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The Incidence of De Novo Hepatocellular Carcinoma After Liver Transplantation: A Retrospective Case-Control Study

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Abstract:

Background:

The American Association for the Study of Liver Diseases (AASLD) recommends screening post-transplant patients with a prior diagnosis of hepatocellular carcinoma (HCC) or recurrent liver cirrhosis. In contrast, de novo HCC is a rare disease, and transplant recipients without a diagnosis of HCC at the time of transplantation without liver cirrhosis are not screened. The goal of this study was to emphasize the importance of HCC screening in post–liver transplant patients who had no history of HCC or liver cirrhosis.

Method:

A retrospective study was conducted using de-identified data from the national health database of the Healthcare Cost and Utilization Project (HCUP). We assessed the incidence of HCC in transplant recipients after excluding patients with a prior diagnosis of HCC or liver cirrhosis.

Results:

The incidence of HCC was 76.47 per 100,000 liver transplant recipients after excluding cirrhotic patients, whereas it was 19.57 per 100,000 in patients without any history of liver transplant. The odds of transplant recipients developing HCC was 3.22 times higher after adjusting for demographics, socioeconomic factors, and known risk factors for HCC such as hepatitis B and hepatitis C, etc. Patients in the HCC cohort were more likely to have a history of hepatitis C compared to the non-HCC group (OR = 3.88, 95% CI, 2.36–6.37, P < 0.001). Alcohol use was higher in the HCC cohort (OR = 3.56, 95% CI, 1.44–8.77, P =0.006F).

Conclusion:

HCC was shown to be more common in liver transplant recipients in this study. The fact that variables other than a prior history of HCC or liver cirrhosis may play a role in the development of HCC is highlighted. Further studies are needed to determine the risk of HCC in liver transplant patients to formulate recommendations about de novo HCC screening in patients other than those with a history of liver cirrhosis.

Key Words: liver cirrhosis; de novo; hcc; liver transplant

Introduction:

Hepatocellular carcinoma (HCC) is the fifth most common malignancy in men and the ninth most common malignancy in women. It is the second most common cause of death from malignancy [1]. Orthotopic liver transplantation (OLT) is the treatment of choice for HCC and end-stage liver disease [2,4]. With advances in the treatment of HCC, the outcomes of OLT have improved over the last few decades. Due to the aging liver transplant population, clinicians are required to become more familiar with the complications seen in this population, which include acute or chronic organ rejection, biliary complications, recurrence of the primary liver disease, or complications related to immunosuppression.

The incidence of malignancy is higher in liver transplant recipients compared to the general population [5]. This is believed to be partially related to the duration and intensity of immunosuppressive therapy, which may affect tumor development and progression [6]. Skin cancer is the most common malignancy seen in liver transplant recipients [7]. Although HCC is one of the indications for OLT, it recurs in 20% of patients [8], which is likely a result of extrahepatic tumor dissemination before OLT [8], leading to HCC recurrence within or outside the liver [9,12].

Another type of carcinogenesis that may affect the graft is de novo HCC. De novo HCC is the occurrence of HCC in a liver transplant recipient with no prior history of HCC [13]. The incidence of de novo HCC was reported to be 25 per 100,000 liver transplant recipients in the U.S. registry data [14]. The AASLD's screening guidelines for de novo HCC in patients with recurrent liver cirrhosis include abdominal imaging every 6–12 months [13]. After excluding the cirrhotic liver population, there is no data in the medical literature on the incidence of de novo HCC in liver transplant recipients. As a result, if the patient does not have liver cirrhosis, there are not de novo HCC screening recommendations. The aim of this study was to estimate de novo HCC incidence and any risk factors associated with it in the post–liver transplant population in the United States, excluding liver cirrhosis.

Methods:

Data Source:

The study used the National Inpatient Sample (NIS) database, which was developed for the Healthcare Cost and Utilization Project (HCUP). The NIS is the largest publicly available inpatient database. It records more than seven million inpatient hospital stays each year. When it is weighted, it contains more than 35 million hospital admissions. It includes data from more than 97% of U.S. states participating in HCUP. It contains data about patients' demographics (age, sex, race, and median household income), primary and secondary diagnosis, hospital characteristics, hospital length of stay, and hospital cost as well as severity and comorbidity measures. The primary diagnosis is the main reason for the hospitalization.

Study Population:

We identified hospital stays with a diagnosis of liver transplant from 2011–2014 using the International Classification of Diseases, Ninth Revision (ICD-9) secondary diagnostic codes V42.7. ICD-9 V42.7 is a code for a history of liver transplantation. We extracted HCC as a primary diagnosis from the database using ICD 9 codes diagnostic codes 155.0. We identified a history of chronic viral hepatitis B (070.32 and 070.33) and chronic viral hepatitis C (070.44 and 070.54) as secondary diagnoses among liver transplant patients by using ICD-9 codes. The ICD-9 codes and Healthcare Cost and Utilization Project (HCUP) clinical classification software codes were used for other comorbidities. The exclusion criteria included patients with a history of HCC and liver cirrhosis.

Study outcomes:

The primary outcome was to assess the incidence of hepatocellular carcinoma among patients who underwent liver transplant. The secondary outcome was to determine any demographic (e.g., age, sex, race, and social-economic) that might be a risk factor for the development of HCC.

Statistical Analysis:

We used Chi-square test and Student's t-test for categorical and continuous variables, respectively, to evaluate the patient demographics and hospital diagnosis of two cohorts of hospitalized patients. P <0.05 was considered statistically significance. Univariate analysis was initially performed to calculate the unadjusted odds ratio. A logistic regression model was performed after adjusting for age, sex, race, median household income, and other risk factors such as alcohol use, obesity, non-alcoholic steatohepatitis (NASH), and chronic hepatitis B and C to evaluate the risk factors among HCC population. Logistic regression was expressed as adjusted odds ratio (aOR) with a 95% confidence interval (CI) and P-value. IBM SPSS statistics 23.0 was used to perform statistical analysis. We used the NIS database for this study. The NIS database does not contain any identifiers of patients; therefore, we did not require institutional review board permission for this study.

Results:

A total of 339,053 hospital visits were identified—134,682 with history of liver transplant and 204,371 with no history of liver transplant. Comparing the OLT cohort with the control group, in terms of sex, 79,127 patients in the OLT cohort were male (58.8%) vs. 85,493 (41.9%) in the control group(P <0.001, odds ratio [OR] = 1.98, 95% CI, 1.95–2.00); in terms of race, 88,514 (70.5%) patients in the OLT cohort were white vs. 124, 416 (65.6%) in the control group (P <0.001, OR = 1.23, 95% CI, 1.21–1.25 (see Table 1); 6,495 (4.8%) patients in the OLT cohort were obese vs. 11, 841 (5.8%) in the control group(P <0.001, OR = 0.82, 95% CI, 0.80–0.85); 11, 492 (8.5%) patients in the OLT cohort were smokers vs. 24, 487 (12%) in the control group (P <0.001, OR= 0.69, 95% CI, 0.67–0.70); 103 patients in the OLT cohort had a history of HCC vs. 40 patients in the control group (P <0.001, OR = 3.91, 95% CI, 2.71–5.63); 1,563 (1.2%) patients in the OLT cohort used alcohol vs. 3,205 (1.6%) in the control group (P <0.001, OR = 0.74, 95% CI, 0.70–0.78); 1,034 (0.8%) patients in the OLT cohort had a history of chronic hepatitis B vs. 184 (0.1%) in the control group (P <0.001, OR = 8.59, 95% CI, 7.34–10.05); 7,139 (5.3%) patients in the OLT cohort had a history of chronic hepatitis C vs. 927 (0.5%) in the control group (P <0.001, OR = 12.28, 95% CI, 11.47–13.16); 1,050 (0.8%) patients in the OLT cohort had a history of non-alcoholic fatty liver disease (NASH) vs. 1,341 (0.7%) in the control group (P = 0.06, OR = 1.19, 95% CI, 1.1–1.29). The incidence of HCC was 76.47/100,000 in the OLT population and 19.57/100,000 in the control group.

Comparing patients who had HCC vs. patients without HCC in the OLT population, HCC patients were more likely to be male than female (OR = 2.20; 95% CI, 1.40–3.44; P <0.001). More patients in the HCC vs. the no HCC cohort had a median income below $51,000 (67.1% vs. 51.5%). No patients in the HCC cohort had a history of obesity or smoking. Patients in the HCC cohort were more likely to have a history of hepatitis C (OR = 4.05; 95%

CI, 2.45–6.67; P <0.001). Alcohol use was higher in the HCC cohort (OR = 4.37; 95% CI, 1.77–10.71; P <0.01). There was no statistical difference between the HCC and the no HCC cohorts in terms of age, race, chronic hepatitis B, and NASH (shown in table 2).

In liver transplant recipients, the risk of developing HCC increased by 322% (aOR [adjusted odds ratio], 3.22; 95% CI, 2.21–4.72; P 0.0001). The HCC cohort had a higher likelihood of having a median household income in the 26th–50th percentile compared to the 76th–100th percentile (OR, 2.11; 95 percent CI, 1.29–3.42; P =0.003). Chronic hepatitis C was more common in the HCC population (OR, 3.88; 95 percent CI, 2.36–6.37; P 0.001) (Table 3).

Factors	**History of Liver transplant group** N = 134,682	**No history of liver transplant group** N = 204,371	**P-Value**
Age – mean + SD	54.02 ± 18.45	48.77 ± 27.64	P <0.0001
Sex Male – n (%) Female	 79,127 (58.8%) 55,536 (41.2%) Missing 19	 85,493 (41.9%) 118,720 (58.1%) Missing 158	P <0.0001
Race – n (%) White Black Hispanic Asian or Pacific Islander Native American Other	 88,514 (70.5%) 12,632 (10.1%) 16,241 (12.9%) 3,231 (2.6%) 536 (0.4%) 4,314 (3.4%) (missing 9,215)	 124,416 (65.6%) 28,772 (15.2%) 23,029 (12.1%) 5,245 (2.8%) 1289 (0.7%) 6863 (3.6%) (missing 189,614)	P <0.0001
Median household income $1–39,999 $40,000 – 50,999 $51,000 – 65,999 $66,000+	 33,994 (26.4%) 33,252 (25.1%) 33,810 (25.5%) 30,360 (22.9%) Missing 2266	 59678 (29.9%) 50474 (25.2%) 49166 (24.6%) 40584 (20.3%) Missing 4469	P <0.0001

Table 1: Demographics of the liver transplant population vs. non-liver transplant population

	HCC N = 103	No HCC N = 134,575	P-value
Age – mean + SD	52.93 ± 21.28	54.03 ±18.46	0.5
Sex Male – n (%) Female	 78 (75.6%) 25 (24.4%)	 79,049 (58.7%) 55,526 (41.3%)	0.001
Race – n (%) White Black Hispanic Asian or Pacific Islander Native American Other	 63 (71.6%) <10 10 (11.4%) <10 0 <10 (missing 15)	 88,461, (70.5%) 12,627 (10.1%) 16,231 (12.9%) 3,226 (2.6%) 536 (0.4%) 4,309 (3.4%) (missing 125,389)	0.23
Median household income $1–39,999 $40,000 – 50,999 $51,000 – 65,999 $66,000+	 29 (28.4%) 40 (38.7%) 15 (14.2%) 19 (18.8%)	 34,970 (26.4%) 33,223 (25.1%) 33,795 (25.5%) 30,341 (22.9%) Missing 2266	0.03
Obesity	0	6495 (4.8%)	0.01
Smoking	0	11492 (8.5%)	0.0001
Alcohol	<10	1558 (1.2%)	0.01
Hepatitis B	0	1034 (0.8%)	0.37
Hepatitis C	19 (18.8%)	7120 (5.3%)	0.0001
NASH*	0	1050 (0.8%)	0.36

Table 2: The ethnic-racial and socioeconomic factors in the development of hepatocellular carcinoma in patients who underwent a liver transplant. (*Non-alcoholic steatohepatitis)

	Adjusted Odds Ratio	Lower limt	Upper limit	P-value
Age	0.98	0.98	0.99	0.01
Male vs. Female	1.15	0.79	1.56	0.529
White vs. AA*	0.95	0.60	1.50	0.837
Hispanic vs.AA	0.87	0.46	1.65	0.665
Asian vs. AA	1.67	1.73	4.41	0.30
Native American vs. AA	0.00	0.00	0.00	0.99
Median household income 1^{st} – 25^{th} vs. 76th – 100th	1.74	1.05	2.88	0.03
Percentile 26^{th}– 50^{th} vs. 76th – 100th	2.11	1.29	3.42	0.003
Percentile 51th –75^{th} vs. 76th – 100th	1.02	0.58	1.78	0.957
Obesity	0.66	0.27	1.62	0.367
Smoking	0.30	0.12	0.72	0.008
Alcohol	3.56	1.44	8.77	0.006
NASH	0.00	0.00	0.00	0.99
Hepatitis B	0.00	0.00	0.00	0.99
Hepatitis C	3.88	2.36	6.37	<0.0001
Liver transplant	3.22	2.21	4.72	<0.0001

Table 3: Multivariate logistic regression test for Hepaticelluar Carcinoma. (*African American).

Discussion:

The main findings of the study were that the incidence of HCC was 290.75% higher in the OLT population. Patients who developed HCC were more likely to be male, and 15.6% more HCC patients had a lower socioeconomic status with a median household income in the 1–50^{th}. Hepatitis C and alcohol use were higher in the HCC patients compared to the non-HCC patients.

A study has shown that sustained excessive alcohol consumption (>20 g/day for women and >30 g/day for men) decreased the five-year survival rate of transplant recipients by 26% [15]. The

resumption of alcohol after OLT is a risk factor for graft injury [16], as highlighted in this study, which showed that that alcohol use after OLT was associated with higher chances of HCC development.

Obesity is associated with metabolic syndrome, increased risk of complications, and poor outcomes following a liver transplant. The AASLD recommends dietary counseling for WHO class 1 and 2 obese patients and relative contraindication of liver transplant in grade 3 obesity. Most likely, liver transplant centers are following these recommendations, as obesity was less prevalent in the OLT population. Tobacco smoking is associated with a higher risk of cardiovascular disease, hepatic artery thrombosis, and oropharyngeal and another neoplasm following OLT [17]. The AASLD recommends tobacco cessation in OLT receipts. In agreement with this, this study showed that tobacco use was less in the liver transplant cohort.

In our study, the risk of developing HCC was higher in the liver transplant cohort even after adjusting for demographics, socioeconomic factors, and known risk factors for HCC, such as hepatitis B, hepatitis C, obesity, NASH, and alcohol use. One possible explanation is that the graft can be affected by chronic hepatitis (viral, metabolic, or toxic) [18]. Another hypothesis is that it might be related to donor exposure to risk factors such as a history of smoking, alcohol use, or environmental exposure to HCC carcinogens. A further possibility is that it might be due to post OLT exposure to environmental hepatocarcinogens, such as aflatoxin B 1, vinyl chloride, pesticides, arsenic, and cigarette smoking [18].

Another known risk factor for HCC recurrence is immunosuppression therapy following liver transplant [19,20], which facilities cancer development, first, by depressing the immune system and, second, by the diabetogenic effect of the calcineurin inhibitors (CNI) cyclosporine and tacrolimus due to pancreatic B cell apoptosis and impaired insulin secretion [21,23]. A retrospective analysis showed that a higher level of cyclosporine was associated with recurrent HCC in patients who undergo OLT for HCC [19]. Retrospective studies have shown that the newer immunosuppression agent sacrolimus had a lower risk of post-transplant HCC recurrence compared to other immunosuppressive agents (tacrolimus and CSA) [24,28].

In our study, the incidence of de novo HCC was higher in the liver transplant population. There is less data available in the medical literature about the incidence of de novo HCC after excluding liver cirrhosis. Several case reports have been published about the development of de novo HCC post–liver transplant that showed patients developed de novo HCC due to hepatitis B [29,32]. In our study, the percentage of patients with chronic hepatitis B was higher in the liver transplant group; however, considering the ethnic-racial and socioeconomic factors for the development of hepatocellular carcinoma in patients, chronic hepatitis B did not play any role and was not statistically significant. One possible explanation could be that we excluded liver cirrhotic patients.

Case reports have shown the recurrence of chronic hepatitis C as the possible cause of de novo HCC in liver transplant recipients [33,36]. In our study, chronic hepatitis C was more common in liver transplant recipients. Although we excluded liver cirrhotic patients, the odds of having chronic hepatitis C were still higher in HCC patients. One possibility is that these patients might have advanced stages of liver fibrosis [37,38] without cirrhosis.

Although case reports have shown an association between alcohol liver cirrhosis and de novo HCC [39,40], and in this study, alcohol use was greater among the HCC patients, there were no cirrhotic alcohol patients in our population. There are multiple explanations for this; first, alcohol may act synergistically with other coexisting HCC risk factors such as viral hepatitis [41] or obesity [42]. Secondly, HCC might be caused by liver fibrosis.

The limitation of this study lies in the use of the NIS-HCUP database. Since NIS is an inpatient database, the incidence of outpatient de novo HCC cannot be addressed using this database. Further, this database uses ICD-9 codes, which are inherently variable, and thus, there might be issues with proper use of codes or reporting systems.

Conclusion:

HCC was shown to be more common in liver transplant recipients in this study. The fact that variables other than a prior history of HCC or liver cirrhosis may play a role in the development of HCC is highlighted. There are no screening recommendations for these patients. More clinical studies are needed to evaluate the risk factors associated with de novo HCC so that appropriate screening recommendations can be developed.

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Statement of Ethics:

The NIS database does not contain any identifiers of patients; therefore, we did not require institutional review board permission for this study.

Disclosure Statement:

No conflits of interest to declare

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Author Contributions:

Saleem - conception and design of this work, the analysis of the data, and writing
Inayat- the analysis of the data, and writing
Aziz– conception and design
Malik - analysis and writing
Ishtiaq- conception and design
Then – conception and writing
Gaduputi – supervision, conception and writing

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