

World Journal of *Methodology*

World J Methodol 2022 January 20; 12(1): 1-63



MINIREVIEWS

- 1 Ophthalmological instruments of Al-Halabi fill in a gap in the biomedical engineering history
Saad MN
- 20 Severe acute respiratory syndrome coronavirus 2 pandemic related morbidity and mortality in patients with pediatric surgical diseases: A concerning challenge
Vaos G, Zavras N
- 32 Liver transplant allocation policies and outcomes in United States: A comprehensive review
Latt NL, Niazi M, Pyrsopoulos NT
- 43 Interrogating the interplay of angiogenesis and immunity in metastatic colorectal cancer
Kampoli K, Foukas PG, Ntavatzikos A, Arkadopoulos N, Koumarianou A

ORIGINAL ARTICLE**Retrospective Study**

- 54 Phenomenology of obsessive-compulsive disorder in children and adolescents: Sample from a tertiary care center in Istanbul, Turkey
Cifter A, Erdogan AB

ABOUT COVER

Peer Reviewer of *World Journal of Methodology*, Angela Domínguez Camacho, DDS, MEd, Professor, Department of Orthodontics, Unico-Cali, Colombia. angela.dominguezc@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Methodology* (WJM, *World J Methodol*) is to provide scholars and readers from various fields of methodology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJM mainly publishes articles reporting research results obtained in the field of methodology and covering a wide range of topics including breath tests, cardiac imaging techniques, clinical laboratory techniques, diagnostic self-evaluation, cardiovascular diagnostic techniques, digestive system diagnostic techniques, endocrine diagnostic techniques, neurological diagnostic techniques, obstetrical and gynecological diagnostic techniques, ophthalmological diagnostic techniques, otological diagnostic techniques, radioisotope diagnostic techniques, respiratory system diagnostic techniques, surgical diagnostic techniques, *etc.*

INDEXING/ABSTRACTING

The WJM is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Rui-Rui Wu, Production Department Director: Xu Guo, Editorial Office Director: Ji-Hong Lin.

NAME OF JOURNAL

World Journal of Methodology

ISSN

ISSN 2222-0682 (online)

LAUNCH DATE

September 26, 2011

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Bruno Megarbane

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/2222-0682/editorialboard.htm>

PUBLICATION DATE

January 20, 2022

COPYRIGHT

© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/gerinfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Liver transplant allocation policies and outcomes in United States: A comprehensive review

Nyan L Latt, Mumtaz Niazi, Nikolaos T Pyrsopoulos

ORCID number: Nyan L Latt 0000-0002-5251-6573; Mumtaz Niazi 0000-0002-4740-5131; Nikolaos T Pyrsopoulos 0000-0002-6950-8174.

Author contributions: Latt NL and Niazi M researched, planned, outlined and wrote the entire manuscript; Pyrsopoulos NT advised the outline, reviewed and edited the manuscript.

Conflict-of-interest statement: Dr. Pyrsopoulos reports grants from MALLINCKRODT, grants from VALEANT, grants from GILEAD, grants and other from BAYER, grants from BEIGENE, grants from GENFIT, grants from PROMETHEUS, grants from GRIFOLS, grants from INTERCEPT, grants from ZYDUS, grants and other from EISAI, other from ROCHE, grants from ABBVIE, grants from NOVARTIS, outside the submitted work.

Country/Territory of origin: United States

Specialty type: Medical laboratory technology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Nyan L Latt, Mumtaz Niazi, Nikolaos T Pyrsopoulos, Division of Gastroenterology and Hepatology, Department of Medicine, Rutgers-New Jersey Medical School, Newark, NJ 07101-1709, United States

Corresponding author: Nikolaos T Pyrsopoulos, MD, PhD, Professor, Division of Gastroenterology and Hepatology, Department of Medicine, Rutgers-New Jersey Medical School, 185 S. Orange Avenue MSB H Rm-536, Newark, NJ 07101-1709, United States.
pyrsopni@njms.rutgers.edu

Abstract

Liver transplant allocation policies in the United States has evolved over 3 decades. The donor liver organs are matched, allocated and procured by the Organ Procurement and Transplantation Network which is administered by the United Network of Organ Sharing (UNOS), a not-for-profit organization governed by the United States human health services. We reviewed the evolution of liver transplant allocation policies. Prior to 2002, UNOS used Child-Turcotte-Pugh score to list and stratify patients for liver transplantation (LT). After 2002, UNOS changed its allocation policy based on model for end-stage liver disease (MELD) score. The serum sodium is the independent indicator of mortality risk in patients with chronic liver disease. The priority assignment of MELD-sodium score resulted in LT and prevented mortality on waitlist. MELD-Sodium score was implemented for liver allocation policy in 2016. Prior to the current and most recent policy, livers from adult donors were matched first to the status 1A/1B patients located within the boundaries of the UNOS regions and donor-service areas (DSA). We reviewed the disadvantages of the DSA-based allocation policies and the advantages of the newest acuity circle allocation model. We then reviewed the standard and non-standard indications for MELD exceptions and the decision-making process of the National Review Liver Review Board. Finally, we reviewed the liver transplant waitlist, donation and survival outcomes in the United States.

Key Words: Liver transplant; Allocation; Distribution; Waiting list; Policies; Acuity circles; Transplant exceptions; National Review Liver Review Board

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Grade A (Excellent): 0
 Grade B (Very good): 0
 Grade C (Good): 0
 Grade D (Fair): 0
 Grade E (Poor): 0

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Received: February 24, 2021

Peer-review started: February 24, 2021

First decision: May 6, 2021

Revised: June 21, 2021

Accepted: November 12, 2021

Article in press: November 12, 2021

Published online: January 20, 2022

P-Reviewer: Zhu YY

S-Editor: Fan JR

L-Editor: A

P-Editor: Fan JR



Core Tip: The liver transplant donor allocation and distribution policies have evolved over three decades. The liver donor distribution policy has recently changed from donor-service area-based policy to the acuity circle model. The new policy is believed to work more efficiently and equitably for waitlist candidates across the United States.

Citation: Latt NL, Niazi M, Pyrsopoulos NT. Liver transplant allocation policies and outcomes in United States: A comprehensive review. *World J Methodol* 2022; 12(1): 32-42

URL: <https://www.wjgnet.com/2222-0682/full/v12/i1/32.htm>

DOI: <https://dx.doi.org/10.5662/wjm.v12.i1.32>

INTRODUCTION

In the United States, organ transplantation is regulated by the United Network Of Organ Sharing (UNOS). UNOS is a not-for-profit and scientific organization which manages the Organ Procurement and Transplantation Network (OPTN), the sole network which is responsible for procuring, matching and allocating donated human organs in the United States by maintaining the national organ transplant database (UNet)[1,2]. UNOS was first established by the United States Congress *via* the National Organ Transplant Act in 1984. OPTN began its operations in 1986. In 2000, "the Final Rule" was published by the United States Department of Health and Human Services establishing federal regulations on OPTN policies including listing requirements, organ procurement, identification of organ recipient, allocation of donated organs, designated transplant program requirements, reviews, evaluation and enforcement of transplant programs[3]. Similar to UNOS, National Health Service Blood and Transplant is responsible for the matching, procurement and allocation of organ transplantation in the United Kingdom[4]. In Europe, the Eurotransplant network is responsible for organ procurement and allocation[5].

The two primary goals of OPTN/UNOS are (1) The equitable distribution of donated organs; and (2) The appropriate care of minority candidates. It is crucial not to discriminate transplantation on age, gender, ethnicity and socioeconomic backgrounds. The National Organ Transplant Act published in 1984 indicates UNOS to establish medical criteria when organs are being allocated. The medical criteria were put in place to ensure justice and reinforce equity. The Final Rule which was later published in 1999 elaborated the national framework for matching, allocation and distribution of the donated organs. The OPTN must institute equitable allocation policies which are based on medical judgement in order to achieve the best outcomes of donated organs and to promote the access to transplantation. Policy 3.6 requires the OPTN to standardize medical criteria for determining suitable transplant candidates and set priority rankings based on objective and measurable medical criteria. The rankings must be sequenced from the most medically urgent to the least and the geographic area must be feasible for organ distribution in order of decreasing medical urgency[6].

CHILD-PUGH SCORE

Prior to 2002, UNOS used Child-Turcotte-Pugh (CTP) score to list and stratify patients for liver transplantation (LT). CTP score was first developed in 1973 to risk stratify patients undergoing portosystemic shunt surgery. CTP score includes blood tests such as serum total bilirubin, serum albumin, international normalized ratio (INR) as well as the severity of symptoms such as ascites and hepatic encephalopathy[7]. One of the disadvantages of using symptoms in CTP scoring was the lack of standardization of perceived symptom severity. Different transplant physicians might interpret the severity of ascites and hepatic encephalopathy in different manners. Moreover, CTP score was not able to predict which patients were in greater need of an orthotopic LT (OLT).

MODEL FOR END-STAGE LIVER DISEASE SCORE

In 2001, Kamath *et al*[8] from Mayo Clinic developed the model for end-stage liver disease (MELD), a mathematical model using all objective tests such as serum bilirubin, INR, serum creatinine, to predict poor survival among cirrhotic patients undergoing transjugular intrahepatic portosystemic shunts[8]. MELD score was also shown to accurately predict disease severity and survival outcome in patients with chronic liver disease[9]. Brown *et al*[10] demonstrated that the MELD score is superior to CTP score in estimating pre-OLT disease severity and optimize the timing of OLT [10]. The OPTN/UNOS committees developed the LT allocation policy based on MELD score. This allocation policy was approved by the OPTN/UNOS Board of Directors in November 2001 and went into effect in February 2002[11].

MELD-SODIUM SCORE

Hyponatremia is the independent risk factor which negatively impacts the survival in patients with cirrhosis. The degree of hyponatremia correlates with the severity of chronic liver disease. In 2005, Biggins *et al*[12] from University of California San Francisco demonstrated that serum sodium level < 126 mEq/L at liver transplant listing or while listed for OLT is a strong independent predictor of mortality. The researchers concluded that addition of serum sodium to MELD score can increase the accuracy to predict 3- and 6-mo mortality in patients with cirrhosis[12]. In their 2008 study, Kim *et al*[13] studied OPTN data of 1781 participants who underwent OLT and 422 who died within 90 d after registration on the waiting list. The MELD and serum sodium combined score was significantly higher than the MELD score alone in patients who died on the waiting list. This data indicated that the priority assignment of MELD-sodium score might have resulted in OLT and prevented mortality[13].

The MELD-sodium score Policy 9.1 was approved by the OPTN/UNOS Board of Directors in June 2014 and implemented in January 2016[14].

PEDIATRIC END-STAGE LIVER DISEASE SCORE

The pediatric end-stage liver disease (PELD) score calculates the pediatric version of the MELD score for liver cirrhosis severity. In addition to serum bilirubin and INR, patient's age, growth failure and serum albumin are included in the mathematical formula of PELD score, contrast to MELD score[15].

Evolution of liver transplant organ allocation systems

Liver transplant organ allocation systems have evolved tremendously over two decades to reduce disparity, increase equity and access to liver transplant based on new evidence-based data with the primary goal of increased "best use" of donated livers.

Allocation priorities based on UNOS status

Patients who are listed as status 1A on UNOS waiting list have acute onset liver failure and are deemed not likely to survive more than a few days without an OLT. Status 1B is reserved for extremely sick, chronically ill pediatric patients with cirrhosis who are younger than 18 years of age-pediatric population. Status 1A and 1B patients are usually less than 1% of overall waitlisted patients at any given time.

Historical background of liver distribution–donor-service areas-based policy

Prior to the current and most recent policy, livers from adult donors were matched first to the status 1A adult patients, then to status 1B pediatric patients located within the boundaries of the same region as the donor hospital but could be outside of donor-service area (DSA). There are 11 UNOS regions and 58 DSAs catered by various organ-procurement organizations (OPO) in the United States. "Share-35 rule", implemented in June 2013, mandated that the waitlisted patients with MELD-sodium score of 35 or above would be offered donated livers outside of the OPO and within the same region. While "Share-35" policy increased the number of OLT by 6% and the number of regional sharing by 11%, there was no impact on the overall waitlist mortality, the post-transplant survival and the overall liver discard rate. The UNOS/OPTN leadership considered a concept of restructuring 11 UNOS regions to 8 districts to

lower geographic disparity, waitlist mortality and the high variability of MELD-sodium at the time of transplant among various liver transplant centers across the regions. The statistical model for “Region Redistricting” was limited by the minimum number of transplant centers *per* district which was set to be 6 centers and maximum of 3 h allotted travel time between the DSAs in the same district.

New liver distribution policy-acuity circles

Due to the disadvantages of DSA-based liver distribution policy and geographic inequities in access to OLT, the OPTN Board of Directors mandated a thorough review process for system improvement since 2014. The new liver policy was proposed by transplant experts, reviewed, and debated by organ recipients, donor families with thousands of public comments on UNOS website. The priority of the new distribution policy is to ensure that the organ distribution is equal for waitlisted candidates where they live or wish to seek a transplant. DSA-based donation boundaries had led waitlisted patients to get more than one wait list (*i.e.*; dual listing practice) or travel to different regions in the country to get access to transplant. The new process is simple with a measure of distance from donor hospital to the transplant hospital in nautical miles, eliminating DSAs. The sole benefit of the December 2018 policy is that it is projected to save more lives by lowering waitlist mortality by 100 lives annually[16].

According to UNOS data, organ donation from deceased donors set an all-time high record in 2020 despite the global COVID-19 pandemic. 36548 organs from deceased donors were transplanted resulting in 33309 people receiving life-saving transplants [17]. The implementation of the December 2018 acuity circles (AC) policy is projected to reduce the impact of where waitlist candidates live, or what hospital they choose for their care. The new policy is believed to work more efficiently and equitably for waitlist candidates across the United States.

AC-status 1A/1B

Under the new policy, livers from all deceased donors are offered for status 1A and 1B candidates listed at transplant hospitals within a radius of 500 nautical miles from the donor hospital.

AC-non-donating upon cardiorespiratory death donors younger than age 70

For the deceased liver donors which are not donating upon cardiorespiratory death (DCD) and under age 70, waitlist candidates with MELD or PELD score of 37 or higher are prioritized after status 1A/1B candidates. The initial offers will go out to the candidates at transplant hospitals within a radius of 150 nautical miles from the donor hospital. The next sequence offers will go out to the candidates within a radius of 250 nautical miles from the donor hospital. Then, the offers will go out to the candidates within a radius of 500 nautical miles from the donor hospital. The MELD/PELD score ranges will progressively continue from 33 to 36, from 29 to 32 and from 15 to 28.

AC-DCD donors and/or adult donors older than 70

For the deceased liver donors who are donating DCD and/or adult donors older than 70 years of age, the new liver distribution policy prioritizes the candidates more local to the donor hospital with earlier access to transplant. The candidates with MELD or PELD of 15 or higher are offered these donated livers after status 1A/1B candidates. The sequence of distribution is for candidates within a radius < 150 nautical miles, then 150-500 nautical miles and lastly > 500 nautical miles from the donor hospital[17].

Challenges of the new liver distribution policy

The new liver distribution policy with AC allocation was approved in December 2018 after a lawsuit was filed in New York by patients who stated that their wait time was longer than other patients with lower MELD score in other parts of the country. The new AC policy went into effect on May 14, 2019. However, a United States federal judge in Atlanta, Georgia temporarily blocked the new policy on May 17, 2019, citing that waitlist candidates and hospitals in less-populated areas would suffer if the AC distribution model rules remained in effect. The liver allocation policy was reverted to DSA-based distribution on May 23, 2019. On February 4, 2020, the OPTN/UNOS reinstated the new AC model distribution policy. This model was supported by the Scientific Registry of Transplant Recipients’ (SRTR) 2018 analysis which projected that the AC model would decrease the variability of MELD score at the time of transplant (MMaT) across DSAs. The model predicted a substantial decrease from 9.97 to 4.33 based on historical statistics[17].

Chyou *et al*[18] compared the center- and DSA-level changes in the 6-mo period pre-AC model era (August 8, 2019 to February 3, 2020) and post-AC era (March 5, 2020 to August 31, 2020) using OPTN/UNOS data. The focus was on non-status 1A adult deceased donors on following metrics: Transplant volume, MMaT, procurements requiring flights and termed “flight-consistent distance” procurements. The volume of adult non-status 1A deceased liver donors decreased by 2.7% during this post-AC era. The DSA-level MMaT ranged from 18.5 to 32 in the pre-AC era while it ranged from 18 to 33 in the post-AC era. The median change in MMaT was +1 MELD point. The DSA-level variance in MMaT was unchanged: 12.2 pre-AC era *vs* 12.1 post-AC era. The number of “flight-consistent distance” procurements increased: 42.5 % pre-AC era *vs* 60.5% post-AC era. The post-AC era has coincided with the coronavirus disease 2019 (COVID-19) global pandemic and the transplant volumes could be affected by the COVID-19 restrictions and hospital constraints. However, these early data have raised the concern that the AC model projection based on mathematical simulations may not match the real-world transplant metrics. Longer-term data are needed to evaluate the benefits of the AC distribution model[18].

NATIONAL LIVER REVIEW BOARD

The OPTN/UNOS Liver and Intestinal Organ Transplantation Committee has established regulation/guidance for both hepatocellular carcinoma (HCC) and non-HCC adult MELD exceptions and extensions requests. MELD exception policies allow opportunity to have a diseased donor liver transplant for the patient whose natural MELD score does not reflect the true liver related mortality risk. These MELD-exceptions could be standardized or non-standardized. All standardized MELD-exceptions requests do not need to be approved by the National Liver Review Board (NLRB) but all non-standardized MELD exceptions must be submitted to the NLRB.

In January 2017, the OPTN/UNOS liver and Intestinal Organ Transplantation Committee proposed NRRB and on May 14, 2019, NLRB replaced the Regional Review Boards (RRB) for each individual 11 OPTN regions for MELD exception scores approval. According to the briefing paper from OPTN/UNOS, the need for this change was warranted secondary to wide range (75.8% to 93.5%) of MELD exception requests being approved among different regions[19]. The NLRB is a nationwide peer review system that provides fair and increase consistency in providing MELD exception scores candidates of all liver transplant programs in United States and has eliminated the regional differences for granting MELD exception points. NLRB reviewers are assigned from a pool of nationwide liver transplant physicians and surgeons. NLRB has three boards, one for HCC exception requests, 2nd for non-HCC exception request and 3rd for pediatrics. NLRB is responsible for approval or denying exception points for patients who do not qualify for standardized MELD exception points. The liver transplant program may request MELD exception points to NLRB, if the calculated MELD score does not accurately reflect the severity of the candidate's disease. The candidate's respective transplant center must submit a request to NLRB with specific MELD score and justification why candidate's current status does not accurately reflect urgency for LT. The initially all cases are reviewed by five randomly assigned reviewers and four out five has to approve the request. According to the current OPTN policy[20]: (1) The NLRB is responsible to review MELD exceptions/extensions requests within 3 wk after the request has been submitted to the OPTN. If the NLRB is unable to complete the decision within 3 wk, candidate will be assigned the requested MELD score; (2) The candidate's transplant program as a right to appeal within 2 wk to the NLRB if the MELD exceptions/extension request has been denied. The appeal must be reviewed by the NLRB within 3 wk after submission to the OPTN, if the decision could not be reached within 3 wk, the candidate will be assigned the requested MELD score; (3) Upon denial of appeal by the NLRB, the candidate's transplant program has a right to further appeal to the appeals review team (ART) within 1 wk after denial notification. Each ART team has 9 members but 5 needs to be present at given time to review the case and must review the request within 2 wk after submission to OPTN. If ART unable to make the final decision within assigned 2 wk' period, candidate will be assigned requested MELD exceptions/extension points; and (4) Upon denial the MELD exception/extension request by ART, the candidate's respective liver transplant program has a right to appeal within 1 wk after denial notification to Liver and Intestinal Organ Transplantation Committee.

MELD-exception for HCC

HCC is the 5th most common cancer and 3rd most common cancer related death in both sexes and in all ages[21]. Incidence of HCC in United States is rapidly rising secondary to chronic hepatitis C related cirrhosis. LT is an effective and curative treatment for non-resectable HCC since removal of both tumor and cirrhotic liver will maximize recurrence-free patient survival. MELD score predicts 3 mo' mortality for majority of the patient with cirrhosis but unfortunately underestimates mortality in the patients with HCC and hence high probability of weight list mortality and weight list dropout secondary to tumor progression while waiting for OLT[22].

Since HCC patients historically have low MELD score, without MELD exception points, realistically will not be able to get diseased donor LT. The liver transplant allocation system designates MELD exception points to patients with HCC if they meet MILAN criteria, which is defined as one lesion to 5 cm or up to 3 lesions each \leq 3 cm without radiologic evidence of macrovascular invasion or metastatic disease[23]. The MELD exception points for patients with HCC, decreases wait-list mortality and increases priority for LT. By for the commonest indication of MELD exception point is HCC in united states.

The 1st HCC exception points policy was implemented on February 27, 2002. Since then, significantly high number of patients with HCC have been transplanted. Secondary to donor organ shortage and high number of patients being transplanted for HCC, needing multiple revisions of UNOS MELD-exception allocation policy for HCC over the last 2 decades (Table 1). In comparison to policy change in October 2015 which focused on timing of exception and incremental increase in tumor MELD exception points with maximum points of 34, the most recent organ allocation policy change in May 2019 does not allow incremental increase in MELD exception points. The current organ allocation policy mandates to list the patient with actual Na-MELD of the patient and after 3 mo, request a MELD extension. Once 6 mo' observation period is finished and the patient is still in with in MILAN criteria, the patient will be granted HCC-MELD exception points. The maximum points are median MELD at transplant (MMaT) 2. The MMaT remains fixed score and does not increase every 3 mo. By using previous 12 mo' data, the median MELD is recalculated every 6 mo and subsequently MMaT is readjusted. The purpose of this change was to promote more balanced allocation of donor organs between HCC and non-HCC patients on liver transplant wait list. 6 mo wait list observation period for HCC patients also will provide better understanding to assess the tumor biology.

The OPTN/UNOS Liver and Intestinal Organ Transplantation Committee has established regulation for adult MELD exceptions for HCC. The following is the summary of summary of current UNOS Policy for HCC exception points[20].

Documentation of number and sizes by multiphasic CT or MRI of all OPTN class 5 lesions (5A or 5B), ruling out metastatic disease, AFP and candidate being not eligible for resection (Tables 2 and 3).

Wait listed patient within MILAN criteria (T2 lesion) and AFP \leq 1000 ng/mL will be eligible for standardized MELD exception points. If AFP > 1000 ng/mL with T2 lesion, candidates may be treated with local-regional therapy (LRT): (1) After treatment if AFP < 500 ng/mL, eligible for standardized MELD exception points; and (2) After treatment if AFP > 500 ng/mL, candidate would need to be referred to and NLRB for MELD exception points.

Standardized MELD exception points if the lesions meet the down staging protocols (Tables 2 and 3) and after LRT the lesion meets the definition of T2 lesion, demonstrated on CT or MRI. If candidates do not meet initially the downstaging protocol and subsequently down staged to T2 lesions must go through NLRB for MELD exception points.

After initial automatic approval of MELD exception points, extensions of HCC exception points would need to be requested every 3 mo. Automatic MELD exception points will be granted as long as lesions do not progress beyond T2 criteria, AFP < 500 ng/mL.

The candidates who meet the standardized MELD score exception, will be granted calculated MELD score on initial and first extension request. After 6 mo (second extension request), the candidate will be granted 3 points below MMaT.

Non-HCC standard MELD-exceptions

In February 2002, non-HCC MELD exception points policy was implemented which allowed exception points for hepatopulmonary syndrome (HPS), familial amyloidosis and primary oxaluria. Subsequently familial amyloidosis and primary oxaluria were removed in 2009 from UNOS/OPTN policy as standard MELD exceptions. According

Table 1 Model for end-stage liver disease exception points granted

Year of policy implementation	MELD exception points granted	
	T2 lesion (A single nodule with diameter ≥ 2 cm and ≤ 5 cm or 2-3 lesions each between 1-3 cm)	T1 lesion (A single nodule ≥ 1 cm and < 2 cm)
February 2002	29 points	24 points
February 2003	24 points	20 points
April 2004	24 points	No exception points
March 2005	22 points	No exception points
October 2015	Natural MELD score at the time of listing	No exception points
	28 points after 6 mo with maximum 34 exception points	
May 2019	MMaT-3	No exception points

MELD: Model for end-stage liver disease; MMaT-3: Median MELD at transplant-3.

Table 2 Lesions eligible for downstaging protocols

Number of lesions	Size	Description
1	> 5 cm and ≤ 8 cm	
2-3	At least one lesion > 3 cm and all ≤ 5 cm	Total diameter of all lesions ≤ 8 cm
4-5	Each < 3 cm	Total diameter of all lesions ≤ 8 cm

Table 3 Organ procurement and transplantation network imaging classification for class 5 lesions in patients with cirrhosis

OPTN class	Description	Comments
0	Incomplete are technically in adequate study	No MELD exception points
5A	Lesion size ≥ 1 cm and ≤ 2 cm	Increased contrast enhancement in the late hepatic arterial phase along with either: (1) Wash out during late contrast phases and peripheral rim enhancement (capsule or pseudocapsule); and (2) Biopsy consistent with HCC
5A-g	Lesion size ≥ 1 cm and ≤ 2 cm	Increased contrast enhancement in the late hepatic arterial phase along with growth $\geq 50\%$ documented on serial CT or MR obtained ≤ 6 mo apart
5B	Lesion size ≥ 2 cm and ≤ 5 cm	Increased contrast enhancement in the late hepatic arterial phase along with either: (1) Wash out during late contrast phases; (2) Peripheral rim enhancement (capsule or pseudocapsule); (3) Growth $\geq 50\%$ documented on serial CT or MR obtained ≤ 6 mo apart in the absence of ablative therapy; and (4) Biopsy consistent with HCC
5T	Prior local regional therapy for HCC	Any residual lesion or perfusion defect at the site of prior class 5A, 5A-g, 5B lesion

OPTN: Organ procurement and transplantation network; MELD: Model for end-stage liver disease; HCC: Hepatocellular carcinoma.

to the OPTN policy change from November 2009 several non-HCC conditions were granted standardized MELD-exceptions, without the need to go through the evaluation process by RRB and now RRB has been replaced by NLRB. This OPTN/UNOS policy change was the results of recommendations made by the MELD exception study group and conference (MESSAGE) in 2006[24,25].

Following is the summary of all non-HCC conditions eligible for standardized MELD exception points according to the current OPTN/UNOS policy and MELD extension request are valid for 90 d after submission[26] (Table 4).

Cholangiocarcinoma

In order to be eligible for MELD exception points of MMaT-3, the candidate must meet all the criteria. The center needs to have written protocol including selection criteria,

Table 4 Conditions eligible for non-hepatocellular carcinoma standard model for end-stage liver disease-exceptions

Condition	Requirements for exception points	MELD score assigned
CCA	Un-resectable hilar CCA with biopsy/cytology consistent with malignancy or CA19-9 > 100 U/mL or aneuploidy Center must have written protocol regarding selection of criteria, neoadjuvant therapy, operative staging for metastatic disease Imaging to exclude metastatic disease	MMaT-3
HPS	Evidence of portal hypertension without any evidence of underlying significant pulmonary disease PaO ₂ < 60 mmHg on room air ECHO or lung scan confirming intra-pulmonary shunt	MMaT-3
POPH	Evidence of portal hypertension along with MPAP > 35 mmHg and PVR > 3 woods unit MPAP < 35 mmHg and PVR < 5.1 woods unit post treatment of pulmonary hypertension	MMaT-3
FAP	Biopsy proven amyloid along with TTR gene mutation and able to walk independently Must be on heart transplant wait list or EF > 40% on ECHO within 30 d	MMaT-3
Cystic fibrosis	Genetic analysis confirmation needed FEV1 below 40% of predicted FEV1 with 30 d prior to initial request	MMaT-3
HAT	HAT within 2 wk of OLT	40
Primary hyperoxaluria	AGT deficiency proven on liver biopsy/genetic analysis On kidney transplant list with eGFR ≤ 25 mL/min on two instances 42 d apart	MMaT

CA19-9: Carbohydrate antigen 19-9; FEV1: Forced expiratory volume at one second; TTR: Transthyretin; AGT: Alanine glyoxylate aminotransferase; MELD: Model for end-stage liver disease; CCA: Cholangiocarcinoma; HPS: Hepatopulmonary syndrome; MPAP: Mean pulmonary artery pressure; FAP: Familial amyloid polyneuropathy; HAT: Hepatic artery thrombosis; PVR: Pulmonary vascular resistance; POPH: Portopulmonary hypertension.

neoadjuvant therapy prior to transplant and operative staging to exclude metastatic disease. Needs to be unresectable hilar cholangiocarcinoma (CCA) and meeting the diagnostic criteria for CCA with malignant appearing stricture on cholangiography with either biopsy/cytology consistent with malignancy or aneuploidy or carbohydrate antigen 19-9 > 100 U/mL without cholangitis. Imaging studies showing one lesion < 3 cm without metastatic disease. After completion of neoadjuvant therapy, operative staging to assess involvement of regional nodes and peritoneal metastases prior to considering for transplant. The biopsy of the original lesion must be avoided secondary to high risk of tumor seeding.

Cystic fibrosis

The candidate will be eligible for MELD exception points of MMaT-3 if has genetic analysis confirmation for cystic fibrosis (CF) and the forced expiratory volume at one second (FEV1) is < 40% of predicted FEV1 within one month prior to initial exception request. After 90 d' extension request needed to be submitted.

HPS

The candidate will be eligible for MELD exception points of MMaT-3 if the candidate has evidence of portal hypertension (ascites, varices, splenomegaly, or thrombocytopenia) in the presence of intrapulmonary shunt confirmed with contrast echocardiogram (ECHO) or lung scan. Also, the partial pressure of oxygen (PaO₂) < 60 mmHg on room air within one month prior to submission of initial MELD exception request along with no underlying significant primary lung disease. To be eligible for MELD extension, the candidate must have PaO₂ < 60 mmHg within last 1 mo.

Portopulmonary hypertension

To be eligible for MELD exception points of MMaT-3, the candidate must have evidence of portal hypertension along with mean pulmonary artery pressure (MPAP)

> 35 mmHg and pulmonary vascular resistance (PVR) > 3 woods unit or ≥ 240 dynes/sec/cm⁵. The candidates must have documentation of treatment for pulmonary hypertension with improvement in MPAP < 35 mmHg along with post treatment PVR < 5.1 woods unit or 400 dynes sec/cm⁵. For MELD extension request cardiac catheterization needs to be repeated every 3 mo with confirmation of MPAP < 35 mmHg.

Familial amyloid polyneuropathy

The candidate will be eligible for MELD exception points of MMaT-3 if the candidate has biopsy-proven Amyloid along with confirmation of transthyretin (TTR) gene mutation with good functional status (able to ambulate without assistance). The candidate must be on liver transplant list or has ejection fraction (EF) > 40% on ECHO been performed within last 1 mo. To be eligible for extension, the candidate must be on active heart transplant list and ECHO showing EF > 40% within last 4 mo.

Primary hyperoxaluria

MELD exception points of MMaT will be granted if the candidates have alanine glyoxylate aminotransferase (AGT) deficiency on liver biopsy sample analysis or genetic mutation analysis and on active kidney transplant list with estimated the glomerular filtration rate (eGFR) ≤ 25 mL/min on two instances at least 42 d apart.

Hepatic artery thrombosis

The candidate will be eligible for MELD exception points of 40 if hepatic artery thrombosis (HAT) is within 2 wk after LT and does not meet the criteria of status 1A which includes HAT within 7 d of liver transplant along with aspartate aminotransferase ≥ 3000 and at least 1 of the following (INR ≥ 2.5 or arterial pH ≤ 7.3 or venous pH ≤ 7.2 or lactate \leq for mmol/L).

Liver transplant outcomes in the United States

The OPTN/SRTR publishes annual liver transplant outcomes report in the United States every year. The most recent reported liver transplant outcomes in the United States were from the year 2018 and they were published in January 2020[27].

Waiting list outcomes

The deceased donor OLT rate had increased to 54.5 *per* 100 waitlist-years in 2018 regardless of the recipients' geographic location (metropolitan and rural), gender and age. This trend has been rising since 2012. Historically, minorities such as Asian and Latino liver transplant candidates were not favored to received OLT, compared to their Caucasian and African American counterparts. This gap has narrowed to 10%, 44 and 48 *per* 100 waitlist-years for Asians and Latinos, compared to 56 and 62.5 for Caucasians and African Americans. The OLT rate was 66% higher for HCC candidates than for non-HCC candidates. This gap has been steadily narrowing since 2006. The overall median time from UNOS listing to transplant was 10.8 mo. The overall pre-OLT mortality rate was 13.2 *per* 100 waitlist-years in 2018. Age 65 or older candidates, candidates listed with acute liver failure, candidate listed with status 1A and MELD ≥ 35 had higher waitlist mortality. However, pre-OLT waitlist mortality of candidates listed at status 1A or MELD ≥ 35 had decreased since the regional "Share 35" rule implemented in 2013. Pre-OLT waitlist mortality also varied significantly by candidates' DSA regions geographically, ranging from 6.5 to 37.4 *per* 100 waitlist-years. That was one of the chief reasons for the UNOS/OPTN to change the liver distribution policy from DSA-based allocation model to the AC model.

Liver donation outcomes

The number of deceased liver donations continued to increase in 2018. There were total of 7766 deceased liver donations. The use of hepatitis C virus (HCV) exposed donor livers has increased steadily since 2013. Approximately 8% of deceased donor OLTs in 2018 were from HCV donors. This trend has increased due to the effective HCV direct-acting antiviral (DAA) therapies and increased anoxic brain deaths from drug overdose secondary to national opioid epidemic. The liver donor organ discard rate has been trending down since 2012. The liver donor organ discard rate in 2018 was 8.4%. HCV-exposed donor livers were more likely to be utilized.

Liver transplant outcomes

In 2018, the annual volume of OLTs was the highest in the United States history, recording 8250 transplants in a single year. In comparison, this number was a huge 31% increase from 2008 when only 6319 OLTs were performed. The percentage of

DCD donations also increased to 6.9% in 2018, compared to 4.8% in 2008. Although the majority of OLT recipients were Caucasian males between 50 to 64 years of age, the number of Asian and Latino transplant recipients increased by 15% and 11% respectively. The two most common diagnoses were alcohol-associated liver disease and cryptogenic disease, which are, in many cases, undiagnosed burnt-out non-alcohol steatohepatitis in etiology. The third most common diagnosis for OLT was HCC. The number of OLT recipients with HCV continued to decline in 2018. Only 10% of OLT recipients had the primary diagnosis of HCV-related chronic liver disease.

Overall and graft survival of OLTs continued to rise in 2018. 1-year and 3-year liver graft failure rates of deceased donor liver transplant were 8.8% and 16% respectively. 1-year and 3-year graft failure rates of living donor liver transplant were 7.8% and 14.6% respectively. 5-year overall and graft survival outcomes for the recipients with HCV diagnosis were comparable to the recipients with other etiologies. This trend was due to the effective DAA therapies for recurrent HCV infection after OLT. While the OLT recipients with HCC had better 1-year graft survival rate than the recipients with non-HCC diagnosis (90% *vs* 88%), they both had a similar 5-year graft survival rate (77% *vs* 76%)[27].

CONCLUSION

In summary, we reviewed the evolution of liver transplant allocation policies in the United States over 3 decades; from CPT score system to MELD score to MELD-sodium score. We reviewed the liver transplant distribution policies; from older DSA-based distribution to the newer AC model and its potential advantages and drawbacks. We also reviewed the indications for both standard and non-standard MELD exceptions granted by the National Liver Review Board. Finally, we reviewed the liver transplant waitlist, donation and survival outcomes in the United States.

REFERENCES

- 1 **OPTN.** Organ Procurement and Transplant Network. [cited 9 January 2021]. Available from: <https://optn.transplant.hrsa.gov/>
- 2 **GAO@100.** United Network for Organ Sharing. [cited 9 January 2021]. Available from: <https://www.gao.gov/products/b-416248>
- 3 **The official Web site for Code of Federal Regulations.** For further information on OPTN policies by HHS. [cited 9 January 2021]. Available from: <https://ecfr.federalregister.gov/current/title-42/chapter-I/subchapter-K>
- 4 **ODT CLINICAL.** For further information on NHS Blood and Transplant. [cited 10 January 2021]. Available from: <https://www.odt.nhs.uk/>
- 5 **The official Web site.** For further information on European Transplant. [cited 10 January 2021]. Available from: <https://www.eurotransplant.org/>
- 6 **Chapter 1–Public Health Service.** Department of Health and Human Services. Part 121–Organ Procurement and Transplantation Network. 1999. [cited 10 January 2021]. Available from: https://optn.transplant.hrsa.gov/policiesandbylaws/final_rule.asp/
- 7 **Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R.** Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649 [PMID: 4541913 DOI: 10.1002/bjs.1800600817]
- 8 **Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR.** A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470 [PMID: 11172350 DOI: 10.1053/jhep.2001.22172]
- 9 **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* 2000; **31**: 864-871 [PMID: 10733541 DOI: 10.1053/he.2000.5852]
- 10 **Brown RS Jr, Kumar KS, Russo MW, Kinkhabwala M, Rudow DL, Harren P, Lobritto S, Emond JC.** Model for end-stage liver disease and Child-Turcotte-Pugh score as predictors of pretransplantation disease severity, posttransplantation outcome, and resource utilization in United Network for Organ Sharing status 2A patients. *Liver Transpl* 2002; **8**: 278-284 [PMID: 11910574 DOI: 10.1053/jlts.2002.31340]
- 11 **MELD.** Model for end-stage liver disease. [cited 10 January 2021]. Available from: https://unos.org/wp-content/uploads/unos/MELD_PELD.pdf
- 12 **Biggins SW, Rodriguez HJ, Bacchetti P, Bass NM, Roberts JP, Terrault NA.** Serum sodium predicts mortality in patients listed for liver transplantation. *Hepatology* 2005; **41**: 32-39 [PMID: 15690479 DOI: 10.1002/hep.20517]
- 13 **Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau**

- TM. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med* 2008; **359**: 1018-1026 [PMID: 18768945 DOI: 10.1056/NEJMoa0801209]
- 14 **The official Web site for UNOS.** The policy change of adding serum sodium to MELD score. [cited 9 January 2021]. Available from: <https://unos.org/news/policy-and-system-changes-adding-serum-sodium-to-meld-calculation/>
- 15 **UNOS.** The official Web site for UNOS's liver distribution policy. [cited 10 January 2021]. Available from: <https://unos.org/policy/Liver-distribution/>
- 16 **UNOS.** The official Web site for UNOS's transplants annual trends. [cited 9 January 2021]. Available from: <https://unos.org/news/deceased-organ-donation-and-transplant-annual-trend-continues-2020/>
- 17 **The official Web site for OPTN.** Liver and Intestine Distribution Using Distance from Donor Hospital Briefing Paper published in 2018. [cited 9 January 2021]. Available from: https://optn.transplant.hrsa.gov/media/2766/Liver_boardreport_201812.pdf
- 18 **Chyou D,** Karp S, Shah MB, Lynch R, Goldberg DS. A 6-month report on the impact of the OPTN/UNOS Acuity Circles policy change. *Liver Transpl* 2020 [DOI: 10.1002/lt.25972]
- 19 **Callahan LR.** Briefing Paper Liver Review Board Guidance Documents OPTN/UNOS Liver and Intestinal Organ Transplantation Committee. [cited 9 January 2021]. Available from: <https://optn.transplant.hrsa.gov/resources/by-organ/Liver-intestine/guidance-on-meld-peld-exception>
- 20 **OPTN.** The official Web site for OPTN policies. [cited 9 January 2021]. Available from: https://Optn.Transplant.Hrsa.Gov/Media/1200/Optn_policies.Pdf
- 21 **WHO.** Cancer today. [cited 10 January 2021]. Available from: <https://Gco.Iarc.Fr/Today/Data/Factsheets/Cancers/39-All-Cancers-Fact-Sheet.Pdf>
- 22 **Wiesner R,** Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R; United Network for Organ Sharing Liver Disease Severity Score Committee. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91-96 [PMID: 12512033 DOI: 10.1053/gast.2003.50016]
- 23 **Mazzaferro V,** Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]
- 24 **Freeman RB Jr,** Gish RG, Harper A, Davis GL, Vierling J, Lieblein L, Klintmalm G, Blazek J, Hunter R, Punch J. Model for end-stage liver disease (MELD) exception guidelines: results and recommendations from the MELD Exception Study Group and Conference (MESSAGE) for the approval of patients who need liver transplantation with diseases not considered by the standard MELD formula. *Liver Transpl* 2006; **12**: S128-S136 [PMID: 17123284 DOI: 10.1002/lt.20979]
- 25 **Massie AB,** Caffo B, Gentry SE, Hall EC, Axelrod DA, Lentine KL, Schnitzler MA, Gheorghian A, Salvalaggio PR, Segev DL. MELD Exceptions and Rates of Waiting List Outcomes. *Am J Transplant* 2011; **11**: 2362-2371 [PMID: 21920019 DOI: 10.1111/j.1600-6143.2011.03735.x]
- 26 **OPTN.** Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review. [cited 10 January 2021]. Available from: <https://optn.transplant.hrsa.gov/resources/guidance/Liver-review-board-guidance/>
- 27 **Kim WR,** Lake JR, Smith JM, Schladt DP, Skeans MA, Noreen SM, Robinson AM, Miller E, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2017 Annual Data Report: Liver. *Am J Transplant* 2019; **19** Suppl 2: 184-283 [PMID: 30811890 DOI: 10.1111/ajt.15276]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

