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Liver transplantation for hepatocellular carcinoma: Role of inflammatory and immunological state on recurrence and prognosis

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Abstract

Criteria for liver transplantation (LT) for hepatocellular carcinoma (HCC) and post-LT indicators of prognosis are historically based on the measurement of the tumor mass. Recently, high throughput technologies have increased the prediction of recurrence, but these tools are not yet routinely available. The interaction between HCC and the immune system has revealed an imbalance of lymphocyte phenotypes in the peritumoral tissue, and the increase of regulatory T cells with respect to cytotoxic lymphocytes has been linked to a higher rate of post-LT HCC recurrence. Moreover, some inflammatory markers have shown good reliability in predicting cancer reappearance after surgery, as a result of either a systemic inflammatory response or a decreased capacity of the organism to control the tu-

mor growth. Among these markers, the neutrophil-to-lymphocyte ratio appears to be the most promising and easily available serum parameter able to predict HCC recurrence after LT and following other types of treatment, although the exact mechanisms determining its elevation have not been clarified. Post-LT immunosuppression may impact on cancer control, and the exposure to high levels of calcineurin inhibitors or other immunosuppressants has recently emerged as a negative prognostic factor for HCC recurrence and patient survival. Despite the absence of prospective randomized trials, inhibitors of the mammalian target of rapamycin have been shown to be associated with lower rates of tumor recurrence compared to other immunosuppressors, suggesting their use especially in patients with HCC exceeding the conventional indication criteria for LT.

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Key words: Liver transplantation; Hepatocellular carcinoma; Inflammation; Immunosuppression; Recurrence

Core tip: This review focuses on inflammatory markers recently emerged as indicators of tumor biological behavior and on immune state of patients submitted to liver transplantation for hepatocellular carcinoma (HCC), with a particular reference to the role of neutrophil-to-lymphocyte ratio. The impact of post-transplant immunosuppression on HCC recurrence is also analyzed according to the most relevant evidences published so far, which outline the importance of minimization of the use of calcineurin inhibitors and the protective role of inhibitors of the mammalian target of rapamycin.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, and its incidence is increasing in Western countries^[1]. For patients with HCC and cirrhosis, liver transplantation (LT) represents the treatment of choice and provides excellent oncological results and a cure for cirrhosis.

Prognostic factors for tumor recurrence and patient outcome have mainly been recognized as an expression of tumor burden and of its biological aggressiveness. Among these factors, the number and size of HCC nodules, the degree of differentiation, the presence of hepatic vascular invasion and elevated serum levels of alpha-fetoprotein (AFP) are the ones most widely utilized to define the indications for LT and to predict the outcome^[2-8]. Since it is often difficult to safely and/or reliably obtain histological parameters before LT^[9,10], radiological tumor criteria and AFP levels are the main preoperative indicators of prognosis.

The role of markers of inflammation and of the patient's immunological state have recently emerged as predictors of outcome, providing information on the environment in which the tumor grows and on the systemic response to its expansion^[11-20]. These markers are often correlated with dimensional and histological factors determining a high risk of recurrence, but the mechanisms by which they are expressed are still largely unexplored. While waiting for more precise molecular markers^[21-23] to become of routine use in defining the indications for and the prognosis of LT, the above parameters of inflammation may help to predict the biological behavior of HCC.

Since post-LT pharmacological immunosuppression can ideally impact on the ability to control tumor reappearance, the type, duration and total load of immunosuppressors have also been investigated in recent years as predictors of HCC recurrence^[7,8,24-33].

The role of inflammatory markers and of post-LT immunosuppression on tumor recurrence and patient prognosis after LT for HCC are the subject of the present review. For this purpose, an extensive review of the English literature using the PubMed database was performed independently by two authors (Cescon M, Bertuzzo VR), separately selecting papers pertinent to the key terms "liver transplantation", "hepatocellular carcinoma", "recurrence" and "inflammation" for the investigation of the impact of inflammatory markers, and to the terms "liver transplantation", "hepatocellular carcinoma", "recurrence" and "immunosuppression" to assess the post-LT impact of pharmacological immunosuppression.

RELATIONSHIP BETWEEN INFLAMMATORY AND IMMUNOLOGICAL MARKERS, AND OUTCOME AFTER LIVER TRANSPLANTATION FOR HCC

In the last two decades, Virchow's hypothesis, which postulates that a relationship exists between inflammation and cancer, has permitted new insights into the phenomenon of carcinogenesis^[34]. Given the importance of the peritumoral (micro)-environment, researchers have focused on markers that could be an expression of the relationship between liver cancer and surrounding tissue, with a possible consequent change of systemic inflammatory response.

Infiltration of pro-inflammatory macrophages, cytokines and chemokines in the tumor microenvironment has been shown to enhance tumor growth, invasion and metastases^[34-36], allowing the use of inflammation parameters as tumor markers^[37,38] and the development of new therapeutic strategies^[35,36].

C-reactive protein (CRP)^[37-41] and erythrocyte sedimentation rate (ESR)^[42-45] were the first serum inflammation indicators used as tumor markers. Elevated preoperative CRP, an acute-phase reactant synthesized by hepatocytes in response to systemic inflammation, has been recognized as a risk factor for incidental colorectal cancer^[39] and as an adverse prognostic factor in patients undergoing hepatectomy for HCC^[40], whereas ESR has been identified as an indicator of poor prognosis in patients with clear cell renal cell carcinoma and in children with Hodgkin's lymphoma^[42,45].

Inflammatory cytokines such as interleukin-6 (IL-6) and IL-1b are linked to transcriptional signaling pathways associated with carcinogenesis, tumor growth, and invasion^[36,46]. IL-6 is known as one of the main regulators of CRP production.

The neutrophil-to-lymphocyte ratio (NLR) is another inflammation index that has been evaluated as a tumor marker^[47-53]. Originally used as a systemic inflammatory response index in critically ill patients, it is obtained by dividing the absolute neutrophil count by the absolute lymphocyte count. According to published literature, an $NLR \geq 5$ can be considered a valid cut-off^[48,50,51].

Some studies have demonstrated the relationship between NLR and tumor progression in patients with colon cancer, liver metastases from colorectal cancer, pancreatic cancer, breast cancer, esophageal cancer, cholangiocarcinoma, and HCC; in addition, a higher incidence of HCC recurrence has been observed in patients with high NLR and undergoing hepatic resection^[47-53].

An elevation of NLR could be related to a relative increase of neutrophils - as a consequence of some sort of inflammatory response - to a decrease of lymphocyte count - reflecting a lower immunological control of tumor growth - or to both phenomena, with several studies supporting each of these hypotheses.

LT for HCC represents a particular field of investiga-

tion of inflammatory markers and local immunological activation as possible expressions of tumor invasiveness and biological behavior. Although the visible tumor mass is usually treated preoperatively with neoadjuvant treatments, and then entirely removed with hepatectomy, some parameters detected in the serum may help in recognizing a systemic response to cancer relapse due to viable cancer cells still in the patient's circulation or in remote organs, at any time during the waiting time to LT, and following the procedure.

The role of CRP has been analyzed for prediction of post-LT outcomes of HCC patients^[14]. In a series of 85 patients, those with high CRP levels (≥ 1 mg/dL) at the time of LT had higher total bilirubin levels, Child-Pugh grade, Model for End-Stage Liver Disease score, maximal tumor size, and frequency of intrahepatic metastasis compared to patients with low CRP levels (< 1 mg/dL).

By multivariate analyses, HCC beyond the Milan criteria, a high CRP level, and microvascular invasion were associated with tumor recurrence, while a high CRP level and microvascular invasion were related to lower overall survival. In addition, high CRP level was an independent factor for predicting poor outcomes in patients with HCC beyond the Milan criteria, but not in patients with HCC within the criteria^[14]. Taken together, these findings suggest that CRP is related to poor liver function and higher tumor invasiveness, but the precise molecular mechanisms for its increase in such circumstances are not clarified. Moreover, another study^[16] failed to detect any relationship between CRP (and ESR) and post-LT HCC recurrence.

Unitt *et al*^[11] studied the tumor CD4⁺, CD8⁺, CD25⁺ and Foxp3⁺ lymphocyte infiltrate in the explant tissue of 69 patients transplanted due to HCC. On multivariate analysis, CD4:CD8 ratio, vascular invasion, tumor size, and reduced lymphocyte infiltration were significant independent predictors of recurrence. The presence of regulatory T cells (Tregs; CD4⁺, CD25⁺, Foxp3⁺ T-lymphocytes) was not predictive of recurrence, but was associated with tumor vascular invasion. These data suggest that a reduced immunological response against cancer expressed as prevalence of Tregs and a lower expression of cytotoxic lymphocytes is associated with poor prognosis.

The above findings were partly supported by another study by Mathai *et al*^[12], who assessed the phenotype of tumor-infiltrating lymphocytes in 131 histology sections of patients undergoing LT or liver resection for HCC. An increased Foxp3:CD3 ratio was associated with poorly differentiated HCC and higher Edmonson-Steiner nuclear grade. An increased Foxp3:CD8 ratio was also associated with poorer differentiation, higher Edmonson-Steiner nuclear grade, tumor recurrence, decreased overall survival, and decreased disease-free survival.

Although not focused on LT recipients, other studies showed that patients with HCC have increased numbers of CD4⁺ CD25⁺ Tregs not only among tumor-infiltrating lymphocytes, but also in the peripheral blood; furthermore, the abundance of this cell population correlated with tumor progression. These cells were anergic toward

T-cell receptor stimulation and, when cocultured with activated CD4⁺ CD25⁻ cells, potently suppressed their proliferation and cytokine secretion. Concomitantly, the expression of granzyme A, granzyme B, and perforin was decreased dramatically in tumor-infiltrating CD8(+) T cells, confirming their inefficacy in controlling tumor expansion^[54,55].

In summary, an imbalance between Tregs and CD8 lymphocytes, with a prevalence of the former and a defective function of the latter, does reflect an aggressive behavior of HCC and the inability of the organism to control the disease. While these findings potentially pave the way to new treatments, they cannot be unequivocally correlated with markers easily available by means of common lab tests, such as NLR (see below).

Nevertheless, novel methods for assessing the immune function of transplanted patients could be useful in the future. The Immu-Know assay, which measures the amount of adenosine triphosphate (ATP) produced by activated CD4⁺ T cells, has been used to evaluate the global immune status, and thus the tendency to develop rejection or, on the contrary, post-LT infections^[56].

This tool has also proven to be reliable in predicting post-LT HCC recurrence, with recipients diagnosed with recurrent tumors having significantly lower values of ATP compared to those without recurrence^[13]. This refined measurement of the immune state of LT recipients could replace the more indirect evaluation allowed by systemic exposure to immunosuppressive agents.

Several studies have demonstrated that an increased NLR is an independent factor for lower recurrence-free survival and/or overall survival in LT HCC patients^[15-20]. These studies are reported in Table 1. A total of 892 patients were included. The chosen cutoff value of NLR ranged from 3 to 5, with most studies using the value of 5^[15,16,18], while others identified lower values^[17,19,20].

In the groups of patients with NLR above the selected risk thresholds, overall survival ranged between 14% and 57%, and recurrence-free survival was between 6% and 42%. Only one study reported both the NLR at diagnosis of HCC and NLR at transplant, showing that this variable had a similar negative impact on outcome at the two chosen time points^[18].

High NLR was an independent predictor of outcome in all studies, in most cases together with other commonly recognized risk factors. Interestingly, in two studies NLR was not correlated with histological, serological and dimensional features with a recognized, negative impact on recurrence^[15,18].

In the above reports, different explanations for the alteration of NLR were provided but, though reasonable, most of them were speculative. Only one group, which produced two different analyses on this topic, investigated the correlation between NLR and the alterations of phenotype/function of leucocytes or other cells in tissues surrounding neoplastic nodules^[19]. Interestingly, the Authors found that serum and peritumoral IL-17 levels were significantly higher in patients with high NLR, and that the density of peritumoral CD163-positive tumor

Table 1 Studies reporting the negative impact of increased neutrophil-to-lymphocyte ratio measured at transplant on the outcome of liver transplantation for hepatocellular carcinoma

Ref.	Patients (n)	Type of LT	NLR cut-off level for poor prognosis	Other factors associated with worse outcome	5-yr RFS with high vs low NLR	5-yr OS with high vs low NLR	Parameters positively correlated with increased NLR
Halazun <i>et al</i> ^[15]	150	NA	5	Tumor size AFP	25% vs 75% ¹	28% vs 64%	None
Bertuzzo <i>et al</i> ^[16]	219	DDLT	5	Microvascular invasion	6% vs 89%	14% vs 73%	Micro/macro vascular invasion Tumor grading AFP CRP Outside MC
Wang <i>et al</i> ^[17]	101	DDLT	3	Tumor number Macrovascular invasion	28% vs 65% ¹	19% vs 62%	Macrovascular invasion AFP Tumor size Outside MC Outside UCSF criteria Outside Hangzhou criteria
Limaye <i>et al</i> ^[18]	160	NA	5	Microvascular invasion AFP	27% vs 79%	38% vs 68%	None
Motomura <i>et al</i> ^[19]	158	LDLT	4	Outside MC	30% vs 89%	57% vs 84%	Serum/peritumoral IL-17 Density of peritumoral CD163 CRP
Yoshizumi <i>et al</i> ^[20]	104	LDLT	4	Nodule size + number ≥ 8.0	42% vs 86%	Not reported	Tacrolimus vs cyclosporine Microvascular invasion Tumor grading

¹In these studies, disease-free survival instead of recurrence-free survival rates were reported (and displayed in the present table); ²This study was performed by the same authors as the previous one^[19], and included only patients with surgical and/or locoregional treatment preceding living donor liver transplantation (LDLT). Thus, the patient population is probably at least partly included in the population of the previous study from the same Institution. NLR: Neutrophil-to-lymphocyte ratio; LT: Liver transplantation; HCC: Hepatocellular carcinoma; RFS: Recurrence-free survival; OS: Overall survival; NA: Not assessable; AFP: Alpha-fetoprotein; CRP: C-reactive protein; MC: Milan criteria; DDLT: Deceased donor liver transplantation; UCSF: University of California at San Francisco.

associated macrophages (TAM) was both correlated with the density of peritumoral IL-17-producing cells, and significantly higher in subjects with elevated NLR. Conversely, tumor, peritumoral and serum expression of vascular endothelial growth factor (VEGF) and of IL-8, *i.e.*, two recognized angiogenesis and tumor growth factors, was similar between high and low NLR groups. Tumor expression of IL-17, CD68, and CD163 was also comparable in patients with elevated or normal NLR.

A positive correlation between CRP and NLR, the absence of correlation between NLR and tumor markers, number and size of nodules, and microvascular invasion, the association between high NLR and an increased serum neutrophil count, and the absence of correlation between NLR and total serum lymphocytes were other important findings^[19].

Consistently with previous studies^[57-61], the authors came to the following conclusions: (1) contrary to other investigations, the elevation of NLR seems correlated with an increase of neutrophil number rather than of lymphocytes, suggesting a dependence of tumor relapse on the inflammatory state rather than on an impaired host immune response; (2) elevated neutrophils are thought to be a reservoir of VEGF, but the expression of VEGF and of IL-8 did not have any impact on NLR, suggesting that NLR elevation is not directly responsible for augmented HCC-related neo-angiogenesis; (3) IL-17 is a pro-inflammatory cytokine that promotes HCC

growth and neutrophil recruitment, thus it could be a key molecule in the relationship between NLR (which is supposed to increase due to expansion of neutrophils following recruitment) and HCC recurrence; and (4) the authors' results are consistent with the demonstrated relationship between IL-7-producing T cells and TAMs. IL-7-producing T cells promote the differentiation of tissue macrophages in peritumoral tissue into TAMs, which in turn promote tumor proliferation and angiogenesis. In fact, monocytes are recruited from the circulation into local tissue or malignant sites, where they are recognized by CD68-positive residential macrophages. Under the effect of inflammatory cytokines released by tumors, some of these macrophages differentiate into CD163-positive TAMs that, contrary to CD68⁺ macrophages, are suppressors of the anti-tumor immune response.

IL-17-producing cells interact with TAMs in patients with HCC, and both IL-17-producing cells and CD163⁺ TAMs generate the same family of chemokines promoting the recruitment of monocytes and neutrophils^[19,57-61].

Finally, it should be considered that in the authors' series splenectomy was performed during LT in patients with hepatitis C virus-positive or significant portal hypertension, and splenectomy itself could have had a role in the balance between neutrophil and lymphocyte count. Moreover, TAMs have been demonstrated to originate from splenic monocytes. However, splenectomy itself was not associated with HCC recurrence in this study,

Table 2 Studies reporting the effect of different basal immunosuppression schedules on the outcome of liver transplantation for hepatocellular carcinoma

Ref.	Evaluated immunosuppressor	Evaluated parameter	Patients (n)	Overall recurrence rate	Outcome parameters	P value
Vivarelli <i>et al</i> ^[24]	CsA cumulative dosage 1 st yr	Low dosage 1 st yr vs high dosage 1 st yr	39 vs 30	12.20%	5 yr RFS: 93% vs 5 yr RFS: 76%	0.0100
Kneteman <i>et al</i> ^[25]	SRL	in MC vs out MC	19 vs 21	12.50%	4 yr RFS: 81.1% vs 4 yr RFS: 76.8%	0.4800
Vivarelli <i>et al</i> ^[26]	CsA	Low exposure vs high exposure	49 vs 21	10.00%	RR: 0% vs RR: 33.3%	< 0.0010
Decaens <i>et al</i> ^[27]	CNI	CsA vs TAC	264 vs 119	31.80%	5 yr RFS: 52.5% vs 5 yr RFS: 70.8%	0.0030
Decaens <i>et al</i> ^[27]	ATG/OKT3	Not administered vs administered	356 vs 55	31.80%	5 yr RFS: 58.8% vs 5 yr RFS: 45.4%	0.0200
Vivarelli <i>et al</i> ^[7]	TAC	Low exposure vs high exposure	44 vs 16	20.00%	RR: 9.1% vs RR: 50%	0.0010
Zhou <i>et al</i> ^[28]	TAC and SRL	TAC vs SRL	46 vs 27	27.40%	2 yr OS: 50.9% vs 2 yr OS: 80.6%	0.0110
Zimmerman <i>et al</i> ^[29]	in patients outMC					
	TAC and SRL	TAC + MMF vs TAC + SRL	52 vs 45	12.40%	5 yr RFS: 54.0% vs 5 yr RFS: 78.8%	-
Chinnakotla <i>et al</i> ^[8]	TAC and SRL	TAC + MMF vs SRL	106 vs 121	11.00%	5 yr RFS: 60% vs 5 yr RFS: 80%	0.0001
Vivarelli <i>et al</i> ^[30]	TAC and SRL	TAC vs TAC + SRL	31 vs 31	25.80%	3 yr RFS: 56% vs 3 yr RFS: 86%	0.0400
Toso <i>et al</i> ^[31]	SRL	Not administered vs administered	2382 vs 109	-	5 yr OS: 68.7% vs 5 yr OS: 83.1%	≤ 0.0500
Xing <i>et al</i> ^[32]	Basiliximab and steroids in patients in MC	TAC + MMF + basiliximab vs TAC + MMF + steroids	28 vs 36	-	5 yr OS: 88.9% vs 5 yr OS: 57.4%	0.0220
Rodríguez-Perálvarez <i>et al</i> ^[33]	CNI	Low exposure 1 st mo vs high exposure 1 st mo	171 vs 48	16.40%	5 yr RR: 14.7% vs 5 yr RR: 27%	0.0070

LT: Liver transplantation; HCC: Hepatocellular carcinoma; CsA: Cyclosporine A; RFS: Recurrence free survival; SRL: Sirolimus; MC: Milan criteria; RR: Recurrence rate; CNI: Calcineurin inhibitors; TAC: Tacrolimus; ATG: Anti-thymocyte globulins; OS: Overall survival; MMF: Mycophenolate mofetil.

even though in the group of patients with elevated NLR, splenectomy led to significantly better recurrence-free survival than the abstention from this procedure, suggesting the supply of splenic TAMs with high IL-17 concentrations after LT^[19].

The same authors confirmed the relevant role of NLR on HCC recurrence in patients undergoing living donor liver transplantation for tumor recurrence after surgical resection and/or locoregional treatment^[20], and in those submitted to liver resection^[62].

By evaluating 958 patients who underwent hepatectomy without preoperative therapy for HCC, multivariate analysis showed that NLR was an independent prognostic factor of lower overall and recurrence-free survival, the best cutoff being 2.81. Again, CD163-positive cell counts were significantly higher in tumors of patients with high NLR than in those with low NLR^[62].

Finally, one of the advantages of an easily obtainable serum marker is to assess the response to pre-LT treatments of HCC and the probability of dropout from the waiting list. NLR has been shown to be a good predictor of the risk of dropout, while platelet-to-lymphocyte ratio has been related to post-LT HCC recurrence^[63]. On the other hand, since multimodal treatments are usually adopted while on the waiting list for LT, it has also been shown that NLR, or NLR postoperative changes, correlate with HCC recurrence and patient outcome after radiofrequency ablation^[64,65].

EFFECT OF IMMUNOSUPPRESSION ON HCC RECURRENCE AFTER LIVER TRANSPLANTATION

At present, there is a general consensus on the negative

impact of pharmacological immunosuppression on the outcome of LT for HCC^[7,8,24-33]. Specifically, two clinical pieces of evidence have emerged: (1) the higher the exposure to calcineurin inhibitors (CNI), *i.e.*, cyclosporine and tacrolimus, the higher the risk of post-LT HCC recurrence; and (2) one specific class of immunosuppressors, *i.e.*, inhibitors of the mammalian target of rapamycin (mTORi), have a favorable effect in reducing the incidence of post-LT HCC recurrence compared to standard immunosuppressors (CNI). Everolimus and sirolimus, the two mTORi currently in use in solid organ transplantation, interfere with hepatocarcinogenesis through the inhibition of the PI3K/Akt/mTOR pathway, which is a key regulator of cellular proliferation and angiogenesis^[66,67].

Several studies led to the above conclusions^[7,8,24-33], although it is of relevance that none of these is a prospective, randomized trial. Table 2 depicts the retrospective clinical studies published so far on this topic, with the exclusion of reports with less than 20 patients and previous reviews or meta-analyses.

Overall recurrence rates ranged between 12% and 32%. Four out of 13 reported studies showed that among patients immunosuppressed with CNI, those exposed to higher dosages had unfavorable outcomes, with significantly higher HCC recurrence rates or lower recurrence-free survival rates compared to patients receiving lower dosages^[7,24,26,33]. One study reported a lower recurrence-free survival in patients treated with cyclosporine vs those treated with tacrolimus^[27].

In 5 studies, patients treated with sirolimus (most frequently in combination with low dosages of tacrolimus) showed higher overall or recurrence-free survival rates compared to patients receiving standard CNI-based immunosuppression^[8,28-31]. In one study^[25], patients treated

with sirolimus had similar recurrence-free survival rates, irrespective of fulfillment of the Milan criteria.

One study showed a detrimental effect of the use of monoclonal antibodies (anti-thymocyte globulins or OKT3), with a lower recurrence-free survival in patients receiving these drugs compared to those not administered them^[27]. Another study revealed that the use of steroids *vs* basiliximab led to significantly lower overall survival rates^[32].

A definitive validation of the benefit of mTORi in LT for HCC is expected to be provided in 2014 by an international multicenter, prospective, randomized trial comparing the outcomes of patients administered or not administered sirolimus following post-LT histological confirmation of HCC^[68]. However, at present the use of mTORi in LT for HCC seems justified on the basis of the above reported results and according to a recent meta-analysis conducted on 5 studies and 474 patients, which showed a lower recurrence rate, longer recurrence-free survival and overall survival, and lower recurrence-related mortality in sirolimus-treated patients in comparison with CNI-treated patients^[69].

CONCLUSION

Recent insights into the interactions between tumor, peritumoral tissue, and systemic inflammatory and immune response have offered new indicators for prognosis of patients with HCC undergoing various types of treatment, including LT. NLR has proven to be a reliable and easily available inflammatory marker of tumor biological aggressiveness, making its use advisable along with common dimensional indexes in assessing the response to treatments and the indication for LT, and to predict the outcomes. Although recent reports provided a reasonable molecular basis for the alteration of NLR and, more in general, for the tumor-related imbalance between immune cells in terms of number and function, much remains to be explored to expand targeted diagnostic and therapeutic tools. On the other hand, despite the lack of prospective, randomized studies, there is sufficient evidence for the minimization of immunosuppression and for the use of mTORi in LT for HCC, especially in the case of extended indications for transplant.

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