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Minireview

Toward a Better Liver Graft Allocation That Accounts for Candidates With and Without Hepatocellular Carcinoma

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In some countries where the Model for End-Stage Liver Disease (MELD) score is used for graft allocation, selected patients with hepatocellular carcinoma (HCC) receive a fixed number of exception points at listing, and increasing priority on the list by accruing additional exception points at regular time intervals. This system originally aimed at balancing the risks of HCC patients of developing contraindications and of non-HCC patients of dying before transplantation, is not ideal because it appears to offer an advantage to HCC patients, regardless of tumor characteristics and response to loco-regional treatment. Scores modulated by HCC characteristics have been proposed. They are based on a more refined estimate of the risk of pretransplant drop-out or of the posttransplant transplant benefit expressed as the life-years gained for each graft. This review describes the newly proposed systems, and discusses their advantages and drawbacks. We believe that the current exception points allocation should be revised and that drop-out-equivalent or transplant benefit-equivalent models should be studied further. As with all policy changes, these should be done under close monitoring that allows subsequent revisions.

Abbreviations: AFP, alpha fetoprotein; deMELD, drop-out equivalent MELD; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; OPO, organ procurement organization; OPTN, Organ Procurement and Transplantation Network; UNOS, United Network for Organ Sharing

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Current Allocation Systems

Many organ allocation systems around the world have implemented the Model for End-Stage Liver Disease (MELD) system for the allocation of liver grafts for patients with chronic nonmalignant (i.e. non-hepatocellular carcinoma [HCC]) liver disease (1,2). The model is based on international normalized ratio, bilirubin and creatinine, and predicts the probability of death at 3 months. Despite some drawbacks, MELD-based liver allocation meets the goal of having a relatively simple, accountable and transparent system. The introduction of the MELD system has been associated with increased transplantation rates in most areas of the world while maintaining acceptable posttransplant outcomes for patients transplanted with cirrhosis (3).

In parallel to the introduction of MELD, the transplant community has seen an increasing demand for listing patients with HCC, promoted by the excellent results for transplantation of patients with early stage HCC (defined by restrictive criteria, such as Milan Criteria) and further enhanced by the acceptance of some carefully expanded criteria showing preserved posttransplant outcomes (4–6). Currently, the proportion of patients transplanted for HCC exceeds 40% in some areas of the world.

Because most patients with HCC are more likely to progress to advanced cancer stages before their cirrhotic liver disease becomes a significant mortality risk, the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) developed a method to offer an exception to pure laboratory value-based MELD allocation by assigning additional MELD points for documented HCC within Milan Criteria. Under the current OPTN/UNOS system, all T2 HCC patients (patients within Milan criteria, having at least one nodule $\geq$2 cm) receive 22 points at the time of listing if they meet imaging criteria (7). HCC patients gain additional priority every 3 months if they continue to meet criteria by being granted increases in

Table 1: HCC exception point models in use in selected liver allocation systems

OPO	Countries/centers	Exception points at listing	Exception point progression	Qualifying for exception points
OPTN/UNOS	USA	22 points at listing	Add point equivalent to a 10% increase in candidate mortality every 3 months	T2
Eurotransplant	Austria, Belgium, Luxembourg, Germany, the Netherlands, Slovakia, Croatia	22 points at listing	Add point equivalent to a 10% increase in candidate mortality every 3 months (according to Table 2)	T2
Human Organ Procurement and Exchange Program	Alberta (Canada)	22 points at listing	Add two points every 2 months	TTV/AFP, except T1
Human Organ Procurement and Exchange Program	Ontario (Canada)	22 points at listing	Add three points every 3 months	TTV/AFP, except T1
Brazil	Brazil	20 points at listing	Increase to 24 at 3 months and to 29 at 6 months	T2
Organització Catalana de Trasplantaments	Catalonia (Spain)	19 points at listing	Add one point every 3 months	Single HCC <3 cm and AFP >200 ng/mL, or single HCC ≥3 cm and <5 cm, or two or three HCCs ≤3 cm
Swisstranplant	Switzerland	14 points at listing	Add 1.5 points every month	All patients qualifying for transplant (according to centers)
Agence de la biomédecine	France		Flexible model taking into account MELD, time on the list and distance between the retrieval and transplantation locations	T2, excluding patients with AFP score >2[1]
Nord Italian Transplant	Italy	No exception points	System under assessment	

AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; OPO, organ procurement organization; OPTN, Organ Procurement and Transplantation Network; TTV, total tumor volume; UNOS, United Network for Organ Sharing.
[1]According to Duvoux et al Gastroenterology 2012; 143: 986–994.
T1: 1 HCC <2 cm; T2: 1 HCC ≥2 cm and <5 cm or 2–3 HCCs <3 cm.

MELD score equivalent to a 10% increase in the candidates' theoretical risk of mortality (Table 1 and Figure 1, www.unos.org). Several other organ allocation systems have adopted similar MELD exception point systems with or without minor modifications, including Eurotransplant (http://www.eurotransplant.org), the largest Canadian programs, Brazil and Switzerland (8,9). The French model is more complex and includes variables such as MELD, time on the list, and distance between the retrieval and transplantation locations (www.agence-biomedecine.fr) (Table 1). These exception point models have provided a framework for including patients who do not have a high short-term risk of dying of their intrinsic liver disease into a mortality risk-based liver allocation system (10), but a number of limitations remain:

(1) HCC patients receiving priority under the US system have been consistently advantaged over non-HCC candidates, with a lower risk of drop-out (3.2–5.4%

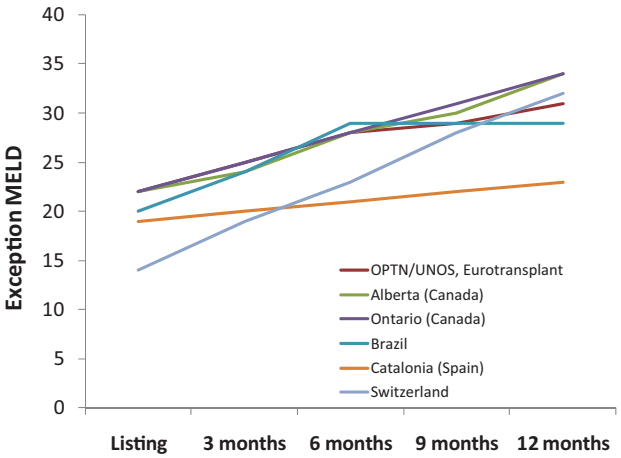

Figure 1: Waitlist exception Model for End-Stage Liver Disease (MELD) point progression in selected liver allocation systems.

Table 2: Proposed HCC characteristic-weighted allocation models

Score	Year of publication	First author	Proposed continuous model
HCC-MELD	2006	Freeman R.B.	$1 - 0.920\ \exp[0.09369\ (\text{MELD} - 12.48) + 0.00193\ (\text{AFP} - 97.4) + 0.1505\ (\text{size} - 2.59)]$
Adjusted MELD	2007	Piscaglia F.	MELD + stage score + waiting time score[1]
deMELD	2011	Toso C.	$-25 + 0.1 \times \text{age} + 1.6 \times \text{MELD} + 1.6 \times \text{size} + 1.3 \times \text{LogAFP} + 6$ if >1 HCC − 1 if HBV + 3 if alcohol + 3 if NASH + 1 if hemochromatosis + 1 if other liver disease
MELD-HCC	2013	Vitale A.	$1.27 \times \text{MELD} - 0.51 \times \text{LogAFP} + 4.59$
New deMELD	Unpublished	Toso C.	$-37.8 + 1.9 \times \text{MELD} + 5.9$ if HCC Nb $\geq 2 + 5.9$ if AFP $> 400 + 21.2$ if HCC size >1 cm

deMELD, dropout equivalent MELD; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease.
[1]Stage score: single HCC ≤ 3 cm = 5 points, single HCC >3 cm or multiple HCCs = 8 points, downstaging protocol = 12 points; waiting score = 1 × waiting time in months.

vs. 8.4–11.5% at 3 months) and a privileged access to transplantation (transplant rate of 46% vs. 29.3% at 3 months) (11–14).

(2) The arbitrary assignment of points to HCC patients needs to be reevaluated periodically because the mortality risk for standard MELD patients should be the number to which the HCC drop-out should be compared. Because the waiting mortality risk changes depending on the relative availability of donor organs (fewer organs or more candidates), HCC priority will need to be adjusted accordingly, and this relative availability of organs can vary both in time and between regions/centers (15). This point was highlighted in an analogy to a pharmacologic model where the rates of effective clearance (transplantation) and of toxic clearance (drop-out/death) of two competing pools of patients have to be maintained in equilibrium. HCC patients could potentially saturate the system when the scarcity of liver grafts lengthens the waiting time: they keep increasing their MELD points without dying, and accumulate at the top of the list. The recent experience documenting that an increasing proportion of candidates with HCC are receiving transplants in the United States, suggests that this may be happening to some degree already (16).

(3) In the US system the same number of points is given to all HCC (T2) patients, as if the risk of drop-out progressed evenly among HCC patients. HCC characteristics, including tumor size, tumor number and alpha fetoprotein (AFP) can approximate the risk of drop-out (13,17,18), and a score integrating these parameters appears desirable. As a future step, more sophisticated indicators, including molecular markers for favorable or unfavorable tumor biology, could be introduced in such a score (19–21).

(4) The modern waitlist management of HCC candidates includes close monitoring and loco-regional treatments (22,23), aiming at minimizing drop-outs and improving posttransplant outcomes (18,24). Recent studies have reported very low drop-out rates for patients with HCC lesions 2–3 cm who respond to loco-regional treatments as documented by complete radiologic and biochemical responses (18). There is no uniform policy as yet to address these results fairly in liver allocation systems.

The above-mentioned faults of the exception point models motivated the effort to move from a ''one size fits all'' approach and to seek alternatives, as detailed below.

Models Centered on the Risk of Drop-Out (Urgency-Based) Integrating HCC Characteristics

Description of the models

As a proof of concept, the Bologna group introduced an adjusted MELD model in 2003, to move away from the relatively arbitrary allocation of exception priority points for HCC candidates (Table 2) (25). The model was calculated by summing the laboratory defined MELD score, adding one point per month for waiting on the list, and a tumor score (Table 2). The model was designed as a trial-and-error construct and led to a higher probability of transplantation for patients with HCC compared to patients without HCC (25). In a subsequent version (2004), the number of points given to start was lowered. In addition, since 2005, T1 patients with a single HCC <2 cm were listed according to their laboratory defined MELD score only. The Bologna adjusted MELD score had the advantage of integrating HCC variables, but did not include AFP, an important predictor of drop-out, nor did it include the potential response to loco-regional HCC treatment (13,17,24). Also, the system gave priority to patients enrolled in downstaging protocols, a controversial point as recent evidence suggests that successfully downstaged patients have better long-term survival after transplantation, and have less urgency for transplant due to reduced risk for drop-out from the list. This balance between justice on the list and overall utility of organ transplantation for HCC patients remains to be resolved. Finally, the results of the recent adjustments of the Bologna system are still to be confirmed.

Other investigators have determined that variables such as AFP, HCC size, HCC number, and MELD itself independently predicted the risk of drop-out in cohorts from the OPTN/UNOS (13,17,18). Freeman et al were the first to assess MELD and HCC variables such as tumor size and AFP in a combined model (Table 2) (17). This model provided an estimate of the risk of drop-out (reported scores ranged from 0.034 to 1 (26)), and was validated externally (27). Of note, the score provided an estimate of the risk of drop-out for HCC patients only, and did not account for the competing risks of drop-out, transplantation and continued waiting that are all possible outcomes for patients on a liver transplant waiting list.

The group in Geneva proposed the drop-out equivalent MELD (deMELD) model; a dynamic urgency model that was calibrated on MELD so that HCC and non-HCC patients with the same deMELD and MELD scores, respectively, had similar risks of drop-out (12). In a first version, deMELD favored the transplantation of older patients, which introduced concerns in terms of utility, as older patients have lower expected posttransplant outcomes. In a revised version (new deMELD), only MELD and HCC variables (AFP, size and number) were included (14). Similar to deMELD, the new deMELD is calibrated on MELD, and increases in an incremental fashion according to the risk of drop-out.

Advantages

Under the current MELD exception systems (Table 1), the assigned priority points do not necessarily correspond to the patients' real risk of drop-out. To illustrate, US HCC patients who are—as a principle—given 22 points, in reality drop-out at a rate (2.7–6.3% at 3 months) similar to patients with calculated MELD scores of 11–15 (14). With the alternative models proposed, the risk of drop-out increases more realistically (it is calculated for each individual patient), and the accuracy is significantly improved (C-indices of 66.2–73.7% for new deMELD vs. 52.7–56.6% for exception MELD) (14).

In addition, models taking HCC characteristics into account (HCC-MELD, deMELD, new deMELD) allow updating the risk of drop-out according to the response to HCC treatment (28,29). To illustrate, a patient with two 3 cm-HCCs, calculated MELD 15 and AFP 410 ng/mL would have a new deMELD decreasing from 24 to 18 after local treatment if the AFP is reduced below 400 ng/mL (Table 2).

Disadvantages

Whatever the modifications, if the system seeks to be equitable in terms of providing equal access for both HCC and non-HCC patients, it must also prove that it provides at least the same amount of utility for both HCC and non-HCC patients. Some HCC variables predicting drop-out from the waiting list are also associated with poorer posttransplant survival and higher rates of tumor recurrence (26,29). In addition, the degree to which variables associated with drop-out influence survival depends, at least in part, on the duration of waiting time. Whatever system is implemented will need to be closely monitored over time so that both waiting list and posttransplant results are optimized and tumor recurrence is minimized.

Some investigators have suggested, to minimize the potential increase in the risk of posttransplant recurrence/death in HCC recipients who have aggressive, rapidly advancing biology or who do not respond to loco-regional treatment, a 3-month delay in assigning increased priority for HCC (12). This would decrease the risk of transplanting patients with rapidly progressing lesions, probably the strongest predictor of recurrence, and help to balance the tension between principles of urgency and of utility. Of note, the length of the ''no listing'' or ''no transplant'' period deserves better exploration; the 3-month limit was inspired by the proposed 3-month minimum waiting time after downstaging, but has not been formally evaluated (30,31).

The strongest potential disadvantage, however, concerns the gap from theory to practice: if the proposed dynamic scores were to be implemented, the most optimal results would likely be achieved if patients are managed with similar pretransplant loco-regional treatments, response monitoring and delisting criteria. Such practices should be enforced within each liver allocation system. They would be essential to help the very refined models detailed above achieve the principle of equity that they aim to respect (7).

Models Centered on the Transplant Benefit (Utility-Based) Integrating HCC Characteristics

Description of the models

The previously described models are based on the risk of drop-out (equity in urgency). They do not take transplantation outcomes into account, nor the impact of alternative therapies. Some investigators have therefore proposed that liver graft allocation would be better performed according to the principle of utility, such as represented by the number of life-years gained by transplantation, or better calculated as the transplant *benefit* (the number of years gained by the transplant *minus* the number of years offered by alternative treatments) (32–34). In non-HCC patients, transplant benefit has been used to demonstrate that patients with a MELD <15 may not improve their risk of death by receiving a transplant compared to remaining on the list (35). A transplant benefit calculation could also be used when a liver graft is available to help identify the candidate for whom there will be the maximum number of life-years gained for that liver graft (33,34).

As opposed to non-HCC patients, all HCC candidates appear to have a measurable 5-year survival benefit after transplantation (32,36,37). Vitale et al have developed a

MELD-HCC score using transplant benefit as outcome (Table 2) (38). The model is strongly and positively influenced by MELD, and marginally and negatively by AFP. The transplant benefit increased similarly across MELD and MELD-HCC strata, and the models could be used for the combined management of candidates with and without HCC. As an added tool, the authors also provide an equation calculating the maximum possible MELD/AFP combination in order to reach an acceptable 50% 5-year survival (38).

Advantages

A transplant benefit approach combines both pre- and post-transplant outcomes, integrates the results of alternative treatment strategies, makes obvious the survival targets that would be unacceptable for transplantation, and allows comparison between HCC and non-HCC patients. In principle, liver allocation systems based on transplant benefit are more relevant compared to models based on drop-out, and they underline that avoiding drop-out should not be the only aim in itself, and that long-term (at least 5-year, but ideally much longer) survival should be taken into account for liver allocation policy.

Disadvantages

Transplant benefit is based on the assumption that the survival probability for a specific patient and treatment is relatively uniform and predictable. Since these survival models are built on populations of patients, however, there will always be outliers for whom the survival models don't apply. Indeed, the consensus on the need for non-HCC-MELD exceptions already reflects the concern for outliers, and the system has to be flexible enough to take these exceptions into account (39).

Also, the current knowledge that allows to categorize patients into prognostic strata has to be improved: the model by Vitale et al was built using data for T2 HCC patients only, and the relevance of the score for other HCC patients, especially those with more advanced disease, has not been established (38). Also, their model only included AFP among HCC variables, which is not expressed in a large proportion of HCC patients, and may not accurately reflect the response to loco-regional HCC treatment (at least in patients with low AFPs) (40).

In addition, the model took remaining in the list as the only alternative to transplantation, rather than the full range of possible treatments, and was constructed on the basis of 5-year survival rather than on the 10–20 year horizon, two reasons probably skewing the transplant benefit in favor of more advanced stages (37).

It is clear that such models need to be refined if they have to replace the current, simpler allocation rules. If a survival benefit approach for HCC candidates is considered, long-term survival benefit results should match the results of non-HCC patients, possibly already implementing prerequisites such as 5-year survival in excess of 50%, or an acceptable recurrence rate of less than 15%.

Also, more generally, changing to a utility-based system such as transplant benefit for graft allocation would represent a radical change from the current practice, and may be difficult to accept by some patients who may be excluded from transplantation. In addition, current measures of utility often incorporate quality adjusted or disability adjusted life-years gained or lost as a measure of treatment efficacy. These measures are more desirable because they take patient preferences into account; however, they become increasingly complex and opaque. The more objective, straightforward an allocation system, the more transparent and accessible it will be for patients and donors who ultimately must have confidence that the system is fair.

Summary and Future Perspectives

All allocation systems should be constantly assessed and critically examined to be sure they are accomplishing their defined goals and that they are relevant to the current candidate and donor pool characteristics. This is good medicine and good policy. The lower risk of drop-out for HCC patients compared with patients with nonmalignant chronic liver disease, the failure to incorporate additional HCC characteristics that now are known to be associated with tumor growth, and the need to account for the effects of loco-regional treatment argue for a revision of the current MELD-HCC exception point system. Moreover, more consistent polices for removal from the list and giving more weight to longer-term posttransplant outcome for HCC should be incorporated into liver allocation systems for HCC.

The Bologna model is currently the only urgency-based allocation model that has been tested prospectively (25), however, it has limitations as outlined above. Alternative models such as deMELD (based on drop-out) and MELD-HCC (based on transplant benefit) may be promising with scales calibrated on MELD. The choice between the two can be debated. deMELD has been validated externally and is in line with the current systems of liver graft allocation based on urgency (drop-out). In contrast, MELD-HCC is based on utility, would need a change of conceptual approach to implement, but may be worth trying on a pilot program for certain subgroups.

Ultimately, there are limitations and challenges inherent to all systems. Policymakers' views on the goals of transplantation that are transmitted via the organ allocation policies they develop, whether intuitive or intellectualized may vary, but ultimately must reflect the values that the society holds as important. Transparency and accountability through robust data tracking and utilization of objective variables are

essential for gaining the public's trust that indeed the polices do reflect their values. Balancing equity for individual patients against overall population utility is a constant principle to which all plans should strive, knowing that no system will meet every need. Fortunately the transplant community has developed evidence-based assessments, is committed to monitoring of the results of our systems, and constant trialing of new ideas in an effort to improve (41).

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