during

| Characteristics | All patients (n = 184) |
|-----------------|-----------------------|
| Events occurring within one year of PCT removal | |
| One-year recurrence | 17 (9.2) |
| One-year cholecystectomy | 60 (32.6) |
| One-year death | (2.7) |

* SD, standard deviation
† PCT, percutaneous cholecystostomy tube

Table 1. (Continued)
Table 2. Clinical Characteristics Stratified by Outcome of One-Year Cholecystectomy.

| Characteristics                                      | Patients with one-year cholecystectomy (n = 60) | Patients without one-year cholecystectomy or death (n = 119) | P value |
|------------------------------------------------------|-------------------------------------------------|-------------------------------------------------------------|---------|
| Age, years (SD*)                                      | 64.5 (14.1)                                     | 73.2 (15.5)                                                 | <0.001  |
| Male, n (%)                                          | 35 (58.3)                                       | 76 (63.9)                                                   | 0.516   |
| Comorbidity, n (%)                                    |                                                 |                                                             |         |
| Diabetes mellitus                                    | 22 (36.7)                                       | 46 (38.7)                                                   | 0.871   |
| Cerebral vascular disease                            | 4 (6.7)                                         | 31 (26.1)                                                   | 0.002   |
| Myocardial infarction                                | 0 (0)                                           | 6 (5.0)                                                     | 0.181   |
| Congestive heart failure                             | 0 (0)                                           | 7 (5.9)                                                     | 0.097   |
| Cirrhosis                                            | 3 (5.0)                                         | 5 (4.2)                                                     | 1       |
| Malignancy                                           | 5 (8.3)                                         | 16 (13.4)                                                   | 0.461   |
| Charlson comorbidity index (SD)                      | 0.92 (1.2)                                      | 1.6 (1.6)                                                   | 0.005   |
| Bedridden status, n (%)                              | 0 (0)                                           | 8 (6.7)                                                     | 0.053   |
| Previous abdominal surgery, n (%)                    | 15 (25.0)                                       | 27 (22.7)                                                   | 0.714   |
| Clinical symptoms and signs on presentation at emergency department | | | |
| Abdominal pain, n (%)                                | 47 (78.3)                                       | 87 (73.1)                                                   | 0.473   |
| Onset of symptoms before presentation, days (SD)     | 3.1 (3.4)                                       | 2.3 (2.6)                                                   | 0.043   |
| Onset of symptoms before presentation ≥3 days, n (%) | 30 (50.0)                                       | 43 (36.1)                                                   | 0.079   |
| Body temperature, °C (SD)                            | 37.1 (0.9)                                      | 37.3 (1.0)                                                  | 0.189   |
| Body temperature ≥38°C, n (%)                        | 13 (21.7)                                       | 32 (26.9)                                                   | 0.473   |
| Mean arterial pressure, mm Hg (SD)                   | 101.6 (24.1)                                    | 98.0 (17.7)                                                 | 0.531   |
| Mean arterial pressure ≥60 mm Hg, n (%)              | 2 (3.3)                                         | 4 (3.4)                                                     | 1       |
| White blood cell count, 10³/μL (SD)                  | 12.3 (5.6)                                      | 13.2 (5.5)                                                  | 0.194   |
| White blood cell count ≥18 000/μL, n (%)             | 8 (13.3)                                        | 18 (15.1)                                                   | 0.825   |
| Sepsis, n (%)                                        | 21 (35.0)                                       | 51 (42.9)                                                   | 0.337   |
| Diagnostic tools, n (%)                              |                                                 |                                                             |         |
| Ultrasonography                                      | 23 (38.3)                                       | 53 (44.5)                                                   | 0.522   |
| Computed tomography                                  | 55 (91.7)                                       | 109 (91.6)                                                  | 1       |
| Findings on ultrasonography or computed tomography, n (%) | | | |
| Gall bladder stones or sludge                         | 47 (78.3)                                       | 87 (73.1)                                                   | 0.473   |
| Complicated cholecystitis                            | 13 (21.7)                                       | 27 (22.7)                                                   | 1       |
| Severity grade by Tokyo guidelines, n (%)            |                                                 |                                                             |         |
| Grade I                                              | 31 (51.7)                                       | 58 (48.7)                                                   | 0.753   |
| Grade II                                             | 29 (48.3)                                       | 47 (39.5)                                                   | 0.267   |
| Grade III                                            | 0 (0)                                           | 14 (11.8)                                                   | 0.003   |
| Early operation not suggested by surgeons, n (%)      | 37 (61.7)                                       | 65 (54.6)                                                   | 0.425   |
| Early operation rejected by patients, n (%)          | 17 (28.3)                                       | 34 (28.6)                                                   | 1       |
| Duration after presentation at emergency department, days (SD) | | | |
| Parenteral antibiotics                               | 13.5 (7.0)                                      | 14.9 (9.9)                                                  | 0.260   |
| Fever                                                | 2.0 (2.0)                                       | 1.8 (2.0)                                                   | 0.385   |
| Parenteral analgesic use                              | 1.3 (1.2)                                       | 1.1 (1.5)                                                   | 0.079   |
| Nil per os (NPO)                                     | 3.1 (2.8)                                       | 3.3 (2.3)                                                   | 0.511   |
| Hospital stay                                        | 17.0 (10.5)                                     | 17.7 (10.2)                                                 | 0.351   |
| PCT† drainage                                        | 17.0 (14.2)                                     | 20.9 (29.9)                                                 | 0.647   |

* SD, standard deviation
† PCT, percutaneous cholecystostomy tube

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### Table 3. Clinical Characteristics Stratified by Outcome of One-Year recurrence.

| Characteristics                                      | Patients with one-year recurrence (n = 17) | Patients without one-year recurrence, cholecystectomy or death (n = 102) | P value |
|------------------------------------------------------|------------------------------------------|------------------------------------------------------------------------|---------|
| Age, years (SD*)                                      | 75.8 (12.6)                              | 72.7 (15.9)                                                            | 0.464   |
| Male, n (%)                                           | 13 (76.5)                                | 63 (61.8)                                                              | 0.287   |
| Comorbidty, n (%)                                     |                                         |                                                                       |         |
| Diabetes mellitus                                     | 7 (41.2)                                 | 39 (38.2)                                                              | 0.796   |
| Cerebral vascular disease                            | 4 (23.5)                                 | 27 (26.5)                                                              | 1       |
| Myocardial infarction                                 | 1 (5.9)                                  | 5 (4.9)                                                               | 1       |
| Congestive heart failure                              | 1 (5.9)                                  | 6 (5.9)                                                               | 1       |
| Cirrhosis                                            | 1 (5.9)                                  | 4 (3.9)                                                               | 0.544   |
| Malignancy                                           | 3 (17.6)                                 | 13 (12.7)                                                              | 0.699   |
| Charlson comorbidity index (SD)                       | 1.6 (1.4)                                | 1.6 (1.6)                                                              | 0.614   |
| Bedridden status, n (%)                               | 1 (5.9)                                  | 7 (6.9)                                                               | 1       |
| Previous abdominal surgery, n (%)                    | 9 (52.9)                                 | 18 (17.6)                                                              | 0.003   |
| Clinical symptoms and signs on presentation at        |                                         |                                                                       |         |
| emergency department                                  |                                         |                                                                       |         |
| Abdominal pain, n (%)                                 | 13 (76.5)                                | 74 (72.5)                                                              | 1       |
| Onset of symptoms before presentation, days (SD)      | 2.8 (3.1)                                | 2.2 (2.5)                                                              | 0.572   |
| Onset of symptoms before presentation ≥3 days, n (%)  | 8 (47.1)                                 | 35 (34.3)                                                              | 0.414   |
| Body temperature, °C (SD)                             | 37.2 (0.8)                               | 37.4 (1.1)                                                             | 0.543   |
| Body temperature ≥38°C, n (%)                         | 1 (5.9)                                  | 31 (30.4)                                                              | 0.039   |
| Mean arterial pressure, mm Hg (SD)                    | 99.1 (20.8)                              | 97.8 (17.3)                                                            | 0.912   |
| Mean arterial pressure ≥60 mm Hg, n (%)               | 1 (5.9)                                  | 3 (2.9)                                                               | 0.465   |
| White blood cell count, 10³/μL (SD)                   | 14.0 (5.6)                               | 13.1 (5.5)                                                             | 0.341   |
| White blood cell count ≥18 000/μL, n (%)              | 4 (23.5)                                 | 14 (13.7)                                                              | 0.287   |
| Sepsis, n (%)                                         | 6 (35.3)                                 | 45 (44.1)                                                              | 0.601   |
| Diagnostic tools, n (%)                               |                                         |                                                                       |         |
| Ultrasonography                                       | 8 (47.1)                                 | 45 (44.1)                                                              | 1       |
| Computed tomography                                   | 17 (100.0)                               | 92 (90.2)                                                              | 0.354   |
| Findings on ultrasonography or computed tomography, n |                                         |                                                                       |         |
| Gall bladder stones or sludge                         | 13 (76.5)                                | 74 (72.5)                                                              | 1       |
| Complicated cholecystitis                             | 8 (47.1)                                 | 19 (18.6)                                                              | 0.024   |
| Severity grade by Tokyo guidelines, n (%)             |                                         |                                                                       |         |
| Grade I                                               | 6 (35.3)                                 | 52 (51.0)                                                              | 0.298   |
| Grade II                                              | 9 (52.9)                                 | 38 (37.3)                                                              | 0.285   |
| Grade III                                             | 2 (11.8)                                 | 12 (11.8)                                                              | 1       |
| Early operation not suggested by surgeons, n (%)      | 7 (41.2)                                 | 58 (56.9)                                                              | 0.295   |
| Early operation rejected by patients, n (%)           | 6 (35.3)                                 | 28 (27.5)                                                              | 0.565   |
| Duration after presentation at emergency department,  |                                         |                                                                       |         |
| days (SD)                                             |                                         |                                                                       |         |
| Parenteral antibiotics                                | 12.6 (7.2)                               | 15.2 (10.2)                                                            | 0.148   |
| Fever                                                 | 1.4 (2.3)                                | 1.8 (2.0)                                                              | 0.142   |
| Parenteral analgesic use                              | 0.8 (1.0)                                | 1.1 (1.6)                                                              | 0.628   |
| Nil per os (NPO)                                      | 4.1 (2.7)                                | 3.2 (2.2)                                                              | 0.135   |
| Hospital stay                                         | 14.7 (7.4)                               | 18.3 (10.6)                                                            | 0.129   |
| PCT† drainage                                         | 36.8 (68.4)                              | 18.3 (15.8)                                                            | 0.233   |

* SD, standard deviation
† PCT, percutaneous cholecystostomy tube

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cholecystectomy should be counted as “successful PCT treatment” remains undefined. The result might be biased if these patients were pooled in analysis because these patients were not at risk for recurrence due to the persistent drainage by PCT. Therefore, in our study, we defined that only patients free of persistent PCT drainage were those treated successfully by PCT and observed for recurrence.

The recurrence rate after PCT placement ranged from 4% to 22% [8, 23, 27, 28]. In our study, the one-year recurrence rate was relatively low, 17/184 (9.2%), with most recurrences within two months (12/184, 6.5%) after successful PCT treatment. This low recurrence rate might be explained by two reasons. First, patients considered high for recurrence was discharged with PCT in situ until cholecystectomy (86/279; 30.8%) (Fig 1). In our hospital, the PCT could usually be removed after temporary clamping of the drain had been shown to be well-tolerated. Some clinicians favored performing a cholangiography via the drain before withdrawal to ensure the absence of leakage or an obstructed cystic duct, but this policy was not systematic [13]. Second, some of the patients after successful PCT treatment received IC

Table 4. Multiple Logistic Regression Model with One-Year Outcome as the Dependent Variable.

| Independent variable† | Odds ratio | 95% confidence interval | P value‡ |
|-----------------------|------------|------------------------|---------|
| **Outcome: One-year cholecystectomy‡** |            |                        |         |
| Age <70 years         | 4.00       | 2.02–8.22              | <0.001  |
| Cerebral vascular disease | 0.25     | 0.07–0.72              | 0.018   |
| **Outcome: One-year recurrence§** |            |                        |         |
| Complicated cholecystitis | 4.67     | 1.44–15.70             | 0.010   |
| Parenteral antibiotics duration >10 days | 0.21 | 0.05–0.68              | 0.013   |
| PCT* drainage duration >32 days | 4.92 | 1.03–23.53             | 0.046   |

† The display of independent variables is arranged in order of P value
‡ For model of one-year cholecystectomy: Goodness-of-fit assessment: n = 179; adjusted generalized $R^2 = 0.206$; the estimated area under the receiver operating characteristic (ROC) curve = 0.725; and modified Hosmer-Lemeshow F test P value = 0.17.
§ For model of one-year recurrence: Goodness-of-fit assessment: n = 119; adjusted generalized $R^2 = 0.206$; the estimated area under the receiver operating characteristic (ROC) curve = 0.742; and modified Hosmer-Lemeshow F test P value = 0.92.

* PCT, percutaneous cholecystostomy tube
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Table 5. Multiple Logistic Regression Model with Two-Month Outcomes as the Dependent Variable.

| Independent variable* | Odds ratio | 95% confidence interval | P value* |
|-----------------------|------------|------------------------|---------|
| **Outcome: Two-month cholecystectomy†** |            |                        |         |
| Age <70 years         | 3.84       | 1.76–8.75              | < 0.001 |
| Grade II by Tokyo guidelines | 3.04 | 1.41–6.80              | 0.005   |
| Charlson comorbidity index | 0.68 | 0.48–0.91              | 0.018   |
| **Outcome: Two-month recurrence‡** |            |                        |         |
| Complicated cholecystitis | 5.94     | 1.57–23.96             | 0.009   |
| White blood cell count ≥18 000/μL | 5.16 | 1.14–22.34             | 0.027   |
| Parenteral antibiotics duration >10 days | 0.25 | 0.06–0.92              | 0.042   |

* The display of independent variables is arranged in order of P value
† For model of two-month cholecystectomy: Goodness-of-fit assessment: n = 183; adjusted generalized $R^2 = 0.224$; the estimated area under the receiver operating characteristic (ROC) curve = 0.767; and modified Hosmer-Lemeshow F test P value = 0.97.
‡ For model of two-month recurrence: goodness-of-fit assessment: n = 143; adjusted generalized $R^2 = 0.236$; the estimated area under the receiver operating characteristic (ROC) curve = 0.788; and modified Hosmer-Lemeshow F test P value = 0.97.
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within one year (60/184; 32.6%) (Fig 1). Clearly, these patients receiving IC would not be susceptible to recurrence. Including these patients in the denominator for calculation might underestimate the actual recurrence rate. Nevertheless, excluding these patients in the rate calculation would also make it difficult for clinicians to apply the analysis results to predict the prognosis of an incoming patient without knowing in advance whether he/she would receive IC within one year.

There have been no recommendations proposed for the optimal duration of PCT drainage. The duration of drainage ranged from three to six weeks, one month on the average, in previous investigations [8]. In our cohort, the mean PCT drainage duration was 20 days. According to previous reports, ≥2 weeks were required for tract maturation for the transhepatic approach and 3 weeks were required for the transperitoneal approach [29, 30]. Nevertheless, the result showed that the PCT drainage duration longer than one month was associated with one-year recurrence (OR: 4.92). Few studies examined the association between drainage duration with recurrence. Hsieh et al. [15] indicated that a drainage duration ≥2 weeks was associated with increased recurrence within two months of the initial AC attack, probably caused by irritation of the gallbladder mucosa by the PCT [31, 32] or bacterial colonization of the tube [33]. While these theories [31–33] might help explain increased short-term recurrence, they might not account for increased one-year recurrence. In our study, patients whose PCT could not be removed earlier might be those who could barely tolerate temporary clamping of PCT or had an obstructed cystic duct on cholangiography, which suggested that these patients might have a higher recurrence probability. Therefore, we suggested that for patients who needed PCT drainage longer than one month should have PCT kept in situ until cholecystectomy if possible. This suggestion might be contradictory to the result of the study by Hsieh et al. [15]. However, Hsieh et al. [14] did not explicitly reveal the timing and the risk stratification method for PCT removal, which made it difficult to compare the results of the current analysis to that of Hsieh et al. [15].

Currently, there are no specific recommendations for antibiotic therapy in association with PCT drainage. In our previous study [34], we noted that in patients receiving antibiotic therapy alone for AC, a duration of parenteral antibiotic use >8 days was associated with decreased recurrence. The Tokyo guidelines [35] suggested for AC of grade II and III, 4–7 days of antibiotic administration was recommended. Nevertheless, the developers of the guidelines [35] also admitted that there were very few data available for the treatment duration of AC and their recommendations [35] referred to the duration of antibiotic therapy for complicated intraabdominal infections suggested by SIS-NA/IDSA 2010 guidelines [36]. In the current analysis, we noted that the duration of parenteral antibiotic use >10 days was associated with both decreased one-year and two-month recurrence, which might serve as a reference for the duration of antibiotic administration for patients requiring PCT drainage. Nevertheless, although we controlled most clinical and laboratory variables in our model, we might still overlook some important variables to eliminate the bias of confounding by indication. Furthermore, the administered antibiotics in the current analysis were heterogeneous, which might also limit the applicability of this result.

Complicated cholecystitis and elevated WBC counts ≥18,000/μL were noted to correlate with an increased risk of recurrence. Both factors were used to define AC of severity grade II in the Tokyo guidelines [12] because the presence of these factors suggested severe gallbladder inflammation, which might be associated with increased operative difficulty when performing early cholecystectomy. For these patients with AC of grade II, the Tokyo guidelines [22] suggested IC be performed after the improvement of the acute inflammatory process. Our analysis demonstrated that patients with AC of grade II were indeed more likely to receive IC within two months after successful PCT treatment (OR: 3.04), as recommended by the guidelines.
in contrast, if they did not receive IC, they were also more likely to suffer a two-month recurrence (complicated cholecystitis, OR: 5.94; WBC count ≥18 000/μL; OR: 5.16). This information might be important to corroborate the necessity of IC in these patients. However, as the regression analysis indicated, age and comorbidities were still important surgical considerations for IC. For patients with old age or advanced comorbidities suffering from AC of grade II, the uncertainties remained about whether they should receive IC to prevent recurrence or receive repeated PCT drainage to avoid perioperative morbidity.

In our study, we used multivariable regression analysis sequentially to identify independent factors significantly associated with each outcome. We could have conducted a survival analysis by fitting a Cox’s proportional hazards model. Nevertheless, because the duration of PCT drainage might correlate with the observation duration for each outcome, in violation of the independent censoring assumption required by a Cox’s proportional hazards model, we decided to adopt the current analysis method.

The efficacy of PCT treatment in high-risk patients has been acknowledged by previous studies [23–25]. For these high-risk patients, even if they had been medically optimized, they might still suffer from significant perioperative comorbidities if they agreed to receive IC [3–7]. Therefore, it might be less debatable that PCT could serve as a definitive treatment for them. Nevertheless, it was noted that there was a trend toward PCT being increasingly used in less morbid patients [11]. For these patients, a complete benefit-risk profile might be important for them to consider whether elective cholecystectomy was mandatory because our analysis showed that even if faced with emergent conditions, up to 28.8% (53/184) of patients still did not want to undergo early cholecystectomy. Our study addressed some concerns for these less morbid patients; nevertheless, only a prospective study like the ongoing CHOCOLATE trial [37], could illustrate the complete risk-benefit picture for them.

Limitations
First, this was an observational study and as such, we were only able to establish an association, rather than a causal relationship, between independent and outcome variables. Second, although our hospital provided all levels of care, the cohort from a single medical center may still introduce selection bias. Third, the recurrence rate in our study might be underestimated because we could not exclude the possibility that patients would receive treatment for recurrence at other hospitals. However, all patients visited our emergency department at the time of initial AC, suggesting that many might utilize the same emergency medical services again in the case of recurrence. This might compensate to some extent for the underestimation. Also, this kind of misclassification bias usually leads to an underestimated association between independent and dependent variables, which might be a less problem for those identified statistically significant independent variables.

Conclusions
The recurrence rate after successful PCT treatment was low. Patients with complicated cholecystitis, elevated WBC counts, or need for prolonged PCT drainage were more likely to experience recurrence.

Supporting Information
S1 Dataset. Raw data used in statistical analysis.
(XLSX)
S1 Table. Clinical Characteristics Stratified by Outcome of Two-Month Cholecystectomy. (DOCX)

S2 Table. Clinical Characteristics Stratified by Outcome of Two-Month Recurrence. (DOCX)

Author Contributions
Conceived and designed the experiments: CHW CYW JCTY WCL. Performed the experiments: CHW HPW KLL YMW SCC. Analyzed the data: CHW CYW JCTY WCL HPW KLL YMW SCC. Contributed reagents/materials/analysis tools: CHW. Wrote the paper: CHW CYW JCTY WCL.

References
1. van der Linden W, Sunzel H. Early versus delayed operation for acute cholecystitis. A controlled clinical trial. Am J Surg. 1970; 120: 7–13. PMID: 5426869
2. Gurusamy K, Samraj K, Gluud C, Wilson E, Davidson BR. Meta-analysis of randomized controlled trials on the safety and effectiveness of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Br J Surg. 2010; 97: 141–150. doi: 10.1002/bjs.6870 PMID: 20035546
3. Huber DF, Martin EW Jr., Cooperman M. Cholecystectomy in elderly patients. Am J Surg. 1983; 146: 719–722. PMID: 6650754
4. Pessaux P, Regenet N, Tuech JJ, Rouge C, Bergamaschi R, Arnaud JP. Laparoscopic versus open cholecystectomy: a prospective comparative study in the elderly acute cholecystitis. Surg Laparosc Endosc Percutan Tech. 2001; 11: 252–255. PMID: 11525370
5. Decker G, Goergen M, Philippart P, Mendes da Costa P. Laparoscopic cholecystectomy for acute cholecystitis in geriatric patients. Acta Chir Belg. 2001; 101: 294–299. PMID: 11868506
6. Houghton PW, Jenkinson LR, Donaldson LA. Cholecystectomy in the elderly: a prospective study. Br J Surg. 1985; 72: 220–222. PMID: 3978383
7. Margiotta SJ Jr., Willis IH, Wallack MK. Cholecystectomy in the elderly. Am Surg. 1988; 54: 34–39. PMID: 3337481
8. McGillicuddy EA, Schuster KM, Barre K, Suarez L, Hall MR, Kaml GJ, et al. Non-operative management of acute cholecystitis in the elderly. Br J Surg. 2012; 99: 1254–1261. doi: 10.1002/bjs.8536 PMID: 22829411
9. Okamoto K, Takada T, Strasberg SM, Solomkin JS, Pitt HA, Garden OJ, et al. TG13 management bundles for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2013; 20: 55–59. doi: 10.1007/s00534-012-0562-2 PMID: 23307002
10. Leveau P, Andersson E, Carlgren I, Willner J, Andersson R. Percutaneous cholecystostomy: a bridge to surgery or definite management of acute cholecystitis in high-risk patients? Scand J Gastroenterol. 2008; 43: 593–596. doi: 10.1080/00365520701851673 PMID: 18415753
11. Smith TJ, Manske JG, Mathiason MA, Kallies KJ, Kohari SN. Changing trends and outcomes in the use of percutaneous cholecystostomy tubes for acute cholecystitis. Ann Surg. 2013; 257: 1112–1115. doi: 10.1097/SLA.0b013e3182747778c PMID: 23263191
12. Yokoe M, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Gomi H, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2013; 20: 35–46. doi: 10.1007/s00534-012-0568-9 PMID: 23340953
13. Venara A, Carretier V, Lebigot J, Lermite E. Technique and indications of percutaneous cholecystostomy in the management of cholecystitis in 2014. J Visc Surg. 2014; 151: 435–439. doi: 10.1016/j.jviscsurg.2014.06.003 PMID: 25168577
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40: 373–383. PMID: 3558716
15. Hsieh YC, Chen CK, Su CW, Chan CC, Hwu TI, Liu CJ, et al. Outcome after percutaneous cholecystostomy for acute cholecystitis: a single-center experience. J Gastrointest Surg. 2012; 16: 1860–1868. PMID: 22929241
16. Radder RW. Ultrasonically guided percutaneous catheter drainage for gallbladder empyema. Diagn Imaging. 1986; 49: 330–333. PMID: 7215096
17. Werbel GB, Nahrwold DL, Joehl RJ, Vogelzang RL, Rege RV. Percutaneous cholecystostomy in the diagnosis and treatment of acute cholecystitis in the high-risk patient. Arch Surg. 1989; 124: 782–785. PMID: 2742479

18. Winbladh A, Gullstrand P, Svanvik J, Sandstrom P. Systematic review of cholecystostomy as a treatment option in acute cholecystitis. HPB (Oxford). 2009; 11: 183–193.

19. Davis CA, Landercasper J, Gundersen LH, Lambert PJ. Effective use of percutaneous cholecystostomy in high-risk surgical patients: techniques, tube management, and results. Arch Surg. 1999; 134: 727–731. PMID: 10401823

20. Browning PD, McGahan JP, Gerscovich EO. Percutaneous cholecystostomy for suspected acute cholecystitis in the hospitalized patient. J Vasc Interv Radiol. 1993; 4: 531–537. PMID: 8353351

21. Kiviniemi H, Mäkelä JT, Autio R, Tikkakoski T, Leinonen S, Siniluoto T, et al. Percutaneous cholecystostomy in acute cholecystitis in high-risk patients: an analysis of 69 patients. Int Surg. 1998; 83: 299–302. PMID: 10096746

22. Miura F, Takada T, Strasberg SM, Solomkin JS, Pitt HA, Gouma DJ, et al. TG13 flowchart for the management of acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2013; 20: 47–54. doi: 10.1007/s00534-012-0563-1 PMID: 23307003

23. Chang YR, Ahn YJ, Jang JY, Kang MJ, Kwon W, Jung WH, et al. Percutaneous cholecystostomy for acute cholecystitis in patients with high comorbidity and re-evaluation of treatment efficacy. Surgery. 2014; 155: 615–622. doi: 10.1016/j.surg.2013.12.026 PMID: 24548617

24. Zerem E, Omerovic S. Can percutaneous cholecystostomy be a definitive management for acute cholecystitis in high-risk patients? Surg Laparosc Endosc Percutan Tech. 2014; 187–191. doi: 10.1097/ SLE.0b013e31828fa45e PMID: 24686358

25. de Mes de Mestral C, Gomez D, Haas B, Zagorski B, Rotstein OD, Nathens AB. Cholecystostomy: a bridge to hospital discharge but not delayed cholecystectomy. J Trauma Acute Care Surg. 2013; 74: 175–179. doi: 10.1097/TA.0b013e31827890e1 PMID: 23271093

26. Sanjay P, Mittapalli D, Marioud A, White RD, Ram R, Alijani A. Clinical outcomes of a percutaneous cholecystostomy for acute cholecystitis: a multicentre analysis. HPB (Oxford). 2013; 15: 511–516.

27. Li M, Li N, Ji W, Quan Z, Wan X, Wu X, et al. Percutaneous cholecystostomy is a definitive treatment for acute cholecystitis in elderly high-risk patients. Am Surg 2013; 79: 524–527. PMID: 23635589

28. Wise JN, Gervais DA, Akman A, Harisinghani M, Hahn PF, Mueller PR. Percutaneous cholecystostomy catheter removal and incidence of clinically significant bile leaks: a clinical approach to catheter management. AJR Am J Roentgenol. 2005; 184: 1647–1651. PMID: 15855132

29. Hatjidakis AA, Karampekos S, Prassopoulou P, Xynos E, Raisissi M, Vasilakis SI, et al. Maturation of the Tract After Percutaneous Cholecystostomy with Regard to the Access Route. Cardiovasc Intervent Radiol. 1998; 20: 36–40. PMID: 9473544

30. Morris CR, Hohl RP, Ivy AC. An experimental study of the role of stasis in the etiology of cholecystitis. Surgery. 1952; 32: 673–685. PMID: 12984284

31. Roslyn JJ, DenBesten L, Thompson JE Jr, Silverman BF. Roles of lithogenic bile and cystic duct occlusion in the pathogenesis of acute cholecystitis. Am J Surg. 1980; 140: 126–130. PMID: 7396076

32. Cnich CJ, Drinka P. Medical device-associated infections in the long-term care setting. Infect Dis Clin North Am. 2012; 26: 143–164. doi: 10.1016/j.cinc.2011.09.007 PMID: 22284381

33. Wang CH, Chou HC, Liu KL, Lien WC, Wang HP, Wu YM. Long-term outcome of patients with acute cholecystitis receiving antibiotic treatment: a retrospective cohort study. World J Surg. 2014; 38: 347–354. doi: 10.1007/s00268-013-2311-3 PMID: 24178182

34. Gomi H, Solomkin JS, Takada T, Strasberg SM, Pitt HA, Yoshida M, et al. TG13 antimicrobial therapy for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2013; 20: 60–70. doi: 10.1007/ s00534-012-0572-0 PMID: 23340954

35. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010; 50: 133–164. doi: 10.1086/649554 PMID: 20034345

36. Kotram K, van Ramshorst B, Bollen TL, Besselink MG, Gouma DJ, Karsten T, et al. Acute cholecystitis in high risk surgical patients: percutaneous cholecystostomy versus laparoscopic cholecystectomy (CHOCOLATE trial): study protocol for a randomized controlled trial. Trials. 2012; 13: 7. doi: 10.1186/ 1745-6215-13-7 PMID: 22236534