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Who should get a liver graft?☆

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1. Introduction (Richard Freeman)

Determining who should get one of the extremely scarce deceased donor liver grafts is becoming an increasingly complex and difficult problem. In the early stages of the liver transplantation field, centers became aware of potential donors, decided whether to accept this donation, and chose which candidate should receive the graft without much consideration for the other centers and patients outside of their own area. However, with the increasing success of liver transplantation, maturation of the hepatitis C virus (HCV) epidemic, and broadening of the indications for liver transplantation to malignancies such as hepatocellular cancer and other previously contraindicated diagnoses, the demand for liver grafts has far outpaced the supply. This widening gap has prompted governments and medical policy-makers to develop strategies to address the question of who should get the liver graft. In some cases, liver allocation systems allow the transplant center to assign the donated liver graft to a waiting candidate while, in other systems, individual grafts are offered to individual patients.

With the understanding that the donor pool will never be sufficient for the demand, liver transplant practitioners have tried to expand the criteria that define what grafts are acceptable for transplantation while recognizing that these broader criteria also often confer additional risks to recipients. Some of the most difficult decision-making has centered on determining which patients with acute liver failure should receive transplants since most will die without immediate transplantation but also realizing that only a fraction will recover. In the first case, organ allocation systems must deliver grafts in a very timely fashion to save a life. In second instance, transplantation of a patient who would have otherwise recovered condemns that recipient to the life-long complications associated with immunosuppressive medicine and deprives another candidate of a graft that was not needed for the first candidate.

In this forum, the authors will address all of these areas and focus on better defining "Who should get the liver graft?", if not completely answering the question outright. Ultimately, society at large, especially the public who is supplying the organs for transplantation, will determine which candidates should or should not get the graft.

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Abbreviations: NSCAG, National Specialist Commissioning Advisory Group; UKELD, United Kingdom Model for End-stage Liver Disease; MELD, Model for End-stage Liver Disease; PELD, Pediatric End-stage Liver Disease Model; OPTN, Organ Procurement and Transplantation Network; ECD, expanded criteria donor; DCD, donation after cardiac death [non heart beating donor]; DRI, donor risk index; HCV, hepatitis C virus; HCC, hepatocellular cancer; ALF, acute liver failure; KCC, King's College Criteria.

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2. Should the center get the graft or the patient? (Neville Jamieson)

In the United Kingdom the number of centers has been centrally regulated and there remain only seven liver transplant units for a population of 61 million. In other countries the number of centers proliferated and inequalities of access to transplantation became apparent. Systems to address these issues were introduced with variable levels of effectiveness. In this section I will highlight differences, comparing the UK center-based system with a patient-based system such as that used in the US.

2.1. Center-based systems

2.1.1. The current British model

Liver allocation in the UK was initially based on each center being allocated a portion of the nation's donor pool reflecting its previous transplant activity and its nationally contracted (and funded) activity with the National Specialist Commissioning Advisory Group (NSCAG). The donor area allocated to each center being varied at regular intervals reflecting changes in transplant activity and the number of donors in the hospitals in the center's donor region. This did not reflect a center's waiting list size, waiting list mortality or the acuity of illness in the transplanted patients. Units were however required to target recipients with an expected post transplant survival of more than 50% at 5 years [1]. Predictably, waiting times and waiting list mortality varied widely.

Proposals for change raised issues about the value of waiting time and waiting list deaths if the patients listed by different units had different levels of illness highlighting the need for more precise, patient-based measures to be included in the allocation system. Therefore agreed national minimal listing criteria [2] were introduced with a minimum disease severity based on the United Kingdom Model for End-stage Liver Disease (UKELD) (Table 1). This has allowed movement to a system of allocation of donor zone size based on numbers of patients listed annually by each center meeting these patient specific criteria. Overriding this center-based allocation remains a national super urgent scheme with specified criteria where the only further allocation principle is time on the super urgent list. Additionally for donors meeting specific criteria (Table 2) offering the liver for splitting is obligatory, the left lateral segment going to a child at one of three national paediatric centers and the remaining right liver to the retrieving center.

Thus UK organ allocation defines donor pools based on patient-specific characteristics, but organ allocation to individual patients remains at the center's discretion. Following listing UKELD is currently only used internally by units in allocating available organs to their own cases. A perceived advantage of this system is that the recipients chosen for transplantation can be tailored to the organ available. An organ with identified donor risk factors and a high donor risk index (see section by Robert J. Porte) can be targeted appropriately to an intermediate risk patient passing over a sicker patient in the anticipation that the center will be able to allocate a better quality graft from their retrieval zone in the near future. Similarly, it allows greater comfort in splitting organs routinely to optimize graft availability for children with center-based selection of appropriate smaller adult recipients for the right liver graft.

Further refinement of the system allowing a national or regional "top band" listing placed just below the super urgent category remains under discussion to allow the sickest patients on the waiting list priority between centers over a wider area reflecting a donor population of approximately 20 million. This banding represents a patient-specific approach based on the UKELD score.

The British model is arguably not applicable to other health systems without central control over the number, location and activity of units. Even in the UK, the center-based system may be reaching the end of the road with the introduction of a national organ retrieval service as part of an initiative to improve organ donation which specifically separates the donation process from organ allocation [3]. Implementation will initially be based on retrieval zones and teams from the liver transplant centers but may still require a new patient-based organ allocation system to be developed based on UKELD to determine where the retrieved organs will be implanted.

Table 1
UKELD calculation.

$$UKELD = 5 \times \{1.5 \times \ln(INR) + 0.3 \times \ln(Creat) + 0.6 \times \ln(Br) - 13 \times \ln(Na) + 70\}$$

where
INR = international normalized ratio
Creat = serum creatinine (μmol/l)
Br = serum bilirubin (μmol/l)
Na = serum sodium (mmol/l)

Table 2
Splitting criteria.

Donor livers should be split if not required for super urgent transplantation or multivisceral grafting and the following criteria are met:

1. Donor age <40
2. Weight >50 kg
3. ICU stay less than 5 days

The decision to split is based solely on these criteria and if a segmental graft is required for a child in any paediatric center the splitting process should be initiated independent of any decision on allocation of the right liver to an adult patient.

2.2. Patient-based models

Dissatisfaction with inequality of access in the US on the old waiting-time weighted system led to the revolution of the introduction of Model for End-stage Liver Disease (MELD) into organ allocation [4,5]. Initially aimed at the admirable challenge of reducing waiting list death, it fortunately also did not impact patient survival [6]. Interest in the system rapidly developed and MELD is now widely applied as at least one parameter in allocation in many countries. However this is not without its own inequities. Additional points are required to allow patients with tumors to be transplanted in a timely fashion [6], particularly when the internal flexibility inherent in a center-based system is removed. Likewise, conditions outside the standard run of intrinsic liver diseases require "exception" status to allow patients with significant disease burden but with a low MELD to be transplanted. This requires complex, sometimes arbitrary, calculations to allow appropriate additional weighting and maintain equity of access.

A patient-based system obliges a center to consider an organ for a single patient. If they pass over the offer for their patient they may lose the organ to another center, this introduces an element of pressure to accept a specific organ even though the surgeon may have reservations about using this organ for a specific patient. The next step in the development of allocation algorithms is to match donor and recipient risk index to optimize individual outcomes, patients with the lowest disease burden also have to most to lose from a poor quality graft [7]. These calculations require accurate candidate and donor specific information. Implementing such systems requires a patient-based allocation system or a fully transparent center-based system in which the center's internal organ allocation principles are precisely defined.

There is a strong tide flowing in the direction of patient-based allocation even in the UK where the center-based system has persisted to date. Much remains to be done to refine the existing allocation algorithms with outstanding issues in defining appropriate matching of donor and recipient risk characteristics. The overall aim remains optimal donor to recipient matching to optimize organ usage, patient outcomes, and achieve a fair distribution of access to transplantation over large populations. Clearly, it is the patient who must always be the central figure in the process if inequity is to be avoided.

3. Urgency versus utility versus survival benefit? (Douglas E. Schaubel)

The persistent shortage of donor livers only increases the pressure on organ allocation policies to make the best possible use of available organs. In this section we compare and contrast the most frequently discussed organ allocation schemes, in the context of deceased-donor livers. Medical urgency, utility and (more recently) transplant benefit are three frequently discussed organ allocation schemes [8–16]. Under an allocation system based on medical urgency (i.e., "sickest-first"), priority for transplantation is based on predicted outcome in the absence of transplantation. With reference to liver transplantation and assuming that mortality is the outcome of interest, the wait list would be sequenced in decreasing order of predicted pre-transplant mortality. Conversely, under a utility-based system, patients would be prioritized with respect to predicted post-transplant survival. An allocation system based on the concept of transplant survival benefit incorporates elements of both urgency- and utility-based systems. Specifically, a survival benefit-based system would sequence wait-listed patients in decreasing order of the predicted difference between post- versus pre-transplant survival.

3.1. Urgency, utility and survival benefit

There are advantages and disadvantages to each of the urgency, utility, and survival benefit allocation schemes. The preference for a particular organ allocation scheme over its alternatives should be based on the objectives of the allocation process. An allocation system-based on medical urgency generally reduces the number of wait list deaths by allocating donor livers to patients subject to the highest wait list mortality. Conversely, there would be fewer post-transplant deaths if allocation was based on utility. Unlike either urgency- or utility-based systems, survival benefit-based allocation would reduce the total number of deaths (wait list + post-transplant).

Allocation systems based on urgency and utility are subject to one substantial limitation not shared by those based on survival benefit. Specifically, urgency-based allocation is generally at the expense of utility and vice-versa; stemming from the fact that wait list and post-transplant mortality are positively correlated. By selecting patients with the highest wait list death rate, urgency-based allocation may select for transplantation patients with the worst post-transplant outcomes. Conversely, by giving the highest priority to patients with the highest post-transplant survival, utility-based allocation may result in the transplantation of patients unlikely to die on the wait list and, as a result, a higher wait list mortality for the patient population as a whole. Survival benefit-based allocation does not seek to minimize either wait list or post-transplant mortality, *per se*. In fact, compared to a survival benefit-based system, it would be expected that an urgency-based system would result in fewer wait list deaths, and that utility-based

allocation would lead to fewer post-transplant deaths. However, if the objective of the allocation system is to minimize the total number of deaths to the patient population, then it would appear that a survival benefit-based system is indicated.

3.2. What are the pros and cons of the MELD system?

February 2002 marked the implementation of a medical urgency allocation system based on the MELD score [17–19]. It is useful to consider the pros and cons the MELD system. First, although MELD is a very strong predictor of wait list mortality, it is a much weaker predictor of post-transplant mortality [8]. This should not be viewed as a liability in and of itself, though. If MELD were an equally strong predictor of post-transplant mortality, the MELD score would identify which patients would die with or without a liver transplant, which of course would be undesirable since allocation by MELD would then merely shift mortality from pre- to post-transplant. Second, several recent efforts have been directed at improving the MELD score, including re-weighting the MELD components [20] and including serum sodium [21,22]. Third, if liver allocation was driven by survival benefit there would be some reordering of patients compared with ordering patients solely by MELD alone. Merion et al. [8] reported that liver transplant survival benefit increases as MELD increases, but this claim should be interpreted as "on average". If MELD were the only predictor of both wait list and post-transplant mortality, then allocation by survival benefit would indeed be equivalent to allocation by MELD. However, there are several factors in addition to MELD which predict wait list and also post-transplant mortality [16]. In order to maximize the lives saved through liver transplantation, allocation should ideally be based on both utility and urgency. In response, a transplant survival benefit allocation system is currently under consideration by the OPTN Liver and Intestine Committee, with the proposed benefit score computed, using patient specific variables.

Under a survival benefit system, care should be taken to ensure that various patient subgroups will not be disadvantaged. The benefit score distributions in the OPTN database are quite similar across subgroups defined by age, gender and race; which makes sense for several reasons. Gender and race were deliberately excluded from the benefit score calculation and, age is only one of several patient characteristics. Moreover, age is a weaker predictor of benefit since it affects both wait list and post-transplant survival in the same direction. Details of the proposed survival benefit score are available in Schaubel et al. [16].

4. What to do with the expanded criteria graft? (Robert J. Porte)

Most current organ allocation systems are based on the assumption that all donor livers carry the same risk of failure [23]. This, however, is not the case, and it has been shown in numerous studies that the risk of graft failure and recipient mortality differs depending on the quality of the donor liver [24–27]. Donor quality represents a continuum of risk rather than a dichotomous diversion between "good" or "bad". Increasing awareness of the growing diversity in donor organ quality has stimulated the debate on how this should be considered in organ allocation policies to avoid futility and local differences in organ acceptance [23,27].

4.1. What is an expanded criteria donor graft?

An expanded criteria donor (ECD) implies a higher risk in comparison with a reference donor. It has been proposed not to use the term "marginal donors" in an era of scarcity where every offer for donation should receive the highest respect [28,29]. In the past a reference, or ideal, donor was defined as a donor with the following characteristics: age below 40 years, trauma as cause of death, hemodynamically stable, no steatosis, and no transmittable disease [28,29]. Although one could categorize any donor not meeting these criteria as ECD, this would be impractical because the use of donors that do not meet all of these criteria has become common practice [29,30]. Most reports have defined an ECD liver as an organ with an increased risk of poor function or failure that may subject the recipient to greater risks of morbidity or mortality [30,31]. In contrast to the low-risk grafts, which form a relatively homogenous group, ECD grafts are quite heterogeneous. Although the impact of donor risk factors on outcome has been analyzed in several studies, many of these variables are not determined or known at the time of organ procurement, such as duration of the cold and warm ischemia times [26,28]. Therefore, it has been proposed that these variables should not be included in the definition of ECD livers [29].

There is a second category of ECD livers: grafts that carry an increased risk of transmission of infection or malignancy to the recipients. Although this group of ECD livers may pose a (more long-term) risk to the recipient, these livers may have characteristics that are otherwise close to that of the reference donor [29,30]. This category of ECD livers should therefore not be included in studies on ECD livers that carry a risk of graft failure. We here propose to separate these two types of ECD donors and refer to them as type A (livers with an increased risk of graft failure) and type B ECD livers (livers that carry an increased risk of disease transmission).

Donor variables that have previously been identified as risk factors for early graft failure (ECD donors type A) include age (>60 years), female donor (especially in male recipients), steatosis, race, elevated liver function tests, hypotension/ increased vasopressor use, non-heart-beating donor (also known as donation after cardiac death donors or DCD), split liver grafts, elevated serum sodium levels, and prolonged cold ischemia time (>12 h) [24,26,28,29]. Not all of these variables have been unequivocally identified in all studies and the clinical relevance of some remains debated (i.e. gender match, race, elevated sodium levels). The three donor variables that are most frequently encountered in daily practice and that have been associated with a well-established increased risk of early graft failure are moderate to severe graft steatosis, advanced donor age, and DCD.

4.2. Not all ECD livers carry the same risk

Although the qualitative effects of individual donor variables are well documented, the quantitative risk associated with combinations of characteristics are much less clear. In an attempt to develop a quantitative donor risk index (DRI), Feng et al. identified seven donor characteristics that independently predict a significantly increased risk of graft failure [28]. Donor age over 40 years (and particularly over 60 years), DCD, and split grafts were strongly associated with graft failure, while African-American race, less height, cerebrovascular accident and 'other' causes of brain death were more modestly associated with graft failure. This quantitative assessment of the risk of donor liver graft failure using a DRI is an essential first element in the development of an allocation system that takes both recipient and donor variables into consideration. However, several donor-related variables that are not included in this DRI may be relevant as well, including length of stay in the ICU and degree of steatosis [29,32].

4.3. Who should be offered an ECD liver?

While few studies have focused on defining the combinations of donor and recipient profiles, many centers would traditionally not use an ECD liver for a high-risk candidate [27,30]. Several studies have shown, for example, that outcome after split liver transplantation is worse when split grafts are used for very sick patients, whereas good results can be obtained in stable recipients [27,30]. However, recent studies have challenged the conventional wisdom that high-risk donor livers should not be used for high-risk patients [11,33]. In a study based on a Markov simulation, Amin et al. [33] concluded that patients with a high MELD score likely have a lower probability of death overall if they accept a higher-risk organ compared with waiting for a lower-risk organ. Using US data from the SRTR, Schaubel et al. [11] calculated the survival benefits of liver transplantation as a function of candidate disease severity as expressed by the MELD score and donor quality as expressed by the DRI [28]. All recipients with MELD $\geqslant 20$ had a significant survival benefit from transplantation, regardless of DRI. These authors concluded that pairing of high-DRI livers with low-MELD candidates fails to maximize survival benefit and may deny lifesaving organs to high-MELD candidates who are at high risk of death without transplantation. The main limitation of this study, however, is that it is based on observational data of patients who have been transplanted according to the conventional wisdom of preferably not using high-risk donor organs in high-risk recipients. These data may become less accurate when applied to other populations which may receive a different pattern of care. Moreover, such models which are valid for populations usually have wide confidence intervals when applied to individuals [2]. More importantly, the DRI used in the study by Schaubel et al. does not include data on the amount of graft steatosis. Although such livers may be used with acceptable outcome in the more stable recipients with a low-MELD score [34,35], it remains to be seen if the steatotic ECD graft will confer a survival benefit for the more ill candidate.

Apart from the severity of sickness, the etiology of liver disease may play a role when matching donors and recipients. For example, there is accumulating evidence that grafts from donors with advanced age are associated with more aggressive recurrence of HCV-related liver disease and subsequently lower graft survival rates [23,29,35]. Therefore, it may be advisable not to use some ECD livers for recipients with HCV. However, a recent study by Majella Doyle et al. [36] has shown that advanced donor age may have no significant impact on medium-term results after transplantation for HCV-related liver disease provided the cold ischemia time is kept very short. Moreover, a strategy of not using older donor livers for HCV-positive recipients would also result in a dilemma with the risk of inequality among recipients, because other recipients with different etiologies of liver disease would also prefer to have a young donor. This exemplifies the complexity of developing an allocation system that considers in detail both recipient and donor profiles.

On the other hand, specific ECD livers (here proposed as type B ECD livers) could be well used for a specific group of recipients, whereas one should be very reluctant to offer such a liver to other potential recipients. For example, livers from hepatitis B core-positive or HCV-positive donors can be used under certain conditions to treat patients with end-stage liver disease due to HBV or HCV, respectively.

Development of an ideal model to determine who should get the ECD graft will be very difficult given

the complexity and large number of donor and recipient factors that may affect outcome after transplantation. Moreover, an allocation model based on matching valid in one area may not be automatically applicable in another area, given the significant heterogeneity among different countries and regions regarding organ shortage, waiting list mortality, legislation, and the presence of alternatives to deceased donor liver transplantation [29,30]. Therefore, in the absence of precise models for specific situations, any (new) system for allocation will need to include a mechanism for ensuring that the responsible clinician has the final decision in determining whether to use a given graft [2]. In addition, rigorous attempts to keep the cold ischemia time as short as possible may provide significant compensation for the two most clinically relevant and prevalent donor risk factors: age and steatosis [34,29,30]. Finally, novel strategies to reduce graft injury during organ preservation, including machine preservation and pharmacological interventions, may prove to be critical to improve outcome after transplantation of certain types of ECD livers.

5. How do we assign priority to patients with hepatocellular cancer (HCC)? (Richard Freeman)

In the US around 2000, policy-makers recognized the need for more objective, patient-based measures to define liver transplant need [37]. The most obvious, objective condition that precludes a favorable LT outcome is death on the waiting list. This was the rationale for incorporating the MELD score. With reasonable accuracy, the MELD score defines the risk of dying on the waiting list for candidates with chronic liver disease using only patient defined variables not subject to observer biases [38]. However, there are other conditions that do not necessarily carry an immediate risk of dying without a transplant in the near term but do offer a good survival probability with liver transplantation, and for which quality of life is superior to not performing the transplant [39]. Among these is HCC.

5.1. What is an unfavorable stage of HCC for liver transplantation?

For HCC candidates, in order to employ the organ allocation concept of "risk of progression" to an unfavorable stage while waiting requires that "unfavorable stage" needs to be defined. The Milan criteria (single tumor <5 cm or no more than 3 tumors the largest <3 cm) have been widely accepted and validated as a good measure of a favorable stage and several studies suggest that offering LT to patients who progress beyond Milan Criteria can result in inferior outcomes [40]. Other less well validated criteria have been suggested such as the UCSF [41] or Pittsburg [42] criteria and these could be used as newer definitions of the boundaries for defining unfavorable stage. Although not firmly established, many observers have argued that an arbitrary definition of <50% 5-year patient survival should set the limit of an unfavorable outcome, so whatever definition of unfavorable stage is used, most would agree that this should define a post LT outcome that is less than 50% patient survival 5 years after transplant.

Once unfavorable stage definitions have been established, creating organ allocation policy using this progression to an unfavorable HCC stage concept requires development of a statistical model to predict progression beyond the unfavorable stage endpoint. MELD was not designed to accurately predict HCC progression beyond Milan Criteria or any other HCC stage (e.g. UCSF criteria). In order to construct a predictive model for progression beyond the Milan Criteria endpoint, patient-specific predictors of the risk of removal (so-called drop out risk) need to be elucidated. Since death also causes drop out for HCC patients, MELD should be combined with tumor characteristics to adequately estimate tumor progression and death reasons for drop out as has been advocated by the Bologna group [43].

5.2. What factors predict drop out for HCC candidates?

Using the US OPTN database, Freeman et al. constructed a Cox model to identify variables associated with waiting list drop out for HCC candidates. We found that, in addition to age, AFP, maximum tumor size and MELD score were all predictive of drop out on the waiting list [44]. In applying this model, MELD was just as accurate in discerning those who would drop out from the list as the combination of MELD, AFP and maximum tumor size since most of the patients on the waiting list have underlying viral disease as well. The resulting MELD-HCC score can be applied to derive a risk of wait list drop out analogous to the MELD-defined risk of waitlist drop out (death) for LT candidates who do not have HCC. More recent updates of these analyses have again confirmed that the same variables: MELD score, maximum tumor size, and AFP, are associated with drop out from the waiting list for HCC candidates. This is true even when a competing risk analysis is used (Fig. 1). Note that all of these variables are relatively objective, patient-based parameters. In all of these studies, tumor number was not associated with drop out rate, a finding consistent with several reports in the literature indicating that size of HCC lesions, not number, is more often associated with vascular invasion and a more aggressive phenotype.

In all of these analyses, administration of loco-regional treatments such as radiofrequency ablation, transarterial chemoembolization, percutaneous ethanol injection to ablate HCC lesions, (ablative treatments

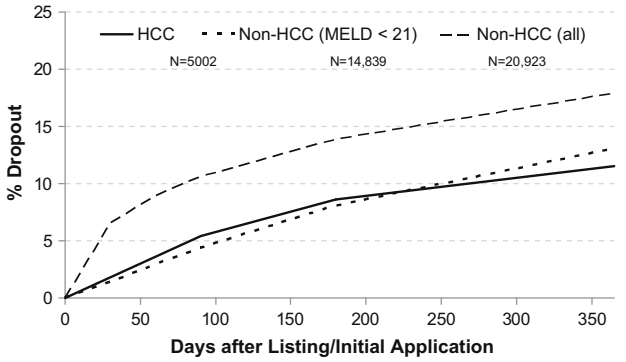

Fig. 1. Overall dropout rates for HCC and non-HCC candidates, listed 4/14/04-12/31/07 on the UNOS/OPTN liver transplant waiting list using a competing risks statistical technique. All calculations are done from time of listing for non HCC patients and from time of first HCC application acceptance for HCC patients. (courtesy of Dr. Erick Edwards, used with permission.)

[AT]) did not influence drop out rates. This is likely due to HCC candidates receiving enough priority on the waiting list so that most are transplanted within 180 days of listing, a time period too short to see a significant effect of AT arresting tumor progression. Nonetheless, there appears to be a positive selection effect for AT in that responders to AT prior to transplant appear to have superior post LT survival [45,46] and in some single center studies, responders to AT who are downstaged from beyond Milan Criteria to within Milan Criteria, have excellent post transplant survivals [47]. Based on these results, some have argued that response to AT, down staging to within Milan Criteria, or at least arresting of progression of HCC by the AT that allows for more prolonged waiting on the list without progression, should be used as a positive selection factor in allocation policy for HCC candidates.

5.3. Are there better ways of assigning the liver graft for HCC candidates?

Using a HCC-MELD score scheme for liver prioritization offers several advantages over the current US system. It provides a continuous rather than categorical grading of need. In contrast to the current system a HCC-MELD score, by maintaining the MELD score within HCC allocation ensures that some priority based on the underlying liver disease severity is included. The contribution of the underlying liver disease to drop out on the waiting list for HCC candidates has been appreciated by other groups [43].

In summary, we now have a wealth of data suggesting that LT offers the best oncologic option for patients with HCC. Prioritizing who gets this treatment however, depends, not only on balancing individual justice and utility for the HCC candidates, it requires taking into account the other candidates who do not have malignancy and their likely success rates. Making progress in achieving a reasonable balance requires that objective, patient-based measures and endpoints are used for candidates with HCC and those without HCC alike.

6. Which Patients with fulminant hepatitis should get a liver graft and how do we assign Priority? (Federico G. Villamil)

Acute liver failure (ALF) results in 70–80% mortality unless liver transplantation (OLT) is performed [48]. Based on the low rates of spontaneous recovery a simple answer to the question of which patients with ALF should get a liver graft is "the majority". However, due to current organ scarcity and the consequences of life-long immunosuppression, maximal efforts are required to avoid unnecessary OLT. The keys for success in managing patients with ALF are early assessment of prognosis and availability of an organ donor in a timely fashion. Ideal prognostic markers should be able to distinguish, shortly after referral, patients who will survive with medical therapy, and thus with no need for OLT, from those with poor outcome who should be transplanted early and before the onset of irreversible complications or multi-organ failure. In addition, effective prognostic markers should be simple-to-use and universally applicable to all patients with ALF irrespective of etiology or geography.

Many clinical, laboratory, radiological and histological markers and composite scores have been proposed to assess prognosis in ALF but at present none of them can predict outcome with absolute certainty [49]. Of all prognostic scores, the King's College Criteria (KCC), with separate models for acetaminophen and other causes of ALF, are today the most widely accepted and are used as the standard to which new scores are compared [50]. Reported experience has shown that KCC are accurate for predicting death (positive predictive values of 80–100%) but are less effective to identify patients who will recover spontaneously (negative predictive values of 23–70%) [51]. Despite this limitation, the score is clinically useful because it identifies patients requiring OLT irrespective of the severity of encephalopathy.

6.1. Comparing models for predicting mortality risk from ALF

Kremers et al. demonstrated that among 312 patients with non-acetaminophen ALF listed in the US as Status 1, the Model for End-stage Liver Disease (MELD) was a statistically significant predictor of mortality and overall survival [52]. Yantorno et al. recently showed that MELD was significantly more accurate (concordance statistics) than KCC and Clichy's Criteria [53] to predict

30-day mortality in 120 patients with ALF not due to acetaminophen. Concordance scores were 0.95, 0.74 ($p = 0.003$) and 0.68 ($p = 0.001$), respectively. More recently we confirmed that the superiority of MELD was independent of etiology and clinical variants of the disease [54].

Even though our results have not been fully confirmed in other series that evaluated different cut-off values for MELD [55–58], the challenging question is whether prognosis of ALF should be assessed with continuous or categorical scores including laboratory values that remain fixed above the defined threshold and thus limit its discriminatory ability. When using KCC, patients with serum bilirubin values of 18 or 40 mg/dL and INR values of 3.6 or 6.0 are assigned to the same prognostic category. In contrast, MELD score progressively increases with worsening of its components and may better identify individual patients with higher risk of death. Whether to use categorical or continuous scores in ALF is an important issue and resembles the controversy of whether MELD or the Child-Pugh score are preferable to assess outcome of patients with cirrhosis. Overall, no prognostic score will completely replace good clinical judgment because at present there is no perfect formula to indicate OLT but one would expect models that more closely resemble the continuous nature of clinical disease are likely to be more useful. The course of ALF is largely unpredictable and therefore in clinical practice severity of encephalopathy, coagulopathy and extrahepatic complications are evaluated on a day-to-day and even hour-to-hour basis and many times the final decision to proceed or not with OLT is made when an organ becomes available.

OLT is a true life-saving procedure for patients with ALF. However, the rapidity of disease progression allows a narrow window for performance of OLT in a timely fashion. Patients with ALF are given the top priority for graft allocation worldwide. Still, a substantial number of patients die on the waiting list, especially in areas where deceased donors are not readily available. OLT should not be indicated too early in patients with favorable prognosis but definitely not too late at a point where the procedure may be futile loosing both the patient and the donor organ. ALF is an heterogeneous condition. Patients with hyperacute forms rapidly progress to grade 4 coma due to cerebral edema [59]. In contrast, subacute forms are characterized by slowly progressive coagulopathy and encephalopathy and in most cases death occurs in weeks rather than in days. Despite having poor outcome without OLT, the time-period to find a suitable organ in subacute forms is much longer than in the hyperacute variants. Therefore, it is likely that among candidates with ALF listed in the emergency category there are subgroups with more severe disease and more urgent need for OLT.

6.2. Should "sickest first" apply to liver allocation for acute liver failure?

A relevant question to be addressed is whether "the sickest first" principle should also be applied to ALF. Kremers et al. showed that among 720 candidates listed as Status 1 in the US, MELD scores were significantly higher in patients with ALF than in those requiring emergency re-OLT for primary non-function or hepatic artery thrombosis [52]. In addition, this study showed that patients with non-acetaminophen ALF had the highest waitlist mortality, the best outcome when OLT was performed expeditiously and therefore the greatest transplant benefit. These findings suggest that criteria for allocation of donor organs to patients in the emergency category should be redefined. Instrumentation of such a new policy will require stratification of listed patients by MELD or other continuous disease severity scale using patient-based variables. Improved fairness of the allocation system may increase the applicability of OLT in ALF and reduce the need for live donors.

7. Summary and conclusions (Richard Freeman)

Assigning priority to receive any scarce resource has remained the subject of intense ethical debates for centuries. In the US, Federal law mandates that a sickest first system should be employed for ranking candidates for liver transplantation (LT) based on "medical need" [60].

Need for LT be conceptualized by defining a risk to progressing to a condition that precludes a favorable outcome with LT. In the past this need was mostly defined by clinicians observing patients and, since these observations were clinician-based, they were subject to all the biases and subjective judgments each clinician brought with him or her to the priority decision-making process. These subjective priority measures were also inconsistently interpreted, sometimes in favor of transplant centers, or institutional allegiances, more than individual patient's best interests.

The preceding discussion makes a few points clear. Increasingly, no matter whether allocation policy offers the graft directly to the patient or to the center, determining "who should get the liver graft" is being done with more sophisticated prognostic modeling based on patient-specific, rather than observer-defined measures. As discussed by Jamieson, even in a primarily center-based system, the most urgent candidates are prioritized by patient specific variables and UKELD is used within centers to decide "who should get the liver graft." In patient-based allocation systems, physicians still decide whether the graft offered to the individual patients should be used in that circumstance, but organ offers and the measurement of physician behavior is more readily defined by objective, patient-based variables. In

either case, these decisions are based on implicit or explicit survival benefit calculations as outlined by Schaubel that are not possible without well defined measures. Included in the "who should get the liver graft" deliberations, are assessments of graft viability and function probabilities, particularly for the less than optimal grafts as described earlier by Robert J. Porte. These donor assessments are also increasingly being measured by specific donor criteria although standardizing and including all of the relevant variables has not been fully realized to date. The increasing prevalence of HCC worldwide introduces the need to define more precisely, not only the immediate short-term risks of cancer progression, but also the long-term risks of tumor recurrence as well as patient survival. Perhaps the most critical decision-making for the acute liver failure patients is not "*who* should the graft", but who should *not* get the graft. As outlined by Villamil, the clinician is faced with models that are very good at predicting which patient will likely die of acute liver failure but our models are less helpful in determining which patients will *not* die without the graft.

We have tried to provide the additional data and insight for liver transplant professionals facing the question of "who should get the liver graft" based on the evidence and point out where the evidence is weak. Hopefully this will stimulate further research in these areas.

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