



Striving for more just allocation of liver allografts between patients with and without hepatocellular carcinoma: successes and challenges

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Purpose of review

Recently the United Network for Organ Sharing (UNOS) adopted new rules for the allocation of liver allografts for recipients with hepatocellular carcinoma (HCC) in hopes of removing regional variation in HCC practice and regional differences in patient survival. Understanding how previous changes to HCC allocation have both succeeded and failed to match the pretransplant mortality of HCC and non-HCC patients on the waitlist will help us to better evaluate these changes and predict where we may again fail.

Recent findings

Previous revisions of the HCC allocation rules were successful in more accurately matching the waitlist mortality of HCC and non-HCC patients. Efforts to select for less aggressive tumor biology have resulted in better disease free and patient survival. Several articles have also supported the practice of using locoregional therapies to downstage the patients to within Milan criteria. New rules seek to reduce the amount of geographic disparity in the allocation system.

Summary

Over time UNOS has steady improved the liver allocation policies to attempt to match pretransplant mortality for patients with HCC and without HCC. The latest changes to the organ allocation rules succeed in implementing some of these best practices. However, one can also predict several ongoing challenges to fair allocation that may not have been addressed by recent changes.

Keywords

hepatocellular carcinoma, liver transplant, organ allocation

INTRODUCTION

Liver transplant is an efficacious cure for many cases of hepatocellular carcinoma (HCC). For HCC that has not spread outside the liver, transplant offers several advantages over either liver resection or locoregional therapy, including: complete curative resection, the ability to address multiple lesions simultaneously, and the treatment of unidentified synchronous lesions [1]. For patients with HCC that falls within Milan criteria [2], it is widely accepted that liver transplant is treatment of choice and offers superior patient and disease-free survival. However, unlike the mortality related to the patients' underlying cirrhosis, the risk of death or waitlist dropout from HCC is not reflected in the patient's model of endstage liver disease (MELD) score. Thus, United Network for Organ Sharing (UNOS) developed a policy of granting MELD exception points for patients with HCC to allow them to compete for organs with other listed patients. Over time, the system of granting exception points has been

revised in the hope of matching the risk of pretransplant mortality between HCC-exception patients and the other patients on the list. Recently, UNOS adopted a new policy for HCC allocation which hopes to address the regional variations in practice and mortality [3]. Although the HCC allocations changes were introduced with changes in the overall distribution of liver allografts, the distributional changes have been blocked in the courts. The purpose of this review is to recap the history of the UNOS rules guiding organ allocation for HCC patients in the United States, describe the new rules of allocation, and discuss how well the new policy is

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KEY POINTS

- The UNOS rules for allocating liver allografts have been revised multiple times to reduce the access advantage that HCC patients receive over non-HCC patients.
- The rules now designate a 6-month wait time prior to granting MELD-exception points for HCC patients, which has shown to improve posttransplant outcomes.
- The newest rules standardize the criteria for downstaging patients to allow more patients to qualify for HCC exception points.
- The rule revisions have not sought to address concerns that the Milan criteria may be too restrictive.
- The newest rule revision may create new challenges, in that, it is likely to offer dramatically different access to organs for patient with different blood types and in to patients who reside in areas with different levels of competition.

set to meet the goal of providing fair access for liver transplant to patients with and without HCC.

HISTORY OF UNITED NETWORK FOR ORGAN SHARING POLICY FOR HEPATOCELLULAR CARCINOMA EXCEPTIONS

Prior to 2002, potential liver transplant recipients with HCC were listed with their native MELD scores (Table 1). In 2002, all patients within Milan criteria were granted MELD exception points and listed with either their native MELD score or their exception MELD score, whichever is higher. 29 points were allocated to all patients with a T2 lesion (single tumor >2 and <5 cm), or up to three tumors as com as they were all under 3 cm, no macrovascular invasion and no extrahepatic disease [2]. 24 points were granted to patients with a T1 lesion (single lesion >1 and <2 cm). One year later it was determined that this allocation policy unfairly advantaged HCC exception patients and the scores were revised to 24 exception points of T2 lesions and 20

exception points for T1 lesions. In 2004, it was determined that a survival advantage was not present for patients with T1 lesions and the lower exception score was dropped.

In 2005, it was recognized that the risk of tumor progression for patients with HCC was not a static risk but one that worsened over time. As system was adopted that granted 22 exception points at the time of listing and a subsequent increase in exception points granted every 3 months, if the disease did not progress on subsequent imaging. There was no cap on the maximum allocation score (other than the cap of 40 for all patients).

In 2015, two substantial changes were made. The first was a recognition that some degree of wait-time prior to transplant helps to predict tumor biology and improve long-term survival after transplant [4,5]. It was determined that a minimum 6-month period without disease progression should be utilized prior to transplant and patients would not receive any MELD exception points until 6 months after listing. It was also determined that the mortality from HCC never approaches the mortality rates of very high MELD patients waiting for an organ [6] and a maximum exception score of 34 points was added into the system.

In 2019, UNOS set out to revise the entire liver allocation system to eliminate the use of donor services areas (DSAs) as arbitrary geographic boundaries to transplant and to reduce the regional disparities in organ availability. The majority of these changes were blocked by the courts and are outside the scope of this review. However, as part of this major overhaul of the allocation system, significant changes were made to the rules for HCC exception. The most substantial change was a recognition that the median MELD score at transplant varies widely in different portions of the country. Thus, HCC exception points were not set at an arbitrary value but set at score that varied depending on the local availability of organs. Specifically, according to the new rules, patients with T2 HCC disease are awarded points equal to the median MELD score in the DSA minus 3. Every 3 months, UNOS calculates the

Table 1. Rules regarding hepatocellular carcinoma allocation in the US over time.

Year implemented	Initial exception score for T2 (within Milan) lesions	Mandatory wait time	Score escalation	Maximum possible score
2002	29 (24 for T1)	None	None	N/A
2003	24 (20 for T1)	None	None	N/A
2004	24	None	None	N/A
2005	22	None	3 Points per 3 months	None
2015	28	6 Months	3 Points per 3 months	34
2019	Median MELD – 3 points	6 Months	None	N/A

median MELD score at transplant in a DSA for the last 2 years. All patients who meet HCC exception criteria are granted this score minus 3. The mandatory 6-month wait-time was preserved and no escalation points are given [7].

The new rules also created a national liver review board to eliminate regional variations in the granting of MELD exception points for HCC [8]. This change was aimed at reducing regional variation in the granting of exception points for patients who do not meet standard criteria (i.e., within Milan). Several regional review boards would allow patients who initially presented outside of Milan criteria to be listed with exception points if the patient's tumor responded to locoregional therapy. The new rules establish a National downstaging protocol to recognize this practice. Under the new criteria, patients are eligible for MELD exception point if they present beyond T2 disease but with a single lesion less than 8 cm, two to three lesions less than 5 cm and a total less than 8 cm, or four to five lesions less than 3 cm and total less than 8 cm. Vascular invasion and extrahepatic disease are also exclusion criteria. Patient's alpha-fetoprotein levels must also be less than 1000. The patients then have to undergo any available locoregional therapy and get to residual disease within Milan. The patients must remain within Milan for 3 months before they are granted the exception points.

EVIDENCE THAT CHANGES IN ALLOCATION HAVE TRENDED TOWARD FAIRNESS OVER TIME

Changes in allocation have reduced the access advantage for hepatocellular carcinoma patients over nonhepatocellular carcinoma patients since implementation

Since the original HCC exception policy, HCC patients have been advantaged compared with rest of patients on the waitlist [6,9^{***}]. However, the changes that have previously been implemented have trended toward fairness. A systemic review of the Scientific Registry of Transplant Recipients database showed that HCC candidates before 2015 were 3.6 times as likely to be transplanted as their non-HCC counterparts. After the changes in 2015, patients with HCC were only 2.2 times as likely to receive a transplant [9^{***}]. Simulation models of the new allocation system are not expected to change the overall mortality rates of patients with HCC but hope to reduce mortality for the non-HCC population [8]. Thus, the new system should continue to reduce this advantage but it is too early to tell how successful the new system will be.

Implementation of mandatory wait-times improves posttransplant survival

The most crucial change implemented in 2015 was the addition of mandatory wait-times before granting MELD exception points. Although Milan criteria selects for patients with a high recurrence-free survival, 10% of patients will still suffer from recurrent disease [10]. The initial size of the tumor burden does not always reflect the tumor biology and some tumors are much more likely to spread. It is thought that a mandatory wait period of 6 months will help select against the most biologically aggressive tumors and reduce the rate of early recurrence. This theory has been supported by UNOS data which demonstrated that regions with short wait times have a 1.5 times risk of posttransplant mortality in HCC patients [11]. Likewise, multicenter data shows that patients who wait less than 6 months have three times the recurrence of those with wait-times between 6 and 18 months [12,13^{*}].

New criteria allow patients who present outside Milan to be eligible for transplant

The landmark article defining the 'Milan criteria' showed that overall survival (OS) of patients within the criteria have survival rates of 85% while those outside the criteria had survival rates of 50% [2]. These criteria became the selection criteria adopted by UNOS in 2002. Multiple studies have independently validated that posttransplant survival for patients with HCC are similar to those transplanted for other indications [14,15]. However, several subsequent studies have suggested that these criteria are too restrictive [14]. To work within the system, several US centers developed the practice of treating patients outside of Milan criteria with locoregional therapy to reduce the patient's disease burden. Radiofrequency ablation, transarterial chemoembolization, microwave ablation, radioactive bead embolization, and single beam radiation therapy have all been utilized to treat tumor burden. If the patients respond to these therapies and the post treatment burden is 'within Milan' and the disease did not progress over the next 3 months, the patients were considered down-staged and listed for transplant. Several regional review boards recognized this practice and granted MELD exception points to 'down-staged patients'. This approach revealed 5-year posttransplant survival of 80% which was comparable with patients who presented within Milan criteria [16]. A meta-analysis compiled by Parikh *et al.* [17] nicely compiles the data in support of this approach. In terms of posttransplant survival, this system has also been rigorously studied and compared with competing models of allocation.

The current allocation system is predicted to achieve a 5-year posttransplant OS advantage of 80%. It compares favorably with other models which have been published. These comparisons are nicely reviewed in Mehta *et al.* [18].

One of the most important changes in the 2019 allocation system is the adoption of this practice on a national level with clear guidelines for exception point eligibility. Adopting this practice nationally should dramatically expand the number of patients who are eligible for transplant with HCC.

The new allocation policy addressed regional differences in organ availability that subjected hepatocellular carcinoma patients to different levels of advantage in different parts of the country

One of the current challenges to liver organ allocation is the overall disparity in organ availability in different parts of the country. One way to measure this disparity is the median MELD at transplant. In areas with more potential recipients or less potential donors the patients must get significantly sicker to receive an organ. UNOS published the median MELD at transplant for all the DSAs currently utilized as geographic boundaries for organ allocation. The median MELD at transplant varied from 21 to 35 [19]. Because, the exception MELD scores utilized prior to 2015 were the same no matter which region of the country the patient was listed in, HCC exception patients had disproportionate access to organs in areas with lower median MELD scores at the time of transplant (i.e., areas with lower demand for organs). This trend toward quicker transplant for HCC patients in lower MELD areas has been documented in several studies [11,13[¶]]. The new liver allocation policy hopes to resolve this policy by assigning every HCC patient with a median MELD score for their DSA minus 3. This should allow HCC patients to compete for organs but not outcompete the sickest patients on the transplant list. This system also has the advantage of allowing the score to adjust over time. Thus, the relative competition between HCC and non-HCC patients will be consistent over time, as well as, consistent across the nation.

AREAS OF CONCERN THAT HAVE NOT YET BEEN ADDRESSED BY THE CURRENT SYSTEM

The Milan criteria may be too restrictive

Although there is an ample amount of evidence suggesting that patients within Milan criteria have excellent posttransplant outcomes, it is less well established that patients who are modestly outside

Milan would not. In fact, several groups have reported different selection criteria that also yield satisfactory results [14]. As discussed above, the practice of downstaging patient has allowed more patients to qualify for transplant and the widespread adoption of this practice should increase access to transplant. However, further study is warranted to insure that we are not denying patients who would benefit from transplant.

Patients with different blood types have dramatically different access to organs with the recently adopted MELD exception scores

The move to set MELD exception scores based on regional differences in organ access should reduce the disparity in access for HCC patients across different regions. However, within all regions there is also significant variability in organ competition based on blood type. Because the organ allocation system allows blood type O organs to be utilized for high MELD B patients, and both A and B organs can be utilized for AB patients there has been a gradual shunting of organs from the O and A blood groups to the B and AB groups. This has led to a significant difference in the MELD at transplant between these groups. O and A patients demand a significantly higher MELD score to compete for organs. On the contrary, this variation was not acknowledged or addressed in the latest rule revision.

Since patients are assigned exception points based on the median MELD for the region, regardless of blood type, patients with HCC in the B or AB blood group have much greater access to liver allografts than patients in the O or A blood groups. This disparity could easily be addressed by assigning blood-type-specific median MELD scores for each region.

The new system may trade a score-based bias for a competition-based bias in hepatocellular carcinoma allocation

Although the new system was developed with the goal of reducing regional variability in access to organs, it may be less effective than planned because the other planned changes to the organ allocation system have not been implemented. The original plan was couple the changes in HCC allocation with broader sharing of organs based on geographic distances rather than the arbitrary DSA areas that are held over from the past. The introduction of the new HCC score, utilizing the median MELD minus 3, was predicted to give HCC exception patients intermittent access to quality organs when the local and regional demand for organs was lower than average. However, this new system may replace a score-based bias (where HCC is more competitive is lower MELD

areas), with a competition based bias. Hypothetically, DSAs and regions with more patients and more competition for organs will see less quality organs fall to median MELD-3 than DSAs and regions with less competition. Since the broader sharing proposal has been delayed in the courts, there will remain a significant competition variance between DSAs [20]. One would predict that areas with less competition will yield better access for HCC patients that more competitive regions. This should be a focus of future study as we determine the effectiveness of the new policy.

CONCLUSION

Over time the changes in liver allocation for HCC patients have made significant progress in seeking to match the survival of HCC and non-HCC liver patients on the liver transplant waitlist. By studying the successes and failure of previous allocation systems and anticipating new challenges, we are better prepared to assess the effectiveness of the newest changes to the system.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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