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MELD-GRAIL-Na: Glomerular filtration rate and mortality on Liver-Transplant Waiting List

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Abbreviations: GRAIL: GfR Assessment In Liver disease; SCr: serum creatinine; CKD: Chronic Kidney Disease; CKD-EPI: *Chronic Kidney Disease* Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease; LT: Liver transplantation.

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Abstract

Background & Aims: Among patients with cirrhosis awaiting liver transplantation, prediction of waitlist (WL) mortality is adjudicated by Model for End Stage liver disease-sodium (MELD-Na) score. Replacing serum creatinine (Scr) with estimated glomerular filtration rate (eGFR) in the MELD-Na score may improve prediction of WL mortality, especially for women and highest disease severity.

Methods: We developed (2014) and validated (2015) a model incorporating eGFR using national data (n=17,095) to predict WL mortality. Glomerular Filtration Rate (GFR) was estimated using **G**f**R** **A**ssessment **I**n **L**iver disease (**GRAIL**) developed amongst patients with cirrhosis (Asrani SK Hepatology.2018; www.bswh.md/grail). Multivariate Cox proportional hazards analysis models were utilized to compare predicted 90-day WL mortality between MELD-GRAIL-Na (re-estimated bilirubin, INR, sodium and GRAIL) vs. MELD-Na.

Results: Within 3 months, 27.8% were transplanted, 4.3% died on the WL and 4.7% were delisted for other reasons. GFR as estimated by GRAIL (HR 0.382, 95% CI 0.344-0.424) and the re-estimated model MELD-GRAIL-Na (HR 1.212, 95% CI 1.199-1.224) were significant predictors of mortality or being delisted on the WL within 3 months. MELD-GRAIL-Na was a better predictor of observed mortality at highest deciles of disease severity (≥27-40). For score ≥32 (observed mortality 0.68), predicted mortality was 0.67 (MELD-GRAIL-Na) and 0.51 (MELD-Na). For women score ≥32 (observed mortality 0.67), predicted mortality was 0.69 (MELD-GRAIL-Na) and 0.55 (MELD-Na). In 2015, use of MELD-GRAIL-Na as compared to MELD-Na resulted in reclassification of 16.7% (n=672) of patients on the WL.

Conclusion: Incorporation of eGFR likely captures true GFR better than Scr, especially among women. Incorporation of MELD-GRAIL-Na instead of MELD-Na may impact outcomes for 12-17% awaiting transplant and affect organ allocation.

Though survival after liver transplantation (LT) is excellent in the current era, mortality while awaiting LT is high; this is often driven by deterioration in a patient's condition in the face of organ shortage. Accurate estimation of waitlist (WL) mortality is therefore crucial for patient care as well as decisions regarding transplantation. Current models of organ allocation rely on accurate assessment of medical urgency and mortality on the WL. This is estimated by predictive models Model for End stage Liver Disease with and without serum sodium (MELD and MELD-Na) using objective laboratory elements that includes bilirubin, INR, creatinine, and serum sodium. (1)

There are however, several limitations of current models based on urgency. The MELD and MELD-Na are excellent predictors of WL mortality. However, as compared to when these were developed over a decade ago, the transplant population has changed.(2) Patients in the current era (2016 vs. 2006) are sicker (MELD score≥30, 3.2 vs. 0.4%), older (age ≥65 years, 24% vs. 12%), have more co-morbidities (diabetes, 28.8% vs. 23.5%) and are less likely to be transplanted for viral hepatitis (17.6% vs. 25.2%).(2-4) Whether the performances of current models are similar in the current era is unknown. Second, performance of current models may be limited in patients with the highest disease severity, where reliance on these models matter most for decisions regarding transplant. Finally, gender disparity is a known limitation of current models; women are disadvantaged under current organ allocation given that renal dysfunction, an integral part of predictive models, may not be as adequately captured by changes in Scr.(5-7)

Renal dysfunction is a primary driver of morbidity and mortality among patients awaiting LT.(8) Though incorporation of both Scr and sodium in the MELD-Na score serves as surrogates of glomerular filtration rate, they do not completely capture the risk attributed to renal dysfunction in the setting of liver disease.(9),(10) Addition of glomerular filtration rate in lieu of Scr may further improve prediction of WL mortality. (9)

Methods

Aim: The primary aim of the study was to assess whether incorporation of eGFR in the MELD and MELD-Na score in lieu of Scr improves prediction of mortality on the WL especially among women. The secondary aim was to assess changes in performance of MELD and MELD-Na score over time.

Data source: We examined all data submitted to Scientific Registry of Transplant Recipients (SRTR) on adult (age≥18 years) recipients in US listed for a receipt of LT alone during 2014 and 2015.(11) Patients that were listed as status 1 or fulminant hepatic failure or were re-transplantation or dual organ transplant candidates were excluded. The SRTR data system includes data on donors, waitlisted candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). Specifically, it contains relevant variables (bilirubin, INR, creatinine, sodium) as well as outcomes (death on the WL, withdrawal from the WL, and transplantation). The study was approved by the institutional IRB.

Estimation of GFR:

Estimated GFR was introduced in a novel model to predict WL mortality.

GRAIL: We recently developed a model for **G**F**R** **A**ssessment **I**n **L**iver disease (**GRAIL**) before and after liver transplantation (LT).(www.bswh.md/grail).(12) GRAIL was derived in cirrhotic patients using objective variables (creatinine, blood urea nitrogen, age, gender, race, albumin) to estimate GFR. It was developed and validated against measured GFR by iothalamate clearance (n=12,122) collected by protocol at our center and validated using national data (n=68,217). BUN is not included in national data and imputation was performed using center data (**see supplementary methods**). (12) GRAIL had less bias, was more accurate and precise as compared to CKD-EPI, MDRD-4 and MDRD-6 at time points before/after LT. It was a better predictor of incident chronic kidney disease and need for kidney after liver transplantation. Simultaneous calculations were made for eGFR using MDRD-6 and CKD-EPI equations.(13, 14)

Statistical Methods

Model building: We used data from 2014 to develop a predictive model and data from 2015 to independently validate the model. The primary outcome was WL mortality or delisting within 3 months of listing. Specifically, patients that were delisted for deterioration in condition (too sick to transplant) or unspecified other reasons not related to improvement in status were also considered as having the event of interest. Other patients were censored at 90 days after WL registration, receipt of LT within 90 days or time of withdrawal from the WL.

The primary predictors of interest were the MELD score(15), MELD-Na score(1) and newly derived MELD-GRAIL and MELD-GRAIL-Na. We examined the relationship between bilirubin, INR, sodium and GRAIL with risk of death. Smoothing splines were utilized to determine the non-linear association of each variable with risk of death, adjusted for the other variables. Based on clinical judgement and assessing the relationship of the variable of interest using splines, upper and lower caps were created. Multivariable Cox proportional hazards analysis models were utilized to assess the association between MELD-GRAIL

(bilirubin, INR, GRAIL) and MELD-GRAIL-Na (bilirubin, INR, sodium and GRAIL) and 90-day mortality on the WL. The score was adjusted to values between 6 and 40 by rescaling.

The final equations were

MELD-GRAIL= 28.848 + 11.183*log (inr) + 3.150*log(br) -5.078*log (grail).

MELD-GRAIL-Na= 29.751 + 10.836* log (inr) + 3.039* log(br) -5.054* log (grail)-0.372*log(Na)

where the lower and upper bounds were bilirubin in mg/dL (1, infinity), INR (1,3), sodium in meq/L (125,140), GRAIL ml/min/1.73m^2 (15, 90), and the presence of dialysis was assigned a GFR=15 ml/min/1.73m^2.

Subset analysis: We also examined the performance of the various models by gender as well as categories of disease severity (6-15, 15-24, 25-34, ≥35).

Other Analysis: We examined several alternatives to the MELD-GRAIL and MELD-GRAIL-Na model. We examined whether simple addition of gender or race to existing MELD score improved the model. We further examined whether addition of any eGFR equation (e.g. CKD-EPI or MDRD-6) instead of GRAIL improved the performance characteristics of a model to predict WL mortality. For this latter scenario, the relation between eGFR, bilirubin, INR and sodium with mortality were re-estimated and similar upper and lower bounds were applied.

Discrimination and calibration: Model characteristics were assessed in 2015 data. Discrimination was assessed based on Harrell's concordance statistic. The bootstrap

method using 100 samples was used to calculate p-values to compare Harrell's concordance statistic. Discrimination assesses the extent to which a predictive model (e.g. MELD-GRAIL-Na) predicts a higher probability of death on the WL among patients that do than do not have the event. MELD based scores already have high discrimination.(1, 15) In cases whereby c-statistic with current models may already be high, discrimination utilizing the c –statistic may be insensitive to changes in absolute risk estimates.(16) Hence, calibration is equally important. Calibration reflects the extent to which absolute risk (predicted versus observed) is correctly estimated by a new model (e.g. MELD-GRAIL-Na) as compared to the old model (MELD-Na). We assessed the relative improvement in calibration using Hosmer–Lemeshow test statistic modified to apply to censored data.(17-19) We compared the performance of MELD-Na and MELD-GRAIL-Na by examination of observed (Kaplan Meier estimates) and predicted mortality (Cox regression) within deciles of risk. We used D'Agnostino and Nam's modification of the Hosmer-Lemeshow formula to calculate the test statistic and evaluated it using a chi-square test with 9 degrees of freedom. Follow-up within-decile comparisons were used to determine which deciles were best described by each model.

Finally, we also calculated the absolute net reclassification index (aNRI) by MELD-GRAIL-Na as compared to MELD-Na.(16) The absolute NRI calculates the absolute number of patients correctly reclassified and consists of the net reclassification of patients with the event (correctly identify patients with WL mortality) and net reclassification of patients without the event (correctly identify patients alive on the WL) divided by the total number of patients. It ranges from -100% to 100% representing the percent of patients incorrectly or correctly reclassified.

Reporting of the data followed guidance provided by "Standards for Reporting Diagnostic accuracy studies" (STARD). All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics (Table 1): There were 17,095 patients in the study. Overall, the median (interquartile) age at listing was 57 years (33-68), 37.8% female, 70.5% Caucasian, and calculated MELD at listing 19 (7-40). Within 3 months, 27.8% were transplanted, 4.3% died on the WL and 4.7% were delisted for other reasons. There were no clinical differences between 2014 and 2015, except that the percentage of persons transplanted for hepatitis C decreased from 20.5% to 16.0% with a concomitant increase in alcohol related disease (25.4% in 2014 and 28.1% in 2015). More patients were transplanted within 3 months in 2015 as compared to 2014 (29.4% vs. 26.1%, $p<0.001$)

Performance of MELD and MELD-Na, 2005-2015

The performance of MELD and MELD-Na remained excellent, though worsened over time. **(Figure 1)** For women, discrimination as measured by the concordance statistic decreased from 0.87 to 0.81 from 2005 to 2015 for both scores. The performance for MELD and MELD-Na scores varied by disease severity. The concordance statistic decreased from 0.69 to 0.61 for MELD 15-24. For MELD 25-34 the concordance statistic increased slightly from 0.61 to 0.62, and for MELD 35-40 it increased from 0.53 to 0.57.

Model performance, 2015

GFR (lower GFR worse) as estimated by GRAIL (HR 0.382, 95% CI 0.344-0.424) was a significant predictor of WL mortality even after adjusting for other relevant factors. MELD-

GRAIL (HR 1.209, 95% CI 1.197-1.221) and MELD-GRAIL-Na (HR 1.212, 95% CI 1.199-1.224) were significant predictors of mortality on the WL.(**Table 2**) Given that MELD-Na is the current model used for organ allocation, model performance for MELD-GRAIL-Na as compared to MELD Na is provided below. Similar findings were noted for MELD-GRAIL versus MELD.

Discrimination:

Overall: MELD-GRAIL-Na was a significant predictor of WL mortality (**Figure 2**) MELD GRAIL Na (c=0.83) had better discrimination than MELD (c=0.81) and MELD-Na (c=0.82) (p<0.001)

Strata of MELD **(Supplemental Table 1)*:*** Discrimination by MELD-Na was lower when limited to strata of severity. Discrimination by MELD-GRAIL-Na was similar for scores 15-24 but significantly better for scores above 25 as compared to MELD-Na.

Gender: Similarly, among women MELD-GRAIL-Na had higher discrimination across all subgroups. As an example, discrimination for low MELD score (0-14) was 0.58 vs. 0.52, p<0.001 and for MELD score >35 was 0.59 vs. 0.55, p<0.001. Discrimination was better for older women (age >60 years) (c=0.81 vs. 0.80 p<.001) and for the sicker older women (age >60, MELD>35), 0.58 vs. 0.53, p<0.01. Malnutrition may also play a role. The number of patients with a BMI less than 18 was low (1.54%). However, performance was better for lean and underweight women combined (c=0.75 vs. 0.72, p<0.01).

Calibration:

Overall calibration was improved (MELD-GRAIL Na chi-square 101.9, p<0.001 vs. MELD-Na chi square 220.8, <0.001) as assessed by the Hosmer–Lemeshow test statistic. **Figure 3a** shows differences in observed and predicted mortality between MELD GRAIL-Na versus MELD-Na by deciles of disease severity. For the lowest deciles of disease severity, both

MELD-GRAIL-Na and MELD-Na underestimated disease severity. For low deciles of disease severity (scores 14-22), the differences between observed and predicted mortality were lowest for MELD-Na. MELD-GRAIL-Na was a better predictor of observed mortality at highest deciles of disease severity (≥27-40). For score ≥32 (observed mortality 0.68), predicted mortality was 0.67 (MELD-GRAIL-Na) and 0.51 (MELD-Na). For women, MELD-GRAIL-Na was a better predictor of observed mortality starting at a score of 23.(**Figure 3b**) Among the sickest patients, for women score ≥32 (observed mortality 0.67), predicted mortality was 0.69 (MELD-GRAIL-Na) and 0.55 (MELD-Na). Further, classification by MELD-GRAIL-Na as compared to MELD-Na did not shift risk of mortality from the pre transplant setting to post transplantation. (**Supplemental figure 1**).

Finally, we examined the absolute Net Reclassification Index (aNRI) to quantify differences in observed versus predicted events. Overall, use of MELD-GRAIL-Na as compared to MELD-Na resulted in reclassification of 16.7% of patients on the WL. Applied to 2015 data, this would suggest that 672 patients would have been reclassified as either having higher or lower risk of mortality as compared to the MELD-Na score. The aNRI increased by 10.9% and 12.3% for women and MELD>35, respectively.

Alternative models: Addition of gender (aNRI 1.96%) or race alone to MELD or MELD Na did not improve performance of models. Additionally, re-estimating the equation using CKD-EPI (aNRI 7.4%) or MDRD-6 (aNRI 15.5%) also improved calibration. However, improvement in calibration was highest for MELD-GRAIL-Na. We compared MELD-MDRD6-Na versus MELD GRAIL-Na. Incorporation of MELD GRAIL-Na had a higher aNRI as compared to MELD-MDRD6-Na.(difference 3.8%). MELD-GRAIL-Na was a better predictor of observed mortality as compared to MELD-MDRD-6-Na which overestimated morality at highest deciles of disease severity. For score ≥32 (observed mortality 0.68), predicted mortality was 0.67 (MELD-GRAIL-Na) and 0.72 (MELD-MDRD-6-Na).

We also examined whether the performance would be impacted by select patient characteristics. When limited to those with ascites, overall calibration was improved by MELD-GRAIL-Na (chi square 92.324, $p<0.01$) as compared to MELD-Na (chi square =200.411, $p<0.01$). Among patients with ascites, MELD-GRAIL-Na was a better predictor of observed mortality at highest deciles of disease severity (≥27-40). **(Supplemental Figure 2)** Similar patterns were seen when limited to patients with alcohol related cirrhosis (**Supplemental figure 3**) or NASH/cryptogenic cirrhosis. (**Supplemental figure 4**) In addition, performance was similar when limited to African Americans as compared to non-African Americans.

Discussion

Accurate prediction of mortality among patients awaiting transplantation is important as it forms the backbone of urgency-based organ allocation. This need is further highlighted by recent approved changes in liver distribution policy that adjudicates sharing of organs for patients with the highest disease severity. (https://optn.transplant.hrsa.gov/news/optnunos-board-approves-updated-liver-distribution-system/) First, MELD and MELD-Na remain excellent predictors of WL mortality even in the current era, though decreased over the last decade. Second, performance of current models may be suboptimal when stratified by disease severity and in relevant subsets (e.g. by gender). Third, renal dysfunction is the penultimate expression of risk for mortality in the natural history of decompensated cirrhosis. (20-23) In independent validation, incorporation of eGFR by any of the current estimating equations instead of Scr improves calibration. However, among eGFR equations, incorporation of GRAIL has the highest calibration with improvement in the net reclassification and predicted mortality aligning closest with expected mortality. Finally, incorporation of eGFR allows for improved discrimination and calibration among women and those with highest risk of premature mortality on the WL. In addition, mortality after LT is not

worsened by reclassification by MELD-GRAIL-Na as compared to MELD-Na. We estimate that incorporation of these models may impact outcomes for 12-17% of registrants awaiting transplant. MELD-GRAIL-Na may serve as an improvement in the model for prediction of WL mortality and organ allocation policy compared to current state.

Women may be currently disadvantaged in a system that uses MELD based organ allocation.(24) This may be driven by several factors including differences in height, socioeconomic factors and inability for Scr to accurately capture renal dysfunction given the prevalence of lower muscle mass. Though eGFR still includes serum creatinine, addition of gender specific eGFR may abrogate some of the disparity. Indeed, MELD-GRAIL-Na had better performance across all strata of disease severity. This superseded a model that simply added gender suggesting that the accurate estimation of renal function in women is important. The ability to further improve performance in the older, underweight and sicker women may also be beneficial.

Finally, performance of prior models in more recent waitlisted patients may be less optimal than previously thought. First, over time the performance of MELD and MELD-Na has decreased. Performance of MELD and MELD-Na may have changed over time which aligns with changes observed in center practices and patient population being evaluated for transplantation in the current era. Second, though over the entire range of patients, a model may be able to predict that a registrant with a higher MELD-Na score has an elevated risk of mortality than someone with lower MELD-Na score (e.g. score 40 vs. 6), the ability of any statistical model to parse out differences in relevant strata (e.g. 35 vs. 32) may be difficult. Among patients with high MELD-Na scores, extra hepatic factors such as infection may play a role to diminish model performance.(25-27) Hence, reliance of any singular predictive model may be fraught by influence of other drivers of mortality. Regardless, incorporation of eGFR appears to improve prediction of WL mortality.

Our study has several strengths. First, we examined current national data and confirmed our findings in an independent data set. We re-estimated the model coefficients to assess its impact in the current era. Specifically, we examined deciles of disease severity that align with relevant considerations under the recently approved organ allocation policy. We restrained use to parsimonious variables that are routinely collected agnostic of diagnosis. We explored gender disparity and assessed whether incorporation of eGFR could mitigate some of the differences.

There were limitations of modeling. We were unable to use measured GFR or other surrogate biomarkers (e.g. cystatin C), that may better capture true renal function. Indeed, addition of measured GFR may also obviate the need for addition of serum sodium in the model as is currently done. (9) However, mGFR is not universally obtained and is cumbersome to obtain. Addition of GRAIL, developed among patients with cirrhosis using measured GFR by iothalamate clearance as a gold standard, may provide less bias and overestimation. Serum cystatin C is not routinely collected across centers; further studies are ongoing whether cystatin based MELD score may be even better for organ allocation.(28) It is unclear how changes in prognostic variables, such as albumin administration will impact outcomes. It is also unclear how MELD-GRAIL-Na may affect decisions regarding simultaneous liver kidney transplantation. Our next step is to assess the impact of the proposed model with SRTR data using the liver simulated allocation model (LSAM), to study the impact of our alternate model on organ allocation. The conclusions are also limited by analyses of large datasets that are retrospective in nature and summarize practice patterns. These inherently do not account for regional variation, center-based variation and diverse listing practices. In addition, patients that are on the waitlist may be systematically different that similar patients that never get listed. Prospective studies that harmonize listing practices and homogeneous methods of determining renal function may needed, albeit difficult to conduct.

In summary, incorporation of eGFR with the GRAIL model in the MELD or MELD-Na score may improve prediction of mortality on the WL. Further studies are needed to assess whether MELD-GRAIL-Na may serve to improve organ allocation through liver simulated allocation models as well as in when applied to data outside of the United States.

Figures

Figure 1: Performance of MELD and MELD-Na over time, 2005-2015

Figure 2: Association of MELD-GRAIL-Na and mortality on the waitlist

Figure 3a: Comparison of observed as compared to predicted mortality for MELD-GRAIL-Na as compared to MELD-Na across deciles of risk scores overall. Hosmer-Lemeshow p<0.001

Figure 3b: Comparison of observed as compared to predicted mortality for MELD-GRAIL-Na as compared to MELD-Na across deciles of risk scores among women. Hosmer-Lemeshow p<0.001

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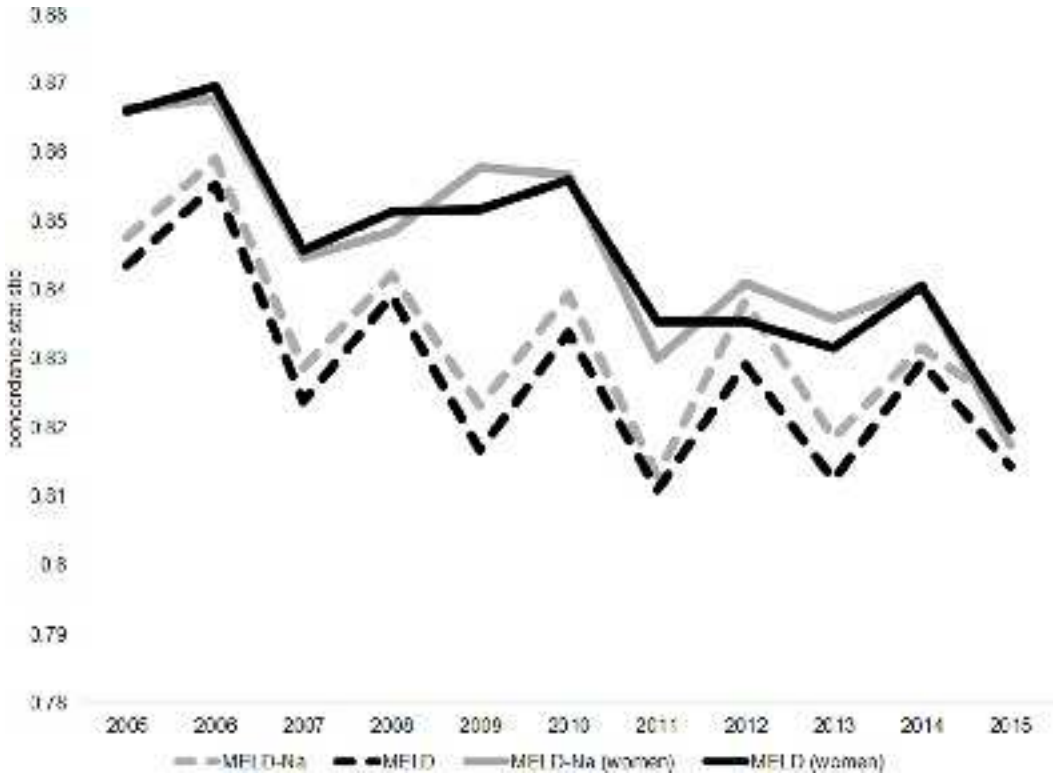
Table 1: Characteristics of patients on the waitlist, 2014-2015

	Overall	2014	2015	P (2015 vs 2014)
	17095	8581	8514	
Age	57.00 [33.00, 68.00]	57.00 [33.00, 68.00]	57.00 [33.00, 68.00]	0.192
Gender	6464 (37.8)	3240 (37.8)	3224 (37.9)	0.8871
Race/Ethnicity				0.2911
Asian	693 (4.1)	343 (4.0)	350 (4.1)	
African American	1499 (8.8)	745 (8.7)	754 (8.9)	
Hispanic	2577 (15.1)	1246 (14.5)	1331 (15.6)	
Other	267 (1.6)	136 (1.6)	131 (1.5)	
Caucasian	12059 (70.5)	6111 (71.2)	5948 (69.9)	
Etiology				<.0001
Alcohol	4572 (26.7)	2183 (25.4)	2389 (28.1)	
Cryptogenic/NASH	3413 (20.0)	1650 (19.2)	1763 (20.7)	
HCV	3124 (18.3)	1763 (20.5)	1361 (16.0)	
Other	5986 (35.0)	2985 (34.8)	3001 (35.2)	
Median MELD at listing	17.00 [7.00, 40.00]	17.00 [7.00, 40.00]	17.00 [7.00, 40.00]	0.146
Median MELD at LT	30.00 [10.00, 40.00]	30.00 [10.00, 40.00]	30.00 [9.00, 40.00]	0.407

Dialysis	1590 (9.3)	743 (8.7)	847 (10.0)	0.004
Serum Creatinine (mg/dL)	1.00 [1.00, 4.00]	1.00 [1.00, 4.00]	1.00 [1.00, 4.00]	0.089
Bilirubin	2.80 [1.00, 27.60]	2.80 [1.00, 26.20]	2.80 [1.00, 28.60]	0.327
INR	1.42 [1.00, 3.38]	1.43 [1.00, 3.30]	1.40 [1.00, 3.40]	0.491
Serum Na (mEq/L)	137.00 [127.00, 143.00]	137.00 [127.00, 143.00]	137.00 [127.00, 143.00]	0.337
Albumin (mg/dL)	3.10 [2.00, 4.30]	3.10 [2.00, 4.20]	3.10 [2.00, 4.30]	0.001
Diabetes	4800 (28.1)	2350 (27.4)	2450 (28.8)	0.0446
Transplanted within 3 months	4744 (27.8)	2239 (26.1)	2505 (29.4)	<0.001
Delisted within 3 months	799 (4.7)	425 (5.0)	374 (4.4)	
Died within 3 months on waitlist	739 (4.3)	739 (4.3)	367 (4.3)	

Table 2: Association between components of MELD –GRAIL and MELD-GRAIL-Na and waitlist mortality.

	Hazard Ratio (95% CI)	P
INR	8.329 (6.335,10.951)	<.0001
Bilirubin	1.817 (1.675, 1.970)	<.0001
GRAIL	0.382 (0.344, 0.424)	<.0001
MELD-GRAIL	**1.209 (1.197, 1.221)**	**<0.001**
INR	8.064 (6.127,10.613)	<.0001
Bilirubin	1.791 (1.651, 1.944)	<.0001
GRAIL	0.380 (0.342, 0.423)	<.0001
Sodium	0.017 (0.002, 0.146)	<.0001
MELD-GRAIL-Na	**1.212 (1.199, 1.224)**	**<.0001**



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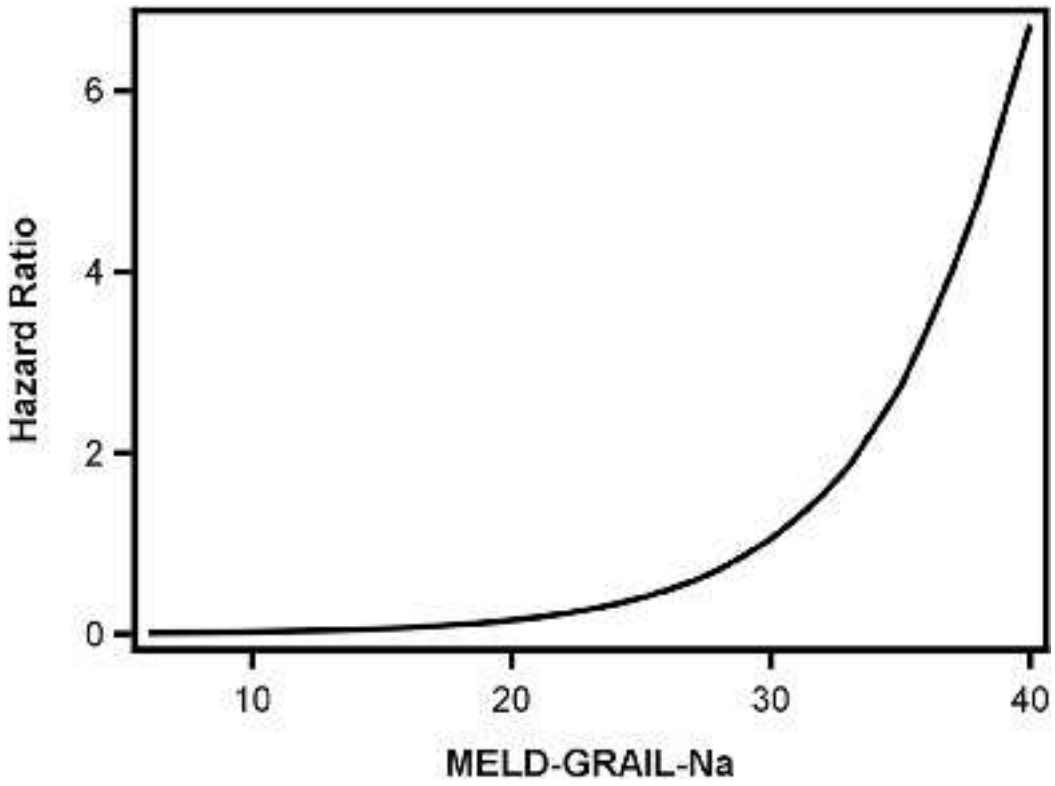

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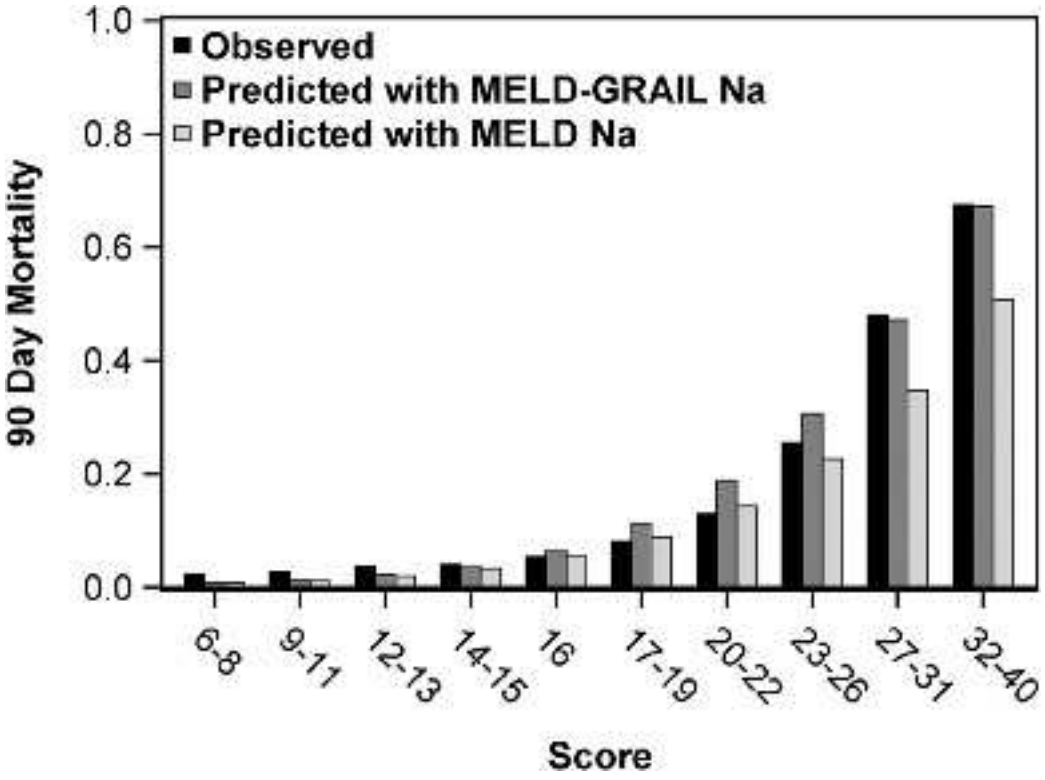

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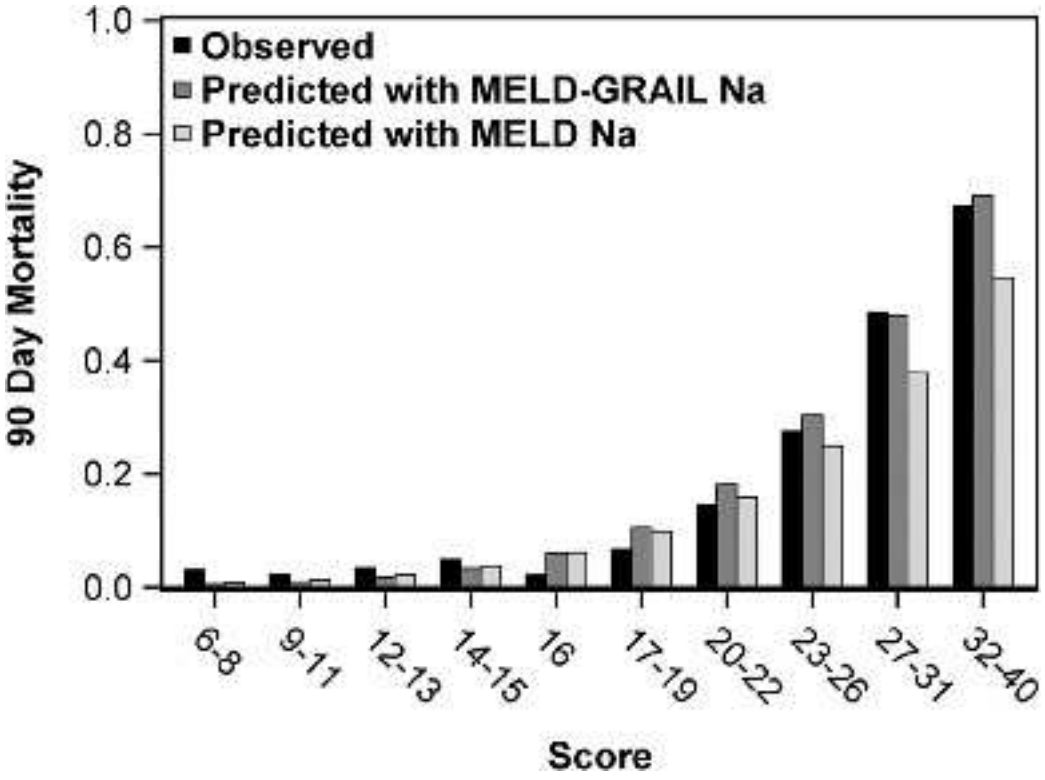

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