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Incidence and Risk Factors for Hepatocellular Carcinoma Following Solid Organ Transplantation[1]

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Abstract

Background—Solid organ transplant recipients commonly are infected with hepatitis viruses, are immunosuppressed, and have other potential hepatocellular carcinoma (HCC) risk factors.

Methods—We studied *de novo* HCC incidence arising after transplant using U.S. registry data (223,660 recipients, 1987–2005). We used proportional hazards regression to identify HCC risk factors and calculated standardized incidence ratios (SIRs) to compare HCC risk to that in the general population.

Results—Based on 74 cases reported by transplant centers to the registry, HCC incidence was 6.5 per 100,000 person-years among kidney, heart, and lung (non-liver) recipients and 25 per 100,000 person-years among liver recipients. HCC incidence among non-liver recipients was independently associated with hepatitis B surface antigenemia (HBsAg) (hazard ratio [HR] 9.7, 95%CI 2.8–33), hepatitis C virus (HCV) infection (HR 6.9, 95%CI 2.5–19), and diabetes mellitus (HR 2.8, 1.2–6.6). Among liver recipients, HCC incidence was associated with advancing age ($p<0.001$), male sex (HR 4.6, 95%CI 1.4–16), HCV infection (HR 3.1, 1.3–7.2), and diabetes mellitus (HR 2.7, 1.2–6.2). Among non-liver recipients, overall HCC incidence was similar to the general population (SIR 0.8) but elevated among those with HCV (3.4) or HBsAg (6.5). HCC incidence among liver transplant recipients was elevated overall (SIR 3.4) and especially among those with HCV (5.0) or diabetes mellitus (6.2).

Conclusions—HCC incidence is elevated among liver transplant recipients and subsets of non-liver recipients. These risk factors indicate the need for improved control of viral hepatitis following solid organ transplantation.

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Keywords

solid organ transplantation; hepatocellular carcinoma; immunosuppression; hepatitis C virus; hepatitis B virus

Introduction

Several malignancies occur with increased frequency among recipients of solid organ transplants (1–5). Relative to the general population, incidence is particularly high for non-Hodgkin lymphoma and Kaposi sarcoma. These cancers are thought to arise in transplant recipients because of immunosuppressive medications administered to prevent organ rejection, leading to a loss of immunologic control of infection with oncogenic viruses (Epstein Barr virus and human herpesvirus 8, respectively).

Like non-Hodgkin lymphoma and Kaposi sarcoma, hepatocellular carcinoma (HCC) can be caused by chronic viral infection. World-wide, chronic viral hepatitis, due to either hepatitis B virus (HBV) or hepatitis C virus (HCV), is the leading cause of HCC (6). Factors identified with increased risk of HCC, in addition to chronic HBV and HCV infection, include alcohol abuse, diabetes mellitus, exposure to aflatoxin or other toxins, iron overload, male sex, and advancing age (7–9). HCC incidence is also elevated in persons infected with human immunodeficiency virus (HIV), although the increase appears due to exposures common in this population, such as HCV infection and alcohol abuse, rather than HIV-induced immunosuppression (10). In the general population in the United States (U.S.), HCC occurs at a rate of 2.9 per 100,000 person-years (11).

An elevated incidence of HCC might be expected in solid organ transplant recipients, given the high prevalence of HCV and HBV infection among this group (12;13) and the possible contribution of immunosuppression in inducing loss of control of these infections. However, an increased incidence of HCC has not been consistently reported following solid organ transplantation (2;4;14). Here we describe HCC incidence among a large cohort of recipients of kidney, heart, and lung (non-liver) transplants and liver transplants, and evaluate recipient and donor factors associated with development of HCC.

Materials and Methods

Study subjects and ascertainment of outcome and exposures

We analyzed risk of *de novo* HCC among solid organ transplant recipients who received a transplant between October 1, 1987 and October 31, 2005 using data from the U.S. Scientific Registry of Transplant Recipients (SRTR). These data are provided to the SRTR by the Organ Procurement and Tissue Network (OPTN), the U.S. transplant network that includes all U.S. organ procurement organizations and transplant centers. Transplant centers in OPTN routinely provide recipient and donor clinical data at the time of transplantation and follow-up data on recipients six months after transplantation and yearly thereafter. In 1999, changes occurred in the collection of follow-up data, including a shift to a web-based system of reporting that resulted in an apparent increase in the number of cancer cases. Because this change indicated that HCC reporting was less reliable before 1999, we included only follow-up time in 1999 and after in our analyses (see below).

We included two groups of individuals receiving a first solid organ transplant: (1) liver recipients and (2) non-liver (kidney, heart, or lung) recipients. We censored follow-up time after receiving any subsequent organ transplants and excluded recipients of pancreas, kidney/pancreas, heart/lung, or kidney/liver transplants, because of the small percentage of the total

population receiving these transplant types and the difficulty in analyzing donor characteristics and HLA mismatch with multiple donors.

The outcome of interest was *de novo* (i.e., new onset or non-recurrent) HCC. We therefore excluded liver recipients with liver cancer diagnosed prior to transplant, either listed as the indication for transplant or (beginning in 2002) for purposes of assigning priority on the wait list, and recipients with tumors detected on liver explant. Among remaining subjects, we defined *de novo* HCC as an OPTN transplant center report of HCC on routine patient follow-up reporting. All recipients of non-liver organs were assumed not to have hepatocellular carcinoma at the time of transplantation, as this would have been a contraindication to transplantation.

Recipient and donor demographic characteristics, medical conditions (including any history of prior cancer among donors), and HLA matching were identified by baseline records in the SRTR. Data on immunosuppressive medication regimen at the time of initial hospital discharge were also obtained from baseline records. Additional data from one-year follow-up included diagnosis or treatment of acute rejection during the first year. HCV infection among recipients and donors was identified by enzyme immunoassay (EIA) for HCV antibodies. Initially, a first generation HCV EIA was used (1989–1992), which was replaced by a second generation assay in 1992. Results of confirmatory HCV recombinant immunoblot assay (RIBA) or RNA polymerase chain reaction testing were available for only 50.0% of the subjects with positive HCV EIA; therefore, we did not use confirmatory test results in the analysis. Nonetheless, among those individuals with a positive HCV EIA who had confirmatory testing, HCV infection was confirmed for 85.6%. HBV testing in recipients included hepatitis B core antibody (anti-HBc) and hepatitis B surface antigen (HBsAg) by EIA. For donors, HBsAg was the only available serology result. To simplify the presentation, we describe all recipient characteristics below without the modifier “recipient,” and specifically note all references to donor characteristics.

Statistical analysis

We calculated HCC incidence among transplant recipients. Follow-up time began with first organ transplantation or January 1, 1999 (i.e., the change to web-based reporting), whichever was later; and ended with the earliest of HCC diagnosis or censoring due to diagnosis of another liver cancer (i.e., cholangiocarcinoma), organ graft failure, second organ transplantation, death, loss to follow-up, or the end of the study period (November 1, 2005). Thus, subjects transplanted before 1999 contributed follow-up on HCC incidence for only part of their post-transplant time. Confidence intervals (CIs) for HCC incidence were calculated using an exact method.

We used Cox proportional hazards modeling to measure associations with potential risk factors for HCC separately for liver and non-liver recipients. When assessing the association between rejection occurring during the first year post-transplant and subsequent HCC risk, we began follow-up time starting one year following transplant, to insure that rejection episodes had occurred prior to HCC outcomes. Multivariate models were designed by initially including all of the independent variables that were individually significantly ($p<0.05$) associated with HCC and then choosing the final models through backward stepwise selection. In addition, we compared characteristics of HCC cases among liver recipients, according to the time of HCC onset (i.e., early cases arising <5 years post-transplant vs. late cases arising 5+ years post-transplant), using the chi-square test.

We calculated standardized incidence ratios (SIRs) to compare HCC incidence among transplant recipients to that in the U.S. general population. HCC rates specific to age, sex, race/ethnicity, and calendar period were obtained from the U.S. Surveillance, Epidemiology, and

End Results Program (15) and applied to the follow-up time in the cohort to calculate the number of expected HCC cases. We then calculated the SIR as the ratio of the observed and expected number of HCC cases. CIs for the SIR were calculated using an exact method. When calculating the SIR, we included only subjects with known race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or Asian). In addition, we calculated SIRs stratified according to factors associated with HCC in multivariate analysis. STATA 9.2 (StataCorp, College Station, TX) was used for all calculations.

Results

Study subjects and incidence of hepatocellular carcinoma (HCC)

Between 1987 and 2005, a total of 301,314 individuals received a first liver, heart, kidney, or lung transplant in the U.S. Of these, 5331 recipients were excluded from analysis because HCC was identified prior to transplantation or was identified in the explanted organ, 68,700 recipients were excluded because follow-up time ended before 1999 (9 of whom exited prior to 1999 because of HCC), and 3623 were excluded because there were no follow-up data following transplantation. Of the remaining 223,660 individuals, the most common organ transplanted was a kidney (n=140,985), followed by liver (n=45,293), heart (n=27,670), and lung (n=9,712). Non-liver and liver recipients contributed 556,110 person-years total (median 2.9 years per person, interquartile range 1.0–5.2 years) and 149,737 person-years total (median 3.1 years, interquartile range 1.0–5.7 years), respectively, in follow-up at risk for HCC.

As shown in Table 1, most recipients were white and male, and the plurality of recipients was between 40 and 59 years of age. Diabetes mellitus was especially common among non-liver recipients (24.5%), while HBsAg and HCV antibody were more commonly detected among liver recipients than non-liver recipients. One-sixth of transplant recipients experienced acute rejection during the first year post-transplant.

HCC incidence was 6.5 (95%CI 4.7–9.0) per 100,000 person-years among non-liver recipients (n=36 cases) and 25 (95% CI 18–35) per 100,000 person-years among liver recipients (n=38 cases). Among non-liver recipients, annual incidence remained relatively steady across time following transplant, while among liver recipients, there was a suggestion that HCC incidence was highest early after transplant, declined, and then began a slight rise six years post-transplantation (data not shown). Information regarding prior donor malignancy was available for 51 HCC cases. Of these, only one case (a kidney recipient) had a donor with a previously diagnosed malignancy (prostate cancer).

Risk factors for HCC in non-liver transplant recipients

As shown in Table 2, among recipients of a non-liver transplant, HCC risk was significantly higher among males (hazard ratio [HR] 3.1), older individuals ($p<0.001$ for trend), and individuals with diabetes mellitus (HR 3.0). The highest risk occurred among individuals with chronic viral hepatitis. Recipients who were HBsAg positive had a 13-fold increased risk of HCC, while those with HCV had an 8.4-fold increased risk. We did not find significant associations with HCC risk based on organ type (kidney, heart, or lung), other recipient characteristics (race, education, anti-HBc status), other donor characteristics (donor age, donor type, donor alcohol abuse), HLA-mismatch, use of specific immunosuppressive medications, or diagnosis or treatment of acute rejection during the first year post-transplant (data not shown).

In multivariate regression models for non-liver transplant recipients, sex and age were not associated with HCC, because both were strongly associated with HCV antibody status, HBsAg status, and diabetes mellitus. In addition, donor HCV status lost significance when recipient

HCV status was considered, because recipients of an organ from an HCV antibody positive donor were usually HCV antibody positive themselves. The final regression model demonstrated that HCC risk was independently associated with HBsAg (HR 9.7, 95% CI 2.8–33), HCV antibody (HR 6.9, 2.5–19), and diabetes mellitus (HR 2.8, 1.2–6.6).

Risk factors for hepatocellular carcinoma in liver transplant recipients

Among liver recipients, HCC risk was associated in univariate analyses with male sex (HR 4.9), older age at transplant (p for trend <0.001), diabetes mellitus (HR 3.4), HBsAg (HR 4.2), HCV antibody (HR 3.3), and older donor age (≥30 years compared to <30 years, HR 2.4) (Table 2). Alcohol abuse by the liver donor was associated with borderline increased HCC risk (HR 1.8, 95% CI 0.82–4.1).

In a multivariate regression analysis among liver recipients, HBsAg status and donor alcohol abuse were not significant predictors of HCC when HCV or diabetes mellitus was included in the model. When age was added as a categorical variable, the multivariate model was unstable, so age was included as a three-level ordinal variable. In the final multivariate regression model, HCC was independently associated with age at transplant (HR 4.0, 95% CI 9.5-8.5, per age category of less than 40, 40–59, and 60+ years; p<0.001), male sex (HR 4.6, 1.4–16), HCV antibody (HR 3.1, 1.3–7.2), and diabetes mellitus (HR 2.7, 1.2–6.2).

Finally, we compared early onset vs. late onset HCC cases among liver recipients (n=24 and n=14, respectively; Table 3). Early onset HCC cases tended to be older at transplant than late onset cases (p=0.03). Compared with early onset HCC cases, late onset cases were more likely to be HBsAg positive (p=0.03).

HCC incidence compared to the general population (standardized incidence ratios)

Among recipients of non-liver transplants overall, HCC incidence was similar to that in the general population (SIR 0.8, 95% CI: 0.5–1.0; Table 4). However, HCC incidence was significantly elevated among non-liver recipients who were HCV antibody positive (SIR 3.4, 95%CI 1.2–7.4) or HBsAg positive (SIR 6.5, 95%CI 1.8–16). In comparison, HCC incidence was elevated among all liver transplant recipients (SIR 3.4, 95%CI 2.4–4.6) and among most subgroups (Table 4). Thus, although many liver recipients (36.8%) were HCV antibody positive, HCV infection did not entirely account for the increased incidence of HCC, because HCC incidence was also elevated for HCV antibody negative liver recipients (SIR 2.0, 95% CI 0.9–3.9). Likewise, incidence was elevated among liver recipients who were HBsAg negative or did not have diabetes mellitus.

Discussion

In this study of 223,660 recipients of a solid organ transplant, the incidence of *de novo* HCC was notably increased among recipients of a liver but not of a non-liver transplant when compared with the general population. The absence of an overall elevated risk among non-liver transplant recipients is consistent with results from studies of kidney transplant recipients in Canada (4) and solid organ transplant recipients in Sweden (84% of whom were kidney recipients) (14). It contrasts with a recent Australian study that reported a three-fold elevated risk of liver cancer following kidney transplantation (2). These prior studies were much smaller than the present study (i.e., 5,931–11,155 vs. 178,367 non-liver recipients). Also unlike the present study, which relied upon transplant center reports of HCC, the prior studies utilized linked data from cancer registries (2;4;14). Therefore, the apparent differences in HCC risk across these four studies could be due to imprecision in risk estimates due to the rarity of HCC, differences in cancer ascertainment, or differences in the prevalence of HCC risk factors. To

our knowledge no large study reporting incidence of *de novo* HCC in liver recipients exists with which to compare our findings.

Differentiation between *de novo* and recurrent HCC among liver recipients is essential to measure incidence and assess risk factors. Among liver recipients, part of the elevated HCC incidence within the first years after transplantation may represent recurrence of occult tumors not detected during pre-transplantation screening or on examination of the explanted organ. Recurrent HCC has typically been described to arise within several years of transplantation (median time to HCC recurrence 11–21 months) (16;17). This early recurrence is also consistent with the doubling time of HCC (80–200 days) (18). Although delayed recurrence of HCC has been reported (19), the occurrence of HCC later after transplant is most consistent with the development of *de novo* tumors. Given the rarity of other cancers in donors, we believe that unsuspected transmission of other cancer types, with subsequent seeding of the liver, did not contribute substantially to our results.

Although overall HCC incidence was not elevated among non-liver recipients, we identified several risk factors associated with increased HCC risk in this population. As seen in the general population, HCV infection, HBV infection, and diabetes mellitus were all strongly associated with development of HCC. In addition, the hazard ratios that we estimated were similar to relative risks reported for the general U.S. population, i.e., 1.3–17 fold for HCV antibody positivity (20;21), 5–15 fold for HBsAg positivity (22), and 2.5 for diabetes mellitus (7). Among people with AIDS (another immunosuppressed population), HCV infection is estimated to increase HCC risk 2.4-fold (10). Two other risk factors associated with HCC in the general population, age and male sex, were associated with HCC incidence in univariate analyses but were no longer significant in a multivariate regression model because of their relationships with HCV status, HBsAg status, and diabetes mellitus.

Among liver transplant recipients, HCC risk was associated with HCV infection, diabetes mellitus, male sex, and older age at transplant. We did not find an association between HBsAg positivity and HCC in multivariate modeling overall, although HCC cases arising late after transplant were more likely to be HBsAg positive (Table 3). Our finding of a lower risk related to HBV infection than previously reported in other populations may reflect the slow progression of HBV-mediated HCC (23), and with long-term follow-up greater than 10 years, it is possible that a greater impact of HBV will be observed. Another potential reason for not finding an independent increased risk conferred by HBV in the liver transplant population is the intensive prophylactic therapy used among patients with chronic HBV. Since 1999, standard practice has been to administer hepatitis B immune globulin and a prolonged course of lamivudine to HBsAg positive transplant recipients (6). The association between HCV infection and HCC risk was also noticeably weaker among liver recipients than in the general population, perhaps because of the potential for HCV to increase risk for graft failure or death from other causes. These competing risks arise from rapid re-infection of the liver graft by HCV following transplantation and progressive liver disease (6;24).

Several negative observations should be addressed. First, the lack of association of HCC risk with rejection during the first year post-transplant or level of HLA mismatch (which correlates with more frequent rejection episodes) argues against a major effect of pulse doses of immunosuppression on HCC risk. In addition, HCC risk for non-liver recipients did not appear to increase over time from organ transplant (data not shown), which is consistent with a lack of a cumulative effect of immunosuppression. Similarly, HCC risk was not associated with use of specific immunosuppressive agents (data not shown). However, we had no information on medication dosage, we had few subjects on some medications that might modify cancer risk, including sirolimus, (25) and we did not have data on medication changes over time.

Strengths of our study include its large size, representation of both non-liver and liver transplant recipients, and availability of data on several important HCC risk factors. Our study also has several limitations. First, we did not have complete follow-up on subjects. Individuals transplanted before 1999 contributed only to later follow-up, while those transplanted after 1999 contributed to earlier follow-up. If there have been substantial changes in HCC risk factors over time, this difference in follow-up could have introduced bias. Therefore, we were unable to reliably examine changes in HCC incidence according to time since transplantation. An additional limitation is that, while many subjects contributed follow-up time for various intervals in the first 10 years post-transplant, there was little follow-up beyond this period, so we could not fully evaluate late HCC risk. Second, we may have missed some cases of HCC. We evaluated follow-up time starting with 1999, but even with improvements in follow-up, we may still lack a complete record of HCC cases. Furthermore, under-ascertainment may have been higher for kidney recipients and could have increased over time since transplant, because such transplant recipients may have transferred their care back to community providers. If under-ascertainment occurred, the incidence for the non-liver recipients may have been underestimated and the SIR for the non-liver group incorrectly low. An additional limitation is that we were missing data on important characteristics for some recipients. For example, information regarding HCV status was unavailable for 25% of the subjects. Furthermore, approximately 20% of individuals with HCV antibodies do not have active infection as a result of earlier clearance (26). We did not have complete data on plasma HCV RNA levels, which would have allowed us to distinguish between chronic and resolved infection, and including individuals with resolved HCV infection may have slightly attenuated the association between HCV and HCC. In addition, we anticipate some misclassification among liver allograft recipients who had occult HCC at the time of transplant and developed recurrent rather than *de novo* HCC. Finally, HCC is rare, limiting the study's power to fully explore factors potentially associated with HCC.

In conclusion, we identified an increased risk of HCC among liver transplant recipients, as well as several strong risk factors for HCC in both liver and non-liver recipients. This information may be useful for management of patients post-transplant. Our findings support the value in suppressing chronic viral hepatitis infections among solid organ recipients, both liver and non-liver. Furthermore, our results suggest a positive impact related to suppression of chronic HBV infection and add further reason to accelerate efforts to develop therapy to suppress HCV replication and protect liver allografts from HCV infection when transplanted to an HCV positive recipient. Continued long-term follow-up will be important to further assess the impact of viral hepatitis infection and to explore the long-term impact of immunosuppression on development of HCC.

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Table 1

Characteristics of U.S. transplant recipients and their donors (n=223,660)

Characteristic	Non-liver recipients(N=178,367), n (%)*	Liver recipients (N=45,293), n (%)*
Sex		
Female	68,693 (38.5)	18,571 (41.0)
Male	109,674 (61.5)	26,722 (59.0)
Age at transplant, years		
<40	58,309 (32.7)	11,369 (25.1)
40–59	86,747(48.6)	26,629 (58.8)
≥ 60	33,311 (18.7)	7,295 (16.1)
Race/ethnicity		
Non-Hispanic white	114,385 (64.3)	34,483 (76.3)
Non-Hispanic black	35,628 (20.1)	3,786 (8.4)
Hispanic	18,759 (10.5)	5,154 (11.4)
Asian	6,463 (3.6)	1,387 (3.1)
Other/unknown	2,537 (1.4)	409 (0.9)
Diabetes mellitus		
No	107,242 (75.6)	30,996 (85.0)
Yes	34,707 (24.5)	5,489 (15.0)
HBsAg		
Negative	155,294 (98.6)	36,547 (94.3)
Positive	2,240 (1.4)	2,204 (5.7)
HCV antibody		
Negative	132,186 (96.1)	19,858 (63.2)
Positive	5,330 (3.9)	11,586 (36.8)
Donor Type		
Living	55,642 (31.2)	2,468 (5.4)
Deceased	122,725 (68.8)	42,825 (94.6)
Donor age, years		
<30	68,458 (38.4)	20,225 (44.7)
≥30	109,893 (61.6)	25,050 (55.3)
Donor alcohol abuse		
No	70,031 (80.8)	25,611 (83.4)
Yes	16,608 (19.2)	5,095 (16.6)
Donor HCV antibody		
Negative	142,887 (98.5)	37,104 (98.2)
Positive	2,132 (1.5)	677 (1.8)
HLA mismatch		
0–2	44,825 (26.4)	1,331 (5.3)
3–4	72,416 (42.7)	9,906 (39.8)
5–6	52,288 (30.8)	13,630 (54.8)
Acute rejection during first year		
No	150,765 (84.5)	36,963 (81.6)

Characteristic	Non-liver recipients* (N=178,367), n (%)	Liver recipients (N=45,293), n (%)*
Yes	27,602 (15.5)	8,330 (18.4)

Abbreviations: HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus

* Subjects with missing values for a specific characteristic are not included in calculating percentages.

Table 2

Risk factors for hepatocellular carcinoma among U.S. transplant recipients (univariate models)

Characteristic	Non-liver recipients			Liver recipients		
	HCC, n	Incidence, per 100,000 person-years	Hazard ratio(95%CI) Univariate analysis	HCC, n	Incidence, per 100,000 person-years	Hazard ratio(95%CI) Univariate analysis
Sex						
Female	6	2.8	1.0	5	7.8	1.0
Male	30	8.7	3.1 (1.3–7.5)	33	39	4.9 (1.9–13)
Age at transplant, years						
<40	4	2.1	1.0*	1	2.4	1.0*
40–59	20	7.3	3.6 (1.2–10)	22	25	11 (1.4–80)
≥ 60	12	13	6.8 (2.2–21)	15	67	28 (3.7–220)
Diabetes mellitus						
No	14	4.4	1.0	19	20	1.0
Yes	12	13	3.0 (1.4–6.5)	10	68	3.4 (1.6–7.4)
HBsAg						
Negative	22	4.5	1.0	26	21	1.0
Positive	4	63	13 (4.5–38)	7	91	4.2 (1.8–9.8)
HCV antibody						
Negative	20	5.0	1.0	9	14	1.0
Positive	6	42	8.4 (3.4–21)	16	47	3.3 (1.4–7.4)
Donor age						
<30	15	6.6	1	11	15	1
≥30	21	6.4	1.0 (0.5–1.9)	27	36	2.4 (1.2–4.9)
Donor alcohol abuse						
No	15	6.4	1.0	22	24	1.0
Yes	5	9.1	1.5 (0.5–4.0)	8	46	1.8 (0.8–4.1)
Donor HCV antibody						
Negative	22	5.2	1.0	29	25	1.0
Positive	3	56	10 (3.1–35)	1	59	2.3 (0.3–17)

Abbreviations: HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HCC, hepatocellular carcinoma, CI confidence interval

Note: Subjects with missing data were excluded from analysis.

* p<0.001 for trend, among non-liver and liver recipients.

Table 3

Characteristics of early and late hepatocellular carcinoma cases among liver transplant recipients

Characteristic	HCC cases with characteristic, n (%)*		p-value
	HCC onset <5 years post-transplant	HCC onset 5+ years post-transplant	
Male	21 (88)	12 (86)	0.87
Age at transplant, years			
< 40	0 (0)	1 (7)	0.03‡
40–59	11 (46)	11 (78)	
≥60	13 (54)	2 (14)	
HBsAg positive	2 (10)	5 (42)	0.03
HCV antibody positive	12 (60)	4 (80)	0.41

Abbreviations: HBsAg, hepatitis B surface antigen: HCV, hepatitis C virus; HCC, hepatocellular carcinoma

*Overall, there were n=24 early HCC cases (onset <5 years post-transplant) and n=14 late HCC cases (onset 5+ years post-transplant). However, the percentages reflect variation in the denominator due to missing data on the characteristic being evaluated.

‡p for trend

Table 4

Standardized incidence ratios for hepatocellular carcinoma among U.S. transplant recipients

Characteristic	Non-liver recipients		Liver recipients	
	HCC cases	SIR (95%CI)	HCC cases	SIR (95%CI)
All subjects	35	0.8 (0.5–1.0)	38	3.4 (2.4–4.6)
Sex				
Male	30	0.7 (0.5–1.1)	33	3.6 (2.5–5.0)
Female	5	0.8 (0.3–2.0)	5	2.6 (0.9–6.2)
Age at transplant, years				
<40	4	1.8 (0.5–4.6)	1	2.9 (0.1–16)
40–59	19	0.7 (0.4–1.1)	22	3.0 (1.8–4.5)
≥ 60	12	0.8 (0.4–1.3)	15	4.5 (2.5–7.4)
HCV antibody				
Negative	19	0.6 (0.4–0.9)	9	2.0 (0.9–3.9)
Positive	6	3.4 (1.2–7.4)	16	5.0 (2.9–8.2)
HBsAg				
Negative	21	0.5 (0.3–0.8)	26	2.9 (1.9–4.4)
Positive	4	6.5 (1.8–16)	7	7.4 (3.0–15)
Diabetes mellitus				
No	13	0.6 (0.3–1.0)	19	2.8 (1.7–4.3)
Yes	12	1.1 (0.6–2.0)	10	6.2 (3.0–11)

Abbreviations: HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HCC, hepatocellular carcinoma, SIR standardized incidence ratio; CI, confidence interval

Standardized incidence ratio calculations exclude subjects of unknown race/ethnicity (2,537 non-liver recipients, including one HCC case; 409 liver recipients, zero HCC cases), because expected cancer rates were not available for these subjects.