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Hyponatremia and Mortality among Patients on the Liver-Transplant Waiting List

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Abstract

BACKGROUND—Under the current liver-transplantation policy, donor organs are offered to patients with the highest risk of death.

METHODS—Using data derived from all adult candidates for primary liver transplantation who were registered with the Organ Procurement and Transplantation Network in 2005 and 2006, we developed and validated a multivariable survival model to predict mortality at 90 days after registration. The predictor variable was the Model for End-Stage Liver Disease (MELD) score with and without the addition of the serum sodium concentration. The MELD score (on a scale of 6 to 40, with higher values indicating more severe disease) is calculated on the basis of the serum bilirubin and creatinine concentrations and the international normalized ratio for the prothrombin time.

RESULTS—In 2005, there were 6769 registrants, including 1781 who underwent liver transplantation and 422 who died within 90 days after registration on the waiting list. Both the MELD score and the serum sodium concentration were significantly associated with mortality (hazard ratio for death, 1.21 per MELD point and 1.05 per 1-unit decrease in the serum sodium concentration for values between 125 and 140 mmol per liter; $P<0.001$ for both variables). Furthermore, a significant interaction was found between the MELD score and the serum sodium concentration, indicating that the effect of the serum sodium concentration was greater in patients with a low MELD score. When applied to the data from 2006, when 477 patients died within 3 months after registration on the waiting list, the combination of the MELD score and the serum sodium concentration was considerably higher than the MELD score alone in 32 patients who died (7%). Thus, assignment of priority according to the MELD score combined with the serum sodium concentration might have resulted in transplantation and prevented death.

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CONCLUSIONS—This population-wide study shows that the MELD score and the serum sodium concentration are important predictors of survival among candidates for liver transplantation.

The allocation of grafts for liver transplantation from deceased donors in the United States is based on medical urgency, which is estimated according to the Model for End-Stage Liver Disease (MELD) score. The MELD score is based on the results of three readily available, objective, and reproducible laboratory tests: the total serum bilirubin concentration, the international normalized ratio (INR) for the prothrombin time, and the serum creatinine concentration.[1–4] In the United States, the MELD score has been used in determining priorities for organ allocation in liver transplantation since 2002.

In addition to the MELD score, the serum sodium concentration has been recognized as an important prognostic factor in patients with liver cirrhosis. For example, hyponatremia has been associated with the hepatorenal syndrome,[5–9] ascites,[6–10] and death from liver disease.[5,8,10–14] The serum sodium concentration, like the components of the MELD score, is readily available, objective, and reproducible; this makes the serum sodium concentration a reasonable candidate for consideration in a model of liver allocation. Several studies have shown that among patients on the waiting list for liver transplantation, the serum sodium concentration is an important predictor of mortality, over and above the MELD score.[15–18] Furthermore, it has been suggested that there may be an interaction between the MELD score and the serum sodium concentration in patients with a very high MELD score and that, among these patients, the addition of the serum sodium concentration may not have as important an effect on mortality as it does among patients with a low MELD score.[16,18] The small size of the studies conducted to date has precluded adequate examination of the interaction between the MELD score and the serum sodium concentration. We used the Organ Procurement and Transplantation Network (OPTN) database to measure the effect of the MELD score, the serum sodium concentration, and the interaction between the two in predicting mortality among patients on a waiting list for liver transplantation.

METHODS

STUDY DATA

Data on all patients who were registered on the waiting list in the United States were obtained from the OPTN. These data were available from the Standard Transplant Analysis and Research file as of May 1, 2007. The predictor variables in this analysis consisted of the MELD score and the serum sodium concentration at the time of registration on the waiting list. The data file also included the outcome of waiting (i.e., transplantation, death, or withdrawal from the list for other reasons), which was used to define the outcome variable in the analysis — namely, death before transplantation and within 90 days after registration.

Since our data spanned 2 calendar years, we adopted a strategy to build a prediction model based on data from 2005 and to validate the model using the 2006 data. Since we planned to assign a prognostic score based on the MELD score and the serum sodium concentration to the current and future registrants on the waiting list, it was important that a model derived from one calendar year remain valid when it was applied to another year. Our target

population was all adults with cirrhotic liver disease in the United States who were listed for a first liver transplantation. Therefore, among all registrants on the waiting list, we excluded those who were younger than 18 years of age, those with liver disease other than cirrhosis (e.g., acute liver failure or hepatocellular carcinoma), and those listed for repeat liver transplantation, as well as patients for whom complete laboratory data were not available within 5 days after they had been placed on the waiting list. In addition, since we were interested in the effects of hyponatremia, a small proportion of patients with hypernatremia (se- rum sodium concentration >150 mmol per liter) (24 of 6793 patients, or 0.4%) were excluded from the model development. However, patients with hypernatremia were included in the model validation in order to ensure that the new score could be applied globally. In candidates listed at more than one center concurrently, we identified the first date of registration on the waiting list, using a de-identified unique candidate code.

STATISTICAL ANALYSIS

The MELD score was calculated with the use of the standard formula, which adds multiples of the natural logarithm (ln) of the values for the INR, creatinine, and bilirubin as follows: $11.2 \times \ln(\text{INR}) + 9.57 \times \ln(\text{creatinine, in milligrams per deciliter}) + 3.78 \times \ln(\text{bilirubin, in milligrams per deciliter}) + 6.43$ (an intercept), with a lower limit of 1 for all variables and with creatinine capped at 4; creatinine was set at 4 if the patient was receiving renal-replacement therapy. The MELD score (rounded to the nearest integer) ranges from 6 to 40, with higher values indicating more severe disease.

A multivariable Cox proportional-hazards analysis of the 2005 data was conducted to describe the relationships among the MELD score, the serum sodium concentration, and 3-month mortality. Patients who were withdrawn from the list and subsequently died were counted as having died. The remaining patients were excluded at the time of withdrawal from the waiting list, at the time of liver transplantation, or 90 days after registration on the waiting list. The Cox model assumed that excluded patients had the same risk as patients with the same covariate values who were not excluded. In other words, the model assumed that the selection of liver-transplant recipients among candidates with an identical MELD score was random. Thus, once the MELD score was taken into account in the model, the concern about potential biases (e.g., informative censoring) in the analysis because of exclusion at the time of liver transplantation was minimized.

Generalized additive models with smoothing splines were used to determine whether the serum sodium concentration had a nonlinear effect on the risk of death. The resulting smooth curves permit depiction of the relationship between the MELD score and mortality in several strata of sodium values. The interaction between the MELD score and the serum sodium concentration was formally evaluated by means of multivariable Cox regression analysis. To maintain consistency with the MELD score, the final model was constrained such that the new score (the MELD score combined with the serum sodium concentration) would have the lower and upper bounds of 6 and 40, respectively, for all strata of sodium values.

Once the prediction model had been finalized, it was applied to the 2006 data to examine whether the calibration and discrimination of the score based on the new model (the

MELDNa score) were superior to those of the MELD score. Calibration describes how closely the predicted probabilities agree numerically with the actual outcomes.[19] To test the calibration of the MELDNa score, for each decile of MELD scores for the 2005 data, we calculated the probability of death at 90 days and compared that probability with those predicted by the MELD score alone and the MELD score combined with the serum sodium concentration. We applied the Hosmer–Leme-show statistic, as modified by D'Agostino and Nam,[20] as a measure of calibration (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). Discrimination refers to the ability of the model to correctly distinguish between two classes of outcomes such as death and survival.[4,19] Statistical measures of discrimination, including the concordance statistics (C statistics) and integrated discrimination improvement (see the Supplementary Appendix), were computed.[21,22] P values for the comparison of C statistics were calculated with the use of the bootstrap method. Finally, a reclassification table was created to estimate the magnitude of changes in ranking between the MELD score alone and the MELDNa score.[21]

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 14,130 adults on the waiting list for liver transplantation met the inclusion criteria in 2005 and 2006. Predictor and outcome variables were complete for 13,940 patients (99%). Characteristics of the patients are shown in Table 1. At registration on the waiting list, the median MELD score was 15 (range, 6 to 40) and the median serum sodium concentration was 137 mmol per liter (range, 112 to 168). Overall, 31% of the patients had hyponatremia (serum sodium concentration <135 mmol per liter), and in 2.5% of the patients, the serum sodium concentration was less than 125 mmol per liter.

MELD SCORE, SERUM SODIUM, AND MORTALITY

In 2005, a total of 422 patients died and 1781 underwent liver transplantation within 90 days after registration on the waiting list. As expected, there was a near-linear relation between the MELD score and mortality among patients on the waiting list. On average, the risk of death increased by 21% (hazard ratio, 1.21; 95% confidence interval [CI], 1.20 to 1.22; P<0.001) per unit increase in the MELD score.

Figure 1 shows that a decrease in the serum sodium concentration was associated with an increase in the risk of death while patients were on the waiting list, even after adjustment for the MELD score. The most meaningful differential effect of hyponatremia on mortality appeared to occur at a serum sodium concentration between 125 and 140 mmol per liter. This effect was verified by model fitting: a Cox model with these upper and lower bounds for the sodium concentration was superior to the model with continuous, untruncated sodium values. The model fit did not improve by allowing the risk for patients with a serum sodium concentration of less than 123 mmol per liter to differ from the risk for patients with a serum sodium concentration of 123 to 127 mmol per liter, or by allowing the risk for patients with a serum sodium concentration of more than 142 mmol per liter to differ from the risk for those with a serum sodium concentration of 138 to 142 mmol per liter (data not shown). A Cox model, adjusted for the MELD score, showed an increase in the risk of death of 5%

(hazard ratio, 1.05; 95% CI, 1.03 to 1.08; P<0.001) per unit decrease in the serum sodium concentration when the serum sodium concentration was between 125 and 140 mmol per liter.

EFFECT OF SERUM SODIUM AT DIFFERENT MELD SCORES

The result of the multivariable Cox regression analysis for the interaction between the MELD score and the serum sodium concentration (i.e., the MELDNa score) is summarized by the following formula:

$$\mathrm{MELDNa} = \mathrm{MELD} - \mathrm{Na} - [0.025 \times \mathrm{MELD} \times (140 - \mathrm{Na})] + 140,$$

where the serum sodium concentration (Na) is bound between 125 and 140 mmol per liter. Like the MELD score, the MELDNa score is rounded to the nearest integer.

The result can also be depicted as the additional allocation points a patient would receive for a given MELD score and serum sodium concentration (Fig. 2). Patients with hyponatremia could have up to 13 points added to their MELD score, which would equate their risk of death to the risk for patients with normal sodium concentrations. The majority of the patients in this study (61%) had serum sodium concentrations above 135 mmol per liter; for these patients, the MELDNa score was essentially identical to the MELD score. Similarly, for patients with MELD scores above 30, the effect of hyponatremia was quite small. However, for patients with moderate MELD scores, the effect could be substantial. For example, a patient with a MELD score of 10 and a serum sodium concentration of 125 mmol per liter would have a MELDNa score of 21 (i.e., 11 points added to the MELD score), because the risk of death would be equivalent to the risk for a patient with a MELD score of 21 and a normal serum sodium concentration.

CALIBRATION AND DISCRIMINATION OF THE MELDNa SCORE

A total of 2159 patients underwent transplantation and 477 patients died within 90 days after registration in 2006; these data were used to examine the calibration and discrimination of the MELDNa score. Figure 3 compares the calibration of the MELD and MELDNa scores in predicting the probability of death at 90 days. The observed probability of death and the probability predicted by the MELDNa score based on the 2005 data are shown, as well as the observed probability of death and that predicted by the MELDNa and MELD scores based on the 2006 data. The probability of death predicted by the MELDNa score was similar to the observed probability for both data sets. As expected, the discrepancy was a bit larger for the validation data from 2006. More important, the 2006 data show that the mortality predicted by the MELDNa score matched the observed mortality at 90 days better than did the mortality predicted by the MELD score in virtually all deciles of MELD scores that were tested. The Hosmer–Lemeshow statistic (as modified by D'Agostino and Nam[20] for survival data) was 17.8 for the MELDNa score and 51.3 for the MELD score. There was less discrepancy between the actual and predicted probabilities with the MELDNa score than with the MELD score (see the Supplementary Appendix for details).

In this study, discrimination refers to the ability to rank patients correctly according to their risk of death. Discrimination of the MELD and MELDNa scores may be assessed by means of the C statistic, a conventional metric of discrimination, which was modestly, yet significantly higher with the MELDNa score than with the MELD score (0.883 vs. 0.868, P<0.001). Assessment of the integrated discrimination improvement (i.e., the average improvement in the predicted probability of death) indicated that the net improvement in the risk score — although numerically small and of uncertain clinical significance — was statistically significant (integrated discrimination improvement, 1.1%; P<0.001) (see the Supplementary Appendix).

The potential effect of the use of the MELDNa score in liver allocation is shown in Figure 4, which shows how the 477 patients who died within 90 days after registration in 2006 would have been reclassified if the MELDNa score had been used instead of the MELD score. For 363 patients, the MELD and MELDNa scores were similar, whereas for 110 patients (23% of the patients who died), the difference between the MELDNa and MELD scores was sufficiently large that the priority for liver allocation might have been altered if the MELDNa score had been used. On the basis of the probabilities of transplantation with the use of the MELD score in 2006, we estimated that if the MELDNa score had been used for organ allocation, the incremental increase in the number of transplantations would have been 32, suggesting that 7% of the 477 deaths might have been prevented (Fig. 4).

DISCUSSION

Since the MELD score was adopted in 2002 as the standard by which priority for liver allocation is determined, mortality among patients on the waiting list has decreased substantially in the United States.[23] However, the MELD score may not accurately reflect the risk of death in some groups of patients. Previous studies have shown that one such group is patients with hyponatremia.[15–18] Our study involved the entire waiting list of registrants in the United States; this large sample provided sufficient statistical power to accurately characterize and validate the interaction between the MELD score and the serum sodium concentration as predictors of mortality.[16,18] Our data show that the effect of hyponatremia gradually diminished as the MELD score increased, as shown in Figure 2.

The current approach to liver transplantation in the United States is to prioritize the allocation of liver grafts on the basis of urgency (i.e., the estimated risk of death for a patient on the waiting list).[24–29] In this study, we found that as compared with the MELD score, the MELDNa score provides better calibration and discrimination of the risk of death among candidates for liver transplantation; thus, use of the MELDNa score may reduce mortality among patients on the waiting list. Since the MELDNa score differs substantially from the MELD score only for patients with hyponatremia, the proportion of candidates for liver transplantation who would be affected by the use of this combined score would be modest. Among such patients, however, we found that the magnitude of the difference between the MELD score and the MELDNa score was often large enough to make a real difference in the probability of receiving a liver transplant and averting death (Fig. 4). Common measures of discrimination such as the C statistic are insensitive to this difference, since they gauge only the proportion of patients whose ranks change, without consideration of the magnitude

of the change in ranks. Our analysis suggests that as many as 7% of waiting-list deaths could be averted if the MELDNa score were used for liver allocation; this would project to 90 lives saved (7% of 1291 patients who died) for the period from 2005 to 2006. Although this may be a modest number, we believe that the use of the MELDNa score could be an important improvement in identifying a subgroup of patients with cirrhosis who have severe fluid retention and a high risk of death.

In our previous research in selected academic transplantation centers, the effect of the serum sodium concentration was modeled as a linear variable, with a lower bound for the serum sodium concentration of 120 mmol per liter and an upper bound of 135 mmol per liter.[18] The current study, with a large sample that permitted formal testing of these lower and upper bounds, updates the range to 125 to 140 mmol per liter. This change is clinically preferable in considering the MELDNa score for liver allocation. Hyponatremia at the time of liver transplantation has been associated with increased morbidity (e.g., due to central pontine myelinolysis[30–32]) and mortality in the immediate postoperative period.[33,34] Whether this association is attributable to hyponatremia itself or reflects the fact that patients with hyponatremia tend to be ill in general remains to be determined. Nonetheless, an allocation system that excessively favors patients with severe hyponatremia may diminish the overall outcome after liver transplantation. Ultimately, once an organ is allocated to a patient with hyponatremia, it should remain the responsibility of the individual physicians to determine whether the patient is at too high a risk to undergo liver transplantation.

Our analysis has limitations. First, the data on serum sodium concentrations were obtained at a single time point — when a patient was placed on the waiting list. Serum sodium concentrations may vary depending on factors such as the volume status and use or nonuse of diuretics. Since the data from the waiting list were collected without a specific protocol for these variables, the data on serum sodium concentrations may entail a significant degree of variability. However, published data and common clinical observations indicate that hyponatremia in patients with cirrhosis is difficult to alter.[35,36] In addition, the consistency of the effect of the serum sodium concentration on short-term mortality between the 2005 and 2006 data ensures the validity of our observation. Second, this analysis is based on a waiting-list registry, rather than on a database specifically created for the study, which makes heterogeneity in the data inevitable.[37–40] Nonetheless, since the OPTN conducts periodic, mandatory audits of data at each center, we believe that most of our data are accurate. Third, we held the MELD score intact rather than refitting coefficients for its components, since our primary objective was to define the relationships among the MELD score, the serum sodium concentration, and short-term mortality in our patients. Having been validated and used extensively, the MELD score is familiar to liver-transplantation personnel. However, if the MELDNa score is to be adopted for organ allocation, further adjustment of the model may be required before implementation.

Despite these shortcomings, we believe our analysis shows that the MELDNa score may provide significantly better prediction of mortality among registrants on the waiting list for liver transplantation. We think that with the priority for organ allocation based on urgency for liver transplantation, adoption of the MELDNa score should be tested to see whether it reduces mortality among patients on the waiting list.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology. 2000; 31:864–71. [PubMed: 10733541]
2. Freeman RB Jr, Wiesner RH, Harper A, et al. The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl. 2002; 8:851–8. [PubMed: 12200791]
3. Wiesner RH, McDiarmid SV, Kamath PS, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl. 2001; 7:567–80. [PubMed: 11460223]
4. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001; 33:464–70. [PubMed: 11172350]
5. Ginès A, Escorsell A, Ginès P, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology. 1993; 105:229–36. [PubMed: 8514039]
6. Porcel A, Díaz F, Rendón P, Macías M, Martín-Herrera L, Girón-González JA. Dilutional hyponatremia in patients with cirrhosis and ascites. Arch Intern Med. 2002; 162:323–8. [PubMed: 11822925]
7. Arroyo V, Colmenero J. Ascites and hepatorenal syndrome in cirrhosis: pathophysiological basis of therapy and current management. J Hepatol. 2003; 38(Suppl 1):S69–S89. [PubMed: 12591187]
8. Cosby RL, Yee B, Schrier RW. New classification with prognostic value in cirrhotic patients. Miner Electrolyte Metab. 1989; 15:261–6. [PubMed: 2682175]
9. Borroni G, Maggi A, Sangiovanni A, Cazzaniga M, Salerno F. Clinical relevance of hyponatraemia for the hospital outcome of cirrhotic patients. Dig Liver Dis. 2000; 32:605–10. [PubMed: 11142560]
10. Fernández-Esparrach G, Sánchez-Fueyo A, Ginès P, et al. A prognostic model for predicting survival in cirrhosis with ascites. J Hepatol. 2001; 34:46–52. [PubMed: 11211907]
11. Llach J, Ginès P, Arroyo V, et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology. 1988; 94:482–7. [PubMed: 3335320]
12. Shear L, Kleinerman J, Gabuzda GJ. Renal failure in patients with cirrhosis of the liver. I. Clinical and pathologic characteristics. Am J Med. 1965; 39:184–98. [PubMed: 14320684]
13. Earley LE, Sanders CA. The effect of changing serum osmolality on the release of antidiuretic hormone in certain patients with decompensated cirrhosis of the liver and low serum osmolality. J Clin Invest. 1959; 38:545–50. [PubMed: 13641405]
14. Arroyo V, Rodes J, Gutiérrez-Lizárraga MA, Revert L. Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. Am J Dig Dis. 1976; 21:249–56. [PubMed: 1266841]
15. Ruf AE, Kremers WK, Chavez LL, Descalzi VI, Podesta LG, Villamil FG. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. Liver Transpl. 2005; 11:336–43. [PubMed: 15719386]
16. Heuman DM, Abou-Assi SG, Habib A, et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology. 2004; 40:802–10. [PubMed: 15382176]
17. Biggins SW, Rodriguez HJ, Bacchetti P, Bass NM, Roberts JP, Terrault NA. Serum sodium predicts mortality in patients listed for liver transplantation. Hepatology. 2005; 41:32–9. [PubMed: 15690479]

18. Biggins SW, Kim WR, Terrault NA, et al. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology. 2006; 130:1652–60. [PubMed: 16697729]
19. D'Agostino RB, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA. 2001; 286:180–7. [PubMed: 11448281]
20. D'Agostino, RB.; Nam, B-H. Evaluation of the performance of survival analysis models: discrimination and calibration measures. In: Balakrishnan, N.; Rao, CR., editors. Advances in survival analysis. Amsterdam: Elsevier; 2004. p. 1-25.
21. Pencina MJ, D'Agostino RB, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med. 2008; 27:157–72. [PubMed: 17569110]
22. Heagerty PJ, Zheng Y. Survival model predictive accuracy and ROC curves. Biometrics. 2005; 61:92–105. [PubMed: 15737082]
23. Kamath PS, Kim WR. The Model for End-Stage Liver Disease (MELD). Hepatology. 2007; 45:797–805. [PubMed: 17326206]
24. Onaca N, Levy MF, Netto GJ, et al. Pretransplant MELD score as a predictor of outcome after liver transplantation for chronic hepatitis C. Am J Transplant. 2003; 3:626–30. [PubMed: 12752320]
25. Saab S, Wang V, Ibrahim AB, et al. MELD score predicts 1-year patient survival post-orthotopic liver transplantation. Liver Transpl. 2003; 9:473–6. [PubMed: 12740789]
26. Freeman RB, Harper A, Edwards EB. Excellent liver transplant survival rates under the MELD/PELD system. Transplant Proc. 2005; 37:585–8. [PubMed: 15848465]
27. Ghobrial RM, Steadman R, Gornbein J, et al. A 10-year experience of liver transplantation for hepatitis C: analysis of factors determining outcome in over 500 patients. Ann Surg. 2001; 234:384–94. [PubMed: 11524591]
28. Nair S, Verma S, Thuluvath PJ. Pretrans-plant renal function predicts survival in patients undergoing orthotopic liver transplantation. Hepatology. 2002; 35:1179–85. [PubMed: 11981768]
29. Rimola A, Gavaler JS, Schade RR, el-Lankany S, Starzl TE, Van Thiel DH. Effects of renal impairment on liver transplantation. Gastroenterology. 1987; 93:148–56. [PubMed: 3556303]
30. Wijdicks EF, Blue PR, Steers JL, Wiesner RH. Central pontine myelinolysis with stupor alone after orthotopic liver transplantation. Liver Transpl Surg. 1996; 2:14–6. [PubMed: 9346623]
31. Bronster DJ, Emre S, Boccagni P, Sheiner PA, Schwartz ME, Miller CM. Central nervous system complications in liver transplant recipients — incidence, timing, and long-term follow-up. Clin Transplant. 2000; 14:1–7. [PubMed: 10693627]
32. Abbasoglu O, Goldstein RM, Vodapally MS, et al. Liver transplantation in hyponatremic patients with emphasis on central pontine myelinolysis. Clin Transplant. 1998; 12:263–9. [PubMed: 9642521]
33. Londoño M, Guevara M, Rimola A, et al. Hyponatremia impairs early posttransplantation outcome in patients with cirrhosis undergoing liver transplantation. Gastroenterology. 2006; 130:1135–43. [PubMed: 16618408]
34. Dawwas MF, Lewsey JD, Neuberger JM, Gimson AE. The impact of serum sodium concentration on mortality after liver transplantation: a cohort multicenter study. Liver Transpl. 2007; 13:1115–24. [PubMed: 17663412]
35. Gerbes AL, Gülberg V, Ginès P, et al. Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: a randomized double-blind multicenter trial. Gastroenterology. 2003; 124:933–9. [PubMed: 12671890]
36. Wong F, Blei AT, Blendis LM, Thuluvath PJ. A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: a multicenter, randomized, placebo-controlled trial. Hepatology. 2003; 37:182–91. [PubMed: 12500203]
37. Tripodi A, Chantarangkul V, Primignani M, et al. The international normalized ratio calibrated for cirrhosis (INR(liver)) normalizes prothrombin time results for model for end-stage liver disease calculation. Hepatology. 2007; 46:520–7. [PubMed: 17659574]

38. Bellest L, Eschwège V, Poupon R, Chazouillères O, Robert A. A modified international normalized ratio as an effective way of prothrombin time standardization in hepatology. Hepatology. 2007; 46:528–34. [PubMed: 17654598]

39. Trotter JF, Brimhall B, Arjal R, Phillips C. Specific laboratory methodologies achieve higher Model for Endstage Liver Disease (MELD) scores for patients listed for liver transplantation. Liver Transpl. 2004; 10:995–1000. [PubMed: 15390325]

40. Trotter JF, Olson J, Lefkowitz J, Smith AD, Arjal R, Kenison J. Changes in international normalized ratio (INR) and model for endstage liver disease (MELD) based on selection of clinical laboratory. Am J Transplant. 2007; 7:1624–8. [PubMed: 17511686]

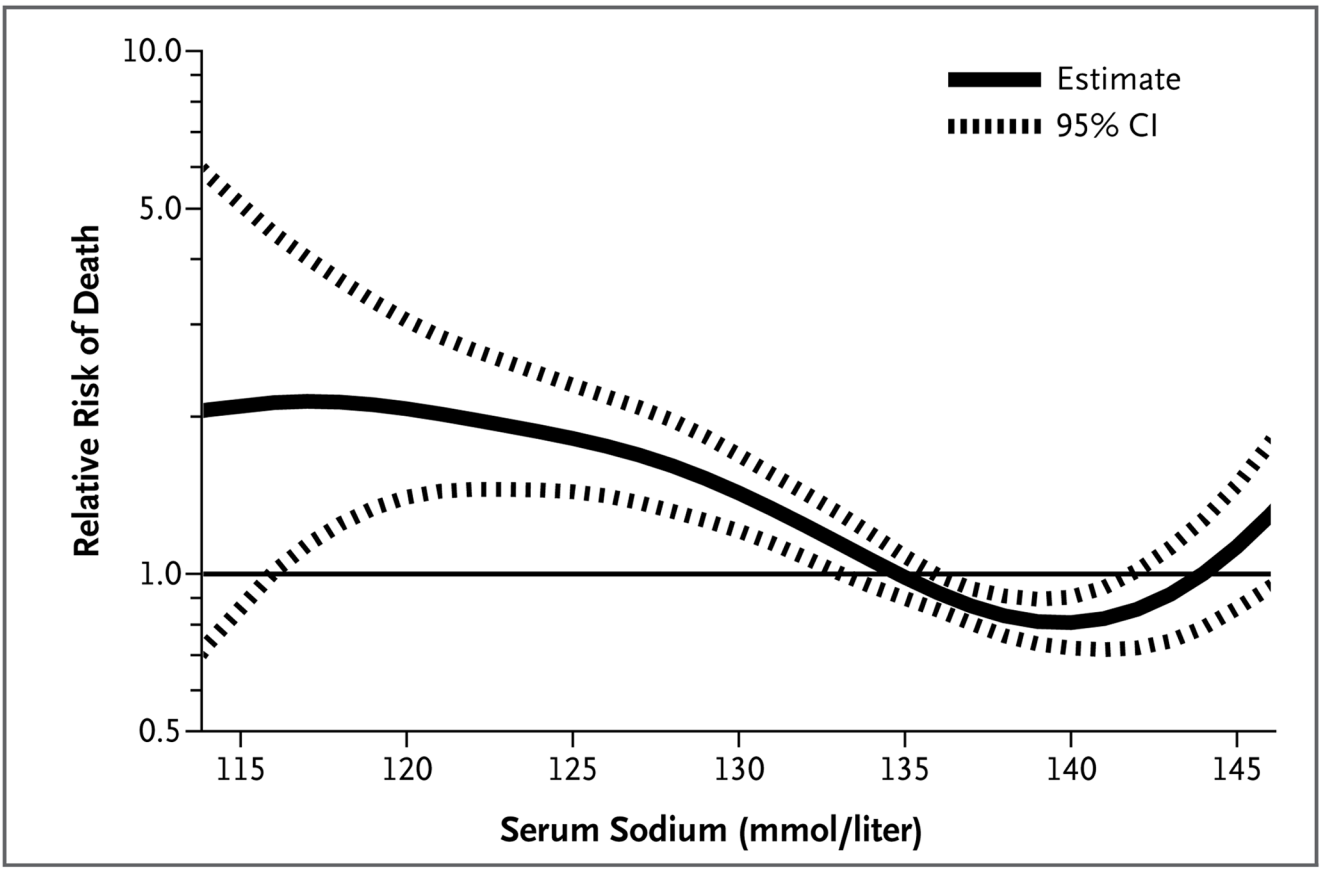

Figure 1.
Serum Sodium Concentration and the Relative Risk of Death after Adjustment for the MELD Score.

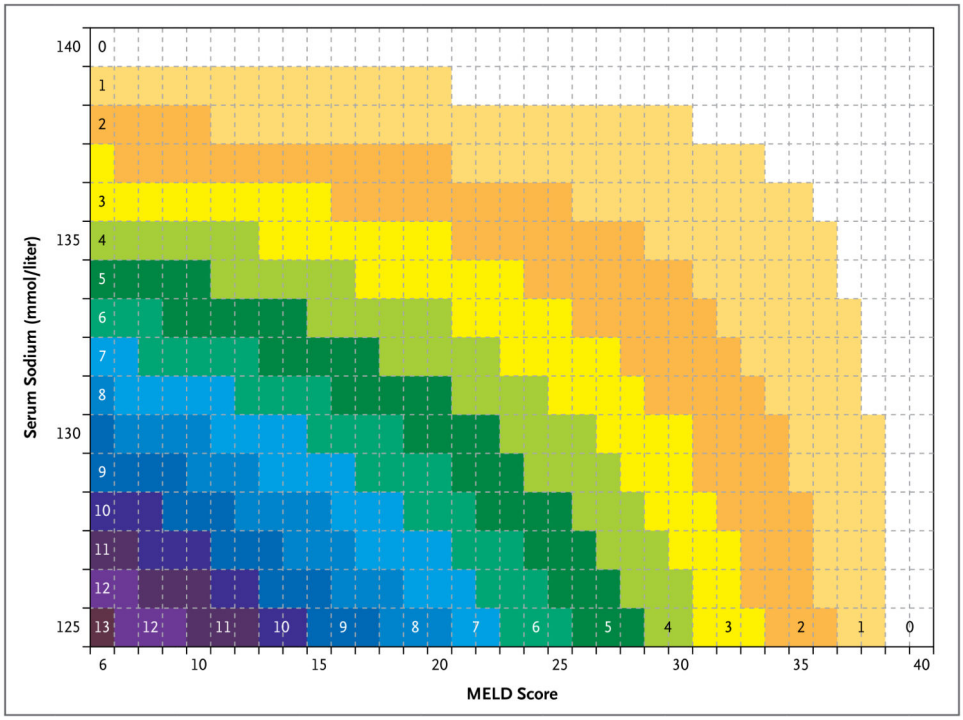

Figure 2. Computation of the MELDNa Score on the Basis of the MELD Score and the Serum Sodium Concentration

The graph shows the allocation points a patient would receive for a given Model for End-Stage Liver Disease (MELD) score and serum sodium concentration. Boxes of the same color share the same allocation points.

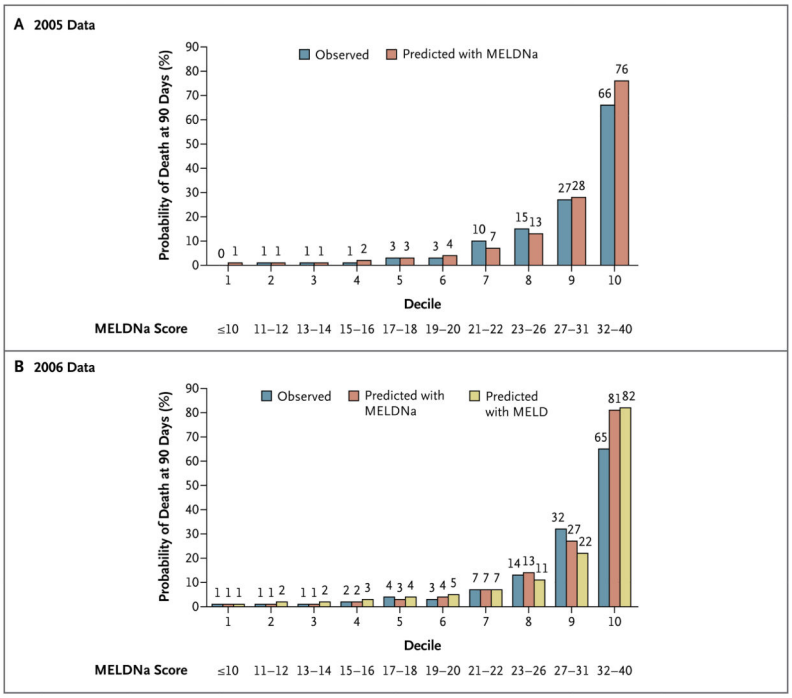

Figure 3. Observed and Predicted Probability of Death at 90 Days

Panel A shows the observed probability of death for the 2005 data and the predicted probability according to the Model for End-Stage Liver Disease–sodium (MELDNa) score in 10 groups (deciles) of patients. Panel B shows the observed probability of death for the 2006 data and the predicted probability according to the MELDNa and MELD scores in 10 groups (deciles) of patients.

MELD Score	MELDNa Score					Total
	<10	10–19	20–29	30–39	40	
	no. of patients					
<10	5	4	–	–	–	9
10–19	–	54	67	–	–	121
20–29	–	–	122	43	–	165
30–39	–	–	–	116	–	116
40	–	–	–	–	66	66
Total	5	58	189	159	66	**477**

Figure 4. Distribution of MELD and MELDNa Scores among the 477 Patients Who Died while on the Waiting List, 2006

Dark orange cells represent patients in whom the Model for End-Stage Liver Disease (MELD) score and the MELDNa score were similar. Light orange cells correspond to the 110 patients with a MELDNa score that was higher than the MELD score and in a range that might have made an organ available for transplantation. In 2006, the probability of receiving a liver transplant increased from 18.5% for a patient with a MELD score from 10 to 19 to 58.4% for a patient with a MELD score from 20 to 29 and to 70.4% for a patient with a MELD score from 30 to 39. If the MELDNa score had been used for liver allocation, the expected number of transplantations would have increased by 32, as calculated with the following formula: 67 × (58.4% − 18.5%) + 43 × (70.4% − 58.4%). Thus, 7% of deaths (32 of 477) that occurred within 3 months after registration on the waiting list might have been prevented.

Table 1

Characteristics of Registrants on the Waiting List for Liver Transplantation.*

Variable	Calendar Year		Total (N = 13,940)
	2005 (N = 6769)	2006 (N = 7171)	
Male sex — no. (%)	4397 (65)	4644 (65)	9041 (65)
Age — yr			
Median	53	53	53
Range	18–83	18–79	18–83
Race or ethnic group — %†			
White	75	75	75
Black	8	8	8
Hispanic	14	14	14
Other	17	17	17
Blood type — %			
A	38	39	38
B	12	11	12
O	46	46	46
AB	4	4	4
Diagnosis — %			
Hepatitis C	40	40	40
Alcoholic liver disease	17	19	18
Cholestatic liver disease	8	8	8
Other	35	33	34
MELD score			
Median	15	15	15
Range	6–40	6–40	6–40
Bilirubin, total — mg/dl			
Median	2.5	2.5	2.5
Range	0.1–91.1	0.1–73.8	0.1–91.1

Variable	Calendar Year		Total (N = 13,940)
	2005 (N = 6769)	2006 (N = 7171)	
Creatinine — mg/dl			
Median	1.0	1.0	1.0
Range	0.3–19.1	0.2–15.7	0.2–19.1
Prothrombin time — international normalized ratio			
Median	1.4	1.4	1.4
Range	0.6–11.5	0.7–14.9	0.6–14.9
Sodium			
Median — mmol/liter	137	137	137
Range — mmol/liter	112–149	112–168	112–168
<135 mmol/liter — no. (%)	2077 (31)	2233 (31)	4310 (31)
<125 mmol/liter — no. (%)	181 (3)	171 (2)	352 (3)
Status 3 mo after registration on waiting list — no. (%)			
Underwent transplantation	1781 (26)	2159 (30)	3940 (28)
Died	422 (6)	477 (7)	899 (6)
Withdrawn from waiting list	50 (1)	64 (1)	114 (1)

*To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for creatinine to micro-moles per liter, multiply by 88.4. MELD denotes Model for End-Stage Liver Disease.

†Race and ethnic group were determined and reported by the health providers in the hospitals where the patients were registered.