Received: 12 March 2019 | Revised: 12 March 2019 | Accepted: 2 April 2019

DOI: 10.1111/ajt.15389

EDITORIAL

Moving toward personalizing MELD exceptions in liver transplantation for hepatocellular carcinoma

Hepatocellular carcinoma (HCC) has become a leading indication for liver transplantation (LT) in the United States over the past 2 decades, accounting for nearly 25% of all LTs conducted yearly.[1] Access to HCC-related LT has been accomplished primarily through granting Model for End-Stage Liver Disease (MELD) exception points, which aim to balance the risk of death and waitlist dropout with post-LT HCC recurrence. Given the finite number of organs, this increase in HCC-related LT has come at the expense of patients with end-stage liver disease. Thus, in order to better balance waitlist dropout between HCC and non-HCC listed patients, MELD exception policies have undergone several changes since instituted in 2002.[2] Nevertheless, inequities exist in waitlist mortality and survival benefit from LT between HCC and non-HCC candidates.[3] Furthermore, all eligible HCC patients meeting Milan criteria (1 HCC less than 5 cm or up to 3 HCCs, each less than 3 cm) receive the same MELD exception prioritization, despite having variable rates of tumor progression, waitlist dropout, and post-LT recurrence based on their individual tumor biology. In the face of this inadequate one-size-fits-all paradigm, continual efforts are necessary to optimize prioritization for HCC patients.

To define characteristics of HCC-exception eligible patients that portend a low risk of waitlist dropout, Mehta et al[4] retrospectively analyzed the United Network for Organ Sharing (UNOS) database from 2011 to 2014. The authors restricted their analysis to regions with protracted average wait times for LT, and identified 4 independent predictors associated with low risk of waitlist dropout including Child Pugh A cirrhosis, MELD score <15, alpha fetoprotein <20, and a unifocal HCC 2-3 cm in maximum diameter. Patients meeting all 4 criteria comprised 11.9% of all HCC patients with MELD exceptions and had a lower risk of waitlist dropout (5.5% vs 20.0%; $P < .001$) and a higher intention to treat survival (94.0% vs 78.5%; $P < .001$) when compared to all other HCC patients at 1 year from listing. These criteria maintained good performance characteristics (c-statistic = 0.69) in a national validation cohort from 2015 to 2016, which included the period after the institution of the most recent MELD-exception policies requiring a 6-month waiting period prior to the granting of exception points. The authors conclude that patients with this lowest risk of dropout should receive less priority for LT than average-risk patients. This is compatible with a recent policy proposal from UNOS to exclude patients with a unifocal 2-3 cm HCC who demonstrate a complete radiographic response to locoregional therapy from attaining a MELD exception.[5] Although the policy was not ultimately adopted, the results of the analysis from Mehta et al suggest that it should be revisited.

There are, however, notable limitations to this analysis that should temper the conclusions from the authors. First, the UNOS database lacks important granularity, particularly dynamic changes on the waitlist and missing data on locoregional therapies. These deficiencies resulted in the proposal of a static model based solely on listing characteristics, which can be problematic. A "low-risk" patient with a single tumor, compensated liver disease, and low alpha fetoprotein at listing may develop declining liver function, new tumors, and rising alpha fetoprotein, which would limit application of locoregional therapy and/or alter their risk profile. Similarly, postlocoregional therapy decompensation may change the waitlist dropout in otherwise low-risk candidates. In these and other circumstances, a safety net framework would be necessary to salvage these patients. Second, the analyses included a large proportion of patients who did not receive locoregional therapy prior to LT. With utilization of pre-LT locoregional therapy now a universal practice in the era of a 6-month mandatory wait time HCC exception policy, and with forthcoming changes in the regional median MELD at transplantation, the result of this study may not apply entirely to contemporary HCC patient populations. Finally, deprioritizing these lowest risk HCC patients may lead to an "enrichment" of higher risk candidates, with the unintended effect of increasing the rate of post-LT HCC recurrence and consequently the risk of short-term mortality. A dynamic model simultaneously evaluating the evolution of both liver function and tumor burden over the waitlist period, although more complex, may ultimately be necessary to truly maximize the transplant benefit of scarce donor organs.

In summary, Mehta et al make a compelling argument that low-risk patients with HCC should have a for lower priority for HCC exception, which is a welcomed step to differentially prioritize HCC candidates based on individualized factors. Implementation of such a policy requires further data and modeling of its impact on waitlist mortality and access to LT. Ultimately, validation of better biomarkers of tumor biology through either direct sampling or noninvasive means (ie, circulating tumor cells, DNA methylation patterns, radiomics, and so on) may better guide transplant priority decision-making. While these technologies are being developed and refined, defining and deprioritizing low-risk HCC patients is a practical approach toward harmonizing benefits and risks for all patients on the LT waitlist.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

KEYWORDS

cancer/malignancy/neoplasia, editorial/personal viewpoint, liver transplantation/hepatology, waitlist management

Neehar D. Parikh[1]
Vatche G. Agopian[2]

[1]*Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan*
[2]*Division of Liver and Pancreas Transplant, David Geffen School of Medicine at UCLA, Los Angeles, California*

Correspondence
Neehar D. Parikh
Email: ndparikh@med.umich.edu

ORCID

Neehar D. Parikh https://orcid.org/0000-0002-5874-9933

REFERENCES

1. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2017 annual data report: liver. *Am J Transplant*. 2019;19(suppl 2):184-283.
2. Rich NE, Parikh ND, Singal AG. Hepatocellular carcinoma and liver transplantation: changing patterns and practices. *Curr Treat Options Gastroenterol*. 2017;15(2):296-304.
3. Berry K, Ioannou GN. Comparison of liver transplant–related survival benefit in patients with versus without hepatocellular carcinoma in the United States. *Gastroenterology*. 2015;149(3):669-680.
4. Mehta N, Dodge JL, Hirose R, Roberts JP, Yao FY. Predictors of low risk for dropout from the liver transplant waiting list for hepatocellular carcinoma in long wait time regions: implications for organ allocation [published online ahead of print 2019]. *Am J Transplant*. https://doi.org/10.1111/ajt.15353.
5. Prentice MA. Changes to HCC criteria for auto approval. OPTN/UNOS Liver and Intestinal Organ Transplantation Committee. 2016. https://optn.transplant.hrsa.gov/media/1922/liver_hcc_criteria_for_auto_approval_20160815.pdf. Accessed March 10, 2019.