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REVIEW

Impact of non-oncological factors on tumor recurrence after liver transplantation in hepatocellular carcinoma patients

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary neoplasm of the liver and is one of the leading causes of cancer-related death worldwide. Liver transplantation (LT) has become one of the best curative therapeutic options for patients with HCC, although tumor recurrence after LT is a major and unaddressed cause of mortality. Furthermore, the factors that are associated with recurrence are not fully understood, and most previous studies have focused on the biological properties of HCC, such as the number and size of the HCC nodules, the degree of differentiation, the presence of hepatic vascular invasion, elevated serum levels of alpha-fetoprotein, and the tumor stage outside of the Milan criteria. Thus, little attention has been given to factors that are not directly related to HCC (*i.e.*, "non-oncological factors"), which have emerged as predictors of tumor recurrence. This review was performed to assess the effects of non-oncological factors on tumor recurrence after LT. The identification of these factors may provide new research directions and clinical strategies for the prophylaxis and surveillance of tumor recurrence after LT, which can help reduce recurrence and improve patient survival.

Key words: Liver transplantation; Immunosuppressive agents; Hepatocellular carcinoma; Recurrence; Living donor; Deceased donor

Core tip: Liver transplantation (LT) has become one of the best curative therapeutic options for patients with hepatocellular carcinoma (HCC). This review discusses the effects of non-oncological factors on tumor recurrence after LT in patients with HCC. These non-oncological factors include the use of immunosuppressive agents, transplant type, hepatitis

virus infection, recipient characteristics, and graft-related factors. Our review provides new research ideas and clinical strategies for the prophylaxis and surveillance of post-LT tumor recurrence, and can help the reader improve their management of, and outcomes among, patients with HCC after LT.

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INTRODUCTION

After > 50 years of research, liver transplantation (LT) has been adopted as the final curative option for many kinds of end-stage liver disease. After reviewing the history of LT, we found that its application in hepatocellular carcinoma (HCC) is typically considered in the context of specific disease stages. However, the selection of LT usually takes a tortuous course, which often includes a preliminary attempt with unrealistic expectations, failure to fulfil these expectations, reconsideration of the approach, and ultimately acceptance that the LT had failed. Clinical practice data indicate that tumor recurrence after LT is the leading factor that affects the prognosis of patients with HCC who undergo LT, and standardizing the indication criteria is an effective measure for improving post-LT outcomes. Nevertheless, Western countries that strictly follow these criteria also have an estimated recurrence rate of 15%-20%[1]. Therefore, improving the post-LT prognosis among patients with HCC remains a major challenge.

As both the tumor and the entire liver are removed during LT to minimize the tumor load, this procedure is fundamentally different from hepatectomy. However, LT outcomes are influenced by various "non-oncological" factors, which include long-term immunosuppressive therapy, the degree of graft preservation, and the characteristics of the donor liver. Previous studies regarding the mechanism for recurrence after LT have mainly focused on the biological properties of HCC, such as the number and size of the HCC nodules, the degree of differentiation, the presence of hepatic vascular invasion, elevated serum levels of alpha-fetoprotein (AFP), and the tumor stage outside of the Milan criteria[2]. Research regarding these oncological factors has achieved outstanding results, and has demonstrated that postoperative recurrence is independently predicted by the degree of differentiation, the presence of hepatic vascular invasion, and elevated serum AFP levels[3,4]. Therefore, transplant centers use formulated selection criteria to guide clinical practice, such as the Milan criteria[5], the University of California, San Francisco criteria[6], the up-to-seven criteria (the new Milan criteria)[7], and the Hangzhou criteria[8]. Although several of these selection criteria are not evidence-based, they still play an important role in reducing recurrence and improving post-LT survival. However, non-oncological factors can also predict recurrence, and these factors include the tumor's location and the systemic response to its expansion, although the studies that reported these associations typically lack accurate conclusions and an overall understanding of HCC. Furthermore, non-oncological factors can be classified as either modifiable or non-modifiable, and further studies are needed to examine which non-oncological factors can be modified to delay post-LT tumor recurrence. Therefore, we have reviewed the clinical and experimental evidence regarding the relationships between non-oncological factors and post-LT recurrence among patients with HCC.

ROLE OF IMMUNOSUPPRESSIVE AGENTS AND THE IMMUNOLOGICAL STATE

There is a general consensus that pharmacological immunosuppression or a poor immunological state negatively affects post-LT outcomes of HCC and increases the risk of postoperative recurrence[9]. In this context, the innate immune system normally locates and destroys circulating clusters of tumor cells in the early HCC stages and prevents HCC progression. However, the administration of high-dose post-LT immunosuppressive agents reduces innate immune activity and contributes to tumor recurrence[10], which has been confirmed *via* clinical, *in vitro*, and animal data[11]. Studies have also demonstrated that calcineurin inhibitors (CNIs) reduce interleukin (IL)-2 expression and increase transforming growth factor (TGF)-β1 expression, which inhibits IL-2-stimulated T-cell proliferation. In addition, TGF-β1 suppresses the natural killer cell-mediated anti-tumor response and is associated with metastases[12,13]. Several studies have also demonstrated that higher CNI doses are correlated with a higher risk of HCC recurrence and lower post-LT overall or recurrence-free survival rates[10,14,15]. A random and homogeneous cohort study recently reported a reduced HCC recurrence rate after receiving only the minimum CNI dose during the first post-LT month, with or without other immunosuppressive drugs[10]. Furthermore, a 10 ng/mL dose of tacrolimus (TC) increased the risk of HCC recurrence, which confirms the findings of an earlier study[14]. However, the exact mechanism for TC-induced immune system impairment, and its possible relationship with tumor recurrence, remains unclear. The aforementioned study also demonstrated that the concomitant use of steroids (even high-dose boluses) for treating LT rejection did not increase the risk of disease recurrence after LT among patients with HCC[10]. Moreover, Vivarelli

Table 1 Studies with different basal immunosuppression schedules for patients with hepatocellular carcinoma after liver transplantationv

Ref.	Year	Immunosuppressor type	Evaluated parameters	Recurrence rate	*P* value
Rodríguez-Perálvarez *et al*[10]	2013	CNI	Low exposure 1st *vs* high exposure 1st	27.7% *vs* 14.7% at 5 yr	0.007
Vivarelli *et al*[16]	2005	CSA	Low exposure *vs* high exposure	0% *vs* 33.3%	< 0.001
Vivarelli *et al*[14]	2008	TAC	Low exposure *vs* high exposure	9.1% *vs* 50%	0.001
Menon *et al*[21]	2013	SRL and CNIs	SRL *vs* CNIs	4.9%-12.9% *vs* 17.3%-38.7%	NA
Cholongitas *et al*[22]	2014	CNIs and mTORi	CNIs *vs* mTORi	22% *vs* 44%	< 0.050

CNI: Calcineurin inhibitors; CsA: Cyclosporine A; TAC: Tacrolimus; SRL: Sirolimus; mTORi: The mammalian target of rapamycin inhibitors; NA: Not analyzed.

et al[16] also reported that HCC recurrence was not related to the cumulative steroid dose, although it was associated with cyclosporin A exposure. Nevertheless, the small sample size and short-term follow-up of that study limits the ability to interpret whether high-dose steroids might affect HCC recurrence after LT, and further studies are needed to clarify this issue.

Inhibition of the mammalian target of rapamycin (m-TOR) protein provides effective anti-tumor activity[17,18], and different mouse models have revealed that rapamycin inhibits cancer by blocking angiogenesis *via* the impairment of vascular endothelial growth factor (VEGF) production and VEGF-induced vascular endothelial cell stimulation[19,20]. In the clinical setting, m-TOR inhibitors (m-TORis; which include both sirolimus and everolimus) are considered immunosuppressive agents that can reduce tumor recurrence among patients with HCC who are undergoing LT. Menon *et al*[21] performed a systematic review and meta-analysis and concluded that, compared to CNI-treated patients, sirolimus-treated patients exhibited a lower recurrence rate and longer recurrence-free survival and overall survival (OS). A study by Cholongitas *et al*[22] in 2014 also demonstrated that patients who were treated using CNIs developed HCC recurrence significantly more frequently than patients who were treated using m-TORis ($P < 0.001$), although the CNI-treated patients exhibited more frequent recurrence using the Milan criteria (74% *vs* 69%) and lower rates of microvascular invasion, compared to m-TORi-treated patients (22% *vs* 44%) ($P < 0.05$). These studies' findings indicate that m-TORi is favored over CNI to control HCC recurrence after LT (Table 1). Various trials have confirmed two important conclusions: 1) lower doses and reduced exposure to CNIs (*e.g.*, cyclosporine and TC) after LT prevented HCC recurrence, and 2) m-TORis are a new class of immunosuppressants that provide antineoplastic properties and reduce the post-LT HCC recurrence rate compared to CNIs[21].

In addition to the effects of immunosuppressants, several studies have reported that poor nutritional status and impaired immune response were associated with HCC recurrence by impairing function of $CD4^+$ T-cells, as measured using adenosine triphosphate levels[11,23,24]. For example, human immunodeficiency virus (HIV)-infected patients have compromised immune responses, due to $CD4^+$ T lymphocyte depletion and a significant reduction in the numbers of peripheral blood lymphocytes, which increase their risks of HCC incidence, progression, and mortality. Several studies have also demonstrated that HIV-infected patients experience a more aggressive course of HCC and a poorer OS compared to HIV-negative patients, which suggests that an HIV-related protein might predispose normal hepatocytes to the oncogenic effects of carcinogens, induce growth signals, and ultimately contribute to the initiation and progression of HCC[25-27]. However, HIV infection has a minimal effect on the risk of tumor recurrence among patients who are undergoing LT for HCC. For example, Di Benedetto *et al*[28] compared 30 HIV-positive patients who underwent LT for HCC and 125 HIV-negative patients with HCC and found that their HCC recurrence rates were 6.7% and 14.4%, respectively ($P = 0.15$). Therefore, the authors concluded that HIV infection did not predict recurrence or mortality. Similarly, Vibert *et al*[29] reported that HIV-positive and HIV-negative patients exhibit similar rates of survival and HCC recurrence. Nevertheless, the value of LT in HIV-positive patients with HCC remains debatable, due to these studies' limited number of HIV-infected patients who underwent LT and the high dropout rate while the patients waited for surgery.

TRANSPLANT TYPE

The need for LTs exceeds the number of deceased donors, which increases waiting times and contributes to a high drop-out rate among patients who experience tumor progression while awaiting surgery[30,31]. Thus, living donor LT (LDLT) provides patients with HCC better access to timely treatment. However, several recent studies have demonstrated that LDLT is associated with an increased incidence of post-LT HCC recurrence, compared to deceased donor LT (DDLT)[32-34]. Vakili *et al*[34] also found that LDLT recipients experienced higher HCC recurrence rates than DDLT recipients (28.6% *vs* 12.1%, $P < 0.05$), and Park *et al*[32] reported higher rates of cancer recurrence after LDLT compared to after DDLT (cumulative 5-year recurrence rates, 19.3% *vs* 6.0%, $P < 0.05$). Multivariate analyses have

Table 2 Disadvantages and rates of tumor recurrence after living donor liver transplantation and piggyback liver transplantation compared to deceased donor liver transplantation and conventional orthotropic liver transplantation, respectively

Transplant type	Disadvantages	Rate of tumor recurrence
LDLT *vs* DDLT	The small-sized graft, the "fast-tracking effect", the sparing of the inferior vena cava, and more extensive manipulation	28.6% *vs* 12.1%, $P < 0.05$[34]; 19.3% *vs* 6%, $P < 0.05$ (cumulative 5-yr)[32]
PB-LT *vs* CON-LT	The positive vena cava margin and greater manipulation of the diseased liver	6.3% *vs* 10.1%, $P > 0.05$[48]

LDLT: Living donor liver transplantation; DDLT: Deceased donor liver transplantation; PB-LT: Piggyback liver transplantation; CON-LT: Conventional orthotropic liver transplantation.

revealed that LDLT was an independent risk factor for HCC recurrence, and that smaller LDLT grafts were associated with a higher post-LT recurrence rate. Therefore, in addition to the advanced tumor characteristics of the LDLT recipient[35], there are three suggested mechanisms by which LDLT might increase the risk of HCC recurrence. The first mechanism is the release of growth factors that mediate the regeneration of the hemiliver and increase the vascular inflow during the rapid regeneration of the partial grafts from living donors, which might contribute to tumor progression and recurrence[36-38]. Furthermore, small-sized grafts are more likely to cause acute phase graft injury, which results in cell adhesion, angiogenesis, and migration; all of these factors may promote tumor recurrence[38,39]. The second mechanism is the "fast-tracking effect", whereby patients who undergo LDLT have a shorter waiting time, which might preclude the detection of an aggressive tumor before surgery[40,41] and increase the risk of recurrence. The third mechanism is the LDLT technique itself might directly contribute to a higher recurrence rate, due to the sparing of the inferior vena cava (which is necessary for complete tumor removal) and more extensive liver manipulation during the LDLT[33,42]. All of these factors might contribute to the high recurrence rates after LDLT compared to after DDLT.

Despite these potential mechanisms by which LDLT might increase HCC recurrence, other studies have reported that LDLT recipients have a similar recurrence rate and comparable recurrence-free survival compared to patients who underwent DDLT[43-45]. In these studies, the authors attributed the inferior outcomes after LDLT for HCC to the tumor's characteristics and biology. Although there is no clear evidence regarding whether LDLT is associated with a higher recurrence rate, the conflicting data suggest that different indication criteria may be appropriate for LDLT and DDLT.

As an alternative to the conventional LT method, the piggyback technique has become the preferred approach in some centers, as it provides a shorter procedure time, a shorter anhepatic phase and warm ischemia period, fewer blood transfusions, and a shorter stay in the intensive care unit[46,47]. This technique has gained widespread acceptance for many end-stage liver diseases, but not for HCC, because it theoretically carries a higher risk of positive vena cava margins and requires greater manipulation of the diseased liver, which could increase the risk of HCC spread[48]. However, it is debatable whether piggyback transplantation increases HCC recurrence in the transplantation setting. For example, Mangus *et al*[48] reported no significant difference between the two techniques in terms of their survival and recurrence rates and suggested that the presence of HCC should not preclude the use of piggyback transplantation. In addition, Grąt *et al*[47] found that piggyback transplantation provided superior long-term survival among patients with HCC and potentially decreased the risk of post-transplant recurrence, as compared to the conventional technique. Therefore, piggyback transplantation might be considered for patients with HCC, although further studies are needed to validate this approach. A summary of the disadvantages and recurrence rates after LDLT and piggyback LT, compared to DDLT and conventional LT, respectively, is listed in Table 2.

HEPATITIS VIRUSES

There is growing evidence that the hepatitis B virus (HBV) contributes to hepatocarcinogenesis *via* direct malignant transformation and other indirect effects[49-51]. Furthermore, persistent HBV infection can increase genetic instability by causing hepatocyte destruction and regeneration[52]. Moreover, HBV load is involved in post-LT HCC recurrence[53,54] and increases the risk of post-LT recurrence through an inflammatory effect after HBV or hepatitis C virus (HCV) allograft re-infection[55]. Li *et al*[53] retrospectively analyzed 340 HBV-positive patients who underwent orthotropic LT (OLT) and found that HBV relapse was an independent predictor of HCC recurrence ($P = 0.03$), and that high pre-transplant levels of HBV DNA were associated with HCC recurrence. Wu *et al*[56] also performed a retrospective study of 78 patients with HBV-related HCC who underwent LT, and found that 13 patients (16.6%) experienced HCC recurrence and 18 patients (23.1%) experienced HBV relapse. Therefore, the authors concluded that HBV relapse was closely related to HCC recurrence ($P = 0.004$) and led to a shorter OS after LT. Thus, HBV relapse and HCC recurrence may have a reciprocal causative relationship in the post-transplantation setting[53].

Antiviral therapy can reduce the risk of recurrence in patients with HCC, which supports a role for hepatitis virus infection in HCC recurrence after LT. For example, Kohli *et al*[57] retrospectively compared patients who were and were not receiving post-LT interferon and found that the rates of HCC recurrence in these groups were 4.1% and 27.3%, respectively ($P < 0.05$). This finding suggests that interferon markedly reduces the risk of HCC recurrence and related mortality among patients who are undergoing LT for HCV-related HCC. Anselmo *et al*[58] have also reported that combined treatment with hepatitis B immunoglobulin and lamivudine after OLT markedly reduced the HBV relapse rates and significantly improved the 1-year and 3-year recurrence-free survival rates.

RECIPIENT CHARACTERISTICS

Overweight and obese patients who undergo OLT for HCC have a relatively high recurrence rate, and these patients exhibit a significantly shorter time to recurrence compared to non-obese patients[59]. The proposed mechanism for this increased risk of recurrence and shorter OS is the altered expression of adipokines (leptin and adiponectin) in obese patients, as these molecules can increase proliferation and suppress apoptosis in cancer cell lines and can also increase cell invasion and upregulate the expression of VEGF and other angiogenesis-related cytokines in HCC[60-63]. Siegel *et al*[64] retrospectively analyzed 342 consecutive HCC patients who underwent LT and found that a body mass index (BMI) of > 30 kg/m^2 was an independent predictor of poor OS and recurrent disease. In addition, Mathur *et al*[59] found that the rate of HCC recurrence in overweight (15%) and obese (15%) patients was double that in non-obese patients (7%) ($P < 0.05$). Therefore, BMI is a potentially significant predictor of post-LT tumor recurrence.

In general, there is an arbitrary age limit for LT, due to the increased incidence of age-related comorbidities among elderly patients with HCC[65,66]. Several studies have reported that elderly patients who underwent LT exhibited a lower survival rate and higher rates of HCC malignancy, which may be associated with their increased risk of adverse outcomes due to chronic comorbidities, immunosuppression, and immunosenescence[66,67]. Age-related immunological changes and immunosenescence can increase the susceptibility of elderly patients to infection, autoimmune disease, and cancer[68]; and long-term immunosuppressive therapy after LT might increase these patients' risks of morbidity and mortality compared to their younger counterparts[69]. However, other studies have reported that LT is not contraindicated for elderly patients[65,70,71], and Ballarin *et al*[70] reported similar short- and middle-term survival outcomes and morbidities (*e.g.*, HCC recurrence) among young and elderly patients. Moreover, Kim *et al*[69] demonstrated that OS was prolonged among younger patients who underwent OLT for HCC, although there were no significant differences in HCC-specific survival among the various age groups. Therefore, these findings suggest that carefully selected elderly patients with HCC could experience a benefit from OLT that is equal to the benefit that is experienced by younger patients.

Several studies have reported sex-specific differences in the incidences of HCC among mice and in the survival of patients with HCC[72,73]. For example, estrogen inhibited the production of IL-6 in Kupffer cells that were exposed to necrotic hepatocytes, and diethylnitrosamine-treated male mice exhibited reduced circulating concentrations of IL-6, which reduced inflammation-induced carcinogenesis[72]. Moreover, Yang *et al*[73] demonstrated that survival among women was superior to that among men when they evaluated patients with HCC who were 18-44 years old and 45-54 years old, respectively, which suggests that menopausal status might be related to HCC outcomes and that estrogen might protect against hepatocarcinogenesis and promote a more favorable HCC outcome. This difference was especially pronounced among patients who underwent surgical resection, although there was no difference among patients who underwent LT. Therefore, as the mean age at transplantation is increasing, a growing number of elderly women are being considered for LT. However, these women may be menopausal and may not experience estrogen's protective effect, which might lead to poorer survival and increased HCC recurrence compared to those among younger patients. Nevertheless, only limited data are available to support this hypothesis, and it remains unclear whether sex influences post-LT survival and tumor recurrence; further clinical studies are needed to examine this issue.

GRAFT-RELATED FACTORS

Changes in transplant-related factors, such as the allograft excision, organ allocation, transportation of the liver graft, and timing of the recipient surgery, might lead to prolonged periods of cold and warm ischemia. Furthermore, experimental and clinical evidence indicate that ischemia-reperfusion injury may affect HCC recurrence after LT. Nagai *et al*[74] retrospectively evaluated 391 patients from two transplant centers who underwent LT for HCC and found that prolonged cold ischemia times (> 10 h, $P = 0.03$; HR = 1.9) and warm ischemia times (> 50 min; $P = 0.003$; HR = 2.84) were independent risk factors for HCC recurrence after LT. These relationships were especially pronounced among patients with other risk factors, such as poor differentiation, micro- and macrovascular invasion, HCC exceeding the Milan criteria, and AFP levels > 200 ng/dL. Prolonged ischemia was also significantly associated with recurrence within 1 year. A number of biological mechanisms have been proposed to explain how ischemia-reperfusion

injury can affect cancer outcomes, based on *in vivo* and *in vitro* experiments[75-77]. For example, the exposure of micrometastases to hypoxia could lead to the activation of several distinct pathways and the abnormal expression of genes and cytokines that contribute to angiogenesis, cellular proliferation, growth, and adhesion[75,78]. Hypoxia also stabilizes and activates the transcription factor for hypoxia-inducible factor, which is a key oxygen response regulator that activates the transcription of genes (*e.g.*, *VEGF-A*) that stimulate angiogenesis[79-81]. Moreover, as the reperfusion progresses, microcirculatory disturbances might exacerbate intrahepatic hypoxia. Therefore, it has been speculated that recipients who receive allografts from donation after brain death (DBD) might experience a lower recurrence rate compared to patients who receive allografts from donation after cardiac death (DCD). Furthermore, patients with HCC exhibit shorter survival after receiving DCD allografts compared to those receiving DBD allografts, even after adjusting for the inherent inferiority of the DCD allografts and other known risk factors[82]. Thus, the survival difference might reflect an increased rate of HCC recurrence. However, the same researchers subsequently reported conflicting results, which indicated that HCC recurrence occurred at equal rates among patients who received DBD or DCD allografts. With respect to donor sex, experimental and clinical observations indicate that livers from women are more susceptible to hepatic reperfusion injury and have a higher sensitivity to reoxygenation damage after prolonged cold storage[83,84], although, to our knowledge, there are only limited data available regarding the effect of donor sex on tumor recurrence after LT among patients with HCC.

Age is another donor factor that is associated with HCC recurrence[85]. For example, the median donor age for patients with HCC recurrence was older than that for patients who did not experience recurrence (49 years *vs* 36 years, $P = 0.008$), which suggests that livers from older donors are poorly preserved and have a greater susceptibility to cold ischemia and age-related immune changes, which can lead to inferior outcomes. However, other studies have reported that recipients of livers from elderly donors experienced excellent outcomes, and that age-matched patients were more likely to exhibit better graft survival[86-88]. The authors attributed these findings to the reduced cold storage times for these organs, although the relationship between donor age and HCC recurrence after LT continues to be debated.

ABO-incompatible (ABO-I) LT is exclusively used when a donor liver is urgently needed in pediatric cases, due to the risk of hyperacute or antibody-mediated humoral graft rejection because of the graft's ABO blood group and the antibodies in the recipient's blood[89,90]. B-cells and T-cells play a major role in this process, and various procedures have been proposed to overcome this rejection, such as plasma exchange, splenectomy, local infusion of the grafts, and more aggressive immunosuppression[91,92]. All of these protocols have achieved good outcomes. Furthermore, as new monoclonal antibodies (*e.g.*, rituximab and basiliximab) have been developed, ABO-I LDLT has been widely performed, and good results have been reported[93]. However, Miyagi *et al*[94] found that strong immunosuppressive therapies, such as steroid pulses and rituximab for ABO-incompatible cases, may have a negative effect on tumor recurrence after LT. In addition, Lee *et al*[93] retrospectively studied 20 patients who underwent ABO-I LDLT due to HCC or liver cirrhosis, using an ABO-I LDLT protocol that included rituximab, plasma exchange, basiliximab, and intravenous immune globulin. The authors found that the proportion of natural killer (NK) cells decreased with declining absolute peripheral blood counts during the early phase of ABO-I LDLT, which contributed to a weakening of the innate immune response to HCC or the hepatitis virus. In this context, NK cells play a critical role in the immune surveillance of liver tumors, through the expression of FasL, perforin, granzyme B, and functional tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)[95]. Therefore, these cells play an important role in preventing HCC recurrence, and caution is needed when performing ABO-I LDLT, especially in cases with advanced HCC.

Data from our center suggest that the use of moderate-to-severe fatty liver grafts might be related to the incidence of post-LT liver cancer recurrence[96]. Other studies have reported that ischemia-reperfusion injury was much more severe in moderate-to-severe steatotic grafts, and that steatotic livers exhibited a decreased tolerance to ischemia-reperfusion injury[97-99]. These injuries led to an increased release of lipid peroxides, downregulation of adipokines (*e.g.*, adiponectin and resistin) that can protect the steatotic liver grafts[100], and a series of secondary inflammatory reaction cascades, which in turn led to increased angiogenesis that ultimately promotes tumor recurrence. However, there were no significant differences in patient and graft survivals according to steatosis after LT[101]. The mechanism that underlies this process is similar to those for small-for-size graft injuries and regeneration. Table 3 shows a summary of studies that compared the effects of recipient characteristics and graft-related factors on tumor recurrence after LT among patients with HCC patients.

OTHER FACTORS

One study reported that the extent of intraoperative packed red blood cell transfusion was associated with HCC recurrence after LT[74], and intraoperative blood transfusion was hypothesized to have a negative effect on tumor recurrence among patients with various types of cancers[102-104]. This detrimental effect is thought to be caused by suppression of the host's immune system (including reduced NK-cell and phagocyte activity),

Table 3 Studies comparing the effects of recipient and donor characteristics on tumor recurrence among patients with hepatocellular carcinoma after liver transplantation

Ref.	Year	Characteristics	Evaluated parameter	Recurrence rate	*P* value
Recipient					
Mathur *et al*[59]	2014	Overweight or obese	Overweight *vs* obese *vs* non-obese	15% *vs* 15% *vs* 7%	< 0.050
Ballarin *et al*[70]	2011	Age	Elderly *vs* younger	7.1% *vs* 4.8%	> 0.050
Yang *et al*[73]	2014	Gender	Male *vs* female	NA	NA
Donor					
Nagai *et al*[74]	2014	Ischemia times	CIT >10 h *vs* < 10 h and WIT > 50 min *vs* ≤ 50 min	NA	0.015
Sharma *et al*[85]	2012	Age	Median donor age for patients with HCC recurrence *vs* without HCC recurrence	NA	0.008
Miyagi *et al*[94]	2012	ABO-I graft	Strong imunosuppressive therapy *vs* other imunosuppressive therapy	NA	NA
Teng da *et al*[96]	2012	Steatosis donor liver	Grafts with no steatosis *vs* mild steatosis *vs* moderate-to-severe steatosis	15.8% *vs* 8.3% *vs* 33.3% at 1 yr; 28.7% *vs* 20.8% *vs* 50% at 3 yr	> 0.050

CIT: Cold ischemia times; WIT: Warm ischemia times; HCC: Hepatocellular carcinoma; ABO-I: ABO-incompatible; NA: Not analyzed.

increased suppressor T-cell activity with inhibition of IL-2 secretion, and sFAS ligand and soluble human leukocyte antigen (sHLA) molecule transfusion[102,105-110]. In addition, systemic inflammation and cytokine production that is caused by impaired oxygen delivery to vital organs due to massive hemorrhage can reduce antitumor immunity[111]. However, Kaido *et al*[112] found that the immunosuppressive effect of homologous blood transfusion in LT was unclear and suggested that any immunosuppression would be minimized by the potent action of immunosuppressive drugs.

CONCLUSION

In conclusion, this review summarized the effects of select non-oncological factors on tumor recurrence after LT, although we did not consider the effects of several non-oncological factors (*e.g.*, diabetes mellitus or smoking), due to a lack of data. Although several studies of non-oncological factors made conclusions that were based on insufficient clinical evidence, these studies have provided new research ideas and clinical strategies for the prophylaxis and surveillance of post-LT tumor recurrence. Furthermore, there is strong evidence for an intricate and close connection between injury, infection, inflammation, regeneration, immune imbalance, and a series of physiological occurrences. Therefore, non-oncological factors might also be intrinsically connected to the deactivation of anti-tumor immunity, tumor recurrence, and tumor progression. Thus, closely considering both oncological factors ("seeds") and non-oncological factors ("soil and environment") might help to improve the outcomes after LT for patients with HCC.

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