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ORIGINAL ARTICLE

Intent-to-Treat Analysis of Liver Transplant for Hepatocellular Carcinoma in the MELD Era: Impact of Hepatitis C and Advanced Status

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Abstract
Background/Aim Liver transplantation is a well-recognized treatment for non-resectable hepatocellular carcinoma (HCC); however, the overall survival and waiting list removal rates for hepatitis C virus (HCV)-related HCC have not been assessed.
Methods The present study included 11,146 patients with HCC and 64,788 patients without HCC, listed for liver transplantation on the Scientific Registry of Transplant Recipients database between 2003 and 2010.
Results In a multivariate analysis, HCV infection was an independent predictor of being transplanted or remaining on the waiting list in HCC candidates (HR 0.65, 95 % CI 0.60–0.71, $p < 0.001$). However, patients in the advanced status (model for end-stage liver disease score over 20, tumor stage exceed tumor-node-metastasis stage II, or alpha fetoprotein lover 400 ng/ml) but without HCV had better post-transplant survival than patients in the advanced status and with HCV (64 vs. 47 % at 5 years, $p < 0.001$), and comparable survival to patients with HCV but not in the advanced status (62 %, $p = 0.461$).
Conclusions HCC candidates with HCV infection are more likely to be transplanted, remain on the waiting list for longer, and have worse post-transplant survival. Patients in the advanced status but without HCV also could share a similar post-transplant survival to those not in the advanced status but with HCV.

Keywords Liver transplantation · Patient selection · Primary hepatic malignancy · Registry · Waiting list

Abbreviations

AFP	Alpha fetoprotein
CDRG	Chronic Disease Research Group
CI	Confidence interval
DRI	Donor risk index
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HHS	Health and Human Services
HR	Hazard ratio
HRSA	Health Resources and Services Administration
ICU	Intensive care unit
LT	Liver transplantation
MELD	Model for end-stage liver disease

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MMRF	Minneapolis Medical Research Foundation
NASH	Non-alcoholic steatohepatitis
OPO	Organ Procurement Organization
OPTN	Organ Procurement and Transplantation Network
RFA	Radio frequency ablation
SRTR	Scientific Registry of Transplant Recipients
TACE	Transcatheter arterial chemoembolization
TNM	Tumor-node-metastasis
UNOS	United Network for Organ Sharing
US	United States

Introduction

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy worldwide and the third most common cause of cancer-related death, with an annual incidence of nearly 1 million cases, resulting in 250,000–1 million deaths [1]. Cirrhosis is regarded as the most important risk factor for the development of HCC, the relative risk of which varies with the etiology of the cirrhosis [2, 3]. For example, chronic viral hepatitis infection is a major cause of cirrhosis in many areas, and numerous studies have established a clear association between hepatitis infection and development of HCC [4, 5].

Liver transplantation (LT) is a well-recognized treatment for selected patients with non-resectable HCC, offering radical resection of HCC tumors and cure of the underlying disease with liver replacement. Previous experience with LT for HCC was disappointing, but a landmark study by Mazzaferro et al. [6] demonstrated an excellent post-transplant outcome due to careful patient selection, named the Milan criteria, which included patients with a single tumor up to 5 cm in diameter or up to three tumors, none larger than 3 cm. Improved outcomes have been subsequently validated by several studies [7–9], and the Milan criteria have been adopted by the Organ Procurement and Transplantation Network (OPTN) for allocation of organs in the USA. Although excellent results can be achieved when the Milan criteria are implemented, recent studies have recommended that they are too restrictive and similar acceptable results can be achieved with more liberal selection criteria [10].

For over 20 years, researchers have been committed to the study of hepatitis-related HCC, and several clinical studies have compared the post-transplantation outcomes of HCV-infected recipients with those without HCV infection in patients with HCC [11, 12]. Indeed, most of these studies have shown that HCV infection significantly impairs graft and patient survival following LT. Although all of these retrospective studies showed similar trends, they included limited numbers of patients, as such; possible confounding variables could not be taken into account due to the limited sample size, and none of these studies were performed on an intent-to-treat strategy. The present study is based on a large registry transplant population and on an intent-to-treat basis. We evaluated the impact of HCV infection on patient survival, and the risk predictors for candidate dropout and patient mortality that could help with the selection of the most appropriate transplant recipients from candidates with HCC.

Patients and Methods

Data Collection and Definitions

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the US, submitted by the members of the OPTN, and has been described elsewhere. The Health Resources and Services Administration (HRSA), US Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors [13]. The whole study was reviewed and approved by the Ethical Committee at Zhejiang University.

The study population included all candidates listed for deceased donor liver transplantation from January 2003 to January 2010, and our exclusion criteria were as follows: age <18; patients with incidental tumors; patients with missing data; and patients relisted for transplantation. In order to ensure that the HCV infection status of all candidates was known, only individuals whose status of HCV infection was available were selected for further analysis. HCV infection was identified based upon positive results for HCV serology or pre-transplantation diagnosis of HCV infection. The patients without HCV infection were all entered into the non-HCV-infected group, and their disease etiology included hepatitis B virus (HBV) infection, alcoholic cirrhosis, primary or secondary biliary cirrhosis, and metabolic disease. Overall, 3,576 (4.5 %) candidates out of a total of 79,510 listed for LT during the study period were excluded from further analysis (Fig. 1).

Statistical Analysis

First, we analyzed candidates with a diagnosis of HCC in the waiting list only. Subjects with all other types of liver cancer such as cholangiocarcinoma, hepatoblastoma, and unspecified liver cancers were excluded. Patient survival was assessed from the time of listing (intent-to-treat) and time from transplantation (post-transplantation). Of note,

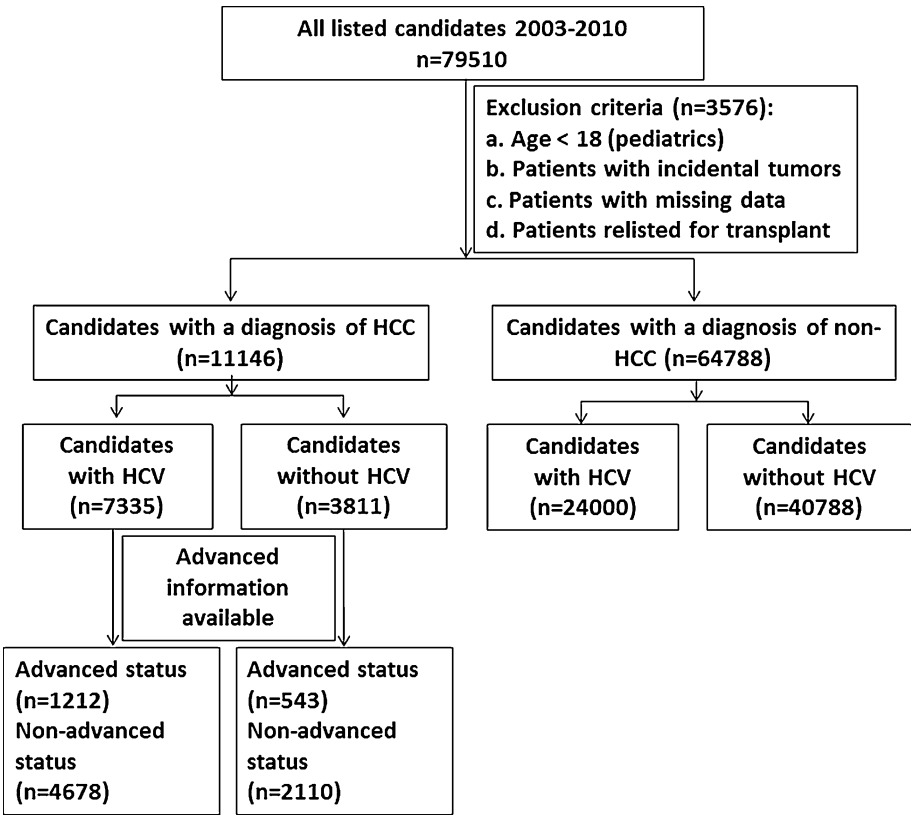

Fig. 1 Flow chart of included patients

intent-to-treat analysis included all listed patients who subsequently dropped out, were transplanted, or are still active on the waiting list. Dropout was defined as death on the waiting list or delisting due to patient disease deterioration or tumor progression. Waiting time was defined as the time from initial listing until removal from the waiting list due to a transplant being performed from either a living or deceased donor. The waiting time before dropout was the time from initial listing until removal from the waiting list due to death, disease deterioration, or tumor progression.

Probability curves for dropout and survival were constructed according to the Kaplan–Meier method, and intergroup comparisons were performed using a log-rank test. In the analysis of dropout probability, patient dropout was considered as an event, whereas LT was considered as a censor point. On the intent-to-treat analysis, we defined dropout from the waiting list and patient's death as the endpoint, but patient's death was the unique variable when post-transplant survival was analyzed. The occurrence and the date of death were obtained from data reported to the SRTR by the transplant centers and supplemented by data from the US Social Security Administration and OPTN. Of note, the SRTR had no access on the use of variables such as HCC or hepatitis recurrence. As a consequence, some patients may have been alive with an HCC recurrence and were not considered an event in the survival analyses.

We further conducted a stepwise multivariate Cox regression analysis, and the results were corrected for the following covariates: age, gender, race, blood type, etiology of liver disease (HCV vs. non-HCV), laboratory model for end-stage liver disease (MELD) scores, tumor size and number, OPTN region, pre-transplant treatment, alpha fetoprotein (AFP), TNM staging, donor risk index (DRI) [14], and use of the immunosuppressive agent sirolimus and the induction drug anti-CD25 antibody. Number and size variables were based on pre-transplant radiological assessment and were available for all HCC candidates. TNM staging was performed according to the American Liver Tumor Study Group Modified Tumor-Node-Metastasis Staging Classification, which is currently being utilized by the OPTN.

In an effort to understand whether the observed results were specific to the candidates with a diagnosis of HCC, or a more general phenomenon, we further conducted the same univariate and multivariate analyses on candidates without HCC listed for LT during the same time period. Similar variables and covariates were used, except for those directly applicable to HCC candidates, i.e., tumor size and number, pre-transplant treatment, AFP, and TNM staging were not applicable.

Table 1 Demographics of HCC and non-HCC candidates

	HCC candidates	Non-HCC candidates	*p* value
Number of patients	11,146	64,788	
Age at listing (years ± SD)	56.4 ± 7.8	47.5 ± 16.9	<0.001
Gender (female/male)	2,486/8,660	25,344/ 39,444	<0.001
Race (%)			
White	7,180 (64.6)	46,126 (71.2)	<0.001
Hispanic/Latino	1,617 (14.5)	9,534 (14.7)	0.572
Asian	1,211 (10.9)	2,243 (3.5)	<0.001
African American	1,012 (9.1)	6,116 (9.4)	0.232
Other/multirace	126 (1.1)	769 (1.2)	0.632
Etiology of underlying disease (%)			
Hepatitis C	7,335 (65.8)	24,000 (37.1)	<0.001
Hepatitis B	972 (8.7)	1,891 (2.9)	<0.001
Alcohol	879 (7.9)	9,072 (14.0)	<0.001
NASH	405 (3.6)	3,862 (6.0)	<0.001
Autoimmune	378 (3.4)	3,845 (5.9)	<0.001
PSC	219 (2.0)	4,968 (7.7)	<0.001
PBC	184 (1.7)	4,213 (6.5)	<0.001
Other	774 (17.6)	12,937 (20.0)	<0.001
Pre-transplant treatment (%)			
TACE	3,966 (35.6)	NA	
RFA	1,393 (12.5)	NA	
Other	1,125 (10.1)	NA	
No treatment	4,662 (41.8)	NA	
Laboratory MELD score at listing (±SD)	12 ± 4	21 ± 10	<0.001
Maximum tumor diameter at listing (cm ± SD)	2.6 ± 1.2	NA	
Total tumor diameter at listing (cm ± SD)	3.2 ± 1.5	NA	
Number of tumor at listing (±SD)	1.4 ± 0.7	NA	
AFP at listing (ng/ml ± SD)	309 ± 2,232	NA	
Dropped out patients	2,035 (18.3)	21,429 (33.1)	<0.001

HCC hepatocellular carcinoma, *MELD* model for end-stage liver disease, *AFP* alpha fetoprotein, *TACE* transcatheter arterial chemoembolization, *RFA* radio frequency ablation, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis, *NASH* non-alcoholic steatohepatitis

In comparative analyses of different subgroups, continuous and categorical variables were compared using Student's *t* tests and chi-square tests, respectively. Results were provided as mean ± SD unless otherwise indicated. A standard α level of 0.05 indicated statistical significance. All statistical analyses were performed using SPSS 15.0 (SPSS, Chicago, IL, USA).

Table 2 Demographics of HCC patients on the waiting list

Variables	HCV group	Non-HCV group	*p* value
Number of patients	7,335	3,811	
Age at listing (years ± SD)	55.6 ± 6.6	57.8 ± 9.6	<0.001
Gender (female/male)	5,805/1,530	2,855/956	<0.001
Race (%)			
White	4,896 (66.7)	2,284 (59.9)	<0.001
Hispanic/Latino	1,124 (15.3)	493 (12.9)	0.003
Asian	439 (6.0)	772 (20.3)	<0.001
African American	792 (10.8)	220 (5.8)	<0.001
Other/multirace	84 (1.2)	42 (1.1)	0.921
Etiology of underlying disease (%)			
HBV infection	NA	972 (25.5)	
Alcohol related	NA	879 (23.1)	
Pre-transplant treatment (%)			
TACE	2,628 (35.8)	1,338 (35.1)	0.453
RFA	974 (13.3)	419 (11.0)	0.001
Other	708 (9.7)	417 (10.9)	0.033
No treatment	3,025 (41.2)	1,637 (43.0)	0.085
Laboratory MELD score at listing (±SD)	12 ± 4	12 ± 4	0.380
Maximum tumor diameter at listing (cm ± SD)	2.6 ± 1.2	2.7 ± 1.3	<0.001
Total tumor diameter at listing (cm ± SD)	3.2 ± 1.5	3.3 ± 1.6	<0.001
Number of tumor at listing (±SD)	1.35 ± 0.74	1.37 ± 0.73	0.374
AFP at listing (ng/ml ± SD)	281 ± 1,764	362 ± 2,927	0.073
Donor risk index (±SD)	1.41 ± 0.36	1.48 ± 0.39	<0.001
Dropped out patients (%)	1,132 (15.4 %)	903 (23.7 %)	<0.001

Donor risk index was defined according to Ref. [14]

HCV hepatitis C virus infection, *HCC* hepatocellular carcinoma, *MELD* model for end-stage liver disease, *AFP* alpha fetoprotein, *TACE* transcatheter arterial chemoembolization, *RFA* radio frequency ablation, *NA* non-applicable

Results

General Characteristics

During the study period, 11,146 candidates were listed for LT with a diagnosis of HCC and 64,788 with a non-HCC diagnosis (Table 1). HCC candidates included more males (female/male ratio: 1/3.5 vs. 1/1.6; $p < 0.001$) and were significantly older than non-HCC candidates (56.4 ± 7.8 vs. 47.5 ± 16.9 years; $p < 0.001$). Hepatitis C virus infection was the most common etiology of underlying liver disease, followed by HBV infection and alcoholic liver disease, and the latter two comprised almost 50 % of the non-HCV-infected HCC group. Furthermore, the

incidence of HCV-related liver disease was higher ($p < 0.001$), and the dropout rate was lower ($p < 0.001$) among HCC candidates. Finally, MELD scores unadjusted for tumor exception points were lower in the HCC group versus the non-HCC group (12 ± 4 vs. 21 ± 10; $p < 0.001$).

Analysis of HCC Candidates

Patient Characteristics

Our first analysis only included candidates with a diagnosis of HCC. The clinical and demographic characteristics of both the HCV-infected group and the non-HCV-infected group are presented in Table 2. The mean candidate age at listing was similar between the HCV-infected group and the non-HCV-infected group (55.6 ± 6.6 vs. 57.8 ± 9.6 years, respectively). There were fewer female candidates in the HCV-infected group (20.9 %) compared with the non-HCV-infected group (25.1 %). The non-HCV-infected group had more Asian candidates (20.3 %) than the HCV-infected group (6.0 %); we believe this was due to the number of HBV-infected candidates in the non-HCV group being predominantly Asian.

Tumor Characteristics and MELD Score

As the SRTR registry is based in the USA where HCC recipient selection is performed according to Milan criteria, most candidates had a limited tumor burden with a mean total tumor diameter of 3.2 ± 1.5 cm and a mean tumor number of 1.36 ± 0.74 at listing. There were only 559 (5.0 %) patients exceeding T2 criteria at listing, which is a confirmed cut-off associated with increased risk of recurrence and death after transplantation [6]. The tumor characteristics of both groups were similar in terms of total tumor diameter and number of tumors (Table 2). The maximum tumor diameter in the non-HCV-infected group was slightly larger than that in the HCV-infected group (2.7 ± 1.3 vs. 2.6 ± 1.2 cm, respectively). The level of AFP showed a wide distribution, with a mean of 281 ± 1,764 ng/ml in the HCV-infected group and 362 ± 2,927 ng/ml in the non-HCV-infected group. The average MELD score of candidates from the two groups at listing was both 12 ± 4. Overall, the mean MELD score, total tumor diameter, and AFP level remained stable on the waiting list.

Pre-transplant Treatment

Pre-transplant treatments for HCC during the waiting period are listed in Table 2. Among them, 41.2 % in the HCV-infected group and 43 % in the non-HCV-infected group did not undergo any treatment while awaiting LT. The most common treatments were transcatheter arterial chemoembolization and radio frequency ablation, accounting for over 46 % of candidates, respectively.

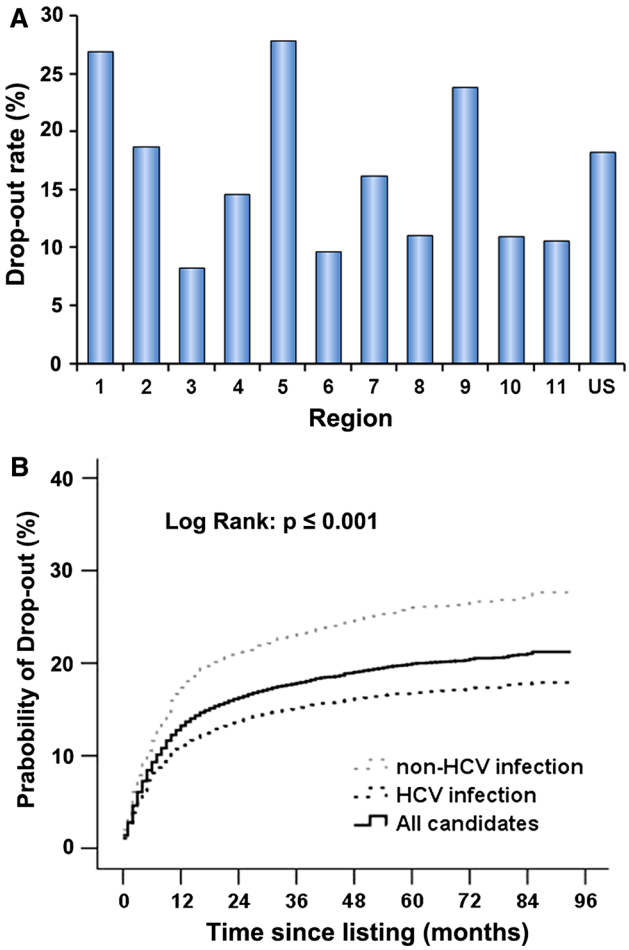

Fig. 2 Analysis of candidate dropout from the LT waiting list. The rate of dropout from the LT waiting list is shown for each OPTN region and for the USA as a whole (**a**). The probability of dropout from the waiting list for all candidates with a diagnosis of HCC and HCV group versus the non-HCV-infected group is also shown (**b**)

Dropout from the Waiting List

The mean time between listing and dropout from the waiting list because of death, disease deterioration, or tumor progression was 11.23 ± 13.76 months for all HCC candidates. Considerable variability was noted for dropout rates based on the different OPTN regions (Fig. 2a). For all candidates with a diagnosis of HCC, the 1- and 3-year probability of dropout was 13 and 18 %, respectively (Fig. 2b). Compared with those with HCV infection, candidates without HCV infection were significantly more likely to drop out from the waiting list due to tumor

Table 3 Univariate and multivariate analysis for predictors of dropout from the waiting list for candidates with HCC

Parameters	HR (95 % CI)	*p* value
Univariate analysis		
Age (years)	1.02 (1.01–1.02)	<0.001
Gender (male)	1.02 (0.91–1.13)	0.784
Race (white vs. others)	0.83 (0.76–0.90)	<0.001
Blood type (type O vs. others)	1.26 (1.16–1.38)	<0.001
HCV infection	0.62 (0.57–0.68)	<0.001
Pretreatment	0.99 (0.91–1.08)	0.870
Laboratory MELD score >20	1.82 (1.52–2.17)	<0.001
AFP >400 ng/ml	2.04 (1.82–2.29)	<0.001
Maximum tumor diameter (cm)	1.05 (1.01–1.08)	0.010
Total tumor diameter (cm)	1.06 (1.03–1.09)	<0.001
Number of tumor	1.02 (0.96–1.08)	0.499
Exceed T2 (TNM staging)	1.39 (1.16–1.66)	<0.001
Region		<0.001
3	0.41 (0.33–0.50)	
5	1.86 (1.70–2.04)	
9	1.38 (1.21–1.56)	
Multivariate analysis		
HCV infection	0.65 (0.60–0.71)	<0.001
Age (years)	1.01 (1.01–1.02)	<0.001
Total tumor diameter (cm)	1.20 (1.11–1.29)	<0.001
Laboratory MELD score >20	1.73 (1.44–2.07)	<0.001
AFP >400 ng/ml	2.11 (1.88–2.38)	<0.001

HR hazard ratio, *CI* confidence interval, *HCV* hepatitis C virus infection, *HCC* hepatocellular carcinoma, *MELD*: model for end-stage liver disease, *AFP* alpha fetoprotein, *TNM staging* tumor-node-metastasis staging classification

progression, disease deterioration, or death (23 vs. 15 %, respectively; $p < 0.001$, Fig. 2b).

Significant predictors of removal from the waiting list based on univariate analysis are listed in Table 3. The risk factors that predicted dropout were older candidate age, blood type O, laboratory MELD score >20, AFP >400 ng/ml, the maximum tumor, total tumor number, exceeding T2 stage, and being listed in region 5 or 9. Univariate factors predicting a decreased risk for dropout from the waiting list included white patients, HCV infection, and being listed in region 3. On multivariate analysis, corrected for age, gender, race, blood type, etiology of liver disease, laboratory MELD score, tumor size and number, OPTN regions, pre-transplant treatment, AFP, and TNM staging, the independent predictors of dropout included age [hazard ratio (HR) 1.01, 95 % confidence interval (CI) 1.01–1.02], total tumor diameter (HR 1.20, 95 % CI 1.11–1.29), laboratory MELD score >20 (HR 1.73, 95 % CI 1.44–2.07), and AFP >400 ng/ml (HR 2.11, 95 % CI 1.88–2.38; Table 3). Significantly, the only independent predictor of being transplanted or remaining on the liver waiting list rather than dropping out was HCV infection (HR 0.65, 95 % CI 0.60–0.71).

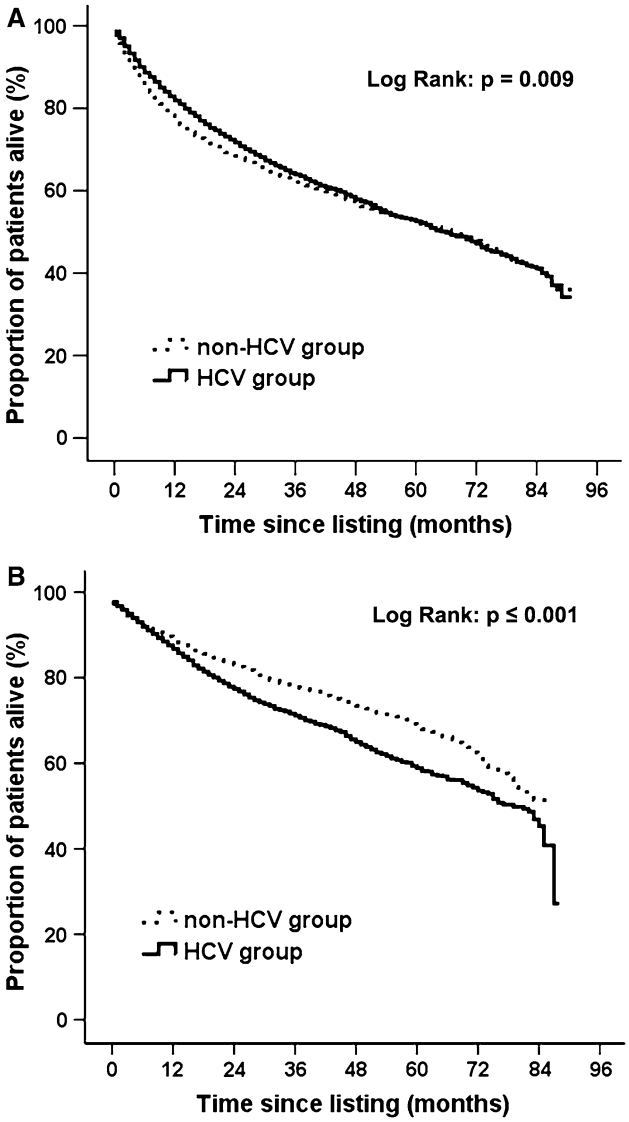

Fig. 3 Comparison of overall survival rates of HCC patients with and without concurrent HCV infection. The proportion of surviving HCC patients with HCV infection is plotted against the proportion of surviving patients without HCV infection for the time since listing (intent-to treat analysis; **a**) and the time since transplantation (**b**)

Intent-to-Treat Survival

The HCV-infected population had a slightly higher patient survival rate according to intent-to-treat analysis (Fig. 3a). The overall intent-to-treat survival in the HCV-infected group from listing was 83, 64, and 53 % at 1, 3, and 5 years, respectively, compared with the 78, 62, and 52 % in the non-HCV-infected group at the same time points ($p = 0.009$). To identify independent predictors for

Table 4 Multivariate Cox analyses of survival

	HR	95 % CI	*p* value
Intent-to-treat survival from listing ($n = 11,146$)			
HCV infection	0.92	0.86–0.98	0.017
Age (years)	1.02	1.01–1.02	<0.001
Laboratory MELD score >20	1.73	1.51–1.98	<0.001
AFP >400 ng/ml	1.95	1.79–2.13	<0.001
Exceed T2 (TNM staging)	1.31	1.14–1.50	<0.001
Blood type (type O vs. others)	1.08	1.02–1.15	0.012
Survival since transplant ($n = 8,543$)			
HCV infection	1.50	1.34–1.68	<0.001
Age (years)	1.02	1.01–1.02	<0.001
AFP >400 ng/ml	1.79	1.56–2.06	<0.001
Laboratory MELD score >20	1.42	1.13–1.79	0.003

HR hazard ratio, *CI* confidence interval, *HCV* hepatitis C virus infection, *AFP* alpha fetoprotein, *MELD* model for end-stage liver disease

survival on an intent-to-treat basis for all liver transplant candidates with HCC, we then performed a multivariate analysis, corrected for age, gender, race, blood type, etiology of liver disease, laboratory MELD score, tumor size and number, OPTN region, pre-transplant treatment, AFP, and TNM staging, finding that HCV infection was the only variable associated with improved survival (Table 4).

Post-transplant Survival

In contrast to the data obtained for our intent-to-treat analysis, post-transplant survival in the HCV-infected group was 87, 71, and 59 % at 1, 3, and 5 years, respectively, which was significantly worse than that in the non-HCV-infected group (89, 77, and 69 % at 1, 3, and 5 years, respectively, $p < 0.001$; Fig. 3b). Our multivariate analysis corrected for age, gender, race, blood type, etiology of liver disease (HCV vs. non-HCV), laboratory MELD score, tumor size and number, OPTN region, pre-transplant treatment, AFP, TNM staging, donor risk DRI, and the use of immunosuppressive agent sirolimus and the induction drug anti-CD25 antibody, and HCV infection remained significantly associated with poor survival (Table 4).

The discrepancy in survival rate between our intent-to-treat analysis and post-transplant analysis was primarily due to different dropout rates. On the intent-to-treat analysis, we defined dropout from the waiting list as an endpoint, and it is plausible that patients who dropped out had a poor outcome. Furthermore, HCC candidates with HCV infection always had a lower probability of dropout from the waiting list; however, they also had worse post-transplant survival compared with those without HCV infection.

Advanced Status Analysis

Further analyses were conducted with the impact of underlying disease's development or tumor's progression on post-transplant survival of HCC patients. There were three allowable items: (1) MELD score over 20; (2) HCC exceeding OPTN/UNOS T2 criteria in accordance with the modified tumor-node-metastasis (TNM) Stage Classification; (3) an AFP level of >400 ng/ml. These cutoffs were chosen from previous studies [6, 15–20]. Patients meeting any one criterion above mentioned will be defined as advanced status. All patients were grouped according to whether they were infected HCV and whether they had developed into advanced status at transplant. Four groups were created, and post-transplant survival was analyzed (Fig. 4).

Among patients not in advanced status, those without HCV infection had significantly better survival rates than those with HCV infection (70 vs. 62 % at 5 years, $p < 0.001$, Fig. 4a) and this was also the case for patients in advanced status (64 vs. 47 % at 5 years, $p < 0.001$). When the advanced status was assessed, patients not in the advanced status enjoyed more satisfactory survival than those in the advanced status among the HCV group ($p < 0.001$) or the non-HCV group ($p = 0.004$), respectively. As expected, the HCV-infective patients in the advanced status experienced the worst patient survival compared with other groups. However, it was interesting that patients with HCV infection but not in the advanced status had similar post-transplant survival rates as those without HCV infection but in the advanced status ($p = 0.461$). Likewise, similar patterns of post-transplant survivals were observed when only considering MELD score (Fig. 4b), tumor TNM stages (Fig. 4c) or AFP level (Fig. 4d). The annual rate of patients undergoing liver transplantation in advanced status remained stable and fluctuated around 20 % from 2003 to 2009 (Fig. 5).

Finally, a further multivariate analysis was computed to examine the impact of advanced status and HCV infection. Recipients with HCV infection but also in the advanced status meanwhile had the markedly worst post-transplant survival, with a 2.4-fold increase in the mortality risk compared with those without HCV infection or in the advanced status ($p < 0.001$); however, recipients without HCV infection but in the advanced status had a similar mortality risk to those with HCV infection but not in the advanced status ($p = 0.955$) (Table 5).

Analysis of Candidates Without HCC

In an effort to understand whether the impact of HCV infection on intent-to-treat survival and post-transplant survival were linked to a unique phenomenon in HCC patients, or a general effect associated with LT, we

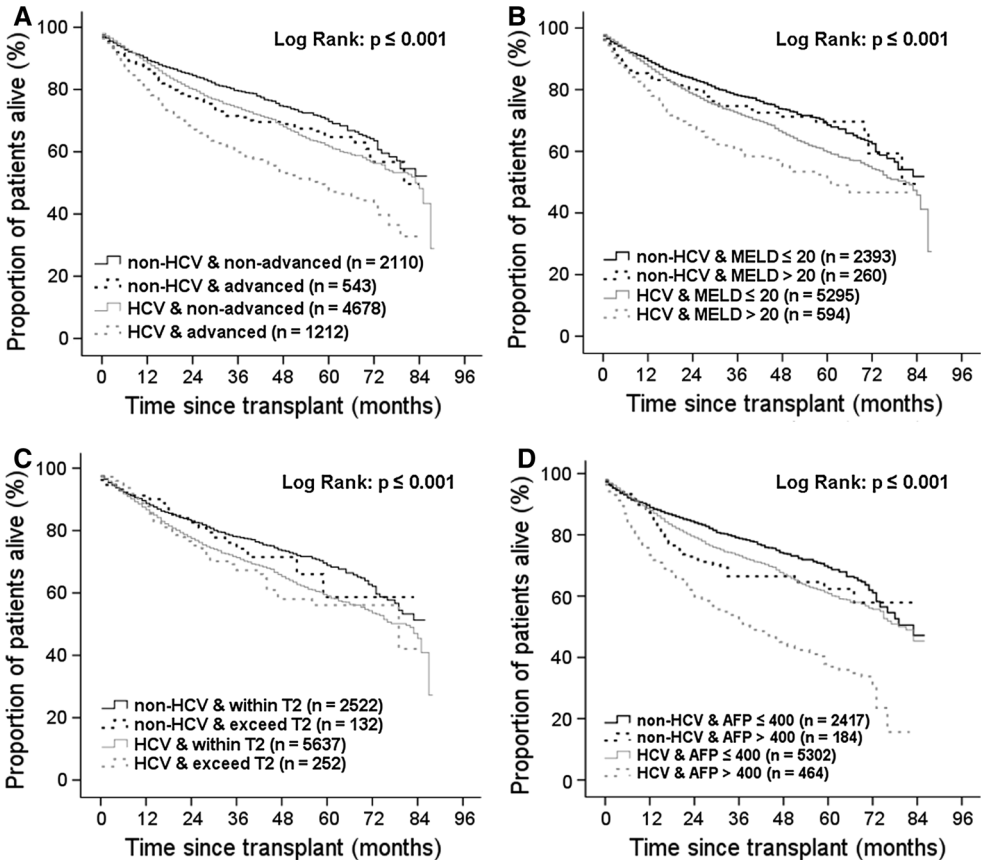

Fig. 4 Survival rates according to whether HCV infection and advanced status at transplant in HCC patients. **a** Overall, **b** MELD score, **c** tumor TNM stage, **d** AFP level

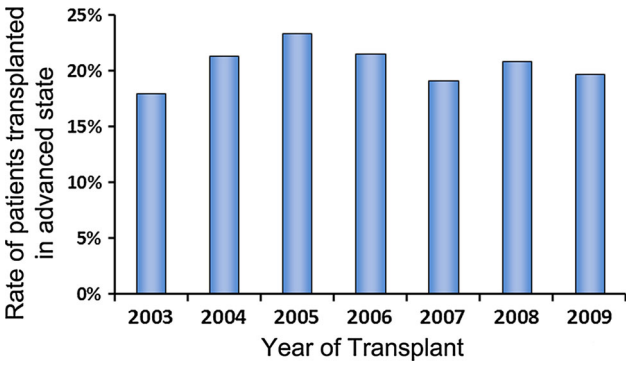

Fig. 5 Rate of patients who underwent liver transplantation in advanced status from 2003 to 2009

Table 5 Multivariate Cox regression evaluating post-transplant survival

	HR	95 % CI	*p* value
Non-HCV and non-advanced status	Reference		
Non-HCV and advanced status	1.409	1.132–1.755	0.002
HCV and non-advanced status	1.417	1.246–1.612	≤0.001
HCV and advanced status	2.409	2.067–2.807	≤0.001

Results were adjusted for age at transplant, patient gender, patient weight, pre-transplant treatment, donor risk index, waiting time between listing and transplant, use of sirolimus at discharge and use of anti-CD25 antibody induction

HR hazard ratio, *CI* confidence interval, *HCV* hepatitis C virus infection

conducted the same analysis as described above on the non-HCC group. Based on this analysis, HCV infection having an opposite effect on the HCC group and the same effect on the non-HCC group should be assumed to be unique to HCC patients. This could be the case for HCV-related HCC patients. Conversely, the impacts of HCV infection on both HCC and non-HCC patients should be assumed to act on the outcome of LT in general. When looking at the non-HCC group, the probability of dropout from the waiting list due to disease deterioration or death was similar between the HCV group and the non-HCV group ($p = 0.774$; Fig. 6a), and the intent-to-treat survival and post-transplant survival in the HCV group were both significantly worse than that in the non-HCV-infected group ($p < 0.001$; Fig. 6b, c). Multivariate analysis also confirmed the above results.

Discussion

According to the present analysis of the SRTR database, among candidates with HCC, those with HCV infection

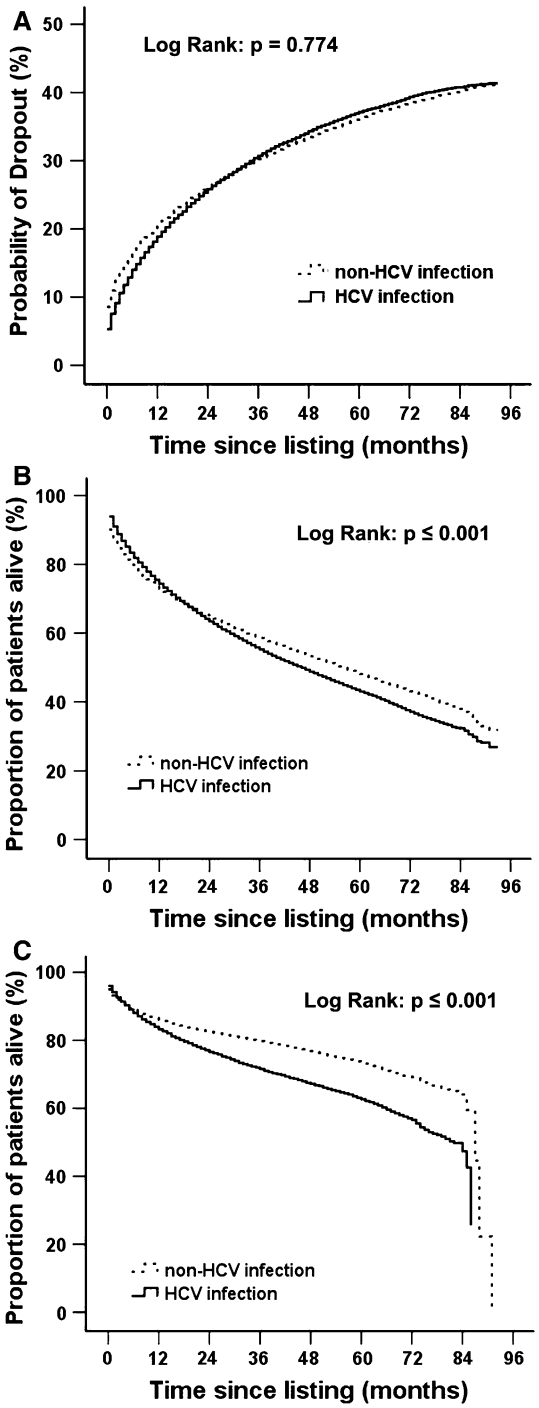

Fig. 6 Survival and waiting list dropout rate for candidates without HCC. An analysis of LT candidates without HCC was performed; data are presented regarding the effect of HCV infection on the probability of candidate dropout (**a**), the survival rate of candidates since listing (intent-to treat analysis; **b**) and the survival rate since transplantation (**c**)

were significantly more likely to be transplanted or remain on the LT waiting list, compared with those without HCV infection; furthermore, HCV infection was associated with a worse post-transplantation life expectancy. HCC patients with high MELD score (over 20), advanced tumor stage (exceed TNM stage II), or high AFP level (over 400 ng/ml) in the non-HCV group also had the similar survival rate as those without the above advanced status in the HCV group.

Extensive research over the past years has identified a number of molecular biomarkers that may contribute to the development of HCC, and recent studies using microRNA studies, combinatorial chemistry, and bioinformatics have provided new insights into the gene and protein expression profiles during various stages of the disease [21]; however, the molecular mechanism underlying HCC is still unknown. Many studies have indicated that liver cirrhosis is closely related to the development of HCC [22–24], although numerous stimuli have been identified that can lead to cirrhosis. For example, it is generally accepted that hepatitis and alcohol both play important roles in the etiology of cirrhosis [25]. Furthermore, different causes of liver disease have different routes of pathogenesis and disease progression, for example, compared with HCV-related HCC patients, non-HCV-infected HCC patients often have larger tumors [26], and more severe pre-transplant disease, as in the ICU [27], which are both risk factors for candidate dropout from the LT waiting list [28]. In agreement with this, in our study, patients with HBV- or alcohol-related HCC comprised almost 50 % of the non-HCV-infected group, and the total tumor size and AFP level in this group were significantly higher than the HCV-infected group. This observation might explain the higher dropout probability in the non-HCV-infected group. Furthermore, in our study, we defined dropout as one of endpoints of the intent-to-treat analysis, and it is plausible that patients who dropped out had extremely poor outcomes. As such, the fact that there were more patients who dropped out of the non-HCV-infected group provides a reasonable explanation for the discrepancy in the survival comparison between the intent-to-treat analysis and the post-transplant analysis.

According to the policies of the OPTN [29], candidates should be removed from the LT waiting list due to disease deterioration or tumor progression; however, whether patients were infected with HCV was not considered. In our multivariate dropout risk model, independent predictors for increased probability of dropout from the waiting list in HCC patients included MELD score, AFP level, total tumor diameter, and patient age. These results suggested that weaker patients and those with larger and more aggressive tumors have a higher rate of dropout from the waiting list, in agreement with OPTN policies. Our study also confirmed that HCV infection was the only independent predictor of being transplanted or remaining on the liver waiting list rather than dropping out. However, those non-HCV patients, even if they were in advanced status

(MELD over 20, exceed TNM T2 stage, and AFP over 400 ng/ml), which could be thought having met the standards of dropout from the waiting list, still had a similar post-transplant survival to those with HCV but in a non-advanced status.

LT has gradually developed as an optimal choice for the treatment of HCC, as it eliminates both the tumor and the cirrhotic liver. However, initial results with LT for HCC were disappointing due to the high rate of HCC recurrence and the extremely low survival rate [30–32]. Application of the Milan criteria for patient selection was associated with improved post-transplant survival rates [6]; however, in recent years, many centers have challenged the Milan criteria as being too restrictive and have found that candidate selection criteria could be expanded without compromising long-term survival [8–10, 20]. Moreover, the Milan criteria only take morphological parameters of the tumor into consideration (i.e., tumor size and number), while increasing evidence suggests that biological parameters, such as AFP, may be equally as important [9, 20, 33]. It has further been shown that the Milan criteria loses its predictive power when applied to patients without HCV infection [34], and Schmitt et al. [35] reported that patients with T3 lesions had higher waiting list mortality, but similar survival, following LT compared with T1 and T2 lesions. Our results clearly confirm that HCV-infected HCC patients had a markedly decreased relative risk of dropout from the waiting list, but an extremely poor post-transplant survival rate compared with non-HCV-infected HCC patients. We believe this means that the selection criteria for HCC candidates with different etiologies should not be regarded equally and that HCV infection should be considered. Thus, some patients may be predicted to dropout from the waiting list but could have an acceptable post-transplant survival if they were not infected with HCV. A plausible explanation can be traced back to the limited number of patients and the variable characteristics of the patient population, i.e., in a study of the Milan criteria, 34 out of 48 patients had HCV-related cirrhosis and other etiologies were not evaluated [6].

Overall survival and graft survival following LT have been reported to be inferior for patients with HCV infection compared with patients receiving LT for other chronic liver diseases, irrespective of concomitant HCC [11]. Our results confirmed these findings and also demonstrated that patients without HCV infection had significantly higher survival rates than HCV-infected HCC patients, reaching a 10 % advantage 5 years after LT. Additionally, a multivariable analysis controlling for confounding factors demonstrated that patients without HCV infection had a significantly decreased relative risk of death in comparison with those with HCV infection. There was a similar result in the non-HCC population. Poor outcome following LT in patients with HCV has been primarily ascribed to factors like immunosuppressive treatment regimens, the natural characteristics of HCV, HCV recurrence, and the absence of effective anti-HCV drugs [12, 36]. Over the last decade, major progress has been made in the prevention and treatment of recurrent HBV post-transplantation, which is associated with greatly increased graft and patient survival. Unfortunately, until recently, HCV recurrence after LT has continued to be a clinical problem.

The use of the SRTR in this study has several limitations. Specifically, this is a retrospective study using the SRTR, and this database has no data on tumor and hepatitis recurrence; thus, we were not able to evaluate these endpoints. There is also variability among the different transplant centers in patient selection criterion and donor assessment that could not be controlled for in our study. Despite this limitation, we analyzed patients without HCC, which was helpful to understand whether our data concerning HCV infection were associated specifically with HCC, or a more general phenomenon.

In conclusion, the strengths of our study emphasize that HCV-infected patients have poorer post-transplant survival in the HCC population; furthermore, they are more likely to be transplanted or remain on the LT waiting list, rather than dropout due to rapid disease deterioration or tumor progression. However, patients in the advanced status but without HCV infection have a similar post-transplant survival to those not in the advanced status but with HCV infection. Our findings should help clinicians prioritize selection of candidates with HCC for LT based on statistically expected outcomes. In line with the principle of decreasing the rate of dropout from LT waiting lists and improving post-transplant survival, future studies containing sufficient numbers of patients that compare the effects of different variables on the outcome of LT for HCC based on the underlying liver disease etiology (such as HCV, HBV, or alcohol) are warranted.

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Conflict of interest None.

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