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Optimal Timing of Cholecystectomy in Secondary Choledocholithiasis Patients Who Underwent Preoperative Endoscopic Retrograde Cholangiopancreatography

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Abstract: Secondary choledocholithiasis occurs when stones leave the gallbladder. After therapeutic endoscopic retrograde cholangiopancreatography (ERCP) with stone removal, cholecystectomy should be performed to prevent recurrence. However, the optimal timing for cholecystectomy in secondary choledocholithiasis patients is unclear. The aim of this study was to determine the optimal timing for laparoscopic cholecystectomy in patients with secondary choledocholithiasis. In total, 22,996 patients in the Taiwan National Health Insurance Research Database (NHIRD) who underwent laparoscopic cholecystectomy for acute cholecystitis from 1998–2015 were divided into three groups according to whether they underwent surgery as an inpatient (early cholecystectomy (ELC)), within 2 months of admission (intermediate cholecystectomy (ILC)), or 2 months after admission (delayed cholecystectomy (DLC)). The primary outcomes included the recurrence, complication, and mortality rates. After adjusting for confounders, according to the 2013 Tokyo guidelines (cut-off at 2013), a subgroup analysis showed that, compared to the ELC group, the ILC group had lower recurrence, complication, and mortality rates, whereas the DLC group exhibited statistically significantly higher recurrence and mortality rates. In conclusion, the optimal timing of cholecystectomy in secondary choledocholithiasis patients after preoperative ERCP is within 2 months (ILC) after hospital admission. Moreover, ELC is associated with a measurable risk of complications.

Keywords: secondary choledocholithiasis; intermediate cholecystectomy; ERCP

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Citation: Ye, S.-L.; Hsu, S.-D.; Chien, W.-C.; Chung, C.-H. Optimal Timing of Cholecystectomy in Secondary Choledocholithiasis Patients Who Underwent Preoperative Endoscopic Retrograde Cholangiopancreatography. *Appl. Sci.* **2022**, *12*, 4574. https://doi.org/10.3390/app12094574

Academic Editor: Thomas Lindner

Received: 17 March 2022
Accepted: 29 April 2022
Published: 30 April 2022

1. Introduction

Choledocholithiasis is defined by the presence of stones within the common bile duct and occurs in up to approximately 20% of patients with cholelithiasis [1].

Therapeutic endoscopic retrograde cholangiopancreatography (ERCP) with stone removal followed by elective cholecystectomy or cholecystectomy with an intraoperative common duct exploration/postoperative ERCP are the treatment possibilities for the individuals who are at high risk for CBD stones [2]. Most of the treatment options for patients are determined by the local surgical and endoscopic expertise and the patient's preference [3].

ERCP is recognized as the first-line treatment of cholangitis to provide bile drainage after the appropriate management of sepsis and any other systemic complications [4]. In most US centers, when bile duct stones are present, ERCP is usually followed by a laparoscopic cholecystectomy [5].

In Taiwan, the present-day treatment of bile duct stones is endoscopic retrograde cholangiopancreatography (ERCP), or, in some cases, a laparoscopic cholecystectomy with a bile duct exploration.

Many studies have shown that the advantages of having surgery over not having surgery have been well established. Choledocholithiasis mostly results from gallstones passing through the cystic duct into the common bile duct. After the resolution of acute inflammation with the appropriate medical treatment and after internal drainage with therapeutic endoscopic retrograde cholangiopancreatography (ERCP) stone removal, a cholecystectomy should be performed to prevent recurrence [2,6–8].

However, the optimal timing of cholecystectomy in secondary choledocholithiasis patients has rarely been directly studied. There has been minimal previous evidence provided for this issue, and since blinding cannot be achieved in these comparisons and the outcomes have been subjective, all of the trials were deemed to be at a high risk of bias [9–11].

The Tokyo 2013 guidelines have proposed that the appropriate treatment of acute cholangitis should be performed in accordance with the severity grade, and a frequent reassessment with reclassification is indicated based on the response to the initial conservative medical treatment. The two most important aspects of treatment are biliary drainage and antimicrobial therapy. Acute cholecystitis can occur alongside acute cholangitis in some patients. The treatment strategy for patients with acute cholangitis and acute cholecystitis should be determined based on the severity of the disease, as well as the patient's surgical risk [12].

In this study, we attempted to employ a big data analysis of a health insurance database to investigate the most suitable surgical time for patients who underwent cholecystectomy following ERCP based on patients' disease severity and according to 2013 Tokyo guidelines (cut-off during the year 2013 after the announcement of the Tokyo guidelines in 2013) and further categorized the patients into early cholecystectomy (ELC), intermediate cholecystectomy (ILC), and delayed cholecystectomy (DLC) groups.

This study aimed to determine the optimal timing for laparoscopic cholecystectomy in patients with secondary choledocholithiasis.

2. Materials and Methods

This study was approved by the Institutional Review Board (IRB) of Tri-Service General Hospital, Taiwan. The IRB waived the need for informed consent for this retrospective study based on the NHIRD. All methods were performed in accordance with the relevant guidelines and regulations while under the surveillance of the IRB of Tri-Service General Hospital.

2.1. Study Design

This study is a population-based retrospective cohort study based on Taiwan's NHIRD, which covers more than 99% of the entire population [13]. The NHIRD has been described in detail in previous studies [14,15].

The patients with choledocholithiasis were selected from two million random samples from the NHIRD between 1998 and 2015 using the Codes of International Statistical Classification of Diseases and Related Health Problems, Ninth Edition (ICD-9) that were recorded during admission.

The acute cholangitis or choledocholithiasis patients were selected using ICD-9 574–576; a therapeutic ERCP was defined as an endoscopic retrograde cholangiopancreatography (ERCP; OP51.10), an endoscopic retrograde cholangiography (ERC; OP51.11), an endoscopic sphincterotomy, or an endoscopic papillary balloon dilatation (EST or EPBD; OP51.8) during the index admission from 1998 to 2015. The patients who previously underwent biliary surgery or biliary treatment (OP51.3) or who had biliary cancer (155.1 and 156) were excluded. The observation period that was selected was from January 1998 to December 2015.

A total of 104,053 patients with symptomatic choledocholithiasis who underwent therapeutic ERCP were selected from the nationwide population databases of two million random samples. We excluded patients who underwent gallbladder drainage or other gallbladder treatments, who had gallbladder cancer, and patients younger than 20 years of age. The recurrence, mortality, and complication rates were investigated.

This nationwide, population-based study on the timing of cholecystectomy (CCY) evaluated 22,996 patients who were newly undergoing therapeutic endoscopic retrograde cholangiopancreatography (ERCP) for choledocholithiasis, and the patients were obtained from the Taiwan National Health Insurance Research Database (NHIRD) between 1998 and 2015.

These patients were further divided into three major groups: early cholecystectomy (ELC, inpatient, performed within 7 days), intermediate laparoscopic cholecystectomy (ILC, performed between 7 days and two months after hospital admission), and delayed laparoscopic cholecystectomy (DLC, performed two months after hospital admission).

The details of this study's design are shown in Figure 1. Table 1 shows the age, sex, comorbidities, hospital classification, economic status, and living area conditions of the entire study population. The recurrence rate, mortality, complications and economic costs were compared between these three groups.

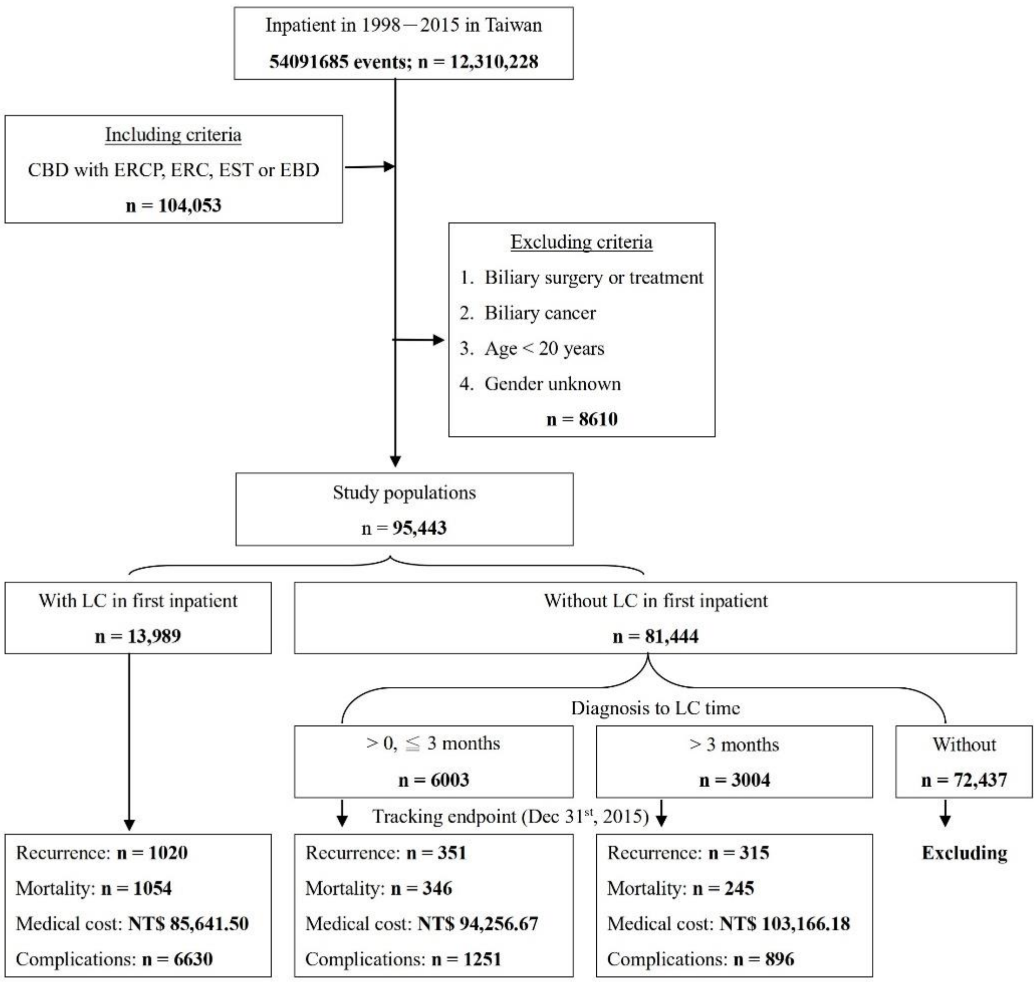

Figure 1. The flowchart of the study sample selection.

Table 1. Characteristics of the study.

Diagnosis to LC (Months)	Total		Group A: 0 (at the Same Time)		Group B: >0, ≤2		Group C: >2		p
Variable	*n*	%	*n*	%	*n*	%	*n*	%	
Total	22,996	62.18	13,989	60.83	5970	25.96	3037	13.21	
Gender									<0.001
Male	11,006	50.04	6484	46.35	2969	49.73	1553	76.24	
Female	10,990	49.96	7505	53.65	3001	50.27	484	23.76	
Age (years)	58.85 ± 16.29		58.19 ± 16.23		58.69 ± 16.59		62.22 ± 15.54		<0.001
IHD									0.876
Without	22,125	96.21	13,458	96.20	5749	96.30	2918	96.08	
With	871	3.79	531	3.80	221	3.70	119	3.92	
HCVD									0.004
Without	22,620	98.36	13,790	98.58	5858	98.12	2972	97.86	
With	376	1.64	199	1.42	112	1.88	65	2.14	
Stroke									0.032
Without	22,635	98.43	13,776	98.48	5886	98.59	2973	97.89	
With	361	1.57	213	1.52	84	1.41	64	2.11	
PUD									<0.001
Without	20,020	87.06	11,821	84.50	5432	90.99	2767	91.11	
With	2976	12.94	2168	15.50	538	9.01	270	8.89	
IBD									0.885
Without	22,991	99.98	13,986	99.98	5969	99.98	3036	99.97	
With	5	0.02	3	0.02	1	0.02	1	0.03	
DM									<0.001
Without	19,587	85.18	12,024	85.95	5072	84.96	2491	82.02	
With	3409	14.82	1965	14.05	898	15.04	546	17.98	
HF									0.025
Without	22,813	99.20	13,875	99.19	5935	99.41	3003	98.88	
With	183	0.80	114	0.81	35	0.59	34	1.12	
CKD									0.001
Without	22,844	99.34	13,907	99.41	5936	99.43	3001	98.81	
With	152	0.66	82	0.59	34	0.57	36	1.19	
Liver cirrhosis									<0.001
Without	21,640	94.10	13,048	93.27	5708	95.61	2884	94.96	
With	1356	5.90	941	6.73	262	4.39	153	5.04	
Pancreatitis									<0.001
Without	20,143	87.59	11,627	83.12	5631	94.32	2885	95.00	
With	2853	12.41	2362	16.88	339	5.68	152	5.00	
Recurrence									<0.001
Without	21,310	92.67	12,969	92.71	5621	94.15	2720	89.56	
With	1686	7.33	1020	7.29	349	5.85	317	10.44	
Mortality									<0.001
Without	21,351	92.85	12,935	92.47	5631	94.32	2785	91.70	
With	1645	7.15	1054	7.53	339	5.68	252	8.30	
Complications									<0.001
Without	14,219	61.83	7359	52.61	4749	79.55	2111	69.51	
With	8777	38.17	6630	47.39	1221	20.45	926	30.49	

p: Chi-square/Fisher exact tests were used to evaluate the categorical variables, and a one-way ANOVA with a Scheffé post hoc test was used to evaluate the continuous variables.

Recurrence in our study was defined as any admissions or emergency room (ER) visits that were associated with a diagnosis of cholelithiasis, choledocholithiasis, chol-ecystitis, cholangitis and pancreatitis.

The financial analysis of the admission and ER visits is complete in our national health insurance system data. The visits for recurrence, mortality, and complications were compared between these three groups by using data from Taiwan's national health insurance system.

2.2. Data Processing and Statistical Analysis

The National Health Insurance Research Database (NHIRD), with two million patients who are representative of the nationwide population between 1995 and 2015 in Taiwan, was processed using Microsoft SQL Server 2008 R2 (Microsoft Corporation, Redmond, WA, USA) with the SQL programming language. Statistical analysis was performed using OpenEpi: open-source epidemiological statistics for public health, version 3.01. A Kaplan–Meier survival analysis was performed using R version 3.4.3. The data obtained from the study were processed using chi-square ($\chi 2$) tests for categorical variables, one-way ANOVA (analysis of variance) for continuous variables, and log-rank (Mantel–Cox) tests for disease-free survival curves. A two-tailed *p*-value of 0.05 was considered statistically significant in this study.

3. Results

A total of 22,996 choledocholithiasis patients who underwent therapeutic ERCP were selected from the nationwide population databases of two million random samples. The data for 22,996 patients who underwent therapeutic ERCP, ERC, EST, and EBD for choledocholithiasis with cholecystectomy were collected. The mean age of the patients was 58.85 $\pm$ 16.29; 47.86% of the patients were male. In Taiwan, the medical evaluation systems are divided into medical centers, regional hospitals, and local hospitals. Of the patients in this study, 46.56% received medical treatment at medical centers, and 36.46% were living in cities. Further detailed information of the study population is shown in Table 1.

The timing of the operations was as follows: 60.83% of these patients had surgery as an inpatient, 25.96% had surgery within 2 months after admission, and 13.21% had surgery 2 months or more after admission. We tried to analyze the recurrence events and subsequent outcomes between the early cholecystectomy, intermediate cholecystectomy, and delayed cholecystectomy groups of patients.

In our analysis, 13,989 (60.83%) of the 22,996 patients underwent an early cholecystectomy, 5970 (25.96%) of the 22,996 patients underwent a cholecystectomy within 2 months of therapeutic ERCP, and only 3037 (13.21%) patients underwent a cholecystectomy after 2 months of therapeutic ERCP.

3.1. Comorbidity Profile

The age, sex, and other comorbidities were compared between the early cholecystectomy, intermediate cholecystectomy, and delayed cholecystectomy groups. The results showed significant differences in age, hypertension, hypertensive cardiovascular disease, stroke, peptic ulcer disease, diabetes, underlying congestive heart failure, chronic kidney disease, liver cirrhosis, and pancreatitis between the three groups of patients.

The oldest patients were found in the delayed cholecystectomy group, followed by the intermediate cholecystectomy group. The delayed cholecystectomy group had the highest proportion of patients with congestive heart failure and chronic kidney diseases, and the early cholecystectomy group had the second-highest proportions. The early cholecystectomy group had the highest proportions of patients with peptic ulcer disease, liver cirrhosis, and pancreatitis. The general conditions of the patients were worse in the delayed cholecystectomy group in our real-world study. All of the comorbidity profile comparison results are shown in Table 2.

3.2. Recurrence Rates

For the analysis of the recurrent biliary events, the recurrent biliary events were also divided into three time periods after the index admission: inpatient, within two months, and after two months.

The results showed that patients with comorbidities had a significantly increased risk of recurrent biliary events, particularly diabetes (95% CI 0.716–0.951), liver cirrhosis (95% CI 0.594–0.991), and pancreatitis (95% CI 0.725–0.991).

Table 2. Factors associated with the outcomes after using Cox regression, linear regression, and logistic regression.

Variable	Recurrence				Mortality				Complications			
	Adjusted HR	**95% CI**	**95% CI**	***p***	**Adjusted HR**	**95% CI**	**95% CI**	***p***	**Adjusted OR**	**95% CI**	**95% CI**	***p***
Diagnosis to LC (months)												
0	Reference				Reference				Reference			
>0, ≤2	0.967	0.855	1.094	0.596	1.116	0.985	1.265	0.085	0.296	0.275	0.318	<0.001
>2	1.704	1.498	1.939	<0.001	1.511	1.313	1.739	<0.001	0.487	0.446	0.513	<0.001
Gender												
Male	1.153	1.047	1.269	0.004	1.500	1.359	1.654	<0.001	1.079	1.021	1.142	<0.001
Female	Reference				Reference				Reference			
Age group (years)	0.999	0.996	1.003	0.719	1.030	1.026	1.034	<0.001	1.010	1.009	1.012	0.008
HTN												
Without	Reference				Reference				Reference			
With	1.090	0.963	1.233	0.171	1.292	1.147	1.455	<0.001	0.882	0.820	0.949	0.001
IHD												
Without	Reference				Reference				Reference			
With	0.975	0.778	1.222	0.824	0.810	0.651	1.007	0.057	1.200	1.039	1.387	0.013
HCVD												
Without	Reference				Reference				Reference			
With	0.890	0.617	1.283	0.533	1.148	0.844	1.562	0.378	0.645	0.513	0.812	<0.001
Stroke												
Without	Reference				Reference				Reference			
With	1.106	0.777	1.574	0.577	1.921	1.473	2.506	<0.001	1.063	0.851	1.328	0.589
PUD												
Without	Reference				Reference				Reference			
With	0.964	0.833	1.116	0.624	1.195	1.043	1.370	0.010	1.843	1.699	1.999	<0.001
IBD												
Without	Reference				Reference				Reference			
With	0.000	-	-	0.858	0.000	-	-	0.916	0.000	-	-	0.999
DM												
Without	Reference				Reference				Reference			
With	0.825	0.716	0.951	0.008	1.303	1.153	1.472	<0.001	1.216	1.121	1.319	<0.001
HF												
Without	Reference				Reference				Reference			
With	0.861	0.498	1.489	0.593	2.739	2.023	3.710	<0.001	1.861	1.364	2.540	<0.001
CKD												
Without	Reference				Reference				Reference			
With	1.077	0.623	1.861	0.791	2.138	1.477	3.093	<0.001	2.889	2.044	4.084	<0.001
Liver cirrhosis												
Without	Reference				Reference				Reference			
With	0.735	0.594	0.991	0.005	1.286	1.092	1.516	0.003	1.338	1.192	1.503	<0.001
Pancreatitis												
Without	Reference				Reference				Reference			
With	0.848	0.725	0.991	0.038	1.044	0.903	1.207	0.562	1.240	1.141	1.347	<0.001

The location had multicollinearity with the urbanization level. The dependent variable of medical cost after using a logarithmic transformation to fit the data into a normal distribution. Adjusted HR, adjusted hazard ratio: the adjusted variables are listed in the table after the Cox regression; Adjusted OR, adjusted odds ratio: the adjusted variables are listed in the table after the logistic regression, and the Nagelkerke R-square value was 0.130; adjusted RR, adjusted relative risk: the adjusted variables are listed in the table after the linear regression, and the R-square was 0.181; CI, confidence interval.

There were no significant differences ($p = 0.596$) in the recurrent biliary event rates between the early cholecystectomy group and intermediate cholecystectomy group (aHR: 0.967, 95% CI: 0.855–1.094); however, there were significant differences ($p \leq 0.001$) between the early cholecystectomy group and delayed cholecystectomy group (aHR: 1.704, 95% CI: 1.498–1.939) in the multivariable analysis. The recurrent biliary event-free survival was analyzed with Kaplan–Meier statistics, as shown in Figure 2.

In our subgroup analysis, as shown in Table 3, from 1998–2013 and by the time of the announcement of the 2013 Tokyo guidelines, 19,686 choledocholithiasis patients who underwent therapeutic ERCP were selected from the nationwide population databases.

These patients were also further divided into 4,894 (24.86%) intermediate cholecystectomies, 2,365 (12.01%) delayed cholecystectomies, and 12,427 (62.13%) early cholecystectomies.

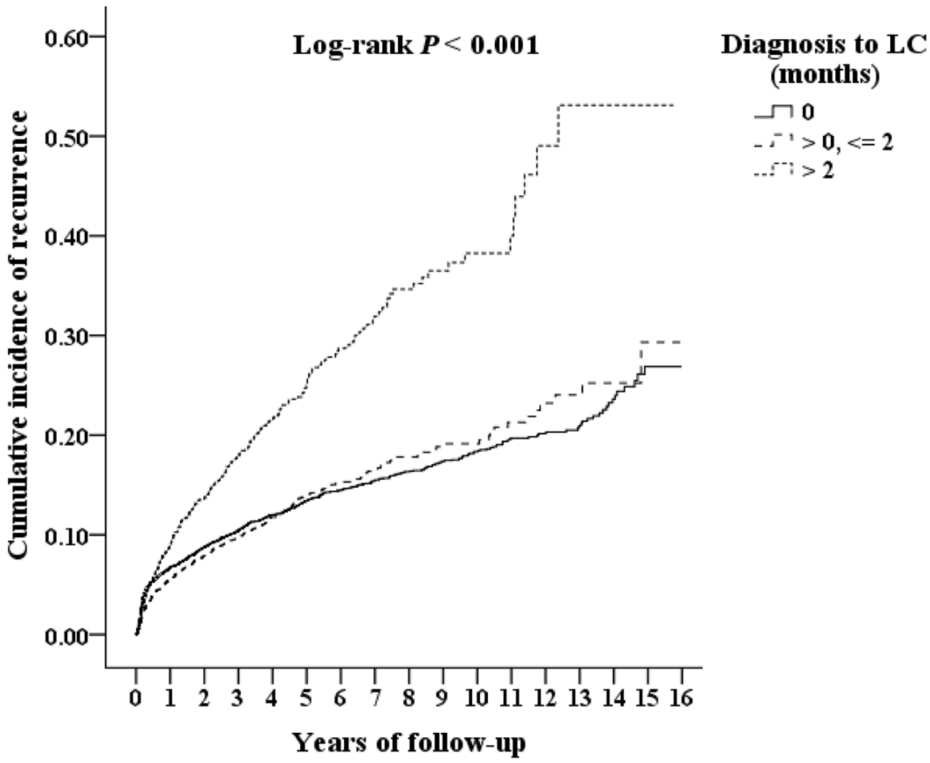

Figure 2. Kaplan–Meier for cumulative incidence of recurrence aged 20 and over stratified by diagnosis to LC months with log-rank test.

Table 3. Characteristics of the study.

Variable	Total		1998–2013		2014–2015		*p*
	n	%	*n*	%	*n*	%	
Total	22,996	53.88	19,686	85.61	3310	14.39	
Diagnosis to LC (months)							<0.001
Group A: 0 (at the same time)	13,989	60.83	12,427	63.13	1562	47.19	
Group B: >0, ≤2	5970	25.96	4894	24.86	1076	32.51	
Group C: >2	3037	13.21	2365	12.01	672	20.30	
Gender							<0.001
Male	11,006	47.86	9282	47.15	1724	52.08	
Female	11,990	52.14	10,404	52.85	1586	47.92	
Age (years)	58.85 ± 16.29		58.29 ± 16.18		62.19 ± 16.55		<0.001
Recurrence							0.012
Without	21,310	92.67	18,208	92.49	3102	93.72	
With	1686	7.33	1478	7.51	208	6.28	
Mortality							<0.001
Without	21,351	92.85	18,110	91.99	3241	97.92	
With	1645	7.15	1576	8.01	69	2.08	
Complications							0.562
Without	14,219	61.83	12,157	61.75	2062	62.30	
With	8777	38.17	7529	38.25	1248	37.70	

p: Chi-square/Fisher exact tests were used to evaluate the categorical variables, and a one-way ANOVA with a Scheffé post hoc test was used to evaluate the continuous variables.

We compared the recurrence rates between the early cholecystectomy group and the other two groups. All of the comparison results are shown in Table 4. There were no significant differences ($p = 0.582$) in the recurrent biliary event rates between the intermediate cholecystectomy group and the intermediate cholecystectomy group (aHR 0.963, 95% CI 0.843–1.100). There were significant differences ($p \leq 0.001$) in the recurrent biliary event rates between the delayed cholecystectomy groups (aHR 1.769, 95% CI 1.540–2.031).

Table 4. Factors associated with the outcomes in the different study periods after using Cox regression, linear regression, and logistic regression.

	Outcome	**Recurrence**				**Mortality**				**Complications**			
Year	**Variable**	**Adjusted HR**	**95% CI**	**95% CI**	***p***	**Adjusted HR**	**95% CI**	**95% CI**	***p***	**Adjusted OR**	**95% CI**	**95% CI**	***p***
Overall	Diagnosis to LC (months)												
	0	Reference				Reference				Reference			
	>0, ≤2	0.967	0.855	1.094	0.596	1.116	0.985	1.265	0.085	0.296	0.275	0.318	<0.001
	>2	1.704	1.498	1.939	<0.001	1.511	1.313	1.739	<0.001	0.487	0.446	0.513	<0.001
1998–2013	Diagnosis to LC (months)												
	0	Reference				Reference				Reference			
	>0, ≤2	0.963	0.843	1.100	0.582	1.116	0.982	1.269	0.093	0.305	0.281	0.330	<0.001
	>2	1.769	1.540	2.031	<0.001	1.508	1.304	1.743	<0.001	0.504	0.457	0.555	<0.001
2014–2015	Diagnosis to LC (months)												
	0	Reference				Reference				Reference			
	>0, ≤2	0.813	0.579	1.143	0.234	0.983	0.546	1.770	0.955	0.243	0.202	0.293	<0.001
	>2	1.024	0.717	1.461	0.897	1.209	0.668	2.187	0.531	0.387	0.317	0.473	<0.001

The location had a multicollinearity with the urbanization level. The dependent variable of medical cost after using a logarithmic transformation to fit the data into a normal distribution. Adjusted HR, adjusted hazard ratio: the adjusted variables are listed in the table after the Cox regression; Adjusted OR, adjusted odds ratio: the adjusted variables are listed in the table after the logistic regression, and the Nagelkerke R-square values were 0.130 (overall), 0.124 (1998–2013), and 0.182 (2014–2015), respectively; Adjusted RR, adjusted relative risk: the adjusted variables are listed in the table after the linear regression, and the R-square values were 0.181 (overall), 0.179 (1998–2013), and 0.194 (2014–2015), respectively; CI, confidence interval.

For the 2014–2015 subgroup, 3310 choledocholithiasis patients who underwent therapeutic ERCP were also further divided: 1076 patients (32.51%) in the intermediate cholecystectomy group, 672 (20.30%) patients in the delayed cholecystectomy group, and 1562 (47.19%) patients in the early cholecystectomy group.

We compared the recurrence rates between the early cholecystectomy group and the other two groups. There were no significant differences ($p = 0.234$) in the recurrent biliary event rates in the intermediate cholecystectomy group (aHR 0.813, 95% CI 0.579–1.143), and there were no significant differences ($p = 0.897$) in the recurrent biliary event rates in the delayed cholecystectomy group (aHR 0.897, 95% CI 0.717–1.461).

3.3. Complications

There were 6630 compilations that occurred in 13,989 early cholecystectomy patients, 1221 compilations that occurred in 5970 intermediate cholecystectomy patients, and 926 compilations that occurred in 3037 delayed cholecystectomy patients.

The complication rates were 47.93% in the early cholecystectomy group, 20.45% in the intermediate cholecystectomy group, and 30.49% in the delayed cholecystectomy group. There were significant differences ($p \leq 0.001$) between the three complication rates in the three groups.

The complication rates were compared between the early cholecystectomy group and the other two groups. There were significant differences ($p \leq 0.001$) in the complication rates between the intermediate cholecystectomy group and the intermediate cholecystectomy group (aHR 0.296, 95% CI 0.275–0.318). There were significant differences ($p \leq 0.001$) in the complication rates of the delayed cholecystectomy group (aHR 0.487, 95% CI 0.446–0.513) in the multivariable analysis.

For the 1998–2013 or 2014–2015 subgroups, the complication rates were significantly different between the early cholecystectomy group and the other two groups, and there were also significant differences ($p \leq 0.001$) in the complication rates between the intermediate cholecystectomy group and the delayed cholecystectomy group.

3.4. Mortality

The mortality rate was 7.53% in the 13,989 patients who had an early cholecystectomy, 5.68% in the 5,970 patients who had an intermediate cholecystectomy, and 8.3% in the 3037 patients who had a delayed cholecystectomy. There were significant differences ($p \leq 0.001$) in the rates of the recurrent biliary events between these three groups.

Comparison of the mortality rates between the early cholecystectomy group and the other two groups showed that there were no significant differences ($p = 0.085$) in the mortality rates in the intermediate cholecystectomy group (aHR 1.116, 95% CI 0.985–1.265). There were significant differences ($p \leq 0.001$) between the mortality rates in the delayed cholecystectomy group (aHR 1.511, 95% CI 1.313–1.739).

In our subgroup analysis of the time before the announcement of the Tokyo guidelines, with total 19,686 choledocholithiasis patients in 1998–2013, we made a comparison of the mortality rates between the early cholecystectomy group and the other two groups. There were also no significant differences ($p = 0.093$) in the mortality rates in the intermediate cholecystectomy group compared to the other two groups (aHR 1.116, 95% CI 0.982–1.269). There were significant differences ($p \leq 0.001$) between the mortality rates in the delayed cholecystectomy group compared to the other two groups (aHR 1.508, 95% CI 1.304–1.743). These results are consistent with the raw data analysis.

For the 2014–2015 subgroup analysis, which included 3310 choledocholithiasis patients, the mortality rate was compared between the early cholecystectomy group and the other two groups. There were no significant differences ($p = 0.955$) in the mortality rates between the intermediate cholecystectomy group (aHR 0.983, 95% CI 0.546–1.770) and the delayed cholecystectomy group (aHR 1.209, 95% CI 0.668–2.187).

4. Discussion

In our study, the data were collected from patients (with or without acute cholecystitis) who underwent therapeutic ERCP for choledocholithiasis. We found that the subgroup analysis (conducted after the publication of the Tokyo guidelines cut-off at the end of 2013) showed that the proportion of inpatients who had a cholecystectomy during the same hospitalization (defined as the early cholecystectomy group) had decreased from 63.13% to 47.19%. The percentage of patients who had an intermediate cholecystectomy had increased from 24.86% to 32.51%. In the delayed cholecystectomy group, the rate had increased from 12.01% to 20.3%. Since the 2013 Tokyo guidelines for the surgical treatment of acute cholecystitis advocated a different approach, depending on the grade of severity, new diagnostic criteria and surgical indications for surgeons have been established [12].

Laparoscopy-related complications such as bile duct injury (including biloma, bile peritonitis, sepsis, multiple organ dysfunction syndrome, external biliary fistula, cholangitis, liver abscess, and others) are often associated with concomitant vascular injury [16,17] or even haemobilia, in some rare cases [18]. We discovered that the intermediate cholecystectomy group was associated with significantly fewer complications than the early cholecystectomy group. In the 1998–2013 subgroup, both the intermediate and delayed cholecystectomy groups had lower complication rates than the early cholecystectomy group; this reveals that there was a greater improvement in the 2013–2015 subgroup, which is consistent with the evidence from the 2013 Tokyo guidelines, which had previously given suggestions regarding the severity assessment of acute cholecystitis patients with or without cholangitis.

We also noticed that after analyzing the group of intermediate cholecystectomy patients in the original data from 1998–2015, the recurrence rates and mortality rates in the 1998–2013 subgroup and in the 2014–2015 group were found to be statistically insignificant compared to the early cholecystectomy group. However, a lower complication rate was found in the cohort compared to the early cholecystectomy group in the original data from 1998–2015 (aHR 0.296, 95% CI 0.275–0.318, $p \leq 0.001$) and the 1998–2013 subgroup (aHR 0.305, 95% CI 0.281–0.330, $p \leq 0.001$), and the same phenomenon was found to be even more pronounced in the 2014–2015 subgroup (aHR 0.243, 95% CI 0.202–0.293, $p \leq 0.001$).

Aspects of the analysis of the delayed cholecystectomy group revealed that, in the raw data from 1998–2015 (aHR 1.704, 95% CI 1.498–1.939, $p \leq 0.001$) and in the 1998–2013 subgroup (aHR 1.769, 95% CI 1.540–2.031, $p \leq 0.001$), the recurrence rate was higher compared to the early cholecystectomy group. However, according to the cut-off year when the 2013 Tokyo guidelines were published, no significant difference in the recurrence rates was found for the delayed cholecystectomy group after 2014–2015 (aHR 1.024, 95% CI 0.717–1.461, $p = 0.897$).

A higher mortality rate of the patients who had a delayed cholecystectomy was found in the raw data from 1998–2015 (aHR 1.511, 95% CI 1.313–1.739, $p \leq 0.001$) and in the 1998–2013 subgroup (aHR 1.508, 95% CI 1.304–1.743, $p \leq 0.001$) compared to the patients who had an early cholecystectomy. No significant difference in the mortality rates was found for the delayed cholecystectomy group after 2014–2015 (aHR 1.209, 95% CI 0.668–2.187, $p = 0.531$). Nevertheless, a lower complication rate was also found in the cohort compared to the early cholecystectomy group in the original data from 1998–2015, the 1998–2013 subgroup, and the 2014–2015 subgroup.

This could be due to a variety of factors. First, the recurrence rates may have decreased as a result of increased surgical expertise, the improvements in the quality of ERCP, as well as various endoscopic techniques [8]. Therefore, we can see that both of the intermediate cholecystectomy and delayed cholecystectomy groups showed decreasing trends in the recurrence rates. Second, prior to 2013, the majority of the patients who had a delayed cholecystectomy had a higher surgical risk and more comorbidities, as well as a higher mortality rate. After 2013, however, the surgeons followed the 2013 Tokyo guidelines, which suggested that patients should generally undergo surgery after their condition had improved following internal drainage. By delaying the surgical time in the patients who were previously at a lower surgical risk, the mortality rate of delayed cholecystectomy has improved.

In most prospective studies, early laparoscopic cholecystectomy was shown to be safe and effective and was shown to provide a better quality of life than initially having conservative treatment followed by delayed surgery [19–21]. It appears likely that ELC is superior to either ILC or DLC, and ELC is strongly recommended. If ELC cannot be performed (because adequate surgical expertise is not available), DLC appears to be superior to ILC [9]. Several trials have advocated the performance of laparoscopic cholecystectomy within 3 days after ERCP [20,21]. However, evidence of moderate quality has been found, mainly because of the lack of blinding in the trials. Furthermore, there is no evidence of a difference between DLC and ILC, and the ACDC trial comparing ELC versus ILC showed that a significant proportion of patients undergoing ILC developed serious adverse events [22]. Our results, on the other hand, demonstrate the opposite outcome. The recurrence rate and the mortality rate were found to be statistically insignificant compared to early cholecystectomy. We found that the intermediate cholecystectomy after ERCP group, with recurrence and mortality rates equivalent to those of the early cholecystectomy group, had a lower complication rate. It appears likely that ILC is superior to either ELC or DLC, and DLC appears to be superior to ELC.

The primary reason for this could be that these studies focused on acute cholecystitis rather than focusing on patients with secondary choledocholithiasis. The optimal timing of the cholecystectomy in secondary choledocholithiasis patients has rarely been directly studied to date.

After reviewing the development of laparoscopic cholecystectomy, it is obvious that the earlier concerns about the development of fibrosis in Calot's triangle following the resolution of the initial bout of inflammation after acute cholecystitis have been considered the main causal factor for a technically difficult surgery, and the development of fibrosis is associated with a higher risk of bile duct injury [4]. However, when simply analyzing the definition of acute obstructive cholangitis, which is characterized by a complete obstruction of the common bile duct with the accumulation of purulent material under pressure, the obstruction is most commonly due to calculi in the common bile duct, and strictures, neoplasms, pancreatitis, and parasites may also be other provoking agents [23]. All of the obstructions in our study were due to calculi only. In other words, if the condition is due to isolated cholangitis and when the inflammation is improved by internal drainage, ELC may not be the appropriate timing for cholecystectomy, as described in the literature. In our analysis, ILC is a superior alternative.

In comparison with the existing literature, our study is characterized by a large sample size and revealed differences between early, intermediate, and delayed cholecystectomy while using an improved patient characterization, including comorbidities and standardized methods for the evaluation of patient parameters, and by a precise subgroup analysis. From our study results, it is obvious that the best time to perform a laparoscopic cholecystectomy in individuals who undergo therapeutic ERCP for choledocholithiasis should be ILC (within 2 months after admission). ELC is associated with a measurable risk of complications.

Limitations

On the basis of the study design, three potential limitations must be taken into account.

As stated in the 2013 Tokyo guidelines, patients with acute cholangitis sometimes also suffer simultaneously with acute cholecystitis. A treatment strategy for patients with both acute cholangitis and cholecystitis should be determined after considering disease severity and the patient's surgical risk [12]. The associated common bile duct stones, the identification of "high-risk" patients, the surgical timing, and the type of treatment, including the surgical procedure, should all be evaluated [9].

Secondly, due to the fact that this was a retrospective study, the national insurance companies' databases may be biased due to the need to enter requests for diagnosis reimbursement. Therefore, an overrepresentation of information may have occurred.

Several systems have been developed to risk-stratify patients with the goals of determining the need and candidacy for a cholecystectomy. As examples, the 2018 Tokyo guidelines classify patients into grade I (mild), II (moderate), or III (severe) cholecystitis; the American Association of Surgery of Trauma (AAST) system grades patients from I to V. However, because the health insurance database only has the characteristics of a large database, it was not possible to separately classify and risk-stratify the patients who chose to undergo surgery at different time points. The recurrence rates and mortality rates can be analyzed after the risk stratification. We expect that future papers will use more sophisticated experimental designs or methods to examine the recurrence rates and mortality rates in a hierarchical manner after risk stratification.

5. Conclusions

In conclusion, the optimal timing of cholecystectomy in secondary choledocholithiasis patients who underwent preoperative ERCP is within 2 months after hospital admission; this is associated with recurrence and mortality rates that are equivalent to the early cholecystectomy group. There are statistically significant advantages in terms of postoperative complications compared with early cholecystectomy.

Author Contributions: Conceptualization, S.-D.H.; methodology, S.-D.H.; software, W.-C.C.; validation, W.-C.C. and C.-H.C.; formal analysis, W.-C.C. and C.-H.C.; investigation, W.-C.C. and C.-H.C.; resources, W.-C.C. and C.-H.C.; data curation, W.-C.C. and C.-H.C.; writing—original draft preparation, S.-L.Y.; writing—review and editing, S.-D.H. and S.-L.Y.; visualization, S.-D.H. and

S.-L.Y.; supervision, S.-D.H.; project administration, S.-D.H. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board (or Ethics Committee) of TSGH (protocol code: B-111-12; date of approval: 1 March 2022).

Informed Consent Statement: Patient consent was waived as all of the participants were de-identified.

Data Availability Statement: All of the data are included in the manuscript.

Acknowledgments: Andy Brandt, Ph.D. Research Communication Partner.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Molvar, C.; Glaenzer, B. Choledocholithiasis: Evaluation, treatment, and outcomes. *Semin. Intervent. Radiol.* **2016**, *33*, 268–276. [CrossRef] [PubMed]
2. Cianci, P.; Restini, E. Management of cholelithiasis with choledocholithiasis: Endoscopic and surgical approaches. *World J. Gastroenterol.* **2021**, *27*, 4536–4554. [CrossRef] [PubMed]
3. Buxbaum, J.L.; Abbas Fehmi, S.M.; Sultan, S.; Fishman, D.S.; Qumseya, B.J.; Cortessis, V.K.; Schilperoort, H.; Kysh, L.; Matsuoka, L.; Yachimski, P.; et al. ASGE guideline on the role of endoscopy in the evaluation and management of choledocholithiasis. *Gastrointest. Endosc.* **2019**, *89*, 1075–1105.e15. [CrossRef] [PubMed]
4. Garancini, M.; Redaelli, A.; Dinelli, M.; Leni, D.; Fior, D.; Giardini, V. Updates in the management of cholecystitis, cholangitis, and obstructive jaundice. In *Operative Techniques and Recent Advances in Acute Care and Emergency Surgery*; Aseni, P., De Carlis, L., Mazzola, A., Grande, A.M., Eds.; Springer International Publishing: Cham, Switzerland, 2019; pp. 455–468.
5. McNicoll, C.F.; Pastorino, A.; Farooq, U.; St Hill, C.R. *Choledocholithiasis*; StatPearls Publishing: Treasure Island, FL, USA, 2021.
6. Boerma, D.; Rauws, E.A.J.; Keulemans, Y.C.A.; Janssen, I.M.C.; Bolwerk, C.J.M.; Timmer, R.; Boerma, E.J.; Obertop, H.; Huibregtse, K.; Gouma, D.J. Wait-and-see policy or laparoscopic cholecystectomy after endoscopic sphincterotomy for bile-duct stones: A randomised trial. *Lancet* **2002**, *360*, 761–765. [CrossRef]
7. Lau, J.Y.; Leow, C.K.; Fung, T.M.; Suen, B.-Y.; Yu, L.-M.; Lai, P.B.; Lam, Y.-H.; Ng, E.K.; Lau, W.Y.; Chung, S.S.; et al. Cholecystectomy or gallbladder in situ after endoscopic sphincterotomy and bile duct stone removal in Chinese patients. *Gastroenterology* **2006**, *130*, 96–103. [CrossRef]
8. Wang, C.C.; Tsai, M.C.; Wang, Y.T.; Yang, T.W.; Chen, H.Y.; Sung, W.W.; Huang, S.M.; Tseng, M.H.; Lin, C.C. Role of cholecystectomy in choledocholithiasis patients underwent endoscopic retrograde cholangiopancreatography. *Sci. Rep.* **2019**, *9*, 2168. [CrossRef]
9. Pisano, M.; Allievi, N.; Gurusamy, K.; Borzellino, G.; Cimbanassi, S.; Boerna, D.; Coccolini, F.; Tufo, A.; Di Martino, M.; Leung, J.; et al. 2020 World Society of Emergency Surgery updated guidelines for the diagnosis and treatment of acute calculus cholecystitis. *World J. Emerg. Surg.* **2020**, *15*, 61. [CrossRef]
10. Mann, K.; Belgaumkar, A.P.; Singh, S. Post-endoscopic retrograde cholangiography laparoscopic cholecystectomy: Challenging but safe. *JSLS* **2013**, *17*, 371–375. [CrossRef]
11. Schiphorst, A.H.; Besselink, M.G.; Boerma, D.; Timmer, R.; Wiezer, M.J.; van Erpecum, K.J.; Broeders, I.A.M.J.; van Ramshorst, B. Timing of cholecystectomy after endoscopic sphincterotomy for common bile duct stones. *Surg. Endosc.* **2008**, *22*, 2046–2050. [CrossRef]
12. Miura, F.; Takada, T.; Strasberg, S.M.; Solomkin, J.S.; Pitt, H.A.; Gouma, D.J.; Garden, O.J.; Büchler, M.W.; Yoshida, M.; Mayumi, T.; et al. TG13 flowchart for the management of acute cholangitis and cholecystitis. *J. Hepatobiliary Pancreat. Sci.* **2013**, *20*, 47–54. [CrossRef]
13. Cheng, T.M. Taiwan's new national health insurance program: Genesis and experience so far. *Health Aff.* **2003**, *22*, 61–76. [CrossRef] [PubMed]
14. Wu, C.Y.; Kuo, K.N.; Wu, M.S.; Chen, Y.J.; Wang, C.B.; Lin, J.T. Early Helicobacter pylori eradication decreases risk of gastric cancer in patients with peptic ulcer disease. *Gastroenterology* **2009**, *137*, 1641–1648.e2. [CrossRef] [PubMed]
15. Wu, C.Y.; Chan, F.K.; Wu, M.S.; Kuo, K.N.; Wang, C.B.; Tsao, C.R.; Lin, J.T. Histamine2-receptor antagonists are an alternative to proton pump inhibitor in patients receiving clopidogrel. *Gastroenterology* **2010**, *139*, 1165–1171. [CrossRef] [PubMed]
16. Strasberg, S.M.; Helton, W.S. An analytical review of vasculobiliary injury in laparoscopic and open cholecystectomy. *HPB* **2011**, *13*, 1–14. [CrossRef] [PubMed]
17. Machado, N.O. Biliary complications postlaparoscopic cholecystectomy: Mechanism, preventive measures, and approach to management: A review. *Diagn. Ther. Endosc.* **2011**, *2011*, 967017. [CrossRef] [PubMed]
18. Romano, L.; Lazzarin, G.; Varrassi, M.; Di Sibio, A.; Vicentini, V.; Schietroma, M.; Carlei, F.; Giuliani, A. Haemobilia secondary to a cystic artery pseudoaneurysm as complication of VLC. *Acta Biomed.* **2021**, *92*, e2021125. [CrossRef] [PubMed]

19. Wilson, E.; Gurusamy, K.; Gluud, C.; Davidson, B.R. Cost-utility and value-of-information analysis of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Br. J. Surg.* **2010**, *97*, 210–219. [CrossRef] [PubMed]
20. Friis, J.P.C.; Rothman, J.; Burcharth, J. Rosenberg Optimal timing for laparoscopic cholecystectomy after endoscopic retrograde cholangiopancreatography: A systematic review. *Scand J. Surg.* **2018**, *107*, 99–106. [CrossRef]
21. Reinders, J.S.; Goud, A.; Timmer, R.; Kruyt, P.M.; Witteman, B.J.M.; Smakman, N.; Breumelhof, R.; Donkervoort, S.C.; Jansen, J.M.; Heisterkamp, J.; et al. Early laparoscopic cholecystectomy improves outcomes after endoscopic sphincterotomy for choledochocystolithiasis. *Gastroenterology.* **2010**, *138*, 2315–2320. [CrossRef]
22. Gutt, C.N.; Encke, J.; Köninger, J.; Harnoss, J.C.; Weigand, K.; Kipfmüller, K.; Schunter, O.; Götze, T.; Golling, M.T.; Menges, M.; et al. Acute cholecystitis: Early versus delayed cholecystectomy, a multicenter randomized trial (ACDC study, NCT00447304). *Ann. Surg.* **2013**, *258*, 385–393. [CrossRef]
23. Reynolds, B.M.; Dargan, E.L. Acute obstructive cholangitis; a distinct clinical syndrome. *Ann. Surg.* **1959**, *150*, 299–303. [CrossRef] [PubMed]