The risk of *de novo* hepatocellular carcinoma still exists in the in the direct acting antiviral era

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Hepatitis C (HCV) has contributed substantially to the near doubling of hepatocellular carcinoma (HCC) incidence over the last 20 years. HCC represents the most common primary hepatic malignancy the 5th most common malignancy worldwide and the 2nd leading cause of cancer related death (1). HCC is the leading cause of death among patients with cirrhosis. HCC has the fastest growing death rate of any cancer in the United States (1). Currently, HCV is the leading indication for liver transplantation (LT) in the United States (2), without treatment HCV recurrence in the transplant allograft is nearly universal.

Successfully treating patients with HCV can lead to a sustained virologic response (SVR) and lower incidence of HCC. Research has shown that patients with SVR have lower recurrence rates compared to patients who do not achieve SVR (3). Interferon (IFN)-based therapy has demonstrated to reduce the risk of HCC in patients with cirrhosis (4,5). The estimated level of risk reduction in patients achieving SVR was 77% according to a recent meta-analysis among patients treated with IFN (5). Unfortunately, IFN based therapy is not suitable for patients with advanced disease, and often precludes use in patients with advanced liver disease listed for liver transplant. Prior to the release of DAAs many hepatologists would forego treatment in patients with advanced liver disease or require them to be listed for transplant prior to IFN based therapy.

Recently, direct-acting antivirals (DAA) have revolutionized HCV treatment and transplant outcomes. The rate of SVR in HCV patients treated with DAAs is in the vicinity of 95–98% (6). Furthermore, DAAs are better tolerated by patients with liver dysfunction, which may allow for treatment of patients at higher risk of developing HCC; such as patients with advanced liver disease. Therapy with DAAs is expected to lead to a progressive decrease in HCV-related HCC. Initially a cumulative increase of HCC may be observed because a longer at-risk period among older patients with treated HCV. The period at-risk for HCC development may be longer due to the lower risk of liver decompensation and the higher survival expectancy of cirrhotic patients with SVR following DAA therapy (7). With DAA treatment, achieving SVR may reduce the risk of HCC recurrence and occurrence (8,9). In addition, HCV treatment may result in improved liver health as evidenced by fibrosis regression, improvements in portal hypertension, and liver function (10). Importantly, HCC patients with prior SVR and compensated cirrhosis at the time of tumor diagnosis have prolonged overall survival than viremic patients (11). Therefore, DAA therapy may not only clear virus but also lead to better quality of life and overall survival. It is known that, even after SVR, the risk of HCC, although lower, persists mainly in patients already with cirrhosis (11). If patients treated with DAAs live longer there is more potential for HCC development, even if the virus is eradicated. Further research is needed to determine...
the appropriate HCC surveillance and characteristics that suggest increased risk.

Recent retrospective studies have questioned the safety of treatment with DAAs suggesting that DAA therapy is associated with higher HCC incidence and recurrence rates (12,13). A study by Reig et al. suggested that DAA therapy may increase the risk of HCC recurrence by reduced immune surveillance dysregulating the anti-tumor response allowing for the growth of microscopic HCC tumor clones (13). Conti et al. found that patients previously treated for HCC have still a high risk of tumor recurrence suggesting that DAA-induced SVR does not seem to reduce occurrence of HCC (12). Both studies created significant controversy with respect to the efficacy and safety of DAA therapy. The increase in the risk of HCC may have been confounded by a shift in demographics as well as the clinical presentation where older patients with more advanced liver disease are being treated. This could be related to the better tolerability of DAAs compared to IFN.

Recently, a meta-analysis found no difference in HCC incidence or recurrence following SVR from DAA and IFN-based therapy (14). Following statistical adjustment for study follow-up time and age, there was no trend toward higher risk for HCC in DAA treated patients (14). A study performed within the Veterans’ Affairs Health System found a 71% reduction in HCC risk, and no additional risk of HCC when DAA-induced SVR is compared to IFN based therapy (7).

In the current study Kwong et al. reported the association between HCC and listing era, specifically the incidence of de novo HCC in the DAA era (15). Those researchers conducted a retrospective analysis of registrants listed for LT in the Scientific Registry for Transplant Recipients database from January 2003 to December 2015. The authors divided patients into 3 eras based on listing date: Eras 1 [2003–2010], 2 [2011–2013] and 3 [2014–2015]. Era 3 is the era in which DAA based therapy became available. In order to ascertain incidence and not prevalent HCC, patients with HCC at listing or HCC exception within 180 days were excluded. The authors found the incidence of HCC was 49% higher in the DAA era. Additionally, multivariate analysis demonstrated a higher hazard of HCC in the DAA era compared to the earliest era (HR 1.22; 95% CI, 1.01–1.48). Importantly, after analysis adjusting for the competing risks of death and LT for HCC incidence, era was no longer associated with HCC (sHR 0.83; 95% CI, 0.69–1.00).

We believe this is an important study for the following reasons; firstly, this is one of the largest population-based observational cohort studies to describe HCC incidence among patients listed for LT in the United States. Importantly, the authors’ methods excluded prevalent HCC cases from the analysis within the limits of the SRTR data. Secondly, the data corroborate a rising incidence of HCC in patients with HCV. The higher HCC risk among patients treated with DAA can be explained by the fact that the patients are older and have more advanced disease when compared to patients treated with IFN (14). Thirdly, the competing risk analysis appropriately considers that waitlist candidates have three potential outcomes HCC development, LT and death. Conventional survival analysis would likely censor LT and death. Importantly, one of the reasons for the increase in HCC seen in the DAA era it that HCV patients have longer waitlist time, which highlights the importance of accounting for the competing risks. The longer at-risk period is evidenced by less frequent waitlist removal for death or being too sick to undergo transplant.

In summary, this study provides very important information. It recognizes the shift in patients’ demographics as well as the presentation and course of liver disease as potential risk factors for the increased risk of HCC in the DAAs era. Hence, the incidence of HCC amongst HCV patients with advanced cirrhosis, remains high. The controversy regarding HCC incidence and recurrence in patients treated with DAAs, remains a subject of debate. Meanwhile, we should all recognize the additional emphasis on close HCC surveillance in patients with advanced liver disease, especially as the age of transplant candidates increases.

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**Footnote**

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**References**


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