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PRE-TRANSPLANT ASSESSMENT OF THE HCC RECURRENCE RISK

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Summary

Liver transplantation (LT) remains the most effective curative treatment for hepatocellular carcinoma (HCC), as it removes both the tumor and the underlying liver disease. However, post-transplant recurrence continues to pose a significant clinical challenge, affecting approximately 20% of recipients and leading to poor outcomes. Traditional selection criteria, such as the Milan criteria, have improved patient outcomes but fail to fully capture individual recurrence risks. Advances in pre-transplant risk assessment now integrate tumor biology, molecular markers, and imaging-based features to enhance candidate selection and predict recurrence more accurately. Serum biomarkers, including alpha-fetoprotein (AFP) and des – carboxy prothrombin (DCP), have emerged as significant predictors of aggressive tumor behavior, while genomic and transcriptomic profiling offer novel insights into tumor biology. Advanced imaging techniques such as radiomics and artificial intelligence-driven models further refine risk stratification by identifying microvascular invasion and other high-risk features. The incorporation of scoring systems like RETREAT and Metroticket 2.0 enhances individualized risk prediction, optimizing transplant decision-making. Additionally, systemic inflammation and immune microenvironment factors, including neutrophil-to-lymphocyte ratio and tumor-infiltrating macrophages, are increasingly recognized as contributors to recurrence. Despite advancements, challenges remain in integrating dynamic biomarkers and treatment response evaluations into standardized pre-transplant protocols. Future research should focus on validating predictive models, incorporating liquid biopsy techniques, and refining artificial intelligence applications to achieve personalized risk assessment. Ultimately, a comprehensive, multi-modal approach to risk stratification is essential to minimize recurrence, improve post-LT surveillance, and enhance long-term outcomes for HCC patients undergoing liver transplantation.

Key words: liver transplantation, hepatocellular carcinoma, Milan criteria, living donor liver transplantation, microvascular invasion

Abbreviations

LT: liver transplantation
HCC: hepatocellular carcinoma

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MC: Milan criteria
LDLT: living donor liver transplantation
MVI: microvascular invasion

INTRODUCTION

As liver transplantation (LT) for hepatocellular carcinoma (HCC) has become more prevalent, the need for refined risk assessment in transplant decision-making has grown, emphasizing tumor biology, pre-transplant recipient factors, and donor characteristics that influence survival and recurrence. Traditional eligibility criteria provided a binary classification but often failed to capture individualized recurrence risks. However, as our understanding of HCC biology has evolved, it has become evident that tumor burden alone does not fully capture the complexity of recurrence risk [1].

Importance of pre-transplant risk assessment in candidate selection

HCC accounts for 90% of primary liver cancer worldwide, presenting as the second most frequent cause of cancer related death. LT [2-4] is considered the most effective curative treatment, as it removes both the tumor and the diseased liver. However, its efficacy is limited by the risk of tumor recurrence, which results in rapid death and graft loss in patients who are not selected appropriately, making LT futile. Various prognostic models have also been developed and recurrence risk has been accurately predicted but recurrence still occurs in 20% of recipients transplanted for HCC and is generally associated with poor outcomes [5-7]. Therefore, pre-transplant risk assessment is essential to optimize liver transplantation outcomes in HCC (Fig. 1).

Overview of current transplant criteria and limitation in predicting recurrence

The morphological characteristics of HCC, such as the number of nodules and their size, were adopted to develop the Milan Criteria (MC), proposed in 1996 by Mazzaferro et al. [8]. Criteria include single tumor diameter ⩽ 5 cm or up to 3 nodules with the diameter of each tumor ⩽ 3 cm, without vascular invasion and extrahepatic metastasis [8]. After LT, the 5-y overall survival (OS) and recurrence-free survival (RFS) of HCC patients within MC were 85% and 92%, respectively, while outside MC were only 50% and 59%, respectively. Thus, considering only the morphologic characteristics of the tumor(s), in 2001, Yao et al. [9] from the University of California, San Francisco, proposed the UCSF standard to expand the MC. The criteria included a single tumor diameter of ⩽ 6.5 cm, or up to 3 nodules with a maximum diameter of ⩽ 4.5 cm and a total tumor diameter of ⩽ 8.5 cm, with a 5-y OS of 75.2%. The introduction of the UCSF standard means that more patients will be able to access LT opportunity, maintaining a high survival rate after LT [9]. The above MC and UCSF criteria are based on the results of European and American cohort studies. Meanwhile, in Asia, Japan and South Korea [10,11] were introduced specific criteria for living donor liver transplantation (LDLT) [12], including the 5–5 rule (2007) and the Asian Medical Center (AMC) criteria (2008). The 5–5 rule allows up to 5 tumors, each ⩽ 5 cm, with 5-y OS and RFS rates of 75% and 90%, respectively. The AMC criteria expand eligibility further, permitting up to 6 tumors ⩽ 5 cm without MVI, achieving a 5-y OS of 76%. Recognizing the limitations of strict morphological selection, Mazzaferro et al. (2009) [13] proposed the up-to-7 criteria, defined as the sum of tumor number and the largest tumor diameter being ⩽ 7 cm, with a 5-y OS of 71.2%. However, as radiological assessments cannot always detect microvascular invasion or extrahepatic metastases, research has increasingly focused on integrating serological markers to refine prognostic predictions and optimize LT candidate selection.

Impact of HCC recurrence on post-transplant outcomes

Recurrent HCC should be categorized as early (within 2 years from LT) or late-onset, as this is considered the most important factor for long-term survival [13]. Early recurrence is associated with a poor prognosis and is likely due to pre-existing or undetected tumor cells at the time of transplantation [14,15]. Some investigators suggest that neo-oncogenesis could be responsible for late hepatic recurrences, especially in patients with untreated viral infections and recurrent cirrhosis [16,17]. However, with current antiviral therapies this is a less likely scenario. Aside from an early recurrence, the most significant adverse factors for survival are not being amenable to curative-intent treatments and an AFP level greater than 100 ng/mL at the time of recurrence [18]. Currently, there are no established consensus guidelines addressing the management of HCC recurrence after OLT. Treatment options are potentially curative interventions (surgery/ablation), loco-regional treatments (LRTs) and systemic therapies, which are not mutually exclusive, but a combination of all 3 may be employed depending on the clinical scenario.

BIOLOGICAL AND MOLECULAR RISK FACTORS FOR HCC RECURRENCE

Understanding the biological and molecular risk factors associated with recurrence is essential for refining patient selection criteria, improving surveillance, and developing targeted interventions. Additionally, histopathological factors, including microvascular invasion and tumor

differentiation, play a crucial role in recurrence dynamics. Histologically, differentiation of HCC is graded using the Edmondson-Steiner system, ranging from well-differentiated (grade I) to poorly differentiated (grade IV), based on cellular architecture, nuclear atypia, and mitotic activity. Microvascular invasion (MVI), a key prognostic factor, is defined by tumor cells in small vessels (portal or hepatic venules) near the tumor and is classified as minor (≤ 5 invaded vessels, localized) or major (> 5 invaded vessels, more widespread), impacting recurrence and survival after resection or transplantation. HCC with MVI is more aggressive, often infiltrating the tumor capsule and lymph nodes, leading to irregular margins and metastases [19]. MVI correlates with higher recurrence rates after LT and poorer survival [20,21]. Beyond MVI, histological grade further reflects tumor invasiveness and recurrence risk post-LT. However, the diagnosis of HCC in cirrhotic patients is primarily based on radiological criteria according to current guidelines, with liver biopsy reserved for cases with atypical imaging and information on MVI is often unavailable before transplantation. Although not routinely performed, histological analysis can provide valuable insights into tumor grading. In 2004, Cillo et al. [22] reported that patients with moderately to well-differentiated HCC at pre-LT biopsy had a favorable 5-year survival rate of 75% and a recurrence-free survival rate of 92%, despite approximately one-third of them failing to meet the Milan criteria at explanted liver examination. To increase the prognostic accuracy of the predictive models of HCC recurrence based exclusively on morphological data, some authors explored using the histological characteristics of HCC obtained by nodule biopsy performed before LT [21]. With respect to MVI, Shah et al. evaluated 155 patients with confirmed HCC after LT that satisfied the Milan criteria, then assessed the presence of MVI via pathological analysis, founding that MVI+ was significantly associated with both the number and size of the nodules and, more importantly, 68% of patients who developed HCC recurrence were positive for MVI [23]. AFP is a surrogate marker of HCC differentiation and vascular invasion [24,25] so, pre-transplant AFP serum levels have been proposed for identifying patients at high risk of HCC recurrence [26]. While AFP is a simple and effective predictor of recurrence, there is no consensus on the precise threshold values that best discriminate risk [27]. The "Toronto criteria [28]" were derived from a general assumption that acceptable survival rates in LT for HCC can be achieved for any size or number of HCC, provided that: imaging studies ruled out vascular invasion, the HCC was confined to the liver, and the HCC was not poorly differentiated on biopsy. The authors demonstrated that by applying these criteria, the only pre-transplant variable associated with 5-year disease-free survival was an AFP serum level value > 400 IU/mL at the time of transplant [28]. The relative simplicity

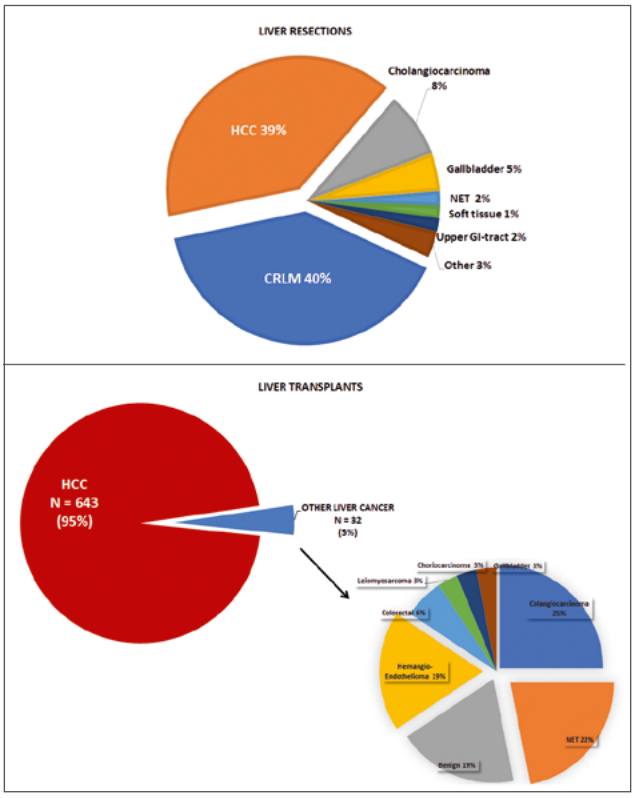


Figure 1. Hepatic surgery on oncologic patients at ISMETT (Palermo, Italy) between 1999 and 2025. 675 liver transplants were performed in adult oncologic patients out of 1829 liver transplants overall. 1426 liver resections were performed in adult oncologic patients out of 1915 total liver resections in adult patients.

of calculating the size and number of nodules in addition to AFP serum levels as surrogate biological markers of the tumor, make these models suitable for extensive and standardized use. An important innovation of these models is their possibility of being used "dynamically", to evaluate the evolution of the tumor in the patient before the transplant. This implies that these models could be used in addition with the response to neo-adjuvant treatments as the reference criteria for defining transplant feasibility in patients with HCC. Elevated DCP levels in HCC patients are correlated with tumor aggressiveness [29], including intrahepatic metastases, capsule infiltration, and portal vein invasion. Furthermore, HCC cases with normal AFP levels but increased DCP levels tend to exhibit lower differentiation and a higher incidence of MVI [30]. Due to these associations, DCP has been proposed as a stronger predictor of HCC recurrence after LT than AFP [31]. Two Japanese research groups [32,33] have incorporated DCP levels into their LDLT selection criteria, alongside tumor size and nodule count. The Kyoto criteria allow for LT in patients with up to 10 HCC nodules, each ≤ 5

cm in diameter, provided that DCP serum levels remain ≤ 400 mAU/mL. Notably, patients who exceeded the MC but met the Kyoto criteria showed HCC recurrence rates comparable to those within the Milan criteria, suggesting that incorporating DCP may help refine LT eligibility without compromising outcomes. Several studies have explored the role of molecular biomarkers in predicting HCC recurrence after liver LT [34]. Among DNA alterations and mutations detectable in liver tissue, the presence of TP53 mutations, high fractional allelic loss, significant hypomethylation of eight tumor suppressor genes, and the absence of CTNNB1 mutations have been identified as markers of a molecular subclass of aggressive HCC [35]. In a study of 132 liver transplant recipients with HCC beyond the Milan criteria, Miltiadous et al. [36] demonstrated that the S2 molecular subclass and progenitor cell markers (CK19 signature) were independent predictors of overall survival and post-LT HCC recurrence, respectively.
One study proposed a prognostic score combining the expression levels of miR-214 and miR-3187 in liver tissue with the Milan criteria, significantly improving recurrence prediction compared to the Milan criteria alone [37]. Nakano et al. [38] demonstrated that circulating exosomal miR-92b could serve as a predictor of post-LT HCC recurrence, but we have to consider the low sensitivity and lack of reproducibility across different technological platforms.

IMAGING-BASED RISK ASSESSMENT

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and computed tomography (CT) are pivotal in the pre-transplant assessment of HCC, particularly in detecting and characterizing liver lesions, assessing tumor size, number, vascular invasion, and extrahepatic spread, factors integral to determining transplant eligibility and the risk of post-transplant recurrence. The Liver Imaging Reporting and Data System (LI-RADS) standardizes the interpretation of liver imaging in patients at risk for HCC [39]. On the other hands, radiomics, combined with artificial intelligence (AI), has emerged as a promising approach for risk stratification in HCC. Particularly, radiomics facilitates the extraction of detailed imaging features that, when analyzed using AI, can improve the accuracy of HCC diagnosis and provide insights into tumor behavior and patient outcomes [40]. Integrating radiomics with clinical data has led to the development of predictive models for early recurrence of HCC post-surgery [41]. Conversely, the treatment response prediction might be influenced because of AI-driven radiomics models have been utilized to predict responses to various HCC treatments, aiding in personalized therapy decisions [42]. In the pre-transplant assessment of HCC, identifying MVI and satellite nodules is crucial, as both are significant predictors of post-transplant recurrence, even considering patients who met the MC. This finding underscores the importance of thorough pre-transplant imaging to detect such nodules, ensuring better risk stratification and patient selection [43,44]. Nevertheless, it is important to differentiate between tumor thrombus and bland thrombus, as the former significantly impacts treatment decisions and prognosis [45]. Positron Emission Tomography/Computed Tomography (PET/CT) utilizing ^18F-fluorodeoxyglucose (^18F-FDG PET/TC) may help evaluate metabolic parameters and tumor aggressiveness. In particular, Metabolic Tumor Volume (MTV) represents the volume of tumor tissue with elevated ^18F-FDG uptake. Larger MTVs have been linked to poorer outcomes after transplantation. It's been demonstrated that volumetric and metabolic activity indices from ^18F-FDG PET are effective predictors of post-transplantation HCC recurrence. These indices should be considered alongside clinicopathologic factors in selecting liver transplantation candidates [46].

RISK STRATIFICATION MODELS AND SCORING SYSTEMS

Risk stratification models and scoring systems are crucial in managing HCC patients as they help predict disease prognosis, guide treatment decisions, and optimize patient outcomes. Common scoring systems, such as the Barcelona Clinic Liver Cancer (BCLC) staging, Child-Pugh score, and ALBI grade, provide valuable insights into liver function, tumor burden, and treatment eligibility. AFP-based models have become integral in assessing the risk of HCC recurrence in patients undergoing liver transplantation. These models enhance traditional selection criteria by incorporating tumor biomarkers, offering a more nuanced evaluation of tumor biology and aggressiveness. The French AFP Model was developed to refine candidate selection beyond the Milan Criteria, incorporating tumor size, number of nodules and AFP Level and is particularly used in patients with viral hepatitis-related cirrhosis undergoing LT [24]. Each parameter is assigned a score, and the cumulative score determines transplant eligibility. A lower total score correlates with reduced recurrence risk post-transplantation [24]. The Model of Recurrence After Liver Transplantation (MoRAL) Score integrates AFP levels and protein induced by vitamin K absence or antagonist-II (PIVKA-II) to predict HCC recurrence risk [47]. Higher MoRAL scores are associated with increased recurrence risk. Studies have demonstrated that the MoRAL score provides a simple, highly accurate tool for predicting recurrence and risk stratification both pre- and post-operatively, outperforming traditional criteria. Composite models that integrate radiological and biological parameters are the Metroticket 2.0 [48] and RETREAT scores [49].

The Metroticket 2.0 model predicts HCC-specific survival post-liver transplantation by incorporating the sum of the number of tumors and their maximum diameter in centimeters and serum AFP concentration, expressed as log10 of the AFP value [48]. This model was developed through a competing-risk regression analysis of 1,018 patients who underwent liver transplantation for HCC. The findings indicated that both the combined tumor number and size, along with the log10 AFP level, were significantly associated with HCC-specific mortality. For instance, to achieve a 70% chance of HCC-specific survival five years post-transplant, patients with an AFP level below 200 ng/mL should have a combined tumor number and size not exceeding 7. The Metroticket 2.0 model demonstrated superior predictive accuracy compared to traditional criteria, such as MC and UCSF criteria. The Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score is a prognostic tool that estimates the risk of HCC recurrence following liver transplantation by integrating microvascular invasion (determined from the explanted liver), AFP level at liver transplantation, and the sum of largest viable tumor diameter and number of viable tumors (histologic examination) [49]. The RETREAT score ranges from 0 to 5 or higher, with higher scores indicating an increased risk of post-transplant HCC recurrence. This model has been validated in multiple studies, demonstrating its effectiveness in stratifying patients' recurrence risk and aiding in tailoring post-transplant surveillance and management strategies [49,50].

Recent advancements have led to the development of both nomograms and machine learning algorithms to enhance personalized risk prediction in pre-transplant assessments. Nomograms are graphical tools that provide a statistical prognostic model to predict clinical events. A study by Zhang et al. [51] developed nomograms to predict 5-year overall survival (OS) and early recurrence in HCC patients post-curative resection. The models incorporated factors such as BCLC stage, tumor margin characteristics, tumor size, microvascular invasion, age, aspartate aminotransferase levels, and differentiation status. The nomograms demonstrated good predictive performance, with concordance indices (C-index) of 0.787 in the training cohort and 0.711 in the testing cohort, suggesting their potential utility in clinical decision-making. Machine learning (ML) techniques have been increasingly applied to predict HCC recurrence. For instance, a study by Kucukkaya et al. [52] employed convolutional neural networks (CNNs) to analyze pre-treatment magnetic resonance imaging (MRI) data, aiming to predict HCC recurrence in patients with early-stage HCC. The model demonstrated promising performance, with area under the receiver operating characteristic curve (AUROC) values ranging from 0.71 to 0.85 across different time intervals, indicating its potential in aiding pre-transplant assessments. Additionally, Zeng et al. developed a machine learning-based model to predict early recurrence in HCC patients after curative resection [53]. The random survival forests (RSF) model incorporated variables such as tumor size, vascular invasion, tumor multiplicity, and alpha-fetoprotein levels. The RSF model outperformed traditional models, demonstrating superior predictive performance and the ability to stratify patients into different risk groups, thereby aiding in personalized patient management [53]. These advancements in nomograms and machine learning algorithms offer valuable tools for personalized risk prediction in pre-transplant assessments of HCC recurrence, potentially leading to improved patient selection and outcomes.

ROLE OF SYSTEMIC INFLAMMATION AND IMMUNE MICROENVIRONMENT IN RECURRENCE

HCC recurrence following LT is influenced by a complex interplay of tumor biology, immune responses, and systemic inflammation [54]. While traditional risk factors such as tumor size, number, and vascular invasion remain key prognosticators, emerging evidence highlights the role of the immune microenvironment and systemic inflammatory markers in modulating recurrence risk. The liver is an immunologically unique organ with a tolerogenic microenvironment, making it particularly susceptible to immune evasion mechanisms exploited by HCC cells [55]. Furthermore, post-transplant immunosuppressive therapy alters immune surveillance, further impacting recurrence dynamics. Understanding the interplay between systemic inflammation and immune responses is crucial for improving post-transplant surveillance and therapeutic interventions [55]. One of the most important factors within the microenvironment, are tumor-associated macrophages (TAMs). It is suggested that they could be used as prognostic or predictive factors [55]. Several studies have suggested that CD68 expression has negative prognostic value [56], even if recently published meta-analysis showed that it's not associated with patients' prognosis [57,58]. In the era of immunotherapy, it is important to highlight that a recently published study indicated that CD68 M1 TAMs were associated with the induction of programmed death-ligand 1 (PD-L1) in HCC cells, which suggested their pro-tumor role [59]. The inflammatory state of body has an important impact on the prognosis of malignant tumors. Studies have shown that there is a correlation between high NLR levels before treatment and poor prognosis. NLR is gradually used as a prognostic indicator for recurrence and survival of HCC patients after LT [58]. Duda et al. [60] retrospectively evaluated circulating biomarkers of angiogenesis and inflammation in a cohort of HCC patients

treated with LR therapy or LT, analyzed their correlation with prognosis, and found that survival outcomes after LR or LT were differentially associated with angiogenic and inflammatory biomarkers. Sun et al. [61] detected 40 inflammatory cytokines in the serum of HCC patients before LT, and established a Pretransplant Serum inflammatory Cytokine-associated Risk Assessment Model (pre-SCRAM). The results showed that the levels of B-lymphocyte chemoattractant (BLC) and interleukin-12p40 (IL-12p40) in serum before transplantation were significantly correlated with the prognosis of HCC patients. The addition of cytokines to the model can optimize HCC recurrence risk assessment models that exceed the MC or AFP models and can maximize the survival benefits of patients. HCC typically arises from chronic liver disease, including hepatitis B (HBV), hepatitis C (HCV), alcohol-related liver disease, and metabolic dysfunction-associated steatotic liver disease (MASLD). Chronic inflammation is a key cancer hallmark, contributing to genomic instability, tumor proliferation, and immune evasion [62]. The tumor immune landscape significantly impacts disease progression and response to immunotherapy. HCC tumors can be classified into three immune phenotypes based on immune cell infiltration and positioning within the tumor microenvironment (TME), which influence their responsiveness to treatment [63]. From more responsive to less responsive: Immune-Inflamed (Hot Tumors), Immune-Excluded and Immune-Desert (Cold Tumors) [64].

INTEGRATION OF RISK ASSESSMENT IN TRANSPLANT DECISION-MAKING

The Metroticket model, first introduced in 2013 and updated in 2018, incorporates both static factors (tumor size and number) and dynamic biological markers, as explicated before, to provide a more individualized prognosis, aligning with the "two-hit hypothesis", which acknowledges that both tumor burden and underlying liver function significantly influence post-LT outcomes [48]. Given the multifactorial nature of HCC recurrence, recent approaches have incorporated additional biological, radiological, and pre-transplant treatment response factors to enhance risk stratification. Despite improved selection criteria, recurrence rates following LT remain a persistent challenge, ranging between 8% and 16%, with a median time to recurrence of 15-23 months. Even patients meeting Milan criteria carry an estimated 10%–15% recurrence risk within five years, highlighting the need for more precise predictive models [51-53]. Several prognostic tools, such as the UCLA Nomogram, RETREAT score, and post-MORAL model, have been developed to refine recurrence predictions and improve patient monitoring post-LT. The RETREAT score, introduced by Mehta et al. in 2017 [49], focuses on Milan criteria-compliant patients and incorporates microvascular invasion, AFP at LT, and the sum of viable tumor size plus number to stratify recurrence risk, ranging from < 3% for a score of 0 to > 75% for scores of 5 or higher. However, RETREAT's limitation lies in its restriction to Milan criteria patients, excluding a broader range of transplant candidates. To address this gap, the RELAPSE score, proposed by Tran et al. in 2023, offers a more comprehensive approach by including all HCC patients receiving LT, without upfront radiological size restrictions [65]. Analyzing data from the US Multicenter HCC Transplant Consortium (UMHTC) database, this model evaluates key pre- and post-transplant factors such as waitlist time, pre-LT AFP response, immediate pre-LT AFP, neutrophil-lymphocyte ratio (NLR), tumor differentiation, and vascular invasion. Ultimately, vascular invasion, tumor diameter, AFP max, and the number of LRT were identified as the strongest predictors of recurrence. Patients with vascular invasion and a tumor diameter > 3 cm exhibited a 49% probability of recurrence within five years, whereas those without vascular invasion, AFP max ⩽ 203.3, tumor diameter < 3.8 cm, and undergoing < 2 or > 2 LRT had significantly better outcomes, with 91%-96% five-year recurrence-free survival. Beyond recurrence risk, OS prognostic factors such as vascular invasion, tumor diameter, hepatitis C cirrhosis etiology, NLR, and age have been identified as key determinants. For instance, patients without vascular invasion, hepatitis C cirrhosis, and an NLR ⩽4.5 demonstrated five-year OS rates between 78% and 85%, whereas those with hepatitis C and aged < 58.2 years had OS rates of 71%-76%, dropping to 67% in older patients. Higher-risk patients, particularly those with vascular invasion and a tumor diameter > 2.8 cm, had significantly poorer five-year OS outcomes of 65% and 47%, respectively, emphasizing the necessity of distinguishing patient risk categories based on these critical factors. Integrating these refined risk assessment models into transplant decision-making has direct implications for organ allocation policies, ensuring that LT is offered to those with the greatest potential for long-term survival while minimizing futile transplants in high-risk individuals. Ethical considerations play a crucial role in this process, as balancing fairness with utility remains a fundamental challenge. Expanding eligibility criteria must be weighed against the need to maintain acceptable survival outcomes, particularly given the ongoing scarcity of donor organs. Ultimately, these advancements in risk stratification represent a continuous effort to refine patient selection, personalize post-LT surveillance, and optimize transplant outcomes, reflecting a broader commitment to evidence-based, ethically sound decision-making in liver transplantation for HCC [66-68].

FUTURE DIRECTIONS AND UNMET NEEDS

The field of liver transplantation has undergone significant transformations over the past decade, driven by expanding indications, advancements in transplant oncology, increased use of donations after cardiac death (DCD), the advent of organ perfusion machines, novel surgical techniques, and evolving prioritization strategies for waitlisted recipients [69]. A major paradigm shifts in clinical decision-making, as outlined in the 2022 revision of the Barcelona Clinic Liver Cancer (BCLC) guidelines, underscores the importance of prognosis-driven treatment selection based on tumor burden, liver function, disease stage, and comprehensive patient characterization [70]. The growing emphasis on re-evaluating patients at different time points in their disease course, particularly following successful downstaging protocols, has introduced more dynamic transplant eligibility criteria. This shift enables stage migration strategies, offering LT as a viable treatment option for selected HCC patients who respond favorably to LRTs, such as trans-arterial chemoembolization (TACE), radiofrequency ablation (RFA), and selective internal radiation therapy (SIRT), where TACE remains the most effective. Notably, the XXL trial, led by Mazzaferro et al. in 2020 [71] introduced surgical resection as part of a downstaging protocol when performed laparoscopically, demonstrating its potential to convert partial LRT responses into complete tumor removal. Moreover, systemic therapies, particularly the atezolizumab-bevacizumab combination, are emerging as promising downstaging-to-transplant strategies for intermediate-to-advanced HCC within ongoing investigations such as the Immuno-XXL trial. Given the increasing number of downstaging options and refined acceptance criteria for waitlisted candidates, it is essential to identify additional factors influencing post-LT tumor recurrence beyond traditional recipient and HCC-related variables. Recent data from a retrospective study by the Cleveland group (2024) [72] involving 569 patients, of whom 75 (13.2%) experienced recurrence, stratified patients based on Milan criteria status and highlighted that increasing tumor size, number, and AFP levels correlated with higher recurrence rates and reduced time-to-recurrence. Notably, pre-LT chemoembolization was associated with a higher recurrence rate in high-risk cohorts, while a predicted mortality of less than 87.5% according to the Metroticket 2.0 scale emerged as a robust predictor of recurrence and survival in both overall and high-risk populations. Importantly, this study challenged the utility of the Model for End-Stage Liver Disease (MELD) score as a selection tool for LT in HCC patients, emphasizing instead the need for a more nuanced risk assessment approach. Donor-specific risk factors, including total ischemic time (TIT > 6 hours) and the use of DCD donors, were identified as particularly detrimental in high-risk recipients, such as those undergoing downstaging, reinforcing the concept that precise donor-recipient matching is critical to optimizing transplant outcomes. The integration of machine perfusion technologies and surgical innovations further offers the potential to mitigate organ scarcity while enhancing graft viability. As risk assessment becomes increasingly sophisticated, emerging biomarkers and predictive tools are playing a pivotal role in refining pre-transplant evaluations. The advent of artificial intelligence (AI) and machine learning algorithms has revolutionized risk stratification by integrating vast datasets encompassing tumor biology, inflammatory markers, imaging characteristics, and patient-specific clinical variables. AI-driven models can now predict post-LT recurrence with greater accuracy by dynamically analyzing individualized responses to treatment, thereby improving patient selection and organ allocation strategies. Several multi-center studies are currently underway to validate scoring systems such as RETREAT, RELAPSE, and Metroticket 2.0 in diverse patient populations, aiming to enhance their predictive performance. Future research must also focus on integrating molecular and genetic biomarkers, such as circulating tumor DNA (ctDNA) and immune signatures, to further personalize transplant decision-making. Ultimately, numerous factors influence both overall survival (OS) and recurrence-free survival (RFS) after LT for HCC, spanning the entire transplantation process—from patient selection and donor evaluation to intraoperative surgical techniques and post-transplant immunosuppression strategies [73]. Recipient tumor stage, biology, downstaging response, waitlist duration, donor characteristics (living donor liver transplant [LDLT] vs. donation after brain death [DBD] vs. DCD), cause of donor death, procurement variables (preservation method and ischemia time), transplant surgical technique, intraoperative management, and post-LT immunosuppressive regimens all contribute to long-term outcomes. By continuously refining pre-transplant risk assessment through AI integration, biomarker discovery, and dynamic listing criteria, the field of LT is advancing toward a more personalized, precision-medicine approach that optimizes survival and minimizes recurrence in HCC patients.

CONCLUSIONS

In summary, accurate pre-transplant risk assessment is essential for optimizing outcomes in LT for HCC. Key factors influencing post-transplant recurrence include tumor burden, biological markers such as AFP, presence of vascular invasion and satellite nodules, response to

downstaging therapies, and donor-related variables. The ability to personalize recurrence risk prediction is crucial for refining patient selection, guiding organ allocation, and tailoring post-transplant surveillance strategies. Emerging predictive tools, such as the Metroticket 2.0 and RETREAT models, offer more nuanced assessments by integrating both radiological and biological parameters, enhancing the accuracy of risk stratification [74]. While AFP-based models contribute to a more comprehensive evaluation of HCC recurrence risk, the integration of radiomics and AI has the potential to revolutionize pre-transplant assessments by analyzing vast datasets and identifying patterns beyond human capability. Future research should focus on validating novel risk assessment models in prospective, multi-center studies and incorporating molecular biomarkers to further refine patient selection, integrating AI-driven tools. By bridging the gap between radiological imaging, tumor biology, and machine learning, the future of LT for HCC is moving towards a more personalized, precision-medicine approach. Ultimately, the integration of these advancements into routine clinical practice will optimize transplant outcomes, improve resource allocation, and enhance long-term survival for HCC patients.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

DP, VF: had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; DP, VF, MCG, DC, SG: concept and design, critical revision of the manuscript for important intellectual content; DP, VF, MCG, DC: acquisition, analysis, or interpretation of data; drafting of the manuscript; DP, SG.

Role of the funder/sponsor

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data sharing statement

The data that support the findings of this study are available from ISMETT but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of corresponding (SG) and first authors (DP).

Ethical consideration

Not applicable.

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