Subsequent Cholecystectomy Is The Most Important Factor for Recurrent Biliary Event-Free Survival in High-Risk Acute Cholecystitis Patients after Gallbladder Drainage

Chi-Chih Wang

Chung Shan Medical University Hospital

Ming-Chang Tsai

Chung Shan Medical University Hospital

Yen-Pin Huang

Changhua Christian Hospital

Wen-Hsin Huang

China Medical University Hospital

Tsung-Yu Tsai

China Medical University Hospital

Wen-Wei Sung

Chung Shan Medical University Hospital

Tzu-Wei Yang

Chung Shan Medical University Hospital

Jaw- Town Lin

China Medical University Hospital

Chun-Che Lin

China Medical University Hospital

Hsu-Heng Yen (✉ blaneyen@gmail.com)

Changhua Christian Hospital

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Abstract

Background and Aims: Cholelithiasis is a disease with increasing prevalence over the decades. Gallbladder drainage is an alternative choice in critically ill patients who cannot tolerate early surgery for acute cholecystitis. In previous data, early or delayed cholecystectomy leads to less recurrent biliary events comparing to using a wait-and-see strategy. We wondered if the subsequent cholecystectomy strategy is the most important factor to improve recurrent biliary event-free survival after gallbladder drainage. The present study aimed to explore the most important factor to improve the clinical outcome after percutaneous transhepatic gallbladder drainage.

Methods: We studied 211 adult acute cholecystitis patients who received percutaneous transhepatic gallbladder drainage during index admission between July 2017 and December 2018 in Chung Shan Medical University Hospital and Changhua Christian Hospital. Patients who died during the index admission or lost follow-up within 30 days were excluded. We further divided these patients into those who received subsequent cholecystectomy within 2 months and those who received no cholecystectomy within 2 months. Recurrent biliary events, mortality and biliary event-related mortality were compared. Multivariate analysis was applied to find the most important factors of recurrent biliary event-free survival.

Results: There were 8 cases (13.6%) in the subsequent cholecystectomy group that experienced recurrent biliary events, while 39 cases (32.2%) experienced recurrent biliary events in the no cholecystectomy within 2 months group. The proportion and average recurrent biliary events per person were all significantly lower in the subsequent cholecystectomy group. The recurrent biliary event-related mortality difference is insignificant. The most decisive factor to determine recurrent biliary event-free survival is whether a subsequent cholecystectomy performed or not (HR:0.485, 95% CI: 0.250-0.941, $p=0.032$).

Conclusion: Subsequent cholecystectomy can decrease further recurrent biliary events and improve recurrent biliary event-free survival in high risk patients with acute cholecystitis that accepted percutaneous transhepatic gallbladder drainage initially.

Introduction

Cholelithiasis is a disease with increasing prevalence in both developed[1, 2], and less developed areas nowadays[3]. Cholecystitis is an inflammatory process located in the gallbladder[4] that occurs in patients with a history of symptomatic gallstones[5, 6]. Acalculous cholecystitis occurs sometimes[7, 8]. Clinical management of acute cholecystitis, such as early cholecystectomy (CCY), percutaneous transhepatic gallbladder drainage (PT-GBD), and endoscopic ultrasonography guide gallbladder drainage (EUS-GBD), are based on disease severity [9]. PT-GBD and EUS-GBD were selected especially in critically ill patients who cannot tolerate surgery initially[10, 11].

According to the timing of CCY, it can be further classified as early CCY, which is performed initially after cholecystitis diagnosis, or delayed CCY. As previous literature showed[12-14], compared to delayed CCY,

early CCY for cases within 72 hours of symptom onset was associated with lower mortality rates and complication rates in the majority of cases. Meanwhile, early CCY is a better choice than delayed CCY regarding hospital stay and medical expenses for treatment in some studies[14]. Still some references show that delayed CCY has a higher proportion of laparoscopy intervention[15] and a lower complication rate[16]. Although CCY is the only definitive therapy for acute cholecystitis[4, 9, 17], there are patients with high short-term comorbidity risk for surgery. The patients who need surgery intervention are suggested to be evaluated using the Charlson Comorbidity Index (CCI)[18-20] or the American Society of Anesthesiologists physical status classification (ASA-PS)[21, 22]; PT-GBD is useful for managing high surgical risk patients compared with conservative treatment[9, 23, 24]. CCY can decrease further recurrent biliary events (RBEs) [25, 26], while the surgery timing after patients with acute cholecystitis have undergone PT-GBD is still in debate[27-32]. Currently, there is no strong evidence to suggest who has survival benefits from subsequent CCY after initial PT-GBD, but a similar concept in choledocholithiasis demonstrated that a prophylactic CCY in acute cholangitis patients who underwent sphincterotomy showed survival benefit compared to the wait-and-see approach[33].

In general, most subsequent CCY was expected to be beneficial and performed within 2 months after initial PT-GBD, so we conduct a retrospective hospital base cohort study to evaluate the most valuable factors to RBE-free survival after initial PT-GBD for complicated acute cholecystitis.

Methods

This is a retrospective cohort study collecting cases of accepted PT-GBD during index admission from July 2017 to December 2018 in Chung Shan Medical University Hospital (CSMUH) and Changhua Christian Hospital (CCH). This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of CSMUH and CCH (No. 200402); documentation of informed consent was waived because the study was conducted retrospectively.

Study design

We collected 211 adult patients with accepted PT-GBD during index admission from July 2017 to December 2018 in CSMUH and CCH. Patients who underwent PT-GBD for cancer obstruction were excluded. The diagnosis of acute cholecystitis was based on Tokyo Guideline 2018. Some patients suffered from both acute cholangitis and acute cholecystitis were managed by PT-GBD and endoscopic retrograde cholangiopancreatography in our study population. Because the purpose of this study was to evaluate the most important factors that affect RBE free survival after initial PT-GBD insertion, patients who died during index admission were excluded. Patients who are alive and lost follow-up within 30 days were excluded from further analysis. We further divided these patients into those with CCY within 2 months before PT-GBD removal (subsequent CCY) and those with no CCY within 2 months after the index admission. All the patients were followed up to their expired date if happened, up to their last hospital visit record or December 31, 2019.

We compared the demographic data, like age, gender, follow-up time, the decisive diagnosis image methods, disease severity at index admission, laboratory (lab) data, baseline CCI score, underlying diseases, and the proportion of laparoscopic/open CCY procedures between the subsequent CCY group and no CCY within 2 months group. The definition of RBE included ER visits and admissions due to biliary events, such as cholangitis, acute biliary pancreatitis and cholecystitis. We evaluate the outcomes of these patients using average RBEs, RBE case numbers, overall mortality, and RBE-related mortality. RBE-related mortality was defined as mortality events due to RBEs during hospitalization or mortality events after critical discharge. We evaluate the decisive factors using multi-variate analysis for clinical conditions, laboratory data, interventions and comorbidity after acute cholelithiasis underwent PT-GBD by RBE-free survival to build the adequate clinical practice and possible outcomes.

Data processing and statistical analysis

The raw data were collected using Microsoft Excel Office Open XML. Kaplan–Meier survival analyses were conducted using SPSS version 19. The important clinical parameters and parameters that achieve statistically significant differences in univariate analysis of RBE-free survival in table 3 are evaluated using multivariate analysis with cox regression model.

The data obtained from the study were processed using chi-square (χ^2) tests or Fisher's exact test for categorical variables, one-way analyses of variance (ANOVA) for continuous variables, and Kaplan–Meier survival for disease-free survival curves. A two-tailed P-value of 0.05 was considered statistically significant

Results

A total 211 of adult patients who underwent PT-GBD were selected from the hospital database from July 2017 to December 2018 in CSMUH and CCH. After exclusion of 10 patients who expired during index admission and 8 patients who accepted PT-GBD as a rescue treatment for bile duct cancer obstruction, we included 193 adult patients who underwent PT-GBD at index admission for acute cholecystitis. We further excluded 13 cases, who were alive because of lost follow up within 30 days after discharge. Among 180 patients selected for analysis, 59 patients underwent subsequent CCY and the other 121 patients didn't accept CCY within 2 months before PT-GBD removal as a definite treatment. Eventually, there were 11 patients who underwent CCY because of RBEs or frequent biliary colic in the no CCY within 2 months group. The flow chart of this study is shown in Figure 1.

Subsequent CCY group vs. No CCY within 2 months group

The average age in the subsequent CCY group was 71.1 ± 14.6 , which is significantly younger than those in the no CCY within 2 months group ($p=0.022$), with an average age of 76.4 ± 14.1 in. We could find that the proportion of sepsis, the proportion of underlying dementia, and CCI score (4.2 ± 2.2 vs. 5.4 ± 2.3 , $p < 0.001$) were significantly higher in the no CCY within 2 months group. Other underlying diseases of the parameters of the CCI score were similar between the two groups. Regarding the status of CCY, only 11

patients (9.1 %) underwent CCY in the no subsequent CCY within 2 months group, while 94.9% patients underwent laparoscopic CCY under a subsequent CCY strategy in CCY within 2 months group. Only 81.8% of patients underwent laparoscopic CCY if CCY was chose as a rescue management in the no CCY within 2 months group when RBEs occurred. But the proportion of laparoscopic CCY did not meet statistical significance between these 2 groups. The detailed demographic data are shown in table 1.

There were 8 cases, which represent 13.6% of patients, that experienced RBEs once in the subsequent CCY group, while 39 cases (32.2%) experienced RBEs in the no CCY within 2 months group (1 RBE: 27 patients, 2 RBEs: 10 patients, 3 RBEs: 1 patient, 4 RBEs: 1 patients). The average number of RBE is higher in the no CCY within 2 months group comparing CCY within 2 months group (0.446 vs. 0.136). The overall mortality rate is 16.5% in the no CCY within 2 months group, and it is significantly higher than the overall mortality rate (5.1%) in the subsequent CCY group. But RBE-related mortality didn't reach statistical significance between these two groups. The outcome comparisons are listed in table 2.

Decisive factors of RBE-free survival

We evaluate the true value of treatment for cholelithiasis using RBE-free survival, which demonstrated a survival curve free from RBEs and overall mortality. In univariate analysis, those age $\geq$ 79 had 1.682 times the risk for RBEs or mortality (95% CI: 1.014-2.790, p=0.044), while gallbladder (GB) rupture in index admission had 2.665 times the risk (95% CI: 1.069-6.644, p=0.036) comparing to no GB rupture. The group with no CCY within 2 months had increased risk (HR:2.383, 95% CI: 1.244-4.564, p=0.009) in RBE-free survival compared to the subsequent CCY group. The detailed information about univariate analysis of disease severity, demographic data, CCI score, underlying disease condition, and CCY status is listed in table 3. After placing age (<79 vs. $\geq$ 79), GB rupture and subsequent CCY attempt and CCI score ($\leq$ 8 vs >8) into multivariate analysis, only subsequent CCY maintained a significantly decreased risk of RBE-free survival, with 2.061 times the risk (CI: 1.063-3.998, p= 0.032) if subsequent CCY is not performed. Age (HR:1.477, 95% CI: 0.885-2.467, p=0.136), GB rupture (HR: 2.191, 95% CI: 0.873-5.501, p=0.095), and CCI score >8 (HR: 1.616, 95% CI: 0.763-3.425, p=0.210) had slightly increased risk in RBEs or mortality without statistical significance. Detailed multivariate analysis of RBE-free survival according to the clinical parameters is demonstrated in table 4.

RBE-free survival

RBE-free survival of patients who underwent PT-GBD due to acute cholecystitis was significantly better (p=0.007) if subsequent CCY was performed, with RBE-free survival being 81.9% in the next year and 75.0% at the end of the follow-up period, compared to 56.6% in the first year and 48.2% at the end of the follow-up period if subsequent CCY is not performed. The results are shown in Figure 2.

Discussion

We found only 59 among 180 patients, which represent 32.78% of total patients, who accepted subsequent CCY after PT-GBD for acute cholecystitis in our data from two medical centers. At the same

time, the subsequent CCY strategy can have a higher laparoscopic CCY proportion (94.9%) than the wait-and-see policy (81.8%). When comparing the benefits of laparoscopic CCY versus open CCY in previous literature, laparoscopic CCY results in a shorter hospital stay[34-36], less post-operative complications[36], being safer in the early trimester of pregnancy[37], and having a lower mean use of analgesia[35]. Although some studies expose laparoscopic CCY as not being a cost-effective investment under economic analysis[38], laparoscopic CCY provides more benefits than open CCY. A subsequent CCY policy is better than the wait-and-see policy theoretically. In our study, subsequent CCY can significantly decrease the RBE cases without affecting the RBE mortality compared to the no CCY within 2 months policy. In a previous systemic review or randomized control trial, comparisons between CCY and no further surgical treatment are relatively rare. But one randomized control trial showed non-significant differences in the laparoscopic CCY group and no further intervention group regarding RBEs [39] and overall mortality[40], which means non-operative management may be an option in specific patients. Our results indicate that having no CCY within 2 months after acute cholecystitis after PT-GBD increases further RBEs, but such a decision does not significantly affect the survival rate directly. There are similar results comparing the outcomes of laparoscopic CCY and PT-GBD in high-risk cholecystitis patients without significant differences in mortality rate[41].

GB rupture, CCI > 8, age older than 79 years-old, and subsequent CCY play important roles in RBE-free survival, but multivariate analysis showed that only subsequent CCY significantly influenced the RBE-free survival after those with acute cholecystitis underwent PT-GBD. Acute cholecystitis patients usually accepted risk evaluation by ASA-PS or CCI score after initial diagnosis, and the patients that underwent PT-GBD initially represent either those in older age or those with some severe underlying disease. Although the severity of underlying diseases is important to future outcomes, our result showed the most important factor of RBE-free survival was whether subsequent CCY was performed or not. Subsequent CCY should be planned after the clinical condition of patient improves if laparoscopic CCY was not performed right after acute cholecystitis was diagnosed. The method of CCY, either laparoscopic or open, had little protective effect if not performed as a subsequent CCY strategy.

There are limitations and some questions in our study. Although surgery is the standard of treatment for patients with gallbladder drainage, lots of patients in Taiwan refused further CCY because of old age and influence of traditional culture. That's why many cases in our study do not accept subsequent CCY even after PT-GBD treatment. Because this is a retrospective cohort study, the decision of surgical intervention, even subsequent CCY, is highly associated with current patient condition and experience of physicians. We noticed that patients were older, had higher CCI scores, and there was a higher proportion of dementia in the no CCY within 2 months group; this is an important selection bias. We believed this is the reason for significantly higher overall mortality in the no CCY within 2 months group rather than the influences of the differences of further RBEs. Meanwhile, RBE-free survival was chosen as an evaluation method that can balance RBE effect and mortality events due to invasive intervention. But the overall mortality rate is low in our analysis, and the RBE-free survival mainly reflects the reality of RBEs.

In conclusion, we found that subsequent CCY can decrease further RBEs and improve RBE-free survival in patients of acute cholecystitis who accepted PT-GBD initially.

Declarations

Competing interests statement:

All authors declare no potential financial and non-financial conflicts of interest.

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Author contributions statement:

Conceptualization, Chi-Chih Wang and Ming-Chang Tsai; Data curation, Yen-Pin Huang; Formal analysis, Tsung-Yu Tsai, Wen-Wei Sung and Tzu-Wei Yang; Funding acquisition, Hsu-Heng Yen; Investigation, Tzu-Wei Yang; Methodology, Chi-Chih Wang and Chun-Che Lin; Supervision, Chun-Che Lin and Hsu-Heng Yen; Validation, Ming-Chang Tsai, Tsung-Yu Tsai, Wen-Wei Sung and Jaw- Town Lin; Writing – original draft, Chi-Chih Wang; Writing – review & editing, Yen-Pin Huang and Wen-Hsin Huang.

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Tables

Table 1 Demographic data of patients underwent percutaneous transhepatic gallbladder drainage

Study group	Subsequent CCY within 2 months N=59		No CCY within 2 months, N=121		P value
	N	SD; %	N	SD; %	
Age (SD)	71.1	14.6	76.4	14.1	0.022
Gender					
Male	36	61.0%	75	62.0%	0.900
Female	23	39.0%	46	38.0%	
Follow up time (days)	354	234	370	215	0.645
Diagnosis tool					NA
CT	52	88.1%	96	79.3%	
MRI	1	1.7%	4	3.3%	
Sonography	6	10.2%	21	17.4%	
Disease severity					
Sepsis	12	20.3%	42	34.7%	0.048
Combined cholangitis	21	35.6%	35	28.9%	0.364
GB rupture	1	1.7%	6	5.0%	0.288
Lab data					
WBC	13462	6291	13608	5981	0.880
T/B (gm/dl)	2.4	2.2	2.6	2.6	0.736
Cr	1.4	1.6	1.5	1.6	0.743
CRP	15.0	10.1	11.9	9.8	0.151
Comorbidity					
CCI score	4.2	2.2	5.4	2.3	<0.001
MI	4	6.8%	11	9.1%	0.598
CHF	9	15.3%	28	23.1%	0.219
PVD	1	1.7%	3	2.5%	0.738
CVA	12	20.3%	23	19.0%	0.832
Dementia	1	1.7%	20	16.5%	0.004

Chronic pulmonary disease	1	1.7%	11	9.1%	0.062
Rheumatologic disease	0	0.0%	0	0.0%	N/A
Peptic ulcer disease	14	23.7%	27	22.3%	0.832
Mild liver disease	3	5.1%	6	5.0%	0.971
Diabetes	23	33.8%	45	37.2%	0.816
Diabetes with chronic complication	0	0.0%	3	2.5%	0.301
Hemiplegia or paraplegia	5	8.5%	4	44.4%	0.135
Renal disease	1	1.7%	9	7.4%	0.119
Malignancy ; including leukemia and lymphoma	0	0.0%	1	0.8%	0.672
Moderate or severe liver disease	3	17.6%	14	11.6%	0.163
Metastatic solid tumor	0	0.0%	5	4.1%	0.134
AIDS	0	0.0%	1	0.8%	0.672
Total CCY	59	100%	11	9.1%	<0.0001
Laparoscopic CCY proportion	56	94.9%	9	81.8 %	0.122
Open CCY proportion	3	5.1%	2	18.2 %	

SD= standard deviation, GB= gallbladder, CT= Computed Tomography, MRI= Magnetic resonance imaging, WBC= white blood cell, T/B= total bilirubin, Cr = creatinine, CRP= C reactive protein, CCI score= Charlson Comorbidity Index score, MI= Myocardial infarction, PVD= Peripheral vascular disease, CVA= cerebrovascular disease, AIDS= acquired immune deficiency syndrome, NA= Not Applicable

Table 2 Outcomes of patients underwent percutaneous transhepatic gallbladder drainage

Study group	Subsequent CCY within 2 months, N=59		No CCY within 2 months, N=121		P value
	N	Rang; %	N	Rang; %	
RBEs*	0	0-1	0	0-4	0.003
RBE case number	8	13.6%	39	32.2%	0.007
Overall mortality	3	5.1%	20	16.5%	0.031
RBE related mortality	1	1.7%	5	4.1%	0.392

CCY= cholecystectomy, SD= standard deviation, RBE= recurrent biliary event

*Median and range due to non-normal distribution

Table. 3 Univariate analysis of RBE-free survival according to the clinical parameters.

	N	HR	95%CI	p
Age (<79 vs ≥79)	89/91	1.682	1.014-2.790	0.044
Gender (F vs M)	69/111	1.421	0.868-2.325	0.162
Sepsis	126/54	1.085	0.640-1.842	0.762
Combined cholangitis	124/56	0.784	0.450-1.366	0.391
GB rupture	173/7	2.665	1.069-6.644	0.036
CCI score (≤5 vs >5)	112/68	1.238	0.755-2.031	0.397
CCI score (≤6 vs >6)	137/43	1.215	0.710-2.080	0.477
CCI score (≤7 vs >7)	154/26	1.723	0.952-3.117	0.072
CCI score (≤8 vs >8)	167/13	2.026	0.965-4.253	0.062
Any comorbidity ¹	91/89	1.008	0.617-1.646	0.975
Comorbidity ² (≤3 vs >3)	164/16	1.232	0.562-2.703	0.603
Comorbidity (≤2 vs >2)	143/37	1.101	0.617-1.965	0.746
Comorbidity (≤1 vs >1)	97/83	1.233	0.755-2.015	0.403
MI	165/15	0.847	0.340-2.111	0.721
CHF	143/37	0.932	0.497-1.747	0.826
PVD	176/4	1.329	0.325-5.444	0.692
CVA	154/35	0.986	0.535-1.814	0.963
Dementia	159/21	1.653	0.863-3.166	0.130
Chronic pulmonary disease	168/12	0.794	0.288-2.188	0.656
Rheumatologic disease	180/0	NA	NA	NA
Peptic ulcer disease	139/41	0.988	0.554-1.764	0.968
Mild to severe liver disease	154/26	1.509	0.820-2.775	0.186
Moderate or severe liver disease	163/17	1.316	0.627-2.763	0.468
Diabetes	112/68	1.209	0.736-1.987	0.453
Hemiplegia or paraplegia	171/9	0.045	0.001-4.611	0.189
Renal disease	170/10	1.331	0.534-3.318	0.539
Malignancy; including leukemia and lymphoma	179/1	4.344	0.595-31.717	NA
Metastatic solid tumor	168/12	0.925	0.336-2.547	0.881

AIDS	179/1	88.999	8.070-981.503	NA
Any CCY status	110/70	0.583	0.335-1.017	0.057
Subsequent CCY vs others	59/121	2.383	1.244-4.564	0.009
CCY (No vs Laparoscopic)	110/65	0.588	0.333-1.038	0.067
CCY (No vs Laparotomy)	110/5	0.509	0.070-3.699	0.505

RBE= recurrent biliary event, GB= gallbladder, WBC= white blood cell, T/B= total bilirubin, Cr = creatinine, CRP= C reactive protein, CCI score= Charlson Comorbidity Index score, MI= Myocardial infarction, PVD= Peripheral vascular disease, CVA= Cerebrovascular disease, AIDS= acquired immune deficiency syndrome, NA= Not Applicable

¹ Include any MI, CVA, COPD, CHF, liver disease (moderate to severe)

² Numbers of comorbidity within CCI score system

Table. 4 Multivariate analysis of RBE free survival according to the clinical parameters. (N=178)

	N	HR	95%CI	p
Age (<79 vs ≥79)	89/91	1.477	0.885-2.467	0.136
GB rupture	173/7	2.191	0.873-5.501	0.095
CCI score (≤8 vs >8)	167/13	1.616	0.763-3.425	0.210
No CCY within 2 months vs subsequent CCY	121/59	0.485	0.250-0.941	0.032

RBE= recurrent biliary event, GB= gallbladder, CCI score= Charlson Comorbidity Index score, CCY= cholecystectomy

Figures

Figure 1

CSMUH= Chung Shan Medical University Hospital (75), CCH= Changhua Christian Hospital (136)

Figure 1

Flow chart for case selection and study design CSMUH= Chung Shan Medical University Hospital, CCH= Changhua Christian Hospital, PTGBD= percutaneous transhepatic gallbladder drainage, CCY= cholecystectomy

Figure 2

Figure 2

Recurrent biliary event-free survival comparison between subsequent CCY group and no CCY within 2 months group RBE= recurrent biliary event, CCY= cholecystectomy