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ORIGINAL RESEARCH ARTICLE

Liver transplantation outcomes in stage I hepatocellular carcinoma and intrahepatic cholangiocarcinoma: A Surveillance, Epidemiology, and End Results-based study

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Abstract

Introduction: Liver transplantation (LT) offers a curative option for early-stage hepatocellular carcinoma (HCC). However, its role in intrahepatic cholangiocarcinoma (ICC) remains controversial, with limited comparative evidence on long-term outcomes, especially for early-stage disease.

Objective: To assess long-term survival outcomes and identify prognostic risk factors among patients with HCC and ICC who have undergone LT.

Methods: The Surveillance, Epidemiology, and End Results database (2004–2015) was used to identify patients with American Joint Committee on Cancer 6th edition stage I HCC or ICC who underwent LT. The primary endpoints were cancer-specific survival (CSS) and overall survival (OS). Kaplan–Meier analysis, log-rank tests, and Cox proportional hazards regression were used for survival comparison analyses, and random subsampling and bootstrap resampling were performed to assess the robustness of the results.

Results: Among 944 eligible patients, 925 had HCC, and 19 had ICC. The five-year OS and CSS rates were significantly higher for HCC patients (OS: 95.1%; CSS: 97.7%) compared to ICC patients (OS: 82.3%; CSS: 82.3%) ($p < 0.001$). Multivariate Cox analysis for HCC identified age and marital status as independent risk factors for OS, and tumor size for CSS. For ICC, given the limited sample size, only descriptive analysis and univariate comparisons were performed. Tumor size showed a potential association with OS in exploratory analysis, but these findings require validation in larger cohorts.

Conclusion: LT provides excellent long-term survival for patients with early-stage HCC. In contrast, outcomes for early-stage ICC patients after LT are significantly inferior, with an approximate 15% absolute difference at five years. Prognostic factors differ between the two histological types, underscoring the need for distinct LT selection criteria and management strategies. Given the small ICC sample size and inherent database limitations, these findings underscore the urgent need for larger multicenter studies that incorporate comprehensive clinical and molecular profiling to identify ICC subpopulations that may benefit from LT.

Keywords: Liver transplantation; Hepatocellular carcinoma; Intrahepatic cholangiocarcinoma; Stage I Surveillance, Epidemiology, and End Results database

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1. Introduction

Primary liver cancer ranks as the sixth most common malignant tumor globally and the fourth leading cause of cancer-related deaths. Its incidence continues to rise, posing a severe challenge to public health systems worldwide.[1] Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) constitute the predominant subtypes, accounting for approximately 75% and 15% of all cases, respectively.[2] Hepatic resection remains the preferred treatment for early-stage primary liver cancer, particularly in patients with localized tumors and adequate liver reserve.[3-5] However, its feasibility is often limited by the severity of underlying liver disease, insufficient residual liver volume post-surgery, and the failure to address the underlying liver pathology at its root.[6] Therefore, for patients with early-stage primary liver cancer complicated by chronic liver diseases such as cirrhosis, liver transplantation (LT) demonstrates irreplaceable value—it not only achieves negative oncological margins and eradicates intrahepatic micrometastases but also completely resolves the underlying liver disease.[7-9]

However, the applicability of LT in ICC treatment remains highly controversial. Most studies suggest that ICC is more invasive and prone to early micrometastasis, often rendering it unsuitable for LT.[10-12] While transplant oncology concepts have expanded indications for LT, its efficacy for early-stage ICC patients remains unclear.[13,14]

Current studies comparing LT outcomes between HCC and ICC are predominantly single-center retrospective or small-sample analyses, yielding limited evidence. There is a particular lack of large-scale, long-term comparative studies focusing on early-stage (American Joint Committee on Cancer [AJCC] stage I) patients, hindering our understanding of the true efficacy of LT for primary liver cancers at early tumor stages.

This study offers several distinct contributions to the existing literature. First, by strictly limiting inclusion to AJCC 6th edition stage I patients, we eliminate stage-related confounding factors that have plagued previous comparative studies, providing the first population-based "head-to-head" comparison of LT outcomes for very early-stage HCC and ICC. Second, beyond simply comparing survival outcomes, we systematically investigate and contrast the prognostic factor profiles between the two histological types, revealing fundamental differences in what determines post-transplant survival. Third, leveraging the Surveillance, Epidemiology, and End Results (SEER) database's population-level coverage, this real-world study complements findings from highly selected clinical trials and single-center series, offering generalizable evidence for clinical decision-making. The National Cancer Institute's SEER database, covering approximately 28% of the United States population, provides an ideal platform for this large-scale, long-term real-world investigation.

Using cancer-specific survival (CSS) and overall survival (OS) as primary endpoints, this study aims to evaluate long-term survival outcomes and prognostic risk factors in HCC and ICC patients who underwent LT and met the AJCC 6th edition stage I criteria, thereby informing clinical practice and highlighting future research priorities.

2. Methods

2.1. Patient selection

Based on the United States' SEER database, patients diagnosed with HCC and ICC between 2004 and 2015 were identified. ICC was defined by primary site code C22.1 and ICD-O-3 histology code 8160/3, while HCC was defined by C22.0 with an ICD-O-3 code 8170/3. The study included patients who underwent LT (surgery of primary site = 61). Data collected included age, race, marital status, tumor size, receipt of chemotherapy and radiotherapy, number of lymph nodes removed, and survival outcomes.

2.1.1. American Joint Committee on Cancer staging consistency

To ensure accurate stage classification, we utilized the AJCC 6th edition-specific staging field (SEER variable "AJCC6") rather than derived stage variables. This approach maintained consistency across the entire study period (2004–2015), regardless of the concurrent availability of later edition staging data.

2.1.2. Liver transplantation selection criteria

It should be noted that the SEER database does not record critical clinical parameters such as the model for end-stage liver disease score, the presence of portal hypertension, detailed liver function status, or performance status. Consequently, we cannot definitively ascertain whether patients in this cohort strictly adhered to classic criteria such as the Milan criteria. Instead, this study captured the real-world clinical practice of LT for AJCC stage I liver cancers, representing patients deemed suitable for transplantation based on contemporary clinical judgment.

2.1.3. Exclusion criteria

We excluded patients younger than 18 years and those with missing data for any of the following variables: race, marital status, tumor size, chemotherapy status, radiotherapy status, number of lymph nodes examined, or survival status. Since the SEER database provides publicly accessible anonymized data, no institutional review board approval or explicit consent was required.

2.2. Statistical analysis

The primary endpoints were CSS and OS. CSS was defined as the time (in months) from HCC or ICC diagnosis to death caused by HCC or ICC; patients who died from other causes or were lost to follow-up were censored at the time of last follow-up or death. OS was defined as the time (in months) from diagnosis to death from any cause, with patients lost to follow-up censored at the time of last follow-up.

2.2.1. Data description and intergroup comparisons

Normality of quantitative data was assessed using the Kolmogorov–Smirnov test. Normally distributed quantitative data were expressed as mean ± standard deviation, while skewed quantitative data were presented as median and interquartile range (IQR). Intergroup comparisons were performed using the Mann–Whitney *U* test. Categorical data were expressed as frequency and percentage, with intergroup comparisons performed using the chi-square (χ^2) test or Fisher's exact test.

2.2.2. Survival analysis and prognostic factor evaluation

Continuous variables were dichotomized using X-tile 3.6.1 to determine optimal cutoff points. For the HCC group, univariate Cox proportional hazards regression models were used to analyze the relationship between each variable and CSS or OS. For each variable, the hazard ratio and its 95% confidence interval were calculated, and the corresponding two-sided *p*-value was reported. Variables showing statistical significance ($p < 0.05$) in univariate analysis were included in multivariate Cox proportional hazards regression models to identify independent prognostic factors. For the ICC group, given the extremely small sample size ($n = 19$), only descriptive analyses and univariate comparisons (Kaplan–Meier with log-rank test) were performed; multivariate Cox regression was not conducted due to the risk of unstable estimates and overfitting. X-tile-derived cutoffs for ICC were used only for exploratory descriptive purposes and require validation in larger cohorts. All analyses were performed using Statistical Package for Social Sciences 22.0.

2.2.3. Handling of sample size imbalance

To assess the robustness of survival comparisons between the heavily imbalanced groups (925 HCC vs. 19 ICC), we conducted two sensitivity analyses:

(i) Random subsampling: We randomly selected 19 HCC patients (matched for age and tumor size where possible) and repeated survival comparisons across 1,000 iterations.

(ii) Bootstrap resampling: We performed 1,000 bootstrap resamples of the ICC group to estimate the stability of five-year CSS estimates. These analyses confirmed that the observed survival differences were unlikely to be artifacts of sample size imbalance.

Survival curves were plotted using the Kaplan–Meier method, and intergroup survival differences were compared using the log-rank test. All hypothesis tests were two-sided with a significance level of $\alpha = 0.05$. Statistical analyses were performed using the Statistical Package for Social Sciences 22.0 and R 4.5.1 software.

3. Results

3.1. Patient characteristics

A total of 944 patients were included, comprising 925 in the HCC group and 19 in the ICC group. The Kolmogorov–Smirnov test indicated that tumor size and age in both groups did not follow a normal distribution ($p < 0.05$). The median tumor size was 22 mm (IQR: 15–32 mm) in the HCC group and 20 mm (IQR: 15–35 mm) in the ICC group; median age was 57 years (IQR: 53–62 years) in the HCC group and 60 years (IQR: 53–64 years) in the ICC group. No statistically significant differences were observed between groups in baseline characteristics (Table 1).

3.2. Survival analysis

The one-, three-, and five-year OS rates for patients with HCC undergoing LT were 99.7%, 97.9%, and 95.1%, respectively, with corresponding CSS rates of 99.2%, 99.1%, and 97.7%. In contrast, among patients with ICC who underwent LT, the one-year, three-year, and five-year OS rates were 97.8%, 94.7%, and 82.3%, respectively, while the CSS rates were 97.8%, 94.7%, and 82.3%, respectively. Comparisons revealed that both OS and CSS rates were significantly lower in ICC patients than in HCC patients (log-rank $p < 0.001$ for both) (Table 2, Figures 1 and 2).

3.3. Sensitivity analysis

To assess whether the observed survival differences were robust to the extreme sample size imbalance, we performed random subsampling (selecting 19 HCC patients, repeated 1,000 times). In all 1,000 iterations, HCC patients demonstrated significantly better survival than ICC patients (log-rank $p < 0.05$ in 100% of iterations). Bootstrap resampling of the ICC group (1,000 iterations) estimated the five-year CSS at 81.5% (95% confidence interval: 72.1–90.5%), which remains significantly lower than the HCC estimate of 97.7% (95% confidence interval: 96.8–98.6%), with non-overlapping confidence intervals. These analyses support the robustness of the primary finding.

Table 1. Baseline characteristics of hepatocellular carcinoma and intrahepatic cholangiocarcinoma patients

Variable	Hepatocellular carcinoma (*n* = 925)	Intrahepatic cholangiocarcinoma (*n* = 19)	*p*-value
Age (years)			0.334
Median	57	60	
Interquartile range	53–62	53–64	
Sex			0.312
Male	680 (73.5%)	12 (63.1%)	
Female	245 (26.5%)	7 (36.9%)	
Race			0.725
White	744 (80.4%)	16 (84.2%)	
Black	85 (9.2%)	2 (10.5%)	
Other	96 (10.4%)	1 (5.3%)	
Tumor size (mm)			0.864
Median	22	20	
Interquartile range	15–32	15–35	
Marital status			0.929
Married	624 (67.5%)	13 (68.4%)	
Unmarried	301 (32.5%)	6 (31.6%)	
Chemotherapy			0.545
Done	281 (30.4%)	7 (36.8%)	
None	644 (69.6%)	12 (63.2%)	
Radiation			1.000
Done	15 (1.6%)	0 (0%)	
None	910 (98.4%)	19 (100%)	
Number of lymph nodes examined			0.682
None	665 (71.9%)	12 (63.1%)	
1–3	233 (25.2%)	6 (31.6%)	
≥4	27 (2.9%)	1 (5.3%)	

Note: Data presented as *n* (%), unless stated otherwise.

Table 2. Survival outcomes of patients with hepatocellular carcinoma and intrahepatic cholangiocarcinoma

Outcome	Hepatocellular carcinoma (*n* = 925)	Intrahepatic cholangiocarcinoma (*n* = 19)	*p*-value
Overall survival			<0.001
One-year	99.7%	97.8%	
Three-year	97.9%	94.7%	
Five-year	95.1%	82.3%	
Cancer-specific survival			<0.001
One-year	99.2%	97.8%	
Three-year	99.1%	94.7%	
Five-year	97.7%	82.3%	

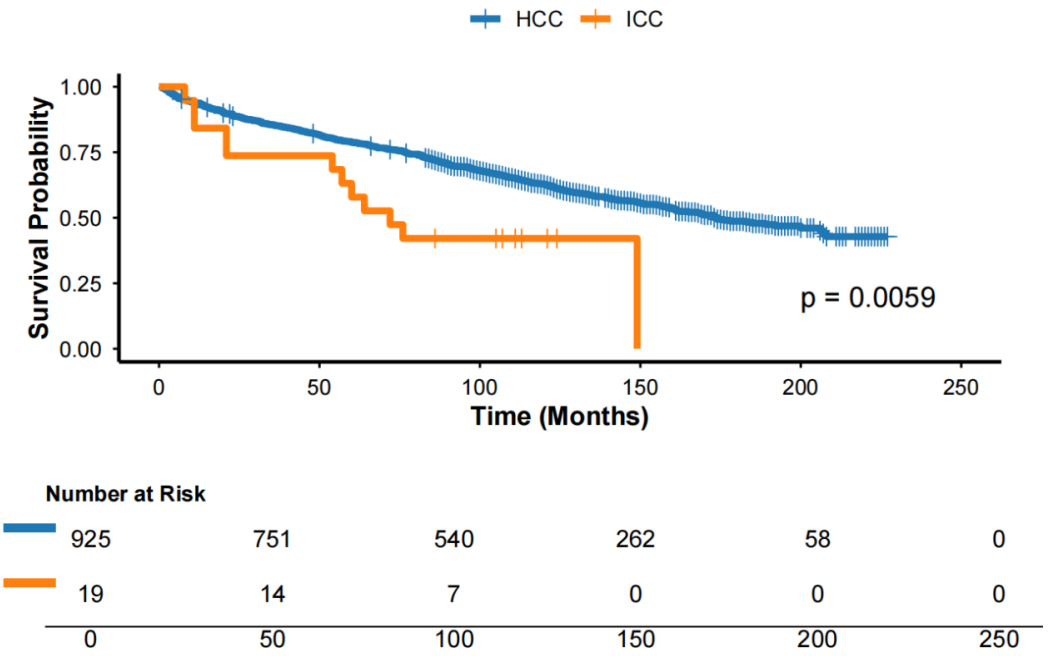

Figure 1. Kaplan–Meier curves for cancer-specific survival (CSS) in hepatocellular carcinoma (HCC; $n = 925$) and intrahepatic cholangiocarcinoma (ICC; $n = 19$) patients after liver transplantation (log-rank $p < 0.001$).
Note: Time is displayed in months, and tick marks were automatically generated based on the distribution of follow-up durations. For reference, 12, 36, and 60 months correspond to 1-, 3-, and 5-year intervals, respectively.

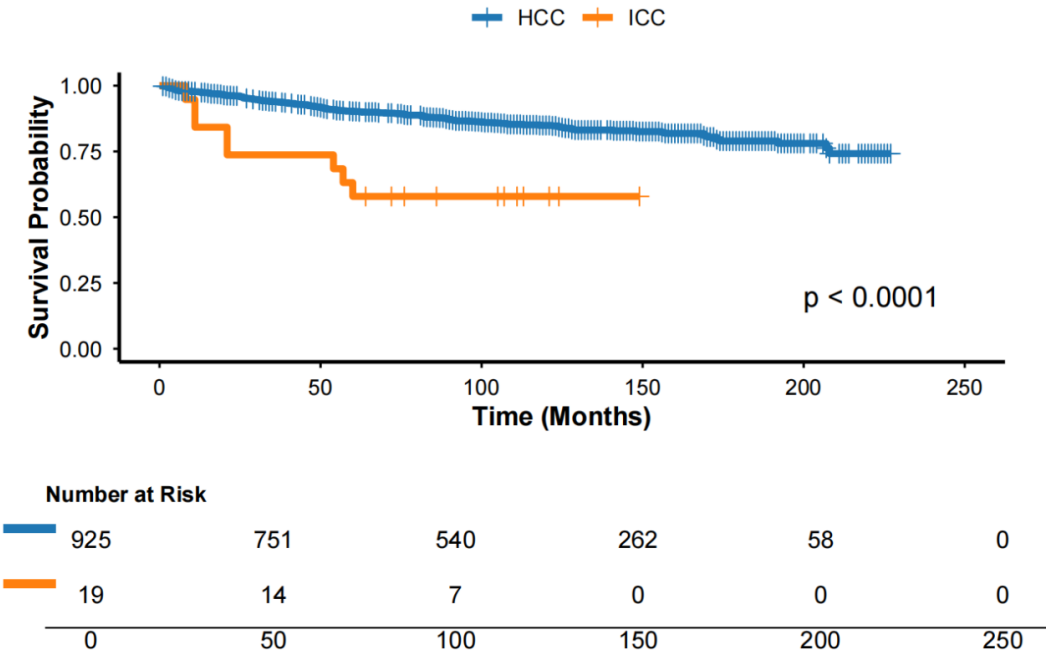

Figure 2. Kaplan–Meier curves for overall survival (OS) in hepatocellular carcinoma (HCC; $n = 925$) and intrahepatic cholangiocarcinoma (ICC; $n = 19$) patients after liver transplantation (log-rank $p < 0.001$).
Note: Time is displayed in months, and tick marks were automatically generated based on the distribution of follow-up durations. For reference, 12, 36, and 60 months correspond to 1-, 3-, and 5-year intervals, respectively.

3.4. Univariate and multivariate analysis of hepatocellular carcinoma

Among 925 HCC patients who underwent LT, the optimal cutoff values for continuous variables were determined using X-tile software and converted into binary variables: age was stratified at 63 years for OS analysis (Figure 3) and at 64 years for CSS analysis (Figure 4); tumor size was stratified at 43 mm for both OS and CSS analyses (Figures 5 and 6). In univariate Cox regression analysis, age and marital status were significant predictors of OS. Multivariate analysis further confirmed both as independent risk factors for OS (Table 3). Regarding CSS, univariate analysis indicated that tumor size and age were associated with CSS, whereas multivariate analysis identified tumor size as an independent risk factor (Table 4).

3.5. Analysis of intrahepatic cholangiocarcinoma patients

Among 19 patients with ICC who underwent LT, the continuous variables age and tumor size were converted into categorical variables using optimal cutoff points determined by X-tile software for exploratory descriptive purposes: age was categorized at 60 years for OS analysis (Figure 7) and at 47 years for CSS analysis (Figure 8); tumor size was categorized at 29 mm for OS analysis (Figure 9) and at 13 mm for CSS analysis (Figure 10). Given the extremely small sample size (n = 19), multivariate Cox regression was not performed due to the risk of overfitting and unstable estimates. Univariate analysis using Kaplan–Meier methods with log-rank tests suggested that tumor size (cutoff 29 mm) was associated with OS (log-rank p = 0.037; Table 5). No statistically significant factors were identified for CSS (Table 6). Given that these findings are exploratory and hypothesis-generating, they should be interpreted with extreme caution and require validation in larger, independent cohorts.

4. Discussion

This study, based on the SEER database, compared long-term survival outcomes and risk factors following LT in patients with stage I HCC and ICC according to the 6th edition of the AJCC staging system. Results revealed distinct characteristics between HCC and ICC: ICC patients had significantly lower five-year OS and CSS than HCC patients. Significant differences in prognostic risk factors were also observed between the two groups. Findings support the critical importance of considering tumor histological type in developing LT strategies and assessing prognosis for early-stage primary liver cancer.

4.1. Survival outcomes and biological aggressiveness

Survival analysis revealed that the five-year OS and CSS rates in the ICC group were both 82.3%, significantly lower than those in the HCC group (OS: 95.1%; CSS: 97.7%). The magnitude of this difference—approximately 15 percentage points at five years—is substantial. Importantly,

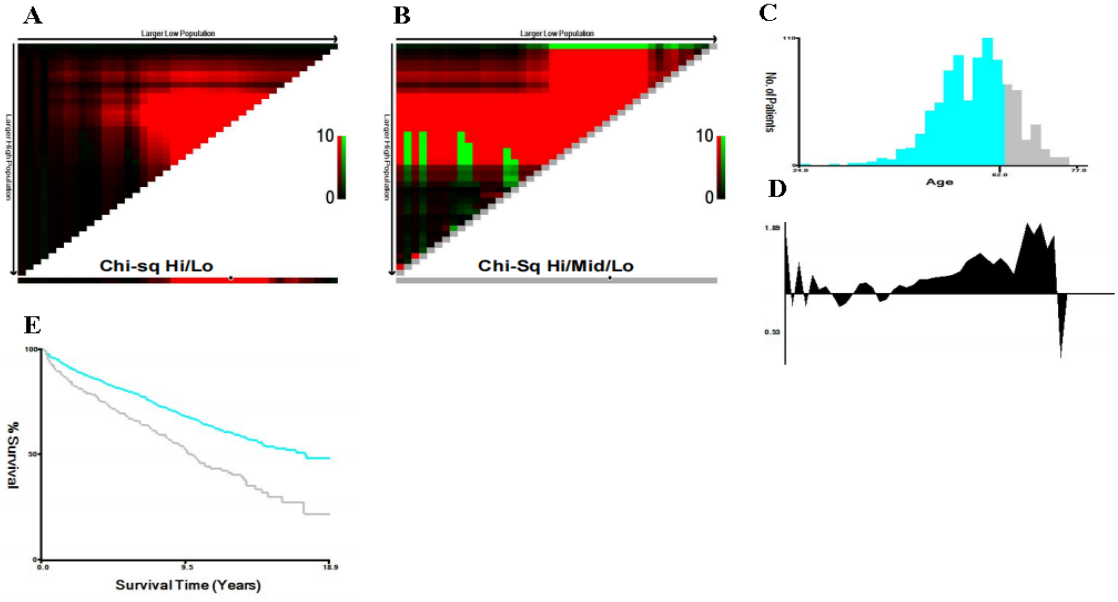

Figure 3. X-tile plot identifying the optimal age cutoff for overall survival in hepatocellular carcinoma patients (cutoff: 63 years). (A) Two-group cut-point analysis (high vs. low) based on maximal log-rank χ^2 statistics. (B) Three-group cut-point analysis (high, intermediate, and low) based on maximal log-rank χ^2 statistics. (C) Age distribution. (D) Association between age and survival. (E) Kaplan–Meier curves stratified by selected cutoff(s).

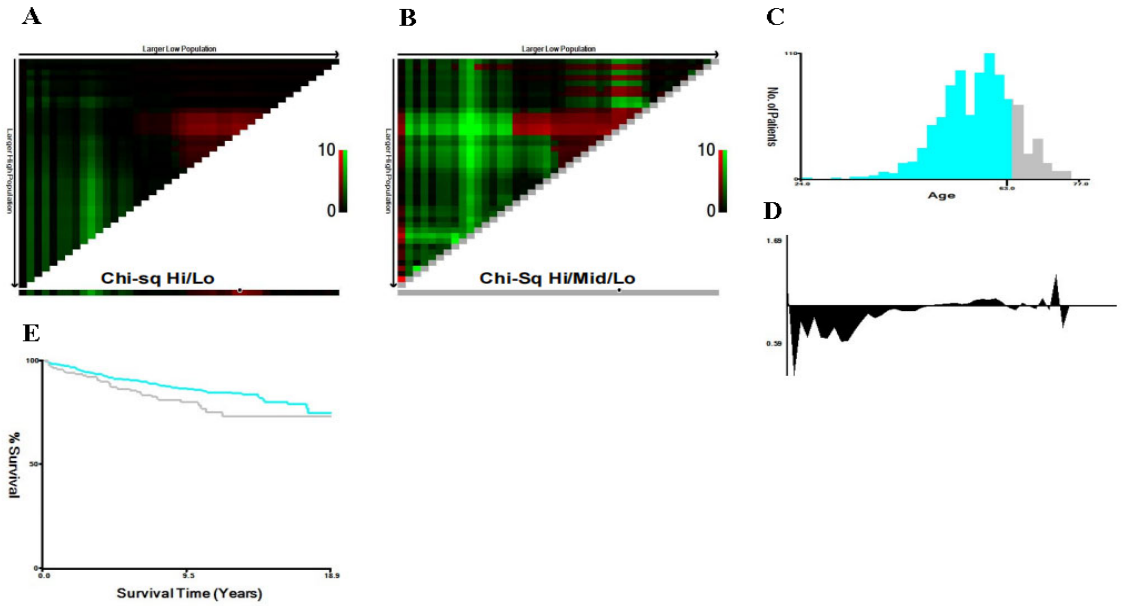

Figure 4. X-tile plot identifying the optimal age cutoff for cancer-specific survival in hepatocellular carcinoma patients (cutoff: 64 years). (A) Two-group cut-point analysis (high vs. low) based on maximal log-rank χ^2 statistics. (B) Three-group cut-point analysis (high, intermediate, and low) based on maximal log-rank χ^2 statistics. (C) Age distribution. (D) Association between age and survival. (E) Kaplan–Meier curves stratified by selected cutoff(s).

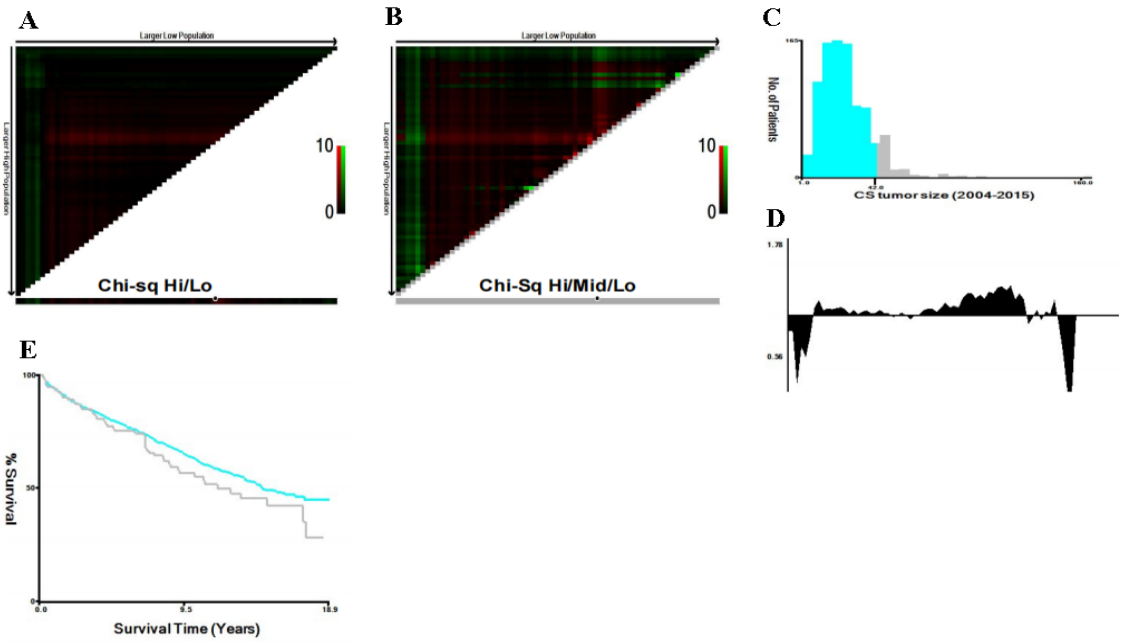

Figure 5. X-tile plot identifying the optimal tumor size cutoff for overall survival in hepatocellular carcinoma patients (cutoff: 43 mm). (A) Two-group cut-point analysis (high vs. low) based on maximal log-rank χ^2 statistics. (B) Three-group cut-point analysis (high, intermediate, and low) based on maximal log-rank χ^2 statistics. (C) Tumor size distribution. (D) Association between tumor size and survival. (E) Kaplan–Meier curves stratified by selected cutoff(s).

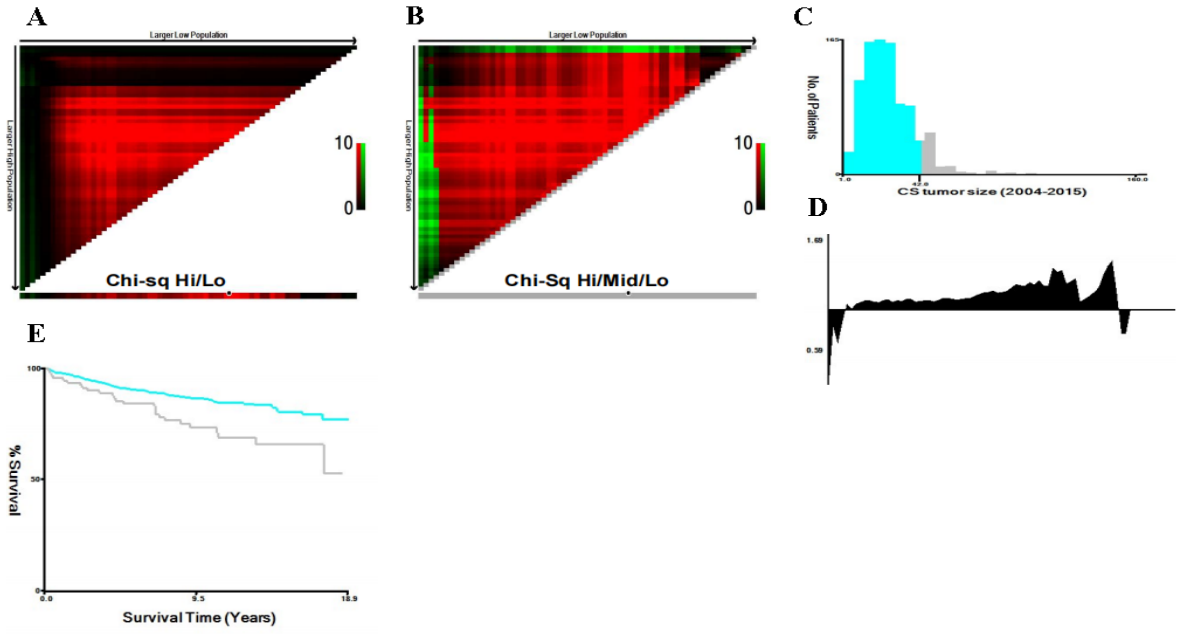

Figure 6. X-tile plot identifying the optimal tumor size cutoff for cancer-specific survival in hepatocellular carcinoma patients (cutoff: 43 mm). (A) Two-group cut-point analysis (high vs. low) based on maximal log-rank χ^2 statistics. (B) Three-group cut-point analysis (high, intermediate, and low) based on maximal log-rank χ^2 statistics. (C) Tumor size distribution. (D) Association between tumor size and survival. (E) Kaplan–Meier curves stratified by selected cutoff(s).

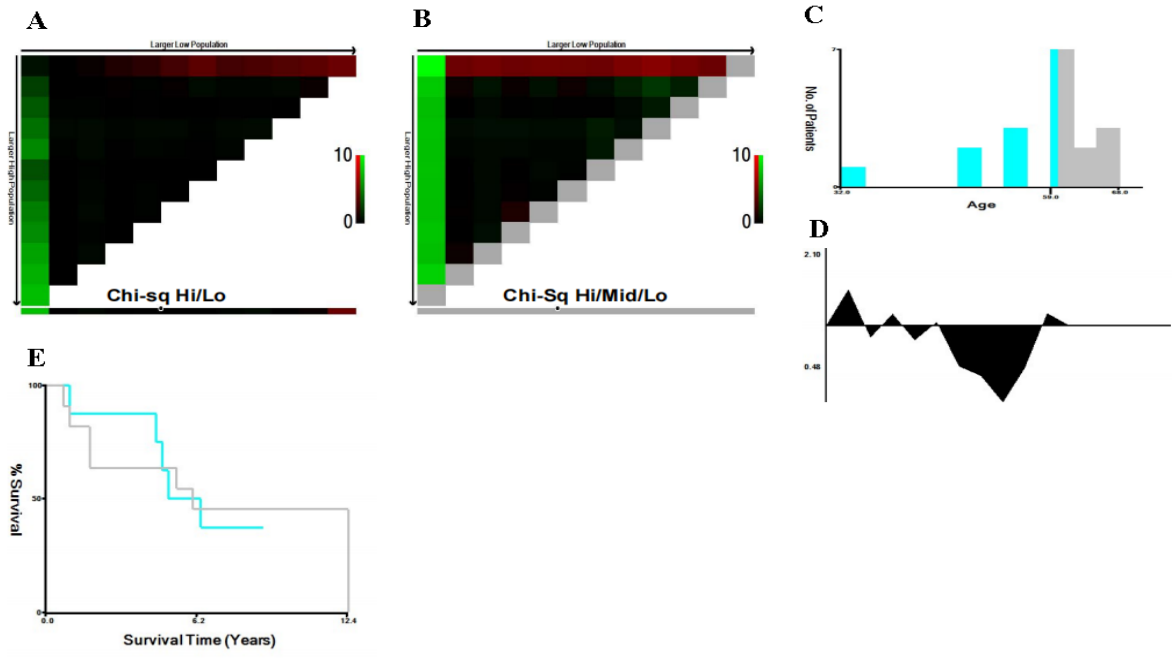

Figure 7. X-tile plot identifying the optimal age cutoff for overall survival in intrahepatic cholangiocarcinoma patients stratified by age (cutoff: 60 years; log-rank $p = 0.889$). (A) Two-group cut-point analysis (high vs. low) based on maximal log-rank χ^2 statistics. (B) Three-group cut-point analysis (high, intermediate, and low) based on maximal log-rank χ^2 statistics. (C) Age distribution. (D) Association between age and survival. (E) Kaplan–Meier curves stratified by selected cutoff(s).

Table 3. Univariate and multivariate analyses for overall survival in hepatocellular carcinoma patients

Variable factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age				
≥63 years	Ref		Ref	
<63 years	0.559 (0.452–0.691)	0.001	0.557 (0.451–0.689)	0.001
Sex				
Female	Ref			
Male	0.948 (0.785–1.185)	0.639		
Race				
Other	Ref			
White	1.161 (0.826–1.631)	0.391		
Black	1.510 (0.967–2.356)	0.070		
Marital status				
Unmarried	Ref		Ref	
Married	0.799 (0.652–0.980)	0.032	1.260 (1.027–1.545)	0.027
Chemotherapy				
None	Ref			
Done	3.079 (0.923–10.273)	0.067		
Radiation				
None	Ref			
Done	1.161 (0.576–2.337)	0.677		
Tumor size				
≥43 mm	Ref			
<43 mm	0.793 (0.587–1.072)	0.132		
Number of lymph nodes				
≥4	Ref			
None	1.147 (0.628–2.095)	0.655		
1–3	1.218 (0.654–2.267)	0.534		

Abbreviations: CI: Confidence interval; HR: Hazard ratio.

if selection bias exists, it would likely favor the ICC group, as patients with ICC are typically subjected to more rigorous preoperative evaluation and are often required to meet stricter criteria for LT candidacy given the controversial nature of this indication.[15] Thus, the observed survival difference likely represents a conservative estimate of the true biological disparity between these two tumor types. This finding aligns with most literature reports, potentially attributable to ICC's more aggressive biological behavior—such as higher tendencies for lymph node metastasis, nerve invasion, and vascular invasion—which substantially increases postoperative recurrence risk.[16-18] Even after rigorous selection, long-term oncological outcomes for ICC remain unfavorable, perpetuating ongoing debate regarding the indications and efficacy of LT in ICC treatment.[19,20] The excellent outcomes observed in HCC patients (five-year OS 95.1%) confirm the established role of LT as a highly effective curative therapy for early-stage HCC when performed within appropriate selection criteria.

4.2. Heterogeneity in prognostic factors

Cox regression analysis further revealed heterogeneity in prognostic factors between the two patient groups. Among HCC patients, age and marital status were independent risk factors for OS, while tumor size was an independent risk factor for CSS. Age and marital status primarily influence long-term survival by affecting patients' overall

Table 4. Univariate and multivariate analyses for cancer-specific survival in hepatocellular carcinoma patients

Variable factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age				
≥64 years	Ref		Ref	
<64 years	0.639 (0.432–0.944)	0.025	0.681 (0.459–1.010)	0.056
Sex				
Female	Ref			
Male	0.712 (0.500–1.015)	0.060		
Race				
Other	Ref			
White	0.710 (0.441–1.145)	0.161		
Black	0.931 (0.470–1.846)	0.838		
Marital status				
Unmarried	Ref			
Married	0.755 (0.536–1.062)	0.107		
Chemotherapy				
None	Ref			
Done	1.269 (0.897–1.795)	0.178		
Radiation				
None	Ref			
Done	1.252 (0.399–3.930)	0.700		
Tumor size				
≥43 mm	Ref		Ref	
<43 mm	0.484 (0.316–0.740)	0.001	1.970 (1.283–3.025)	0.002
Number of lymph nodes				
≥4	Ref			
None	0.868 (0.353–2.131)	0.757		
1–3	0.945 (0.371–2.404)	0.905		

Abbreviations: CI: Confidence interval; HR: Hazard ratio.

health management and support systems: advanced age is a strong predictor of multiple non-tumor-related deaths, and elderly patients face higher risks of postoperative complications and slower recovery.[21-23] Marital status, as a key indicator of social support, correlates with better treatment adherence, psychological well-being, and caregiving, thereby reducing mortality from non-cancer-specific causes.[24-26]

Tumor size directly reflects tumor burden and malignant potential, serving as a core biological determinant of recurrence and cancer-specific mortality.[27,28] However, in ICC patients, only tumor size showed a potential association with OS in univariate analysis, and no significant risk factors for CSS were identified. Given the small sample size, these findings should be considered hypothesis-generating rather than definitive. This observation may suggest a fundamental difference in ICC biology. The inherent high invasiveness of ICC may result in a uniformly elevated and relatively homogeneous risk of postoperative recurrence, such that conventional clinical-pathological variables struggle to further differentiate cancer-specific mortality risk. This suggests that prognosis in ICC may depend more on deeper biological contexts such as molecular subtypes and microenvironmental characteristics.[29-32]

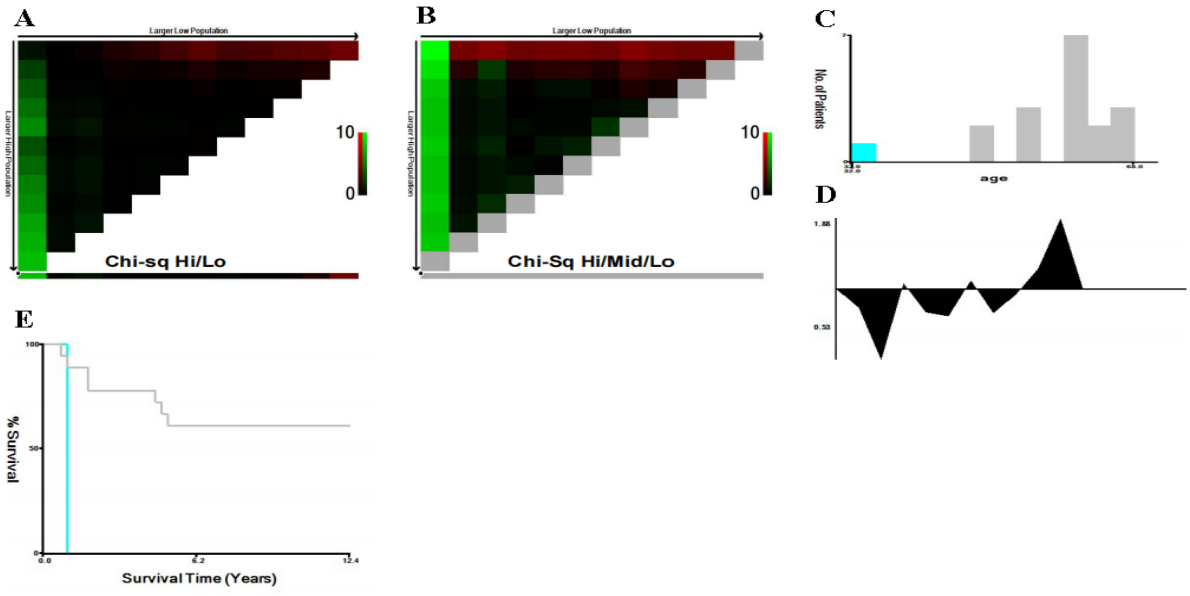

Figure 8. X-tile plot identifying the optimal age cutoff for cancer-specific survival in intrahepatic cholangiocarcinoma patients stratified by age (cutoff: 47 years; log-rank $p = 0.078$). (A) Two-group cut-point analysis (high vs. low) based on maximal log-rank χ^2 statistics. (B) Three-group cut-point analysis (high, intermediate, and low) based on maximal log-rank χ^2 statistics. (C) Age distribution. (D) Association between age and survival. (E) Kaplan–Meier curves stratified by selected cutoff(s).

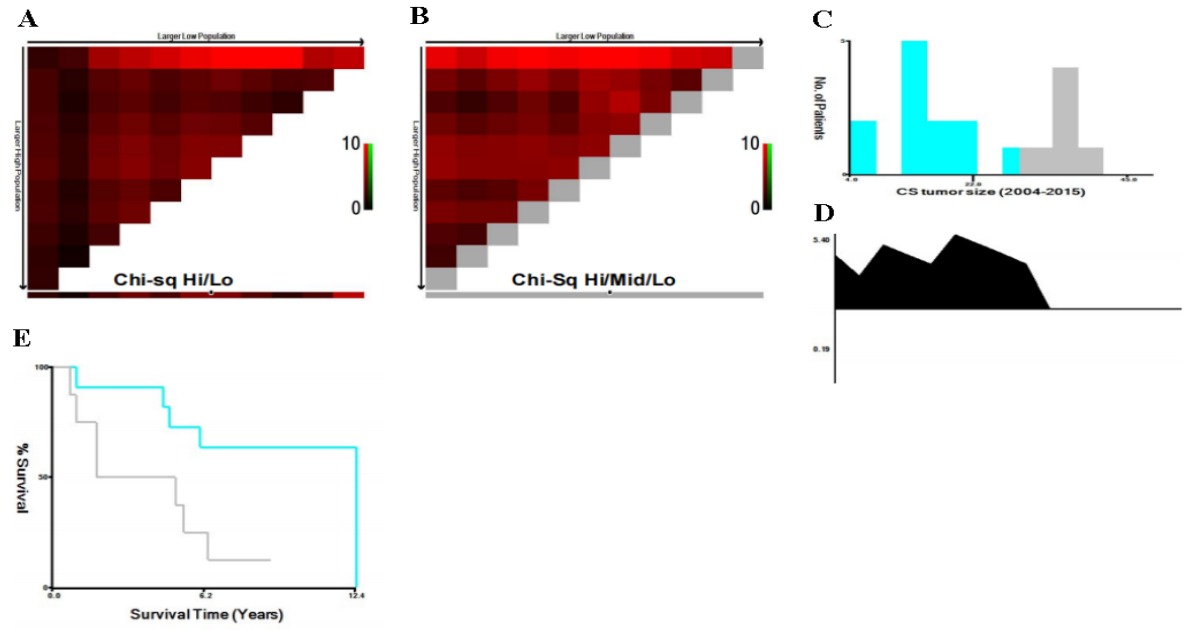

Figure 9. X-tile plot identifying the optimal tumor size cutoff for overall survival in intrahepatic cholangiocarcinoma patients stratified by tumor size (cutoff: 29 mm; log-rank $p = 0.037$). (A) Two-group cut-point analysis (high vs. low) based on maximal log-rank χ^2 statistics. (B) Three-group cut-point analysis (high, intermediate, and low) based on maximal log-rank χ^2 statistics. (C) Tumor size distribution. (D) Association between tumor size and survival. (E) Kaplan–Meier curves stratified by selected cutoff(s).

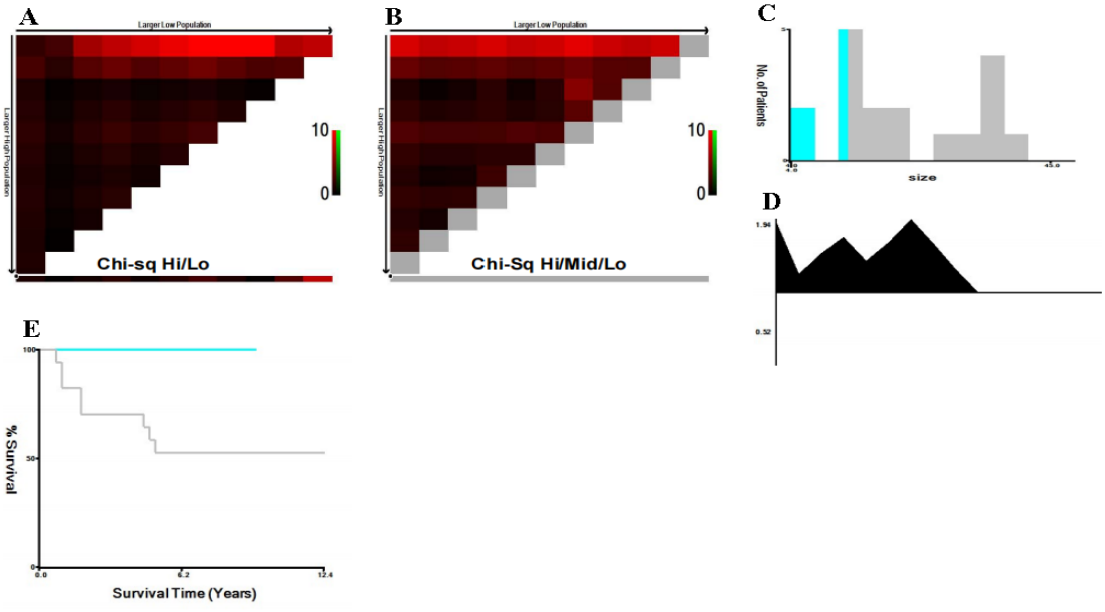

Figure 10. X-tile plot identifying the optimal tumor size cutoff for cancer-specific survival in intrahepatic cholangiocarcinoma patients stratified by tumor size (cutoff: 13 mm; log-rank $p = 0.483$). (A) Two-group cut-point analysis (high vs. low) based on maximal log-rank χ^2 statistics. (B) Three-group cut-point analysis (high, intermediate, and low) based on maximal log-rank χ^2 statistics. (C) Tumor size distribution. (D) Association between tumor size and survival. (E) Kaplan–Meier curves stratified by selected cutoff(s).

4.3. Clinical implications and recommendations

Based on the study findings, we propose the following clinical recommendations. For HCC patients, given the excellent post-transplant outcomes, the priority should shift toward optimizing patient selection and perioperative management. Specifically, elderly patients (≥63 years) and unmarried patients merit enhanced postoperative surveillance and comprehensive supportive care, as they face higher risks of non-cancer-specific mortality. For patients with tumors ≥43 mm, closer oncological follow-up is warranted given their increased risk of cancer-specific mortality.

For ICC patients, the current evidence suggests that LT for ICC, even at stage I, yields significantly inferior outcomes compared to HCC. Therefore, extreme caution is warranted when considering LT as a treatment option for ICC. Preoperative evaluation should be particularly rigorous, with careful assessment of tumor size and exclusion of extrahepatic disease. Given the limited efficacy under current selection paradigms, LT for ICC should ideally be confined to prospective clinical trials or to highly selected cases in which no alternative curative options exist.

4.4. Future research directions

The findings of this study highlight several critical directions for future research. First, the establishment of multicenter ICC LT cohorts is urgently needed. The small number of ICC cases identified in this large national database (19 cases over 12 years) underscores the rarity of this practice and the necessity of collaborative efforts to generate adequately powered datasets. International consortia pooling data from multiple transplant centers could achieve sufficient sample sizes for meaningful multivariable analyses and subgroup identification.

Second, incorporating molecular and genomic biomarkers is essential for identifying ICC subpopulations that may benefit from LT. Recent advances in ICC molecular subtyping have revealed distinct subtypes with different prognoses and treatment responses.[29,30] For instance, the proliferative subtype, characterized by oncogenic pathways such as KRAS, BRAF, and MET mutations, may exhibit more aggressive behavior, whereas the inflammatory subtype with active immune infiltration may show different treatment responses.[31] Future studies should integrate these molecular classifiers into transplant selection criteria, moving beyond traditional clinical-pathological variables.

Third, the role of neoadjuvant and adjuvant therapies in ICC patients undergoing LT warrants investigation. As transplant oncology concepts evolve, strategies such as

Table 5. Univariate analysis for overall survival in intrahepatic cholangiocarcinoma patients

Variable factors	Hazard ratio (95% confidence interval)	*p*-value
Age		
≥60 years	Ref	
<60 years	1.088 (0.331–3.576)	0.889
Sex		
Female	Ref	
Male	1.108 (0.324–3.789)	0.871
Race		
Other	Ref	
White	0.342 (0.040–2.933)	0.328
Black	0.975 (0.084–11.343)	0.984
Marital status		
Unmarried	Ref	
Married	1.315 (0.348–4.970)	0.686
Chemotherapy		
None	Ref	
Done	0.901 (0.724–1.122)	0.353
Radiation		
None	Ref	
Done	-	-
Tumor size		
≥29 mm	Ref	
<29 mm	0.265 (0.076–0.922)	0.037
Number of lymph nodes		
≥4	Ref	
None	21,017.908 (0.000–4.599E + 153)	0.955
1–3	47,289.001 (0.000–1.035E + 154)	0.951

Note: Multivariate analysis was not performed due to the extremely small sample size (n = 19).

neoadjuvant chemotherapy or locoregional therapy may help select biologically favorable tumors and improve post-transplant outcomes.[13,14] The impact of these approaches on ICC patients specifically requires a dedicated study.

4.5. Limitations

This study has several limitations that should be acknowledged. First, as a retrospective analysis of the SEER database, it is subject to inherent selection bias. We attempted to minimize this by applying strict inclusion criteria, but unmeasured confounding factors may persist. Specifically, the SEER database lacks critical variables that determine transplant eligibility, including performance status (Eastern Cooperative Oncology Group), model for end-stage liver disease score, portal hypertension status, and whether patients met Milan or University of California, San Francisco criteria. The direction of potential bias is important to consider: if ICC patients were more rigorously selected than HCC patients (as is typical in clinical practice), any bias would likely overestimate ICC outcomes relative to HCC, making our finding of inferior ICC outcomes more conservative.

Second, the sample size in the ICC group is extremely small ($n = 19$). While this accurately reflects the real-world rarity of LT for ICC, it severely limits the statistical power and precision of our analyses. As a result, we refrained from performing multivariate Cox regression for the ICC group, and the univariate findings should be interpreted as hypothesis-generating rather than definitive. The substantial imbalance between groups (925 vs. 19) further complicates direct comparison, though our sensitivity

Table 6. Univariate analysis for cancer-specific survival in intrahepatic cholangiocarcinoma patients

Variable factors	Hazard ratio (95% confidence interval)	*p*-value
Age		
≥47 years	Ref	
<47 years	8.662 (0.785–95.550)	0.078
Sex		
Female	Ref	
Male	1.029 (0.246–4.311)	0.968
Race		
Other	Ref	
White	0.376 (0.044–3.200)	0.371
Black	0.631 (0.039–10.342)	0.747
Marital status		
Unmarried	Ref	
Married	1.391 (0.281–6.899)	0.686
Chemotherapy		
None	Ref	
Done	3.629 (0.858–15.356)	0.080
Radiation		
None	Ref	
Done	—	—
Tumor size		
≥13 mm	Ref	
<13 mm	0.040 (0.001–323.602)	0.483
Number of lymph nodes		
≥4	Ref	
None	7,306.582 (0.000–5.596E + 116)	0.947
1–3	15,039.791 (0.000–1.152E + 117)	0.942

Note: Multivariate analysis was not performed due to the extremely small sample size (n = 19). HR estimates were unstable due to sparse events and should not be interpreted.

analyses (random subsampling and bootstrap resampling) suggest the observed survival differences are robust.

Third, and most importantly, the SEER database lacks several critical clinical and pathological variables that are known to influence post-LT outcomes. Table 7 summarizes the potential impact of these missing variables.

The absence of these variables means we cannot fully account for their confounding effects, particularly in explaining the poorer outcomes observed in ICC patients. However, it is noteworthy that ICC patients in this cohort likely represent a highly selected subset (given the controversy surrounding LT for ICC), which would bias toward better outcomes in this group. Despite this potential bias favoring ICC, we still observed significantly inferior survival, reinforcing the conclusion that biological differences between these tumor types are substantial.

Fourth, the study period (2004–2015) may not fully reflect contemporary advances in transplant oncology, including newer immunosuppressive strategies, improved perioperative care, and evolving patient selection practices.

Despite these limitations, the study provides valuable real-world evidence on the comparative outcomes of LT for early-stage HCC and ICC, highlighting critical differences that should inform clinical decision-making and future research priorities. The consistency of our findings with external literature, coupled with sensitivity analyses demonstrating robustness, supports the validity of the primary conclusions despite inherent database constraints.

Table 7. Potential impact of missing variables

Missing variable	Impact on HCC conclusion	Impact on ICC conclusion
Vascular invasion/ microvascular invasion	May lead to overestimation of HCC outcomes if excluded (some patients with vascular invasion may be inappropriately included)	ICC has an inherently higher propensity for vascular invasion; absence may underestimate the true recurrence risk in ICC
Tumor differentiation grade	Prevents assessment of biological aggressiveness beyond size	Particularly important for ICC prognosis
Alpha fetoprotein level	Key marker for HCC biological behavior and recurrence risk	Less relevant for ICC
Liver function (Child–Pugh/ MELD)	Affects non-cancer mortality; may influence OS but less so for CSS	ICC patients often lack underlying cirrhosis, so the impact is limited
Immunosuppressive regimen	Unable to assess the impact of different protocols on recurrence	Equally important for both groups
Neoadjuvant/adjuvant therapy details	Cannot evaluate perioperative treatment effects	Particularly relevant given the ongoing debate about ICC neoadjuvant strategies

Abbreviations: CSS: Cancer-specific survival; HCC: Hepatocellular carcinoma; ICC: Intrahepatic cholangiocarcinoma; MELD: Model for end-stage liver disease; OS: Overall survival.

5. Conclusion

In summary, LT offers excellent long-term survival for patients with early-stage HCC, with five-year survival rates exceeding 95%. Age, marital status, and tumor size serve as important prognostic factors in this population. In contrast, the therapeutic value of LT for early-stage ICC remains limited, with significantly inferior outcomes and no identifiable independent prognostic factors based on conventional clinical variables. The magnitude of the survival difference (~15% at five years) and its consistency across sensitivity analyses support the conclusion that this reflects genuine biological differences rather than an artifact of sample imbalance or selection bias. These findings underscore the need for distinct selection criteria and management strategies for the two histological types. The limited utility of LT for ICC under current selection paradigms emphasizes the urgent need for larger multicenter studies incorporating comprehensive clinical, pathological, and molecular profiling to identify the specific ICC subpopulations that may derive benefit from this treatment modality. Until such evidence emerges, LT for ICC should be approached with extreme caution and ideally within the context of clinical trials.

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Conflict of interest

The authors have disclosed no conflicts of interest.

Author contributions

Conceptualization: Chuan Jiang
Data curation: All authors
Writing–original draft: All authors
Writing–review & editing: Chuan Jiang

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

The data supporting the findings of this study are publicly available in the Surveillance, Epidemiology, and End Results (SEER) Program database at https://seer.cancer.gov/.

References

1. Jiang Z, Zeng G, Dai H, *et al*. Global, regional and national burden of liver cancer 1990-2021: a systematic analysis of the global burden of disease study 2021. *BMC Public Health*. 2025;25(1).

   doi: 10.1186/s12889-025-22026-6

2. Yao J, Liang X, Liu Y, Li S, Zheng M. Trends in Incidence and Prognostic Factors of Two Subtypes of Primary Liver Cancers: A Surveillance, Epidemiology, and End Results-Based Population Study. *Cancer Control*. 2022;29.

   doi: 10.1177/10732748211051548

3. Liao K, Yang K, Cao L, *et al*. Laparoscopic Anatomical Versus Non-anatomical hepatectomy in the Treatment of Hepatocellular Carcinoma: A randomised controlled trial.

Int J Surg. 2022;102:106652.

doi: 10.1016/j.ijsu.2022.106652

4. Chen B, Wu JX, Cheng SH, *et al*. Phase 2 Study of Adjuvant Radiotherapy Following Narrow-Margin Hepatectomy in Patients With HCC. *Hepatology*. 2021;74(5):2595-2604.

doi: 10.1002/hep.31993

5. Du C, Cao W, Liu J, *et al*. Utility of a novel scoring system for difficulty of pure laparoscopic hepatectomy for intrahepatic cholangiocarcinoma. *Sci Rep*. 2024;14(1).

doi: 10.1038/s41598-024-83413-4

6. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. *Lancet*. 2022;400(10360):1345-1362.

doi: 10.1016/S0140-6736(22)01200-4

7. Sun D, Lv G, Dong J. Liver Transplantation for Intrahepatic Cholangiocarcinoma: What Are New Insights and What Should We Follow? *Front Oncol*. 2022;11.

doi: 10.3389/fonc.2021.841694

8. Elzein SM, Brombosz EW, Kodali S. Liver Transplantation for Cancer-Current Challenges and Emerging Solutions. *J Clin Med*. 2025;14(15):5365.

doi: 10.3390/jcm14155365

9. Wei P, Ma D, Lo C, *et al*. Liver transplantation for intrahepatic cholangiocarcinoma: Insights from a National Registry Study in China. *Medicine*. 2025;104(42):e44942.

doi: 10.1097/MD.0000000000044942

10. Huang G, Song W, Zhang Y, Yu J, Lv Y, Liu K. Liver transplantation for intrahepatic cholangiocarcinoma: a propensity score-matched analysis. *Sci Rep*. 2023;13(1).

doi: 10.1038/s41598-023-37896-2

11. Kim J, Joo DJ, Hwang S, *et al*. Liver transplantation for combined hepatocellular carcinoma and cholangiocarcinoma: A multicenter study. *World J Gastrointest Surg*. 2023;15(7):1340-1353.

doi: 10.4240/wjgs.v15.i7.1340

12. Krenzien F, Nevermann N, Krombholz A, *et al*. Treatment of Intrahepatic Cholangiocarcinoma-A Multidisciplinary Approach. *Cancers*. 2022;14(2):362.

doi: 10.3390/cancers14020362

13. Dasari BVM, Line PD, Sapisochin G, *et al*. Liver transplantation as a treatment for cancer: comprehensive review. *BJS Open*. 2025;9(3).

doi: 10.1093/bjsopen/zraf034

14. Andraus W, Ochoa G, de Martino RB, *et al*. The role of living donor liver transplantation in treating intrahepatic cholangiocarcinoma. *Front Oncol*. 2024;14.

doi: 10.3389/fonc.2024.1404683

15. Kodali S, Kulik L, D'Allessio A, *et al*. The 2024 ILTS-ILCA consensus recommendations for liver transplantation for HCC and intrahepatic cholangiocarcinoma. *Liver Transpl*. 2025;31(6):815-831.

doi: 10.1097/LVT.0000000000000589

16. Kim KM, Na JE, Shim SG, Sinn DH. Comparison of ICC patients with hepatitis B infection to those with no major risk factors for HCC. *HPB*. 2021;23(6):945-953.

doi: 10.1016/j.hpb.2020.10.011

17. Liguori C, Cacciaguerra AB, Giampieri R, *et al*. Is it a new era for intrahepatic cholangiocarcinoma? *Crit Rev Oncol Hematol*. 2025;215:104923.

doi: 10.1016/j.critrevonc.2025.104923

18. Endo Y, Kawashima J, Woldesenbet S, *et al*. Characteristics of "Very Early" Intrahepatic Cholangiocarcinoma Undergoing Liver Resection and Its Relationship With Carbohydrate Antigen 19-9. *J Surg Oncol*. 2025;132(5):924-934.

doi: 10.1002/jso.70071

19. Sugawara Y, Hibi T. Recent trends and new developments in liver transplantation. *Biosci Trends*. 2024;18(3):206-211.

doi: 10.5582/bst.2024.01176

20. Schwenk L, Rohland O, Ali-Deeb A, Dondorf F, Settmacher U, Rauchfuß F. Liver Transplantation for Incidental Cholangiocarcinoma or Combined Hepatocellular Carcinoma/Cholangiocarcinoma-Own Experiences and Review of the Literature. *Cancers*. 2023;15(14):3609.

doi: 10.3390/cancers15143609

21. Alim A, Karataş C. Prognostic Factors of Liver Transplantation for HCC: Comparative Literature Review. *J Gastrointest Cancer*. 2021;52(4):1223-1231.

doi: 10.1007/s12029-021-00730-x

22. Niazi S, Schneekloth T, Taner CB. Elderly recipients of liver transplantation: impact of age and psychosocial variables on outcome. *Curr Opin Organ Transplant*. 2017;22(6):588-592.

doi: 10.1097/MOT.0000000000000469

23. Avanaz A, Doğru V, Kisaoglu A, *et al*. Impact of older age on the long-term survival in living-donor liver transplantation: A propensity score matching analysis. *Asian J Surg*. 2022;45(11):2239-2245.

doi: 10.1016/j.asjsur.2021.11.061

24. Krajc K, Miroševič Š, Sajovic J, *et al*. Marital status and survival in cancer patients: A systematic review and meta-analysis. *Cancer Med*. 2023;12(2):1685-1708.

doi: 10.1002/cam4.5003

25. Chen F, Wu Y, Xu H, Song T, Yan S. Impact of marital status on overall survival in patients with early-stage hepatocellular carcinoma. *Sci Rep*. 2022;12(1).

doi: 10.1038/s41598-022-14120-1

26. Song L, Guan T, Guo P, *et al*. Health behaviors, obesity, and marital status among cancer survivors: a MEPS study. *J Cancer Surviv*. 2023;17(2):499-508.

doi: 10.1007/s11764-022-01269-x

27. Shehta A, Elsabbagh AM, Medhat M, *et al*. Impact of tumor size on the outcomes of hepatic resection for hepatocellular carcinoma: a retrospective study. *BMC Surg*. 2024;24(1).

doi: 10.1186/s12893-023-02296-w

28. Zhang D, Love T, Hao Y, *et al*. Tumor Size, Not Small Vessel Invasion, Predicts Survival in Patients With Hepatocellular Carcinoma. *Am J Clin Pathol*. 2022;158(1):70-80.

doi: 10.1093/ajcp/aqac001

29. Zeng L, He C, Li X. Prognosis for intrahepatic cholangiocarcinoma after liver transplantation by size of tumor. *Surgery*. 2023;174(4):1094.

doi: 10.1016/j.surg.2022.12.014

30. De Santis A, Zhu L, Tao J, Reißfelder C, Schölch S. Molecular subtypes of intrahepatic cholangiocarcinoma. *Trends Mol Med*. 2025;31(8):755-769.

doi: 10.1016/j.molmed.2025.01.008

31. Huang H, Chen F. Molecular and Histological Profiles and Relevant Imaging Signatures of Intrahepatic Cholangiocarcinoma. *J Clin Transl Hepatol*. 2025;13(6):504-515.

doi: 10.14218/JCTH.2024.00410

32. Czauderna C, Kirstein MM, Tews HC, Vogel A, Marquardt JU. Molecular Subtypes and Precision Oncology in Intrahepatic Cholangiocarcinoma. *J Clin Med*. 2021;10(13):2803.

doi: 10.3390/jcm10132803