Improving Liver Allocation: MELD, PELD, Status 1A, Status 1B

OPTN Liver and Intestinal Organ Transplantation Committee
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Purpose of Proposal

- Create a more **equitable** and **efficient** liver allocation system by updating policy for:
  - Model for end-stage liver disease (MELD) score
  - Pediatric end-stage liver disease (PELD) score
  - Status 1A and 1B requirements

Proposal: MELD 3.0

- MELD 3.0 Overview:
  - Adds two new variables: **current sex and albumin**
  - **Updates coefficients** for existing variables (sodium, bilirubin, creatinine, and international normalized ratio (INR))
  - Introduces **interaction terms** between bilirubin and sodium and between albumin and creatinine
  - **Caps creatinine** at 3.0 mg/dL

Proposal: MELD 3.0

- Current MELD:
  - Calculated using **objective laboratory values** to predict likelihood of 90-day mortality for waitlist candidates
  - Decreasing ability to predict likelihood of waitlist mortality since implementation in 2001
  - Use of creatinine in the MELD score **disadvantages female candidates**:
    - Females have decreased odds of liver transplantation within three years of listing compared to males
    - Females are more likely than males to die waiting for transplant or be removed from waitlist for being too sick for transplant

Proposal: MELD 3.0

- "MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era" published in December 2021 *Gastroenterology* by Kim et al.
- MELD 3.0 is calculated as follows:

$$MELD\ 3.0 = 1.33\ (if\ female) + [4.56 \times \log_e(bilirubin)] + [0.82 \times (137\text{-}Sodium)] - [0.24 \times (137\text{-}Sodium) \times \log_e(bilirubin)] + [9.09 \times \log_e(INR)] + [11.14 \times \log_e(creatinine)] + [1.85 \times (3.5\text{-}albumin)] - [1.83 \times (3.5 - albumin) \times \log_e(creatinine)] + 6$$

Proposal: MELD 3.0

- MELD 3.0 **better predicts candidate waitlist mortality** compared to MELD Na
  - MELD 3.0 C-statistic: 0.869
  - MELD Na C-statistic: 0.862

Proposal: MELD 3.0

Gastroenterology LSAM Modeling Results

MELD Model	Waitlist Deaths	Change in Waitlist Deaths	P-value
MELD Na	7,850	Not applicable	Not applicable
MELD 3.0 with albumin	7,788	-62	.02
MELD 3.0 without albumin	7,814	-36	.12

Only MELD 3.0 with albumin produced a significant decrease in the predicted number of waitlist deaths when compared to MELD Na

MELD 3.0 impact modeled separately by Gastroenterology paper authors and SRTR.

Proposal: MELD 3.0

SRTR LSAM Modeling Results

MELD Model	Transplant Rate	Transplant Count	Waitlist Mortality Rate	Waitlist Mortality Count	2 Year Post-Tx Mortality
MELD Na: Female	38.8 (38,40.2)	2059 (2021,2144)	8.8 (8.5,9.4)	468 (449,492)	17.2 (15.7,18.1)
MELD Na: Male	42.3 (41.2,44)	3751 (3687,3864)	8.9 (8.5,9.2)	787 (758,814)	15.9 (15.2,17.1)
MELD 3.0 with albumin: Female	41.2 (39.6,41.8)	2170 (2100,2216)	8.7 (8.1,9.2)	458 (426,481)	17.2 (15.3,18.5)
MELD 3.0 with albumin: Male	40.8 (40.3,41.6)	3635 (3596,3681)	9 (8.7,9.5)	798 (774,851)	16.2 (15.4,17)

Proposal: MELD 3.0

- eGFR vs. Creatinine:
  - Public comment proposal would require race-neutral eGFR calculations
  - Newer, race-neutral eGFR models, like cystatin-C, are not widely-available
- Sex vs. Height:
  - Impact of sex is larger and more consistent than height
  - Sex more correlated with mortality; height more correlated to access to transplant
- Albumin vs. No Albumin:
  - MELD 3.0 with albumin does better job of predicting mortality risk
  - Only MELD 3.0 with albumin resulted in statistically significant reduction in waitlist mortality
  - As creatinine increases, albumin is given less relative weight

Proposal: MELD 3.0

- **Adolescent candidates (age 12-17) will utilize MELD 3.0** but both male and female candidates will receive 1.33 “female” points
  - No evidence to suggest a sex-based disparity exists for adolescent candidates
  - Providing 1.33 “female” points to both male and female adolescent candidates ensures no unintended disparity is introduced for this group

Proposal: MELD 3.0

- Data Collection Changes:
  - OPTN collects “birth sex”
  - Data collection will be updated to allow transplant programs to report a **candidate’s current sex** when it differs from his or her birth sex

Rationale: MELD 3.0

- Improved ability to predict waitlist mortality
- Reduce sex-based disparity in liver allocation
- Clinical input of Committee members and subject matter experts

Member Actions

- Transplant programs will need to:
  - Inform candidates of any potential **changes in their MELD score**
  - Be aware of any changes to **lab updates schedules** as a result of new scores
  - Submit **albumin** values for all MELD candidates
  - Provide candidate's **current sex** if different than sex at time of birth

PELD Cr, Status 1A, Status 1B

Proposal: PELD Cr

- PELD Cr Overview:
  - Adds **creatinine variable** as measure of renal function
  - Updates parameters for current variables (albumin, bilirubin, INR)
  - Includes **continuous variables** for age and growth failure instead of categorical variables
  - Incorporates **age-adjusted mortality** factor to align with risk of mortality in the adult population

Proposal: PELD Cr

- Current PELD:
  - Calculated using **objective laboratory values** and predicts likelihood of 90-day mortality for pediatric waitlist candidates (age less than 12)
  - Not updated since it was developed in 2000
  - Current PELD **under predicts waitlist mortality** risk by as much as 17%
  - Almost two-thirds of pediatric candidates **listed with an exception score**
  - Categorical growth failure variable creates "**growth failure gap**" where candidates with growth failure inappropriately lose six to seven PELD points
  - No measure of renal function

Proposal: PELD Cr

	If the value is:	Then the value's contribution to PELD is:
Candidate Age (fractional calendar year)	< 1	-0.1967 * 1
	1 to 5.5	-0.1967 * age at the time of most recent lab reported for use in the PELD score (fractional calendar year)
	> 5.5 and < 12	-0.1967 * 5.5
Albumin (g/dL)	1 to 1.9	-1.842 * ln(albumin)
	> 1.9	-1.842 * ln(1.9)
Total bilirubin (mg/dL)	1 to 4	0.7854 * ln(bilirubin) + 0.3434 * ln(4)
	> 4 to 40	0.7854 * ln(4) + 0.3434 * ln(bilirubin)
	> 40	0.7854 * ln(4) + 0.3434 * ln(40)
INR	1 to 2	1.981 * ln(INR) + 0.7298 * ln(2)
	> 2 to 10	1.981 * ln(2) + 0.7298 * ln(INR)
	> 10	1.981 * ln(2) + 0.7298 * ln(10)
Minimum of CDC height or weight Z-score	< -5.0	-0.1807 * (-5)
	-5.0 to -2.1	-0.1807 * (minimum z-score)
	> -2.1	-0.1807 * (-2.1)
Creatinine (mg/dL)	< 0.2	1.453 * ln(0.2)
	0.2 to 1.3	1.453 * ln(creatinine)
	> 1.3	1.453 * ln(1.3)

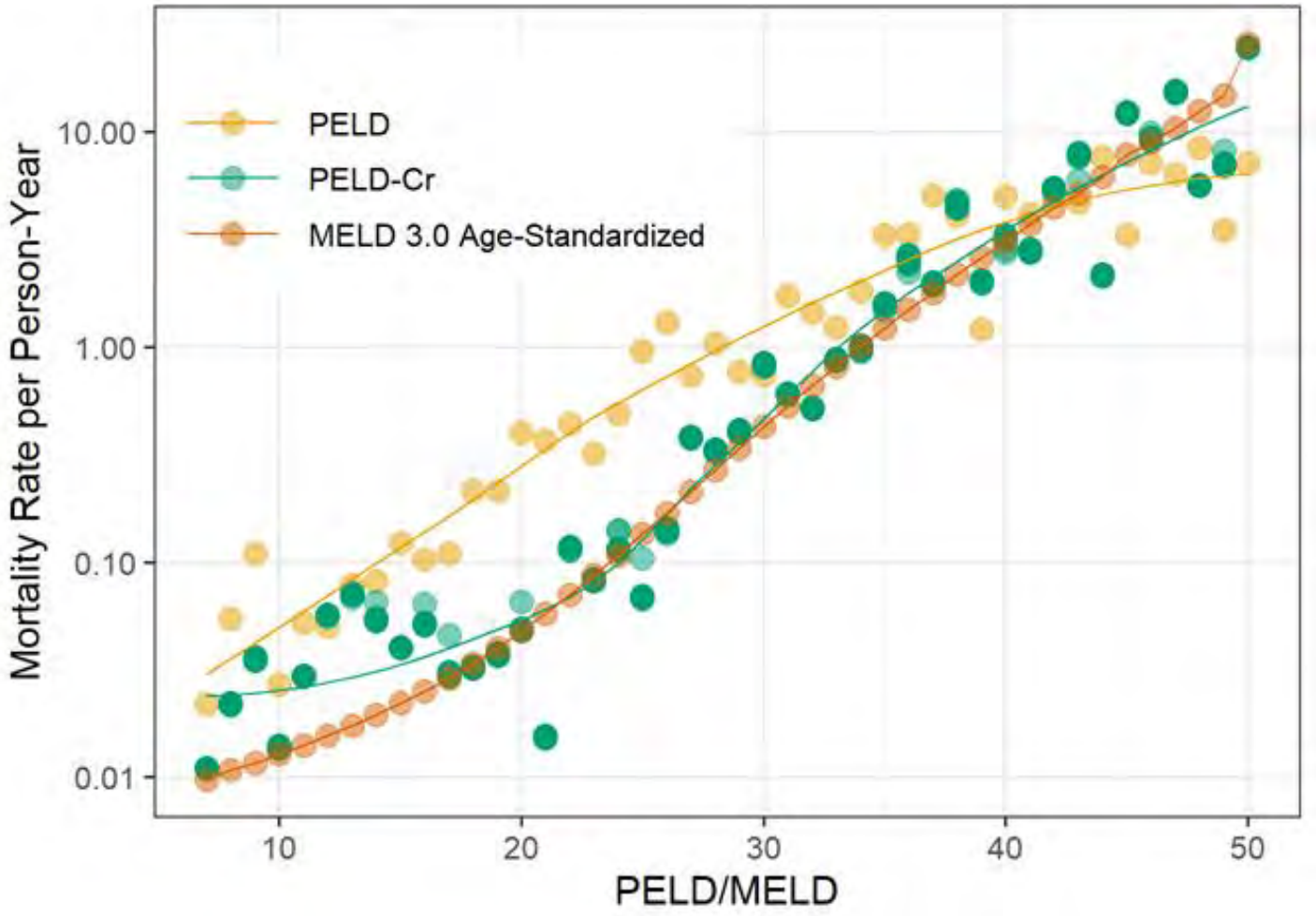
PELD Cr = (sum of all terms + 1.5287) x 10 + 2.82

Proposal: PELD Cr

- PELD Cr **better predicts waitlist mortality** risk when compared to PELD:
  - PELD Cr C-statistic: 0.909
  - PELD C-statistic: 0.842
- Age and growth failure converted to **continuous variables** to address “growth failure gap”
- Creatinine incorporated to capture **renal function**
- 2.82 points added to account for **age-adjusted mortality**

Proposal: PELD Cr

- Age-adjusted mortality:



Proposal: Status 1A

- Current policy does not reflect that diagnosing encephalopathy in young children is difficult and may be unreliable

Current Policy	Proposed Policy
Fulminant liver failure, defined as the onset of hepatic encephalopathy within 56 days of the first signs or symptoms of liver disease AND has an INR greater than 2.0	Fulminant liver failure AND candidate either has: • INR greater than or equal to 1.5 and less than 2.0 and a diagnosis of hepatic encephalopathy within 56 days of the first signs for symptoms of liver disease • INR greater than or equal to 2.0

Proposal: Status 1B

- Proposed changes:
  - **MELD/PELD threshold** for candidates with chronic liver disease
  - **Gastro-intestinal (GI) bleeding threshold** for candidates with chronic liver disease
  - **Glasgow Coma Score (GCS) criteria** for candidates with chronic liver disease
  - **Sorting** of candidates within Status 1B classifications

Proposal: Status 1B Criteria for Chronic Liver Disease

- **MELD/PELD 25 Threshold:**
  - Liver-intestine candidates automatically get 23 points
  - Most common reason that liver-alone candidate are listed as Status 1B by exception is because the candidate does not have a calculated MELD or PELD greater than 25; Most (72%) exceptions approved
- Update **GI bleeding threshold** to match definition of persistent mild shock or moderate shock for liver-alone candidates with chronic liver disease
- **GCS criterion** is not clinically relevant and rarely used for Status 1B listing

Proposal: Status 1B

- Blood type points:
  - Identical: 10 points
  - Compatible: 5 points
  - Incompatible: 0 points
- Waiting time points:
  - Candidate with most waiting time at Status 1B: 10 points
  - Fraction of 10 points divided among the remaining status 1B candidates within each classification, based on the potential recipient's total waiting time

Proposal: Status 1B

- Prioritize candidates with chronic liver disease by assigning **diagnosis points**:

Diagnosis	Points
Chronic liver disease (liver-alone and liver intestine)	15 points
Tumor	5 points
Metabolic Disease	0 points
Other	0 points

Rationale

PELD Cr:	Status 1A/1B:
• Improved ability to predict waitlist mortality for pediatric candidates • Clinical input of Committee members and subject matter experts	• Clinical input of Committee members and subject matter experts • OPTN data • Aligning policy with updated clinical guidelines

Member Actions

- Transplant programs will need to:
  - Inform candidates of any potential changes in their PELD score
  - Be aware of any changes to lab updates schedules as a result of new scores
  - Submit creatinine values for all PELD candidates

What do you think?

- Should MELD 3.0 include albumin?
- How should adolescent candidates be handled under the new scoring system?
- Do you support removing the MELD/PELD 25 threshold for Status 1B?
- Do you support the number of points assigned for each diagnosis within Status 1B?