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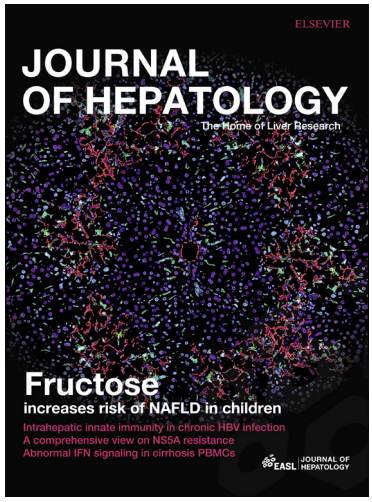

Allocation of Liver Grafts Worldwide Is there a best System?

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Please cite this article as: Tschuor, C., Ferrarese, A., Kümmerli, C., Dutkowski, P., Burra, P., Clavien, P-A., on behalf of theLendoire, J., Imventarza, O., Crawford, M., Andraus, W., D'Albuquerque, L.A.C., Hernandez-Alejandro, R., Dokus, M.K., Tomiyama, K., Zheng, S., Echeverri, G.J., Taimr, P., Fronek, J., de Rosner-van Rosmalen, M., Vogelaar, S., Lesurtel, M., Mabrut, J-Y., Nagral, S., Kakaei, F., Malek-Hosseini, S.A., Egawa, H., Contreras, A.G., Czerwiński, J., Danek, T., Pinto-Marques, H., Gautier, S.V., Monakhov, A., Melum, E., Ericzon, B-G., Kang, K.J., Kim, M.S., Sanchez-Velazquez, P., Oberkofler, C.E., Müllhaupt, B., Linecker, M., Eshmuminov, D., Grochola, L.F., Song, Z., Kambakamba, P., Chen, C-L., Haberal, M., Yilmaz, S., Rowe, I.A., Kron, P.,

Liver Allocation Study Group, Allocation of Liver Grafts Worldwide Is there a best System?, *Journal of Hepatology* (2019), doi: https://doi.org/10.1016/j.jhep.2019.05.025

To appear in: *Journal of Hepatology*

PII: S0168-8278(19)30339-3
DOI: https://doi.org/10.1016/j.jhep.2019.05.025
Reference: JHEPAT 7369

To appear in: *Journal of Hepatology*

Received Date: 11 January 2019
Revised Date: 23 May 2019
Accepted Date: 27 May 2019

Please cite this article as: Tschuor, C., Ferrarese, A., Kümmerli, C., Dutkowski, P., Burra, P., Clavien, P-A., on behalf of theLendoire, J., Imventarza, O., Crawford, M., Andraus, W., D'Albuquerque, L.A.C., Hernandez-Alejandro, R., Dokus, M.K., Tomiyama, K., Zheng, S., Echeverri, G.J., Taimr, P., Fronek, J., de Rosner-van Rosmalen, M., Vogelaar, S., Lesurtel, M., Mabrut, J-Y., Nagral, S., Kakaei, F., Malek-Hosseini, S.A., Egawa, H., Contreras, A.G., Czerwiński, J., Danek, T., Pinto-Marques, H., Gautier, S.V., Monakhov, A., Melum, E., Ericzon, B-G., Kang, K.J., Kim, M.S., Sanchez-Velazquez, P., Oberkofler, C.E., Müllhaupt, B., Linecker, M., Eshmuminov, D., Grochola, L.F., Song, Z., Kambakamba, P., Chen, C-L., Haberal, M., Yilmaz, S., Rowe, I.A., Kron, P., Liver Allocation Study Group, Allocation of Liver Grafts Worldwide Is there a best System?, *Journal of Hepatology* (2019), doi: https://doi.org/10.1016/j.jhep.2019.05.025

Allocation of Liver Grafts Worldwide

Is there a best System?

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Key words: Liver transplantation, Allocation, MELD

Type of article: Original article

Word count: 4951

Figures: 3; 1 supplementary

Tables: 2; 2 supplementary

Conflicts of interest: Patrizia Burra delivered part of this presentation at ELTR/ELITA Meeting in Paris, France, November 25th 2016. PA Clavien delivered part of the material in the manuscript at the AASLD/ILTS postgraduate course in Boston, USA, November 2016.

Financial support statement: None

#**Authors contributions:** For specific questions for accuracy and accountability regarding allocation data from different countries, we kindly ask you to contact directly the contributors of the *Liver Allocation Study Group*. All authors listed contributed to the study concept and design, data collection and writing of the article.

List of Abbreviations:

DBD: deceased brain donors

DCD: deceased cardiac donors

EU: European Union

HCC: hepatocellular carcinoma

LT: liver transplantation

MELD: model of end stage liver disease

NLTR: Nordic Liver Transplant Registry

ONT: Spanish National Transplant Organization

ACO: approved combined organ

AFP: alpha fetoprotein

ALF: acute liver failure

ASH: alcoholic liver disease

BG: blood group

BMI: body mass index

CNT: National Transplantation Center

CTP: Child-Turcotte-Pugh

DCD: donor after cardiac death

ECD: extended criteria donor

ELTR: European Liver Transplant Registry

FAP: familial amyloidotic polyneuropathy

FLAS: French Liver Allocation Score

HAT: hepatic artery thrombosis

HOPE: hypothermic oxygenated perfusion

HPS: hepatopulmonary syndrome

HRS: hepatorenal syndrome

ICU: intensive care unit

INR: international normalized ratio

LDLT: living donor liver transplantation

MDT: multidisciplinary team

NASH: non-alcoholic liver disease

NET: neuroendocrine tumor

NOR: norepinephrine

PH: pulmonary hypertension

PLD: polycystic liver disease

PNF: primary non-function

PPH: portopulmonary hypertension

HHT: hereditary hemorrhagic teleangiectasia

HIV: human immunodeficiency virus

PBC: primary biliary cirrhosis

PSC: primary sclerosing cholangitis

SE: standard exception

SGOT: Serum-Glutamat-Oxalacetat-Transaminase

SGPT: Serum-Glutamat-Pyruvate-Transaminase

TACE: transarterial chemoembolization

TBS: transplant benefit score

TIPS: transjugular intrahepatic portosystemic shunt

Tx: transplantation

UNOS: United Network for Organ Sharing

WL: waiting list

WT: waiting time

Abstract

Background: An optimal allocation system for scarce resources should simultaneously ensure maximal utility, but also equity. The most frequent principles for allocation policies in liver transplantation (LT) are therefore criteria that rely on pre-transplant survival (sickest first policy), post-transplant survival (utility), or on their combination (benefit). Large differences however exist between centers and countries for ethical and legislative reasons.

Aim: To report the current worldwide practice of liver graft allocation and discuss respective advantages and disadvantages.

Methods: Countries around the world performing ≥ 95 or more deceased donor liver transplantations per year were analyzed for donation and allocation policies, as well as recipient characteristics.

Results/Conclusion: The sickest first policy is the most reasonable basis for the allocation of liver grafts. While MELD is currently the standard for this model, many adjustments were implemented in most countries. A future globally applicable strategy should combine donor and recipient factors predicting probability of death on the waiting list, post-transplant survival as well as morbidity, and perhaps costs.

Lay Summary

An optimal allocation system for scarce resources should simultaneously ensure maximal utility, but also equity. While MELD is currently the standard for this model, many adjustments were implemented in most countries. A future globally applicable strategy should combine donor and recipient factors predicting probability of death on the waiting list, post-transplant survival as well as morbidity, and perhaps costs.

Introduction

Liver transplantation (LT) has been undoubtedly one of the most successful procedures developed in the late 20th century, and as a consequence allocation of scarce liver grafts has caused many controversies (Fig. 1-2) [1]. In the early stages of the procedure, from 1980s until mid-1990s, liver grafts were prioritized in the USA based on the degree of sickness and localization of the patients in the hospital [2]. For example, candidates admitted to an intensive care unit (ICU) received the highest priority taking over on patients hospitalized in a non-ICU setting as well as outpatients, somewhat independently of their accumulated waiting time [3]. This policy carried the obvious risk of spoiling the system by forcing competing centers to keep the candidates on the ICU in order to get priority, when an organ became available. Next to the location of the patients, listing time was an important variable; patients listed early in a compensated stage of liver disease could gain much priority [4]. As a consequence, a minimal listing criterion was introduced based on the Child–Turcotte–Pugh (CTP)-score with a minimum of 7 out of 15 points to qualify for listing [5]. The introduction of this additional criterion, however, did not reduce the number of listed candidates because waiting time remained the most important recipient variable for organ allocation, until Freeman et al. reported a lack of correlation between waiting time and waiting list mortality [6]. This has led to a change in paradigm as waiting time was no longer a key criterion for organ allocation [7].

Subsequently, the social and political requests for a better allocation system focusing on patient's medical condition and some notion of justice led to the implementation of the currently widely used allocation policy based on the model for end-stage liver disease (MELD score) [8]. The MELD score is composed of three objective and routine biochemical parameters (serum bilirubin, serum creatinine and

the international normalized ratio (INR) of prothrombin time, which was originally designed as a predictive tool for survival of patients receiving a transjugular intrahepatic portosystemic shunt (TIPS) (supp. Fig. 1) [9, 10]. The model was subsequently validated in a large cohort of patients suffering from chronic liver disease for the prediction of the 3-month mortality irrespective of the etiology of liver disease or presence of portal hypertension [11].

Since 2002, the MELD score has been adopted by the United Network for Organ Sharing (UNOS) in the USA, followed by North Italian transplant (2006), Eurotransplant (2006), Canada (2004-2006), France (2007), Switzerland (2007) and other countries with a high number of transplantations such as China and Brazil (Tbl. 1; Fig. 1-2; supp. Fig 1.) [12, 13]. The MELD-based allocation is consecutively performed by most countries worldwide performing more than 95 LT per year (sup. Tbl. 1) [14]. In contrast, a center specific allocation policy remains popular in other parts of the world, especially in areas with high donation rates, such as Portugal and Scandinavia. As a putative advantage, this policy offers transplant centers the degree of freedom to allocate and match the graft to the presumed optimal recipient. Moreover, some countries like Spain and Canada combine the MELD and the center-specific allocation policy with remarkable outcome results [15]. The UK introduced a new allocation scheme in 2018 based on survival benefit. Priority is given to urgent cases and to those patients on the list with the highest Transplant Benefit Score (TBS), based on the best match of 7 donor and 21 recipient parameters (Tbl. 1; sup. Tbl. 1-2; supp. Fig. 1) [16].

An alternative to these allocations models are scores to define a threshold for declining livers to avoid unfavorable risk accumulation in high MELD patients (BAR, SOFT, D-MELD) (supp. Fig. 1) [7, 17-19]. The BAR score provides a new and simple

scoring system to predict outcome after orthotopic liver transplantation with respect to recipient, donor and graft factors. It was calculated on 37.255 patients in the UNOS (United Network for Organ Sharing) database and identifies the six strongest predictors of post transplantation patient survival. Analysis confirmed the superiority of BAR as compared to other score systems like MELD, D-MELD, DRI and SOFT. The score was validated using the ELTR database. The BAR compared to other scores offers a well-defined cut off for decision making.

The recent extension of transplant indications, for example for malignancy including cholangiocarcinoma, HCC, and colorectal liver metastases, has further aggravated organ shortage and led again to a competition in the allocation for liver grafts (Tbl. 2; supp. Tbl. 2; Fig. 3; supp. Fig. 1) [4, 17, 20-23].

While benchmarking for LT has been implemented in a recent study to define the optimal achievable results in “ideal” candidates [24], it remains however unclear, how non ideal candidates and marginal grafts should be best allocated in face of the huge differences in local legislative regulations, education as well as public attitudes, culture and religion. We report in the following on current distribution systems for liver grafts worldwide (Fig. 1.).

Materials and methods:

To collect data transplant centers from countries around the world performing 95 or more deceased donor liver transplantations per year were contacted (Fig. 1. – 2). A total of 2 email reminders were sent within a period of 4 weeks. All countries replied. All data has been verified multiple times (Tbl. 1 – 2; supp. Tbl. 1 - 2).

Results:

Allocation Systems of Liver Grafts Worldwide

1. Europe

In 2013 more than 7000 liver transplantations, a third of LT worldwide, were performed in Europe (ELTR) [25]. In fact, there is a trend to further increasing LT, mostly due to the increase in donor rates by 25% in several European countries in the past few years [25]. One of the most important findings in the evolution of LT is the significant improvement of results over time, leading to a current 1- and 5-year survival rate of 96% and 82%, respectively (sup. Tbl. 1). Notably, the LT rate in the EU countries vary widely from 8 to more 26 persons per million population (pmp) (Fig. 2). These differences encompass legislation, indications for LT, investments in health care and infrastructure, education, public attitudes, culture, and possibly religion.

1.1. Eurotransplant

Donation policy:	Opt in (DE, NL), Opt out (all others)
Prioritization:	Clinical & MELD
Priority for HCC:	Yes. The Netherlands 10% MELD equivalent, other countries 15% MELD equivalent; additional points: after 90d days 10% MELD equivalent.
Indications for extra points:	Neoplasia, Biliary atresia, PLD, PSC, Haemangioendothelioma, HHT, Cystic fibrosis, FAP, Primary Hyperoxaluria, Urea-cycle disorder, HRS PPH

Eurotransplant is a non-profit organization founded in 1967 covering the international organ-exchange among Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia. While each country in the Eurotransplant program follows its own legislation, including the use of donors after cardiac death (DCD) or prioritization on the waiting list, Eurotransplant has a supra-national mediating role on graft allocation, aiming to prevent graft loss and to achieve a better donor-recipient match. The Eurotransplant region has a population of approx.136 million people. This large donor and recipient pool allows matching between the available donor organs and the patients on the waiting list. Special patient groups like children, high urgent patients or highly immunized patients have therefore a chance of receiving a suitable donor organ in time. A payback rule regulates that a specific country is obliged to offer back a liver – the next available liver with the same bloodgroup - if they have received a liver for a high urgency (ACO) recipient from another Eurotransplant country.

With regard to donation rates, there is a high variability across the Eurotransplant area, ranging from 5.3 pmp in Luxembourg to 37.6 pmp in Croatia. The median deceased donor rate is 14.2 pmp, with an increasing donor age over the past years (current median of 54 years), as the number of octogenarian donors doubled in the last decade. The graft utilization rate is 91% [26].

In the Eurotransplant area, more than 1500 LTs are performed each year in 38 centers. The treaties aim to balance the number of LT considering the high heterogeneity among different countries. LT candidates are listed according to three different prioritization categories: high urgency, combined transplantation with other organs and elective liver transplantation, which accounts for approximately 86% of LT recipients. The main strength caused by the resulting wide donor pool is that patients listed in the first group, in particular urgent re-LT, hepatic artery thrombosis or acute

liver failure, may benefit from a very short waiting time with a median of 2 days. The use of an urgent graft from another country should, however, be compensated by a "payback" graft [27].

LT candidates listed in the elective groups are managed according to national allocation policies. In Germany and the Netherlands, a recipient-driven model determines graft allocation to the sickest patient, regardless of the center. However, in case of donors with hemodynamic instability or technical difficulties, a non-standard allocation model ("extended" or "rescue" allocation systems, accounting for 20-25% LT performed each year) can be used to prevent graft deterioration or loss. In the Eurotransplant program, the MELD score is capped at 40 points, and extra-points are granted to patients with well-defined exceptions such as biliary atresia, primary hyperoxaluria, urea cycle disorder, haemangioendotheloima and others (Tbl. 1-2; supp. Tbl. 1-2; Fig. 1–3 and supp. Fig. 1) [27].

1.2. Scandiatransplant

Donation policy: Opt-out

Prioritization: Clinical, waiting time

Priority for HCC: No

Indications for extra points: Not applicable

In contrast to middle Europe, Nordic European countries are characterized by significant societal and cultural differences reflecting on the prevalence of liver donations and, subsequently LT. According to the Nordic Liver Transplant Registry (NLTR), primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) account for more than 20% of indications for LT, whereas HBV or HCV-related cirrhosis represent less than 10%. The number of candidates active on the waiting list

(110 patients), the waiting time to get a graft and consequently mortality on the waiting list (about 6%) are lower than in any other area around the globe. Given that the MELD score predicts 3-month survival for patients with cirrhosis, it is clearly not a useful tool to assess prioritization in a population with such underlying characteristics. Therefore, Scandinavian countries have kept a center-driven allocation policy.

According to the NLTR, which is managed by Scandiatransplant, > 5000 LT have been performed since the first LT performed in Helsinki in 1982. Supply of grafts is high with donation rates ranging from 15.3 pmp in Denmark to 40 pmp in Iceland [28, 29]. With regard to donor age, Scandiatransplant present data similar to other European countries, with a median donor age of 54 years, and a homogeneous increase in the utilization of organs from septuagenarian and octogenarian donors. One and 5-year post-LT survival is 92% and 81%, respectively [28].

The high organ availability in Scandinavian countries has led to a broadening of indications in LT. For example, a modest expansion of Milan criteria for HCC, which represents only 9% of indications has been adopted according to the Oslo Criteria in 2005 in Norway [28, 30]. Median time on the waiting list for HCC patients is short, probably because of the good balance between the HCC burden on the waiting list and the center-driven allocation policy. Post-LT survival for HCC (1 and 5-year 85% and 57%) is lower than for non-HCC recipients, which is comparable with data from different allocation systems [31].

In addition to expanding the criteria for HCC, the group from Oslo investigated in a single center prospective pilot study the post-LT outcome of 21 patients with non-resectable colorectal liver metastases. After a median follow-up time of 27 months,

the 1- and 5-year estimated post-LT overall survival were 95% and 60%, respectively, and a 35% 1-year disease free survival. Although the authors demonstrated a survival comparable to re-LT patients, data have to be clearly confirmed with larger studies and several ethical and cultural concerns have to be faced before considering non-resectable liver metastases as a stable indication for LT (Tbl. 1-2; supp. Tbl. 1-2; Fig. 1–3 and supp. Fig. 1) [32, 33].

1.3. France

Donation policy:	Opt-out
Prioritization:	Clinical, French Liver Score
Priority for HCC:	Only for recurrent HCC, extra points granted (Recurrence of a treated single HCC within AFP-score)
Indications for extra points:	Recurrent HCC, PLD, HHT, Amyloidosis, Metabolic disease, Recurrent cholangitis, HPS, Ascites

The National transplant program in France is managed by the “Agence de la Biomédecine”, founded in 2004. The LT program has grown over the past decade with the usage of DCD organs after a specific legislation passed in 2010, and the establishment of organ donation as a national priority. HCC has become the lead indication in 2014, followed by alcohol-related cirrhosis (30% and 28% of the indications, respectively) [34].

The allocation rules for DBD have been modified in France in 2007, up to this time allocation followed a center-driven policy with the exception of emergency transplantation. This system was associated with significant differences in waiting list mortality ranging from 3% to 24% depending on the region. A new allocation system,

the French Liver Allocation Score (FLAS), is currently in place affecting nearly 80% of liver grafts in 2015 [15]. This score reflects severity of cirrhosis according to MELD score, but attributes also a defined number of points for the accumulation waiting time. The French allocation system allows to include patients with HCC outside the Milan criteria as well as those undergoing surgical resection before disease recurrence [30]. In addition, the Liver Transplantation French Study Group has shown that the prediction of tumor recurrence is improved significantly by a model that incorporates α fetoprotein (αFP) [35]. With regard to the DCD program, only 5 centers have been authorized to perform organ procurement to date (Tbl. 1-2; supp. Tbl. 1-2; Fig. 1–3 and supp. Fig. 1).

1.4. Italy

Donation policy: Opt-out

Prioritization: Clinical, MELD

Priority for HCC: Yes, extra points granted at listing

Indications for extra points: HCC, Complications of PH

The Italian organ transplantation network is governed by the National Transplantation Center (CNT) with more than 1000 LT since 2014, half of which have been performed in 6 centers in Northern Italy. There are 21 LT centers in 13 regions, grouped into 2 macro areas (central-Northern and central-Southern Italy). Interregional institutions (e.g. the North Italian Transplant programs) have a mediating role among centers granting graft rotations respecting a pay-back system, and directly collaborate with the CNT. In Italy, significant differences exist regarding organ donation between Northern and Southern regions (mean donation rate in Italy

22.6 pmp in 2015, ranging from 9.8 pmp in Sicily to 48 pmp in the region of Tuscany) [36].

Organs are shared nationwide for the most severely ill candidates in a super-urgent setting, by macro-area for patients with MELD ≥ 30 and regionally for patients with MELD < 30. A large cohort of Italian LT recipients (n= 2061) were recently compared with a matched English cohort (n=2121) showing that strategies to drive allocation are lacking in both cohorts, except for split-livers (mainly allocated to non-HCV recipients) and HCC patients who received grafts from older donors [37]. Thus, a recent consensus conference was held to identify new allocation policies respecting criteria for MELD exceptions [38]. A DCD program has been started in Milan Niguarda Hospital since 2015 with 28 liver transplantations performed so far (Tbl. 1-2; supp. Tbl. 1-2; Fig. 1–3 and supp. Fig. 1) [39].

1.5. Spain

Donation policy:	Opt-out
Prioritization:	Clinical, MELD
Priority for HCC:	Yes, extra points granted
Indications for extra points:	HCC (region-specific)

Liver transplantation started in Spain in 1984, currently involving 24 centers, five of which include a pediatric LT program. More than 1000 LT/year are performed in Spain, which translates in the highest European transplant rate (25 pmp) and one of the highest European organ donation rates (39.7 pmp), with an increasing trend over time [40]. Since 2008, a nationwide plan has been put in place to identify potential donors to be referred to appropriate ICUs. The plan encourages the use of extended

donor criteria organs including DCD [41]. The DCD program expanded much since 2014 with the use of controlled DCDs making Spain the third country for the use of DCD organs after the US and UK [42].

The country is subdivided in several regions each with its own particularity regarding the organ allocation process. The National Spanish Organization (ONT) manages organ allocation through a center-oriented strategy, even if nationwide allocation is granted for super-urgent cases. The center-driven allocation policy allows for a clinician-guided decision independent of the degree of sickness of the potential candidates, as the final decision regarding donor-recipient matching is made internally by the local team. In contrast to other countries with a center-driven allocation policy, the Spanish centers also utilize the MELD system to guide patient allocation (Tbl. 1-2; supp. Tbl. 1-2; Fig. 1–3 and supp. Fig. 1) [43].

1.6. Switzerland

Donation policy:	Opt-in
Prioritization:	Clinical, MELD, waiting time
Priority for HCC:	Yes, extra points granted (at listing: 14; additional 1.5 points/month)
Indications for extra points:	Neoplasia, Amyloidosis, Primary Hyperoxaluria, HRS, PPH

The Swisstransplant foundation manages organ allocation throughout the country. Organ donation rates remained low at 14.1 pmp. Only three liver transplant centers are active to cover about 100 -120 liver transplants per year. MELD allocation was introduced in 2007 in view of significant waiting list mortality, with HCC patients receiving 1.5 points per month, starting at MELD 14. Non-standard exceptions are

granted by a national audit group, if needed. Based on poor donations rates to cover many high-risk candidates, the balance of risk (BAR) score was developed in 2011, which sums up six key donor and recipient risk factors (donor age, cold ischemia, recipient age, retransplantation, ventilator dependency, MELD score) for reliable prediction of patient survival [18]. This score has been validated in the UNOS and ELTR databases. A DCD liver transplant program has been started in 2012 in Zurich with the use of a newly designed machine perfusion technique, hypothermic oxygenated perfusion (HOPE), which is applied end-ischemic directly before implantation [44]. Since 2018 both other programs are also using DCD grafts (Tbl. 1-2; supp. Tbl. 1-2; Fig. 1–3 and supp. Fig. 1).

1.7. United Kingdom

Donation policy:	Opt-in
Prioritization:	TBS, UKELD
Priority for HCC:	No
Indications for extra points:	Recurrent cholangitis, Metabolic disease, HPS

The UK LT program is the oldest one in Europe, since the first LT was performed in Cambridge in 1968 [45]. This program accounts for about 850 LT per year covering only 7 centers (one in Scotland and six in England) [46]. There has been an increasing number of donations (20.3 pmp in 2015) and LT's over the past 5 years (+26% from 2011 to 2015), mostly as a consequence of an operative Task Force. The second reason is the wide use of donors after cardiac death (DCD). UK is the second country in terms of the frequency of DCD organ utilization after the US,

which contributes to more than 20% of the donor pool [47]. The donation process is, however, accompanied by a high discard rate (national offer decline rate is 15% for both donors after brain and cardiac deaths), due to a high donor age and predicted high-risk transplantation.

The assessment of waiting list prioritization in the UK was established by UKELD, which was developed after a nationwide evaluation of the English LT scenario [48]. All non-HCC patients listed for LT in the 7 LT centers across the UK from 2003 to 2006 were evaluated, identifying a specific score (comprising sodium, creatinine, INR and bilirubin), that performed better than MELD score in predicting survival. The allocation system has been center-driven until 2018, with designated zones periodically revised and rebalanced among centers, although a prioritization for super-urgent patients (ALF, or early graft failure) is nationally assured. The UK introduced in 2018 a new allocation scheme. Priority is still given to those patients on the 'super urgent' list. However, if there is no patient on the super urgent list, the available liver is then offered to patients on the list with the highest Transplant Benefit Score (TBS) taking into account 7 characteristics from the donor and matching those with 21 recipient characteristics (Tbl. 1-2; supp. Tbl. 1-2; Fig. 1–3 and supp. Fig. 1) [16].

2. North America

2.1 USA

Donation policy:	Opt-in
Prioritization:	MELD-Na

Priority for HCC:	None at listing. Median MELD at transplant at surrounding centers less 3 MELD points starting 6 months after listing.
Indications for extra points:	Neoplasia, Cystic Fibrosis, FAP, Primary Hyperoxaluria, Metabolic Disease, HPS, PPH

Organ allocation is managed in the US by a private non-profit organization, the united network for organ sharing (UNOS). MELD allocation was introduced in 2002 based on increasing deaths on the waiting list. The previously defined status I for urgent transplant was maintained, but MELD replaced status 2A - C. Concerns have been expressed on the increased post-transplant mortality and morbidity when strictly following a sickest-first allocation policy, although most studies failed to show greater mortality with higher MELD recipients, while undoubtedly morbidity and cost significantly increased [49, 50]. The median MELD score at transplant still differs greatly based on geography across the US and efforts are underway to resolve this issue. In 2016, allocation according to the MELD-Na was introduced (Tbl. 1-2; supp. Tbl. 1-2; Fig. 1–3 and supp. Fig. 1) [51]. In 2019, ECD were approved by the Board of directors of the OPTN. The implementation is still pending

2.2 Canada

Donation policy:	Provincially based
Prioritization:	MELD-Na
Priority for HCC:	Yes, extra points granted (22 at listing; 3 points/3 months thereafter)
Indications for extra points:	Neoplasia, PLD, Cystic fibrosis, FAP, Primary Hyperoxaluria, Metabolic disorders, HPS, Failed LDLT / DCD

The organ allocation system in Canada has been historically based on the CanWAIT algorithm, which prioritized patients according to where the patient is located (home, hospital ward *vs.* ICU) and the severity of liver disease [52, 53]. In close similarity to the previously utilized allocation systems based on Child-Pugh criteria, the CanWAIT algorithm relied heavily upon waiting time to break ties within categories. Since the MELD allocation has been shown to be superior to the CanWAIT system for predicting waitlist mortality, centres gradually began to adopt MELD liver transplant allocation regionally for non-urgent status patients. Starting in January 2015, Canada adopted MELD-Na for allocation of liver transplants, although, considerable heterogeneity remained in listing criteria regarding MELD exceptions. For example, British Columbia and Atlantic Canada use the Milan criteria for their patients with HCC. However, they will consider patients with tumors within the UCSF criteria, on a case-by-case basis. In Alberta, London and Ontario, total tumor volume and αFP are used as selection criteria, although patients can also be transplanted within UCSF criteria in the latter two provinces. Due to the regional heterogeneity in listing criteria, there is at present a strong focus on advancing consensus about allocation criteria for LT within Canada (Tbl. 1-2; supp. Tbl. 1-2; Fig. 1–3 and supp. Fig. 1) [54].

3. Latin America (Brazil, Colombia, Argentina and Mexico)

Argentina:

Donation policy:	Opt-in
Prioritization:	MELD
Priority for HCC:	Yes, extra points granted (22 at listing; additional 1 point/3 months)
Indications for extra points:	HCC, PLD, FAP, HPS

Brazil:

Donation policy:	Opt-in
Prioritization:	Clinical, MELD, Waiting time
Priority for HCC:	Yes, extra points granted (20 at listing; 24 points after 3 months, 29 points after 6 months)
Indications for extra points:	Neoplasia, PLD, FAP, Metabolic diseases, Recurrent cholangitis, HPS, Post-LDLT

Colombia:

Donation policy:	Opt-out
Prioritization:	Clinical, MELD, waiting time
Priority for HCC:	Yes, extra points granted (22 at listing)
Indications for extra points:	HCC, Age

Mexico:

Donation policy:	Opt-in
Prioritization:	Clinical, waiting time
Priority for HCC:	No
Indications for extra points:	None

With the recent increase of the number of LT by about 6% per year, Latin America has become a very active part of the world [55]. This region has a population of 589 million, representing 8.5% of the world population, and more than 2,500 LT are performed per year (corresponding to 17% of world activity). The outcome of LT in some Latin America countries, such as Brazil (9.2 pmp) and Argentina (9.0 pmp), is comparable to those in more developed countries. However, LT is still not performed in 35% of Latin American countries, which is mostly due to the lack of adequate financial coverage, education as well as organization. MELD–based allocation has been adopted in Argentina and Brazil. In addition, split, domino, and

living-donor adult and pediatric transplantations are also routinely performed with comparable outcomes to the rest of the world. HCC patients receive standard exception points, e.g. Brazilian patients with tumors > 2cm in diameter within the Milan criteria, receive 24 points after 3 months on the waiting list. In addition, extra points are awarded for a wide variety of conditions such as NET metastases, familial amyloid polyneuropathy or hepatopulmonary syndrome (Tbl. 1-2; supp. Tbl. 1-2; Fig. 1–3 and supp. Fig. 1).

4. Asia-Pacific Region (South Korea, Iran, India, China, Taiwan, Australia/New Zealand)

For details see Tables 1-2 and supp. Tables 1-2

The countries with the highest living donor rates in the Asian-Pacific region have unanimously adopted the allocation systems based on the MELD score for their cadaveric organs. Interestingly, at 28.7 per million population, South Korea has currently one of the highest donor rates per million inhabitants worldwide. However, the deceased organ donation rate remains low. This is due to the fact that the rapid development of LT in South Korea has been spurred by the widespread acceptance and adoption of living donor liver transplantation (LDLT) [56]. Indeed, since the first LT performed in South Korea in 1988, LDLT accounted for approximately 76.5% of all liver transplantations in this country [57].

A large majority of liver transplants performed in India are currently through live donation. However, in some states in the Southern & Western regions deceased donor liver transplants form a substantial proportion [58]. A national body to regulate transplantation called National Organ & Tissue Transplant Organisation (NOTTO) has recently been set up in India. There are currently two broad liver allocation

models. Both these models recognise a super urgent category. Beyond this, allocation is either done by waiting list chronology or by rotational allocation to all the recognised liver transplant centres [58]. There is a growing recognition that the model needs to change to a severity-based allocation, however, given limited regulatory power most states have found this challenging to implement. Data on outcomes of liver transplantation in India is currently very inadequate as there is no national registry.

The Asia-pacific region also hosts the Australia & New Zealand Liver Transplant Registry. All centers share organs for cases of fulminant hepatic failure. The large majority of LT are performed in Australia (281 LT/y). The MELD score is used for organ allocation and 22 extra points are awarded for patients with HCC (>2cm and within UCSF) with an additional 2 points every 3 months (Tbl. 1-2; supp. Tbl. 1-2; Fig. 1–3 and supp. Fig. 1) [59].

Discussion

Both the MELD- and center-based allocation systems suffer from inherent limitations. A center-specific allocation system fails to provide an objective tool in assigning the need for a LT resulting in more deaths on the waiting list, when compared to a MELD score-based policy. This shortcoming certainly holds true especially in countries, which badly suffer from organ shortage. Differences in transplant rates between countries should also include causes of death. A metric that looks at effectiveness of the donation system is really the number of potential donors who become actual donors. Allocation and distribution of livers from deceased donors is a challenge and different jurisdictions have adopted slightly different approaches. In view of the recent and repetitive scandals in the transplant business, an objectively founded allocation process of limited resources appears mandatory [60]. Allocation by recipient's lab MELD score is transparent and objective, but fails taking into account additional relevant patient-specific factors, such as factors related to the quality of life (e.g. refractory pruritus), the presence of recurrent cholangitis or cancer (Fig. 2; supp. Fig. 1) [61].

Limitations of the MELD allocation system are addressed by most players including several countries or allocation systems. First, by adding extra-points to the recipient's laboratory MELD score (so-called standard vs. nonstandard exceptions) to allow candidates not well served by laboratory changes to compete with higher MELD-score recipients [62]. The amount of added points, and its further increase during waiting time remains, however, quite subjective and therefore highly inconsistent among countries (supp. Tbl. 1). Next, all MELD-based allocation systems have been criticized for not defining a threshold for being too sick for transplantation [23, 63-65]. To address the issue of futile LT and waste of available

grafts, i.e. the concept of utility, a variety of additional scores were developed to predict poor outcomes. The most accurate scores combine donor and recipient factors, such as D-MELD, Delta MELD, survival outcome following LT (SOFT), balance of risk (BAR) score, University of California Los Angeles futility risk score (UCLA-FRS) and survival benefit analysis (Fig. 2; supp. Fig. 1)[19, 64, 66-68]. A further development in this direction is the use of artificial neural networks by combing approximately 60 donor, graft, and recipient factors to identify best matches [28, 69]. Despite all these efforts, however, refusing a liver offer for a very sick transplant candidate remained a major challenge and responsibility since outcome prediction, not uncommonly, differs among the many available scores and formulas.

Cancer as an indication for LT requires special attention, as well as the long-term side effects of immunosuppression in this population. For example, twenty years after the introduction of the Milan criteria to select patients with HCC for LT, it is still unclear what would be an acceptable aim in recipients transplanted for cancer, some have suggested 50% 5-year survival rate [70]. Several other models (e.g. UCSF, up to seven, total tumor volume, Kyoto criteria, extended Toronto criteria, MORAL score) have been introduced, which typically claim comparable predictive values [30, 71-74] (Fig. 3.; Tbl. 2; supp. Tbl. 1-2). Microvascular invasion seems to be the predictive key factor, however a reliable and convincing serum or easy available marker is still missing [75]. Furthermore, it is unclear how to include other malignancies qualifying for LT, such as perihilar or intrahepatic cholangiocarcinoma, or colorectal liver metastases [32, 33, 76-79].

The success of LT over the past 30 years is indisputable and indications are likely to widen with the availability of less toxic immunosuppression, leading to an ever increasing need for available grafts. Increasing the donor pool relies on living

donation or the use of marginal organs, such as steatotic livers or livers donated after cardiac death (DCD) [18, 80, 81]. Those liver grafts yield a higher risk for failure (primary non function) after implantation or developing irreversible biliary injury (ischemic cholangiopathy), usually when associated with prolonged warm ischemia inherent to the DCD procurement [82, 83]. Several countries with DCD experience prefer to allocate DCD organs according to a center-specific policy (Tbl. 1.) [42, 84, 85]. Optimizing techniques such as machine perfusion technology is likely to gain wide acceptance to enhance organ quality with an increased availability of grafts for transplantation [86, 87].

In conclusion, while a perfect liver allocation system is currently not available, the sickest first policy represents the most reasonable basis for allocation of liver grafts. MELD is currently the standard, however, adjustments have to be implemented for diseases poorly served by a liver failure score such as for PSC, metabolic disorders or cancer. The BAR score is currently a valuable and easy tool to identify high-risk cases for post-transplant mortality and to compare results among centers. BAR compared to other scores offers a well-defined cut off for decision making. A future globally applicable model should combine donor and recipient factors predicting probability of death on the waiting list, post-transplant survival as well as morbidity including associated costs. Moreover, a globally applicable model of allocation of liver grafts has also to take into account regional ethical, moral, and religious, as well as cultural aspects.

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Table 1. Donation policies worldwide.

	Donation policy	*ECD*	*DCD per year (%)*	*Retrieved livers (n)*	*Livers discarded (%)*	*Livers tx (pmp)*
Portugal[‡]	Opt-out	DCD	low*	290	6.6	26.3
Spain[†]	Opt-out	DCD	13.3	1665	26.8	24.9
United States of America [88][†]	Opt-in	Age >70 years[§] DCD[§]	6.1	8529	8.7	24.1
Italy[†]	Opt-out	Age >65 years DCD	0.9	1599	25.0	20.0
France [89][†]	Opt-out	na	1.7	1327	3.6	19.8
Czech Republic[†]	Opt-out	DCD	low*	260	30.0	19.5
Turkey [90][†]	Opt-out	Age >65 years	Na	598	26.8	17.5
Scandiatransplant[‡] (Sweden, Norway, Finland, Denmark, Iceland, Estonia) [29]	Opt-out	DCD	Norway 1 Overall 0,5	417	na	15.5
United Kingdom[‡]	Opt-in	Center-dependent	22.8	1116	15.0	15.4
Canada [91][†]	Provinci-ally based	DCD	6.2	226	8.0	13.4
Australia & New Zealand [92,93][†]	Opt-in	Age >70 years DCD Steatosis >30%	3.6	304	24.1**	11.5
Switzerland	Opt-in	na	16[‡]	136[#]	4.4[#]	11.4[†]
Eurotransplant[†] (Austria, Belgium, Croatia, Germany, Hungary, Luxem-burg, Netherlands, Slovenia) [94]	Opt-in (DE, NL) Opt-out (all others)	Age >65 years Steatosis >40% ICU stay with ventilation >7 days BMI >30kg/m2 Sodium >165 mmol/l SGPT >105 U/l SGOT >90 U/l Serum Bilirubin >3 mg/dl	NL 37.5 BE 24.9 Overall 8.6	1661	8.5	11.1
Iran[†]	Opt-in	Age >65 years Steatosis >40% Sodium >165mmol/l Intoxication	na	926	16.0	9.5
Brazil[†]	Opt-in	Age >60 years Steatosis ICU stay >7 days NOR >0.5µg/kg/min	na	3488	44.9	9.2
Argentina [95]	Opt-in	na	na	732[‡†]	3.4[‡†]	9.0[†]
South Korea[†]	Opt-in	DCD	na	515	17.3	8.3
Poland[‡]	Opt-out	na	na	343	7.6	8.3
Colombia	Opt-out	na	na	190[#]	na	5.0[†]
Taiwan [96][†]	Opt-in	Age >65 years DCD	Started in 2017	96	10.4	4.7
China[†]	Opt-in	Age >65 years	na	5146	14.4	2.4
Russia [97][†]	Opt-out	Age >65 years	na	375	18.1	2.1
Mexico [98][†]	Opt-in	Age >65 years	na	182	7.7	1.5
India[§§†]	Opt-in	Steatosis	na	45	6.7	na

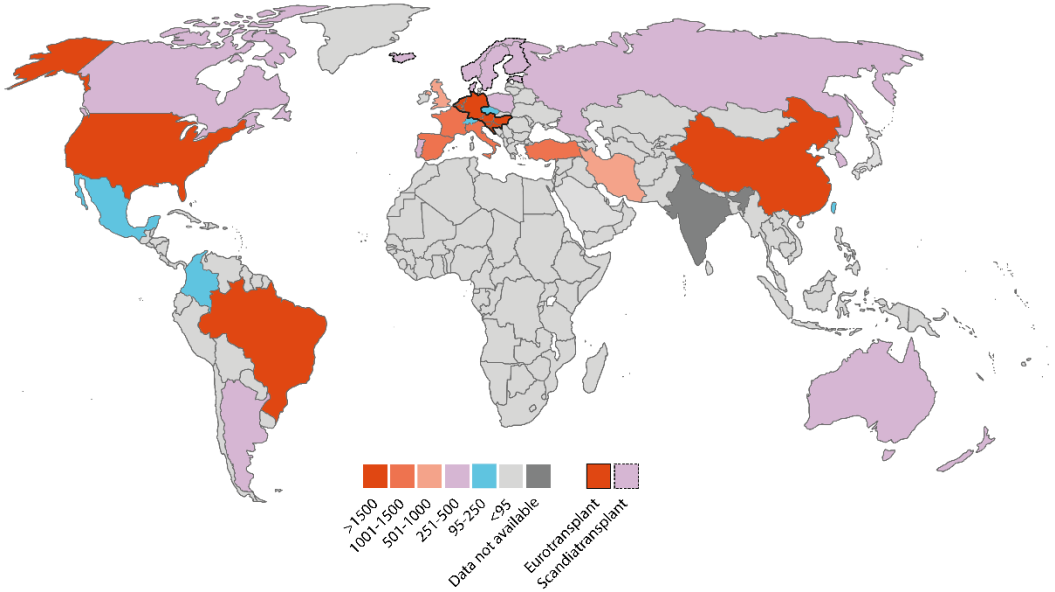
[‡] data from 2016; * less than 5/year; [†] data from 2017; [§] 2019 approved by the Board of Directors of the OPTN. Implementation pending; ** only New South Wales; [#] data from 2018; [§§] Mumbai only;
BE, Belgium; BMI, body mass index; DCD, donor after cardiac death; DE, Denmark; ECD, extended criteria donor; ICU, intensive care unit; na, not available; NL, Netherlands; NOR, Norepinephrine; SGPT, serum-Glutamat-Pyruvate-Transaminase; SGOT, Serum-Glutamat-Oxalacetat-Transaminase; tx, transplanted

Table 2. Allocation for hepatocellular carcinoma.

	Allocation rules	*% of Tx*	*Prioritization*	*Points at listing*	*Additional points*
Portugal	Center-oriented	21.8‡	Milan MELD	None	No
Spain	Regional	28.4†	Milan MELD	Region-specific	Region-specific
United States of America [88]	National incl. regional	20.5†	MELD	None	Median MELD at transplant at surrounding centers less 3 MELD points starting 6 months after listing§
Italy	Center-oriented	22.7†	Milan	Yes	No
France [89]	Patient-oriented	35†	AFP Score	None	Recurrence of a treated single HCC within AFP-score
Czech Republic	Center-oriented	21.2†	Milan	None	6 months after listing
Turkey [90]	Center-oriented	na†	Milan MELD	None	No
Scandiatransplant (Sweden, Norway, Finland, Denmark, Iceland, Estonia) [29]	Center-oriented	13.5‡	Clinical Waiting time	None	No
United Kingdom	Patient-oriented DCD Center-oriented	21‡	TBS Modified Milan UKELD	None	No
Canada [91]	Provincial	31.6†	Milan	22	3 points/3 months
Australia & New Zealand [92, 93]	Center-oriented	19†	UCSF MELD	22	2 points/3 months
Switzerland	Patient-oriented	20.5‡	MELD	14	1.5 points/month (constant); inital value + (number of months)*1.5
Eurotransplant (Austria, Belgium, Germany, Croatia, Luxemburg, Netherlands, Hungary, Slovenia) [94]	Center-oriented (Austria, Slovenia, Croatia, Hungary) Patient-oriented (Netherlands, Belgium, Luxembourg, Germany)	28†	Milan MELD	The Netherlands 10% MELD equivalent (MELD 20), other countries 15% MELD equivalent (MELD 22)	After 90d days 10% MELD equivalent
Iran [99]	Center-oriented	5.2†	Milan MELD	24	No
Brazil [100]	Regional	23.8†	Milan Waiting time	20	24 points after 3 months, 29 points after 6 months
Argentina [95]	National	9†	MELD	22	1 point/3 months
South Korea	National	12.3†	Milan MELD	MELD 0-13: additional 4 points MELD 14-20: additional 5 points	No
Poland	na	3.2†	na	None	No
Colombia	Center-oriented	20†	Milan MELD	22	No
Taiwan [96]	Center-oriented	30.6‡	MELD Waiting time	10% of MELD points	10% of MELD points
China	Patient-oriented	34.5‡	MELD	None	No
Russia [97]	Center-oriented	26,8†	UCSF MELD	None	Depends on center policy
Mexico [98]	Center-oriented	18†	na	None	No
India	Center-oriented	10†	UCSF	None	No

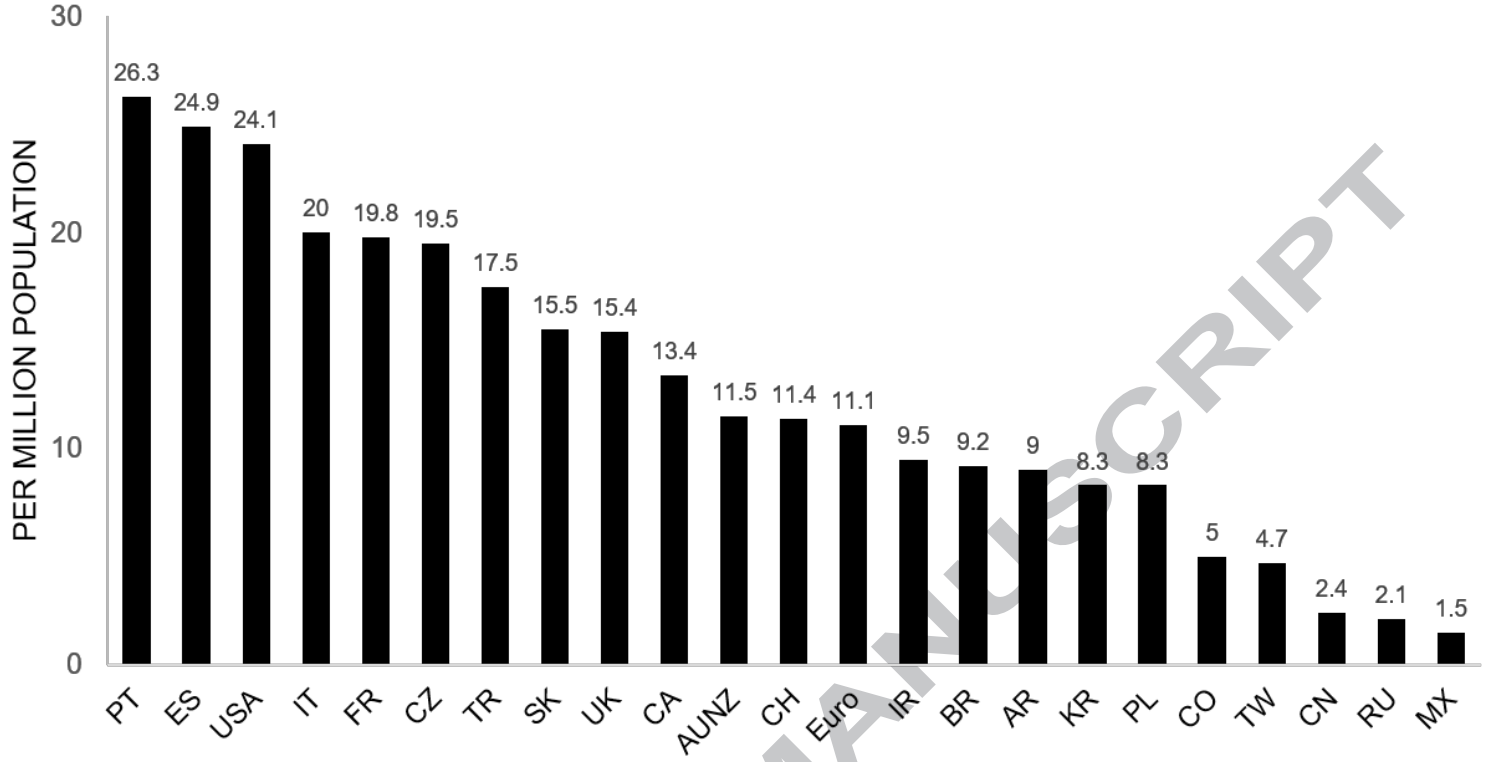
‡ data from 2016; † data from 2017; § 2019 approved by the Board of Directors of the OPTN. Implementation pending;
AFP, alpha fetoprotein; DBD, donor after brain dead; DCD, donor after cardiac death; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; na, not available; MELD-Na, sodium model for end-stage liver disease; SE, standard exception; TACE, transarterial chemoembolization; Tx, transplantation; UCSF, University of California San Francisco

Figure 1: Deceased donor liver transplantation per year



Data from 2016/2017

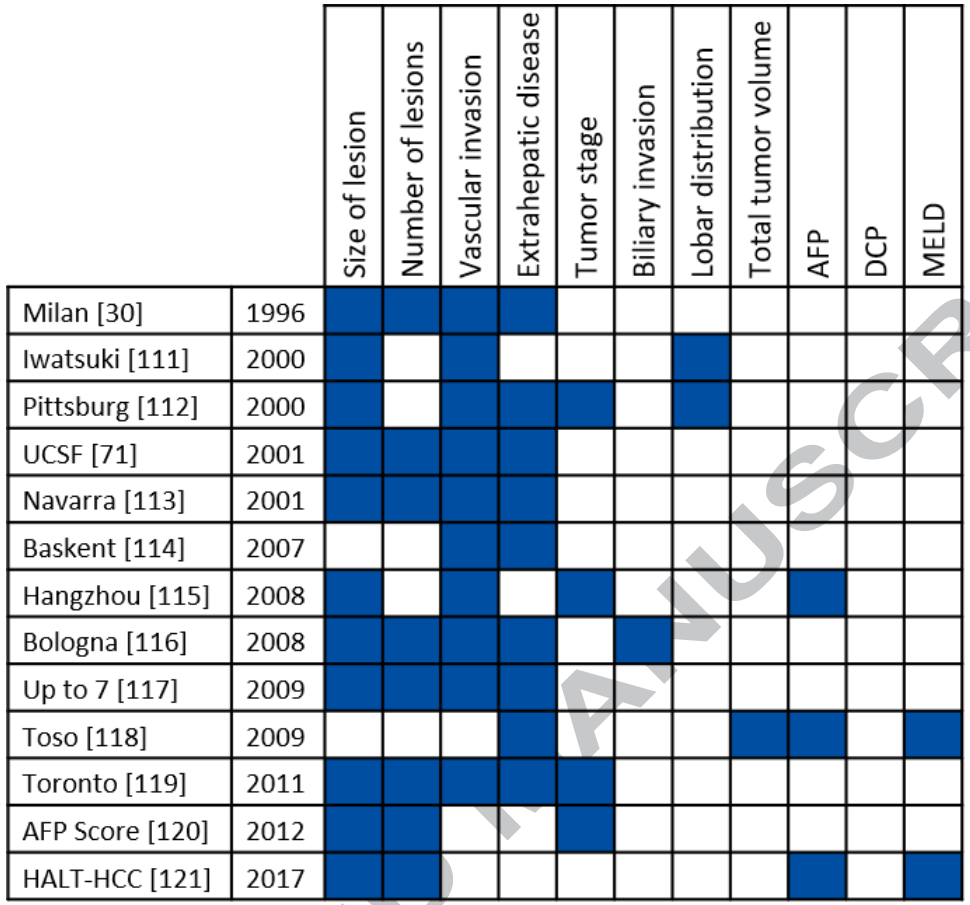
Figure 2: Number of deceased donor liver transplantation per million population



Data from 2016/2017

AR, Argentina; AUNZ, Australia and New Zealand; BR, Brazil; CA, Canada; CH, Switzerland; CN, China; CO, Colombia; CZ, Czech Republic; ES, Spain; Euro, Eurotransplant; FR, France; IR, Iran; IT, Italy; JP, Japan; KR, South Korea, MX, Mexico; PL, Poland; RU, Russia; SK, Scandiatransplant; PT, Portugal; UK, United Kingdom; USA, United States of America; TR, Turkey; TW, Taiwan

Figure 3: Criteria for liver transplantation for HCC



		Size of lesion	Number of lesions	Vascular invasion	Extrahepatic disease	Tumor stage	Biliary invasion	Lobar distribution	Total tumor volume	AFP	DCP	MELD
Milan [30]	1996	■	■	■	■							
Iwatsuki [111]	2000	■		■				■				
Pittsburg [112]	2000	■		■	■	■		■				
UCSF [71]	2001	■	■	■	■							
Navarra [113]	2001	■	■	■	■							
Baskent [114]	2007			■	■							
Hangzhou [115]	2008	■		■		■				■		
Bologna [116]	2008	■	■	■	■		■					
Up to 7 [117]	2009	■	■	■	■							
Toso [118]	2009				■				■	■		■
Toronto [119]	2011	■	■	■	■	■						
AFP Score [120]	2012	■	■			■						
HALT-HCC [121]	2017	■	■							■		■

AFP, Alpha fetoprotein; HALT-HCC, Hazard associated with liver transplantation for hepatocellular carcinoma; MELD, Model for end-stage liver disease; UCSF, University of California San Francisco

Highlights

- An optimal allocation system for scarce resources should simultaneously ensure maximal utility, but also equity.

- Large differences however exist between centers and countries for ethical and legislative reasons.

- A future globally applicable strategy should combine donor and recipient factors predicting probability of death on the waiting list, post-transplant survival as well as morbidity, and perhaps costs.