

# The Impact of Allocation Changes on Patients with Hepatocellular Carcinoma



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## KEYWORDS

- Hepatocellular carcinoma • Organ allocation • Waitlist mortality
- Liver transplantation

## KEY POINTS

- Liver allocation policy for hepatocellular carcinoma (HCC) has continued to evolve steadily over the past 20 years.
- HCC exception candidates have been overprioritized relative to nonexception waitlisted patients, and model for end-stage liver disease inflation.
- National Liver Review Board and Acuity Circle model represent a recent, significant change in the liver allocation system, and the net effect for patients with HCC is uncertain but potentially may ameliorate differences in access for HCC and nonexception patients awaiting LT.

## INTRODUCTION

In the United States, mortality for HCC has increased faster than for any other tumor primarily due to cirrhosis from hepatitis C virus (HCV) as well as other causes such as alcohol, nonalcoholic fatty liver disease (NAFLD), and HBV.<sup>1,2</sup> Although recently the age-adjusted incidence rates seem to be plateauing, the combination of the high disease incidence with the demonstrated effectiveness of liver transplantation (LT) as a treatment of HCC and an allocation policy that prioritized patients with HCC has led to HCC being the most common indication for LT in the United States.<sup>3</sup>

The observation that HCC is now a leading indication for LT is especially notable because the initial experience of LT for patients with HCC was associated with such poor outcome that in 1989 the Department of Health and Human Services listed HCC as a contraindication for LT.<sup>4,5</sup> The early dismal outcomes led to the conclusion that LT was not an acceptable treatment of HCC, although notably LT was used only as a therapy for last resort for those with very extensive tumors. However, patients undergoing LT for other indications noted to have incidental tumors in the explanted liver

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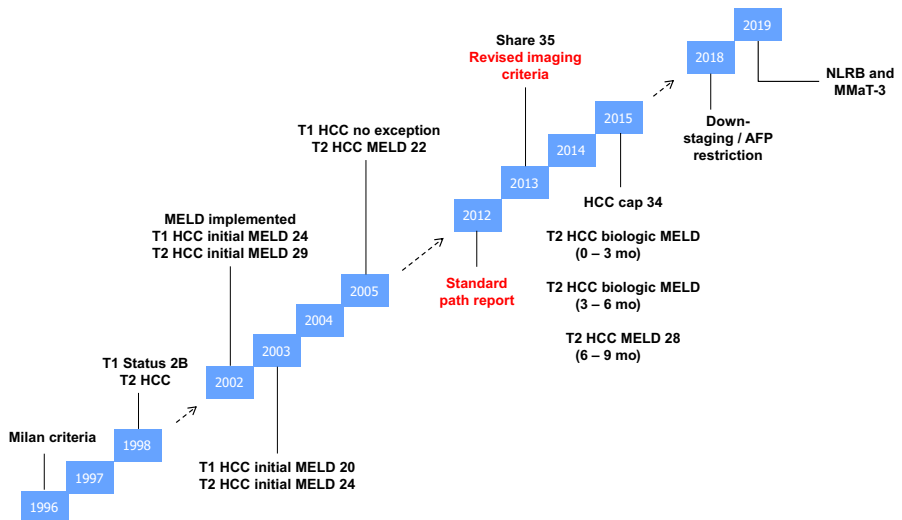
demonstrated low recurrence rates and good survival, suggesting that patients with limited tumor burden may benefit from LT. The landmark publication from Mazzaferro and colleagues<sup>6</sup> in 1996 demonstrated 83% recurrence-free survival and 75% actuarial survival at 4 years for patients undergoing LT for HCC within the Milan criteria (1 tumor between 2–5 cm or 2–3 tumors between 1–3 cm), defining the importance of patient selection and also establishing LT for unresectable HCC as a standard of care.

However, a major remaining challenge is the availability of deceased-donor organs. Because of the extreme shortage, a system of allocation is required. Before 2002, the allocation of deceased donor livers was based on waiting time and medical status (measured by the Child-Turcotte-Pugh score as well as hospitalization/intensive care unit status) and did not offer any additional priority for patients with HCC.<sup>7</sup> Thus, access to transplantation for HCC was very limited as the patient's HCC would progress while their liver function remained relatively stable and priority for transplant remained low. With the adoption of the model for end-stage liver disease (MELD) allocation system, which included additional prioritization for patients with complications of cirrhosis such as HCC, access was markedly improved.

As depicted in **Fig. 1**, the system has undergone multiple revisions to the priority granted for HCC patients, as well as other system enhancements such as a standardized pathology form and standard imaging criteria. More recent changes are anticipated to have a more notable impact on patients with HCC, including the adoption of standard down-sizing criteria, the development of a national liver review board, and the revision of the distribution of allocated livers to a circle-based system, and will require close monitoring.

### **Evolution of Hepatocellular Carcinoma Liver Allocation Policy**

The MELD-based system for allocation of deceased donor livers was adopted in the United States in 2002 and has been associated with a decrease in waitlist mortality and an increase in post-LT survival.<sup>8,9</sup> This system was updated to include sodium in 2016, which has led to a further decrease in waitlist mortality without any impact



**Fig. 1.** OPTN/UNOS HCC policy timeline.

on post-LT survival.<sup>10,11</sup> Patients with HCC as well as other complications of cirrhosis and certain metabolic conditions have an increased mortality risk without access to timely LT, which is not predicted by their calculated MELD or MELD-Na score. Therefore, they are allowed to receive assigned MELD scores commonly referred to as MELD exception scores. Since inception, the MELD system has continued to evolve through multiple revisions as summarized in **Fig. 1**.

The process of awarding exception scores for HCC in the United States is automated for patients whose tumors are within designated criteria. Historically, assigned MELD score exceptions for HCC meeting standard criteria were set at a score intended to reflect a 15% risk of waitlist drop out over a 3-month period, and this score increased every 3 months by a value anticipated to reflect a 10% increased risk of mortality without transplantation. Patients who did not meet standard criteria for HCC could still receive an MELD exception score through a process of appeal to a regional review board system, similar to the process for patients with other indications for MELD score exception that are not covered by allocation policy. Although nearly 70% of MELD exception scores are granted for patients with HCC, there are 6 additional policy-based diagnoses for patients meeting specific criteria (hepatopulmonary syndrome, hilar cholangiocarcinoma, familial amyloidosis, primary hyperoxaluria, portopulmonary hypertension, and cystic fibrosis) who also receive policy-based MELD exception scores.

### ***Problems with the Hepatocellular Carcinoma Exception System***

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Following the adoption of the exception point policy, challenges have arisen. It was immediately identified that the initial scores for patients with HCC were too high and they were reduced twice with T2 HCC starting score going from 28 down to 25, then to 22 and the priority for T1 being eliminated altogether.<sup>12–14</sup> Even with these downward adjustments, with ongoing monitoring it was still evident that patients with HCC were transplanted at a much higher rate than non-HCC patients and removed from the list at lower rates.<sup>15–17</sup>

Another issue that potentially may be related to the system of MELD score exceptions is MELD inflation. Until very recently, there has been a steady increase in the median MELD score at the time of transplant across all regions. In a compelling manuscript by Northup and colleagues,<sup>16</sup> the investigators link the steady increase in the MELD score needed to access transplant to the increased numbers of patients transplanted with exception scores. They proposed the increasing MELD score may be due to the fixed thresholds for exception patients, which included a large number of patients who are relatively stable, and required those with calculated score to increase higher than these thresholds in order to access LT.

Finally, it was noted that there was significant variability in the approval of MELD exception points by regional review boards for patients with HCC not meeting criteria. Some regions were approving patients who had been successfully downsized from UCSF criteria, whereas other regions did not require downstaging. Still others were not allowing any exceptions for patients beyond Milan criteria. There were also concerns about different rates of approval for nonstandard indications for exceptions across the different regions and additional concerns about inefficiencies and delays, as well as concerns about lack of expertise, particularly for pediatric waitlist candidates, and the potential for there to be a conflict of interest when reviewing cases within the same allocation region.

### ***Policy Solutions: National Liver Review Board***

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The overprioritization for patients with HCC was addressed by the “cap and delay” policy revision, which was adopted in 2015.<sup>18</sup> This revision added a 6-month waiting

period before patients could be transplanted based on their assigned HCC exception score; although the score granted after 6 months was MELD 28, the same exception score as they would have had after 6 months under the prior system, which avoided further disadvantaging of patients waiting in high-MELD regions, yet importantly, allowed for biological selection by delaying access to transplant.<sup>19</sup> A recent analysis of transplant rates for patients with HCC and those without HCC in the United States before and after the policy change determined that HCC candidates had a 37% lower risk of waitlist mortality/dropout prepolicy and a comparable risk of mortality/dropout postpolicy and concluded that the revised policy established equity between HCC and non-HCC waitlist candidates.<sup>20</sup>

Addressing the issues of MELD inflation and inconsistent approaches by regional review boards for patients with HCC and those without HCC required more significant change. First, in December 2017, a national downstaging policy was created, incorporating downstaging criteria initially proposed by UCSF to define the allowable tumor burden before downstaging treatment (1 lesion between 5–8 cm; 2–3 lesions with at least one greater than 3 cm although none greater than 5 cm and sum of all less than 8 cm; 4–5 lesions all less than 3 cm and sum <8 cm), as well as a cap on the maximum alpha-fetoprotein at 1000 ng/mL (influencing waitlist and post-LT outcomes).<sup>21</sup> This policy created a standardized approach applied across all regions for patients initially presenting with HCC beyond Milan criteria.

Following the adoption of a unified approach to downstaging, the National Liver Review Board (NLRB) was adopted in May 2019. The primary goal was to improve consistency and efficiency in the allocation of MELD exception points across the United States. However, because it was necessary to set scores using a national board even though there are regional differences in the scores needed to access transplantation, the scoring system was also revised to one that is based on the median MELD at transplant in the area of distribution where the patient is listed.

The newly adopted NLRB has 3 distinct boards:

- Adult HCC: staffed by reviewers with special interest in HCC in order to handle HCC exception requests that do not meet standard exception policy criteria
- Adult other: to address non-HCC adult exception requests
- Pediatric: staffed by reviewers with pediatric expertise

Each case will be reviewed by 5 randomly assigned reviewers from the appropriate board and requires a supermajority (4/5) for approval. Centers with an approved pediatric program may have a representative on the pediatric board, whereas adult centers may provide representation to both the HCC and the adult other boards. If the case is denied, the center may appeal in writing to the same group of 5 reviewers, providing any additional data/information to support their appeal. If the appeal is still not approved, the center may request a conference call with a separate group of pre-selected reviewers called the appeal review team (ART). The ART consists of NLRB reviewers who are expected to serve a 1-month term. If the case is still not approved, the transplant center may appeal to the OPTN Liver/Intestine committee, which is the same final step as under the previous regional review board system.

In addition to changing the structure to 3 separate boards focused on specific content areas, the review process for the 6 other policy-based diagnoses became an automated process done via computer, as it already had been for HCC, instead of requiring a manual review by the chair of the regional review board. In order to try to improve the consistency of the review boards, guidance documents addressing the most common nonpolicy-based scenarios were created for the board and centers to reference when considering or preparing nonpolicy-based exception requests,

including for patients with HCC not meeting policy criteria. However, it is anticipated that the most significant change for patients with HCC is that with the adoption of the NLRB, the MELD scores assigned to exception points are now set at a fixed value (currently set at  $-3$ ) relative to the median MELD score at transplantation (MMA<sub>T</sub>) for the area of organ distribution for the transplant center where the patient is listed, which until February of 2020 was the median for the donor service area. Transplants performed using nationally shared allografts, allografts from DCD donors, and allografts from living donors are excluded from the calculation of MMA<sub>T</sub>.

The purpose of this is 2-fold. First, given that the review board is now a national instead of regional system, it allows the initial awarded score for both policy and nonpolicy-based exceptions to be adjusted to the score needed to access transplantation where the patient is listed. It is also hoped that this fixed point system will reduce or at least prevent further escalation in the MMA<sub>T</sub> and will hopefully also further reduce the imbalance in transplant rate between patients with and without exceptions. The median MELD is recalculated for each center every 6 months based on the prior 12 months of data.

### ***Acuity Circle Model***

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Geographic disparity in access to transplantation has been noted for decades and affects both patients with and without HCC. Following an OPTN Board directive in 2012, the Liver-Intestine Committee began in earnest to attempt to create a system that reduced variability in access to liver transplant. After a very arduous process, a circle-based model of distribution which creates a series of progressively larger circles around the donor hospital was adopted in February 2020. After offering the liver broadly for Status 1A/1B patients, the Acuity circle model then reverts to a 150 mile circle around the donor hospital for patients with an MELD score of 37 to 40. The system only requires sharing over larger circles if the liver is not accepted for a patient within the smaller circle and thus provides an attempted surrogate for population-based circles. The liver is then offered to patients with MELD 37 to 40 within 250 miles of the donor hospital, then 500 miles of the donor hospital. If no suitable patient is identified, the liver is then offered back to the smaller circle for MELD 34 to 36, then if not accepted, it is offered to the 250 nm and subsequently the 500 nm circles for MELD 34 to 36. This continues for MELD 29 to 33 and then for MELD 15 to 28 before being offered nationally. Because the donor service area is no longer the unit of distribution, the calculation of the median MELD at transplant is based on a 250 nm circle around the transplant hospital.

Going forward, it may be necessary to further adjust the size of the circles depending on the performance of the new system, and this adjustment may ideally be made according to population density rather than uniformly being applied across the United States. An additional issue created by the new system, which is specific to exception patients, including those with HCC, is that because organ distribution is based on a circle around the donor hospital, while the MMA<sub>T</sub> is based on a 250 nm circle around the recipient hospital, there will be situations where patients listed at different transplant centers with an exception score for HCC will have different exception scores for the same organ offer even though they both may be within 150 miles of the donor hospital and they both may have been waiting for the same amount of time. Patients from transplant center A will still be eligible for different organ offers from donor hospitals located, for example, north and west of transplant center A, which would not come within 150 nm of transplant center B, which is located east and south. However, it is unknown whether this system will ultimately provide equitable access given that centers and populations are not evenly distributed. A potential revision recently

proposed is to generate equivalent MMaT scores for each donor match run by taking the highest, lowest, or average MMaT for all transplant centers contained within the distribution circle. Although this may be more complex from a programming standpoint, it would allow patients with the same exception score diagnosis to be ranked according to time at score for each organ offer. Consideration for adopting a national MMaT has also been proposed although this would underprioritize HCC in the higher MELD areas and overprioritize HCC (relative to patients without HCC) in the low-MELD areas.

## SUMMARY

Liver transplantation for HCC within defined criteria is an optimal treatment modality, as it addresses both the tumor and also underlying cirrhosis. The cap-and-delay policy has reduced the disparity in access between patients with and without HCC, thus potentially increasing the waiting times for patients with HCC and thus making the role of bridging therapies and living donor liver transplantation more prominent. The creation of national downstaging policy has standardized the approach for patients presenting with HCC beyond Milan. The adoption of the NLRB is expected to increase efficiency and consistency, whereas the new scoring system may reduce MELD inflation and MELD scores overall. However, with the adoption of the Acuity circle model in February of 2020, the calculation of the MMaT moved from a DSA-based calculation to a circle around the transplant center model, creating some match runs where patients have different scores for the same diagnosis, even if they have the same waiting time at that exception score. Thus, it remains essential to have the continued engagement and collaboration of members in order to optimize the new policy through innovative solutions to issues that will continue to arise. A potential next step may include artificial intelligence and machine learning techniques as analysis tools to further optimize the system.

## DISCLOSURE

The authors have nothing to disclose.

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