ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

e-ISSN 2329-0358
© Ann Transplant, 2025; 30: e949241
DOI: 10.12659/AOT.949241

Received: 2025.04.04
Accepted: 2025.09.19
Available online: 2025.11.06
Published: 2025.12.16

Liver Transplantation for Combined Hepatocellular-Cholangiocarcinoma: A Retrospective Registry-Based Study Using the Korean Organ Transplant Registry (KOTRY)

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Financial support: This research was supported by a fund (2014-ER6301-00, 2014-ER6301-01,2014-ER6301-02, 2017-ER6301-00,2017-ER6301-01, 2017-ER6301-02, 2020-ER7201-00) by Research of Korea Centers for Disease Control and Prevention Agency

Conflict of interest: None declared

Background: Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is a rare primary liver tumor with poor prognosis. This retrospective study aimed to evaluate the outcomes and prognostic factors of 40 patients who underwent liver transplantation (LT) for cHCC-CC using data from the Korean Organ Transplant Registry (KOTRY).

Material/Methods: A cohort of 40 LT recipients diagnosed with cHCC-CC was selected from the KOTRY database between 2014 and 2019. Survival analyses were performed according to key clinicopathological variables, and risk factor analyses were conducted for overall survival (OS) and recurrence-free survival (RFS).

Results: During a median follow-up of 21.4 months, 10 patients (25.0%) died and 9 patients (22.5%) experienced tumor recurrence. The 1-, 2-, and 3-year OS rates were 91.8%, 76.2%, and 59.3%, respectively, and the corresponding RFS rates were 88.8%, 70.5%, and 50.2%. Patients with a MELD score <20 (P=0.017) and a single tumor <3 cm (P=0.046) showed significantly better OS. On multivariate analysis, MELD score ≥20 (P=0.04), perineural invasion (P=0.04), and portal vein tumor thrombosis (P=0.005) were independent risk factors for poor OS, whereas microvascular invasion (P=0.01) was an independent risk factor for poor RFS.

Conclusions: LT can be a feasible treatment option for patients with early-stage cHCC-CC, providing favorable long-term survival. As most prognostic factors identified were pathology-related, further studies are needed to refine the selection criteria for LT candidates in this population.

Keywords: Carcinoma, Hepatocellular • Cholangiocarcinoma, Intrahepatic • Liver Transplantation • Survival • Prognosis

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/949241

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Introduction

Combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CC) is a rare form of primary liver carcinoma characterized by the presence of hepatocytic and cholangiocytic differentiation. This tumor represents 2% of all primary liver malignancies [1]. The diagnosis of cHCC-CC relies on routine histopathology with hematoxylin and eosin staining, demonstrating the intermingling of hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) components [1]. The working terminology for diagnostic and research approaches has been recently updated in the 2019 World Health Organization (WHO) histological classification system [1,2]. Liver transplantation (LT) has been established as a therapeutic option for HCC, but LT for cHCC-CC has been sporadically reported to date, due to high tumor recurrence and poor patient survival [3,4]. Only a small number of studies, which report conflicting posttransplant outcomes, have been published [3-7]. Several recent studies have recommended LT for patients with cHCC-CC who meet strict selection criteria, reporting favorable long-term survival outcomes in these patients [3-7]. The Korean Organ Transplantation Registry (KOTRY), established in 2014 and supported by the Korean Center for Disease Control and Prevention, is a nationwide prospective multicenter registry that collects standardized real-world data on organ transplantation in Korea, including donor and recipient demographics, perioperative details, postoperative complications, and long-term outcomes, from most transplant centers across the country [8]. Therefore, in this retrospective study, we aimed to evaluate outcomes from LT for cHCC-CC in 40 patients using data from the KOTRY database.

Material and Methods

Ethics Statement

All patients were registered with the KOTRY before LT and underwent routine outpatient follow-up. The study patients were followed until December 2021 or death, through data updated regularly using institutional medical records. The study was approved by the Institutional Review Board of Asan Medical Center, Seoul, South Korea (approval No. 2023-1402), which waived the requirement for informed consent due to the retrospective nature of this study. This study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki 2013.

Study Design

This study was a retrospective analysis of multicenter data from the KOTRY database. The primary end-point of this study was to evaluate the posttransplant prognosis of cHCC-CC and to analyze associated prognostic factors.

Patient Selection

The KOTRY LT database was searched to identify adult patients aged 19 years or older who underwent primary LT with explant diagnosis of cHCC-CC during a 6-year study period from April 2014 to December 2019. All cases in this study were pathologically confirmed as cHCC-CC based on postoperative examination of the explanted liver graft, as none were identified as cHCC-CC before transplantation. Exclusion criteria were re-transplantation and cHCC-CC combined with other distinct malignancies, such as HCC or intrahepatic cholangiocarcinoma (ICC).

Data Collection

We formally requested data from the KOTRY administrative office regarding patients who underwent LT and had a pathological diagnosis of cHCC-CC. Upon approval, the KOTRY administrative office extracted the relevant data from the KOTRY database and provided them to us in a de-identified format.

The collected preoperative recipient variables included sex, age, underlying etiologies of liver disease, model for end-stage liver disease (MELD) score, Child-Pugh classification, history of intensive care unit admission, and the presence of complications related to liver cirrhosis, such as ascites, variceal bleeding, hepatorenal syndrome, and hepatic encephalopathy. Laboratory parameters at the time of transplantation, including total bilirubin, serum albumin, and international normalized ratio, were also collected. Information on preoperative downstaging treatments for liver tumors was obtained from the registry records.

Postoperative follow-up data included tumor recurrence (date, site, and number), patient survival status, causes of death, recurrence-free survival (RFS), overall survival (OS), total follow-up period, and length of postoperative hospital stay. OS was defined as the time from LT to death from any cause or last follow-up, and RFS was defined as the time from LT to tumor recurrence or last follow-up without recurrence.

Histopathological data were obtained from the patient's pathological report of the explanted liver. The diagnosis of cHCC-CC was confirmed by expert pathologists in the participating centers. The following tumor characteristics were analyzed: the histological type and principal tumor component in cHCC-CC, tumor status according to Milan criteria, tumor location, viable tumor number, totally necrotic tumor number, maximal tumor size, sum of tumor size, differentiation based on Edmondson-Steiner grade, serosa invasion, peliosis or hemorrhage in tumor, fibrous capsule formation, septal formation, fatty change in tumor, capsule invasion, bile duct invasion, perineural invasion, portal vein tumor thrombosis, macrovascular invasion, microvascular invasion, lymph node metastasis, and satellite nodule.

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Table 1. Baseline and clinicopathologic characteristics of recipients.

Variable	N=40
Sex	
Male (%)	32 (80.0)
Female (%)	8 (20.0)
Age (year)	54.5 (49.3-59.8)
Etiology of liver disease	
Hepatitis B virus infection	33 (82.5)
Hepatitis C virus infection	1 (2.5)
Others	6 (15.0)
MELD score	9 (7-15)
Child-Pugh classification	
A	24 (60.0)
B	9 (22.5)
C	7 (17.5)
Pre-LT ICU admission	3 (7.5)
History of decompensation	
Ascites	2 (5.0)
Variceal bleeding	1 (2.5)
Hepatorenal syndrome	0
Hepatic encephalopathy	0
Pre-LT laboratory findings	
Total bilirubin (mg/dL)	1.0 (0.7-2.0)
Albumin	3.7 (3.0-4.1)
INR	1.19 (1.09-1.37)
Pre-LT down staging treatment for liver cancer	
Liver resection	8 (20.0)
TACE/TACI	25 (62.5)
RFA	4 (10.0)
Chemotherapy	2 (5.0)
Radiotherapy	7 (17.5)
Recurrence during follow-up	9 (22.5)
Intrahepatic metastasis	3 (7.5)
Extrahepatic metastasis	5 (12.5)
Both intra- and extra-hepatic metastasis	1 (2.5)

Variable	N=40
Recurrent sites	
Liver	3 (7.5)
Liver and pleura	1 (2.5)
Lung	1 (2.5)
Lung and left adrenal gland	1 (2.5)
Left adrenal gland	1 (2.5)
Bone	1 (2.5)
Peritoneal seeding	1 (2.5)
Mortality during follow-up	10 (25.0)
Causes of mortality	
Recurrent cancer	4 (10.0)
Infection	4 (10.0)
Pneumonia	1 (2.5)
Aorto-esophageal fistula	1 (2.5)
Follow-up period (months)	21.4 (9.4-30.9)
Hospital stay (days)	21 (17-28)
Tumor characteristics	
Preoperative tumor status	
Within Milan criteria	23 (57.5)
Beyond Milan criteria	17 (42.5)
Viable tumor number	
1	18 (45.0)
2	8 (20.0)
≥3	14 (35.0)
Totally necrotic tumor number	
0	31 (77.5)
1	5 (12.5)
≥2	4 (10.0)
Maximum tumor diameter	
≤2 cm	13 (32.5)
2-5 cm	24 (60.0)
>5 cm	3 (7.5)
Sum of diameter of each tumor	4.1 (2.7-5.7)

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Table 1 continued. Baseline and clinicopathologic characteristics of recipients.

Variable	N=40
Differentiation (Edmondson-Steiner grade)	
I	0
II	9 (23.7)
III	21 (55.3)
IV	8 (21.1)
Serosa invasion	7 (17.5)
Peliosis or hemorrhage in tumor	14 (35.0)
Fibrous capsule formation	11 (27.5)
Septal formation	6 (15.0)
Fatty change in tumor	4 (10.0)

Variable	N=40
Capsule invasion	13 (32.5)
Bile duct invasion	3 (7.5)
Perineural invasion	4 (10.0)
Portal vein invasion (portal vein tumor thrombosis)	3 (7.5)
Macrovascular invasion	4 (10.0)
Microvascular invasion	19 (47.5)
Lymph node metastasis	1 (2.5)
Extrahepatic metastasis	0
Satellite nodule	9 (22.5)

Data are shown as median (interquartile range), mean±standard deviation, or n (%).ICU – intensive care unit; LT – liver transplantation; MELD – model for end-stage liver disease; INR – international normalized ratio; TACE – transcatheter arterial chemoembolization; TACI – transcatheter arterial chemoinfusion; RFA – radiofrequency ablation.

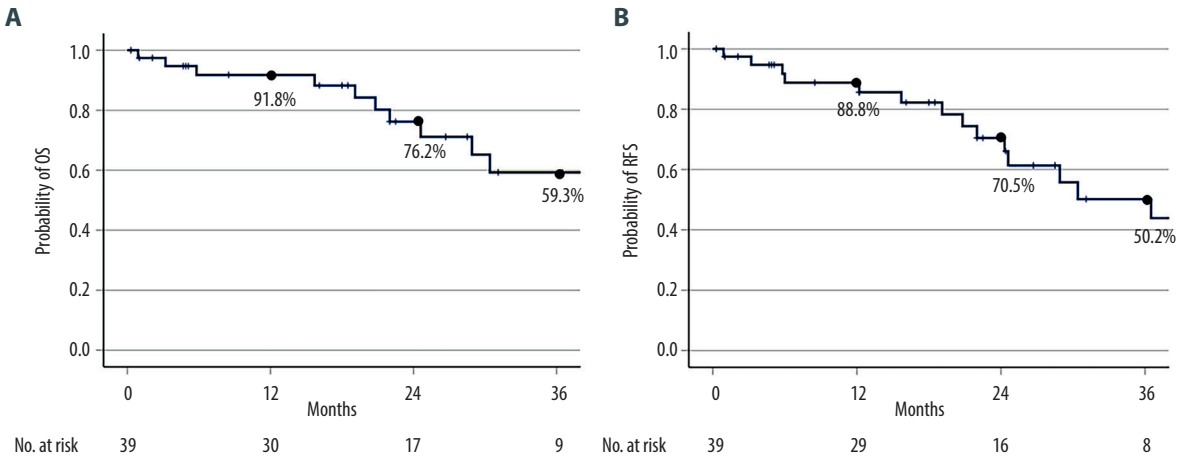

Figure 1. Kaplan-Meier survival curves for 40 patients who underwent liver transplantation for combined hepatocellular carcinoma-cholangiocarcinoma. (**A**) Overall survival (OS) and (**B**) recurrence-free survival (RFS) for the entire cohort.

Statistical Analysis

Continuous variables are expressed as median with interquartile (IQR), and categorical data are presented as counts (n) or percentages (%). The OS and RFS after LT were estimated by the Kaplan-Meier curve and compared using the log-rank test. Univariate and multivariate Cox regression analyses were performed to identify potentially important risk factors for OS and RFS. Significant variables in the univariate analysis (*P*<0.10) were entered into the multivariate backward stepwise Cox regression analysis model as independent risk factors. Cox proportional hazard regression was used for multivariate analysis, and the data presented as the hazard ratio (HR) with 95% CI. A value of *P*<0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 25 (IBM Corp, Armonk, NY, USA).

Results

Patient Demographics and Tumor Characteristics

This retrospective multicenter study based on the KOTRY database included 40 LT recipients diagnosed with cHCC-CC from explanted livers. The baseline characteristics and tumor

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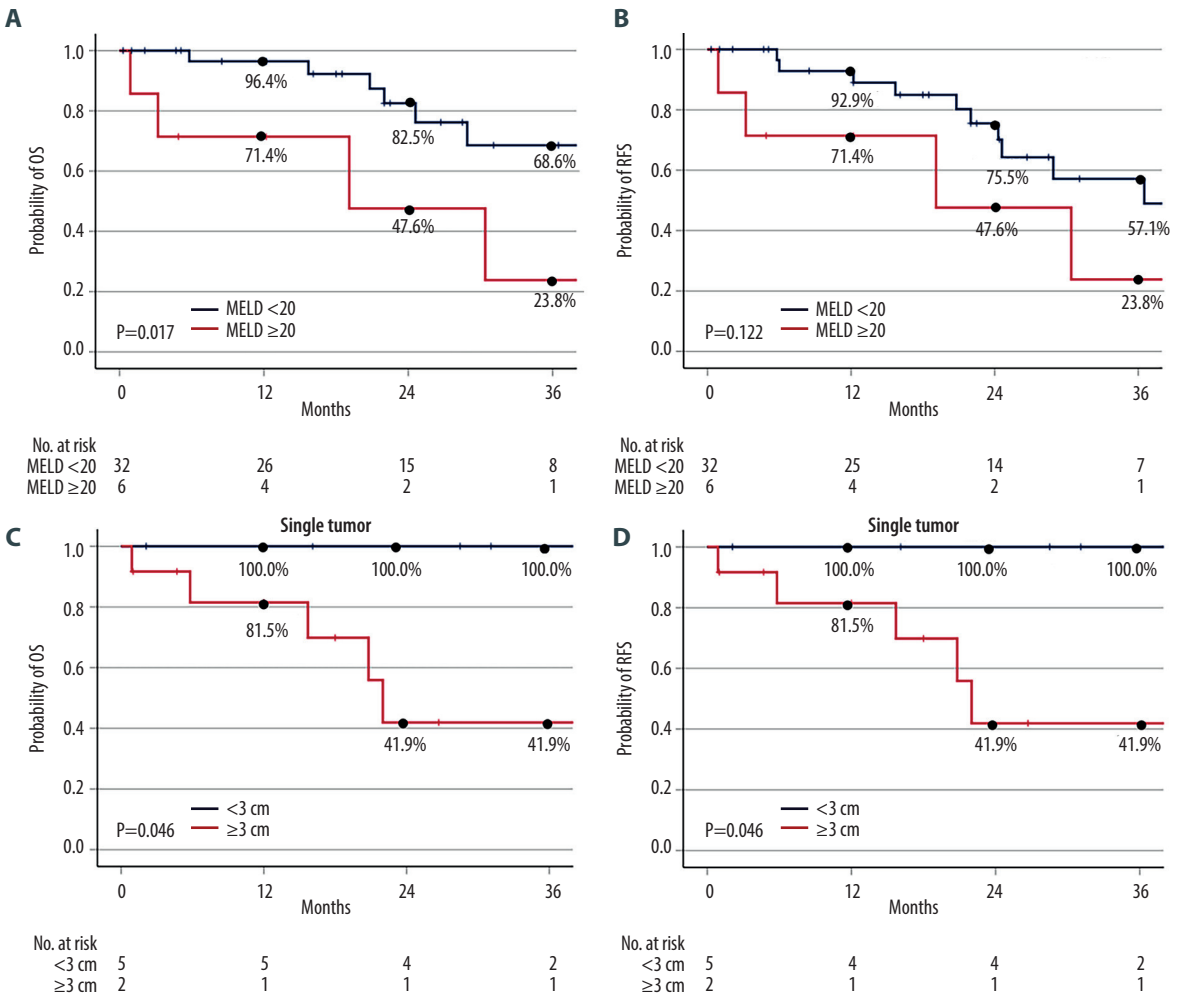

Figure 2. Kaplan-Meier survival curves. (**A**) Overall survival (OS) and (**B**) recurrence-free survival (RFS) according to pretransplant model for end-stage liver disease (MELD) score (<20 vs ≥20). (**C**) OS and (**D**) RFS according to tumor size (<3 cm vs ≥3 cm) in 9 patients with a single tumor.

characteristics as presented in the pathology reports of the recipients are detailed in **Table 1**.

Survival Outcomes in Patients with cHCC-CC

During the median 21.4 months of posttransplant follow-up, 10 cases (25.0%) of mortality and 9 cases (22.5%) of tumor recurrence were observed. During follow-up, the 1-, 2-, and 3-year OS rates were 91.8%, 76.2% and 59.3%, respectively (**Figure 1A**) and the 1-, 2-, and 3-year RFS rates were 88.8%, 70.5%, and 50.23% (**Figure 1B**).

MELD Score <20 vs ≥20

A MELD score ≥20 was associated with a lower long-term survival rate. The 1-, 2-, and 3-year OS rates were 96.4%, 82.5%, and 68.6%, respectively, in patients with a MELD score ≥20, compared with 71.4%, 47.6%, and 23.8% in patients with a MELD score <20 (*P*=0.017; **Figure 2A**). The 1-, 2-, and 3-year RFS rates were 92.9%, 75.5%, and 57.1%, respectively, in patients with MELD score ≥20, compared with 71.4%, 47.6%, and 23.8% in patients with MELD <20; however, there was no statistically significant difference (*P*=0.122; **Figure 2B**).

Single Tumor with Size <3 cm vs ≥3 cm

In the patients with a single tumor (n=18), patients with a small tumor <3 cm had better OS and RFS than the patients with tumor size >3 cm (*P*=0.046). The 3-year OS and RFS rates of 18 patients with a single tumor <3 cm were each 100.0%, whereas the 3-year OS and RFS rates of patients with a single tumor >3 cm were each 49.1% (**Figure 2C, 2D**).

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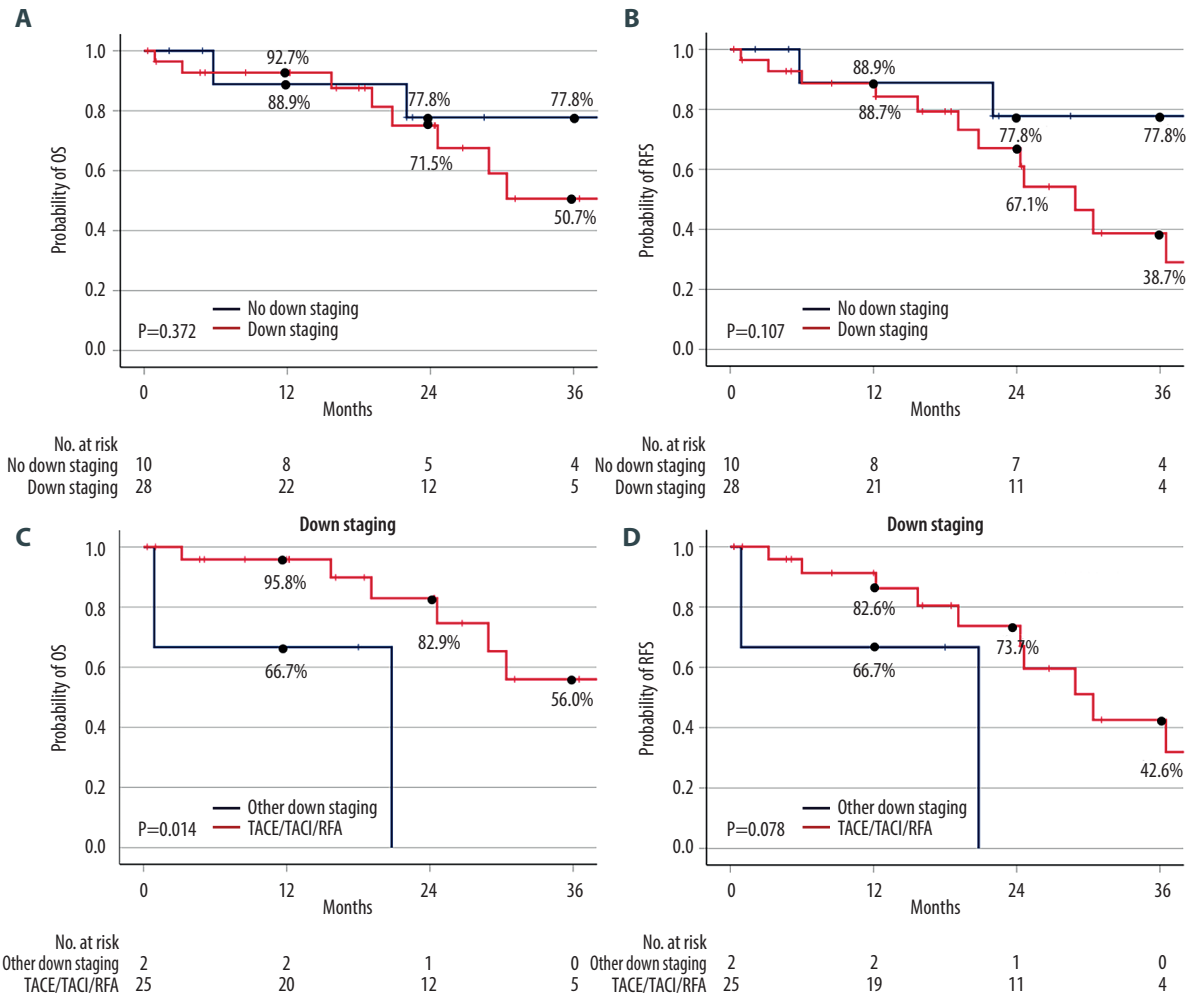

Figure 3. Kaplan-Meier survival curves according to preoperative downstaging treatment. (**A**) Overall survival (OS) and (**B**) recurrence-free survival (RFS) of the patients according to downstaging treatment. (**C**) OS and (**D**) RFS of the 29 patients who underwent downstaging treatments according to treatment type.

Downstaging Treatment

Pretransplant downstaging treatment was not associated with significant improvement of OS *(P*=0.372) and RFS (*P*=0.107; **Figure 3A, 3B**). However, among the 29 patients who underwent preoperative downstaging treatment, those who underwent locoregional treatments as downstaging or curative treatment, including transcatheter arterial chemoembolization (TACE), transcatheter arterial chemotherapy infusion (TACI), and radiofrequency ablation (RFA), had better OS than those who underwent other downstaging treatments, including liver resection, chemotherapy, and radiation therapy (*P*=0.078; **Figure 3C**). RFS appeared to be better in the patients that underwent pretransplant locoregional treatment, but there was no statistically significant difference (*P*=0.078; **Figure 3D**).

Child-Pugh Class, Milan Criteria, Tumor Number, and Tumor Size

Child-Pugh classification (A vs B-C), preoperative Milan criteria (within vs beyond), number of viable tumors (single vs multiple), and maximum tumor size (<5 cm vs ≥5 cm) were not associated with statistically significant differences in OS or RFS (**Figures 4, 5**).

Everolimus Administration

Additional administration of everolimus at 1 and 6 months after transplant was not associated with statistically significant differences in OS or RFS (**Figure 6**).

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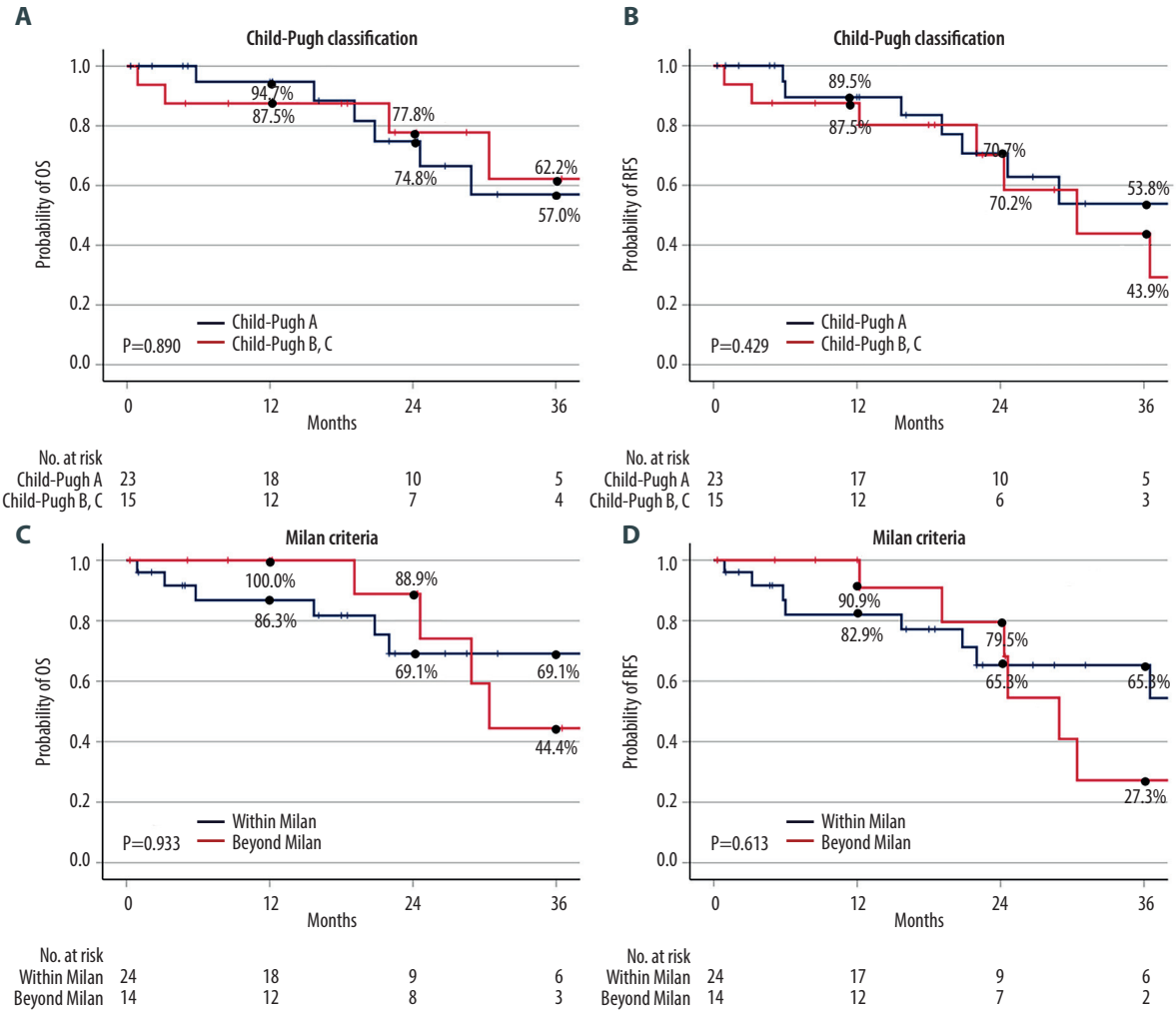

Figure 4. Kaplan-Meier survival curves. (**A**) Overall survival (OS) and (**B**) recurrence-free survival (RFS) according to Child-Pugh classification (A vs B-C). (**C**) OS and (**D**) RFS according to Milan criteria (within vs beyond).

Recurrence

Among 9 cases (22.5%) of tumor recurrence during posttransplant follow-up (median 21.4 months), there were 3 cases (7.5%) of intrahepatic metastasis, 5 cases (12.5%) of extrahepatic metastasis, and 1 case (2.5%) of concurrent intra- and extrahepatic metastases. Tumor recurrence sites were liver (n=3 [7.5%]), liver and pleura (n=1 [2.5%]), lung (n=1 [2.5%]), lung and adrenal gland (n=1 [2.5%]), bone (n=1 [2.5%]), and peritoneum (n=1 [2.5%]) (**Table 1**).

Patients with tumor recurrence (n=9 [22.5%]) appeared to have lower OS than those without tumor recurrence, but there was no statistically significant difference. The 1-, 2-, and 3-year OS rates were 88.9%, 50.8%, and 33.9%, respectively, in patients with recurrence, compared with 93.1%, 88.2%, and 71.9% in patients without recurrence (P=0.069; **Figure 7A**). In patients with tumor recurrence, additional administration of everolimus at 1 month, 6 months, and 1 year after transplant was not associated with improvement in OS (**Figure 7B-7D**).

Risk Factor Analysis

The univariate and multivariate Cox regression analyses of risk factors for OS and RFS in 40 LT recipients with cHCC-CC are summarized in **Tables 2 and 3**. Significant potential factors (P<0.10) in the univariate analysis were entered into the multivariate analysis model. Significant risk factors for OS (P<0.05) in multivariate analysis were as follows: MELD score of 20 or higher (P=0.04; HR=4.27 [95% CI=1.07-17.08]), perineural invasion (P=0.04; HR=5.14 [95% CI=1.07-24.69]), and portal vein tumor thrombosis (P=0.005; HR=13.43 [95% CI=2.17-83.21]) (**Table 2**). The only significant risk factor associated with RFS

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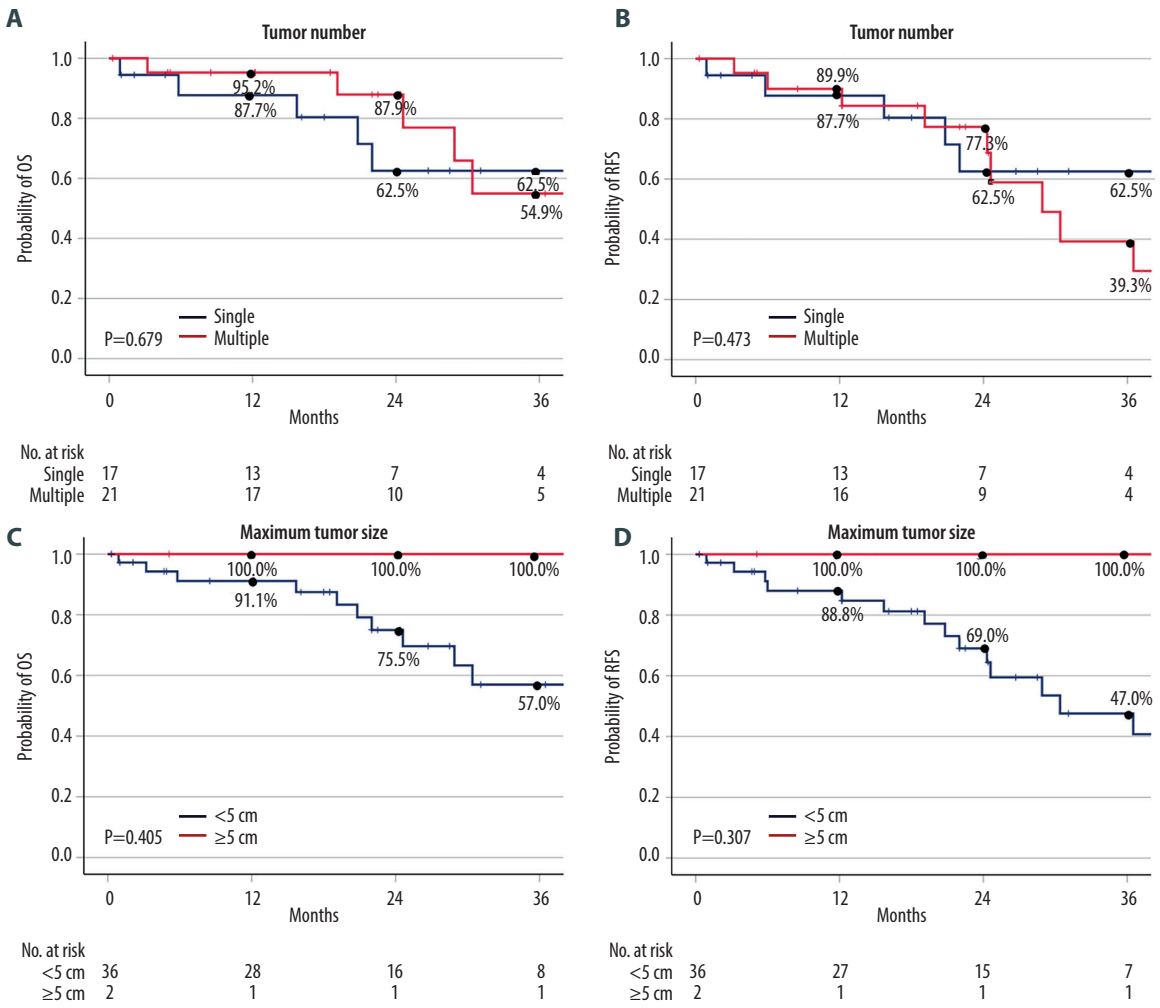

Figure 5. Kaplan-Meier survival curves according to tumor burden. (**A**) Overall survival (OS) and (**B**) recurrence-free survival (RFS) according to the number of viable tumors (single vs multiple). (**C**) OS and (**D**) RFS according to maximum tumor size (<5 cm vs ≥5 cm).

in multivariate analysis was microvascular invasion (*P*=0.01; HR=4.56 [95% CI=1.36-15.22]) (**Table 3**).

Discussion

In this multicenter study of 40 liver transplant recipients with pathologically confirmed cHCC-CC from the KOTRY database, we observed 3-year OS and RFS rates of 59.3% and 50.2%, respectively. Higher MELD scores (≥20), larger single tumors (≥3 cm), perineural invasion, and portal vein tumor thrombosis were associated with poorer OS, while only microvascular invasion was independently associated with worse RFS. Other clinical factors, including Child-Pugh class, Milan criteria status, tumor number, and everolimus use, showed no significant association with outcomes.

Previous studies investigating the clinical outcomes of cHCC-CC showed conflicting results using different classification criteria overtime [2-13]. Overall prognosis of cHCC-CC tends to be worse than that of HCC and similar to that of ICC [14], thus cHCC-CC has been regarded as a contraindication for LT. The present study revealed that the 1-, 2-, and 3-year OS rates were 91.8%, 76.2%, and 59.3%, respectively, and the 1-, 2-, and 3-year RFS rates were 88.8%, 70.5%, and 50.2%, which are comparable or superior to the previous reports [6,9-16].

The treatment options for advanced cHCC-CC that are not amenable to resection include preoperative downstaging treatments, including locoregional therapies, such as TACE, TACI, and RFA, and systemic chemotherapy. However, due to the lack of evidence, there are no consensus clinical guidelines; thus management plans are usually derived from HCC and

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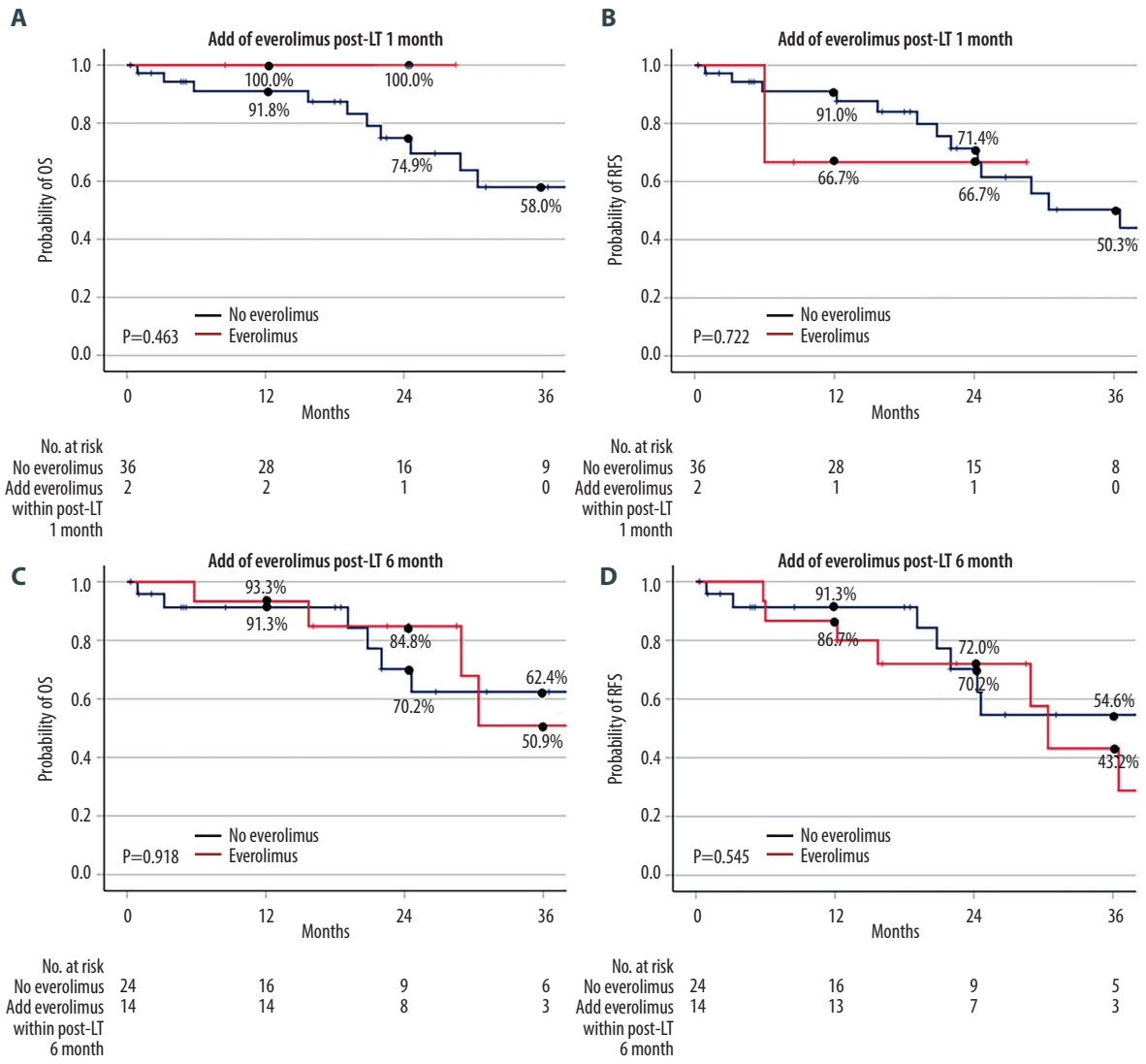

Figure 6. Kaplan-Meier survival curves according to postoperative administration of everolimus. (**A**) Overall survival (OS) and (**B**) recurrence-free survival (RFS) by everolimus use within 1 month after liver transplantation (LT). (**C**) OS and (**D**) RFS within 6 months.

ICC [14]. A few studies have shown the prognostic efficacy of successful downstaging in LT recipients with HCC beyond the Milan criteria [15,16]. In contrast, the present study revealed that pretransplant downstaging treatments for cHCC-CC did not induce improvement in OS.

Prognostic factors have clinical value for predicting prognosis and helping determine the therapeutic plan of individual patients. Previous studies regarding hepatectomy reported the various risk factors associated with long-term survival of cHCC-CC as tumor size more than 5 cm, multiple tumors, elevated serum carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen, decreased serum albumin, surgical margins less than 2 cm, satellite nodules, lymph node metastasis, vascular invasion, high tumor stage, and microvascular and macrovascular thrombus [11,17-20]. However, primarily due to the small number of patients in each study and rarity of cHCC-CC, many of these factors did not meet statistical significance in multivariate analysis [17]. In the present study, we found that a MELD score of 20 or higher, perineural invasion, and portal vein tumor thrombosis were risk factors for OS, while microvascular invasion was a risk factor for RFS in cHCC-CC patients who had undergone LT.

The preoperative or pretransplant diagnosis of cHCC-CC is difficult without histopathologic confirmation, and the imaging

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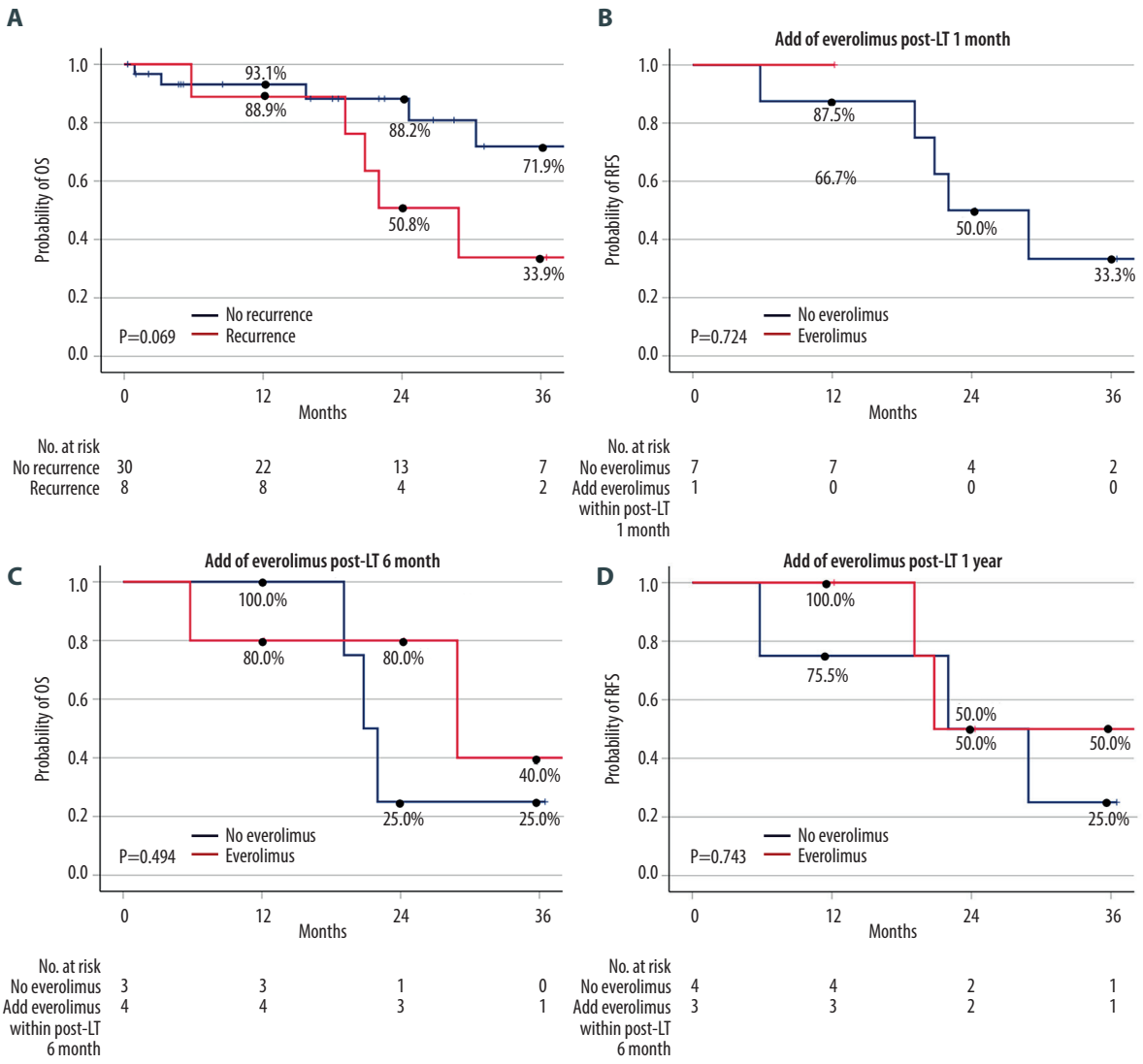

Figure 7. Kaplan-Meier curves for overall survival (OS) according to tumor recurrence. (**A**) OS according to recurrence status. OS of the 9 recipients with recurrence according to everolimus administration within (**B**) 1 month, (**C**) 6 months, and (**D**) 1 year after liver transplantation (LT).

criteria for diagnosis of cHCC-CC have not yet been standardized. HCC is a unique malignancy because its diagnosis is based on noninvasive imaging features; therefore, it is essential to clinically distinguish non–HCC hepatic malignancies from HCC. The radiographic features of cHCC-CC include the similarities of those seen in HCC and ICC, which can lead to preoperative misdiagnosis of cHCC-CC by relying on preoperative imaging. In imaging of cHCC-CC, the arterial hyper-enhancement with corresponding washout appearance can be observed, which is similar to HCC [21-23], or the peripheral gradual arterial hyper-enhancement can be seen, which is similar to ICC [23,24]. Therefore, it is recommended to use preoperative serum tumor markers, such as CA19-9 and α-fetoprotein, and imaging findings together for diagnosis of cHCC-CC [1]. In recent studies, patients with cHCC-CC having similar imaging patterns of HCC with arterial hyper-enhancement showed better long-term survival outcomes than did those having similar imaging features of ICC with non-hypervascular enhancement [25,26], whereas histopathologic classification, which is categorized as HCC-dominant and ICC-dominant according to a cutoff value of 50% of dominant cell composition, failed to show a significant difference in survival outcomes [26]. A recent consensus study from the International Liver Transplant Society recommended that biopsy be performed to refine the diagnosis and rule out pure HCC in cases of atypical imaging findings [27].

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Table 2. Univariate and multivariate analyses for risk factor of overall survival.

Variable	Comparison	Univariate			Multivariate		
		HR	95% CI	*P*	HR	95% CI	*P*
Age	<60 vs ≥60 years	0.81	0.17-3.85	0.79			
Sex	Male vs female	0.04	0.00-49.60	0.37			
Etiology of liver disease	non-HBV vs HBV	2.02	0.25-16.07	0.51			
Pre-LT ICU hospitalization	No vs yes	0.93	0.12-7.44	0.94			
MELD	≤20 vs ≥20	4.17	1.16-14.91	0.03	4.27	1.07-17.08	0.04
Child-Pugh classification	A vs B or C	0.92	0.26-3.24	0.89			
Pre-LT Milan criteria	Within vs beyond	0.83	0.23-2.94	0.77			
Pre-LT down staging	No vs yes	2.00	0.42-9.46	0.38			
Viable tumor number	Solitary vs multiple	0.77	0.22-2.67	0.68			
Maximum tumor diameter	≤5 vs >5 cm	0.05	0.00-319.21	0.59			
Sum of tumor diameter	≤8 vs >8 cm	0.99	0.13-7.89	0.99			
Serosa invasion	No vs yes	1.25	0.26-5.87	0.78			
Peliosis or hemorrhage in mass	No vs yes	0.92	0.24-3.57	0.90			
Fibrous capsule formation	No vs yes	0.35	0.04-2.79	0.32			
Septal formation	No vs yes	0.78	0.10-6.19	0.82			
Fatty change in tumor	No vs yes	0.04	0.00-162.33	0.56			
Capsule invasion	No vs yes	0.29	0.04-2.31	0.24			
Bile duct invasion	No vs yes	2.86	0.60-13.51	0.19			
Perineural invasion	No vs yes	4.36	1.08-17.55	0.04	5.14	1.07-24.69	0.04
Portal vein tumor thrombosis	No vs yes	6.77	1.34-34.13	0.02	13.43	2.17-83.21	0.005
Macrovascular invasion	No vs yes	5.33	1.02-28.00	0.048	Stepwise eliminated		
Microvascular invasion	No vs yes	6.97	1.43-33.86	0.02	Stepwise eliminated		
Lymph node metastasis	No vs yes	0.05	0.00-130.99	0.63			
Satellite nodule	No vs yes	0.32	0.04-2.55	0.28			
Tumor differentiation (E-S grade)	I-III vs IV	2.54	0.63-10.33	0.19			
Everolimus within 1 month after LT	No vs yes	0.05	0.00-1415.69	0.63			
Everolimus within 6 months after LT	No vs yes	0.94	0.26-3.32	0.92			
Everolimus within 1 year after LT	No vs yes	0.84	0.24-2.98	0.79			

HR – hazard ratio; CI – confidence interval; HBV – hepatitis B virus; LT – liver transplantation; ICU – intensive care unit; MELD – model for end-stage liver disease; E-S – Edmondson-Steiner.

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Table 3. Univariate and multivariate analyses for risk factor of recurrence-free survival.

Variable	Comparison	Univariate			Multivariate		
		HR	95% CI	*P*	HR	95% CI	*P*
Age	<60 vs ≥60 years	0.94	0.26-3.40	0.93			
Sex	Male vs female	0.35	0.05-2.70	0.31			
Etiology of liver disease	non-HBV vs HBV	1.18	0.26-5.30	0.83			
Pre-LT ICU hospitalization	No vs yes	0.57	0.07-4.47	0.59			
MELD	≤20 vs ≥20	1.93	0.53-6.99	0.32			
Child-Pugh classification	A vs B or C	1.52	0.53-4.34	0.43			
Pre-LT Milan criteria	Within vs beyond	1.78	0.62-5.15	0.29			
Pre-LT downstaging	No vs yes	3.23	0.72-14.56	0.13			
Viable tumor number	Solitary vs multiple	1.49	0.50-4.45	0.48			
Maximum tumor diameter	<5 vs ≥5 cm	0.04	0.00-424.12	0.51			
Sum of tumor diameter	<8 vs ≥8 cm	0.65	0.08-5.00	0.68			
Serosa invasion	No vs yes	1.26	0.35-4.54	0.72			
Peliosis or hemorrhage in mass	No vs yes	0.79	0.25-2.54	0.70			
Fibrous capsule formation	No vs yes	0.56	0.13-2.53	0.45			
Septal formation	No vs yes	1.33	0.30-5.96	0.71			
Fatty change in tumor	No vs yes	0.04	0.00-382.43	0.50			
Capsule invasion	No vs yes	1.35	0.40-4.52	0.63			
Bile duct invasion	No vs yes	3.00	0.83-10.82	0.09	3.48	0.94-12.83	0.06
Perineural invasion	No vs yes	2.76	0.74-10.28	0.13			
Portal vein tumor thrombosis	No vs yes	4.48	0.95-21.02	0.06	Stepwise eliminated		
Macrovascular invasion	No vs yes	3.36	0.69-16.40	0.13			
Microvascular invasion	No vs yes	4.29	1.32-13.93	0.02	4.56	1.36-15.22	0.01
Lymph node metastasis	No vs yes	0.04	0.00-107.27	0.55			
Satellite nodule	No vs yes	1.16	0.36-3.73	0.80			
Differentiation (E-S grade)	I-III vs IV	2.17	0.66-7.12	0.20			
Everolimus within 1 month after LT	No vs yes	1.45	0.18-11.45	0.72			
Everolimus within 6 months after LT	No vs yes	1.38	0.48-3.95	0.55			
Everolimus within 1 year after LT	No vs yes	1.20	0.42-3.44	0.73			

HR – hazard ratio; CI – confidence interval; HBV – hepatitis B virus; LT – liver transplantation; ICU – intensive care unit; MELD – model for end-stage liver disease; E-S – Edmondson-Steiner.

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Table 4. Literature review of liver transplantation for combined hepatocellular-cholangiocarcinoma.

Study	Country	Study period	N	Follow-up months (median)	Patient mortality	Tumor recurrence	OS			DFS		
							1-year	3-year	5-year	1-year	3-year	5-year
Chan 2007	Hong Kong	1994-2005	3	25		1 (33.3)	100			66.7		
Maganty 2010	USA	1994-2009	3	37.5	2 (66.7)	2 (66.7)	33.3	33.3	33.3	33.3	33.3	33.3
Panjala 2010	USA	1998-2008	12	11.1	7 (58.0)		79	66	16			
Harring 2011	USA	1998-2011	5	26.2	1 (20.0)	1 (20.0)	100	50	50	100	50	50
Park 2013	Korea	1999-2009	15		7 (46.6)	7 (46.6)	66.7	60	60	60	53.3	53.3
Groeschl 2013	USA	1973-2007	19				89	48				
	USA	1994-2007	65		33 (50.8)		75	45	28			
Song 2013	Korea	1995-2012	8	34.5	4 (50.0)	5 (62.5)	75.0	50.0	50.0	50.0	37.5	37.5
Garancini 2014	Italy	1988-2009	61				86.6	62.8	41.1			
Wu 2015	China	2000-2011	21			11 (52.4)	64	39	39	64	30	30
Itoh 2015	Japan	1999-2014	8		3 (37.5)	2 (20.0)	87.5	72.9	72.9	85.7	85.7	85.7
Wu 2016	China	2006-2014	8			4		75				
Vilchez 2016	USA	1994-2013	94				82	47	40			
Chang 2017	Taiwan	2006-2014	10	23.9		4 (40.0)	90.0	61.7	41.1	80.0	46.7	46.7
Jung 2017	Korea	2005-2014	32	48.6 (mean)	11 (34.4)	12 (37.5)	95	72.5	66			
Lunsford 2018	USA	1984-2015	12	27.9		6 (50.0)	75	54	42	66	42	42
Ito 2020	Japan	2005-2018	4	40	1 (25.0)	1 (25.0)	100	66.7	66.7	75.0	75.0	75.0
Dageforde 2020	USA	2009-2017	99			35 (35.3)	84	68	58.4			
Jaradat 2021	Germany	2001-2018	19	42.5	11 (57.9)	11 (64.7)	57.1	38.1				
Chen 2022	China	2004-2015	60				86.7	68.3	56.6			

N – patient number; OS – overall survival; DFS – diseas-free survival.

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Nineteen studies, including single- and multicenter studies, have reported outcomes of cHCC-CC following LT [3-6,9-16,28-37], and the characteristics and survival outcomes of these studies are summarized in **Table 4**. Several studies have presented post-LT outcomes in which cHCC-CC and ICC are mixed together, thereby providing limited information specific to cHCC-CC [7,27,38-40]. Since cHCC-CC is a rare tumor, the outcomes following LT have been shown in few studies, with mostly small sample sizes [41]. Of 15 single-center studies, only 1 study reported improved survival outcomes of cHCC-CC patients after LT, in highly selected cases [3], whereas most studies showed comparable [6,9-13,28-30] or inferior [32,34,37] survival outcomes in cHCC-CC patients undergoing LT, compared with LT recipients chosen with strict inclusion criteria for HCC. A large retrospective cohort study from the Surveillance, Epidemiology, and End Results (SEER) database showed LT for localized cHCC-CC provides survival benefit similar to that of liver resection for cHCC-CC but inferior to that of LT for HCC [33]. However, another large retrospective study from the United Network for Organ Sharing (UNOS) database reported that survival outcomes after LT of patients with HCC were better than those of patients with cHCC-CC [36]. A recent large-scale multicenter study from the United States showed the OS and RFS of cHCC-CC patients after LT were superior to those of patients after hepatectomy, regardless of tumor burden [4]. Another recent multicenter study found the OS of patients with cHCC-CC was clearly lower than that of patients with HCC after LT [5].

The present multicenter study based on the KOTRY has several limitations. First, the KOTRY database contains heterogeneous data and inherent flaws characteristic in multicenter registry databases. Although data from multiple centers participating in the KOTRY registry were prospectively collected, this study has a retrospective nature; thus, there are risks of data loss and institutional differences in collecting and recording data. Second, the patients included in this study were not classified histologically according to the 2019 WHO classification. Third, the sample size of 40 patients was relatively small to achieve statistical significance in the analysis. Further studies with larger sample sizes are necessary to enhance reliability. Fourth, the study patients were selected in Korea, where hepatitis B virus infection is endemic. Fifth, the lack of histopathology images in the KOTRY database precluded the inclusion of representative pathological photomicrographs. Finally, most of our study patients had been diagnosed with HCC before LT, and cHCC-CC was incidentally diagnosed on the pathology report of the explanted livers.

Conclusions

In conclusion, LT can be a feasible treatment option for patients with early-stage cHCC-CC, providing favorable long-term survival. As most prognostic factors identified were pathology-related, further studies are needed to refine the selection criteria for LT candidates in this population.

Acknowledgments

This study was previously reported in abstract form as: Kim S, Hwang S. Liver transplantation for combined hepatocellular-cholangiocarcinoma in the Korean Organ Transplantation Registry (KOTRY) study. Ann Hepatobiliary Pancreat Surg. 2023;27: S195-S195. https://doi.org/10.14701/ahbps.2023S1.LV-PP-5-2.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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