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Hyponatremia Is Associated With Increased Mortality in Children on the Waiting List for Liver Transplantation

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Background. Our aim was to determine whether hyponatremia is associated with waiting list or posttransplantation mortality in children having liver transplantation (LT). **Methods.** A retrospective analysis of the united network for organ sharing/organ procurement transplantation network database on pediatric LT performed between 1988 and 2016 was conducted. Hyponatremia was defined as a serum sodium of 130 mEq/L or below. Subjects were divided into 2 age groups: I (0–6 y old) and II (7–18 y old). Patient survival before and after LT, as well as graft survival, were compared in patients with and without hyponatremia. Multivariable Cox proportional hazards models were constructed for perioperative mortality. **Results.** Data from 6606 children were available for analysis of waiting list mortality, and 4478 for postoperative mortality. The prevalence of hyponatremia at the time of registration was 2.8% and 3.7% at the time of LT. Waiting list mortality in patients with hyponatremia was significantly higher in group I ($P < 0.001$) but not in group II ($P = 0.09$). In group I, the relative risk of mortality adjusted to pediatric end-stage liver disease score was significantly associated with hyponatremia ($P < 0.001$). A sodium level below 130 mEq/L (hazard ratio [HR] = 1.7), younger age (group I) (HR = 2.01), and need for dialysis (HR = 2.3) were independent predictors for increased waiting list mortality. There was no difference in overall postoperative patient or graft survival related to hyponatremia. **Conclusions.** Hyponatremia is associated with increased waiting list mortality for pediatric LT candidates, particularly in younger children. Future studies examining incorporation of age-specific serum sodium levels into organ allocation policies in children seems warranted based on our findings.

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INTRODUCTION

Hyponatremia is a frequent complication of end-stage liver disease (ESLD), largely due to portal hypertension, systemic vasodilation, and hypovolemia, which leads to a compensatory release of antidiuretic hormone and subsequent fluid retention.^{1–3} In several single-center studies, using a threshold of <135 mmol/L for hyponatremia in

adult medical and surgical patients, hyponatremia was found in nearly 50% of patients with ESLD.⁴ Many of these patients were asymptomatic and, it appears, that hyponatremia does not impact their clinical course. For this reason, a threshold below 130 mmol/L has been proposed to define hyponatremia in patients with ESLD because this is the level where the frequency of complications dramatically increases.⁵

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Because of the limited number of studies, the prevalence of hyponatremia in children with ESLD is unknown but is estimated to be similar to that of adults.⁶

Independent of severity, hyponatremia is a well-established risk factor for morbidity and mortality in adult patients with ESLD.^{7–10} It has been demonstrated that hyponatremia is an independent predictor for waiting list mortality in adults.^{7,11–13} In 2016, the importance of hyponatremia as a prognostic factor for preoperative survival in liver transplantation (LT) was acknowledged with the addition of serum sodium to the model for end-stage liver disease.

The effect of hyponatremia on postoperative survival in adults is unclear. A number of studies having conflicting results.^{9,14–19}

Serum sodium, however, has not been included in the pediatric end-stage liver disease (PELD). Reasons for this include the pediatric population is much less homogeneous than adults, the rapidly changing physiology in childhood, adaptive changes in the coagulation profile, and notable differences related to age in the causes of ESLD, some of which present particular challenges in surgical technique. To date, 2 relatively small single-center evaluations have demonstrated hyponatremia is associated with increased waiting list mortality in children.^{6,20} Analysis of larger nationwide databases may aid our understanding of the importance of hyponatremia in children awaiting LT to allow us to develop more effective perioperative management strategies.

In this retrospective database analysis, we evaluated the relationship between hyponatremia and waiting list mortality as well as postoperative patient and graft survival in children. Patients were stratified by age to identify subgroups most susceptible to hyponatremia-related mortality. We hypothesized that hyponatremia was associated with increased waiting list mortality.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board at the Penn State Hershey Medical Center.

Data on all pediatric liver transplants performed in the United States between 1988 and 2016, available in the united network for organ sharing (UNOS) database, were extracted with permission from the organ procurement transplantation network (OPTN). Exclusion criteria included only status 1a indications for LT.

The cutoff for hyponatremia was chosen based on receiver operating characteristic (ROC) for several serum sodium levels. Cutoffs for serum sodium used in previous publications were also taken into consideration.

Data regarding the incidence of hyponatremia in both the entire pediatric population on the waiting list and those transplanted were obtained. Considering the significant differences in pediatric physiology at different stages of development, the prevalence of hyponatremia for each year of life was calculated. Based on these results, age groups (group I: 0–6 and group II: 7–18 y old) evaluated for perioperative mortality were defined.

Other reasons for selecting these age groups were the significant differences in pediatric physiology and the distribution of causes of ESLD.^{21–23} Analysis of overall mortality as well as mortality in different age groups for patients with and without hyponatremia *on the waiting list* (perioperative) and *after*

LT (postoperative) was performed for both groups. Overall graft survival was evaluated in 2 age groups.

We also evaluated the effect of serum sodium on relative risk (RR) of death for both preoperative and postoperative populations overall and stratified to different age groups.

Independent predictive factors for waiting list mortality were chosen based on previous publications and expert opinion. Preoperative variables included serum sodium level at registration, demographics (age, Hispanic, or African American compared with White ethnicity), causes of ESLD (biliary atresia [BA], intrahepatic cholestatic [IC], metabolic, and oncologic), history of preoperative dialysis, and laboratory values at registration (international normalized ratio [INR], serum creatinine, serum albumin). Bilirubin level did not demonstrate statistical significance in any preliminary regression model and was excluded from evaluation.

For evaluation of independent predictive factors for postoperative mortality, we used sodium level at LT, demographics (age, Hispanic, or African American compared with White ethnicity), causes of ESLD (BA, IC, metabolic, and oncologic), type of liver graft (deceased or split compared with living donors), and laboratory values at LT (INR, serum creatinine, and serum albumin).

PELD score components, instead of the PELD score itself, were used for regression analysis. This allowed us to include in the evaluation children registered for LT before the PELD/model for end-stage liver disease era. Bilirubin and diabetes mellitus (DM) did not demonstrate statistical significance in any preliminary regression models and were excluded from evaluation.

Statistical Methods

Means, medians, and SD are presented for continuous variables and frequencies with percentage (%) for categorical variables. To evaluate possible differences between subpopulations, a comparison between the complete dataset and missing data was conducted.

To identify a threshold to define hyponatremia, ROCs were constructed to predict both waiting list and postoperative mortality, and, in particular, the sensitivity and specificity of serum sodium at 3 discrete levels (125, 130, and 135 mmol/L). After all, results were obtained, we defined 2 subgroups for further stratification: group I (age between 0 and 6 y old) and group II (age between 7 and 18 y old). Evaluation of overall survival, as well as survival in each age group (groups I and II), was performed at 2 time points: perioperative (on the waiting list) and postoperative (after LT). Overall graft survival was stratified into 2 age groups and evaluated. Kaplan-Meier curves were plotted by groups with *P* values obtained from log-rank tests for group comparison.

Summary statistics including means, medians, interquartile ranges, and SDs were computed for each continuous variable and frequencies with percentages for categorical variables. For group comparison, 2-sample *t*-tests were utilized for continuous variables and Pearson Chi-square tests for categorical variables.

To assess the effect of sodium on PELD score-related mortality, we also performed an exploratory analysis using sodium as a continuous variable based on a generalized additive model, with smoothing splines on serum sodium to determine its potential nonlinear effect on patient survival with and without adjustment to the calculated PELD score.

A multivariable logistic regression analysis was then performed to identify independent predictive factors for waiting list mortality and postoperative survival. The initial variables were chosen based on previous publications and expert opinion. Several preliminary regression analyses were performed in an attempt to identify the most significant parameters.

All hypothesis tests are 2 sided with a significance level of 0.05. Data were analyzed using R software (version 3.6.1).

RESULTS

Between June 6, 1988, and September 30, 2016, 10428 children (0–18 y old) were registered for LT. Data from 3822 (37%) patients were incomplete (serum sodium at the time of registration was not available) and could not be included. Statistical analysis demonstrated that both the included and excluded populations had similar overall profiles. Data from 6606 pediatric candidates (4251 patients in group I and 2355 patients in the group II) were ultimately available for the evaluation of waiting list mortality. From this population, 535 candidates (8%) died on the waiting list before LT.

During the time period under evaluation, 5661 children underwent LT but 1183 patients (21%) from this cohort were excluded from analysis due to missing data (serum sodium at the time of registration was not available). Statistical analysis has demonstrated that included and excluded populations had a similar overall profile and exclusion of 21% of patients would most likely not affect the final results. Ultimately, 4478 children were included in the evaluation for postoperative mortality (2983 children in group I and 1495 in group II). Observed overall postoperative mortality was 11%.

The best cutoff for hyponatremia was calculated using ROC results.

For preoperative mortality: AUC-ROC=0.55. For serum sodium cutoffs of 125, 130, and 135 mmol/L, sensitivities were 0.009345794, 0.04485981, and 0.2224299, respectively. For serum sodium cutoffs of 125, 130, and 135 mmol/L, specificities were 0.9953879, 0.9738099, and 0.817493, respectively.

For postoperative mortality: AUC-ROC=0.49. For serum sodium cutoffs of 125, 130, and 135 mmol/L, sensitivities were 0.005976096, 0.03386454, and 0.2031873, respectively. For serum sodium cutoffs of 125, 130, and 135 mmol/L, specificities were 0.9909774, 0.9682707, and 0.8261654, respectively.

Even though the most predictive ROC was found for a preoperative serum sodium of 125 mmol/L for both mortality on the waiting list and postoperative mortality, the decision was made to use a serum sodium level of 130 mmol/L as the cutoff for hyponatremia because the accepted definition of hyponatremia in ESLD in the transplantation literature is 130 mmol/L.²⁴ It has been demonstrated in adults (data in children are limited) that the frequency of complications is highest in patients with a serum sodium level below 130 mmol/L.⁴ A level of 125 mmol/L would therefore not correctly represent the entire population.

The prevalence of hyponatremia in patients on the waiting list was 2.8% (3.1% and 2.3% in groups I and II, respectively).

A comparison of groups I and II is demonstrated in Table 1. Children with hyponatremia had both shorter waiting list and preoperative survival time ($P<0.001$), had a higher PELD score both at the time of registration and transplantation ($P<0.001$). Advanced ascites and DM were also associated with hyponatremia ($P<0.001$ and $P=0.012$, respectively). In addition, INR and bilirubin were higher ($P<0.001$) and serum albumin lower in children with hyponatremia ($P<0.001$).

The additive model with smoothing splines on serum sodium has demonstrated that sodium concentration had a statistically significant nonlinear effect on the RR of overall waiting list mortality and specifically in group I ($P<0.0001$). The model remained statistically significant after adjustment to the calculated PELD ($P<0.0001$). In group I, a serum sodium concentration of between 135 and 138 mmol/L had a minimal effect on RR mortality (Figure 1). If the serum sodium concentration was below 130 mmol/L, the RR for mortality increased exponentially in group I but not in group II (Figure 1). In both groups, the RR for mortality was increased when the serum sodium was above 140 mmol/L (142 mmol/L for group II).

If hyponatremia was evaluated as a categorical variable (with a cutoff of 130 mEq/L), overall waiting list mortality in patients with hyponatremia was significantly higher than in patients without hyponatremia ($P<0.001$). Data stratification, based on patient age, demonstrated that this trend was confirmed only in group I ($P<0.001$) (Figure 2) but approached statistical significance in group II ($P=0.09$) (Figure 3).

All 10428 pediatric patients listed for transplantation were included in the regression analysis (Figure 4). Independent predictive factors associated with increased mortality included serum sodium level below 130 mmol/L (HR = 1.7), younger age (0–6 y old) (HR = 2.01), elevated INR (odds ratio [OR] = 1.1), metabolic and oncologic causes of ESLD (HR = 1.3 and 1.9, respectively), and need for dialysis (HR = 2.3).

Factors associated with improved survival were higher albumin level (HR = 0.47) and BA as a cause of hepatic failure (HR = 0.54).

The overall prevalence of hyponatremia at the time of LT was 3.7% (3.9% and 3.3% in groups I and II, respectively). There was no difference in either overall or age-stratified postoperative mortality between patients with and without hyponatremia. There were no observed differences in graft survival in patients with or without hyponatremia.

Data from 5681 pediatric LT were available for evaluation of postoperative mortality (Figure 5). Independent predictive factors associated with increased postoperative mortality included: younger age (0–6 y old) (HR = 2.2), African American population (HR = 1.3), oncologic cause for ESLD (OR = 2.9), and the use of deceased compared with living donor grafts (OR = 1.7).

Factors associated with improved postoperative survival included: higher albumin level (OR = 0.72) and selected causes of ESLD (BA, IC, and metabolic OR = 0.28, 0.81, and 0.77, respectively).

DISCUSSION

This is the first study that uses a large nationwide database for evaluation of possible relationships between perioperative mortality and hyponatremia. This evaluation clearly demonstrated that serum sodium independently predicts waiting list mortality in pediatric patients. This relationship was especially prominent in younger children.

We determined the overall prevalence of hyponatremia in pediatric patients on the waiting list to be 2.8%. This is relatively low in comparison to adults. The reason for this is likely related to several factors associated with the characteristics of ESLD in children.

It has been previously demonstrated that waiting list time for LT in children is about 3 times shorter than for adults.²⁵

TABLE 1.
Baseline characteristics of patients with and without hyponatremia (n=6606)

	Sodium below 130 mmol/L (n = 183)	Sodium above 130 mmol/L (n = 6423)	P
Demographics			
Age at listing, mean (SD)	4.52 (6.37)	5.48 (6.36)	0.046 ^a
African American, mean (%)	27 (14.8%)	1107 (17.2%)	0.57
Caucasian, mean (%)	102 (55.7%)	3325 (51.8%)	–
Asian, mean (%)	19 (10.4%)	593 (9.2%)	–
Hispanic, mean (%)	35 (19.1%)	1398 (21.8%)	–
Cause of ESLD			
Biliary atresia, n (%)	71 (38.8%)	2077 (32.3%)	0.08
Intrahepatic cholestatic, n (%)	22 (12.0%)	625 (9.7%)	0.37
Metabolic, n (%)	35 (19.1%)	1379 (21.5%)	0.50
Oncologic, n (%)	2 (1.1%)	277 (4.3%)	0.051
PELD			
At listing, mean (SD)	20.6 (10.6)	12.0 (11.4)	< 0.001 ^a
At transplant, mean (SD)	21.4 (12.7)	13.5 (12.6)	< 0.001 ^a
Waiting list times			
Time on waiting list (mo), mean (SD)	3.39 (5.90)	5.61 (9.21)	< 0.001 ^a
Waiting list survival time (mo), mean (SD)	4.34 (7.27)	9.73 (17.3)	< 0.001 ^a
Clinical conditions			
Diabetes, n (%)	9 (4.9%)	126 (2.0%)	0.012 ^a
Dialysis preoperative, n (%)	4 (2.2%)	165 (2.6%)	0.93
Primary graft nonfunction, n (%)	4 (2.2%)	94 (1.5%)	0.63
Donor type			
Deceased donor, n (%)	112 (61.2%)	3777 (58.8%)	0.57
Living donor, n (%)	21 (11.5%)	478 (7.4%)	0.06
DCD donor	1 (0.5%)	26 (0.4%)	1
Split donor	73 (39.9%)	2796 (43.5%)	0.013 ^a
Portal hypertension			
Ascites >grade 2 at listing, n (%)	106 (57.9%)	2444 (38.1%)	< 0.001 ^a
Ascites >grade 2 at transplant, n (%)	110 (60.1%)	2806 (43.7%)	< 0.001 ^a
HE >grade 2 at listing, n (%)	60 (32.8%)	2068 (32.2%)	0.93
HE >grade 2 at transplant, n (%)	73 (39.9%)	2374 (37.0%)	0.48
Laboratory values			
INR, at listing, mean (SD)	1.95 (1.53)	1.57 (1.25)	< 0.001 ^a
INR, at transplant, mean (SD)	1.96 (1.09)	1.61 (1.72)	< 0.001 ^a
Serum albumin, at listing, mean (SD)	2.74 (0.666)	3.21 (0.720)	< 0.001 ^a
Serum albumin, at transplant, mean (SD)	2.82 (0.717)	3.15 (0.797)	< 0.001 ^a
Serum bilirubin, at listing, mean (SD)	14.7 (10.4)	8.71 (9.20)	< 0.001 ^a
Serum bilirubin, at transplant, mean (SD)	15.5 (12.9)	9.67 (11.5)	< 0.001 ^a
Serum creatinine, at listing, mean (SD)	0.56 (0.710)	0.51 (0.822)	0.39
Serum creatinine, at transplant, mean (SD)	0.57 (0.740)	0.56 (0.885)	0.80

^aIndicates statistical significance.

DCD, donation after circulatory death; ESLD, end-stage liver disease; HE, hepatic encephalopathy; INR, international normalized ratio; PELD, pediatric model for end-stage liver disease.

Children are usually transplanted relatively early during course of disease before the full development of ESLD-related complications. Other factors likely associated with the low prevalence of hyponatremia in children are related to differences in management. Compared with adults, children are more frequently hospitalized before and after listing for LT and hyponatremia is usually more aggressively treated. The pathogenic profile of ESLD in children is also different in comparison to adults with a high incidence of cholestatic and metabolic diseases responsible for liver failure as opposed to the causes typically seen in adults. The use of diuretics, a contributing factor to hyponatremia in adults, is less frequently seen in children. It has also been demonstrated that the incidence of ascites is slightly less frequent in children in comparison to adults (44% versus 50%).^{26–29} There is currently, however, no scientific evidence that children have either less

severe portal hypertension or an underdeveloped antidiuretic hormone release mechanism. Although the overall prevalence of hypernatremia is low, it reflects the severity of ESLD and helps identify the most vulnerable pediatric patients urgently needing LT.

Our study also found that hyponatremia was associated with an increased mortality on the waiting list for younger children. Although a strong association between mortality and hyponatremia on the waiting list has been demonstrated in adults,^{7,11,12} it has only been shown in a few relatively small, single-center evaluations in children, not in large populations.^{6,20} In a retrospective study, Carey et al⁶ evaluated a cohort of 94 pediatric patients and were able to demonstrate a significant association between hyponatremia (sodium below 130 mEq/L) and waiting list mortality. Pugliese et al evaluated data from 522 pediatric LT and

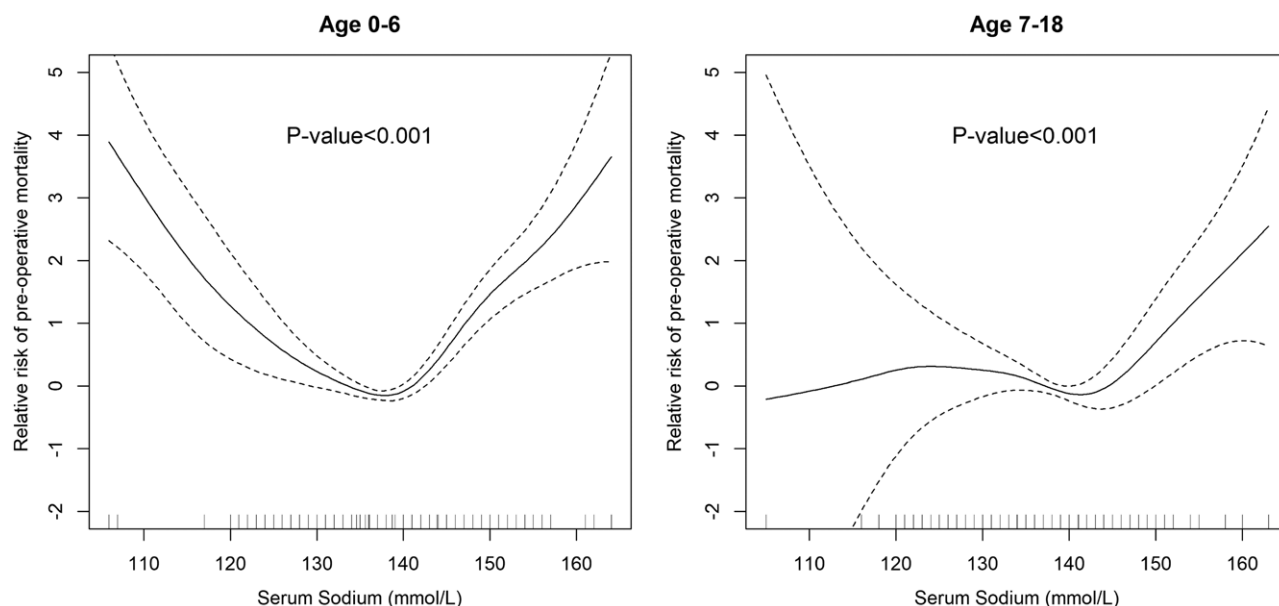


FIGURE 1. Association between relative risk for mortality on the waiting list and serum sodium concentration. Model adjusted to the calculated PELD score for groups I and II. PELD, pediatric end-stage liver disease.

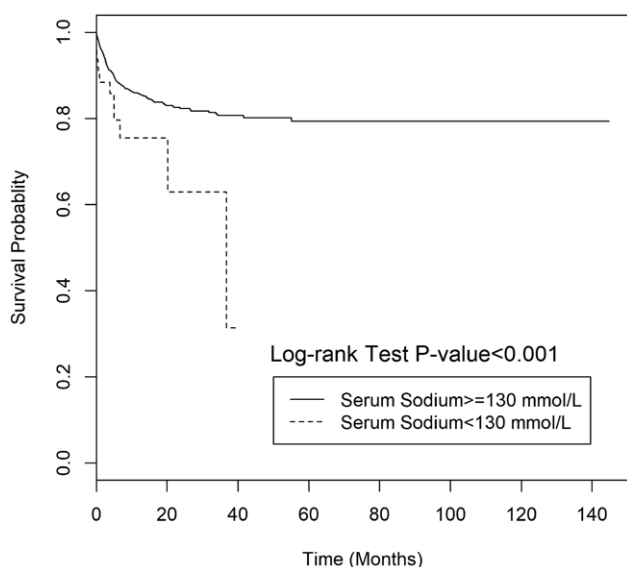


FIGURE 2. Survival on the waiting list in group I (0–6 y old).

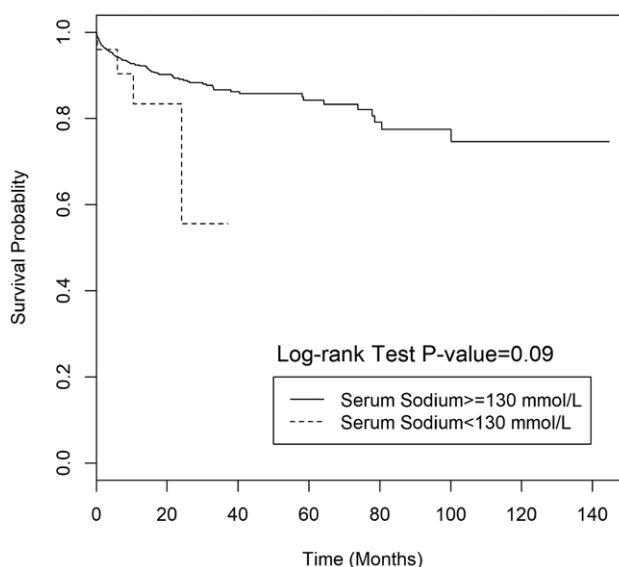


FIGURE 3. Survival on the waiting list in group II (7–18 y old).

also found that hyponatremia (sodium below 130 mEq/L) was associated with decreased survival on the waiting list. Another important finding in these evaluations was that hyponatremia-related mortality was higher in children younger than 1 y of age. In these studies, however, only age groups below and above 1 y old were compared. We found that hyponatremia was an independent predictive factor of waiting list mortality in children younger than 7 y but not in older children. The reason for these results needs to be investigated further. Younger children are much more fragile and do not have mature compensatory mechanisms. As a result, medical management of this population is much more difficult.

Hyponatremia was not associated with an increase in postoperative mortality or with decreased graft survival. This finding might also be related to the shorter waiting time for pediatric patients and likely points to the benefits

of early transplantation, before complications associated with increased portal pressure fully develop. In addition, surgical technique and perioperative management of small children is significantly more demanding.

The effect of preoperative hyponatremia on posttransplant outcomes in adults is unclear. Published evaluations have demonstrated ambiguous results.^{14,16–18} The association between hyponatremia and mortality is likely the result of prolonged waiting times and the advanced stages of ESLD seen in adults. Studies that did not find differences in postoperative survival pointed out that several postoperative complications, such as osmotic demyelization syndrome,¹⁴ renal failure, infections, delirium, and longer hospital stay, were associated with pre-transplant hyponatremia.¹⁵

Our study has demonstrated that serum sodium levels have a significant effect on the PELD adjusted RR for mortality for patients in group I.

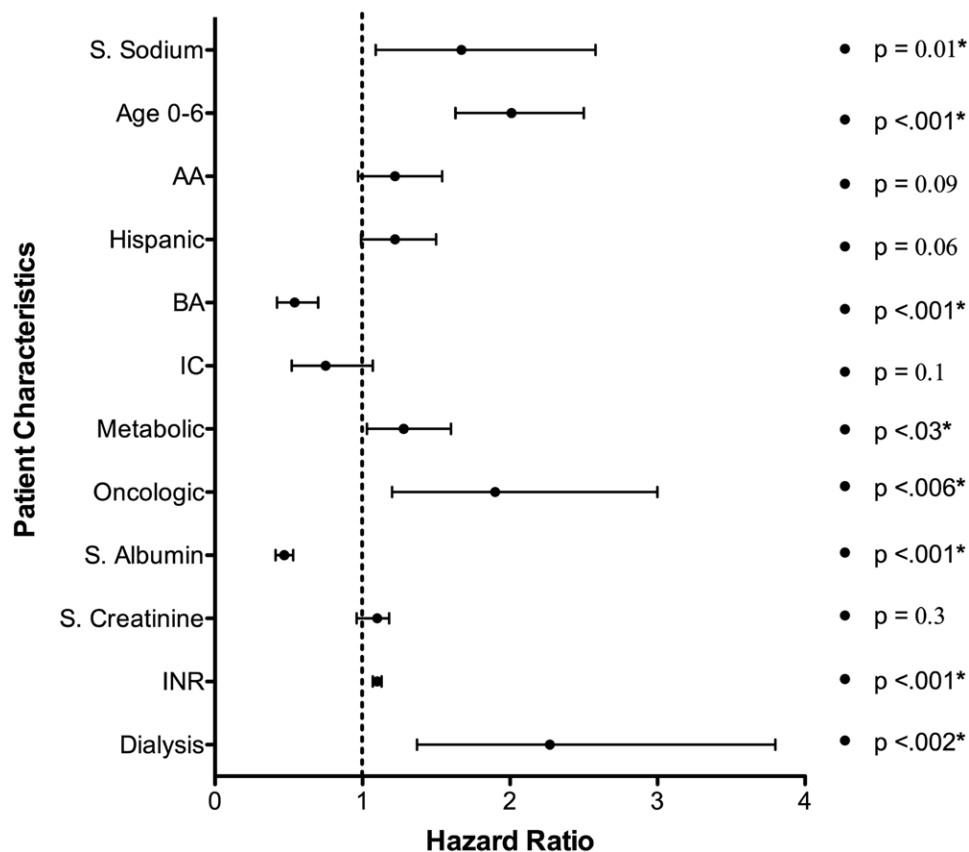


FIGURE 4. Factors associated with mortality on waiting list: a regression analysis. Data are reported as odds ratio and confidence interval. Statistical significance of $P < 0.05$ is indicated by *. Reference group for age was 7–18 y old. AA, African Americans; BA, biliary atresia; IC, intrahepatic cholestatic; INR, international normalized ratio; S. albumin, serum albumin; S. creatinine, serum creatinine; S. sodium, serum sodium.

The PELD score was introduced in February of 2002 and has been shown to decrease waiting list mortality.³⁰ The PELD, however, has significant limitations. In a retrospective investigation, Shneider et al³¹ found that in 44% of patients, the PELD score did not correctly reflect the clinical situation and to be allocated a liver graft at this time, these patients required either a status 1a listing or exception points. It has been previously demonstrated that the current allocation system benefits older children (12 y old and above). Waiting list mortality for this group of patients was about 10% but for younger children, it approached 25%.³² Modification of the current approach with the addition of serum sodium to the PELD score would be helpful to identify the most vulnerable patients, particularly considering that the prevalence of hyponatremia in our study increased between the time of registration and LT from 2.8% to 3.7%. The concept of including sodium in the PELD score has already been discussed.³³ The value of this adjustment is unclear because of the small number of evaluations available, limited number of patients, and borderline significance of the effect of hyponatremia on survival performed without age stratification.²⁰

Although *hypernatremia* was not the topic of our evaluation, we found that when the serum sodium concentration was above 140 mmol/L (142 mmol/L for the group II), there was an associated increased RR for death. *Hypernatremia* in children has not been previously evaluated but in adults is usually the result of the use of diuretics and lactulose, which is used less frequently in children with ESLD.^{34,35} It has been demonstrated in adults that *hypernatremia* is associated with

increased mortality in patients with cirrhosis on the waiting list as well as after LT.^{7,9,34,36} *Hypernatremia* with cirrhosis is always a sign of very advanced liver dysfunction³⁴ and when present in a pediatric patient, needs further detailed evaluation.

In our study, we also investigated other factors associated with perioperative mortality. Regression analysis has demonstrated that both preoperative and postoperative mortality was associated with decreases in serum albumin and increases in INR. This association was previously demonstrated by McDiarmid et al in the study of pediatric liver transplantation (SPLIT). These investigators attempted to identify the most promising components of the PELD score to predict preoperative mortality.³⁷ They found that a model including both serum albumin and INR had the best predictive value.³⁷ It is interesting that serum sodium was neither considered nor discussed in the evaluation. The predictive value of albumin and INR is not surprising because both factors reflect synthetic function of liver.

Regression analysis did not demonstrate an association between serum creatinine and preoperative mortality. This result also reinforces the understanding that the predictive value of hyponatremia on mortality in pediatric patients rather represents the degree of liver disease and not impairment of renal function.³³

Our investigation also demonstrated that patients transplanted for BA had a decreased preoperative and postoperative mortality while transplantation for oncologic causes of ESLD had an increased preoperative and postoperative

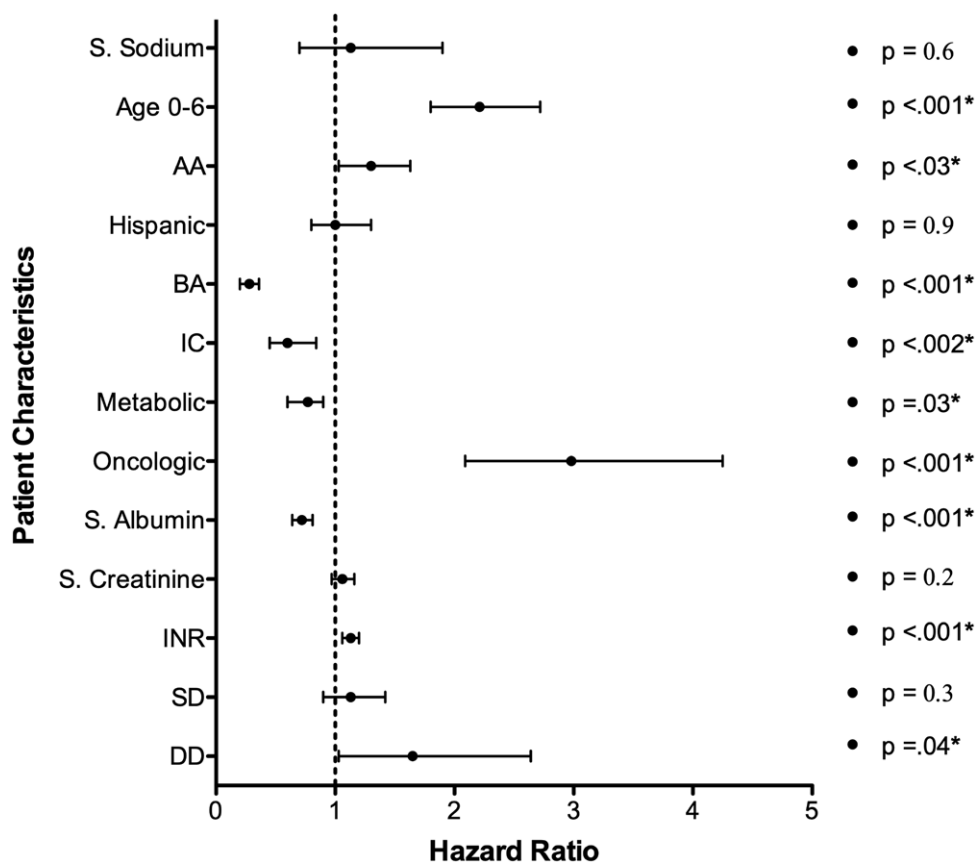


FIGURE 5. Factors associated with mortality after transplantation: a regression analysis. Data are reported as odds ratio and confidence interval. Statistical significance of $P < 0.05$ is indicated by *. Reference group for age was 7–18 y old. Reference group for donor type was living donors. AA, African Americans; BA, biliary atresia; DD, deceased donor; IC, intrahepatic cholestatic; INR, international normalized ratio; S. albumin, serum albumin; S. creatinine, serum creatinine; SD, split donor; S. sodium, serum sodium.

mortality. Similar results for both conditions have been reported.^{38,39} Patients with BA frequently have a relatively low PELD due to a normal albumin and INR; the waiting time to transplantation is relatively short (about 90 d) with a median PELD of 15 at the time of LT, and surgery is performed in a situation where patients are medically stable.⁴⁰ LT in this subpopulation is associated with excellent results, superior in comparison to the Kasai procedure alone.^{41,42} In contrast, hepatic malignancy is associated with increased mortality primarily due to metastatic or recurrence of disease.^{39,43}

Pretransplant dialysis was a significant independent predictive factor of mortality after LT. This relationship has been demonstrated in several investigations in adults^{44,45} and is likely related to the presence of other comorbidities including cardiovascular disease, peripheral vascular disease, and DM,⁴⁶ which are uncommon in children. Other investigators, however, have demonstrated an association between preoperative kidney dysfunction and mortality in children undergoing LT. In a retrospective evaluation of almost 9000 pediatric LT, Ruebner et al⁴⁷ found that a glomerular filtration rate below 60 mL/min/1.73m² was an independent risk factor for death after LT. This study also emphasized that the chronicity of kidney disease in children, and especially the need of dialysis, is associated with an increased postoperative mortality.⁴⁷ The cause of this association in children is unclear. It has been shown that preoperative renal dysfunction is associated with a more complicated postoperative course after LT, including a higher incidence of infection and sepsis.^{48,49}

It has been suggested that in patients with preoperative renal insufficiency, decreasing the intraoperative use of vasopressors can reduce the need for postoperative renal replacement therapy and improve outcome.⁴⁶ Other recommendations include using calcineurin inhibitor sparing immunosuppressive protocols,^{50,51} maintaining tight perioperative blood pressure control,⁵² as well as avoiding the use of nephrotoxic medications.⁵³

Because our preliminary models did not show an association between bilirubin levels and mortality, this variable was removed from regression analysis. A recent large single-center retrospective analysis also failed to demonstrate the significance of bilirubin as an independent predictive factor for either patient or graft survival.³⁹ One other SPLIT evaluation also failed to demonstrate bilirubin as a predictor for mortality in the cohort of children with fulminant hepatic failure.⁵⁴ The association between bilirubin and mortality, however, has been previously shown. In a retrospective evaluation of the SPLIT dataset, Uttereson et al⁵⁵ found that bilirubin was an independent predictive factor for death *before* LT. This investigation evaluated patients with BA, with the majority of being <1 y old. SPLIT evaluation, performed by McDiarmid et al, also found that bilirubin was valuable in predicting mortality in pediatric patients on the waiting list. However, almost half of the 884 patients included in the study were younger than 1 y old and had BA as the cause of ESLD.³⁰ Bilirubin is likely to be a predictor of survival in some subpopulations.

Our study investigated a significantly larger population with a wider range of ages and causes of ESLD. This gives us a broader perspective on mortality associated with a wider variety of comorbidities in pediatric patients.

Our study has several limitations. The most significant limitation is the structure of the UNOS database itself. Serum sodium levels were recorded at only 2 different time points (registration and transplantation), so although progression of hyponatremia could not be evaluated, it is expected that hyponatremia is chronic in patients with ESLD. Information regarding correction of hyponatremia was not available and overall serum sodium might not correctly reflect the actual prevalence of hyponatremia. In addition, some information regarding the status of the child, such as whether the patient was at home or in the hospital at the time of the listing, was not available in the UNOS database. Another limitation relates to potential coding errors because information was pooled from a variety of transplant centers. About 37% of data was not available for evaluation due to missing information, potentially resulting in misinterpretations of our findings. However, a comparison of included and excluded patients demonstrated that both cohorts have comparable characteristics and most likely, excluded patients would not affect our study results. Lastly, as with any retrospective study, the data allows us to assign associations, but not causation.

In conclusion, our study has demonstrated an overall low prevalence of hyponatremia in children with ESLD. This most likely reflects the short waiting time to LT compared with adults as well the specific characteristics of ESLD management in children. Only in younger children was hyponatremia associated with increased mortality on the waiting list. The addition of serum sodium to the PELD score for this subpopulation might be beneficial in improving organ allocation.

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