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Does mTORi base immunosuppression offer survival advantage after liver transplantation for hepatocellular carcinoma? Systematic review and meta-analysis of randomized controlled trials

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Abstract

Recurrence is still a problem after liver transplant for hepatocellular carcinoma (HCC). We performed an updated systematic review and meta-analysis of randomized controlled trials comparing tumor recurrence of mammalian target of rapamycin inhibitors (mTORi) versus Calcineurin inhibitor-based immunosuppression after liver transplantation for HCC. A systematic search was conducted in the following databases: MEDLINE, EMBASE, and Cochrane Central Register of Control Trials databases. The Medical Subject Headings used in the search included: "sirolimus," "everolimus," "mTORi," "HCC," "mTORi," "hepatic transplantation" "randomized controlled trials," and "liver transplantation (LT)". Seven randomized controlled trials were included for meta-analysis. There were a total of 1,365 patients, with 712 of these patients receiving calcineurin inhibitors (CNIs) while 653 had received mTORi. Our meta-analysis revealed that patients that received mTORi-based immunosuppression had superior recurrence-free survival (RFS) at 1 year and 3 years with a hazard ratio of 2.02 and 1.36, respectively. Meta-analysis also showed that within the first 3 years after LT for HCC, patients receiving CNIs-based immunosuppression have a higher recurrence than those receiving mTORi-based immunosuppression. Our meta-analysis revealed that recipients of mTORi-based immunosuppression had a superior OS at 1 year and 3 years. mTORi-based immunosuppression is associated with decreased early recurrence and improved RFS and overall survival.

Keywords: Calcineurin inhibitors; hepatocellular carcinoma; liver transplant; mammalian target of rapamycin inhibitors.

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Introduction

Hepatocellular carcinoma (HCC) is considered the most common primary liver cancer, and the incidence has increased over the past decades. Globally, it is considered the third-most common cause of cancer-related mortality.[1] Although its onset is insidious, the progression is rapid. The significant number of patients with HCC has lost the chance of surgical resection on presentation due to liver cirrhosis, intrahepatic and extrahepatic metastasis. Liver transplantation (LT) is the most effective treatment for HCC with background liver cirrhosis; it completely removes the lesion and the liver cirrhosis.[2,3] HCC currently accounts for up to 20-40% of all LT.[4]

The short-term prognosis of patients with HCC after LT has significantly improved, with most studies reporting a 5-year survival rate of >50%. Despite the improvement of survival, recurrence is still a problem for LT for HCC. Recurrence rate of up to 15-20% has been reported at 5 years post-transplantation.[5,6] One of the several risk factors for post-LT recurrence is the state of the primary tumor. To reduce recurrence after LT, strict patients selection following specified criteria has been adopted, but still, recurrence of 15-20% is been reported by multiple studies.[5-9]

Another factor implicated in the recurrence of HCC after LT is the choice of immunosuppressant after transplantation. Calcineurin inhibitors (CNIs) are immunosuppressants that are routinely used after LT and they have been proven to be an independent risk factor for the recurrence of HCC by promoting cancer cell proliferation and survival.[10-12] The commonly used CNIs are cyclosporine and tacrolimus.

Another class of immunosuppressants, the mammalian target of rapamycin inhibitors (mTORi), has different mechanisms of action. They have been found to have anti-proliferative and anti-angiogenic effects.[3,10-13] The main agents are sirolimus and everolimus. These agents are mainly used because of their low nephrotoxicity profile. Another potential advantage of these agents is the fact that they have been associated with improved survival after LT for HCC with reduced tumor recurrence.[3,10-13]

Multiple retrospective and prospective studies, randomized controlled trials, and meta-analysis have reported the advantage of mTORi-based immunosuppression ahead of mTORi-free immunosuppression.[10,14-16] However, the meta-analysis included both randomized controlled trials, retrospective and prospective studies. This is the first meta-analysis that included only randomized controlled trials for analysis.

We performed an updated systematic review and meta-analysis of randomized controlled trials reporting tumor recurrence and survival outcomes with mTOR inhibitor vs Calcineurin inhibitor-based immunosuppression after LT for HCC.

Materials and Methods

This systematic review was performed in compliance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline. The protocol for this systematic review was prospectively registered on the International Prospective Register of Systematic Reviews, PROSPERO (CRD42022356341). This study did not include patients' participants so ethical clearance from the institutional review board and patients' informed consent were not sought.

Search Strategy

A systematic search was conducted by two independent reviewers. The search was conducted in the following databases: MEDLINE, EMBASE, and Cochrane Central Register of Control Trials databases. Databases were searched from their inception until June 2022. The Medical Subject Headings, Emtree, and text terms used in the search included: "sirolimus," "everolimus," "rapamycin," "rapamune," "mTORi," "mTOR inhibitors," "HCC," "mTORi," "hepatic transplantation", "randomized controlled trials" and "LT." Related articles and reference lists were searched to avoid omission. In case of conflict between the two reviewers, a third reviewer resolves the conflict.

Study Selection Criteria

Studies that fulfilled the following criteria were included in the review.

1. Studies published from 1990 to date
2. Randomized controlled trials that compared the outcomes of mTORi and mTORi free immunosuppression among recipients of LT with HCC
3. Studies with full texts
4. Studies published in all languages.

The exclusion criteria are as follows:

1. Conference presentations, editorials, and commentaries.
2. Lack of relevant data or insufficient data
3. Total study population <10

Quality Assessment and Risk of Bias Assessment

The risk of bias for RCTs was assessed using the Cochrane Collaboration's tool for assessing risk of bias.

Publication Bias

Publication bias was evaluated using the funnel plot and Egger's test if 10 or more studies were included in the meta-analysis of a particular outcome as recommended by the Cochrane handbook.

Data Extraction

Data extraction was performed by two independent researchers. The following information was extracted from each study: first author, published year, country, study design, number of patients, characteristics of patients, intervention, comparison, length of follow-up, and outcome data. Discrepancies between the two researchers were solved by a third researcher.

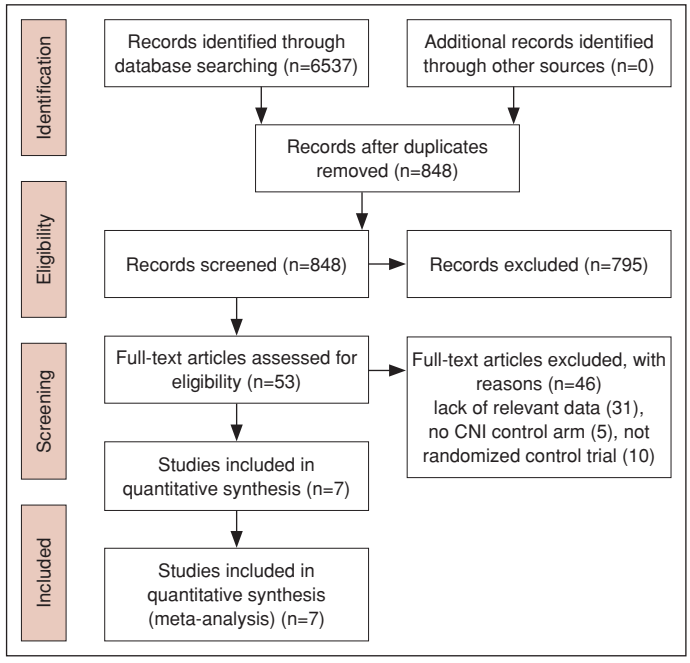

Figure 1. Study selection process.

Outcomes

The primary outcome we considered in this meta-analysis is disease-free survival.

Secondary outcomes include overall survival (OS), recurrence rate, and acute graft rejection.

Statistical Analysis

All statistical analyses were performed using RevMan software (version 5.4.1). For dichotomous variables, the pooled relative risk was calculated with a 95% confidence interval. For continuous variables, the weighted mean difference or standardized mean difference (SMD) with 95% Confidence interval (CI) was calculated. We used a fixed-effects model to calculate the pooled effect sizes if the data were not significantly heterogeneous. Otherwise, a random-effects model was used.

Heterogeneity was evaluated by I^2 statistics. I^2 >50% was considered a statistically significant heterogeneity. Sensitivity analysis was used by omitting each included study in the meta-analysis to identify the main source of heterogeneity. Standard deviation was computed from standard error, confidence interval or from p values if it was not given directly in the articles. If the article included did not provide the mean value, we would use Wan et al.[17] method of computing means from median and range. In survival analysis, the log hazard ratio and variance were obtained by Tierney et al.[18] method of computing the percentage survival at a given time.

Sensitivity analysis was performed by omitting each study and to determine its effect on the overall result. In this meta-analysis, publication bias was assessed by visual inspection of funnel plots for symmetry.

Table 1. Characteristics of included studies

Author	Year of publication	Sample size		Outcomes compared
		CNI	mTORi	
Taperman et al.[23]	2013	42	44	1. Recurrence 2. Recurrence related mortality
Masetti et al.[25]	2010	16	28	1. Recurrence related mortality 2. Acute rejection
Geisler et al.[19]	2016	256	252	1. Acute rejection 2. Overall survival 3. Disease free survival
Jeng et al.[24]	2020	62	56	1. Recurrence
Yujian et al.[22]	2014	31	30	1. Recurrence 2. Overall survival
Schnitzbauer et al.[21]	2020	284	224	1. Overall survival
Lee et al.[20]	2020	21	19	1. Overall survival 2. Disease free survival

CNI: Calcineurin inhibitors; mTORi: Mammalian target of rapamycin inhibitors.

Table 2. Quality assessment of included studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome	Incomplete outcome data	Selective reporting	Other bias
Taperman et al.[23	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear	Low risk
Masetti et al.[25]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear
Geisler et al.[19]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jeng et al.[24]	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear	Unclear
Yujian et al.[22]	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear
Schnitzbauer et al.[21]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lee et al.[20]	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear

Results

Results were reported in accordance with the PRISMA checklist.

Study Selection Process and Description of Selected Studies

We identified 6,537 references during the initial search. Out of these, 5,689 duplicates and 795 irrelevant articles were excluded (Fig. 1). The 53 remaining references were retrieved for assessment of their full text. Forty-six references were excluded for reasons like lack of relevant data (31 studies), lack of CNI control arm (5 studies), and not randomized control trial (10 studies). Seven references were included for the data synthesis and meta-analysis. The studies included were all randomized control trials published between 2010 and 2020. There were a total of 1,365 patients, with 712 of these patients receiving CNIs while 653 had received mTORi. Of the 7 randomized controlled trials included, only 4 were specifically designed to analyze recurrence free survival (RFS) in HCC transplant patients.[19-22] The remaining 3 studies[23-25] primarily addressed the effect of mTORi on renal function but included data on HCC recurrences.

Details of selected studies are displayed in Table 1. The risk of bias assessment is presented in Table 2. In general, the quality of RCTs was high.

Sociodemographic Variables

The two groups did not show any statistical significance in age distribution (SMD= -0.04, 95% CI -0.18–0.10, p=0.60). The gender distribution, however, differs between the two groups, with more males receiving CNI-based immunosuppression compared mTORi based immunosuppression (OR=0.50, 95% CI 0.34–0.74, p=0.0005).

Primary Outcome

RFS

The primary outcome we compared was RFS between patients that received mTORi-based immunosuppression and those that received CNI-based immunosuppression. Three studies[19,20,22] consisting of a total of 611 patients, reported 1-year and 3-year RFS. The heterogeneity between studies was not significant with I^2=0%, so the fixed effect was used to estimate the pooled effect. Our meta-analysis revealed that patients that received mTORi-based immunosuppression had a superior RFS at 1 year and 3 years with a hazard ratio of 2.02 and 1.36, respectively. Figure 2 displays the forest plot of the meta-analysis.

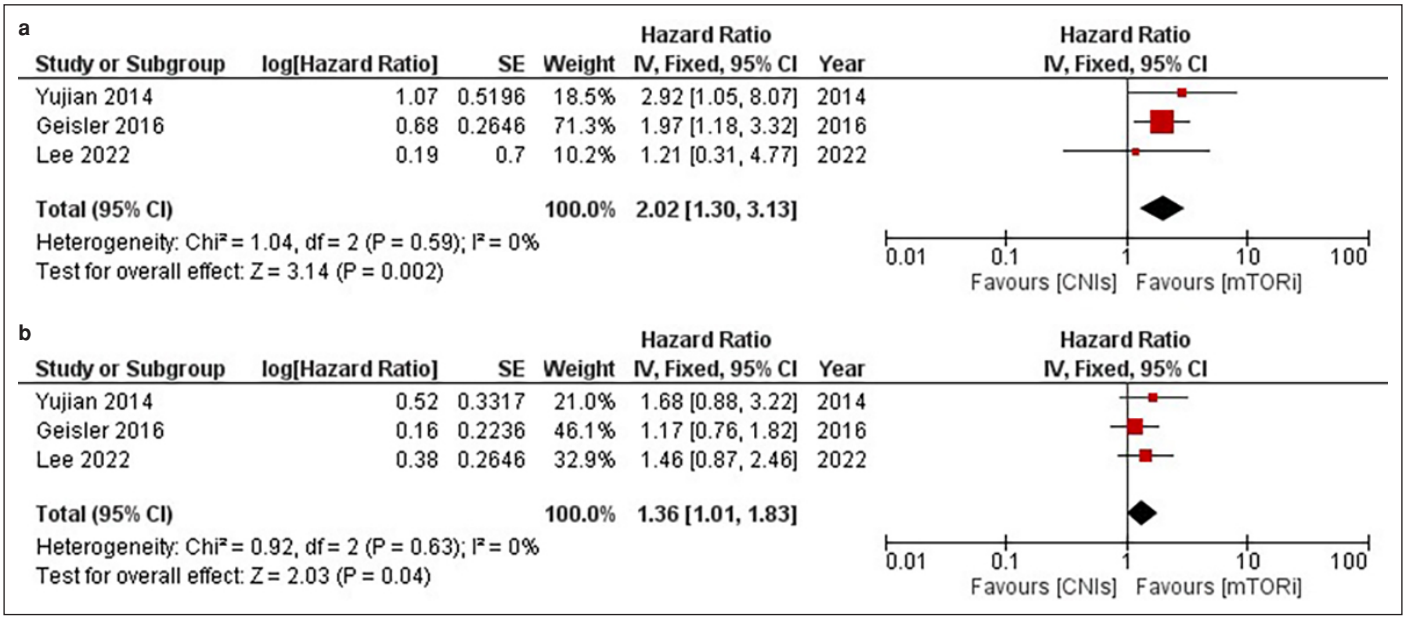

Figure 2. Meta-analysis of recurrence free survival at 1 year **(a)** and 3 years **(b)**.

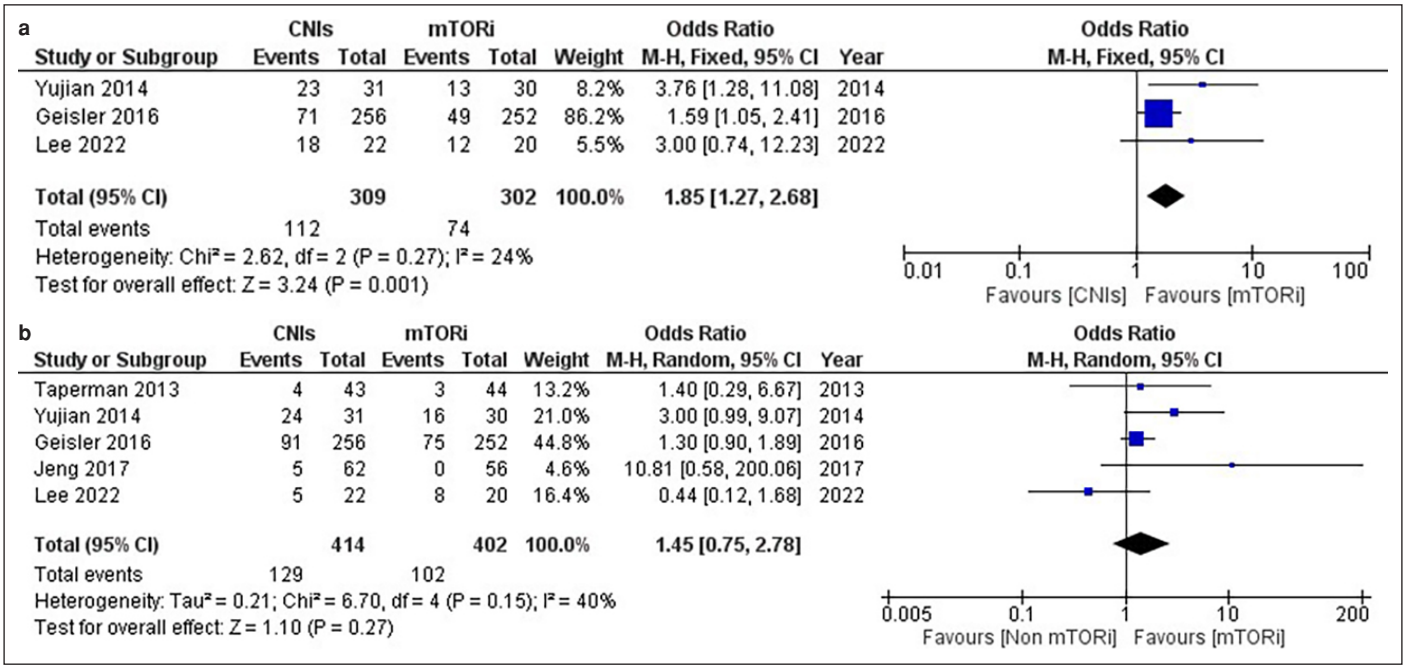

Figure 3. Meta-analysis of post-transplant recurrence at 3 years **(a)** and overall recurrence **(b)**.

Secondary Outcome

Recurrence Rate

Five studies[19,20,22-24] consisting of 804 patients compared overall recurrence between the two groups. There was no statistically significant difference between the two groups in terms of recurrence when we subjected these studies to meta-analysis. The p value was 0.27, with an odd ratio of 1.45. There was no heterogeneity between the studies as I^2=25%. The recurrence at 3 years post-LT was reported by 3 studies[19,20,22] that included 611 patients, and meta-analysis of these studies showed that within the first 3 years after LT for HCC, patients receiving CNIs-based immunosuppression have a higher recurrence compared to patients receiving mTORi based immunosuppression with a p-value of 0.001 and OR of 1.85.

The meta-analysis of the overall recurrence rate and recurrence at 3 years is shown in Figure 3.

OS

Four studies[19-22] consisting of 1,119 patients compared OS between the two groups. Our meta-analysis revealed that recipients of mTORi-based immunosuppression had a superior OS at 1 year and 3 years with hazard ratios of 2.13 and 1.29, respectively. At 5 years after transplantation,

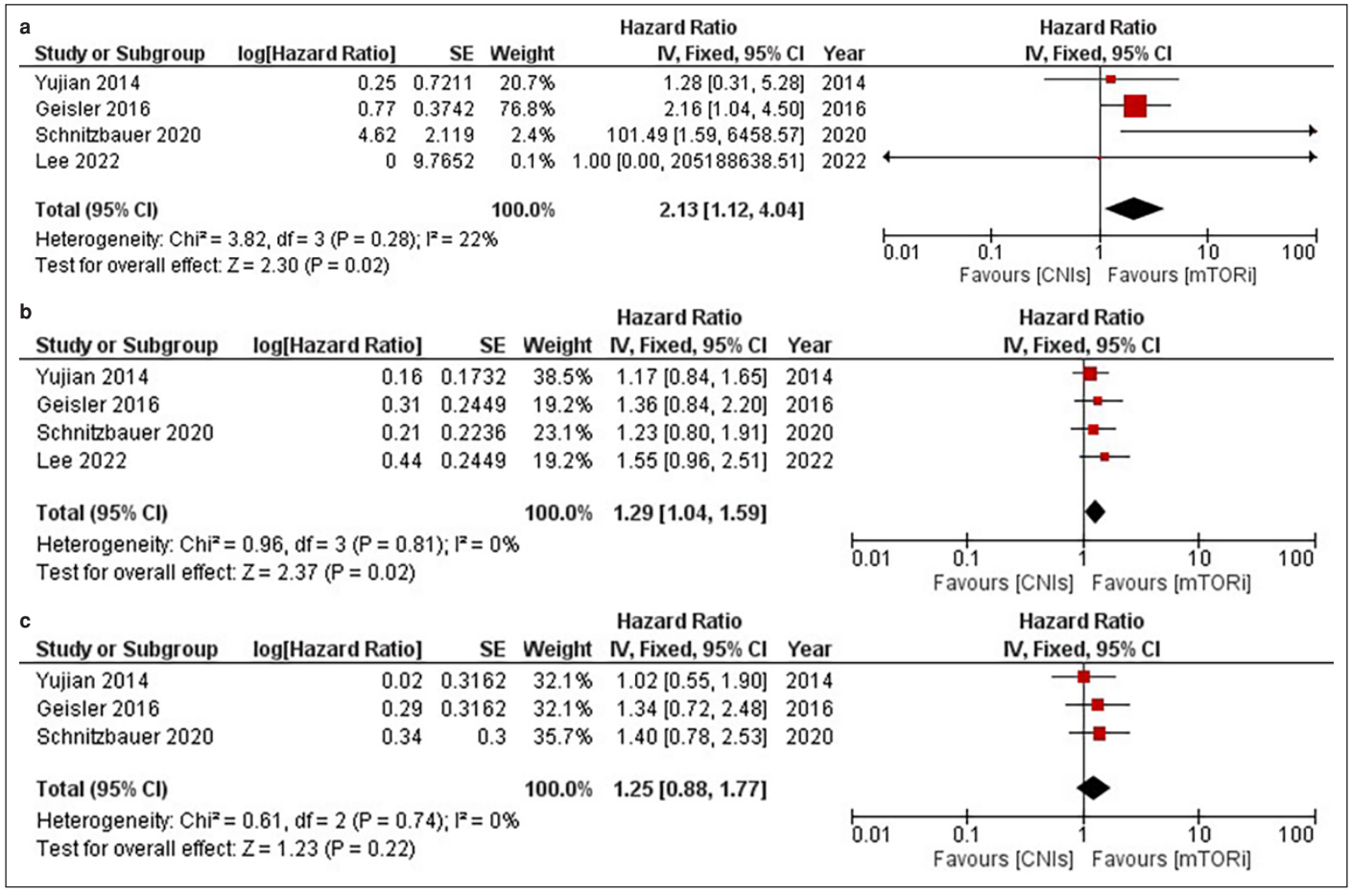

Figure 4. Meta-analysis of overall survival at 1 year **(a)**, 3 years **(b)** and 5 years **(c)**.

there was no statistically significant difference in OS between the two groups (p=0.22). The heterogeneity between studies was not significant with I^2=0%, so the fixed effect was used to estimate the pooled effect. The meta-analysis of OS is displayed in Figure 4.

Hepatic Artery Thrombosis

Two studies[19,25] consisting of 552 patients compared post-transplant hepatic artery thrombosis between patients that received mTORi-based immunosuppression and CNI-based immunosuppression. Meta-analysis of these studies revealed no significant difference in hepatic artery thrombosis between the two groups (p=0.59, OR=1.48).

Acute Cellular Rejection (ACR)

The comparison of acute rejection between patients receiving mTORi-based immunosuppression and those receiving CNI-based immunosuppression was reported in 4 studies,[19,20,23,24] which included 703 patients. Meta-analysis of these studies revealed that there is no statistically significant difference between the two groups in terms of ACR (OR=0.95, p=0.76, I^2=0%).

Discussion

Since liver transplant became accepted as a treatment option for HCC, the disease has become one of the most common indications for transplantation worldwide, accounting for 15%–20% of liver transplants performed in some centers.[4] A persistent problem after liver transplant for HCC is the recurrence of the disease, and there has been an effort to improve outcomes by minimizing the risk of tumor recurrence. One of the factors implicated in the recurrence of HCC after LT is the choice of immunosuppressant after transplantation.[10-12]

CNIs are immunosuppressants that are routinely used after LT and they have been proven to be an independent risk factor for the recurrence of HCC by promoting cancer cell proliferation and survival. CNIs are believed to promote cancer recurrence and progression by direct cellular effect through the production of transforming growth factor-β. They are also believed to induce overexpression of vascular endothelial growth factor (VEGF) and promote a rapid progression of tumor cells.[12] The commonly used CNIs are cyclosporine and tacrolimus. One of the efforts at improving outcomes after liver transplant for HCC was to minimize the use of CNIs-based immunosuppression with increased use of mTORi-based immunosuppression patients that had liver transplant for HCC.

The mTORi has different mechanisms of action compared to CNIs. They have been found to have anti-proliferative and anti-angiogenic effects by interfering with VEGF-mediated pathways.[10,11,13,26] The main agents are sirolimus and everolimus and one of the advantages of these agents is the fact that they have been associated with improved survival after LT for HCC with reduced tumor recurrence.[3,13,21]

In this meta-analysis, we found that RFS in patients that received mTORi-based immunosuppression is superior to those that received CNI-based immunosuppression. The difference was statistically significant at 1 year and 3 years after liver transplant. We also found that mTORi-based immunosuppression is associated with better OS at 1 year and 3 years. This is similar to the findings of Grigg et al.[15] and Yan et al.[14]

Recurrence after LT for HCC carcinoma is reported to occur between 15 and 20% of all transplants.[5,6] Recurrence can be classified as early or late recurrence. Early recurrence occurs within 2 years of LT, while late recurrence occurs between 2 and 5 years after LT.[27,28] Very late recurrence occurring after 5 years has been described in some patients.[29] In our meta-analysis, overall recurrence after liver transplant foe HCC was no affected by the choice of immunosuppression. However, the studies included in the analysis showed variation in the time of measurement of overall recurrence. Some of the studies[20] reported the recurrence at 3 years after LT, while other studies reported the recurrence at 8 years post-LT.[19] To standardize the analysis, we performed a subgroup analysis of studies[19,20,22] that provided results of recurrence within 3 years post-transplant and we found that patients receiving CNIs have a higher risk of recurrence compared to patients on mTORi based immunosuppression. The role of mTORi in improving early recurrence after transplant for HCC may be related to the interference with the VEGF pathway, which may inhibit angiogenesis and vascular invasion.[26] One of the risk factors implicated in early recurrence after liver transplant for HCC is the presence of circulating tumor cell (CTC) in the circulation during the perioperative period.[30,31] CTCs have been reported to express VEGF, VEGF receptors, and hypoxia-inducible factor 1-alpha.[32] These factors play an important role in angiogenesis, recurrence, and metastasis. By interfering with VEGF and VEGFR, mTORi can prevent early recurrence by inhibiting the implantations of CTCs.

One of the initial limitations to the use of mTORi-based immunosuppression was the fear of hepatic artery thrombosis and subsequent graft loss.[13] Initial reports reported a strong association between mTORi-based immunosuppression and hepatic artery thrombosis but subsequent studies by McKenna et al.[33] and De-Simone et al.[16] showed mixed results with some findings reporting a negative association. In this meta-analysis, we found no difference in hepatic artery thrombosis in mTORi-based immunosuppression compared to CNI-based immunosuppression.

ACR occurs in up to 25% of patients that underwent liver transplants. One of the risk factors for acute rejection includes low trough levels of immunosuppressants or noncompliance to immunosuppression regimens. Another risk factor for ACR reported by Massoud et al.[34] is the choice of immunosuppressive agents. In their study, they reported that the use of sirolimus monotherapy is associated with up to 75% of cases of ACR after liver transplant.[34] However, since they reported their findings, there have multiple studies that showed no superiority of CNI-based immunosuppression over mTORi-based immunosuppression in terms of ACR.[13] In this meta-analysis, acute rejection after liver transplant was not statistically different between mTORi-based immunosuppression and CNI-based immunosuppression.

Conclusion

This meta-analysis indicated that mTORi-based immunosuppression is associated with decreased early recurrence and improved RFS and OS up to 3 years after LT for HCC compared to CNIs-based immunosuppression with no additional risk of acute rejection or hepatic artery thrombosis.

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Conflict of Interest: The authors have no conflict of interest to declare.

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