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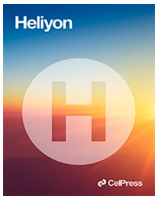

Research article

Sex disparity in clinical characteristics and long-term prognosis after liver resection for patients with intrahepatic cholangiocarcinoma: A propensity score matching analysis

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ABSTRACT

Aim: To compare the survival outcomes between male and female patients with intrahepatic cholangiocarcinoma who underwent liver resection.

Methods: Data from 976 consecutive intrahepatic cholangiocarcinoma patients undergoing liver resection between January 2005 and May 2013 at the Eastern Hepatobiliary Surgery Hospital were prospectively collected and retrospectively reviewed. Patient clinicopathological characteristics, overall survival, and cumulative recurrence rates were compared between male and female patients using propensity score matching.

Results: Propensity score matching generated 313 matched pairs of patients. Among the entire cohort, the 1-, 3-, and 5-year overall survival and recurrence rates of the male and female patients were 60.2 %, 37.3 %, and 27.7 % vs. 65.8 %, 40.4 %, and 31.0 % ($P = 0.380$) and 50.6 %, 67.4 %, and 74.2 % vs. 44.4 %, 63.5 %, and 69.6 % ($P = 0.123$), respectively. In the matched cohort, the 1-, 3-, and 5-year overall survival and recurrence rates of the male and female patients were 60.6 %, 35.9 % and 22.4 % vs. 66.4 %, 40.6 % and 31.1 % ($P = 0.041$) and 51.5 %, 69.3 % and 83.9 % vs. 44.3 %, 63.6 %, and 69.9 % ($P = 0.041$), respectively. After adjustment for other confounding variables by multivariate Cox regression analysis, male sex was independently associated with worse overall survival (hazard ratio = 1.322, 95 % confidence interval: 1.079–1.621, $P = 0.007$) and tumor recurrence (hazard ratio = 1.337, 95 % confidence interval: 1.088–1.645, $P = 0.006$). A subgroup analysis of patients younger than 55 years old after propensity score matching

Abbreviations: ICC, intrahepatic cholangiocarcinoma; HCC, hepatocellular carcinoma; PSM, propensity score matching; TACE, transarterial chemoembolization; PRFA, percutaneous radiofrequency ablation; HBV, hepatitis B virus; HCV, hepatitis C virus; PT, prothrombin time; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; CT, computed tomography; GI, gastrointestinal; MRI, magnetic resonance imaging; PET, Positron emission tomography; OS, overall survival; TTR, time to recurrence; HR, hazard ratios; CI, confidence intervals; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet counts; MVI, microvascular invasion; IQR, interquartile range; BA, bile acid.

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showed that male patients had significantly worse overall survival and higher recurrence rates than female patients after surgery, while no significant difference in long-term overall survival and recurrence was observed between male and female patients older than 55 years old after propensity score matching.
Conclusion: Male sex was an independent risk factor for overall survival and tumor recurrence in patients after liver resection for intrahepatic cholangiocarcinoma.

1. Introduction

Intrahepatic cholangiocarcinoma (ICC), arising from the endothelial cells of segmental or proximal branches of the bile duct [1], accounts for 10–15 % of primary liver cancer [2]. Although relatively rare, its incidence and mortality have been increasing over the last three decades, and it has a rather poor prognosis [3,4]. Currently, liver resection remains the only established therapy to achieve a possible cure for ICC patients [5]. Even after curative-intent resection, the 5-year overall survival (OS) rate is only 25–40 %, with a 5-year recurrence rate as high as 50–70 % [6,7]. For patients with advanced ICC, doublet chemotherapy with gemcitabine and cisplatin has been recommended as the first-line treatment for over 10 years, but recent studies using combined immune checkpoint inhibitors with chemotherapy have begun to shift the paradigm [8,9]. Molecular targeted therapies have recently been approved as second-line treatment for selected patients harboring actionable genomic alterations [10,11].

Numerous attempts have been made to investigate the factors associated with the long-term prognosis of patients undergoing liver resection for ICC, such as aggressive tumor characteristics, hepatitis B virus infection, and treatment strategies [12–15]. For hepatocellular carcinoma (HCC), the most common primary liver cancer, previous studies have reported a significantly higher incidence and poorer long-term survival in male patients than in female patients [16]. The striking disparities can be partly explained by the protective role of estrogen [17]. In clinical practice, similar disparities could be observed in ICC patients—female patients seem to have a relatively better long-term survival than male patients after surgery. However, to our knowledge, no studies focusing on the association between sex and long-term prognosis after liver resection for ICC have been reported.

Therefore, using propensity score matching (PSM) analysis, the current study aimed to elucidate the impact of sex on long-term prognosis after liver resection for ICC.

2. Patients and methods

2.1. Patients

The data of all consecutive patients who underwent liver resection for histologically proven ICC between January 2005 and May 2013 at the Eastern Hepatobiliary Surgery Hospital (EHBH, Shanghai, China) were prospectively collected and retrospectively analyzed. Patients who met the following inclusion criteria were identified: (a) no history of preoperative anticancer treatment, including transarterial chemoembolization (TACE), percutaneous radiofrequency ablation (PRFA), or percutaneous ethanol injection (PEI); (b) no history of other malignancies; (c) underwent R0 resection [18]; and (d) histopathologically proven ICC. Patients were excluded if they met the following criteria: (a) hilar or extrahepatic cholangiocarcinoma, including intrahepatic metastasis of extrahepatic cholangiocarcinoma; (b) tumors of uncertain origin or probable metastatic liver tumor; (c) mixed type of primary liver cancer as confirmed histopathologically; (d) perioperative mortality; (e) incomplete clinical data; and (f) lost to follow-up within 90 days after surgery.

2.2. Ethics and consent

This study was approved by the institutional ethics committee of the EHBH (No. EHBHKY2020-K-027). **Written** informed consent was obtained from all patients before surgery for using their data in the research.

2.3. Preoperative evaluation and liver resection

Before the operation, a detailed history and complete physical examination were conducted for all patients. The routine serological examinations included antigens and antibodies of hepatitis B virus (HBV) and C virus (HCV), liver function test, renal function tests, prothrombin time (PT), α-fetoprotein (AFP), carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19-9). Routine imaging studies included chest radiography or computed tomography (CT) scan, upper gastrointestinal (GI) endoscopy, abdominal ultrasound, contrast-enhanced CT scan and/or magnetic resonance imaging (MRI) of the abdomen. Positron emission tomography (PET) was performed for patients with clinical or radiological suspicion of distant metastases. A preoperative diagnosis of ICC was made mainly based on the combination of the above findings [19]. The status of perihepatic lymph nodes was evaluated with contrast-enhanced CT scan or PET. Considering that the age at which natural menopause occurs is between 45 and 55 years for women worldwide, an age of 55 years was used as a surrogate for menopause, and female patients younger than 55 years were defined as premenopausal [20].

Liver resection was carried out based on Couinaud's segments, sectors, and hemilivers. Major hepatectomy was defined as resection

Table 1
Baseline clinicopathological characteristics between male and female patients before and after propensity score matching.

Variable	Whole cohort (n = 976)			PSM matched cohort (n = 626)		
	Female (n = 322)	Male (n = 654)	P- value	Female (n = 313)	Male (n = 313)	P- value
Age, years						
<55	135 (41.9)	343 (52.4)	**0.002**	186 (59.4)	166 (53.0)	0.126
≥55	187 (58.1)	311 (47.6)		127 (40.6)	147 (47.0)	
Diabetes mellitus						
No	303 (94.1)	609 (93.1)	0.657	294 (93.9)	297 (94.9)	0.728
Yes	19 (5.9)	45 (6.9)		19 (6.1)	16 (5.1)	
Hepatolithiasis						
No	259 (80.4)	587 (89.8)	**<0.001**	256 (81.8)	259 (82.7)	0.834
Yes	63 (19.6)	67 (10.2)		57 (18.2)	54 (17.3)	
HBsAg						
Negative	207 (64.3)	291 (44.5)	**<0.001**	198 (63.3)	195 (62.3)	0.869
Positive	115 (35.7)	363 (55.5)		115 (36.7)	118 (37.7)	
HCV-Ab						
Negative	314 (97.5)	639 (97.7)	1.000	305 (97.4)	306 (97.8)	1.000
Positive	8 (2.5)	15 (2.3)		8 (2.6)	7 (2.2)	
TBIL, mg/dL						
≤1	257 (79.8)	485 (74.2)	0.062	249 (79.6)	238 (76.0)	0.336
>1	65 (20.2)	169 (25.8)		64 (20.4)	75 (24.0)	
ALB, g/L						
< 35	220 (68.3)	541 (82.7)	**<0.001**	216 (69.0)	205 (65.5)	0.394
≥ 35	102 (31.7)	113 (17.3)		97 (31.0)	108 (34.5)	
ALT, IU/L						
≤ 80	255 (79.2)	431 (65.9)	**<0.001**	247 (78.9)	238 (76.0)	0.444
> 80	67 (20.8)	223 (34.1)		66 (21.1)	75 (24.0)	
AST, IU/L						
≤ 80	251 (78.0)	487 (74.5)	0.266	243 (77.6)	255 (81.5)	0.276
> 80	71 (22.0)	167 (25.5)		70 (22.4)	58 (18.5)	
PT, seconds						
≤ 13	300 (93.2)	572 (87.5)	**0.009**	291 (93.0)	287 (91.7)	0.652
> 13	22 (6.8)	82 (12.5)		22 (7.0)	26 (8.3)	
PLT, 10^9/L						
≥100	309 (96.0)	592 (90.5)	**0.004**	300 (95.8)	303 (96.8)	0.671
<100	13 (4.0)	62 (9.5)		13 (4.2)	10 (3.2)	
AFP, μg/L						
≤ 20	270 (83.9)	490 (74.9)	**0.002**	261 (83.4)	267 (85.3)	0.582
> 20	52 (16.1)	164 (25.1)		52 (16.6)	46 (14.7)	
CEA, μg/L						
≤ 10	255 (79.2)	553 (84.6)	**0.046**	249 (79.6)	253 (80.8)	0.764
> 10	67 (20.8)	101 (15.4)		64 (20.4)	60 (19.2)	
CA19–9, IU/mL						
≤ 39	131 (40.7)	312 (47.7)	**0.045**	128 (40.9)	139 (44.4)	0.419
> 39	191 (59.3)	342 (52.3)		185 (59.1)	174 (55.6)	
Child-Pugh grade						
A	301 (93.5)	616 (94.2)	0.768	293 (93.6)	292 (93.3)	1.000
B	21 (6.5)	38 (5.8)		20 (6.4)	21 (6.7)	
Surgery time, h						
< 3	258 (80.1)	545 (83.3)	0.217	252 (80.5)	257 (82.1)	0.608
≥ 3	64 (19.9)	109 (16.7)		61 (19.5)	56 (17.9)	
Blood loss, mL						
<400	230 (71.4)	498 (76.1)	0.111	226 (72.2)	238 (76.0)	0.273
≥ 400	92 (28.6)	156 (23.9)		87 (27.8)	75 (24.0)	
Major hepatectomy						
No	195 (60.6)	461 (70.5)	**0.002**	193 (61.7)	192 (61.3)	1.000
Yes	127 (39.4)	193 (29.5)		120 (38.3)	121 (38.7)	
Tumor diameter, cm						
< 5 cm	111 (34.5)	260 (39.8)	0.123	109 (34.8)	119 (38.0)	0.455
≥ 5 cm	211 (65.5)	394 (60.2)		204 (65.2)	194 (62.0)	
Tumor number						
Solitary	225 (69.9)	448 (68.5)	0.717	218 (69.6)	213 (68.1)	0.730
Multiple	97 (30.1)	206 (31.5)		95 (30.4)	100 (31.9)	
Cirrhosis						
No	292 (90.7)	449 (68.7)	**<0.001**	283 (90.4)	285 (91.1)	0.890
Yes	30 (9.3)	205 (31.3)		30 (9.6)	28 (8.9)	
MVI						
No	286 (88.8)	500 (76.5)	**<0.001**	277 (88.5)	277 (88.5)	1.000
Yes	36 (11.2)	154 (23.5)		36 (11.5)	36 (11.5)	
Nodal metastasis						

(*continued on next page*)

Table 1 (*continued*)

Variable	Whole cohort (n = 976)			PSM matched cohort (n = 626)		
	Female (n = 322)	Male (n = 654)	P- value	Female (n = 313)	Male (n = 313)	P- value
No	252 (78.3)	538 (82.3)	0.159	246 (78.6)	244 (78.0)	0.923
Yes	70 (21.7)	116 (17.7)		67 (21.4)	69 (22.0)	
7th TNM stage						
I	155 (48.1)	288 (44.0)	0.057	151 (48.2)	151 (48.2)	1.000
II	77 (23.9)	203 (31.0)		76 (24.3)	75 (24.0)	
III	9 (2.8)	27 (4.1)		9 (2.9)	9 (2.9)	
IV	81 (25.2)	136 (20.8)		77 (24.6)	78 (24.9)	

Values shown is n (%).
Abbreviations: PSM, propensity score matching; HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; PLT, platelet counts; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; MVI, Microvascular invasion.

of 3 or more segments, while minor hepatectomy was defined as resection of 2 or fewer segments. Routine dissection of lymph nodes in the hepatoduodenal ligament and retropancreatic and/or para-aortic lymph nodes was performed for patients with ICC diagnosed pre- or intraoperatively. The newly found intrahepatic nodules and direct invasions of adjacent structures identified intraoperatively were resected whenever technically possible.

Histopathologic study of the resected specimens was carried out independently by three pathologists who came to a consensus by discussion if there was any controversy [21]. Pathological features, such as tumor diameter, number, tumor capsule, surgical margin, vascular invasion, nodal metastasis and cirrhosis, were documented, and the degree of cell differentiation was determined.

2.4. Follow-up and endpoints

After surgery, patients were followed up once every 2 months for the first 2 years and then every 3–6 months thereafter. Serum levels of CA19-9, CEA, and AFP; liver function tests; and abdominal ultrasound were performed at each visit. Contrast-enhanced CT or MRI was performed once every 6 months or earlier if tumor recurrence was clinically suspected. ICC recurrence or metastasis was defined as the appearance of a newly detected tumor confirmed on two radiologic images, with or without elevation of serum tumor markers. Patients with tumor recurrence were treated with reresection, percutaneous ablation, radiotherapy, TACE, and supportive care, according to the patients' general condition, liver function, and patterns of recurrence.

The primary endpoints were OS and time to recurrence (TTR). OS was measured from the date of liver resection to the date of patient death or last follow-up. TTR was calculated from the date of surgery to the date when recurrence or metastasis was diagnosed.

2.5. Statistical analysis

Demographic and clinicopathological characteristics of all included patients were summarized as frequencies and percentages. Categorical variables were compared using Pearson's chi-squared test or Fisher's exact test as appropriate. Survival curves for OS and tumor recurrence were calculated using the Kaplan–Meier method and compared using the log-rank test. Multivariate Cox regression analysis was carried out to assess the impact of sex on recurrence and survival after adjustment for other potential prognostic factors. Variables with $P < 0.05$ in univariate analysis were subjected to multivariate Cox-regression model using forward stepwise variable selection. The resulting hazard ratios (HRs) and 95 % confidence intervals (CIs) were reported.

PSM analysis was used to reduce the selection bias. Logistic regression was used to create propensity scores for the male and female patients [22–24]. The following variables were included in the propensity model: Age, hepatolithiasis, HBsAg, albumin (ALB), alanine aminotransferase (ALT), platelet counts (PLT), AFP, CEA, CA19-9, resection type, cirrhosis, and microvascular invasion (MVI). The model was used to provide a one-to-one nearest-neighbor match between the two groups, with a caliper width of 0.03 [24].

Statistical analysis was performed using SPSS 19.0 for Windows (IBM Corp, Armonk, NY, http://www.ibm.com) and R software v. 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org). All reported *P* values were two-sided, and *P* values of <0.05 were considered significant.

3. Results

3.1. Clinicopathological characteristics

A total of 976 patients who met the inclusion criteria were included in this study. Comparisons of baseline clinicopathological variables between male and female patients before and after PSM are presented in Table 1. Of the entire cohort, 654 (67.0 %) patients were male, and 322 (33.0 %) patients were female. The median age was 54.0 (interquartile range [IQR], 46.0 to 61.0) years. Significant differences existed between male and female patients in age, hepatolithiasis, HBsAg, ALB, ALT, PT, PLT, AFP, CEA, CA19-9, major hepatectomy, cirrhosis and MVI. PSM created 313 pairs of male and female patients. After PSM, the baseline clinicopathological features were all balanced between the two groups (Table 1).

3.2. Long-term OS and tumor recurrence of male and female patients before PSM

With a median follow-up of 42.5 (IQR, 25.3 to 60.9) months, the median OS of the entire cohort was 20.8 (IQR, 8.2 to 66.8) months. The postoperative 1-, 3-, and 5-year OS rates of the entire cohort were 62.1 %, 38.3 %, and 28.8 %, respectively. The 1-, 3-, and 5-year OS rates of male and female patients were 60.2 %, 37.3 %, and 27.7 % versus 65.8 %, 40.4 %, and 31.0 %, respectively ($P = 0.380$) (Fig. 1A). Multivariate Cox regression analysis demonstrated that ALB, CEA, CA19-9, tumor diameter, multiple tumors, and nodal metastasis were independent prognostic factors for OS after liver resection for ICC (Table 2 & Supplementary Table 1).

The median TTR was 12.9 (IQR, 4.3 to 70) months, and the postoperative 1-, 3-, and 5-year recurrence rates of the entire cohort were 48.2 %, 66.1 %, and 72.5 %, respectively. The postoperative 1-, 3-, and 5-year recurrence rates of male and female patients were 50.6 %, 67.4 %, and 74.2 % versus 44.4 %, 63.5 %, and 69.6 %, respectively ($P = 0.123$) (Fig. 1B). Univariate and multivariate analyses showed that tumor diameter, multiple tumors, MVI and nodal metastasis were independently associated with tumor recurrence after liver resection for ICC (Table 2 & Supplementary Table 1).

3.3. Long-term OS and tumor recurrence of male and female patients after PSM

The median OS in the PSM-matched cohort was 20.3 months (IQR, 8.8–63.2 months), with 1-, 3-, and 5-year OS rates of 63.4 %, 38.0 % and 27.4 %, respectively. Male patients had a significantly worse long-term OS than female patients after liver resection (1-, 3-, and 5-year OS rates: 60.6 %, 35.9 % and 22.4 % vs. 66.4 %, 40.6 % and 31.1 %, $P = 0.041$) (Fig. 1C). After adjustment for other confounding variables by multivariate Cox regression analysis, male sex (HR: 1.322, 95 % CI: 1.079–1.621, P = 0.007) was

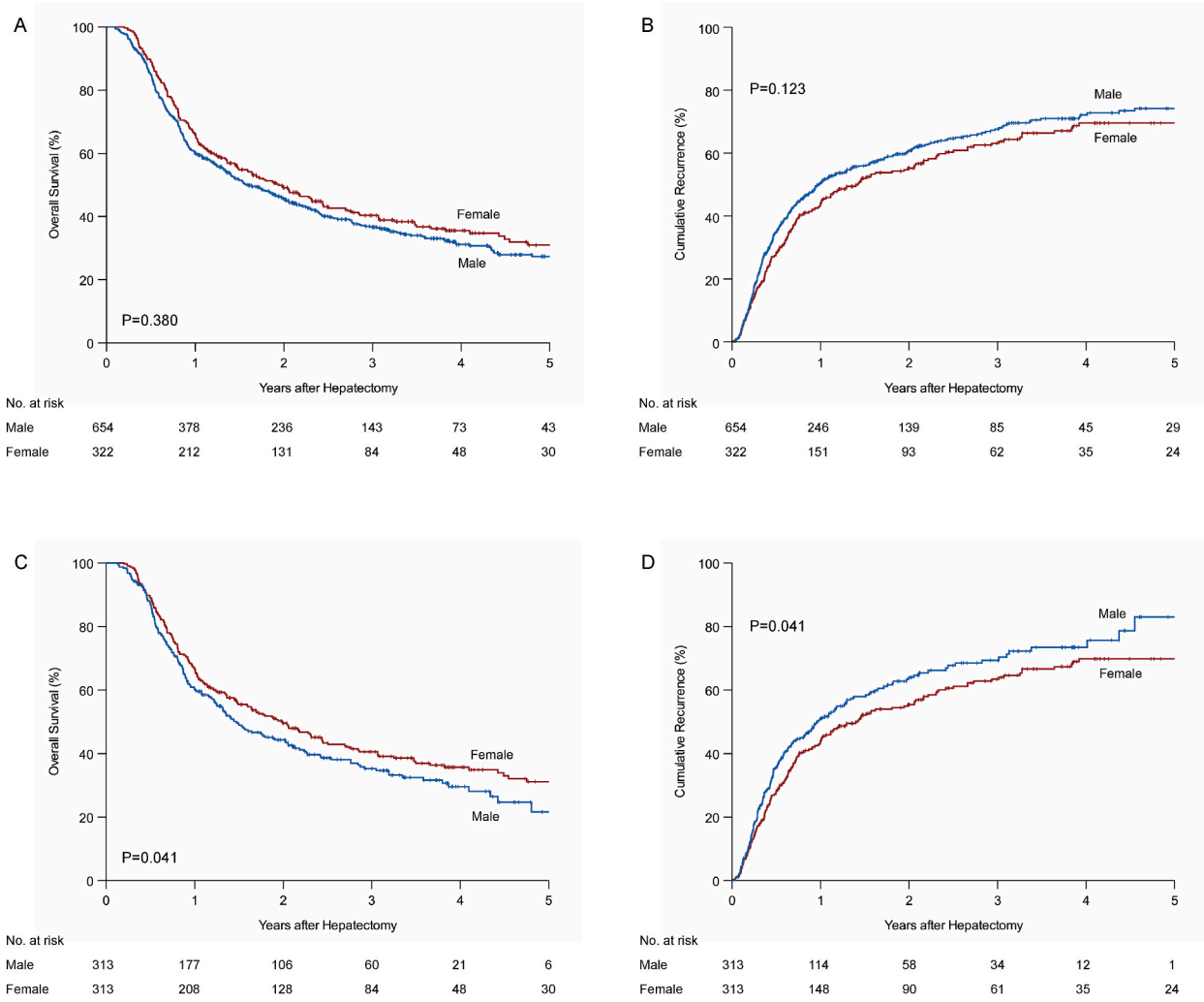

Fig. 1. Overall survival and tumor recurrence between male and female patients undergoing liver resection for intrahepatic cholangiocarcinoma. Overall survival (A) and tumor recurrence (B) of the entire cohort. Overall survival (C) and tumor recurrence (D) of the propensity score matching cohort.

Table 2
Multivariate Cox regression analysis of OS and tumor recurrence in the entire cohort.

Variable	OS			Tumor recurrence		
	HR	95 % CI	P- value	HR	95 % CI	P- value
ALB, g/L, ≥35	0.768	0.643–0.961	0.019			
CEA, μg/L, >10	1.435	1.172–1.757	<0.001			
CA19–9, IU/mL, >39	1.426	1.203–1.690	<0.001			
Tumor diameter, cm, ≥5	1.491	1.248–1.782	<0.001	1.575	1.311–1.891	<0.001
Tumor number, multiple	1.442	1.219–1.705	<0.001	1.465	1.231–1.745	<0.001
MVI, yes				1.428	1.173–1.739	<0.001
Nodal metastasis, yes	1.292	1.061–1.573	0.011	1.249	1.019–1.529	0.032

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; ALB, albumin; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; MVI, Microvascular invasion.

independently associated with worse OS after liver resection for ICC. Other variables independently associated with OS included CEA >10 μg/L (HR: 1.426, 95 % CI: 1.114–1.826, P = 0.005), CA19-9 >39 IU/mL (HR: 1.357, 95 % CI: 1.088–1.691, P = 0.007), tumor diameter ≥5 cm (HR: 1.508, 95 % CI: 1.206–1.887, P < 0.001), multiple tumors (HR: 1.512, 95 % CI: 1.231–1.857, P < 0.001) and ALB ≥35 g/L (HR: 0.701, 95 % CI: 0.559–0.878, P = 0.002) (Table 3 & Supplementary Table 2).

The median TTR in the PSM-matched cohort was 13.4 (IQR, 4.6 to 63.4) months, and the postoperative 1-, 3-, and 5-year recurrence rates were 47.3 %, 66.4 % and 74.1 %, respectively. There was a significant difference in the 1-, 3-, and 5-year recurrence rates between the male and female groups (51.5 %, 69.3 % and 83.9 % vs. 44.3 %, 63.6 %, and 69.9 %, P = 0.041) (Fig. 1D). Univariate and multivariate analyses identified that male sex (HR: 1.337, 95 % CI: 1.088–1.645, P = 0.006), tumor diameter ≥5 cm (HR: 1.631, 95 % CI: 1.293–2.057, P < 0.001), multiple tumors (HR: 1.524, 1.230–1.889, P < 0.001) and MVI (HR: 1.512, 95 % CI: 1.105–2.067, P = 0.010) were independent risk factors for tumor recurrence after liver resection for ICC (Table 3 & Supplementary Table 2).

3.4. Subgroup analysis of patients older or younger than 55 years old

The PSM matched cohort was stratified according to the age of 55 years old. For the 352 patients younger than 55 years old, 166 (47.2 %) patients were male, and 186 (52.8 %) patients were female. Male patients had significantly worse OS and recurrence rates than female patients. The 1-, 3-, and 5-year OS rates between the male and female groups were 59.1 %, 34.9 % and 21.6 % vs. 68.3 %, 42.1 % and 29.3 %, respectively ($P = 0.040$). The corresponding recurrence rates were 51.2 %, 69.8 % and 88.3 % vs. 41.7 %, 59.3 % and 79.6 %, respectively ($P = 0.016$) (Fig. 2A & B).

For the 274 patients older than 55 years after PSM, no significant difference was observed in OS and recurrence between the 147 male patients and 127 female patients. The 1-, 3-, and 5-year OS and recurrence rates of male and female patients were 61.6 %, 36.7 % and 24.2 % vs. 63.8 %, 38.6 % and 32.4 % ($P = 0.443$) and 51.8 %, 68.7 % and 78.0 % vs. 47.4 %, 69.2 % and 73.1 % ($P = 0.782$), respectively (Fig. 2C & D).

4. Discussion

Over the past few decades, progressively more attention has been given to ICC due to its increasing incidence, mortality, and poor prognosis after liver resection. In this study, a large population of 976 patients undergoing R0 resection for ICC was enrolled to investigate the sex differences in major clinical characteristics and long-term prognosis. After PSM, male patients had significantly worse OS and tumor recurrence than female patients. Multivariate Cox regression analysis demonstrated that male sex was an independent risk factor for OS and recurrence after surgery for ICC.

Differences existed in some clinicopathological variables between male and female patients before PSM, such as age, positive serum HBsAg, and cirrhosis (all $P < 0.05$). Consistent with previous reports [25], female patients had a higher incidence of hepatolithiasis

Table 3
Multivariate Cox regression analysis of OS and tumor recurrence in the PSM cohort.

Variable	OS			Tumor recurrence		
	HR	95 % CI	P- value	HR	95 % CI	P- value
Sex, male	1.322	1.079–1.621	0.007	1.337	1.088–1.645	0.006
ALB, g/L, ≥35	0.701	0.559–0.878	0.002	0.766	0.606–0.969	0.027
CEA, μg/L, >10	1.426	1.114–1.826	0.005			
CA19–9, IU/mL, >39	1.357	1.088–1.691	0.007			
Tumor diameter, cm, ≥5	1.508	1.206–1.887	<0.001	1.631	1.293–2.057	<0.001
Tumor number, multiple	1.661	1.357–2.034	<0.001	1.524	1.230–1.889	<0.001
MVI, yes				1.512	1.105–2.067	0.010

Abbreviations: OS, overall survival; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; ALB, albumin; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; MVI, Microvascular invasion.

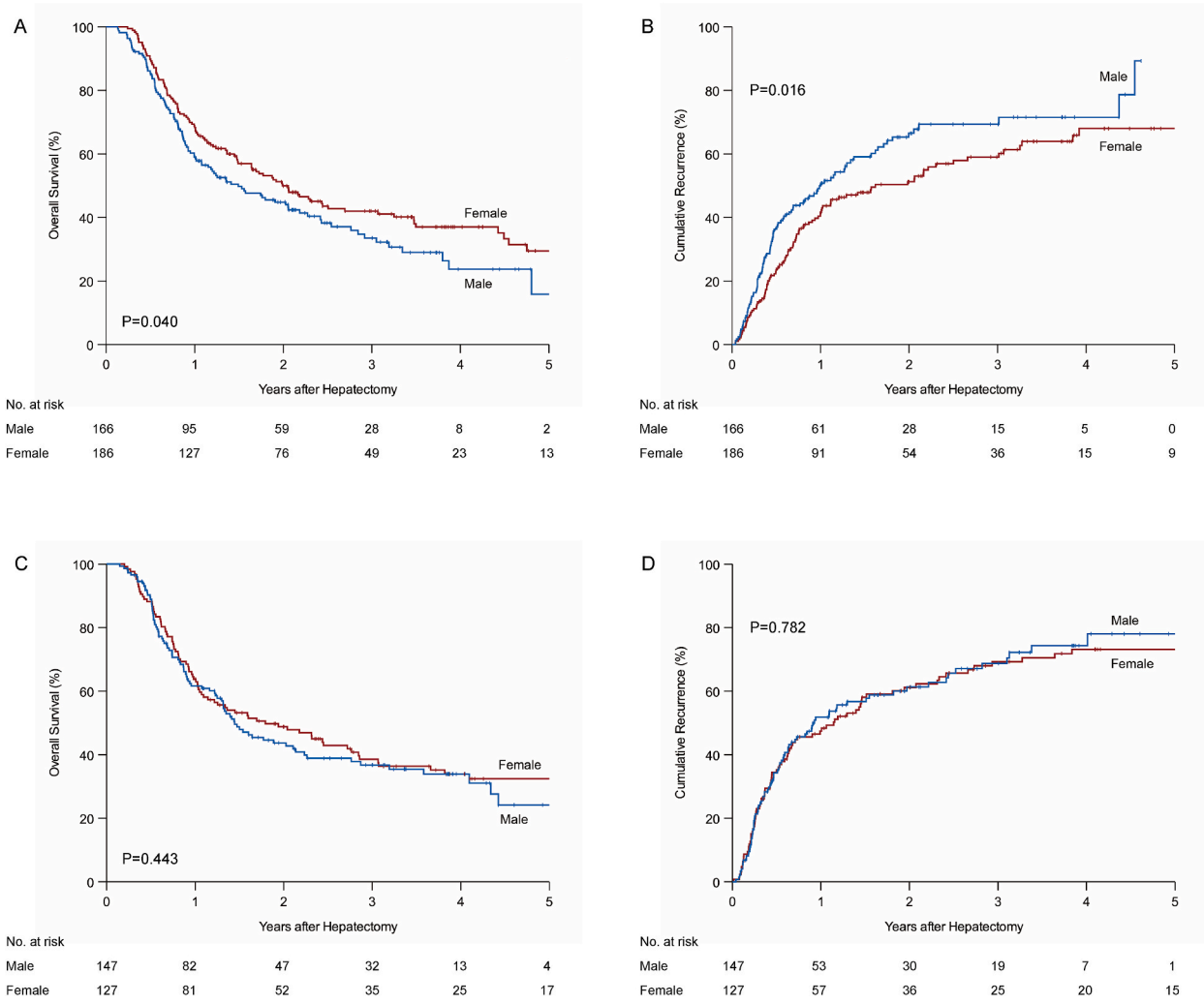

Fig. 2. Overall survival and tumor recurrence between male and female patients undergoing liver resection for intrahepatic cholangiocarcinoma in the propensity score matching cohort. Overall survival (A) and tumor recurrence (B) of patients younger than 55 years old. Overall survival (C) and tumor recurrence (D) of patients older than 55 years old.

than male patients ($P < 0.001$). The occurrence of hepatolithiasis is mainly related to intrahepatic cholestasis, intrahepatic bile duct infection and abnormal bile duct anatomy [26]. In female patients, estrogen-mediated intrahepatic cholestasis is characterized by impaired bile flow and accumulation of bile acid (BA) in the liver [27]. The main mechanism is that estrogen inhibits the transport of BA from liver cells to bile ducts by interfering with the bile salt export pump [28].

One strength of the present study was the use of the PSM method to control for potential confounding variables. Before PSM, no significant differences were observed in 1-, 3-, and 5-year OS and recurrence rates between male and female patients, and further multivariate analysis showed that sex was not independently associated with OS and tumor recurrence. After PSM, the baseline characteristics were all balanced between the two groups, and the real relationship between sex and long-term outcomes after liver resection for ICC was elucidated. Male sex was independently associated with worse OS and recurrence after liver resection for ICC.

The effect of sex hormones should be responsible for the significant difference in long-term prognosis between male and female ICC patients to some extent. Some previous studies have investigated the association between sex hormones and the risk of ICC among women. One recent study on menopausal hormone therapy and the risk of biliary tract cancers revealed that estrogen-only formulations were associated with a lower cholangiocarcinoma risk [29]. Another study reported no association between ICC risk and exogenous hormone use [30]. In the present study, a subgroup survival analysis was performed based on the general menopausal age of females (55 years old). For premenopausal patients younger than 55 years old after PSM, females had a significantly better OS and recurrence than males after liver resection for ICC (all $P < 0.05$). For menopausal patients older than 55 years old after PSM, no significant difference existed in long-term outcomes between male and female patients, thus indicating the potential protective role of sex hormones in females after liver resection for ICC. Mechanistic studies on the relationship between sex hormones and ICC development and progression are still lacking, and further laboratory studies are needed to elucidate its detailed molecular mechanisms.

Patients are currently recommended to be followed up once every 3 months within the first 2 years after surgery and once every 6 months for the next 3 years. The interval could be extended to 1 year for those patients who were alive and recurrence-free 5 years after surgery. The potential of the present study lies in its ability to provide insights into the effect of sex on long-term survival outcomes following liver resection for ICC, which has important implications for the development of personalized follow-up and treatment strategies after surgery. Our findings suggest that a personalized postoperative surveillance regimen should take patients' sex and age into account. In other words, male ICC patients should be followed up more stringently after surgery for lack of protection from sex hormone, as well as menopausal women. In this study, the impact of menopause, estrogen level and hormone therapy on long-term survival after ICC resection was unavailable, because such information was not included in the multicenter database. In our future studies, we will include these data into analysis to clarify the association between sex hormone and recurrence after liver resection for ICC, as well as the potential value of hormone therapy as adjuvant therapy to improve postoperative survival rates. Additionally, ongoing advances in genomic analysis will allow the identification of new biomarkers that predict response to treatment and overall survival in a sex-specific manner.

There were some limitations of our study. First, this study was observational, retrospective, and nonrandomized, which had potential selection bias despite the application of PSM. Second, the study was based on data from a single institution in China. More large-scale multi-institutional studies are necessary to make the conclusion more reliable.

5. Conclusion

In conclusion, our study demonstrated that male sex was an independent risk factor associated with OS and tumor recurrence in patients after liver resection for ICC. In addition, follow-up strategies and treatment after liver resection for ICC should be personalized according to patient sex and age.

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Data availability statement

All data used in the generation of the results presented in this manuscript will be made available upon reasonable request from the corresponding author.

CRediT authorship contribution statement

Yiran Zou: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Xinfei Xu:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Tanyang Wu:** Formal analysis, Data curation, Conceptualization. **Qinjunjie Chen:** Formal analysis, Data curation. **Zheng Li:** Formal analysis, Data curation. **Zhishi Yang:** Data curation. **Kui Wang:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Feng Shen:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29910.

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