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# Impact of Statins on Hepatocellular Carcinoma Recurrence After Living-Donor Liver Transplantation

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Conflict of interest:** None declared

**Background:** Liver transplantation (LT) has been validated widely all over the world as the curative treatment for hepatocellular carcinoma (HCC). Statins have been reported to prevent the progression of HCC. There are many factors that affect recurrence of HCC, but the precise role of statins is unknown. Therefore, we examined whether statin therapy is associated with decreased HCC recurrence in patients who underwent living-donor LT (LDLT) for HCC.

**Material/Methods:** We retrospectively analyzed 844 HCC patients who underwent primary adult-to-adult LDLT in our center between January 2007 and December 2016. Statin therapy was defined as administration of statins for more than 30 cumulative defined daily doses (cDDDs) after LT. We compared HCC recurrence and patient survival between non-statin (n=334) and statin (n=52) groups.

**Results:** The recurrence rate was higher in the non-statin group; however, time-dependent multivariate analysis with Kaplan-Meier curves showed that statin users did not significantly benefit in terms of HCC recurrence-related survival or overall survival. Further, risk factor analysis of HCC recurrence and patient survival confirmed multiple regional treatments ( $\geq 3$  times), high alpha fetoprotein level ( $\geq 100$  ng/mL), large tumor size ( $\geq 3$  cm), and microvascular invasion as risk factors for HCC recurrence, but statin treatment was not associated with a significantly lower recurrence rate of HCC or reduced mortality after adjusting for other risk factors.

**Conclusions:** Statin use might be associated with prevention of HCC progression, but no significant decrease in HCC recurrence rates in LDLT patients was recorded in this study.

**Keywords:** 3-hydroxy-3-methylglutaryl-coenzyme A • Carcinoma, Hepatocellular • HMG-CoA Reductase Phosphatase • Liver Transplantation • Recurrence

**Abbreviations:** LT – liver transplantation; LDLT – living-donor liver transplantation; HMG-CoA – 3-hydroxy-3-methylglutaryl CoA; DDLT – deceased-donor liver transplantation; TACE – transcatheter arterial chemoembolization; cDDD – cumulative defined daily dose

**Full-text PDF:** <https://www.annalsoftransplantation.com/abstract/index/idArt/935604>

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## Background

Liver transplantation (LT) is established widely around the world as the only curative treatment for end-stage liver disease. Moreover, it is expected that LT not only can remove the tumor, but also cure the underlying liver disease. Therefore, LT can be a life-saving intervention in patients with hepatocellular carcinoma (HCC). However, although the survival rate of HCC patients treated with LT has improved steadily, recurrence of HCC remains an important clinical challenge. The first case of recurrent HCC after LT was reported in 1995 [1]. Recently, the recurrence rate of HCC after LT was estimated to range between 10% and 20%, with a median time to recurrence of 14 months after LT and a post-recurrence median survival period of 12.2 months [2-5]. In addition, at Samsung Medical Center, the median length of the recurrence-free period was 9.3 months (range, 0.89-97.25 months), and the median follow-up period after recurrence was 13.4 months (range, 0.59-118.28 months). The 1-, 3-, and 5-year survival rates after recurrence were 65.2%, 34.0%, and 20.5%, respectively [6,7].

Statins, which are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, have a long history of use as treatments for dyslipidemia and cardiovascular disease [8]. However, there has been emerging interest in the potential therapeutic application of statins as anticancer agents given their pro-apoptotic, antiproliferative, cell-cycle regulation, anti-invasive, and immunomodulatory effects [9-11].

For these reasons, many studies have sought to assess the effects of statins in patients with HCC. In previous research, statin use was associated with a reduction in the risk of HCC, and a meta-analysis showed that statin use was associated with a 37% lower risk of HCC [12,13]. Furthermore, statin use has been linked to reduced risk of HCC development in chronic hepatitis B virus (HBV)-infected patients, suggesting that statins have a chemopreventive role in this population [14,15].

However, relatively few studies have investigated the effect of statins on HCC recurrence in patients who underwent living-donor LT (LDLT) for HCC. One retrospective study showed that statin use was associated with a reduction in the risk of HCC recurrence in LT recipients [17]. However, that study included a heterogeneous donor spectrum of clinical conditions, including patients who underwent deceased-donor LT (DDLT). Statins might prevent HCC recurrence in LT recipients, but this association has not been studied fully in patients who underwent LDLT for HCC. Therefore, in the present study, we aimed to investigate the association between statin use and risk of HCC recurrence in LDLT recipients.

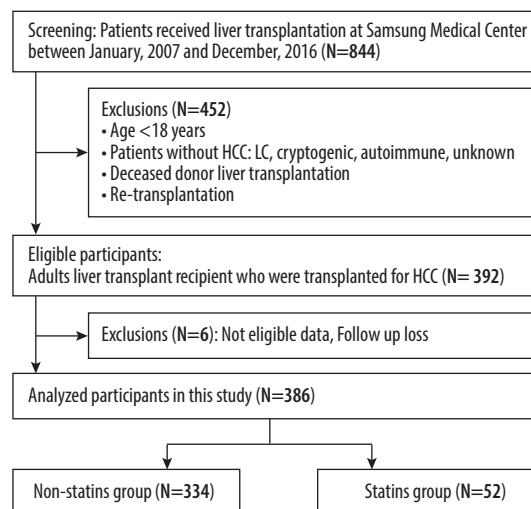


Figure 1. Patient selection.

## Material and Methods

This study was approved by the Samsung Medical Center Institutional Review Board (IRB No. 2021-09-058). The need for consent from the participants was exempted by the IRB.

### Study Population

From January 2007 to December 2016, 844 LTs were performed at Samsung Medical Center (Figure 1). Patients with DDLT or multi-organ transplants (including simultaneous kidney grafts and re-transplantation) and pediatric transplants were excluded from this study (n=226). Additionally, 6 patients with missing follow-up data were excluded, leaving 386 patients in this study.

After enrollment, the study participants were divided into 2 groups, a no-statin-medication group (n=334) and a statin-medication group (n=52). We compared the HCC recurrence and patient survival rates between these 2 groups and conducted a risk factor analysis of HCC recurrence after LDLT.

### Living-Donor Liver Transplantation for Hepatocellular Carcinoma

In our center, we did not set strict criteria for liver transplantation in HCC patients. However, whether to perform LDLT was decided after the discussion of a multidisciplinary team, and HCC invading the main portal vein was considered a contraindication for transplantation. Living donors were selected among family members or relatives if the recipient did not have a matched donor within his or her family members. A graft-recipient weight ratio (GRWR) of 0.8% and future liver remnant of 30% were considered as the cut-off for donation.

## Use of Statins

According to pharmacokinetic features, statins are classified as either lipophilic or hydrophilic. Lipophilic statins include simvastatin, atorvastatin, fluvastatin, and lovastatin, whereas hydrophilic statins include rosuvastatin and pravastatin. Data on the prescription of statins during the study period were extracted from our electronic prescription databases. Statin dosage, type(s), date(s) of prescription, and cumulative number(s) were analyzed. The defined daily dose (DDD) is the standard dose of a statin recommended by the World Health Organization for measuring a prescribed amount of drug. The cumulative DDD (cDDD), which was calculated as the summation of the DDD values of all statins during the follow-up period, considered the exposure duration. Patients who used statins for at least 30 cDDDs during the follow-up period were defined as statin users. For patients who were taking statins before transplantation, the cDDD was counted from the first prescription after transplantation. Statin use and cDDD were considered as time-dependent covariates.

## Immunosuppression Protocol

Depending on routine induction medication, basiliximab was administered at a dose of 20 mg/day at the time of surgery and on the fourth postoperative day. All patients received triple immunosuppressive therapy regimens consisting of tacrolimus, mycophenolate mofetil, and methylprednisolone. Any patient who did not receive this regimen was excluded from the study. Tacrolimus (FK506, Prograf; Astellas Fujisawa, Osaka, Japan, and generic tacrolimus) was started on postoperative day 5 at 0.1 to 0.15 mg/kg/day and adjusted to maintain whole-blood trough level at 8 to 10 ng/mL for 1 month postoperatively and administered at 6 to 8 ng/mL until 3 months and tapered down thereafter. Mycophenolate mofetil (Myfortic; Novartis Pharma AG, Basel, Switzerland) was started at a dose of 500 to 1000 mg/day on postoperative day 3 and adjusted according to the general condition of the recipient considering the potential for opportunistic infection. Methylprednisolone was started on the day of surgery at an intravenous dose of 500 mg/day, administered for 2 days, and then tapered by half every day to 60 mg/day. Thereafter, oral methylprednisolone was administered at 32 mg/day for 7 days, at 16 mg/day for the next 2 weeks, at 8 mg/day for the next month, and at 4 mg/day for maintenance.

## Statistical Analysis

All variables are expressed as mean±standard deviation or number and percentage. Between-group differences of mean values were compared with independent *t* tests, and between-group differences of numbers and percentages were compared with  $\chi^2$  test or Fisher's exact test. Statin use was considered a

time-dependent covariate to consider the immortal time bias of statin on-off time for patients who used statins during the study period. Kaplan-Meier survival curves were used to calculate HCC recurrence-related survival and patient survival to evaluate the impact of statin use. Cox regression analysis was performed with adjustments for significant risk factors in the univariate analysis, as well as other factors previously known to be associated with HCC recurrence, HCC recurrence-related survival, and patient survival. *P* values <.05 were considered statistically significant. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

## Results

### Baseline Characteristics and Postoperative Outcomes

A total of 386 patients who underwent adult LDLT between January 2007 to December 2016 were reviewed. The statin group (*n*=52) and non-statin group (*n*=334) were compared according to demographics and perioperative characteristics (Table 1).

Patients in the statin group were significantly older ( $55.85\pm 7.33$  vs  $53.89\pm 7.54$  years; *P*=0.042) with higher proportion of DM (34.62% vs 18.26%; *P*=0.007) and/or hypertension (28.85% vs 10.78%; *P*<0.001) compared to the non-statin group. Body mass index ( $25.95\pm 3.45$  vs  $24.61\pm 3.19$  kg/m<sup>2</sup>; *P*=0.014) and total cholesterol level ( $141.79\pm 40.75$  vs  $130.29\pm 36.72$  mg/dL; *P*=0.042) were higher in the statin group compared to the non-statin group. The proportions of male patients (78.85% vs 88.92%; *P*=0.041) and HBV carriers (73.08% vs 85.93%; *P*=0.018) were higher in the non-statin group, and more transcatheter arterial chemoembolization (TACE) procedures were performed in the non-statin group than in the statin group ( $1.48\pm 2.13$  vs  $2.64\pm 3.42$  procedures; *P*=0.022).

Regarding operative and postoperative outcomes, the proportion of macroscopic fatty changes in the liver graft ( $8.50\pm 7.01$  vs  $6.99\pm 5.78$ ; *P*=0.026) was greater in the statin group (Table 2). Operation and cold and warm ischemic times as well as pathologic outcomes did not differ between the 2 groups. Postoperative peak levels of liver enzymes were higher in the statin group than in the non-statin group (aspartate aminotransferase, AST,  $463.56\pm 507.85$  vs  $368.02\pm 399.98$ , *P*=0.012; alanine aminotransferase, ALT,  $461.56\pm 363.76$  vs  $395.71\pm 433.17$ , *P*=0.015). Postoperative complication rates were similar between the 2 groups.

The recurrence rate of HCC (9.62% vs 32.34%; *P*<0.001) and mortality rate (5.36% vs 34.24%; *P*<0.001) were significantly higher in the non-statin group than in the statin group.

Table 1. Baseline characteristics.

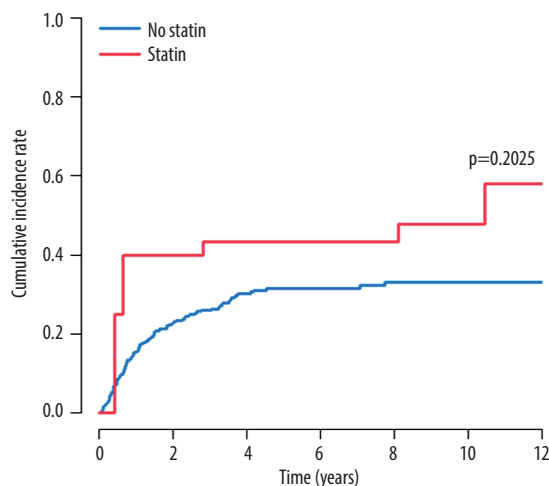
Characteristics	Statin non-user (n=334)	Statin user (n=52)	P-value
<b>Recipient</b>			
Sex (recipient Male/Female)	297/37 (88.92%)	41/11 (78.85%)	0.041
Age (years)	53.89±7.54	55.85±7.33	0.042
Body mass index	24.61±3.19	25.95±3.45	0.014
Hypertension (+)	36 (10.78%)	15 (28.85%)	<0.001
Diabetes (+)	61 (18.26%)	18 (34.62%)	0.007
CTP score	7.15±2.05	7.00±2.16	0.493
MELD score	12.44±5.79	11.87±5.83	0.298
Hepatitis B sAg (+)	287 (85.93%)	38 (73.08%)	0.018
Hepatitis C RNA (+)	19 (5.69%)	4 (7.69%)	0.532
ABO-Incompatible (+)	52 (15.57%)	5 (9.62%)	0.260
<b>Preoperative laboratory findings</b>			
Albumin (g/dL)	3.39±0.64	3.35±0.66	0.805
Total bilirubin (mg/dL)	3.09±5.89	2.45±4.31	0.213
INR (INR)	1.42±0.60	1.40±0.51	0.413
AFP (ng/dL)	1205.85±9865.90	377.98±1319.91	0.906
PIVKA II (mAU/mL)	254.60±1448.08	584.17±3235.49	0.258
Total cholesterol (mg/dL)	130.29±36.72	141.79±40.75	0.042
Triglyceride (mg/dL)	75.48±43.68	83.90±43.17	0.174
HDL (mg/dL)	49.77±19.85	56.88±21.12	0.213
LDL (mg/dL)	87.19±36.47	88.97±26.49	0.858
<b>Locoregional treatment (no. of sessions)</b>			
RFA	0.44±1.01	0.52±0.94	0.350
TACE	2.64±3.42	1.48±2.13	0.022
Radiation therapy	26 (7.81%)	3 (5.77%)	0.781
Operation (hepatectomy)	59 (17.66%)	7 (13.46%)	0.454
ICU stay (days)	7.34±7.05	6.87±2.07	0.462
Hospital stay (days)	36.64±32.40	35.50±19.08	0.500
<b>Statin use</b>			
Lipophilic		25 (48.08%)	
Hydrophilic		27 (51.92%)	
<b>Donor</b>			
Sex (recipient Male/Female)	232/102 (69.46%)	35/17 (67.31%)	0.754
Age (years)	31.36±11.50	32.62±12.19	0.516
Body mass index (kg/m <sup>2</sup> )	23.09±2.89	23.85±4.07	0.299
Hypertension (+)	2 (0.6%)	4 (7.69%)	0.004
Diabetes (+)	1 (0.3%)	0 (0.0%)	1.000
Hospital stay (days)	13.68±6.78	15.39±9.28	0.370

INR – international normalized ratio; RFA – radiofrequency ablation; CPT – Child-Turcotte-Pugh; MELD – Model for End-Stage Liver Disease; AFP – Alpha-Fetoprotein; PIVKA2 – Protein induced by vitamin K absence-II; HDL – High-density lipoprotein; LDL – High-density lipoprotein; TACE – Transcatheter arterial chemoembolization; ICU – Intensive Care Unit.

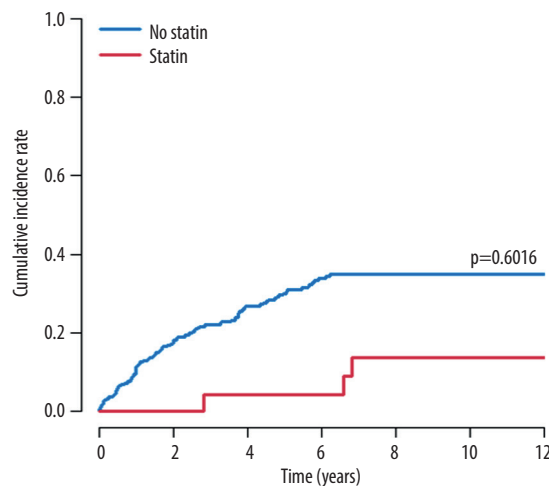
**Table 2.** Postoperative outcomes.

Characteristics	Statin non-user (n=334)	Statin user (n=52)	P-value
Donor fatty change (%)			
Macroscopic	6.99±5.78	8.50±7.01	0.026
Microscopic	9.29±8.00	10.20±7.56	0.293
Graft weight (g)	699.10±128.47	727.96±120.77	0.064
GRWR	1.03±0.22	1.04±0.22	0.683
Operation time (min)	563.89±113.08	553.02±105.91	0.455
Cold ischemic time (min)	88.90±29.18	102.40±64.96	0.981
Warm ischemic time (min)	35.13±14.47	33.31±11.72	0.492
Tumor			
Number	2.44±2.73	1.75±1.08	0.109
Size (largest, cm)	3.03±1.99	2.58±1.60	0.094
Pathologic (Edmonson grade)	2.02±0.50	1.88±0.55	0.080
Microvascular invasion	169 (50.60%)	23 (44.23%)	0.393
Postoperative laboratory findings (at 7 days after LT)			
Peak AST (U/L)	368.02±399.98	463.56±507.85	0.012
Peak ALT (U/L)	395.71±433.17	461.56±363.76	0.015
Peak total bilirubin (mg/dL)	4.10±4.54	4.25±6.26	0.359
Pear prothrombin time (INR)	2.65±0.67	2.52±0.63	0.098
Acute rejection episode	38 (11.38%)	11 (21.15%)	0.049
Complication (Clavien-Dindo)	167 (50.0%)	24 (46.15%)	0.606
I	11	1	
II	44	10	
III	103	12	
IV	3	1	
V	5	0	
Recurrence	108 (32.34%)	5 (9.62%)	<0.001
Intrahepatic	40	2	
Extrahepatic	64	3	
Both	4	0	
Death	113 (34.24%)	3 (5.36%)	<0.001
HCC recurrence related	69	2	

GRWR – graft-recipient weight ratio; AST – aspartate aminotransferase; ALT – alanine aminotransferase; INR – international normalized ratio.



**Figure 2.** Cumulative recurrence rates estimated using an extended Kaplan-Meier method that can be used with time-varying covariates.



**Figure 3.** Cumulative overall survival rates estimated using an extended Kaplan-Meier method that can be used with time-varying covariates.

### Analysis for Recurrence of HCC and Patient Survival

The cumulative recurrence rate was estimated using an extended Kaplan-Meier method that can be used with time-varying covariates (Figure 2). The Kaplan-Meier curve showed similar rates of HCC recurrence-related survival between the 2 groups ( $P=0.602$ ). Furthermore, the results of cumulative overall survival analysis were similar between the 2 groups ( $P=0.203$ ) (Figure 3).

Risk factor analysis of HCC recurrence was performed using Cox proportional hazard models (Table 3). Statin use and cDDD were considered as time-dependent covariates. Three or more locoregional treatments (hazard ratio [HR], 1.775, 95% confidence interval [CI], 1.204-2.616;  $P=0.004$ ) tumor size  $\geq 3$  cm (HR, 1.570; 95% CI, 1.070-2.304;  $P=0.021$ ), AFP level  $\geq 100$  ng/mL (HR, 1.912; 95% CI, 1.293-2.828;  $P=0.001$ ), and microvascular invasion (HR, 3.408; 95% CI, 2.085-5.572;  $P<0.001$ ) showed significant relationships with HCC recurrence. However, statin treatment was not associated with HCC recurrence after adjusting for other risk factors (HR, 0.929; 95% CI, 0.366-2.357;  $P=0.877$ ). Regarding risk factors for overall survival, AFP  $\geq 100$  ng/mL (HR, 1.592; 95% CI, 1.068-2.372;  $P=0.022$ ) and microvascular invasion (HR, 1.966; 95% CI, 1.287-3.002;  $P=0.002$ ) were significantly related to poor prognosis, while statin treatment was not related to prognosis (HR, 0.388; 95% CI, 0.121-1.242;  $P=0.111$ ) (Table 4).

### Discussion

This study investigated the correlation between statin medication and HCC recurrence in patients who underwent LDLT

for HCC. The possibility of administering statins as anticancer agents was evaluated, focusing on recurrence of HCC after LDLT. The background of this study was that several investigations have reported the beneficial impact of statin for various types of cancer [18-20]. Use of statin prior to allograft procurement of kidney transplant reduced the acute kidney inflammatory burden profile and promoted improved kidney function recovery following transplantation [21]. Hence, statins significantly reduced hyperlipidemia and tended to reduce cardiovascular events in kidney transplant recipients [22].

It is not definite which mechanism of statins contributes to prevention of HCC, although HMG-CoA reductase by statins can reduce concentrations of mevalonate pathway metabolites that are essential for cancer cell growth [23]. Various liver disorders, particularly cholestasis, affect cholesterol metabolism and can trigger variable levels of hypercholesterolemia, including the appearance of Lp-X. Mistaking Lp-X for low-density lipoprotein cholesterol can interfere with cardiovascular risk assessment, leading to prescription of futile lipid-lowering therapies [24]. Therefore, it was expected that statins would have a strong effect in the liver, which is a major organ that experiences inflammation caused by steatosis related to lipid metabolism.

However, our study showed no difference in recurrence-free survival rates between the statin and non-statin groups. While the statin group demonstrated a significantly lower recurrence rate (9.62% vs 32.34%;  $P<0.001$ ), our study failed to show a significant relationship with recurrence-free survival in the time-dependent Cox analysis ( $P=0.877$ ). This finding can be attributed to the tendency to prescribe statins to LDLT recipients who experienced prolonged survival. Furthermore, the statin

**Table 3.** The risk factors of hepatocellular carcinoma recurrence analyzed by Cox proportional-hazards regression models.

Recipient characteristics	Univariable			Multivariable					
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Sex (Male)	1.968	0.959-4.039	0.065	1.317	0.634-2.739	0.460	1.321	0.635-2.747	0.457
Age (≥60 years)	0.732	0.455-1.175	0.196						
MELD score (≥20 points)	0.798	0.372-1.716	0.564						
ABO-incompatible LT	1.258	0.767-2.063	0.364						
Regional treatment (≥3 times)	2.381	1.637-3.461	<0.001	1.775	1.204-2.616	0.004	1.784	1.210-2.629	0.004
Tumor size (≥3 cm)	2.347	1.617-3.406	<0.001	1.570	1.070-2.304	0.021	1.561	1.065-2.288	0.022
Tumor number (≥3)	1.877	1.285-2.742	0.001	1.267	0.861-1.864	0.231	1.272	0.863-1.873	0.224
AFP (≥100 ng/dL)	2.923	2.013-4.243	<0.001	1.912	1.293-2.828	0.001	1.911	1.293-2.825	0.001
Poor pathologic finding (Edmonson criteria ≥3)	1.451	0.842-2.501	0.181						
Microvascular invasion	5.373	3.394-8.505	<0.001	3.408	2.085-5.572	<0.001	3.379	2.067-5.523	<0.001
Low GRWR (<0.8)	1.975	1.000-3.903	0.050	1.373	0.689-2.736	0.367	1.379	0.692-2.748	0.361
Statin user	1.277	0.510-3.193	0.602	0.929	0.366-2.357	0.877			
cDDD	1.231	0.813-1.863	0.326				1.107	0.706-1.736	0.658

\* Statin user and, cDDD were considered as time dependent covariates. MELD – model for end-stage liver disease; AFP – alpha-fetoprotein; GRWR – graft-recipient weight ratio; cDDD – cumulative defined daily dose.

group included a smaller proportion of HBV carriers (73.08% vs 85.93%;  $P=0.018$ ), which is the main risk factor for HCC, and fewer sessions of TACE were performed in the statin group ( $P=0.022$ ). In our study, locoregional treatments such as TACE were a significant factor for HCC recurrence.

While statins usually are well-tolerated, they often are associated with various statin-associated symptoms, including statin-associated muscle symptoms (SAMS), DM, and central nervous system problems [25]. SAMS are difficult to treat because there are no validated biomarkers or tests that can be used to confirm patient self-reports of SAMS, and a number of patients who report SAMS have nonspecific muscle pain not attributable to statin therapy [26]. Therefore, in clinical practice, the decision to prescribe statins should be made carefully so as not to result in their misuse or abuse in consideration of the above adverse effects. Furthermore, while the phenomenon of statins acting on lipid metabolism is well established in long-term cumulative studies, the use of statins as anticancer agents has not been established. Therefore, statin prescription with the expectation of an anticancer effect for preventing HCC recurrence should be considered after more

evidence is gathered. Also, in transplant patients, it is necessary to determine whether there are any interactions or adverse effects due to long-term combined administration of immunosuppressant and statin.

A study by Cho et al reported a significant impact of statins on HCC recurrence after LT [17]. However, the population of the abovementioned study was 30% DDLT patients. Thus, our study is the only one to include elective LDLT patients with homogeneous donor factors. However, it is difficult to determine the difference between the results of these 2 similar studies based on the difference between LDLT and DDLT. There are well-known radiologic or pathologic risk factors, such as tumor size larger than the Milan criteria and vascular invasion, that were significant in our study. However, various biologic factors that were not measured in the 2 studies can lead to differences in their results. Recently, several laboratory findings, including AFP as a risk factor for recurrence of HCC, have been reported. The ratio of neutrophils to lymphocytes and des- $\gamma$ -carboxy prothrombin were reported as postoperative independent risk factors associated with HCC recurrence [27,28]. Therefore, study of the relationships between these biologic

**Table 4.** The risk factors of patient survival analyzed by Cox proportional-hazards regression models.

Recipient characteristics	Univariable			Multivariable					
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Sex (Male)	1.536	0.803-2.939	0.194						
Age ( $\geq 60$ years)	0.989	0.639-1.530	0.959						
MELD score ( $\geq 20$ points)	1.168	0.611-2.234	0.638						
ABO-incompatible LT	0.852	0.487-1.490	0.574						
Regional treatment ( $\geq 3$ times)	1.501	1.042-2.164	0.029	1.230	0.844-1.792	0.282	1.268	0.870-1.847	0.217
Tumor size ( $\geq 3$ cm)	1.537	1.067-2.212	0.021	1.229	0.842-1.792	0.285	1.192	0.817-1.741	0.362
Tumor number ( $\geq 3$ )	1.350	0.909-2.003	0.137						
AFP ( $\geq 100$ ng/dL)	2.059	1.414-2.997	<0.001	1.592	1.068-2.372	0.022	1.597	1.072-2.379	0.021
Poor pathologic finding (Edmonson criteria $\geq 3$ )	1.503	0.886-2.549	0.131						
Microvascular invasion	2.398	1.630-3.529	<0.001	1.966	1.287-3.002	0.002	1.908	1.250-2.913	0.003
Low GRWR ( $< 0.8$ )	1.622	0.871-3.019	0.127						
Statin user	0.471	0.148-1.498	0.203	0.388	0.121-1.242	0.111			
cDDD	1.062	0.738-1.529	0.745				0.982	0.673-1.434	0.926

\* Statin user and, cDDD were considered as time dependent covariates. MELD – model for end-stage liver disease; AFP – alpha-fetoprotein; GRWR – graft-recipient weight ratio; cDDD – cumulative defined daily dose.

markers and statins would be helpful in identifying their protective role in HCC recurrence.

There are some limitations to this study. First, it was a retrospective, single-center analysis with a cohort composed of Korean patients; therefore, the results might not be generalizable to other countries or continents. Second, all patients in the statin group had variable statin initiation, maintenance, and termination times after transplantation; however, the exact period and amount of statin exposure were evaluated and adjusted for the analysis. Third, a statistical technique with an on-off period was used, but there is a possibility that the calculated cDDD was different from the actual use. Next, using the retrospective cohort, adjustments were not made for several factors known to be associated with HCC recurrence risk, including alcohol intake, smoking, and family history of HCC. Nevertheless, our well-selected LDLT samples, time-dependent variable analysis to reduce immortal time bias, and careful adjustment for important factors are strengths of this study.

## Conclusions

In conclusion, while recent studies have reported the anticancer potential of statin administration, our study, which included LDLT recipients with HCC, showed that the impact of statin administration after LT was not correlated with recurrence-free survival. As such, a large-scale, prospective, randomized study is needed to investigate the long-term outcomes of statin administration in patients who underwent LDLT for HCC.

## Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.



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