

# Hepatectomy is associated with survival in intrahepatic cholangiocarcinoma

## An observational study by instrumental variable analysis

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### Abstract

Liver resection (LR) is a major treatment modality in select patients with stage I-III Intrahepatic cholangiocarcinoma (ICC), yet many studies demonstrated low rates of resection. The aim of the present study is to evaluate whether increasing resection rates would result in an increase in average survival in patients with stage I-III ICC.

Surveillance, Epidemiology, and End Results 18 registry database for 2004 through 2015 was retrieved for the present study. Propensity score matching was performed to eliminate possible bias. In addition, instrumental variable (IV) analysis was utilized to adjust for both measured and unmeasured confounders.

Among 2341 patients with clinical stage I-III ICC, we identified 1577 (67.4%) and 764 (32.6%) patients who received no treatment or LR, respectively. In the multivariable adjusted cohort, a clear prognostic advantage of LR was observed in overall survival (OS) ( $P < .001$ ) and disease-specific survival (DSS) ( $P < .001$ ) compared to patients who received no treatment. Estimates based on the IV analysis indicated that patients treated with LR had a significantly longer OS ( $P < .001$ ) and DSS ( $P < .001$ ) after adjusting confounding factors. In IV analyses stratified by American Joint Committee on Cancer tumor stage, we found that the better survival effects of LR on OS and DSS were consistent across all subgroups.

Our outcomes indicated that LR was associated with a survival benefit for marginal patients with stage I-III ICC.

**Abbreviations:** AJCC = American Joint Committee on Cancer, CI = confidence intervals, DSS = disease-specific survival, HR = hazard ratios, HSA = Health Service Areas, ICC = intrahepatic cholangiocarcinoma, IV = instrumental variable, LR = liver resection, OS = overall survival, PSM = propensity score matching, SEER = Surveillance, Epidemiology, and End Results.

**Keywords:** instrumental variable analysis, intrahepatic cholangiocarcinoma, liver resection, survival

## 1. Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common liver tumor after hepatocellular carcinoma (accounting for 10%–15% of primary liver tumor), and the overall incidence and cancer-related death of ICC has increased progressively globally in the past decades.<sup>[1,2]</sup> Liver resection (LR) remains the mainstay of potentially radical treatment for ICC.<sup>[3–5]</sup> However,

the radical resection rate of ICC is only 15% to 20%.<sup>[3]</sup> The low resection rate of ICC may be caused by the late-stage and incurable tumor at diagnosis, uncompensated liver function, poor performance status, comorbidities and the medical center where the patient is being treated.<sup>[1,5,6]</sup> If the most suitable cases for LR are already identified and treated, then increasing LR rate could not lead to improved long-term survival.

In this study, we aimed to explore whether increasing LR rates were associated with overall survival for patients with ICC. Instrumental variable (IV) analyses were utilized to explore variation in results across geographical regions different in liver resection rate. The analysis method was theorized to control for potential unmeasured confounding factors in surgical decision makings.<sup>[7,8]</sup> This method was particularly applicable to the Surveillance, Epidemiology, and End Results (SEER) registry, which does not provide detailed prognosis-relevant information. A feasible instrumental variable should be associated with patients' receiving a specific therapy, while not directly correlated with the outcome itself, except through the receipt of therapy. In this study, the LR rate for liver cancer in each Health Services Area (HSA) was used as the instrument. The IV was constructed by calculating the proportion of cases that received hepatectomy for liver malignancy in each HSAs.

## 2. Patients and methods

### 2.1. Patient identification

In this study, all primary clinical data including demographics, tumor characteristics and patient survival information was

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acquired from the SEER 18 registry database from 2004 to 2015 (<https://seer.cancer.gov/>). The patient identification process is as follows: we first confirmed 8171 cases whose pathological diagnosis was ICC (International Classification of Diseases for Oncology, 3rd Edition [ICD-O-3] site code C22.1 for intra-hepatic bile duct and histologic type ICD-O-3 codes 8160 for cholangiocarcinoma) between 2004 and 2015 from the SEER database. The detailed flow chart of this study including inclusion and exclusion criteria is shown in Figure 2. Finally, 2341 cases with American Joint Committee on Cancer (AJCC; 6th) stage I-III ICC meeting the specified eligibility criterion were enrolled in the multivariate analysis and IV analysis. The following SEER codes for ICC treatment were selected: LR: 20-25, 30, 36, 37, 50, 51, and 52; none treatment: 0. The present study was approved by the ethics committee of our hospital.

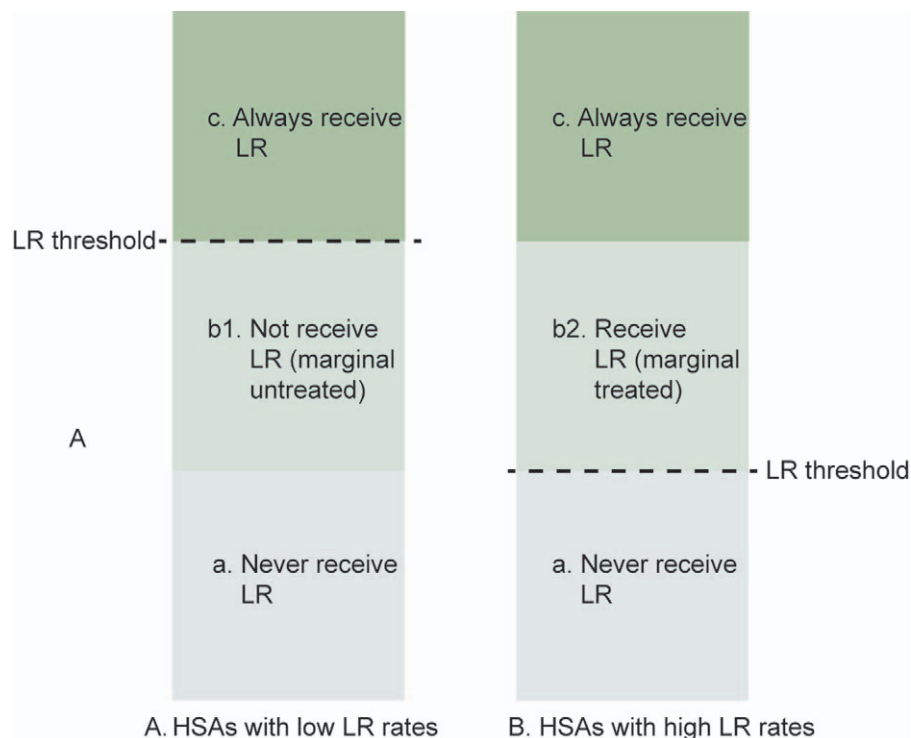
## 2.2. Statistical analysis

All data was analyzed by the R (<http://www.R-project.org>). For categorical variables, chi-square tests or Fisher exact tests were utilized for comparison. For continuous data, *t* tests were applied to examine the statistical differences. Our primary outcomes of interest were overall and disease-specific survival (OS and DSS) among ICC patients. The Kaplan-Meier curve was generated to assess probability of survival stratified by two groups with different treatment method. COX proportional hazards regression models were employed for multivariable analyses, and hazard ratios were presented with 95 percent confidence intervals. The multivariable models were adjusted for: sex, race, age, year of diagnosis, tumor size, lymph node status, AJCC stage, insurance status, marital status, radiotherapy, and chemotherapy.

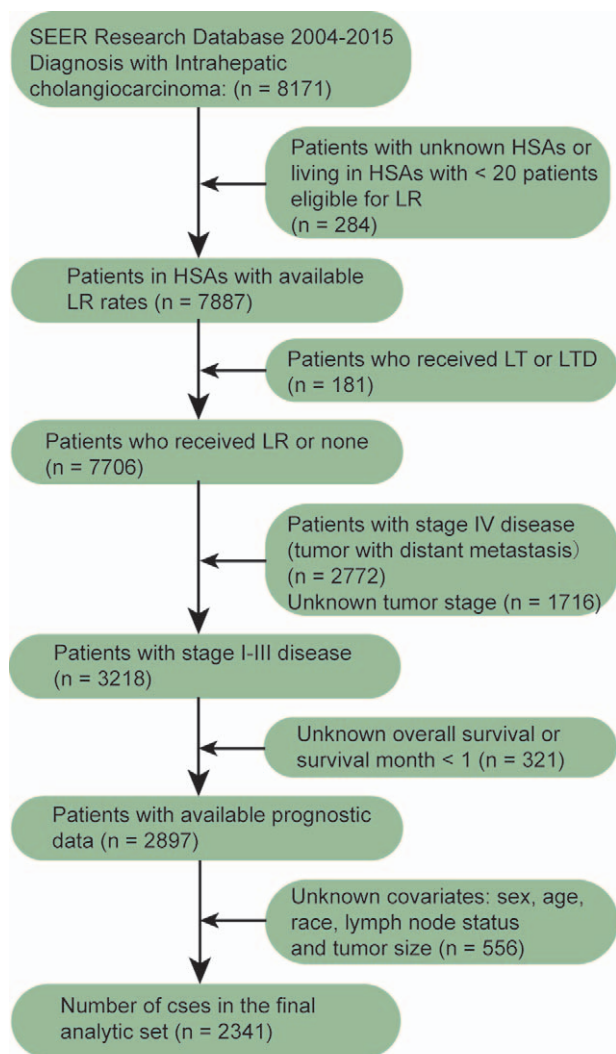
We balanced the baseline characteristics using propensity score matching (PSM) with variables including race, sex, age, year of diagnosis, tumor size, lymph node status and AJCC stage. The LR group and none group were matched by 1:1 with caliper width set as 0.02.

Before using IV analysis, we should understand the definition of “marginal patients,” which represents those whose indications for receiving liver resection are more uncertain. The treatment modality (LR or none) for marginal patients may be influenced by surgeon’s beliefs, preferences, or skills in diverse HSAs. HSA was defined as one or more counties in the USA which provided independent routine medical services.<sup>[7]</sup> Cases with operable ICC would receive LR in a high-use HSA, but not in a low-use HSA.<sup>[9,10]</sup> Results from instrumental variable analyses is on behalf of the adjusted therapy effect in the marginal cases, while not the average therapeutic efficacy (Fig. 1).<sup>[9]</sup>

Instrumental variable analyses are used to adjust both unmeasured and measured confounding factors through using an exogenous instrument. Instrumental variable is a measured variable that should be associated with the course of treatment (instrument relevance property), but are unrelated to unmeasured confounders influencing patient outcomes and without direct effect on outcomes (instrument exogeneity property).<sup>[11]</sup> In the present study, LR rates in HSAs were used as a feasible instrumental variable. We excluded cases in HSAs with no more than 20 cases, because the LR rates were difficult to be accurately confirmed in these HSAs.<sup>[12]</sup> To evaluate the validity of LR rate in HSAs as an instrumental variable, after calculation, we observed that LR rate in a HSA was obviously related to likelihood of a LR-eligible patients in that HSA having undergone LR (with *F* statistic higher than 10), but not related to OS in the multivariate Cox models. In addition, we also explored covariate balance



**Figure 1.** Flowchart representing selection process of patients included in this study.



**Figure 2.** In Fig. 2A, the hospital performs liver resection (LR) less and has a higher threshold for LR while in Fig. 2B, the hospital performs LR more frequently and has a lower threshold for carrying out LR. In both hospitals, there will be a population of patients who would never be performed LR (group “a”) as well as patients who would always be performed LR (group “c”). At the same time, there will be a group of patients who would either not be performed (group “b1”) or would be performed (group “b2”) LR solely because of the hospital to which they presented. These “b” groups together are the marginal population.

across quintiles. The two-stage residual inclusion technique was used in IV analysis.<sup>[13]</sup>

### 3. Results

#### 3.1. Patient characteristics

Among 2341 patients with clinical stage I-III ICC, we identified 1577 (67.4%) and 764 (32.6%) patients treated with none or LR, respectively. Table 1 showed the general demographics of the entire study population according to receipt of treatment. The mean age of cases who underwent LR and none was 63.6 and 66.9 years, respectively. Patients treated by LR were younger, and more patients had smaller tumor size and stage I-II disease. In addition, when patients underwent LR, less patients had lymph node metastasis (17.4% vs. 23.7%).

**Table 1**  
**Clinical features of the included patients with intrahepatic cholangiocarcinoma.**

Variable	None (n=1577)	LR (n=764)	P value
Age (yr)	66.9±12.2	63.6±11.6	<.001
Sex			.492
Female	808 (51.2%)	403 (52.7%)	
Male	769 (48.8%)	361 (47.3%)	
Race			.459
White	1231 (78.1%)	603 (78.9%)	
Black	126 (8.0%)	54 (7.1%)	
Other	216 (13.7%)	107 (14.0%)	
Tumor size (mm)	65.5±37.4	59.3±32.5	<.001
Lymph node status			<.001
Negative	1203 (76.3%)	631 (82.6%)	
Positive	374 (23.7%)	133 (17.4%)	
FS			.030
0–4	135 (67.8%)	125 (78.1%)	
5–6	64 (32.2%)	35 (21.9%)	
AJCC stage			<.001
I	512 (32.5%)	325 (42.5%)	
II	186 (11.8%)	158 (20.7%)	
III	879 (55.7%)	281 (36.8%)	
Insurance			.242
Yes	1323 (97.9%)	666 (98.7%)	
No	28 (2.1%)	9 (1.3%)	
Marital status			<.001
Married	900 (59.1%)	496 (67.1%)	
Divorced or separated	420 (27.6%)	142 (19.2%)	
Single	203 (13.3%)	101 (13.7%)	
Radiotherapy			<.001
Yes	61 (3.9%)	109 (14.3%)	
No	1516 (96.1%)	655 (85.7%)	
Chemotherapy			<.001
Yes	849 (53.8%)	312 (40.8%)	
No	728 (46.2%)	452 (59.2%)	

Data are shown as mean ± SD or n (%). FS=fibrosis score, AJCC=American Joint Committee on Cancer.

#### 3.2. Multivariate COX model

There were 2341 cases with available prognostic information included in survival analysis. For all included patients, the mean OS times for cases undergoing LR and cases who underwent none surgical treatment were 58.2 months and 21.2 months, respectively. The mean DSS for cases with LR and none were 61.6 and 22.3 months, respectively. Cases after LR showed longer DSS ( $P < .001$ ) and OS ( $P < .001$ ) in comparison to cases receiving none surgical therapy (Fig. 3).

After adjusting several available confounders in the multivariate adjusted model, we found that LR was related to a significantly better survival than untreated patients including DSS (HR, 0.33; 95% CI, 0.28–0.39;  $P < .001$ ) and OS (HR, 0.33; 95% CI, 0.28–0.38;  $P < .001$ ) (Table 2). In multivariate analysis subgrouped by AJCC tumor stage, the better survival effects of LR on DSS and OS were observed consistent across all subgroups (Table 3).

#### 3.3. Results based on instrumental variable analyses

In this study, we confirmed the validity in two aspects. Firstly, cases were divided into quintiles based on the percentage of patients within each HSA undergoing LR (Supplementary Table 1, <http://links.lww.com/MD/F825>). The average HSA LR rate (for liver malignancy) ranged from 5% (quintile 1) to

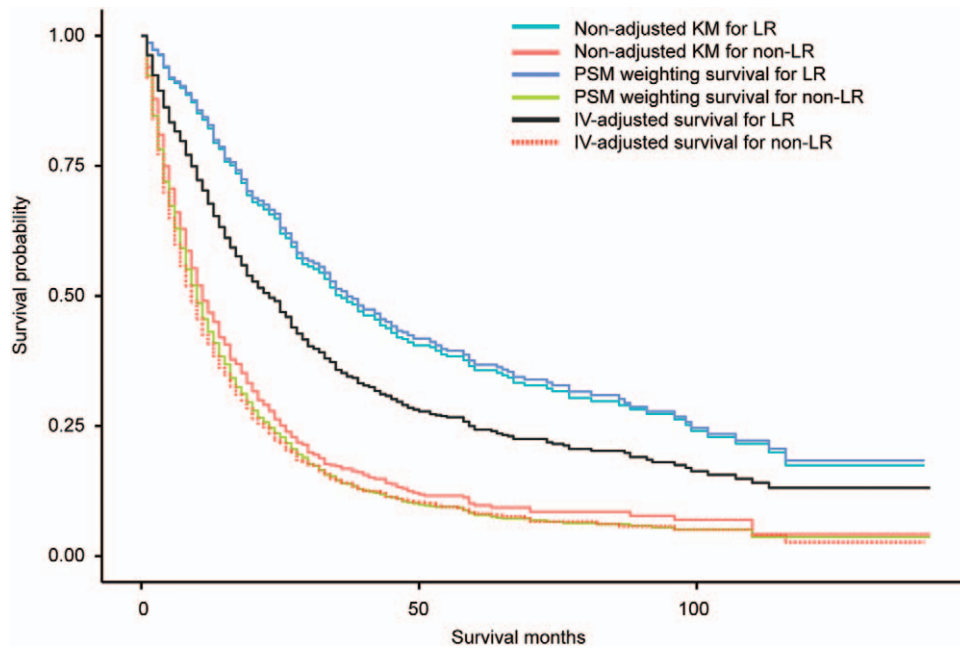


Figure 3. Survival analysis in different statistical models.

12% (quintile 5). In the COX model, we observed no independent association between the instrumental variable and OS (HR 1.53, 95% CI 0.11–21.81,  $P = .755$ ). Besides, the F-values is 58.6 ( $P < .001$ ), which indicated that the IV was significantly associated with the therapy.

Results according to the IV analysis indicated that cases undergoing LR showed an obviously longer DSS (HR 0.18, 95% CI 0.13–0.25,  $P < .001$ ) and OS (HR 0.18, 95% CI 0.13–0.23,  $P < .001$ ) after the confounders were adjusted (Table 4). During instrumental variable analysis stratified by AJCC tumor stage, we observed better survival of LR on DSS and OS in all sub-groups (Table 3).

### 3.4. Outcomes in propensity score matching analysis

In the matched population, most of the covariates were well-balanced for most baseline features (Table S1, <http://links.lww.com/MD/F825>, <http://links.lww.com/MD/F826>). In the PSM-selected cohort, cases with LR had better DSS and OS ( $P$  values  $< 0.001$ ) in comparison with cases in none treatment

cohort (Fig. 3). In the PSM population, the univariate analyses indicated that cases after LR still showed better DSS (HR 0.65, 95% CI 0.56–0.76,  $P < .001$ ) and OS (HR 0.66, 95% CI 0.58–0.76,  $P < .001$ ) compared to cases in the none treatment group (Table 2). As shown in Table 2, results after adjusting the propensity score demonstrated both better DSS (quintile: HR 0.38, 95% CI 0.33–0.44,  $P < .001$ ; continuous: HR 0.39, 95% CI 0.33–0.44,  $P < .001$ ) and OS (quintile: HR 0.38, 95% CI 0.33–0.42,  $P < .001$ ; continuous: HR 0.38, 95% CI 0.34–0.43,  $P < .001$ ) related to LR.

## 4. Discussion

Most of the ICC cases presented with advanced stages at the point of diagnosis.<sup>[14]</sup> And the long-term survival of ICC patients was low.<sup>[15]</sup> Although liver resection is related to better survival for ICC, hepatectomy rates are much lower than expected for cases with localized tumor. Actually, 30% to 66% of patients with ICC do not receive any treatment during the course of their disease.<sup>[16]</sup> The selection of treatment approach is often determined by the

**Table 2**  
Association of liver resection (LR) with patient overall survival in patients with intrahepatic cholangiocarcinoma.

	OS			DSS		
	Number	HR (95%CI)	P value	Number	HR (95%CI)	P value
Non-adjusted	2341	0.34 (0.30, 0.38)	<.001	1736	0.34 (0.29, 0.39)	<.001
Multivariable adjusted model*	1955	0.33 (0.28, 0.38)	<.001	1459	0.33 (0.28, 0.39)	<.001
Matched on propensity score**	1476	0.66 (0.58, 0.76)	<.001	1098	0.65 (0.56, 0.76)	<.001
Regression adjusted with propensity score						
Propensity score, continuous	2341	0.38 (0.34, 0.43)	<.001	1736	0.39 (0.33, 0.44)	<.001
Propensity score, quintile	2341	0.38 (0.33, 0.42)	<.001	1736	0.38 (0.33, 0.44)	<.001

Data are shown as HR (95%CI)  $P$  value.

\* Multivariable adjusted model was adjusted for: age, race, sex, year of diagnosis, tumor size, lymph node status, AJCC stage, insurance status, marital status, radiotherapy and chemotherapy. Propensity score matching model was based on: age, race, sex, year of diagnosis, tumor size, lymph node status and AJCC stage. OS, overall survival; DSS, disease specific survival; HR, hazard ratio; 95% CI, 95% confidence interval.

**Table 3**  
Subgroup analyses according to AJCC tumor stage.

	AJCC stage I	AJCC stage II	AJCC stage III
OS			
Non-adjusted	0.24 (0.20, 0.30) <0.001	0.32 (0.23, 0.43) <0.001	0.51 (0.43, 0.60) <0.001
Adjusted			
Traditional regression model	0.27 (0.22, 0.34) <0.001	0.30 (0.22, 0.41) <0.001	0.53 (0.45, 0.62) <0.001
2SRI IV model	0.15 (0.09, 0.23) <0.001	0.15 (0.08, 0.31) <0.001	0.24 (0.16, 0.37) <0.001
DSS			
Non-adjusted	0.23 (0.18, 0.31) <0.001	0.31 (0.22, 0.44) <0.001	0.52 (0.43, 0.62) <0.001
Adjusted			
Traditional regression model	0.27 (0.20, 0.35) <0.001	0.31 (0.22, 0.45) <0.001	0.53 (0.44, 0.65) <0.001
2SRI IV model	0.13 (0.07, 0.22) <0.001	0.16 (0.07, 0.37) <0.001	0.29 (0.18, 0.47) <0.001

Data are shown as HR (95%CI) P value. \*Adjusted model was adjusted for: age, race, sex, year of diagnosis, lymph node status and tumor size. AJCC, American Joint Committee on Cancer; OS, overall survival; DSS, disease-specific survival; 2SRI, 2 stage residual inclusion; IV, instrumental variable.

surgeon's choice, which may vary by specialty, thus there is significant disparities among treated patients.<sup>[3]</sup> In the present study, by using IV analysis, we found that ICC cases in stage I-III undergoing LR showed better long-term survival than those without LR. We could suggest with greater confidence that if the LR rates were to increase, the long-term survival times could also increase for these patients in the future.

In this study, using the IV analysis, we explored the independent role of primary tumor resection in the long-term prognosis of ICC. Compared to traditional multivariate analysis, IV analysis takes advantage of the natural variation in the use of hepatectomy due to factors other than those which may influence patient prognosis.<sup>[12]</sup> IV analysis is an alternate analytic method which controls for both known and unknown confounding factors in retrospective studies, which is especially applicable if randomized controlled trials (RCTs) were not available or could not be carried out. Given the absence of any published or ongoing RCTs related to LR vs. none for ICC, outcomes from instrumental variable analyses might be the best evidence that help to guide the treatment decision-makings. However, given the precondition of IV analysis, it should be noted that outcomes were only suitable for "marginal" populations and may not represent the average effect of liver resection in the whole population.<sup>[7,9]</sup>

Previous studies have utilized instrumental variable analysis to illustrate the role of primary tumor resection in the long-term prognosis of patients with diverse tumor types.<sup>[7,10,12,13,17,18]</sup> For

example, Mehta, et al. also used the population-based health services record to assess the effectiveness of chemotherapy versus the primary tumor resection as the initial therapy in older cases with stage IV colorectal tumors.<sup>[17]</sup> In this study, they found that chemotherapy as the initial treatment offered similar results (compared to primary tumor resection) in cases with stage IV colorectal tumor, while this conclusion was not observed in conventional multivariate regression analysis. Consequently, for patients with a large burden of disease, surgery can be avoided and combined therapies may be more beneficial. For pancreatic tumors, McDowell, et al. utilized pancreatectomy rates as the instrumental variable to study the role of pancreatic resection in cases with stage I/II pancreatic ductal adenocarcinoma.<sup>[7]</sup> Similarly to our study, they observed that after controlling for confounding factors by IV analysis, pancreatectomy is related to a statistically significant increase in survival for patients with resectable pancreatic ductal adenocarcinoma. In conclusion, after accounting for measurable, as well as unmeasurable confounders, the results would be closer to the actual effect of treatment methods on patient survival.

In this study, LR rates in different HSAs were used as the instrumental variable. We have evaluated the validity of the IV by analyzing the association between LR rates and patient survival. Finally, no direct correlation was observed in the multivariate analysis, and patients who underwent LR for ICC in the centers with high LR rates did not have better long-term survival (thus, it

**Table 4**  
Instrumental variable analysis of the impact of LR on survival for patients with Intrahepatic cholangiocarcinoma in 2SRI IV model.

	OS (n=2341)			DSS (n=1736)		
	HR	95% CI	P-value	HR	95% CI	P-value
LR vs. none	0.176	0.133–0.233	<.001	0.179	0.128–0.249	<.001
Age, years	1.015	1.010–1.019	<.001	1.016	1.011–1.022	<.001
Sex, male vs. female	1.126	1.020–1.243	.019	1.110	0.989–1.247	.078
Race						
Black vs. White	1.213	1.008–1.461	.042	1.236	1.001–1.526	.049
Other vs. White	0.984	0.852–1.136	.825	1.029	0.874–1.212	.730
Tumor size, cm	1.004	1.002–1.005	<.001	1.004	1.002–1.005	<.001
Lymph node status, positive vs. negative	1.133	0.991–1.296	.069	1.210	1.037–1.412	.015
AJCC stage						
II vs. I	1.206	1.023–1.422	.026	1.201	0.986–1.462	.068
III vs. I	1.262	1.103–1.444	<.001	1.267	1.079–1.488	.004
Year of diagnosis, 2010–2015 vs. 2004–2009	0.980	0.964–0.997	.024	0.9832	0.964–1.003	.1016

2SRI = two-stage residual inclusion, AJCC = American Joint Committee on Cancer, DSS = disease-specific survival, LR = liver resection, OS = overall survival.

met the criterion as an instrumental variable). Interestingly, previous studies demonstrated that concentration of treatment leads to both more access to treatment and improved outcomes, which were well described in pancreatic and esophageal cancers.<sup>[19,20]</sup> The distinct observations between previous literatures and ours may be firstly caused by the difference in complexity of hepatectomy and pancreaticoduodenectomy or the other surgical procedures. Actually, the available evidence related to this issue is limited.<sup>[21]</sup> It is necessary to increase the monitoring of the association between concentration of treatment and patient survival in tumor type such as ICC.

Admittedly, the present study subject to some limitations. First, the SEER registry did not provide all significant variables that influence the long-term prognosis of ICC patients, such as liver function and detailed comprehensive treatment procedures, thus we cannot measure the impact of these confounding factors on the results; Second, even though IV analyses is a feasible alternative to RCTs, its validity depends on the specific population. The instrumental variable analyses only evaluate the effect on marginal patients, whereas the marginal patients do not include cases never or always receive LR, focusing on ICC cases who are more hesitating for receiving LR.

This is the first comparative effectiveness research study to use an IV analysis to evaluate the potential OS benefit of LR for ICC. By integrating multivariable COX models, propensity score matching, and IV analysis, our outcomes indicated that LR provided survival benefits for marginal cases with stage I-III ICC. These results indicate that if the LR rate was to increase, long-term survival may also be expected to increase in the future.

## Author contributions

**Conceptualization:** Zhaoping Wu, Lingling Cao.

**Data curation:** Lingling Cao.

**Formal analysis:** Weili Chen.

**Funding acquisition:** Weili Chen.

**Investigation:** Weili Chen.

**Methodology:** Weili Chen, Zhaoping Wu.

**Project administration:** Zhaoping Wu.

**Writing – original draft:** Zhaoping Wu.

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