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Review

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# Liver transplantation for hepatocellular carcinoma - non-cancer factors and implications for improving outcome beyond standard tumor criteria

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## Abstract

Liver transplantation (LT) is recognized as best treatment option in patients with early hepatocellular cancer (HCC) in underlying liver cirrhosis. Apart from tumor size and number implemented in the Milan criteria, which are current worldwide standards for patient selection, several biological tumor factors have been identified to affect cancer-specific outcome. In particular, grading and vascular tumor invasions were shown to correlate with aggressive biological tumor behavior and poor survival following LT. Identifying tumors with favorable biology is one important approach for expanding the pool of eligible liver recipients beyond the Milan burden limits. Improving the immunological state and condition for appropriate defense against circulating cancer cell attack may be another important prognostic aspect. Therefore, there is increasing interest in non-cancer factors related to the peritransplant period that may influence the oncological outcome by providing negative immunomodulatory actions. Considering and modulation of these non-HCC factors of prognosis might contribute in safely expanding the HCC LT selection criteria.

**Keywords:** Hepatocellular carcinoma, liver transplantation, tumor biology, non-cancer factors, outcome

## INTRODUCTION

In the last 40 years, liver transplantation (LT) has developed as a generally accepted standard procedure in the treatment of a wide range of end-stage liver diseases. Especially liver replacement for hepatocellular carcinoma (HCC) in underlying liver cirrhosis became a phenomenal story of clinical success in oncological surgery[1].

Due to cirrhosis-related portal hypertension (PH) and liver dysfunction, these patients are mostly not eligible for hepatic resection, so that only palliative treatment options have frequently been possible in former days[2]. In particular, the implementation of the so-called Milan criteria (MC) in 1996 for realizing a strict and rigid selection process based on radiographic tumor size and number (one tumor nodule ≤ 5 cm, or up to 3 HCC nodules each ≤ 3cm, no macrovascular invasion) established LT as best curative treatment option in early stage HCC patients[3]. The pre-MC era was characterized by high posttransplant tumor recurrence rates and mortality, which was not acceptable in view of donor organ shortage[4,5]. In contrast, numerous validation trials have clearly shown that Milan-based LT for HCC produces excellent long-term survival rates above 70% at 5 years, which was absolutely comparable to those of other transplant indications[6-8]. Therefore, the MC have been implemented as standard selection features in large public allocation systems, such as the United Network of Organ Sharing (UNOS) and Eurotransplant[9,10]. Currently, in times of model for end-stage liver disease (MELD) score based organ allocation, priority is still given to patients with HCC meeting the MC[11,12].

With increasing experience in rescue LT of marginal donor grafts and living donor liver transplantation (LDLT), who are both independent from MELD-based allocation rules, it became evident in recent years that the MC are too rigid and very often unjustifiably preclude patients with beyond MC tumors from potentially curative treatment[13-15]. In order to increase the pool of eligible transplant patients, several expanded macromorphologic tumor selection criteria have been proposed, such as the University of California San Francisco (UCSF) and the registry based Up-to-seven (UTS) criteria[16-18]. However, as shown in the metroticket concept, increasing "distance" from the MC burden limits enhances the oncological risk[18]. In addition, differences between radiologic and pathologic tumor staging additionally hamper the clinical applicability of tumor size based selection approaches[19,20]. Poor differentiation and vascular (micro/macro) invasion of the tumor were identified as most important predictors of unfavorable tumor biology in the LT setting[21-23].

However, both histopathologic features may not adequately be assessed prior to LT by radiographic tools or by using tumor biopsy[24-26].

The identification of patients with aggressive tumor behavior is one important clinical practice to safely expand the pool of eligible liver transplant recipients beyond the MC[27-29]. Different surrogate markers of tumor biology were shown to improve the selection process beyond the MC, such as alpha-fetoprotein (AFP)[30,31], protein induced by Vitamin K absence II (PIVKA-II)[32,33], serological inflammatory markers [C-reactive protein (CRP); neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR)][34], 18F-fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET)[35,36] and tumor downstaging under locoregional treatments[37,38]. Apart from that, there is increasing evidence that not only tumor-specific characteristics, but also non-cancer factors may decisively influence cancer-specific outcome. Beneficial modulations of these non-HCC related factors might probably be another useful approach to improve post-LT prognosis, since HCC recurrence is the major risk factor for poor overall survival (OS). Therefore, it was the major aim of this manuscript to review the current available clinical data on the prognostic impact of non-tumor factors on post-LT HCC recurrence and tumor-specific survival.

### The role of immunology and inflammation

Immunocompetence is a major prognostic factor of outcome in cancer patients. However, a specific characteristic of neoplasia is that it induces a state of inflammation and immunosuppression, which may additionally impair prognosis[39]. Since the postulation of the link between inflammation and cancer by Virchow in 1863, important molecular mechanisms of cancer-induced pro-inflammatory response reactions have been identified. Malignant cells were shown to release inflammatory and immunosuppressive cytokines to their local environment, promoting tumor invasiveness and growth. In addition, cancer itself may induce

systemic immunosuppression through multiple mechanisms and effector cells, such as T-cell exhaustion, T-regulatory cells, myeloid-derived suppressor cells and M2 macrophages[40]. In this context, HCC has an exceptional position, since 90% of the cases develop in underlying cirrhosis and fibrosis, which are promoted by chronic liver inflammation. Liver damage and necroinflammation induced by alcoholic disease, non-alcoholic fatty liver disease (NAFLD) and in particular by chronic viral hepatitis comprise a substantial risk of carcinogenesis[41,42]. Activation of the innate immune system, hepatocyte death with production of damage-associated molecules (DAMPs), T cell exhaustion, and upregulation of pro-inflammatory cytokines [interleukin (IL)-2, IL-7, IL-12, IL-15, IFN-γ] seem to be major molecular mechanisms. Thereby induced local and systemic pro-inflammatory reactions and immunosuppression lead to replication stress, DNA damage and genetic instability, which may result in development of liver cancer and impact cancer treatment[42,43].

Another important aspect is that liver dysfunction is another important prognostic factor enhancing tumor progression. The liver plays a key role in maintaining immunocompetence. In addition to numerous other mechanisms triggered by its unique blood supply, it has an essential capability to remove gut-derived microbial compounds, and hosts a great variety of innate and adaptive immune cells (sinusoidal cells, hepatic stellate cells, Kupfer cells, dendritic cells), and is able to preserve immunotolerance to non-pathogenic and inflammatory triggers. Decrease of these immunological efficacies result in a persistent up-regulation of inflammatory stimuli which may promote carcinogenesis. For example, increased levels of circulating T regulatory cells were shown to be associated with increased mortality of HCC patients[42,43].

Currently, 2 major ways of posttransplant HCC recurrence are postulated: (1) growth of pre-LT undetected extrahepatic micrometastases; and (2) engraftment of circulating tumor cells (CTC) that have been released during transplant procedures[44]. Both ways of metastasis are significantly promoted by immunological dysbalance[34]. In particular, patients with advanced HCC stages are at an extraordinary oncological risk post-LT, since macromorphologic tumor load correlates with unfavorable tumor features, such as poor grading and vascular invasion, and thereby with numbers of CTC[45,46]. A prevailing state of immunosuppression and pro-inflammation in the peritransplant period might, therefore, be particularly dangerous for advanced HCC LT patients. Consequently, recipients' factors (cirrhosis, sarcopenia), liver graft quality, surgical procedure and post-LT immunosuppressive treatment as non-cancer features affecting the immunological state have to be considered in order to safely expand the patient selection criteria.

## Recipients' factors
### *Background liver cirrhosis*
Progressive liver cirrhosis induces complex pro-inflammatory and immunosuppressive mechanisms referred to as cirrhosis-associated immune dysfunction (CAID) syndromes[47]. This may impair outcome following non-surgical treatment and hepatic resection[48,49]. This aspect has not yet been intensively studied in the LT setting so far, which may be due to the fact that most HCC transplant patients present with less severe Child A or B cirrhosis and liver dysfunction are cured by liver replacement, probably implying that CAID has no influence on posttransplant clinical course. However, some interesting recent data have shown that the extent of background native cirrhosis may affect cancer-specific outcome in the LT setting [Table 1]. Already in 2008, Ioannou *et al.*[50] demonstrated in a large study cohort using the UNOS database, that apart from increased AFP level, laboratory (lab.)MELD score ≥ 20 was the most important predictor of poor post-LT survival. Again by using the UNOS dataset of 3519 liver transplants, Halazun *et al.*[51] identified pretransplant rising (lab.)MELD score as an independent predictor of microvascular invasion (MVI) on explant pathology, which in turn was the most important factor of poor cancer-specific outcome. Others have recently confirmed the oncological significance of background cirrhosis severity in the liver transplant setting[52-54]. In a series of 243 transplant candidates with HCC, Faitot *et al.*[55] demonstrated that clinically evident portal PH was

**Table 1. Impact of stage of underlying cirrhosis on post-LT HCC recurrence**

| Ref. | n | Characterization of cirrhosis severity | Impact on post-LT outcome |
|---|---|---|---|
| Ioannou et al.[50] | 4453 | (lab.) MELD score ≥ 20 | Calculated MELD score ≥ 20 was the most important predictor (HR = 1.61; 95%CI 1.3-2.1) of poor post-LT survival, along with AFP level. The risk of post-LT death was almost doubled in patients with either AFP level ≥ 455ng/mL or MELD score ≥ 20 (HR = 1.97; 95%CI 1.6-2.5) |
| Halazun et al.[51] | 3519 | Pre-LT rising (lab.) MELD score | Rising pre-LT MELD score proved to be an independent predictor of MVI on explant pathology (OR: 1.46, CI 1.13-1.88; $P$=0.004), which was the most important factor of poor post-LT outcome |
| Macdonald et al.[52] | 1074 | (lab.) MELD score | Calculated MELD score was identified as an independent predictor of HCC recurrence or death after LT (HR = 1.03; 95%CI 1.01-1.05; $P$ = 0.005), along with AFP level and donor risk index |
| Komorowski et al.[53] | 142 | (lab.) MELD score | Apart from AFP level, pretransplant calculated MELD score turned out to be an independent and significant predictor of RFS (HR = 1.16) |
| Foerster et al.[54] | 304 | (lab.) MELD score ≥ 15 | Calculated MELD score ≥ 15 was an independent promoter of poor OS (HR = 1.028; 95%CI 1.002-1.053: $P$ = 0.033), with HCC relapse to be the major reason of mortality |
| Faitot et al.[55] | 243 | Clinically evident portal hypertension | PH was an independent predictor of drop out from the waiting list due to tumor progression (OR = 2.79; 95%CI 1.02-7.69; $P$ = 0.04). In an intent-to-treat analysis, post-LT OS was significantly lower in PH patients when compared to those without PH ($P$ = 0.044). However, PH had no significant impact on outcome in the transplanted patients |

AFP: alpha fetoprotein; HCC: hepatocellular carcinoma; HR: hazard ratio; LT: liver transplantation; lab: laboratory; MELD: model for end-stage liver disease; MVI: microvascular invasion; OS: overall survival; PH: portal hypertension; RFS: recurrence-free survival

an independent promoter of drop out from the waiting list due to tumor progression. In an intent-to-treat analysis, post-LT OS was significantly lower in PH patients when compared to those without PH. However, PH had no significant impact on outcome in the subgroup of transplanted patients [Table 1].

*Sarcopenia*

Nowadays, it is undoubtedly that recipients' functional status has a major prognostic impact on liver transplant recipients[56,57]. In recent years, involuntary loss of muscle mass and strength, referred to "sarcopenia", was shown to be an early predictor of frailty and poor outcome. Sarcopenia is a feared complication in consuming chronic diseases like cancer, sepsis, renal function and liver cirrhosis[58]. The pathogenesis of sarcopenia in cirrhotics is multifactorial and not fully understood. It seems to be a response to protein-energy malnutrition, metabolic catabolism, and patients' inactivity[59,60]. Although there is currently no worldwide standard measurement and index of sarcopenia, depletion of skeletal muscle mass and function estimated by cross-sectional abdominal imaging were demonstrated to be a significant risk factor for wait list mortality, prolonged intensive care duration, complicated hospital stay, severe infections, metabolic syndrome and overall poor outcome in liver recipients, independent from underlying indication[57,61-63].

The pathophysiological mechanisms accounting for such fatal complications are not completely defined. However, it seems to be quite clear that sarcopenia and in particular sarcopenic obesity negatively affect immunocompetence via pro-inflammatory cytokines and adipokines, such as IL-1, IL-6, tumor necrosis factor (TNF)-α and leptin. Apart from that, secretion of the myokin IL-15 is decreased, which has negative effects on growth and differentiation of B and T lymphocytes, natural killer cells, macrophages and monocytes. Thus, a persistent state of immunosuppression and inflammation arises, which is not only enhancing morbidity and mortality, but may also promote cancer development[64-67]. A large retrospective analysis including 1257 HCC patients following curative and non-curative treatments has recently identified sarcopenia as an independent promoter of mortality and HCC recurrence[68].

Apart from that, several studies on hepatic resection have shown that risk of HCC recurrence is significantly higher in sarcopenic patients compared to those without muscle waste[69-72]. These data suggest that, with special regard to high immunosuppressive load early post-LT, sarcopenia-related depression of the

**Table 2. Impact of sarcopenia on post-LT HCC recurrence**

| Ref. | *n* | Surgical procedure | Impact on overall outcome | Multivariable impact on post-LT HCC relapse |
|---|---|---|---|---|
| Itoh *et al.*[72] | 153 | LDLT | Low SVR was associated with poor RFS (*P* = 0.01) and OS (*P* = 0.03.) | Low SVR was identified as an inde-pendent promoter of poor post-LDLT outcome |
| Kim *et al.*[73] | 92 | LDLT | Cumulative HCC recurrence probability was significantly higher in sarcopenic vs. non-sarcopenic MC Out patients (*P* = 0.044). HCC recurrence rates were 36.1% and 5.0% in sarcopenic and non-sarcopenic patients. | Sarcopenia was identified as an independent predictor of HCC relapse (HR = 2.25; 95%CI 1.18-76.32; *P* = 0.034), along with AFP |
| Sharma *et al.*[74] | 118 | DDLT | Overall post-LT survival was significantly lower in patients with low BMD compared to those with high BMD (*P* = 0.018) | Low BMD was identified as an independent predictor of post-LT mortality in HCC LT patients (HR = 0.90; 95%CI 0.83-0.90; *P* = 0.03) |

BMD: bone mineral density; CI: confidence interval; DDLT: deceased donor LT; HCC: hepatocellular carcinoma; HR: hazard ratio; LDLT: living donor liver transplantation; MC: Milan criteria: SVR: skeletal muscle-to-visceral fat area ratio

immunocompetence may also increase the oncological risk in LT patients [Table 2]. In a subset of 153 patients following LDLT for HCC, low skeletal muscle-to-visceral fat area ratio (SVR) was shown to predict poor recurrence-free survival (RFS) and OS. In addition, low SVR was identified as an independent and significant prognostic factor for post-LT outcome[72]. Kim *et al.*[73] have specifically studied the impact of sarcopenia in series of 92 LDLT patients with Milan Out HCC. Tumor recurrence rate was 36.1% in sarcopenic patients and only 5% in those without muscle depletion. Apart from AFP level and MVI, sarcopenia was identified as an independent and significant promoter of HCC relapse. In series of 118 HCC LT patients, Sharma *et al.*[74] were able to demonstrate that bone mineral density (BMD), an early predictor of sarcopenia, is an independent predictor of post-LT mortality, with HCC recurrence to be the most common cause of death. A recent meta-analysis by Chang *et al.*[75] including 13 studies and 3111 HCC patients after curative treatments concluded that sarcopenia is correlated with both, all-cause mortality (HR = 1.95; 95%CI 1.6-2.37) and tumor recurrence (HR = 1.76; 95%CI 1.27-2.45).

Implementing clinical features of sarcopenia in pretransplant decision making, such as the ability to walk, may significantly improve selection process and outcome[63]. In addition, perioperative interventions like intense physiotherapeutic rehabilitation and nutritional treatment are able to improve posttransplant OS[76-78]. Whether this may have a beneficial impact on oncological outcome post-LT needs to be further assessed.

Immunological dysbalance associated to malnutrition should be discovered early before sarcopenia has been established. In this context, Nagai *et al.*[78] have identified peritransplant lymphopenia, which is considered a surrogate marker of immunosuppression and poor nutritrional status, as an independent predictor of both, impaired OS and RFS following LT for HCC.

## Liver graft injury and marginal liver grafts
*Hepatic ischemia reperfusion (I/R) injury*
I/R injury to the liver graft is an inevitable process during harvesting, preservation, storage and final implantation of the organ, triggered by consecutive cold and warm ischemia periods. Severe hepatic I/R damage increases the risk of posttransplant early allograft failure and immunological complications[79]. Currently, there is growing evidence from experimental studies that immune damage and pro-inflammatory response reaction induced by allograft hypoxia promote the oncological risk[80,81]. Although the precise molecular mechanisms have not yet been identified, it seems to be evident that I/R damage has cancerogenic capabilities via different molecular approaches and levels[82]. Simply put: (1) hepatic I/R produces a pro-cancer microenvironment via microvascular disturbances, tissue hypoxia and angiogenesis; (2) resulting pro-inflammatory response reactions render HCC cells to be more aggressive by supporting mechanisms of cell adhesion, migration and invasion; and (3) hepatic I/R injury stimulates circulatory progenitor and immune cells to support post-LT HCC relapse.

**Table 3. Impact of cold and warm ischemia times on HCC recurrence following LT**

| Reference | n | Impact on tumor-specific outcome post-LT | Impact on tumor-specific outcome in unfavorable HCC phenotype |
|---|---|---|---|
| Nagai et al.[85] | 391 | Cumulative incidence of HCC recurrence was significantly higher in CIT > vs. < 10 h (P = 0.015), and for WIT > vs. < 50 min (P = 0.036). CIT (HR = 1.9; 95%CI 1.06-3.04; P = 0.03) and WIT (HR = 2.84, 95%CI 1.44-4.85; P = 0.003) were both identified as independent predictors of HCC relapse | CIT > 10 h (HR = 2.6; 95%CI 1.23-5.49; P = 0.01) and WIT > 50 min (HR = 3.23; 95%CI 1.24-8.38; P = 0.01) correlated independently with HCC recurrence in patients with vascular tumor invasion but not in those without |
| Kornberg et al.[84] | 103 | Apart from PET+ status, AFP > 400 ng/dL and beyond MC HCC, WIT > 50 min was identified as an independent and significant promoter of post-LT HCC relapse (HR = 52.5; 95%CI 6.0–458.1; P < 0.001). RFS rates at 1 and 3 years post-LT were 97.2% and 92.8% in WIT ≤ 50 min, and 61.4% and 42.0% in WIT > 50 min, respectively (P < 0.001) | In Milan In patients, HCC recurrence rate was 0% in limited but 42.2% in extended WIT (P = 0.001). In the Milan Out subset, 10 of 13 patients with WIT > 50 min (76.9%), but only 6 of 27 patients with WIT ≤ 50 min (22.2%) developed HCC relapse (P = 0.001). WIT was identified as the only independent and significant risk factor in patients with PET+ tumors (OR 15.5; 95%CI 3.0-101.5; P < 0.001) |
| Grat et al.[85] | 90 | Apart from beyond MC tumors, pre-LT AFP level and male donor sex, CO-LT (HR = 5.88; 95%CI 1.86-18.58; P = 0.003) and prolonged total ischemia time (HR = 1.48; 95%CI 1.06-2.07; P = 0.02) were identified as independent predictors of tumor recurrence | In MC In patients, RFS rates at 3 years post-LT were 100% and 66.7% following PB-LT CO-LT (P = 0.003). Corresponding data in MC Out patients were 77.8% and 48.9% (P = 0.031), respectively |
| Orci et al.[86] | 9724 | Warm ischemia time > 19 min was independently associated with HCC recurrence (HR = 4.26; 95%CI 1.20-15.1; P = 0.025) | |

AFP: alpha fetoprotein; CI: confidence interval; CIT: cold ischemia time; CO-LT: conventional liver transplantation; HCC: hepatocellular carcinoma; HR: hazard ratio; MC: Milan criteria; OR: odds ratio; PB-LT: piggy back liver transplantation; PET: positron emission tomography; RFS: recurrence-free survival; WIT: warm ischemia time

Transfer of these insights to the clinical transplant setting is still hampered by lack of clear standards of hepatic I/R injury measurement[83,84]. However, there is convincing evidence that duration of cold (CIT) and warm ischemia times (WIT), which are the major triggers of I/R damage to the liver graft, correlate with risk of HCC recurrence post-LT [Table 3].

In a series of 391 LT patients with HCC, Nagai *et al.*[85] reported that CIT > 10 h and WIT > 50 min were independent and significant predictors of overall and early post-LT HCC recurrence. In addition, both correlated independently with risk of tumor recurrence in patients with but not in those without vascular tumor infiltration.

Our transplant group was able to confirm the prognostic importance of ischemia time in a subset of 103 LT patients with HCC[84]. Both CIT (468 *vs.* 375.5 min; P = 0.001) and WIT (58.4 *vs.* 45.7 min; P = 0.001) were significantly longer in patients with compared to those without HCC relapse. Apart from PET+ status, AFP > 400 ng/dL and beyond MC tumors, WIT > 50 min was identified as an independent and significant promoter of post-LT HCC relapse[84]. RFS rates at 1 and 3 years post-LT were 97.2% and 92.8% in WIT ≤ 50 min, and 61.4% and 42.0% in WIT > 50 min, respectively (P < 0.001). In addition, WIT was able to further stratify the oncological risk in unfavorable HCC phenotype, such as PET+ tumors [Table 3].

Another interesting approach by Grat *et al.*[86] has focused on outcome differences between piggy back (PB) and conventional (Co) LT procedures for HCC. Among others, shorter duration of anhepatic phase and WIT were reported to be major outcome advantages of PB-LT (without clamping and replacement of the inferior caval vein) in comparison to CO-LT (including clamping and replacement of the inferior caval vein). In their series of 90 patients, RFS rates at 1, 2 and 3 years post-LT were 97.0%, 92.2%, and 89.4% for PB-LT, but only 75.6%, 56.0%, and 56.0% for CO-LT, respectively (P = 0.0006). Apart from beyond MC tumors, pre-LT AFP level and male donor sex, CO-LT and prolonged total ischemia time were identified as independent predictors of tumor recurrence. In addition, RFS rates were significantly different in MC In and MC Out patients when being stratified according to transplant procedure [Table 3].

**Table 4. Impact of donor age on HCC recurrence**

| Reference | *n* | Impact on post-LT HCC recurrence |
|---|---|---|
| Sharma *et al.*[95] | 94 | Median donor age was 49 y and 36 y in patients with and without HCC relapse ($P$ = 0.008). Along with number and largest diameter of tumor nodules, donor age was identified as the only pre-LT available independent risk factor of tumor recurrence (HR = 1.06; 95%CI 1.02-1.10; $P$ = 0.002) |
| Vagefi *et al.*[96] | 5002 (UNOS database) | Cumulative incidence of HCC recurrence at 1-, 2-, 3-, and 4-year post-LT was 3%, 5.1% 6.4% and 7.3% in donors < 60 y, but 4.5%, 8.3%, 10.4% and 11.8% in donors > 60 y ($P$ < 0.05). Apart from non-local organ sharing, donor age ≥ 60 years was reported to be the only independent donor-related predictor of HCC recurrence (HR = 1.42; 95%CI 1.09-1.84; $P$ = 0.009) |
| Orci *et al.*[87] | 9724 (SRTR database) | Donor age > 60 y (HR = 1.38; 95%CI 1.10-1.73; $P$ = 0.006) was identified as an independent promoter of HCC relapse |

CI: confidence interval; HCC: hepatocellular carcinoma; HR: hazard ratio; LT: liver transplantation

In another study including 9724 liver transplant recipients of the Scientific Registry of Transplant Recipients (SRTR) database, WIT ≥ 19 min was associated with increased risk of HCC relapse in uni- and multivariable analysis. However, the authors did not stratify data according to MC[87].

*Marginal liver grafts*
The dramatic shortage of appropriate donor livers enhances the risk of patients' drop-out due to tumor progression and/or morbidity or mortality related to cirrhosis progression during waiting times. Therefore, the so-called extended criteria donor grafts (ECD) are increasingly used for decreasing the fatal discrepancy between demand and donor organ availabilities[88]. In order to avoid penalizing patients with standard criteria HCC or other indications, marginal liver grafts, such as steatotic livers, living donor liver grafts, donor livers after cardiac death (DCD) and older donor grafts are currently accepted for patients with advanced HCC stages, not at least as these patients frequently present with compensated liver function. However, such ECD livers are more susceptible to severe I/R damage, which may impair immunological and oncological outcome[89].

**Steatotic donor livers**
In recent years, liver steatosis has become a serious medical issue due to growing rates of diabetes, obesity, metabolic syndrome and alcohol abuse. Consequently, the numbers of explanted, offered and finally accepted steatotic liver grafts has significantly increased in recent years. However, donor graft steatosis is associated with overall poorer outcome post-LT[90]. Based on histopathologic assessment, we distinguish between mild (< 30%), moderate (30%-60%) and severe (> 60%) liver steatosis, whereby particularly recipients of the latter are subject to an extraordinary risk of hepatic I/R damage with risk of post-LT allograft failure[91]. In an experimental setting, Orci *et al.*[92] have shown that I/R injury contributes to more severe intrahepatic and remote HCC recurrence with enhanced liver steatosis. Although statistical significance was lacking, Teng *et al.*[93] reported on a clear trend of higher HCC recurrence rates in recipients of moderate-to-severe steatotic (50%) compared to non-steatotic grafts (28.7%) and mild steatosis (20.8%). In a large registry trial (*n* = 3007), Orci *et al.*[87] reported that graft steatosis > 60% was an independent promoter of HCC recurrence post-LT (HR = 1.65; 95%CI 1.03-2.64; $P$ = 0.037).

**Donor age**
The use of elderly donor livers increases the risk of early post-LT graft loss, arterial and biliary complications, and immunological insults. Particularly presence of hepatitis C and prolonged ischemia times are known triggers of the negative impact of older donor grafts[94]. In recent years, there is growing evidence that donor age may also affect oncological outcome in HCC LT patients [Table 4]. In a retrospective study of 94 liver recipients, Sharma *et al.*[95] were the first to identify donor age as an independent predictor of HCC recurrence, along with number of tumor lesions and size of the largest tumor diameter. Two large registry studies have subsequently confirmed the oncological importance of donor age. Apart from non-local organ sharing, donor

**Table 5. Impact of graft size on outcome in LDLT for HCC**

| Reference | n | Impact of GRWR on post-LDLT outcome | Impact of GRWR on outcome in advanced HCC |
|---|---|---|---|
| Hu et al.[105] | 295 | OS was significantly better in GRWR ≤ 0.8% vs. > 0.8% (P = 0.009). RFS tended to be better in GRWR > 0.8 (P = 0.133). GWRW > 0.8% was identified as independent predictor of poor OS (HR = 2.166; 95%CI 1.173-4.001; P = 0.013), along with vascular invasion | |
| Li et al.[106] | 597 | RFS rates at 1-, 3- and 5 years were 75.9%; 73.3%, and 71.7% in GRWR < 0.8%, and 86.4%, 80.8% and 77.9% in GRWR ≥ 0.8%, respectively (P = 0.17). The corresponding OS rates were 87.8%, 80.3% and 78.7% (GRWR < 0.8%), and 93.5%, 87.1%, and 84.1% (GRWR ≥ 0.8%; P = 0.017) | The 1-, 3- and 5-year RFS rates in MC Out patients were 52.4%, 49.3% and 49.3% in GRWR < 0.8%, and 76.5%, 68.3%, and 64.3% in GRWR ≥ 0.8% (P = 0.049). The corresponding OS rates were 77.1%, 65.3%, and 61.5% (GRWR < 0.8%), and 90.2%, 80.1%, and 77.5% (GRWR > 0.8%, P = 0.047). No significant effect of GRWR on outcome in Milan In patients was found |

CI: confidence interval; GRWR: graft-to-recipient body weight ratio; HR: hazard ratio; OS: overall survival; RFS: recurrence-free survival

age ≥ 60 years was reported to be the only independent donor-related predictor of HCC recurrence in a study of 5002 patients of the UNOS database[96]. Comparably, Orci *et al.*[87] reported on an independent prognostic effect of donor age > 60 years (HR = 1.38; 95%CI 1.10-1.73; *P* = 0.006), when analyzing 9742 patients of the SRTR database. Adequate donor-recipient age matching was shown to improve overall long-term outcome in recipients of older donor grafts[97]. However, no data exists on the oncological impact of such a matching policy.

## Living donor liver grafts
LDLT has been established as an appropriate alternative approach to fight organ shortage and, thereby, to decrease risk of drop out from the waiting list, especially in Eastern countries where the number of deceased donor liver transplants (DDLT) is significantly restricted. Allocation of these organs is not regulated by public institutions, so that the indication is independent of strict tumor size limitations. Therefore, LDLT is particularly attractive for advanced HCC patients, who may otherwise not be offered a transplant option via HCC exceptional MELD allocation, but rather transferred to palliative treatments[98,99]. However, apart from the donors' risks related to major hepatectomy, there are important oncological issues that have to be considered.

Liver grafts from living donors are principally small for size and, thus, exposed to an enhanced acute phase attack, which is an established promoter of cancer[82,100]. Another important oncological aspect is that fast track LDLT without HCC MELD-related waiting time may select more aggressive tumors that otherwise would have been identified and probably rejected[101]. Based on current mainly retrospective studies of the Eastern and Western transplant regions, the impact of reduced liver graft size compared to full-size donor livers on HCC recurrence remains finally unclear. One meta-analysis including 7 studies and 1310 patients did not find significant outcome differences between both transplant procedures, also when stratified according to MC[102]. In contrast, a more recent meta-analysis by Grant *et al.*[103] including 633 LDLT and 1232 DDLT patients provided evidence for reduced RFS following LDLT. Prospective multicenter studies are need, implementing standardized tumor selection criteria, comparable neoadjuvant tumor treatments and intent-to-treat outcome data, which seems to be illusionary with regard to different strategies and mentalities between Eastern and Western countries.

What seems to be equally important is, whether LDLT is principally able to produce acceptable outcome in beyond Milan patients, which by definition may also be lower than those for Milan In patients. Regarding this, it became apparent in recent years that post-LDLT 5-year RFS rates far beyond 50% are possible in MC Out patients when implementing parameters of biological tumor aggressiveness, such as AFP, PIVKA II or PET-status[98,104]. Apart from that, size of the living related donor graft may be another important prognostic factor that should be considered [Table 5]. In a series of 295 HCC patients following LDLT, Hu *et al.*[105]

reported on significantly better 1- and 3- year OS rates in graft-to-recipient body weight ratio (GRWR) ≤ 0.8% *vs.* > 0.8% (*P* = 0.009), whereas the corresponding RFS rates tended to be different (*P* = 0.133). Besides vascular invasion, GRWR was identified as the only independent and significant prognostic factor for OS. Analyzing 597 consecutive LDLT patients, Lee *et al.*[106] were able to demonstrate that RFS in Milan Out patients was significantly better in GRWR < 0.8% (*P* = 0.049) [Table 5].

## DCD

In order to cope with dramatic donor organ shortage, donors after cardiac or circulatory death have been increasingly used in recent years. In comparison to LT using donors after brain death (DBD), DCD LT is characterized by repeat and prolonged WIT, higher susceptibility to I/R damage, increased rate of post-LT graft failure, higher rates of re-transplants, and impaired overall outcome[107,108]. The impact of applying DCD liver grafts on the oncological outcome is currently assessed controversially. Using the SRTR database, Croome *et al.*[109] demonstrated inferior survival after DCD LT (55.86% at 5-year post-LT) compared to DBD LT (63.77% at 5-years post-LT; *P* < 0.001) in HCC patients, without including data on tumor recurrence. More recently, several large single-center studies did not find a significant difference in cancer-related outcome between both transplant procedures[110,111]. Using the SRTR database, Oric *et al.*[87] failed to identify a negative prognostic impact of DCD grafts when being compared to DBD livers. However, WIT exceeding 19 min proved to be an independent predictor of HCC relapse in the subset of DCD liver recipients (HR = 4.26; 95%CI 1.2-15.1, *P* = 0.025).

### Improving cancer-specific outcome by mitigating I/R injury

Several approaches to improve tumor-specific outcome by reducing hepatic I/R injury are currently under experimental and clinical consideration.

Orci *et al.*[112] demonstrated that ischemic preconditioning prior to I/R injury reduced tumor load in an experimental setting of rat liver steatosis to an equal level as in non-steatotic control grafts. The same group recently demonstrated in another experimental study that remote ischemic preconditioning may reduce I/R injury and modulate the gut-liver axis, finally alleviating HCC recurrence[113].

In a retrospective clinical analysis, our transplant group was able to demonstrate that early post-LT treatment with prostaglandin E1 (PGE1) reduces hepatic I/R damage and provides beneficial immunomodulatory capabilities, finally improving cancer-specific outcome[114]. In a series of 106 HCC LT patients, RFS rates at 3- and 5-year post LT were significantly better in the PGE1-treatment group (87.9%; 85.7%) compared to the non-PGE1 subset (65.3%; 63.1%; *P* = 0.003). In addition, rate of early HCC relapse within 1 year from LT was significantly higher without PGE1 treatment (34% *vs.* 5.1%; *P* < 0.001). When stratified according the MC, PGE1-therapy did not exert an independent prognostic impact in Milan In, whereas it was identified as a significant and independent promoter of RFS in patients with MC Out patients (HR = 5.09; 95%CI 1.64-15.76; *P* = 0.005)[114].

The increasing use of different hypo- or normothermic extracorporeal liver perfusion systems may be another promising approach to expand the pool of transplantable ECD livers. Pre-transplant assessment of organ viability and reducing susceptibility to hepatic I/R are the suggested scope of application. In fact, the safety and feasibility of ex-situ machine preservation have already been demonstrated. First clinical trials suggested reduced morbidity and mortality in recipients of high risk organs that were pretreated with extracorporeal machine perfusion devices[115-117]. Just recently, He *et al.*[118] from Guangzhou transplant center presented the first case of "ischemia-free transplantation" of a severely steatotic graft by using normothermic machine perfusion without stopping blood supply, already initiated during donor liver harvesting. So far, there are no

**Table 6. Impact of intraoperative blood loss and red blood cell transfusion on post-LT outcome**

| Reference | n | Overall post-LT outcome | Cancer-specific outcome in unfavorable HCC phenotypes |
|---|---|---|---|
| Teng *et al.*[125] | 223 | IOBL was identified as an independent predictor of OS when stratified according: Milan: HR = 1.039; 95%CI 1.021-1.057; *P* < 0.001 UCSF: HR = 1.039; 95%CI 1.002-1.057; *P* < 0.001 Fudan: HR = 1.035; 95%CI 1.018-1.052; *P* < 0.001 Hangzhou: HR = 1.020; 95%CI 1.000-1.040; *P* = 0.046 | |
| Liu *et al.*[126] | 479 | Cumulative 1- and 3-year RFS rates were 30.5% and 42.0% in IOBL ≤ 4 L, and 52.6% and 62.8% in IOBL > 4 L (*P* < 0.001). IOBL > 4 L was identified as an independent promoter of overall HCC recurrence (HR = 2.32; 95%CI 1.60-3.36; *P* < 0.001) and early post-LT (within 1 year) tumor relapse (HR = 2.45; 95%CI 1.64-3.66; *P* < 0.001). Red blood cell transfusion had no prognostic impact | IOBL > 4 L was identified as an independent predictor of tumor recurrence in tumors with vascular invasion (HR = 2.86; 95%CI 1.76-4.64; *P* < 0.001) but not in those without vascular invasion (HR = 1.57; 95%CI 0.87-2.85; *P* = 0.138) |
| Kornberg *et al.*[127] | 111 | Post-LT RFS rates at 3 and 5 years' post-LT were 91.9% and 91.9% in IOBL ≤ 1500 mL, but only 43.9% and 37.1% in IOBL > 1500 mL (*P* < 0.001). IOBL was identified as independent predictor of beneficial RFS (HR = 3.91; 95%CI 1.496-10.210; *P* = 0.005) of the entire study group, whereas red blood cell transfusion had no independent prognostic significance | IOBL was identified as an independent prognostic factor for RFS in Milan Out patients (HR = 3.66; 95%CI 1.138-11.766; *P* = 0.029) and PET+ patients (HR = 4.13; 95%CI 1.482-11.524; *P* = 0.007). Application of > 3 red blood cell units proved to be an independent oncological factor in Milan Out (HR = 4.98; 95%CI 1.442-17.185; *P* = 0.011) and PET+ patients (HR = 2.98; 95%CI 1.071-8.280; *P* = 0.037) |
| Nagai *et al.*[78] | 391 | Red blood cell transfusion was a strong univariate (HR = 1.03; 95%CI 1.01-1.05; *P* = 0.001) but not an independent (HR = 1.02; 95%CI 0.99-1.05; *P* = 0.14) predictor of post-LT HCC recurrence | |
| Seehofer *et al.*[133] | 336 | Apart from microvascular tumor invasion (*P* < 0.001), blood transfusion was identified as the only significant independent predictor of HCC recurrence (*P* = 0.033) | The negative impact of blood transfusions on RFS was more pronounced in patients with (*P* = 0.023) than in those without vascular tumor invasion |

CI: confidence interval; HR: hazard ratio; IOBL: intraoperative blood loss; LT: liver transplant; OS: overall survival; PET: positron emission tomography; RFS: recurrence-free survival: UCSF: University of California San Francisco

clinical data on the oncological impact of extracorporeal machine perfusion in HCC patients.

**Perioperative complications**

In recent years, postoperative complications, such as bleeding, bile leakage, ascites, liver failure, infection and need of reoperation were shown to significantly impair overall and cancer-specific outcome following liver resection for HCC[119-121]. In the LT setting, surgical complications reduce the overall prognosis in HCC patients. Dai *et al.*[122] have recently identified complications grade IIIA or more according to Clavien-Dindo classification as only independent predictor of poor overall outcome (HR = 1.108; 95% CI 1.45-34.71; *P* = 0.015) in a series of 99 LT patients with HCC. Just recently, a study from Washington DC demonstrated in a series of 428 patients that re-operation following LT was an independent predictor of graft loss (OR = 5.125; 95%CI 1.35819.552; *P* = 0.016)[123].

Intraoperative bleeding is still a major determinant of perioperative complications and a need of early reoperation in HCC patients. In times of increasing MELD scores and decreasing liver graft quality, blood loss remains a critical issue in LT, despite significant improvements in surgical techniques and homeostasis management[124]. There is increasing evidence that the extent of intraoperative blood loss (IOBL) may not only increase early morbidity and mortality, but also promote post-LT HCC recurrence [Table 6].

In a study including 223 HCC LT patients, Teng *et al.*[125] identified IOBL as an independent prognostic factor for poor OS, independent from the selectin criteria applied. However, the authors did not provide data on oncological outcome. The same group subsequently demonstrated in a series of 479 patients that, apart from recipients age, beyond MC status, AFP > 400 ng/mL and vascular invasion, IOBL > 4 L was an independent predictor of overall HCC recurrence and early post-LT (within 1 year) tumor relapse. In addition, IOBL was independently correlated with tumor recurrence in patients with but not in those without vascular invasion[126].

We have recently studied the impact of IOBL with a cut-off value of 1500 mL in 111 LT patients with HCC[127]. Post-LT RFS rates at 3 and 5 years were 91.9% and 91.9% in the low, but only 43.9% and 37.1% in the high IOBL subset ($P < 0.001$). Along with PET-status, tumor grading and AFP level, IOBL was identified as an independent predictor of cancer-specific survival. Furthermore, IOBL correlated independently with cancer relapse in unfavourable tumor phenotypes, such as Milan Out and PET+ tumors, but not in low-risk HCC[127].

Enhanced spread of occult cancer cells, aggravation of I/R injury to the graft and induction of pro-inflammatory and immunosuppressive mechanisms are currently discussed as underlying cancerogenic mechanisms[125-129]. Apart from that, IOBL increases the need of red blood cell transfusion, which in turn enhances the oncological risk by induction of pro-inflammatory and immunosuppressive mechanisms[130,131]. In a meta-analysis including 5635 cases, allogeneic blood transfusion was shown to significantly increase the risk of HCC recurrence at 1, 3, and 5 years following liver resection[132]. Nagai *et al.*[78] identified red blood cell transfusion as a strong univariate factor, but it had no independent prognostic significance on post-LT HCC relapse. In a retrospective analysis including 336 LT patients, Seehofer *et al.*[133] identified red blood cell transfusion as an independent promoter of HCC recurrence, along with vascular tumor invasion. The negative prognostic impact of blood transfusion was particularly evident in patients with vascular invasion. We have recently identified application of > 3 red blood cell units as significant and independent prognostic factor in patients with Milan Out HCC and patients with PET-positive tumors[127].

Whether the observed oncological risks are related to IOBL or rather to transfusion remains still unclear. In any case, limiting the risk of intraoperative bleeding and, thereby, need of red blood cell transfusion seems to be critical for improving post-LT cancer-specific outcome, particularly in patients with unfavourable tumor stages [Table 6]. As has been shown by several recent studies, intraoperative blood salvage and autologous re-transfusion do not increase the oncological risk and should increasingly be considered, in order to avoid allogeneic transfusion[134,135].

### Post-transplant immunosuppression

Post-transplant immunosuppressive treatment is recognized as a major risk factor for HCC recurrence following LT. In an immunocompetent patient, the innate immune system is able to recognize and destroy CTC. But in the transplant setting, postoperatively high immunosuppressive doses are administered in order to achieve liver graft acceptance, which depresses the natural anti-cancer properties of the immunological defence. Apart from development of de-novo cancers, this may lead to acceleration of metastatic spread, implantation and growth of circulating tumor tissue in HCC patients[136,137].

Despite a large number of studies on this topic, the most optimal immunosuppressive concept for HCC LT patients has not yet been defined. This may be due to the fact that the vast majority of trials are of retrospective character with significant differences regarding patients' selection criteria, transplant procedure, applied immunosuppressive protocols and post-LT surveillance program. The major conclusions that can be drawn from current available data are the following: (1) early post-LT reduced exposure to calcineurin inhibitor (CNI) is an important factor of improved tumor-specific outcome post-LT [Table 7]. The CNIs cyclosporine and tacrolimus are still the main immunosuppressants used in the setting of LT. Apart from immunoregulatory properties, CNIs are also able to render oncogenes to promote tumor cell aggressiveness and invasiveness, growth and metastasis[138,139]. As shown by an Italian group, early post-LT dose reduction of CNIs has a favourable effect on cancer-specific outcome[140,141]. In a large 2 European center study including 219 HCC patients, Rodríguez-Perálvarez *et al.*[141] reported that higher exposure to CNI (mean tacrolimus trough level > 10 ng/dL or cyclosporine trough concentrations > 300 ng/dL) within the first months post-LT enhanced the risk of HCC relapse (27.7% *vs.* 14.7% at 5 years; $P = 0.007$). Early post-LT reduced CNI exposure was identified as an

**Table 7. Immunosuppressive approaches to reduce the oncological risk after LT**

| Reference | *n* | Immunosuppressive approach | Impact on tumor-specific outcome |
|---|---|---|---|
| Vivarelli *et al.*[140] | 70 | Reduced CsA exposure (≤ 189.6 ng/mL) | Mean CsA exposure was 278.3 ± 86.4 ng/mL in patients with, and 169.9 ± 33.3 ng/mL in those without HCC recurrence. Reduced CsA exposure was identified as the only independent predictor of HCC recurrence ($P < 0.001$) |
| Vivarelli *et al.*[141] | 130 | Reduced CNI exposure (CsA ≤ 220 ng/mL; Tac ≤ 10 ng/mL) | Apart from tumor grading, MVI and AFP level, exposure to CNI was identified as the only independent predictor of HCC relapse (HR = 4.01; 95%CI 1.33-12.09; $P = 0.014$) |
| Rodriguez-Peralvarez *et al.*[142] | 219 | Reduced CNI exposure (CsA ≤ 300 ng/mL; Tac ≤ 10 ng/mL) | Apart from tumor nodule diameter, micro- and macrovascular invasion, exposure to CNI was identified as independent predictor of HCC relapse (HR = 2.82; 95%CI 1.4-5.8; $P = 0.005$). Reduced CNI exposure resulted in a significantly better RFS in MC Out patients ($P = 0.004$), whereas there was a trend of improved tumor-specific outcome in Milan Out patients ($P = 0.09$) |
| Liang *et al.*[149] | 2950 | SRL-based IS | SRL-based regimens led to improved overall survival at 1 (OR = 4.53; 95%CI 2.31-8.89), 3 (OR = 1.97; 95%CI 1.29-3.00) and 5 years (OR=2.47; 95%CI 0.21-0.83) post-LT. In addition, HCC recurrence rate was significantly decreased (OR = 0.42; 95%CI 0.21-0.83) |
| Menon *et al.*[150] | 474 | SRL-based IS | SRL-based IS resulted in lower recurrence rate (OR = 0.3; 95%CI 0.16-0.55; $P < 0.001$), lower recurrence-related mortality (OR = 0.29; 95%CI 0.20-0.70; $P = 0.005$) and lower overall mortality (OR = 0.35; 95%CI 0.20-0.61; $P < 0.001$) compared to CNI-based IS |
| Cholongitas *et al.*[151] | 3666 | mTORi-based IS | HCC recurrence rate was significantly lower in mTORi-based IS (8%) compared to CNI-based protocol (13.8%; $P < 0.001$) |
| Zhang *et al.*[152] | 7695 | SRL-based IS | SRL-based IS prolonged 1-year (OR = 2.44; 95%CI 1.66-3.59), 3-year (OR = 1.67; 95% CI 1.08-2.58) and 5-year (OR = 1.68; 95%CI 1.21-2.33) OS compared to the control group. SRL resulted in lower HCC recurrence rates (OR = 1.68; 95%CI 0.37-0.98), lower recurrence-related mortality (OR = 0.58; 95%CI 0.42-0.81) and lower overall mortality (OR = 0.62; 95% CI 0.44-0.89) compared to SRL-free regimens |

CI: confidence interval; CNI: calcineurin inhibitor; CsA: cyclosprin A; HCC: hepatocellular carcinoma; IS: immunosuppression; mTORi: mammalian target of rapamycin inhibitor; OR: odds ratio; SRL: sirolimus; Tac: tacrolimus

independent predictor of favourable cancer-specific outcome. Stratified according the pathologic MC, reduced CNI exposure resulted in a significantly better RFS in Milan In patients, whereas there was a clear trend of improved RFS in Milan Out patients ($P = 0.09$), respectively[142]; and (2) the protective effect of sirolimus (SRL) based immunosuppression is still inconclusive.

The use of mammalian target of rapamycine inhibitors (mTORis), such as rapamycine (SRL) and everolimus (EVL) provide anti-cancer effects by inhibiting the PI3K/AKt/mTOR pathway beyond its immunosuppressive capabilities[143,144]. Therefore, many hopes had been placed in this immunosuppressant in recent years for reducing the risk of post-LT HCC recurrence without affecting the immunological outcome[145-148]. Several systematic reviews and meta-analyses in the past suggested a significant benefit of SRL in HCC LT patients[149-151] [Table 7]. Just recently, Zhang *et al.*[152] presented data on an updated meta-analysis including the largest number of patients ($n = 7695$) from a total of 11 studies. The authors reported that patients treated with SRL demonstrated lower recurrence rates, lower recurrence-related mortality and lower overall mortality compared to SRL-free regimens. Whether advanced HCC patients were particularly benefiting from SRL was, however, not adequately assessed. The only prospective, randomized, multicenter, open-label study recently finalized, however, did not find a significant improvement of OS and RFS beyond 5 years[153].

Currently, several approaches to achieve recipient tolerance by IS weaning protocols in order to reduce long-term CNI-induced complications, such as hyperlipidemia, cardiovascular events, renal dysfunction and de-novo carcinoma are under consideration[154-157]. About 25% of liver transplant patients were reported to be suitable for complete IS withdrawal without increasing the risk of patient and graft loss. Probably, the application of non-invasive biomarkers predicting "operational tolerance" might permit significant reduction

in a higher number of liver recipients[154]. As suggested in small study samples, this might be a promising IS-based approach to reduce the oncological risk in LT patients with HCC. However, larger prospective studies are needed.

## CONCLUSION

As pointed out in this review, there are several important non-HCC related factors of prognosis that have to be considered in LT for HCC. However, comparability of related studies is rather limited by their mostly retrospective character and the use of different outcome variables [Tables 1-7]. Nevertheless, there is growing evidence that these non-oncological features trigger a series of unfavorable immunomodulatory processes related to inflammation and immunosuppression, and thereby promoting the oncological risk following LT. This may be particularly relevant for patients with advanced HCC stages, who are per se exposed to an increased risk of HCC recurrence. Therefore, these non-oncological factors should play an important role in individual decision making. The presented data suggest that adequate patient and graft selection, limitation of ischemia time, reduction of surgical complications and minimizing post-LT immunosuppressive drug load may be essential components for preserving immunbalance and, thereby, for improving cancer-specific survival.

Since all of these features are well-known prognostic factors that are generally affecting outcome of LT patients even without underlying malignancy, it is a particular challenge to determine the individual transplant benefit based on both tumor biology data and non-HCC variables. In this context, there is currently no applicable clinical algorithm which is implementing both aspects for risk assessment. However, what became clear from our review is that such an approach should include concepts of mitigating hepatic I/R damage not only to improve early posttransplant patient and graft survival, but to reduce the potency of metastatic tumor cell implantation and growth. Thus, the HCC patients' selection criteria might be safely expanded beyond current macromorphologic tumor burden limits.

## DECLARATIONS

### Authors' contributions
Conceived the study, analyzed data and wrote the manuscript: Kornberg A
Analyzed data and revised the manuscript: Schernhammer M

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Both authors declared that there are no conflicts of interest.

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