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New Scenarios in Liver Transplantation for Hepatocellular Carcinoma

Ezequiel Mauro[1,2] | Manuel Rodríguez-Perálvarez[2,3] | Antonio D'Alessio[4,5] | Gonzalo Crespo[2,6] | Federico Piñero[7] | Eleonora De Martin[8] | Jordi Colmenero[2,6] | David James Pinato[4,5] | Alejandro Forner[1,2]

[1]Barcelona Clinic Liver Cancer (BCLC) Group, Liver Unit, ICMDM, Hospital Clinic Barcelona, IDIBAPS, University of Barcelona, Barcelona, Spain | [2]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain | [3]Department of Hepatology and Liver Transplantation, Hospital Universitario Reina Sofía, Universidad de Córdoba, IMIBIC, CIBERehd, Córdoba, Spain | [4]Department of Surgery & Cancer, Imperial College London, Hammersmith Hospital, London, UK | [5]Division of Oncology, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy | [6]Liver Transplant Unit, Liver Unit, ICMDM, Hospital Clinic Barcelona, IDIBAPS, University of Barcelona, Barcelona, Spain | [7]School of Medicine, Hospital Universitario Austral, Austral University, Buenos Aires, Argentina | [8]AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, INSERM Unit 1193, Université Paris-Saclay, FHU Hepatinov, Villejuif, France

Correspondence: Alejandro Forner (aforner@clinic.cat)

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ABSTRACT

Background and Aims: Despite liver transplantation (LT) is considered the optimal treatment for hepatocellular carcinoma (HCC), particularly in patients with impaired liver function, the shortage of donors has forced the application of very restrictive criteria for selecting ideal candidates for whom LT can offer the best outcome. With the evolving LT landscape due to the advent of direct-acting antivirals (DAAs) and the steady increase in donors, major efforts have been made to expand the transplant eligibility criteria for HCC. In addition, the emergence of immune checkpoint inhibitors (ICIs) for the treatment of HCC, with demonstrated efficacy in earlier stages, has revolutionized the therapeutic approach for these patients, and their integration in the setting of LT is challenging. Management of immunological compromise from ICIs, including the wash-out period before LT and post-LT immunosuppression adjustments, is crucial to balance the risk of graft rejection against HCC recurrence. Additionally, the effects of increased immunosuppression on non-hepatic complications must be understood to prevent them from becoming obstacles to long-term OS.

Methods and Results: In this review, we will evaluate the emerging evidence and its implications for the future of LT in HCC. Addressing these novel challenges and opportunities, while integrating the current clinical evidence with predictive algorithms, would ensure a fair balance between individual patient needs and the overall population benefit in the LT system.

Summary

- Liver transplantation (LT) remains the best treatment option for hepatocellular carcinoma (HCC), but its applicability is limited by a shortage of donors.
- In recent years, several models have been proposed not only for expanding but also for optimising the selection of HCC candidates for LT.
- The development of models for candidate selection and prioritisation should be based on potential outcome maximisation and alignment with local donor availability and waiting list dynamics.
- Immune checkpoint inhibitors (ICIs) have revolutionised the therapeutic approach of HCC patients.
- The integration of ICIs in the setting of LT is challenging, and their efficacy and safety are still a matter of debate.

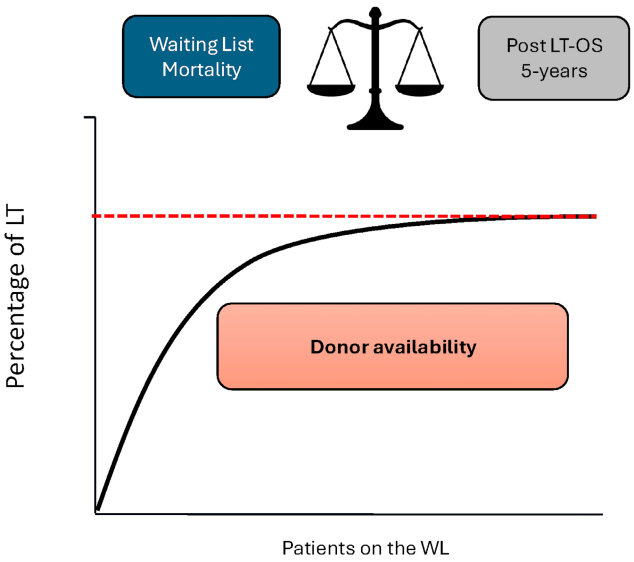

FIGURE 1 | Impact of donor availability on liver transplant system efficiency: Balancing waiting list mortality and 5-year post-transplant survival. LT, liver transplantation; OS, overall suvival; WL, waiting list.

1 | Introduction

Liver transplantation (LT) offers the greatest survival benefit for patients with hepatocellular carcinoma (HCC) [1] due to its dual ability to eliminate the tumour, including undetected hepatic micrometastases, and to fully resolve the underlying chronic liver disease [2]. However, the scarcity of donor organs continues to be a significant barrier, necessitating optimised patient selection to maximise the outcomes [3]. Historically, an expected 5-year post-LT overall survival (OS) rate exceeding 50% has been considered the threshold to ensure the benefits of organ utility [4, 5]. However, given the evolving landscape of LT outcomes, a more appropriate benchmark may be a 5-year OS rate of 60%, aligning with current global standards and comparable to that of patients with non-neoplastic end-stage chronic liver disease [6, 7]. To warrant equitable access to LT and reduce waitlist dropouts due to tumour progression, transplant allocation policies must strike a delicate balance between organ supply and demand (Figure 1) [8]. This involves providing timely access to LT, while allowing an adequate observation period to identify biologically aggressive tumours associated with a higher risk of post-LT recurrence and lower OS [3].

The primary challenge in LT is the shortage of donors amidst a growing number of patients requiring transplantation. However, significant advancements in donor pool expansion and recipient management have emerged in recent decades. Epidemiological shifts, particularly following the introduction of direct-acting antivirals (DAAs), have redefined waitlist indications and etiologies, significantly improving short- and long-term overall survival by eradicating HCV recurrence [9–12]. Concurrently, innovations such as living donors, deceased non-heart-beating donors, and graft-perfusion technologies, including normothermic perfusion, have markedly increased the donor pool and improved LT outcomes [13–17].

While the Milan criteria (MC) have long served as the benchmark for LT selection in HCC [18], recent refinements incorporating biomarkers aimed to refine composite models for LT criteria have demonstrated that long-term outcomes can be maintained or even improved [1, 19]. Additionally, a recent phase 2b/3 randomised trial confirmed the benefits of locoregional treatments aimed at reducing the tumour burden to make patients eligible for LT ("downstaging") [20]. However, uncertainties remain regarding the initial tumour load and biological limits for patient selection for downstaging, acceptable treatment approaches, criteria for staging and defining successful downstaging, observation periods, and the extent to which the tumour load should be reduced [3, 21].

Recent advances in systemic treatments, particularly immune checkpoint inhibitors (ICIs) and their potential combination with locoregional therapies, have sparked a critical debate regarding their role in downstaging or bridging therapies before LT [22–24]. In parallel, optimising immunosuppression regimens in this evolving landscape is paramount. The challenge lies in reducing the risk of graft rejection without increasing the likelihood of HCC recurrence or the incidence of long-term non-hepatic complications, both of which contribute significantly to post-transplant morbidity and mortality. Given these rapid developments, the present review aims to evaluate the emerging evidence and its implications for the future of LT in HCC, addressing these novel challenges and opportunities while highlighting the importance of balancing individual and global survival benefits.

2 | Indications of Liver Transplantation for Hepatocellular Carcinoma

2.1 | Brief History of Liver Transplant Selection Models for Hepatocellular Carcinoma

Over two decades have passed since the publication of the MC and its adoption as the standard LT selection model worldwide for patients with HCC (Figure 2) [18]. However, several authors have considered MC too restrictive, preventing access to LT in

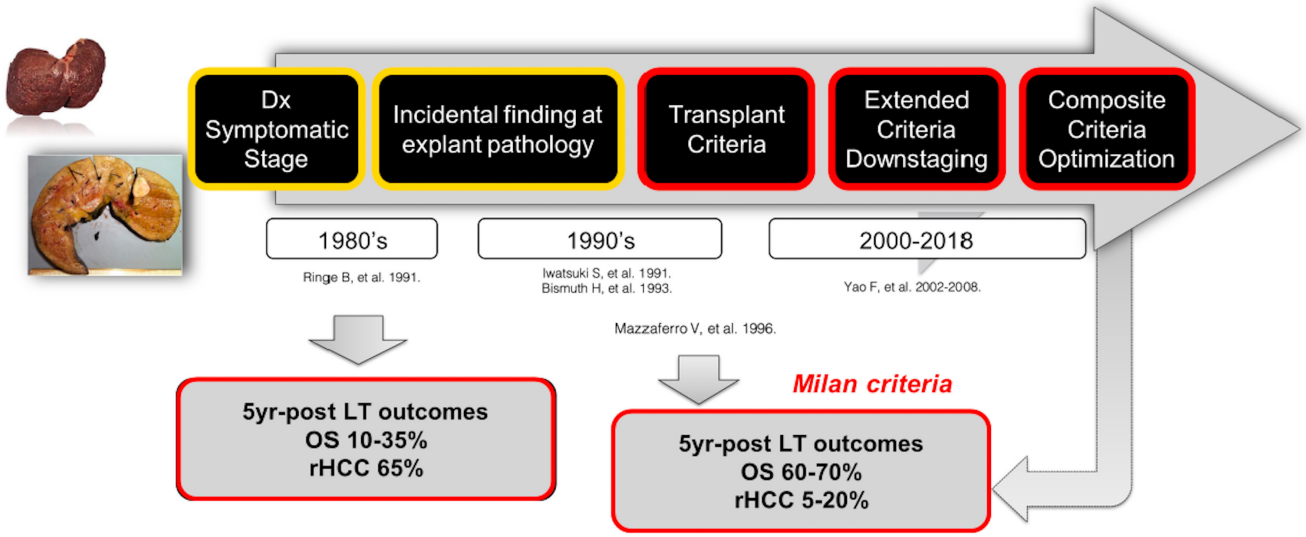

FIGURE 2 | A brief overview of liver transplant selection models for hepatocellular carcinoma. OS, overall survival; rHCC, recurrence rates after transplantation.

a subset of patients beyond the MC who would benefit from LT. Accordingly, several "*extended*" criteria to expand tumour limits for candidate selection have been proposed (Table 1) [18, 19, 25–34]. Regrettably, expansion based solely on number and/or tumour size is questionable because it is associated with higher recurrence and decreased post-LT survival. The efforts to develop new models should not be directed at "*expanding*" (increasing the number of candidates beyond Milan criteria with good post-LT outcomes) but rather at "*optimising*" the transplant selection process (not only expanding but also identifying patients within the MC with worse post-LT outcomes) through the addition of biological markers. As a result, the optimization of LT criteria for HCC will not negatively impact the LT access of non-HCC patients [35].

2.2 | "Optimization" Criteria for Selecting HCC Patients for Liver Transplantation

"*Composite models*" based on the use of biomarkers such as pre-LT alpha-fetoprotein (AFP) have gained ground in improving transplant selection [32, 33]. Pre-LT AFP, whether as a continuous, categorical, or dichotomous variable, is independently associated with HCC recurrence and lower post-LT OS. Importantly, AFP seems not related to inaccurate pre-LT imaging staging, but rather to a pattern of tumour aggressiveness, associated with tumour dedifferentiation or microvascular invasion [36, 37]. An example is the French model developed by Duvoux et al. which combines tumour size, number of nodules, and AFP levels [33]. It ranks from 0 to 9 and scores higher than 2 points identify patients with an increased risk of recurrence and worse post-LT OS, even within MC. It has been implemented in France since 2013 and has been externally validated in European [38], Latin American [39], and Asian [40] cohorts. More recently, Metroticket 2.0 integrates logAFP and the sum of the largest diameter with the number of nodules as continuous variables [19]. Although better discrimination power was initially suggested [19], it did not result in a net improvement in the reclassification of risks compared to the French model [41–44]. Nevertheless, its discrimination power is improved when incorporating the modified RECIST criteria adjusting for the effect of bridging therapies [45]. Recent meta-analyses have suggested that bridging locoregional therapies (LRT) do not significantly improve post-LT outcomes or reduce the risk of waitlist dropout. Their potential benefits may be influenced by selection biases and thus, its use is not fully supported by high-quality data [46, 47].

Other authors have attempted to predict HCC recurrence after LT through dynamic changes in the WL [32, 48]. Nevertheless, these models have not yet been proposed using mixed or joint multivariable regression models, considering intra- and inter-individual variability. Biomarker values [32, 49] and radiological tumour changes [50–52] are important aspects to be considered during patient selection. The New York and California (NYCA) score includes a somewhat arbitrary definition of "biological response" (the difference between the maximum AFP value and the last pre-LT value) [32]. Also, not all tumour progression may be associated with an increased risk of drop-out from WL, or tumour recurrence after LT [53, 54]. Thus, the LT selection process for HCC becomes even more complex and challenges daily practice.

The incorporation of other novel biomarkers may further optimise this selection process, even in patients with normal or very low AFP values [32]. AFP-LP3 and des-gamma-carboxy prothrombin (DCP, also known as PIVKA) have been associated with explant recurrence risk factors [55], tumour progression on the WL [31], and as additional transplant selection tools in patients with low AFP values [56, 57].

2.3 | Reducing Tumour Stage or "Downstaging"

Downstaging is defined as the application of any type of treatment to tumours currently outside of the accepted transplant criteria,

TABLE 1 | Liver Transplant criteria including morphometric and biomarker data.

LT criteria	Tumour imaging features	Biomarkers	Reported outcomes
Milan criteria	1 lesion < 5 cm or 3 lesions up-to 3 cm	None	70% 5-year survival 15% recurrence rate
UCSF criteria	1 lesion < 6.5 cm or 3 lesions up-to 4.5 cm	None	Similar outcomes than Milan criteria but higher recurrence rates. Expansion criteria
AFP model	Scoring model 0–9 points: largest tumour diameter (≤ 3 cm = 0 points, 3–6 cm = 1 point, > 6 cm = 4 points), number of HCC nodules (1–3 nodules = 0 points, ≥ 4 nod- ules = 2 points)	pre-LT AFP levels ng/mL (≤ 100 = 0 points, 101–1000 = 2 points and > 1000 = 3 points)	AFP score ≤ 2 points selects patients within or exceeding Milan with excellent post LT outcomes
Metroticket 2.0	Regression model, coeficients: sum of number and largest diameter	Log AFP values	Continues model with c-statistic > 0.70
AFP tumour volume	Total tumour volume (TTV) > 115 cm^3	AFP > 400 ng/mL	Overall survival < 50% at 3 years
Extended Toronto criteria	Any size or tumour number: dedifferentiated tumours (–), no cancer related symptoms	AFP > 500 ng/mL	Within Toronto: 5-year survival: 69%
Hanghzou criteria	Sum of diameters (≤ 8 cm)	AFP > 400 ng/mL	Within Hanghzou: 5-year survival and recurrence: 70.8% and 35.7%.
Tokio criteria	Tumour number (≤ 5 nodules) Largest diameter (≤ 5 cm)	Beyond Tokio criteria AFP > 250 ng/mL DCP > 450 mAU/mL	2/3 criteria: 5-year survival 20%
Kyoto criteria	Tumour number (≤ 10 nodules) Largest diameter (≤ 5 cm)	DCP > 400 mAU/mL	Beyond Milan & within Kyoto criteria: 5-year recurrence 4%
NYCA score	Tumour number (1, 2–3, > 3 nodules) Largest diameter (0–3, 3–6, ≥ 6 cm)	AFP "response"**: always < 200 ng/mL, > 200–1000 to final < 200 ng/mL, and > 1000 to final < 1000 ng/mL (at least 50% decrease)	NYCA recurrence score: 0–2 points: low risk 3–6 points: intermediate > 6 points: high risk
3-model biomarker approach	Beyond Milan	AFP (> 250 ng/mL) or AFP-L3 (> 35%) or DCP (> 7.5 ng/mL)	Higher recurrence with any of these criteria
AFP-L3 and DCP biomarker profile	Within or exceeding Milan criteria	AFP-L3 < 15% DCP < 7.5 ng/mL	3-year recurrence free survival: negative dual biomarker 97% vs. positive 43%

Note: Not incorporated in the multivariable model for transplant selection.
**AFP response: difference between maximum and final pre-transplant AFP values.

with the aim of reducing the viable tumour burden to allow LT. Despite that several scientific societies have recognised downstaging as an instrumental tool for expanding the indication for LT [58], some aspects are still a matter of debate such as the limits on tumour burden and/or AFP values for attempting downstaging, the degree of tumour response to be achieved, and the duration of response to consider downstaging successful. The most popular and externally validated downstaging protocol is the University of California San Francisco (UCSF-DS: one lesion > 5 cm and ≤ 8 cm; two to three lesions each ≤ 5 cm with a total tumour diameter ≤ 8 cm; or four to five lesions each ≤ 3 cm with a total tumour diameter ≤ 8 cm; AFP values < 1000 ng/mL) [59, 60]. However, external validations in the USA showed worse outcomes, and an AFP < 100 ng/mL is suggested for better candidate eligibility [61]. This highlights the need for combined models in the downstaging setting, with the preconception that the greater the "*expansion*" in terms of number and diameter, the lower AFP values should be requested [62]. The best evidence supporting the use of downstaging comes from the XXL trial, an open-label, multicenter, randomised, controlled, phase 2b/3 trial comparing LT against the best available treatment after successful downstaging [20]. In the intention-to-treat analysis, the 5-year OS was 77.5% (95% CI, 61.9–97.1) in the LT group versus 31.2% (95% CI, 16.6–58.5) in the control group (HR, 0·32; 95% CI, 0·11–0·92; $p = 0·035$).

3 | Potential Role of Immune Checkpoint Inhibitors for Downstaging

3.1 | Immune Checkpoint Inhibitors for Unresectable or Metastatic HCC

Over the past few years, the landscape of HCC treatment has undergone a paradigm shift, with ICI-based therapies rapidly becoming the standard of care for unresectable or metastatic HCC (uHCC) [63]. Compared to the previous standard-of-care treatment with tyrosine-kinase inhibitors (TKI) [64, 65], ICIs provide a longer duration of response, which is key to preventing disease progression while on WL, and an improved safety profile [63].

Four pivotal trials, IMbrave150, HIMALAYA, CARES-310, and CheckMate 9DW, have demonstrated the superiority of ICI combinations over sorafenib or lenvatinib for patients with uHCC [66–69]. The IMbrave150 trial investigated the efficacy of atezolizumab, a monoclonal antibody (mAb) targeting programmed-death ligand 1 (PD-L1), combined with bevacizumab, a mAb that inhibits vascular endothelial growth factor (VEGF). The combination therapy significantly improved the median OS of patients with uHCC from 13.4 months reached in the sorafenib arm to 19.2 months in the ICI regimen. Of note, atezolizumab plus bevacizumab achieved an objective response rate (ORR) of 30% with RECIST v1.1 criteria and 33.2% with modified RECIST (mRECIST) criteria [69, 70]. The HIMALAYA trial explored a different combination using durvalumab (anti-PD-L1) and a single priming dose of tremelimumab (anti-cytotoxic T lymphocyte antigen-4 [CTLA-4]) [68]. The combination met its primary endpoint, with the patients treated in the experimental arm reaching a median OS of 16.4 months versus 13.8 with sorafenib, and with the survival advantage being maintained after 4 years of follow-up [71]. The difference was found to be significant despite a lack of difference in median progression-free survival (PFS) (3.78 vs. 4.07 months for the experimental arm and sorafenib, respectively), while ORR was 20.1% with the experimental regimen and 5.1% with sorafenib, according to RECIST v1.1 criteria.

The CARES-310 study has further expanded the treatment options for patients with uHCC [66]. Patients receiving camrelizumab (anti-PD-1) combined with rivoceranib (a selective VEGF receptor 2 oral inhibitor) reached an unprecedented median OS of 22.1 months versus 15.2 months in the sorafenib arm, with an ORR of 25% and 33.1% per RECIST v1.1 and mRECIST, respectively. Thus, the combination of camrelizumab plus rivoceranib is a potential new first-line treatment for HCC, marking the first ICI to be combined with an oral anti-angiogenic agent in this setting. More recently, the combination of nivolumab (anti-PD-L1) plus ipilimumab (anti CTLA-4) significantly improved the median OS from 20.6 months reached in the sorafenib or lenvatinib arm to 23.7 months in the ICI combination arm (HR, 0.79; 95% CI, 0.65–0.96; $p = 0.0180$) [67]. These landmark studies have established the current recommended options for first-line treatment of patients with uHCC according to international guidelines [1, 72].

3.2 | Combining Immune Checkpoint Inhibitors With Locoregional Therapy

Radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and transarterial radioembolization (TARE) are established LRT for early and intermediate-stage HCC, including pre-LT patients [73]. These therapies work by exerting a targeted anti-tumour effect, either via a direct cytotoxic mechanism or via the embolization of the vascular tumour supply. By triggering the release of tumour antigens and inflammatory cytokines, LRT creates an immunogenic tumour microenvironment, essentially priming the immune-mediated anti-cancer activity [74, 75]. For instance, TACE has been shown to induce immunogenic cell death, while simultaneously promoting Th17 and $CD8^+$ T cell activation and reducing the number of peripheral Tregs [76, 77]. Building upon this rationale and the success of ICI therapy in uHCC, the potential of combining immunotherapy with LRT has been explored in early- and intermediate-stage HCC. In the phase 1b PETAL study, the combination of TACE and PD-1 monotherapy was shown to be safe, and it led to changes both in the tumour microenvironment and in the peripheral immune profile [78]. The recently reported EMERALD-1 trial was the first phase 3 trial investigating the combination of TACE plus an ICI regimen [79]. Patients considered eligible for TACE were randomised to receive TACE plus durvalumab and bevacizumab, TACE plus durvalumab, or TACE plus placebo. The primary endpoint of the study was met, with the addition of durvalumab and bevacizumab to TACE significantly improving median PFS compared to TACE alone (15.0 vs. 8.2 months, HR 0.77, $p = 0.032$). In addition, the ORR increased to 43.6% per RECIST v1.1 criteria versus 29.6% with TACE alone. Intriguingly, a secondary survival analysis showed a lack of PFS benefit between patients treated with durvalumab plus TACE versus TACE alone, thus pointing to a likely synergistic role of bevacizumab with ICI. Finally, the LEAP-012 study recently demonstrated a clinically meaningful and statistically significant improvement in PFS for patients with intermediate-stage HCC treated with lenvatinib + pembrolizumab + TACE compared to dual placebo + TACE (14.6 vs. 10 months, HR: 0.66 [95% CI, 0.51–0.84], $p < 0.001$). A favourable OS trend will be evaluated in future analyses in accordance with the statistical analysis plan (HR: 0.80 [95% CI, 0.57–1.11], $p = 0.086$). The ORR was 46.8% vs. 33.3% by RECIST 1.1 and 71.3% vs. 49.8% by mRECIST, with no new safety concerns identified [80].

3.3 | Adjuvant Treatment for HCC

Patients diagnosed with BCLC 0-A HCC can potentially be cured with tumour ablation or liver surgery. However, relapse rates can be as high as 70% in the first 5 years after resection [81], with a typical bimodal occurrence around 1 and 5 years after surgery [82]. Adjuvant therapies have been explored with the aim of targeting residual micrometastatic disease and reducing relapse rates. After the negative results of the STORM trial, where adjuvant sorafenib failed to improve recurrence-free survival (RFS) [83], in the pre-specified first interim analysis of the phase 3 IMbrave050 trial, the combination of atezolizumab plus bevacizumab significantly prolonged RFS compared to

active surveillance for patients with high-risk disease treated with RFA or liver surgery, with a reduction in the risk of relapse and/or death by 28% (HR 0.72, $p = 0.012$) [84]. Regrettably, after longer follow-up, the updated RFS HR was 0.90 (95% CI, 0.72, 1.12) and thus, the initial benefit in RFS was not sustained [85]. Patients undergoing liver resection with evidence of microvascular invasion on the surgical specimen might also benefit from an adjuvant course with another inhibitor of the PD-1/PDL-1 axis, sintilimab, which achieved a significantly longer RFS in a phase 2 trial compared to active surveillance [86]. Although not an option for transplant patients, adjuvant ICI therapy offers the potential to improve cure rates in patients undergoing radical treatments, though its benefits in terms of RFS and OS still require validation in long-term follow-up analyses. Ongoing phase 3 trials, despite significant heterogeneity in selection criteria, are likely to provide new insights into therapeutic options in this setting (EMERALD-2 [87], CheckMate-9DX [88], KEYNOTE-937 [89]).

3.4 | Challenges and Opportunities for Immune Checkpoint Inhibitors as Downstaging Treatment Strategy

LT is a potential curative option for both cancer and underlying cirrhosis. However, up to ~20% of patients experience HCC recurrence after LT [90], and ICIs are potentially contraindicated in these patients due to an increased risk of graft rejection. Consequently, for LT candidates, the neoadjuvant setting represents the exclusive therapeutic window of opportunity to receive ICIs. Treatment options for recurrent HCC post-LT are limited, and prognosis remains poor [91], therefore reducing the risk of post-LT recurrence is an area of high unmet need. A higher tumour burden and longer waiting time for LT are key determinants of relapse risk, building a case for incorporating ICI in pre-LT management. Sorafenib has been used as part of integrated downstaging strategies, showing the feasibility and the potential survival benefit of systemic treatment prior to LT [20]. An ORR exceeding 40% achieved by ICI-LRT combinations can offer novel opportunities for disease downstaging, potentially increasing the number of patients eligible for LT. In addition, anti PD-1/CTLA-4 inhibition could have the potential to provide durable disease control during WL, potentially reducing the risk of dropout and post-LT relapse. However, the use of ICI is not deprived of the risk of treatment-related adverse events (trAEs), with potential delays in LT [92]. G3-4 trAEs were reported in 25.8% of patients treated with durvalumab-tremelimumab [68] and 43% with atezolizumab-bevacizumab [69], with immunosuppressive treatment for immune-related AEs needed in 20% and 12.5% of patients, respectively. However, as demonstrated in a number of experiences with neoadjuvant ICI prior to liver resection, the risk of treatment-related delays to surgery is negligible, likely due to the limited exposure to ICI prior to surgery [93–97]. The blockade of key immune-regulatory pathways induced by ICIs might entail an increased risk of allograft rejection when ICIs are used prior to LT. Prospective studies are currently investigating the safety of ICI used as a bridge therapy prior to LT (NCT04425226, NCT04443322, NCT05339581, NCT05185505). Several phase 3 trials, such as EMERALD-3 [98] or CheckMate 74W, are expected to be published in the near future, likely expanding the landscape of treatment options combining ICI and LRT. This could potentially broaden the possibilities for downstaging tumours to curative treatments, such as LT, and shed light on the recently proposed concepts of "reverse therapy" and "therapeutic hierarchy" [99].

4 | Relevant ICIs-Related Toxicities That May Impact on Potential LT Candidates

A significant concern regarding the use of ICIs in LT candidates is the potential risk of side effects, which may be particularly complex in this setting and can occur both before and after LT. Regarding the pre-LT period, it should be noted that toxicity can affect any organ, although we focused on heart, liver, and kidney toxicities.

4.1 | Pre-Transplant Toxicities

4.1.1 | Cardiovascular Toxicity

The prevalence of cardiovascular risk factors, including older age and previous cardiovascular events (CVE), is increasingly higher in LT candidates [100, 101] and CVE are among the most frequent causes of death, both in the early post-operative period and in the long-term [102–106]. In a recent study, the prevalence of severe coronary calcifications (Agatston score ≥ 400) in 245 LT candidates undergoing coronary artery calcification score (CACS) was 26%, which increased the risk of post-LT CVE nearly 4-fold. In the same study, 30% of patients undergoing invasive coronary angiography (ICA) had significant coronary artery disease (CAD) [107]. Similarly, in a large American cohort of LT candidates that underwent ICA, 28% had non-obstructive CAD and 16% significant CAD [108]. In addition to this, heart failure is the second most frequent early post-LT CVE [105] and has been associated with the degree of pre-LT cardiac dysfunction [109, 110].

Patients who undergo treatment with angiogenesis inhibitors such as anti-VEGF monoclonal antibodies (i.e., bevacizumab) or TKI (i.e., sorafenib) may be at increased risk of these complications, considering the key role of angiogenesis in the development and function of vasculature. Indeed, angiogenesis inhibition, either with VEGF antibodies or TKI, has been associated with a higher risk of hypertension, cardiac ischemia, arterial thromboembolism, and heart dysfunction in lung, breast, or colorectal cancer [111–114]. In a recent study of patients with HCC, the incidence of CVE in sorafenib-treated patients was 11% and could be predicted with a point-based score (CARDIOSOR) [115], which has been externally validated [116]. The risk of CVE with bevacizumab in HCC patients seems to be similar to that of sorafenib-treated patients [117].

Cardiac toxicity associated with ICIs has heterogeneous manifestations including myocarditis, pericardial disease, vasculitis, including temporal arteritis, and non-inflammatory heart failure and has been underreported [118, 119]. In patients with cirrhosis and HCC, cardiovascular toxicity seems extremely low

at least in clinical trials [92] and in a real-world setting [120]. The association of ICIs and angiogenesis inhibitors seems to increase the risk of high-grade hypertension but not of acute vascular events [121].

Altogether, these data highlight the potential impact of these treatment strategies on peri-LT CV outcomes. Specific guidelines to risk-stratify and manage these patients, particularly in the setting of LT, are lacking. However, it seems crucial to keep the threshold low to consider these patients at risk of CVE and consequently perform a thorough, multidisciplinary evaluation of cardiovascular disease in order to develop strategies to mitigate risk, both before and after LT [122–124].

4.2 | Liver Toxicity

The incidence of ICI-associated hepatotoxicity in patients with cirrhosis treated for HCC is higher and occurs at an earlier stage than in patients who are treated for non-hepatic cancers [125]. Nevertheless, the altered liver tests must be carefully assessed within the context of cirrhosis to determine whether they are attributable to immune-mediated toxicity [126]. In evaluating the severity of the condition, it is necessary to consider liver function tests at baseline [92]. It is noteworthy that hepatic and all organ adverse events did not occur more frequently in Child-Pugh B patients compared to Child-Pugh A patients undergoing anti-PD1 monotherapy [127] or atezolizumab/bevacizumab [128, 129]. To date, only one study has explored the effect of combining immunotherapy with anti-VEGF therapy on the development of hepatic decompensation. This study indicated that decompensation is more common in patients with baseline ALBI score > 1. Additionally, effective etiological treatment was associated with a lower risk of decompensation during systemic therapy. Distinguishing hepatic decompensation from tumour progression can be challenging, underscoring the need for careful patient selection and appropriate management of portal hypertension prior to initiating treatment [130, 131].

4.3 | Nephrotoxicity

The occurrence of renal impairment during ICI and combination therapies for HCC is not exclusively associated with drug toxicity but may also be attributed to cirrhosis [132–134]. This makes differential diagnosis challenging. Bevacizumab is associated with known renal adverse effects, including proteinuria and acute kidney injury (AKI) [135]. Bevacizumab can also result in a distinctive hyaline occlusive glomerular microangiopathy, which should be distinguished from nephrotic syndrome [136]. ICI-induced nephrotoxicity appears to be a rare occurrence in HCC trials [92], although it may be underreported. The incidence rates of ICI-induced renal toxicities (including patients treated for non-hepatic cancer) have been reported to range from 9.9% to 29% [137]. It can present as severe AKI and, although may be partially reversible, concerns persist regarding the renal function sequelae and the possibility of restarting ICI treatment [138].

4.4 | Perioperative Surgical Complications

The risk of perioperative surgical complications may also be a concern when evaluating LT candidates undergoing combinations that include VEGF inhibitors. Bevacizumab has been associated with surgical complications such as dehiscence, ecchymosis, surgical site bleeding, or wound infection [139–141]. While in colon cancer, discontinuation of bevacizumab 6 weeks before surgery is recommended [142], the optimal wash-out period in LT is unknown due to the additional intrinsic peculiarity of the unpredictability of transplant surgery except for living donation. In the few reported cases of patients with HCC receiving bevacizumab before LT the time between treatment completion and LT range between 7 days and 10 months [143–147].

4.5 | Graft Rejection

Early fatal acute graft rejection relative to the use of pre-LT ICI has been described [148, 149], questioning the possibility of using these drugs in the LT setting. However, some reports have highlighted the efficacy of pre-LT ICI and suggested that seeking an appropriate interval between ICI and LT is probably a safe approach [150]. Whether there is a need for a wash-out period, and if so, how long it should be, is still a matter of debate. A case series reported safe transplantation in 9 patients with washout periods ranging from 1 to 253 days [151]. A recent case report described safe LDLT after 6 weeks of ICI discontinuation [152]. A multicenter retrospective study of 83 patients suggested a 30-day wait before proceeding with LT, due to the significantly higher risk of rejection in patients transplanted with a shorter washout period [153]. On the other hand, the most appropriate washout period was found to be 3 months in a small series [154]. Similarly, a recent meta-analysis of 91 patients found that older age and a longer ICIs washout period significantly lowered the risk of allograft rejection. Specifically, each 10-year increase in age reduces the risk by 28%, and each additional week of wash-out decreases the risk by 8% [155]. More recently, a multiregional U.S. study (2016–2023) evaluated 117 HCC patients treated with ICIs prior to LT. Of the cohort, 73.5% were initially beyond MC, who 75.6% were successfully downstaged. A total of 43 patients underwent LT, 19.7% of whom were initially beyond MC. The study found no grade 4–5 adverse events pre-LT, with a 3-year intention-to-treat survival rate of 71.1% and a 3-year post-LT survival rate of 85%. Post-LT rejection occurred in 7 patients, primarily when ICIs were administered within 3 months of LT. Predictors of dropout included exceeding MC, AFP doubling, and poor radiological response. While these findings may support the safe and effective use of ICIs in the peri-transplant setting, they also underscore the variability in the effects of ICIs among individuals [156]. Additionally, it is important to consider the influence of blood product transfusions and estimated blood loss during LT surgery on the likelihood of acute rejection in patients previously treated with ICIs, as these factors can alter ICIs pharmacokinetics and subsequently, the risk of graft rejection. In this context, peri-LT plasmapheresis could help mitigate this risk, particularly in cases with minimal intraoperative blood loss and a short ICIs washout period [157]. Finally, the absence of

data on immunosuppressive regimens and cumulative dose of calcineurin inhibitors complicates the interpretation of existing studies, as these variables are crucial in determining the risk of graft rejection. A more comprehensive understanding of these interactions is essential for safe pre-LT use of ICIs.

5 | Immunosuppression for HCC Patients

Calcineurin inhibitors are the mainstay of immunosuppression in LT, with tacrolimus preferred over cyclosporin [158]. Studies performed in animal models have shown a dose-dependent pro-oncogenic effect of tacrolimus by triggering transforming growth factor beta 1 [159]. In two large cohort studies, patients developing *de novo* malignancies after LT had received higher tacrolimus trough levels than patients remaining cancer-free, with colorectal, lung, and skin tumours being particularly vulnerable to tacrolimus overexposure [160, 161]. According to the manufacturer's recommendations, tacrolimus dose should be titrated to target whole blood trough levels of 5–20 ng/mL within the first week, and 5–15 ng/mL thereafter. However, in patients with HCC undergoing LT, tacrolimus trough levels > 10 within the first month after LT are associated with doubled rates of tumour recurrence [162, 163]. Although cumulative exposure to tacrolimus over time may exert an incremental effect on post-LT malignancy, it seems that minimization within the first weeks after LT are the key to prevent HCC recurrence in the long term [161, 164]. A meta-analysis of randomised controlled trials demonstrated that trough concentrations of tacrolimus < 10 ng/mL within the first month after LT do not increase the risk of rejection but result in lower renal impairment rates compared with higher levels [165]. Therefore, in patients with HCC, tacrolimus trough concentrations between 6 and 10 ng/mL within the first month with a progressive reduction to achieve 4 ng/mL in the long term are considered safe, even in monotherapy, and higher doses should be avoided [166].

The combination of tacrolimus with other immunosuppressants would allow further reduction of blood trough target concentrations and theoretically provide an additional benefit in terms of lowering the risk of tumour recurrence. Inhibitors of the mammalian target of rapamycin (mTOR), sirolimus and everolimus, are considered particularly attractive due to their inherent antiproliferative properties [167]. Indeed, mTOR inhibitors allow to effective reduction of tacrolimus, but there is contrasting evidence regarding its effect on tumour recurrence. Retrospective studies suggest that mTOR inhibitors decrease the risk of HCC recurrence [168], but prospective studies and randomised trials have failed to confirm this effect [169, 170], probably owing to attrition bias: patients who withdrew mTOR inhibitors due to side effects are not accounted for in retrospective studies. The universal prescription of mTOR inhibitors in patients with HCC is not supported by current evidence. However, the combination of minimised tacrolimus and everolimus may be useful in patients with a priori high risk of tumour recurrence (expanded criteria, microvascular invasion, poor histological differentiation, etc.), in whom the theoretical oncological benefit would overcome the side effects associated with everolimus [171, 172]. If this immunosuppression protocol is implemented, it seems reasonable to keep trough concentrations of everolimus high whenever tolerated (i.e., 3–8 ng/mL), with tacrolimus trough levels between 3 and 5 ng/mL [172, 173]. Other immunosuppressive drugs used in LT, such as mycophenolate, induction therapies, or steroids, may not impact on HCC recurrence beyond the indirect effect resulting from tacrolimus minimization. The question arises about how far we can go in tacrolimus minimization to avoid graft loss while preventing HCC recurrence in a particular patient [174]. Very aggressive minimization protocols could increase the risk of formation of *de novo* donor-specific antibodies and acute rejection, particularly in young patients with underlying autoimmune disease [175]. However, most patients with HCC who qualify for LT are men older than 50 years without autoimmune conditions and should be considered at low-moderate risk of rejection [176]. The lowest tacrolimus trough concentrations tolerated should be individually explored under close analytical surveillance within the first weeks after LT for an optimal balance between long term graft viability and minimal risk of HCC recurrence (Table 2).

The recurrence of HCC after LT occurs in up to 20% of patients, mainly within the first 5 years, yet recurrences may also

TABLE 2 | Recommendations for tailoring immunosuppression in patients with hepatocellular carcinoma undergoing liver transplantation.

Mandatory	Suggested	Possible neutral effect
	Explore the lowest tacrolimus trough levels tolerated under close surveillance. Combine tacrolimus with other immunosuppressants to facilitate minimization	Corticosteroids (maintenance or boluses)
Avoid tacrolimus trough concentrations > 10 ng/mL	Combine tacrolimus with other immunosuppressants to facilitate minimization	Induction therapies
	Consider the addition of an mTOR inhibitor as the preferred strategy to achieve early minimization of tacrolimus in patients with risk factors of tumour recurrence	Mycophenolate mofetil

occur beyond that time point. Post-LT HCC recurrence can be divided into disseminated disease or oligo-recurrence inside or outside the liver graft, being lungs and bone the most common extrahepatic sites [177, 178]. Importantly, the early detection of HCC recurrence after LT by implementing periodic imaging surveillance may improve the chances of receiving curative therapies to maximise post-recurrence survival [179]. Early disseminated recurrence usually translates to a more aggressive behaviour than late extrahepatic oligo-recurrence. All patients with post-LT HCC recurrence should be promptly evaluated for an onco-specific approach and reassessment of immunosuppression [180]. There are no established protocols to manage immunosuppression after HCC recurrence, and it is unclear whether these modifications would translate into improved oncological outcomes. Retrospective data in the context of *de novo* malignancies after LT support minimization (or complete withdrawal) of calcineurin inhibitors in favour of mTOR inhibitors, which may be safe in terms of rejection and could have a favourable effect on survival [181–183]. However, most of these *de novo* malignancies occur beyond 5 years after LT, thus claiming caution before extrapolating recommendations to patients with early HCC recurrence. As stated above, LT patients with HCC could display a lower risk for rejection, probably owing to the presence of increased number of myeloid-derived mesenchymal cells in the tumour, which exert immunosuppressive action [184].

ICIs have become first line therapies for patients with advanced HCC; however, their use in the transplant setting raises unanswered questions. Firstly, do patients with ICIs treatment before LT need specific immunosuppressive management after LT? The risk of rejection in patients previously exposed to ICI is higher compared to those not treated with ICIs, especially when using anti-PD1 within 60–90 days prior to LT [22]. Aggressive minimization of calcineurin inhibitors early after LT should be avoided in these patients, but the optimal immunosuppression strategy is unknown. Secondly, is there a role for ICIs after LT in treating HCC recurrence and how to adapt the immunosuppression strategy in such a scenario? Efficacy and safety data of ICIs after LT are lacking, but the shorter the interval from LT to ICIs treatment, the higher the risk of rejection, which could lead to graft loss and death [185]. Preliminary observations suggest that the identification of ICIs molecules within the tumour after LT (i.e., staining of PD-1) could be a potential strategy to predict the response to ICIs therapy and to assess the risk of rejection [186]. Some authors recommend strengthening immunosuppression when starting ICIs in LT patients, particularly by increasing tacrolimus doses, since preclinical studies showed that the antitumoral effects of ICIs would be preserved [187]. Another option would be combining tacrolimus and mTOR inhibitors before starting ICIs. However, it is unclear whether these strategies would reduce the risk of rejection and immune-mediated graft loss. A careful balance of immunological risks and oncological benefits should be made before starting ICIs after LT and the adjustment of immunosuppression should be done on a case-by-case basis, given the paucity of clinical trials [175]. Before starting ICIs, the assessment of donor-specific antibodies and a liver biopsy could be considered to rule out subclinical rejection. However, it is important to emphasise that, as of today, the use of ICIs in the post-LT setting is not recommended due to the significant risk associated with graft loss [188, 189].

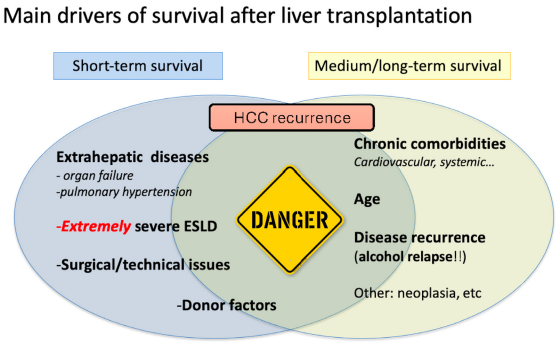

FIGURE 3 | Main drivers of survival after liver transplantation. ESLD, end stage liver disease; HCC, hepatocellular carcinoma.

6 | The Future of LT for HCC in the Era of ICIs

LT is considered the optimal treatment for patients with HCC, especially for those with compromised liver function. However, its implementation has been hindered by a scarcity of donors. This limitation has primed the development of various models to select candidates who are most likely to achieve favourable outcomes and to establish allocation and prioritisation policies. These policies should be tailored to local donor rates and WL dynamics to maximise the OS benefits for HCC patients, without adversely affecting other candidates.

Predicting outcomes after LT has become increasingly challenging owing to the multitude of pre- and post-LT variables that significantly impact prognostic estimations (Figure 3). A particular aspect contributing to this complexity is the rising age of LT candidates, which augments the prevalence of comorbidities and the risk of cardiovascular events, which are currently the leading cause of death post-LT.

Currently, expanding the transplant eligibility criteria for HCC presents a considerable ethical and logistical challenge. It is imperative to ascertain that such expansion not only benefits individuals requiring transplantation, but also optimises organ allocation within the competitive and disproportionate environment of candidates versus available organs. On one hand, we must scrutinise the inherent risks entailed by novel protocols employing ICIs or their combinations, as well as the uncertainties associated with the timing of surgery. Moreover, the risk of HCC recurrence remains a significant concern as selection criteria continue to be pushed further, regardless of the efficacy of new therapeutic strategies. While an intact immune system is crucial for an improved response to pre-LT therapy, in post-LT there is a need to mitigate the potential risk of graft loss resulting from an augmented immune response, which could undermine the oncologic control attained during the WL period. Additionally, it is essential to understand the management of potential immunological compromises associated with ICIs use. This includes not only the wash-out period for ICIs, but also the potential role of adjuvant treatments such as peri-LT plasmapheresis, and the careful adjustment of immunosuppression levels post-LT to balance the benefits of preventing graft rejection against the risk of HCC recurrence. Finally, in a scenario requiring increased immunosuppression to counteract the risk of immunological graft loss, we must understand how this will impact the risk of non-hepatic

complications, such as chronic renal damage, increased cardiovascular events, or even *de novo* tumours development, to ensure that these do not become barriers to long-term OS.

This complex landscape underscores the need to direct future research toward identifying effective strategies that address fundamental aspects, ensuring benefits not only at the individual level but also without compromising the collective benefit of LT across all candidate populations. The integration of clinical evidence and predictive algorithms is crucial to refine decision-making, always guided by the principles of transparency and equity, to maintain a balance between individual needs and overall population benefit.

Authors Contribution

The author takes full responsibility for this article.

Conflicts of Interest

- E. Mauro: Received lecture fees from Roche and Sirtex, and travel funding from MSD.
- M. Rodríguez-Perálvarez: Received lecture fees from Astellas, Chiesi, and Advanz Pharma.
- A. D'Alessio: Received educational support for congress attendance from Roche, and consultancy fees from Roche, Astrazeneca, and Chugai.
- The authors declare no conflicts of interest.
- F. Piñero: Received lecture fees, advisory board and grants from ROCHE, BAYER, LKM Knight, RAFFO and Astrazeneca.
- E. De Martin: Received lecture and consultancy fees from IPSEN, GSK, Chiesi, Astellas
- J. Colmenero: Received lecture fees and travel grants from Chiesi and Astellas.
- D.J. Pinato: Received lecture fees from Astra Zeneca, Roche, EISAI, Boston Scientific, IPSEN and Bayer Healthcare, travel expenses from BMS, Roche, EISAI and Bayer Healthcare; consulting fees for Mina Therapeutics, iTeos, Avamune, EISAI, Roche, IPSEN, DaVolterra, Starpharma, Mursla and Astra Zeneca; received research funding (to institution) from MSD, GSK and BMS.
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Data Availability Statement

The authors have nothing to report.

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