Serum Sodium Predicts Mortality in Patients Listed for Liver Transplantation

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With the implementation of the model for end-stage liver disease (MELD), refractory ascites, a known predictor of mortality in cirrhosis, was removed as a criterion for liver allocation. Because ascites is associated with low serum sodium, we evaluated serum sodium as an independent predictor of mortality in patients with cirrhosis who were listed for liver transplantation and whether the addition of serum sodium to MELD was superior to MELD alone. This is a single-center retrospective cohort of all adult patients with cirrhosis listed for transplantation from February 27, 2002, to December 26, 2003. Listing laboratories were those nearest the listing date ±2 months. Of the 513 patients meeting inclusion criteria, 341 were still listed, while 172 were removed from the list (105 for transplantation, 56 for death, 11 for other reasons). The median serum sodium and MELD scores were 137 mEq/L (range, 110-155) and 15 (range, 6-51), respectively, at listing. Median follow-up was 201 (range, 1-662) days. The risk of death with serum sodium < 126 mEq/L at listing or while listed was increased, with hazard ratios of 7.8 ($P < .001$) and 6.3 ($P < .001$), respectively, and the association was independent of MELD. The c-statistics of receiver operating characteristic curves for predicting mortality at 3 months based upon listing MELD with and without listing serum sodium were 0.883 and 0.897, respectively, and at 6 months were 0.871 and 0.905, respectively. In conclusion, serum sodium < 126 mEq/L at listing or while listed for transplantation is a strong independent predictor of mortality. Addition of serum sodium to MELD increases the ability to predict 3- and 6-month mortality in patients with cirrhosis.
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In the United States, deceased donor livers are allocated for transplantation based on a "sickest first" basis (*i.e.*, those who are most likely to die without a liver transplant are given the highest priority). Since February 27, 2002, the United Network for Organ Sharing has allocated deceased donor livers for chronic liver disease based on the model for end-stage liver disease (MELD) score.[1] Prior to the implementation of MELD, the assessment of medical urgency in liver allocation was based on Child-Turcotte-Pugh score.[2,3] The Child-Turcotte-Pugh score was limited by a narrow range of disease severity (score range, 7-15) and the inclusion of subjective clinical criteria (hepatic encephalopathy and ascites). In contrast, the MELD score as used by the United Network for Organ Sharing stratifies patients into 35 categories (score range, 6-40) and is based solely on three readily available, reproducible, and objective laboratory tests: serum total bilirubin, the international normalized ratio of the prothrombin time, and serum creatinine (minimum, 1 mg/dL; maximum, 4 mg/dL; patient on hemodialysis assigned to 4 mg/dL).

Although the MELD score was originally created to predict mortality after transjugular intrahepatic portosystemic shunt,[4] validation of the MELD score's ability to accurately rank patients with cirrhosis according to risk of death has been performed on five data sets (four independent retrospective, one prospective).[5,6] In these studies, the accuracy of the MELD score was as good as or better than the CPT score in predicting wait-list mortality. Additionally, the MELD score has been shown to predict mortality in chronic liver disease independent of body mass index, etiology of liver disease, and complications of

Abbreviations: MELD, model for end-stage liver disease; HR, hazard ratio; HCC, hepatocellular carcinoma; ROC, receiver operating characteristic; HD, hemodialysis; CVVHD, continuous venous–venous hemodialysis.

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portal hypertension such as hepatic encephalopathy, variceal bleeding, and spontaneous bacterial peritonitis.[5,6] Others have suggested that serum albumin, serum total bilirubin, severity of ascites, and severity of hepatic encephalopathy may be predictive of 90-day mortality independent of MELD score.[7] However, there are clear advantages to preserving the objective nature of the MELD score, and a return to the use of subjective criteria such as severity of ascites or hepatic encephalopathy in allocation is considered undesirable.

Serum sodium, like the components of the MELD score, is a readily available, reproducible, and objective laboratory test. Hyponatremia and impaired solute-free water excretion are well-recognized events in the cascade leading to hepatorenal syndrome[8–11] and ascites,[8,9,11–13] and have been associated with increased liver-related mortality.[10,11,13–17] Therefore, we hypothesized that serum sodium may be useful as a predictor of mortality in patients awaiting liver transplantation, and that the addition of serum sodium to MELD may be useful in determining prioritization for liver transplantation. In this study, we evaluated serum sodium as an independent predictor of death in patients with cirrhosis who were listed for liver transplantation and found that the addition of serum sodium to MELD yields superior accuracy to MELD alone in predicting 3- and 6-month mortality.

Patients and Methods

Study Design and Patient Population. This was a single-center retrospective cohort study of all adults listed for liver transplantation at the University of California–San Francisco from February 27, 2002, to December 26, 2003. Patients with hepatocellular carcinoma (HCC) were included. Patients listed for fulminant hepatic failure, repeat liver transplant, and etiologies without cirrhosis were excluded. Patient demographics, etiology of liver disease, complications at the time of listing, requirement for renal support (dialysis), serum sodium and biological MELD scores at the time of listing and while listed were recorded. The biological MELD score was calculated according to Kamath et al.[5] independent of hemodialysis status and not capped at a MELD score of 40. When a MELD score concurrent with serum sodium was not available, the most recent MELD score prior to the date of the serum sodium result was used for analysis. For laboratory results designated as listing laboratory tests, only those within 2 months of the date of listing were used. Patients who died while listed were no more or less likely to be excluded because of an absence of listing laboratory data compared with patients who did not die ($P = .13$). The time from serum sodium to the next MELD score was 2 or fewer days for 85% of the intervals, 7 or fewer days for 86% of the intervals, and 30 or fewer days for 91% of the intervals. When a patient had more than one laboratory result for the same test within a 24-hour period, the first test result was used. Patients were followed until death, liver transplantation, or the end of the study period. Observations ended after any of these end points. The following additional subanalyses were performed: (1) excluding patients with HCC, (2) censoring data at the onset of hemodialysis, and (3) assigning a serum sodium value of 125 mEq/L at the onset of hemodialysis. In the second subanalysis, patients on hemodialysis at or before listing had all observations deleted. The study was approved by the local institutional review committee.

Statistical Methods. Cox proportional hazard ratios (HRs) for death were estimated with univariate models of baseline demographic and clinical variables, as well as with multivariate models using the biological MELD and serum sodium as predictors at the time of listing and at "any time" during the observation period. HRs for "any time" were calculated with serum sodium and MELD as time varying covariates, using the most recent prior value for each time at which the patient was still at risk. Serum sodium was analyzed as a continuous and as a dichotomous variable with preselected cutoffs for serum sodium of 126 and 131 mEq/L. These cutoffs are similar to those in prior studies.[8,10,17] Testing of proportional hazard assumptions was performed. Additionally, bivariate logistic regression models with listing serum sodium and biological MELD as predictors were used to estimate odds ratios and assess the independent association of serum sodium and waitlist mortality at 3 and 6 months. The c-statistics or area under the receiver operating characteristic (ROC) curves for listing biological MELD with and without listing serum sodium as predictors of 3- and 6-month mortality were assessed using nonparametric methods.[18] All statistical analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC).

Results

Patient Characteristics

There were 554 patients listed for liver transplantation at the University of California–San Francisco from February 27, 2002, to December 26, 2003. A total of 41 patients were excluded from the study: 16 for fulminant hepatic failure, 16 for repeat liver transplant, and 3 for non–cirrhosis-related etiologies. An additional 6 patients were excluded because of the presence of nonliver cancers and other significant comorbidities that were contraindications for liver transplantation. Thus, a total of 513 patients formed the study cohort (Fig. 1). At the end of the study period, 341 patients were still listed and 172 had

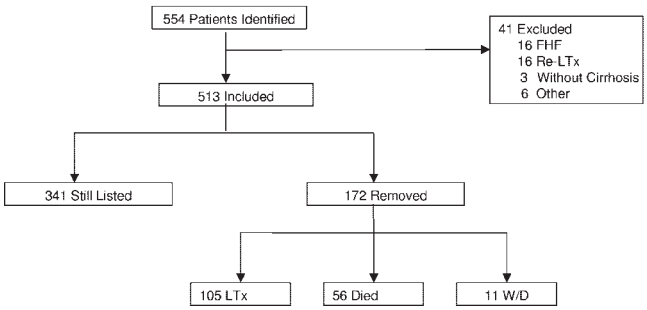

Fig. 1. Flow diagram of patient outcomes. LTx, liver transplantation; Re-LTx, repeat liver transplant; FHF, fulminant hepatic failure; W/D, withdrawn for other reasons.

been removed from the list, with 105 removed for liver transplantation, 56 for death, and 11 for other reasons, including positive toxicology tests, progression of HCC, and transfer of care to another center.

The study cohort was 65% male with a median age of 52 years (range, 20-75); 77% were Caucasian, 15% were Asian, 5% were African American, and 3% were of other races (Table 1). The etiology of cirrhosis was hepatitis C in 55%, alcoholic liver disease in 15%, hepatitis B in 13%, nonalcoholic steatohepatitis in 8%, primary biliary cirrhosis in 4%, autoimmune hepatitis in 2%, primary sclerosing cholangitis in 1%, and other etiologies in 2%. The patients in the cohort had the following complications before the time of listing for liver transplantation: ascites in 54%, encephalopathy in 37%, gastrointestinal bleeding in 29%, HCC in 18%, and bacterial infection in 11%.

Table 1. Patient Characteristics

Patient Characteristic	Entire Cohort
Median age (range)	52 (20–75)
Male (%)	333 (65)
White (%)	395 (77)
Asian (%)	77 (15)
African American (%)	26 (5)
Other (%)	15 (3)
Hepatitis C virus (%)	282 (55)
Alcohol-related liver disease (%)	77 (15)
Hepatitis B virus (%)	67 (13)
NASH/CC (%)	41 (8)
Primary biliary cirrhosis (%)	21 (4)
Autoimmune hepatitis (%)	10 (2)
Primary sclerosing cholangitis (%)	5 (1)
Other (%)	10 (2)
Ascites (%)	277 (54)
Hepatic encephalopathy (%)	190 (37)
Gastrointestinal bleeding (%)	149 (29)
Hepatocellular carcinoma (%)	92 (18)
Infection (%)	56 (11)
Serum sodium at listing (range)	137 (110–148)
Serum sodium any time (range)	137 (115–152)
MELD at listing (range)	15 (6–51)
MELD at any time (range)	27 (10–55)
Median follow-up (range)	201 (1–662)

Abbreviations: NASH, nonalcoholic steatohepatitis; CC, cryptogenic cirrhosis.

Table 2. Univariate Analysis of Variables Associated With Wait-List Mortality

Variable	HR	95% CI	*P* Value
Age (yr)	0.98	0.96–1.02	.41
Female	1.00	–	–
Male	1.67	0.85–3.29	.13
White	1.00	–	–
African American*	0.00	0.00–0.00	.95
Asian	1.43	0.66–3.07	.37
Other	0.74	0.10–5.41	.77
Ascites	1.86	1.01–3.43	.048
Hepatic encephalopathy	1.78	1.01–3.15	.049
Gastrointestinal bleeding	0.47	0.21–1.02	.51
Hepatocellular carcinoma	0.65	0.26–1.66	.37
Infection	0.38	0.10–1.55	.18
HBV/HCV	1.33	0.54–3.30	.53
Alcohol-related liver disease	1.30	0.56–2.78	.58
AIH/PBC/PSC	1.10	0.38–3.15	.86
NASH/CC	0.25	0.03–1.84	.17
Serum sodium list	0.87	0.82–0.91	<.0001
MELD list	1.21	1.15–1.28	<.0001

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; NASH, nonalcoholic steatohepatitis; CC, cryptogenic cirrhosis.

*No African American patients died.

The median listing serum sodium was 137 mEq/L (range, 110-148). The median listing MELD score was 15 (range, 6-51). Stratified by outcome, the median listing MELD scores were 13, 15, and 20 for the still waiting, transplanted, and died groups, respectively, and the median listing serum sodium values were 137, 137, and 134, respectively. The median follow-up for the cohort was 201 days (range, 1-662).

Predictors of Waiting List Mortality

Cox Proportional Hazard Models. In univariate analysis, ascites and hepatic encephalopathy at the time of listing were independent predictors of mortality (HR, 1.86 [95% CI, 1.01-3.43], $P = .048$; and HR, 1.78 [95% CI, 1.01-3.15], $P = .049$, respectively), but hepatocellular carcinoma (HCC), gastrointestinal bleeding, and bacterial infection were not predictive of mortality (Table 2). Also, age, race, sex, and etiology of liver disease were not independent risk factors for mortality. In univariate analysis, increasing MELD and decreasing serum sodium as continuous variables at time of listing were associated with an increased risk of death (HR, 1.21 [95% CI, 1.15-1.28], $P < .0001$; and HR, 0.87 [95% CI, 0.82-0.91], $P < .0001$, respectively).

Table 3. Wait-List Mortality Based on MELD and Serum Sodium at Listing (Models 1–3) and at Any Time While on the Wait List (Models 4–5)

Model and Variable	HR	95% CI	*P* Value
1			
List MELD*	1.20	1.15-1.24	<.001
List SNa†	0.93	0.88-0.99	.027
2			
List MELD*	1.22	1.16-1.28	<.001
List SNa <126‡	7.78	2.71-22.3	<.001
3			
List MELD*	1.20	1.13-1.26	<.001
List SNa <131‡	1.68	0.67-4.23	.27
4			
Recent MELD§	1.18	1.14-1.23	<.001
SNa <126‖	6.26	2.92-13.4	<.001
5			
Recent MELD§	1.19	1.14-1.23	<.001
SNa <131‖	4.99	2.47-10.1	<.001

Abbreviation: SNa, serum sodium.

*MELD score at time of listing for liver transplantation.

†Serum sodium as a continuous variable at the time of listing for liver transplantation.

‡Serum sodium as a dichotomous variable at the time of listing for liver transplantation.

§Most recent MELD score for each time at risk while listed for liver transplantation.

‖Serum sodium as a dichotomous variable at any time while listed for liver transplantation.

In bivariate analysis, including MELD and serum sodium, serum sodium as a continuous variable at the time of listing was negatively associated with risk of death (HR, 0.93 [95% CI, 0.88-0.99], $P = .027$). Each 1-mEq/L increase in serum sodium was associated with a 7% reduction in risk of death while listed for liver transplantation. MELD score was positively associated with risk of death (HR, 1.20 [95% CI, 1.15-1.24], $P < .001$). Each 1-point increase in the MELD score was associated with a 20% increase in the risk of death while waiting for liver transplantation. As a dichotomous variable using *a priori* cutoffs of less than 126 and less than 131 mEq/L, a serum sodium less than 126 mEq/L at listing was associated with an increased risk of death (HR, 7.78 [95% CI, 2.71-22.3], $P < .001$). The 7.8-fold increase in the risk for death associated with a serum sodium less than 126 mEq/L was independent of the MELD score at the time of listing (Table 3). Additionally, a serum sodium less than 126 mEq/L and less than 131 mEq/L at any point while listed for liver transplantation was associated with an increased risk of death (HR, 6.26 [95% CI, 2.92-13.4], $P < .001$; and HR, 4.99 [95% CI, 2.47-10.1], $P < .001$, respectively). The 6.3- and 5-fold increases in the risk of death for serum sodium less than 126 mEq/L and less than 131 mEq/L, respectively, were independent of the MELD score at that time (Table 3). Although a listing serum sodium less than 131 mEq/L was not associated with a statistically significant increase in the risk of death (HR, 1.68 [95% CI, 0.67-4.23], $P = .268$), this result is likely due to insufficient power.

When patients with HCC were excluded (n = 97), the risks of death associated with low serum sodium at listing and at any point while listed for liver transplantation were increased. Serum sodium as a continuous variable at the time of listing remained negatively associated with risk of death (HR, 0.87 [95% CI, 0.82-0.91], $P < .0001$). A serum sodium less than 126 mEq/L at listing and at any point while listed for liver transplantation was associated with an increased risk of death (HR, 11.6 [95% CI, 4.4-30.7], $P < .0001$; and HR, 24.7 [95% CI, 12.2-50.1], $P < .0001$, respectively). A serum sodium less than 131 mEq/L at listing and at any point while listed for liver transplantation was associated with an increased risk of death (HR, 6.2 [95% CI, 2.8-13.9], $P < .0001$; and HR, 13.5 [95% CI, 6.6-27.5], $P < .0001$, respectively).

When patients on hemodialysis were censored at the date of hemodialysis, the risks of death associated with low serum sodium at listing and at any point while listed for liver transplantation again increased. Serum sodium as a continuous varsiable at the time of listing was negatively associated with risk of death (HR, 0.91 [95% CI, 0.86-0.97], $P = .002$). A serum sodium less than 126 mEq/L at listing and at any point while listed for liver transplantation was associated with an increased risk of death (HR 13.5, [95% CI, 4.5-40.7], $P < .0001$; and HR, 9.5 [95% CI, 3.7-24.5], $P < .0001$). A serum sodium less than 131 mEq/L at listing and at any point while listed for liver transplantation was associated with an increased risk of death (HR, 3.1 [95% CI, 1.1-8.7], $P = .033$; and HR, 7.3 [95% CI, 2.8-18.6], $P < .0001$, respectively).

When patients on hemodialysis were included but assigned a serum sodium of 125 mEq/dL at the date of hemodialysis, similar results were obtained. The risk of death increased with lower serum sodium at listing and at any point while listed for liver transplantation. Serum sodium as a continuous variable at the time of listing and at any time point while listed was negatively associated with risk of death (HR, 0.91 [95% CI, 0.86-0.96], $P = .001$; and HR, 0.78 [95% CI, 0.73-0.82], $P < .0001$, respectively).

Logistic Regression Models and ROC Curves of Serum Sodium and MELD as Predictors of Mortality. In bivariate logistic regression models, odds ratios for 3-month and 6-month wait-list mortality were calculated using MELD and serum sodium (as a continuous variable, serum sodium less than 126 mEq/L, or serum sodium less than 131 mEq/L) (Table 4). There was a statistically significant increase in the odds of death for

Table 4. Odds of Wait-List Mortality at 3 and 6 Months Based on Serum Sodium, Controlling for MELD

Model and Variables	3-Month Wait-List Mortality			6-Month Wait-List Mortality		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
1						
List MELD*	1.23	1.10–1.36	<.001	1.31	1.16–1.49	<.001
List SNa†	0.86	0.77–0.96	<.001	0.85	0.76–0.95	.003
2						
List MELD*	1.30	1.16–1.45	<.001	1.38	1.21–1.57	<.001
List SNa <126‡	39.36	5.70–271.9	<.001	60.81	4.91–753.4	.001
3						
List MELD*	1.23	1.10–1.37	<.001	1.30	1.14–1.48	<.001
List SNa <131‡	3.77	0.98–14.5	.054	7.38	1.93–28.3	.004

Abbreviations: OR, odds ratio; SNa, serum sodium.

*MELD score at the time of listing for liver transplantation.

†Serum sodium as a continuous variable at the time of listing for liver transplantation.

‡Serum sodium as a dichotomous variable at the time of listing for liver transplantation.

serum sodium and MELD in each of these models except in the model using serum sodium less than 131 mEq/L to predict 3-month mortality. When the ROC curves generated from the logistic regression models to assess the increase in accuracy in predicting 3- and 6-month wait-list mortality were examined, the addition of serum sodium to MELD, increased the area under the ROC curves (c-statistic) in each model. The area under the ROC curves for predicting 3-month mortality using MELD alone, MELD plus serum sodium as a continuous variable, MELD plus serum sodium less than 126 mEq/L, and MELD plus serum sodium less than 131 mEq/L were 0.883, 0.897, 0.917, and 0.904, respectively. The area under the ROC curves for these same models predicting 6-month mortality were 0.871, 0.905, 0.921, and 0.910, respectively (Figs. 2 and 3; Table 5).

Discussion

The implementation of the MELD score as the measure of medical urgency for liver allocation in the United States demonstrates a firm commitment to the use and further development of evidence-based models to assess wait-list mortality. The prospective validation of MELD in patients listed for liver transplantation by Wiesner et al.[6] provides reassurance that the change from Child-Turcotte-Pugh score to a MELD-based allocation was a "step forward." In the current study, we provide further validation of the prognostic value of the MELD score in predicting wait-list mortality. It is clear that some aspects of medical urgency are not accurately represented by the MELD score. Additional refinement of mortality models should lead to improved generalization and accuracy while maintaining the use of readily available, reliable, reproducible, and objective parameters. In this study, we show that serum sodium provides additional prognostic information, independent of the MELD score, in predicting wait-list mortality for patients with cirrhosis.

Hyponatremia in cirrhosis is primarily the result of solute-free water retention. The proposed mechanism is

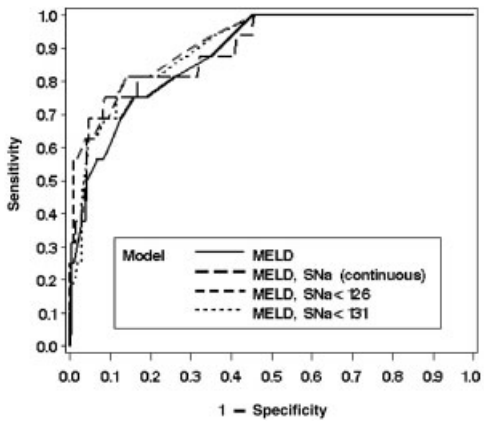

Fig. 2. Receiver operating curves with predictors of listing MELD alone, listing MELD plus listing serum sodium as a continuous variable, listing MELD plus serum sodium as dichotomous variable (<126 mEq/L, <131 mEq/L), and outcomes of 3-month mortality. SNa, serum sodium.

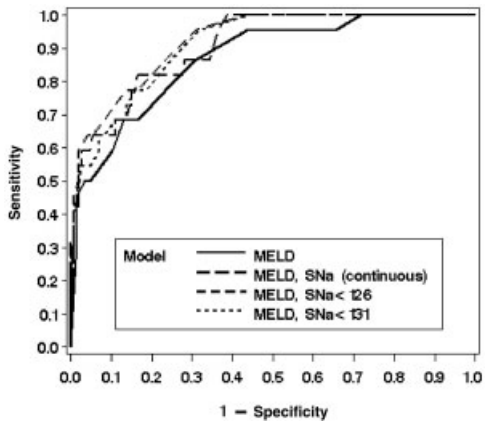

Fig. 3. Receiver operating curves with predictors of listing MELD alone, listing MELD plus listing serum sodium as a continuous variable, listing MELD plus serum sodium as dichotomous variable (<126 mEq/L, <131 mEq/L), and outcomes of 6-month mortality. SNa, serum sodium.

Table 5. AUC for ROC Curves for Prediction of 3- and 6-Month Mortality

Model	AUC for ROC Curve: 3-Month Mortality (c-Statistic)	*P* Value*	AUC for ROC Curve: 6-Month Mortality (c-Statistic)	*P* Value†
MELD	0.883	–	0.871	–
MELD + SNa‡	0.897	.465	0.905	.249
MELD + SNa <126§	0.917	.207	0.921	.143
MELD + SNa <131§	0.904	.219	0.910	.200

Abbreviations: AUC, area under the curve; SNa, serum sodium.

*Comparison of c-statistic for model to MELD alone at 3 months.

†Comparison of c-statistic for model with MELD alone at 6 months.

‡Serum sodium as a continuous function at the time of listing for liver transplantation.

§Serum sodium as a dichotomous function at the time of listing for liver transplantation.

splanchnic arterial vasodilatation leading to reduced systemic vascular resistance and the release of antidiuretic hormone, also known as arginine vasopressin.[6,9,19] A reduced mean arterial pressure is sensed by baroreceptors and leads to activation of compensatory neurohumoral mechanisms, including the sympathetic nervous system and renin–aldosterone–angiotensin system, as well as the release of antidiuretic hormone. The net result of this activation is solute-free water retention, avid renal sodium retention, and dilutional hyponatremia. The degree of activation of these neurohumoral mechanisms and renal impairment correlates directly with the degree of portal hypertension.[20–23] Additionally, therapeutic interventions that decrease portal hypertension (*e.g.*, transjugular intrahepatic portosystemic shunts[23]) or blunt the neurohumoral cascade (*e.g.*, vasopressin receptor antagonists[24,25]) increase serum sodium levels. Therefore, it follows that serum sodium would be a reasonable parameter to reflect the severity of portal hypertension in patients with cirrhosis who are listed for liver transplantation. In the current study, hyponatremia was strongly associated with an increased risk of wait-list mortality. A serum sodium less than 126 mEq/L at the time of listing for liver transplantation or any point while listed was associated with a 6.3- to 7.8-fold increase in risk of death while awaiting a transplant.

A serum sodium less than 126 mEq/mL remained an independent predictor of wait-list mortality after controlling for the contribution of the most recent MELD score. Furthermore, the addition of serum sodium to MELD at the time of listing for liver transplantation was associated with an increase in the accuracy in predicting both 3- and 6-month wait-list mortality with cirrhosis as assessed by area under the curve of the ROC curves. Listing serum sodium less than 126 mEq/L as a dichotomous variable plus MELD led to an increase of the accuracy of predicting 3- and 6-month wait-list mortality by 3.4% (from 0.883 to 0.917) and 5% (from 0.871 to 0.921), respectively. When used as a continuous variable, the addition of listing serum sodium to MELD increased the accuracy of mortality prediction by 1.4% (from 0.883 to 0.897) and 3.4% (from 0.871 to 0.905) for mortality at 3 and 6 months, respectively. These improvements are smaller in magnitude than that reported by Wiesner et al.[6] in their prospective evaluation of MELD versus CPT in predicting 3-month wait-list mortality, in which MELD increased the accuracy by 7% (from 0.76 to 0.83). However, the incremental improvement seen by adding serum sodium to MELD in the current study was sizable considering the already high accuracy of MELD alone. Although the *P* values comparing ROC curves for MELD alone versus MELD plus serum sodium did not achieve statistical significance, the direction of improved accuracy in predicting mortality is consistent across all measures of serum sodium, and both the survival models and logistic regression models demonstrate a strong and independent contribution of serum sodium to 3- and 6-month wait-list mortality.

Like the components of the MELD score, serum sodium can be influenced by factors other than the underlying severity of liver disease. Hemodialysis (HD) and continuous venous–venous hemodialysis (CVVHD) are frequently required for the management of renal complications associated with advanced liver disease. In our cohort of 513 patients, 41 received HD or CVVHD during the observation period. The influence of HD on our findings was assessed by performing our analysis with and without censoring patients at the onset of first dialysis. This showed that inclusion of patients on renal replacement therapy biased our results toward the null. When patients were censored at the time of HD or CVVHD, the HRs associated with lower serum sodium increased. This association is not surprising, because patients requiring HD or CVVHD support are more likely to have iatrogentically corrected serum sodium, thereby masking the relationship between disease severity and serum sodium levels. Future models may need to consider assignment of a specific serum sodium value—such as 125 mEq/dL (similar to serum creatinine in the current

MELD)—to those patients requiring HD. Other possible factors that may influence serum sodium levels but were not assessed in this study include diet, diuretics, free water restriction, intravenous fluids, and osmotic laxative use.[9,26] Although these latter factors certainly can affect serum sodium, including them in an allocation model would be impractical.

To make the study findings more generalizable, we included patients with HCC and used their calculated biological MELD score for analysis. However, we recognized that patients with HCC (1) may have less severe liver disease, and (2) differ from patients with decompensated cirrhosis in terms of the underlying pathophysiology and natural history. In the cohort of 513 patients, 97 had HCC (45 of whom received a liver transplant), 7 died, 40 were still listed, and 64 had another complication of liver disease at the time of listing (gastrointestinal bleeding, encephalopathy, and/or ascites [26 with ascites only]). The influence of including patients with HCC was assessed by repeating the analysis excluding those with HCC. The HRs for death associated with low serum sodium increased when these patients were excluded. As with the effects of HD and CVVHD, inclusion of HCC patients in our cohort introduces a bias toward the null and does not significantly alter the strong association between serum sodium and mortality in our models. Although two thirds of those with HCC had another complication at the time of listing, they had lower median biological MELD scores at the time of listing than those without HCC (11 vs. 15). Additionally, because the MELD score used for assigning priority for liver transplantation was based on the HCC exception policy—not the biological MELD score—in these patients, those with HCC had a higher likelihood of transplant and therefore were also more likely to be censored before progressive decompensation and death.

The retrospective single-center design of this study has its limitations. Because this study reflects the patient population and practice patterns at one center, referral biases likely ocurred. Although serum sodium is a routinely ordered test in patients with liver disease at our center, it was not always ordered concurrently with the MELD laboratory tests. When a concurrent MELD score was not available, the most recent MELD score prior to the date of serum sodium was used for analysis. For laboratory results designated as listing laboratory tests, only those within 2 months of the date of listing were used. As expected, the frequency of laboratory testing varied based on severity of illness and hospitalization status. Patients with high MELD scores who also had more frequent laboratory testing were more likely to have concurrent MELD laboratory tests and serum sodium. Therefore, multicenter prospective studies will be needed to confirm and extend our findings. The Organ Procurement Transplant Network has recently added serum sodium to the list of laboratory tests collected in liver transplant recipients.

To patients whose lives depend upon a liver transplant, the means of prioritizing the receipt of this lifesaving organ is of ultimate importance. Within the current paradigm for deceased liver donor allocation based on medical urgency, we as physicians and patient advocates are obliged to continue to refine our allocation models. In this study, we have shown that serum sodium is an independent predictor of mortality in patients with cirrhosis and may provide improved accuracy if added to the MELD score. Serum sodium as a continuous variable should be considered as an additional parameter to the MELD score, with patients receiving HD assigned a serum sodium value such as 125 mEq/dL.

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