Retrospective Cohort Study

Cholecystectomy reduces subsequent cholangiocarcinoma risk in choledocholithiasis patients undergoing endoscopic intervention

Chi-Chih Wang, Ming-Hseng Tseng, Sheng-Wen Wu, Tzu-Wei Yang, Hsuan-Yi Chen, Wen-Wei Sung, Chang-Cheng Su, Yao-Tung Wang, Chun-Che Lin, Ming-Chang Tsai

ORCID number: Chi-Chih Wang 0000-0002-8222-0503; Ming-Hseng Tseng 0000-0001-8868-1610; Sheng-Wen Wu 0000-0002-0305-8078; Tzu-Wei Yang 0000-0002-1522-8177; Hsuan-Yi Chen 0000-0003-1001-7968; Wen-Wei Sung 0000-0002-2375-0029; Chang-Cheng Su 0000-0002-7211-4192; Yao-Tung Wang 0000-0002-0300-0896; Chun-Che Lin 0000-0002-2474-6734; Ming-Chang Tsai 0000-0002-7687-2329.

Author contributions: Wang CC and Tsai MC contributed to study conception and design; Tseng MH and Wu SW contributed to acquisition of the data; Wang CC, Wang YT, and Wu SW contributed to analysis and interpretation of the data; Wang CC, Yang TW, and Chen HY contributed to drafting of the manuscript; Tsai MC, Yang TW, Sung WW, and Lin CC contributed to critical revision of the manuscript; Tseng MH, Tsai MC, and Su CC contributed to statistical analysis; Tsai MC contributed to supervision.

Supported by Chung Shan Medical University Hospital Research program, No. CSH-2013-C-032.

Institutional review board statement: This study was approved by the Institutional Review Board (IRB) of Chung Shan Medical University Hospital.

Chi-Chih Wang, Tzu-Wei Yang, Hsuan-Yi Chen, Chang-Cheng Su, Ming-Chang Tsai, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Chung Shan Medical University Hospital, and Institute of Medicine, School of Medicine, Chung Shan Medical University, Taichung 40201, Taiwan

Ming-Hseng Tseng, Department of Medical Informatics, Chung Shan Medical University, Taichung 402, Taiwan

Sheng-Wen Wu, Department of Internal Medicine, Chung Shan Medical University Hospital and School of Medicine, Chung Shan Medical University, Taichung 402, Taiwan

Wen-Wei Sung, Department of Urology, Chung Shan Medical University Hospital, and Institute of Medicine, School of Medicine, Chung Shan Medical University, Taichung 40201, Taiwan

Yao-Tung Wang, Division of Pulmonary Medicine, Chung Shan Medical University Hospital, and Institute of Medicine, School of Medicine, Chung Shan Medical University, Taichung 402, Taiwan

Chun-Che Lin, Department of Internal Medicine, China Medical University Hospital and School of Medicine, China Medical University, Taichung 402, Taiwan

Corresponding author: Ming-Chang Tsai, MD, PhD, Assistant Professor, Doctor, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Chung Shan Medical University Hospital, No. 110, Sec. 1, Juanguo N. Road, South District, Taichung 402, Taiwan. tsaimc1110@gmail.com

Abstract

BACKGROUND
Cholangiocarcinoma is a disease with a high mortality rate. Our previous study revealed that cholelithiasis patients who undergo endoscopic sphincterotomy (ES)/endoscopic papillary balloon dilatation are at a higher risk for subsequent cholangiocarcinoma than cholelithiasis patients who undergo cholecystectomy.

AIM
To clarify the relationship between recurrent biliary events and subsequent cholangiocarcinoma risk in choledocholithiasis patients.
Medical University Hospital, Taiwan. All methods were performed in accordance with the relevant guidelines and regulations and under surveillance by the IRB of Chung Shan Medical University Hospital.

Conflict-of-interest statement: Chun-Che Lin has received research funding from Chung Shan Medical University Hospital Research program (CSH-2013-C-032) for national health insurance data collection.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Taiwan

Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

Received: July 4, 2020
Peer-review started: July 4, 2020
First decision: September 18, 2020

INTRODUCTION
Cholangiocarcinoma, which carries a medium incidence and high mortality rate[1], has been under re-evaluation in Asia-Pacific countries[2,3]. Over the past two decades, the incidence of intra-hepatic cholangiocarcinoma (ICC) has increased, while the incidence of extra-hepatic cholangiocarcinoma has declined internationally[4,5-7]. The most important factor for survival in cholangiocarcinoma patients is R0 resection[8], and this means that a surveillance program that can lead to early detection is the key to survival. There are many historical risk factors for cholangiocarcinoma that have been discussed in the previous literature, like primary sclerosing cholangitis[9,10], choledochal cyst disease[11,12], parasite infection[13], cholelithiasis[14-16], diabetes mellitus[17,18], and Helicobacter pylori infection[19,20]. The impact of liver cirrhosis[21], and chronic hepatitis C[22] and B[23,24] virus infections has also been confirmed in recent studies. Because the etiology of cholangiocarcinoma is not fully understood, several
hypotheses were proposed to explain its cause, including chronic inflammation of the bile duct or the destruction of the integrity of the bile duct\cite{35}, such as from endoscopic retrograde cholangiopancreatography. The topic of endoscopic sphincterotomy and endoscopic papillary balloon dilatation (EPBD) and the late complication, like cholangiocarcinoma, is still a matter of debate\cite{36-38}, and the current evidence is insufficient for a conclusion to be drawn. Because cholelithiasis itself is an important risk factor for cholangiocarcinoma, the impact on the incidence of subsequent cholangiocarcinoma from advanced bile duct management is difficult to evaluate.

Although previous studies have shown differing results regarding cholecystectomy (CCY) due to cholelithiasis and subsequent ICC\cite{39} or extra-hepatic cholangiocarcinoma\cite{40-41}, our prior study revealed that cholelithiasis patients who undergo endoscopic sphincterotomy/endoscopic papillary balloon dilatation (ES/EPBD) are at a greater risk for subsequent cholangiocarcinoma, while cholelithiasis patients who undergo CCY have reduced risk for subsequent cholangiocarcinoma\cite{42}. These results can be explained by different inflammation sites or by CCY reducing recurrent biliary events (RBEs)\cite{43} and further decreasing future cholangiocarcinoma rates.

Because of the inconsistent results of the previous evidence, we performed this study using the National Health Insurance Research Database (NHIRD) 2004–2011 of Taiwan to clarify the risk of cholangiocarcinoma after ES/EPBD, ES/EPBD and CCY, and supportive care with no invasive intervention in patients who were admitted to the hospital because of choledocholithiasis.

**MATERIALS AND METHODS**

This study was a population-based retrospective cohort study based on Taiwan’s NHIRD 2004–2011, and the study methods of the NHIRD have been described in detail in previous studies\cite{35-36}. This study was approved by the Institutional Review Board (IRB) of Chung Shan Medical University Hospital, Taiwan. All methods were performed in accordance with the relevant guidelines and regulations and under surveillance by the IRB of Chung Shan Medical University Hospital. All authors declare they have no any conflict of interest to report.

**Study design**

Symptomatic choledocholithiasis cases in patients over 18 years old were obtained from among one million random samples of the NHIRD between January 2005 and December 2009 by the codes of the International Statistical Classification of Diseases and Related Health Problems, ninth revision (ICD-9), which were registered when patients were admitted to hospital. Then, we excluded patients who had already undergone ES/EPBD or CCY in 2004, or who had been diagnosed with cholangiocarcinoma before 2005, or who had been diagnosed with choledocholithiasis prior to being diagnosed with choledocholithiasis. After the study group was selected, we built a control group, matched by sex and age in a 1:3 ratio. The cases for the control group were defined as individuals who had never been diagnosed with cholelithiasis or had never undergone a related medical procedure prior to 2005. The study group was further divided into ES/EPBD, ES/EPBD and CCY, and no intervention groups. Because cholangiocarcinoma patients in Taiwan use a catastrophic illness card to wave medical expenses when the patients seek for medical help using ICD-9 registration of cholangiocarcinoma, we believe that a 1-year exclusion period is enough. Variables such as economic status, place of residence, follow-up time, and historical common risk factors, including chronic hepatitis B (CHB), chronic hepatitis C, *Helicobacter pylori* infection, diabetes mellitus, end-stage renal disease on dialysis, congenital cystic disease of the liver, *Clonorchis/Opisthorchis* infection, and inflammatory bowel disease, were compared among the ES/EPBD, ES/EPBD and CCY, and no intervention groups. We calculated the number and rates for cholangiocarcinoma just after the procedure and then again 6, 12, and 18 mo after the procedure. The study flow chart is shown in Figure 1. The ICD-9 codes for the above diseases and procedure codes are listed in Supplementary Table 1.

Furthermore, we chose cholangiocarcinoma that occurred after the first 18 mo post-ES/EPBD or biliary event to be considered as subsequent cholangiocarcinoma because the incidence of cholangiocarcinoma during the first 18 mo were obviously higher than that in the following years (Figure 2) and this condition was most obvious in the no intervention group. We believed that these cases should be considered as concurrent malignancies rather than subsequent cholangiocarcinoma. The incidence of subsequent cholangiocarcinoma in patients in the ES/EPBD, ES/EPBD and CCY, or no
intervention group was compared with that of the normal population. The time cumulative risk for subsequent cholangiocarcinoma in the different groups was calculated. The definition of RBEs was further ER visits or admission course due to cholangitis, cholecystitis, or biliary pancreatitis. The incidence of RBEs and that of subsequent cholangiocarcinoma were compared in different groups to identify their relationships.

Data processing and statistical analysis
The NHIRD was managed by employing the Microsoft SQL Server 2008 R2 (Microsoft Corporation, Redmond, WA, United States), and the data query and data processing procedures were done using the SQL programming language. Statistical analyses was performed using OpenEpi: Open Source Epidemiologic Statistics for Public Health, version 3.01[38]. Kaplan-Meier survival analyses were completed using SPSS version 19. Person-time analyses were done using OpenEpi version 3.01.

Data obtained from the study were compared by a chi-square ($\chi^2$) test for the categorical variables, $t$-test or one-way ANOVA (analysis of variance) for the continuous variables, and log-rank (Mantel-Cox) test for the survival curves. A Cox regression model was used for analysis of the hazard ratio of subsequent cholangio-
Figure 2 Cholangiocarcinoma cases diagnosed during different follow-up periods in the endoscopic sphincterotomy/endoscopic papillary balloon dilatation group, endoscopic sphincterotomy/endoscopic papillary balloon dilatation and cholecystectomy group, no intervention group, and normal population. ES: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilatation; CCY: Cholecystectomy.

RESULTS

In total, 2204 adult symptomatic choledocholithiasis admission cases were obtained from one million random samples of the NHIRD between January 2005 and December 2009. After excluding 25 cases who had undergone ES/EPBD or CCY in 2004 and 7 cases with confirmed cholangiocarcinoma in 2004, we excluded another 76 cases who had a diagnosis of cholangiocarcinoma prior to a diagnosis of choledocholithiasis. We finally selected 2096 choledocholithiasis patients without prior ES/EPBD, CCY, or cholangiocarcinoma between January 2005 and December 2009. The control group, built with cases without cholelithiasis by matching by age and sex, included 6288 cases. The mean age was 66.18 years in both the study and control groups.

There were 511 patients who had undergone ES/EPBD without CCY, while 100 patients had ES/EPBD with further CCY. At the same time, there were 1485 patients with choledocholithiasis who accepted supportive care without any further intervention during admission because of either disease severity or baseline health condition. Regarding the demographic data, the average age was 67.44 ± 15.23 years in the ES/EPBD group, 59.96 ± 16.87 years in the ES/EPBD and CCY group and 66.16 ± 16.02 years in the no intervention group.

We found that only age, age distribution, and follow-up time had statistically significant differences among the three groups in the demographic data, which also included gender, economic status, place of residence, and comorbidities. Patients who underwent ES/EPBD and CCY were younger than those in the ES/EPBD and no intervention groups, and they had the longest follow-up time, with 47.91 mo vs 42.77 mo and 36.14 mo, respectively. Meanwhile, the proportion of historical risk factors for carcinoma. A two-tailed $P$ value of 0.05 was considered statistically significant in this study.

Choledocholithiasis cases undergoing ES/EPBD, ES/EPBD and CCY, and no intervention

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cholangiocarcinoma, such as CHB, chronic hepatitis C, DM, end-stage renal disease on dialysis, cystic disease of the liver, *Clonorchis/Opisthorchis* infection, and inflammatory bowel disease, were similar in these three groups except that there was a non-significantly lower CHB proportion in the ES/EPBD and CCY group (3% vs 9.78% and 10.37%) in Table 1.

Thirty-nine (7.63%) patients were diagnosed with cholangiocarcinoma in the ES/EPBD group, while 90 cholangiocarcinoma (6.06%) patients were found in the no intervention group and four (4.00%) were diagnosed in the ES/EPBD and CCY group. Because the incidence of cholangiocarcinoma during the first 6 mo was extremely high in all groups and abnormally high during the first 18 mo in the no intervention group, we excluded the cholangiocarcinoma cases that were diagnosed during the first 18 mo after index admission to build the definition of subsequent cholangiocarcinoma. The detailed information is revealed in Figure 2. After the exclusion, 12 (2.35%), 11 (0.74%), and 1 (1.00%) subsequent cholangiocarcinoma cases were diagnosed in the ES/EPBD, no intervention, and ES/EPBD and CCY groups, respectively. The hazard ratio for subsequent cholangiocarcinoma was 3.45 in the ES/EPBD group and 1.31 in the ES/EPBD and CCY group when compared with the no intervention group. The results were similar in that the no intervention group had the lowest subsequent cholangiocarcinoma rate if we excluded the cholangiocarcinoma cases diagnosed within 6 mo or 1 year after index admission. The cumulative cholangiocarcinoma rates in the ES/EPBD, ES/EPBD and CCY, no intervention, and control groups during the 7-year follow-up period revealed that choledocholithiasis patients who needed an ES/EPBD intervention initially had the highest subsequent cholangiocarcinoma rate. The subsequent cholangiocarcinoma rate in the no intervention group exceeded that in the ES/EPBD and CCY group after the 5-year follow-up period. The cumulative subsequent cholangiocarcinoma rates in the ES/EPBD, ES/EPBD and CCY, no intervention, and control groups are shown in Figure 3.

**Incidence of cholangiocarcinoma**

As for the comparisons between the patients who had undergone ES/EPBD, ES/EPBD and CCY, and no intervention for choledocholithiasis and the normal population, the incidence of cholangiocarcinoma after the first 18 mo was compared using incidence rate/1000 person-years. In the ES/EPBD group, the incidence of subsequent cholangiocarcinoma was 7.23 (3.92–12.29) per 1000 person-years, which is more than 25 times the incidence in the normal population. The incidence of subsequent cholangiocarcinoma in the ES/EPBD group was higher especially in females (10.39/1000 person-years) and patients above 70 years old (8.42/1000 person-years).

In the ES/EPBD and CCY group, the incidence of subsequent cholangiocarcinoma was 2.54 (0.13–12.55) per 1000 person-years, which was higher than that of the normal population. As for choledocholithiasis patients without any intervention, the incidence of subsequent cholangiocarcinoma, which was 2.52 (1.35–4.38) per 1000 person-years, was similar to that in the ES/EPBD and CCY group. The incidence of subsequent cholangiocarcinoma was the highest in the ES/EPBD group, and it was almost equal in the ES/EPBD and CCY and no intervention groups. Meanwhile, the incidence of subsequent cholangiocarcinoma was significantly higher for all choledocholithiasis patients as compared to the normal population. The detailed information is shown in Table 2.

**Relationship between RBES and subsequent cholangiocarcinoma rate**

We further analyzed the relationship between RBES and the incidence of subsequent cholangiocarcinoma. Using the RBE incidence rate/1000 person-years of the no intervention group as a reference, the RBE incidence rate/1000 person-years of the ES/EPBD group was 350.06, which was significantly higher than that of the ES/EPBD and CCY and no intervention groups. Meanwhile, the incidence of subsequent cholangiocarcinoma was highest in the ES/EPBD group at 7.23/1000 person-years. Based on the idea that frequent RBES may increase the subsequent cholangiocarcinoma rate, we separated the entire study group into two groups: Patients diagnosed with subsequent cholangiocarcinoma and patients without cholangiocarcinoma. The RBE incidence rates/1000 person-years were 527.79 and 286.69 in the subsequent cholangiocarcinoma group and the without cholangiocarcinoma group, respectively. The RBE event rate and the proportion of RBES in patients with confirmed subsequent cholangiocarcinoma were significantly higher in our results.
Table 1 Comparisons of choledocholithiasis patients who underwent endoscopic sphincterotomy/endoscopic papillary balloon dilatation, endoscopic sphincterotomy/endoscopic papillary balloon dilatation and cholecystectomy, and no intervention

|                                | ES/EPBD, n = 511, mean (SD; %) | ES/EPBD and CCY, n = 100, mean (SD; %) | Without intervention, n = 1485, mean (SD; %) | P value |
|--------------------------------|--------------------------------|----------------------------------------|---------------------------------------------|---------|
| Age, mean (SD)                 | 67.44 (15.23)                  | 59.96 (16.87)                          | 66.16 (16.02)                               | < 0.001 |
| Age, yr                        |                                |                                        |                                             |         |
| 18-49                          | 40.08 (6.91)                   | 39.13 (8.43)                           | 39.48 (6.76)                               |         |
| 50-69                          | 60.48 (5.43)                   | 58.21 (5.88)                           | 60.14 (5.55)                               |         |
| > 70                           | 79.45 (6.02)                   | 77.58 (4.71)                           | 79.89 (6.43)                               |         |
| Gender                         |                                |                                        |                                             | 0.450   |
| Male                           | 282 (55.19)                    | 49 (49.00)                             | 824 (55.49)                                |         |
| Female                         | 229 (44.81)                    | 51 (51.00)                             | 661 (44.51)                                |         |
| Follow-up time (mo), mean (SD) | 42.77 (22.20)                  | 47.91 (20.86)                          | 36.14 (24.87)                              | < 0.001 |
| Economic status                |                                |                                        |                                             | 0.445   |
| MBS                            | 292 (57.14)                    | 54 (54.00)                             | 867 (58.38)                                |         |
| 1-3 times MBS                  | 189 (36.99)                    | 36 (36.00)                             | 536 (36.09)                                |         |
| Above 3 times MBS              | 29 (5.68)                      | 10 (10.00)                             | 82 (5.52)                                  |         |
| Place of residence             |                                |                                        |                                             | 0.154   |
| City                           | 288 (56.36)                    | 68 (68.00)                             | 900 (60.61)                                |         |
| Countryside                    | 213 (41.68)                    | 31 (31.00)                             | 551 (37.10)                                |         |
| Remote village                 | 9 (1.76)                       | 1 (1.00)                               | 33 (2.22)                                  |         |
| Comorbidity                    |                                |                                        |                                             |         |
| CHB                            | 50 (9.78)                      | 3 (3.00)                               | 154 (10.37)                                | 0.057   |
| CHC                            | 23 (4.50)                      | 5 (5.00)                               | 103 (6.94)                                 | 0.127   |
| DM                             | 172 (33.66)                    | 29 (29.00)                             | 504 (33.94)                                | 0.599   |
| ESRD                           | 8 (1.57)                       | 1 (1.00)                               | 32 (2.15)                                  | 0.552   |
| CCDL                           | 12 (2.35)                      | 2 (2.00)                               | 20 (1.35)                                  | 0.289   |
| CO                             | 0 (0.00)                       | 0 (0.00)                               | 0 (0.00)                                   | 1.00    |
| IBD                            | 8 (1.57)                       | 0 (0.00)                               | 32 (2.15)                                  | 0.253   |
| Cholangiocarcinoma             |                                |                                        |                                             |         |
| Number of CC                   | 39 (7.63)                      | 4 (4.00)                               | 90 (6.06)                                  | 0.279   |
| Number of CC after first 18 mo | 12 (2.35)                      | 1 (1.00)                               | 11 (0.74)                                  | 0.013   |
| Hazard ratio                   | 3.45 (1.52-7.82)               | 1.31 (0.17-10.13)                      | 1.00                                        | 0.012   |
| Time to diagnosis of CC (excluding case in first 18 mo), month | 39.71 (18.93) | 25.12 (0.00) | 43.27 (17.98) | 0.624  |
| Overall mortality rate         | 146 (28.57)                    | 12 (12.00)                             | 596 (40.13)                                | < 0.001 |

ES: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilatation; CCY: Cholecystectomy; SD: Standard deviation; MBS: Minimum basic salary; CHB: Chronic hepatitis B; CHC: Chronic hepatitis C; HP: Helicobacter infection; DM: Diabetes mellitus; ESRD: End-stage renal disease; CCDL: Congenital cystic disease of liver; CO: Clonorchis/Oipisthorchis; IBD: Inflammatory bowel disease; CC: Cholangiocarcinoma.

DISCUSSION

Southeast Asia has the highest incidence of cholangiocarcinoma worldwide. Its annual incidence ranges from 0.1/100000 to 71.3/100000 [39,40], and our reports came from this endemic area. Although the most famous risk factor for cholangiocarcinoma in the Western world is primary sclerosing cholangitis [10], this rarely occurs in Asian countries except in Japan. At the same time, choledochal cyst disease contributes to a
Table 2 Incidence of cholangiocarcinoma among patients with choledocholithiasis who underwent therapeutic endoscopic retrograde cholangiopancreatography, endoscopic retrograde cholangiopancreatography and cholecystectomy, or no intervention compared with normal population (excluding cholangiocarcinoma in the first 18 mo)

| Variable                  | Person-years at risk in study cohort | Person-years at risk in control cohort | No. of observed cases of cholangiocarcinoma in study cohort | Incidence rate/1000 person-years (95%CI) in study cohort | Incidence rate/1000 person-years (95%CI) in control cohort | P value |
|---------------------------|-------------------------------------|---------------------------------------|---------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|---------|
| **ES/EPBD**               |                                     |                                       |                                                               |                                                          |                                                          |         |
| Total                     | 1659.70                             | 25360.07                              | 12                                                            | 7.23 (3.92-12.29)                                         | 0.28 (0.12-0.55)                                         | < 0.001 |
| Gender                    |                                     |                                       |                                                               |                                                          |                                                          |         |
| Male                      | 889.95                              | 13822.88                              | 4                                                             | 4.50 (1.43-10.84)                                         | 0.22 (0.06-0.59)                                         | < 0.001 |
| Female                    | 769.76                              | 11537.20                              | 8                                                             | 10.39 (4.83-19.74)                                        | 0.35 (0.11-0.84)                                         | < 0.001 |
| Age, years                |                                     |                                       |                                                               |                                                          |                                                          |         |
| 18-49                     | 253.84                              | 4392.03                               | 1                                                             | 3.94 (0.20-19.43)                                         | 0.00 (0.00-0.00)                                         | < 0.001 |
| 50-69                     | 574.78                              | 8631.76                               | 5                                                             | 6.96 (2.21-16.79)                                         | 0.58 (0.21-1.28)                                         | < 0.001 |
| > 70                      | 831.08                              | 12336.28                              | 7                                                             | 8.42 (3.68-16.66)                                         | 0.16 (0.03-0.54)                                         | < 0.001 |
| **ES/EPBD and CCY**       |                                     |                                       |                                                               |                                                          |                                                          |         |
| Total                     | 393.11                              | 25360.07                              | 1                                                             | 2.54 (0.13-12.55)                                         | 0.28 (0.12-0.55)                                         | 0.011   |
| Gender                    |                                     |                                       |                                                               |                                                          |                                                          |         |
| Male                      | 184.36                              | 13822.88                              | 0                                                             | 0.00 (0.00-0.00)                                         | 0.22 (0.06-0.59)                                         | 0.842   |
| Female                    | 208.75                              | 11537.20                              | 1                                                             | 4.79 (0.24-23.63)                                         | 0.35 (0.11-0.84)                                         | 0.002   |
| Age, yr                   |                                     |                                       |                                                               |                                                          |                                                          |         |
| 18-49                     | 113.01                              | 4392.03                               | 0                                                             | 0.00 (0.00-0.00)                                         | 0.00 (0.00-0.00)                                         | NA      |
| 50-69                     | 143.37                              | 8631.76                               | 1                                                             | 6.98 (0.35-34.40)                                         | 0.58 (0.21-1.28)                                         | 0.004   |
| > 70                      | 136.73                              | 12336.28                              | 2                                                             | 0.00 (0.00-0.00)                                         | 0.16 (0.03-0.54)                                         | 0.882   |
| **Without intervention**  |                                     |                                       |                                                               |                                                          |                                                          |         |
| Total                     | 4364.45                             | 25360.07                              | 11                                                            | 2.52 (1.35-4.38)                                         | 0.28 (0.12-0.55)                                         | < 0.001 |
| Gender                    |                                     |                                       |                                                               |                                                          |                                                          |         |
| Male                      | 2345.22                             | 13822.88                              | 6                                                             | 2.56 (1.04-5.32)                                         | 0.22 (0.06-0.59)                                         | < 0.001 |
| Female                    | 2019.23                             | 11537.20                              | 5                                                             | 2.48 (0.91-5.49)                                         | 0.35 (0.11-0.84)                                         | < 0.001 |
| Age, yr                   |                                     |                                       |                                                               |                                                          |                                                          |         |
| 18-49                     | 871.87                              | 4392.03                               | 0                                                             | 0.00 (0.00-0.00)                                         | 0.00 (0.00-0.00)                                         | NA      |
| 50-69                     | 1528.74                             | 8631.76                               | 6                                                             | 3.93 (1.60-8.16)                                         | 0.58 (0.21-1.28)                                         | < 0.001 |
| > 70                      | 1963.84                             | 12336.28                              | 5                                                             | 2.55 (0.93-5.64)                                         | 0.16 (0.03-0.54)                                         | < 0.001 |

ES: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilatation; CCY: Cholecystectomy; NA: Not applicable.
more than 30-fold higher cholangiocarcinoma risk\cite{10} over that of the normal population, but this kind of disease is as rare as *Clonorchis/Opisthorchis* infection\cite{11} in patients in modern Taiwan. Because hepatolithiasis is associated with a 6- to 50-fold increased risk for ICC\cite{14} and there has been an increase in worldwide incidence of cholelithiasis in recent years\cite{15,16}, we analyzed the relationship between RBEs and the incidence of subsequent cholangiocarcinoma in choledocholithiasis patients who required admission for medical management.

Because we used only age and sex to find three times as many in the normal population without a cholelithiasis diagnosis to be our control group, other risk factors for cholangiocarcinoma may confound the results in our three study groups. Meanwhile, we can observe the distribution of these well-known risk factors for cholangiocarcinoma in the different groups.

We noticed that the subsequent and overall cholangiocarcinoma risks of choledocholithiasis patients were statistically higher than those of the normal population (Table 2 and Figure 3). These results are compatible with the previous literature in proving that cholelithiasis is an important risk factor for cholangiocarcinoma\cite{12,13}.

The comparison among the choledocholithiasis patients who had undergone ES/EPBD, ES/EPBD and CCY, and no intervention showed no statistically significant differences regarding previous risk factors for cholangiocarcinoma. Because the cholangiocarcinoma incidence was obviously higher during the first 6 mo after index admission in the ES/EPBD and ES/EPBD and CCY groups, we considered these events as initial misdiagnoses or concurrent cholangiocarcinoma events. Interestingly, we noticed that the incidence of cholangiocarcinoma in the choledocholithiasis patients who were admitted without any further endoscopic or surgical intervention was still abnormally higher during the 6–12 mo and 12–18 mo after index admission. Because there were no further advanced interventions in this group, we chose to exclude cholangiocarcinoma that occurred within 18 mo after index admission to build up the subsequent cholangiocarcinoma definition in our database. The subsequent cholangiocarcinoma cumulative risk was highest in the ES/EPBD group, and the cumulative risk for subsequent cholangiocarcinoma in the no intervention group gradually exceeded that of the ES/EPBD and CCY group as the observation time went by. The overall subsequent cholangiocarcinoma hazard ratios were 3.45, 1.31, and 1.0 in the ES/EPBD, ES/EPBD and CCY, and no intervention groups, respectively. This phenomenon can be explained by the fact that the greater the severity of the inflammation in the bile duct, the more advanced the interventions performed. Meanwhile, the frequency or severity of bile duct inflammatory events may increase the risk of subsequent cholangiocarcinoma. We believe that the lowest subsequent cholangiocarcinoma risk in the no intervention group comes from having fewer inflammatory events than the other two groups. We further hypothesize that more RBEs result in a higher subsequent cholangiocarcinoma rate. The comparisons between RBE incidence and subsequent cholangiocarcinoma incidence among the ES/EPBD, ES/EPBD and CCY, and no intervention groups showed a strong correlation: The incidence of RBEs was much higher in the choledocholithiasis patients who were later diagnosed with cholangiocarcinoma than in those who were not, which is shown in Table 3. These results prove that RBEs can increase the subsequent cholangiocarcinoma rate.

Second, we attempted to prove that early or delayed CCY can decrease subsequent cholangiocarcinoma risk by reducing future RBEs, and it has already been proved in the previous literature that early or delayed CCY can reduce future RBEs\cite{17,18}. In our study, the risk for subsequent cholangiocarcinoma in the no intervention group was initially low but gradually increased and exceeded that of the ES/EPBD and CCY group, starting with the fifth year after index admission. We believe that this result gives us a clue that CCY after ES/EPBD for choledocholithiasis management maybe reduces long-term subsequent cholangiocarcinoma risk by decreasing RBEs.

There are two major limitations to our study. First, this is a retrospective database cohort study that showed no laboratory data results or clinical images, and this makes concurrent cholangiocarcinoma or misdiagnoses initially hard to identify. That is why we excluded cholangiocarcinoma during the first 18 mo after index admission in our study design. Second, although this study used a representative database sample of one million patients, the incidence of cholangiocarcinoma was low, and we could only find 12, 1, and 11 cases in the ES/EPBD, ES/EPBD, and CCY and no intervention groups, respectively. However, the relationship between the incidence of RBEs and that of subsequent cholangiocarcinoma was statistically meaningful. Further large-scale retrospective or prospective studies are needed on this topic. We have already started to initiate a prospective hospital-based cohort study of cholelithiasis patients.
Table 3 Recurrent biliary event incidence and relationship with cholangiocarcinoma incidence among patients with choledocholithiasis underwent therapeutic endoscopic retrograde cholangiopancreatography, endoscopic retrograde cholangiopancreatography and cholecystectomy, or without intervention (excluding cholangiocarcinoma in the first 18 mo)

| Variable | Number of RBE events | Number of RBE patients | RBE per person (SD) | Incidence proportion (person) | Person-years | Cholangiocarcinoma incidence rate/1000 person-years | RBEs incidence rate/1000 person-years | P value |
|----------|----------------------|------------------------|--------------------|-------------------------------|--------------|---------------------------------|---------------------------------|---------|
| ES/EPBD, n = 511 | 581 | 126 | 1.14 (2.28) | 24.66% | 1659.70 | 7.23 | 350.06 | < 0.001 |
| ES/EPBD and CCY, n = 100 | 70 | 14 | 0.70 (1.36) | 14.00% | 393.11 | 2.54 | 178.07 | < 0.001 |
| Choledocholithiasis without intervention, n = 1485 | 1213 | 286 | 0.82 (1.52) | 19.26% | 4364.45 | 2.52 | 277.93 | Reference |
| Patients had cholangiocarcinoma after 18 mo, n = 24 | 43 | 10 | 1.79 (2.06) | 41.67% | 81.47 | NA | 527.79 | < 0.001 |
| Patients without cholangiocarcinoma, n = 1963 | 1812 | 414 | 0.92 (1.76) | 21.09% | 6320.31 | NA | 286.69 | Reference |

*Z-score. ES: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilatation; CCY: Cholecystectomy; RBE: Recurrent biliary event; NA: Not applicable.*

Figure 3 Cumulative subsequent cholangiocarcinoma risk in the endoscopic sphincterotomy/endoscopic papillary balloon dilatation group, endoscopic sphincterotomy/endoscopic papillary balloon dilatation and cholecystectomy group, no intervention group, and normal population (The cases of cholangiocarcinoma within 18 mo after index admission were excluded). ES: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilatation; CCY: Cholecystectomy.

who have undergone therapeutic endoscopic or surgical interventions to clarify the results that we found in this retrospective cohort study.

**CONCLUSION**

In conclusion, choledocholithiasis patients who have undergone ES/EPBD intervention without further CCY have a 25–26-fold higher subsequent cholangiocarcinoma risk than the normal population. Further CCY in ES/EPBD patients decreases subsequent cholangiocarcinoma risk by reducing RBEs.
ARTICLE HIGHLIGHTS

Research background
Our previous study revealed that cholelithiasis patients who undergo endoscopic sphincterotomy/endoscopic papillary balloon dilatation (ES/EPBD) are at a greater risk for subsequent cholangiocarcinoma, while cholelithiasis patients who undergo cholecystectomy (CCY) have a much lower risk for subsequent cholangiocarcinoma.

Research motivation
Because of problems in prior study’s design, we could not identify whether different inflammation sites or CCY-reduced recurrent biliary events (RBEs) influenced the subsequent cholangiocarcinoma risk in cholelithiasis patients.

Research objectives
To evaluate the relationships of recurrent biliary events with subsequent cholangiocarcinoma risk.

Research methods
We selected symptomatic choledocholithiasis patients older than 18 years who were admitted from January 2005 to December 2009 from one million random samples in the National Health Insurance Research Database of Taiwan.

Research results
This study showed that choledocholithiasis patients who underwent further CCY after ES/EPBD can reduce subsequent cholangiocarcinoma risk from 2.35% to 1%. And the subsequent cholangiocarcinoma risks had a good correlation with RBEs in our study. Choledocholithiasis patients who have undergone an ES/EPBD intervention without further CCY had a 25–26-fold higher subsequent cholangiocarcinoma risk than the normal population.

Research conclusions
Further CCY in ES/EPBD patients decreases subsequent cholangiocarcinoma risk by reducing RBEs.

Research perspectives
This study not only showed different subsequent cholangiocarcinoma risks in the ES/EPBD, ES/EPBD and CCY, and no intervention groups of symptomatic choledocholithiasis patients, but also the significant relationship between the incidence of RBEs and that of subsequent cholangiocarcinoma.

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