A Multistep, Consensus-Based Approach to Organ Allocation in Liver Transplantation: Toward a "Blended Principle Model"

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A Multi-Step Consensus-Based Approach to National Allocation in Liver Transplantation: Towards a "Blended Endpoint Model"

Italian Consensus Conference on Outcome Measures and Allocation Policy in Liver Transplantation

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ABSTRACT

Since the latest revision in Italian liver allocation policy (2012), relevant criticalities, conceptual evolutions, and the need for significant improvements have emerged. Herein we report the results of a national Consensus Conference process promoted by the Italian College of Liver Transplant Surgeons (SITO) and the Italian Association for the Study of the Liver (AISF), aimed at revising, on the bases of scientific evidence, the best indicators for guiding organ allocation policies in the urgency, utility, and benefit models. MELD exceptions and hepatocellular carcinoma were analytically approached in building a priority algorithm for transplantation, considering the inequity of a purely MELD-based system in governing organ allocation. The working groups composed of transplant surgeons and hepatologists prepared a list of statements for each of these topics, attributing a level of evidence and recommendation according to the Centers for Disease Control grading system. The jury that voted on and validated the proposed statements was selected among transplant surgeons, hepatologists, intensivists, infectious disease specialists, epidemiologists, representatives of patient and of organ sharing organizations, transplant coordinators, and ethicists. After a careful revision of the statements, a critical proposal for the implementation of the current liver allocation policy in Italy was prepared and shared among transplant surgeons and hepatologists.

INTRODUCTION

Allocation systems based mainly on the urgency principle, as those based on priority indicated by the MELD score, present several limitations that are related to the fact that the MELD score is a measure of severity of liver disease, but is often inappropriate for predicting outcome after liver transplantation (LT). Furthermore, the MELD score cannot predict the severity of several liver diseases currently defined as "MELD exceptions" and of hepatocellular carcinoma (HCC) in patients with compensated cirrhosis.

This implies that the evaluation of equitable access to LT should distinguish between patients with decompensated cirrhosis in whom the urgency principle based on the MELD score is adopted, and patients with HCC and compensated cirrhosis as a prototype of MELD exceptions for whom a MELD-based system does not capture the risk of dropout related to tumor progression or to development of liver-related complications not influencing the MELD scores. Thus the selection of candidates with or without HCC for LT and their priority in receiving a transplant cannot be predicted simply by models based on the urgency principle (Appendix 1), but by models balancing urgency and utility principles and including the transplant benefit endpoint.

Several models centered on either urgency, utility, or benefit principles or their combinations have been proposed according to score adjustments, donor-recipient matching, and other optimization principles, considering that access to transplantation cannot be an exclusive goal without taking into account de-listing criteria, long-term transplantation outcomes, and availability, as well as expected results of alternative therapies.

The complexity of the issue, the number of variables to be considered, the variety of medical, social and political figures involved, and the vast differences in local and regional scenarios have impeded the translation of all the above elements into a consensual allocation/priority system.

The National Center of Transplantation (CNT) governs the organ transplantation network in Italy. The network is composed of 21 liver transplant centers, distributed in 13 regions, and grouped in 2 macro-areas covering the center-north and the center-south of the country, respectively. Since the

inception of the CNT, liver allocation policies have undergone several modifications. The current liver allocation policy is the result of a 2012 revision, which involved broader regional, macro-area and national sharing of organs on the basis of urgency principles. National sharing is adopted for the sickest recipients, who are classified, in accordance with the UNOS classifications, as Status 1 (super-urgent patients). Macro-area sharing is adopted for recipients with a MELD score ≥30, and regional sharing is applied for recipients with a MELD score ≤29, with a minimum MELD score for listing of 15. This allocation scheme implies local, uncontrolled, and different policies, a lack of balance among different transplant etiologies, and the absence of a common endpoint framework to unify the action of the national liver transplant system.

Given these areas of contention, a national consensus conference process, with the contribution of all interested parties, was proposed in order to fulfill an unmet need for broader discussion of these important issues in Italian liver allocation policies.

The aims of this multistep process were:

1. identification of the best indicators for urgency, utility, and benefit of organ allocation policies;
2. identification of the MELD exceptions and the best indicators for organ allocation policies in the MELD exceptions;
3. preparation of an operative proposal for the implementation of the current allocation system.

Liver allocation to pediatric recipients was not included in this process because of the existence of a national common list, with an independent setting and already agreed upon roles.

This report provides the results of group discussions on the aforementioned topics, and the operative proposal to implement the current allocation policy for LT in Italy.

The methodology and the data from this work should provide a potential model to stimulate discussion on future implementations in liver allocation systems adopted in other countries.

METHODS

Promoters were the Italian College of Liver Transplant Surgeons (SITO) and the Italian Association

for the Study of the Liver (AISF). The Promoters identified a Scientific Board of Experts that was composed of 2 coordinators of scientific societies, 2 liver transplant surgeons, and 2 transplant hepatologists, recognized as leading experts in the field.

The first and second topic were discussed in separate Consensus Conferences, held in 2012 and in 2013. For each topic, the Promoters and the Scientific Board identified a working group equally composed of surgeons and hepatologists, selected on the basis of their expertise and publications in the field of liver disease and transplantation. The working groups independently carried out a systematic review of the literature. While there were specific background presentations that took place in the morning of the forum, the afternoon was devoted to interactive discussion among working groups. At the end of the discussion, each working group proposed definitions and statements referring to each topic, which were graded according to the CDC grading system. The flow chart summarizing the key steps in the Consensus Conferences preparation is reported in Appendix 2.

The proposed statements were voted on by a Jury that was selected among transplant surgeons, hepatologists, intensivists, infectious disease specialists, epidemiologists, patient representatives, representatives of organ sharing organizations, transplant coordinators, and ethicists. None of the Jury members were involved in the selection, preparation or discussion of the topics and statements. During the voting sessions, the chairman of each working group presented the proposed statements referring to the first two aforementioned topics. The format in which the statements were proposed initially provided the formulation of a question, followed by one or more responses based on the level of evidence and the strength of recommendation, according to the CDC grading system scale. A general discussion was held in order to refine the statements and make any possible revision. At the end of the discussion, every proposed statement was voted on by the Jury (valid vote) and by the audience (reference vote).

In February 2015, after further careful revision of the approved statements, a group of experts composed of surgeons and transplant hepatologist group coordinators worked to prepare the

operative scheme reported herein, which will be presented to all parties involved in liver transplantation at a meeting to be held in mid 2015.

CONSENSUS CONFERENCES RESULTS

The approved statements concerning the definition and the outcomes provided by the utility, urgency, and benefit principles are reported in Appendix 3. Based on their relevance for the discussion, benefit statements are also reported in Table 1. Each statement includes, when appropriate, the level of evidence and the grade of recommendation.

MELD exceptions were analytically identified in building a priority algorithm for transplantation on the basis of currently available scientific evidence. Four categories of priority (P) for MELD exceptions were identified and defined as follows:

- P1: Very high priority: need for macro-regional organ sharing (two national areas of 20-25 million inhabitants) as established in Italy for recipients with a MELD score ≥30
- P2: High priority: regional organ sharing (areas of 1-6 million inhabitants), with the possibility of prioritizing in macro-regional areas
- P3: Intermediate priority: regional organ sharing, with the possibility of prioritizing
- P4: Low priority, regional organ sharing, with the possibility of prioritizing

The proposed detailed list of individual MELD exceptions in relation to individual priorities is reported in Table 2 and Appendix 4. In Appendix 5 a detailed list of statements referring to indicators of prioritization in patients with MELD exceptions is reported. A pertinent list of comments that explain in more detail the content of each statement and relative references is also provided (Appendix 5A).

For HCC patients, a new classification (Table 1) and prioritization policy (Table 4) were agreed on. First, patients were defined as Transplantable (TT) (or non Transplantable - T_{NT}) if within/out accepted transplant criteria for acceptable post transplant survival (either conventional or extended criteria, but within minimal accepted post-transplant utility, e.g., Milan Criteria, Up to Seven, TTV) (Table 3). After this basic filter, patents were then classified according to more dynamic categories

(first presentation, early or late recurrence, kind of response to bridge therapy, successful downstaging), and finally classified in 3 different priority strata, according principally to a conceptual benefit endpoint, but also taking into consideration risk of dropout and patient/physician expectations (Table 3). Final priority within the strata will be regulated according to the benefit prognosticators currently available (HCC-MELD), as well as to an agreed definition of disease progression.

Table 4 synthetizes the whole scheme of prioritization, including super-urgent patients as well as MELD patients, MELD exceptions, and HCC patients receiving priority according to a common continual numeric scale. A future implementation of the system from MELD to MELDNa is planned.

Discussion

Organ distribution and allocation is an evolving process in different liver transplantation areas worldwide. European transplant organizations, for example, which base liver allocation criteria on blood group, recipient size, clinical urgency, and waiting time have reported 13 different adaptations of allocation rules from 2006 to 2013. At present, OPTN/UNOS is considering a redesign of liver distribution in the U.S. to reduce variation in access to liver transplantation, exploring a national geographical division of 4 or 8 districts. In the U.K., the last change in policy received final approval from the Transplant Policy Review Committee in March, 2014.

Many other countries, mainly Asian, with relatively recent experience in cadaveric donation are now facing the complexity of this issue, and are creating *de novo* allocation algorithms.

The methodology of these frequent implementations (or *de novo* implementations) varies and includes in most instances an organ-specific advisory board (e.g., Liver Advisory Group on behalf of NHSBT in the U.K.; EUROTX in Europe). In some national transplant experiences (e.g., OPTN/UNOS in the U.S.A.), major distribution/allocation changes are first circulated as "concept documents" to receive valuable input from all interested parties. Resulting proposals are then submitted to the public for further comment and implementation before the Board's final decision.

The results of the Consensus Conferences herein reported had made it clear that changes to existing Italian liver allocation policy were required in order to account for the vastly heterogeneous nature of waitlist patients within the same MELD score intervals, given the emergence of disadvantaged subgroups and potential regional inequities.

The multistep-consensus conference setting we adopted started with a critical review of the scientific evidence, with the contribution of all the players of the system, to produce a sort of "common sense and knowledge" of problems, different available solutions, and relative pros and cons.

In this setting, substantial attention was paid to a critical reconsideration of outcome measures in liver transplantation in light of recent evidence and experience (First Step).

The introduction of the MELD score, in 2002, vastly improved objectivity, transparency, and efficiency of the allocation and prioritization processes in LT. However, a relevant number of patients, including HCC patients with compensated cirrhosis, and the so-called MELD exceptions, still receive priority according to arbitrary national or regional judgments. In many international allocation models, questions about equity and efficiency have been raised, with particular reference to the different endpoints used (urgency vs. utility). An imbalance in transplant opportunities among different etiologies of liver diseases on the same waiting list has also been addressed, and has required subsequent adjustments.

In our consensus on outcome measures (First Step), it emerged that the concepts of utility and urgency used independently in a non-integrated scheme to guide allocation/prioritization have a number of limitations. A "blended endpoint model," also widely including a transplant benefit concept might contribute to the unsolved issue of balance in urgency and post transplant utility in LT. Indeed, transplant benefit adjusted for a minimal accepted post-transplant utility has been considered, in this national process, an attractive outcome measure to be tested in the future to improve equity among different etiologies, and to increase the efficiency of the system at both an individual and population level (Table 1).

As a result of these speculations, in the final operative meeting, held in February 2015, it was decided, while awaiting more robust benefit prognosticators, to design a system that reflects an adequate balance among the different principles, consistent with the Persad et al. fundamental statement: "To achieve a just allocation of scarce medical interventions, society must embrace the challenge of implementing a coherent multi-principle framework rather than relying on simple principles or retreating to the status quo."

An area of pure urgency endpoint was identified, including patients with high short-term risk of death (super-urgent, MELD ≥30 and P1 exceptions) benefitting from a large geographical area of allocation (nation or macro-area) or (P2) having to be granted high time-dependent prioritization.

It was agreed that the two further areas (areas of "benefit" and "pure post transplant utility" endpoints) could be better managed in the context of a regional allocation, where an easier donor-recipient match and greater flexibility may represent a plus.

Within the last two areas and under this unifying "blended endpoint concept," including benefit and pure post transplant utility, other MELD exceptions, including complications of cirrhosis, rare liver diseases or their unusual presentations, and liver tumors were reconsidered in the second Consensus Conference (Second Step). An arbitrary approach for the priority definitions in MELD exception was driven by experts and followed by wide agreement, and aimed, when possible, at focusing on a benefit endpoint.

Balance between MELD patients and Exception patients was also arbitrary, dividing the MELD interval 15-30 in quartiles, and equating each P category at the lowest MELD of the corresponding quartile (e.g., P4 = MELD 15). Time adjustment points were regulated according to the mean waiting time of the disease strata recorded in 2014. Patients with the same score would be served according to waitlist time.

For HCC patients, the difference between expected survival with transplantation versus alternative therapies, when available, is crucial.

With the lack of accurate prognosticators of benefit, treatability with alternative tools, response to therapy, and successful downstaging were considered as benefit surrogates. It was agreed, though, stratifying patients into 3 major priority strata, that very early HCC in compensated cirrhosis or HCC patients with alternative radical therapeutic options available, such as liver resection, have a benefit that is intrinsically too low to deserve priority for transplantation, while impaired liver function in HCC patients, limiting the adoption of any alternative therapy, weighs substantially in increasing the transplant benefit. Avenues for considering priority for efficaciously downstaged HCC patients move in the same direction, again provided that the high benefit achieved by transplant in these patients is "capped" by a minimal accepted post-transplant utility (minimal predicted long-term survival post-transplantation).

The HCC-MELD scoring system, even with a number of important limitations, has been chosen as a priority tool within the HCC strata since it is the only published score that considers a balance between HCC and non-HCC patients, with benefit as endpoint. The score gives a relevant weight to the severity of liver function impairment as a mirror of non-applicability of alternative therapies, and also reflects the negative impact of alpha-fetoprotein on post-transplant prognosis. However, the system needs external validation.

Due to an intrinsically greater benefit, patients in HCC stratum 1 (TT_{DR}, TT_{PR}) would receive a higher prioritization by adding more time-adjusted extra points to the HCC MELD than the other HCC strata (TT_{FR}).

From the open discussion it was clear that transplant benefit as a relevant outcome measure has important limitations. Accuracy of prognostic benefit models is still relatively weak, and there is a substantial lack of evidence on benefit predictors in some numerically relevant indications for liver transplantation, such as HCC and MELD exceptions.

Furthermore, a purely transplant-benefit oriented allocation may intrinsically favor those patients with underlying diseases associated with better post-transplant prognosis (e.g., PBC), as well as younger patients. These equity imbalances could be partially adjusted through an adequate

transplant benefit time horizon specifically chosen (e.g., 10 years post-transplant). Ethical issues will play a relevant role in these adjustments.

As a final step of the process, the group agreed to verify the weight of the main allocation principles in the distribution of national liver donor resources in 2014, as depicted in Figure 1. This model of graphic representation, even though general and somewhat arbitrary, represents a benchmark for future national or international comparisons aimed at optimizing the balance among different principles and guiding future resource investments. For example, a consensus was reached that for the next year transplant centers should have a "pure post-transplant utility area of allocation" of up to 40% of overall donor resources. A yearly remodulation of such prevalence, according to epidemiological studies and waitlist dropout data (in a continually changing scenario), was also decided.

It is worth noting that an agreement to dedicate up to 5% of the national donor liver resources to innovative, multicenter studies was also reached. A crucial commitment was taken to implement prospective studies focused on benefit prognosticators (with particular reference to HCC patients) to adequately validate benefit-oriented allocation models.

One of the contributions to the transplant community of this report is that it comes 8 years after the publication of the International Consensus on MELD Exception, published in *Liver Transplantation* in 2006.

Another interesting and well received Consensus Conference report was published a few years ago However, this was a Consensus Conference specifically dedicated to HCC. The organization of the consensus, and the methodology followed to collect the recommendations were widely appreciated, and then became a point of reference in most liver transplant centers around the world. No other such complete and detailed Consensus Conference Report on LT has been published since.

In conclusion, this multistep consensus-based approach represents a potentially effective response to the complexity of liver allocation, which includes conflicting principles, diverging endpoints, and different clinical presentations in varying degrees. We truly hope our national experience can be a

stimulus for discussion at the international transplant community level, as well as for those countries where liver transplantation has already achieved consolidated results, and for those countries where the deceased donor transplant process is still developing.

Table 1. Statements on Transplant Benefit (in **boldface** the level of evidence and grade of recommendation).

Statements C: BENEFIT

C6.1 Transplant benefit of at least 5 years after transplantation is the best available indicator for maximizing the life-saving potential of procured livers. **E2, R2**

C6.2 Transplant benefit should be regulated according to minimally acceptable post-transplant results (UTILITY), and take into account the risk of dropout from the waiting list (URGENCY). **E2, R2**

C6.3 When measuring transplant benefit, the gain in life years is equivalent to the difference in the mortality ratio of patients with or without liver transplantation. The measure of gain in life expectancy is more understandable than the difference in mortality ratio with or without transplant. **E2**

Most studies on transplant benefit calculation are based on waiting list populations. **E2**

However, the implementation of a national registry to sample prospective cohorts of cirrhotic patients potentially eligible for liver transplantation based on the ITT principle is strongly recommended. **R1**

C6.4 Quality-adjusted life years (QALYs) should be included in the transplant benefit estimation as a relevant endpoint. **E3, R3**

Cost effectiveness should also be evaluated, though neither evidence nor data are available in the transplant benefit estimation. **R3**

C6.5 Evaluation of potential harm to individuals and waiting list populations should be included in the transplant benefit estimation **E2, R2**

Statements C: BENEFIT PREDICTORS

C7.1 The predictors of transplant benefit in cirrhotic patients are, at minimum, the following: MELD and its variables, albumin, donor age, recipient age, previous liver transplant, diagnosis of HCV, and portal vein thrombosis. **E2**

Studies assessing predictors of transplant benefit are warranted.

C7.2 Liver function is a predictor of transplant benefit in HCC patients

Indeed, in patients within criteria for transplantation according to tumor features, BCLC stages seem to predict the magnitude of transplant benefit. **E2**

Applicability of therapies as alternatives to transplantation is a predictor of transplant benefit in HCC patients. **E2**

Studies on transplant benefit, including hepatic function parameters and tumor characteristics, are warranted. **R2**

Statements C: MINIMUM THRESHOLD OF BENEFIT

C8.1 A MELD score of 15 corresponds to a 1-year transplant benefit of 12 months of life gain. This should be the minimum acceptable benefit.

Excluding exceptions, the minimum listing criteria in Italy for patients with end-stage liver disease is MELD 15. **E2, R2**

Table 2. Agreed Priority Stratification of MELD Exceptions and Relative Sharing Area.

Priority and Sharing	LT Indication
P1 (Macro-area sharing once served those with MELD>30)*	- Rendu-Osler-Weber, - Hepatoblastoma (young adult), - Hemangioma (if Kasabach Merritt syndrome), - Acute late ReLT, - FAP (if domino)
P2 (Center-based)	- HCC (center-modulated priority) - Hepato-pulmonary syndrome - PPH - Refractory hydrothorax - Chronic late ReLT - Hepato-renal syndrome (if not automatically equated with MELD) - Previous severe infections
P3 (Center-based)	- Refractory ascites - FAP - Wilson's (with compensated cirrhosis and initial neurologic symptoms) - NET metastases - Hemangioendotheliomas
P4 (Center-based)	- PSC or PBC with intractable pruritus - Polycystic disease - Complicated adenoma - Hemangiomas
P Multidisciplinary (Center-based)	- Hepatic encephalopathy - Fibrolamellar HCC - Liver adenomatosis (not complicated) - Neuroendocrine metastases - Hilar cholangiocarcinoma - CRC metastases

Table 3. Staging and Priority Classification of HCC in Liver Transplantation: The Proposed New Patient Stratification.

Category of transplantable (T) HCC	**Priority according to HCC drop-out models**	**Priority according to transplant benefit**	**Priority based on patient/physician expectations**
$T0_C$	**Very Low**	**Low**	**Low**
No residual tumor after curative treatment of a T-HCC	Very low-risk of dropout in cured HCC	Transplant benefit depending on lab-MELD only	Patients with no tumor should not be transplanted
$T0_L$	**Low-Intermediate**	**Low**	**Intermediate**
No residual tumor after loco-regional embolo-therapies of a TT-HCC	Low-risk of dropout in cured HCC	Transplant benefit depending on HCC-MELD	The patient was transplantable but now can be put on hold because the tumor seems to be cured
$**T0_{NT}$	**Not Applicable**	**Low**	**Low**
No residual tumor after treatment of a NT (Non-Transplantable) HCC	NT HCC should not be listed, as in cases of non-HCC in low MELD patients	Transplant benefit depending on lab-MELD only	The patient was not transplantable and now is cured by other means
T1	**Low**	**Low**	**Low**
Single HCC ≤2cm	Low risk of drop-out in very early HCC	Low benefit in presence of alternative non-transplant treatments	No need to transplant someone who can be treated by other means
$*TT_{FR}$	**Intermediate**	**Intermediate**	**High**
Any Transplantable TT-HCC at presentation or recurrent HCC >2 years after curative treatment of a TT-HCC	Demonstrated increase of dropout risk over time and across T2-HCC sub-stages	Benefit depending on true applicability of alternative non-transplant treatments	This is the patient with the best post-transplant survival (utility)
TT_{PR}	**Intermediate-High**	**High**	**High**
Partial response to bridge therapy (cycle of multimodal therapy)	Risk of selection of biologically aggressive clones with increased proliferative activity	Failure of a bridge therapy with no residual therapeutic alternative	Patients still with good post-transplant expected utility and high need for OLT
TT_{DR}	**Intermediate-High**	**High**	**High**
TT-HCC after downstaging or recurrent HCC < 2 years after curative treatment of any HCC	High dropout risk over time and across T2-HCC sub-stages	Benefit depending on absence of true alternatives among non-transplant treatments	Transplant is a chance to be offered before is too late

*TT-HCC: any HCC within transplantability criteria (either conventional or expanded criteria, after donor rate and dynamics of waiting-list considerations, in agreement with region/state allocation rules)

**NT-HCC: non transplantable HCC: any other conditions not within the T-HCC definitions and/or any conditions of extrahepatic tumor spread and/or macrovascular invasion

Table 4. Proposed and Agreed upon National Waiting List Prioritization Roles and Geographic Distribution of Organ Allocation in Patients with or without HCC and in Those Considered MELD Exceptions.

PRIORITY	PTS CATEGORY	POINTS	ALLOCATION AREA
SUPER-URGENT	FHF, early reOLTx, hepatoblastoma	(first come first served)	NATION
URGENT	MELD > 30	Biochemical MELD	MACROAREA
URGENT	EXCEPTIONS P1	30	MACROAREA
STANDARD	EXCEPTIONS P2	25 + 1/ month	REGION/CENTER
STANDARD	Bioch MELD 15-29	Biochemical MELD	REGION/CENTER
STANDARD HCC Stratum 1	HCC: TT_{DR} - TT_{PR} (downstaged patients or partial responders to bridge therapies)	MELD 22 at entry or HCC-MELD* + increased time adjustment (according to regional choice) § Cap at 29	REGION/CENTER
STANDARD HCC Stratum 2	HCC: TT_{FR} (First presentation or late recurrence)	HCC-MELD* Criteria for time adjustment points and priority class migration on disease progression will be set regionally (regional board approval)# Cap at 29	REGION/CENTER
STANDARD HCC Stratum 3	HCC: $T0_C$ – T1 – T_{NT} - $T0_L$ (complete responders or T1 tumors)	Biochemical MELD	REGION/CENTER
STANDARD	EXCEPTIONS P3	20 + 1 every 2 months	REGION/CENTER
STANDARD	EXCEPTIONS P4	15 + 1 every 2 months	REGION/CENTER

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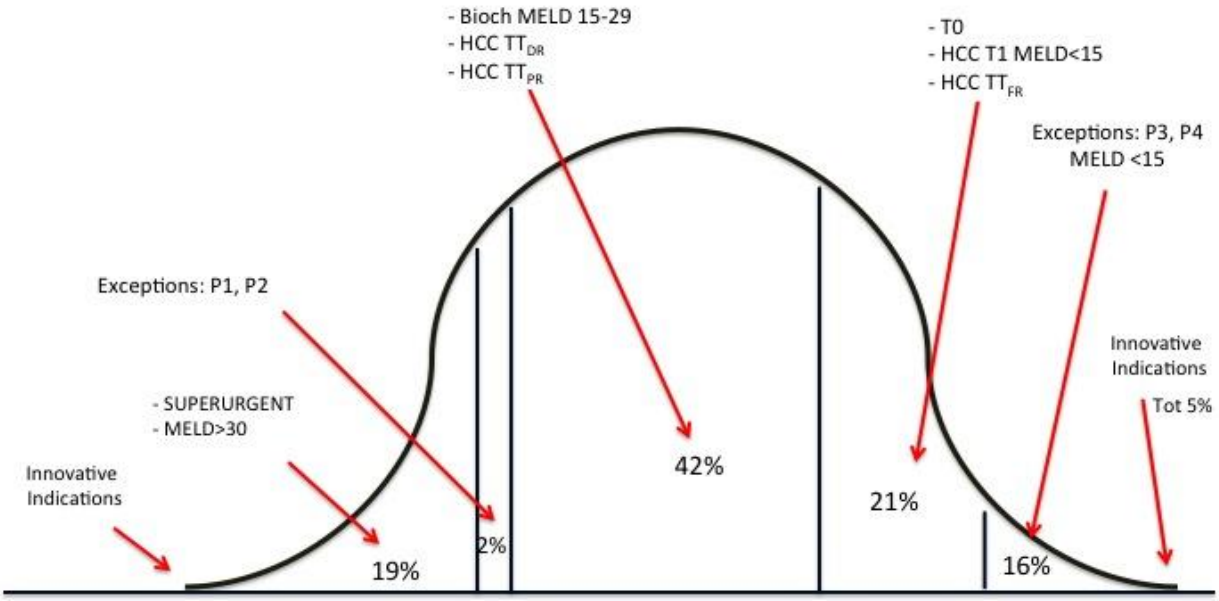
§ Choice between “HCC MELD + increase time adjustment at entry” or “fixed MELD at 22” will be decided on a regional basis.
#Point progression while waiting can be discussed and adjusted (fast vs. slow pace) according to pattern of response or progression within the transplantability criteria. Progression has to be assessed after optimal treatments within defined protocols. In case of vital tumor after 6 months, extrapoints can be allowed.
P1= Rendu-Osler-Weber, young adult hepatoblasoma, Kasabach-Merritt, late “acute” retransplant.
P2= Hepato-pulmunary syndrome, porto-pulmunary hypertension, late “chronic” retransplant, refractory hydrothorax, hepatorenal syndrome, previous severe infections.
P3= Refractary ascites, FAP, Wilson’s with initial neurologic symptoms and well compensated cirrhosis, NET metastases, hemangioenadothelioma.
P4= Complicated adenomatosis, polycystic disease.

Figure 1. Ideogram of Donor Resource Distribution among Prevalent Liver Allocation Principles in Italy.



PRINCIPLE	FUTURE BENEFIT	Pure URGENCY HIGH BENEFIT	Low ALTERNATIVES HIGH BENEFIT	Post OLT UTILITY LOW BENEFIT	FUTURE BENEFIT
PRIORITY	Multidisc	Sickest first	Greater benefit	Waitlist time	Multidisc
PREDICTOR	-----	MELD/time bonus	MELD, HCC-MELD	MELD + time bonus	-----
PREVAL 2014	-----	21%	42%	37%	------
FUTURE AIM	Up to2.5%	To be reduced	To be increased	Not greater than 40%	Up to2.5%

Multidisc: Abitrary multidisciplinary decision on priority for unconventional indications.

PREVAL 2014: Prevalence of national indications for transplant in 2014 stratified according to main allocation principle.

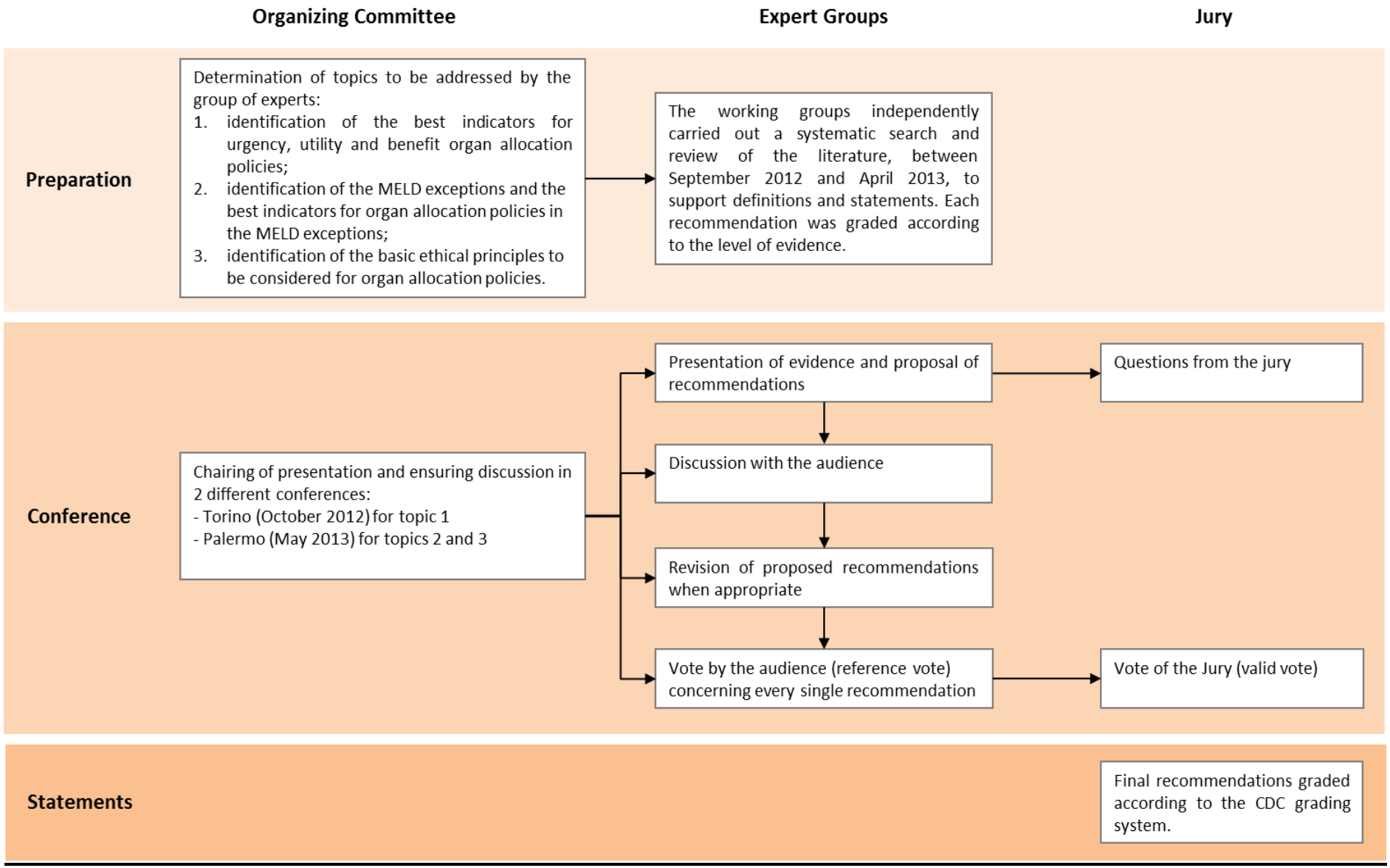
FUTURE AIM: National community agreement on resource distribution goals for the next 3 years

Appendixes

Appendix 1. Differences in the Selection Criteria Adopted for Liver Transplantation Cirrhotic Patients with or without HCC.

Cirrhosis	**HCC + Cirrhosis**
MELD ≥15	Milan Criteria
MELD exceptions (increasing up to 20% of the whole)	Up-to-Seven Criteria UCSF Criteria Non-standardized down-staging and biologic tumour criteria
Access to Tx influenced by: • risk of mortality during waiting time • donor characteristics (HCV+ recipients)	Access to Tx influenced by: • risk of drop-out during waiting time • local or general policy to add MELD points

Appendix 2. Flow chart Showing the Structure and Modalities Adopted for Preparation of the Consensus Conferences.



Appendix 3. Final Recommendation and Statements Voted on in the Consensus Conferences. The Statements Are Divided into Three Sections: Section A Refers to Utility, Section B to Urgency, and Section C to Benefit. The Level of Evidence (E) and the Grade of Recommendation (R) Based on the CDC Grading System Are Provided, When Appropriate, for Each Statement.

SECTION A: UTILITY

Statement A: Utility endpoint	Level of evidence	Strength of recommendation
A1. Intention to treat (ITT) patient-survival of at least 5 years must be preferred to absolute survival for all end-stage liver disease (ESLD) patients, with or without HCC, because ITT analysis can capture the entire therapeutic process, including liver transplantation.	E2	R1
A 1.1. Intention to treat (ITT) analysis is more informative if done not only on single-center data, but also on an entire macro area/nationally-listed populations.	E3	

Statement A: Utility predictor		
A2. Evidence-based prognostic tools have been developed mainly in post-transplant patients and graft survival.	E2	
A2.1 **Cirrhosis**: The use of validated predictors, including both donor and recipient parameters, such as D-MELD or other predictors validated nationwide, is strongly advised.	E2	R1
A2.2 **HCV Patients**: In HCV-positive recipients, a relevant predictive value of the D-MELD score has been identified in a large Italian cohort. Thus, at present, its use is strongly advised for such patients.	E2	R1

Statement A: Minimum survival threshold		
A3. The acceptable survival threshold is 50% at 5 years, regardless of the indication for liver transplantation.	E3	R2
A3.1 The same applies to re-transplantation and fulminant hepatic failure (FHF).		R1
A3.2 It is hoped that in the future this threshold can be more precisely established.		R2

SECTION B: URGENCY

Statement B: Urgency endpoint	Level of evidence	Strength of recommendation
B4.1 Risk of dropout from the waiting list at three months (due mainly to mortality) is the best urgency indicator in cirrhotic patients.	E2	R2
B4.2 MELD-Na is a better predictor than MELD because it identifies patients in greater need of transplantation, particularly in the high ranges of the MELD score.	E2	R1

Statement: B Urgency predictors in patients with HCC		
B5.1 Risk of dropout from the waiting list at three months (due mainly to tumor progression outside the transplant criteria) is, at present, the best indicator of urgency in HCC patients listed for transplantation.	E2	R2
B5.2 Alpha-fetoprotein, diameter of the largest nodule, MELD score, and failure to respond to HCC treatment while on the waiting list are strong predictors of dropouts.	E2	
B5.3 To ensure equity among HCC and cirrhotic patients, validation of prognostic models based on the same endpoint (e.g., HCC-equation, deMELD) is recommended.	E2	R1
B5.4 T1 HCC patients with MELD <15 should not be listed for liver transplantation barring well-motivated exceptions.		R1
B5.5 T2 HCC patients with comparable hepatic function should be stratified according to response to treatment while on the waiting list: responders should receive less priority than partial*or non-responders, or than untreatable patients *(mRECIST criteria vs. EASL criteria).	E2	R1
B5.6 Progression of HCC beyond T2 should be re-evaluated for indication and priority for liver transplantation, considering downstaging strategies in the context of formal protocols.	E2	R2

SECTION C: BENEFIT

Statement C: BENEFIT	Level of evidence	Strength of recommendation
C6.1 Transplant benefit of at least 5 years after transplantation is the best available indicator for maximizing the life-saving potential of procured livers.	E2	R2
C6.2 Transplant benefit should be regulated according to minimally acceptable post-transplant results (UTILITY), and take into account the risk of dropout from the waiting list (URGENCY).	E2	R2

C6.3 When measuring transplant benefit, the gain in life years is equivalent to the difference in the mortality ratio of patients with or without liver transplantation. The measure of gain in life expectancy is more understandable than the difference in mortality ratio with or without transplant. Most studies on transplant benefit calculation are based on waiting list populations. However, the implementation of a national registry to sample prospective cohorts of cirrhotic patients potentially eligible for liver transplantation based on the ITT principle is strongly recommended.	E2 E2	 R1
C6.4 Quality-adjusted life years (QALYs) should be included in the transplant benefit estimation as a relevant endpoint. Cost effectiveness should also be evaluated, though neither evidence nor data are available in the transplant benefit estimation.	E3	R3
C6.5 Evaluation of potential harm to individuals and waiting-list populations should be included in the transplant benefit estimation.	E2	R2

Statement C: BENEFIT PREDICTORS

C7.1 The predictors of transplant benefit in the cirrhotic patients are, at minimum, the following: MELD and its variables, albumin, donor age, recipient age, previous liver transplant, diagnosis of HCV, and portal vein thrombosis. Studies assessing predictors of transplant benefit are warranted.	E2	
C7.2 Liver function is a predictor of transplant benefit in HCC patients Indeed, in patients within criteria for transplantation according to tumor features, BCLC stages seem to predict the magnitude of transplant benefit. Applicability of therapies as alternatives to transplantation is a predictor of transplant benefit in HCC patients. Studies on transplant benefit, including hepatic function parameters and tumor characteristics, are warranted.	E2 E2 E2	R2 R2

Statement C: MINIMUM THRESHOLD OF BENEFIT	Level of evidence	Strength of recommendation
C8.1 A MELD score of 15 corresponds to a 5-year transplant benefit of 12 months of life gain. This should be the minimal acceptable benefit. Excluding exceptions, the minimum listing criteria in Italy for patients with end-stage liver disease is MELD 15.	E2	R2

Appendix 4. Attribution of Priority in Liver Transplantation for MELD Exceptions. Priorities Are Divided into Those Predicted and Unpredicted by MELD Score. In the Latter Group a Coefficient of Priority (P) Is Indicated.

MELD Exceptions	Priority		Described by MELD Na	Priority
Refractory ascites	P3		HRS 1, 2	MELD calculated as for dialysis patients
Hydrothorax	P2		Wilson's	MELD
Hepatic encephalopathy	P multidisciplinary		Hemochromatosis	MELD, if HCC, rules for HCC
FAP	P1 if domino		Alfa-1antitrypsin deficiency	MELD, if HCC, rules for HCC
PPS (if PaO_2 <60mmHg)	P2		HIV	
Late retransplantation	P2 or higher			
Fulminant liver failure	Status 1			
Polycystic disease	P4			
Intractable pruritus	P4			
Hepatoblastoma	P1			
Fibrolamellar HCC, liver adenomatosis, Neuroendocrine metastases, Hilar cholangiocarcinoma, CRC metastases	P multidisciplinary			

Appendix 5. List of Statements Referring to MELD Exceptions Considered for Liver Transplantation and Proposed Tools to Attribute a Level of Priority. MELD Exceptions Are Divided into Two Sections: Section D Refers to Non-Tumor-Related MELD Exceptions, and Section E Refers to Tumor-Related MELD Exceptions. The Level of Evidence (E) and the Grade of Recommendation (R) Based on the CDC Grading System Are Provided, When Appropriate, for Each Statement.

SECTION D

Question

Are the following MELD exceptions to be considered for transplantation, and at which priority?

D9. **Ascites and refractory hydrothorax.** **Statement**	Level of evidence	Strength of recommendation
D9.1 MELDNa should be preferred to standard MELD in all patients with cirrhosis and ascites, both for listing and prioritization. The presence of refractory ascites, defined according to the ICA criteria*, is associated with a worse prognosis, and requires:	E2	R1
1) early listing independent of MELDNa (also if <15) and	E2	R2
2) prioritization at level P3 when a) its management requires at least three large-volume paracenteses (>5 liters) per month within the last three months and b) there is a contraindication for the placement of a TIPS or no response to TIPS.	E3	R2
D9.2 Patients with refractory hydrothorax who need repeated thoracenteses because of either a contraindication for TIPS or no response to TIPS, should receive a higher priority (P2) than those with refractory ascites.	E3	R2

D10

Hepato-renal syndrome

Statement	Level of evidence	Strength of recommendation
D10.1 Type 1 HRS and severe type 2 HRS (serum creatinine >2 mg/dl) should be considered an exception to the MELDNa score.	E1	R1
D10.2 For the patient with type 1 HRS and severe type 2 HRS who responds to terlipressin and albumin, and then maintains an adequate renal function, pre-treatment MELDNa score should be used for prioritization on the waiting list for LT.	E3	R2
D10.3 The patient with continuous recurrence of type 1 or severe type 2 HRS who requires a "long term" treatment with terlipressin and albumin should be considered as though he were on dialysis, and thus receive the same points in the calculation of the MELDNa score.	E3	R2

D11.

Hepatic encephalopathy

Statement		
D11.1 In patients with a chronic encephalopathy grade ≥ 2, with MELD <15, without the presence of precipitating risk factors (with or without TIPS), not responsive to adequate therapy, with poor quality of life, liver transplantation can be proposed as a MELD exception.	E3	R2
D11.2 There is insufficient evidence that these patients deserve priority on the waiting list.		R3

D12.

Rendu-Osler-Weber disease

Statement		
D12.1 Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease) can be considered an exception to the MELD score because of the possible absence of liver function impairment **(AII)**.	E2	
D12.2 Transplant priority for these patients should be just after status I, (P1).	E3	R2

D13.

Wilson's disease

Statement	Level of evidence	Strength of recommendation
D13.1 Decompensated cirrhosis due to Wilson's disease, with or without the presence of mild neurologic symptoms, after failure of copper chelating therapy or interruption, does not represent a MELD exception.	E2	
D13.2 Patients with decompensated cirrhosis due to Wilson's disease with mild clinically evident neurological symptoms and cerebral involvement assessed by PET/SPECT despite copper chelating therapy should be prioritized (P3) on the waiting list.	E2	
D13.3 Liver transplantation is not indicated in the presence of neurological symptoms, without liver disease or with liver disease associated with a severe neuropsychiatric condition, because of the lack of sufficient evidence.	E3	

D14. **Idiopathic hemochromatosis**		
Statement		
D14.1 Idiopathic hemochromatosis as the cause of liver cirrhosis does not represent a MELD exception.	E2	
D14.2 In the presence of HCC, liver transplantation criteria for HCC should be followed, applying the same listing criteria adopted for HCC in patients without hemochromatosis.	E2	

D15.

Alfa-1 antitrypsin deficiency

Statement		
D15.1 Liver cirrhosis due to alfa-1-antitrypsin deficiency does not represent a MELD exception.	E2	
D15.2 In the presence of HCC, liver transplantation criteria for HCC should be respected.	E2	

D16

Familial amyloidotic polyneuropathy

Statement	Level of evidence	Strength of recommendation
D16.1 Patients with familial amyloidotic polyneuropathy should be considered for listing within the first year of the onset of symptoms, and before the occurrence of organ damage.	E3	
D16.2 When the domino transplant procedure is applicable, these patients should be prioritized after status I (P1).	E3	R2
D16.3 Liver cirrhosis due to alfa-1-antitrypsin deficiency does not represent a MELD exception.	E3	R2
D16.4 In the presence of HCC, liver transplantation criteria for HCC should be respected.	E3	R1

D17

Hepato-pulmonary syndrome (HPS)

Statement		
D17.1 Liver transplantation is the only effective therapy for HPS because it can correct hypoxemia and improve survival.	E2	
D17.2 There are no data for considering mild/moderate HPS (PaO_2 80-60 mmHg) as a MELD exception. Differently, P_aO_2 <60mmHg is a sufficient criterion for attributing a high priority (P2).	E3	
D17.3 Because hypoxemia is often progressive, a clinical re-evaluation every 3 months is advised.	E2	

D18

Porto-pulmonary syndrome (PPS)

Statement		
D18.1 Patients with PPS should be listed independent of MELDNa score only if they are responsive to vasoactive therapy (achievement of an MPAP <35 mmHg and PVR <400 dynes.s.cm-5 or normal PVR (<240 dynes.s.cm-5).	E2	
D18.2 MPAP>50 mmHg not corrected by vasoactive therapy is an absolute contraindication to liver transplantation.	E1	
D18.3 High priority (P2) should be given to patients with pre-treatment MPAP>35 mmHg. A re-evaluation with right cardiac catheterization every 3 months is advised.	E2	

D19

Late retransplantation

Statement	Level of evidence	Strength of recommendation
D19.1 Because no clear criteria for late retransplantation are available, the decision regarding a late retransplantation is to be taken on a case-by-case basis.	E3	
D19.2 Late "acute" retransplantation** should have different priority criteria if compared with late "chronic" retransplantation.	E3	
D19.3 While awaiting prospective validation of outcome scores, a high list priority *(P2 or higher – note)* is advised in order to avoid futile retransplantation.	E3	R2

D20

Acute liver failure

Statement		
D20.1 Acute liver failure (ALF) is an indication for urgent transplantation regardless of the MELD score**.** ALF usually has a status 1 priority for transplantation.	E3	R1

D21

Liver transplantation in HIV-positive recipients

Statement		
D21.1 Patients infected with HIV do not represent a MELD exception.	E2	
D21.2 In patients with HIV and HCV co-infection, liver transplantation at lower D-MELD values than patients without HIV infections could be considered.	E3	

D22

Polycystic liver disease

Statement		
D22.1 Polycystic liver disease, when untreatable with surgical procedures, is an indication for liver transplantation as a MELD exception if it is associated with one or more of the following symptoms and signs: persistent abdominal pain, intra-cystic bleeding, infectious and/or hemorrhagic complications hindering regular feeding, severe quality of life impairment (P4).	E2	

D23

Pruritus in cholestatic liver diseases

Statement	Level of evidence	Strength of recommendation
D23.1 In primary and secondary cholestatic liver diseases, intractable pruritus can be considered a criterion for liver transplant listing even when associated with low MELDNa (P4).	E2	

SECTION E

Question

Are the following liver tumors to be considered for transplantation, and at which priority?

E24

Fibrolamellar HCC (FLH)

Statement		
E24.1 Non-resectable FLH can be considered an indication for liver transplantation in the absence of macrovascular invasion and extrahepatic disease.	E1	R2
E24.2 There is insufficient evidence to recommend indications for transplantation based on criteria such as tumor size, and number of nodules.	E2	R2
E24.3 Considering the rarity of the disease, a multidisciplinary approach to diagnosis (pathology) and prioritization is highly recommended.	E3	R1

E25

Liver adenomatosis

Statement

E25.1 LT should be considered for non-resectable adenomatosis with high risk of bleeding and/or rupture, proven or high risk of malignant transformation, and severe impairment of QOL. Low prioritization is required **(P4),** though age, symptoms, and impending complications should be taken into account.	E3	R3
E25.2 Considering the rarity of the disease and the low risk of malignant transformation, there is no rationale for pre-emptive liver transplantation.	E1	R3

E26

Hepatoblastoma

Statement	Level of evidence	Strength of recommendation
E26.1 Liver transplantation is the only effective treatment option for unresectable hepatoblastoma (PRETEXT IV and multifocal III) after neoadjuvant chemotherapy.	E2	R1
E26.2 Macroscopic vascular invasion and/or extrahepatic disease are not contraindications as long as the tumor is removed before or during LT.	E2	R2
E26.3 Timing of transplantation should not be delayed after chemotherapy (P1); therefore, high prioritization is needed (P1).	E2	R1

E27

Liver metastases from neuroendocrine tumors

Statement		
E27.1 Liver transplantation should be offered to select patients with non-resectable neuroendocrine tumor (NET) liver metastases from gastro-entero-pancreatic primaries and absence of extrahepatic disease. Restrictive listing criteria should consider limited tumor burden, low-grade histology, younger age, response to pre-transplant therapies, and a minimum observation time of 6 months. Under such circumstances it is highly likely that transplantation with respect to non-transplant options has an associated survival benefit.	E2	R2
E27.2 There is no evidence suggesting a particular waiting list priority for these patients, even though presence of symptoms and patient compliance should be taken into consideration (P3).	E3	

E28

Cholangiocarcinoma

Statement		
E28.1 In select cases and in association with precise neoadjuvant radio/chemotherapy protocols, 5-year overall survival after transplantation can exceed 50% (68%–75%). Based on these data, in select cases, and after radio/chemotherapy, hilar cholangiocarcinoma could be considered an indication for liver transplantation.	E2	

E28.2 The limitation in alternative therapies for the cirrhotic patient with hilar cholangiocarcinoma increases the potential benefit of liver transplantation in this patient subgroup. Transplantation should be considered only in the context of controlled prospective studies. Such studies are strongly recommended.	E2	
E10.12 To date, intrahepatic cholangiocarcinoma (mass forming) does not represent an indication for liver transplantation.	E2	

E29

Liver metastasis of colorectal cancer

Statement

E29.1 Recent series of liver transplantation for non-resectable colorectal metastasis (NRCRM) do not offer enough evidence for the use of liver transplantation to cure this disease	E3	R2
E29.2 Prospective controlled multicenter studies, better if performed in different countries, are required in order to assess the efficacy of liver transplantation for NRCRM.	E3	R2

Appendix 5A. List of Comments Referring to Statements Illustrated in the MELD Exceptions Sections D and E, Respectively.

D9. Ascites and refractory hydrothorax.

*Contraindications to the placement of a TIPS include: a) history of recurrent episodes of hepatic encephalopathy of grade 2 or more; b) serum bilirubin >4 mg/dL; c) serum creatinine >3 mg/dL; d) a Child-Turcotte-Pugh score >11; e) complete portal vein thrombosis; f) hepatocellular cancer and/or ongoing bacterial infection.

Comment: Although risk of death clearly is increased at high MELD scores, much of the early mortality in patients with cirrhosis still occurs in patients with low initial MELD (< 21). The subset of low MELD score patients with low serum sodium and persistent ascites has substantial early mortality. In the presence of both of these findings, the risk of pre-transplant death within 180 days exceeds 40%. As a result, MELDNa should be used in all these patients [42].

Refractory ascites is a condition characterized by a further increase in mortality and a negative impact on quality of life. The 2-year probability of survival among patients with refractory ascites is

about 30%, while at least 40% of patients with responsive ascites are alive at 5 years [43-45]. Several groups have reported a beneficial effect of TIPS in patients with hepatic hydrothorax [46-48].

D10. Hepato-renal syndrome

****This is essentially the score calculated with the highest serum creatinine value and the lowest value of serum sodium concentration just before starting treatment with terlipressin and albumin, without taking into account the subsequent effects of treatment on these values.

****This is basically the score calculated with the highest serum creatinine value and the lowest value of serum sodium concentration just before starting treatment with terlipressin and albumin, without taking into account the subsequent effects of treatment on these values.

Comment: Patients with HRS have a worse survival expectancy than other populations of patients with cirrhosis with an equal MELD or MELDNa score and for any given value of MELD or MELDNa score. Patients with HRS have a shorter survival expectancy than patients with chronic liver disease who are candidates for LT [49].

Patients with continual recurrence of type 1 HRS, which requires long-term treatment with terlipressin and albumin [50-51] probably have the highest priority for LT, but are at risk of remaining on the waiting list for months simply because their MELD or MELDNa scores are reduced by the treatment. An allocation of priority for LT for in patients with type 2 HRS according to their response to treatment with terlipressin and albumin is a very difficult task [52].

D11. Hepatic encephalopathy

Comment: Further prospective observational studies are needed before modifying the current transplantation policy in relation to hepatic encephalopathy. However, a retrospective study has reported that encephalopathy grade ≥2 is associated with reduced survival in hospitalized patients without TIPS compared with TIPS patients with the same MELD score but not affected with the disease [53]. Scales used to clinically evaluate encephalopathy are subjective, but episodes of encephalopathy needing hospitalization might represent a better surrogate parameter [54]. The

addition of an electroencephalographic index to the MELD may improve the accuracy of MELD [55]. In patients with large portal-systemic shunts and recurrent hepatic encephalopathy, no studies on the outcome are available, and should be investigated. At present, list priority still needs an individually based multidisciplinary decision.

D12. Rendu-Osler-Weber disease

Comment: Patients with hereditary hemorrhagic teleangiectasia (Rendu-Osler-Weber disease) may develop high output cardiac failure due to hepatic arterio-venous malformations. Due to the small number of liver transplantations performed in such patients, the prediction of complications is rather difficult [56-57]. Therefore the priority is usually evaluated on an individual basis, but consensus has been reached that these patients should be listed and transplanted early.

D13. Wilson's disease

Comment: Wilson's disease is an autosomal genetic disorder of copper metabolism resulting in the pathological accumulation of copper in many organs and tissues.

Thus, patients with hepatic disease generally develop neuropsychiatric symptoms 5–10 years earlier than cases with other major initial signs. Hepatic manifestations of Wilson's disease range from asymptomatic hypertransaminasemia to acute liver failure (25% of cases) or inactive cirrhosis (40% of cases), that may be present even when the clinical picture is one of fulminant hepatic failure [58]. Liver transplantation is indicated for all patients with Wilson's disease and decompensated liver cirrhosis unresponsive to medical therapy [59]. Exceptionally, liver transplantation has been considered in patients with Wilson's disease to improve the neurological deterioration, but this approach is debated [60].

D14. Idiopathic hemochromatosis

Comment: Hemochromatosis is a rare disease, which may cause liver cirrhosis. There is insufficient evidence to warrant priority increases in the waiting list. The risk of developing hepatocellular carcinoma, however, should be carefully taken into consideration in the recall policy.

D15. Alfa 1 antitripsin deficiency

Comment: Similarly to hemochromatosis, alpha-1-antitrypsin disease is rare, and may cause liver cirrhosis. There is insufficient evidence to warrant priority increases in the waiting list. If hepatocellular carcinoma develops, liver transplantation priority should follow the criteria applied for hepatocellular carcinoma.

D16. Familial amylodotic polyneuropathy

Comment: The enzyme defect results in deposition of amyloid into cardiac, neurologic and ophthalmic tissues. Liver transplantation restores normal enzyme function. Polyneuropathy, cardiac involvement, and nutritional parameters are usually considered as risk factors for poor outcome despite liver transplantation. Therefore, liver transplantation should be proposed before end-stage of organ diseases [61]. Whereas priority is generally poorly studied and ill defined, the availability of a domino transplantation elides the harm on the waiting list, justifying a high priority.

D17. Hepato-pulmunary syndrome

Comment: Patients with HPS should be listed at the time of diagnosis of HPS independent of MELD score or P_aO_2 values. This indication derives from the very low 5-year expected survival (20%) observed in patients with HPS. Transplant benefit is therefore high, provided that post-transplant results remain acceptable (utility), thus justifying high priority at PaO_2 deterioration.

D18. Porto-pulmunary syndrome

Comment: Patients with POPH should be listed independent of MELD. The efficacy of vasoactive therapy should always be considered to evaluate indication/contraindication for liver transplant.

D19. Late retransplantation

Definition: We here define late retransplantation as organ failure occurring after at least 6 months from the previous transplant, more frequently related to recurrent disease, severe cholestasis associated with multiple intrahepatic biliary strictures or late onset vascular strictures or thrombosis.

Comment: Patients listed for late chronic retransplantation may have a predicted 5-year survival below 50% [62-66]. To avoid a futile retransplant some predictive models have been proposed. Only Markman and Rosen have been validated (the latter including recipient age, bilirubin, and creatinine) [67]. MELD or MELD components, donor-recipient index (DRI) and donor age, albumin, and time interval from previous transplant have been advocated as predictors. Since utility in retransplantation is deeply influenced by MELD (as opposed to first transplant), timing is crucial, with some models recommending retransplantation at MELD <25-28. Priority should be regulated on this basis.

D20. Acute liver failure

Comment The predictive accuracy of scores specific for ALF (e.g., Kings College Criteria) have always proved superior to a suggested MELD ≥30 [1-4]. This is because various parameters not included in the MELD have been shown to influence the prognosis of ALF (age, etiology, severity of encephalopathy, time elapsed between jaundice and encephalopathy, hyper-lactatemia, severity of SOFA and APACHE II scores [67-69].

D21. Liver transplantation in HIV-positive recipients

Comment: In contrast to the excellent outcomes seen in HBV-HIV transplant patients, patients with HCV-HIV have high rates of HCV recurrence after liver transplantation, with lower patient and graft survival [70-72]. The outlook for the future seems favorable as the new DDAs become widely available.

D22. Polycystic liver disease

Comment: Polycystic liver disease is mainly associated with poor quality of life, and less commonly with the risk of hepatic decompensation [73-74]. The early satiety symptoms can cause malnutrition, and malnutrition may compromise the immune response to infections. There is insufficient evidence to warrant priority increases in the waiting list, with priority generally

considered low due to the lack of a significant mortality risk. Liver and kidney polycystic disease associated with kidney failure is an indication for combined liver-kidney transplantation.

D23. Pruritus in cholestatic liver diseases

Comment: Severe pruritus can be observed in patients with cholestatic liver disease. Intractable pruritus affects the quality of life, but does not increase the risk of dying while awaiting a liver transplant. There are no measures to quantify the symptoms. Despite no evidence to increase priority in the waiting list, on a single case evaluation, intractable pruritus can be a criterion for listing [75]. Priority should be decided in the multidisciplinary transplant setting on individual bases as well.

E24. Fibrolamellar hepatocellular carcinoma

Comment: Resection remains the mainstay of treatment of FLH when the disease is arising on an otherwise healthy liver. Retrospective series of transplants performed for unresectable fibrolamellar HCC report up to 50% 5-year survival, but no prognostic criteria based on tumor characteristics can be identified, though tumour volume seems to correlate with outcome. No clear advantage in patient survival after transplantation for post-resection recurrent fibrolamellar HCC has been documented [76-78]. Age consideration at diagnosis, expected survival with non-transplant therapies and QOL consideration should play a role in decision making regarding transplant listing.

E25. Liver adenomatosis

Comment: The risk of malignant transformation in multiple adenomatosis is about 7%. Beta catenin expression represents a relevant prognosticator of transformation in hepatocellular carcinoma [79-81].

E26. Hepatoblastoma

Comment: Five-year patient survival of over 70% is achievable after liver transplantation for unresectable PRETEXT III and IV hepatoblastoma treated with neoadjuvant chemotherapy. Active extrahepatic tumor site untreated with chemotherapy and/or surgery has a severely negative impact

on survival [82-85].

E27. Liver metastases from neuroendocrine tumors

Comment: There is vast evidence suggesting the adoption of restrictive criteria in the candidacy for liver transplant for patients with NET liver metastases. Accordingly, dropout from the waiting list should be considered in case of progression beyond previously defined criteria. Marginal donated grafts in NET patients might be maximized providing that utility endpoints remain achievable through an adequate match between graft quality and the patient's general conditions. Considering the usually slow natural history of this disease, transplant benefit and survival should be evaluated at 10 years, possibly by means of ITT analysis, including quality of life evaluation. There is evidence suggesting that downstaging is associated with a better post-transplant survival, while bridge treatments are recommended in patients with carcinoid syndrome [86-88].

E28. Cholangiocarcinoma

Comment: Some critical issues in the analysis of the available data should be considered for decision making: 1) Positive post-transplant outcome has been observed in those cases with negative/complete response after neoadjuvant treatment; 2) improvement in preoperative diagnosis and staging up to molecular level should be fostered; 3) the underlying chronic cholestatic liver disease (e.g., PSC) may be associated with better DFS. 4) Incidental cholangiocarcinomas diagnosed at explant of the cirrhotic liver seem to be associated with reasonable survival and, therefore, these tumor presentations warrant prospective investigations [89-91].

The role of and response to neoadjuvant therapies are likely to be crucial in priority consideration for those patients with cholangiocarcinoma considered eligible for transplant, whether cadaveric or living-related [92].

E29. Metastases from colorectal cancer

Comment: NRCRC are considered a contraindication for liver transplant according to historical data and natural history of this cancer, which is frequently associated with occult extra-hepatic metastases. Recent data estimate a 60% 5-year survival rate after transplant in select cases of

NRCRC in a specific scenario benefitting from an excess of donated organs [93-95]. Ethical considerations must be addressed, and objective selection criteria have to achieve consensus before liver transplantation can be applied for NRCRC, given the universal organ shortage. If these conditions are satisfied, the survival benefit achievable with liver transplantation for NRCRC liver metastasis should approximate that expected for more conventional indications. Provided sufficient expected benefit and utility, LDLT might potentially contribute to open clinical practice to this indication.