BMJ Open

Postoperative survival of extrahepatic and intrahepatic cholangiocarcinoma after surgery: a population-based cohort

Wei-Wen Liu,[1] Jian-Fei Tu,[1] Xi-Hui Ying,[1] Zheng-Ju Chen,[2] Yun-Bing Wang [3]

To cite: Liu W-W, Tu J-F, Ying X-H, *et al*. Postoperative survival of extrahepatic and intrahepatic cholangiocarcinoma after surgery: a population-based cohort. *BMJ Open* 2022;**12**:e049789. doi:10.1136/bmjopen-2021-049789

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-049789).

W-WL and J-FT contributed equally.

Received 06 February 2021
Accepted 23 March 2022

[1]Department of Radiology, The Fifth Affiliated Hospital of Wenzhou Medical University, Lishui, Zhejiang, China
[2]Laboratory of Pathology, Sichuan University West China Hospital, Chengdu, Sichuan, China
[3]Department of Hepatobiliary Surgery, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China

Correspondence to
Yun-Bing Wang;
wangyunbing@cqmu.edu.cn

ABSTRACT

Objectives The study was designed to clarify the difference between extrahepatic cholangiocarcinoma (ECC) and intrahepatic cholangiocarcinoma (ICC) in postoperative cancer-specific death.

Design Patients diagnosed with ECC and ICC after surgery, who are identified from the Surveillance, Epidemiology and End Results programme, are eligible for this retrospective cohort study.

Setting Survival between groups was compared using the traditional Kaplan-Meier method and the cumulative incidence function (CIF) method. Propensity score-matched (PSM) analysis was conducted to balance the differences in vital variables between groups. The HR and 95% CI for ECC relative to ICC were used to quantify the risk of death. Subgroup analysis was further used to evaluate the stability of the differences between groups.

Results The study included 876 patients with ECC and 1194 patients with ICC. Before PSM, with the Kaplan-Meier method, postoperative overall survival and cancer-specific death for ECC were worse than those for ICC. However, with the CIF method, no difference in postoperative cancer-specific death was found. After PSM, all differences in the considered traits were balanced, and 173 pairs of patients were retained. Survival analysis found that there was no difference in postoperative all-cause death (Kaplan-Meier method, p=0.186) or cancer-specific death (Kaplan-Meier and CIF methods, p=0.500 and p=0.913, respectively), which was consistent with subgroup analysis.

Conclusions ECC and ICC showed no difference in postoperative cancer-specific death, both in the natural state and in multiple variable-matched conditions.

Trial registration number researchregistry4175.

Strengths and limitations of this study

- The study compared the difference between extrahepatic cholangiocarcinoma (ECC) and intrahepatic cholangiocarcinoma (ICC) in postoperative cancer-specific death.
- The main strength of the study is that it contains a large sample size.
- Survival between groups was compared using the traditional Kaplan-Meier method or the cumulative incidence function method. This comparative analysis allowed demonstrating the limitations of the Kaplan-Meier method and the need to use appropriate analytic methods in the presence of competing risk events.
- Propensity score-matched analysis was conducted to balance the differences in vital variables between groups.
- Limitations include the unavailability of some clinical variables, such as the causes of ECC or ICC.

INTRODUCTION

Cholangiocarcinoma (CC) is one of the most common malignant neoplasms arising from the epithelium of the bile duct. During the past several decades, the incidence rate has increased, while the overall mortality has remained high, with a 5-year overall survival below 20%.[1] To date, the therapy for CC remains limited, and surgery is the best curative therapy.[2 3]

Based on the difference of tumour location, CC could be further classified into extrahepatic cholangiocarcinoma (ECC) and intrahepatic cholangiocarcinoma (ICC). Lots of studies did not discriminate between them but rather investigated ECC and ICC together.[1] Obviously, this way was not helpful for adopting individual treatment. Determining whether there was a difference between ECC and ICC is useful for enhancing diagnosis and treatment.

Previously, several studies had elaborated their differences in terms of risk factors for occurrence and pathology.[4] However, few studies were designed to investigate their difference in terms of postoperative survival. In addition, these previous studies showed inconsistent findings regarding the differences between ECC and ICC in postoperative survival.[5–7] As a result, it is still not clear as to whether there was a difference in the postoperative survival between ECC and ICC.

Considering this situation, based on the large amount of data in the Surveillance, Epidemiology and End Results (SEER) database, we conducted a retrospective study to explore whether there was a difference in postoperative survival (in terms of both

cancer-specific death and death from other reasons) between ECC and ICC.

MATERIALS AND METHODS

Data source

Patient data were obtained from the SEER 18 database, which aims to provide information on cancer statistics in an effort to reduce the cancer burden in the US population. We have been authorised to use these data for clinical investigation. All analyses were based on the public data in SEER database, thus no ethical approval and patient consent are required. The study was registered at Research Registry. Furthermore, the study was reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology criteria.[8]

Patient and public involvement

This study is informed by the literature concerning the differences between ECC and ICC in postoperative survival.[5–7] Because this is a retrospective cohort using data from SEER database, the patients included were not involved in the design, recruitment and conduct of this study. Furthermore, study participants will not be notified of the study's results, because we cannot obtain individually identifiable information from SEER database.

Inclusion and exclusion criteria

All patients who were diagnosed with ECC or ICC between 2007 and 2015 in the SEER data were eligible for study inclusion. A retrospective cohort design was used for this study. The histologic diagnosis for each patient was based on the topography code (ECC, C24.0; ICC, C22.1) and morphology code (8160). Only patients undergoing recommended surgery after diagnosis were included.

The exclusion criteria were as follows: (1) patients who had no confirmed diagnosis of ECC or ICC; (2) patients with incomplete or inaccurate vital clinicopathological and follow-up data (eg, the survival month was not known); (3) patients whose cause-specific death classification were missing/unknown.

Variables and outcomes definition

The variables were age, gender, race, marital status, tumour differentiation, clinical stage (based on the Cancer Staging Manual by the American Joint Committee on Cancer (sixth ed., 2002)[9] (referred to as the AJCC clinical stage)), T stage, N stage and M stage. Races included black, white, other or unknown. Marital status was classified as single, married or unknown. Tumour differentiation included grade I/II/III/IV and unknown stage. From tumour differentiation I to IV, the degree of tumour differentiation increased. The primary outcomes in our study were postoperative cancer-specific death, death from other causes (excluding primary cancer-specific death) and death from all causes above. All follow-up data were extracted for survival analysis.

Statistical analysis

The statistical analysis was conducted with R software and SPSS (V.22.0) software. Continuous variables are presented as the mean±SD, and the differences between groups were compared with the t test. Classification variables were presented as the case number and corresponding percentage, and the differences between groups were compared using the χ^2 test. Propensity score-matched (PSM) analysis was used to balance the bias between ECC and ICC groups.[10] The method of nearest neighbour matching was used in PSM analysis. The calliper value was set based on the final difference between both groups considering the included variables. The included variables were age, gender, race, marital status, tumour differentiation, AJCC clinical stage, T stage, N stage and M stage. Survival between groups was compared using the traditional Kaplan-Meier method or the cumulative incidence function (CIF) method. In detail, Kaplan-Meier method and the CIF method were combined with log-rank test and Gray test for analyses, respectively. The CIF method was able to analyse the survival data considering the potential interferences between death from other reasons and cancer-specific death,[11] but the Kaplan-Meier method did not.

To quantify the risk of death for ECC relative to ICC, the HR and corresponding 95% CI were estimated. For competing risk events, subdistribution hazard model was utilised to estimate the HR and 95% CI. When competing risk events were not considered, Cox-proportional hazard (PH) model was used to estimate the HR and 95% CI. Subdistribution hazard model is one kind of competing risk models, which is different from Cox-PH model. For the two models in our study, no covariates were included. These models would be directly used, only if the PH assumption was met. The testing of scaled Schoenfeld residuals and visual assessment of survival curves were utilised to evaluate the PH assumption. When PH assumption was not met, time-axis division method (piecewise regression)[12] would be used to estimate the HR and 95% CI in Cox-PH model or subdistribution hazard model. Subgroup analysis was conducted to validate whether the difference in survival could be presented in various conditions based on different variables. P value<0.05 was considered statistically significant.

RESULTS

Patient selection and general traits

After limiting the cancer to intrahepatic bile duct and other biliary, a total of 22 695 patients were obtained. Based on the description of primary sites (intrahepatic and extrahepatic bile duct), a total of 15 810 cases were selected. An additional 254 patients with unknown survival months were excluded. The patients who were unable to undergo surgery were excluded; therefore, 3585 patients remained. Subsequently, 35 patients were excluded because they died with no detailed description of causes. The ICD-O-3 hist/behaviour was then used to

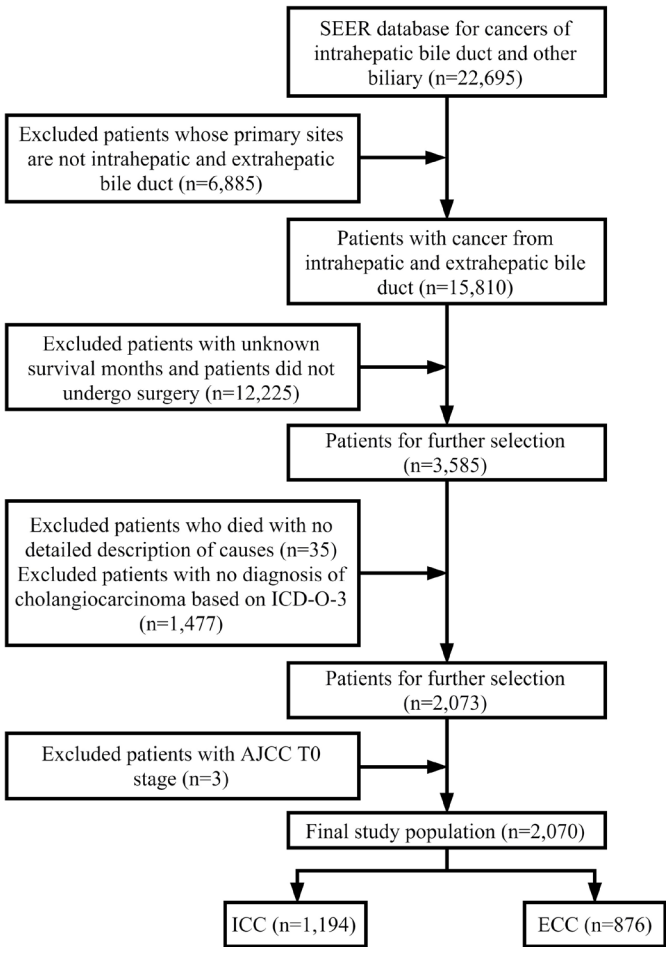

Figure 1 Diagram for patient selection. When selecting the cancer of intrahepatic bile duct and other biliary, we got a total of 22 695 cases. Based on the primary sites (intrahepatic and extrahepatic bile duct), 15 810 cases were left. The patients who had unknown survival months were excluded. Besides, the patients who were unable to undergo surgery were excluded. Subsequently, the patients with no detailed description of causes of death were excluded. The ICD-O-3 hist/behaviour was used to confirm the diagnosis of cholangiocarcinoma. Three patients had a tumour T stage of T0 and were then excluded. In the end, 2070 patients were included for final analysis. AJCC, American Joint Committee on Cancer; ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; SEER, Surveillance, Epidemiology and End Results.

confirm the diagnosis of CC; therefore, 2073 patients remained. Three patients had a tumour T stage of T0 and were excluded. Finally, 2070 patients were identified, including 876 with ECC and 1194 with ICC. The patients' selection diagram was shown in figure 1.

Subsequently, general and clinicopathological traits were compared between ECC and ICC (table 1). The age of the patients in ECC group (66.03±11.19 years) was significantly older than that of the ICC group (63.54±11.78 years) (p<0.001). In the ECC group, 64.73% were male, and in the ICC group, 48.58% of the patients were male. There was also a difference in terms of race: 6.51% black, 74.89% white and 18.49% other races in the ECC group; and 7.12% black, 79.31% white and 13.57% other races in the ICC group. The percent of married patients in

Table 1 General traits between extrahepatic and intrahepatic cholangiocarcinoma

Variable	Extrahepatic group (n=876)	Intrahepatic group (n=1194)	P value
Age (years)	66.03±11.19	63.54±11.78	**<0.001**
Age			**0.001**
≤60 years	254 (29.00%)	427 (35.76%)	
>60 years	622 (71.00%)	767 (64.24%)	
Sex			**<0.001**
Male	567 (64.73%)	580 (48.58%)	
Female	309 (35.27%)	614 (51.42%)	
Race			**0.008**
Black	57 (6.51%)	85 (7.12%)	
White	656 (74.89%)	947 (79.31%)	
Others	162 (18.49%)	162 (13.57%)	
Unknown	1 (0.11%)	0 (0%)	
Marital status			**0.025**
Single	240 (27.40%)	382 (31.99%)	
Married	609 (69.52%)	763 (63.90%)	
Unknown	27 (3.08%)	49 (4.10%)	
Differentiation			**<0.001**
Grade I	97 (11.07%)	105 (8.79%)	
Grade II	368 (42.01%)	510 (42.71%)	
Grade III	274 (31.28%)	305 (25.54%)	
Grade IV	3 (0.34%)	14 (1.17%)	
Unknown	134 (15.30%)	260 (21.78%)	
AJCC clinical stage			**<0.001**
Stage I	246 (28.08%)	448 (37.52%)	
Stage II	418 (47.72%)	206 (17.25%)	
Stage III	108 (12.33%)	382 (31.99%)	
Stage IV	68 (7.76%)	117 (9.80%)	
Unknown	36 (4.11%)	41 (3.43%)	
T stage			**<0.001**
T1	112 (12.79%)	520 (43.55%)	
T2	242 (27.63%)	275 (23.03%)	
T3	366 (41.78%)	210 (17.59%)	
T4	124 (14.16%)	143 (11.98%)	
Tx	32 (3.65%)	46 (3.85%)	
N stage			**<0.001**
N0	474 (54.11%)	933 (78.14%)	
N1	371 (42.35%)	217 (18.17%)	
Nx	31 (3.54%)	44 (3.69%)	
M stage			0.276
M0	785 (89.61%)	1046 (87.60%)	
M1	68 (7.76%)	117 (9.80%)	
Mx	23 (2.63%)	31 (2.60%)	

Bold P values indicate that the corresponding item has statistical significance.
AJCC, American Joint Committee on Cancer.

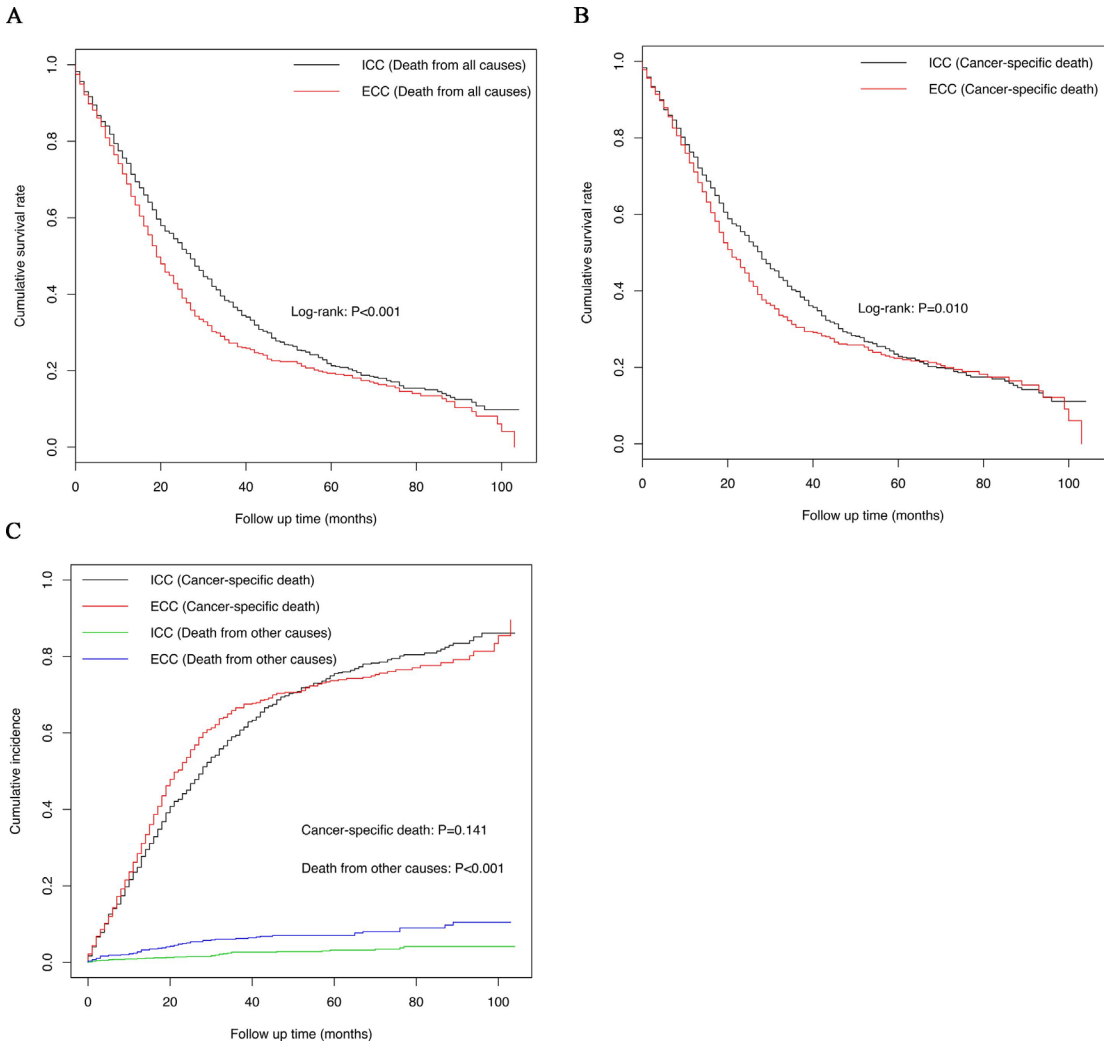

Figure 2 Comparison of postoperative survival between extrahepatic and intrahepatic cholangiocarcinoma before PSM. The postoperative overall survival (cancer-specific death and death from other reasons combined) of ECC was worse than that of ICC (Kaplan-Meier method; p<0.001; A). The cumulative survival (including cancer-specific death only) of ECC was worse than that of ICC (Kaplan-Meier method; p=0.010; B). The postoperative incidences of death from cancer-specific death between ECC and ICC were not different [p=0.141; CIF method; C; however, the postoperative incidence of death from other causes in the ECC group was higher than that of the ICC group (p<0.001; CIF method; C)]. CIF, cumulative incidence function; ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; PSM, propensity score-matched.

the ECC group (69.52%) was higher than that of the ICC group (63.90%). There was a difference in terms of tumour differentiation: 11.07% grade I, 42.01% grade II, 31.28% grade III and 0.34% grade IV in the ECC group; and 8.79% grade I, 42.71% grade II, 25.54% grade III and 1.17% grade IV in the ICC group (p<0.001). In addition, there were significant differences in terms of AJCC clinical stage, T stage and N stage (p<0.001). The percentages of the patients of ECC and ICC with M1 stage were 7.76% and 9.80%, respectively. No significant difference was found between groups in M stage (p=0.276).

Survival analysis before PSM

With all collected data, we next explored whether there was a difference in postoperative survival between the ECC and ICC groups. As shown in figure 2A, when all-cause death (including cancer-specific death and death from other causes) was regarded as the final outcome, the result of Kaplan-Meier method showed that the postoperative cumulative survival rates in the ECC group (3year: 27.21%, 5year: 19.34%, 7year: 13.42%) were significantly lower than those of the ICC group (3year: 37.95%, 5year: 21.28%, 7year: 14.97%; p<0.001). No crossing of Kaplan-Meier curves was observed and meanwhile the test for scaled Schoenfeld residuals showed p=0.15, so the PH assumption was met. The result of Cox-PH model showed that the HR and 95% CI for ECC relative to ICC were 1.23 and 1.11 to 1.37, respectively (p<0.01).

When cancer-specific death was regarded as the only final outcome (death from other causes and remaining survival were considered censored data), the result of Kaplan-Meier method showed that the postoperative cumulative survival rates in the ECC group (3year: 30.42%, 5year: 22.33%, 7year: 17.44%) were still significantly lower than those of the ICC group (3year: 39.81%,

5 year: 22.82%, 7 year: 16.98%; figure 2B; p=0.010). The test for scaled Schoenfeld residuals showed p=0.12 but there was a crossing of Kaplan-Meier curves, so the PH assumption was not met. The result of Cox-PH model showed that the HR for ECC relative to ICC was 1.17 (95% CI: 1.04 to 1.30) in ≤64.7 months' follow-up (p=0.01) and 0.97 (95% CI: 0.51 to 1.85) in >64.7 months' follow-up (p=0.92).

When cancer-specific death and death from other causes were considered a pair of competing risk events, the result of CIF method showed that there were no differences in postoperative cancer-specific death rates between the ECC group (3 year: 66.58%, 5 year: 73.65%, 7 year: 77.62%) and the ICC group (3 year: 59.39%, 5 year: 75.53%, 7 year: 80.91%; figure 2C; p=0.141). There was a crossing of survival curves, so the PH assumption was not met. The result of subdistribution hazard model showed that the HR for ECC relative to ICC was 1.12 (95% CI: 1.00 to 1.26) in ≤50.4 months' follow-up (p=0.05) and 0.81 (95% CI: 0.53 to 1.25) in >50.4 months' follow-up (p=0.34). The result of CIF method showed that the post-operative rates of death from other causes in the ECC group (3 year: 6.22%, 5 year: 7.02%, 7 year: 8.96%) were significantly higher than those of the ICC group (3 year: 2.66%, 5 year: 3.19%, 7 year: 4.12%; figure 2C; p<0.001).

PSM analysis

To balance the difference in general and clinicopathological traits between the ECC and ICC groups, we conducted PSM analysis (table 2). After PSM analysis, no difference was found between groups in terms of age, gender, race, marital status, tumour differentiation, AJCC clinical stage or T/N/M stage (all p>0.05), reflecting the satisfying effect of PSM analysis.

Survival analysis after PSM analysis

To demonstrate whether there was a difference between the ECC and ICC groups in the newly formed cohort, we conducted another survival analysis.

When all-cause death (including cancer-specific death and death from other causes) was regarded as the final outcome, the result of Kaplan-Meier method showed that there were no differences in postoperative cumulative survival rates between the ECC group (3 year: 32.26%, 5 year: 19.60%, 7 year: 14.70%) and the ICC group (3 year: 39.95%, 5 year: 25.25%, 7 year: 17.59%; figure 3A; p=0.186). The test for scaled Schoenfeld residuals showed p=0.93 but there was a crossing of Kaplan-Meier curves, so the PH assumption was not met. The result of Cox-PH model showed that the HR for ECC relative to ICC was 1.16 (95% CI: 0.88 to 1.53) in ≤51.1 months' follow-up (p=0.30) and 1.91 (95% CI: 0.68 to 5.35) in >51.1 months' follow-up (p=0.22).

When cancer-specific death was regarded as the final outcome only (death from other causes and remaining survival were considered censored data), the result of Kaplan-Meier method still indicated that there were no differences in postoperative cumulative survival rates between the ECC group (3 year: 36.14%, 5 year: 21.95%, 7 year: 19.76%) and the ICC group (3 year: 41.56%, 5 year: 26.26%, 7 year: 18.29%; figure 3B; p=0.500). The test for scaled Schoenfeld residuals showed p=0.97 but there was

Table 2 Propensity score-matched analysis

Variable	Extrahepatic group (n=173)	Intrahepatic group (n=173)	P value
Age (years)	66.11±10.63	64.00±11.46	0.077
Age			0.489
≤60 years	52 (30.06%)	58 (33.53%)	
>60 years	121 (69.94%)	115 (66.47%)	
Sex			0.738
Male	108 (62.43%)	111 (64.16%)	
Female	65 (37.57%)	62 (35.84%)	
Race			0.424
Black	3 (1.73%)	3 (1.73%)	
White	151 (87.28%)	143 (82.66%)	
Others	19 (10.98%)	27 (15.61%)	
Marital status			0.594
Single	43 (24.86%)	41 (23.70%)	
Married	124 (71.68%)	129 (74.57%)	
Unknown	6 (3.47%)	3 (1.73%)	
Differentiation			0.488
Grade I	18 (10.40%)	18 (10.40%)	
Grade II	69 (39.88%)	81 (46.82%)	
Grade III	39 (22.54%)	38 (21.97%)	
Unknown	47 (27.17%)	36 (20.81%)	
AJCC clinical stage			0.233
Stage I	86 (49.71%)	82 (47.40%)	
Stage II	8 (4.62%)	10 (5.78%)	
Stage III	45 (26.01%)	60 (34.68%)	
Stage IV	22 (12.72%)	13 (7.51%)	
Unknown	12 (6.94%)	8 (4.62%)	
T stage			0.196
T1	89 (51.45%)	91 (52.60%)	
T2	9 (5.20%)	14 (8.09%)	
T3	14 (8.09%)	5 (2.89%)	
T4	49 (28.32%)	54 (31.21%)	
Tx	12 (6.94%)	9 (5.20%)	
N stage			0.894
N0	128 (73.99%)	130 (75.14%)	
N1	40 (23.12%)	37 (21.39%)	
Nx	5 (2.89%)	6 (3.47%)	
M stage			0.276
M0	148 (85.55%)	156 (90.17%)	
M1	22 (12.72%)	13 (7.51%)	
Mx	3 (1.73%)	4 (2.31%)	

Bold P values indicate that the corresponding item has statistical significance.
AJCC, American Joint Committee on Cancer.

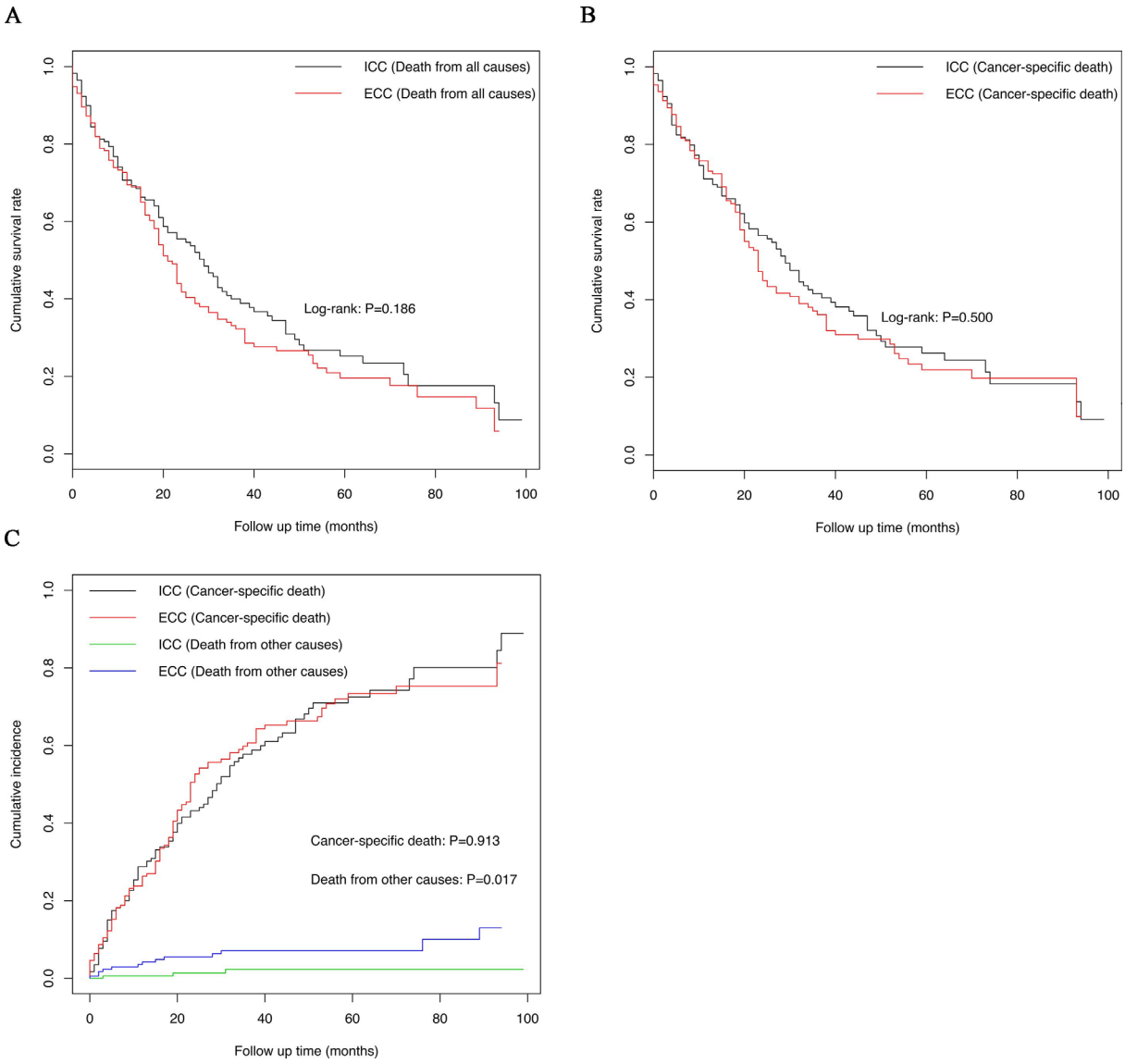

Figure 3 Comparison of postoperative survival between extrahepatic and intrahepatic cholangiocarcinoma after PSM. The postoperative overall survival (combined cancer-specific death and death from other reasons) of ECC and ICC was not different (Kaplan-Meier method; p=0.186; A). The cumulative survival (include cancer-specific death only) of ECC and ICC was also not different (Kaplan-Meier method; p=0.500; B). The postoperative incidences of death from cancer-specific death between ECC and ICC were not different [p=0.913; CIF method; C; however, the postoperative incidence of death from other causes for the ECC group was higher than that of the ICC group (p=0.017; CIF method; C)]. CIF, cumulative incidence function; ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; PSM, propensity score-matched.

a crossing of Kaplan-Meier curves, so the PH assumption was not met. The result of Cox-PH model showed that the HR for ECC relative to ICC was 1.09 (95% CI: 0.82 to 1.45) in ≤50.1 months' follow-up (p=0.57) and 1.32 (95% CI: 0.47 to 3.70) in >50.1 months' follow-up (p=0.60).

Moreover, when cancer-specific death and death from other causes were considered in a competing risk model, the result of CIF method showed that there were no differences in postoperative cancer-specific death rates between the ECC group (3 year: 60.65%, 5 year: 73.31%, 7 year: 75.27%) and the ICC group (3 year: 57.75%, 5 year: 72.45%, 7 year: 80.11%; figure 3C; p=0.913). There was a crossing of survival curves, so the PH assumption was not met. The result of subdistribution hazard model showed that the HR for ECC relative to ICC was 1.05 (95% CI: 0.79 to 1.39) in ≤47 months' follow-up (p=0.75) and 0.87 (95% CI: 0.35 to 2.17) in >47 months' follow-up (p=0.77). The result of CIF method showed that the postoperative rates of death from other causes in the ECC group (3 year: 7.09%, 5 year: 7.09%, 7 year: 10.03%) were significantly higher than those of the ICC group (3 year: 2.30%, 5 year: 2.30%, 7 year: 2.30%; figure 3C; p=0.017).

Subgroup analysis after PSM

We performed subgroup analysis to determine whether the difference in survival could be presented in various conditions based on four variables: age at diagnosis, gender, race and AJCC clinical stage (table 3). We found that there were

Table 3 Subgroup analysis after propensity score-matched analysis

	Cumulative incidence of cancer-specific death			P1 value	P2 value
Variable	**3 years**	**5 years**	**7 years**	**Cancer-specific death**	**Other reasons**
Overall				0.913	**0.017**
ICC	57.75%	72.45%	80.11%		
ECC	60.65%	73.31%	75.27%		
Age					
≤60				0.301	**0.015**
ICC	51.74%	61.29%	69.03%		
ECC	42.40%	57.01%	57.01%		
>60				0.384	0.292
ICC	60.26%	76.76%	85.05%		
ECC	68.39%	80.21%	83.79%		
Sex					
Female				0.370	**0.027**
ICC	53.02%	73.50%	82.61%		
ECC	58.26%	77.39%	77.39%		
Male				0.618	0.168
ICC	60.81%	71.56%	77.73%		
ECC	61.92%	70.54%	73.34%		
Race					
Black				0.096	NA
ICC	0%	NA	NA		
ECC	NA	NA	NA		
White				0.841	0.062
ICC	60.88%	73.76%	81.83%		
ECC	62.16%	71.96%	74.11%		
Others				0.984	0.073
ICC	47.45%	70.44%	70.44%		
ECC	42.88%	NA	NA		
AJCC clinical stage					
Grade I				0.901	0.105
ICC	48.48%	64.49%	82.36%		
ECC	53.05%	66.10%	69.01%		
Grade II				0.364	NA
ICC	44.44%	NA	NA		
ECC	72.66%	NA	NA		
Grade III				0.628	0.442
ICC	67.88%	82.04%	82.04%		
ECC	65.35%	79.78%	NA		
Grade IV				0.927	0.450
ICC	89.20%	NA	NA		
ECC	87.44%	NA	NA		
Unknown				0.721	0.237
ICC	53.13%	53.13%	NA		
ECC	45.95%	57.38%	57.38%		

P1 value and P2 value represent the P values for comparisons of cancer-specific death and death from other causes with cumulative incidence function (CIF) method, respectively.
Bold P values indicate that the corresponding item has statistical significance.
AJCC, American Joint Committee on Cancer; ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; NA, not available.

still no differences in postoperative cancer-specific death rates between ECC and ICC after stratifying the considered variables (p>0.05). In addition, the postoperative death rate from other causes for the ECC group was higher than that for the ICC group in patients aged ≤60 and in female patients (p=0.015 and p=0.027, respectively).

DISCUSSION

In the past several decades, statistical methods for survival analysis have undergone much development.[13] Current methods most used for comparing differences of survival primarily include the traditional Kaplan-Meier method and the recently proposed CIF method. The latter has received much attention in recent years because it considers potential interference of competing risks of non-cancer-specific death. Our study compared the difference of these two methods in analysing postoperative survival of ECC and ICC, hoping to conduct a more rigorous survival analysis with an exception of the interference of non-cancer-specific death.

In this paper, with the traditional Kaplan-Meier method, we showed that postoperative death (for death from all causes and for cancer-specific death) of the ECC group was higher than that of the ICC group in the natural state. Subsequently, after excluding the potential influence of competing events of non-cancer death, survival analysis using the CIF method showed that there were no differences in postoperative cancer-specific deaths, while death from other reasons in the ECC group was higher than that of the ICC group. Taken together, these data indicated that the general understanding regarding the worse prognosis of ECC compared with ICC might be interfered by non-cancer specific death. Postoperative survival was more inclined to be no different in the natural state. So, adopting CIF analysis has successfully helped us to clarify the difference of ECC and ICC in postoperative survival. The Kaplan-Meier method is not an appropriate approach to estimate survival in the presence of competing risks.

Biased variables existing in the compared groups might interfere with the comparison of postoperative survival. Therefore, in the present study, PSM analysis acted as an advanced statistical method to balance the differences between the compared groups. It would become more comparable to evaluate the differences of postoperative survival between the ECC and ICC groups under nearly the same extent of disease. After PSM analysis, surprisingly, we found that there were no differences in postoperative all-cause death (Kaplan-Meier method), cancer-specific death (Kaplan-Meier method) and cancer-specific death (CIF method). In particular, although there was a difference in death from other causes, the postoperative all-cause death still showed no differences between the groups. To quantify the risk of death for ECC relative to ICC, the HR and 95% CI were estimated using Cox-PH model or subdistribution hazard model. Importantly, the results of these two models supported the results obtained from the Kaplan-Meier method and the CIF method. Additionally, the subgroup analysis validated that there were no differences in postoperative cancer-specific death in various stratified conditions between the ECC and ICC groups. Taken together, there was enough evidence to conclude that no difference could be found between the ECC and ICC groups in terms of postoperative cancer-specific death, both in the natural disease state and also in multiple variable-matched conditions.

After reviewing the published articles, we found that previous studies in the investigation of ECC and ICC mainly focused on their risk factors, together or individually.[14] With respect to risk factors, one study including the SEER database over 10 years found that risk factors for incidence of ECC and ICC were similar.[15] Similarly, one systematic review and meta-analysis found hepatitis C virus (HCV) was the same risk factor for ECC and ICC occurrence.[16] Furthermore, one study investigated the demographic patterns and geographical variation of ICC, ECC and hepatocellular carcinoma (HCC) and found that ICC and ECC (but not HCC) were more likely to belong to the same type of tumour.[17] In addition, another study investigated whether tumour location had an influence on ECC by dividing it into proximal, middle and distal; they found that tumour location was unable to independently predict cancer-specific survival after resection.[18] For the ECC and ICC, as we supposed, tumour location (extrahepatic or intrahepatic) could also not independently predict cancer-specific survival after therapy. We found no difference in postoperative cancer-specific survival between the ECC and ICC groups. Therefore, the data suggested that the prognosis of the same pathological type of CC would seldom be influenced by tumour location.

However, some studies showed that there were differences between ECC and ICC in some other aspects. One study reviewed the literature and found some potential risk factors have a differential effect on the occurrence of ECC and ICC.[19] Another study included 61 ICC patients and 129 ECC patients and concluded that there was a difference in risk factors for tumour occurrence.[20] In addition, one study (including three ECC patients and eight ICC patients) investigated the change in genomics between ECC and ICC, and found there was a difference in gene mutations.[21] It is regrettable that this study was restricted by small sample size and that no further validation was given. In addition, one systematic review and meta-analysis investigated the differences in biomarkers between ECC and ICC and concluded that there were differences in marker expression between ECC and ICC.[22] From the difference in methylation profiles between ECC and ICC, another study concluded that they owned unique biological processes.[23]

As for the difference of postoperative survival for ECC and ICC, previous studies showed inconsistent results. Guglielmi *et al* found that ICC have longer survival rate compared with ECC (perihilar CC).[5] Mukkamalla *et al* found that ECC have longer survival rate compared with ICC.[6] Ercolani *et al* showed that there was no difference in overall survival between ICC and ECC (peri-hilar and distal CC).[7] In our opinion, the cytological type might primarily determine the behaviour characteristics of CC as well as postoperative cancer-specific survival. ECC and ICC might be different certainly in some aspects, such as risk factors, but they were the same in pathology, so the prognosis of them showed no difference.

The current study was large but had several potential limitations. First, as we found, the causes of ECC or ICC

were not reported in detail in the SEER database. This might be a confounding factor influencing the final result. Therefore, more original studies should include this variable and should make a further analysis. Second, our study was conducted on USA population. For patients from other countries, whether same conclusion could be obtained still needed to be determined in the future. Despite these potential limitations, the present study included a large population from multiple centres, utilising a competing risk model to compare postoperative cancer-specific death rates, and it was therefore a reliable and convincing study.

In conclusion, our study found that there were no differences in postoperative cancer-specific death rates between ECC and ICC both in the natural state and also in multiple variable-matched conditions.

Contributors W-WL, J-FT and X-HY are responsible for data cleaning, management and analysis. Z-JC contributed to the study's design and analysis. Y-BW is responsible for all aspects of the study including conceiving of and designing the study, acquiring the data, analysing and interpreting the data and drafting and submitting manuscripts. All authors critically revised the manuscript and approved of the final version. Y-BW is the guarantor.

Funding The study was funded by Chongqing medical scientific research project (Joint project of Chongqing Health Commission and Science and Technology Bureau: No. 2021MSXM139). The present study was also financially supported by the Programme for Science and Technology Department of Zhejiang Province (Grant No. LGF18H220001), the Zhejiang Province Health Department (Grant No. 2018253605) and the Science and Technology Department of Lishui City (Project No. 2017ZDXK05).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID iD

Yun-Bing Wang http://orcid.org/0000-0002-7159-2299

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