의학석사 학위논문

간이식을 시행한 간세포암 환자에서 LI-RADS 기반 영상의학적 평가와 병리학적 평가에 따른 Milan 기준의 일치도 및 예후적 연관성에 관한 연구

Performance of the LI-RADS-based Milan criteria and its prognostic implication in potential transplant candidates with hepatocellular carcinoma

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지 도 교 수 심 주 현

이 논문을 의학석사 학위 논문으로 제출함

2024 년 2 월

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Abstract

Background/Aims: Given the limited availability and feasibility for pathologic confirmation of every hepatic lesion, imaging diagnosis is primarily used to assess Milan criteria in candidates for liver transplantation (LT) with hepatocellular carcinoma (HCC). There is little data on the correlation between explant pathology and radiologic measurement based on LI-RADS in determining LT eligibility in HCC patients. This study aimed to investigate the radio-pathologic correlation of Milan criteria using LI-RADS-based diagnosis, and also to identify factors affecting discordance and its prognostic impact.

Methods: This retrospective study included 267 patients who had any hepatic lesion identified on dynamic liver CT within 3 months prior to LT and/or in the explant livers at Asan Medical Center. Two radiologists reviewed CT examinations, evaluating nodules and the Milan criteria based on LI-RADS v2018. Analyses were performed on a per-lesion and per-patient basis, comparing radiologic lesions with their matched pathology. LR-5 or LR-TR-V nodules were regarded as HCC to determine LI-RADS Milan criteria (MC). Overall survival (OS) and recurrence-free survival (RFS) were measured according to LI-RADS MC and pathologic MC, applying a competing risk analysis to 259 patients, excluding cases of in-hospital mortality.

Results: In per-lesion analysis, among 79 LR-5 lesions and 48 LR-3/LR-4 lesions, 72 lesions (91.1%) and 37 (77.1%) were identified as HCCs, respectively. The 189 LR-TR-V lesions were matched with 176 HCCs (93.1%) in pathology. According to per-patient analysis, an overall concordance rate of 87.3% was presented between LI-RADS MC and pathologic MC. These concordances were not affected by pre-LT chemoembolization and type of LT. The 5-year OS and RFS were significantly greater for patients meeting the MC, compared to the counterparts: 96% vs. 86% and 90% vs. 62% for pathologic MC; and 96% vs. 76% and 90% vs. 45% for LI-RADS MC, respectively (Ps<0.003). When cases meeting LI-RADS MC and pathologic MC were compared, there were no significant differences in OS and RFS. Multivariate Cox-proportional hazard models indicated that being outside LI-RADS MC independently predicted OS and RFS (hazard ratios, 6.51 and 6.34; 95% confidence intervals: 2.37-17.86 and 3.38-11.88, respectively). The presence of nodules other than LR-5/LR-TR-V did not affect survivals.

Conclusions: The LI-RADS-based radiology presented high concordance and comparable prognostic performance with explant pathology in determining the MC. LT eligibility could likely be judged by CT LI-RADS in patients with HCC.

Keywords: LI-RADS v2018, LI-RADS treatment response algorithm, liver transplantation, hepatocellular carcinoma

목 차

표 및 그림 목차

INTRODUCTION

Liver transplantation (LT) provides curable results to hepatocellular carcinoma (HCC) patients with limited tumor burden, which prefers to hepatectomy especially in cirrhotic with significant portal hypertension, though availability is limited by an extreme shortage of liver allografts.(1) Among selection approaches for patients with HCC, the Milan criteria (MC) are the most widely validated and globally applied in clinical practice.

The MC is originally based on pathological examination of explanted livers, not pre-LT radiologic measurement.(2) Pathological features in the explanted liver including not just tumor size and number of nodules but also satellite lesions and microvascular invasion must be the most accurate prognosticator in liver recipients.(3) However, given the limited availability and feasibility for liver biopsy before LT, imaging diagnosis as a realistic alternative is mainly used to assess MC in LT candidates with HCC. Despite incremental technological advances in cross-sectional imaging techniques with CT and MRI, it is important to note that classical imaging methods (i.e., arterial phase hyperenhancement with washout in the portal venous or delayed phases) can under- or over-estimate the extent of HCC in up to 25% of cases, compared with pathological findings of explant liver.(4-8)

In the context of heterogeneity and uncertainty in imaging criteria for HCC diagnosis, LI-RADS was developed to standardize the imaging evaluation of HCC. The system has undergone several updates, and the most recent version was introduced in 2018 (LI-RADS v2018). Since the introduction of LI-RADS, numerous studies have investigated its performance for HCC diagnosis, consistently reporting excellent specificity of LR-5 (i.e., definitely HCC) for HCC. LI-RADS has been integrated into the most recent guideline by the American Association for the Study of Liver Diseases (AASLD), thereby facilitating its clinical use.(9) LI-RADS categories, specifically LR-5 and LR-M, have also shown tremendous potential in HCC prognostication in predicting postsurgical recurrence and survival of HCC.(9-13) However, there have been little data on the correlation with explant pathology and radiologic measure based on LI-RADS in determining LT eligibility in HCC patients. Therefore, the goal of our study is to investigate the radio-pathologic correlation of MC using LI-RADS-based diagnosis, and also to identify factors affecting discordance and its prognostic impact.

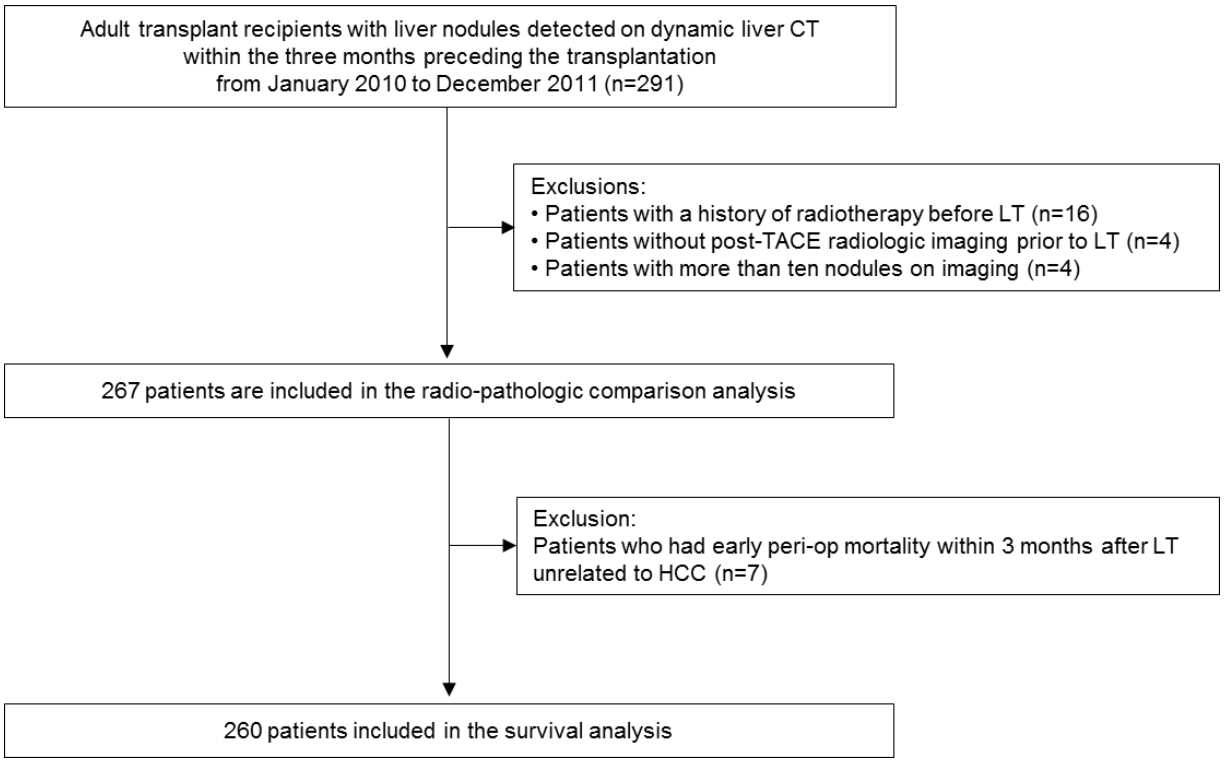
METHODS

Study population

Searching through radiologic database and electronic medical records of Asan Medical center from January 2010 through December 2011, a total of 291 patients were identified who met the following inclusion criteria: 1) those who underwent LT for liver nodule with a contrast-enhanced dynamic liver CT within 3 months before LT (n=285), and 2) patients with HCC in the explanted liver following transplantation, even in cases where the nodule was not discernible on pre-transplant imaging (n=6). The 3-month interval between CT and LT was selected in consideration of the volume doubling time of HCC.(14) The study did not have restrictions on whether LT was the first-line treatment option or followed bridging/down-staging treatments, including RFA, TACE and resection. Among these patients, 24 patients were excluded in the following reasons: 1) patients receiving radiotherapy prior to LT in whom imaging evaluation of tumor viability would be ambiguous (n=16), 2) patients who underwent LT without any CT evaluation after TACE (n=4), and 3) patients with more than 10 nodules in whom it was difficult to accurately describe the individual nodules in pathology specimen (n=4). Radiologic and pathologic analyses were finally performed on a total of 267 patients. Within three months after LT, seven patients experienced early perioperative mortality unrelated to HCC, categorized as in-hospital deaths. These cases were subsequently excluded from the survival analyses.

The flow of patient selection is expressed in **Figure 1**. This retrospective study was approved by the institutional review board of the Asan Medical center (No. 2023-1016).

Figure 1. Patient flow diagram. LT, liver transplantation; TACE, transarterial chemoembolization



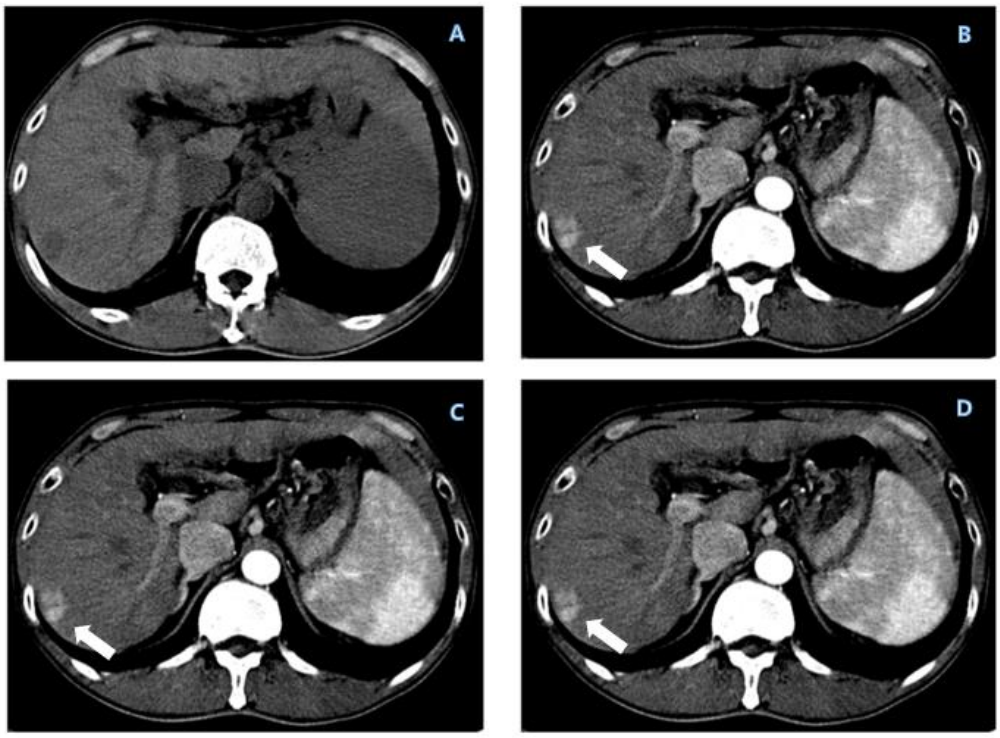
The LI-RADS categorization

The categories LR-1 (definitely benign) and LR-2 (probably benign) range from cysts to LR-2 distinctive nodules. An LR-2 distinctive nodule is defined by its size (<20 mm) and the absence of any major features of HCC, any features of LR-M, or any ancillary features of malignancy. LR-3 (intermediate probability of HCC) includes some perfusion alterations that have a nodular shape and true nodules with one or two malignant features. The malignant categories range from probable to definite malignancy and include LR-4 (probably HCC), LR-5 (definitely HCC), LR-M (probably or definitely malignant, not specific for HCC), and LR-TIV (malignancy with tumor in vein). We applied the LI-RADS treatment response algorithm with multiphase CT to assess response after local-regional therapy. Similar to the modified Response Evaluation Criteria in Solid Tumors (mRECIST), the LI-RADS algorithm is based on unidimensional measurements of the largest enhancing component of a treated tumor, excluding areas of non-enhancement. The LI-RADS algorithm expands on the mRECIST approach not only by defining viable disease (LR-TR-V) but also by providing non-evaluable (LR-TR-NE), equivocal (LR-TR-E), and nonviable (LR-TR-NV) treatment response categories.(15)

Two expert abdominal radiologists, blinded to the histopathologic findings, reviewed pre-LT contrast-enhanced dynamic CT and classified the lesions in consensus. For each patient, the imaging features

and categories according to LI-RADS v2018, along with the tumor size, number, and presence or absence of tumor in vein, were evaluated. Every nodule that fitted LR-3/LR-4 and LR-5, LR-M, LR-TIV, LR-TR-V, LR-TR-NV and LR-TR-E categories was subclassified, while LR-1 and LR-2 nodules were not included in this analysis because of their extremely low probability (ranging from 0 to 16%) for harboring HCC. Examples of radiologic assessment of each nodule via LI-RADS criteria are expressed in **supplementary figure 1**.

Supplementary figure 1. Hepatocellular carcinoma categorized as Liver Imaging Reporting and Data System category LR-5 in a 62-year-old male.



Two centimeter mass in liver S7, showing arterial phase hyperenhancement and washout on portal and delayed phases. LI-RADS category 5 nodule (arrow). A. Non-contrast phase. B. Late arterial phase. C. Portal venous phase. D. Delayed phase.

Definition of variables

Patient age, gender, etiology of liver disease (hepatitis B virus infection, hepatitis C virus infection, alcohol, liver cirrhosis and other etiologies), together with degree of alcohol consumption (heavy drinking, moderate drinking, and no alcohol drinking) according to the National Institute on Alcohol

Abuse and Alcoholism (NIAAA) guidelines, were evaluated. NIAAA defines heavy drinking as follows: (a) for men, consuming five or more drinks on any day or 15 or more per week, and (b) for women, consuming four or more on any day or 8 or more drinks per week. The amounts and/or volumes of 1 standard drink per various alcoholic beverages are 1.5 ounces (approximately 45 mL) of liquor (40%), 5 ounces (approximately 150 mL) of wine (12%), and 12 ounces (approximately 350 mL) of beer (4.5%). One standard drink of Soju (20%) is 1/4 bottle (approximately 90 mL).(16) People who drank alcohol below the standard for heavy drinking were classified as moderate drinking. Donation type (defined as donation from deceased donor or living donor) was reviewed and laboratory tests performed up to 24 hours before LT were identified in this study. Whether the presence of decompensation before LT was investigated by reviewing electronic medical records. Albumin-Bilirubin score and Child-Pugh classification and the model for end-stage liver disease (MELD) 3.0 score were also calculated from these clinical data and laboratory tests. Tumor markers such as alpha-fetoprotein, prothrombin induced by vitamin K absence-II (PIVKA-II) which were measured up to 6 months before LT was assessed in this study. Previous treatments including loco-regional and surgical approaches with either bridging or down-staging intent were also recorded. After LT, all patients underwent clinical and radiologic follow-up regularly every 3 to 6 months. If a patient died, the date and cause of death were recorded. Last follow up date and the date of recurrence were also monitored.

All the explanted liver specimens were reviewed by expert liver pathologists. Histopathologic diagnoses after LT were used as the standard of reference, which included number and size of HCC nodules, microvascular invasion, satellite nodules, presence of liver cirrhosis. For patients with multiple tumors, all evaluable observations were assessed and the largest observation was selected as the representative for statistical analysis. MC (a single nodule <5 cm in diameter or 3 or fewer nodules with individual diameters <3 cm without macrovascular invasion) was employed to view the explanted liver. Pathologic reports were described as maximal tumor size with percentage of necrosis, and maximal tumor size was considered as the basis for classifying pathologic MC.(2) Based on the explanted liver, patients were categorized as within pathologic MC and beyond pathologic MC. Based on the pre-transplant liver dynamic CT, the number and size of HCC were evaluated, and whether the MC was met or not was reviewed and defined as within LI-RADS MC and beyond LI-RADS MC, respectively. Only lesions corresponding to LR-5 and LR-TR-V were regarded as HCC to determine in evaluating LI-RADS MC. For the LR-M & LR-TIV category, considering the possibility of malignancy other than HCC and macrovascular invasion of HCC, respectively, patients with LR-M & LR-TIV were classified beyond LI-RADS MC. If the nodules were classified as LR3 or 4, even if considering a possibility of LR3/4 nodules being malignancy, these nodules were not classified as HCC first.

Study outcomes

Concordance rate of MC was reviewed as a per-patient analysis and the rate was subcategorized according to specific status (whether the presence of hepatitis B and C, deceased donor or living donor, presence of liver cirrhosis and chemoembolization were performed or not prior to LT). Per-lesion analysis was performed to match the nodules identified through imaging evaluated via LI-RADS and pathology. OS and RFS were evaluated to see if there were a difference in the long-term outcome between pathologic MC and LI-RADS MC. Factors that had a significant impact on overall survival (OS) and recurrence-free survival (RFS) were also analyzed through statistical analysis.

Statistical analysis

Continuous data are expressed as median with interquartile ranges (IQR). Categorical data are reported as counts and percentages. The agreement of patient allocation according to the MC based on LI-RADS and pathology was calculated and correlation analysis was performed by Chi-square or Fisher's exact test. The Kaplan-Meier method was used to measure OS and RFS rates, and significance was compared using the log-rank test. OS was defined as the interval between the date of LT and the date of the last reported visit or death. RFS was defined as the interval between the date of LT and either the date of the last reported imaging examination that confirmed the presence or absence of recurrent disease or the date of death. Competing risk analysis was carried out to calibrate between cancer-associated death (after recurrence) and other causes of death. A Cox proportional hazard regression model was utilized for univariate and multivariate analyses of preoperative factors related to OS, RFS after LT, including age, sex, alcohol consumption, comorbidity, etiology of liver disease, presence or absence of cirrhosis, Child-Pugh class, ALBI grade, MELD 3.0 score, prior treatment (including bridging or down-staging) of HCC, living or deceased donor liver transplantation, size of tumor, number of tumor, alpha-fetoprotein, PIVKA-II, LI-RADS category and LI-RADS MC. All variables with P values of <0.05 in the univariate analysis were included for the multivariate analysis using a stepwise Cox hazards regression module. All reported P-values were two-sided, and a P-value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed using R software (version 4.3.2; The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

The baseline characteristics of 267 patients included in the radio-pathologic analysis are presented in **Table 1**. The cohort consisted of 219 male and 48 female patients with a median age was 53 (interquartile range: 50–58). Hepatitis B viral infection was present in 85.8% of patients, while 7.5% had hepatitis C. The Child-Pugh classification of the patients was as follows: 110 (41.2%) were classified as Child-Pugh A, 101 (37.8%) as Child-Pugh B, and 56 (21.0%) as Child-Pugh C. Living donor LT was performed in 64.4% of patients. Prior to LT, 25.9% of patients had not undergone any down-staging or bridging therapy, whereas 74.1% had received such therapies in the following distribution: trans-arterial chemoembolization in 65.8%, radiofrequency ablation in 24.4%, and resection in 10.9%. Radiologic assessment prior to LT revealed that the median diameter of the largest nodule (LR-5 or LR-TR-V) was 2.1 cm (IQR, 1.6–2.8 cm). There were 79 LR-5 and 189 LR-TR-V nodules present in 138 patients. In the pre-transplant CT, 129 patients (48.3%) had no LR-5/LR-TR-V nodules. Eighty-three (31.1%) and twenty-four (9.0%) patients had one and two LR-5/LR-TR-V nodules, respectively, while 12 patients (4.5%) had three nodules, 9 patients (3.4%) had four nodules, and 10 patients (3.7%) had more than five nodules.

Histologic analysis revealed that 256 patients (95.9%) had liver cirrhosis at the explant liver. Microvascular invasion was present in 36 (13.5%) of patients and satellite nodules were found in 11 (4.2%) of explanted liver. The 479 HCC nodules identified in the explanted livers were distributed among 214 patients (110 patients with one HCC, 45 patients with two HCCs, 28 patients with three HCCs, 9 patients with four HCCs, and 22 patients with more than five HCCs). Median size of HCC in explanted liver was 2.3 cm (IQR: 1.5–3.2 cm). Regarding the MC, 205 patients (76.8%) were within the pathologic MC, and 62 patients (23.2%) were beyond it. When the MC were applied to radiologic analysis, 227 patients (85.0%) were within the LI-RADS MC, and 40 patients (15.0%) were beyond these criteria.

Table 1. Characteristics of the 267 transplant patients

Variable	Entire population (n=267)
Demographic variable	
Age	53 (50–58)
Male sex	219 (82.0%)
Alcohol consumption	
None / moderate / heavy	100 (37.4%) / 124 (46.4%) / 43 (16.1%)
Diabetes	59 (22.2%)
Liver-related factor	
Etiology of liver disease	
Hepatitis B virus infection	229 (85.8%)
Hepatitis C virus infection	20 (7.5%)
Child-Pugh class	7 (6–9)
Child-Pugh A / B / C	110 (41.2%) / 101 (37.8%) / 56 (21.0%)
ALBI grade	-1.7 (-2.2– -1.2)
Grade 1 / 2 / 3	23 (7.6%) / 153 (57.3%) / 91 (34.1%)
MELD 3.0	12 (9–18)
Living donor liver transplantation	172 (64.4%)
HCC-related factor before transplantation	
Diameter of largest tumor* (cm)	2.1 (1.6–2.8)
Number of tumors*	1 (1–3)
0 / 1 / 2 / ≥3	129 (48.3%) / 83 (31.1%) / 24 (9.0%) / 31 (11.6%)
LI-RADS Milan criteria	
Within Milan criteria	227 (85.0%)
Beyond Milan criteria	40 (15.0%)
Prior HCC treatments[†]	
None	69 (25.9%)
Resection	29 (10.9%)
Radiofrequency ablation	65 (24.4%)
Trans-arterial chemoembolization	175 (65.8%)
Serum AFP[‡] (ng/mL)	11.0 (4.1–50.6)
Serum PIVKA-II[§] (mAU/mL)	24.0 (16.0–42.0)
Pathological factor at explant liver	
Diameter of largest HCC[¶] (cm)	2.3 (1.5–3.2)
Number of HCC	
0 / 1 / 2 / ≥3	53 (19.9%) / 110 (41.2%) / 45 (16.9%) / 59 (22.0%)
Pathologic Milan criteria	

Within Milan criteria	205 (76.8%)
Beyond Milan criteria	62 (23.2%)
Liver cirrhosis	256 (95.9%)
Microvascular invasion	36 (13.5%)
Satellite nodule	11 (4.2%)

Values are presented as number (%) or median (interquartile range).

* Only nodules classified as LR-5 and LR-TR, which are indicative of viable HCC, were assessed for their diameter and number using pre-transplantation dynamic CT scans of the liver.

† Sixty-six patients underwent at least two modalities of HCC treatment prior to liver transplantation.

‡ AFP values at the time their lesions were detected were not available for two patients.

§ PIVKA-II values at the time their lesions were detected were not available for four patients.

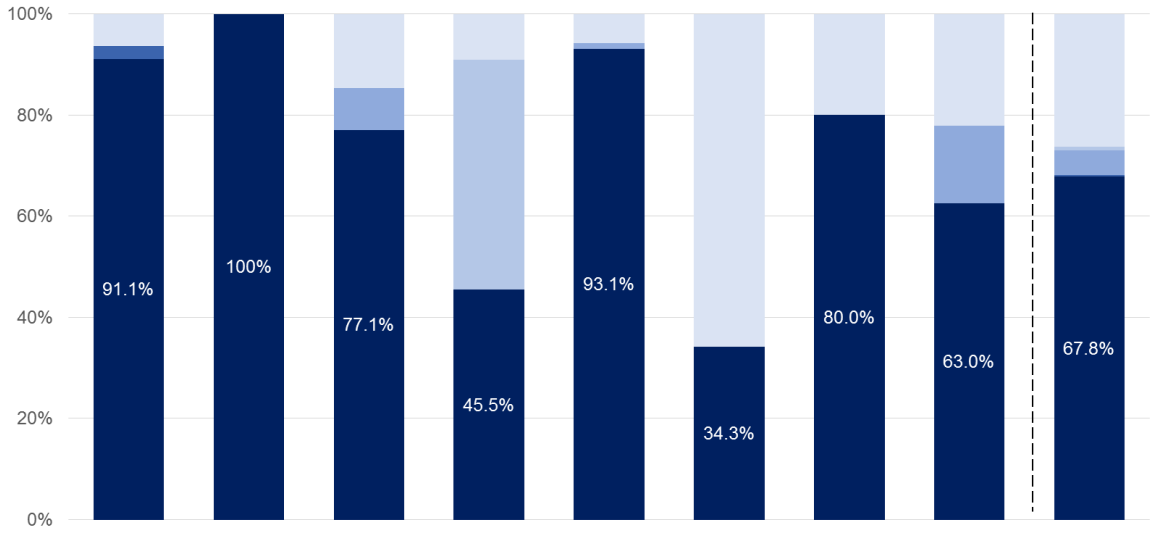
¶ This measurement was taken from 214 patients with histologically confirmed HCC.

Abbreviations: ALBI, albumin-bilirubin; MELD, model for end-stage liver diseases; LI-RADS, liver imaging reporting and data system; HCC, hepatocellular carcinoma; AFP, Alpha-fetoprotein; PIVKA-II, Protein induced by vitamin K absence or antagonist II

Correlation of LI-RADS Categorization with Histopathological Findings in Hepatic Lesions

The per-lesion analysis correlating LI-RADS categories with matched pathological nodules is detailed in **Figure 2**. The median diameters were 1.9 cm (IQR: 1.5–2.5) for LR-5, 1.4 cm (IQR: 1.1–2.0) for LR-3/LR-4, and 1.9 cm (IQR: 1.4–2.5) for LR-TR-V categories. Of the 79 LR-5 lesions and 48 LR-3/LR-4 lesions, 72 (91.1%) and 37 (77.1%) were histologically confirmed as HCC, respectively. Pathological analysis identified seven non-HCC LR-5 lesions, which consisted of two combined hepatocellular carcinoma-cholangiocarcinoma (HCC-CCA), one necrotic lesion, and four unmatched lesions in explanted liver. In the LR-TR-V category, 176 out of 189 lesions (93.1%) were identified as HCCs, compared to 62 of 181 (34.3%) in LR-TR-NV and 8 of 10 (80.0%) in LR-TR-E. The 11 LR-M lesions comprised 5 HCCs, 5 epithelioid hemangioendotheliomas, and 1 benign lesion. Notably, 119 HCC nodules, 29 dysplastic nodules, and other benign lesions observed in explanted livers were not detected in CT scans, classifying them as LR-invisible nodules.

Figure 2. Radiologic and Pathologic Characteristics of Hepatic Nodules Classified by LI-RADS Criteria



Class	LR-5	LR-TIV	LR-3/4	LR-M	LR-TR-V	LR-TR-NV	LR-TR-E	LR-invisible	Total
Number	79 (11.1%)	4 (0.6%)	48 (6.7%)	11 (1.5%)	189 (26.6%)	181 (25.4%)	10 (1.4%)	189 (26.6%)	712 (100%)
Size (cm)	1.9 (1.5–2.5)	-	1.4 (1.1–2.0)	3.6 (3.2–4.5)	1.9 (1.4–2.5)	1.6 (1.2–2.6)	2.2 (1.7–2.4)	-	1.6 (1.2-2.4)

Per-patient correlation between radiological and pathologic Milan criteria

In the per-patient analysis, the relationship between radiological LI-RADS MC and the pathologic MC is detailed in **Table 2**. Out of 267 patients, 227 were categorized within the LI-RADS MC, with 199 (87.7%) of these also fulfilling the pathologic MC. Conversely, among the 40 patients outside the LI-RADS MC, 34 (85.0%) did not meet the pathologic criteria, demonstrating a significant correlation (Pearson's chi-squared p-value < 0.001). The concordance rate, depicted in **Figure 3**, stood at 87.3% overall. Subgroup analyses revealed a consistent concordance rate above 80%, accounting for variables like prior trans-arterial chemoembolization, hepatitis B and C infections, liver cirrhosis, and the type of liver transplantation.

Table 3 delineates the specific causes of discordance. Reasons for classification within the LI-RADS MC but outside the pathologic MC included: HCCs in explanted livers classified as LR-TR-NV (13 cases), LR-TR-E (1 case), or invisible on CT scans (16 cases), and HCCs classified as LR-3/LR-4 on CT (6 cases). Additionally, two cases were found to have macrovascular invasion on explanted liver and two cases presumed to be metastasis-free pre-transplantation were found to have peritoneal seeding during surgery. Another four cases fell within the radiological criteria but exceeded the Milan criteria due to size thresholds (**Supplementary figure2**). One case with LR-5 nodule in pre-operative CT was found to have combined HCC-CCA in explanted liver. Furthermore, six cases were beyond the LI-RADS MC but within the pathologic MC as follows: (a) three patients with presence of LR-M nodules, which were later verified as HCCs in the explanted liver, (b) one patient with LR-TIV but without macrovascular invasion detected on pathology, and (c) 2 patients fell within pathologic MC but beyond LI-RADS MC due to size thresholds.

Table 2. Correlation between LI-RADS and pathologic Milan criteria in the patients undergoing transplantation (n=267).

		Pathologic Milan criteria	
		Within Milan	Beyond Milan
LI-RADS Milan criteria	Within Milan	199 (87.7%)	28 (12.3%)
	Beyond Milan	6 (15.0%)	34 (85.0%)

Abbreviations: LI-RADS, liver imaging reporting and data system.

Figure 3. Concordance rate between LI-RADS and pathologic Milan criteria according to baseline status

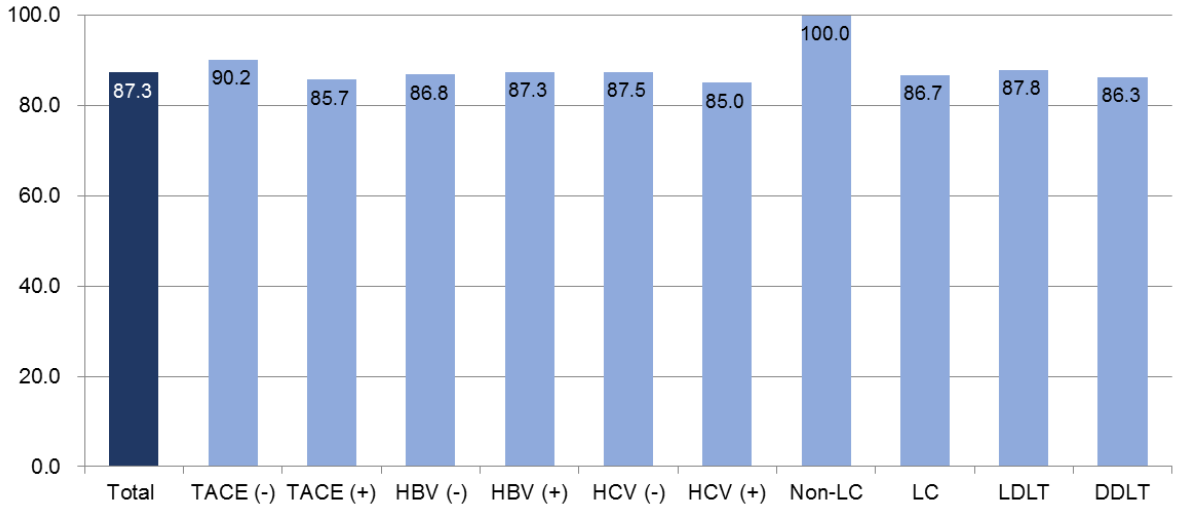


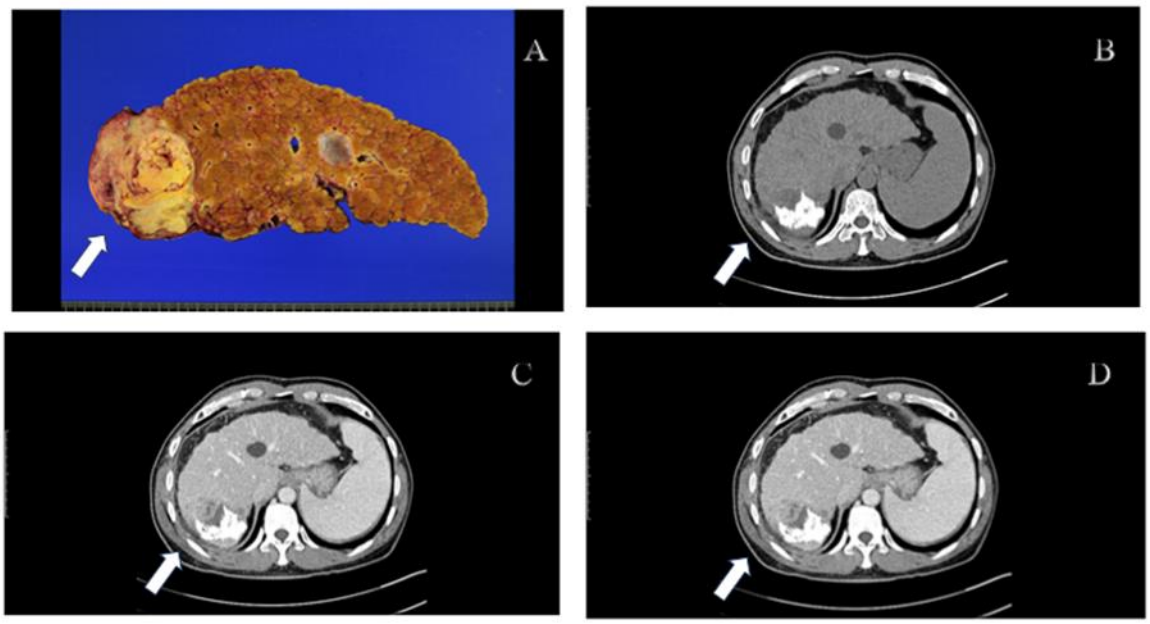
Table 3. Causes of discordance between LI-RADS and pathologic Milan criteria (n=34)

Causes	Number of patients
Within LI-RADS Milan criteria, but beyond pathologic Milan criteria (n=28)*	
LR-invisible corresponding to HCC on pathology	16
LR-3/4 consistent with HCC on pathology	6
LR-5 identified as combined HCC-CCA on pathology	1
LR-TR-NV matched with HCC on pathology	13
LR-TR-E matched with HCC on pathology	1
Macrovascular invasion newly identified on pathology	2
HCC exceeding the Milan size limit on pathology	4
Peritoneal seeding found during surgery not previously known	2
Beyond LI-RADS Milan criteria, but within pathologic Milan criteria (n=6)	
LR-M confirmed as HCC on pathology	3
LR-TIV but without macrovascular invasion detected on pathology	1
HCC meeting the Milan size limits on pathology	2

* 15 patients were identified as having two or more causative factors within LI-RADS MC, but beyond pathologic MC.

Abbreviations: LI-RADS, liver imaging reporting and data system; HCC, hepatocellular carcinoma; AFP

Supplementary figure 2. Size discrepancy (within LI-RADS MC but beyond pathologic MC)



Case beyond pathologic MC, but within LI-RADS MC because of size discrepancy. Images show HCC in a 60-year-old man who underwent TACE before LT. A 6.2cm-sized HCC (30% necrosis) in segment 7 (arrow) in seen in explanted liver (A). Lipiodol uptake is seen segment 7 (arrow) in precontrast phase (B). There is a portion of arterial phase enhancement around the lipiodol uptake site in segment 7 (arrow), suggesting a viable tumor, and its size is measured at approximately 3.8 cm (LR-TR viable) (C). Viable tumor (arrow) is suspected in portal phase in segment 7 (D)

Survival Analysis and Outcome Correlations with LI-RADS and Pathologic Milan Criteria in Liver Transplant Patients

For survival analysis, 260 patients were observed over a median period of 11.9 years (IQR, 7.2-12.5 years). **Figure 4** depicts OS rates based on LI-RADS MC and pathologic MC, utilizing a competing risk analysis. Significantly higher 5-year and 10-year OS rates were observed for patients within the MC than those outside: 96% vs. 76% and 96% vs. 70% for LI-RADS MC; 96% vs. 86% and 96% vs. 84% for pathological MC (all $P<0.003$). RFS rates, shown in **Figure 5** using a cause-specific hazard function, also favored patients within the MC: 90% vs. 45% and 89% vs. 40% for LI-RADS MC; 90% vs. 62% and 89% vs. 57% for pathologic MC (all $P<0.001$). Comparison of OS and RFS between patients within LI-RADS MC and within pathologic MC (**Figure 6**) revealed no significant survival differences ($P=0.840$ and $P=0.940$, respectively). Subgroups were divided according to whether they met the LI-RADS MC and pathologic MC, and the corresponding OS and RFS are depicted in **Figure 7**.

The OS and RFS of the subgroup within pathologic MC and beyond LI-RADS MC and the subgroup both beyond MC are significantly lower compared to the subgroup both within MC (P<0.001).

Univariate analysis of pre-LT variables identified predictors for OS and RFS using the Cox proportional hazards model in **Tables 4-5**. In univariate and subsequent multivariate analyses, high AFP ≥20 ng/mL (adjusted HR, 4.28; 95% CI: 1.34–13.62; P=0.014), child B class (adjusted HR, 0.17; 95% CI: 0.04–0.78; P=0.023) and LI-RADS MC (adjusted HR, 6.51; 95% CI: 2.37–17.86; P<0.001) were significant factor. As for RFS, LI-RADS MC (adjusted HR, 6.34; 95% CI: 3.38-11.88; P<0.001) was only significant factor.

Figure 4. Cumulative estimates of overall survival according to the (A) LI-RADS Milan criteria and (B) Pathologic Milan criteria

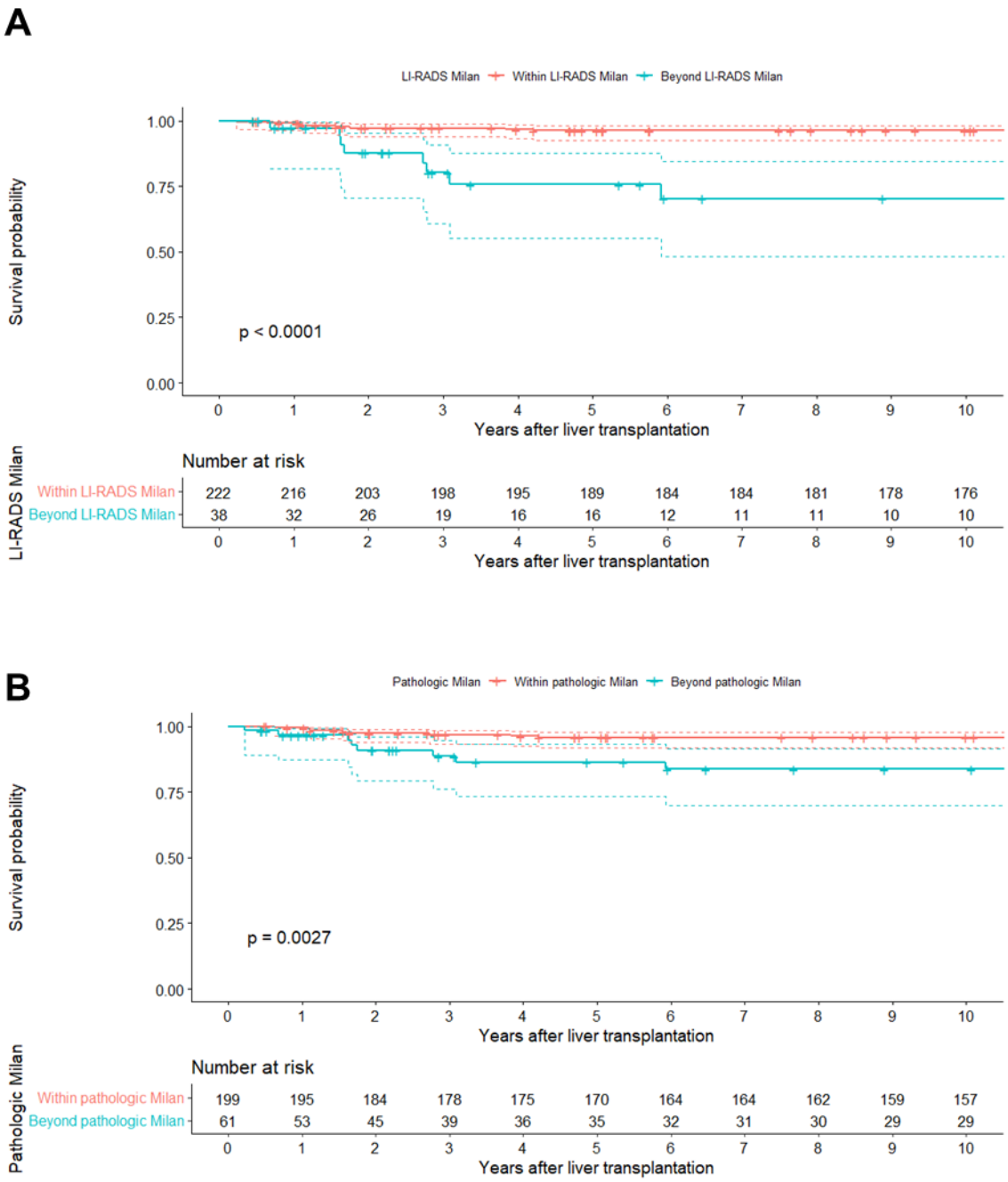


Figure 5. Cumulative estimates of recurrence-free survival according to the (A) LI-RADS Milan criteria and (B) Pathologic Milan criteria

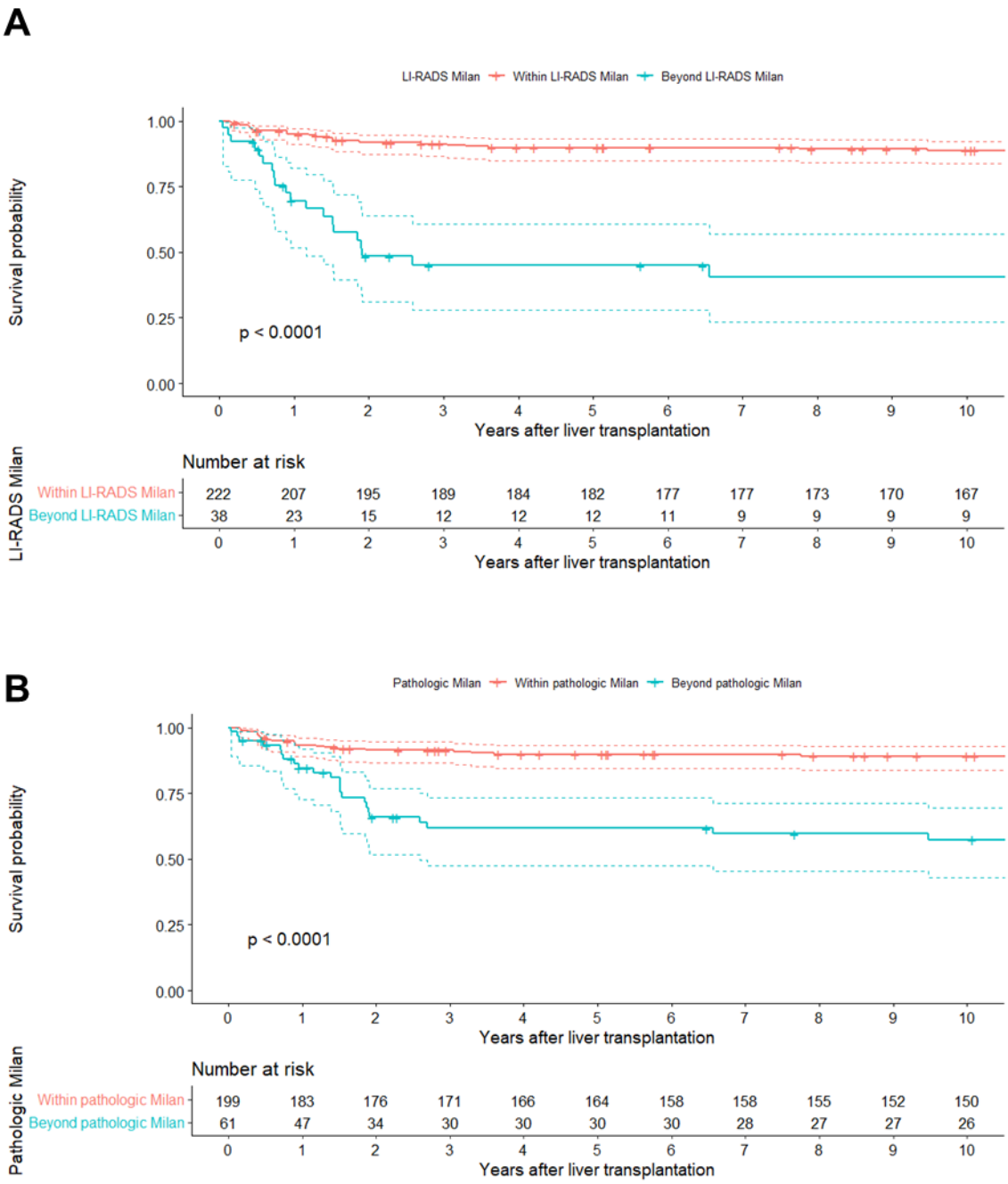


Figure 6. Cumulative estimates of (A) overall survival and (B) recurrence-free survival in patients with LI-RADS and (B) pathologic Milan criteria

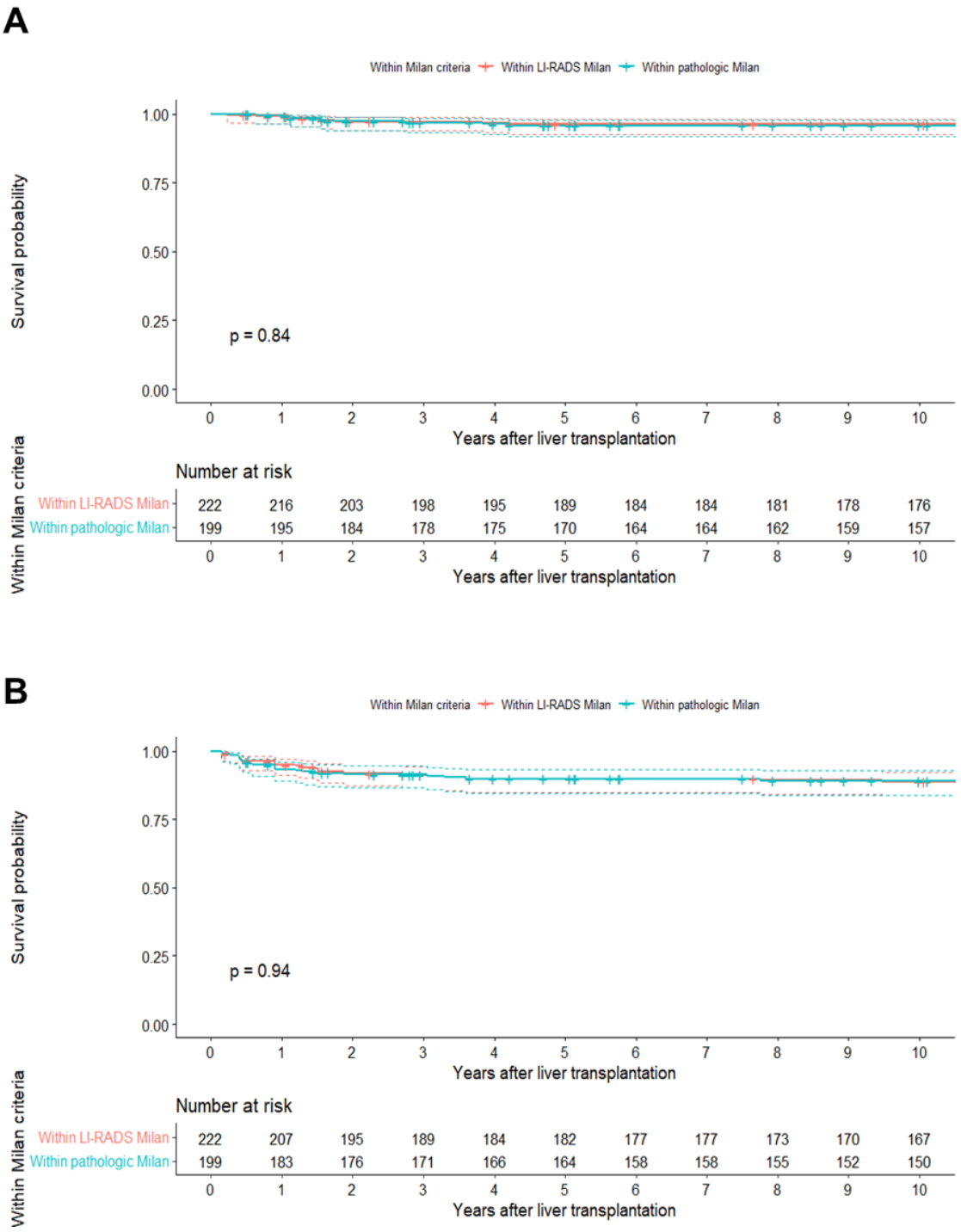
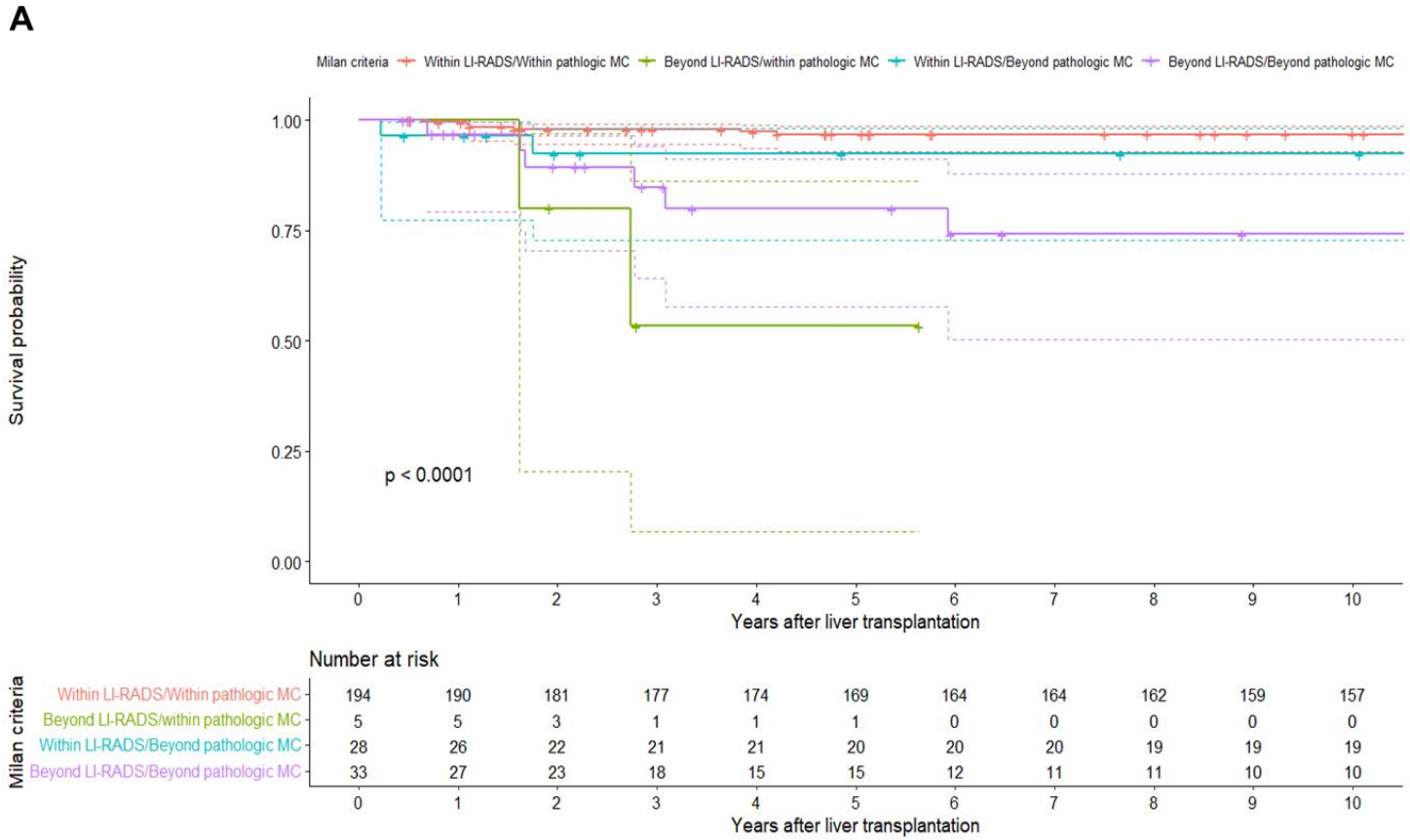
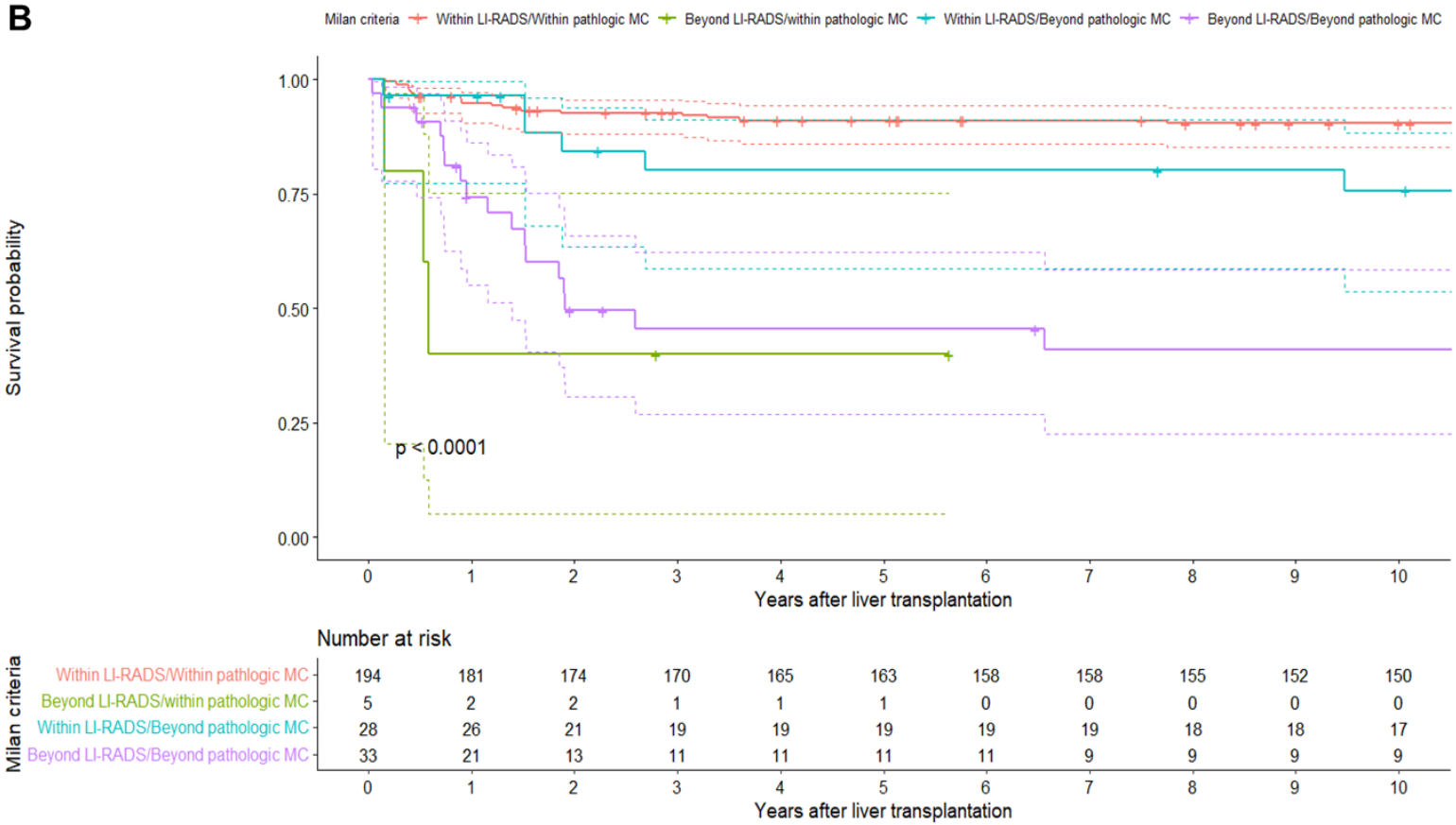


Figure 7. (A) Overall survival and (B) recurrence-free survival following liver transplantation according to status of LI-RADS and pathologic Milan criteria



P value by group comparison	Within Milan criteria by both methods	Within pathologic- & beyond LI-RADS MC	Beyond pathologic- &within LI-RADS MC
Within pathologic- &Beyond LI-RADS MC	<0.001	-	-
Beyond pathologic- &Within LI-RADS MC	0.235	0.094	-
Beyond pathologic-&Beyond LI-RADS MC	<0.001	0.216	0.076

B



	Within pathologic- &within LI-RADS MC	Within pathologic- &Beyond LI-RADS MC	Beyond pathologic- &Within LI-RADS MC
Within pathologic- &Beyond LI-RADS MC	<0.001	-	-
Beyond pathologic- &Within LI-RADS MC	0.047	0.0023	-
Beyond pathologic-&Beyond LI-RADS MC	<0.001	0.431	0.011

Table 4. Independent predictors of overall survival following liver transplantation (n=260)

Characteristic	Univariate analysis			Multivariate analysis*		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age ≥55 years	1.24	0.47–3.31	0.666			
Male sex	1.57	0.36–6.90	0.551			
Alcohol consumption						
None	ref.					
Moderate	0.71	0.24–2.11	0.535			
Heavy	0.95	0.25–3.67	0.941			
Diabetes	2.16	0.78–5.93	0.137			
HBV infection		0.00–Inf	0.997			
HCV infection	0.88	0.11–7.04	0.904			
CTP class						
CTP A	ref.					
CTP B	0.18	0.04–0.79	0.023	0.17	0.04–0.78	0.023
CTP C	0.31	0.07–1.40	0.130			
ALBI grade						
Grade 1	ref.					
Grade 2	0.63	0.14–2.90	0.548			
Grade 3	0.58	0.11–3.02	0.521			
MELD 3.0	0.94	0.86–1.03	0.175			
Prior HCC treatment	1.58	0.45–5.53	0.477			
Deceased donor LT	1.04	0.38–2.86	0.942			
AFP ≥20 ng/mL	6.26	2.02–19.4	0.001	4.28	1.34–13.62	0.014
PIVKA II ≥400mAU/mL	3.85	0.87–17.0	0.075			
Largest tumor diameter	1.28	0.98–1.68	0.073			
Multiple tumors	2.39	0.76–7.53	0.138			
LR-5	0.68	0.15–2.98	0.606			
LR-TIV	4.93	0.65–37.6	0.124			
LR-M	6.39	1.45–28.2	0.014			
LR-3/4	0.35	0.05–2.67	0.313			
LR-TR-V	3.59	1.30–9.88	0.013			
LR-TR-NV	0.78	0.29–2.10	0.627			
LR-TR-E		0.00–Inf	0.997			
LI-RADS Milan criteria						
Within Milan	ref					
Beyond Milan	7.96	2.96–21.4	<0.001	6.51	2.37–17.86	<0.001

* Due to the insufficient number of events associated with the two variables, hepatitis B, liver cirrhosis, and LR-TR-E, conducting a Cox Proportional-Hazard model was not feasible.

* Only variables with a *P* value <0.05 in the univariate analysis were included in the multivariate analysis.

Abbreviations: HR, hazard ratio; CI, confidence interval; ref, reference; HBV, hepatitis B virus; HCV, hepatitis C virus; CTP, Child-Turcotte-Pugh; ALBI, albumin-bilirubin; MELD, model for end-stage liver diseases; HCC, hepatocellular carcinoma; LT, liver transplantation; AFP, Alpha-fetoprotein; PIVKA-II, Protein induced by vitamin K absence or antagonist II. LI-RADS, liver imaging reporting and data system;

Table 5. Independent predictors of recurrence-free survival following liver transplantation (n=260)

Characteristic	Univariate analysis			Multivariate analysis*		
	HR	95% CI	*P*	HR	95% CI	*P*
Age ≥55 years	0.85	0.47–1.55	0.594			
Male sex	2.33	0.83–6.51	0.107			
Alcohol consumption						
None	ref.					
Moderate	1.54	0.72–3.27	0.265			
Heavy	1.38	0.67–2.84	0.384			
Diabetes	0.91	0.44–1.89	0.800			
HBV infection	1.02	0.43–2.40	0.972			
HCV infection	0.68	0.16–2.92	0.607			
Liver cirrhosis	0.77	0.19–3.19	0.721			
CTP class						
CTP A	ref.					
CTP B	0.82	0.43–1.54	0.535			
CTP C	0.42	0.16–1.10	0.076			
ALBI grade						
Grade 1	ref.					
Grade 2	0.41	0.18–0.96	0.040			
Grade 3	0.48	0.20–1.18	0.111			
MELD 3.0	0.97	0.92–1.01	0.160			
Prior HCC treatment	1.23	0.61–2.49	0.565			
Deceased donor LT	0.89	0.48–1.67	0.721			
AFP ≥20 ng/mL	1.95	1.07–3.55	0.028			
PIVKA II ≥400mAU/mL	3.57	1.40–9.06	0.008			
Largest tumor diameter	1.37	1.18–1.60	<0.001			
Multiple tumors	2.49	1.23–5.05	0.011			
LR-5	1.05	0.49–2.27	0.894			
LR-TIV	7.06	2.17–22.9	0.001			
LR-M	4.43	1.37–14.3	0.013			
LR-3/LR-4	0.25	0.06–1.03	0.055			
LR-TR-V	2.60	1.43–4.70	0.002			
LR-TR-NV	0.82	0.45–1.48	0.509			
LR-TR-E	0.99	0.14–7.19	0.992			
LI-RADS Milan criteria						
Within Milan	ref.					
Beyond Milan	7.45	4.08–13.6	<0.001	6.34	3.38–11.88	<0.001

* Only variables with a *P* value <0.05 in the univariate analysis were included in the multivariate analysis.

Abbreviations: HR, hazard ratio; CI, confidence interval; ref, reference; HBV, hepatitis B virus; HCV, hepatitis C virus; CTP, Child-Turcotte-Pugh; ALBI, albumin-bilirubin; MELD, model for end-stage liver diseases; HCC, hepatocellular carcinoma; LT, liver transplantation; AFP, Alpha-fetoprotein; PIVKA-II, Protein induced by vitamin K absence or antagonist II. LI-RADS, liver imaging reporting and data system;

DISCUSSION

In the context of selecting optimal LT candidates among patients with HCC, MC remains a cornerstone in clinical practice. Although MC is crucial for post-LT prognosis evaluation, it primarily relies on pathology.(2, 6) However, due to bleeding risks and other practical constraints, pre-transplant liver biopsies are not feasible in all cases, necessitating reliance on radiologic evaluations for LT eligibility. A study by Seo et al., adhering to European Association for the Study of the Liver (EASL) guidelines, reported an 81.9–83.3% concordance rate for 216 patients between radiologic and pathologic MC.(17) This contrasted with Sugimachi et al.'s finding of a 71.6% concordance rate using similar criteria.(6) Investigations into the LI-RADS v2018 criteria for HCC diagnosis have consistently shown high diagnostic accuracy for LR-5 categorization for HCC.(18-20) Lee et al. reported a notable 88.9–92.1% concordance rate for 63 recipients between pathologic MC and pre-operative radiologic MC using LI-RADS with MRI, where LR-4 and 5 nodules were indicative of HCC. This study also highlighted that the concordance between radiologic and pathologic MC did not significantly influence OS or RFS.(7) Similarly, Bae et al. demonstrated the high accuracy (85.3–92.7%) of LR-5 observations on CT in assessing LT eligibility in high-risk patients, considering LR-TIV and LR-M as contraindications for LT, as in our study.(1) However, this study excluded patients treated with down-staging or bridging loco-regional therapy prior to LT, thus not assessing the impact of the LI-RADS treatment response algorithm in LT eligibility assessment. Notably, the LI-RADS treatment response algorithm has shown better specificity than mRECIST for viable HCC diagnosis post loco-regional therapy, with no significant difference in sensitivity.(21) In our radiologic-pathologic correlation study, evaluating LR-5 and LR-TR-V nodules as HCC indicators, LI-RADS MC demonstrated an agreement rate exceeding 85% with the pathologic MC on a per-patient basis. Moreover, we observed comparable OS and RFS outcomes between patients categorized within LI-RADS MC and pathologic MC in competing risk models.

In evaluating LI-RADS and pathologic MC, some patients exhibited discordance between the two criteria. Specifically, in the subgroup classified beyond LI-RADS MC but within pathologic MC, discordance was attributed to: (a) size discrepancies in 2 patients, (b) 1 patient with LR-TIV, and (c) 3 patients with LR-M nodules matching HCC. In the size discrepancy cases, LR-TR-V nodules measuring 4 cm and 6.9 cm corresponded to 3 cm and 4.7 cm HCCs in explanted livers, respectively. One patient survived beyond 5 years post-LT without HCC recurrence, while the other survived approximately 3 years post-LT, eventually succumbing to colon cancer (a competing event). On the contrary, the patient with the LR-M nodule experienced perioperative mortality within 90 days of LT and the remaining patients (1 with TIV and 2 with LR-M nodules) faced HCC recurrence about 6 months post-LT. Vascular invasion on imaging, known as tumor in vein, signals highly invasive tumor behavior, correlating with

poor outcomes and is considered an absolute contraindication for LT.(5, 22) Andreou et al. identified macrovascular invasion as a significant factor, increasing the risk of HCC recurrence post-LT by 2.45-fold.(23) LI-RADS v2018 defines tumor in vein diagnosis as the presence of "unequivocal enhancing soft tissue within the vein," ensuring high specificity and positive predictive value.(24) A study of 366 HCC patients using gadoxetic acid-enhanced MRI found that enhancement in the thrombus had excellent accuracy for diagnosing tumor in vein, with sensitivity ranging from 70–84% and specificity between 89–96%.(25) LR-M HCCs are associated with poor prognosis, more aggressive cancer behavior like microvascular invasion, poor differentiation, and macrotrabecular-massive type.(11-13, 26-28) For example, Lee et al. reported that LR-M categorized HCC was a stronger independent predictor of recurrence post-living donor LT compared to LR-4/5 HCCs. LR-M HCCs also exhibited significantly more microvascular invasion than LR-4/5 HCCs (57.1% vs. 17.5%).(11) Considering the adverse nature of LR-M nodules, even in pathologically confirmed HCCs, it might be prudent to classify their presence as MC-out at least in cases where biopsy is challenging. Our study revealed poor OS and RFS in the LI-RADS-out and pathologic MC-in subgroups, primarily due to the presence of LR-M and LR-TIV. This suggests that cases outside LI-RADS MC, particularly due to LR-M and LR-TIV, may be indicative of a poor prognosis post-LT.

In the subgroup within LI-RADS MC, but beyond pathologic MC, the reasons for discordance were as follows: (a) 4 size discrepancies, (b) 1 LR-5 combined HCC-CCA, (c) 16 CT-invisible HCCs, (d) 6 LR-3 or LR-4 HCCs, (e) 13 LR-TR-NV HCCs, (f) 1 LR-TR-E HCC, (g) 2 portal vein invasions in the explanted liver, or (h) 2 peritoneal seeding on pathology. In cases of size discrepancy, HCC nodules with partial necrosis in the explanted liver (>3 cm) were matched as LR-TR-V nodules (<3 cm). The LI-RADS system is known to be applicable in differentiating between HCC and combined HCC-CCA. The majority of combined HCC-CCA cases reviewed against the LI-RADS criteria demonstrated ancillary features favoring non-HCC malignancy, sufficient for them to be recorded as LR-M.(29) Furthermore, studies suggest that specific radiological features can be used to provide prognostic information about combined HCC-CCA.(30) Tumors with a predominant HCC component may exhibit arterial phase signal enhancement (hyperintensity) and delayed venous phase signal dropout (hypointensity) on contrast-enhanced CT and MRI, resembling HCC characteristics. In contrast, lesions with a predominant CCA component demonstrate peripheral rim enhancement in the arterial phase with progressive centripetal enhancement in the delayed venous phase, similar to mass-forming CCA.(31) Tumors that exhibit a radiological predominance of HCC features tend to have a more favorable prognosis compared to CCA-predominant subtypes.(30) According to one study, the long-term outcomes of tumor recurrence and patient survival following liver LT were similar in patients with combined HCC-CCA (n=8) and HCC (n=170), reporting 5-year OS and disease-free survival after LT

for combined HCC-CCA were 72.9% and 85.7%, respectively.(32) Based on the data obtained from the United Network for Organ Sharing (UNOS) database collected between 1994 and 2013, patients who underwent LT for combined HCC-CCA (n=94) had overall 1-, 3-, and 5-year OS rates of 82%, 47%, and 40%, respectively, and a median survival duration of 29 months.(33) Although the prognosis after LT in combined HCC-CCA is known to be generally poor(34), this case suggests that a relatively good prognosis may be expected if radiological characteristics are consistent with HCC according to LI-RADS.

According to one systematic review, the LR-3 and LR-4 categories in LI-RADS were reported to represent HCCs in 40% and 80% of the cases, respectively.(35) In our study, LR-3 or LR-4 nodules were confirmed as HCCs in 80% of cases upon examination of the explanted liver. LI-RADS recommends that LR-4 observations be discussed at multidisciplinary conferences and potentially undergo biopsy due to their high probability of malignancy.(36) Centonze et al. reported that LR-5 nodules showed a higher prevalence of microvascular invasion, satellitosis, and capsule infiltration when compared with LR-3/LR-4 nodules in cases where HCC was confirmed pathologically.(9) Regarding the criteria for LT, several groups have argued that the MC should be expanded, given the shortage of liver grafts and the potential benefits of transplantation for many patients with HCC exceeding these criteria.(8, 37) Additionally, the MC are quite stringent, which can lead to the exclusion of patients from waitlists who could indeed benefit from LT. Many studies have shown that comparable survival outcomes can be achieved after extending the MC. Criteria such as the Navarra criteria (single tumors ≤6 cm or 2–3 nodules ≤5 cm) and Asan criteria (≤6 tumors all ≤5 cm in diameter) were developed as expansions of the MC, both of which identified additional HCC patients who could benefit from LT without compromising the results.(38, 39) Subsequently, the total tumor diameter or volume has emerged as an essential factor. Patients with HCC meeting the University of California, San Francisco (UCSF) criteria (single tumors ≤6.5 cm in diameter or no more than 3 lesions ≤4.5 cm in diameter and a total tumor diameter ≤8 cm) were reported to have similar 5-year OS and disease-free survival rates when compared to MC.(40) In 2007, Mazzaferro et al. conducted a large retrospective study in which 283 patients within the 'up-to-seven criteria' (the sum of the size of the largest tumor, in cm, and the number of tumors ≤7) achieved a 5-year OS of 71.2%.(41) A study from Spain reported that patients beyond MC but within the Valencia criteria (1–3 tumors ≤5 cm and a cumulative tumor burden ≤10 cm) had a similar 5-year OS to patients within MC.(42) These expanded criteria suggest that the maximal diameter of tumors may be a more crucial factor than the specific number of tumors. According to one meta-analysis that reviewed 74 studies, tumor size rather than the number of tumors was a significant factor in overall survival after LT.(43) Even if LR-3 and LR-4 nodules are proven to be HCC, there is a possibility that these nodules are associated with less aggressive histological features.

Furthermore, it can be inferred that even if a case exceeds the MC due to pathologically proven LR-3 and LR-4 nodules, and the size of these nodules is not significantly large, LR-3 and LR-4 nodules might have a minimal impact on prognosis after LT. LI-RADS MC might have demonstrated comparable outcomes with the pathologic MC, considering that MC is quite strict criteria for LT, and several expanded criteria have shown comparable survival outcomes when compared to MC

Chaudhry et al. reported that 60% (32 out of 53, totaling 36 patients with 53 lesions) of the treated nodules were categorized as LR-TR-NV. Among these, 26 out of the 32 LR-TR-NV lesions were found to be completely necrotic on histopathology. This observation was made by reviewing patients who underwent ablation therapy for presumed HCC followed by LT. The LR-TR-NV category demonstrated a specificity of 81–85% in predicting complete tumor necrosis.(44) Similarly, Yoon et al. also reported that the LR-TR-NV category exhibited a sensitivity ranging from 73.3% to 80.0% and a specificity ranging from 78.9% to 89.5% in predicting complete necrosis. This finding was based on a review of patients who underwent radioembolization for HCC followed by surgery, involving a total of 27 patients with 34 lesions.(45) Furthermore, several studies have reported superior survival outcomes for patients with LR-TR-NV nodules after local or surgical treatments compared to the LR-TR-V group.(46-48) Based on these observations, it can be inferred that even in cases where there is a viable portion within the entire tumor, and this nodule is classified as LR-TR-NV according to LI-RADS v2018, the prognostic impact of this discordance after LT might be minimal.(46-48)

This study has several limitations. Firstly, there is a selection bias as it was conducted retrospectively on patients who underwent LT for HCC. However, conducting a prospective study on all LT candidates is unfeasible due to ethical and social issues, given the significant risks associated with LT and the problem of donor shortage. Secondly, the extent of necrosis was expressed as a percentage, and the total diameter with necrosis was documented in the pathological reports. When evaluating the pathologic MC, the total diameter, including portions of necrosis, was the standard for classifying the pathologic MC. In cases where a large portion of the tumor is necrotic, the size of the tumor might have been overestimated. Thirdly, our study only evaluated pre-transplantation dynamic CT images for assessing nodules using LI-RADS v2018. Follow-up studies that also include MRI images are needed to provide a more comprehensive evaluation. Due to the relatively small number of patients, a subgroup analysis of those who underwent chemoembolization could not be performed in this study. Further analysis will be conducted in the future through a larger-scale cohort in a variety of pre-LT settings.

In conclusion, the LI-RADS MC, which considers LR-5 and LR-TR-V nodules as HCC, demonstrates a high level of agreement and comparable survival outcomes with the pathological MC when using competing risk models. This validates LI-RADS v2018 and the treatment response algorithm as

valuable tools for evaluating eligibility for LT. Future studies that assess transplant eligibility using different extended criteria, while applying LI-RADS v2018, are needed to provide clinicians and surgeons with more informative and practical data.

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국문요약

배경: 밀란기준은 간세포암의 간이식후 예후 평가를 위해 사용되나 병리적 분석에 기초하고 있다. 기존 연구에 따르면 간영상 보고 및 자료체계(liver imaging reporting and data system; 이하 LI-RADS)는 간세포암 진단에 높은 정확도를 보이고, LI-RADS 치료반응(LI-RADS treatment response; 이하 LR-TR) 또한 간세포암에 대해 국소치료를 시행한 환자에서 mRECIST 기준과 비교하여 비슷한 진단적 정확성을 보이는 것으로 알려져 있다. 이 연구에서는 LI-RADS v2018 과 LR-TR 을 적용한 영상학적 밀란기준과 및 병리기반 밀란기준의 일치도를 평가하고, 불일치와 예후의 영향을 미치는 요인을 식별하여 LI-RADS 와 LR-TR 의 이식전 예후평가로서의 역할을 평가하였다.

연구방법: 2010 년부터 2011 년까지 서울아산병원의 간결절로 간이식을 시행하고, 이식전 3 개월 이내에 삼중시기 나선식 CT 를 촬영한 267 명의 환자를 대상으로 후향적 분석을 수행하였다. 영상의학과 의사에 의하여 LI-RADS 기준으로 CT 를 분석하였고, 이식후 적출된 간의 병리소견과 비교평가하였다. LI-RADS 상 LR-5 와 LR-TR Viable 결절을 간세포암으로 간주하였다. 영상과 병리상 확인된 결절에 대해 각 결절별로 분석을 수행하였다. LI-RADS 기반 밀란기준과 병리기반 밀란기준의 일치도를 확인하고 불일치의 요인과 그 예후적 영향에 대해 평가하였다. 수술 전후 사망한 환자를 제외하고, LI-RADS 와 병리기반 밀란기준간의 생존율 및 무병생존율을 경쟁위험회귀모형을 통해 평가하였다. Cox 비례위험 모형을 통해 생존율과 무병생존율에 대한 요인을 확인하였다.

결과: 병변별 분석에서 79 개의 LR-5 및 189 개의 LR-TR viable 병변이 각각 적출된 간에서 72 개(72/79, 91.1%) 및 176 개(176/189, 93.2%)의 간세포암과 일치하였다. LI-RADS 와 병리기반 밀란기준 사이에 87.27%의 일치도가 확인되었다. LI-RADS 밀란기준 내에 속하는 환자와 병리기반 밀란기준내에 속하는 환자들은 전체 생존율(p=0.84)과 무병 생존율(p=0.94)이 유의한 차이가 없었다. 하위그룹분석상 LI-RADS 밀란기준 이상에 속하나 병리기반 밀란기준내 속하는 환자군(n=5)의 예후가 다른 하위그룹에 비해 생존율 과 무병생존율이 유의하게 가장 낮았다(p<0.001). 이 환자군은 주로 LR-M (비특이적 악성 간병변) 및 LR-TIV (확실한 정맥 내 종괴)를 포함하고 있었다. Cox 비례위험 모형을 적용한 다변량분석에서 LI-RADS 밀란기준은 생존율 (HR 7.76[2.73-22.09, p=0.000] 과 무병생존율(HR 7.86[4.28-14.43], p=0.000)에 대한 유의미한 변수로 확인되었다.

결론: LR-5 와 LR-TR viable 결절을 간세포암으로 간주하는 LI-RADS 밀란기준은 병리기반 밀란기준과 높은 일치도를 보이고, 경쟁위험회귀모형을 통해 비슷한 생존율과 무병생존율을 보여 LI-RADS 와 LR-TR 이 이식전 예후를 평가하는 기준으로 사용될 수 있음을 확인하였다.

중심단어: 간영상 보고 및 자료체계, LI-RADS 치료 반응, 간이식, 간세포암