Modest Impact of Liver Transplantation on Hepatocellular Carcinoma Mortality in the United States, Findings from The Transplant Cancer Match (TCM) Study

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ABSTRACT

Liver transplantation is considered the most curative treatment for patients with localized hepatocellular carcinoma (HCC). Recent organ allocation policies have reduced the priority of patients with HCC for liver transplantation, which might affect overall liver transplantation usage and HCC-specific mortality among patients with HCC. Therefore, studies on the impact of liver transplantation on population-level HCC-specific mortality rates are necessary and essential. Mahale and colleagues used comprehensive, linked population databases on both HCC cancer cases and liver transplantation recipients and applied incidence-based mortality (IBM) analysis to evaluate the overall impact of liver transplantation on HCC mortality in the United States. Although liver transplantation rates continue to rise in the United States, the authors showed that liver transplantation has had modest impact over time on HCC-specific mortality at the population level (liver transplantation was associated with a 0.5% reduction in the annual rate of increase in the IBM rate vs. nontransplant). Considering these findings, HCC screening and surveillance for early detection should be a priority, meanwhile, increased availability of liver transplantation for patients with HCC and other HCC curative-intent treatment modalities are also necessary to improve HCC survival. Moreover, HCC risk factors, viral hepatitis and nonalcoholic fatty liver disease prevention and treatment should also be incorporated in future HCC mortality research.

See related article by Mahale et al., p. 513 (1)

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and third most common cause of cancer-related mortality in the United States (2). The incidence of HCC has increased substantially in the United States over the past three decades and continues to rise. HCC incidence is characterized by a strong male predominance and HCC is more common among Asians/Pacific Islanders and Hispanics compared with non-Hispanic whites (3). The overall survival rates for patients diagnosed with HCC are poor (5-year survival < 20%; ref. 2), with disparities in survival strongly related to differences in the distribution of stage at diagnosis and whether or not the patient receives curative-intent treatment (4). Studies have shown that early detection and early curative-intent treatment, such as ablation, surgery resection, and liver transplantation, are associated with improved survival in patients with HCC (5). Among them, liver transplantation is considered the most effective curative treatment for patients with localized HCC (i.e., those patients who met the Milan criteria; ref. 6) because liver transplantation removes both the tumor and underlying cirrhosis (7). However, only a small fraction of all patients with HCC is eligible for liver transplantation and, with potentially improving mortality rates among non-transplanted HCC patients, it is suggested that liver transplantation has had limited impact on population–level HCC-specific mortality rates in the United States. In fact, in 2019, the organ allocation policy from the Organ Procurement and Transplantation Network and United Network for Organ Sharing has reduced the priority of HCC patients for liver transplantation, which will affect overall liver transplantation usage among patients with HCC in the United States and might adversely influence population-level HCC-specific mortality rates.

A number of studies have attempted to quantify the impact of liver transplantation on population-level HCC-specific mortality rates, which have conflicting results due to methodologic differences and other shortcomings. For example, while some studies have demonstrated survival benefit of liver transplantation in patients with HCC over other treatment modalities (8, 9), these studies did not take into consideration the background rising incidence rates for HCC, and therefore likely underestimated the impact of liver transplantation on population-level HCC-specific mortality rates (10). Furthermore, most prior studies used only data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, which has limited information about the cancer and only first line treatment data (11), or from the SEER-Medicare database, which rely on inpatient/outpatient claims data to characterize the patient's personal and clinical history (8). Moreover, none of these prior studies linked the cancer registry data with data for transplanted patients in the U.S. Scientific Registry of Transplant Recipients (SRTR). In this issue, Mahale and colleagues (1) address these shortcomings by using data from the Transplant Cancer Match (TCM) study, which linked patient-level data from the United States SRTR with data from national cancer registries, and covered approximately 50% of all solid tumor transplants in United States. To more accurately quantify population-level impact and address the issue of underestimation of liver transplantation impact in prior studies, the authors used incidence-based mortality (IBM) analysis to evaluate the impact of liver transplantation on HCC-specific mortality rates in United States. IBM analysis (where the numerator is the number of HCC-specific deaths linked to a prior HCC diagnosis, and the denominator is the person-time in the

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general population), which differs from traditional survival analysis, incorporates both incidence and mortality data and is able to decompose population–level mortality rates according to specific cancer attributes (7). Because the 5-year cumulative probability of death following HCC diagnosis is around 95%, the authors utilized a 5-year burn-in period to capture all deaths due to HCC. In addition, the authors applied counterfactual methods to evaluate the impact of liver transplantation on population-level HCC-specific mortality rates, calculating the HCC-specific mortality rates for cases with localized cancer who did not receive liver transplantation and applying these rates to the person-time observed following liver transplantation. Therefore, it yielded the number of deaths that would have occurred among localized HCC cases who received liver transplantation if they had not received those transplants. Moreover, they applied joint analysis to provide a detailed time trend on HCC incidence, liver transplantation and IBM rates related to HCC. Finally, they took consideration of different calendar periods on participating cancer registries by conducting a sensitivity analysis on each individual cancer registry region, which helps illustrate the potential heterogeneity related to registry.

The primary finding from the IBM analysis was that population–level HCC-specific mortality would have been higher than that observed, in the absence of liver transplantation, but that the impact of liver transplantation on HCC-specific mortality at the population level was modest (liver transplantation was associated with a 0.5% reduction in the annual rate of increase in the IBM rate versus what would have been expected in the absence of transplantation for localized HCC; Mahale et al., **Fig. 4**; ref. 1). Specifically, HCC incidence increased between 1987 to 2017 at an average rate of 4.0% per year. Among all transplantations, HCC accounted for only 1% in 1987 but 40.0% in 2011 after Model for End-Stage Liver Disease (MELD) exception points were introduced. The proportion of all HCC cases who received a liver transplantation within 5 years of their diagnosis increased from 0.6% in 1987 to 15.5% in 2006 then declined to 12.4% in 2013. The IBM rate increased on average 2.9% per year, with the highest rate of change (annual percent change = 4.8%) observed among the subgroup of HCC patients with localized disease at diagnosis and eligible for liver transplantation. Without transplantation for localized HCCs, IBM rates for localized HCCs would have increased 5.3% annually instead of 4.8% annually. HCC-specific mortality among localized HCC cases declined for both liver transplantation receivers and liver transplantation non-receivers and the proportion of cases diagnosed with local stage HCC who receive a transplant has been declining since 2002 despite the increasing fraction of liver transplantation recipients that have HCC. However, the authors did not show whether there was potential age, sex and race/ethnicity disparity on these findings, which has been reported in previous studies (12, 13) and this information is very important to help guide the allocation of transplantation resource.

This is the first comprehensive study using TCM data, linkage of cancer registries and the SRTR, and using IBM methods to evaluate the impact of liver transplantation on population-level HCC-specific mortality rates. IBM rates for localized HCC are not increasing as steeply as the HCC incidence rate for localized HCC, indicating the improved survival over time among all patients with localized HCC. Meanwhile, they also applied a reliable algorithm to classify deaths as HCC specific to avoid the potential misclassification (14). Nonetheless, the study has some limitations. There was some mismatching for cancer registries and SRTR and 2% of cancer registry cases were reclassified to local stage cancers, which might potentially affect the final results. Notably, other curative treatment modalities for HCC, such as surgery resection and ablation were not taken into consideration in this study because cancer registry data did not differentiate multiple surgical procedures and the time order for these procedures.

On the back of improvement in mortality rates among non-liver transplantation patients, limited availability of liver transplantation and the continued diagnosis of many HCC cases at advanced stages (and therefore not qualifying for liver transplantation), this United States–based study demonstrated that liver transplantation has had modest impact on HCC-specific mortality at the population level. Given established differences in HCC incidence among subgroups of the U.S. population, future studies should take into consideration age, sex and race/ethnicity as potential effect modifiers on the effect of liver transplantation on HCC-specific mortality. These findings also highlight the need for prioritizing HCC screening and surveillance for early detection, as well; as the need for increased availability of liver transplantation for patients with HCC and other HCC curative-intent treatment modalities. We should also incorporate the prevention and treatment HCC risk factors, such as hepatitis C virus infection, alcohol abuse and non-alcoholic fatty liver disease, in the future HCC mortality research, so that a more comprehensive and precise network of HCC prevention, screening and treatment could be built and implemented in clinical practice.

Authors' Disclosures

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