

Received: 2026.06.22

Accepted: 2026.09.22

Available online: 2026.10.19

Published: 2026.XX.XX

Prognostic Prediction in Living Donor Liver Transplantation Recipients With Complete Pathological Response of Hepatocellular Carcinoma: Single-Center Development and Korea-Nationwide Multi-Center Validation Studies

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 **Woo-Hyoung Kang** 
ABCDEF 1 **Shin Hwang** 
BCE 1 **Chul-Soo Ahn**
BCE 1 **Deok-Bog Moon**
BCE 1 **Gi-Won Song**
BCE 1 **Dong-Hwan Jung** 
and collaborators*

1 Department of Surgery, Asan Medical Center,
University of Ulsan College of Medicine, Seoul, South Korea

Corresponding Author:

* A full list of authors is available on the website

Shin Hwang, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine,
88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea

Phone: +82-2-3010-3930, Fax: +82-2-3010-6701, e-mail: shwang@amc.seoul.kr

Financial support:

This research was supported by the funds 2014-ER6301-00, 2014-ER6301-01, 2014-ER6301-02, 2017-ER6301-00, 2017-ER6301-01, 2017-ER6301-02, 2020-ER7201-00, 2020-ER7201-01, 2020-ER7201-02, 2023-ER0805-00, and 2023-ER0805-01 by the Research of Korea Centers for Disease Control and Prevention Agency

Conflict of interest:

None declared

Background:

Complete pathological response (CPR) after locoregional treatments (LRTs) predicts better outcomes in patients with hepatocellular carcinoma (HCC) after living donor liver transplantation (LDLT). This study aimed to find risk factors associated with HCC recurrence in patients with LRT-induced CPR of HCC.

Material/Methods:

Prognostic factors were identified from a development cohort of 313 patients from a high-volume single-center LDLT database and validated using a nationwide cohort of 418 patients from the Korean multi-center transplantation registry.

Results:

In the development study, 380 LRT sessions were performed on 313 patients, while the validation study included 482 sessions for 418 patients. Cumulative tumor recurrence and overall survival rates in the development study showed recurrence rates of 2.0%, 3.9%, 3.9%, and 4.5% and overall survival rates of 97.1%, 93.5%, 91.4%, and 89.2% at 1, 3, 5, and 10 years, respectively, respectively. In the validation study, tumor recurrence rates were 3.4%, 5.6%, and 7.7%, and overall survival rates were 98.6%, 96.0%, and 93.5% at 1, 3, and 5 years, respectively. Multiplicity of non-viable tumors was identified as a significant risk factor for tumor recurrence ($P = 0.001$; HR = 9.83) and overall survival ($P = 0.021$; HR = 2.91) in the development study, whereas the composite AFP-PIVKA-II score did not show significance. The validation study confirmed that the multiplicity of non-viable tumors was the only significant risk factor for tumor recurrence ($P = 0.026$; HR = 2.47) and overall survival ($P = 0.017$; HR = 2.82).

Conclusions:

This study demonstrates that LDLT recipients exhibiting LRT-induced CPR with multiple non-viable tumors constitute a high-risk subgroup and may require intensive posttransplant surveillance.

Keywords:

Carcinoma, Hepatocellular • Necrosis • Recurrence • Response Evaluation Criteria in Solid Tumors • Transplantation

Full-text PDF:

<https://www.annalsoftransplantation.com/abstract/index/idArt/954574>

 2918 1 8 28

Publisher's note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent and lethal cancers globally, particularly affecting individuals with chronic liver disease or cirrhosis [1]. Liver transplantation (LT) stands out as a crucial treatment modality, effectively addressing both HCC and coexisting liver cirrhosis, offering a potential cure for selected patients. In many Asian countries, HCC is the primary reason for living donor liver transplantation (LDLT).

Owing to challenges such as limited donor availability and stringent transplantation criteria, many patients undergo downstaging therapies while awaiting LDLT. These therapies encompass a range of locoregional treatments (LRTs), including transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA), and external beam radiotherapy [2-5]. However, the prognostic implications of tumor responses to these LRTs after transplantation remain unclear. This ambiguity arises from inconsistent assessment of treatment response and varying degrees of tumor necrosis achieved following LRTs [2,3,6,7].

Complete pathological response (CPR), characterized by the absence of viable tumor cells in the explanted liver, is frequently observed in LT recipients, particularly in the LDLT population. Indicators of CPR include complete radiological response and significant reductions in tumor markers such as α -feto-protein (AFP) and protein induced by vitamin K antagonist-II (PIVKA-II) [8]. CPR is a strong predictor of enhanced survival and lower recurrence rates after LT [9-11]. Furthermore, the AFP-PIVKA-II (AP) score, which integrates these 2 serum biomarkers, serves as a practical tool for forecasting outcomes following hepatic resection and LT [12,13].

This study aimed to assess the prognosis of LDLT recipients who attain CPR following pretransplant LRTs. Specifically, we intended to explore the risk factors associated with HCC recurrence in patients with CPR, utilizing data from a high-volume single-center cohort for model development, which was then validated in a multi-center cohort from the Korean Organ Transplantation Registry (KOTRY), a nationwide prospective registry of organ transplant recipients in South Korea.

Material and Methods

Study Design

This study consisted of 2 retrospective cohort studies. The first, a development study, utilized a comprehensive cohort from the high-volume single institution, whereas the second served as a validation study, drawing data from the Korean multicenter transplantation registry.

Patient Selection for Development Study

The institutional LT database at a Korean high-volume transplantation center was systematically reviewed to identify patients who underwent primary LDLT for HCC between January 2014 and December 2023. The exclusion criteria were applied to patients who had not received any preoperative LRT. This study focused on patients exhibiting CPR in explanted livers. The selection flow of the patients for the development study is depicted in **Figure 1A**. The inclusion criteria were LDLT, CPR of HCC, and pretransplant measurement of serum AFP and PIVKA-II levels ($n = 313$). Patients without either pretransplant AFP or PIVKA-II levels were regarded as incomplete data cases ($n = 39$) and thus excluded from this study. The medical records of the enrolled individuals were meticulously examined, with follow-up conducted through April 2026 or until death, utilizing institutional medical records and data from the National Health Insurance Service. The study protocol was approved by the Institutional Review Board of the Korean high-volume transplantation center (IRB No. 2025-1387), which waived the requirement for informed consent due to the retrospective design and the use of de-identified data with minimal risk to participants. All procedures adhered to the ethical standards outlined in the Declaration of Helsinki (2013 revision).

Patient Selection for Validation Study

The multi-center LT database was explored to identify adult patients aged 19 years and older who underwent primary LDLT following an HCC diagnosis during the study period from April 2014 to May 2023. This study included patients who demonstrated LRT-induced CPR in explanted livers. The selection flow of the patients for the validation is shown in **Figure 1B**. The inclusion criteria were LDLT, CPR of HCC, and pretransplant measurement of serum AFP and PIVKA-II levels ($n = 418$). Patients who did not provide information on pretransplant AFP or PIVKA-II levels were regarded as incomplete data cases ($n = 118$) and thus excluded from this study. Approval for this study protocol was granted by the Institutional Review Board of the Korean high-volume transplantation center (IRB No. 2026-0875). The requirement for additional informed consent was waived because the study used anonymized registry data and a retrospective design. Participants had provided consent for KOTRY enrollment at their respective centers.

Data Sources

In the development cohort, data were obtained from the institutional LT database of a single high-volume transplantation center and supplemented by review of medical records. Patient survival follow-up was supplemented with data from the National Health Insurance.

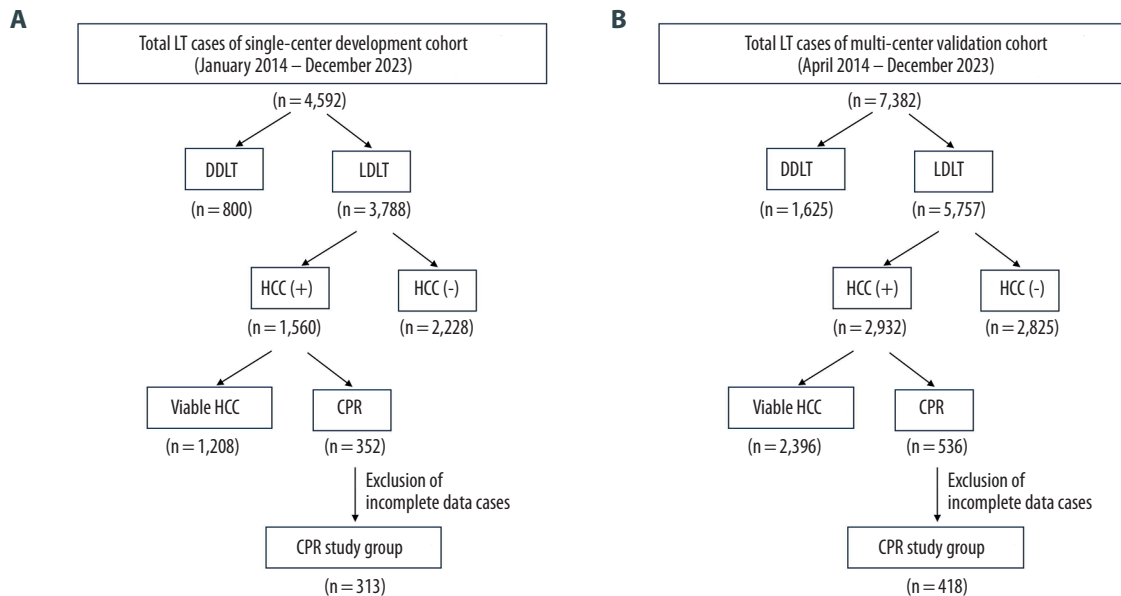


Figure 1. Flow of patient selection for the single-center development (A) and multi-center validation (B) studies. Abbreviations: DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation; HCC, hepatocellular carcinoma; CPR, complete pathological response.

In the validation cohort, data were obtained from KOTRY, a nationwide registry of organ transplant recipients that collects standardized clinical, laboratory, pathological, and follow-up data from participating transplant centers. An anonymized dataset was provided by the KOTRY after review and approval of a data-access request. Pathological diagnoses, including CPR, were taken from each center's pathology report. Registry data are entered by participating centers into iCReaT (Internet-based Clinical Research and Trial management system), which is operated by the Korea Disease Control and Prevention Agency. The development and validation cohorts were independent because patients from the development center were excluded from the validation cohort.

Pretransplant LRTs and Pathological Assessment

Pretransplant LRTs, including TACE, RFA, external beam radiotherapy, microwave ablation, transcatheter arterial radioembolization, and percutaneous ethanol injection, serve diverse roles, including curative intent, palliative tumor reduction, downstaging, and evaluation of transplant eligibility, often in combination. Most patients in this study underwent multiple LRT sessions before LT, following the national Korean guidelines [14].

CPR was defined as complete necrosis of the tumor tissue with no viable cancer cells detected in any sampled lesion. Consequently, the diagnosis of HCC was based solely on pretransplant imaging and tumor marker assessment due to the absence of viable tumor cells.

AFP-PIVKA-II Score Calculation

The AP score is a composite biomarker index calculated as the product of serum AFP concentration (ng/mL) and PIVKA-II concentration (mAU/mL). To standardize this composite measure for clarity, a logarithmic transformation using base-10 was used to yield the final AP score, expressed as $\log_{10}(\text{AFP} \times \text{PIVKA-II})$ [12,13].

Statistical Analysis

Descriptive statistics for continuous variables are presented as medians with ranges or means $\pm$ standard deviations, depending on the distribution of the data. Categorical or incidence data were evaluated using the chi-Square test, while numeric continuous data were tested with either the parametric *t* test or the non-parametric Mann-Whitney U test, chosen based on whether the data followed a normal distribution. Two time-to-event endpoints were analyzed in both cohorts. Tumor recurrence was defined as imaging- and/or biopsy-confirmed HCC recurrence at any site after LDLT, and overall survival as death from any cause. For both endpoints, time was measured from the date of LDLT. Patients without the event were censored at the date of last follow-up or at the end of the follow-up window (April 2026 in the development cohort and December 2025 in the validation cohort). For tumor recurrence, patients who died without HCC recurrence were censored at the date of death; therefore, cumulative recurrence rates are 1 minus the Kaplan-Meier estimate and do not treat death as

a competing event. Survival curves were compared with the log-rank test. All tests were 2-sided, with $P < 0.05$ considered significant. Three candidate prognostic factors, all measured in the explanted liver or pretransplant samples, were entered into a separate univariate Cox proportional hazards model: (1) number of non-viable tumors, coded as multiple (≥ 2) vs single (reference); (2) maximum diameter of non-viable tumors, coded as greater than 2 cm vs 2 cm or less (reference); and (3) AP score, calculated as $\log_{10}(\text{AFP} \times \text{PIVKA-II})$ from the last pretransplant measurements before LDLT and categorized in 1.0-log intervals (reference = lowest category and analyzed as continuous per 1.0-log increase). Univariate Cox proportional hazards analysis was used for calculation of hazard ratios (HRs) with 95% confidence intervals (CIs). No multivariable model was fitted, and all HRs are unadjusted. Patients with missing pretransplant AFP or PIVKA-II were excluded, to perform complete-case analysis. The proportional-hazards assumption was not formally tested; given the small number of events, HRs should be interpreted as average effects over follow-up. All statistical analyses were performed using SPSS version 22.0 (IBM Corp, Armonk, NY, USA) and MedCalc version 23.4.5 (MedCalc Software Ltd, Ostend, Belgium).

Results

Patient Demographics of the Development Study

From the single-center LDLT database, 313 patients were selected for inclusion in the study. A total of 380 LRT sessions were performed on these 313 patients. The median pretransplant serum levels of AFP and PIVKA-II were 3.5 ng/mL (range, 1.0–282.1 ng/mL) and 24 mAU/mL (range, 8–19 623 mAU/mL), respectively. Analysis of the explanted livers revealed single non-viable tumors in 242 patients (77.3%) and 2 or more (multiple) non-viable tumors in 71 patients (22.7%). The median size of the largest non-viable tumor was 1.8 cm, with a range of 0.3 to 6.8 cm. Further details regarding the patient characteristics are summarized in **Table 1**.

Tumor Recurrence and Overall Patient Survival Outcomes After LDLT in the Development Study

Patients were monitored for a median duration of 65 months (range, 2–149 months) after LT. Of the 313 patients, only 13 (4.2%) experienced HCC recurrence during the follow-up period. In total, 28 patients (8.9%) died from various causes, with 8 deaths directly linked to HCC recurrence. The cumulative tumor recurrence rates at 1, 3, 5, and 10 years after transplantation were 2.0%, 3.9%, 3.9%, and 4.5%, respectively (**Figure 2A**). The overall survival rates were 97.1%, 93.5%, 91.4%, and 89.2% at the same intervals (**Figure 2B**).

Prognostic Factor Analysis in the Development Study

Univariate analysis identified that the presence of multiple non-viable tumors was a significant risk factor for HCC recurrence ($P = 0.001$; **Figure 3A**), but a maximum diameter of non-viable tumors exceeding 2 cm was not ($P = 0.152$; **Figure 4A**). No significant difference in tumor recurrence was noted based on AP scores with 1.0 log intervals ($P = 0.383$; **Figure 5A**). Regarding overall patient survival, the presence of multiple non-viable tumors emerged as a significant risk factor ($P = 0.021$; **Figure 3B**), whereas the maximum size of non-viable tumors exceeding 2 cm did not yield significant associations with survival outcomes ($P = 0.244$; **Figure 4B**). There was no notable difference in overall patient survival related to AP scores ($P = 0.402$; **Figure 5B**). These findings indicate that multiplicity of non-viable tumors was a significant risk factor for both tumor recurrence (HR = 9.83 [95% CI: 2.65–36.4]) and overall survival (HR = 2.91 [95% CI: 1.18–7.19]), while the maximum size of non-viable tumors and AP scores were not significant.

Patient Demographics of the Validation Study

From the multi-center database, 418 patients with HCC were selected for this validation study. A total of 482 LRT sessions were performed on these 418 patients. The median pretransplant serum concentrations of AFP and PIVKA-II were 3.7 ng/mL (range, 0.6–441 ng/mL) and 22 mAU/mL (range, 4–18,841 mAU/mL), respectively. Examination of the explanted livers indicated that 293 patients (70.1%) had single non-viable tumors, whereas 125 patients (29.9%) exhibited multiple non-viable tumors. Further patient characteristics are presented in **Table 1**. Notably, patient demographics were largely comparable between the development and validation cohorts, with differences observed only in AFP expression levels and the prevalence of multiple non-viable tumors.

Tumor Recurrence and Overall Patient Survival Outcomes After LDLT in the Validation Study

Participants were followed up for a median of 59.5 months (range, 4–121 months) after LDLT. Of the 418 patients, 29 (6.9%) experienced HCC recurrence during follow-up. In total, 26 patients (6.2%) died from various causes, with 15 deaths attributed to HCC recurrence. At 1, 3, and 5 years following LDLT, cumulative tumor recurrence rates were 3.4%, 5.6%, and 7.7%, respectively (**Figure 6A**), whereas overall survival rates were 98.6%, 96.0%, and 93.5%, respectively (**Figure 6B**).

Prognostic Factor Analysis in the Validation Study

Univariate analysis of the validation cohort identified multiple non-viable tumors as a significant predictor of tumor recurrence ($P = 0.026$; **Figure 7A**). No significant differences in

Table 1. Clinicopathological features of living donor liver transplant recipients with hepatocellular carcinoma who achieved complete pathological responses in response to pretransplant locoregional treatments.

Cohort	Development cohort	Validation cohort	P value
Parameters	Values	Values	
Case No.	313	418	
Age (yrs) (Mean ± SD)	55.8 ± 7.1	56.9 ± 7.6	0.056*
Sex (Male/Female) (n)	258 / 55	330 / 88	0.240
Background liver disease (n)			0.623
HBV	253	323	
HCV	13	25	
ALD	28	43	
Others	19	27	
Preoperative blood laboratory profiles (Mean±SD)			
Albumin (g/dL)	3.6 ± 0.8	3.5 ± 0.6	0.334*
AST (IU/L)	55.3 ± 28.4	NA	NA
ALT (IU/L)	31.2 ± 27.3	NA	NA
Total bilirubin (mg/dL)	4.9 ± 8.2	1.6 ± 3.6	0.167*
Platelet count (10 ³ /μL)	82.4 ± 52.4	NA	NA
Prothrombin time (INR)	1.56 ± 0.98	1.23 ± 0.29	0.153*
AFP (ng/mL) shortly before transplantation			0.013**
Mean ± SD	43.8 ± 256.6	12.2 ± 40.2	
Median (range)	4.5 (0.2-3,630)	3.7 (0.6-441)	
≤ 7.5 / > 7.5 ng/mL (n)	232 / 116	323 / 95	
PIVKA-II (mAU/mL) shortly before transplantation			0.153**
Mean ± SD	199.3 ± 1499.3	160.1 ± 1270.4	
Median (range)	25 (8-19,623)	22 (4-18,841)	
≤ 40 / > 40 mAU/m (n)	269 / 79	328 / 90	
MELD score (Mean ± SD)	11.3 ± 5.9	10.6 ± 4.6	0.056*
Pretransplant locoregional treatments			0.865
TACE	280	343	
RFA	68	96	
EBRT	24	33	
Others	8	10	
Maximum non-viable tumor size (cm)			NA
Mean ± SD	2.1 ± 1.1	NA	
Median (range)	1.8 (0.3-6.8)	NA	

Table 1 continued. Clinicopathological features of living donor liver transplant recipients with hepatocellular carcinoma who achieved complete pathological responses in response to pretransplant locoregional treatments.

Cohort	Development cohort	Validation cohort	P value
Parameters	Values	Values	
Case No.	313	418	
Non-viable tumor number (n)			0.029
Single	242	293	
Multiple (≥ 2)	71	125	
ABO incompatible LDLT (n)	51	57	0.316
Type of transplantation (n)			0.056
Living right liver graft	304	406	
Living left liver graft	2	9	
Living dual liver graft	7	3	
GRWR	1.08 ± 0.27	1.04 ± 0.33	0.091

Abbreviations: SD, standard deviation; NA, not available; HBV, hepatitis B virus; HCV, hepatitis C virus; ALD, alcoholic liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalization ratio; AFP, α -fetoprotein; PIVKA-II, proteins induced by vitamin K antagonist or absence-II; MELD, model for end-stage liver disease; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; EBRT, external beam radiotherapy; GRWR, graft-to-recipient weight ratio. Data are presented as mean $\pm$ SD or median (range). Categorical or incidence data are compared using the chi-square test. Numeric continuous data are tested with the *t* test (*) or the Mann-Whitney U test (**), depending on data distribution. Other pretransplant locoregional treatments included transcatheter arterial radioembolization and percutaneous ethanol injection. Microwave ablation was included in RFA.

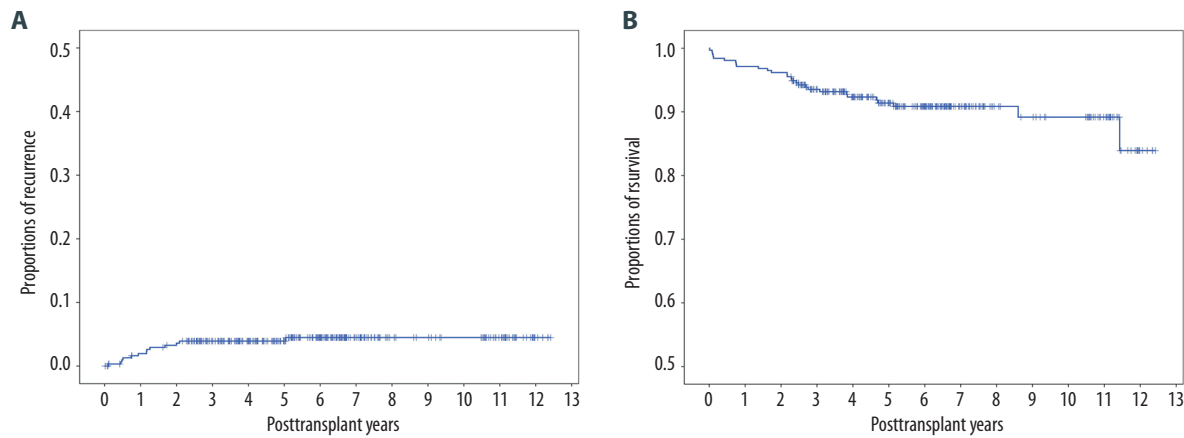


Figure 2. Kaplan-Meier survival analysis depicting posttransplant tumor recurrence (A) and overall survival (B) among living donor liver transplant recipients who exhibited complete pathological response of hepatocellular carcinoma following various locoregional treatments. Data are from the single-center development cohort.

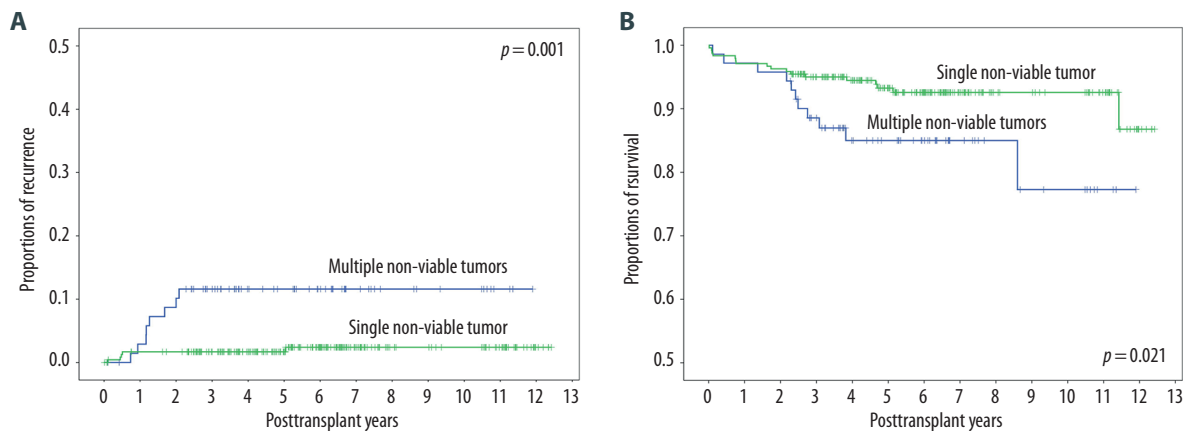


Figure 3. Kaplan-Meier survival analysis illustrating posttransplant tumor recurrence (A) and overall survival (B) in living donor liver transplant recipients with complete pathological response of hepatocellular carcinoma stratified by the number of non-viable tumors. Data are drawn from the single-center development cohort.

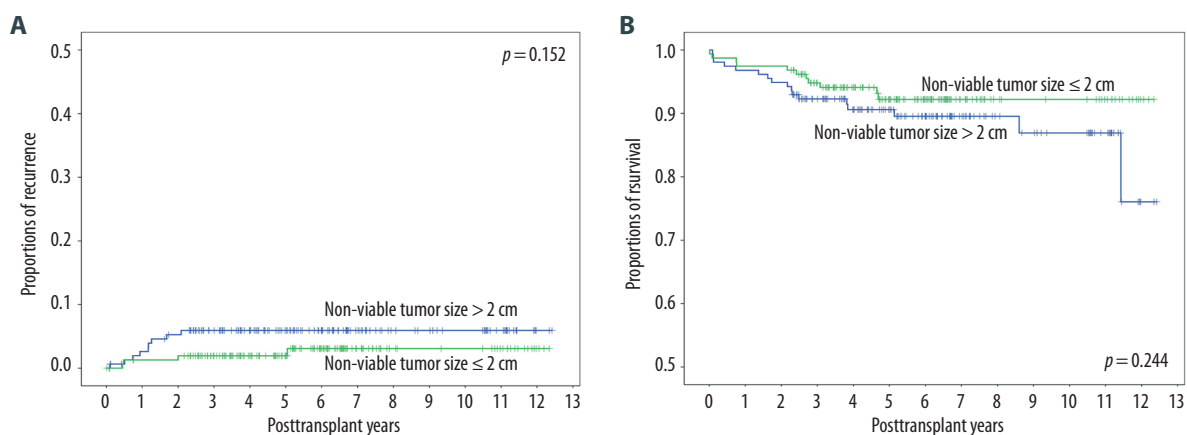


Figure 4. Kaplan-Meier survival analysis of posttransplant tumor recurrence (A) and overall survival (B) in living donor liver transplant recipients with complete pathological response of hepatocellular carcinoma based on the maximum size of non-viable tumors. Data are sourced from the single-center development cohort.

tumor recurrence were found regarding AP scores with 1.0 log intervals ($P = 0.551$; **Figure 8A**). In terms of overall survival, the presence of multiple non-viable tumors was again a significant risk factor ($P = 0.017$; **Figure 7B**), whereas AP scores were not significant ($P = 0.357$; **Figure 8B**). The validation study confirmed that the multiplicity of non-viable tumors was a significant risk factor for both tumor recurrence (HR = 2.47 [95% CI: 1.11-5.49]) and overall survival (HR = 2.82 [95% CI: 1.20-6.58]), but AP scores were not significant in this analysis.

Discussion

CPR resulting from various LRTs is a well-established prognostic indicator in patients with HCC [2,4,5,8]. In the present study,

those who achieved LRT-induced CPR exhibited significantly reduced recurrence rates and impressive long-term survival, outcomes comparable to those of LT recipients who met the rigorous super-selection criteria [11,15]. The real-world prognostic effect of CPR was identified in a high-volume single-center cohort and confirmed through an external validating analysis using the multi-center database, a nationwide resource for organ transplantation in South Korea.

The incidence of CPR following LRTs varies widely among patients. Owing to the heterogeneous responses to TACE, many patients with HCC undergo multiple treatment sessions to optimize outcomes and address new lesions. Prior research indicated that 31.6% of patients attained CPR after an average of 2.2 TACE procedures [11]. Another study involving 67 LT

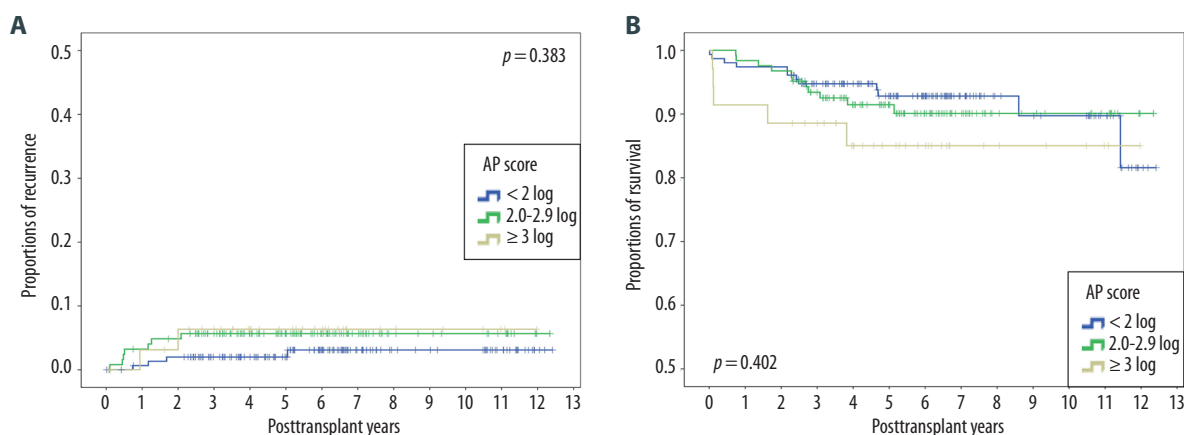


Figure 5. Kaplan-Meier survival analysis assessing posttransplant tumor recurrence (A) and overall survival (B) in living donor liver transplant recipients with complete pathological response of hepatocellular carcinoma according to the AP score. The AP score is defined as $\log_{10}(\text{AFP} \times \text{PIVKA-II})$, where AFP = α -fetoprotein (ng/mL) and PIVKA-II = protein induced by vitamin K antagonist-II (mAU/mL). Data are from the single-center development cohort. *P* values were calculated using the log-rank test.

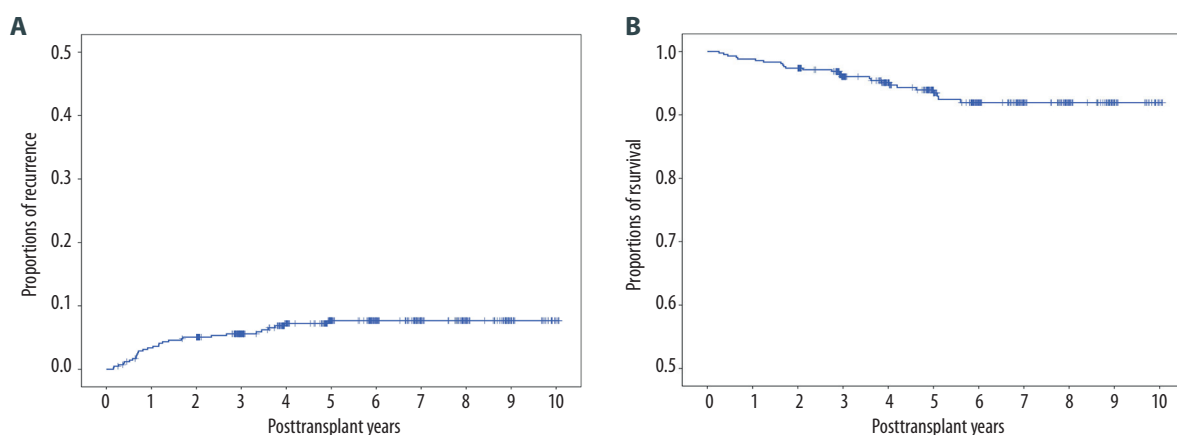


Figure 6. Kaplan-Meier survival analysis of posttransplant tumor recurrence (A) and overall survival (B) in living donor liver transplant recipients with complete pathological response of hepatocellular carcinoma following various locoregional treatments in the multi-center validation cohort. Data are sourced from the multicenter validation cohort.

recipients with HCC tumors under 5 cm revealed that 44 patients (65.7%) achieved complete radiological responses, with CPR confirmed in 53 of 95 nodules (55.8%) displaying complete radiological resolution [16]. Although LRTs, such as TACE and RFA, can produce complete radiological responses, many patients still require LT due to advanced liver cirrhosis. Achieving a complete radiological response and normalizing tumor markers after LRT may defer LT for selected patients with small tumors and well-preserved liver function [17,18].

Addressing tumor recurrence after LDLT remains a pivotal challenge, as effective therapies for recurrence are still lacking. LRTs serve various roles, including curative intent, tumor

downstaging, and assessment of tumor biology to determine the candidacy for LDLT. Several studies suggest that pretransplant LRT, which is primarily conducted for downstaging rather than as a definitive therapy, often has only modest prognostic significance [19-22]. Nonetheless, CPR is considered as a reliable surrogate for substantial tumor cell eradication, potentially lowering the risk of HCC recurrence after LT [9,10].

Our prior findings indicated that tumor recurrence rates were particularly low among LT recipients who fulfilled the super-selection criteria, which aligns with rates seen in patients achieving CPR [15,23,24].

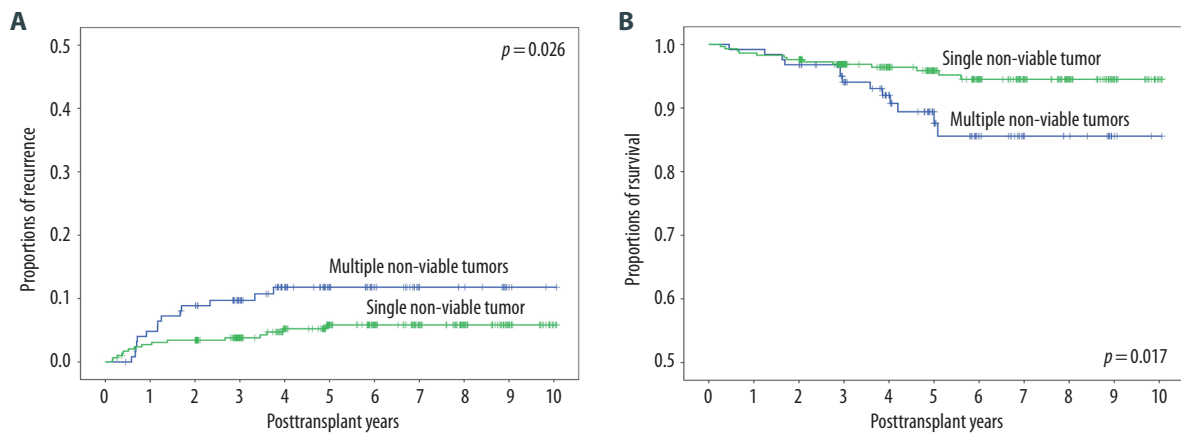


Figure 7. Kaplan-Meier survival analysis depicting posttransplant tumor recurrence (A) and overall survival (B) in living donor liver transplant recipients with complete pathological response of hepatocellular carcinoma categorized by the number of non-viable tumors in the multi-center validation cohort. Data are gathered from the multicenter validation cohort.

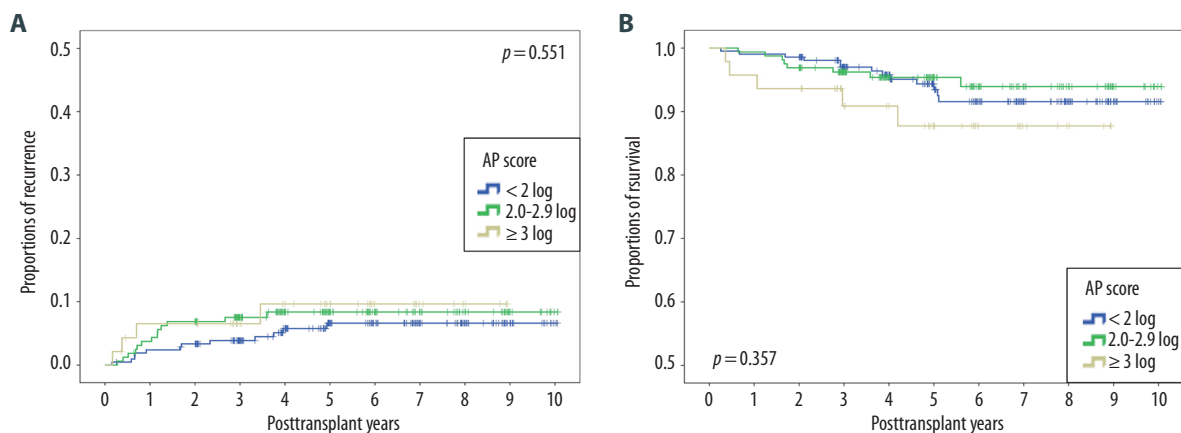


Figure 8. Kaplan-Meier survival analysis assessing posttransplant tumor recurrence (A) and overall survival (B) in living donor liver transplant recipients with complete pathological response of hepatocellular carcinoma based on the AP score. The AP score is defined as $\log_{10}(\text{AFP} \times \text{PIVKA-II})$, where AFP = α -fetoprotein (ng/mL) and PIVKA-II = protein induced by vitamin K antagonist-II (mAU/mL). Data originate from the multicenter validation cohort. *P* values were calculated using the log-rank test.

CPR signifies the thorough elimination of viable HCC cells after LT, suggesting that patients with CPR may have an oncologic burden comparable to that of patients with very early-stage HCC. Our previous single-center investigation identified the presence of multiple non-viable lesions and the maximum diameter of non-viable tumors exceeding 2 cm as independent predictors of post-transplant recurrence and overall survival. The study indicated that patients achieving CPR can be stratified into high-risk (with multiple non-viable tumors > 2 cm) and low-risk categories [25].

Conversely, the present study indicated that only the multiplicity of non-viable HCC tumors correlated with elevated recurrence and decreased survival rates. This association was

validated in the present analysis. The number of non-viable lesions is consistently detailed in pathology reports from explanted livers, allowing transplant surgeons to accurately assess the prognostic effect of non-viable tumors. Therefore, we propose that the quantity of non-viable HCC lesions be considered the primary prognostic factor, and the levels of AFP and PIVKA-II do not need to be considered for this purpose.

Previous evaluations of pretransplant HCC tumor marker levels demonstrated that among 166 LT recipients achieving CPR, the median serum AFP and PIVKA-II levels were 4.2 ng/mL and 20 mAU/mL, respectively, which was comparable to the levels in control groups without HCC [26]. However, receiver operating characteristic curve analyses failed to yield definitive

cutoff values differentiating HCC patients who achieved CPR from those without HCC. These findings suggest that normalization of AFP and PIVKA-II levels may indicate CPR, although elevated levels persisted in some patients who achieved CPR. The variability in AFP and PIVKA-II expression among patients undergoing LT complicates prognostic assessments, particularly in those with advanced liver cirrhosis [27,28].

In patients with CPR, levels of AFP and PIVKA-II likely decrease to values similar to those without HCC, diminishing their prognostic relevance after LT. Previous receiver operating characteristic curve analyses have reinforced that no firm cutoff values can reliably distinguish between patients with CPR and those without HCC [26]. While the AP score has been recognized as a promising predictive tool following hepatic resection and LT, our findings indicate that it did not correlate with prognosis among LDLT recipients who achieved CPR [12,13].

This study had several limitations. The retrospective nature of this study, conducted in a region where hepatitis B virus infection is prevalent, may restrict the generalizability of the results. The diagnostic significance of CPR warrants further

validation in diverse geographic and etiology-based contexts as well as in deceased donor liver transplantation. The retrospective cohort design had limitations to establish a causal effect of tumor multiplicity or other evaluated factors on recurrence or survival outcomes. Moreover, our study exclusively focused on patients who achieved CPR without contrasting them with those who did not.

Conclusions

This study demonstrates that LDLT recipients exhibiting LRT-induced CPR with multiple non-viable tumors constitute a high-risk subgroup and may require intensive posttransplant surveillance, although CPR is a predictor of favorable posttransplant prognosis.

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.

References:

- Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet*. 2018;391:1301-14
- Chang Y, Jeong SW, Young Jang J, Jae Kim Y. Recent updates of transarterial chemoembolization in hepatocellular carcinoma. *Int J Mol Sci*. 2020;21:8165
- Wallace D, Cowling TE, Walker K, et al. Liver transplantation outcomes after transarterial chemotherapy for hepatocellular carcinoma. *Br J Surg*. 2020;107:1183-91
- Patel KR, Menon H, Patel RR, et al. Locoregional therapies for hepatocellular carcinoma: A systematic review and meta-analysis. *JAMA Netw Open*. 2024;7:e2447995
- Yoon SM. External beam radiotherapy for hepatocellular carcinoma: A review of the current guidelines in the East and the West. *J Liver Cancer*. 2021;21:25-33
- Zhou WP, Lai EC, Li AJ, et al. A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma. *Ann Surg*. 2009;249:195-202
- Kaibori M, Tanigawa N, Kariya S, et al. A prospective randomized controlled trial of preoperative whole-liver chemolipiodolization for hepatocellular carcinoma. *Dig Dis Sci*. 2012;57:1404-12
- Amorim J, França M, Perez-Girbes A, et al. Critical review of HCC imaging in the multidisciplinary setting: Treatment allocation and evaluation of response. *Abdom Radiol (NY)*. 2020;45:3119-28
- Park HW, Hwang S, Ahn CS, et al. Long-term survival outcomes for living donor liver transplant recipients with pathologically nonviable hepatocellular carcinoma. *Transplant Proc*. 2013;45:3032-34
- Allard MA, Sebah M, Ruiz A, et al. Does pathological response after transarterial chemoembolization for hepatocellular carcinoma in cirrhotic patients with cirrhosis predict outcome after liver resection or transplantation? *J Hepatol*. 2015;63:83-92
- Kang WH, Hwang S, Song GW, et al. Prognostic effect of transarterial chemoembolization-induced complete pathological response in patients undergoing liver resection and transplantation for hepatocellular carcinoma. *Liver Transpl*. 2017;23:781-90
- Choi M, Hwang S, Kaibori M, Jo M; Collaboration of Korean Association of Hepato-Biliary-Pancreatic Surgery; Japanese Society of Hepato-Biliary-Pancreatic Surgery. Prediction of microvascular invasion and post-resection prognosis using ADV, AFP-PIVKA-II, and MoRAL scores in hepatocellular carcinoma patients: An international multicenter cohort study with 9,061 patients. *Ann Surg Treat Res*. 2026;110(5):317-30
- Won DH, Hwang S, Ahn CS, et al. AFP-PIVKA-II (AP) score as a simplified quantifiable surrogate biomarker for hepatocellular carcinoma recurrence following living donor liver transplantation. *Ann Liver Transplant*. 2026;6:25-32
- Cho Y, Choi JW, Kwon H, et al; Research Committee of the Korean Liver Cancer Association. Transarterial chemoembolization for hepatocellular carcinoma: 2023 expert consensus-based practical recommendations of the Korean Liver Cancer Association. *Korean J Radiol*. 2023;24:606-25
- Hwang S, Ahn CS, Kim KH, et al. Super-selection of a subgroup of hepatocellular carcinoma patients at minimal risk of recurrence for liver transplantation. *J Gastrointest Surg*. 2011;15:971-81
- Golfieri R, Cappelli A, Cucchetti A, et al. Efficacy of selective transarterial chemoembolization in inducing tumor necrosis in small (< 5 cm) hepatocellular carcinomas. *Hepatology*. 2011;53:1580-89
- Kim BK, Kim SU, Kim KA, et al. Complete response at first chemoembolization is still the most robust predictor for favorable outcome in hepatocellular carcinoma. *J Hepatol*. 2015;62:1304-10
- Henry JC, Malhotra L, Khabiri H, et al. Best radiological response to transarterial chemoembolization for hepatocellular carcinoma does not imply better outcomes. *HPB (Oxford)*. 2013;15:196-202
- Ravaioli M, Grazi GL, Ercolani G, et al. Partial necrosis on hepatocellular carcinoma nodules facilitates tumor recurrence after liver transplantation. *Transplantation*. 2004;78:1780-86
- Chapman WC, Majella Doyle MB, Stuart JE, et al. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. *Ann Surg*. 2008;248:617-25
- Otto G, Schuchmann M, Hoppe-Lotichius M, et al. How to decide about liver transplantation in patients with hepatocellular carcinoma: Size and number of lesions or response to TACE? *J Hepatol*. 2013;59:279-84
- Kim HD, Shim JH, Kim GA, et al. Optimal methods for measuring eligibility for liver transplant in hepatocellular carcinoma patients undergoing transarterial chemoembolization. *J Hepatol*. 2015;62:1076-84
- Lee SG, Hwang S, Moon DB, et al. Expanded indication criteria of living donor liver transplantation for hepatocellular carcinoma at one large-volume center. *Liver Transpl*. 2008;14:935-45
- Hwang S, Moon DB, Ahn CS, et al. Risk-based long-term screening for hepatocellular carcinoma recurrence after living donor liver transplantation. *Transplant Proc*. 2013;45:3076-84

25. Jeong JJ, Hwang S, Ahn CS, et al. Long-term prognostic significance of TACE-induced complete pathological response in patients with hepatocellular carcinoma who have undergone liver transplantation. *Ann Transplant.* 2025;30:e950787
26. Kim MJ, Kang WH, Hwang S, et al. Expression patterns of tumor markers in liver transplant recipients showing complete pathological response of hepatocellular carcinoma. *J Clin Med.* 2022;11:5897
27. Kim Y, Park YH, Hwang S, et al. Diagnostic role of blood tumor markers in predicting hepatocellular carcinoma in liver cirrhosis patients undergoing liver transplantation. *Ann Transplant.* 2016;21:660-67
28. Kang WH, Hwang S, Kim JM, et al. Diagnostic role of tumor markers for hepatocellular carcinoma in liver transplantation candidates: An analysis using the Korean organ transplantation registry database. *Ann Transplant.* 2022;27:e936937