Addition of Serum Sodium Into the MELD Score Predicts Waiting List Mortality Better Than MELD Alone

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In this study, we investigated the prognostic value of serum sodium and hyponatremia (≤130 mEq/L) in 262 cirrhotic patients consecutively listed, 19 of which died (7%), 175 survived (67%), and 68 underwent liver transplantation (26%) during 3 months of follow-up. Hyponatremia was present in 63% of patients who died, compared to 13% of those who survived ($P < .001$), whereas the proportion with elevated creatinine (≥1.4 mg/dL) was low and similar in both groups (10.5 vs. 3%). Prevalence of hyponatremia was higher than that of elevated serum creatinine across all model for end-stage liver disease (MELD) categories. Using logistic regression, hyponatremia and serum sodium were significant predictors of mortality with concordance statistics (c-statistics) .753 for hyponatremia, .784 for sodium, .894 for MELD, .905 for MELD plus hyponatremia ($P = .006$ vs. MELD alone), and .908 for MELD plus serum sodium ($P = .026$ vs. MELD alone). Risk of death across all MELD scores was higher for patients with hyponatremia than without hyponatremia. Cox regression considering data within 6 months of follow-up yielded qualitatively similar results, with hyponatremia being a significant predictor of greater mortality risk with an odds ratio of 2.65 ($P = .015$). Each increase of 1 mEq/L of serum sodium level was associated with a decreased odds ratio of .95 ($P = .048$). Our results indicate that hyponatremia appears to be an earlier and more sensitive marker than serum creatinine to detect renal impairment and / or circulatory dysfunction in patients with advanced cirrhosis. In conclusion, addition of serum sodium to MELD identified a subgroup of patients with poor outcome in a more efficient way than MELD alone and significantly increased the efficacy of the score to predict waitlist mortality. (*Liver Transpl 2005; 11:336–343.*)

The model for end-stage liver disease (MELD) is based on 3 biochemical variables that are readily available, reproducible, and objective: serum bilirubin, serum creatinine, and the international normalized ratio (INR) of prothrombin time. MELD has been found to be an excellent predictor of 3-month mortality among cirrhotic patients listed for orthotopic liver transplantation (OLT).[1] Since February 2002, allocation of organ donors in the United States has been based on the MELD score. With the exception of patients with fulminant hepatic failure and those requiring emergency retransplantation who are listed as United Network for Organ Sharing status 1, cirrhotic patients are stratified on the waiting list and are given priority for OLT according to their MELD scores.[2] Recently reported data showed that death or removal from the waiting list for being too sick for OLT has decreased in the MELD / pediatric end-stage liver disease era, both for children and adults.[3] Despite the usefulness of MELD, an appropriate question to be raised is whether the efficiency of the score can be further improved, at least for some patient cohorts.

Ascites is a major complication of cirrhosis and is therefore an indication for OLT.[4] Serum creatinine is strongly powered in the MELD formula. However, increase in serum creatinine is a late event in patients with ascites. The Consensus Conference of the International Ascites Club reported by Arroyo et al.[5] established that chronologically elevation of serum creatinine occurs only after the onset of sodium retention and impaired ability to excrete free water. In addition, patients with type 1 hepatorenal syndrome may develop rapidly progressive renal failure, which in turn is associated with increased morbidity and mortality following OLT.[6,7] Previous studies have shown that parameters estimating systemic hemodynamics and renal function are better predictors of survival in patients

Abbreviations: MELD, model for end-stage liver disease; INR, international normalized ratio; OLT, orthotopic liver transplantation; c-statistic, concordance statistic.

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with cirrhosis and ascites than those routinely used to measure hepatic function. Examples of these are glomerular filtration rate, urinary sodium excretion, plasma renin activity, renal water excretion after a water load test, dilutional hyponatremia, mean arterial pressure, and norepinephrine concentration.[6,8–10] Dilutional hyponatremia is a frequent event in cirrhotic patients with ascites and is associated with elevated in hospital mortality.[11] Moreover, hyponatremia has been found to be an independent predictor of long-term survival and of hepatorenal syndrome, and is also considered a surrogate marker for circulatory dysfunction following large volume paracentesis.[6,10,12,13] Therefore, the objectives of this study were to investigate the prognostic value of serum sodium and hyponatremia in patients with cirrhosis listed for OLT and whether the addition of serum sodium into the MELD would increase the accuracy of the score to estimate waitlist mortality.

Materials and Methods

The study included 262 consecutive patients aged ≥18 years with decompensated cirrhosis listed for OLT in our center from June 1995 to January 2003. INR and serum bilirubin, creatinine, and sodium were obtained on the same day, at the time of listing. MELD was calculated according to the United Network for Organ Sharing formula.[2] Scores were rounded to the nearest 10th. Serum bilirubin, INR, or serum creatinine <1.0 were set to a value of 1.0 to preclude negative scores, whereas serum creatinine levels were capped at 4.0, although no patient in this series was on hemodialysis. Hyponatremia was defined as serum sodium ≤130 mEq/L. This cutoff value was utilized in previously reported studies analyzing the prevalence, prognosis, and therapy of hyponatremia in cirrhotic patients with ascites.[11–18] Elevated serum creatinine was defined as values ≥1.4 mg/dL. The rationale for this threshold was to select a value of serum creatinine that has significant impact by itself on the MELD score. Therefore, in a given patient with normal bilirubin and INR, a serum creatinine of 1.4 mg/dL results in a MELD score of 10. Moderate or large ascites (grade 2 or 3) was defined as symmetrical abdominal distension, easily detectable on clinical examination.[4] Candidates for living-donor liver transplantation or combined transplantation and those with hepatocellular carcinoma, parenchymal renal disease, or on anticoagulant therapy were excluded from the analysis. Patients were followed until death or OLT during the 6 months after the time of listing. Argentina has a single national waiting list including 3 categories: 1) emergency: fulminant hepatic failure and emergency retransplantation for primary nonfunction or hepatic artery thrombosis with liver failure; 2) urgency: serum bilirubin >20 mg/dL and prothrombin activity <60% for patient with chronic cholestasis, and bilirubin >8 mg/dL, prothrombin activity <35% and serum creatinine >1.7 mg/dL (2 of 3 variables) for patients with hepatocellular causes of cirrhosis; and 3) elective: all other listed patients.

Logistic regression was used to assess the accuracy of serum sodium, hyponatremia, and MELD as predictors of death within 3 months of listing; patients transplanted within 3 months were dropped from analysis. The concordance statistic (c-statistic), which is equivalent to the area under the receiver operating characteristic curve, was also calculated.[19] For our setting, when considering all pairs of patients in which 1 patient died and the other survived, the c-statistic is the fraction of the pairs in which the model correctly identifies (ranks) the patient that died. A c-statistic >0.8 indicates excellent diagnostic accuracy, and a model with a c-statistic over 0.7 should be considered clinically useful.[1] Next, a Cox proportional hazards model was fit using data within 6 months from the time of listing and concordance was calculated;[20] transplants were treated as censorings. Considering all pairs of patients in which at least 1 patient died, concordance for the Cox model and our setting is the fraction of pairs in which the model correctly identifies the patient that died or the patient who died first. The logistic model for the 3-month outcome is used as the primary analysis, as it allows the direct quantification of early mortality risk. The predictive accuracy from the Cox model may be influenced by the ability to distinguish between later events. For univariate comparisons, the Wilcoxon and Fisher exact test were also used. Statistical significance was concluded at the 2-sided 5% level. The study was approved by the institutional review board.

Results

Mean (± standard deviation) age of the patients was 49 ± 12 years (range 18-69 years). A total of 47% were females (n = 123) and 53% were males (n = 139). Etiology of cirrhosis was hepatitis C in 66 (25%), chronic cholestasis in 59 (23%), autoimmune hepatitis in 36 (14%), alcoholic liver disease in 35 (13%), cryptogenic in 31 (12%), hepatitis B in 17 (6%), and other causes in 18 (7%) patients. MELD score was 17.8 ± 6.5 (range 6-44).

Three-Month Data

For the 3-month time period following listing, 19 of the 262 patients died (7%), 175 survived (67%), and 68 underwent OLT (26%). The 194 patients who either died or survived without OLT were included in this analysis. Clinical ascites was present at listing in 100 / 194 patients (51.5%). The overall prevalence of hyponatremia was 17.5% (34 / 194). All patients with hyponatremia had ascites. Therefore, the prevalence of hyponatremia in patients with ascites was 34% (34 / 100). Patients who died had more advanced cirrhosis com-

Table 1. Severity of Liver Failure, Renal Function, and Prevalence of Ascites and Hyponatremia in Patients Who Died Within 3 Months or Survived 3 Months Without Liver Transplantation

	Survived 3 months (n = 175)	Died within 3 months (n = 19)	*p* Value
Clinical ascites	83 (47%)	17 (89.5%)	<.001
Serum bilirubin (mg/dL)	5.1 ± 5.3	17.8 ± 9.3	<.001
INR	1.5 ± .5	2.5 ± 1.3	<.001
MELD score	15.3 ± 4.9	26.4 ± 7.7	<.001
Serum creatinine (mg/dL)	.8 ± .3	.9 ± .4	.043
Elevated serum creatinine	6 (3%)	2 (10.5%)	.18
Serum sodium (mEq/L)	136 ± 5	130 ± 6	<.001
Hyponatremia	22 (13%)	12 (63%)	<.001
Elevated serum creatinine in subset of patients with hyponatremia	1 / 22 (4.5%)	2 / 12 (17%)	.28

pared to those who survived, as reflected by a significantly higher prevalence of ascites, hyperbilirubinemia, coagulopathy, and MELD score (Table 1). All patients died from major complications of cirrhosis. Etiology of cirrhosis did not differ between patients who survived or died. The prevalence of hyponatremia was 13% in patients who survived and 63% in those who died ($P <$ .001) (Table 1). In contrast, the proportion of patients with elevated serum creatinine was similar in the 2 groups. Among the 34 patients with hyponatremia, only 3 (9%) had elevated serum creatinine (4.5% in patients who survived and 17% in those who died; $P =$ .28). The prevalence of hyponatremia was higher than that of increased serum creatinine across all MELD categories (Fig. 1). Characteristics of patients with hyponatremia (n = 34) and without (n = 160) hyponatremia at the time of listing are shown in Table 2. Patients with hyponatremia differed significantly from those without hyponatremia with regard to prevalence

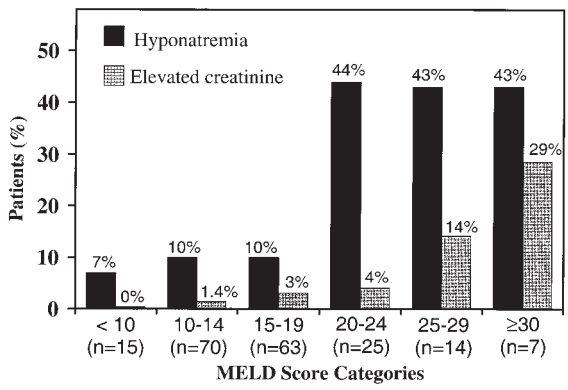

Figure 1. Prevalence of hyponatremia and elevated serum creatinine according to MELD score categories in 194 patients who either died within 3 months or survived 3 months without liver transplantation

of clinical ascites, severity of liver failure (bilirubin, INR, MELD), and risk of death. However, mean serum creatinine and the proportion of patients with increased serum creatinine were not significantly different between both groups. Mortality during the study period progressively increased, in parallel to the MELD score. Risk of death according to MELD score categories was 0% (0 / 15) in <10, 1.4% (1 / 70) in 10–14, 4.7% (3 / 63) in 15–19, 16% (4 / 25) in 20–24, 42.8% (6 / 14) in 25–29, and 71.4% (5 / 7) in ≥30. Death rates across all MELD categories were higher for patients with hyponatremia compared to those with normal serum sodium (Fig. 2).

Results from the logistic regression are given in Table 3. The c-statistics for hyponatremia and serum sodium were 0.753 and 0.784, respectively, values in the range of clinical usefulness. When used alone, the efficacy of these parameters to predict risk of death was inferior to the MELD score, which had an excellent c-statistic of 0.894. However, addition of hyponatremia or serum sodium to the MELD score increased the c-statistic to 0.905 and 0.908, respectively. The accuracy of MELD score plus hyponatremia or plus serum sodium to predict waitlist mortality was significantly higher than MELD score alone ($P = 0.006$ and $P = 0.026$, respectively). Though not depicted in Table 3, interactions between MELD and hyponatremia and between MELD and serum sodium were not statistically significant ($P = 0.29$ and $P = 0.18$, respectively). The estimated mortality rate as a function of MELD score and hyponatremia status, when excluding and including a MELD × hyponatremia interaction term, is depicted in Figure 3A and B. Including a MELD × hyponatremia interaction term, the estimate of mortality rate was greater for patients with than for patients without hyponatremia over most of the range of MELD

Table 2. Prevalence of Ascites, Severity of Liver Failure, Renal Function, and Mortality According to Hyponatremia Status in Patients Not Transplanted Within 3 Months

	No hyponatremia (n = 160)	Hyponatremia (n = 34)	p Value
Serum sodium (mEq/L)	138 ± 3	127 ± 4	<.001
Clinical ascites	66 (41%)	34 (100%)	<.001
Total bilirubin (mg/dL)	5.3 ± 5.9	11.1 ± 9.1	<.001
INR	1.5 ± 0.5	1.9 ± 1.1	<.001
MELD score	15.4 ± 5.2	21.1 ± 7.9	<.001
Serum creatinine (mg/dL)	.8 ± .3	.8 ± .4	.28
Elevated serum creatinine	5 (3%)	3 (9%)	.14
3-month mortality	7 (4%)	12 (35%)	<.001

scores, with the estimates approaching each other only at MELD scores below 12. For patients with MELD scores below 12, no deaths were observed and estimates of mortality rates were below 2% regardless of hyponatremia status. Note: The models including interaction terms should be interpreted with caution as there are fewer than 10 events per model term and the asymptotes used for derivation of the *P* values may be in question.[20]

Six-Month Data

For the 6-month time period, 29 (11%) patients died and 94 (36%) underwent OLT. No patient was lost to follow-up. Results for the Cox regression, considering data within 6 months of listing, are similar to those from the logistic regression for the 3-month time period, with hyponatremia being a significant predictor of greater mortality risk (Table 4). Interactions between MELD and hyponatremia and between MELD and serum sodium were not statistically significant ($P = 0.45$ and $P = 0.84$, respectively).

The estimated mortality rates as a function of MELD score and hyponatremia status, when excluding and including a MELD × hyponatremia interaction term, are depicted in Figure 3C and D. Including a MELD × hyponatremia interaction term, the estimated mortality rate is greater for patients with than without hyponatremia over the entire range of MELD scores.

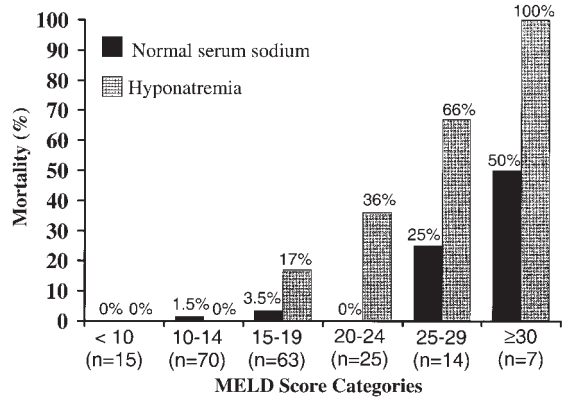

Figure 2. Observed 3-month mortality rates according to MELD score categories in 34 patients with hyponatremia and 160 patients with normal serum sodium

Discussion

This study shows that the presence of hyponatremia is associated with increased risk of death in patients with decompensated cirrhosis listed for OLT. As depicted in Figure 2, the observed mortality rate is greater for patients with hyponatremia than for patients without hyponatremia for all MELD score categories. Increased risk of death associated with hyponatremia is further indicated by the statistical significance, both univariately and multivariately, in conjunction with the MELD score, in both logistic and Cox regression models. The generality of the association between hyponatremia and increased risk of death across the range of MELD scores is supported by lack of significance of the MELD × hyponatremia and MELD × serum sodium interaction terms in both the logistic and Cox regression models and by the estimated mortality rates when including interaction terms, as depicted in Figure 3B and D.

When added to the MELD, hyponatremia significantly increased the efficacy of the score to predict waitlist mortality. Whereas the c-statistic increased by only about 1%, this increase is highly significant, with the small increment in the c-statistic being due to the relative infrequency of hyponatremia. In our data, hypona-

Table 3. Univariate and Multivariate Logistic Regression Summaries for MELD, Hyponatremia, and Serum Sodium in Predicting 3-Month Mortality

Model terms	c-Statistic	Odds ratio	95% CI	*P* Value
Hyponatremia	.753	11.92	4.34–35.21	<.001
Serum sodium (mEq/L)	.784	.84	.76–.91	<.001
MELD score	.894	1.33	1.20–1.50	<.001
MELD score plus hyponatremia	.905	1.302	1.175–1.478	<.001
		5.85	1.70–21.38	.006
MELD score plus serum sodium (mEq/L)	.908	1.307	1.180–1.483	<.001
		.89	.80–.98	.026

Abbreviation: CI, confidence interval.

tremia was associated with an estimated 2.65-fold increase in the instantaneous risk of mortality in the Cox model, even after controlling for MELD score. Therefore, due to its *P* value, hyponatremia is statistically significant and, due to the magnitude of its effect, medically significant. Considering serum sodium levels directly, as opposed to dichotomizing to hyponatremia status, each increase of 1 mEq/L is associated with a decreased odds ratio of 0.95 after controlling for MELD score. Decreased serum sodium level, univariately and after controlling for MELD score, was also associated with increased risk of mortality, but hyponatremia was the stronger predictor as judged by the level of statistical significance.

The reported prevalence of hyponatremia in patients with cirrhosis and ascites ranges from 27 to 44%,[6,11,15–17] in agreement with the 34% observed in our study. Dilutional hyponatremia occurs in patients with decreased free-water clearance driven by nonosmotic secretion of antidiuretic hormone, secondary to circulatory dysfunction and effective hypovolemia.[14] Although the prognostic value of hyponatremia in patients with cirrhosis and ascites has been established in a number of previous reports, it has been somehow underestimated in the assessment of the

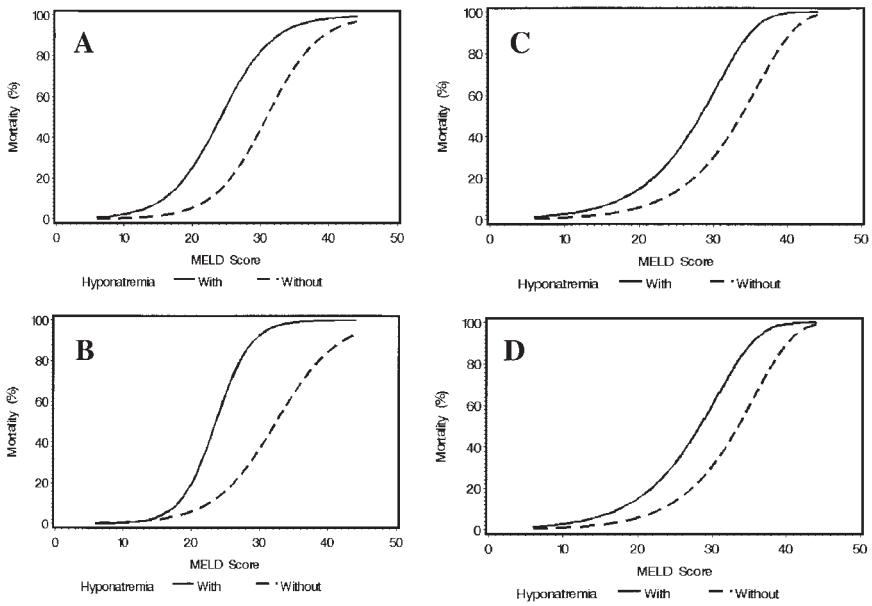

Figure 3. Three-month mortality rates according to MELD score and hyponatremia status. (A-B) A logistic regression model was fit based upon the 194 patients who either died within 3 months or survived 3 months without transplant. (C-D) A Cox regression model was fit based upon all 262 patients and transplantation was treated as censoring. (A,C) No interaction terms were included in the models; (B,D) MELD score × hyponatremia interaction terms were included.

Table 4. Univariate and Multivariate Cox Regression Summaries for MELD, Hyponatremia, and Serum Sodium in Predicting Death Considering 6-Month Follow-Up Data

Model terms	c-Statistic	Hazard ratio	95% CI	*P* Value
Hyponatremia	.671	4.93	2.36–10.29	<.001
Serum sodium (mEq/L)	.741	.91	.86–.95	<.001
MELD score	.841	1.21	1.15–1.27	<.001
MELD score plus hyponatremia	.850	1.20	1.14–1.26	<.001
		2.65	1.23–5.70	.015
MELD score plus serum sodium (mEq/L)	.855	1.20	1.14–1.26	<.001
		.95	.90–.996	.048

Abbreviation: CI, confidence interval.

risk of death, and therefore has not been utilized to prioritize patients on the waiting list. Hyponatremia was found to be an independent predictor of death in patients with cirrhosis and ascites, both in observational studies[11] and randomized controlled trials of large volume paracentesis or transjugular intrahepatic portosystemic shunting.[10,13,17,21] Borroni et al.[11] showed that in-hospital mortality was significantly higher in patients with hyponatremia compared to those without this complication (26 vs. 9%), with the highest risk of death (48%) in the subgroup with serum sodium <125 mEq/L. In agreement with our study, the proportion of patients with renal dysfunction was similar in the groups with or without hyponatremia. Mean survival after transjugular intrahepatic portosystemic shunting, as reported by Schepke et al.,[17] was significantly shorter in patients with than without hyponatremia (7.6 vs. 49.1 months). Hepatorenal syndrome, renal failure following spontaneous bacterial peritonitis, and circulatory dysfunction after large volume paracentesis are known to be associated with decreased short- and long-term survival. Gines et al.[6] showed that increased plasma renin activity and hyponatremia, but not bilirubin or coagulopathy, were independent predictors of hepatorenal syndrome in 234 cirrhotic patients with ascites. Renal failure is a frequent complication of spontaneous bacterial peritonitis. In the study reported by Follo et al.,[22] serum sodium before the onset of spontaneous bacterial peritonitis was an independent predictor of renal dysfunction triggered by this infectious complication. Sort et al.[23] recently demonstrated that combined treatment with cefotaxime and volume expansion with intravenous albumin infusion in patients with spontaneous bacterial peritonitis was associated with a significant reduction in the incidence of renal failure as compared with cefotaxime alone. Patients randomized to receive cefotaxime without albumin infusion developed a significant decrease in serum sodium and a significant increase in plasma renin activity on days 3, 6, and 9 after therapy.[23] Finally, hyponatremia has been found to be a surrogate marker for circulatory dysfunction following large volume paracentesis.[12,13] In the study by Ruiz del Arbol et al.,[12] a significant decrease in serum sodium was found in 40% of patients who developed circulatory dysfunction compared to none of those without this complication. Taken together, these findings suggest that dilutional hyponatremia should be regarded as an early prognostic marker of poor outcome, announcing the development of more serious complications.

In our study, the prevalence of hyponatremia was significantly higher in patients who died within 3 months (63%) than in those who survived 3 months (13%) (Table 1). Similarly, patients with hyponatremia had significantly more advanced liver failure compared to those with normal serum sodium (Table 2). Irrespective of the pathogenic mechanisms involved, our results indicate that the presence of hyponatremia identifies a subgroup of cirrhotic patients with poor outcome and thus with a more urgent need for OLT. Serum creatinine is strongly powered in the MELD score. However, the proportion of patients with elevated creatinine in our study was not significantly different among those who died or survived without OLT and in the cohorts of cirrhotic patients with or without hyponatremia, as described in Tables 1 and 2. In addition, the prevalence of hyponatremia was much higher than that of renal dysfunction across all MELD categories (Fig. 1). Therefore, although hyponatremia ultimately reflects renal impairment, it appears to be a more accurate and earlier marker of poor outcome than serum creatinine in candidates for OLT with advanced cirrhosis. Development of renal dysfunction is an established prognostic factor in patients with cirrhosis and ascites.[6] Previous studies have shown that measurement of serum creatinine, although practical, is not a good parameter to assess renal function in this patient population, mostly

due to decreased hepatic synthesis, increased tubular secretion, and decreased skeletal muscle mass.[24] Our results suggest that serum sodium is an earlier and more sensitive test than creatinine to detect circulatory dysfunction resulting in renal failure and / or death. This conclusion is supported by the studies of Vila et al.[15] and Porcel et al.,[16] who showed that patients with hyponatremia had significantly higher plasma concentrations of epinephrine, higher aldosterone and renin activity, significantly reduced mean arterial pressure, and elevated resistance of renal arteries when compared to patients without hyponatremia.

MELD score was an excellent predictor of 3-month mortality in our patient population, as indicated by the c-statistic of .894, which was similar or even higher than that observed in the studies that validated the usefulness of this score in the United States.[1,25] No patient with a MELD score of <10 died. In addition, mortality on the waiting list was only 1.4% in the 70 patients with MELD scores of 10–14. Risk of death progressively increased with higher scores, from 4.7% (MELD 15-19) to 71% (MELD ≥ 30). These data reinforce the idea of establishing minimal listing criteria based on MELD score. Despite the high efficacy of MELD to predict waitlist mortality in our study, incorporation of serum sodium into the formula significantly increased the c-statistic, to 0.908 (Table 3). This was due to the ability of hyponatremia, but not MELD score alone, to identify a subgroup of high-risk patients who died during the study period. Mortality of patients with hyponatremia was higher across all MELD scores, as described in Figures 2 and 3. As an example, mortality within the MELD 25–29 category was 25% for patients without hyponatremia and 66% for those with hyponatremia.

Similarly to bilirubin, INR, and creatinine, serum sodium is an objective, quantitative, and reproducible laboratory test, and therefore attractive to be incorporated into a mathematical formula such as the MELD score. It may be argued that serum sodium concentration may decrease with fluid overload and use of diuretics, and for these reasons it should be relatively easy to manipulate. However, the same drawbacks are true for serum creatinine.

In conclusion, this study shows that hyponatremia is an excellent predictor of outcome in patients with advanced cirrhosis and significantly increases the efficacy of MELD to predict waitlist mortality. The potential benefits of incorporating serum sodium into the MELD formula should be confirmed in other independent and larger series.

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