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Authors

Swenson, Sonja M
Roberts, John P
Rhee, Sue
et al.

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Impact of the Pediatric End-Stage Liver Disease (PELD) growth failure thresholds on mortality among pediatric liver transplant candidates

Sonja M. Swenson[1], **John P. Roberts**[2], **Sue Rhee**[3], **Emily R. Perito**[3,4]

[1]School of Medicine, University of California, San Francisco, San Francisco, California

[2]Department of Surgery, University of California, San Francisco, San Francisco, California

[3]Department of Pediatrics, University of California, San Francisco, San Francisco, California

[4]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California

Abstract

The Pediatric End-stage Liver Disease (PELD) score is intended to determine priority for children awaiting liver transplant. This study examines the impact of PELD's incorporation of "growth failure" as a threshold variable, defined as having weight or height <−2 standard deviations below the age and gender norm (z-score<−2). First, we demonstrate the "growth failure gap" created by PELD's current calculation methods, in which children have z-score

<−2 but do not meet PELD's growth failure criteria—thus losing 6–7 PELD points. Second, we utilized United Network for Organ Sharing data to investigate the impact of this "growth failure gap." Among 3,291 pediatric liver transplant candidates, 26% met PELD-defined growth failure, and 17% fell in the growth failure gap. Children in the growth failure gap had a higher risk of waitlist mortality than those without growth failure (adjusted SHR: 1.78, 95%CI:1.05–3.02, p=0.03). They also had a higher risk of post-transplant mortality (adjusted HR 1.55, 95%CI 1.03–2.32, p=0.03). For children without PELD exception points (n=1,291), waitlist mortality risk nearly tripled for those in the gap (SHR: 2.89, 95%CI:1.39– 6.01, p=0.005). Current methods for determining growth failure in PELD disadvantage candidates arbitrarily and increase their waitlist mortality risk. PELD should be revised to correct this disparity.

Correspondence: Sonja M. Swenson, Sonja.Swenson@ucsf.edu.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of this article.

1. Introduction

Although liver transplant has transformed end-stage liver disease in children from a fatal to fixable condition, 1 in 10 infants and 1 in 20 children listed for liver transplant in the United States still die on the waitlist.[1, 2] The primary goal of our current waitlist priority ranking, which relies on the Pediatric End-Stage Liver Disease (PELD) score for children age 0–11 years old, is to minimize waitlist mortality. PELD, and the Model for End-Stage Liver Disease (MELD) score for adults, were derived to predict the risk of short-term waitlist mortality using objective, quantitative measures.[3] PELD includes bilirubin, International Normalized Ratio (INR), and albumin, with additional points for age <1 year and "growth failure." (FIGURE 1) However, PELD scores have been shown to underestimate waitlist mortality by as much as 17%.[4]

Currently, almost two-thirds of pediatric liver transplant candidates have their waitlist priority determined by something other than calculated PELD; 13% receive a standardized increase for conditions in which PELD does not reflect disease severity, and 44% receive "non-standard" PELD points based on their transplant center's subjective narrative on their individual risks.[5]

Some have argued that reliance on calculated PELD could be improved by recalibration—adding points to all PELD scores so children can compete with adult MELD scores. However, this does not address aspects of current PELD calculation that limit its ability to discriminate fairly between pediatric candidates, and to be trusted by transplant providers for priority ranking.[4, 7]

We previously identified "growth failure" as the most common justification provided in appeals for extra PELD points—despite "growth failure" already being factored into the PELD equation.[8] This suggests pediatric liver transplant providers do not trust that growth failure is adequately accounted for by the current PELD score.

Growth failure, often multifactorial, has been identified as a risk factor before and after liver transplant.[3, 9–19] Malnutrition increases vulnerability to infections, bleeding and hypoalbuminemia, which may exacerbate ascites. Smaller size may also limit availability of a suitable liver for transplant. Although nutritional support is a mainstay of treatment for pediatric candidates, growth failure prevalence remains high.[1520]

PELD defines growth failure as present or absent, based on a stated threshold of less than 2 standard deviations below mean height or weight for age and sex (z-score <−2).[21] Although weights and heights are measured along a continuous spectrum, PELD's growth failure threshold leads to 6–7 point shifts in the calculated score, when a child shifts from meeting to exceeding growth failure criteria. Additionally, PELD calculations currently rely on weight and height thresholds for growth failure that shift in 3-month age increments. For example, the threshold weight and height by which growth failure are defined do not change as a baby ages from 6 to 7 to 8 months, but at 9 months the height and weight threshold change. This holds for 3-month age increments, ages 0–144 months.[21]

The impact of PELD's growth failure threshold and its definition in 3-month age increments on PELD scores, and on pediatric waitlist outcomes, has not been previously elucidated. In this analysis, we used the Organ Procurement and Transplant Network (OPTN) PELD calculator to illustrate the impact of growth failure thresholds on PELD scores across the age spectrum, and to highlight the "growth failure gap" created by its calculation methods. We used Organ Procurement and Transplantation Network (OPTN) data on all U.S. pediatric liver transplant candidates to evaluate the impact of growth failure thresholds on waitlist outcomes.

2. Methods:

The University of California San Francisco Committee on Human Research approved this analysis (IRB 18–26475).

2.1 Calculator Simulation

To map PELD growth failure thresholds and their impact on PELD scores, we entered combinations of height, weight, age, and sex into OPTN's PELD calculator.[22] OPTN policy 9.1.E defines "growth failure" as "more than 2 standard deviations below the candidate's expected growth based on age and sex, using the most recent Centers for Disease Control and Prevention (CDC) National Center for Health Statistics pediatric clinical growth chart."[23] Other PELD components were held constant at values representing moderate illness severity, in a PELD range matching median allocation PELD at waitlist removal for young children (PELD score 19–23, FIGURE 1, eFIGURE 1).[1] Starting with age 1 day, 50th percentile weight and height for age and sex (using CDC charts[24–27]) were entered, and corresponding PELD score calculated. Weight was then decreased in 0.01 kilogram increments to identify the threshold weight that triggered "growth failure" points, holding height constant. We then reset weight to the 50th percentile and repeated the process for height, decreasing in 0.01 centimeter increments to identify the height threshold that triggered "growth failure" points. This process was repeated for boy and girls ages 1 day to 144 months, in 2-week age intervals. These threshold values matched supporting documentation for the OPTN MELD/PELD calculator and were confirmed as identical to those used by OPTN to calculate listing PELD scores. ([21,] United Network for Organ Sharing, written communication, November 2018) PELD weight and height threshold values, by age and sex, were plotted on CDC 2000 growth charts.[24–27]

CDC 2000 z-scores equivalent to each PELD weight and height threshold value, throughout its 3-month age interval, were then calculated.[28] For each month of age (0–144), three datapoints per month per sex were used, corresponding to ages at the beginning, middle, and end of the month (e.g., ages 2.0, 2.5 and 2.97 months). For ages 0–24 months, CDC 2000 growth charts for children 0–36 months old were used. For ages 24.5–144 months, charts for ages 2–20 years were used.[24–27]

The OPTN PELD calculator was then used to quantify the change in other PELD components that produced a score change equivalent to the shift from "no growth failure" to "growth failure" at three ages (0.5, 1.5, and 6.0 years). Each calculation started with 50th percentile height and weight for age and sex, bilirubin=14 mg/d, INR=1.5, and albumin=3.0

mg/dL. PELD component values were altered individually, holding other variables constant, to identify the change in each that produced a PELD score shift equivalent to crossing the growth failure threshold.

2.2 Retrospective Cohort Study

We next utilized data from the Organ Procurement and Transplantation Network (OPTN)[29] with supplemental birthdate data, to examine the discrepancy between growth z-scores at listing and PELD growth failure thresholds – and the impact of these discrepancies on waitlist outcomes. The OPTN data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere. The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN contractor.

Our cohort included all U.S. liver transplant candidates <12 years old at listing, listed for primary liver transplant 1/1/2003–12/31/2014, followed through 6/8/2018. We excluded Status 1A/1B listings because their priority is independent of calculated PELD (n=2,107), multi-organ listings (n=1,038), duplicate listings (n=253), and those with biologically implausible weight/height z-scores (<−5 or >5) (n=31).[30] Children with only a weight or height z-score were categorized according to available z-score. Children with a weight or height that met PELD growth failure criteria but had both weight and height z-scores ≥−2 were excluded (n=14, all transplanted).

Using calculated z-scores at listing, children were categorized as Growth Failure (GF) (weight or height z-score <−2 and weight or height at or below PELD growth failure threshold), Growth Failure Gap (GF Gap; weight or height z-score <−2 but both weight and height above PELD thresholds for age and gender), or No Growth Failure (No GF; (weight and height z-scores ≥−2 and above the PELD thresholds). We focused on measures at listing, as have previous PELD and MELD derivation papers. Data on ascites was missing for 36% of children (TABLE 1), preventing adjustment for this variable.

Waitlist mortality was defined as removal from the waitlist for death or being too sick to transplant within 6 months of listing. If a child was removed from the waitlist for any reason other than transplant, relisted, and then died before transplant, only the last listing was included. For transplanted children, death within 3 years post-transplant was assessed.

“On life support” was defined as being on a ventilator, receiving breathing support, or receiving dialysis.

Statistical analysis: Descriptive statistics were performed with chi-squared, Kruskal-Wallis, or Fisher’s exact testing as appropriate. Predictors of waitlist mortality were identified by competing risks regression, and of post-transplant death by Cox Proportional Hazards. Models were derived using backward stepwise regression, with variables $p<0.1$ retained from univariate analysis and final variables retained if $p<0.05$. Cumulative incidence curves, compared with logrank testing, were used to examine waitlist mortality by growth failure category. Analyses performed with Stata v15.1.

3. Results

3.1 Calculator Simulation

3.1.1 PELD's growth failure threshold falls below a z-score of −2—Growth failure thresholds identified by the OPTN PELD calculator–the weight and height at which a child gains PELD growth failure points for a given age and sex, keeping all other PELD components constant – do not match a z-score of −2 for weight or height, for children of most ages and both sexes (FIGURE 1; eFIGURE 2). The gap between PELD's threshold and z = −2 is largest for the youngest children, who grow most rapidly, because the weight and height thresholds change in 3-month age intervals. When lab values are held constant, PELD score is the same for any weight above the growth failure threshold (e.g. PELD=17 for infants<1 years and =13 for children 1–11 years in FIGURE 1) and any weight below the threshold (PELD=24 for infants, =19 for children in FIGURE 1).

Figure 2 shows the range of z-scores that correspond to weight and height values used as the PELD growth failure thresholds across the age spectrum. This range is a consequence of PELD relying on weight and height thresholds that shift every 3 months. Across all ages evaluated in the simulation (3 data points per month of age), the median z-score corresponding to the weight growth failure threshold was −2.55 (range −4.85 to −1.71). The median z-score corresponding to the height growth failure threshold in the simulation was −2.14 (range −4.93 to −1.48).

3.1.2 Magnitude of PELD score shifts—For infants <1 year old, PELD score increases by 7 points with a shift across the growth failure threshold—which could occur with a weight loss of 10 grams or a height measured as 0.1 millimeters shorter.[10] To increase PELD by 7 points without growth failure, infants would need to have a bilirubin rise from 14 to >50 mg/dL, an INR increase of 1.5 to 2.2, or an albumin decrease from 3.0 to 1.1 g/dL. For children 1–11 years old, PELD score increases by 6 points when they meet growth failure criteria. To increase PELD by 6 points without growth failure, children would require a bilirubin rise from 14 to 48 mg/dL, an INR increase from 1.5 to 2.1, or an albumin decrease from 3.0 to 1.2 g/dL.

3.2 Retrospective Cohort Study

Among 3,291 pediatric liver transplant candidates listed 2003–2014, 26% had GF, by z-score <−2 and PELD growth failure criteria; 17% fell into the GF Gap—with listing weight or height z-score <−2 but both above the PELD growth failure threshold, and 57% met neither definition for growth failure.

Most children (71%) were in the same growth failure group at listing and at waitlist removal. Among children in the GF Gap at listing, 87% remained in the GF or GF Gap groups at removal; 95% of children in the GF group at listing were either GF or GF Gap at removal (data not shown).

3.2.1 Children in the GF Gap—Children in the GF Gap were more likely to be <1 year old (83%) than children with GF (46%) or No GF (44%, p<0.001). The majority of children in the GF Gap were transplanted for biliary atresia (72%). The GF Gap and GF groups had

slightly higher bilirubin and lower sodium than the No GF group, with no difference in creatinine (TABLE 1). Compared to No GF, GF Gap and GF children had higher calculated PELD scores at listing and at waitlist removal and a lower likelihood of receiving PELD exception points. However, allocation PELD scores (calculated scores for those without exceptions and exception scores for those with approved exceptions) did not differ among the three groups. Perhaps related to this adjustment of allocation PELD scores by exception points, median length of time on the waitlist also did not differ significantly (TABLE 1).

Among children in the GF Gap, 35% of infants <1 year old had allocation PELD scores at least 7 exception points higher than final calculated PELD. Among children 1–11 years, 56% had allocation PELD scores at least 6 exception points higher than final calculated PELD.

Infants were more likely to fall in the GF Gap than older children (27% vs. 6% of children 1–11 years old, p< 0.001). (FIGURE 3) For infants, weight was more often in the GF Gap for age and sex (29%) than height (16%). Infants were also less likely to have GF than older children (23% vs. 29%, p=0.002).

There was not statistically significant variation in prevalence of GF or GF Gap by OPTN region (p=0.10, data not shown).

3.2.2 Children with GF—The GF group had the highest proportion of Black children and children with public insurance, followed by GF Gap. Non-cirrhotic metabolic diseases were also more prevalent in the GF group. (TABLE 1)

3.2.3 Waitlist mortality—Compared to children with No GF, risk of waitlist mortality was higher among children with GF (unadjusted subhazard ratio (SHR) 1.80, 95% confidence interval (CI) 1.15–2.83, p=0.011), and among those in the GF Gap (unadjusted SHR 1.87, 95%CI 1.12–3.10, p=0.016). Mortality risk did not differ between the GF Gap and GF groups (unadjusted SHR 0.97, 95%CI 0.57–1.64, p=0.90).

After adjusting for additional predictors of waitlist mortality (see eTABLE 1), children in the GF Gap still had a significantly higher waitlist mortality risk compared to children with No GF (adjusted SHR 1.78, 95%CI 1.05–3.02, p=0.032; TABLE 2, FIGURE 4).

Hispanic ethnicity was associated with a higher waitlist mortality risk in multivariate analysis (TABLE 2).

In a sensitivity analysis including only children who remained in the same growth failure group between listing and removal (n=2,338), waitlist mortality risk remained higher for those in the GF Gap (unadjusted SHR: 2.70, 95% CI: 1.32–5.54, p=0.007) and those with GF (unadjusted SHR: 1.81, 95% CI: 1.09 – 3.00, p=0.021) compared to No GF. Differences between GF Gap and GF did not reach statistical significance (data not shown).

Among children removed for death or being “too sick” more than 6 months after listing (n=15), 47% were GF and 13% were GF Gap at listing.

3.2.4 Waitlist mortality by exception status—Among children in the GF Gap, having PELD exception points (n=309) was associated with a lower risk of waitlist mortality than having no exception points (n=245) (unadjusted SHR: 0.41, 95%CI: 0.18–0.98, p=0.044). However, the waitlist mortality risk associated with having at least 6–7 exception points (7 for infants; 6 for children 1–11 years old) (n=215) compared to no exception points did not reach statistical significance (unadjusted SHR: 0.37, 95%CI: 0.14—1.03, p=0.056). For those who received fewer than 6–7 exception points (<7 for infants; <6 for children 1–11 years old) (n=94), waitlist mortality was not different compared to children without exception points (unadjusted SHR: 0.51, 95%CI: 0.15—1.76, p=0.29).

Among children without PELD exception points (n=1,291), being in the GF Gap more than doubled the waitlist mortality risk (unadjusted SHR: 2.46; 95%CI: 1.23–4.92; p=0.011) compared to No GF. For these children, having no PELD exception points nearly tripled the risk after adjusting for transplant indication, PELD score, being “on life support” at listing, and OPTN region (adjusted SHR 2.89; 95%CI: 1.39–6.01; p=0.005; data for other variables not shown). Those with GF but no exception points also had increased waitlist mortality risk in univariate (unadjusted SHR: 2.31, 95%CI: 1.22—4.38, p=0.010) and multivariate analysis (adjusted SHR: 2.30, 95%CI: 1.15–4.59, p=0.019; data for other variables not shown) compared to children with No GF.

For children with exception points (n=2,000), waitlist mortality risk was not increased for those in the GF Gap (unadjusted SHR 1.24; 95%CI: 0.56–2.76; p=0.59) or those with GF (unadjusted SHR 1.29, 95%CI 0.66–2.53, p=0.45) compared to No GF.

Children in the GF Gap with exception points (n=309) had no increased risk of waitlist mortality compared to children with No GF and no exception points (n=680) (unadjusted SHR: 1.02, 95%CI: 0.44–2.37, p=0.96).

3.2.5 Post-transplant mortality—Among transplanted children (n=3,041), risk of death within 3 years post-transplant was higher for children in the GF Gap and GF groups at listing, compared to No GF. After adjusting for additional predictors (eTABLE 2), the GF Gap group still had a higher post-transplant mortality risk than No GF (adjusted hazard ratio (HR) 1.55, 95%CI: 1.03–2.32, p=0.034) (TABLE 3).

4. Discussion:

The methods currently used to incorporate growth failure into the PELD score are inadequate. The use of weight and height thresholds that shift in 3-month age intervals creates a “growth failure gap,” in which children can have a weight or height z-score <−2 but not receive PELD’s “growth failure” points. The PELD growth failure threshold falls below a z-score of −2 for weight at every age and height at almost every age, from birth through 12 years. The stepped PELD growth failure threshold does not accurately represent children’s growth trajectories (eFIGURE 2), and particularly disadvantages infants (FIGURE 3) and those at the older range of each 3-month age group.

Our comparisons highlight the significant role in prioritization for transplantation that the growth threshold plays. The 6–7 point shift that growth failure triggers in PELD is

equivalent to the impact of large changes in PELD's biochemical components. INR, bilirubin, and albumin would all need to worsen from values suggestive of moderate liver dysfunction to severe liver failure to achieve the same PELD shift. This can shift an "average" child's PELD from achieving to falling substantially below a score at which they are likely to be transplanted (eFIGURE 1). The growth failure thresholds can also lead to a substantial decrease in PELD score because of clinically insignificant shifts in weight or height. The use of growth failure thresholds – particularly weight-based thresholds – may be especially inappropriate for children with severe liver disease due to the prevalence of ascites in this population. With the current variable, weight fluctuations associated with fluid accumulation and removal can result in a 6–7 point difference in a child's PELD score depending on when the weight was measured. Other methods of assessing growth failure (e.g., skin fold measurements, cross-sectional imaging for sarcopenia) in children with ascites should be explored and validated in all age groups.

In considering the impact of PELD's growth failure threshold on a comprehensive retrospective cohort of pediatric liver transplant candidates, we found that almost one-fifth fall into the "growth failure gap". This includes more than one-quarter of infants, who are at the highest risk of waitlist death.[1] Being in the GF Gap significantly increases the risks of waitlist and post-transplant mortality, even after adjusting for other patient and illness characteristics. Already vulnerable populations, particularly publicly insured children, are overrepresented in the GF and GF Gap groups. Additionally, almost 90% of children in the GF Gap at listing remain in the GF Gap or develop GF by waitlist removal. Thus, our analysis supports the importance of "growth failure" as an "objective and measurable" predictor of waitlist mortality among pediatric liver transplant candidates; it also highlights that current PELD calculation methods do not adequately account for this predictor.[31]

Weight and height z-scores provide a continuous measure of growth adequacy in children, normalized for age and sex. More severely depressed z-scores are likely indicative of more severe chronic liver disease—and higher mortality risk. Thus, children in the growth failure gap may represent an intermediate risk group. This risk spectrum could explain why children in the gap did not have significantly different mortality risk than those meeting PELD's growth failure criteria. Children with z-scores below the PELD growth failure threshold have more severe growth failure than those in the gap, but their waitlist mortality risk may be mitigated by their extra PELD points.

Boosting PELD scores with exception points may be masking the growth failure gap's effect on waitlist mortality. This is evidenced by the strong impact of this gap on children without exception points but not on those with exception points. In addition, median allocation PELD scores – which incorporate exception points for those with approved exceptions – converged at allocation. Among children in the gap, over half of children and one third of infants were eventually granted at least 6–7 exception points, respectively—mathematically offsetting the effect of being in the gap. However, receiving at least 6–7 exception points did not completely reverse the increased risk of waitlist mortality for these children. They may have already accumulated life-threatening morbidity by the time exception points were awarded. This may be also related to crossover among groups between listing and removal, or underpowered sub-analyses.

Continued reliance on non-standard exceptions undermines the intended objectivity and broad applicability of PELD.[32] Although planned changes to the non-standard exception review process aim to promote consistency across regions—including the National Liver Review Board,[33] the process still relies on individual centers to submit appeals. Recent OPTN guidance for PELD/MELD exceptions states there is "insufficient evidence" to support awarding exception points based on broad definitions of growth failure but suggests consideration of exception points for failure to gain weight with tube feedings, parenteral nutrition dependence, and height/weight/skinfold thickness<5th in addition to height/weight z-score<−2.[33] However, this definition would not reduce reliance on non-standard PELD exceptions.

Re-calibrating PELD has been proposed to ensure that children can compete appropriately with adults for deceased donor livers.[7] But, as this analysis shows, reliance on PELD as currently calculated disadvantages children at arbitrary age intervals. The PELD equation was derived in a cohort of 779 patients listed between 1995–2000.[3] MELD has undergone revision (MELD-Na) while PELD has not.[34] Revising PELD with a larger cohort may help address disparities not apparent in the original analysis by using a cohort that comprehensively includes all U.S. pediatric transplant candidates.[2] We now have 20 years of additional data with which to refine the PELD equation. Historical data should be leveraged to refit all five variables in PELD and to consider inclusion of different variables like sodium and creatinine.

Turning continuous z-scores into a binary "growth failure" variable is no longer justifiable. In a revised PELD equation, "growth failure" should be reconfigured as a continuous variable that awards points in proportion to severity. Incorporating additional predictors related to growth, such as ascites, infections, and growth trajectory on the waitlist should also be explored. Simpler modifications to PELD like setting the threshold to z-score=−2 and dropping the 3-month age intervals could be implemented temporarily while PELD undergoes revision, but an updated PELD is ultimately needed. Future research should leverage accumulated OPTN data to revise PELD so it can objectively—and fairly—guide waitlist priority ranking for pediatric liver transplant candidates.

Limitations of this analysis include its reliance on retrospective data and incomplete data on some confounders of interest, particularly ascites. This may have caused underestimation of growth failure prevalence and its impact on waitlist mortality. Additionally, only anthropometrics at listing were considered as predictors. Future analyses should consider additional measurements to evaluate the impact of changes that occur while a child is listed. Among adults, MELD score increases of ≥30% within seven days are associated with waitlist mortality.[35] Future analyses should examine whether PELD score spikes are similarly associated with waitlist mortality—and perhaps warrant additional priority.

5. Conclusion

Current methods for determining "growth failure" in PELD disadvantage candidates at arbitrary age intervals and increase the risk of waitlist mortality for many of these children. The PELD equation should be revised: The growth failure variable used to calculate PELD

score should be reconfigured, leveraging z-scores as inherently continuous variables, to avoid the threshold effect and erase the “growth failure gap.”

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CDC	Centers for Disease Control and Prevention
CI	confidence interval
GF	Growth Failure
HR	Hazard Ratio
INR	International Normalized Ratio
MELD	Model End-stage Liver Disease
OPTN	Organ Procurement and Transplant Network
PELD	Pediatric End-stage Liver Disease
SHR	subhazard ratio
STAR	Standard Transplant Analysis and Research
UNOS	United Network for Organ Sharing

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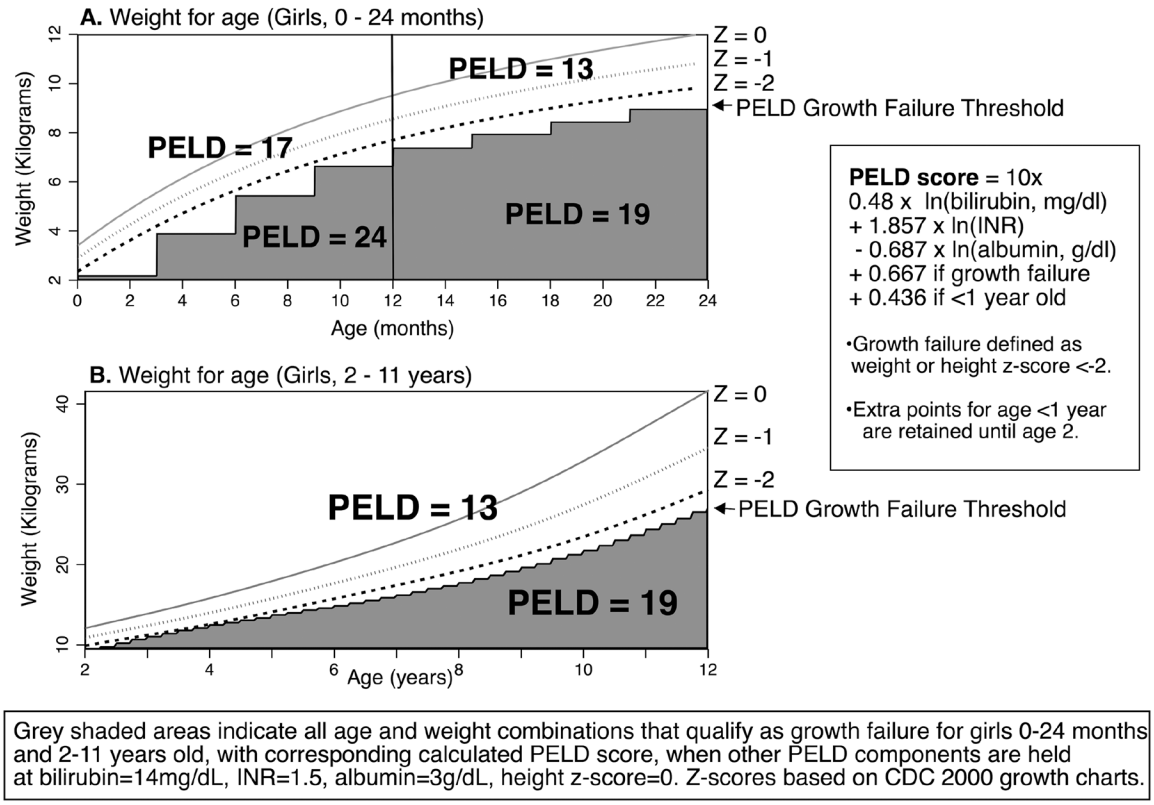

FIGURE 1: (PELD calculator simulation):

Impact of PELD's growth failure thresholds on PELD score, as illustrated by weight thresholds in girls (A) 0 to <24 months old and (B) 2 to 11 years old. See impact of weight threshold on boys' PELD scores and height threshold for boys' and girls' scores in eFigure 2. All weights below the threshold qualify as growth failure (grey-shaded); all weights above are not considered growth failure (white). When laboratory values and height are held constant, PELD score is the same for any weight in the grey area and for any height in the grey area. The threshold is stepped because PELD-defined weight thresholds for growth failure change in 3-month increments. Growth failure thresholds for each graphs calculated using the OPTN PELD calculator[22], as described in Methods.

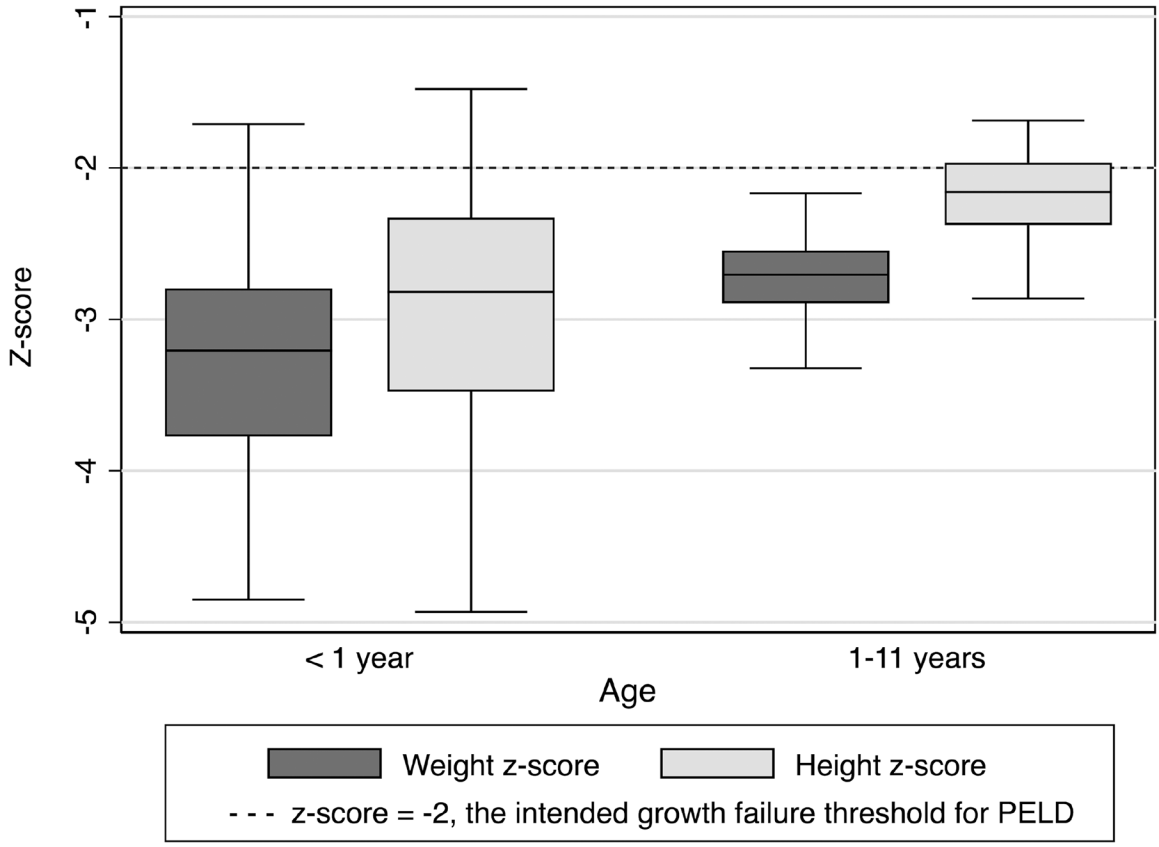

FIGURE 2. (PELD calculator simulation):
Weight and height z-scores equivalent to the PELD growth failure threshold used for current PELD calculations, by age group. Median (middle line), interquartile range (box), and minimum/maximum (whiskers) of weight and height z-scores equivalent to the PELD-defined growth failure threshold in each age group (3 data points per month of age, n=443 total data points per sex, see Methods).

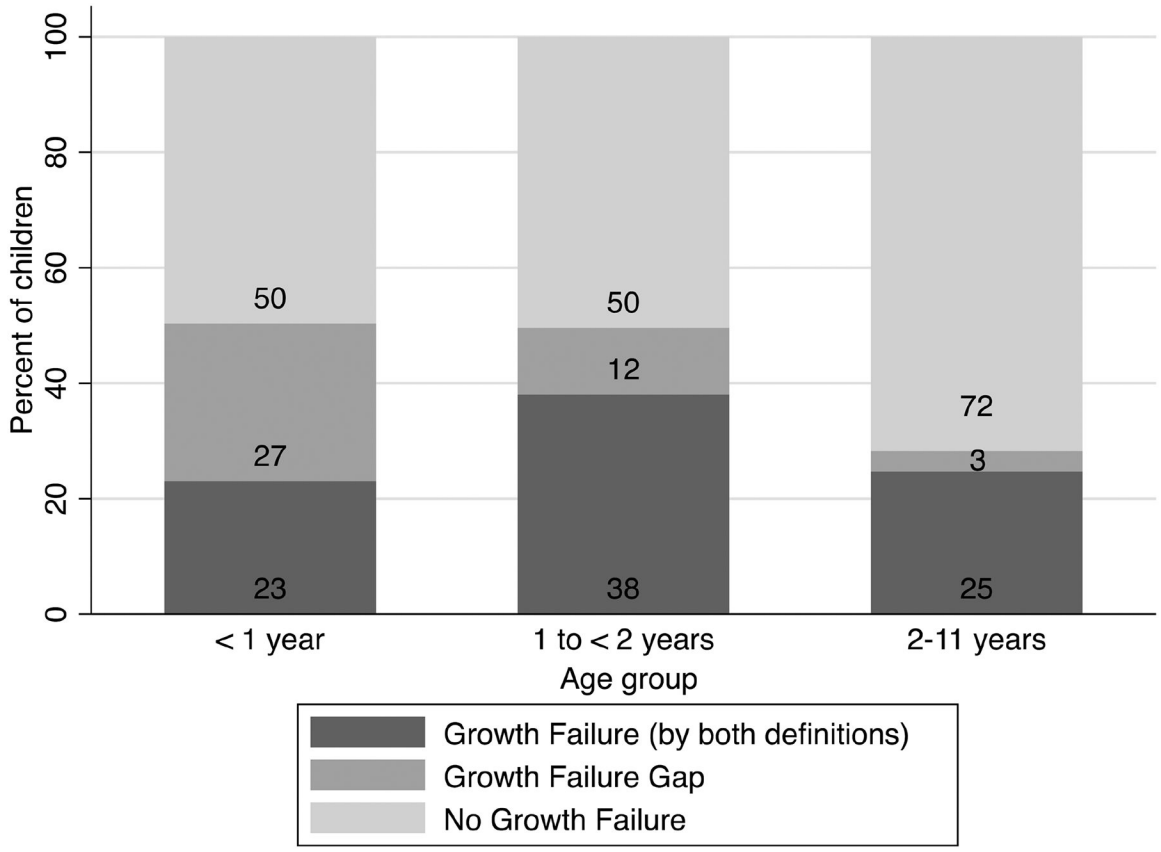

FIGURE 3:

Prevalence of growth failure, by age and growth failure definition. Light grey shading indicates percent of children in each age group who had both weight and height z-scores greater than or equal to −2, and therefore met neither definition of growth failure. Medium grey shading indicates percent of children in the Growth Failure Gap, who had a weight or height z-score <−2 but did not meet PELD growth failure criteria. Dark grey shading indicates children who had a weight or height z-score <−2 and also met PELD growth failure criteria. Younger children (<1 year old) were more likely to fall in the Growth Failure Gap (27.4%) compared to children ages 1 to <2 years old (11.4%, p<0.001) and children 2–11 years old (3.5%, p<0.001).

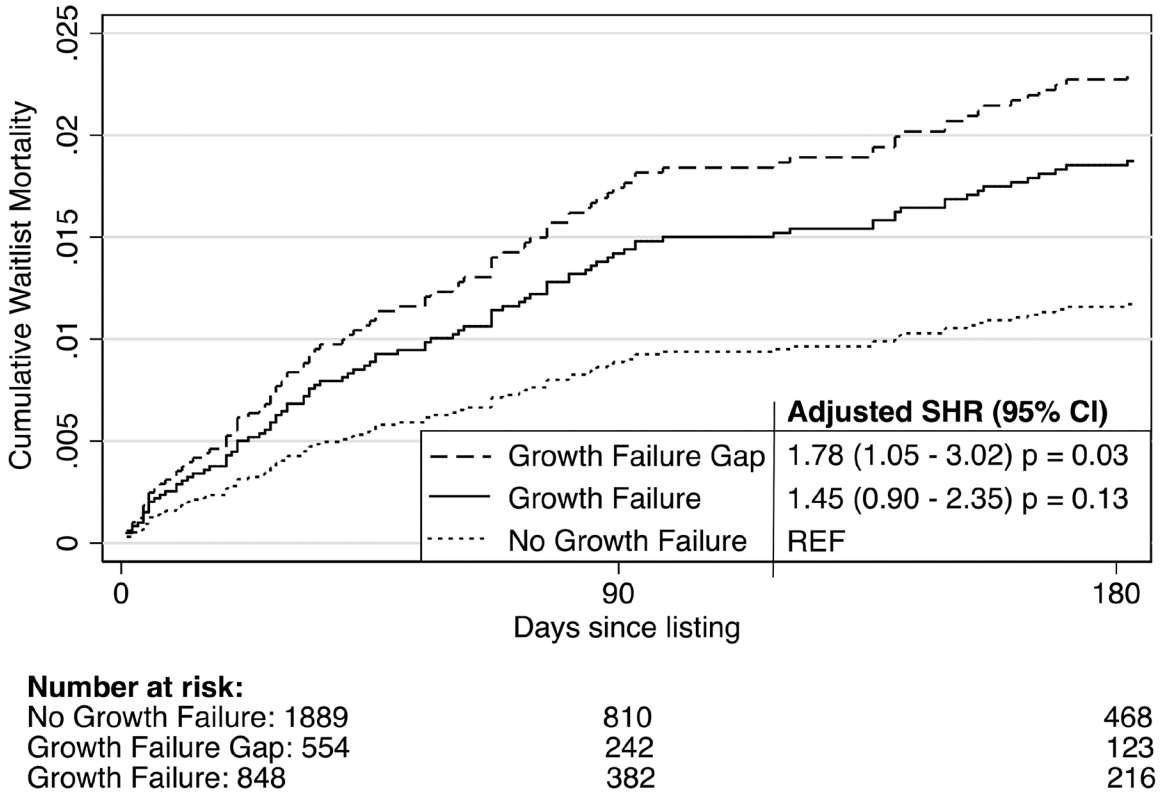

FIGURE 4:

Mortality on the pediatric liver transplant waitlist within 6 months of listing, by growth failure group. Graph depicts cumulative mortality risk, by growth failure group, adjusted for other significant predictors and the competing risk of liver transplant, in multivariate analysis. (Table 2)

TABLE 1:

Pediatric liver transplant candidates, by growth failure category

		Growth Failure (n=848)	Growth Failure Gap (n=554)	No Growth Failure (n=1889)	*P* value
Age at listing, years, median [IQR]		1.1 [0.7–3.5]	0.6 [0.4–0.8]	1.3 [0.5–5.8]	<0.001
Age group at listing	0 to < 1 year	386 (46)	459 (83)	833 (44)	< 0.001
	1 to < 2 years	181 (21)	55 (10)	240 (13)	
	2 – 11 years	281 (33)	40 (7)	816 (43)	
Female		458 (54)	296 (53)	1040 (55)	0.57
Race/ethnicity [a]	Caucasian, Asian, Other	485 (57)	341 (62)	1191 (63)	0.001
	Black	171 (20)	91 (16)	257 (14)	
	Hispanic	192 (23)	122 (22)	441 (23)	
Transplant indication [b]	Biliary atresia	396 (47)	398 (72)	955 (51)	<0.001
	Other cirrhotic	144 (17)	62 (11)	312 (17)	
	Acute liver failure	7 (1)	10 (1)	60 (3)	
	Non-cirrhotic	254 (30)	71 (13)	446 (24)	
	Tumor	44 (5)	16 (3)	116 (6)	
Listed for kidney or pancreas		38 (4)	10 (2)	46 (2)	0.003
Insurance	Private/Self	331 (39)	250 (45)	969 (51)	<0.001
	Public	514 (61)	297 (54)	907 (48)	
	Missing	3 (<1)	7 (1)	13 (1)	
Laboratory values at listing, mean (SD)					
Albumin (g/dL) [c]		3.3 (0.7)	3.2 (0.7)	3.3 (0.7)	0.018
Bilirubin, total (mg/dL) [d]		9.7 (9.0)	11.1 (8.4)	7.6 (8.2)	<0.001
INR		1.4 (1.0)	1.4 (0.6)	1.5 (2.4)	0.35
Sodium (mmol/L)		136.8 (4.1)	136.7 (4.2)	137.4 (3.8)	<0.001
Creatinine, serum (mg/dL) [e]		0.41 (0.74)	0.35 (0.84)	0.38 (0.59)	0.27
PELD at listing, median (IQR)		15 (5–21)	12 (6–18)	5 (−4–15)	<0.001
Anthropometrics at listing, median (IQR)					
Weight z-score		−2.76 (−3.52– −1.76)	−2.28 (−2.64– −1.94)	−0.37 (−1.11– 0.44)	<0.001
	Missing	42 (5)	0 (0)	12 (1)	<0.001
Height z-score		−2.98 (−3.67– −2.44)	−2.05 (−2.36– −1.52)	−0.56 (−1.20–0.20)	<0.001
	Missing	47 (6)	1 (<1)	42 (2)	<0.001
BMI/Weight-for-length z-score [f]		−0.06 (−1.28–0.90)	−0.95 (−1.76–0.19)	0.22 (−0.60–1.02)	<0.001
	Missing	89 (10)	1 (<1)	54 (3)	<0.001
Ascites at listing	Moderate	83 (10)	66 (12)	250 (13)	0.08
	Slight/absent	464 (55)	277 (50)	969 (51)	
	Missing	301 (35)	211 (38)	670 (35)	

	Growth Failure (n=848)	Growth Failure Gap (n=554)	No Growth Failure (n=1889)	*P* value
On life support at listing [g]	31 (4)	9 (2)	42 (2)	0.030
Days on waitlist, median (IQR)	75 (28 – 182)	74 (32 – 166)	69 (25 – 178)	0.25
Calculated PELD at waitlist removal, median (IQR)	15 (6–23.5)	18 (10–25)	8 (−2–19)	<0.001
PELD at allocation, median (IQR)	24 (15–32)	24 (15–32)	24 (13–30)	0.68
Allocation PELD higher than calculated PELD at waitlist removal [h]	482 (57)	309 (56)	1209 (64)	<0.001

Abbreviations: IQR, interquartile range; SD, standard deviation, INR, International Normalized Ratio; PELD, pediatric end-stage liver disease; BMI, body mass index.

[a]Other race includes: Native American/Alaskan, Pacific Islander/Hawaiian, multiracial, and unknown.

[b]Other cirrhotic disease includes Alagille syndrome, α_1-antitrypsin deficiency, choledochal cyst, cystic fibrosis, glycogen storage disease, progressive intrahepatic cholestatic syndromes, total parenteral nutrition cholestasis, primary sclerosing cholangitis or primary biliary cirrhosis, idiopathic cholestasis, congenital hepatic fibrosis, autoimmune hepatitis cirrhosis, drug toxicity, hepatitis C cirrhosis, nonalcoholic steatohepatitis cirrhosis, unknown cirrhosis, chronic rejection/graft failure, inborn errors in bile acid metabolism, and Wilson disease. Acute liver failure includes diagnoses coded or text described as “acute liver failure,” “fulminant liver failure,” or “fulminant” without other specifying diagnosis. Other noncirrhotic disease includes primary hyperoxaluria, maple syrup urine disease, trauma, urea cycle defects, mitochondrial disease/encephalopathy, ethylmalonic encephalopathy, Budd-Chiari, Crigler-Najjar, tyrosinemia, and hyperlipidemia/homozygous hypercholesterolemia. Tumor includes hepatoblastoma, hepatocellular carcinoma, cholangioma, cholangiocarcinoma, Klatzkin tumor, and secondary hepatic malignancy.

[c]International System of Units (SI) conversion factors: to convert albumin to g/L, multiply by 10

[d]SI conversion factors: to convert total bilirubin to μmol/L, multiply by 17.104

[e]SI conversion factors: to convert serum creatinine to μmol/L, multiply by 88.4

[f]Weight-for-length was used for children < 2 years; BMI was used for children 2–11 years old.

[g]Life support includes a ventilator, breathing support, or dialysis. Patients listed as “on life support” for whom mode of life support was specified only as enteral or parenteral nutrition were excluded from this category.

[h]A child was determined to have received exception points if allocation PELD score > final calculated PELD lab score.

TABLE 2:

Predictors of waitlist mortality within 6 months of listing for transplant, multivariate analysis [ab]

Variable	SHR	95% CI	p-value
Growth failure group			
No growth failure	REF	REF	REF
Growth failure (z-score + PELD criteria)	1.45	0.90–2.35	0.129
Growth failure gap	1.78	1.05–3.02	0.032
Age at listing			
< 1 year	1.81	1.11 – 2.95	0.016
1–11 years	REF	REF	REF
Race/Ethnicity			
White/Asian/other [c]	REF	REF	REF
Black	0.81	0.43–1.53	0.514
Hispanic	1.80	1.11–2.93	0.018
Diagnostic condition category [d]			
Biliary atresia	REF	REF	REF
Other cirrhotic	2.05	1.20–3.51	0.009
Acute liver failure	4.14	1.90–9.01	<0.001
Non-cirrhotic	1.27	0.70–2.29	0.435
Tumor	3.67	1.61–8.38	0.002
Calculated PELD at listing (per 1-point increase) [e]	1.04	1.03–1.06	<0.001
On life support at listing [f]	5.23	2.74–9.99	<0.001

SHR, subhazard ratio; CI, confidence interval; REF, reference; PELD, pediatric end-stage liver disease.

[a] Variables with p-value <0.1 in the univariate analysis (See eTable 1) were considered for inclusion in the multivariate analysis.

[b] Model adjusted for UNOS region (REF = region 5). Only UNOS Region 6 had a statistically significant difference in subhazard ratio (SHR: <0.001; 95%CI: 0.000 - <0.001; p <0.001) data for other Regions not shown).

[c] Other race includes: Native American/Alaskan, Pacific Islander/Hawaiian, multiracial, and unknown.

[d] Other cirrhotic disease includes Alagille syndrome, α_1-antitrypsin deficiency, choledochal cyst, cystic fibrosis, glycogen storage disease, progressive intrahepatic cholestatic syndromes, total parenteral nutrition cholestasis, primary sclerosing cholangitis or primary biliary cirrhosis, idiopathic cholestasis, congenital hepatic fibrosis, autoimmune hepatitis cirrhosis, drug toxicity, hepatitis C cirrhosis, nonalcoholic steatohepatitis cirrhosis, unknown cirrhosis, chronic rejection/graft failure, inborn errors in bile acid metabolism, and Wilson disease. Acute liver failure includes diagnoses coded or text described as “acute liver failure,” “fulminant liver failure,” or “fulminant” without other specifying diagnosis. Other noncirrhotic disease includes primary hyperoxaluria, maple syrup urine disease, trauma, urea cycle defects, mitochondrial disease/encephalopathy, ethylmalonic encephalopathy, Budd-Chiari, Crigler-Najjar, tyrosinemia, and hyperlipidemia/homozygous hypercholesterolemia. Tumor includes hepatoblastoma, hepatocellular carcinoma, cholangioma, cholangiocarcinoma, Klatzkin tumor, and secondary hepatic malignancy.

[e] All PELD scores <0 all set to 0 for analysis.

[f] Life support includes a ventilator, breathing support, or dialysis. Patients listed as “on life support” for whom mode of life support was specified only as enteral or parenteral nutrition were excluded from this category.

TABLE 3:

Predictors of post-transplant mortality at 3 years among liver transplant recipients (n=3,041), multivariate analysis [ab]

Variable	HR	95% CI	p-value
Growth failure group			
No growth failure	REF	REF	REF
Growth failure (z-score + PELD criteria)	1.41	0.99–2.00	0.056
Growth failure gap	1.55	1.03–2.32	0.034
Age at listing			
< 1 year	1.93	1.35 – 2.76	<0.001
1–11 years	REF	REF	REF
Insurance type			
Private	REF	REF	REF
Public	1.52	1.10–2.10	0.011
Diagnostic condition category [c]			
Biliary atresia	REF	REF	REF
Other cirrhotic	2.32	1.51–3.56	<0.001
Acute liver failure	1.28	0.31–5.26	0.73
Non-cirrhotic	1.47	0.96–2.24	0.08
Tumor	4.03	2.28–7.13	<0.001
Ascites	1.64	1.10–2.45	0.016

HR, hazard ratio; CI, confidence interval; REF, reference; PELD, pediatric end-stage liver disease.

[a]Variables with p-value <0.1 in the univariate analysis (See eTable 2) were considered for inclusion in the multivariate analysis.

[b]Model adjusted for UNOS region (REF = region 5). Statistically significant differences in mortality risk were found for Region 3 (HR: 2.17; 95%CI: 1.21–3.88; p=0.009), Region 4 (HR: 2.96, 95%CI: 1.68–5.22, p<0.001), Region 10 (HR: 2.52, 95%CI: 1.33–4.76, p=0.004), and Region 11 (HR: 2.18, 95%CI: 1.06–4.49, p=0.034). Data for other Regions not shown.

[c]Other cirrhotic disease includes Alagille syndrome, α_1-antitrypsin deficiency, choledochal cyst, cystic fibrosis, glycogen storage disease, progressive intrahepatic cholestatic syndromes, total parenteral nutrition cholestasis, primary sclerosing cholangitis or primary biliary cirrhosis, idiopathic cholestasis, congenital hepatic fibrosis, autoimmune hepatitis cirrhosis, drug toxicity, hepatitis C cirrhosis, nonalcoholic steatohepatitis cirrhosis, unknown cirrhosis, chronic rejection/graft failure, inborn errors in bile acid metabolism, and Wilson disease. Acute liver failure includes diagnoses coded or text described as “acute liver failure,” “fulminant liver failure,” or “fulminant” without other specifying diagnosis. Other noncirrhotic disease includes primary hyperoxaluria, maple syrup urine disease, trauma, urea cycle defects, mitochondrial disease/encephalopathy, ethylmalonic encephalopathy, Budd-Chiari, Crigler-Najjar, tyrosinemia, and hyperlipidemia/homozygous hypercholesterolemia. Tumor includes hepatoblastoma, hepatocellular carcinoma, cholangioma, cholangiocarcinoma, Klatzkin tumor, and secondary hepatic malignancy.