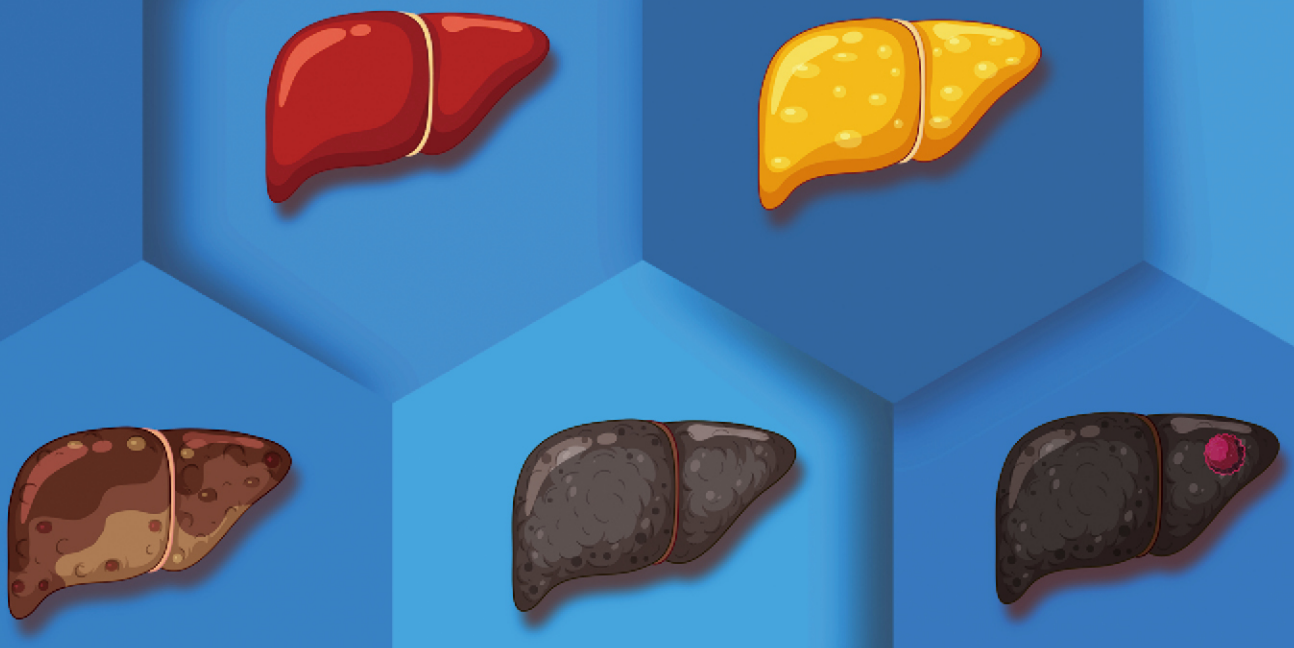
VOLUME 31 SUPPLEMENT February 2025
pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases



KASL 2025 MASLD clinical practice guidelines

Prognostication of MASLD

Epidemiology of MASLD

Precision medicine and MASH

Microbiome-centered therapies for MASLD

KASL

pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2024.0323
Clinical and Molecular Hepatology 2025;31(Suppl):S285-S300

Review

Criteria and prognostic models for patients with hepatocellular carcinoma undergoing liver transplantation

Meng Sha[1,*], Jun Wang[2,*], Jie Cao[1,*], Zhi-Hui Zou[3,*], Xiao-ye Qu[1], Zhi-feng Xi[1], Chuan Shen[1], Ying Tong[1], Jian-jun Zhang[1], Seogsong Jeong[4], and Qiang Xia[1]

[1]Department of Liver Surgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [2]State Key Laboratory of Systems Medicine for Cancer, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [3]Department of Hepatic Surgery VI, Eastern Hepatobiliary Surgery Hospital, Naval Military Medical University, Shanghai, China; [4]Department of Biomedical Informatics, Korea University College of Medicine, Seoul, Korea

Hepatocellular carcinoma (HCC) is a leading cause of cancer-associated death globally. Liver transplantation (LT) has emerged as a key treatment for patients with HCC, and the Milan criteria have been adopted as the cornerstone of the selection policy. To allow more patients to benefit from LT, a number of expanded criteria have been proposed, many of which use radiologic morphological characteristics with larger and more tumors as surrogates to predict outcomes. Other groups developed indices incorporating biological variables and dynamic markers of response to locoregional treatment. These expanded selection criteria achieved satisfactory results with limited liver supplies. In addition, a number of prognostic models have been developed using clinicopathological characteristics, imaging radiomics features, genetic data, and advanced techniques such as artificial intelligence. These models could improve prognostic estimation, establish surveillance strategies, and bolster long-term outcomes in patients with HCC. In this study, we reviewed the latest findings and achievements regarding the selection criteria and post-transplant prognostic models for LT in patients with HCC. **(Clin Mol Hepatol 2025;31(Suppl):S285-S300)**

Keywords: Hepatocellular carcinoma; Liver transplantation; Standards; Nomogram

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer globally, causing more than 900,000 new cases each year. HCC is also the third-leading cause of cancer-associated mortality globally, with a relative 5-year survival rate of only 18%.[1,2] Liver transplantation (LT) is a primary curative treatment for HCC that eliminates both

Corresponding author : Qiang Xia
Department of Liver Surgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China
Tel: +86-21-68383775, Fax: +86-21-58737232, E-mail: xiaqiang@shsmu.edu.cn
https://orcid.org/0000-0001-9482-6951

Seogsong Jeong
Department of Biomedical Informatics, Korea University College of Medicine, 73 Goryeodae-ro, Seongbuk-gu, Seoul 02841, Korea
Tel: +82-2-3407-4085, E-mail: seogsongjeong@korea.ac.kr
https://orcid.org/0000-0003-4646-8998

*These authors share first authorship as equal contributors to this work.

Editor: Ju Hyun Shim, University of Ulsan, Korea

Received : Apr. 30, 2024 / **Revised :** Aug. 11, 2024 / **Accepted :** Aug. 12, 2024

the tumor and the underlying liver disease simultaneously.[3,4] With advances in immunosuppression and surgical techniques, the average 5-year post-LT survival currently exceeds 70%.[5] To balance the shortage of available organs and best outcomes for HCC, the Milan criteria, initially introduced by Mazzaferro in 1996,[6] serve as the main criteria for selecting patients with HCC suitable for LT globally. For patients meeting the Milan criteria, the 4-year overall survival (OS) and recurrence-free survival (RFS) rates have reached 75% and 83%, respectively. However, the strict selection criteria based on morphological characteristics result in the exclusion of many patients who could benefit from LT.[7] Additionally, the post-LT tumor recurrence rate of 10–16% represents a major concern and impedes the chance of cure for patients with HCC.[8] Therefore, many centers have proposed extended criteria that incorporate larger tumor size, favorable tumor biological markers, and dynamic response to pre-LT treatments, and these criteria have displayed comparable performance as the Milan criteria and permitted the selection of more patients for LT.[9-12] In addition, with the rapid development of statistics and artificial intelligence, several prognostic models for predicting HCC recurrence have been constructed.[13-15] The ability to predict tumor recurrence could help guide HCC surveillance strategies after LT. This study reviews the current data on the selection criteria for LT in patients with HCC. Moreover, the latest prognostic models predicting HCC recurrence risk are discussed.

SELECTION CRITERIA FOR LT IN PATIENTS WITH HCC

Criteria based on morphological characteristics

Traditional morphological criteria based on the number and size of tumors were easily accessed through preoperative imaging and regarded as surrogate markers of HCC recurrence after LT (Table 1). Because the Milan criteria restrict the number of patients eligible for LT, several groups achieved comparable post-LT outcomes by expanding the original morphological criteria. Among the most commonly used expanded criteria were those proposed by Yao et al. in 2001, known as the University of California, San Francisco (UCSF) criteria (single tumor ≤6.5 cm in size, up to three tumors ≤4.5 cm in size, total tumor diameter ≤8 cm.[16] Using an expanded tumor size and total tumor diameter, the 5-year RFS rate reached 81% while expanding the number of patients eligible for LT by 5–20% versus the Milan criteria.[9] The UCSF criteria were further validated by the University of California Los Angeles group in a larger cohort of patients, demonstrating a 5-year survival rate of 64% for patients beyond the Milan criteria but within the UCSF criteria.[17] In 2009, Mazzaferro et al.[18] proposed the "up-to-seven criteria" based on the findings in 1,556 patients within 36 LT centers. The criteria illustrated that HCC with a total sum of tumor size and number not exceeding 7, but without microvascular invasion (MVI), could achieve equivalent survival outcomes as the Milan criteria. The 5-year survival rate of 283 patients was 71.2% within the up-to-seven criteria, similar to the rate of 73.3% for those within the Milan criteria. The main limitation of these criteria was the difficulty in obtaining histological features of MVI in the pretransplant setting, which limited its widespread adoption globally.

Apart from tumor diameter and number, the total tumor volume (TTV), first introduced by Toso et al.[19] in 2008, is another morphometric selection criterion adopted by several Canadian groups. The results indicated that patients with TTV within 115 cm^3 had a similar survival rate as those within the Milan criteria (5-year OS rate 74% vs. 79%, P=0.3; 5-year RFS rate 78% vs. 80%, P=0.3). Additionally, the use of TTV significantly increased the number of included recipients compared with both the Milan (28–53% increase) and UCSF criteria (16–26% increase). These results were further validated in patients at centers in Toronto and Colorado.[20]

Although the expansion of morphological features has permitted the identification of more patients with acceptable post-LT outcomes, there are differences in accuracy

Abbreviations:

AFP, alpha-fetoprotein; AUC, area under the curve; CT, computed tomography; DCP, des-gamma-carboxyprothrombin; HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; LDLT, living donor liver transplantation; LRT, locoregional therapy; LT, liver transplantation; MRI, magnetic resonance imaging; MVI, microvascular invasion; OS, overall survival; RFS, recurrence-free survival; SII, systemic immune–inflammation index; TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors; TTV, total tumor volume; UCSF, University of California, San Francisco; ^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography

https://doi.org/10.3350/cmh.2024.0323

in detecting liver lesions because of the great heterogeneity in liver imaging techniques. In addition, increasing numbers of studies have suggested that the traditional tumor number and diameter do not precisely reflect tumor biology, which necessitates the use of other tumor biological markers.[21]

Criteria based on markers of tumor biology

Alpha-fetoprotein (AFP) is among the most commonly adopted serum biomarkers for HCC development and differentiation, and it has been adopted by United Network for Organ Sharing (UNOS) and multiple centers to screen patients on waiting lists.[22,23] Hameed et al.[24] identified an AFP cutoff of 1,000 ng/mL as the independent predictor of vascular invasion and tumor recurrence. Patients with AFP levels lower than 1,000 ng/mL had a 5-year RFS rate of 80.3%, significantly exceeding the rate of 52.7% for patients with elevated AFP levels. Consequently, several criteria have incorporated AFP levels and morphological characteristics to better screen patients. The Hangzhou criteria select patients with HCC for LT based on a tumor diameter smaller than 8 cm or a tumor size exceeding 8 cm but with concurrent AFP serum levels <400 ng/mL and a histological grade of I or II.[25] The 5-year OS rate for patients meeting these criteria was 70.7%, comparable with that among patients meeting the Milan criteria. In 2009, Toso et al.[20] proposed similar criteria combining AFP levels and TTV. Recipients with AFP levels <400 ng/mL and TTV <115 cm^3 experienced significantly better survival after LT. Another selection model was developed by the Liver Transplantation French Study Group based on a large cohort from 1988 to 2001.[26] This model categorized patients according to AFP levels of <100, 100–1,000, and >1,000 ng/mL and assigned different scores to each variable. Patients were considered at high risk of HCC recurrence if the final score exceeded 3 points. This model has replaced the Milan criteria for liver allocation in France and has been validated in various countries,[27-29] confirming its utility in predicting excellent outcomes beyond the Milan criteria. Several other models, including RETREAT, MORAL and Metroticket 2.0, also classified survival risk by incorporating AFP levels and tumor number, size, or grade, and these models outperformed the original Milan criteria (Table 2).[30-33]

The limitations of the aforementioned criteria are attributed to the difficulty in consistently measuring AFP levels. The fluctuation of AFP levels during the waiting interval could lead to inconsistent outcomes. Thus, variations in AFP levels, rather than a cutoff, are considered more accurate for predicting post-LT outcomes. In 2009, Vibert et al.[34] reported that an increase in AFP levels of more than 15 μg/L per month was a negative prognostic factor in waiting recipients. The results were further validated by Lai et al.[35], who recorded superior 5-year outcomes in patients with an AFP change of less than 15 ng/mL per month (5-year OS rate 66.0% vs. 36.7%; 5-year RFS rate 92.3% vs. 53.8%).[29] More recently, Halazun et al.[36] proposed a novel system using dynamic AFP levels to predict RFS. In a study consisting of 1,450 patients, the change in AFP levels between the maximum and final value was identified as an independent prognostic factor. It was demonstrated that patients with persistent AFP levels of <200 ng/mL had the best outcomes. Moreover, patients with the last recorded AFP level of <1,000 ng/mL and a >50% decrease had a comparable prognosis as those with a maximum AFP level of 200–1,000 ng/mL and a decrease to <200 ng/mL.

Table 1. Results and criteria based on morphological characteristics for liver transplantation in patients with HCC

Criterion, study	Year	No. of patients	Parameters	OS (%)	RFS (%)
Milan Mazzaferro et al.[6]	1996	48	Solitary tumor ≤5 cm; or 2–3 tumors ≤3 cm	85.0% at 4 years	92.0% at 4 years
UCSF Yao et al.[16]	2001	70	Solitary tumor ≤6.5 cm; or 2–3 tumors ≤4.5 cm and total diameter ≤8 cm	75.2% at 5 years	NR
Up-to-7 Mazzaferro et al.[18]	2009	1,556	Sum of number of tumors and diameter (cm) of the largest tumor ≤7	71.2% at 5 years	NR
TTV Toso et al.[19]	2008	288	TTV<115 cm^3	74% at 5 years	78% at 5 years

HCC, hepatocellular carcinoma; OS, overall survival; RFS, recurrence-free survival; TTV, total tumor volume; NR, not reported.

Apart from AFP levels, other serum markers reflective of tumor biology have been considered important in patient selection. Des-gamma-carboxyprothrombin (DCP), also known as protein induced by vitamin K absence or antagonist II, is an abnormal prothrombin caused by the absence of vitamin K, and it is expressed by some HCC cells.[37,38] DCP has been widely used in Asian countries to predict outcomes after LT, especially following living donor liver transplantation (LDLT). In a Japanese study, Todo et al.[39] found that patients who were beyond Milan criteria with DCP <100 mAU/mL and AFP <200 ng/mL had a 5-year RFS rate of 83.5% after LDLT.[33] Another large-scale Korean study confirmed that patients with a combined AFP+DCP level of <300 experienced 5-year RFS rates exceeding 50%, even among those with multiple tumors >10 cm in size.[40] Most recently, Norman et al.[41] proposed selection criteria based on AFP-L3 (fraction of AFP bound to Lens culinaris agglutinin) and DCP. A dual-biomarker combination of AFP-L3 ≥15% and DCP ≥7.5 mAU/mL predicted 61.1% of HCC recurrences, which outperformed AFP with C-statistics of 0.81 and 0.86, respectively, compared with 0.74 for AFP alone. The 3-year RFS rate was 43.7% for patients with dual-positive biomarkers, compared with 97.0% for all others. However, DCP levels can be elevated in certain situations other than HCC, such as biliary obstruction and vitamin K deficiency caused by malnutrition. Additionally, DCP levels can be strongly influenced by drugs including rifampicin and warfarin. In addition, the cutoff of DCP remains under debate because of variability in measurement techniques. Considering these limitations, AFP remains the most useful biomarker for predicting the clinical outcomes of patients with HCC post-transplant.

Using the aforementioned biomarkers, the selection of patients with HCC for LT has greatly improved beyond simple morphometrics. Recent developments in downstaging therapy, including multikinase inhibitors and locoregional

Table 2. Results and criteria based on tumor biology for liver transplantation in patients with HCC

Criterion, study	Year	No. of patients	Parameters	OS (%)	RFS (%)
Hangzhou Zheng et al.[25]	2008	195	Tumor ≤8 cm in diameter or >8 cm if associated with AFP serum levels <400 ng/mL and histological grade I-II	70.7% at 5 years	62.4% at 5 years
Toronto DuBay et al.[30]	2011	294	No tumor size or number restriction No systemic symptoms and macro-VI Not poorly differentiated cancer (if beyond MC)	79.0% at 5 years	76.0% at 5 years
AFP Duvoux et al.[26]	2012	972	Score ranged from 0 to 9 using AFP level (≤100 ng/mL, 100–1,000 ng/mL, >1,000 ng/mL), tumor diameter and number	71.7% when score≤2 42.2% when score >2	AFP <100: 16% AFP 100–1,000: 27% AFP >1,000: 53%
RETREAT Mehta et al.[31]	2017	1,062	Score ranged from 0 to 8 using AFP, micro-VI, tumor diameter and number of explants	NR	97.1% when score 0
MORAL Halazun et al.[32]	2017	339	Pre-MORAL: NLR, maximum AFP and tumor size; Post-MORAL: tumor grade, vascular invasion, tumor size and number on pathology	Low risk within Milan: 90% Low risk outside Milan: 80%	Low risk outside Milan: 78% High risk outside Milan: <50%
Metroticket 2.0 Mazzaferro et al.[33]	2018	1,359	1. If AFP <200 ng/mL, sum of number and size ≤7 2. If 200≤AFP<400 ng/mL, sum of number and size ≤5 3. If 400≤AFP<1,000 ng/mL, sum of number and size ≤4	79.7% at 5 years	89.6% at 5 years

HCC, hepatocellular carcinoma; OS, overall survival; RFS, recurrence-free survival; MC, Milan criteria; VI, vascular invasion; NLR, neutrophil-to-lymphocyte ratio; AFP, alpha-fetoprotein; NR, not reported.

https://doi.org/10.3350/cmh.2024.0323

therapy (LRT), have displayed promising effects on advanced HCC during the waiting interval. Therefore, selection criteria based on the response to downstaging treatments with greater accuracy are gaining increasing attention (Fig. 1).

Criteria based on the response to bridging and downstaging treatments

Tumor "bridging" describes treatments for accepted HCC transplant candidates aimed at reducing the risk of waiting list dropout, whereas "downstaging" defines treatments that reduce the tumor burden to meet acceptable criteria and thus achieve expected survival.[42,43] The advantage of both approaches is that they permit dynamic assessments of tumor biology over time. Additionally, a positive response to pre-LT anti-HCC treatments often implies favorable tumor biology, aiding in the selection of suitable candidates and improving post-LT outcomes.[44]

Regarding downstaging treatments, the priority is determining the extent to which we aim to reduce the tumor burden. Many studies have used the Milan criteria as the endpoint of downstaging. In 2015, Yao et al.[45] revealed that patients beyond the Milan criteria who underwent downstaging to within the Milan criteria had similar 5-year OS (77.8% vs. 81%) and RFS rates (90.8% vs. 88%) as patients within the Milan criteria without downstaging. Similar outcomes were demonstrated in other studies.[46,47] However, less than 10% of successfully downstaged patients underwent LT. This might be attributable to discrepancies in the original tumor burden between studies before downstaging. Therefore, the current UNOS policy uses the upper limits of the tumor burden defined by the UCSF group in 2008, including ≤8 cm for one tumor, ≤5 cm each for two or three tumors and sum of the maximal tumor diameters ≤8 cm, and ≤3 cm each for four or five tumors and sum of the maximal tumor diameters ≤8 cm (UCSF downstaging criteria).[48] Using the upper limits of the UCSF group, Sinha et al.[49] recorded a lower dropout rate (25% vs. 54%) and superior survival outcomes (56% vs. 21%) compared with those in no limit group. The Italian Bologna group proposed the criteria of ≤6 cm for one tumor, ≤5 cm each for two tumors, and ≤4 cm each for three to five tumors with a sum of maximal diameters ≤12 cm.[50]

In addition to the original tumor burden and downstaging criteria, the response of HCC to downstaging treatments is the most crucial marker for survival. The modified Response Evaluation Criteria in Solid Tumors represent a method for measuring treatment response,[51] which is divided into several categories: complete response (disappear-

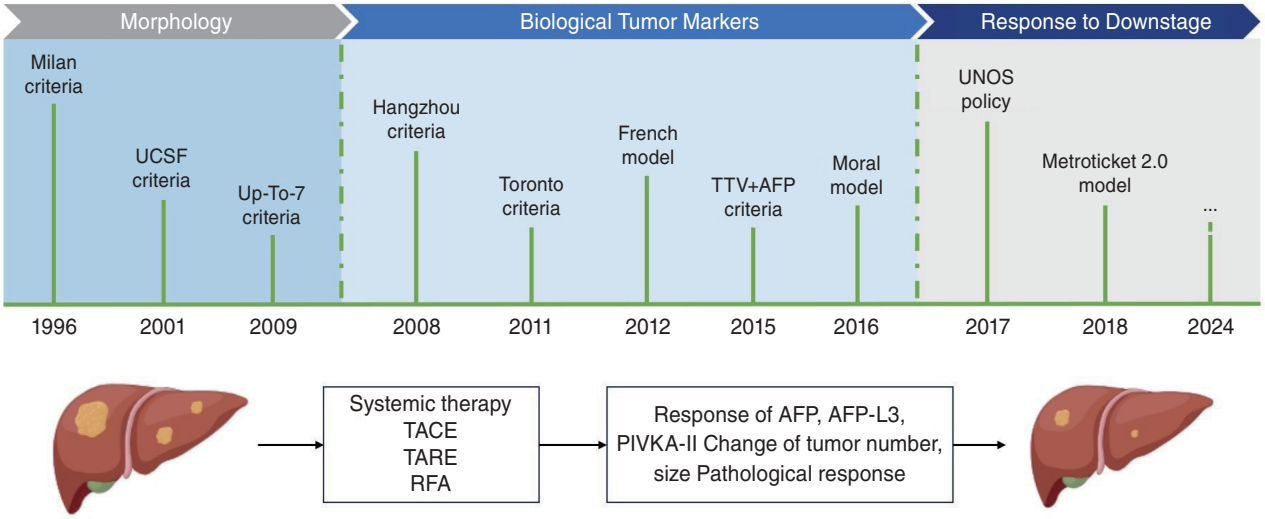


Figure 1. Evolving criteria for the selection of patients with hepatocellular carcinoma for liver transplantation. After the introduction of the Milan criteria in 1996, the subsequently expanded criteria mainly focused on the morphological characteristics of the tumor. Starting in 2008, the addition of biological markers facilitated further expansion of the original Milan criteria. More recently, new concepts for patient selection focused on successful downstaging and the response after locoregional or systemic treatment. UCSF, University of California, San Francisco; TTV, total tumor volume; AFP, alpha-fetoprotein; UNOS, United Network for Organ Sharing; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; RFA, radiofrequency ablation; PIVKA-II, vitamin K absence II.

ance of arterial enhancement in the tumor), partial response (a minimum of 30% reduction in the sum of the diameters of viable tumors versus baseline), and stable disease (neither partial response nor progressive disease). DiNorcia et al.[52] reviewed data from the United States Multicenter HCC Transplant Consortium to evaluate whether complete pathological response following pre-LT LRT affects post-LT outcomes.[45] Their results illustrated that patients with complete response had significantly lower 1-, 3-, and 5-year recurrence rates than those without complete response. Another large-scale European study confirmed that a poor radiological response after bridging treatment represented a strong independent risk factor for post-LT recurrence.[53]

As previously mentioned, the AFP response is another surrogate marker of successful downstaging. Patients with persistent AFP levels >1,000 ng/mL despite anti-HCC treatment before LT achieved 5-year OS and RFS rates of only 49% and 35%, respectively.[54] A significant decrease in AFP from >1,000 ng/mL to <500 ng/mL was associated with a 3-fold reduction in HCC recurrence. Thus, the AFP response has been implemented in the US allocation system. Along with the response to downstaging treatments, the waiting time can also be used to identify tumor aggressiveness and biology. The "ablate and wait" strategy suggests at least 3 months of observation to ensure the absence of tumor progression and success of downstaging. Halazun et al.[55] conducted a large-scale study including more than 6,000 patients from the UNOS database. Patients in long wait-listing regions (median, 7.6 months) were more likely to drop out, resulting in tumor progression. However, the OS rate in long wait-listing regions was significantly better than that in short wait-listing regions (median, 1.6 months; 75% vs. 67%). The results were further validated by Mehta et al.[56], who recorded an increased 3-year survival rate in patients waiting for >9 months than for those waiting for <3 and 3–9 months (92% vs. 79% vs. 73%). To date, the optimal waiting period from downstaging to LT has not been clarified. A minimum observation period of 6 months is mandated by the UNOS policy for recipients with HCC (Table 3).[57]

The treatment options for downstaging represent another important issue. Transarterial chemoembolization (TACE), transarterial radioembolization, and radiofrequency abla-

Table 3. Results and criteria based on the response to downstaging treatments for liver transplantation in patients with HCC

Study	Year	No. of patients	Comparison	OS (%)	RFS (%)
Otto et al.[43]	2006	96	DS vs. No downstage	DS: 80.9% No DS: 51.9%	DS: 94.5% No DS: 35.4%
Ravaioli et al.[50]	2008	177	DS from single tumor 5–6 cm or 2 tumors ≤5 cm or less than 6 tumors ≤4 cm and sum diameter ≤12 cm vs. Milan criteria	DS: 56% Milan criteria: 62.8%	DS: 71% Milan criteria: 71%
Yao et al.[45]	2015	606	DS from T2 to Milan/UNOS vs. T2	DS: 77.8% T2: 81%	DS: 90.8% T2: 88%
Sinha et al.[49]	2019	207	UCSF-DS to Milan vs. AC	UCSF-DS: 78.5% All-comers: 50%	UCSF-DS: 86.1% All-comers: 40%
Mehta et al.[54]	2019	407	Dynamic AFP level post DS	AFP>1,000: 49% AFP=101–499: 67% AFP≤100: 88%	AFP>1000: 35% AFP=101–499: 13.3% AFP≤100: 7.2%
Kardashian et al.[47]	2020	789	DS vs. no DS vs. untreated	NR	DS: 64% Treated, no DS: 61% Untreated: 60%
Assalino et al.[46]	2020	41	DS in macrovascular invasion with AFP < vs. ≥10	AFP<10: 83% AFP≥10: 27%	AFP<10: 72% AFP≥10: 33%
Mehta et al.[56]	2020	3,819	UNOS-DS criteria vs. All-comers DS	Milan criteria: 83.2% UNOS-DS: 79.1% AC-DS: 71.4%	Milan criteria: 95.6% UNOS-DS: 90.8% AC-DS: 89.3%

DS, downstage; HCC, hepatocellular carcinoma; OS, overall survival; RFS, recurrence-free survival; AFP, alpha-fetoprotein; AC, all-comers; NR, not reported.

https://doi.org/10.3350/cmh.2024.0323

tion are the most commonly used LRTs.[58] In addition to LRT, tyrosine kinase inhibitors (TKIs) including sorafenib and lenvatinib have displayed excellent effects as bridging treatments to LT.[59] In 2018, Golse et al.[60] reported a case series of five patients with HCC who received sorafenib as a downstaging therapy before LT. No recurrence was observed after 27 months of follow-up.[60] Another study from France in 2022 found that 62 of 327 patients with HCC were treated with TKIs. Of these patients, 26 underwent LT, and their 5-year RFS and OS rates were 48% and 77%, respectively.[61] Combination therapy with LRT and TKIs has also been investigated. In 2022, a retrospective study of 128 patients with HCC discovered that those who received TACE plus TKIs before LT achieved significantly better 5-year RFS rates than those who underwent TACE alone.[62] Apart from TKIs, immune checkpoint inhibitors (ICIs) have also exerted dramatic antitumor effects and led to prolonged survival in HCC in recent years.[63] Tabrizian et al. reported a case series of nine patients with HCC who received nivolumab and successfully bridged to LT.[64] Surprisingly, there was no tumor recurrence or death at a median of 16 months after LT. Similar results were also reported by several case studies.[65,66] To improve bridging strategy, the integration of ICIs and TKIs was further investigated. Abdelrahim et al. reported a patient who received atezolizumab plus bevacizumab prior to LT, and no recurrence occurred after 12 months of follow-up.[67] Another cohort of seven patients with HCC who received lenvatinib in combination with ICI therapy prior to LT also experienced satisfactory survival outcomes.[68] However, it must be noted that acute rejection after LT is a major concern in the context of ICI treatment. A safe washout period before LT and cautious post-LT immunosuppression strategies are required.[69]

PROGNOSTIC MODELS FOR PATIENTS WITH HCC AFTER LT

Risk scoring systems based on tumor clinicopathological features

Several scoring models combining tumor clinicopathological features have been proposed to predict the risk of HCC recurrence after LT (Fig. 2). In 2000, Iwatsuki et al.[70] proposed a Cox proportional hazards regression-based prognostic scoring system that included the bilobar tumor distribution, maximum tumor size, and vascular invasion.

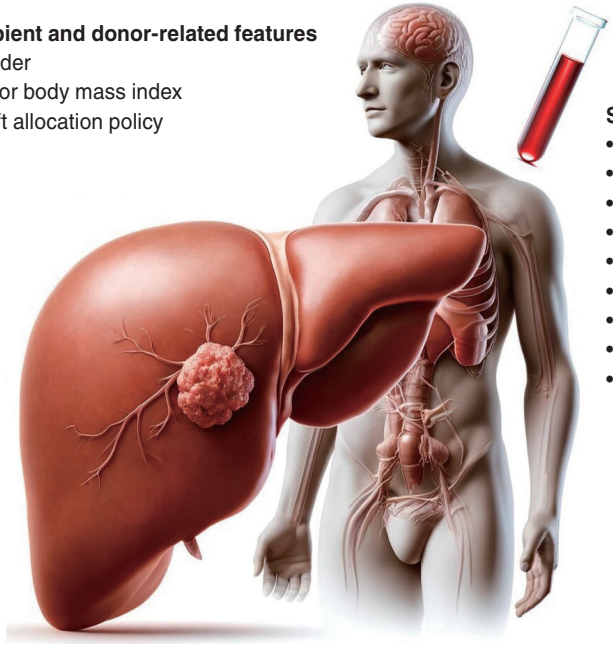


Figure 2. Features used to develop risk scoring systems for predicting the prognosis of patients with hepatocellular carcinoma after liver transplantation. The parameters included recipient features, tumor clinicopathological characteristics, and serological biomarkers.

This scoring system classified patients into five grades and found that higher grades were associated with a lower tumor-free survival rate. In 2008, another study proposed and validated a prognostic score based on three different preoperative variables (maximum tumor size, tumor differentiation, and number of nodules), and this score had better accuracy than the Milan criteria in predicting HCC recurrence after LT.[71] Interestingly, this study revealed that tumor differentiation alone has no significant additive value for predicting HCC recurrence.

Based on its ability to reflect tumor biology and screen patients, the AFP level is also an important parameter predicting tumor recurrence after LT. A Cox score threshold of 0.7 from the AFP model, consisting of the largest tumor size, number of nodules, and $\log_{10}$AFP, was deemed useful in stratifying patients with HCC at higher risk of recurrence after LT (50.6% vs. 8.8%).[26] Another Cox proportional hazards regression-based model consisting of the Child–Pugh score, positive HBV detection time, number of tumors, tumor size, AFP levels, and tumor differentiation grade was proposed, and its sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) were 72.5%, 90.7%, and 0.887, respectively.[72] A Japanese study evaluated the prognostic impact of AFP and DCP, finding that satisfying two or more of the identified criteria (tumor size ≤5 cm for ≤5 tumors, AFP <250 ng/mL, DCP <450 ng/mL) was associated with higher 5-year RFS (96.8% vs. 20.0%) and OS rates (84.0% vs. 20.0%).[73] In addition to the pre-LT AFP level, Ma et al.[74] found that AFP levels 7 days after LT are predictive of HCC recurrence. A model based on tumor size, tumor thrombus, MVI, and 7-day postoperative alanine aminotransferase and AFP levels was validated to predict recurrence with an AUC of 0.732.

Some other parameters have also been incorporated into risk score models. The systemic immune–inflammation index (SII), calculated as absolute platelet count × absolute neutrophil count/absolute lymphocyte count, was reported to be more effective than the platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio in patients with HCC after LT within the Hangzhou criteria.[75] Although a high SII did not significantly distinguish patients at higher risk of recurrence (5-year RFS rate 64.1% vs. 78.4%), it was significantly predictive of worse OS (5-year OS rate 56.1% vs. 82.4%). Wang et al.[76] developed a model including D-dimer and plasma fibrinogen levels (0.91×fibrinogen concentration+0.967×D-dimer

Table 4. Summary on the multivariable-based risk scoring systems based on clinicopathological features

Authors	Parameters	Survival outcomes	Model performance
Iwatsuki et al.[70]	HBsAg, HCV antibody, tumor number, tumor distribution, tumor size, vascular invasion, tumor differentiation, cirrhosis, chemotherapy, surgical margins, lymph node metastasis, distant metastasis	5-year RFS grade 1: 100% 5-year RFS grade 2: 61% 5-year RFS grade 3: 40% 5-year RFS grade 4: 5%	NR
Wang et al.[72]	Child-Pugh score, positive HBV detection time, tumor number, tumor size, AFP, tumor differentiation	5-year OS low risk: 77.1%	AUC=0.887
Shindoh et al.[73]	Tumor size, tumor number, DCP	5-year RFS low risk: 96.8% 5-year RFS high risk: 20.0%	AUC (AFP)=0.88 AUC (DCP)=0.76
Ma et al.[74]	Age, tumor size, thrombus, microvascular invasion, AFP at day 7, ALT at day 7	2-year RFS low risk: 67.8% 2-year RFS high risk: 20.8%	AUC=0.732
Fu et al.[75]	Platelet count, neutrophil count, lymphocyte count	5-year RFS low SII: 64.1% 5-year RFS high SII: 78.4%	AUC=0.632
Wang et al.[76]	Fibrinogen concentration, D-dimer, AFP, Milan criteria, microvascular invasion	NR	AUC=0.764
Kornberg et al.[77]	Albumin, lymphocyte count	5-year RFS low risk: 94.7% 5-year RFS high risk: 43.7%	AUC=0.896
Huang et al.[78]	Albumin-globulin score, skeletal muscle index	5-year RFS grade 1: 82.5% 5-year RFS grade 2: 70.8% 5-year RFS grade 3: 57.9%	AUC=0.700

HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; RFS, recurrence-free survival; NR, not reported; AUC, area under curve; OS, overall survival; DCP, des-gamma-carboxyprothrombin; ALT, alanine aminotransferase; SII, systemic immune-inflammation index.

https://doi.org/10.3350/cmh.2024.0323

concentration+0.585×AFP concentration+1.623×Milan criteria+0.68×MVI−3.159), and the model had satisfactory performance in predicting recurrence (AUC=0.828) and survival (AUC=0.764). Kornberg et al.[77] evaluated the prognostic nutritional index (10×albumin (g/dL)+0.005×lymphocyte count) for predicting HCC recurrence and identified a cutoff of 42 as a threshold for predicting tumor recurrence (AUC=0.896). Huang et al.[78] found that the combination of the preoperative albumin–globulin score and skeletal muscle index achieved predictive accuracy for OS (AUC=0.710) and RFS (AUC=0.700). The summarized results of the multivariable risk scoring systems are presented in Table 4.

Imaging radiomics features

The relationship between glucose metabolism, as evaluated by ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET), and HCC progression has been acknowledged by several studies.[79,80] Lee at al.[81] demonstrated that the ratio of the tumor maximum standardized uptake value to the normal liver tumor maximum standardized uptake value as determined by ^{18}F-FDG PET significantly distinguished patients with a higher risk of recurrence after LT (1-year RFS rate 97% vs. 57%, P<0.001). A study from 16 Japanese centers further confirmed a PET-positive status (increased FDG uptake in the tumor as compared with non-tumor liver tissue) as an independent risk factor for HCC recurrence after LT.[82]

Computed tomography (CT)-based radiomics features, including both non-textural and textural features, were reported to be effective in predicting HCC recurrence after LT.[83] The AUCs of an arterial phase radiomics model for predicting HCC recurrence among patients within and exceeding the Milan criteria were 0.748 and 0.661, respectively. Another integrated study of contrast-enhanced CT-based features, clinical characteristics, and laboratory values demonstrated that a model including peritumoral enhancement, tumor number, tumor size, AFP levels, and the presence of a tumor capsule had good utility (5-year AUC=0.85) for predicting HCC recurrence after LT.[84]

In addition, magnetic resonance imaging (MRI) has also been adopted in prognostic prediction in patients with HCC after LT. Kim et al.[85] found identified the presence of satellite nodules and peritumoral hypointensity in the hepatobiliary phase as independent predictors of HCC recurrence after LT. Specifically, the researchers reported that patients with least one of two MRI features had a 3-year RFS of 27.5%, versus 84.6% for the remaining patients. Another study of 140 cases of pretransplant contrast-enhanced MRI in patients with treatment-naïve HCC found that patients with probable or definitive HCC based on the Liver Imaging Reporting and Data system had a 5-year RFS rate of 36.9%, compared with 95.8% for those with probable or definite malignancy but not specific for HCC.[86] In addition, Chiang et al.[87] revealed that the transverse relaxation rate

Table 5. Summary on the prognostic effects of imaging radiomics features-involved models

Authors	Parameters	Survival outcomes	Model performance
Lee et al.[81]	Tumor maximal standardized uptake value to normal-liver maximum standardized uptake value from ^{18}F-FDG PET	1-year RFS low risk: 97% 1-year RFS high risk: 57%	AUC=0.887
Takada et al.[82]	Increased FDG uptake in the tumor as compared to non-tumor liver tissue, Milan criteria, and AFP	5-year RFS group 1: 94% 5-year RFS group 2: 81% 5-year RFS group 3: 47%	NR
Guo et al.[83]	Radiomics score for CT image in arterial phase, HBsAg, BCLC stage	NR	AUC=0.789
Hoang et al.[84]	Peritumoral enhancement in CT, tumor lesions, tumor size, AFP, and presence of tumor capsule	NR	AUC=0.85
Kim et al.[85]	Presence of hepatobiliary phase satellite nodules and peritumoral hypo-intensity on MRI	3-year RFS low risk: 84.6% 3-year RFS high risk: 27.5%	NR
Lee at al.[86]	Liver Imaging Reporting and Data system category from MRI	5-year RFS low risk: 95.8% 5-year RFS high risk: 36.9%	NR

^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography; RFS, recurrence-free survival; AUC, area under curve; AFP, alpha fetoprotein; NR, not reported; CT, computed tomography; HBsAg, hepatitis B surface antigen; BCLC, Barcelona Clinic Liver Cancer; MRI, magnetic resonance imaging.

https://doi.org/10.3350/cmh.2024.0323

attributable to the characteristics of tissue and field inhomogeneity on blood oxygen level-dependent MRI is significantly associated with liver rejection after liver transplantation (AUC=0.878). The summarized results of the imaging radiomics feature-involved models are presented in Table 5.

Biological marker-based models

In addition to AFP, several other serum biomarkers have been discovered to be closely associated with HCC recurrence after LT (Fig. 3). Fiorentino et al.[88] reported that the MIB-1 proliferation index, E-cadherin level, and nuclear beta-catenin level are effective in identifying patients at a higher risk of HCC recurrence after LT. The presence of any biomarker alone and that of all three biomarkers were associated with recurrence rates of 88% and 99%, respectively. Another study utilized Feulgen staining and semi-automatic image analyses, which automatically calculate the DNA index by comparing the DNA content of the peak tumor cells to that of diploid reference cells. The results found that DNA index ≤1.5 is associated with higher 5- and 10-year survival rates (86% and 80%, respectively) than DNA index >1.5 (27% and 6%, respectively).[89,90]

In addition, a CpG island methylator phenotype based on the P16, CDH1, SOCS1, GSTP1, STK, XAF1, and DAPK1 genes identified patients with HCC and a lower 3-year RFS rate after LT (25% vs. 64%).[91] Campillo et al.[92] identified high expression of angiogenesis and proliferation markers (COX2, VEGF, and VEGF-2) in the cirrhotic liver, but not in the tumor, as predictive of recurrence in patients with HCC and liver cirrhosis after LT. The study evaluated preoperative plasma VEFG levels and indicated that 5-year RFS levels were significantly worse in patients with plasma VEFG levels >44 pg/mL (47.7% vs. 8.7%). In addition, Atanasov et al.[93] revealed that the hepatic infiltration of TIE2-expressing monocytes and $CD68^+$ tumor-associated macrophages was predictive of decreased survival after LT in patients with HCC.

A microRNA (miRNA) microarray was adopted to predict the prognosis of patients with HCC after LT. Liese et al.[94] found that addition of miR-214 and miR-3187 expression to the Milan criteria more effectively stratified patients at higher risk of recurrence after LT (AUC=0.869) than the Milan criteria alone (AUC=0.640). Meanwhile, Ng et al.[95] identi-

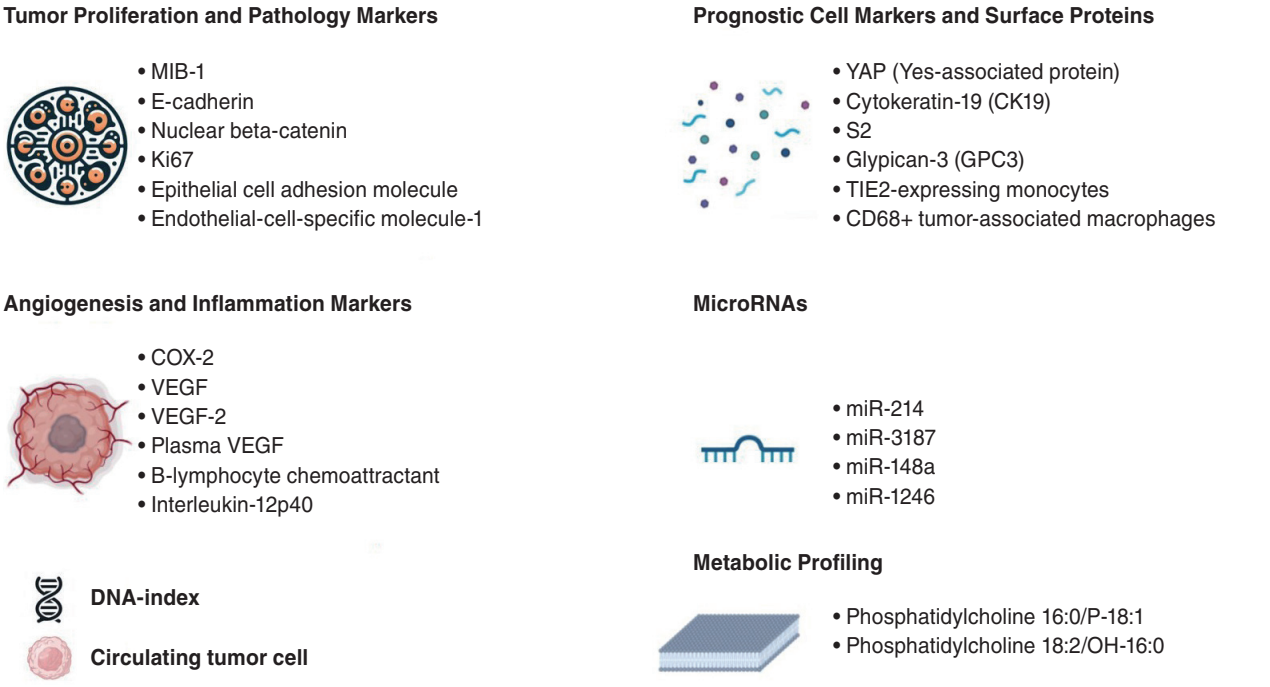


Figure 3. Features of biological marker-based models for predicting the prognosis of patients with hepatocellular carcinoma after liver transplantation. The markers can be divided into tumor proliferation and pathology markers, angiogenesis and inflammatory markers, circulating tumor cells, microRNAs, and metabolic profiling.

https://doi.org/10.3350/cmh.2024.0323

fied circulating miRNAs as predictors of recurrence (miR-148a and miR-1246) and survival (miR-1246) in patients with HCC after LT. Plasma metabolomics profiling identified phosphatidylcholine 16:0/P-18:1 and 18:2/OH-16:0 as independent predictors of HCC recurrence after LT.[96] Wang et al.[97] reported that peripheral blood circulating tumor cell count ≥1/5 mL is predictive of HCC recurrence after LT.

Artificial intelligence-based prognostic models

In 1997, a pilot study first developed fully connected artificial neural network models to predict HCC recurrence after LT based on the lymph node status, margins, vascular invasion, sex, tumor size and number, lobar distribution, age, and the presence of hepatitis B or C virus infection.[98] The mean AUC was 0.971±0.034 in the test set. However, the single-center-based nature and small number of patients (n=178) were cited as limitations. With the rapid development of artificial intelligence, novel models based on machine learning algorithms have been constructed to predict HCC recurrence after LT. Liu et al.[99] developed a deep learning model from pathology images that was trained using a pre-trained U-net. The images were fed into the MobileNetV2 model (a convolutional neural network model), and aggregation was performed using a generalized mean with a sign. The predictive accuracy was significantly higher (0.75) at 12 months after LT than that of American Joint Committee on Cancer staging. Using clinical variables, the US Multicenter HCC Transplant Consortium constructed a random survival forest machine learning model, achieving an AUC of 0.82 for predicting 5-year recurrence.[100] Most recently, Qu et al.[101] established a deep pathomics score for predicting tumor recurrence after LT. The results identified immune cells as the most significant tissue category for predicting post-LT recurrence (hazard ratio 1.907, 95% confidence interval 1.490–2.440).

CONCLUSION

HCC carries a heavy burden of illness globally. To increase the number of patients who can benefit from LT, the criteria for LT have been greatly expanded from the Milan criteria using features ranging from simple morphometrics to tumor biological behavior. Recently, the response to LRT or systemic treatments, combined with dynamic tumor serum markers, has gained acceptance for better patient selection. For post-LT surveillance, a number of prognostic models have been constructed to predict the HCC recurrence risk and guide antitumor treatment strategies. However, room for improvement in accuracy and satisfaction exists for both the current criteria and prognostic models. Future research integrating clinicopathological characteristics, imaging radiomics features, and biological features could be promising for developing better criteria and prognostic models for patients with HCC undergoing LT. In addition, the development of artificial intelligence models with the ability to make individualized decisions is expected to improve the survival outcomes of patients with HCC. The efforts in establishing better criteria and prognostic models could be beneficial in selecting optimal candidates, estimating prognosis, developing surveillance strategies, and eventually improving long-term outcomes in patients with HCC undergoing LT in the clinical setting.

Authors' contributions

Meng Sha, Jun Wang, Jie Cao and Zhi-Hui Zou: Design of the work, write the manuscript; Xiao-ye Qu, Zhi-feng Xi and Chuan Shen: Figure drawing; Ying Tong and Jian-jun Zhang: Data collection; Seogsong Jeong: Critical revision of the article; Qiang Xia: Supervision of design.

Acknowledgements

We thank Medjaden Inc. for scientific editing of this manuscript.

This study was supported by the National Natural Science Foundation of China (81902379), Chenguang Program of Shanghai Education Development Foundation and Shanghai Municipal Education Commission (21CGA20), and Cultivation Foundation of Renji Hospital (RJPY-LX-011).

Conflicts of Interest

The authors have no conflict of interest to declare.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN es-

timates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-249.
2. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet 2022;400:1345-1362.
3. Brown ZJ, Tsilimigras DI, Ruff SM, Mohseni A, Kamel IR, Cloyd JM, et al. Management of hepatocellular carcinoma: a review. JAMA Surg 2023;158:410-420.
4. Terrault NA, Francoz C, Berenguer M, Charlton M, Heimbach J. Liver transplantation 2023: status report, current and future challenges. Clin Gastroenterol Hepatol 2023;21:2150-2166.
5. Serper M, Asrani S, VanWagner L, Reese PP, Kim M, Wolf MS. Redefining success after liver transplantation: from mortality toward function and fulfillment. Liver Transpl 2022;28: 304-313.
6. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-699.
7. Lingiah VA, Niazi M, Olivo R, Paterno F, Guarrera JV, Pyrsopoulos NT. Liver transplantation beyond Milan criteria. J Clin Transl Hepatol 2020;8:69-75.
8. Toniutto P, Fumolo E, Fornasiere E, Bitetto D. Liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a comprehensive review. J Clin Med 2021;10: 3932.
9. Yao FY, Xiao L, Bass NM, Kerlan R, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. Am J Transplant 2007;7:2587-2596.
10. Silva M, Moya A, Berenguer M, Sanjuan F, López-Andujar R, Pareja E, et al. Expanded criteria for liver transplantation in patients with cirrhosis and hepatocellular carcinoma. Liver Transpl 2008;14:1449-1460.
11. Guiteau JJ, Cotton RT, Washburn WK, Harper A, O'Mahony CA, Sebastian A, et al. An early regional experience with expansion of Milan Criteria for liver transplant recipients. Am J Transplant 2010;10:2092-2098.
12. Nagy G, Gerlei Z, Haboub-Sandil A, Görög D, Szabó J, Kóbori L, et al. Optimizing survival for hepatocellular carcinoma after liver transplantation: a single-center report and current perspectives. Transplant Proc 2022;54:2593-2597.
13. Bhat M, Rabindranath M, Chara BS, Simonetto DA. Artificial intelligence, machine learning, and deep learning in liver transplantation. J Hepatol 2023;78:1216-1233.
14. Jamtani I, Lee KW, Choi Y, Choi Y, Lee JM, Han ES, et al. Tailored prediction model of survival after liver transplantation for hepatocellular carcinoma. J Clin Med 2021;10:2869.
15. Kim SJ, Kim JM. Prediction models of hepatocellular carcinoma recurrence after liver transplantation: a comprehensive review. Clin Mol Hepatol 2022;28:739-753.
16. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394-1403.
17. Duffy JP, Vardanian A, Benjamin E, Watson M, Farmer DG, Ghobrial RM, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. Ann Surg 2007;246:502-509; discussion 509-511.
18. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al; Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35-43.
19. Toso C, Trotter J, Wei A, Bigam DL, Shah S, Lancaster J, et al. Total tumor volume predicts risk of recurrence following liver transplantation in patients with hepatocellular carcinoma. Liver Transpl 2008;14:1107-1115.
20. Toso C, Asthana S, Bigam DL, Shapiro AM, Kneteman NM. Reassessing selection criteria prior to liver transplantation for hepatocellular carcinoma utilizing the Scientific Registry of Transplant Recipients database. Hepatology 2009;49:832-838.
21. Amado V, Rodríguez-Perálvarez M, Ferrín G, De la Mata M. Selecting patients with hepatocellular carcinoma for liver transplantation: incorporating tumor biology criteria. J Hepatocell Carcinoma 2018;6:1-10.
22. Özdemir F, Baskiran A. The importance of AFP in liver transplantation for HCC. J Gastrointest Cancer 2020;51:1127-1132.
23. Ruch B, Wagler J, Kumm K, Zhang C, Katariya NN, Garcia-Saenz-de-Sicilia M, et al. Hepatocellular carcinoma, alpha fetoprotein, and liver allocation for transplantation: past, present and future. Curr Oncol 2022;29:7537-7551.
24. Hameed B, Mehta N, Sapisochin G, Roberts JP, Yao FY. Alpha-fetoprotein level > 1000 ng/mL as an exclusion criterion for liver transplantation in patients with hepatocellular carcinoma meeting the Milan criteria. Liver Transpl 2014;20:945-951.
25. Xu X, Lu D, Ling Q, Wei X, Wu J, Zhou L, et al. Liver transplantation for hepatocellular carcinoma beyond the Milan

https://doi.org/10.3350/cmh.2024.0323

criteria. Gut 2016;65:1035-1041.
26. Duvoux C, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, et al; Liver Transplantation French Study Group. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012;143:986-994.e3; quiz e14-e15.
27. Notarpaolo A, Layese R, Magistri P, Gambato M, Colledan M, Magini G, et al. Validation of the AFP model as a predictor of HCC recurrence in patients with viral hepatitis-related cirrhosis who had received a liver transplant for HCC. J Hepatol 2017;66:552-559.
28. Piñero F, Tisi Baña M, de Ataide EC, Hoyos Duque S, Marciano S, Varón A, et al; Latin American Liver Research, Education and Awareness Network (LALREAN). Liver transplantation for hepatocellular carcinoma: evaluation of the alpha-fetoprotein model in a multicenter cohort from Latin America. Liver Int 2016;36:1657-1667.
29. Rhu J, Kim JM, Choi GS, Kwon CHD, Joh JW. Validation of the α-fetoprotein model for hepatocellular carcinoma recurrence after transplantation in an Asian population. Transplantation 2018;102:1316-1322.
30. DuBay D, Sandroussi C, Sandhu L, Cleary S, Guba M, Cattral MS, et al. Liver transplantation for advanced hepatocellular carcinoma using poor tumor differentiation on biopsy as an exclusion criterion. Ann Surg 2011;253:166-172.
31. Mehta N, Heimbach J, Harnois DM, Sapisochin G, Dodge JL, Lee D, et al. Validation of a risk estimation of tumor recurrence after transplant (RETREAT) score for hepatocellular carcinoma recurrence after liver transplant. JAMA Oncol 2017;3:493-500.
32. Halazun KJ, Najjar M, Abdelmessih RM, Samstein B, Griesemer AD, Guarrera JV, et al. Recurrence after liver transplantation for hepatocellular carcinoma: a new MORAL to the story. Ann Surg 2017;265:557-564.
33. Mazzaferro V, Sposito C, Zhou J, Pinna AD, De Carlis L, Fan J, et al. Metroticket 2.0 model for analysis of competing risks of death after liver transplantation for hepatocellular carcinoma. Gastroenterology 2018;154:128-139.
34. Vibert E, Azoulay D, Hoti E, Iacopinelli S, Samuel D, Salloum C, et al. Progression of alphafetoprotein before liver transplantation for hepatocellular carcinoma in cirrhotic patients: a critical factor. Am J Transplant 2010;10:129-137.
35. Lai Q, Inostroza M, Rico Juri JM, Goffette P, Lerut J. Delta-slope of alpha-fetoprotein improves the ability to select liver transplant patients with hepatocellular cancer. HPB (Oxford) 2015;17:1085-1095.
36. Halazun KJ, Tabrizian P, Najjar M, Florman S, Schwartz M, Michelassi F, et al. Is it time to abandon the Milan criteria?: results of a bicoastal US collaboration to redefine hepatocellular carcinoma liver transplantation selection policies. Ann Surg 2018;268:690-699.
37. Kim DY, Toan BN, Tan CK, Hasan I, Setiawan L, Yu ML, et al. Utility of combining PIVKA-II and AFP in the surveillance and monitoring of hepatocellular carcinoma in the Asia-Pacific region. Clin Mol Hepatol 2023;29:277-292.
38. Dong L, Qiu X, Gao F, Wang K, Xu X. Protein induced by vitamin K absence or antagonist II: experience to date and future directions. Biochim Biophys Acta Rev Cancer 2023;1878:189016.
39. Todo S, Furukawa H; Japanese Study Group on Organ Transplantation. Living donor liver transplantation for adult patients with hepatocellular carcinoma: experience in Japan. Ann Surg 2004;240:451-459; discussion 459-461.
40. Lee HW, Song GW, Lee SG, Kim JM, Joh JW, Han DH, et al. Patient selection by tumor markers in liver transplantation for advanced hepatocellular carcinoma. Liver Transpl 2018;24:1243-1251.
41. Norman JS, Li PJ, Kotwani P, Shui AM, Yao F, Mehta N. AFP-L3 and DCP strongly predict early hepatocellular carcinoma recurrence after liver transplantation. J Hepatol 2023;79:1469-1477.
42. Di Martino M, Ferraro D, Pisaniello D, Arenga G, Falaschi F, Terrone A, et al. Bridging therapies for patients with hepatocellular carcinoma awaiting liver transplantation: a systematic review and meta-analysis on intention-to-treat outcomes. J Hepatobiliary Pancreat Sci 2023;30:429-438.
43. Otto G, Herber S, Heise M, Lohse AW, Mönch C, Bittinger F, et al. Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma. Liver Transpl 2006;12:1260-1267.
44. Crocetti L, Bozzi E, Scalise P, Bargellini I, Lorenzoni G, Ghinolfi D, et al. Locoregional treatments for bridging and downstaging HCC to liver transplantation. Cancers (Basel) 2021;13:5558.
45. Yao FY, Mehta N, Flemming J, Dodge J, Hameed B, Fix O, et al. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. Hepatology 2015;61:1968-1977.
46. Assalino M, Terraz S, Grat M, Lai Q, Vachharajani N, Gringeri

E, et al. Liver transplantation for hepatocellular carcinoma after successful treatment of macrovascular invasion - a multicenter retrospective cohort study. Transpl Int 2020;33:567-575.
47. Kardashian A, Florman SS, Haydel B, Ruiz RM, Klintmalm GB, Lee DD, et al. Liver transplantation outcomes in a U.S. multicenter cohort of 789 patients with hepatocellular carcinoma presenting beyond Milan criteria. Hepatology 2020;72: 2014-2028.
48. Yao FY, Kerlan RK Jr, Hirose R, Davern TJ 3rd, Bass NM, Feng S, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. Hepatology 2008;48:819-827.
49. Sinha J, Mehta N, Dodge JL, Poltavskiy E, Roberts J, Yao F. Are there upper limits in tumor burden for down-staging of hepatocellular carcinoma to liver transplant? Analysis of the all-comers protocol. Hepatology 2019;70:1185-1196.
50. Ravaioli M, Grazi GL, Piscaglia F, Trevisani F, Cescon M, Ercolani G, et al. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. Am J Transplant 2008;8:2547-2557.
51. Llovet JM, Lencioni R. mRECIST for HCC: performance and novel refinements. J Hepatol 2020;72:288-306.
52. DiNorcia J, Florman SS, Haydel B, Tabrizian P, Ruiz RM, Klintmalm GB, et al. Pathologic response to pretransplant locoregional therapy is predictive of patient outcome after liver transplantation for hepatocellular carcinoma: analysis from the US multicenter HCC transplant consortium. Ann Surg 2020;271: 616-624.
53. Manzia TM, Lai Q, Iesari S, Perera MTPR, Komuta M, Carvalheiro A, et al. Impact of remnant vital tissue after locoregional treatment and liver transplant in hepatocellular cancer patients, a multicentre cohort study. Transpl Int 2018 Mar 23. doi: 10.1111/tri.13153.
54. Mehta N, Dodge JL, Roberts JP, Hirose R, Yao FY. Alpha-fetoprotein decrease from > 1,000 to < 500 ng/mL in patients with hepatocellular carcinoma leads to improved posttransplant outcomes. Hepatology 2019;69:1193-1205.
55. Halazun KJ, Patzer RE, Rana AA, Verna EC, Griesemer AD, Parsons RF, et al. Standing the test of time: outcomes of a decade of prioritizing patients with hepatocellular carcinoma, results of the UNOS natural geographic experiment. Hepatology 2014;60:1957-1962.
56. Mehta N, Dodge JL, Grab JD, Yao FY. National experience on down-staging of hepatocellular carcinoma before liver transplant: influence of tumor burden, alpha-fetoprotein, and wait time. Hepatology 2020;71:943-954.
57. Roberts JP, Venook A, Kerlan R, Yao F. Hepatocellular carcinoma: ablate and wait versus rapid transplantation. Liver Transpl 2010;16:925-929.
58. Kostakis ID, Dimitrokallis N, Iype S. Bridging locoregional treatment prior to liver transplantation for cirrhotic patients with hepatocellular carcinoma within the Milan criteria: a systematic review and meta-analysis. Ann Gastroenterol 2023; 36:449-458.
59. Mou L, Tian X, Zhou B, Zhan Y, Chen J, Lu Y, et al. Improving outcomes of tyrosine kinase inhibitors in hepatocellular carcinoma: new data and ongoing trials. Front Oncol 2021;11: 752725.
60. Golse N, Radenne S, Rode A, Ducerf C, Mabrut JY, Merle P. Liver transplantation after neoadjuvant sorafenib therapy: preliminary experience and literature review. Exp Clin Transplant 2018;16:227-236.
61. Minoux K, Lassailly G, Ningarhari M, Lubret H, El Amrani M, Canva V, et al. Neo-adjuvant use of sorafenib for hepatocellular carcinoma awaiting liver transplantation. Transpl Int 2022; 35:10569.
62. Abdelrahim M, Victor D, Esmail A, Kodali S, Graviss EA, Nguyen DT, et al. Transarterial chemoembolization (TACE) plus sorafenib compared to TACE alone in transplant recipients with hepatocellular carcinoma: an institution experience. Cancers (Basel) 2022;14:650.
63. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al; IMbrave150 Investigators. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020; 382:1894-1905.
64. Tabrizian P, Florman SS, Schwartz ME. PD-1 inhibitor as bridge therapy to liver transplantation? Am J Transplant 2021; 21:1979-1980.
65. Chen Z, Hong X, Wang T, Guo Y, Huang C, Li M, et al. Prognosis after liver transplantation in patients treated with anti-PD-1 immunotherapy for advanced hepatocellular carcinoma: case series. Ann Palliat Med 2021;10:9354-9361.
66. Schnickel GT, Fabbri K, Hosseini M, Misel M, Berumen J, Parekh J, et al. Liver transplantation for hepatocellular carcinoma following checkpoint inhibitor therapy with nivolumab. Am J Transplant 2022;22:1699-1704.
67. Abdelrahim M, Esmail A, Umoru G, Westhart K, Abudayyeh A, Saharia A, et al. Immunotherapy as a neoadjuvant therapy for a patient with hepatocellular carcinoma in the pretransplant

https://doi.org/10.3350/cmh.2024.0323

setting: a case report. Curr Oncol 2022;29:4267-4273.
68. Qiao ZY, Zhang ZJ, Lv ZC, Tong H, Xi ZF, Wu HX, et al. Neoadjuvant programmed cell death 1 (PD-1) inhibitor treatment in patients with hepatocellular carcinoma before liver transplant: a cohort study and literature review. Front Immunol 2021;12:653437.
69. Kuo FC, Chen CY, Lin NC, Liu C, Hsia CY, Loong CC. Optimizing the safe washout period for liver transplantation following immune checkpoint inhibitors with atezolizumab, nivolumab, or pembrolizumab. Transplant Proc 2023;55:878-883.
70. Iwatsuki S, Dvorchik I, Marsh JW, Madariaga JR, Carr B, Fung JJ, et al. Liver transplantation for hepatocellular carcinoma: a proposal of a prognostic scoring system. J Am Coll Surg 2000;191:389-394.
71. Marelli L, Grasso A, Pleguezuelo M, Martines H, Stigliano R, Dhillon AP, et al. Tumour size and differentiation in predicting recurrence of hepatocellular carcinoma after liver transplantation: external validation of a new prognostic score. Ann Surg Oncol 2008;15:3503-3511.
72. Wang LY, Zheng SS, Xu X, Wang WL, Wu J, Zhang M, et al. A score model for predicting post-liver transplantation survival in HBV cirrhosis-related hepatocellular carcinoma recipients: a single center 5-year experience. Hepatobiliary Pancreat Dis Int 2015;14:43-49.
73. Shindoh J, Sugawara Y, Nagata R, Kaneko J, Tamura S, Aoki T, et al. Evaluation methods for pretransplant oncologic markers and their prognostic impacts in patient undergoing living donor liver transplantation for hepatocellular carcinoma. Transpl Int 2014;27:391-398.
74. Ma E, Li J, Xing H, Li R, Shen C, Zhang Q, et al. Development of a predictive nomogram for early recurrence of hepatocellular carcinoma in patients undergoing liver transplantation. Ann Transl Med 2021;9:468.
75. Fu H, Zheng J, Cai J, Zeng K, Yao J, Chen L, et al. Systemic immune-Inflammation index (SII) is useful to predict survival outcomes in patients after liver transplantation for hepatocellular carcinoma within Hangzhou criteria. Cell Physiol Biochem 2018;47:293-301.
76. Wang C, Liu Z, Chen J, Rao W, Dong S, Yang M, et al. A model integrated fibrinogen and D-dimer for prediction of hepatocellular carcinoma recurrence following liver transplantation: a multicentre study. Am J Transl Res 2022;14:572-581.
77. Kornberg A, Kaschny L, Kornberg J, Friess H. Preoperative prognostic nutritional index may be a strong predictor of hepatocellular carcinoma recurrence following liver transplantation. J Hepatocell Carcinoma 2022;9:649-660.
78. Huang Y, Wang N, Xu L, Wu Y, Li H, Jiang L, et al. Albumin-globulin score combined with skeletal muscle index as a novel prognostic marker for hepatocellular carcinoma patients undergoing liver transplantation. J Clin Med 2023;12:2237.
79. Khan MA, Combs CS, Brunt EM, Lowe VJ, Wolverson MK, Solomon H, et al. Positron emission tomography scanning in the evaluation of hepatocellular carcinoma. J Hepatol 2000;32:792-797.
80. Shiomi S, Nishiguchi S, Ishizu H, Iwata Y, Sasaki N, Tamori A, et al. Usefulness of positron emission tomography with fluorine-18-fluorodeoxyglucose for predicting outcome in patients with hepatocellular carcinoma. Am J Gastroenterol 2001;96:1877-1880.
81. Lee JW, Paeng JC, Kang KW, Kwon HW, Suh KS, Chung JK, et al. Prediction of tumor recurrence by 18F-FDG PET in liver transplantation for hepatocellular carcinoma. J Nucl Med 2009;50:682-687.
82. Takada Y, Kaido T, Shirabe K, Nagano H, Egawa H, Sugawara Y, et al; LTx-PET study group of the Japanese Society of Hepato-Biliary-Pancreatic Surgery and the Japanese Liver Transplantation Society. Significance of preoperative fluorodeoxyglucose-positron emission tomography in prediction of tumor recurrence after liver transplantation for hepatocellular carcinoma patients: a Japanese multicenter study. J Hepatobiliary Pancreat Sci 2017;24:49-57.
83. Guo D, Gu D, Wang H, Wei J, Wang Z, Hao X, et al. Radiomics analysis enables recurrence prediction for hepatocellular carcinoma after liver transplantation. Eur J Radiol 2019;117:33-40.
84. Hoang TPT, Schindler P, Börner N, Masthoff M, Gerwing M, von Beauvais P, et al. Imaging-derived biomarkers integrated with clinical and laboratory values predict recurrence of hepatocellular carcinoma after liver transplantation. J Hepatocell Carcinoma 2023;10:2277-2289.
85. Kim AY, Sinn DH, Jeong WK, Kim YK, Kang TW, Ha SY, et al. Hepatobiliary MRI as novel selection criteria in liver transplantation for hepatocellular carcinoma. J Hepatol 2018;68:1144-1152.
86. Lee S, Kim KW, Jeong WK, Jeong SY, Hwang JA, Choi JS, et al. Liver imaging reporting and data system category on magnetic resonance imaging predicts recurrence of hepato-

cellular carcinoma after liver transplantation within the Milan criteria: a multicenter study. Ann Surg Oncol 2021;28:6782-6789.
87. Chiang HJ, Chou MC, Chuang YH, Li CW, Lin CC, Eng HL, et al. Use of blood oxygen level-dependent magnetic resonance imaging to detect acute cellular rejection post-liver transplantation. Eur Radiol 2022;32:4547-4554. Erratum in: Eur Radiol 2023;33:7355.
88. Fiorentino M, Altimari A, Ravaioli M, Gruppioni E, Gabusi E, Corti B, et al. Predictive value of biological markers for hepatocellular carcinoma patients treated with orthotopic liver transplantation. Clin Cancer Res 2004;10:1789-1795.
89. Hiddemann W, Schumann J, Andreef M, Barlogie B, Herman CJ, Leif RC, et al. Convention on nomenclature for DNA cytometry. Committee on Nomenclature, Society for Analytical Cytology. Cancer Genet Cytogenet 1984;13:181-183.
90. Jonas S, Al-Abadi H, Benckert C, Thelen A, Hippler-Benscheid M, Saribeyoglu K, et al. Prognostic significance of the DNA-index in liver transplantation for hepatocellular carcinoma in cirrhosis. Ann Surg 2009;250:1008-1013.
91. Wu LM, Zhang F, Zhou L, Yang Z, Xie HY, Zheng SS. Predictive value of CpG island methylator phenotype for tumor recurrence in hepatitis B virus-associated hepatocellular carcinoma following liver transplantation. BMC Cancer 2010;10:399.
92. Campillo A, Solanas E, Morandeira MJ, Castiella T, Lorente S, Garcia-Gil FA, et al. Angiogenesis and proliferation markers in adjacent cirrhotic tissue could predict hepatocellular carcinoma outcome after liver transplantation. Eur J Gastroenterol Hepatol 2014;26:871-879.
93. Atanasov G, Dino K, Schierle K, Dietel C, Aust G, Pratschke J, et al. Recipient hepatic tumor-associated immunologic infiltrates predict outcomes after liver transplantation for hepatocellular carcinoma. Ann Transplant 2020;25:e919414.
94. Liese J, Peveling-Oberhag J, Doering C, Schnitzbauer AA, Herrmann E, Zangos S, et al. A possible role of microRNAs as predictive markers for the recurrence of hepatocellular carcinoma after liver transplantation. Transpl Int 2016;29:369-380.
95. Ng KT, Lo CM, Wong N, Li CX, Qi X, Liu XB, et al. Early-phase circulating miRNAs predict tumor recurrence and survival of hepatocellular carcinoma patients after liver transplantation. Oncotarget 2016;7:19824-19839.
96. Lu D, Yang F, Lin Z, Zhuo J, Liu P, Cen B, et al. A prognostic fingerprint in liver transplantation for hepatocellular carcinoma based on plasma metabolomics profiling. Eur J Surg Oncol 2019;45:2347-2352.
97. Wang PX, Xu Y, Sun YF, Cheng JW, Zhou KQ, Wu SY, et al. Detection of circulating tumour cells enables early recurrence prediction in hepatocellular carcinoma patients undergoing liver transplantation. Liver Int 2021;41:562-573.
98. Marsh JW, Dvorchik I, Subotin M, Balan V, Rakela J, Popechitelev EP, et al. The prediction of risk of recurrence and time to recurrence of hepatocellular carcinoma after orthotopic liver transplantation: a pilot study. Hepatology 1997;26:444-450.
99. Liu Z, Liu Y, Zhang W, Hong Y, Meng J, Wang J, et al. Deep learning for prediction of hepatocellular carcinoma recurrence after resection or liver transplantation: a discovery and validation study. Hepatol Int 2022;16:577-589.
100. Tran BV, Moris D, Markovic D, Zaribafzadeh H, Henao R, Lai Q, et al. Development and validation of a REcurrent Liver cAncer Prediction ScorE (RELAPSE) following liver transplantation in patients with hepatocellular carcinoma: analysis of the US Multicenter HCC Transplant Consortium. Liver Transpl 2023;29:683-697.
101. Qu WF, Tian MX, Lu HW, Zhou YF, Liu WR, Tang Z, et al. Development of a deep pathomics score for predicting hepatocellular carcinoma recurrence after liver transplantation. Hepatol Int 2023;17:927-941.

https://doi.org/10.3350/cmh.2024.0323