Transplant International

ORIGINAL ARTICLE

The RETREAT score provides valid predictions regarding hepatocellular carcinoma recurrence after liver transplantation

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SUMMARY

Prediction of hepatocellular carcinoma (HCC) recurrence after liver transplantation (LT) with knowledge of explant data is important for guiding post-LT surveillance and treatment. The RETREAT score was recently introduced for this purpose, but has not been validated outside the USA. In a retrospective single-center study of 169 consecutive patients undergoing LT in Gothenburg, through 2000–2017 (mean age 57 years, 80% men), there were 34 HCC recurrences during a median 4.6-year follow-up. The 5-year cumulative incidence of HCC recurrence was 0% with RETREAT scores of 0–1 (18%), 11–22% with scores of 2–4 (58%), and 65% with scores of 5–8 (24%). The C-statistic, as a measure of discrimination for prediction of HCC recurrence was 0.762, 0.664, 0.616, and 0.717, for the RETREAT score, Milan criteria, UCSF criteria, and post-MORAL criteria. The RETREAT score had no significant impact on patient survival after HCC recurrence (HR 1.00, $P = 0.97$). In conclusion, the RETREAT score provided valid predictions of post-LT HCC recurrence in a European setting, with the ability to discriminate between high, intermediate, and low risk for HCC recurrence in a clinically important way. Prognosis after recurrence did not differ according to the RETREAT score in our study.

Transplant International 2021; 34: 2869–2874

Key words
HCC, LT, prognostic, recurrence

Received: 12 May 2021; Revision requested: 28 October 2021; Accepted: 6 November 2021; Published online: 22 November 2021

Introduction

Hepatocellular carcinoma (HCC) is an important indication for liver transplantation (LT); much of the existing research has focused on identifying the best patient selection criteria. Recently, traditional criteria based uniquely on radiographic findings, such as tumor size and number, have, in many centers, been replaced by criteria incorporating markers of tumor biology, such as α-fetoprotein (AFP), growth rate, response to pretransplant treatments, or even biopsy findings [1]. However, even with improved selection precision, tumor recurrence still occurs after LT.

To the best of our knowledge, there are no guidelines on how to perform surveillance for HCC recurrence after LT. A consensus conference recommended computed tomography or magnetic resonance imaging surveillance every 6–12 months during the first 3–5 years [2]. A fixed schedule such as this could lead to both over- and underuse of radiological surveillance.

doi:10.1111/tri.14159

Although this has yet to be clearly defined, there may be subgroups of patients who could benefit from individualized immunosuppression after LT for HCC [3].

Therefore, there is a need to stratify patients based on risk after LT to guide further surveillance and possible immunosuppression adjustment. The RETREAT score, combining pre-LT variables (alfa-fetoprotein) with explant pathology data (size and number of tumors and microvascular invasion), was recently developed and validated in US cohorts to predict post-LT HCC recurrence risk [4,5] and was shown to outperform both the Milan and University of California San Francisco (UCSF) criteria in the post-LT setting [4,5].

As the RETREAT score lacks validation outside the USA, we performed external validation analyses at a single center in Sweden and compared the prognostic performance of the RETREAT score with that of other prognostic indices.

Patients and methods

This was a retrospective single-center study of consecutive patients with HCC who underwent LT at Sahlgrenska University Hospital in Gothenburg, Sweden, between 2000 and 2017. Patients were identified from the hospital's surgical registry and the Nordic Liver Transplant Registry (NLTR). The inclusion criteria were a diagnosis of HCC as confirmed via histopathology of the explanted liver and age $\geq$ 18 years. We excluded cases without evidence of HCC in the explanted liver despite not receiving locoregional therapy before LT (i.e., HCC misdiagnosis), combined hepatocellular cholangiocarcinoma, death within 2 months from LT, and those for whom the RETREAT score could not be calculated due to missing data.

Data were collected from hospital records, the Nordic Liver Transplant Registry (NLTR), pretransplant radiology reports, and histology reports of explanted livers. We collected data on tumor size, number of nodules, degree of differentiation according to the Edmondson–Steiner classification, presence of vascular invasion, tumor viability, and fulfillment of the Milan (a single lesion $\leq$5 cm, up to three lesions $\leq$3 cm each, no evidence of vascular invasion, nor any regional nodal or extrahepatic metastases) and UCSF criteria (a single lesion $\leq$6.5 cm, up to three lesions $\leq$4.5 cm each with a total tumor burden of no more than 8 cm, with no evidence of vascular invasion, nor any regional nodal or extrahepatic metastases). The Milan and UCSF criteria were based on explant pathology. For a tumor with 100% necrosis, the tumor size was regarded as zero, in line with the guidelines. AFP was the last value before LT. We also recorded the Child–Pugh score, etiology of cirrhosis, viral hepatitis status, and preoperative locoregional treatments. Study follow-up was conducted until September 2018. The study was approved by the Regional Ethical Review Board in Gothenburg (diary number 934-14 and T773-18).

Statistical analyses

For comparing groups, we used the chi-square or Mann–Whitney U test, as appropriate. External validation of the RETREAT score, Milan [6], UCSF [7], and post-MORAL [8] criteria were assessed by considering these scores/criteria as covariates in separate Cox regression models with time to recurrence as the outcome. Model discrimination was assessed using Harrell's C-statistic. Cumulative recurrence risk and recurrence-free survival with the RETREAT score were estimated using the Kaplan–Meier method. A Cox regression model was used to assess the possible impact of various scores/criteria on patient survival after HCC recurrence. To analyze the potential calendar-time effect in the performance of the RETREAT score, we included an interaction term between the RETREAT score and year of LT in Cox models separately for predicting the HCC recurrence and predicting the patient survival after HCC recurrence. Statistical significance was set at $P < 0.05$. Data were analyzed using the R software version 4.0.2.

Results

The study included 169 patients with a mean age of 57 years, 79% men, 28% with alcoholic cirrhosis, and 59% with hepatitis C (Table 1). Based on the explant pathology data, 38% were outside the Milan criteria and 27% were outside the UCSF criteria. The mean AFP level at the last measurement before LT was 555 ng/ml.

Of the patients, 18% had a RETREAT score of 0–1, 58% had a score of 2–4, and 24% had a score of 5–8 (Table 2). The distribution of the RETREAT score in relation to the Milan and UCSF criteria as well as according to HCC recurrence is shown in Table 2.

Median follow-up until HCC recurrence, death or end of study was 4.08 years (mean 5.07 years, IQR 2.68–7.16 years, range 0.22–18.25 years, 856.63 person-years of follow-up). During follow-up, 34 patients had HCC recurrence, and 46 patients died. Of the 34 patients with HCC recurrence, 29 died during the follow-up period.

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Table 1. Baseline recipient, donor, and liver transplant (LT) characteristics.

	Mean (SD) or n (%)
Patients	169
Recipient age (years)	57.4 (7.8)
Men	134 (79.3)
Recipient body mass index, kg/m^2	27.9 (4.7)
Child-Pugh score	
A	73 (43.5)
B	61 (36.3)
C	29 (17.3)
Hepatitis C	100 (59.2)
Hepatitis B	30 (17.9)
Alcohol-related liver disease	48 (28.4)
Cold ischemia time, min	474 (143)
Donor age, years	55.7 (16.1)
Donor body mass index, kg/m^2	25.5 (4.4)
Tumor characteristics	
Size of largest nodule, mm	32.8 (19.9)
Number of nodules	
0–1	76 (45.0)
2–3	63 (37.3)
>3	30 (17.8)
Largest diameter (cm) plus number of viable tumors	
0	4 (2.4)
1.1–4.9	55 (32.5)
5.0–9.9	94 (55.6)
≥10	16 (9.5)
Alpha-fetoprotein, ng/ml	555.2 (2562.4)
0–20	102 (60.4)
21–99	33 (19.5)
100–999	21 (12.4)
≥1000	13 (7.7)
Microvascular invasion	69 (40.8)
Differentiation degree (Edmondson-Steiner)	
1–2	54 (35.3)
3–4	87 (56.9)
Missing	12 (7.8)
Pretransplant locoregional therapies	60 (35.7)
Within Milan criteria	104 (61.5)
Within UCSF criteria	123 (72.8)
RETREAT score	
0	2 (1.2)
1	29 (17.2)
2	46 (27.2)
3	20 (11.8)
4	32 (18.9)
5	18 (10.7)
6	12 (7.1)
7	8 (4.7)
8	2 (1.2)
Post-MORAL criteria	
1	86 (54.8)
2	61 (38.9)
3	7 (4.5)
4	3 (1.9)

Table 2. The distribution of the RETREAT score (numbers of patients) in relation to Milan and UCSF criteria as well as according to hepatocellular carcinoma (HCC) recurrence.

RETREAT score	Patients	HCC Recurrence	Milan criteria		UCSF criteria	
			In	Out	In	Out
0	2	0	2	0	2	0
1	29	0	29	0	29	0
2	46	5	30	16	38	8
3	20	3	15	5	15	5
4	32	6	14	18	19	13
5–8	40	20	14	26	20	20

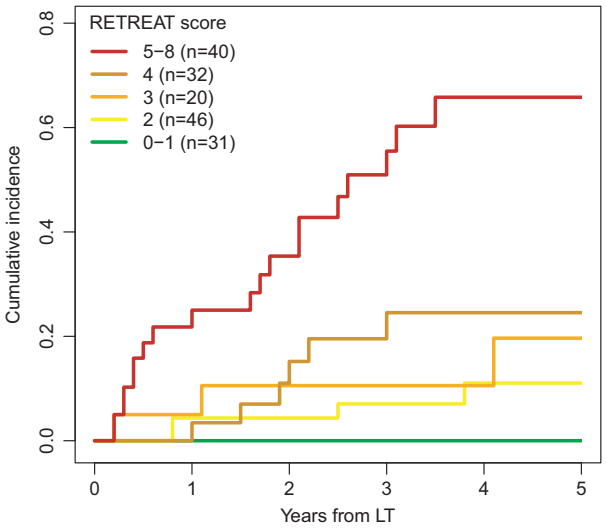

Figure 1 Recurrence of hepatocellular carcinoma (HCC) after liver transplantation (LT) according to the RETREAT score.

The 5-year cumulative incidence of HCC recurrence was 0% in patients with a RETREAT score of 0–1, 11–22% in those with a score of 2–4, and 65% in those with a score of ≥5 (Fig. 1). Figure 2 shows the recurrence-free survival curves according to the RETREAT score.

The C-statistic of the RETREAT score for the prediction of HCC recurrence was 0.762, compared with 0.664 for the Milan criteria, 0.616 for the UCSF criteria, and 0.717 for the post-MORAL criteria (Table 3). The C-statistic was significantly higher for the RETREAT score than for the Milan or UCSF criteria, but non-significant compared with the post-MORAL criteria. The interaction term between RETREAT score and year of LT in the Cox model for the prediction of HCC recurrence was nonsignificant (P = 0.96), indicating no

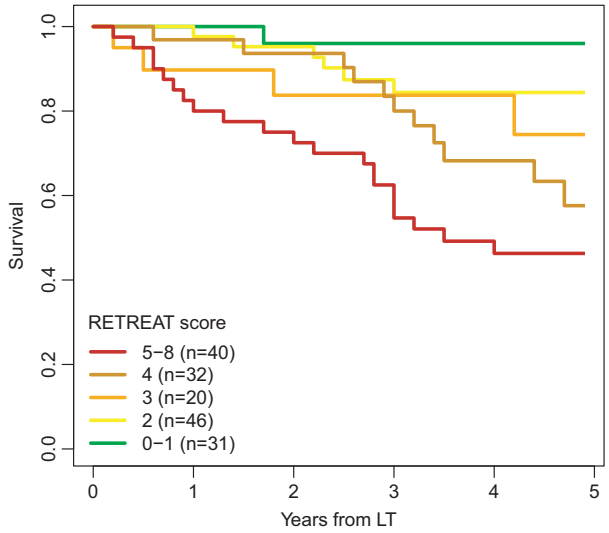

Figure 2 Recurrence-free patient survival after liver transplantation (LT) according to the RETREAT score.

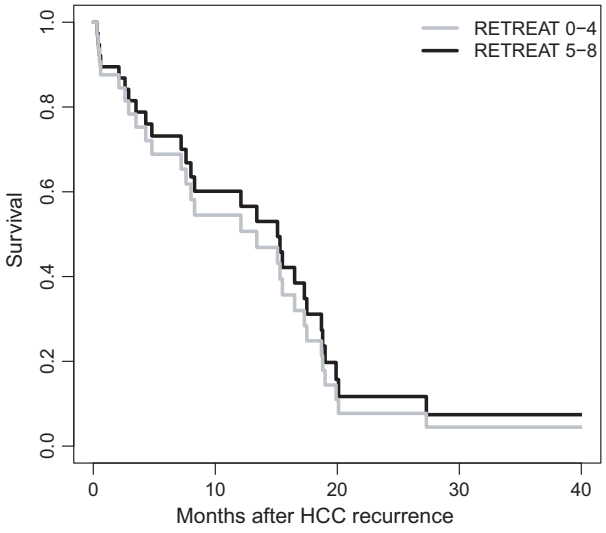

Figure 3 Patient survival after recurrence of hepatocellular carcinoma (HCC) according to the RETREAT score.

Table 3. Model discrimination using the C-statistic for the prediction of recurrence of hepatocellular carcinoma (HCC) after liver transplantation (LT).

	C-statistic	95% CI	*P* (compared with RETREAT)
RETREAT	0.762	0.689–0.835	
Milan criteria	0.664	0.601–0.727	0.035
UCSF criteria	0.616	0.547–0.685	<0.001
Post-MORAL criteria	0.717	0.623–0.811	0.347

significant calendar-time effect for the performance of the RETREAT score for predicting HCC recurrence.

The RETREAT score had no significant impact on patient survival after HCC recurrence (HR 1.00, 95% CI 0.78–1.30, $P = 0.97$) (Fig. 3). The interaction term between the RETREAT score and year of LT in the Cox model for mortality after HCC recurrence was non-significant ($P = 0.43$), indicating no significant calendar-time effect.

Discussion

The RETREAT score provided valid predictions of post-LT HCC recurrence in a European setting, with the ability to discriminate between high, intermediate, and low risk for HCC recurrence in a clinically important manner. Selection criteria are more liberal in Sweden than in the US; consequently, this cohort included more advanced tumors compared with the cohorts with which the RETREAT score was developed and validated, with a higher proportion outside the Milan criteria and having more microvascular invasion [4,5]. Even if the RETREAT score was developed in a cohort with a relatively limited tumor burden, the included variables have previously been proven to be prognostic in many different types of cohorts, which is a strength of this study [8–12]. As expected, when combining multiple independent markers of tumor biology in a prognostic model posttransplantation, the discriminating power improved [8,11]. Consequently, the prognostic power of the RETREAT score was improved compared with that of the Milan or UCSF criteria, similar to the preoperative selection setting. Compared with the post-MORAL score, RETREAT includes fewer prognostic variables, but the use of multiple categories instead of simple cut-offs for variables with incremental risks takes better advantage of their prognostic value [4]. The simplicity of the RETREAT score, including only AFP and explant pathology facilitates its use in clinical practice.

Prognosis after HCC recurrence did not differ according to the RETREAT score. This suggests that the ability of the RETREAT score to predict HCC is not merely a reflection of more severe tumor biology. Although prognosis is generally poor in patients with recurrent HCC after liver transplantation [12], post-transplant tumor surveillance can be justified, because treatment leading to good long-term prognosis is possible in some patients [9]. The RETREAT score could potentially be used to individualize the radiology surveillance of HCC patients after LT, as was recently suggested [5].

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There is a general consensus in oncology that immunosuppression can impact the risk of tumor recurrence and outcomes in cancer. In the setting of posttransplant HCC, there is still no solid evidence for such an impact. Although debated, mammalian target of Rapamycin (mTOR) inhibitors is mostly regarded as an antitumor alternative, despite the failure to demonstrate a significant effect in the randomized SILVER study [3,13]. In addition, some data suggest that early posttransplant calcineurin inhibitor (CNI) reduction is associated with a reduced rate of tumor recurrence [14]. In addition, a possible association between posttransplant HCC recurrences and acute rejection was recently published [15], which suggests that simply reducing the load of immunosuppression might not be the solution. Even though more research is needed to clarify whether patients with high or intermediate RETREAT scores benefit from adjuvant therapies or specific immunosuppression protocols, such as early CNI minimization or an early switch to everolimus/sirolimus-based regimens, a posttransplant prognostic score could help stratify patients with more accuracy in future studies in this field, which could lead to the identification of improved and individualized immunosuppression strategies, taking into account the tumor recurrence risk.

Efficient adjuvant therapies after curative treatment for HCC are still lacking, but the large increase in available systemic therapies has recently provided new hope for such options [16]. Again, the RETREAT score, if proven relevant in different kinds of cohorts, could be useful for stratification in future studies.

The retrospective single-center design is a limitation of our study. Larger multicenter validation studies are warranted.

In conclusion, the RETREAT score provides valid predictions of HCC recurrence after liver transplantation and can be used for guiding posttransplant surveillance and management.

Authorship

F.Å. – designed research, performed analyses, wrote the manuscript; J.A. – collected data, critical revision; W.B. – critical revision; A.S. – critical revision; M.R. – designed research, critical revision, supervised the project; M.S-E. – designed research, collected data, wrote the manuscript.

Funding

The authors have declared no funding.

Conflict of interest

The authors have declared no conflicts of interest.

Ethical approval

The study was approved by the regional ethical review board of Gothenburg (diary number 934-14 and T773-18).

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