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NON-TUMOR-RELATED RISKS OF POST-TRANSPLANT HEPATOCELLULAR CARCINOMA (HCC) RECURRENCE: A STATE-OF-THE-ART REVIEW

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Summary

Hepatocellular carcinoma recurrence after liver transplantation remains a significant challenge and is influenced not only by tumor biology but also by non-tumoral factors that affect metastatic growth. This comprehensive review consolidates current evidence on how recipient etiology and comorbidities, systemic inflammation and metabolic dysfunction, donor and graft quality, ischemia–reperfusion injury, perioperative events, and the intensity and composition of immunosuppression contribute to the risk. The interaction of these factors alters immune surveillance, angiogenesis, and the liver microenvironment, thereby influencing recurrence patterns. A practical framework that combines non-tumoral factors with established tumor metrics to guide patient selection, customize immunosuppressive strategies, reduce ischemic injury, and personalize monitoring should aim to shift practice toward mechanism-based, patient-specific management while ensuring graft safety. Future priorities include prospective validation of combined risk models, development of biomarkers linked to modifiable pathways, and intervention studies testing antiviral strategies, ischemia reduction, and immunosuppressive sequencing. A thorough understanding of non-oncological factors can improve long-term cancer outcomes following liver transplantation.

Key words: hepatocellular carcinoma, liver transplantation, recurrence, immunosuppression, ischemia-reperfusion injury

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INTRODUCTION

Liver transplantation (LT) offers the best chance for cure in carefully selected patients with hepatocellular carcinoma (HCC). While morphological and serological criteria have reduced recurrence rates, post-LT recurrence still ranges from about 8% to 20%, depending on the criteria and follow-up period [1–3].
Traditionally, risk stratification has mainly focused on tumor morphology, with patients beyond Milan criteria [4] considered at higher risk. Consequently, most predictive scores for HCC recurrence, such as RETREAT [5], include factors like alpha-fetoprotein (AFP), tumor size, and number of nodules.
However, many factors influencing recurrence go beyond explant pathology (Fig. 1). The type and intensity of immunosuppression, graft quality and

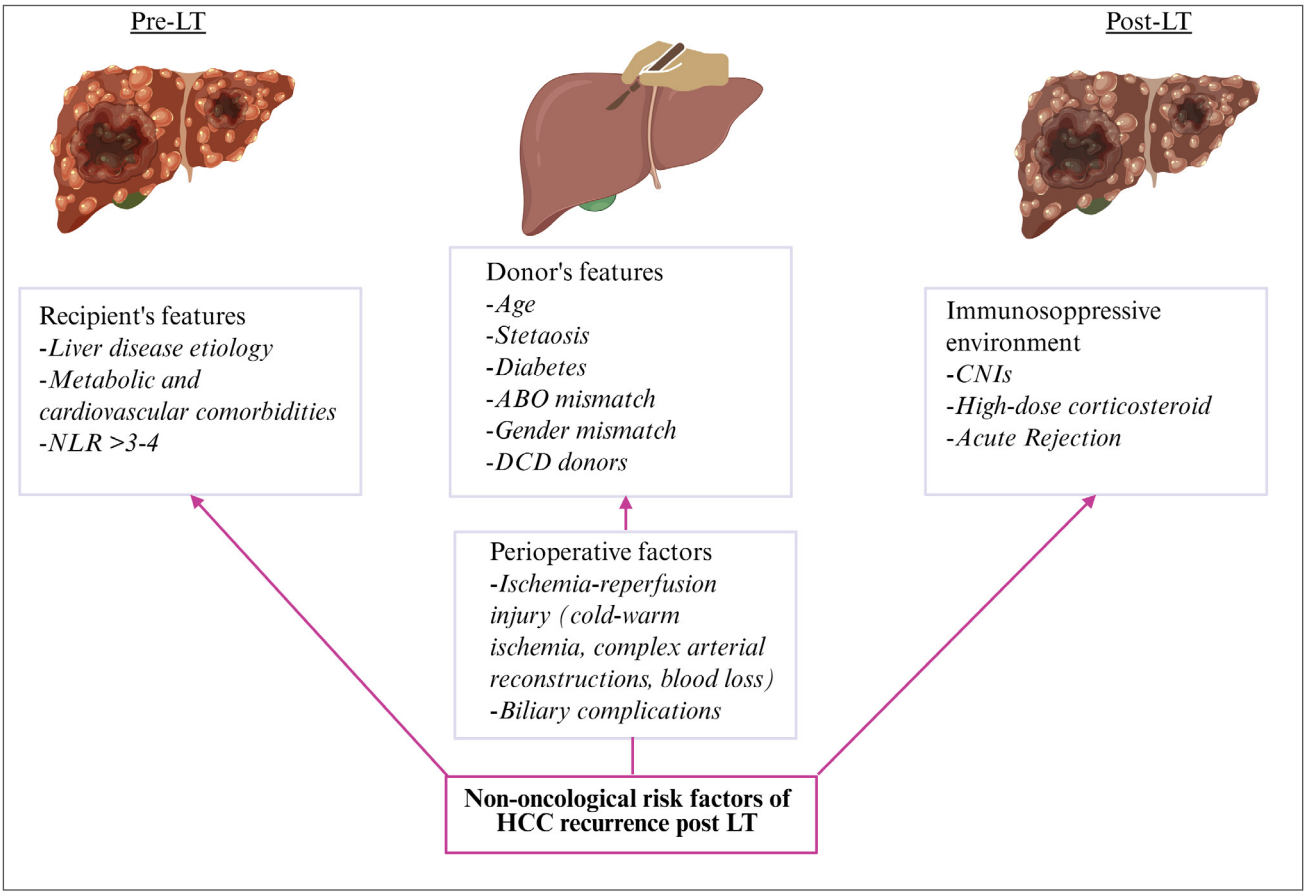

Figure 1. Non-tumoral risk factors of HCC recurrence after liver transplantation. NLR: neutrophil-to-lymphocyte ratio; HCC: hepatocellular carcinoma; DCD: donation after circulatory death; CNIs: calcineurin inhibitors.

management, perioperative physiology, the recipient's systemic inflammatory and metabolic condition, and the timing and method of transplantation all affect recurrence risk. Recognizing, assessing, and, when possible, modifying these non-tumor-related risks is essential for achieving better long-term outcomes.

RISK FACTORS ASSOCIATED WITH THE RECIPIENT

Underlying liver disease etiology

The etiology of liver disease is crucial in HCC recurrence after LT [6,7]. Recurrence rates are highest in HBV-related HCC (18%) compared to hepatitis C (11%), alcohol-related liver disease (10%), and nonalcoholic steatohepatitis (8%), due to HBV's inherent cancer-causing potential and the persistence of viral DNA that can seed remaining malignant clones [8].

Antiviral preventive treatment after transplantation using high-genetic barrier nucleos(t)ide analogs (NUCs) with or without hepatitis B immunoglobulins (HBIG) enhances recurrence-free survival by inhibiting viral replication and reducing both graft reinfection and the pro-oncogenic signals that may encourage micrometastatic growth [9].

Although regimens without HBIG, combined with potent NUCs such as entecavir or tenofovir, have shown promising results, the standard treatment remains lifelong HBIG plus NUCs to prevent HBV reactivation and reduce conditions that promote residual HCC cell growth. The goal is long-term viral suppression rather than eradication, since covalently closed circular or integrated HBV DNA can stay in the graft.

In contrast, treating HCV before LT does not clearly lower the risk of HCC recurrence after transplantation [10,11]. Some studies suggest that patients who achieve sustained virologic response (SVR) with direct-acting antivirals (DAAs) before LT may have a similar or even higher risk of post-LT HCC recurrence compared to those who remain viremic at transplantation [12]. This paradoxical finding, observed in retrospective cohort studies, may relate to unique biological effects of DAAs or to longer wait-list times that allow occult malignancies to develop.

However, when comparing SVR achieved through DAAs to that achieved via interferon-based therapies, recurrence rates seem similar, suggesting that the specific antiviral regimen might influence outcomes [13].

The relationship between metabolic dysfunction-associated steatotic liver disease (MASLD) and HCC recurrence is more complex. In current LT cohorts, recurrence rates in patients with MASLD are generally similar to those for other causes. In a large U.S. multicenter study, the cumulative incidence of post-transplant HCC recurrence in MASLD-related cases was 3.1% at 1 year, 9.1% at 3 years, and 11.5% at 5 years, compared to 4.9%, 10.1%, and 12.6% for non-MASLD causes, with no statistically significant difference ($p = 0.36$) [14]. Current data therefore suggest that MASLD as the underlying liver disease does not increase the risk of post-transplant HCC recurrence, and long-term recurrence patterns closely resemble those of non-MASLD groups. Evidence indicates that with effective metabolic management after LT, patients with MASLD may have longer recurrence-free survival compared to those with other causes. Conversely, failing to control metabolic factors or resuming alcohol intake in patients with alcohol-related HCC seems to raise the risk of recurrence [15,16].

Other risk factors related to recipient

Metabolic and cardiovascular comorbidities

The presence of metabolic and cardiovascular comorbidities has become a significant non-oncological risk factor affecting HCC recurrence after LT. The complex interaction between metabolic dysfunction, systemic inflammation, and oncogenic pathways creates a microenvironment that encourages tumor recurrence, even without traditional tumor-related risk factors.

Obesity has been extensively studied concerning post-transplant HCC recurrence. The risk of developing HCC in patients with obesity and diabetes is roughly five times higher than in those without these metabolic conditions [17].

The mechanisms behind this increased oncogenic risk are multifactorial, involving complex interactions among hepatic steatosis, chronic inflammation, insulin resistance, altered lipid metabolism, intestinal dysbiosis, and genetic predisposition [18-20].

Clinical evidence shows that higher body mass index (BMI) is linked to increased tumor vascular invasion, higher recurrence rates, and poorer overall survival [21] Some studies suggest that obesity doubles mortality after LT in HCC patients, with an increased risk of vascular invasion and a tendency for more frequent recurrences with shorter recurrence-free survival [22,23].

The proposed oncogenic mechanisms include disruption of the balance between adiponectin and leptin levels, leading to increased vascular endothelial growth factor (VEGF) activity, which stimulates angiogenesis and promotes tumor growth [22-24].

However, the link between obesity and HCC recurrence remains complex and somewhat inconsistent. Recent long-term follow-up studies have questioned whether obesity should be regarded as a predictor of recurrence when selecting HCC patients for LT [25].

These conflicting results might be due to variations in patient groups, follow-up times, and research methods across studies.

Diabetes mellitus, especially type 2 diabetes, is an important metabolic comorbidity that influences HCC recurrence risk. Recent evidence indicates that the coexistence of obesity and diabetes increases the risk of late recurrence through combined effects, highlighting the importance of ongoing postoperative surveillance beyond 5 years [26,27].

The molecular mechanisms connecting diabetes to HCC recurrence involve chronic hyperinsulinemia, activation of the insulin-like growth factor-1 (IGF-1) pathway, formation of advanced glycation end products, and ongoing low-grade inflammation [28].

The hyperinsulinemic state characteristic of insulin resistance promotes hepatocyte proliferation through direct mitogenic effects and indirect mechanisms involving IGF-1 receptor activation. Additionally, diabetes-related oxidative stress and chronic inflammation create a protumorigenic microenvironment that may promote both de novo carcinogenesis and metastatic progression [29].

Also, other cardiovascular comorbidities such as arterial hypertension and dyslipidemia can be associated with a higher risk of HCC recurrence [30].

Emerging evidence suggests that hypertension may independently affect HCC outcomes. Studies in hepatectomy patients have shown that renin-angiotensin system (RAS) inhibition is linked to reduced recurrence risk, lower rates of extrahepatic metastasis, and longer survival in HCC patients with primary hypertension [31].

This finding indicates potential therapeutic targets for managing hypertensive HCC patients after transplantation.

Moreover, the cardiovascular risk profile of transplant recipients is further complicated by immunosuppressive medications, which can worsen pre-existing metabolic abnormalities and lead to the development of new cardiovascular risk factors.

The dual role of the recepient's immune system

The recipient's immune system plays a vital dual role in HCC recurrence after LT, acting both as a protective barrier against tumor growth and as a therapeutic target that must be suppressed to prevent allograft rejection. This delicate balance between maintaining immune tolerance to the transplanted organ and supporting anti-tumor

defenses is one of the most challenging aspects of post-transplant cancer management.

During LT, residual micrometastases and circulating tumor cells may remain despite seemingly complete tumor removal, creating a reservoir for potential recurrence [2,32].

The extensive immunosuppression needed to prevent allograft rejection fundamentally changes immune surveillance mechanisms that detect and remove residual malignant cells. This level of immunosuppression creates a permissive environment where microscopic disease, previously kept in check, may progress to noticeable recurrence [32,33].

The post-transplant immune environment features complex cellular interactions that can support tumor progression. Platelets, neutrophils, and myeloid-derived suppressor cells help create a pro-metastatic microenvironment through different mechanisms. These cells boost tumor growth by releasing pro-angiogenic growth factors, especially VEGF, which encourages new blood vessel formation needed for tumor growth and metastasis [24,34-36].

Furthermore, these cell populations create protective shields around circulating tumor cells, effectively shielding them from immune attack and allowing their successful colonization at distant sites [37].

The mechanistic understanding of immune-tumor interactions indicates that non-tumor factors are not merely associated with recurrence outcomes but are central drivers of recurrence biology [38], with significant implications for both risk assessment and therapeutic strategies during the post-transplant period.

Inflammatory biomarkers as prognostic indicators

Systemic inflammatory markers have become important predictors of cancer outcomes after LT for HCC. The neutrophil-to-lymphocyte ratio (NLR) has shown especially strong prognostic value in several recent studies and meta-analyses [39].

Elevated NLR (> 3-4) is linked to early tumor recurrence, with preoperative elevation significantly increasing recurrence risk in patients undergoing LT for HCC [40,41].

The mechanistic basis of these inflammatory biomarkers lies in their roles in supporting key steps of the metastatic process, as neutrophils promote tumor progression through various pathways, including vascular invasion, endothelial adhesion, and immune evasion mechanisms [42,43].

The platelet-to-lymphocyte ratio (PLR) has also shown prognostic value in the transplant setting. While NLR effectively predicts the risk of dropout from the waiting list, PLR is especially useful in predicting post-LT recurrence risk. Including these markers may provide additional tools to improve selection criteria for HCC liver recipients [44].

Additionally, recent evidence shows that elevated NLR or PLR is linked to worse outcomes for patients with HCC, and both markers can be considered reliable and affordable biomarkers for clinical decision-making regarding HCC treatment [42,45,46].

Immunosuppressive regimens and cancer risk

Calcineurin inhibitors

Calcineurin inhibitors (CNIs), the cornerstone of post-transplant immunosuppression, present a fundamental challenge in HCC management because of their potential pro-tumorigenic effects. Multiple observational studies [47-49] have shown associations between higher early tacrolimus or cyclosporine exposure and increased recurrence risk after liver transplantation for HCC, supporting clinical strategies aimed at early CNI minimization when clinically feasible.

However, recent evidence shows a more complex view of CNI exposure effects. While some authors have observed the association between early tacrolimus exposure and recurrence, others indicate that aggressive minimization strategies might paradoxically increase all-cause mortality, highlighting the importance of maintaining adequate immunosuppression to prevent rejection-related issues [50,51].

The practical approach, therefore, involves avoiding unnecessarily high trough levels while ensuring adequate immunosuppression to protect the graft, requiring personalized management based on individual patient risk factors [52].

mTOR inhibitors

Mammalian target of rapamycin (mTOR) inhibitors, including sirolimus and everolimus, have gained significant attention for their dual immunosuppressive and antineoplastic effects. Recent clinical evidence strongly supports the oncological benefits of mTOR inhibitors in liver transplant patients with HCC. At a median follow-up of 4.4 years after transplantation, patients receiving everolimus demonstrated lower recurrence risk compared to tacrolimus (7.7% *versus* 16.9%; RR = 0.45; p = 0.002) [53], making this one of the most compelling recent pieces of evidence supporting mTOR inhibitor use in post-transplant HCC patients.

A comprehensive 2022 systematic review and meta-analysis confirmed that sirolimus and everolimus can lower relapse rates after liver transplantation for hepatocellular carcinoma, although mTOR inhibitor-based immunosuppression increases adverse side effects [54].

The benefits of mTOR inhibition seem most significant in specific patient subgroups, with recent evidence showing that mTOR inhibitors have anticancer effects especially in patients with active tumors [55].

The optimal timing, duration, and patient selection criteria for mTOR inhibitor use are still being actively studied, with

new evidence indicating that early initiation, especially in higher-risk tumors or as part of CNI-sparing regimens, may enhance oncological outcomes [56].

Corticosteroids

High-dose corticosteroid treatment, especially for acute cellular rejection, remains linked to significantly higher HCC recurrence rates in clinical studies [57].
Clinical approaches that emphasize steroid-sparing primary immunosuppressive regimens and early steroid withdrawal have proven safe in many LT populations and seem especially advantageous for HCC patients, as long as the risk of rejection remains acceptably low [58].

Acute rejection

Biopsy-proven acute rejection (AR) within the first 1-2 years after LT is strongly associated with an increased risk of HCC recurrence [59].
This relationship probably stems from several interconnected factors, including immune activation causing rejection, increased immunosuppression needed for rejection treatment, and possible changes in the immune microenvironment that support tumor growth [60].
The clinical significance of this association is considerable. Patients experiencing AR episodes may benefit from enhanced monitoring strategies that include more frequent imaging and laboratory tests. Additionally, managing AR in HCC patients should focus on prompt, effective treatment with minimal immunosuppressive escalation to avoid extended immune suppression.

DONOR CHARACTERISTICS

Donor traits such as age, body mass index, diabetes, and steatosis are linked to higher HCC recurrence rates after LT. Older donors tend to cause increased inflammation and changes in the immune environment of the liver graft, which may support tumor growth and spread. Recent research shows that donors over 60 years old have a significantly higher risk of HCC recurrence, with hazard ratios from 1.8 to 2.4 in multivariable studies [61,62].
This likely relates to age-related changes in hepatic stellate cells, decreased regenerative ability, and different cytokine levels that can promote angiogenesis and tumor growth [63].
Steatotic liver grafts are more prone to ischemia-reperfusion injury (IRI), which later fosters an inflammatory environment that promotes tumor recurrence. A multicenter study published in 2019 showed that moderate to severe donor steatosis (> 30% macrovesicular) was linked to a 2.1-fold higher risk of HCC recurrence (95% CI: 1.4-3.2, $p < 0.001$) compared to grafts with minimal steatosis [64].
The underlying mechanisms include increased production of pro-inflammatory cytokines, changes in lipid metabolism, and heightened oxidative stress within the graft.
Donor diabetes mellitus is another important metabolic factor that impacts HCC recurrence. Diabetic donor organs show chronic inflammatory changes, advanced glycation end products, and altered immune cell populations that may promote tumor cell engraftment and growth. Recent registry analyses have indicated that organs from diabetic donors have a 40-60% higher risk of HCC recurrence compared to those from non-diabetic donors [65].
Although ABO incompatible LT is feasible, emerging evidence suggests potential oncological risks. A recent single-center study involving 847 HCC patients showed that ABO incompatible transplantation was linked to a 1.8-fold higher risk of HCC recurrence ($p = 0.034$), possibly due to increased inflammatory responses and altered immune surveillance [66].
Finally, donor-recipient gender mismatch has been linked to various transplant outcomes, and recent studies suggest possible effects on HCC recurrence. Male recipients of female donor livers showed a trend toward higher recurrence rates in several cohort studies, possibly due to differences in immune responses and hormonal influences on tumor biology [67].

Extended criteria donors and donation after circulatory death (DCD)

The use of extended criteria donors, including donation after circulatory death (DCD) donors, has increased due to organ shortages. These donors often include individuals with advanced age, significant liver steatosis, transmissible infections, or DCD status. Recent large-scale studies have provided detailed insights into the link between DCD donation and HCC recurrence [68,69]. One study using the UNOS database compared recurrence-free survival and overall survival after liver transplantation among HCC patients transplanted with MELD exception between 2012 and 2016 [68]. While the study found no overall difference in recurrence-free survival between patients receiving donors after brain death (DBD) versus DCD donors, a subset analysis of patients at higher risk of post-LT recurrence based on the RETREAT score favored DBD donors.
This finding indicates that the effect of DCD donation on HCC recurrence might be risk-stratified, with higher-risk recipients experiencing worse outcomes when receiving DCD organs. The extended warm ischemia time associated with DCD donation could worsen ischemia-reperfusion injury, leading to an inflammatory environment that encourages tumor recurrence in already vulnerable patients [68].

Clinical implications of donor-related factors

The growing evidence about how donor factors influence HCC recurrence has several key clinical implications.

Including donor characteristics in current recurrence prediction models could enhance their accuracy and usefulness in clinical settings. High-risk HCC patients might benefit more from receiving optimal donor organs, while those with a low risk of recurrence could be suitable candidates for extended criteria donors. Patients with organs from higher-risk donors may need more intensive post-transplant surveillance. Understanding donor-related risk factors can help guide the selection of adjuvant therapies and immunosuppressive regimens.

TECHNICAL SURGICAL FEATURES AND ISCHEMIA-REPERFUSION INJURY

The technical aspects of LT, especially those related to IRI, have become key factors in HCC recurrence. The inflammatory response triggered by IRI creates a microenvironment that supports tumor growth, blood vessel formation, and spread.

Hepatic IRI is a leading cause of LT failure and has become increasingly important due to the expanded use of extended criteria livers for transplantation. The pathophysiology involves a complex interplay of cellular and molecular events that can elevate the risk of HCC recurrence [70–72]. IRI causes hepatocyte necrosis, sinusoidal endothelial cell dysfunction, and Kupffer cell activation, leading to an inflammatory environment. Pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and chemokines (CXCL10, CCL2) are released, supporting tumor cell survival and growth. IRI also triggers the release of angiogenic factors, including VEGF, promoting neovascularization that can support tumor growth. Paradoxically, IRI can also induce immunosuppression by activating regulatory T cells and recruiting myeloid-derived suppressor cells.

Cold and warm ischemia: innovative surgical techniques to minimize IRI

Multiple studies have demonstrated a strong association between prolonged cold ischemia time (CIT) and the recurrence of HCC. In a comprehensive cohort, 60 patients (15.3%) experienced recurrence, with a median time of approximately 0.9 years. The cumulative recurrence curves highlight that CIT has a significant impact on recurrence rates. Notably, the pivotal study by Kornberg et al. found that each additional hour of cold ischemia time increased the risk of HCC recurrence by 1.3 times (95% CI: 1.1-1.5, p = 0.002). Patients with CIT exceeding 8 hours showed markedly worse recurrence-free survival compared to those with CIT under 6 hours, with 3-year RFS rates of 58% *versus* 78%, respectively (p < 0.001) [73].

In fact, recent analyses indicate threshold effects for cold ischemia time, with the most significant impact occurring beyond 6 to 8 hours. A multicenter European study demonstrated that the relationship between CIT and recurrence is non-linear, with minimal effect below 6 hours but risk increasing exponentially after 8 hours [74].

Warm ischemia time, although generally shorter than cold ischemia time, can have an even greater impact on HCC recurrence due to the metabolically active state during warm ischemia. Complex surgical procedures involving prolonged anhepatic phases or difficult vascular reconstructions are linked to a higher risk of recurrence. A recent study showed that warm ischemia time over 45 minutes was independently associated with HCC recurrence (HR: 1.9, 95% CI: 1.3-2.8, p < 0.001) after adjusting for tumor features and cold ischemia time [73].

Ischemia-free liver transplantation (IFLT) is a new procedure that greatly reduces or even prevents IRI. A pioneering study from Sun Yat-sen University [75] showed remarkable results with IFLT. In Kaplan-Meier analysis, the recurrence-free survival rates at 1 and 3 years after LT in recipients with HCC in the IFLT group were 92.2% and 86.7%, respectively, significantly higher than those (73% and 46.3%) in the conventional LT group (p = 0.006). Additionally, multivariate analysis revealed that pretransplant AFP (⩾ 300 μg/L *vs* < 300 μg/L) (HR 2.262, 95% CI 1.597-4.318, p < 0.001), microvascular invasion (HR 2.309, 95% CI 1.403-3.801, p < 0.001), and surgical procedure (conventional LT *vs* IFLT) (HR 3.728, 95% CI 1.172-11.861, p = 0.026) were independent factors affecting disease-free survival in HCC patients after LT. The technique involves continuous normothermic machine perfusion from procurement to implantation, completely avoiding cold preservation. Histological analysis showed no significant increase in injury scores or apoptotic hepatocytes during the transplant process in the IFLT group, proving the technique's effectiveness in preventing IRI.

Machine perfusion has been a focus of research in recent years and could expand the organ donor pool, helping to address current liver donor shortages. Various perfusion strategies have shown promise in reducing IRI and potentially improving oncological outcomes. Hypothermic oxygenated perfusion (HOPE) has demonstrated particular promise. One recent European retrospective study examined the impact of HOPE on post-liver transplant HCC recurrence in DCD liver donor recipients, revealing a significant difference in 5-year recurrence-free survival (92% *vs* 73%; p = 0.027) between HOPE DCD liver donor recipients and non-perfused DBD recipients [76]. Normothermic machine perfusion (NMP) maintains physiological temperature and oxygenation, potentially providing better preservation compared to static cold storage [77]. Preliminary studies suggest improved liver function and reduced inflammatory markers, though oncological outcomes need further investigation.

Other perioperative factors

Complex arterial reconstructions, especially those involving conduits or multiple anastomoses, are linked to longer ischemia times and increased technical complexity. A multicenter study showed that patients needing arterial conduits faced a 1.6-fold higher risk of HCC recurrence (p = 0.018) compared to those with standard arterial anastomoses [78].

Additionally, while biliary complications themselves do not directly increase HCC recurrence, the inflammatory response related to bile duct issues and subsequent interventions may promote conditions that support tumor growth. Patients with biliary strictures requiring multiple procedures showed higher recurrence rates in several cohort studies [79].

Finally, extensive intraoperative blood loss and transfusion requirements have been associated with higher HCC recurrence, likely due to the immunosuppressive effects of blood products and systemic inflammatory responses. A recent showed that blood transfusions are a risk factor for hepatocellular carcinoma after LT [80]. Intraoperative hemodynamic instability, especially hypotension and low cardiac output states, can worsen ischemia-reperfusion injury. Maintaining adequate perfusion pressure and cardiac output during transplantation is essential for reducing the risk of IRI-related HCC recurrence.

CONCLUSIONS AND FUTURE DIRECTIONS

After LT for HCC, recurrence is not just a property of the explant; it results from how we shape the hepatic environment.

Therefore, we should move beyond a "tumor-only" perspective and embrace oncologic stewardship of non-tumoral factors. This approach includes establishing specific CNI targets with scheduled exposure periods and early initiation of mTOR in high-risk profiles; actively avoiding ischemia-reperfusion injury (IRI) as part of cancer management; and matching donors and recipients while steering clear of inflammatory or steatotic grafts in patients with additional risks.

The field should now prioritize testing strategies through prospective pathways that jointly manage: (i) carefully calibrated immunosuppressive sequencing; (ii) minimization of IRI from allocation to operative workflow; and (iii) surveillance intensity tailored to fluctuating NLR/PLR ratios and ischemia exposure. To improve patient outcomes, collaborative research efforts and personalized approaches are essential.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

PB, AZ: conceptualized the study, made critical revisions; EP: AZ wrote the preliminary draft. All authors prepared the draft and approved the final version.

Ethical considerations

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