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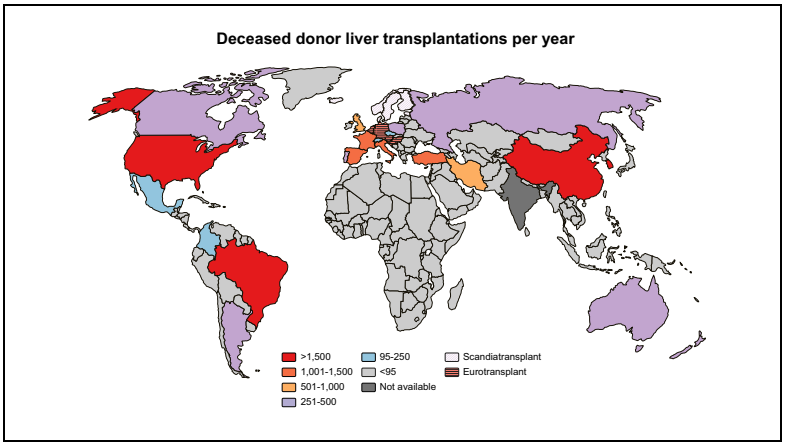
Allocation of liver grafts worldwide – Is there a best system?

Graphical abstract



Highlights

- An optimal allocation system for scarce resources should simultaneously ensure maximal utility, but also equity.
- Large differences exist between centers and countries for ethical and legislative reasons.
- A future globally applicable strategy should combine donor and recipient factors.
- This strategy must predict probability of death on the waiting list, post-transplant survival and morbidity, and costs.

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Lay summary

An optimal allocation system for scarce resources should simultaneously ensure maximal utility, but also equity. While the model for end-stage liver disease 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 and morbidity, and perhaps costs.

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Allocation of liver grafts worldwide – Is there a best system?

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See Editorial, pages 654–656

Background & Aims: 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 are therefore criteria that rely on pre-transplant survival (sickest first policy), post-transplant survival (utility), or on their combination (benefit). However, large differences exist between centers and countries for ethical and legislative reasons. The aim of this study was to report the current worldwide practice of liver graft allocation and discuss respective advantages and disadvantages.

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

Results: Most countries use the model for end-stage liver disease (MELD) score, or variations of it, for organ allocation, while some countries opt for center-based allocation systems based on their specific requirements, and some countries combine both a MELD and center-based approach. Both the MELD and center-specific allocation systems have inherent limitations. For example, most countries or allocation systems address the limitations of the MELD system by adding extra points to recipient's laboratory scores based on clinical information. It is also clear from this study that cancer, as an indication for liver transplantation, requires special attention.

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 and morbidity, and perhaps costs.

Lay summary: An optimal allocation system for scarce resources should simultaneously ensure maximal utility, but also equity. While the model for end-stage liver disease 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 and 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 (Figs. 1, 2).[1] In the early stages of the procedure, from the 1980s until the 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, ahead of patients hospitalized in a non-ICU setting and 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 led to a change in the paradigm of organ allocation as waiting time ceased to be a key criterion.[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

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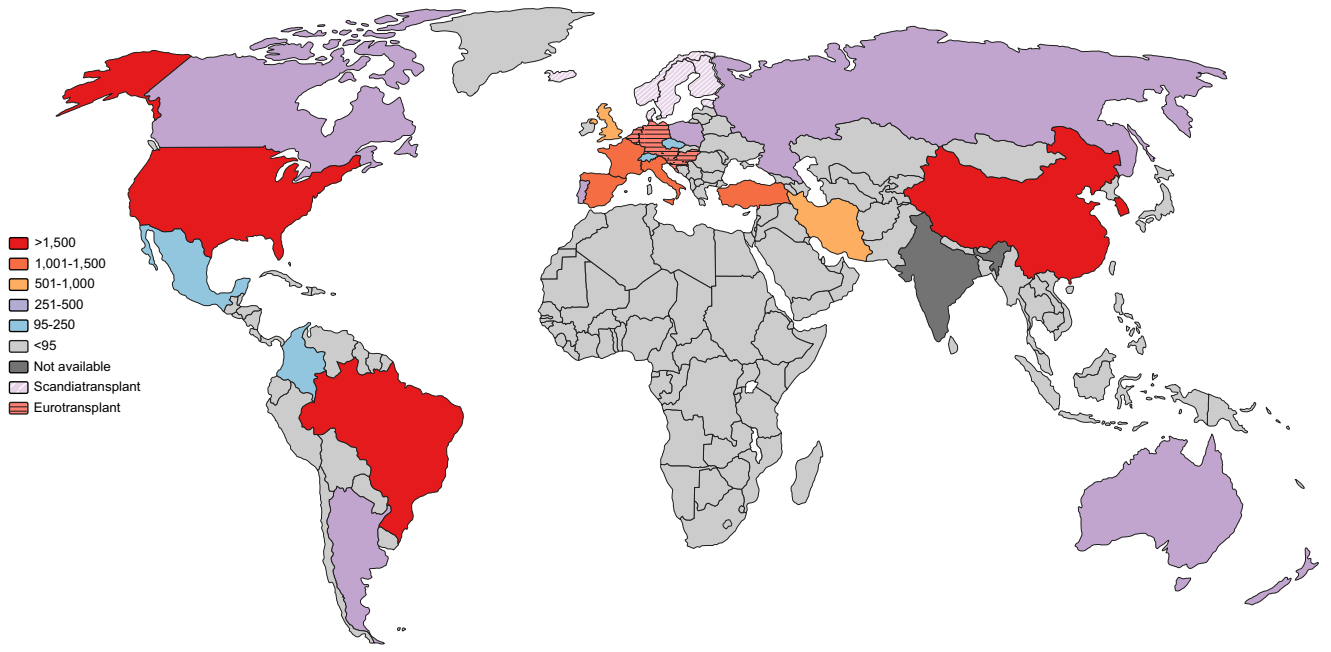

Fig. 1. Deceased donor liver transplantation per year. Data from 2016/2017. (This figure appears in colour on the web.)

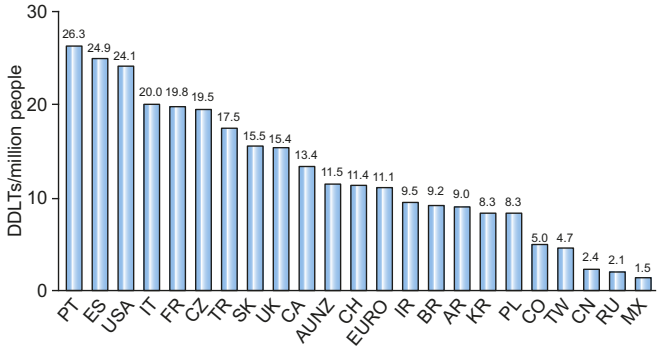

Fig. 2. Number of deceased donor liver transplantations per million people. Data from 2016/2017. AR, Argentina; AUNZ, Australia and New Zealand; BR, Brazil; CA, Canada; CH, Switzerland; CN, China; CO, Colombia; CZ, Czech Republic; DDLTs, deceased donor liver transplantations; ES, Spain; Euro, Eurotransplant; 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.

currently widely used allocation policy based on the model for end-stage liver disease (MELD score).[8] The MELD score is composed of 3 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 [Fig. S1]).[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 (Table 1; Figs. 1, 2; Fig. S1).[12,13] The MELD-based allocation is used by most countries worldwide that perform more than 95 LT per year (Table S1).[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 (Table 1; Tables S1, S2; Fig. S1).[16]

An alternative to these allocations models are scores that define a threshold for declining livers to avoid unfavorable risk accumulation in patients with high MELD (balance of risk [BAR], survival outcome following LT [SOFT], product of donor age and MELD [D-MELD]) (Fig. S1).[7,17–19] The BAR score provides a new and simple scoring system to predict outcome after orthotopic LT with respect to recipient, donor and graft factors. It was calculated on 37,255 patients in the UNOS database and identifies the 6 strongest predictors of post transplantation patient survival. Analysis confirmed the superiority of BAR compared to other score systems like MELD, D-MELD, disease risk index (DRI) and SOFT. The score was validated using the European Liver Transplant Registry (ELTR) database. Compared to other scores, the BAR offers a well-defined cut-off for decision making.

The recent extension of transplant indications, for example for malignancy including cholangiocarcinoma, hepatocellular carcinoma (HCC), and colorectal liver metastases, has further aggravated organ shortages, leading to competition in the allocation for liver grafts (Table 2; Table S2; Fig. 3; Fig. S1).[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 unclear how non-ideal candidates and marginal grafts should be best allocated in the face of huge dif-

Table 1. Donation policies worldwide.

	Donation policy	ECD	DCD per year (%)	Retrieved livers (n)	Livers discarded (%)	Livers (pmp)
Portugal[‡]	Opt-out	DCD	low[*]	290	6.6	26.3
Spain[†]	Opt-out	DCD	13.3	1,665	26.8	24.9
United States of America[85†]	Opt-in	Age >70 yr[§] DCD[§]	6.1	8,529	8.7	24.1
Italy[†]	Opt-out	Age >65 yr DCD	0.9	1,599	25.0	20.0
France[86†]	Opt-out	n.a.	1.7	1,327	3.6	19.8
Czech Republic[†]	Opt-out	DCD	low[*]	260	30.0	19.5
Turkey[87†]	Opt-out	Age >65 yr	n.a.	598	26.8	17.5
Scandiatransplant[‡] (Sweden, Norway, Finland, Denmark, Iceland, Estonia)[29]	Opt-in (Denmark, Estonia, Iceland) Opt-out (Sweden, Finland, Norway)	DCD	Norway 1, Overall 0.5	417	n.a.	15.5
United Kingdom[‡]	Opt-in	Center-dependent	22.8	1,116	15.0	15.4
Canada[88†]	Provincially based	DCD	10.6	226	8.0	13.4
Australia & New Zealand[89,90†]	Opt-in	Age >70 yr DCD Steatosis >30%	3.6	304	24.1[**]	11.5
Switzerland	Opt-in	n.a.	16[‡]	136[#]	4.4[#]	11.4[†]
Eurotransplant[†] (Austria, Belgium, Croatia, Germany, Hungary, Luxemburg, Netherlands, Slovenia)[91]	Opt-in (DE, NL[=]) Opt-out (all others)	Age >65 yr Steatosis >40% ICU stay with ventilation >7 days BMI >30 kg/m^2 Sodium >165 mmol/L ALT >105 U/L AST >90 U/L Serum Bilirubin >3 mg/dl	NL 37.5 BE 24.9, Overall 8.6	1,661	8.5	11.1
Iran[†]	Opt-in	Age >65 yr Steatosis >40% Sodium >165 mmol/L Intoxication	n.a.	926	16.0	9.5
Brazil[†]	Opt-in	Age >60 yr Steatosis ICU stay >7 days NOR >0.5 μg/kg/min	n.a.	3,488	44.9	9.2
Argentina[92]	Opt-in	n.a.	n.a.	732[‡†]	3.4[‡†]	9.0[†]
South Korea[†]	Opt-in	DCD	n.a.	515	17.3	8.3
Poland[‡]	Opt-out	n.a.	n.a.	343	7.6	8.3
Colombia	Opt-out	n.a.	n.a.	190[#]	n.a.	5.0[†]
Taiwan[93†]	Opt-in	Age >65 yr DCD	Started in 2017	96	10.4	4.7
China[†]	Opt-in	Age >65 yr	n.a.	5,146	14.4	2.4
Russia[94†]	Opt-out	Age >65 yr	n.a.	375	18.1	2.1
Mexico[95†]	Opt-in	Age >65 yr	n.a.	182	7.7	1.5
India[#]	Opt-in	Steatosis	n.a.	500	n.a.	n.a.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BE, Belgium; BMI, body mass index; DCD, donor after cardiac death; DE, Denmark; ECD, extended criteria donor; ICU, intensive care unit; n.a., not available; NL, Netherlands; NOR, norepinephrine; OPTN, Organ Procurement and Transplantation Network; pmp, per million people; tx, transplanted.

‡ 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.
= opt-out from July 1st 2020 on.

ferences in local legislative regulations and education, as well as public attitudes, culture and religion. Herein, we report on current distribution systems for liver grafts worldwide (Fig. 1).

Materials and methods

To collect data, we contacted transplant centers from countries around the world that perform 95 or more deceased donor LTs per year (Figs. 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 (Tables 1, 2; Table S1, S2).

Results

Europe

In 2013 more than 7,000 LTs, a third of the worldwide total, were performed in Europe (ELTR).[25] In fact, there is a trend to further increasing LT, mostly due to the increase in donor rates

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[85]	National incl. regional	20.5†	MELD	None	Median MELD at transplant at surrounding centers less 3 MELD points starting 6 months after listing§
Italy[37]	Center-oriented	22.7†	Milan	Yes	According to tumour stage
France[86]	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[87]	Center-oriented	n.a.†	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[88]	Provincial	31.6†	Milan	22	3 points/3 months
Australia & New Zealand[89,90]	Center-oriented	19†	UCSF MELD	22	2 points/3 months
Switzerland	Patient-oriented	20.5‡	MELD	14	1.5 points/month (constant), initial value + (number of months)*1.5
Eurotransplant (Austria, Belgium, Germany, Croatia, Luxemburg, Netherlands, Hungary, Slovenia)[91]	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 90 days 10% MELD equivalent
Iran[96]	Center-oriented	5.2†	Milan MELD	24	No
Brazil[97]	Regional	23.8†	Milan Waiting time	20	24 points after 3 months, 29 points after 6 months
Argentina[92]	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	n.a.	3.2†	n.a.	None	No
Colombia	Center-oriented	20†	Milan MELD	Center-oriented	No
Taiwan[93]	Center-oriented	30.6‡	MELD Waiting time	10% of MELD points	10% of MELD points
China	Patient-oriented	34.5‡	MELD	None	No
Russia[94]	Center-oriented	26,8†	UCSF MELD	None	Depends on center policy
Mexico[95]	Center-oriented	18†	n.a.	Center-oriented	No
India	Center-oriented	n.a.†	UCSF	None	No

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

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 in results over time, leading to current 1- and 5-year survival rates of 96% and 82%, respectively (Table S1). 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.

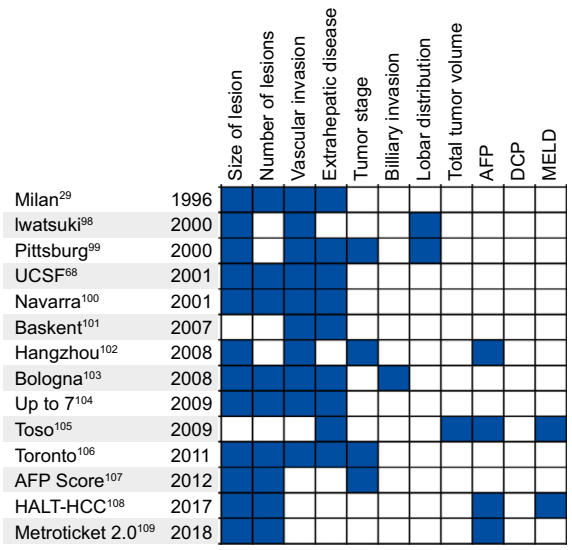

Fig. 3. Criteria for liver transplantation for HCC. AFP, alpha-fetoprotein; DCP, des-carboxy-prothrombin; HALT-HCC, hazard associated with liver transplantation for hepatocellular carcinoma; MELD, model for end-stage liver disease; UCSF, University of California San Francisco. (See above-mentioned references for further information.) (This figure appears in colour on the web.)

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 90 days 10% MELD equivalent.
Indications for extra points: Neoplasia, biliary atresia, polycystic liver disease (PLD), primary sclerosing cholangitis (PSC), hemangioendothelioma, hereditary hemorrhagic teleangiectasia (HHT), cystic fibrosis, familial amyloidotic polyneuropathy (FAP), primary hyperoxaluria, urea cycle disorder, hepatorenal syndrome (HRS), portopulmonary hypertension (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 in international prioritized exchange and the role of 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 improves matching between the available donor organs and the patients on the waiting list. Special patient groups like children or high urgent patients therefore have 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 (HU) or approved combined organ 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 1,500 LTs are performed each year in 38 centers. The treaties aim to balance the number of LTs considering the high heterogeneity among different countries. LT candidates are listed according to 3 different prioritization categories: high urgency, combined transplantation with other organs and elective LT, which accounts for approximately 86% of LT recipients. The main strength of 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.[27]

LT candidates listed in the elective groups are managed according to national allocation policies. In Germany, Belgium and the Netherlands, a recipient-driven MELD model determines graft allocation to the sickest patient, regardless of the center. For all countries within Eurotransplant in case of marginal donors or donors with hemodynamic instability, 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, hemangioendothelioma and others (Tables 1, 2; Tables S1, S2; Figs. 1–3 and Fig. S1).[27]

Scandiatransplant

Donation policy: Opt-in (Denmark, Estonia, Iceland)
Opt-out (Sweden, Finland, Norway)
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, which reflect the prevalence of liver donations and, subsequently LT. According to the Nordic Liver Transplant Registry (NLTR), PSC and primary biliary cholangitis 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 3%) 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, >6,000 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 24 pmp in Finland.[28] 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 uti-

lization 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 13.5% of indications has been adopted according to the Oslo Criteria in 2005 in Norway.[29,30] Median time on the waiting list for patients with HCC is short, probably because of the good balance between the HCC burden on the waiting list and the center-driven allocation policy. Although lower than patients without HCC, the post-LT survival for HCC (1- and 5-year 85% and 57%) 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, with a 1-year disease free survival of 35%. 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 (Tables 1, 2; Table S1, S2; Figs. 1–3 and Fig. S1).[32]

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 alpha-fetoprotein (AFP)-score)
Indications for extra points: Recurrent HCC, PLD, HHT, amyloidosis, metabolic disease, recurrent cholangitis, hepatopulmonary syndrome (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 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).[33]

The allocation rules for DBD were modified in France in 2007, up to this point the 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, is currently in place affecting nearly 80% of liver grafts in 2015.[15] This score reflects severity of cirrhosis according to MELD score, but also attributes a defined number of points for the accumulated waiting time. The French allocation system allows for inclusion of patients with HCC outside the Milan criteria as well as those undergoing surgical resection before disease recurrence. In addition, the Liver Transplantation French Study Group has shown that the prediction of tumor recurrence is improved significantly by a model that incorporates AFP.[34] With regard to the DCD program, 22 centers have been authorized to perform organ procurement to date (Tables 1, 2; Tables S1, S2; Figs. 1–3 and Fig. S1).

Italy

Donation policy: Opt-out
Prioritization: Clinical, MELD
Priority for HCC: Yes, extra points granted
Indications for extra points: HCC, complications of pulmonary hypertension

The Italian organ transplantation network is governed by the National Transplantation Center (CNT) with more than 1,000 LT/year 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 based on a pay-back system, and directly collaborating with the CNT. In Italy, significant differences exist regarding organ donation between Northern and Southern regions (mean donation rates in Italy 22.6 pmp in 2015, ranging from 9.8 pmp in Sicily to 48 pmp in Tuscany).[35]

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 = 2,061) were recently compared with a matched English cohort (n = 2,121) 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.[36] Thus, a recent consensus conference was held to identify new allocation policies respecting criteria for MELD exceptions.[37] A DCD program has been started in Milan Niguarda Hospital since 2015 with 28 LTs performed so far (Tables 1, 2; Tables S1, S2; Figs. 1–3 and Fig. S1).[38]

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, 5 of which include a pediatric LT program. More than 1,000 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.[39] 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 ECD organs including DCD.[40] The DCD program has expanded greatly since 2014 with the use of controlled DCDs, making Spain the third biggest user of DCD organs after the US and UK.[41]

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 alloca-

tion 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 (Tables 1, 2; Tables S1, S2; Figs. 1–3 and Fig. S1).[42]

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 3 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 patients with HCC receiving 1.5 extra points per month, starting at MELD 14. Non-standard exceptions are granted by a national audit group, if needed. Based on donation rates which are too low to cover many high-risk candidates, the BAR score was developed in 2011, which sums up 6 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 was 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.[43] Since 2018 both other programs are also using DCD grafts (Tables 1, 2; Tables S1, S2; Figs. 1–3 and Fig. S1).

United Kingdom

Donation policy: Opt-in
Prioritization: TBS, UK end-stage liver disease score
Priority for HCC: No
Indications for extra points: Recurrent cholangitis, metabolic disease, HPS

The UK LT program is the oldest in Europe, since the first LT was performed in Cambridge in 1968.[44] This program accounts for about 850 LT per year covering only 7 centers (1 in Scotland and 6 in England).[45] The number of donations (20.3 pmp in 2015) and LTs has increased 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 DCD. The UK is second in terms of the frequency of DCD organ utilization after the US, which contributes to more than 20% of the donor pool.[46] 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 the UK end-stage liver disease score, which was developed after a nationwide evaluation of the English LT scenario.[47] 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 the MELD score in predicting survival. The allocation system was 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. In 2018, the UK introduced 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 TBS taking into account 7 characteristics from the donor and matching those with 21 recipient characteristics (Tables 1, 2; Tables S1, S2; Figs. 1–3 and Fig. S1).[16]

North America

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 USA by a private non-profit organization, the 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 2 A-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.[48,59] 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 (Tables 1, 2; Tables S1, S2; Figs. 1–3 and Fig. S1).[50] In 2019, extended criteria donors were approved by the Board of directors of the OPTN. The implementation is still pending.

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 historically been 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.[51,52] In close similarity to the previously utilized allocation systems based on CTP 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, centers 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 AFP are used as selection criteria, although patients can also be transplanted within UCSF criteria in the latter 2 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 (Tables 1, 2; Tables S1, S2; Figs. 1–3 and Fig. S1).[53]

Latin America

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 living donation.

Colombia

Donation policy: Opt-out
Prioritization: Clinical, MELD, waiting time
Priority for HCC: Center-oriented extra points
Indications for extra points: HCC, age, same/compatible blood group, post living donation, Intention to donate

Mexico

Donation policy: Opt-in
Prioritization: Clinical, waiting time
Priority for HCC: Center-oriented
Indications for extra points: Center-oriented

With the number of LTs performed increasing by about 6% per year, Latin America has become a very active part of the world.[54] This region has a population of 589 million, representing 8.5% of the world population, and more than 2,500 LTs 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.[42] Patients with HCC receive standard exception points, *e.g.* Brazilian patients with tumors >2 cm 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 neuroendocrine tumor metastases, familial amyloid polyneuropathy or HPS (Tables 1, 2; Tables S1, S2; Figs. 1–3 and Fig. S1).

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

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 currently has 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).[55] Indeed, since the first LT performed in South Korea in 1988, LDLT accounted for approximately 76.5% of all LTs in this country.[56]

A large majority of LTs 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.[57] A national body to regulate transplantation called National Organ & Tissue Transplant Organisation has recently been set up in India. There are currently 2 broad liver allocation models. Both these models recognize a super-urgent category. Beyond this, allocation is either done by waiting list chronology or by rotational allocation to all the recognized liver transplant centers.[57] 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 LT in India are currently very inadequate but number of liver transplants are increasing rapidly and a national registry is being set up.

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 (>2 cm and within UCSF) with an additional 2 points every 3 months (Tables 1, 2; Tables S1, S2; Figs. 1–3 and Fig. S1).[58]

Details provided in Tables 1, 2 and Tables S1, S2.

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 an LT resulting in more deaths on the waiting list, when compared to a MELD score-based policy. This shortcoming certainly holds true in countries which suffer badly from organ shortages. Differences in transplant rates between countries should also include causes of death. A metric that looks at the 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.[59] Allocation by recipient's lab MELD score is transparent and objective, but fails to consider 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; Fig. S1).[60]

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.* non-standard exceptions) to allow candidates not well served by laboratory changes to compete with higher MELD-score recipients.[37] The amount of added points, and its further increase during waiting time remains, however, quite subjective and therefore highly inconsistent among countries (Table S1). Next, all MELD-based allocation systems have been criticized for not defining a threshold for being too sick for transplantation.[23,60–62] 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, SOFT, BAR score, University of California Los Angeles futility risk score and survival benefit analysis (Fig. 2; Fig. S1).[19,61,63–65] A further development in this direction is the use of artificial neural networks by combining approximately 60 donor, graft, and recipient factors to identify best matches.[66] Despite all these efforts, however, refusing a liver offer for a very sick transplant candidate remains 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. So too do the long-term side effects of immunosuppression in this population. For example, 20 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 a 5-year survival rate of 50%.[67] Several other models (*e.g.* UCSF, up to 7, total tumor volume, Kyoto criteria, extended Toronto criteria, MORAL score) have been introduced, which typically claim comparable predictive values[68–71] (Fig. 3; Table 2; Tables S1, S2). Microvascular invasion seems to be the key predictive factor, however a reliable and convincing serum or easy available marker is still missing.[72] Furthermore, it is unclear how to include other malignancies qualifying for LT, such as perihilar or intrahepatic cholangiocarcinoma, or colorectal liver metastases.[32,33,73–76]

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 DCD livers.[18,77,78] 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.[79,80] Several countries with DCD experience prefer to allocate DCD organs according to a center-specific policy (Table 1).[42,80–82] 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.[83,84]

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 and morbidity, including associated costs. Moreover, a globally applicable model for the allocation of liver grafts must also consider ethical, moral, religious and cultural factors.

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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.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

For specific questions relating to the 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.

Supplementary data

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References

Author names in bold designate shared co-first authorship

[1] Zarrinpar A, Busuttil RW. Liver transplantation: past, present and future. Nat Rev Gastroenterol Hepatol 2013;10:434–440.

[2] Taniguchi M. Liver transplantation in the MELD era–analysis of the OPTN/UNOS registry. Clin Transpl 2012:41–65.
[3] Lau T, Ahmad J. Clinical applications of the Model for End-Stage Liver Disease (MELD) in hepatic medicine. Hepat Med 2013;5:1–10.
[4] European Association for the Study of the Liver, Electronic address eee. EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol 2016;64:433–485.
[5] United Network for Organ Sharing. Components of the CTP score employed in the previous liver allocation policy. Available at: <http://www.unos.org> accessed 06.12.2018.
[6] Freeman Jr RB, Edwards EB. Liver transplant waiting time does not correlate with waiting list mortality: implications for liver allocation policy. Liver Transplant 2000;6:543–552.
[7] **Akkina SK**, **Asrani SK**, Peng Y, Stock P, Kim WR, Israni AK. Development of organ-specific donor risk indices. Liver Transplant 2012;18:395–404.
[8] Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91–96.
[9] Angermayr B, Cejna M, Karnel F, Gschwantler M, Koenig F, Pidlich J, et al. Child-Pugh versus MELD score in predicting survival in patients undergoing transjugular intrahepatic portosystemic shunt. Gut 2003;52:879–885.
[10] Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology (Baltimore, MD) 2000;31:864–871.
[11] Weismuller TJ, Negm A, Becker T, Barg-Hock H, Klempnauer J, Manns MP, et al. The introduction of MELD-based organ allocation impacts 3-month survival after liver transplantation by influencing pretransplant patient characteristics. Transpl Int 2009;22:970–978.
[12] **Dutkowski P**, **De Rougemont O**, Müllhaupt B, Clavien PA. Current and future trends in liver transplantation in Europe. Gastroenterology 2010;138(802–809) e804.
[13] Freeman Jr RB, Wiesner RH, Roberts JP, McDiarmid S, Dykstra DM, Merion RM. Improving liver allocation: MELD and PELD. Am J Transplant 2004;4(Suppl 9):114–131.
[14] http://www.transplant-observatory.org/summary/ Accessed 07.12.2018.
[15] Francoz C, Belghiti J, Castaing D, Chazouilleres O, Duclos-Vallee JC, Duvoux C, et al. Model for end-stage liver disease exceptions in the context of the French model for end-stage liver disease score-based liver allocation system. Liver Transplant 2011;17:1137–1151.
[16] https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/policies-and-guidance/ accessed 09.04.2019.
[17] Dutkowski P, Linecker M, DeOliveira ML, Mullhaupt B, Clavien PA. Challenges to liver transplantation and strategies to improve outcomes. Gastroenterology 2015;148:307–323.
[18] **Dutkowski P**, **Oberkofler CE**, Slankamenac K, Puhan MA, Schadde E, Mullhaupt B, et al. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. Ann Surg 2011;254:745–753.
[19] Halldorson JB, Bakthavatsalam R, Fix O, Reyes JD, Perkins JD. D-MELD, a simple predictor of post liver transplant mortality for optimization of donor/recipient matching. Am J Transplant 2009;9:318–326.
[20] Hoti E, Adam R. Liver transplantation for primary and metastatic liver cancers. Transpl Int 2008;21:1107–1117.
[21] Testa G, Klintmalm GB. Liver transplantation for primary and metastatic liver cancers. Ann Transplant 1997;2:19–21.
[22] Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. Surgery 1991;110:726–734, discussion 734–725.
[23] Linecker M, Krones T, Berg T, Niemann CU, Steadman RH, Dutkowski P, et al. Potentially inappropriate liver transplantation in the era of the "sickest first" policy - A search for the upper limits. J Hepatol 2018;68:798–813.
[24] Muller X, Marcon F, Sapisochin G, Marquez M, Dondero F, Rayar M, et al. Defining benchmarks in liver transplantation: A multicenter outcome analysis determining best achievable results. Ann Surg 2018;267:419–425.
[25] http://www.eltr.org/Evolution-of-LTs-in-Europe.html accessed 06.12.2018.
[26] http://statistics.eurotransplant.org/index.php?search_type=donors+deceased&search_organ=liver accessed 06.12.2018.
[27] Jochmans I, van Rosmalen M, Pirenne J, Samuel U. Adult liver allocation in eurotransplant. Transplantation 2017;101:1542–1550.
[28] http://www.scandiatransplant.org/data/scandiatransplant-figures accessed 06.12.2018.
[29] Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–699.
[30] Fosby B, Melum E, Bjoro K, Bennet W, Rasmussen A, Andersen IM, et al. Liver transplantation in the Nordic countries - An intention to treat and post-transplant analysis from The Nordic Liver Transplant Registry 1982–2013. Scand J Gastroenterol 2015;50:797–808.
[31] Hagness M, Foss A, Line PD, Scholz T, Jorgensen PF, Fosby B, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg 2013;257:800–806.
[32] Dueland S, Foss A, Solheim JM, Hagness M, Line PD. Survival following liver transplantation for liver-only colorectal metastases compared with hepatocellular carcinoma. Br J Surg 2018;105:736–742.
[33] https://www.agence-biomedecine.fr/?lang=fr accessed 18.12.2018.
[34] **Duvoux C**, **Roudot-Thoraval F**, **Decaens T**, Pessione F, Badran H, Piardi T, et al. Liver transplantation for hepatocellular carcinoma: a model including alpha-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012;143:986–994.
[35] http://www.trapianti.salute.gov.it/cnt/cnt.jsp accessed 22.12.2018.
[36] Carbone M, Nardi A, Marianelli T, Martin K, Hudson A, Collett D, et al. International comparison of liver transplant programmes: differences in indications, donor and recipient selection and outcome between Italy and UK. Liver Int 2016;36:1481–1489.
[37] Cillo U, Burra P, Mazzaferro V, Belli L, Pinna AD, Spada M, et al. A multistep, consensus-based approach to organ allocation in liver transplantation: toward a "blended principle model". Am J Transplant 2015;15:2552–2561.
[38] De Carlis R, Di Sandro S, Lauterio A, Botta F, Ferla F, Andorno E, et al. Liver grafts from donors after circulatory death on regional perfusion with extended warm ischemia compared with donors after brain death. Liver Transpl 2018;24:1523–1535.
[39] Matesanz R, Marazuela R, Dominguez-Gil B, Coll E, Mahillo B, de la Rosa G. The 40 donors per million population plan: an action plan for improvement of organ donation and transplantation in Spain. Transplant Proc 2009;41:3453–3456.
[40] Matesanz R, Dominguez-Gil B, Coll E, Mahillo B, Marazuela R. How Spain reached 40 deceased organ donors per million population. Am J Transplant 2017;17:1447–1454.
[41] Hessheimer AJ, Dominguez-Gil B, Fondevila C, Matesanz R. Controlled donation after circulatory determination of death in Spain. Am J Transplant 2016;16:2239–2240.
[42] http://www.ont.es/Paginas/Home.aspx accessed 22.12.2018.
[43] **Dutkowski P**, **Schlegel A**, de Oliveira M, Mullhaupt B, Neff F, Clavien PA. HOPE for human liver grafts obtained from donors after cardiac death. J Hepatol 2014;60:765–772.
[44] Calne R, Williams R. Early liver transplantation in Europe. Transplantation 2013;96:e48–49.
[45] Neuberger J. Liver transplantation in the United Kingdom. Liver Transplant 2016;22:1129–1135.
[46] https://www.odt.nhs.uk/ accessed 20.12.2018.
[47] Barber K, Madden S, Allen J, Collett D, Neuberger J, Gimson A, et al. Elective liver transplant list mortality: development of a United Kingdom end-stage liver disease score. Transplantation 2011;92:469–476.
[48] **Dutkowski P**, **Oberkofler CE**, Bechir M, Mullhaupt B, Geier A, Raptis DA, et al. The model for end-stage liver disease allocation system for liver transplantation saves lives, but increases morbidity and cost: a prospective outcome analysis. Liver Transplant 2011;17:674–684.
[49] Neuberger J. The introduction of MELD-based organ allocation impacts 3-month survival after liver transplantation by influencing pretransplant patient characteristics Invited Commentary on Weissmuller et al.. Transplant Int 2009;22:979–981.
[50] Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008;359:1018–1026.
[51] Burak KW, Meeberg GA, Myers RP, Fick GH, Swain MG, Bain VG, et al. Validation of the model of end-stage liver disease for liver transplant allocation in Alberta: implications for future directions in Canada. Can J Gastroenterol Hepatol 2016;2016:1329532.
[52] Burak KW, Meeberg GA, Myers RP, Fick GH, Swain MG, Bain VG, et al. Validation, current use and future directions of the Model for End-stage Liver Disease for liver transplant allocation in Canada. Can J Gastroenterol Hepatol 2015.
[53] https://www.canadiantransplant.com/ accessed 20.12.2018.
[54] Salvalaggio PR, Caicedo JC, de Albuquerque LC, Contreras A, Garcia VD, Felga GE, et al. Liver transplantation in Latin America: the state-of-the-art and future trends. Transplantation 2014;98:241–246.

[55] http://www.irodat.org/?p=database&c=KR&year=2016#data accessed 07.12.2018.
[56] Lee SG, Moon DB, Hwang S, Ahn CS, Kim KH, Song GW, et al. Liver transplantation in Korea: past, present, and future. Transplant Proc 2015;47:705–708.
[57] Nagral S, Nanavati A, Nagral A. Liver transplantation in India: at the crossroads. J Clin Exp Hepatol 2015;5:329–340.
[58] McCaughan GW, Munn SR. Liver transplantation in Australia and New Zealand. Liver Transplant 2016;22:830–838.
[59] Cholongitas E, Burroughs AK. The evolution in the prioritization for liver transplantation. Ann Gastroenterol 2012;25:6–13.
[60] Aberg F, Nordin A, Makisalo H, Isoniemi H. Who is too healthy and who is too sick for liver transplantation: external validation of prognostic scores and survival-benefit estimation. Scand J Gastroenterol 2015;50:1144–1151.
[61] Petrowsky H, Rana A, Kaldas FM, Sharma A, Hong JC, Agopian VG, et al. Liver transplantation in highest acuity recipients: identifying factors to avoid futility. Ann Surg 2014;259:1186–1194.
[62] Sharpton SR, Feng S, Hameed B, Yao F, Lai JC. Combined effects of recipient age and model for end-stage liver disease score on liver transplantation outcomes. Transplantation 2014;98:557–562.
[63] Rana A, Hardy MA, Halazun KJ, Woodland DC, Ratner LE, Samstein B, et al. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. Am J Transplant 2008;8:2537–2546.
[64] **Dutkowski P**, **Oberkofler CE**, Slankamenac K, Puhan MA, Schadde E, Mullhaupt B, et al. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. Ann Surg 2011;254:745–753, discussion 753.
[65] **Dutkowski P**, **Schlegel A**, Slankamenac K, Oberkofler CE, Adam R, Burroughs AK. The use of fatty liver grafts in modern allocation systems: risk assessment by the balance of risk (BAR) score. Ann Surg 2012;256:861–868, discussion 868–869.
[66] Cucchetti A, Vivarelli M, Heaton ND, Phillips S, Piscaglia F, Bolondi L, et al. Artificial neural network is superior to MELD in predicting mortality of patients with end-stage liver disease. Gut 2007;56:253.
[67] Clavien P-A, Lesurtel M, Bossuyt PMM, Gores GJ, Langer B, Perrier A, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol 2012;13:e11–e22.
[68] Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology (Baltimore, MD) 2001;33:1394–1403.
[69] Ito T, Takada Y, Ueda M, Haga H, Maetani Y, Oike F, et al. Expansion of selection criteria for patients with hepatocellular carcinoma in living donor liver transplantation. Liver Transplant 2007;13:1637–1644.
[70] Sapisochin G, Goldaracena N, Laurence JM, Dib M, Barbas A, Ghanekar A, et al. The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: A prospective validation study. Hepatology (Baltimore, MD) 2016;64:2077–2088.
[71] Halazun KJ, Najjar M, Abdelmessih RM, Samstein B, Griesemer AD, Guarrera JV, et al. Recurrence after liver transplantation for hepatocellular carcinoma: a new MORAL to the story. Ann Surg 2017;265:557–564.
[72] Grat M, Stypulkowski J, Patkowski W, Bik E, Krasnodebski M, Wronka KM, et al. Limitations of predicting microvascular invasion in patients with hepatocellular cancer prior to liver transplantation. Sci Rep 2017;7:39881.
[73] De Vreede I, Steers JL, Burch PA, Rosen CB, Gunderson LL, Haddock MG, et al. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoirradiation for cholangiocarcinoma. Liver Transplant 2000;6:309–316.
[74] Darwish Murad S, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology 2012;143, 88–98.e83; quiz e14.
[75] Sapisochin G, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, et al. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: International retrospective study supporting a prospective assessment. Hepatology (Baltimore, MD) 2016;64:1178–1188.
[76] Toso C, Pinto Marques H, Andres A, Castro Sousa F, Adam R, Kalil A, et al. Liver transplantation for colorectal liver metastasis: Survival without recurrence can be achieved. Liver Transplant 2017;23:1073–1076.
[77] Pezzati D, Ghinolfi D, De Simone P, Balzano E, Filipponi F. Strategies to optimize the use of marginal donors in liver transplantation. World J Hepatol 2015;7:2636–2647.
[78] Monbaliu D, Pirenne J, Talbot D. Liver transplantation using Donation after Cardiac Death donors. J Hepatol 2012;56:474–485.
[79] Blok JJ, Detry O, Putter H, Rogiers X, Porte RJ, van Hoek B, et al. Longterm results of liver transplantation from donation after circulatory death. Liver Transplant 2016;22:1107–1114.
[80] Foley DP, Fernandez LA, Leverson G, Anderson M, Mezrich J, Sollinger HW, et al. Biliary complications after liver transplantation from donation after cardiac death donors: an analysis of risk factors and long-term outcomes from a single center. Ann Surg 2011;253:817–825.
[81] Selck FW, Grossman EB, Ratner LE, Renz JF. Utilization, outcomes, and retransplantation of liver allografts from donation after cardiac death: implications for further expansion of the deceased-donor pool. Ann Surg 2008;248:599–607.
[82] Hodgson R, Young AL, Attia MA, Lodge JPA. Impact of a national controlled donation after circulatory death (DCD) program on organ donation in the United Kingdom: a 10-year study. Am J Transplant 2017;17:3172–3182.
[83] **Dutkowski P**, **Polak WG**, **Muiesan P**, Schlegel A, Verhoeven CJ, Scalera I, et al. Comparison of hypothermic oxygenated PErfusion versus static cold storage of human donation after cardiac death liver transplants: an international-matched case analysis. Ann Surg 2015;262:764–770, discussion 770–761.
[84] Ploeg RJ, Friend PJ. New strategies in organ preservation: current and future role of machine perfusion in organ transplantation. Transpl Int 2015;28:633.
[85] https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/ accessed 11. June 2018.
[86] https://www.agence-biomedecine.fr/annexes/bilan2016/donnees/sommaire-organes.htm accessed 20.12.2018.
[87] https://organ.saglik.gov.tr accessed 21.12.2018
[88] https://www.cihi.ca/en/access-data-and-reports accessed 10. july 2018.
[89] https://www3.anzltr.org/wp-content/uploads/Reports/29thReport.pdf accessed 17. december 2018.
[90] https://www.tsanz.com.au/organallocationguidelines/documents/ClinicalGuidelinesV1.1May2017.pdf accessed 17. december 2018.
[91] http://statistics.eurotransplant.org/index.php?search_type=donors+deceased&search_organ=liver accessed 06. december 2018.
[92] https://www.argentina.gob.ar/salud/incucai accessed 17. december 2018.
[93] https://www.torsc.org.tw/transplant/transplant_15.jsp?uid=40&pid=11#north_4 accessed 20. december 2018.
[94] Gautier SG, Moysyuk YN, Poptsov VN, Kornilov MB, Yaroshenko EV, Pogrebnichenko IY, et al. Long-term outcomes of deceased donor liver transplantation. Russ J Transplantol Artif Organs 2014;16(3):45–53.
[95] http://cenatra.salud.gob.mx/transparencia/trasplante_estadisticas.html accessed 21. december 2018.
[96] Malek Hosseini SA, Nikeghbalian S, Salahi H, Kazemi K, Shemsaeifar A, Bahador A, et al. Evolution of liver transplantation program in Shiraz, Iran. Hepat Mon 2017;17 e60745.
[97] www.abto.org.br. accessed 22. december 2018
[98] Iwatsuki S, Dvorchik I, Marsh JW, Madariaga JR, Carr B, Fung JJ, et al. Liver transplantation for hepatocellular carcinoma: a proposal of a prognostic scoring system. J Am Coll Surg 2000;191:389–394.
[99] Marsh JW, Dvorchik I, Bonham CA, Iwatsuki S. Is the pathologic TNM staging system for patients with hepatoma predictive of outcome? Cancer 2000;88:538–543.
[100] Herrero JI, Sangro B, Quiroga J, Pardo F, Herraiz M, Cienfuegos JA, et al. Influence of tumor characteristics on the outcome of liver transplantation among patients with liver cirrhosis and hepatocellular carcinoma. Liver Transplant 2001;7:631–636.
[101] Moray G, Karakayali F, Yilmaz U, Ozcay F, Bilezikci B, Haberal M. Expanded criteria for hepatocellular carcinoma and liver transplantation. Transpl Proc 2007;39:1171–1174.
[102] Zheng SS, Xu X, Wu J, Chen J, Wang WL, Zhang M, et al. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. Transplantation 2008;85:1726–1732.
[103] Ravaioli M, Grazi GL, Piscaglia F, Trevisani F, Cescon M, Ercolani G, et al. Liver transplantation for hepatocellular carcinoma: results of downstaging in patients initially outside the Milan selection criteria. Am J Transplant 2008;8:2547–2557.
[104] Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepato-

cellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35–43.
[105] Toso C, Asthana S, Bigam DL, Shapiro AM, Kneteman NM. Reassessing selection criteria prior to liver transplantation for hepatocellular carcinoma utilizing the Scientific Registry of Transplant Recipients database. Hepatology (Baltimore, MD) 2009;49:832–838.
[106] **DuBay D**, **Sandroussi C**, Sandhu L, Cleary S, Guba M, Cattral MS, et al. Liver transplantation for advanced hepatocellular carcinoma using poor tumor differentiation on biopsy as an exclusion criterion. Ann Surg 2011;253:166–172.
[107] **Duvoux C**, **Roudot-Thoraval F**, **Decaens T**, Pessione F, Badran H, Piardi T, et al. Liver transplantation for hepatocellular carcinoma: a model including alpha-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012;143, 986–994.e983; quiz e914–985.
[108] **Sasaki K**, **Firl DJ**, Hashimoto K, Fujiki M, Diago-Uso T, Quintini C, et al. Development and validation of the HALT-HCC score to predict mortality in liver transplant recipients with hepatocellular carcinoma: a retrospective cohort analysis. Lancet Gastroenterol Hepatol 2017;2:595–603.
[109] Mazzaferro V, Sposito C, Zhou J, Pinna AD, De Carlis L, Fan J, et al. Metroticket 2.0 model for analysis of competing risks of death after liver transplantation for hepatocellular carcinoma. Gastroenterology 2018;154:128–139.