REVIEW

The trials and tribulations of liver allocation

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SUMMARY

Allocation policies are necessary to ensure a fair distribution of a scarce resource. The goal of any liver transplant allocation policy is to achieve the best possible outcomes for the waiting list population, irrespective of the indication for transplant, whilst maximizing organ utilization. Organ allocation for liver transplantation has evolved from simple centre-based approaches driven by local issues, to complex, evidence-based algorithm prioritizing according to need. Despite the rapid evolution of allocation policies, there remain a number of challenges and new approaches are required to ensure transparency and equity on the decision-making process and the best possible outcomes for patients on the waiting list. New ways of modelling, together with novel outcome criteria, will be required to enable a dynamic adaptability of the allocation policies to the ever changing demographics of the donor population and the changing landscape of indications for transplantation.

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Introduction

Liver grafts are a scarce and precious resource. There are many approaches to the problem of graft scarcity, including increasing donor rates and improving alternative treatments for liver diseases and hepatocellular cancer. Whilst these solutions focus on improving the organ supply or reducing the demand for liver transplantation, liver allocation policies are aimed at the immediate problem of graft scarcity for current as well as future patients. The goal of any liver transplant allocation policy is to achieve the best possible outcomes for the waiting list population, within the limited resources available at a given point in time. Changes in the aetiology of cirrhosis over time (Fig. 1) in addition to recent expansion of indications for liver transplantation (including cholangiocarcinoma and colorectal liver metastases) in some countries has increased demand for scarce allografts further [1,2]. Thus, the challenge of how we should allocate livers for transplantation is an ongoing and relevant issue. Although changes in allocation policies have largely been incremental, overall these have led to substantial modifications over the last 30 years. However, as allocation policies serve the needs of specific population groups within different geo-political and social environments, they differ considerably between countries and geographical regions.

A brief history

Following the first liver transplant by Dr Starzl *et al.* [3], procurement and allocation of donor organs was performed locally by individual hospital-based teams. As the operative mortality from liver transplantation progressively declined (to <10% by 1984 [4]), demand for donor organs soared. This led to a series of high

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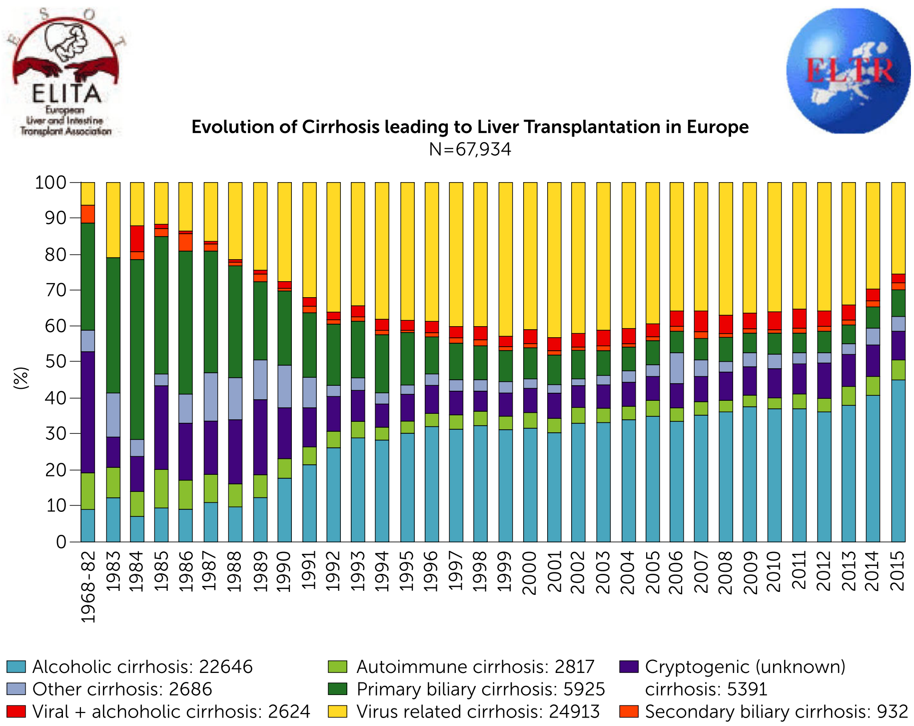

Figure 1 Evolution of cirrhosis leading to liver transplantation in Europe (1968–2015). Source: European Liver Transplant Registry.

profile controversial transplants with accusations of bias, arbitrary decision-making and manipulation of transplant waiting lists in return for financial donations [5]. In 1984, the National Organ Transplant Act was passed into law in the United States, establishing the principle of donor organs as a national asset and criminalizing financial compensation for donor organs [6]. Regional networks for organ procurement and distribution were established with the aim of transferring the responsibility for organ allocation from individual physicians to evidence-based, objective and transparent algorithms based primarily on clinical need [7]. Similar fundamental principles were subsequently adopted by all countries and centres starting liver programmes although the basis of the allocation algorithms varied according to the local medical and societal realities and needs.

Principles of organ allocation

Despite the differences in liver allocation policy worldwide, common ethical principles drive allocation and complex and sometimes conflicting considerations such as equity, utility, justice and fairness require a delicate balance (Table 1). These ethical principles may overlap with the regulatory framework of liver allocation policy, such as the need for transparency and efficiency and any system for prioritization needs to be acceptable and relevant to the society it serves.

In the current global environment, an organ allocation system should balance considerations of equity (all patients who need a transplant should have equal opportunity to receive one), need (to reduce mortality on the transplant waiting list), benefit (optimizing outcomes from each organ transplanted) and utility (maximizing the overall life-years-gained) [8]. ‘Good’ can be defined in different ways, including patient survival, graft survival or quality of life measures. However, in the context of liver allocation, where there is a severe supply shortage, the individual ‘good’ is often at odds with the ‘good’ of the wider population. As such, unintuitive allocation decisions arise when equity and utility are considered separately. Futile liver transplants may result if only medical need is considered, (by prioritizing organs for critically unwell patients with little chance of long-term survival). Conversely, allocation of a liver to a patient with a predicted long-term survival on the transplant waiting list reduces the utility (life-years gained) of that specific organ. Critical in achieving the right balance is the definition of ‘best outcomes’, and one may consider individual patient survival (either from listing or from transplant), the quality of life or the costs of care as acceptable criteria. However, in the context of liver transplantation where there is no

Table 1. Desirable criteria for organ allocation systems and possible approaches for achieving these.

Criteria for an organ allocation system	Possible approaches
Justice and fairness: equity of access to transplant, and transplant waitlist	Treat all people equally ('first come, first served')
Utility: maximization of net benefit to the community	Needs-based: sickest patient first (i.e. MELD-based)
Respect for autonomy: for example, directed living donor donation	Utility-based: maximize lives saved or life-years saved (prioritize those with most favourable prognosis)
Efficiency: minimize potential organ and resource wastage, maximize benefit obtained from each organ	Youngest patient first ('fair innings')
Transparency: stakeholders should understand how the allocation system works	Prioritize patients who have not engaged in risky behaviour that may have contributed to their condition (for example, nonalcoholic liver disease)
	Prioritize on a patient's instrumental value (i.e. prioritize those who have made or will make relevant contributions, such as having previously been a living donor)
	Combination of approaches (for example, transplant benefit)

alternative life-sustaining therapy, the allocation of the scarce resource has been centred primarily around the life-sustaining benefit offered by the transplant.

Evolution of liver allocation

In the early days of liver transplantation, practicalities of graft ischaemic times and limited availability of suitably trained specialists necessitated a centre-based approach to organ allocation. Within each centre, priority was roughly accorded to prospective transplant patients based on surrogate markers of clinical need, such as need for admission to the intensive care unit [9]. As outcomes improved and liver transplantation became an established life-saving treatment, the opaque, arbitrary decision-making and widespread geographical variation inherent with a centre-based approach to organ allocation became unacceptable and patient-based systems began to emerge.

Evidence-based liver allocation has evolved as the problem of liver graft scarcity continued to grow. Prior to 1997, waiting list time and hospitalization status were the determinants of waitlist prioritization in the United States. The establishment of large transplant databases encouraged an evidence-based approach to waitlist prioritization. Waiting time was demonstrated not to correlate with waitlist mortality [10], which shifted the emphasis for prioritization from the length of waiting time to the severity of liver disease. The Child-Turcotte-Pugh (CTP) classification was considered in the first attempt to objective allocation. CTP is based on clinically assessed variables of ascites and encephalopathy, as well as laboratory measurements of serum bilirubin, albumin and prothrombin time. It was originally developed to predict post-operative survival in cirrhotic patients with bleeding varices and was modified in 1973 to replace the nutritional status with prothrombin time [11]. In 1997, medical urgency-based allocation was introduced in the United States and incorporated CTP classification in the assessment of urgency although waiting time remained a factor for prioritization [5]. In 1998, the US Department of Health and Human Services published the 'Final Rule', which outlined that the principles of organ allocation should be based on objective criteria of medical urgency, rather than waiting time [12]. Although it provided some objectivity, CTP classification-based allocation had several limitations. Assessments of encephalopathy and ascites in CTP scoring are considerably subjective. CTP classification also failed to consider renal function as a prognostic variable, and the score does not discriminate between patients who have high bilirubin above 3 mg/dl or albumin below 28 g/dl [13]. As a result, a more accurate score as a basis for allocation was needed.

The MELD era

The model for end-stage liver disease (MELD) score was initially developed as an objective and reproducible measure for survival prediction in patients undergoing transjugular intrahepatic portosystemic venous shunts [14]. The original MELD score was based on laboratory values of bilirubin, creatinine and international normalized ratio (INR) to predict three-month mortality for these patients. MELD was subsequently validated as predictor of waitlist mortality in liver transplant patients [15,16] and accurately predicted three months mortality for most patients [17] with a superior predictive power to CTP [15]. Therefore, MELD score-based allocation was introduced to the United States in February 2002 and implemented by many countries since. This change resulted in a reduction in waiting list mortality (by transplanting the sickest patients first) [18], but also had the effect of a small overall increase in early post-transplant mortality [19,20]. A further limitation of prognostication with MELD is failure of the score to account for elevations in INR and creatinine for reasons other than liver disease or inaccurate laboratory results [21].

Model for end-stage liver disease was further refined by the addition of serum sodium (MELD-Na or UKELD – UK model for end-stage liver disease), which took account of the poor outcomes associated with hyponatraemia in cirrhosis. This improved the predictive ability of MELD for short-term survival in both chronic liver disease and fulminant settings [22,23]. However, MELD scoring has limitations as a tool for liver allocation. Firstly, MELD has been shown to systematically bias against women (largely due to disparities in height), leading to lower transplantation rates and increased waitlist mortality [24]. Secondly, MELD does not always reflect the severity of disease in conditions such as polycystic liver disease and hepatopulmonary syndrome. Thirdly, it particularly fails to reflect the benefit of transplantation in patients with hepatocellular cancer (HCC). Over time, MELD-based allocation systems have tried to compensate for these disparities with various corrective measures ('exception points' added to the score for patients with HCC, for example) and alternative listing criteria [25].

Whilst MELD score-based allocation aims to maximize waitlist survival outcomes, it does not consider the importance of expected post-transplant outcomes, which may be due to donor and intraoperative factors, as well as recipient factors not measured by MELD scoring [26]. In addition, the specific interactions between donor and recipient may affect graft survival and overall survival outcomes of liver transplantation. Donor and recipient population characteristics have changed over time and will continue to change in the future [27]. Donors have become older with more medical comorbidities, and there are increased numbers of expanded criteria donors, such as donation after circulatory death [28]. Donor–recipient matching is a balance of an individual recipient's risk of waitlist mortality, and their expected post-transplant outcome with a specific donor liver. Donor–recipient matching becomes particularly important in the context of increasing demand for liver transplants worldwide, ever-increasing graft scarcity and expansion of donor criteria [29].

Until recently, donor livers in the United States were distributed according to historical arbitrary geographical 'donor service areas' and transplant regions. This led to significant variation in the MELD score at which patients were transplanted depending on where they resided or, with sufficient financial resources, which hospital's list they chose to join [30]. In January 2020, the United Network for Organ Sharing (UNOS) implemented a new system for prioritization of liver transplant candidates: organs are now offered to patients above a specified threshold MELD score in a sequence of progressive distances from the donor hospital (i.e. to transplant units within 150, 250 then 500 nautical miles) [31]. Outcomes from the new system are awaited, but it is anticipated that this change should dramatically reduce geographical (and therefore indirectly socioeconomic) inequities for patients in need of liver transplantation in the United States. This change highlighted that whilst need can be defined by MELD (or a similar score), the offering and distribution of organs need to follow additional rules to ensure an equitable access to the resources across a wide range of societally accepted factors.

'Allocations schemes' are really 'offering' systems, which ensure that any given donated graft is offered to the most suitable recipient according to the respective algorithm in use in a particular country. This, however, does not guarantee complete equity of access to transplantation as further inequity could be introduced by variation in organ utilization rates in each transplanting centre. To address this, in the UK, this data are continually monitored and made publicly available [32] together with additional outcome measures (such as median waiting time to transplantation at each centre) that should identify any such variation.

The variation in acceptance increases the risk of grafts not being allocated (late declines, increased cold ischaemic time), and therefore, correction systems should be in place. In the UK, such a system ('fast-track offering') is triggered when the liver graft is not accepted by three centres in the standard offering sequence or the process has exceeded five hours. This allows centres with a more aggressive risk appetite to utilize the livers which otherwise may be lost.

Post MELD-era liver allocation

Historically, outcomes were measured in terms of 5-year survival from the time of transplantation; this has moved to survival from the time of listing for transplantation and future challenges will include comparative survival over additional time periods (e.g. 10 or 15 years) and estimation of patient longevity if liver disease was excluded. Choosing the optimal time horizon in an offering scheme remains a challenge as by using a longer horizon there is a risk of discriminating against age, as seen with several proposals of benefit-based approach in kidney allocation.

After almost two decades of needs-based allocation based on MELD scoring, there has been a gradual shift towards optimizing outcomes for the entire transplant population. Consideration of expected post-transplant outcomes is paramount in prioritizing patients for transplant and as such, a transplant benefit-based allocation is a way to consider both waitlist and post-transplant outcomes in designing the prioritization of waitlist patients.

Transplant survival benefit is quantified by the difference in an individual patient's expected survival with and without a transplant. The time over which transplant survival benefit is measured is generally accepted as mean or median survival over 5–10 years [33]. Transplant benefit-based allocation provides a method of balancing medical urgency and utility in allocation decisions. Additionally, it can be used to potentially equitably prioritize patients with differing indications for transplant, such as patients with hepatocellular cancer and those with end-stage liver disease. The relevance of the concept of transplant benefit is recognized in the US MELD-based allocation system by the granting MELD-exception points for patients with HCC. However, there is continuing debate regarding the extent to which patients with HCC should be prioritized to achieve best outcomes for the whole transplant population [34–36]. This reflects the challenge of how to quantify the transplant benefit.

Predicting the expected survival for an individual patient with and without a transplant is challenging. Calculation of transplant benefit incorporates the challenges of predicting survival outcomes both for patients on the waiting list and after receiving a transplant and is therefore reliant on accurate statistical modelling of survival outcomes. This is necessarily based on retrospective data which contains inherent selection bias that may not be overcome by statistical methods [37]. This is particularly problematic for predictions of waitlist survival, as the sickest patients are usually transplanted first, and the majority of waitlist patients are censored by transplant [38]. Additionally, specific donor–recipient matching must also be considered in order to calculate the patient's expected post-transplant survival. Complex mathematic models are required to quantify transplant benefit. The equity and utility of transplant benefit-based allocation is reliant on these complex models. This raises concerns regarding transparency, the generalizability of such models, and the ability of such models to dynamically respond to future changes in variables in the transplant (and donor) population. Despite these issues, the concept of transplant benefit-based allocation represents progress in liver allocation policy in the current context of graft quality and availability.

Prior to 2018, donor livers in the United Kingdom were allocated on a regional basis, with priority given to the transplant centre assigned to a designated organ recovery zone. Each individual centre subsequently allocated organs to patients on their waiting list according to compatibility (size and blood group) and greatest need (as determined by UKELD). This system offered obvious logistical benefits and the potential for minimizing graft cold ischaemic times, but did perpetuate some ongoing geographical inequity in organ allocation. To address this, in April 2018, the United Kingdom introduced a transplant benefit-based liver offering scheme, whereby livers are allocated nationally to a named patient who is predicted to gain the most survival benefit from receiving the particular liver graft on offer [39]. Allocation for the majority of adult patients is now based on the Transplant Benefit Score (TBS), which is calculated according to 21 recipient criteria and seven donor criteria (Table 1), and measures the difference between predicted post-transplant survival and survival on the transplant waiting list over a 5-year period (Fig. 2). Mathematical modelling of this scheme was compared to the status quo based on a simulation period from 1st January to 31st December 2013 encompassing 629 donors. This analysis predicted that an additional 45 lives could be saved per year on the transplant waiting list compared to the status quo [39]. Following launch of the new allocation system, a monitoring committee with representation from hepatologists, transplant surgeons and patient groups was established to identify and address any inequities in allocation that develop of time.

Whilst the national transplant benefit-orientated allocation system makes some strides towards demonstrably transparent and equitable organ allocation, some challenges persist. 'Variant syndromes' such as polycystic liver disease constitute a parallel waiting list to which organs are allocated on a proportionate basis with (at present) 10% of grafts offered to the variant list and 90% to the chronic liver disease list. The proportion of offers allocated to each list is reviewed on a regular basis, but despite this, a perception of disadvantage to

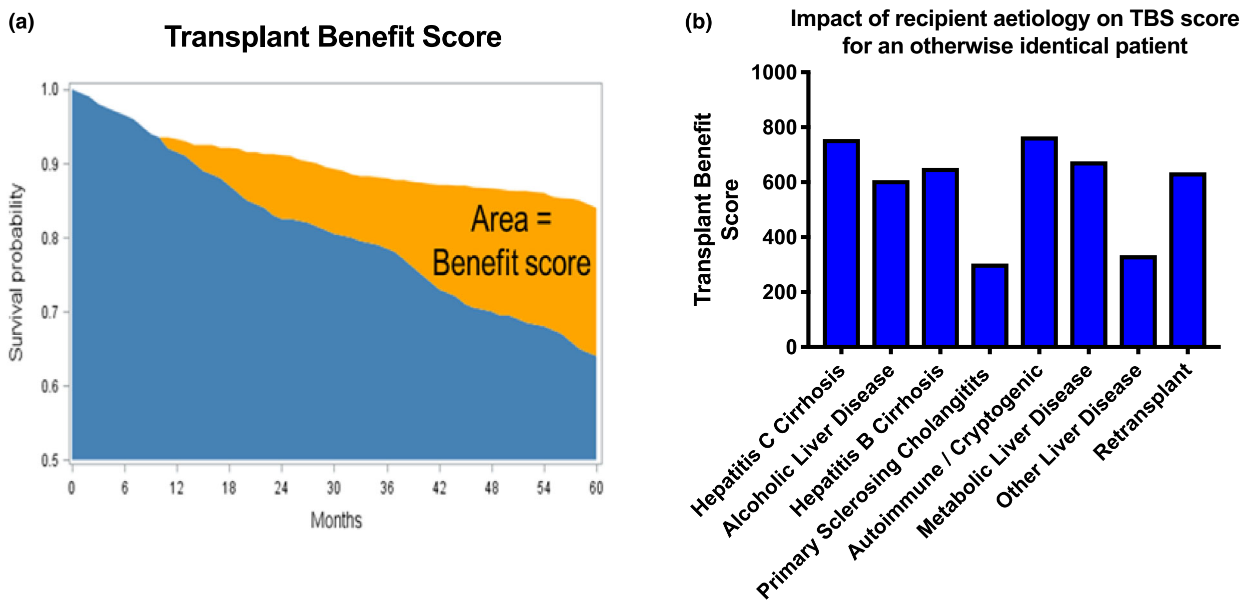

Figure 2 (a) Transplant Benefit Score (TBS) – calculated by subtracting the area under the waiting list survival curve from the area under the predicted post-transplant survival curve. (b) Impact of chronic liver disease aetiology on the TBS (1 of 28 variables that infulence the score). Adapted from NHSBT – National Liver Offering Scheme (2019).

some specific patient groups (in particular those with HCC and preserved liver function) persists [40]. Several additional priority tiers exist – 'super-urgent' (those patients that meet agreed criteria and are expected to live less than 7 days without a transplant) [41], hepatoblastoma/paediatric recipients, multi-visceral transplant recipients and split liver recipients; all of whom are offered livers ahead of patients on the main elective waiting list. In some instances, the potential benefit to an individual on the transplant waiting list vs the waiting list as a whole can be at odds with one another. For example, a patient at the top of the waiting list might be best served waiting for a good-quality organ, whist the remainder of the waiting list might benefit if that patient accepted a poor-quality marginal graft. At present, the new UK liver allocation system only applies to DBD organs; DCD livers continue to be allocated separately on a regional basis. Finally, logistical practicalities and the objective to maximize organ utilization necessitates additional mechanisms such as fast-track offers (available to any patient on the waiting list) made after an organ has been declined for a named patient. All of these factors continue to challenge the equity of the system as a whole. Since the introduction of the new UK liver allocation system in 2018, analysis of outcomes at 3 and 6 months has shown a marginal decrease in mortality on the transplant waiting list [42], but publication of comparative outcomes post-transplantation is still awaited.

What is the future of liver allocation?

The main problem that drives the need to optimize liver allocation is the scarcity of liver grafts. Measures aimed at increasing the supply of deceased donor livers and decreasing the need for transplantation are therefore essential. However, with the current drive to reduce the scarcity of liver grafts, there are many changing trends in donor and recipient populations worldwide that will affect how liver allocation can achieve best outcomes or indeed how these 'best outcomes' are defined. There have been several key changes in indication for liver transplantation with progress in the medical treatment of liver diseases such as direct-acting antivirals for hepatitis C, whilst nonalcoholic steatohepatitis as an indication for liver transplant is increasing [43]. It is likely, however, that indications for liver transplant will continue to expand, to likely include transplantation for colorectal metastases and cholangiocarcinoma. Liver allocation policy must adapt in response to these changes in donor, recipient and disease characteristics. There are several areas that will undoubtedly have a significant impact on liver allocation policies in the near future, including the impact of machine perfusion in improving organ quality with consequential effect on organ–recipient matching. The development of integrated offering systems considering all these issues but also accounting to individual patient situation are desirable and may be achieved by using innovative modelling including large dataset analysis, AI and qualitative data to inform the development of such schemes.

A different way of modelling

As discussed above, serial refinements of liver disease severity and transplant benefit scoring systems have led to marginal gains in equity of access to transplantation and reducing mortality on the transplant waiting list. However, novel validated disease scoring systems and biomarkers are rapidly emerging [44–46] and compensatory scoring 'rules' to address under-served populations (such as patients with HCC) are an imperfect solution [47]. Utilization of artificial intelligence with machine learning that can incorporate evolving biomarkers for prognostication (such as AFP to predict HCC recurrence) [48] and adapt to changes in donor and recipient characteristics in real time presents the prospect of a possible field change in organ allocation in the near future.

Consider the use of expanded criteria grafts

Increasing numbers of expanded criteria donors, including donation after circulatory death donors, has driven progress in techniques to improve organ utilization rates. Normothermic regional perfusion and ex-situ liver perfusion have improved assessment of organ viability [49–51]. These techniques also improve organ preservation and have the potential to re-condition expanded criteria liver grafts or rescue grafts that otherwise would have not been transplanted. Thus, increasing utilization of expanded criteria liver grafts may reduce scarcity of deceased donor grafts but will challenge the current donor risk classification and therefore donor–recipient matching will require re-evaluation at this stage. Criteria to determine which potential recipients may gain the greatest transplant benefit from such grafts are yet to be established.

Allow for expansion of recipient selection criteria

If we accept that liver allocation should be according to transplant benefit, this will have substantial implications for referral criteria for transplant. It has been suggested that liver transplantation should be restricted to patients who are expected to have a comparable 5-year post-transplant survival as patients with end-stage liver disease [52,53]. The Milan criteria for HCC are a prime example of such an approach, defining transplant selection criteria for patients with HCC who are likely to have superior post-transplant survival (a single tumour <5 cm, or up to three tumours, each <3 cm, without evidence of extrahepatic or vascular involvement) [54]. However, some patients outwith the Milan criteria may also have good outcomes from transplantation. Further expansions of the Milan criteria, such as the University of California San Francisco criteria, have been shown to have recurrence-free survival rates close to those achieved by the Milan criteria [55]. Under a transplant benefit allocation scheme, absolute criteria of tumour size and number may not correspond with transplant benefit. Instead, with the use of potentially curative locoregional therapies and considering all patient and disease factors (such as tumour biology), it may be possible to selectively prioritize patients with HCC who will have the greatest transplant benefit [56].

In some countries, the indications for liver transplantation have been extended, where a donor organ can be used if no suitable recipient can be found in the donor country on the general waiting list. In selected patients with unresectable colorectal cancer metastases, 5-year overall survival may be comparable to patients with HCC within Milan criteria (despite having lower disease free survival) [57]. The expected 5-year survival without transplant for patients with unresectable metastatic colorectal cancer is around 10% [58]. Given the length of survival benefit conferred by transplant in a purely transplant benefit-based allocation would demand that these patients should be prioritized for transplantation. Similarly, select patients with early cholangiocarcinoma may have a significant transplant benefit [59–61]. Even without a surplus of donor grafts, it would be inequitable to deny such patients access to transplant if they are expected to have a comparable transplant benefit with patients within currently accepted transplant indications. The use of transplant benefit may help redefine how transplant can help patients with diseases outside current indications.

Interaction with living donor transplantation

Another solution to the shortage of deceased donor grafts may be to expand living donor programs. Expansion of living donation programs in the West has been limited due to the availability of deceased donors, valid ethical concerns of donor safety and the technical difficulties of adult living donor liver transplantation [62,63]. The benefits of living donor transplantation are well rehearsed, but consideration should also be given to the fact that it increases the availability of deceased donor organs to patients who do not have access to a potential living donor [64]. However, there are ethical concerns in prioritizing living donation over deceased donation, including nonmaleficence with the overall reported mortality risks for donors of approximately 0.2% [65,66].

The risk of graft complications (particularly biliary complications) and graft loss may be higher with living donor liver transplantation [67]. However, some waitlist patients stand to derive particular transplant benefit from living donor grafts, such as those whose MELD score does not reflect mortality risk [68,69] and patients with HCC who are at risk of tumour progression beyond transplant criteria with increasing waiting time [70]. The overall consequences of expanding living donor programs and particularly the use of deceased donor grafts as rescue grafts if living donor transplant fails must also be considered.

In 2008, Israel introduced a controversial organ allocation scheme designed to specifically incentivize donation [71]. Medical need was taken into account, but organs were then allocated according to tiers of priority: first for those individuals who have already been a living donor in the past, or those with a first-degree relative that has been a deceased donor. Second, to those who chose to register as a donor. And third, to those with a first-degree relative that choses to register as a donor. This system has been widely criticized for not allocating organs on objective medical considerations alone; however, proponents point out that many systems around the world also give priority to nonmedical considerations (such as death of an intended living donor).

Going beyond traditional outcomes – quality of life measures

The benefit of transplantation has largely been defined in terms of survival benefit: the number of life-years gained or saved. However, quality of life considerations may be at least as relevant to prioritizing waitlisted patients and are an important outcome measure from a patient perspective of the benefit of liver transplantation. At present, the subjective nature of assessing quality of life has restricted inclusion in allocation scoring; but it may be possible to objectively assess the quality of life benefit of transplantation by quantifying the expected difference in quality of life with and without a transplant. This would allow, for example, a parallel waiting list to which donor organs are proportionally offered (e.g. 1 in 10) in a similar arrangement to the 'variant syndromes' list in the new UK National Liver Offering Scheme [39]. Such a change could play an important role in optimizing the impact of liver transplantation to society as a whole by maximizing return to gainful employment.

Conclusion

Progress in organ allocation is defined by the adaptability of organ allocation policy to meet the needs of the transplant population. The changes in allocation policy from an emphasis on waiting times to medical severity and refinements of MELD scoring may have been incremental but have led to significant and continuing progress. The UK adoption of a national transplant benefit-based liver offering system is a substantial change from the needs-based liver allocation, which is still widely applied in practice and may be considered by other systems too. However, progress in organ allocation should be judged on how well it meets the needs of the transplant population it serves.

There is increasing recognition that allocation systems need to continuously evolve to account for changing indications for liver transplantation, improvements in alternative treatments and novel technologies such as machine perfusion that may abrogate many geographical considerations. Continuous monitoring of outcomes categorized according to donor characteristics (indication for transplant, ethnicity, location, etc) will allow for inevitable refinements to be made so that any objective inequity can be minimized. Strategies to improve organ allocation will continue to dynamically evolve and adapt to changes in the transplant population for as long as there is a gap between demand and supply.

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