IMPACT OF MODEL FOR END STAGE LIVER DISEASE SODIUM (MELD-NA) PRIORITIZATION FOR LIVER TRANSPLANTATION ON WAITLIST SURVIVAL

By

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A THESIS

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CERTIFICATE OF APPROVAL

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LIST OF ABBREVIATIONS

CI	Confidence interval
HCC	Hepatocellular carcinoma
IQR	Interquartile range
LT	Liver transplant
MELD	Model for End-Stage Liver Disease
MELD-Na	Sodium MELD exception
OPTN	Organ Procurement and Transplantation Network
STAR	Standard Transplant Analysis and Research
TX	Transplant
UNOS	United Network for Organ Sharing
WL	Waitlist

ABSTRACT

Background: Patients are prioritized for liver transplantation (LT) by their anticipated 90-day waitlist mortality using the MELD score, however the MELD underestimates waitlist mortality when hyponatremia is present. A revised MELD that incorporates the added mortality due to hyponatremia, the MELD-Na, was shown to reduce waitlist mortality in hyponatremic patients in a modeling study. In UNOS Region 6, regional agreement has resulted in prioritization of cirrhotic patients with hyponatremia for LT using a MELD-Na exception since 2008.

Research question: Does the use of a MELD-Na exception decrease 90-day mortality for hyponatremic patients on the liver transplant waitlist in Region 6.

Specific Aims:

(1) Identify and describe characteristics of the following groups from the UNOS transplant database:
    a. 'MELD-Na' group: Region 6 patients who received a MELD-Na exception
    b. 'Normonatremic' group: Region 6 normonatremic patients
    c. 'Hyponatremic without MELD-Na' group: Region 6 hyponatremic patients who did not receive a MELD-Na exception
(2) Evaluate whether patients receiving MELD-Na exceptions in Region 6 have similar 90 day waitlist mortality as normonatremic patients in Region 6.
(3) Compare waitlist mortality in patients with MELD-Na exceptions to hyponatremic patients who did not receive a MELD-Na exception.
(4) Evaluate the influence of other predictors on waitlist mortality, using competing risk regression.

Methods: In the UNOS registry, we selected all patients listed for liver transplant in Region 6 from January 2010 to June 2014 who received a MELD-Na prioritization exception based on regional agreement. We compared waitlist mortality of the groups using competing risk regression.

Results: The sub hazard ratio for death was 52% lower in the MELD-Na group relative to the hyponatremic without exceptions group when taking into account the competing risk of LT and adjusted for MELD score, age, and encephalopathy (SHR=0.48, 95% CI 0.27-0.87, p=0.016). The sub hazard ratio of death was 43% lower in the MELD-Na group compared to the normonatremic group, taking into account the competing risk of LT, and adjusted for MELD score, year on the waitlist, age, and etiology (SHR=0.57, 95% CI 0.30 - 1.07, p=0.081). Age was an influential predictor in normonatremic and hyponatremic patients without an exception.

Conclusion: There is a strong association of decreased mortality in hyponatremic patients who received a MELD-Na exception compared to hyponatremic patients without the exception. Therefore, the MELD-Na score had the intended effect of decreasing waitlist mortality in hyponatremic patients. I did not find a significant difference in mortality between MELD-Na exception patients and normonatremic patients, but the evidence for this lack of difference is not strong, and there may be a difference that this study could not detect. This raises the question of whether the MELD-Na exception conferred a waitlist survival benefit to hyponatremic patients. Before being adopted as the new determinant for LT priority there should be further research examining a possible survival benefit conferred by the MELD-Na to hyponatremic patients.

INTRODUCTION

Liver transplantation is the most effective treatment for patients with end-stage liver disease. Patients who are waitlisted for liver transplantation in the United States are closely tracked by the United Network for Organ Sharing (UNOS). The allocation of organs for liver transplantation is prioritized by medical urgency, which is determined by the Model for End-stage Liver Disease (MELD) score, which has been shown to predict 90-day waitlist mortality in patients awaiting liver transplantation.[1] Since 2002, the MELD score has been used for liver allocation and MELD-based allocation and has led to a marked reduction in deaths on the transplant waitlist.[1] The MELD score incorporates 3 laboratory values: serum bilirubin, serum creatinine, and the international normalized ratio (INR) to generate a score ranging from 6 to 40, with higher scores representing more severe liver disease and correlating with lower 90-day survival.[1] Patients awaiting liver transplant (LT) with higher MELD scores have higher priority for liver transplantation.[1]

The MELD score does not accurately reflect the risk of death in hyponatremic patients on the LT waitlist (WL). Low sodium is associated with complications of cirrhosis such as impaired renal function, ascites, and a high mortality rate, [2-4]. It has been shown that serum sodium is a significant predictor of early mortality in patients awaiting liver transplantation,[5-8] and the serum sodium is not incorporated into the MELD score.

It has been proposed that assignment of priority according to a MELD score that incorporates serum sodium may more effectively prioritize patients with low sodium for liver transplantation. In 2008, Kim et al. developed a MELD-Na score that better predicted 90-day mortality in patients with low serum sodium than the standard MELD score[9]. They predicted that the use of this MELD-Na score would prevent 7% of LT waitlist deaths[9].

Compared to the MELD score, the MELD-Na has shown to be the best predictor of 90-day drop off from the LT waitlist. The MELD-Na score used by Kim et al. is calculated as follows: MELDNa = MELD − Na − [0.025 × MELD × (140 − Na)] + 140, rounded to the nearest integer.[9]

Since 2008, Organ Procurement and Transplantation Network (OPTN) Region 6 (Alaska, Hawaii, Idaho, Montana, Oregon, and Washington) has been using MELD-Na exceptions. Region 11 has incorporated the MELD-Na score with capping of the MELD points at 22.[10] A prospective study comparing the waitlist mortality of MELD-Na exception patients in region 11, standard MELD patients in region 11, and standard MELD patients in other regions found that MELD-Na scored patients were transplanted faster and had lower waitlist mortality compared to standard MELD scored patients in other regions[10]. In 2013, The Oregon Procurement and Transplantation Network (OPTN) Liver and Intestinal Organ Transplantation Committee proposed adding serum sodium to the MELD score for all patients using the MELD-Na equation.[11] The proposed MELD-Na score allows a maximum of 40 points without capping of points received.[11] waitlist mortality in patients receiving a MELD-Na exception in a manner similar to that proposed for adoption by OPTN has not yet been assessed. Furthermore, waitlist mortality has not been assessed when taking into account the competing risk of transplantation. Region 6 has been granting MELD-Na exceptions for patients with serum sodium <130 on the LT waitlist in a manner similar to that proposed for adoption, without capping of scores. MELD-Na exceptions are not automatically granted in Region 6, and only approved for patients who applied for the MELD-Na exception. This would allow for a natural control group to which to compare MELD-Na patients. The MELD-Na score used by Region 6 is the same as that used by Kim et al.'s prediction model.[9]

Assessment of waitlist mortality in patients with a MELD-Na exception in Region 6, and taking into account the competing risk of transplantation, would help determine if OPTN's proposed MELD-Na score decreases waitlist mortality.

A MELD score with the incorporation of serum sodium (MELD-Na) has been proposed for adoption as the new determinant for LT allocation based on prediction models. waitlist mortality of the MELD-Na has not been assessed in OPTN regions that grant MELD-Na exceptions using the method proposed by OPTN. Region 6 has been granting MELD-Na exceptions since 2008 using a method similar to that proposed for adoption. Determining if OPTN's proposed MELD-Na score decreases waitlist mortality would provide support to accept a new method of liver allocation that more accurately predicts waitlist mortality than the current MELD score.

RESEARCH QUESTION AND SPECIFIC AIMS

Does the use of a MELD-Na exception decrease 90-day mortality for hyponatremic patients on the liver transplant waitlist in Region 6.

Specific Aims

(1) Identify and describe characteristics of the following groups from the UNOS transplant database:
    a. 'MELD-Na' group: Region 6 patients who received a MELD-Na exception
    b. 'Normonatremic' group: Region 6 normonatremic patients
    c. 'Hyponatremic without MELD-Na' group: Region 6 hyponatremic patients who did not receive a MELD-Na exception
(2) Evaluate whether patients receiving MELD-Na exceptions in Region 6 have similar 90 day waitlist mortality as normonatremic patients in Region 6.
(3) Compare waitlist mortality in patients with MELD-Na exceptions to hyponatremic patients who did not receive a MELD-Na exception.
(4) Evaluate the influence of other predictors on waitlist mortality, using competing risk regression.

I hypothesized that there would be no difference in waitlist mortality for persons who have received a MELD-Na exception when compared to normonatremic persons. I also hypothesized that waitlist mortality would be lower in those who have received a MELD-Na exception compared to hyponatremic patients without a MELD-Na exception.

METHODS

Data source

I used the Standard Transplant Analysis and Research (STAR) registry, which is maintained and prospectively collected by United Network for Organ Sharing (UNOS) for the Organ Procurement and Transplantation Network (OPTN), under contract with the Health Resources and Services Administration (HRSA) of the U.S. Department of health and Human Services. This dataset includes prospectively collected data for all solid organ transplants reported to OPTN since October 1st, 1987[12]. The STAR dataset also includes data on the Death Master File (DMF) of the Social Security Administration (SSA) which was used to confirm and ascertain mortality. The STAR dataset in this dataset was up to date as of December 15, 2014.

Study design

This is a retrospective cohort study, performed as a secondary analysis using the prospective STAR registry.

Study population

The study population included all U.S. patients listed for first-time cadaveric liver transplantation from January 1st, 2010 to June 30th, 2014. A start date of 2010 was chosen because that is when the majority of MELD-Na exceptions began being granted in Region 6. The study excluded pediatric patients (<18 years of age), prior LT recipients, patients with hepatocellular carcinoma, patients listed as status 1A, patients with MELD exceptions other than a MELD-Na exception, and split liver recipients. Three study groups were selected.

1. **'MELD-Na' group**: Region 6 patients who received a MELD-Na exception.

2. '**Normonatremic' group**: Region 6 normonatremic patients selected by a random sample of MELD scores within the same range of the MELD-Na scores based on the initial distribution of the MELD-Na scores in Group 1.
3. **'Hyponatremic without MELD-Na**' group: Region 6 hyponatremic patients who did not receive a MELD-Na exception.

The normonatremic and hyponatremic without MELD-exception group served as control groups for the MELD-Na group. Normonatremic is defined as serum sodium ≥ 130. Hyponatremia is defined as serum sodium <130.

Predictors and outcomes

The primary outcome was waitlist mortality, defined as death after waitlist registration and before transplantation. waitlist mortality included patients who died while on the LT waitlist and patients who were removed from the waitlist and subsequently died. Patients who were removed from the waitlist as too sick to be transplanted were not counted as dead without a documented death because less than 35% of these patients have been shown to have died within 90 days of delisting.[13] Receipt of liver transplantation was included as a competing outcome to waitlist mortality. The rationale for including a competing outcome is described in the statistical analysis section below.

Predictors that have been shown to influence mortality in patients on the LT waitlist were included. Covariates that have been shown to be predictors of death in cirrhotic patients include increasing age,[14] female gender,[15] ascites,[14] encephalopathy[14], and alcoholic etiology.[14] Patients with higher MELD score has been shown to have increased waitlist mortality[1] and higher diseased donor LT rates.[16] Female gender has been shown to have

lower rates of liver transplantation[16] and increased risk of death on the LT waitlist.[15] Hispanic ethnicity,[17] Asian ethnicity at high MELD score,[17] dialysis,[16] and blood type O[18] have been shown to have lower rates of liver transplantation. Later eras on the transplant waitlist, compared to earlier eras, have been shown to have longer time to transplantation, however the risk of death is not necessarily different.[18] Etiology of hepatitis C has been shown to have higher transplantation rates.[16] Presence of ascites or encephalopathy have been shown to be predictors of death on the LT waitlist and associated with higher rates of diseased donor liver transplantation.[16] Age has also been shown to be associated with higher rate of diseased donor liver transplantation.[16]

Covariates therefore included in the analysis were age, gender, ethnicity, etiology of liver disease, presence of clinical characteristics (ascites, encephalopathy, dialysis status), blood type, MELD score, and the year the patient was on the waitlist when entering the study. The UNOS MELD score was categorized as tertiles based on the distribution of the sodium MELD exception score granted to the MELD-Na group. Clinical characteristics were dichotomous variables indicating presence or absence of the clinical characteristic. Ethnicity was categorized into Caucasian and other ethnicities. Etiology of liver disease was categorized into viral and non-viral etiology. Blood type was categorical indicating blood type A, B, AB, or O. Age and waitlist year were continuous variables. For a summary of the independent variables, please see Methods Table 1 below.

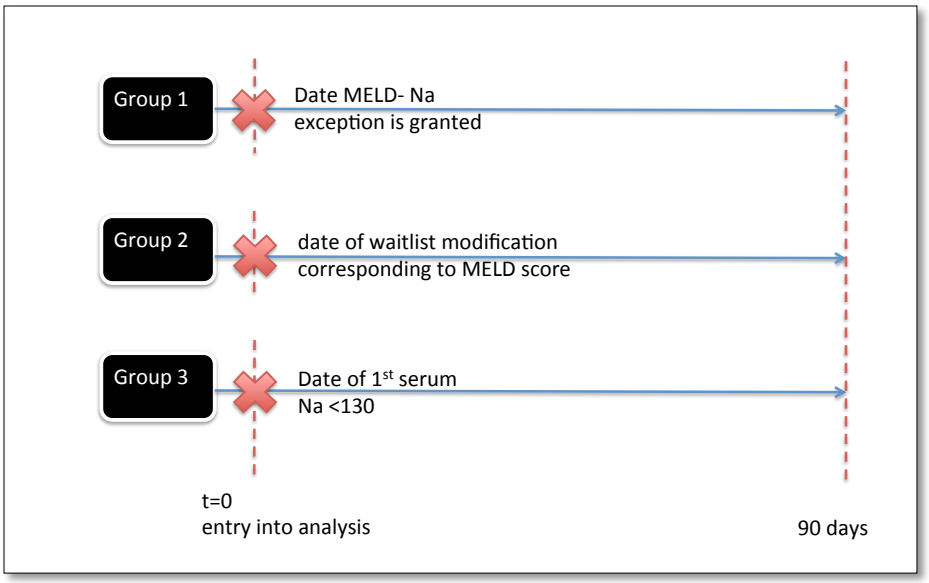
The clinical and demographic variables included in analysis were those recorded at the time of study entry for each group. The time of entry into the data analysis for the MELD-Na group was the time the MELD-Na exception is granted because that is when the MELD exception points were granted and the patient was listed on the waitlist with the new,

higher MELD score. For the normonatremic group, time of entry was date of waitlist modification corresponding to each patient's respective MELD score. The time of entry into the data analysis for the hyponatremic without MELD-Na exception group was the date of first serum sodium <130. The time of entry into analysis for each group is illustrated in Methods Figure 1 below.

Methods Table 1: Variables for data analysis

Variables	
Dependent variable	Time to event
Primary independent variable	Group
Other independent	Recipient age Recipient gender (male, female) Recipient ethnicity (Caucasian, other) UNOS MELD status (≤24, 25-28, ≥29) Etiology of liver disease (viral, non-viral) Presence of ascites (yes, no) Presence of encephalopathy (yes, no) Recipient dialysis status (yes, no) Recipient blood type (A, B, AB, O) Year of recipient WL study entry
Primary Outcome	Death while on the WL or after WL removal
Competing Outcome	Receipt of liver transplantation
Censoring	Survival to end of data collection, WL dropout with no recorded death after dropout, or last reported follow-up without death or liver transplantation

Methods Figure 1: The time of entry into data analysis for each group



Statistical analysis

To address the first aim, *identify and describe characteristics of the following groups from the UNOS transplant database*, I used descriptive statistics to show frequencies and means or medians of age, gender, ethnicity, etiology of liver disease, clinical characteristics (ascites, encephalopathy, dialysis status), blood type, and year of waitlist registration. The mean MELD status, MELD-Na, and serum sodium of the groups were also described. Normally distributed variables were expressed as mean ± standard deviation, and non-normally distributed variables were expressed as median ± interquartile range (IQR). The characteristics between groups were compared using t-test or Wilcoxon rank sum test for continuous variables, or chi-squared or Fisher's exact test for dichotomous or categorical variables. Appropriate functional form of continuous variables were assessed by plotting histograms and martingale residuals of transformed and non-transformed variables.

To address the second and third aims, *evaluate whether patients receiving MELD-Na exceptions have similar waitlist mortality as normonatremic patients,* and *compare waitlist mortality in patients with MELD-Na exceptions to hyponatremic patients who did not receive a*

MELD-Na exception, I used competing risk regression analysis. Competing risk regression is based on the method by Fine and Gray,[19] which is an alternative to traditional time to event analysis with Cox proportional hazards regression and takes into account a competing event to the outcome of interest.

The traditional method to evaluate mortality on the transplant waitlist is Kaplan-Meier (KM) survival analysis, however these methods overestimate the risk of death by failing to account for a competing risk.[20] In KM survival analysis, patients who have not experienced the primary outcome by the end of the study are considered censored. An assumption of KM analysis is that censored patients will experience the event if followed for a long enough period of time. However, if a patient is censored for an outcome that impedes the occurrence of the outcome of interest, then the results of the study must be interpreted in a hypothetical world where the outcome that impedes the outcome of interest does not exist.

Competing risk regression takes into account those outcomes that impede the occurrence of the outcome of interest. In this study, the receipt of liver transplantation impedes the future occurrence of waitlist death and affects whether or not a patient will die on the waitlist. Receipt of liver transplantation is therefore considered a competing risk to waitlist mortality. In this study, the competing event of transplantation was a significant proportion of the outcome events and could not be treated as censored without affecting the interpretation of the results. Therefore, the use of competing risk regression analysis is most appropriate for this study.

Estimation with competing risk regression will produce sub distribution hazard ratios, or sub hazard ratios, for the risk of the occurrence of the primary outcome when taking into

account a competing event. To graphically summarize the cumulative failure of the outcome of interest over time, a cumulative incidence curve can be created that includes covariate effects on a cumulative incidence function, taking the competing outcome into account.

In this study, the primary outcome, waitlist mortality, was compared between the groups using a sub-distribution hazard ratio of waitlist mortality, which takes into account the competing risk of liver transplantation. Patients were censored in the analysis if they survived to end of data collection or last reported follow-up without death or liver transplantation, or waitlist dropout with no recorded death after dropout. The end of the study was set at 90 days in order to obtain a sub hazard ratio of waitlist mortality within 90 days.

In using competing risk regression to answer the second and third aims, I created separate statistical models for each aim to compare the sub distribution hazard ratio of waitlist mortality between groups. To create the statistical models, I began by performing univariable competing risk regression for all covariate predictors of waitlist mortality with the criterion for inclusion in multivariable regression modeling $p<0.25$. Group and MELD score was included in the model *a priori.* Group and MELD were forced into the model since group was our primary independent variable of interest and MELD score is the used to prioritize waitlist candidates and has been shown to predict 90 day mortality. Variable selection for a multiple regression of the competing risk regression model was done by a combination of automated sequential backwards and forwards stepwise selection and manual review with group and MELD score a required covariate in the final model. After univariable selection, all independent variables with $p<0.25$, in addition to MELD score and group, were entered simultaneously in a multivariable model. Independent variables with

$p<0.05$ were then removed one at a time from the full model until the model contained only variables with $p<0.05$ and those chosen a priori.

During manual review, models were compared using Akaike information criterion (AIC). All variables removed from the initial full model were added back one at a time to the preliminary effects model to assess for confounding. Variables not included in after univariable analysis were added back one at a time to the model to assess for importance, and were kept in the model if their p value was <0.05. Multicollinearity was assessed using variable inflation factors. I evaluated all plausible pairwise interactions of interest.

Once a final model was selected, I evaluated group specific predictors in the model by stratifying by group. The proportional hazard of each model was tested by assessing the individual time varying covariates and visualizing Schoenfeld-type plots.[21] Goodness of fit was evaluated with C statistics[22] and plotting Cox Snell residuals. Outliers were assessed by plotting the likelihood displacement values and outliers were assessed for influence by comparing their effect when removed from the model.

A two sided p value was considered to be statistically significant. Analysis was performed using Stata/IC version 13.1 for Macintosh OS X. The study was reviewed by the OHSU IRB and determined not to be human subjects research.

RESULTS

1,413 patients were listed on the LT waitlist in Region 6 between Jan. 1, 2010 to June 30, 2014. After exclusions, 91 patients received MELD-Na exceptions, 201 were normonatremic and with MELD scores in the same distribution of MELD scores in the MELD-Na group, and 255 were hyponatremic that did not receive a MELD-Na exception. Sodium exceptions granted were found to increase, from 6 exceptions granted in 2010 to 24 exceptions granted in 2012. Sodium exceptions remained steady from 2012-2014. 2014 had 18 exceptions granted as of June 30th.

Patients in all three groups were more frequently male and white. There was no significant difference between gender and age between groups. MELD-Na exception patients were of significantly more Caucasian ethnicity than normonatremic patients. MELD-Na exception patients had significantly more viral etiology than normonatremic patients and did not have a significant difference in etiology compared to hyponatremic patients without exceptions. MELD-Na exception patients had significantly more ascites than normonatremic and hyponatremic patients without exceptions. MELD-Na patients were significantly less likely to be on dialysis than either normonatremic patients or hyponatremic patients without exceptions. There was no significant difference in encephalopathy, blood type, or year the patient was on the waitlist when entering the study between groups.

Serum sodium was found to be significantly lower in MELD-Na patients compared to hyponatremic patients but not significantly different than hyponatremic patients without exceptions. MELD-Na patients had similar median serum sodium to hyponatremic patients without exceptions. A median increase of 7 points was awarded to hyponatremic patients

after a MELD-Na exception was granted. When the MELD-Na score was calculated for all groups using lab values, there was a median increase in 1 point added to the normonatremic group and a median increase in 6 points added to the hyponatremic without exception group. The lab calculated MELD-Na score was significantly higher in the normonatremic and hyponatremic without exception group when compared to the MELD-Na group.

52% of MELD-Na patients received a LT and 10% died within 90 days compared to 36% and 15% in the normonatremic group and 39% and 18% in the hyponatremic without exception group, respectively. Significantly more patients in the MELD-Na group received a LT in 90 days compared to either the normonatremic or hyponatremic without exception group. The median days to transplant were 28 (IQR 13-47), 11 (IQR 5-22), and 9 (IQR 3-23) days for MELD-Na, normonatremic, and MELD-Na without exceptions group respectively. The MELD-Na group received LT significantly slower in 90 days compared to either the normonatremic or hyponatremic without exception group. The median days until death were 39 (IQR 23-51), 10 (IQR 5-24), and 16 (IQR 7-44) days for MELD-Na, normonatremic, and MELD-Na without exceptions group respectively. The MELD-Na group had significantly longer time to death in 90 days when compared to the normonatremic group. In all three groups, most waitlist dropouts were due to clinical deterioration. No patients were lost to follow up within the 90 day period. All censored patients were those surviving to the end of the observation period of 90 days. Detailed descriptive statistics are available in Results Table 1 in the tables and figures for results section.

Evaluating 90 day waitlist mortality between MELD-Na exception patients and normonatremic patients.

In univariable analysis, age, year on the waitlist, and etiology were associated with the primary outcome of mortality in the competing risk regression model ($p<0.25$) (Results Table 2). These variables were included in the final multivariable model. When assessing for outliers, one of the patients in the MELD-Na group was considered an influential outlier. Deleting this observation increased the Harrell's C value from 0.7228 to 0.7355. Additionally, the overall significance of the model increased when the observation was deleted from the model. I therefore excluded this observation from the model. All variables in the final multivariable regression model were significant with the exception of group and MELD score, which were included *a priori*.

The final multivariable model had a reasonably good fit of the data, with plotting of Cox-Snell residuals confirming an adequate model with slope approximately equal to one and Harrell's concordance statistic greater than 0.7, which is considered acceptable discrimination of the data.[23] There were no significant interactions found among the variables at the level of significance $p<0.05$. The proportional hazard assumption was not violated by time varying covariates age or year on the waitlist.

Because MELD score is predictive of death, I initially planned to stratify by categories of MELD score; however, it was not statistically necessary to stratify by MELD score, as MELD score did not interact with other variables. Also, stratifying by MELD score did not create significant difference in mortality between the groups. MELD score was not found to be a cofounding or an effect modifier. I chose to include MELD score in the final model because of the clinical implications of the MELD score used in prioritizing patients on the LT waitlist and being predictive of 90 day mortality.

The final regression model included the MELD-Na and normonatremic groups, MELD score, year, age, and etiology (Results Table 3) The sub hazard ratio of death was 43% lower in the MELD-Na group compared to the normonatremic group, taking into account the competing risk of LT, and adjusted for MELD score, year on the waitlist, age, and etiology (SHR=0.57, 95% CI 0.30 - 1.07, p=0.081). The confidence interval was wide and encompassed the null, ranging from 0.30 - 1.07, and had a p value of 0.081. Graphically, the cumulative incidence of mortality, adjusted for MELD score, year, and age, was lower in the MELD-Na group compared to the hyponatremic group (Results Figure 1).

The other covariates in the model show the influence of the predictors averaged over the 2 groups. MELD score did not have a statistically significant influence on mortality averaged over the two groups (95% CI 0.84-3.23 for MELD 25-28 and 95% CI 0.81-2.90 for MELD ≥ 29, p=0. 257) when taking into account group, year on the waitlist, age, or etiology. Year, age, and etiology were significant overall predictors in the model. Averaged over the two groups and taking into account the competing risk of LT, each subsequent year on the waitlist decreased mortality by 28%, each increase year in age increased mortality by 5%, and non-viral etiology, compared to viral etiology, decreased mortality by 43%.

In group specific models, only year and age were found to be significant influential predictors of death in the normonatremic group. (Results Table 4). Increasing age significantly predicted increased mortality in the normonatremic group, with each one year increase in age increasing mortality by 4% for normonatremic patients on the LT waitlist, taking into account LT as a competing risk to mortality and adjusted for MELD status, age, and etiology (95% CI 1.01-1.08, p=0.019). Being on the LT waitlist on years after 2010 predicted decreased waitlist mortality in the normonatremic group, with each subsequent

year of being on the LT waitlist after 2010 decreasing mortality by 36% in the normonatremic group, adjusted for MELD status, age, and etiology and taking into account the competing risk of LT (95% CI 0.51-0.79, p<0.001). No significant interactions were found in the group specific models.

Evaluating 90 day waitlist mortality between MELD-Na exception patients and hyponatremic patients who did not receive a MELD-Na exception.

In univariable analysis, age and encephalopathy were associated with the primary outcome of mortality in the competing risk regression model, taking into account the competing risk of LT (p<0.25) (Results Table 5). Encephalopathy was initially removed from the model since it had a p value >0.05, however when comparing models using AIC, the model was improved with encephalopathy included. When assessing for outliers, again one of the patients in the MELD-Na group was considered an influential outlier. Deleting this observation increased the Harrell's C value from 0.6863 to 0.7001. Additionally, the overall significance of the model increased when the observation was deleted from the model. I therefore excluded this observation from the model. All variables in the final multivariable regression model were significant with the exception of group and MELD score, which were included *a priori*.

The final multivariable model included age, encephalopathy and the *a priori* group and MELD score. The final multivariable model had a reasonably good fit of the data, with plotting of Cox-Snell residuals confirming an adequate model with slope approximately equal to one and Harrell's concordance statistic greater than 0.7 (Harrell's C=0.7001). There were no significant interactions found among the variables at the level of significance

$p<0.05$. The proportional hazard assumption was not violated by time varying covariates age and encephalopathy.

MELD score was not considered a confounder or effect modifier on the model. Again stratifying by MELD score did not make statistical sense, as MELD score did not interact with the other variables, and stratifying by it did not create significant difference in mortality between the groups. I chose to include MELD score in the final model because of the clinical implications of the MELD score used in prioritizing patients on the LT waitlist and being predictive of 90 day mortality.

The final regression model included the MELD-Na and normonatremic groups, MELD score, age, and encephalopathy (Results Table 6). The sub hazard ratio for death was 52% lower in the MELD-Na group relative to the hyponatremic without exceptions group when taking into account the competing risk of LT and adjusted for MELD score, age, and encephalopathy (SHR=0.48, 95% CI 0.27-0.87, p=0.016). Graphically, the cumulative incidence of mortality, adjusted for MELD score, age, and encephalopathy, was lower in the MELD-Na group compared to the hyponatremic without MELD-Na exceptions group (Results Figure 2).

The other covariates in the model show the influence of the predictors averaged over the 2 groups. MELD score did not have a statistically significant influence on mortality averaged over the two groups (95% CI 0.7 - 2.49 for MELD 25-28 and 95% CI 0.62 - 1.92 for MELD ≥ 29, overall p=0. 525) when taking into account group, year on the waitlist, age, or etiology. Age was the only significant overall predictor in the model. Averaged over the two groups

and taking into account the competing risk of LT, each increasing year of age increased mortality by 6% (95% CI: 1.03 - 1.09, p<0.001).

In group specific models, only age were found to be a significant influential predictor of death in the normonatremic group. (Results Table 7). Increasing age significantly predicted increased mortality in the normonatremic group, with each one year increase in age increasing mortality by 6% for normonatremic patients on the LT waitlist, taking into account LT as a competing risk to mortality and adjusted for MELD status, age, and etiology (95% CI 1.02-1.09, p<0.001). No interactions were significant in the group specific models.

DISCUSSION

In this retrospective cohort study, the application of the MELD-Na score did achieve the intended goal of decreasing waitlist deaths in hyponatremic patients, and the use of the MELD-Na exception was the likely cause of difference in mortality between hyponatremic patients in Region 6. I could not reject the possibility of a lack of difference in mortality between MELD-Na exception patients and normonatremic patients, but the evidence for this lack of difference is not strong, and there may be a difference in mortality that this study could not detect. The regional implementation of MELD-Na exceptions accomplished the intended effect of decreasing waitlist mortality in hyponatremic patients and these findings validate the proposed LT waitlist survival benefit of applying a MELD-Na score to hyponatremic patients. However, this study raises a question about whether or not the MELD-Na exception may have over-advantaged hyponatremic patients by possibly decreasing their waitlist mortality and increasing their frequency of LT relative to normonatremic patients.

Comparing mortality between the MELD-Na group vs. hyponatremic without exceptions group

I demonstrated that the use of MELD-Na exceptions decreased mortality in hyponatremic patients compared to hyponatremic patients who did not receive exceptions. The sub hazard ratio of death was 52% lower in the MELD-Na group compared to the hyponatremic group that did not receive exceptions. The use of the MELD-Na exception was the likely cause of difference in mortality between hyponatremic patients. In reviewing alternate explanations for the observed association, chance is unlikely to explain the observed decrease in mortality, as the 95% confidence interval (0.27-0.87), though wide, does not

cross the null. The wide range in the confidence interval may be from a small number of events in MELD-Na group (9 observed deaths).

Selection bias may have influenced the findings, given that the study groups were not randomized. Ideally, the hyponatremic patients compared in the two groups should have only differed by the receipt of the MELD-Na exception, and should be identical in all other regards. Because the groups were not randomized, there were some uncontrollable differences that suggest that the group that did not receive the MELD-Na exception was a sicker group. The two groups are similar in most regards, including serum sodium, however, the MELD-Na group's MELD-Na score, calculated from lab values, was significantly higher than the calculated MELD-Na score of the hyponatremic group that did not get the exception. This may suggest that the hyponatremic group that did not get MELD-Na exceptions is a possibly a sicker group with potentially greater initial baseline mortality. A possible explanation for the difference in lab MELD-Na score between the groups is that patients receiving a MELD-Na exception may have increased access to care since a MELD-Na exception is granted based on approval of an application by a referring physician and may have received better and earlier healthcare, thus they would be less sick at the time of referral compared to other patients with similar serum sodium. Further supporting the idea of the exception group being less sick is that MELD-Na exception patients were significantly less likely to be on dialysis, and dialysis is an indicator of increased time to LT.[16]

Furthermore, the MELD status at time of study entry was not different between the groups. Keeping in mind that the time of study entry in the hyponatremic without exception group is approximately when the MELD-Na exception could have been granted, I would have anticipated that MELD status at time of study entry would have been different between the

two groups since there was a median addition of 7 points granted to the exception group by the MELD-Na score. The median MELD status prior to being granted an exception was 19 in the MELD-Na group, versus a median MELD score of 24 in at study entry in the hyponatremic without exception group.

If the MELD-Na group was a less sick group, then this would negatively bias the association of mortality difference between groups away from the null and likely increase the magnitude of the observed difference. Thus, the actual difference in mortality may be a lower magnitude. Although selection bias may have played a role in the inflating the study's difference in mortality, the bias is unlikely to be the sole reason to explain the difference in observed mortality between the groups.

Another difference between the two groups is that the MELD-Na patients had significantly more ascites than hyponatremic patients without exceptions. The likely explanation for this is due to selection criteria requiring the presence of ascites to grant exceptions. Comparing patients with and without ascites in the hyponatremic group that did not receive exceptions showed that a significant majority of the non-exception group, 91%, had ascites. Ascites is therefore less likely to be a significant contributor to the observed difference in mortality.

Confounding is unlikely to influence the observed association since I did not detect confounding with the covariates included in my analysis. I cannot exclude the potential for residual confounding from unmeasured confounders since there are many factors that affect mortality, however I accounted for the ones most influential on patients on the LT waitlist based on literature. Support for external validity for a decrease in waitlist mortality when using the MELD-Na score is supported by Kim et al., who predicted that the MELD-Na

score would prevent 7% of waitlist deaths compared to the standard MELD score.[9] However it is important to note that the magnitude of the decrease in this study has no comparison in literature since there are no other studies directly comparing mortality between hyponatremic patients who received MELD-Na exceptions to those who did not.

Of the predictors, only increasing age was significantly associated with increased mortality in the hyponatremic without exceptions group. This is consistent with increasing age being a predictor of death in cirrhotic patients.[14]

Although the association of decreased mortality in the hyponatremic with MELD-Na exceptions group does not fulfill all the epidemiologic criteria for causation, it is nevertheless a strong association. Excluding chance and confounding as possible alternate explanations for the observed difference, and taking into account the selection bias, the difference in mortality is most likely due to the MELD-Na exception, however the actual association may have a smaller magnitude. The association between receipt of MELD-Na exception and decreased mortality is strong, with a large magnitude of association with the 52% decrease in mortality, and internally consistent across stratification. The decrease in mortality is also externally consistent with Kim et al.'s prediction of a decrease in mortality with application of the MELD-Na.[9] Given the positive criteria for causation and taking into account that selection bias may have decreased the observed strength of association, I concluded that the MELD-Na exception is most likely to have contributed to the difference in mortality between MELD-Na patients and hyponatremic patients without the MELD-Na exception.

Comparing mortality between the MELD-Na group vs. normonatremic group

In reducing the mortality of hyponatremic patients on the LT waitlist with the MELD-Na score, the MELD-Na was expected to equalize mortality between hyponatremic and normonatremic patients on the LT waitlist. This study could not reject the possibility of a lack of mortality difference between normonatremic patients and MELD-Na exception patients on the waitlist. I did not find a statistically significant difference in mortality between the MELD-Na or normonatremic group. The 95% CI of the association encompassed the null and was wide (95% CI: 0.30-1.07). Although not statistically significant, the large magnitude of decreased mortality in MELD-Na exception patients warrants special attention. The overall magnitude of association was large, and only the upper tail of the confidence interval crossed the null, with the sub hazard ratio of death 43% lower in the MELD-Na group compared to the normonatremic group. The magnitude of the association, in conjunction with a wide confidence interval where only the upper tail crossed the null, raises the question of whether there was a difference in mortality between the groups this study did not detect. I did not perform a post-hoc analysis of power because power calculations are most appropriately used in prediction of data and not in interpretation of results.[24]

Selection bias may have influenced the findings, as the groups were not randomized. Hyponatremic patients with MELD-Na exceptions may have been a less sick group of patients on the LT waitlist compared to hyponatremic patients without the MELD-Na exception, as described above, therefore the hyponatremic patients compared to normonatremic patients may have had a lower baseline mortality compared to all hyponatremic patients in Region 6. This would bias the association of mortality between the MELD-Na and normonatremic groups in this study toward the null in the MELD-Na group,

and the true association, had all hyponatremic patients who qualified for exceptions received them, would show a greater difference in mortality than that observed. This demonstrates that bias may have masked a possible greater difference. The association of decreased mortality between normonatremic and MELD-Na exception patients may be different, and perhaps is underestimated given selection bias.

The two groups were similar in most regards, however the MELD-Na group was significantly of more Caucasian ethnicity, of more viral etiology, less likely to be on dialysis, and more likely to have ascites. Increased ascites can be explained by the presence of hyponatremia.[25] The difference in Caucasian ethnicity and dialysis may be explained by the theory that hyponatremic patients who received exceptions had better access to care and therefore are less likely to be an ethnic minority or be sick enough to be on dialysis compared to hyponatremic patients who did not receive exceptions. The larger proportion of viral etiology in the MELD-Na group was a unique finding. Although there was a chance for unknown confounders to influence the findings, I accounted for most factors that influence mortality on the waitlist based on literature and it was unlikely that confounding affected the findings of this study.

In regards to external validity, although there is prior literature by Fischer et al. supporting a similarity of mortality between MELD-Na exception patients and normonatremic patients,[10] I am tentative to apply it to this study as evidence of eternal validity. Fischer et al.'s Region 11 study investigating the difference in mortality with the application of the MELD-Na exception was done in a manner very different to this study. That study capped MELD-Na scores at 22, whereas in this study, patients would only be considered for a MELD-Na score is there total points were 22 or greater. Depending on the LT Region,

capping the MELD-Na score at a maximum of 22 points may not give the number of points necessary to create a difference in survival on the waitlist relative to the rest of the patients on the waitlist. Additionally, this study used a different methodology. Fischer et al.'s Region 11 study compared the total proportion of patients who died or were 'too sick' among four comparison groups (two of which were MELD-Na exception recipients and standard MELD patients) using ANOVA,[10] and not by time to event testing with survival analysis as in this study. Furthermore, defining mortality as 'too sick' in addition to death would overestimate mortality.[13] Therefore, their finding of no difference in death between MELD-Na exception patients and standard MELD patients cannot be applied to this study, and their findings may have overestimated death between the two groups.

Increasing age was associated with increased mortality in the normonatremic group, which is consistent with increasing age being a predictor of death in cirrhotic patients.[14] Furthermore, each subsequent year on the LT waitlist showed a 36% decrease in mortality in the normonatremic group. A possible explanation for this is care for patients awaiting LT has improved over the years, leading to better management on the waitlist.

This study could not reject the possibility of a lack of mortality difference between normonatremic patients and MELD-Na exception patients on the waitlist. Excluding confounding as a possible explanation, the lack of a statistically significant difference could be due to selection bias or chance given that the magnitude of the association between mortality and MELD-Na group to normonatremic group is large and only crosses the null on the upper tail of the confidence interval. Furthermore, prior literature showing a lack of difference in mortality had different methodology than this study and should not be used in this study as evidence of external consistency for a lack of difference in mortality. This could

mean there is an actual difference in mortality that this study failed to detect. This raises a question of whether there could be a difference in mortality that this study did not detect. An explanation for a possible difference in mortality is that the equation for the MELD-Na score was derived from a model using cox proportional hazard analysis by Kim et al.[9], which overestimates the risk of death when a competing risk, such as transplantation is present.[20] An equation which overestimates the risk of death would grant an excess number of points, thus leading to an decrease in mortality of the exception group. A possible decrease in mortality in MELD-Na exception patients raises the question of a possible advantage in waitlist survival in hyponatremic patients with the MELD-Na exception relative to normonatremic patients.

Further adding to this question of over-advantage, this study showed that significantly more patients in the MELD-Na group are receiving transplants compared to the normonatremic group (57% versus 36%) (Results Table 8). This was also observed by Fisher et al.'s study in Region 11 (90% MELD-Na versus 49% standard MELD score)[10]. Massie et al. reported that exception patients overall, including HCC and non-HCC exceptions separately and together, had higher rates of transplantation.[26] Higher rates of transplantation in MELD-Na exception patients may disadvantage those who do not receive transplantation. It has not been shown how the MELD-Na score would affect transplantation rates in hyponatremic patients if the MELD-Na score were applied to all patients on the waitlist. This would be important to assess since hyponatremia is not a rare outcome on the LT waitlist, and of patients on the LT waitlist globally, 22% have serum sodium <130 and 49% have serum sodium <135.[27] If a significantly decreased association in mortality in MELD-Na patients compared to normonatremic patients was to be found from a future study, then the MELD-

Na, although improving mortality in hyponatremic patients, would be doing so at the cost of increasing mortality in normonatremic patients.

Strengths and limitations

This study has several strengths and limitations. This study took into account that transplant is a competing outcome for mortality and used a database with excellent data on LT candidates with few missing data (only 4 total data points missing). Furthermore, by restricting comparisons to a single LT region, I reduced confounding based on geographic variability, differences in LT practices, and differences in incorporation of the MELD-Na exception score. This study has several limitations. By restricting my analysis to one LT region, this study has reduced generalizability to other LT regions. The study groups were not randomized, which introduced selection bias. Also, this study uses data prospectively collected, not intended for this study. Mortality ascertainment was done using a combination STAR database and linking patients to SSDMF data, which may not have captured all deaths since as of November 2011. The percentage of deaths accessible in the SSDMF data decreased due to data release issues with the Social Security Administration.[28]

Conclusion

In conclusion, I found that there is an association of decreased mortality between hyponatremic patients who have received the MELD-Na exception, and there is good support for this association given the positive criteria for causation and taking into account how selection bias may have decreased the observed strength of association. I could not reject the possibility of a lack of difference in mortality between MELD-Na exception patients and normonatremic patients, but the evidence for this lack of difference is not

strong and may be explained by chance or selection bias. Therefore there may be a difference in mortality that this study could not detect. Region 6 has been granting MELD-Na exceptions in a manner that is similar to that being proposed for national adoption, and I showed that the application of the MELD-Na score decreases waitlist mortality in hyponatremic patients in Region 6. This study raises the question of a possible waitlist survival and transplantation advantage in MELD-Na exception patients. Before being adopted as the new determinant for LT priority, there should be further research examining a possible survival benefit conferred by the MELD-Na to hyponatremic patients.

Future studies

The MELD-Na score is being proposed for adoption as the new determinant for LT priority. This study was unable to answer conclusively whether there was no difference in waitlist mortality between hyponatremic patients with MELD-Na exceptions and normonatremic patients without raising some questions about a possible survival benefit and transplantation advantage in using a MELD-Na score. The ascertainment of mortality difference in hyponatremic and normonatremic patients prioritized by the MELD-Na score should be determined prior to widespread adoption of the MELD-Na score. Following this cohort for 180 days instead of 90 days may lead to an increased number of events and may lead to a detectable difference in mortality between the MELD-Na exception and normonatremic group. Additionally, the MELD-Na score has only been used as an exception and has not yet been applied to an entire population on the LT waitlist, as it was intended to be used. It would important to determine if there is a mortality difference or difference in LT receipt between hyponatremic and normonatremic patients in a single or multiple LT regions where the MELD-Na has been applied to all patients since a survival benefit to either one group would disadvantage the other. Furthermore, the post-transplant mortality

outcomes of patients prioritized with the MELD-Na score have not yet been determined. A study evaluating post-transplant survival in patients prioritized with the MELD-Na score would add information about the long-term survival benefit of the MELD-Na score on hyponatremic patients.

DISCLAIMER

This work was supported in part by Health Resources and Services Administration contract 234-2005-370011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

TABLES AND FIGURES FOR RESULTS

Results Table 1: Demographics and Clinical Characteristics of Liver Transplant Patients in Study Groups

	MELD-Na	Normonatremic	Hyponatremic without MELD-Na	MELD-Na vs Normonatremic	MELD-Na vs Hyponatremic without MELD-NA
	N=90	N=201	N=255	P value	P value
Male gender, n (%)	61 (67%)	125 (61%)	156 (61%)	0.32*	0.321*
Age, mean ± sd	56.5 ± 7.5	53.2 ± 12.8	55.7 ± 8.7	0.137***	0.537***
Ethnicity, n (%)				0.024*	0.253*
White	78 (87)	153 (75)	208 (82)		
Other	12 (13)	50 (25)	47 (18)		
Etiology, n (%)				0.002*	0.204*
Viral	47 (53)	67 (33)	112 (44)		
Non-viral	44 (47)	138 (67)	143 (56)		
Clinical characteristics, n (%)					
Ascites	89 (98)	176 (86)	223 (91)	<00.001*	0.002*
Encephalopathy	80 (88)	165 (80)	219 (86)	0.107*	0.335*
Dialysis	2 (2)	22 (11)	24 (9)	0.011**	0.022**
Blood group n, (%)				0.235**	0.244**
A	35 (39)	90 (44)	121 (48)		
B	15 (16)	20 (10)	24 (9)		
AB	3 (3)	3 (1)	8 (3)		
O	37 (42)	92 (45)	102 (40)		
Year, n (%)				0.656**	0.177**
2010	6 (7)	24 (12)	39 (15)		
2011	19 (21)	35 (17)	51 (20)		
2012	24 (26)	48 (23)	46 (18)		
2013	23 (13)	54 (26)	65 (26)		
2014	18 (14)	44 (20)	54 (21)		
Serum sodium, median (IQR) (mEq/L)	125(122-128)	136 (134-139)	126 (123-128)	<0.001***	0.73***
MELD status, median (IQR)	26 (24-28)	27 (23-31)	24 (18-31)	0.2379***	0.1281***
UNOS MELD prior to being granted exception, median (IQR)	19 (16-22)	-	-	-	-
Lab MELD-Na, median (IQR)	26 (24-28)	28 (24-32)	30 (26-34)	0.004***	<0.001***

* Chi-square test, **Fisher's exact test, ***t test

Results Table 2: Univariable competing risk regression of MELD-Na exception patients and normonatremic patients

	SHR	95% CI	P value
Group			0.302
Normonatremic	ref	ref	
MELD-Na	0.74	0.42 - 1.31	
MELD status			0.643
≤24	ref	ref	
25-28	1.32	0.71 - 2.46	
≥29	1.25	0.67 - 2.34	
Year	0.76	0.63 - 0.90	0.002
Age	1.04	1.00 - 1.07	0.031
Male gender	1.03	0.61 - 1.75	0.901
Ethnicity			0.397
Caucasian	ref	ref	
Other	1.3	0.71-2.36	
Etiology			0.027
viral	ref	ref	
non-viral	0.56	0.34 - 0.94	
Ascites	1.05	0.42 - 2.61	0.914
Encephalopathy	1.42	0.66 - 3.05	0.366
Dialysis	2.06	0.99 - 4.24	0.051
Blood Type			0.433
A	ref	ref	
B	1.84	0.88 - 3.85	
AB	1.12	0.13 - 9.84	
O	1.33	0.75 - 2.37	

Results Table 3: Competing risk regression sub hazard ratio for death for MELD-Na exception patients and normonatremic patients

	SHR	95% CI	P value
Group			0.081
Normonatremic group	1.00	referent	referent
MELD-Na group	0.57	0.30 - 1.07	
MELD status			0.257
≤24	referent	referent	
25-28	1.65	0.84-3.23	
≥29	1.53	0.81-2.90	
Year	0.72	0.60-0.87	0.001
Age	1.05	1.01-1.09	0.007
Etiology – non-viral	0.57	0.35-1.01	0.037

Results Table 4: Influence of other predictors on waitlist mortality, using competing risk regression model, stratified by group

	Normonatremic group			MELD-Na group		
	SHR	**95% CI**	**P>z**	**SHR**	**95% CI**	**P>z**
MELD status			0.199			0.982
≤24	referent	referent		referent	referent	
25-28	1.95	0.90-4.21		1.02	0.36-3.39	
≥29	1.56	0.79-3.07		0.98	0.15-6.46	
Year	0.64	0.51-0.79	>.001	1.02	0.60-1.72	0.947
Age	1.04	1.01-1.08	0.019	1.10	0.98-1.23	0.119
Etiology - viral	0.65	0.35-1.19	0.169	0.36	0.12-1.07	0.065

Results Table 5: Univariable competing risk regression of MELD-Na exception patients and hyponatremic patients without MELD-Na exceptions

	SHR	95% CI	P value
Group			0.060
Normonatremic group	ref	ref	
MELD-Na group	0.59	0.34 - 1.02	
MELD status			0.801
≤24	ref	ref	
25-28	0.88	0.52 - 1.51	
≥29	0.85	0.49 - 1.46	
Year	0.91	0.78 - 1.07	0.270
Age	1.05	1.02 - 1.09	0.004
Male gender	1.04	0.66 - 1.63	0.858
Ethnicity	0.95	0.53 - 1.68	0.847
Caucasian	ref	ref	
Other			
Etiology			0.938
viral	ref	ref	
non-viral	1.01	0.66 - 1.57	
Ascites	1.75	0.57 - 5.44	0.330
Encephalopathy	1.79	0.80 - 4.03	0.157
Dialysis	0.62	0.22 - 1.69	0.355
Blood Type			0.793
A	ref	ref	
B	1.14	0.57 - 2.29	
AB	0.40	0.05 - 3.00	
O	1.06	0.66 - 1.68	

Results Table 6: Competing risk regression sub hazard ratio for death for MELD-Na exception patients and hyponatremic patients without MELD-Na exceptions

	SHR	95% CI	P>z
Group			0.016
Hyponatremic no exception	1	ref	ref
MELD-Na	0.48	0.27-0.87	
MELD status			0.525
≤24	ref	ref	
25-28	1.40	0.7 - 2.49	
≥29	1.09	0.62 - 1.92	
Age	1.06	1.03 - 1.09	<0.001
Encephalopathy	1.75	0.77 - 3.97	0.181

Results Table 7: Influence of other predictors on waitlist mortality, using competing risk regression model, stratified by group

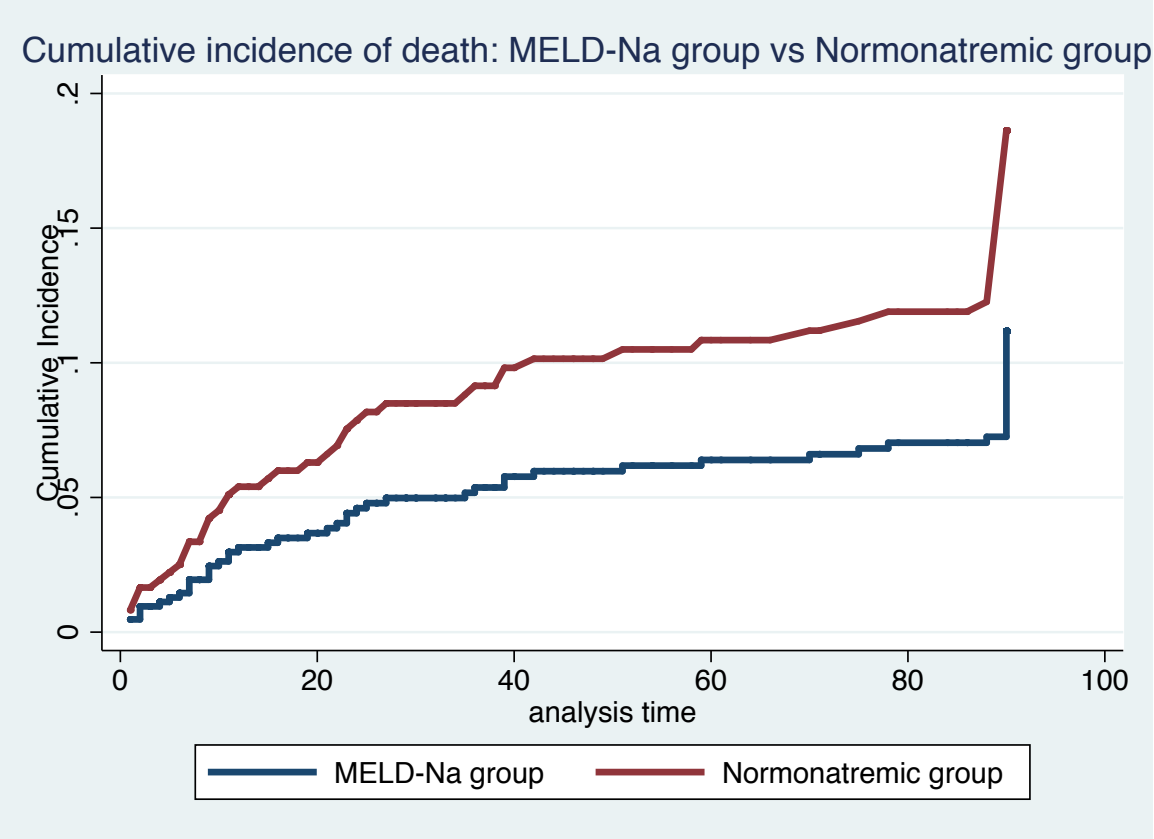
	Hyponatremic no exception group			MELD-Na group		
	SHR	**95% CI**	**P value**	**SHR**	**95% CI**	**P value**
MELD status			0.653			0.868
≤24	ref	ref		ref	ref	
25-28	1.37	0.70-2.69		1.35	0.44-4.17	
≥29	1.09	0.60-1.97		1.28	0.30-5.59	
Age	1.06	1.02-1.09	<0.001	1.01	0.89-1.15	0.826
Encephalopathy	1.85	0.76-4.47	0.174	1.65	0.21-13.17	0.636

Results Table 8: Frequency of and time to LT or death in study groups

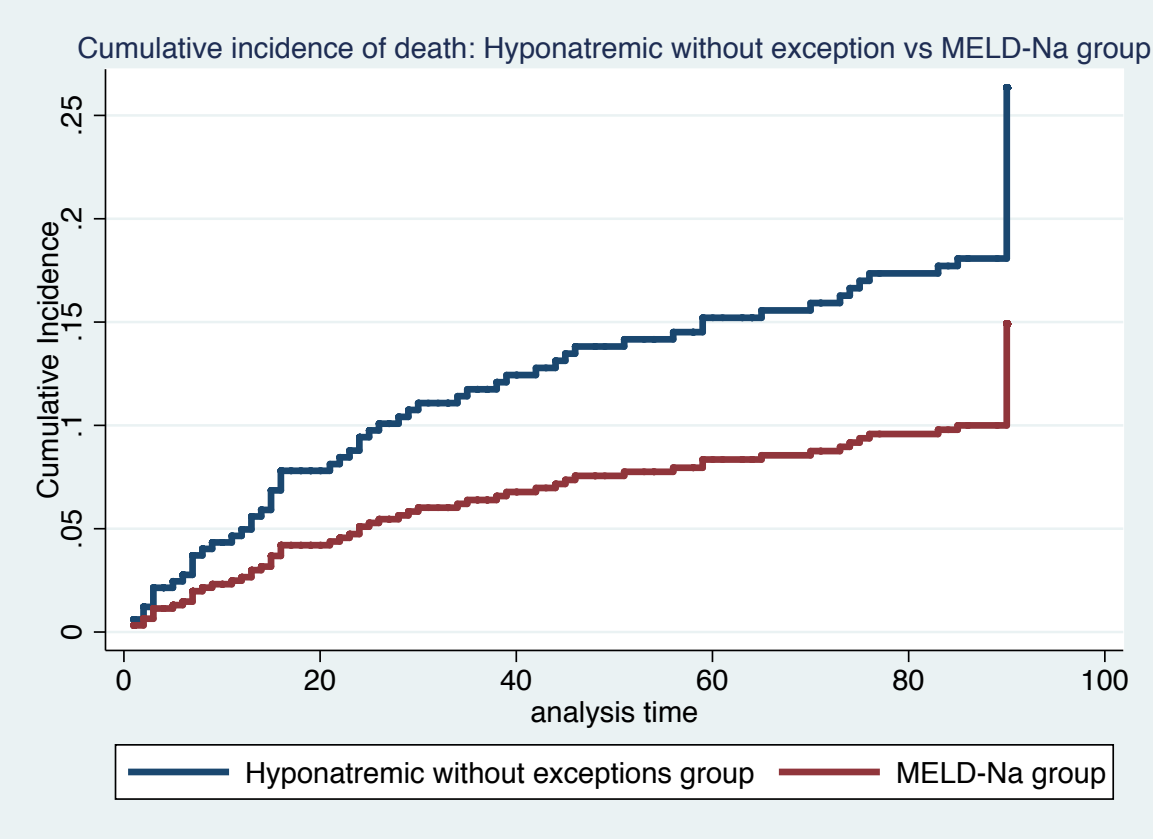
	MELD-Na	Normonatremic	Hyponatremic without MELD-Na	MELD-Na vs Normonatremic	MELD-Na vs Hyponatremic without MELD-NA
				P value	P value
Received LT, n(%)	52 (57)	72 (36)	99 (39)	0.001*	0.002*
Died on WL or after WL removal	9 (10)	31 (15)	47 (18)	0.203*	0.058*
Dropped off WL, n(%)	11 (12)	36 (18)	47 (18)	0.21*	0.164*
Died on WL, n(%)	5 (5)	13 (6)	26 (10)	0.749*	0.178*
Dropped of WL due to clinical deterioration, n(%)	10 (11)	29 (14)	31 (12)	0.424*	0.767*
Dropped of WL due to clinical deterioration and died, n(%)	4 (4)	18 (9)	18 (7)	0.128**	0.267**
Dropped off WL and died, n(%)	4 (4)	18 (9)	21 (8)	0.128**	0.164**
Died on WL or dropped off due to clinical deterioration, n(%)	15 (16)	42 (21)	57 (22)	0.378*	0.236*
Time to tx within 90, median (IQR)	28 (13-47)	11 (5-22)	9 (3-23)	<.001***	0.003***
Time to death in 90, median (IQR)	39 (23-51)	10 (5-24)	16 (7-44)	0.028***	0.212***

* Chi-square test, **Fisher's exact test, ***t test

Results Figure 1: Cumulative incidence function graph for mortality between MELD-Na group and the normonatremic group



Results Figure 2: Cumulative incidence function graph for mortality between MELD-Na group and the hyponatremic without exceptions group



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