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ORIGINAL ARTICLE

Elevated serum sodium in recipients of liver transplantation has a substantial impact on outcomes

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SUMMARY

Dysnatremias are a rare but significant event in liver transplantation. While recipient pre-transplant hypernatremia has been demonstrated to increase post-transplant mortality, the degree of hypernatremia and the impact of its resolution have been less well characterized. Here, we used multivariate Cox regression with a comprehensive list of donor and recipient factors in order to conduct a robust multivariate retrospective database study of 54,311 United Network for Organ Sharing (UNOS) liver transplant patients to analyze the effect of pre-transplant serum sodium on post-transplant mortality, post-transplant length of hospitalization, and post-transplant graft survival. Mortality and graft failure increased in a stepwise fashion with increasing pre-transplant hypernatremia: 145 −150 mEq/L (HR = 1.118 and HR = 1.113), 150–155 mEq/L (HR = 1.324 and HR = 1.306), and > 155 mEq/L (HR = 1.623 and HR = 1.661). Pre-transplant hypo- and hypernatremia also increased length of post-transplant hospitalization: < 125 mEq/L (HR = 1.098), 125–130 mEq/L (HR = 1.060), 145 −150 mEq/L (HR = 1.140), and 150–155 mEq/L (HR = 1.358). Resolution of hypernatremia showed no significant difference in mortality compared with normonatremia, while unresolved hypernatremia significantly increased mortality (HR = 1.254), including a durable long-term increased mortality risk for patients with creatinine < 2 mg/dL and MELD < 25. Pre-transplant hypernatremia serves as a morbid prognostic indicator for post-transplant morbidity and mortality.

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Key words
graft survival, hypernatremia, hyponatremia, length of stay, mortality

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Introduction

In all types of patients, dysnatremias are challenging and can serve as a potential surrogate for mortality. Hypernatremia alone has been correlated with increased inpatient mortality, vascular rupture, and intracranial bleeding [1–3], and hyponatremia has been found to increase mortality in any surgical patient with concomitant heart failure [4,5]. In fact, even mild hyponatremia in an ambulatory setting is associated with increased

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mortality [6]. Dysnatremias are of particular interest in the context of liver transplantation [7,8]. In patients with end-stage liver disease, hyponatremia is a common and ominous sign, associated with increased mortality in cirrhotic patients [7]. The influence specifically of hyponatremia led to an amendment of the gold-standard, MELD scoring system, resulting in the production of the Na-MELD score and an increased ability to predict mortality in cirrhotic patients on the waitlist [8,9].

There is also significant evidence that dysnatremias impact outcomes after liver transplantation. Pre-transplant hypernatremia has been found to have a substantial impact on mortality rates in the post-liver transplant period. Multiple studies have found that pre-transplant hypernatremia was not only associated with increased hospital length of stay and risk-adjusted mortality, but that the mortality risk could be directly correlated with the unit increase in serum Na^+ >145 mEq/L [7,10].

Even more common in the pre-transplant setting than hypernatremia is hyponatremia, but the risk of pre-transplant hyponatremia on post-transplant outcomes is less clear. In a multicenter cohort study, pre-transplant hyponatremia had a higher risk-adjusted mortality at 3 years with excess mortality was noted in the first 90 days [10]. Multiple other studies based on liver transplant and national databases found no impact or modest benefit on 90-day survival [7,11,12]. Unlike hypernatremia, correction of hyponatremia poses substantial risk of neurological demise if corrected rapidly [13].

The aim of this study is to clarify the impact of pre-transplant serum sodium level on post-transplant mortality, post-transplant length of hospitalization, and post-transplant graft survival using a large retrospective database study of 54,311 UNOS liver transplant patients. Additionally, this study aims to investigate the effect of resolution of hypernatremia. While increased mortality has been observed for hypernatremia in previous reports, to the authors' knowledge, such a large dataset has not yet been utilized to perform a robust multivariate analysis for resolution of serum sodium before transplant and for post-transplant length of hospitalization and graft survival with the specific intent of isolating the effect of pre-transplant serum sodium. This massive sample size will allow for the novel stratification of sodium levels for a dose–response analysis. Understanding the significance of pre-transplant serum sodium on post-transplantation outcomes could lead to more mindful management of these transplant patients and improved outcomes in patient care. With this in mind, this study could help to illuminate the impact of dysnatremias on outcomes in liver transplantation, and better understanding of these parameters could lead to improved management and prognostication of patients with end-stage liver disease.

Patients and methods

Study population

De-identified UNOS data from patients receiving liver transplants from Jan 1, 2008 to Jan 1, 2018 were used for retrospective analysis. All transplant recipients were age 18 years or older. No organs from executed prisoners were used. Living donor liver transplants were excluded (n = 2238). Patients undergoing transplants of other organs were excluded from the study (n = 5519). Patients that lacked pre-transplant serum sodium levels were also excluded from the study (n = 2). Patients were followed from the date of transplant until either death (n = 10,507) or loss to follow-up (n = 1,176). The final analysis included 54,311 liver transplant patients across 10 years (Table 1).

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Patient consent and study approval were waived by the institutional review board of Baylor College of Medicine because patient information was de-identified and not reported in the study. All patient data used in the drafting of this manuscript have been de-identified to preserve patient confidentiality.

Statistical analysis

Data were analyzed using a standard statistical software package, Stata® 16.1 (Stata Corp, College Station, TX). Continuous variables were reported as a mean ± standard deviation. Post-transplant mortality, graft survival, and length of hospital stay analyses were performed using Kaplan–Meier with log rank test methods. Kaplan–Meier with log rank test was used for long-term mortality and graft survival up to 5 years and hospitalization up to 60 days.

Univariate and multivariate proportional hazards Cox regression were conducted for short-term mortality and graft survival. Primary outcomes were defined in separate analyses for post-transplant mortality at 90 days for mortality, length of stay in hospital, and graft survival. These data points are standardized within UNOS. For

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Table 1. Demographics characteristics.

	Recipient			
	Hyponatremia	Normonatremia	Hypernatremia	Donor
No. Patients	22,399	29,851	2,061	54,311
Age	54.7 ± 9.9	55.5 ± 10.6	52.7 ± 12.7	41.6 ± 16.5
% Female	32.3	32.68	44.59	40.4
% African American	7.86	10.24	14.12	18.0
Height (cm)	172.5 ± 10.2	171.9 ± 10.2	170.1 ± 10.2	171.3 ± 10.8
Weight (kg)	85.4 ± 20.0	85.2 ± 19.4	81.6 ± 19.5	81.5 ± 20.6
INR	2.08 ± 1.37	1.84 ± 1.16	2.46 ± 1.58	NA
Creatinine (mg/dL)	1.52 ± 1.13	1.29 ± 0.956	1.59 ± 1.01	1.6 1.8
MELD	24.7 ± 9.6	20.1 ± 11.4	28.3 ± 10.9	N/A
Cause of liver failure				
Acute hepatic necrosis	2.60%	3.99%	16.64%	N/A
Cholestatic liver disease	7.91%	7.14%	6.84%	N/A
Metabolic liver disease	3.21%	2.19%	2.18%	N/A
Malignancy	19.28%	34.12%	17.27%	N/A
Hepatitis C	20.79%	17.10%	14.75%	N/A
Hepatitis B	1.34%	15.50%	2.09%	N/A
Alcoholic cirrhosis	17.14%	10.48%	11.74%	N/A
Cold ischemia time (hours)	N/A	N/A	N/A	6.41 ± 2.68
Cause of Death				
CVA	N/A	N/A	N/A	65.57%
Trauma	N/A	N/A	N/A	32.34%

length of hospital stay analysis, patients that lacked information on discharge date were excluded from analysis (n = 4907), leaving 49,404 patients in the analysis.

Serum sodium at the time of transplant (pre-transplant serum sodium) at all levels was included in the multivariate Cox regression analyses, even if not found to be significant in univariate analyses. For all other variables, covariates found to be significant in univariate Cox regression (defined as $P < 0.05$) were included in adjusted multivariate regression. Full adjusted multivariate values are provided in supplementary tables. The results are represented in Cox proportional hazard ratio with HR > 1 representing increased probability of mortality at 90 days or graft failure. For the length of hospitalization, HR > 1 represents an increased likelihood of prolonged hospital course post-transplant and conversely HR < 1 indicated more likely to be discharged post-transplant.

For further hypernatremia sensitivity analyses, the serum sodium at the time of listing was compared with the serum sodium at the time of transplant (pre-transplant). Status 1A patients were excluded from analysis (n = 2117). Multivariate proportional hazards Cox regression was done in a similar fashion with covariates significant in univariate proportional hazards Cox regression included in the multivariate regression excluding resolved hypernatremia (> 145 mEq/L at listing but normonatremic at time of transplant), unresolved hypernatremia (> 145 mEq/L at both listing and time of transplant), and normonatremia (135–145 mEq/L at both listing and time of transplant) which were automatically included in the analysis. The Cox proportional hazards ratio for HR > 1 indicates increased likelihood of mortality and conversely HR < 1 indicates less likelihood of mortality.

Results

Study population

The study population contained 54,311 liver transplant patients for analysis from 2008 to 2018. The demographic data are summarized in Table 1 and substratified based on hyponatremia (< 135 mEq/L, n = 22,399), normonatremia (135 – 145 mEq/L, n = 29,851), and hypernatremia (> 145 mEq/L, n = 2061). The cause of liver failure varied somewhat between the groups with acute hepatic necrosis, occurring more frequently in hypernatremia and hepatocellular carcinoma and Hepatitis B in normonatremia.

Risk factors and entry completion

Risk factors considered for univariate and multivariate analyses for both donors and recipients are included in Table 2. The entry completion rate for all variables was > 99% for all variables except for deceased donor after cardiac death (Table S1). Variable cutoffs were determined using clinical expertise and rounding to nearest numbers. The distribution of serum sodium at the time of transplant was consistent with previously published results with both hyper- and hyponatremia as rare occurrences (Table 1, Figure S1).

Serum sodium and mortality and graft survival

The short-term effects of serum sodium level at the time of transplant were evaluated in relation to post-transplant recipient mortality within 90 days of transplant. First, a univariate Cox regression was used to isolate factors that significantly altered hazard ratio (Table 3, Table S1). Severe hyponatremia (< 125 mEq/L) was protective (HR = 0.840 (0.748, 0.943), $P = 0.003$); however, hyponatremia closer to normonatremia (135 – 145 mEq/L) was not significant in univariate Cox regression (Table 3). Hypernatremia at all levels significantly increased the hazard ratio for mortality in a dose-dependent manner with increasing levels of serum sodium (Table 3, $P < 0.001$). Graft survival in relation to pre-transplant serum sodium was also evaluated with univariate Cox regression and held similar patterns to univariate Cox regression for 90-day mortality (Table 3).

In order to properly control for factors relevant to mortality at 90 days, all factors significant in univariate analysis were included in a multivariate Cox regression (Table 3, see Table S2). As expected, the protective factor of severe hyponatremia lost significance in multivariate analysis (HR 0.900 (0.799, 1.014), $P = 0.083$). Hypernatremia at all levels remained associated with increased adjusted mortality and retained the stepwise increase in mortality in multivariate analysis (Table 3). Adjusted graft survival was also evaluated in multivariate Cox regression and had stepwise results consistent with multivariate Cox regression for mortality at 90 days (Table 3, Table S2).

The long-term effect of pre-transplant dysnatremia was evaluated with overall 5-year survival Kaplan–Meier Curves and log rank comparisons (Fig. 1a.). Consistent with univariate Cox regression, severe hyponatremia (< 125 mEq/L) was the only hyponatremic state that significantly differed from the normonatremic reference range in terms of mortality by log rank test ($P = 0.003$). All the hypernatremic curves presented with significant difference in comparison to the normonatremic reference range. The stepwise nature of the hypernatremic mortality at 90 days in univariate and multivariate analysis was reflected in the overall survival and 5 years in Kaplan–Meier (Fig. 1b). Graft survival had similar results when applying the same Kaplan–Meier Curve with log rank comparisons (Fig. 2).

Serum sodium and length of hospital stay

In addition to mortality, length of post-transplant hospital stay is another indication of successful transplantation and a surrogate of post-transplant morbidity. Pre-transplant serum sodium was evaluated first in univariate Cox regression. Extreme hyponatremia (< 125 mEq/L) and moderate hyponatremia (125 – 130 mEq/L) presented with a marginally lengthened hospital stay (HR = 1.088 (1.038, 1.140) $P < 0.001$ and HR = 1.063 (1.033, 1.094) $P < 0.001$ respectively) (Table 3). Hypernatremia significantly increased post-transplant hospital course in all cases in univariate analysis (Table 3).

To evaluate for the true effect of serum sodium on post-transplant length of hospital stay by controlling for other clinically relevant factors, a multivariate Cox regression was carried out (Table 3, Table S2). Adjusted length of hospitalization for hyponatremia at < 125 mEq/L and 125 – 130 mEq/L remained significantly increased (HR = 1.098 (1.046, 1.153) $P < 0.001$, and HR = 1.060 (1.028, 1.093) $P < 0.001$ respectively). However, hyponatremia closer no normonatremia failed to reach significance ($P = 0.107$). Adjusted length of hospitalization for only hypernatremia at 145 −150 mEq/L and 150–155 mEq/L significantly increased hospital stay (HR = 1.140 (1.080, 1.203) $P > 0.001$, and HR = 1.358 (1.210, 1525) $P < 0.001$ respectively), while more severe hypernatremia (>155 mEq/L) failed to reach significance ($P = 0.21$) (Table 3). Given the increased mortality within the first 90 days at more severe hypernatremia, it is likely that more patients were deceased during the 60-day hospitalization period analyzed. Post-transplant hospital stays for up to 60 days were evaluated with Kaplan–Meier Curves and log rank comparison, which found that all curves differed significantly from the reference range and were associated with increased length of hospital stays (Fig. 3). The increased length of hospitalization implies that mild and moderate hypernatremia increase post-transplant morbidity.

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Table 2. Variables considered for analysis.

Donor	Recipient
Donor Age < 10	Serum Sodium < 125 mEq/L
Donor Age 10–15	Serum Sodium 125–130 mEq/L
Donor Age 15–20	Serum Sodium 130–135 mEq/L
Donor Age 20–30	Serum Sodium 145 −150 mEq/L
Donor Age 45–55	Serum Sodium 150–155 mEq/L
Donor Age 55–60	Serum Sodium > 155 mEq/L
Donor Age 60–70	Hemodialysis Prior to Transplant
Donor Age > 70	Incompatible Blood Type
Deceased Donor after Cardiac Death	Recipient Age 18–30
Cold Ischemia Time < 6 hrs	Recipient Age 60–65
Cold Ischemia Time 12–14 hrs	Recipient Age > 65
Cold Ischemia Time > 14 hrs	Albumin 2.0–2.5 g/dL
Creatinine Donor 1.5–2.0	Albumin 1.5–2.0 g/dL
Creatinine Donor > 2.0	Albumin < 1.5 g/dL
Donor Distance 500–1000 miles	Ascites at Transplant
Donor Distance 1000–10,000 miles	Spontaneous Bacterial Peritonitis
Regional Allocation	BMI 30 – 35
National Allocation	BMI 35 – 40
Hepatitis C Serology in Donor	BMI > 40
African American Donor	High School Dropout
Height Difference of 30–60 cm	High School Education
Height Difference of > 60 cm	Technical Degree
Height Difference of −30–60 cm	Bachelors Degree
Height Difference of > −60 cm	Doctorate Degree
Donor pH 7.1–7.2	Encephalopathy
Donor pH 7.0–7.1	African American Recipient
Donor pH < 7.0	Hepatocellular Carcinoma
SGOT/AST 90–140 u/L	Functional Status 10%
SGOT/AST > 140 u/L	Functional Status 20%
ALT 60 −100 u/L	Functional Status 50%
ALT > 100 u/L	Functional Status 60%
Regional Procurement	Functional Status 70%
National Procurement	Functional Status 80%
Total Bilirubin Donor 1–1.8 mg/dL	Functional Status 90%
Total Bilirubin Donor > 1.8 mg/dL	Functional Status 100%
Weight Difference 45–70 lbs	INR 2.0–2.5
Weight Difference > 70 lbs	INR 2.5–3.0
Weight Difference–70–45 lbs	INR 3.0–3.5
Weight Difference > −70 lbs	INR 3.5–4.0
Employment Status	INR > 4.0
	Life Support for Transplant Patient
	In ICU Pre-Transplant
	Hospitalized not in ICU Pre-Transplant
	2nd Transplant Within 90 Days of 1st Transplant
	2nd Transplant After 90 Days of 1st Transplant
	3rd Transplant Within 90 Days of 1st Transplant
	3rd Transplant After 90 Days of 1st Transplant
	More Than 3 Transplants
	On Ventilator at Transplant
	History of Portal Vein Thrombosis at Registration
	History of Portal Vein Thrombosis at Transplant
	Private Insurance
	Medicaid
	Previous Abdominal Surgery
	Total Bilirubin < 2 mg/dL

Table 2. Continued.

Donor	Recipient
	Total Bilirubin 8–16 mg/dL
	Total Bilirubin 16–32 mg/dL
	Total Bilirubin > 32 mg/dL
	Transjugular Intrahepatic Portacaval Stint Shunt
	Region: CT, ME, MA, NH, RI
	Region: DE, DC, MD, NJ, PA, N. VA, WV
	Region: AL, AR, FL, GA, LA, MS, PR
	Region: OK, TX
	Region: AZ, CA, NV, NM, UT
	Region: AK, HI, ID, MT, OR, WA
	Region: IL, MN, ND, SD, WI
	Region: CO, IA, KS, MO, NE, WY
	Region: NY, VT
	Region: IN, MI, OH
	Region: KY, NC, SC, TN, VA

Hypernatremia resolution analyses

Given that hypernatremia displayed increased short- and long-term mortality at all levels, we hypothesized that resolution of hypernatremia before transplant could signal improved post-transplant outcomes. To analyze the short-term mortality benefit, we compared 90-day post-transplant mortality in patients who were hypernatremic at transplant listing (> 145 mEq/L) and had their serum sodium resolved to normonatremia (135 – 145 mEq/L) immediately before transplantation to patients who were either hypernatremic or normonatremic at both listing and immediately before transplant using univariate and multivariate Cox regression analysis. Resolution of hypernatremia with no time limit between listing and transplant, 1 month between listing and transplant, and 2 weeks between listing and transplant all demonstrated no significant increase in adjusted mortality when controlling for relevant factors denoted by multivariate Cox proportional hazard ratios with 95% confidence intervals that overlap with 1 (Table 4, Table S4). However, unresolved hypernatremia was associated with significantly increased adjusted mortality at all time points, denoted by multivariate Cox proportional hazard ratios > 1 (Table 4).

Consistent with the short-term mortality trend, long-term mortality using Kaplan–Meier curve and log rank test demonstrated significant increase in mortality for unresolved hypernatremia compared with both resolved hypernatremia and normonatremia (Fig. 4a.). To further isolate resolution of hypernatremia from declining hepatic and renal function, subgroups of patients with MELD < 25 (Fig. 4b), Creatinine < 2 mg/dL (Fig. 4c), and both MELD < 25 and Creatinine < 2 mg/dL (Fig. 4d) were analyzed using Kaplan–Meier curves and log rank tests. Similar to the Fig. 4a, log rank tests for all subgroups demonstrated significant increases in mortality for unresolved hypernatremia compared with both resolved hypernatremia and normonatremia.

Discussion

This analysis found that pre-transplant hypernatremia significantly increased adjusted mortality and decreased adjusted graft survival in a dose-dependent pattern across a broad range of serum sodium. Furthermore, hypernatremia was found to have a significant and negative impact on adjusted length of hospitalization, with both mild and moderate hypernatremia increasing length of stay. Finally, a brief retrospective analysis demonstrates that resolved hypernatremia provides adjusted mortality benefit similar to or equivalent to normonatremia, even in relatively preserved liver and kidney function. The large dataset in this analysis allowed for the stratification of serum sodium levels across a broad range for both hyponatremia and hypernatremia. Thus, the degree of impact that hypernatremia had on a patient could be directly correlated with severity of the electrolyte imbalance. Even though some of these serum sodium levels are rarer, this stratification allowed us to decipher the general principle that consist increases in serum sodium led to dose-dependent worse outcomes. This study is novel because it allowed for the stratification of serum sodium to

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Table 3. Univariate and multivariate cox proportional hazards regression of hypo- and hypernatremia.

	Univariate Cox Proportional Hazards Regression					
		Mortality at 90 Days		Graft Survival at 90 Days		Length of Hospitalization
	No. Patients	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value
Serum Sodium < 125 mEq/L	1,903	0.840 (0.748, 0.943)	**0.003**	0.849 (0.761, 0.946)	**0.003**	1.088 (1.038, 1.140)	<**0.001**
Serum Sodium 125–130 mEq/L	5,542	0.935 (0.875, 0.999)	**0.048**	0.945 (0.888, 1.006)	0.077	1.063 (1.033, 1.094)	<**0.001**
Serum Sodium 130–135 mEq/L	14,954	0.959 (0.918, 1.002)	0.063	0.966 (0.927, 1.007)	0.103	1.000 (0.981, 1.020)	0.995
Serum Sodium 135 −145 mEq/L	29,851	1 (Reference Range)		1 (Reference Range)		1 (Reference Range)	
Serum Sodium 145 −150 mEq/L	1,615	1.352 (1.219, 1.500)	<**0.001**	1.315 (1.189, 1.454)	<**0.001**	1.476 (1.401, 1.556)	<**0.001**
Serum Sodium 150–155 mEq/L	349	1.743 (1.435, 2.119)	<**0.001**	1.647 (1.354, 2.004)	<**0.001**	1.901 (1.696, 2.131)	<**0.001**
Serum Sodium > 155 mEq/L	97	2.116 (1.511, 2.963)	<**0.001**	2.118 (1.534, 2.925)	<**0.001**	1.659 (1.312, 2.097)	<**0.001**
	Multivariate Cox Proportional Hazards Regression					
		Adjusted Mortality at 90 Days		Adjusted Graft Survival at 90 Days		Adjusted Length of Hospitalization
	No. Patients	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value
Serum Sodium < 125 mEq/L	1,903	0.900 (0.799, 1.014)	0.083	0.899 (0.804, 1.005)	0.062	1.098 (1.046, 1.153)	<**0.001**
Serum Sodium 125–130 mEq/L	5,542	0.952 (0.887, 1.021)	0.171	0.963 (0.901, 1.029)	0.261	1.060 (1.028, 1.093)	<**0.001**
Serum Sodium 130–135 mEq/L	14,954	0.958 (0.914, 1.004)	0.073	0.968 (0.927, 1.012)	0.154	1.017 (0.996, 1.039)	0.107
Serum Sodium 135 −145 mEq/L	29,851	1 (Reference Range)		1 (Reference Range)		1 (Reference Range)	
Serum Sodium 145 −150 mEq/L	1,615	1.118 (1.004, 1.244)	**0.043**	1.113 (1.003, 1.235)	**0.043**	1.140 (1.080, 1.203)	<**0.001**
Serum Sodium 150–155 mEq/L	349	1.324 (1.084, 1.616)	**0.006**	1.306 (1.069, 1.595)	**0.009**	1.358 (1.210, 1.525)	<**0.001**
Serum Sodium > 155 mEq/L	97	1.623 (1.155, 2.282)	**0.005**	1.661 (1.198, 2.303)	**0.002**	1.162 (0.918, 1.471)	0.21

Bold values indicate statistical significance (*P*-value < 0.05).

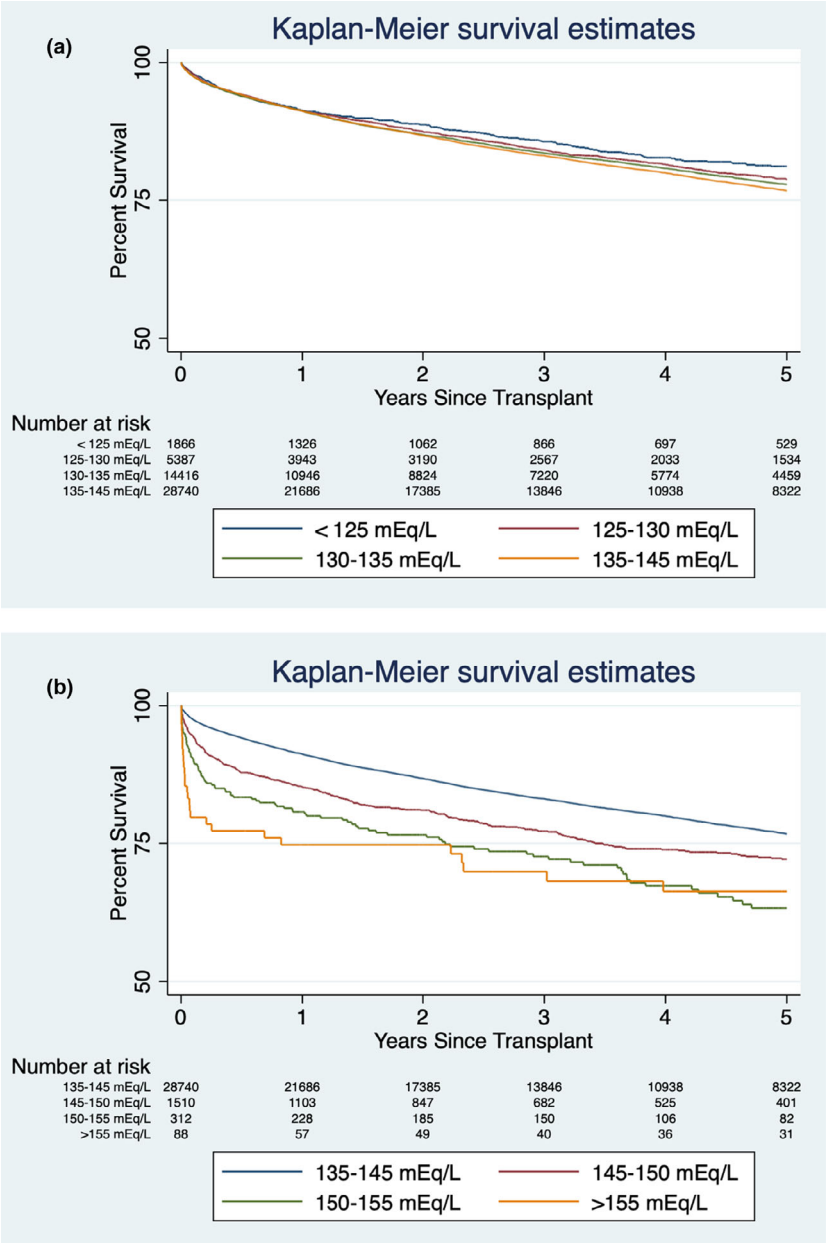

Figure 1 Kaplan–Meier Curve for Mortality. (a) Pre-transplant hyponatremia significant difference with 135–145 mEq/L at < 125 mEq/L (log rank, $P = 0.003$). Other individual log rank comparisons insignificant for 125–130 mEq/L (log rank, $P = 0.051$) and for 130–135 mEq/L (log rank, $P = 0.1$) (b). Pre-transplant hypernatremia significantly different from 135–145 mEq/L for 145–150 mEq/L, 150–155 mEq/L, > 155 mEq/L (log rank, $P < 0.001$ each respectively).

examine a dose–response curve and demonstrates that resolved Na levels from listing to transplant are associated with better outcomes.

Mortality with dysnatremia has been evaluated before, but previous studies have not expanded to include other measures of outcomes of morbidity. This study allowed for direct examination of substratified pre-transplant serum sodium and its effect on graft survival and length of hospital stay, both novel analyses. This is significant because extended length of hospital stay is associated with post-operative morbidity including increased incidence of post-transplant infection, gastrointestinal bleed, renal failure, and allograft rejection [14].

Though stratification of risk and dose–response by various degrees of hypernatremia increasing mortality in a stepwise fashion has not yet been demonstrated in the current literature, other studies have generally

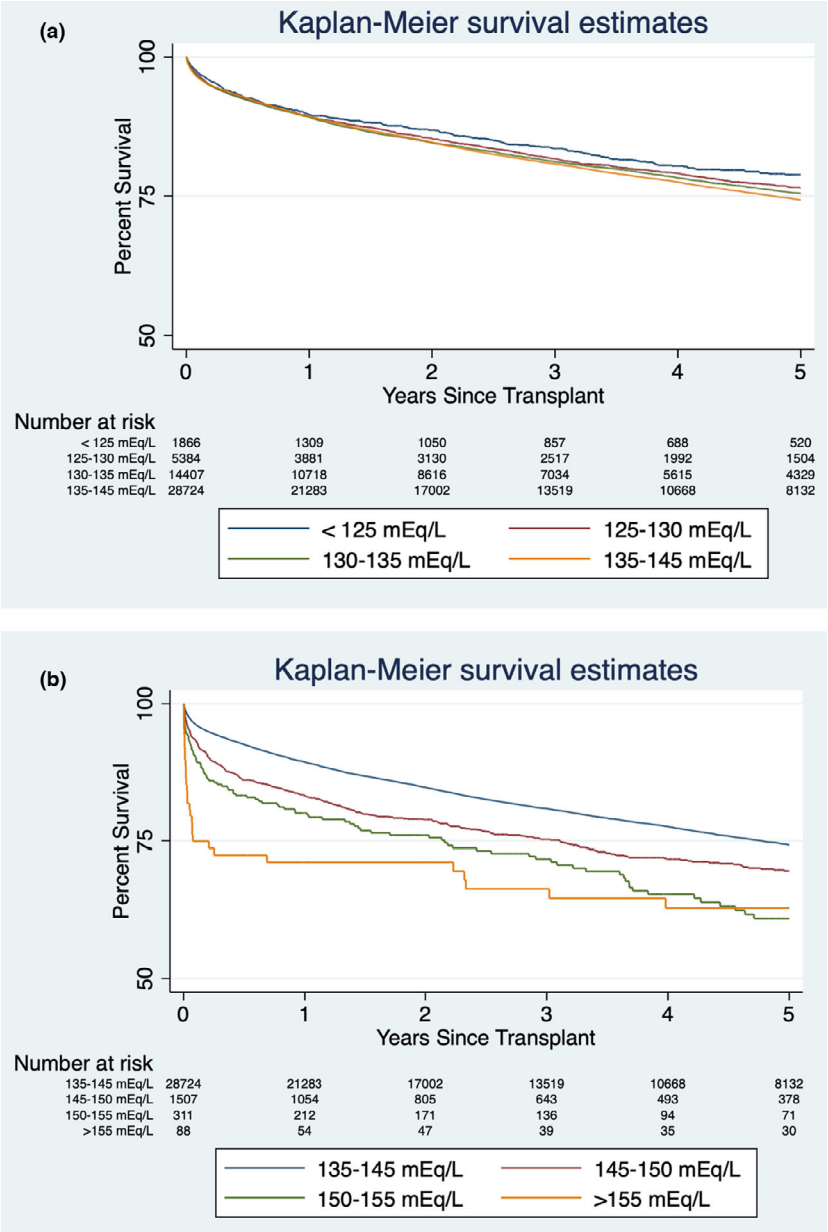

Figure 2 Kaplan–Meier Curve for Graft Survival. (a) Pre-transplant hyponatremia significant difference with 135–145 mEq/L at < 125 mEq/L (log rank, $P = 0.003$). Other individual log rank comparisons insignificant for 125–130 mEq/L (log rank, $P = 0.081$) and for 130–135 mEq/L (log rank, $P = 0.14$) (b). Pre-transplant hypernatremia significantly different from 135–145 mEq/L for 145–150 mEq/L, 150–155 mEq/L, > 155 mEq/L (log rank, $P < 0.001$ each respectively).

supported the findings of this analysis. One cohort multicenter study of 5125 patients found that the patients who had pre-transplant hypernatremia had a greater risk-adjusted mortality at 90 days after transplantation [10]. Another database study of 19,637 liver transplants from 2003 to 2008 showed that 464 hypernatremic patients had increased in-hospital mortality and a diminished 90-day survival [7]. Hyponatremia has also been evaluated in previous studies, but the results have been mixed. Multicenter cohort studies have provided a range of conclusions, from identifying it as a risk for increased mortality to being of no significance [10,11]. Alternatively, other studies have found hyponatremia to be insignificant or even protective if MELD > 11 [7,12]. This study contributes to the current literature on the effects of hyponatremia because its multivariate analysis of a large dataset has shown minimal impact on post-transplant patient outcomes, likely because the liver

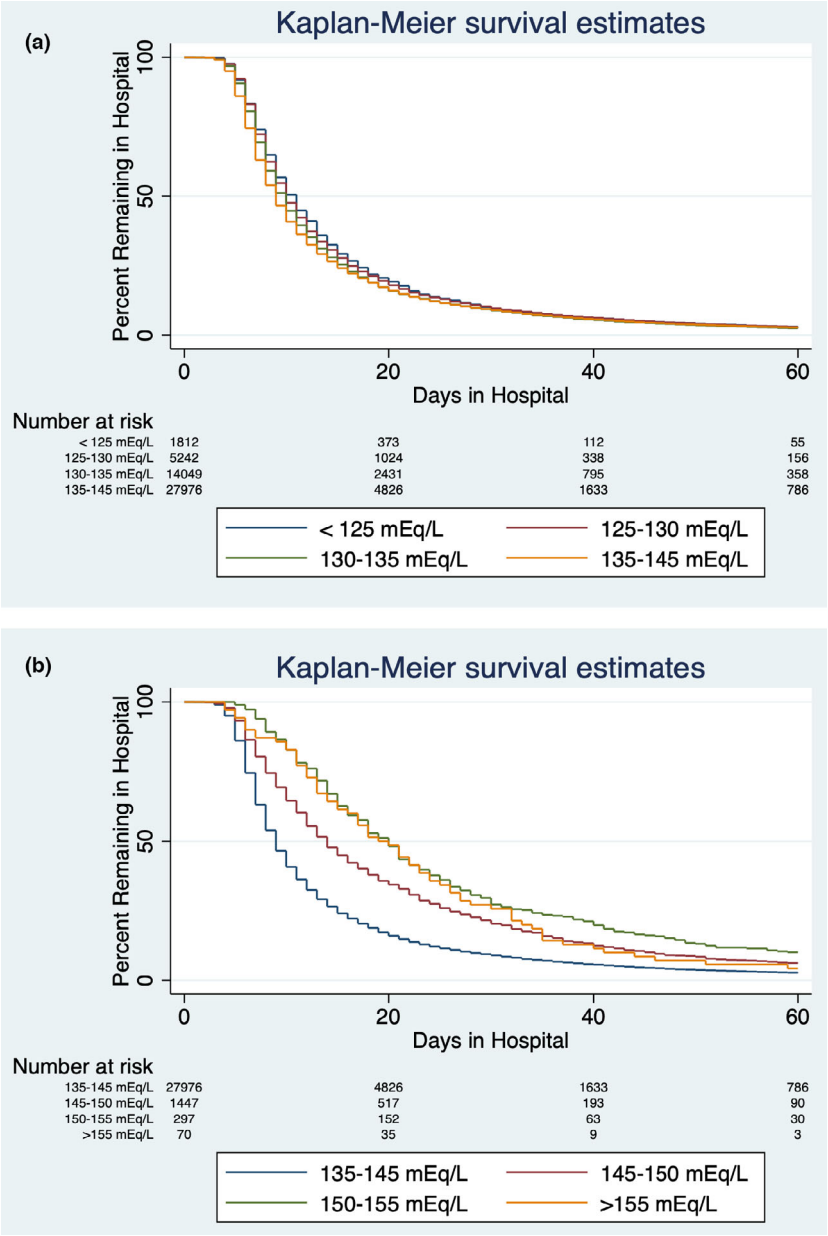

Figure 3 Kaplan–Meier Curve for Length of Hospital Stay (a) Pre-transplant hyponatremia significant difference with 135–145 mEq at all levels (log rank, $P < 0.001$ each respectively). (b). Pre-transplant hypernatremia significantly different from 135–145 mEq/L for 145–150 mEq/L, 150–155 mEq/L, > 155 mEq/L (log rank, $P < 0.001$ each respectively).

transplant itself serves to solve the ascites underlying the hyponatremia. Because extremely hyponatremic patients will have increased MELD-Na scores and be justifiably prioritized for transplant, it is logical that it provides no increased risk for adjusted mortality if the new liver eliminates the underlying source of hyponatremia.

Hypernatremia more likely serves as a poor prognostic indicator in and of itself rather than being the sole determinant of poor outcomes. Hypernatremia in end-stage liver disease can be the result of lactulose use, nasogastric suction, gastrointestinal bleed, or parenteral nutrition [15]. Hypernatremia occurs more often in patients in the ICU or on hemodialysis, both of which are risk factors for early post-transplantation mortality [16,17]. Additionally, severe hepatic encephalopathy is sometimes treated with more aggressive doses of lactulose, which can precipitate hypernatremia [18,19]. It is likely that hypernatremia is serving as a surrogate for patient condition. This means our findings for

Table 4. Univariate and multivariate cox proportional hazards regression of resolved hypernatremia.

		Mortality at 90 Days			
		No Time Limit Between Listing and Transplantation			
		Univariate		Multivariate (Adjusted)	
	No. Patients	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value
Normonatremic at Listing and Transplant	21,971	0.951 (0.914, 0.990)	**0.014**	0.988 (0.947, 1.031)	0.587
Resolved Hypernatremia	1,073	1.089 (0.959, 1.237)	0.189	0.977 (0.859, 1.112)	0.729
Unresolved Hypernatremia	466	1.701 (1.433, 2.020)	<**0.001**	1.254 (1.050, 1.498)	**0.013**
		1 Month Between Listing and Transplant			
		Univariate		Multivariate (Adjusted)	
	No. Patients	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value
Normonatremic at Listing and Transplant	5,829	1.037 (0.967, 1.112)	0.311	0.977 (0.908, 1.052)	0.545
Resolved Hypernatremia	372	1.499 (1.227, 1.830)	<**0.001**	1.183 (0.963, 1.455)	0.11
Unresolved Hypernatremia	391	1.763 (1.466, 2.119)	<**0.001**	1.405 (1.158, 1.706)	**0.001**
		2 Weeks Between Listing and Transplant			
		Univariate		Multivariate (Adjusted)	
	No. Patients	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value
Normonatremic at Listing and Transplant	4,286	1.016 (0.935, 1.103)	0.711	0.993 (0.911, 1.082)	0.866
Resolved Hypernatremia	305	1.426 (1.140, 1.784)	**0.002**	1.153 (0.914, 1.454)	0.23
Unresolved Hypernatremia	370	1.754 (1.449, 2.123)	<**0.001**	1.417 (1.157, 1.736)	**0.001**

Bold values indicate statistical significance (*P*-value < 0.05).

unresolved hypernatremia are likely indicative of poorer underlying conditions in the patient.

The results of this study serve to corroborate the findings of multiple previous studies, but with a more substantial dataset and highly rigorous multivariate analysis. Both existing literature and this analysis have shown that pre-transplant hypernatremia is a significant prognostic factor when determining the morbidity and mortality of liver transplant patients. Our sensitivity analysis of resolved hypernatremia is novel and demonstrates that it does not significantly increase adjusted mortality, while unresolved hypernatremia does significantly increase adjusted mortality. Some studies have suggested re-stratifying waitlist mortality for Status 1A patients including extremely hypernatremic patients, which aligns with the concept that hypernatremia serves as a surrogate for overall patient condition [20]. Our study also demonstrated that resolved hypernatremia had better mortality outcomes long term for the subgroup of patients with relatively preserved kidney and liver functions with MELD < 25 and Creatinine < 2.0 mg/dL. This implies that pre-transplant hypernatremia itself plays some role in long-term outcomes. While not yet formally attempted in a clinical trial for liver transplant patients, a retrospective study of hospitalized patients who received rapid reversal of hypernatremia appears safe, unlike correction of hyponatremia, which is much more and has been associated with worsened outcomes and increased mortality in the context of liver transplantation [13,21]. Our results analyzing resolution of hypernatremia do not imply active correction. Furthermore, these results should be considered with caution, as correction of hypernatremia is not always feasible nor advised in patients. Suggesting the correction of hypernatremia is also outside of the scope of this study and would be better evaluated in a clinical trial setting.

Limitations

Though data entry is mandatory in all US transplant centers, all patient registries suffer from variability. This study was based on a very large database from UNOS, and it therefore is not likely to have been impacted by small amounts of missing or incorrect data. Furthermore, due to prevalence, the sample size for hypernatremia was inherently limited. Pre-transplant serum sodium was not

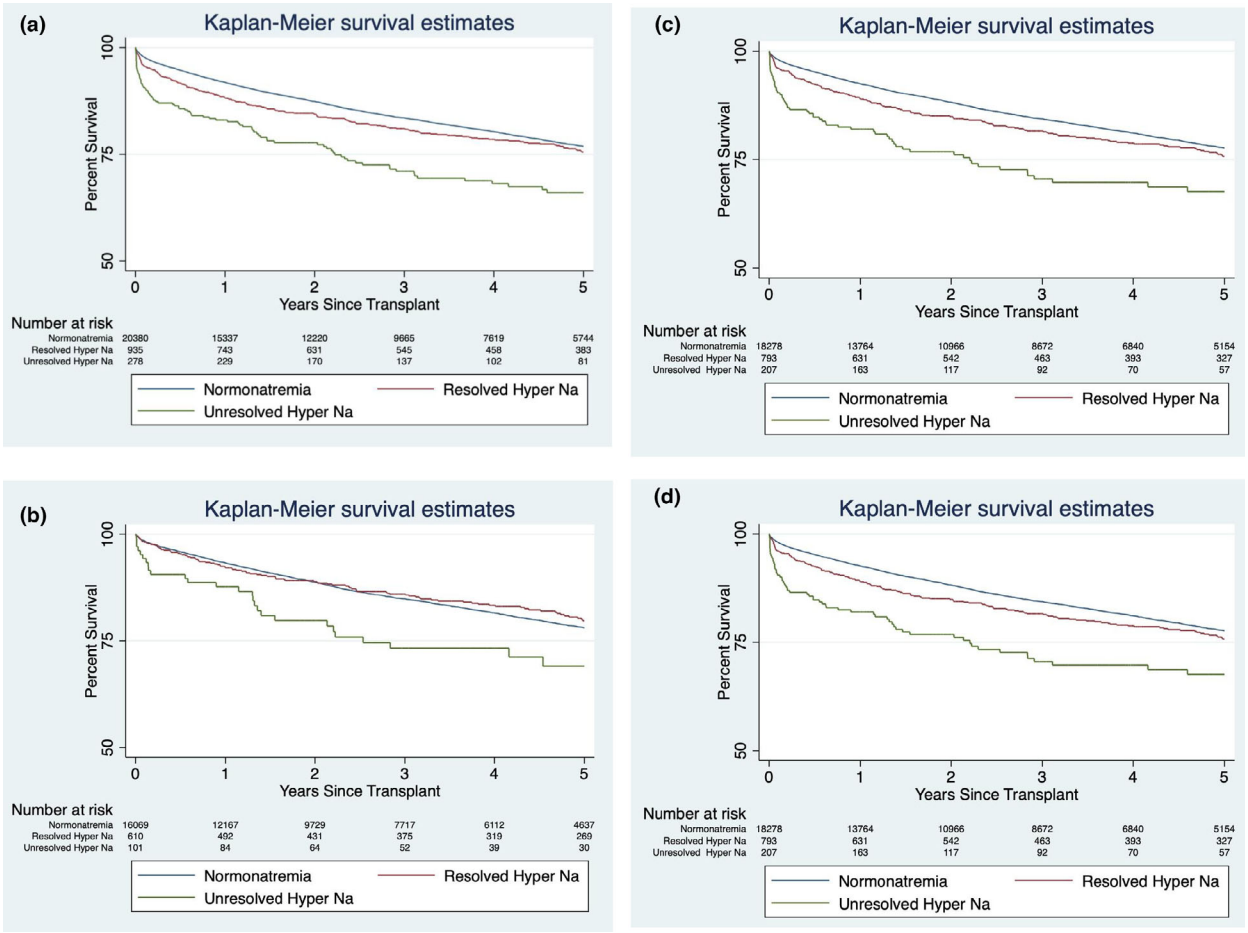

Figure 4 Hypernatremia Resolution Analyses (a) Resolution of pre-transplant hypernatremia (> 145 mEq/L) to normonatremia (135 – 145 mEq/L) not significantly different from normonatremia (log rank, $P = 0.098$). Unresolved hypernatremia (> 145 mEq/L) significantly different from normonatremia (log rank, $P < 0.001$) and resolved hypernatremia (log rank, $P < 0.001$). (b) For subgroup of patients with MELD score < 25, resolved pre-transplant hypernatremia not significantly different from normonatremia (log rank, $P = 0.4658$). Unresolved hypernatremia (> 145 mEq/L) significantly different from resolved hypernatremia (log rank, $P < 0.002$) and normonatremia (log rank, $P < 0.002$). (C). For subgroup of patients with creatinine < 2 mg/dL, resolved pre-transplant hypernatremia not significantly different from normonatremia (log rank, $P = 0.1156$). Unresolved hypernatremia (> 145 mEq/L) significantly different from resolved hypernatremia (log rank, $P = 0.001$) and normonatremia (log rank, $P < 0.001$). (D). For subgroup of patients with MELD score < 25 and creatinine < 2 mg/dL, resolved pre-transplant hypernatremia not significantly different from normonatremia (log rank, $P = 0.5612$). Unresolved hypernatremia (> 145 mEq/L) significantly different from resolved hypernatremia (log rank, $P = 0.018$) and normonatremia (log rank, $P = 0.017$).

consistently recorded in our database until 2008; therefore, the study population was limited to transplant patients after 2008. Lastly, hypernatremia resolution analyses were inherently limited by the lack of granularity between the clinical management of the patient between the listing and transplant serum sodium.

Conclusion

Our retrospective, multivariate analysis of 54,311 liver transplant patients found that pre-transplant hypernatremia significantly impacts post-transplant outcomes in liver transplant recipients by both increasing adjusted mortality and impairing graft survival and that resolution of hypernatremia is associated with improved post-transplant adjusted mortality. Mild and moderate pre-transplant hypernatremia also have a significant increase on adjusted length of hospital stay. On the other hand, pre-transplant hyponatremia appears to have less significant impact on mortality and graft survival.

Authorship

MFM, AR, and THM conceptualized and designed the experiments. MFM performed the experiments. MFM,

AR, THM, AA, CRG, and GC analyzed the data. MFM, SCB, SSK, and CRC wrote the manuscript. AR, CRG, GC, TG, FK, and JG edited the manuscript.

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Conflicts of interest

The authors of this manuscript declare no conflicts of interest.

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Data availability statement

Data are available upon request.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Univariate cox proportional hazards regression hypo- and hypernatremia.

Table S2. Multivariate cox proportional hazards regression of hypo- and hypernatremia.

Table S3. Univariate cox proportional hazards regression resolved hypernatremia.

Table S4. Multivariate cox proportional hazards regression resolved hypernatremia.

Figure S1. Distribution of pre-transplant serum sodium.

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