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Liver-allocation policies for patients affected by HCC in Europe

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Abstract

The main goal of organ allocation systems is to guarantee an equal access to the limited resource of liver grafts for every patients on the waiting list, balancing between the ethical principles of *equity, utility, benefit, need, and fairness*. The European health care scenario is very complex, as it is essentially decentralized and each Nation and Regions inside the nation, operate on a significant degree of autonomy. Furthermore the epidemiology of liver diseases and HCC, which is different among European countries, clearly impacts on indications and priorities. The aims of this review are to analyze liver allocation policies for hepatocellular carcinoma, among different European.

The European area considered for this analysis included 5 macro-areas or countries, which have similar policies for liver sharing and allocation: Centro Nazionale Trapianti (CNT) in Italy; Eurotransplant (Germany, the Netherlands, Belgium, Luxembourg, Austria, Hungary, Slovenia, and Croatia); Organizacion Nacional de Transplantes (ONT) in Spain; Etablissement français des Greffes (EfG) in France; NHS Blood & Transplant (NHSBT) in the United Kingdom and Ireland; Scandiarttransplant (Sweden, Norway, Finland, Denmark, and Iceland). Each identified area, as network for organ sharing in Europe, adopts an allocation system based either on a policy *center oriented* or on a policy *patient oriented*. Priorization of patients affected by HCC in the waiting list for deceased donors liver transplant worldwide is dominated by 2 main principles: *urgency* and *utility*.

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Conflict of Interest

Mario Strazzabosco, Stefano Okolicsanyi, Vincenzo Buscemi, Leonardo Centonze, Luciano De Carlis, Riccardo De Carlis, Stefano Di Sandro, Fabio Ferla, Andrea Lauterio, Raffaella Sguinzi, and Luca Saverio Belli declare no conflict of interest.

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Human and Animal Rights and Informed Consent

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Despite the absence of a common organs allocation policy over the European countries, long-term survival patients listed for transplant due to HCC are comparable to the long-term survival reported in the UNOS register. However, as the principles of allocation are being re-discussed and new proposals emerge, and the epidemiology of liver disease changes, an effort toward a common system is highly advisable.

Keywords

Hepatocellular Carcinoma; liver transplantation; Europe; allocation policy

Introduction

The first attempts to perform liver transplantation (LT) for hepatocarcinoma (HCC) were reported almost fifty years ago, at the beginning of 1967 (1); these cases resulted in early tumor recurrence and death within few months after transplantation. Because of these negative outcomes, HCC was widely recognized as a contraindication for LT (2) until the mid 90's, when the Milan group led by Vincenzo Mazzaferro published his pioneering results showing that the post-transplant survival of patients with early HCC similar to that of non-cancer patients (3). Since then, LT has become the standard of care for early HCC in cirrhotic patient worldwide, and nowadays the so-called "Milan criteria" are universally accepted as the benchmark for patient selection (*for LT in HCC*). When discussing liver transplantation for HCC, one has to distinguish two aspects: one the indication for transplant (Milan criteria, San Francisco criteria, up-to-seven, etc), the other is how to prioritize HCC patients among themselves and as respect to non-oncologic indications.

As highlighted by a recent analysis of ELTR data progressively more LT have been performed for HCC during the last decade (4) a trend confirmed also in UNOS database (5) in US. The growing number of patients with HCC in transplant waiting lists created a new scenario in which HCC patients compete with end stage-liver disease (ESLD) patients for graft allocation. The imbalance between the increasing number of candidates for LT and the limited pool of donors makes it crucial to establish allocation and prioritization policies that ensure fair and equal access.

The goal of allocation systems is to to guarantee equal access to the limited resource of liver grafts for every patients on the waiting list (i.e. cirrhotic patients with ESLF, cirrhotic patients presenting HCC or CCA, metabolic and rare disorders), finding a balance between the ethical principles of *equity, utility, benefit, and fairness*. In 2002, UNOS adopted the Model for End-stage Liver Disease (MELD) scoring system for liver allocation, in order to reduce list mortality and consequently drop-out. The more recent Na-MELD score is based on objective measures, such as total bilirubin and creatinine levels, INR international normalized ratio (INR) and sodium concentration. MELD score provides accurate information about short-term mortality. However, in a number of clinical conditions the risk can not be accurately quantified using the MELD score. These "MELD exceptions" include a diverse array of conditions in addition to cholangiocarcinoma and HCC.

Indeed, most HCC patients present with low MELD scores and their mortality risk is determined by progression of the neoplasm, rather than by further decrease in liver function. To overcome this structural problem and reduce the drop-out from the list, UNOS has recognized HCC as a “MELD exception, and attributed additional MELD points to HCC patients, thereby increasing their priority. This has resulted in a sizable increase in the number of patients transplanted for HCC. UNOS has adjusted this priority a number of times as it was felt to favor HCC patients over those listed for ESLD.

In Europe, there is no central organ that coordinates liver procurement and allocation at a pan-european level (similar to the UNOS/OPTN in US),; rather, there are multiple organ exchange organization, with different rules and systems that operate in different countries and geographical areas. The aim of this review is to analyse liver allocation policies for HCC among these organizations.

Principles of liver allocation policies

The European areas considered for this analysis included 5 macroareas or countries with a similar liver sharing and allocation policy. The 5 areas identified are shown in table 1.

The allocation policy of the livers from deceased donors is dominated by 2 main principles, urgency and utility. The principle of *urgency* is based on the clinical severity of the patient and its prognosis. As the number of patients waiting for liver transplantation is higher than the number of available organs, every liver transplant candidate is exposed to a sizable risk of death or dropout from the waiting list. The urgency policy by calling “the seekest first”, prioritises patients in order to decrease their risk of dropout/death. Centers who adopt an urgency-based policy consider variables such as MELD score, time from listing, and size/numbers of nodules to assign additional MELD points give points to reduce the risk of patient dropout. (6,7,8). Leading models based on the urgency policy for HCC are the HCC-MELD, the deMELD, the new de-MELD) (9). This policy allows the reassessment of risk based on the tumor response to the pre-transplant locoregional treatments. However, in the urgency-based models the outcome of transplantation weighs less than the necessity to provide a possibly life-saving treatment. Unfortunately, the seekest patient does not always represents the ideal patient for transplant because of the higher transplant-related mortality as respects to patients at earlier stage of the liver disease.

On the contrary, for *the utility-based models* the best candidate for transplantation is the patient who may gain the highest number of life-years by transplantation. Therefore, by maximizing the utility of allocation, this model evaluates the survival benefit obtained from the transplant (number of years gained) as respect to those provided by the alternative treatments. This model takes into account both pre- and post-transplant outcomes, including the results of alternative treatments, in view to achieve the best survival benefit from the transplant. Therefore, this model reduces the priority for transplant of patients which gain survival compared to alternative treatments (10, 11, 12) is lower. The limits of this model are essentially related to the outliers. The ideal survival benefit should take into account all the factors that may impair survival of patients before and after transplantation, not only variables related to the underlying disease, but also variables related to the patient baseline

characteristics and lifestyle. Even though appealing from a theoretical point of view, this model may result less effective when applied on the entire cohort of patients waiting for the transplant. Indeed in practice it is extremely difficult to factor-in all the variables affecting survival in a model that accurately fits all needs. Furthermore, the leading studies on the benefit model, were constructed on the basis of 5-year survival rather than on the 10-horizon; this may limit the real appreciation of the benefit of the transplant in comparison to the alternative treatments.

Besides the principles of urgency and benefit, each of the five European areas adopts either a center-oriented or a patient-oriented policy. *Center-oriented* policy means that the organ procurement agency assigns the organ to a specific center, based of geographic and/or other rotational criteria, and subsequently the specific center associates that donor to a proper recipient among those listed at the same center. On the other hand, the *patient-oriented* policy implies that, regardless the geographic distribution or centers rotation, livers are allocated in a common shared list based the patient's absolute priority. The UNOS system may be considered a clear example of a patient-oriented policy.

In Europe, there are several policies in between the two extreme, usually mitigating the center-based policy with nation- or region-wide urgent priority for patients with high MELD score.

European leading policies

The following paragraphs report the allocation and prioritization criteria adopted in the leading 5 European organ sharing systems (see Table 1):

Centro Nazionale Trapianti – Italy

Centro Nazionale Trapianti (CNT) coordinates organ allocation in Italy. Indications for transplant are made following the Milan criteria or the “up to seven”. Liver allocation is center-oriented, and patients are prioritized according to MELD score. There is no central policy about liver allocation for HCC: organs are allocated within each center's waiting-list independently. During the last years, the Bologna group has reported a preferential use of elderly grafts for low-MELD HCC patients (13), and described its internal model of HCC prioritization according to tumor stage and waiting time (14). The Padua group has recently developed and validated a new allocation model for prioritizing both HCC and non-HCC patients according to the common end-point of survival benefit, the so-called “HCC-MELD”, which has been computed according to liver function and AFP level, and calibrated to the survival benefit of non-HCC patients expressed by MELD score (15)

Eurotransplant - Germany, the Netherlands, Belgium, Luxembourg, Austria, Hungary, Slovenia, and Croatia

Eurotransplant (ET) area covers the whole central Europe. Organ allocation is patient-oriented in four countries within ET (Germany, Belgium, the Netherlands, Luxembourg), and center-oriented in the other half (Austria, Hungary, Slovenia and Croatia). Patients are generally selected according to Milan criteria: patients eligible for LT are those presenting with a single nodule <5cm or up to 3 nodules >3cm or patients down-staged within such

criteria. Patients are prioritized according to MELD score. Allocation protocol is well defined inside the ELAS (Eurotransplant Liver Allocation System), and is based upon medical criteria such as blood group, weight, size, and recipient MELD. HCC is considered a MELD exception: those patients receive a starting MELD score equivalent to a 15% probability of death within 3-months at the time of listing (except from Netherlands, where such initial score equals a 10% 3-months mortality risk), and +10% MELD equivalent bonus every three months, provided they remain eligible for LT (i.e. stable disease within Milan Criteria) (16).

Organizacion Nacional de Transplantes – Spain

Organizacion Nacional de Transplantes (ONT) manages organ procurement and allocation in Spain.

Liver allocation is center oriented. Patients are selected according to Milan criteria: patients eligible for LT are those presenting with a single nodule <5cm or up to 3 nodules >3cm or patients down-staged within such criteria. MELD score is adopted for list prioritization. HCC is considered a MELD exception. Allocation rules are decided by consensus among professionals from every transplant center and approved by the representatives from regional health authorities. These rules are updated annually after analyzing in detail the liver transplant activity and taking into account several aspects: donor and recipient characteristics, waiting list time, mortality on the waiting list, probability of being transplanted for different groups of patients, and emergency and retransplantation rates per hospital. A recent survey among 17 Spanish groups highlighted how most of transplant teams actually prioritize HCC patients according to MELD score, assigning extra points according to tumor stage and waiting time (17). National guidelines recommend to prioritize HCC patients assigning 15 to 19 extra points at the time of listing, with the periodical gain of additional points with increasing waiting time (18)

Etablissement français des Greffes – France

Coordinates the whole process of liver procurement and allocation in France. Patients are selected according to Milan criteria: patients eligible for LT are those presenting with a single nodule <5cm or up to 3 nodules >3cm or patients down-staged within such criteria. Liver allocation is patient-oriented. The French Liver Allocation System (FLAS) has been implemented in 2007, takes into account the severity of cirrhosis, which is evaluated with the Model for End-Stage Liver Disease (MELD) score, but it also considers other frequent conditions (eg, HCC and the need for retransplantation) that are not necessarily associated with high MELD scores: for each indication for liver transplantation, specific formulas have been computed according to a national retrospective analysis by the Agency of Biomedicine. Points are given to patients with HCC in addition to the MELD score, which is usually not very high. The number of points depends on the MELD score (the higher the MELD score is, the higher the point maximum is); the maximum point total with the lowest MELD score of 6 is 360 for patients with T1 HCC and 450 for those with T2 HCC. These points are progressively acquired by patients on the waiting list, and the progression rate varies with the HCC stage. For patients with T1 HCC who have a low and stable score and do not progress on the waiting list in the first months, the slope increases until 12 to 18 months; this

ideally leads to access to a graft within a year. In contrast, patients with T2 HCC must obtain access faster. No initial delay is considered, and points are continuously given from the time of listing until the point maximum is obtained; this theoretically leads to access to a liver graft after 6 months. Again, patients with high MELD scores and HCC obtain access to transplantation more rapidly than patients with low MELD scores. (19)

NHSBT - UK, Ireland

NHSBT provides essential support for organ procurement via the new National Organ Retrieval Service introduced in the UK on April 1, 2010. Liver allocation in the UK is center oriented, patient on the waiting list are prioritized by the application of UKELD (a modified MELD including Na as a variable) (20). Patients are selected according to Milan criteria: patients eligible for LT are those presenting with a single nodule <5cm or up to 3 nodules >3cm or patients down-staged within such criteria. Currently the United Kingdom does not award any priority points for HCC patients awaiting liver transplantation, though the outcomes of this policy in terms of waiting list drop out are unknown. (21) The allocation priority at each center is decided by transplant surgeons and physicians on call. National guidelines currently do not specify which patient to select when a liver suitable for more than one recipient is offered. There is a significant number of factors influencing the decision of the transplant professional, including quality and size of the donated liver, blood group, health condition of the potential recipient, and logistics of pressure on intensive care unit beds and on staff. The decision whether a liver should be transplanted into an individual should take account of both recipient and donor factor.

Scandiatransplant (Sweden, Norway, Finland, Denmark, and Iceland)

Scandiatransplant is a collaboration of all organ transplant centers in the Nordic countries - Sweden, Norway, Finland, and Denmark. Liver allocation is center oriented. Patients are selected according to Milan criteria: patients eligible for LT are those presenting with a single nodule <5cm or up to 3 nodules >3cm or patients down-staged within such criteria. The Nordic countries have generally had a favorable organ donation rate with short waiting lists. For this reason, the MELD score is currently not used to prioritize patients for LTX in this region. In some instances, it is used locally at the individual centres to help match an available organ with the patient in greatest need. (22). Center-oriented allocation is used, and each transplant center has its own waiting list and the right to transplant livers procured from a defined geographical area. The MELD score and/or the Child-Turcotte-Pugh scores are usually used in conjunction with clinical (e.g., medical urgency, recipient size, recipient age) and nonclinical parameters (e.g., waiting time) to select patients to be transplanted.

Conclusions

A common organ allocation policy among European countries is still lacking. Most European organizations adopt a center-oriented policy, but no data is available on how the organs are subsequently assigned to actual patients in the waiting list. Differently from the patient-oriented systems, each center establishes its own criteria of prioritization of patients in the waiting list. Interestingly, the leading studies on European patient cohorts report a favorable long term survival and intention-to-treat survival, regardless the policy of organs allocation

(23). It is possible that these differences in transplant policies among the European areas may actually play a favorable role, by allowing flexible adaption to the different local demands, including HCC and ESLD prevalence, donation rates and pool. Patients input into the transplant list is obviously influenced by the indication/allocation policies, and unfortunately, information about patients that are not listed is not available. Thus, despite the favorable general survival, we do not have reliable data to analyze the ability to satisfy the needs, including access and the crucial ethical principles of equity and transparency in the organs allocation policy (3–18).

An urgency-based patient-oriented was used over the past decade by UNOS, and applied by individual European centers. The system was in part utility-based, as only patients inside the Milan criteria (i.e. with better a priori prognosis) were listed. Patients with HCC received a modified and progressive MELD score supposed to reflect the time-based dropout risk that during their waiting time for a given oncologic stage (T1 or T2). Additional points were awarded independently to the response to intermediate treatments. This system created a greater likelihood of transplant patients with HCC compared to patients with non-neoplastic diseases, creating a disadvantage for the latter (12–19).

The *survival benefit* approach is supposed to be more uniform and predictable. Thus, several authors have proposed prioritization models that include variables having a strong impact on the individual patient risk of dropout and post-transplant outcome, such as alpha-fetoprotein (AFP) and MELD score itself. Models based on the survival benefit should promote an ideal balance between the principles of urgency and utility. Vitale et al have proposed a unique method (called HCC-MELD) to equalize the priority among patients with and without HCC, by converging on the common goal to maximize the survival benefit. The HCC-MELD is an upward continuous score that assigns a survival benefit based on variables defining the years of life that a patient earns with the transplant compared to alternative treatments to transplant. This model does not neglect the principle of utility as it also poses a minimum threshold of post-transplant survival of 50% at 5 years, excluding therefore the patients who do not have that expected prognosis. The performance of this model is awaiting validation (15).

Mazzaferro V. (25) recently published a manuscript intended to square the circle in the arena of transplant indication and graft allocation in patients with HCC. The model proposed applies only to BCLC A and B patients, as those with vascular invasion, extrahepatic metastases, or other contraindications are excluded from the transplant, and patients with high MELD would be prioritized according to liver function. The patients who meet inclusion criteria were defined as having a “Transplantable Tumor” (TT). Eight groups of patients affected by TT and otherwise low MELD cirrhosis received a priority basing on tumor characteristics and modality and efficacy of alternative treatments. The lowest priority was assigned to patients that previously underwent radical treatment of HCC and had no viable tumor into the liver at the time of listing (TT_{0c}) or last follow-up. The highest priority, on the other hand, went to patients with recurrent HCC after initial downstaging or after resection performed less than 2 years before the recurrence diagnosis (TT_{DR}). In between of these two stages, the author considered 6 more classes of priority from the lowest to the highest: patients with no viable tumor after effective locoregionale chemo or radio

embolization (TT_{0L}), patients with single active HCC <2 cm (TT₁), patients effectively downstaged with a not transplantable HCC at the time of tumor diagnosis (TT_{NT}), patients with HCC >T1 or recurrent HCC after resection performed longer than 2 years before tumor recurrence diagnosis (TT_{FR}); patients not amenable to alternative treatments of HCC because of ascites, but tumor compatible with transplant criteria (TT_{UT}); patients with not complete response to the bridging loco-regional treatment and viable tumor into the liver (TT_{PR}) (25, 26).

This model aims to overcome the limits of the previous adopted models that considered tumor size and number as the leading risk factors to assess the risk of drop out from before transplantation list and/or a proxy of transplantation outcome. Only recently, few authors have begun to assess the actual weight of tumor response to the bridging loco-regional treatment as a tool to re-assess priority for the patients candidate to LT (26,27). Patients at the same tumor stage in terms of size and number of nodules may have different outcomes based on tumor biology and the response to treatment. The response to the locoregional treatment performed while on the waiting list defines the risk of drop-out (26). The model proposed by Mazzaferro appears able to contemplate the different scenarios of HCC presentation and management and in setting the priorities. By assigning higher priority to those at higher risk of progression after alternative treatment, it makes the best use of the transplant resource (population utility) while still prioritizing the sickest. This model is awaiting to be validated, while further work is needed to balance urgency/utility with the goal to achieve the best benefit in patient survival.

In conclusion, the allocation of livers for patients waiting for transplantation in Europe changes areas-by-areas and sometimes centers-by-centers. Despite that, long-term survival of the community of patients listed for transplant due to HCC results acceptable and comparable to the long-term survival reported in the UNOS register. Physicians should keep exploring alternative allocation policies with the aim to continuously improve the equity and transparency and to improve the effectiveness of the liver transplantation. Future policies should strongly take into account two parameters: the impact of alpha-fetoprotein in candidates and the tumor response to the loco-regional treatments performed while patients are waiting for the transplant. The general scenario is changing at a fast pace because of the impact of Hepatitis C cure worldwide. This will force physicians to re-assess the global allocation policies and indications for liver transplantation in the very next future time.

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•Of importance

••Of major importance

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Table 1

Table reports the 5 european areas identified for the review of the leading allocation systemes for liver tranplant in HCC affected patients ion Europe.

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- Centro Nazionale Trapianti (CNT) in Italy
 - Eurotransplant (Germany, the Netherlands, Belgium, Luxembourg, Austria, Hungary, Slovenia, and Croatia)
 - Organizacion Nacional de Transplantes (ONT) in Spain
 - Etablissement français des Greffes (EfG) in France
 - NHS Blood & Transplant (NHSBT) in the United Kingdom and Ireland
 - Scandiatransplant (Sweden, Norway, Finland, Denmark, and Iceland)
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Table 2

Liver allocation policy for each european area, focusing on HCC prioritization scheme

<i>Country/organization</i>	<i>Center vs Patient Oriented</i>	<i>Allocation system</i>	<i>HCC prioritization</i>
Eurotransplant	Patient oriented	MELD	Extra points
France	Patient oriented	FLAS	FLAS
UK & Ireland	Center oriented	UKELD	NO extra points
Spain	Center oriented	MELD	Extra points (depending on transplant group policy)
Italy	Center oriented	MELD	Extra points (depending on transplant group policy)
Scanditransplant	Center oriented	No MELD	–

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