9-27-2021

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Recommended Citation

Ivanics T, Leonard-Murali S, Mouzaihem H, Moonka D, Kitajima T, Yeddula S, Shamaa T, Rizzari M, Collins K, Yoshida A, Abouljoud M, and Nagai S. Extreme Hyponatremia as a Risk Factor for Early Mortality after Liver Transplantation in the MELD-Sodium Era. Transpl Int 2021.

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Transplant International

ORIGINAL ARTICLE

Extreme hyponatremia as a risk factor for early mortality after liver transplantation in the MELD-sodium era

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SUMMARY

The impact of hyponatremia on waitlist and post-transplant outcomes following the implementation of MELD-Na-based liver allocation remains unclear. We investigated waitlist and postliver transplant (LT) outcomes in patients with hyponatremia before and after implementing MELD-Na-based allocation. Adult patients registered for a primary LT between 2009 and 2021 were identified in the OPTN/UNOS database. Two eras were defined; pre-MELD-Na and post-MELD-Na. Extreme hyponatremia was defined as a serum sodium concentration ≤120 mEq/l. Ninety-day waitlist outcomes and post-LT survival were compared using Fine-Gray proportional hazard and mixed-effects Cox proportional hazard models. A total of 118 487 patients were eligible (n = 64 940: pre-MELD-Na; n = 53 547: post-MELD-Na). In the pre-MELD-Na era, extreme hyponatremia at listing was associated with an increased risk of 90-day waitlist mortality ([ref: 135–145] HR: 3.80; 95% CI: 2.97–4.87; $P < 0.001$) and higher transplant probability (HR: 1.67; 95% CI: 1.38–2.01; $P < 0.001$). In the post-MELD-Na era, patients with extreme hyponatremia had a proportionally lower relative risk of waitlist mortality (HR: 2.27; 95% CI 1.60–3.23; $P < 0.001$) and proportionally higher transplant probability (HR: 2.12; 95% CI 1.76–2.55; $P < 0.001$) as patients with normal serum sodium levels (135–145). Extreme hyponatremia was associated with a higher risk of 90, 180, and 365-day post-LT survival compared to patients with normal serum sodium levels. With the introduction of MELD-Na-based allocation, waitlist outcomes have improved in patients with extreme hyponatremia but they continue to have worse short-term post-LT survival.

Transplant International 2021;

Key words
hyponatremia, MELD-Na, post-transplant survival, United Network of Organ Sharing, waitlist

Received: 27 May 2021; Revision requested: 17 August 2021; Accepted: 20 September 2021

Introduction

In cirrhotic patients, a primary mechanism, contributing to abnormal sodium homeostasis, is disproportionate free-water retention resulting from arginine vasopressin hypersecretion in the setting of circulatory dysfunction [1]. These changes are typically manifestations of advanced disease [1] and can be associated with

doi:10.1111/tri.14123

refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and death [1,2]. Hyponatremia in cirrhotic patients is relatively common (up to 57% of inpatients by some reports) and, historically, has been an independent risk factor for both waitlist dropout and short-term (90-day) mortality following liver transplantation (LT) [2–5].

In January 2016, the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) implemented allocation based on the Model for End-Stage Liver Disease (MELD)-Na score. The MELD-Na score is a modification of the original MELD score that incorporates serum sodium into the formula [6]. The purpose of this new score in liver graft allocation was to account for the adverse impact conferred by hyponatremia on waitlist mortality and improve overall waitlist prognostication [6]. Our group recently reported that the introduction of MELD-Na-based allocation was associated with improved waitlist outcomes with lower waitlist mortality and higher transplant rates [7]. The MELD-Na score is calculated and implemented only if a patient has a MELD of at least 11 using the original MELD equation. In addition, the MELD-Na equation does not give additional points for serum sodium levels less than 125 mEq/l, and patients with severe hyponatremia may not receive higher scores than patients with more moderate hyponatremia. Although the incorporation of serum sodium into the allocation algorithm improves waitlist mortality by improving access to LT, it is unclear how this impacts survival benefit and if there is variation in outcomes based on the degree of hyponatremia. The post-LT impact of MELD-Na-based allocation on candidates with extreme hyponatremia remains to be clarified. In this study, we evaluate post-LT outcomes in patients with pre-LT hyponatremia and the effect of MELD-Na-based allocation on these outcomes.

Patient and methods

Patient selection

This study uses data from the OPTN/UNOS Standard Transplant and Research file, which contains information from all patients registered for liver transplantation in the USA until March 5, 2021. For the analysis of waitlist outcomes, patients with multiorgan transplant listing (except liver-kidney), re-listing, recipient age <18 at listing, acute liver failure, status 1A, or who were listed between January 10, 2016 and February 10, 2016 were excluded. The latter was regarded as a one-month washout period between the implementation of the new policy and the defined date of the post-MELD-Na era. The same exclusion criteria were applied for the analysis of post-LT outcomes, except patients were excluded if they were younger than 18 years old at transplant, underwent a living donor liver transplant (LDLT), or had missing follow-up data. Patients who were listed in the pre-MELD-Na era and transplanted in the post-MELD-Na era were excluded from the post-transplant outcome analysis. A Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) compliant figure of full patient inclusion and exclusion criteria is shown in Fig. 1. The study was approved for an institutional review board (IRB) waiver after IRB review.

Because MELD-Na based allocation was introduced on January 11, 2016, two time periods were defined according to the date of LT listing: a pre-MELD-Na era from January 1, 2009 to January 10, 2016, and a post-MELD-Na era from February 11, 2016 to March 5, 2021. As mentioned previously, a one-month washout period was allowed between the eras. Liver disease etiology was defined by the primary or secondary diagnostic codes or manual text entries in the dataset and grouped into alcohol-related liver disease (ALD), hepatitis C virus-related liver disease (HCV), nonalcoholic steatohepatitis liver disease (NASH), hepatocellular carcinoma (HCC), malignant and biliary etiologies.

Patients were categorized into six groups according to the serum sodium level (mEq/l) at listing and at the time of LT: extreme hyponatremia (Na ≤120), severe hyponatremia (Na 121–124), moderate hyponatremia (Na 125–129), mild hyponatremia (Na 130–134), normal sodium (Na 135–145), and hypernatremia (Na >145). Recipient demographics at LT were collected, including age, gender, MELD, body mass index (BMI). Donor characteristics at LT were collected, including gender, age, BMI, donation after circulatory death (DCD), hepatitis C virus (HCV) antibody, comorbidities, and cold ischemia time (CIT).

Analysis of waitlist outcomes

Ninety-day waitlist outcomes were analyzed using a competing risk analysis with outcomes, including improvement on the waitlist (removal code 12), transplantation (removal codes 2–4, 14, 18, 19, 21, and 22), or death, including removal for being too sick (removal codes 5, 8, and 13). Data was censored if none of the above-mentioned events had occurred before the end of the set period. Patients who received LDLT were censored at the time of LDLT receipt. Because differences in follow-up

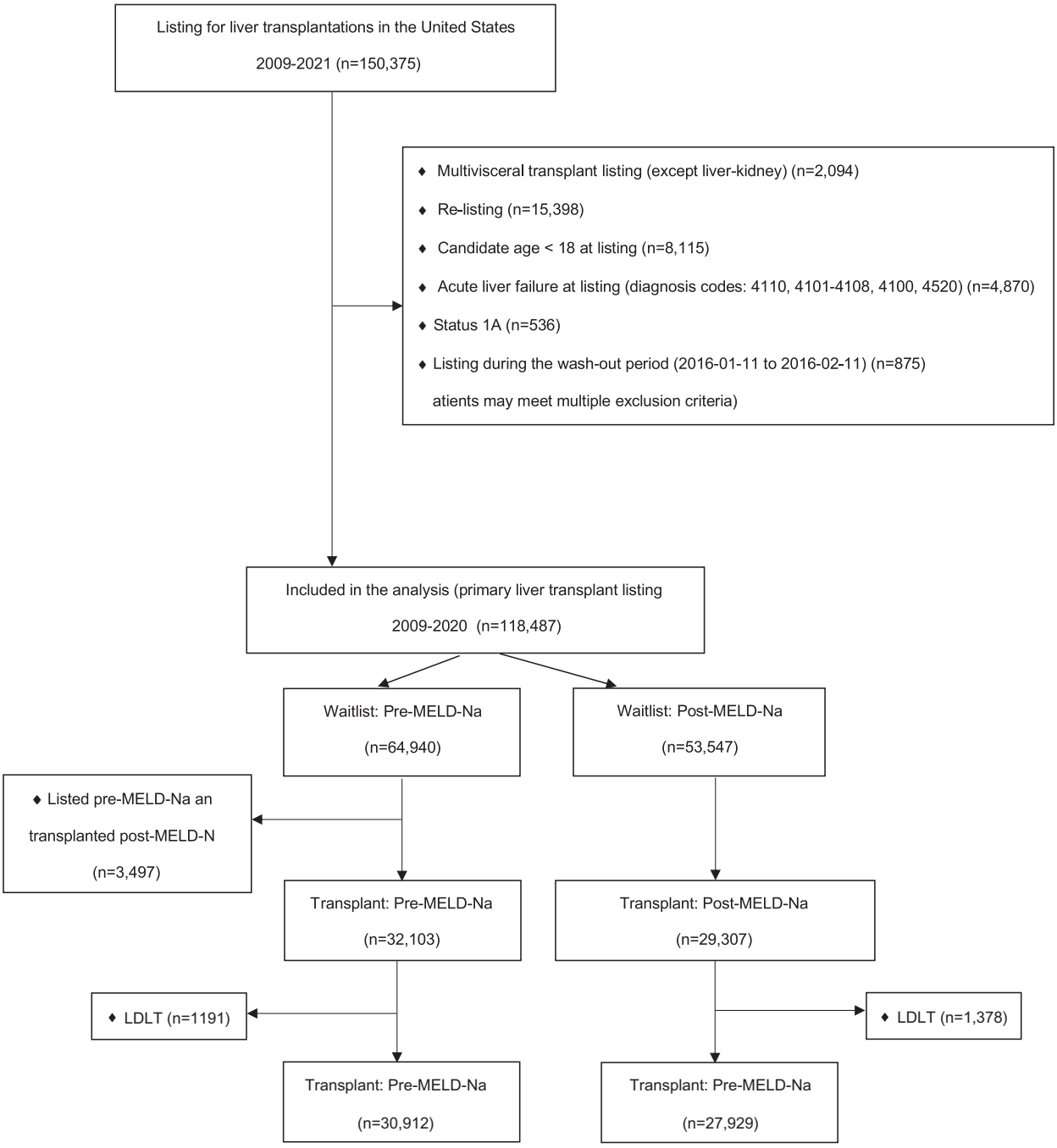

Figure 1 STROBE diagram of cohorts included and excluded.

time can result in withdrawal bias, patients registered in each era were censored on the last day of that era (January 11, 2016, and March 5, 2021, respectively).

Analysis of post-LT outcomes and comparison of the hazard of mortality

Short-term post-LT outcomes were evaluated and compared between eras, including 90-day and 1-year patient survival. Both unadjusted and adjusted survival analyses were performed. Risk factors for post-LT mortality were evaluated adjusting for the following variables present at the time of LT: recipient age, encephalopathy, ascites, recipient life support, MELD exception, disease etiology, hyponatremia levels, recipient diabetes, recipient BMI, International normalized ratio (INR), Creatinine, Bilirubin, liver-kidney listing, dialysis requirement during the week before LT, CIT, Karnofsky score, waitlist time,

donor age, donor BMI, and DCD donor. In the pre-MELD-Na era, the MELD score is the MELD score, whereas, in the post-MELD-Na era, the MELD represents the MELD-Na. To overcome this differential calculation in the MELD score, adjustments were made for the individual MELD score components (bilirubin, INR, and creatinine). A mixed-effects cox regression model was constructed where the transplant center was treated as a random effect. The interaction between the sodium categories and the MELD-Na era were evaluated in the adjusted multivariable models. The primary cause of death was captured by the variable name COD and up to two contributory causes of death were captured by the COD2 and COD3 variables, respectively.

Statistical analysis

Descriptive data for continuous variables were expressed as means with standard deviation if the distribution was normal and medians with interquartile range (IQR) if the distribution was non-normal. These were compared using the Student *t*-test and Mann-Whitney *U* test, respectively. Categorical variables were expressed as numbers and percentages and were compared using chi-square and Fischer exact test. Patients were analyzed from the time of LT using Kaplan-Meier analysis with log-rank tests. Multiple pairwise comparisons between groups with corrections for multiple testing were performed using the Benjamini-Hochberg method. Cox proportional hazard regression models were constructed to evaluate the association of extreme hyponatremia on post-LT patient survival. For the waitlist analysis, instead of a Kaplan-Meier approach, which censors for competing events, a cumulative incidence approach was used to account for the presence of competing risks of transplant and waitlist dropout due to mortality [8]. The cumulative incidence was calculated using sub-distribution estimates for each cause. A Gray's modified log-rank test was used to compare sub-distribution estimates for each cause (unadjusted incidence estimated) of waitlist event. Multiple pairwise comparisons between groups with corrections for multiple testing were performed using the Bonferroni method. For assessing the relative change in the hazard of waitlist dropout due to mortality, a Fine-Gray proportional sub-distribution hazard model was used to account for transplant as a competing event [9]. Flexible hazard ratio curves were constructed using "smoothing splines" to allow for the nonlinear aspect of serum sodium as a continuous predictor of survival. A *P*-value <0.05 was considered statistically significant for all analyses. All statistical analyses were performed using R (R version 4.0.3 [2020-10-10], R foundation for Statistical Computing, Vienna, Austria URL http://www.R-project.org/). Competing risk analysis was performed using the package 'cmprsk'. Mixed-effects cox regression was performed using the package 'survival' and 'coxme'.

Results

Waitlist outcome analysis

A total of 118 487 patients were identified for the analysis of waitlist outcomes (N = 64 940 Pre-MELD-Na and N = 53 547 Post-MELD-Na). Waitlist characteristics are compared between eras in Table 1. The majority of patients had a normal serum sodium concentration at listing in both the pre- and post-MELD-Na era (135–145, 68.1% vs. 67.3%; $P < 0.001$). Patients with a serum sodium concentration of ≤ 120 at listing comprised 0.5% of patients in the pre-MELD-Na era and 0.6% in the post-MELD-Na era ($P < 0.001$). Of the extreme hyponatremic cohort at listing (n = 295 and n = 207 in the pre- and post-MELD-Na era, respectively), 3 (1.0%) required dialysis in the week prior to listing in the pre-MELD era and 6 (2.9%) in the post-MELD era (Table S1). Patients with extreme hyponatremia had a higher 90-day cumulative incidence of waitlist dropout due to death compared to patients with higher (135–145, 130–134, 125–129, and 121–124) sodium levels in the pre-MELD-Na era ($P < 0.001$) but similar rates compared to patients with the highest serum sodium concentrations (>145; Fig. 2a). Similarly, patients with extreme hyponatremia had a higher transplant probability compared with patients with higher sodium levels (135–145, 130–134) in the pre-MELD-Na era ($P < 0.001$; Fig. 2b). Significant differences were also observed in the post-MELD-Na era, where patients with extreme hyponatremia had similar 90-day waitlist mortality as patients with higher serum sodium concentration (121–124, 125–129, >145) but higher waitlist mortality than patients with a serum sodium concentration of 130–134 and 135–145 (Fig. 3a). The cumulative 90-day transplant probability was highest in patients with extreme hyponatremia than all other serum sodium concentrations except for patients with a serum sodium concentration between 121 and 124 mEq/l (Fig. 3b).

In patients with extreme hyponatremia, the cumulative incidence of 90-day waitlist dropout due to death was lower post-MELD-Na ($P < 0.001$; Fig. S1a), and the cumulative incidence of 90-day transplant probability was higher post-MELD-Na ($P < 0.001$; Fig. S1b) compared to

Table 1. Patient characteristics (waitlist).

	Pre-MELD-Na (*N* = 64 940)	Post-MELD-Na (*N* = 53 547)	*P* value
Serum sodium concentration at listing, mEq/l, *n* (%)			
N-missing	40	28	<0.001*
135–145	44 194 (68.1%)	36 041 (67.3%)	
130–134	14 270 (22.0%)	11 737 (21.9%)	
125–129	4347 (6.7%)	3950 (7.4%)	
120–124	1118 (1.7%)	1009 (1.9%)	
≤120	330 (0.5%)	307 (0.6%)	
>145	641 (1.0%)	475 (0.9%)	
Recipient sex, *n* (%)			
Female	22 335 (34.4%)	19 623 (36.6%)	<0.001*
Male	42 605 (65.6%)	33 924 (63.4%)	
Recipient age (years), median (Q1, Q3)	58 (52, 63)	58 (50, 64)	<0.001†
MELD score at listing, median (Q1, Q3)	15 (11, 21)	18 (11, 26)	<0.001†
Days on waitlist, median (Q1, Q3)	204 (50, 572)	140 (25, 348)	<0.001†
Hepatocellular carcinoma, *n* (%)	14 964 (23.0%)	11 476 (21.4%)	<0.001*
Malignant indication, *n* (%)	15 289 (23.5%)	11 994 (22.4%)	0.047*
Alcohol-related liver disease, *n* (%)	18 358 (28.3%)	20 654 (38.6%)	<0.001*
Hepatitis C virus-related liver disease, *n* (%)	26 033 (40.1%)	10 339 (19.3%)	<0.001*
Non-alcoholic steatohepatitis, *n* (%)	8804 (13.6%)	12 682 (23.7%)	<0.001*
Biliary etiology of liver disease, *n* (%)	4889 (7.5%)	4068 (7.6%)	0.657*
Recipient diabetes, *n* (%)	18 148 (28.1%)	16 215 (30.6%)	<0.001*
(Missing)	332	581	
Functional status, *n* (%)			
10–30%	7906 (12.5%)	8336 (16.0%)	<0.001*
40–100%	55 464 (87.5%)	43 855 (84.0%)	
(Missing)	1570	1356	
Dialysis week prior to listing, *n* (%)	4216 (6.5%)	4694 (8.8%)	<0.001*
(Missing)	15	24	
Exception points, *n* (%)	15 467 (23.8%)	8317 (15.5%)	<0.001*
Life support at listing, *n* (%)	1353 (2.1%)	1519 (2.9%)	<0.001*
Missing	3	498	

*Pearson's Chi-squared test.

†Kruskal-Wallis rank sum test.

pre-MELD-Na. Similar findings were observed for patients without extreme hyponatremia (Fig. S2a,b).

In extreme hyponatremic patients, using Fine-Gray proportional hazard models, the post-MELD-Na era was protective for 90-day waitlist survival [sub-distribution HR (sHR) 0.44, 95% CI 0.28–0.68; $P < 0.001$] and was associated with an increased chance for receiving a transplant within 90 days (HR 1.89, 95% CI 1.48–2.41; $P < 0.001$; Fig. S2). In the pre-MELD era, extreme hyponatremia at listing was associated with an increased risk of 90-day waitlist mortality (ref: 135–145, sHR 3.80, 95% CI 2.97–4.87; $P < 0.001$) and a higher likelihood of transplant within 90-days (ref: 135–145, sHR 1.67, 95% CI 1.38–2.01; $P < 0.001$; Fig. S3a,b). In the post-MELD-Na era, extreme hyponatremia had a proportionally lower risk (although statistically significantly higher) of 90-day waitlist mortality (ref: 135–145, sHR 2.27, 95% CI 1.60–3.23; $P < 0.001$) and a proportionally higher chance of transplant (ref: 135–145, sHR 2.12, 95% CI 1.76–2.55; $P < 0.001$) as patients with normal serum sodium levels at listing (Fig. S2a,b).

Analysis of patients who underwent LT

A total of 58 841 patients were analyzed, including 30 912 in the Pre-MELD-Na era and 27 929 in the Post-MELD-Na Era (Fig. 1). There was a small (0.5%) and a similar proportion of patients with serum sodium ≤120 pre- and post-MELD-Na. MELD scores were higher in the post-MELD-Na era [median (IQR) 21 (13–31) vs. 24 (16–32) $P < 0.001$], and the median overall time on the waitlist was shorter post-MELD-Na [days (IQR) 91 (20–256) vs. 61 (11–226); $P < 0.001$]. A higher proportion of DCD LTs was performed in the

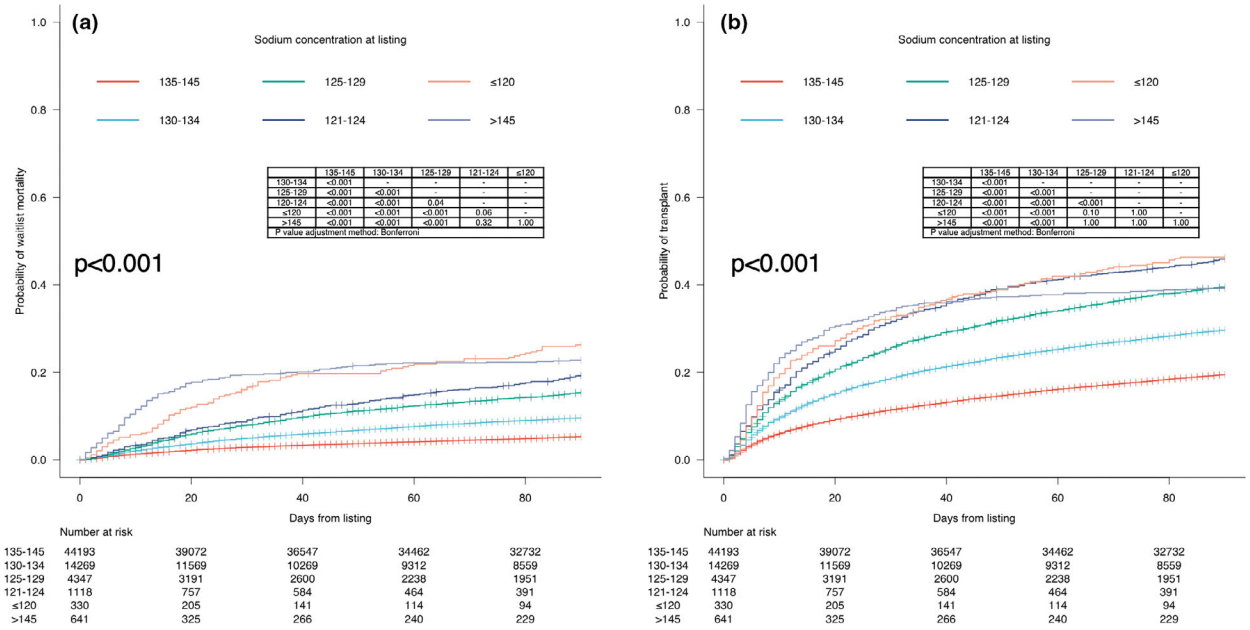

Figure 2 (a) Pre-MELD-Na era 90-day waitlist dropout for death or too sick by serum sodium concentration. (b) Pre-MELD-Na era 90-day transplant probability by serum sodium concentration. (c) Post-MELD-Na era 90-day waitlist dropout for death or too sick by serum sodium concentration. (d) Post-MELD-Na era 90-day transplant probability by serum sodium concentration.

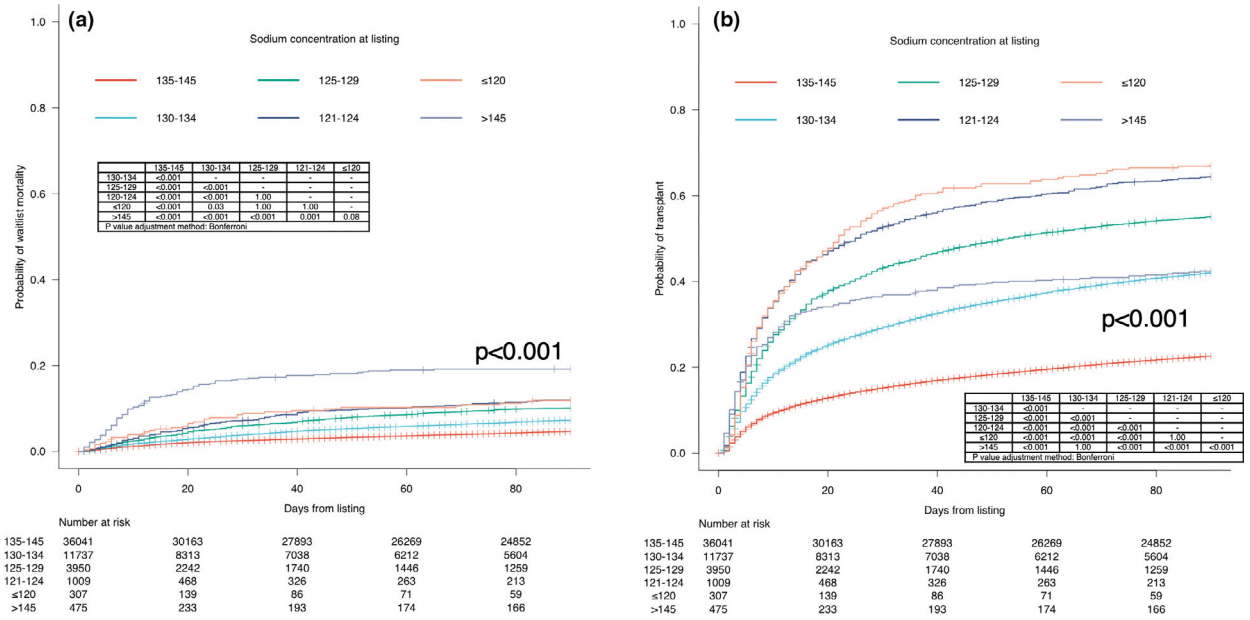

Figure 3 (a) Post-MELD-Na era 90-day waitlist dropout for death or too sick by serum sodium concentration. (b) Post-MELD-Na era 90-day transplant probability by serum sodium concentration.

post-MELD-Na era (5.7% vs. 8.7%; $P < 0.001$; Table 2). Patient characteristics stratified by serum sodium concentration at LT for the pre-MELD-Na and post-MELD-Na eras can be seen in Tables S2 and S3. For extreme hyponatremic patients who underwent transplant (154 and 143 in the pre- and post-MELD-Na era, respectively) 7 (4.5%) required dialysis in the week prior to LT in the pre-MELD era and 4 (2.8%) in the post-MELD era (Table S1).

Unadjusted post-LT survival analysis

The 30, 90, 180-, and 365-day post-LT survival in patients with extreme hyponatremia in the pre-MELD-

Table 2. Patient characteristics (LT).

	Pre-MELD-Na (*N* = 30 912)	Post-MELD-Na (*N* = 27 929)	*P* value
Serum sodium concentration at liver transplant, mEq/l, *n* (%)			
135–145	19 729 (63.8%)	16 715 (59.9%)	<0.001*
130–134	7292 (23.6%)	7031 (25.2%)	
125–129	2540 (8.2%)	2915 (10.4%)	
121–124	566 (1.8%)	719 (2.6%)	
≤120	154 (0.5%)	143 (0.5%)	
>145	629 (2.0%)	402 (1.4%)	
(Missing)	2	4	
Recipient sex, *n* (%)			
Female	9724 (31.5%)	9638 (34.5%)	<0.001*
Male	21 188 (68.5%)	18 291 (65.5%)	
Recipient age (years), Median (Q1, Q3)	57 (51, 62)	58 (50, 64)	<0.001†
In intensive care unit at liver transplant, *n* (%)	3662 (11.8)	3816 (13.7)	<0.001*
MELD at liver transplant, median (Q1, Q3)	21 (13, 31)	24 (16, 32)	<0.001†
Days on the waitlist, median (Q1, Q3)	91 (20, 256)	61 (11, 226)	<0.001†
Recipient diabetes, *n* (%)	8533 (27.8%)	8378 (30.0%)	<0.001*
N-missing	164	37	
Functional status, *n* (%)			
N-missing	266	333	<0.001*
40–100%	22 033 (71.9%)	19 394 (70.3%)	
10–30%	8613 (28.1%)	8202 (29.7%)	
Dialysis in the week prior to liver transplant, *n* (%)	4516 (14.6%)	4903 (17.6%)	<0.001*
(Missing)	0	143	
Hepatocellular carcinoma, *n* (%)	8764 (28.4%)	5856 (21.0%)	<0.001*
Malignant indication, *n* (%)	8861 (28.7%)	6090 (21.8%)	<0.001*
Alcohol-related liver disease, *n* (%)	8250 (26.7%)	11 260 (40.3%)	<0.001†
Hepatitis C virus-related liver disease, *n* (%)	12 858 (41.6%)	5379 (19.3%)	<0.001†
Non-alcoholic steatohepatitis, *n* (%)	4063 (13.1%)	6691 (24.0%)	<0.001†
Biliary etiology of liver disease, *n* (%)	2217 (7.2%)	1973 (7.1%)	0.612†
Follow-up time, days, Median (Q1, Q3)	2165 (1427, 2905)	384 (184, 863)	<0.001†
Length of stay, Median (Q1, Q3)	10 (7, 16)	10 (7, 16)	<0.001†
Recipient BMI, Median (Q1, Q3)	28.0 (24.5, 32.3)	28.4 (24.7, 32.8)	<0.001†
Donor sex, *n* (%)			
Female	12 452 (40.3%)	10 941 (39.2%)	0.044*
Male	18 460 (59.7%)	16 988 (60.8%)	
Donor BMI, Median (Q1, Q3)	26.69 (23.37, 30.99)	27.25 (23.67, 31.76)	<0.001†
Donation after circulatory death, *n* (%)	1767 (5.7%)	2423 (8.7%)	<0.001*
Exception points, *n* (%)	11 633 (44.8%)	6430 (25.2%)	0.172†
N-missing	4920	2427	
Life support at liver transplant, *n* (%)	2180 (7.1%)	2303 (8.2%)	<0.001*
N-missing	0	12	

BMI, body mass index; MELD, model for end-stage liver disease; Q1, Q3, interquartile range.

*Pearson's Chi-squared test.

†Kruskal-Wallis rank sum test.

Na era were 95.5% (95% CI 92.2–98.8), 93.5% (95% CI 89.7–97.5), 89.6% (95% CI 84.9–94.5), and 85.6% (95% CI 80.3–91.4), respectively, compared to 97.6% (95% CI 97.3–97.8), 95.8% (95% CI 95.5–96.1), 94.0% (95% CI 93.7–94.3), and 91.3% (95% CI 90.9–91.7), respectively, in patients with normal serum sodium levels (30-day $P = 0.17$, 90-day $P = 0.32$, 180-day $P = 0.06$, and 365-day $P = 0.03$). The 30, 90, 180, and 365-day post-LT survival in patients with extreme hyponatremia in the post-MELD-Na era were 95.6% (95% CI 92.3–99.1), 93.3% (95% CI 89.2–97.6), 91.0% (95% CI 86.2–96.0), and 89.3% (95% CI 84.1–94.8), respectively, compared to 97.7% (95% CI 97.5–98.0), 96.3% (95% CI 96.0–96.6), 95.1% (95% CI 94.7–95.4), and 92.7% (95% CI

92.3–93.2) in patients with normal serum sodium levels (30-day $P = 0.18$, 90-day $P = 0.14$, 180-day $P = 0.06$, 365-day $P = 0.17$; Figs 4 and S4).

In the pre-MELD-Na era, patients with hypernatremia (Na >145) had the worst 90-day post-LT survival compared to all sodium levels except compared to patients with extreme hyponatremia where the unadjusted survival was equivalent ($P = 0.43$; Fig. 4a). In the post-MELD-Na era, patients with extreme hyponatremia had a statistically significantly worse 90- and 365-day post-LT survival compared to a serum sodium concentration of 121–124, and a nonstatistically significant different unadjusted survival from a serum sodium concentration of 125–129, 130–134, 135–145, and over 145 (Fig. 4b).

Patients with extreme hyponatremia had a similar 90-day and 365-day post-LT survival in both the pre-MELD-Na and post-MELD-Na eras (Fig. S5).

Cox proportional hazard analysis

On the mixed-effects multivariable Cox proportional hazard analysis for 90-day post-LT survival where transplant center was treated as a random effect, adjusting for bilirubin at LT, creatinine at LT, INR at LT, DCD, recipient age, encephalopathy, ascites, etiology of liver disease, recipient diabetes, recipient BMI, functional status, recipient life support at LT, exception points, donor age, donor BMI, simultaneous liver-kidney transplant listing, dialysis status pre-LT, and Era (pre-MELD-Na reference), both extreme hyponatremia and hypernatremia were associated with patient death (HR 2.28, 95% CI 1.43–3.64; $P = 0.03$ and HR 2.05, 95% 1.59–2.64; $P < 0.001$). These findings persisted up to 180-days (extreme hyponatremia (ref: 135–145) HR 2.45, 95% CI 1.67–3.61; $P < 0.001$) and up to 365-days post-LT (extreme hyponatremia (ref: 135–145) HR 2.16, 95% CI 1.53–3.04; $P < 0.001$). In none of the models did the association of extreme hyponatremia with death vary depending on the era [serum sodium concentration * MELD-era (interaction)].

In the pre-MELD-Na era, extreme hyponatremia had a higher risk for post-LT 90-day mortality as a normal serum sodium level (HR 2.13, 95% CI 1.08–4.18; $P = 0.03$; Fig. 5a) The risk remained higher up to 180-days post-LT (ref: 135–145, HR 2.42, 95% CI 1.43–4.09; $P < 0.001$) and up to 365-days post-LT (ref: 135–145, HR 2.10, 95% CI 1.32–3.35; $P = 0.001$; Fig. S6a). In the post-MELD-Na era, extreme hyponatremia had a higher hazard for post-LT 90-day mortality relative to a normal serum sodium concentration (HR 2.40, 95% CI 1.21–4.75; $P = 0.01$; Fig. 5b). This effect persisted up to 180-days post-LT (ref: 135–145, HR 2.51, 1.39–4.53; $P = 0.002$) and up to 365-days post-LT (ref: 135–145, HR 2.16, 95% CI 1.25–3.73; $P = 0.005$; Fig. S6b). A steeper increase in hazard below a serum sodium concentration of 120 was observed in the post-MELD-Na era compared to the pre-MELD-Na era when serum

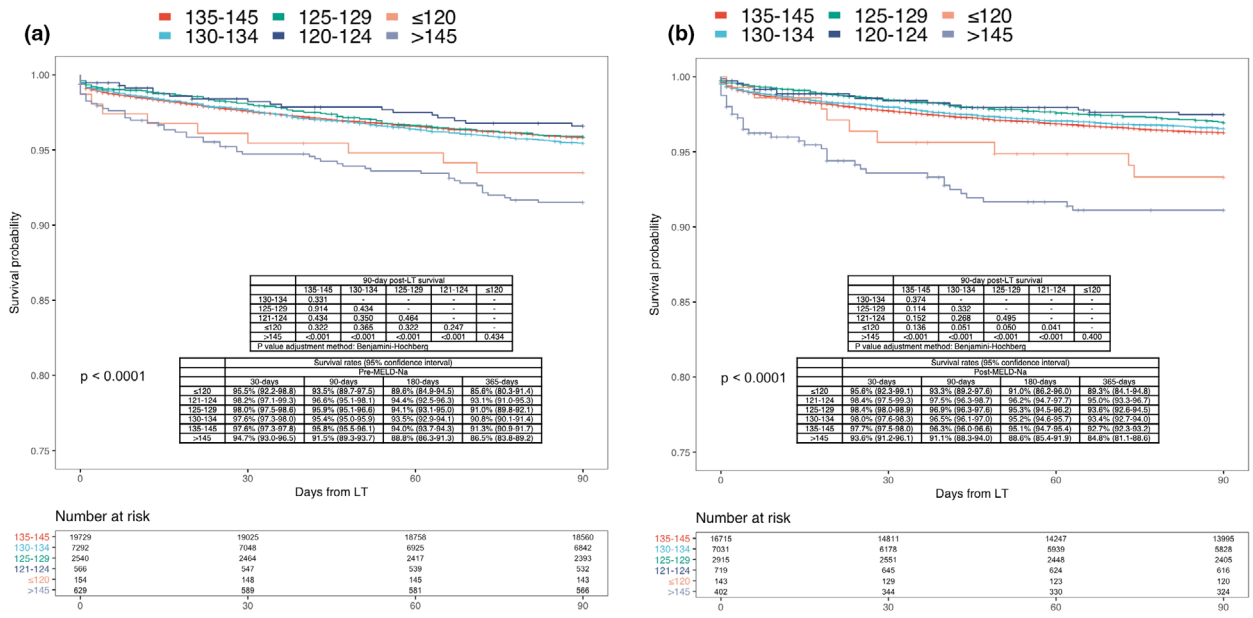

Figure 4 (a) 90-day post-LT survival stratified by serum sodium at LT (pre-MELD-Na era). (b) 90-day post-LT survival stratified by serum sodium at LT (post-MELD-Na era).

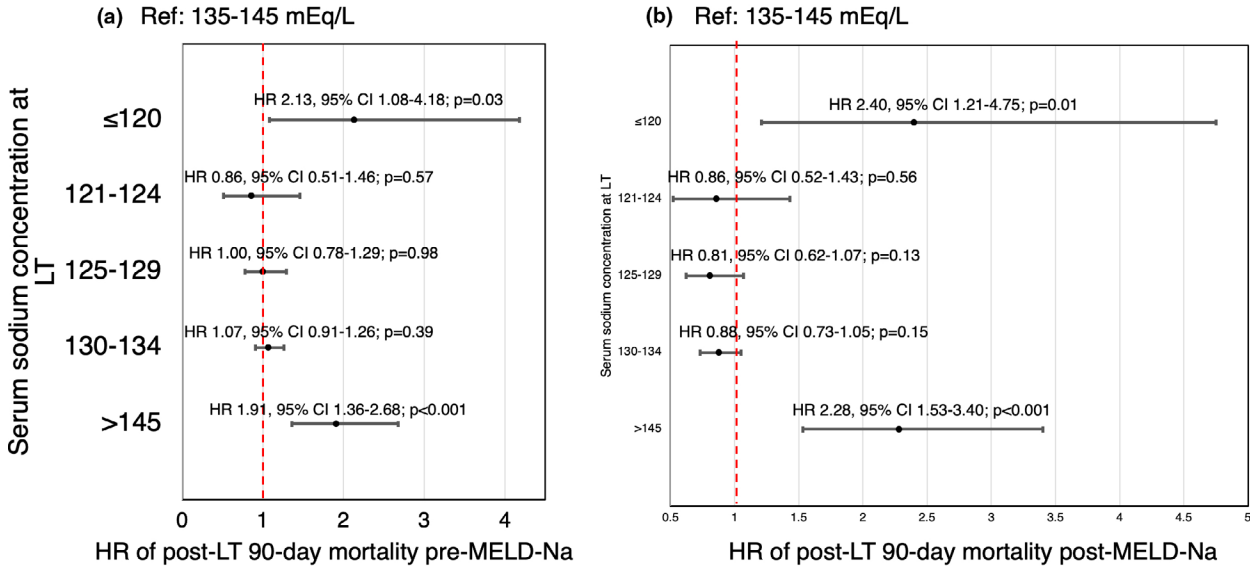

Figure 5 (a) Mixed effects Cox proportional hazard model forest plot for post-LT 90-day mortality in pre-MELD-Na era by serum sodium concentration (ref: serum sodium concentration 135–145 mEq/l). Adjusted for recipient factors (sodium level at LT, age, encephalopathy, ascites, liver disease etiology [ALD, HCV, NASH, HCC], life support, diabetes, bilirubin, INR, creatinine, dialysis requirement, BMI, functional status, exception points, liver kidney listing), and donor factors (DCD, CIT, age, BMI), and era. (b) Cox proportional hazard model forest plot for post-LT 90-day mortality in post-MELD-Na era by serum sodium concentration (ref: serum sodium concentration 135–145 mEq/l. Adjusted for recipient factors (sodium level at LT, age, encephalopathy, ascites, liver disease etiology [ALD, HCV, NASH, HCC], life support, diabetes, bilirubin, INR, creatinine, dialysis requirement, BMI, functional status, exception points, liver kidney listing), and donor factors (DCD, CIT, age, BMI), and era.

sodium concentration was modeled using penalized smoothing spline on adjusted analysis (Fig. S7).

Discussion

This study demonstrates that while waitlist outcomes for extremely hyponatremic patients have improved through lower waitlist mortality rates (ref: normal serum sodium, risk-adjusted sHR 2.27, 95% CI 1.60–3.23; $P < 0.001$) and higher transplantation rates (ref: normal serum sodium, risk-adjusted sHR 2.12, 95% CI 1.76–2.55; $P < 0.001$), the same patients continue to have worse short-term post-LT outcomes (ref: normal serum sodium, risk-adjusted mortality HR 2.40, 95% CI 1.21–4.75; $P = 0.01$) relative to other serum sodium concentrations in the post-MELD-Na era. Our group recently reported the effects of the MELD-Na-based allocation on waitlist and post-LT outcomes and demonstrated that the new allocation score was associated with improved waitlist outcomes in patients with hyponatremia [7]. This present study further investigated the impact of the policy change, concentrating on patients with extreme hyponatremia. An evaluation specifically focused on patients with extreme hyponatremia has not been performed, and they are often grouped with abnormal yet higher serum sodium concentrations (e.g., <125 mEq/l). Consequently, the better outcomes of patients with higher sodium levels (i.e., >120 but <125) may mask the specific outcomes in the extremely hyponatremic group. This study's findings highlight that caution should be exercised in proceeding with LT in these patients, and efforts should be made to optimize patients for LT to mitigate adverse short-term post-LT outcomes.

The MELD-Na score was developed over several renditions [3,5]. Biggins *et al.* [3] incorporated Na into the MELD score using a prospective multicenter database of 753 patients. In this model, the lower and upper limits of serum sodium were established at 120 and 135, assuming a linear relationship between those limits and waitlist mortality. The lower limit was selected because a linear relationship for worse outcomes did not extend past this cutoff, there were few patients below this point and the perceived need for a "cap" similar to creatinine in the original MELD formula [3]. The authors highlighted that incorporating of sodium into the allocation system might favor severely hyponatremic patients at risk of neurologic problems following transplantation and that it was the transplant center's responsibility to identify patients who were too high risk to undergo

transplantation [3,5]. The present MELD-Na score limits sodium in the range of 125–140 mEq/l, and concentrations beyond these cutoffs do not result in higher scores. Concerns have been raised that the prioritization of hyponatremic patients by the present MELD-Na system might adversely affect post-LT outcomes [10]. Our study demonstrates this is predominantly limited to patients with extreme hyponatremia.

Several studies have demonstrated an independent association between hyponatremia and worse waitlist and short-term transplant outcomes, primarily due to neurological disorders, renal failure, and infection [11–13]. Hyponatremia is considered a marker of advanced cirrhosis and results, in part, from significant hemodynamic abnormalities that lead to impairment in body water homeostasis [1,14]. The LT allocation policy in the USA is based on allocating grafts according to the "sickest first" to rescue patients from likely death. Allocation is not based on transplant survival, which is left to individual centers to risk assess guided, in part, by regulatory guardrails. Because the MELD score's ability to predict mortality was suboptimal in hyponatremic patients, the MELD-Na score was developed to improve accuracy. While this has resulted in overall favorable outcomes for hyponatremia patients, patients with extreme hyponatremia appear to have worse short-term post-LT outcomes than other degrees of hyponatremia. Apart from the aforementioned pathophysiologic reasons, extremely hyponatremic patients have overall higher MELD scores, shorter waitlist times, and worse functional status than patients without extreme hyponatremia. The exact reason why the difference in transplant survival is more pronounced in the post-MELD-Na era is not entirely clear. One explanation may be that the accelerated waitlist process, supported by a shorter waitlist time in extreme hyponatremic patients in the post-MELD-Na era, while increasing the chance of LT, may result in less opportunity for preoperative optimization decrease the likelihood of poorer candidates dropping off the waitlist and instead of proceeding to LT. While risk factors could not be determined within the extremely hyponatremic group, given the small number of events, potentially modifiable donor factors associated with decreased 90-day post-LT survival were the use of DCD grafts and longer CIT. Recipient selection could reflect the increased early mortality risk seen with older recipient age, higher recipient BMI, worse functional status, and need for life support. Thus, these should be considered when mitigating the risk of early mortality post-LT by avoiding compounding factors. For instance, patients with extreme hyponatremia might potentially benefit from additional medical optimization rather than proceeding more rapidly to LT with a marginal graft such as a DCD liver.

Data on the management of patients with severe hyponatremia entering into LT are limited and there are no succinct society or working group guidelines in this specific setting. An absolute sodium level cutoff below which proceeding with LT is contraindicated has not been established due to the complex physiology it represents. The sodium level is a dynamic variable that can be acutely or chronically altered, especially with diuretic therapy, medical intervention, and dialysis. The latter was adjusted for in our multivariable analysis. Consequently, serum sodium levels should be taken in the context of the entire clinical picture of any transplant candidate. Leise *et al.* [15] described results of a survey administered to 20 moderate to large-sized LT programs in the USA, which highlighted that only 45% (9 out of 20) had an absolute threshold of serum sodium for not proceeding with transplantation. This threshold ranged between $\leq$125 and $\leq$120 mEq/l. Moreover, an even smaller minority (30%) of programs had standard protocols for managing hyponatremia [15]. It should be recognized that preoperative optimization may not be feasible in all hyponatremic patients, given the urgent need for LT. Consequently, if the emphasis is placed on preoperative sodium correction, there is a risk that a patient may deteriorate and lose their opportunity for transplantation.

Several critical observations might help guide therapy of hyponatremia in patients undergoing imminent transplant. In the general patient population, the risk of osmotic demyelination syndrome (ODS) is greatest when serum sodium is corrected more than 12 mEq/l within 24 h [16]. For patients in general, a European expert group recommends that serum sodium correction not exceed 10 mEq/l in the first 24 h [17] and a US expert group limits the correction to 8 mEq/l per day [18]. In addition, Yun *et al.* [10] using a multicenter US database demonstrate a pretransplant sodium of <125 mEq/l is significantly associated with post-transplant CPM at an incidence of 4.6%. At our center, we build on these observations to inform our approach to pretransplant hyponatremia. At the time of donor offer, we use conventional measures, including the use of saline or hypertonic saline, to increase serum sodium to at least 120 mEq/l. In patients with a sodium between 120 and 125 mEq/l entering into surgery, we use an intraoperative continuous veno-venous hemofiltration (CVVH) protocol to facilitate a controlled and gradual increase in the serum concentration [16] and have not seen ODS or other adverse outcomes. In the unusual case that the sodium

cannot be increased to 120 mEq/prior to surgery, the transplant is typically cancelled.

The use of intra-operative CVVH protocols [19] to control sodium stabilization is particularly useful in LT, where potential requirements for intraoperative fluid and blood product administration can lead to rapid sodium fluctuations with the potential for (ODS) [10,20]. Gradual sodium correction can be achieved using hypotonic replacement fluid composed of successively higher sodium concentrations [21]. The trend in serum sodium correction is measured with frequent measurements (0, 1, and every 2 h) [19]. The slow and continuous sodium correction that CVVH can achieve has been demonstrated to be safe and feasible in patients with severe hyponatremia with and without underlying liver dysfunction [21,22]. Moreover, one small study demonstrated the use of CVVH to be associated with a nonstatistically improved post-LT survival in high MELD-score patients with acute kidney injury (1-year survival 86% with CVVH vs. 71% without CVVH), a scenario that has become increasingly common in the Share 35 era [23,24]. Additionally, the intra-operative use of CVVH has not been found to be associated with an increased operative time or blood product requirement [23].

This study is limited by its retrospective nature, with the potential for misclassification and selection bias. Although covariate adjustments were made for group comparisons, there is always a potential for residual and unmeasured confounding. The sodium levels were analyzed at only two time points, listing, and LT. Information on diuretic use and volume status is not captured in the dataset. However, within this context, it should be noted that chronic hyponatremia in cirrhotic patients is difficult to alter [25]. One of the potential risks of LT in patients with extreme hyponatremia are neurological complications, including ODS. We attempted to determine a possible association, but the mortality numbers available for patients with extreme hyponatremia are too limited. Moreover, intra-operative CVVH use is not captured in the database, and it thus remains unclear whether the use of such strategies may lead to improved outcomes. The OPTN/UNOS registry lacks other detailed clinical information. Lastly, operative variables, including treatment administered to correct serum sodium abnormalities and the degree to which sodium was adjusted, are unavailable in the database and may have impacted short-term post-LT outcomes.

This study demonstrates that waitlist outcomes have improved for patients with extreme hyponatremic in the post-MELD era. In contrast, these patients continue to have worse short-term post-LT survival in the post-MELD-Na era relative to higher serum sodium concentrations. This highlights the need to optimize patients in the perioperative period and the need to define algorithms to identify serum sodium levels beyond which proceeding with LT exceeds the risk of remaining on the waitlist.

Authorship

TI and SN: Conception of project, literature review, data analysis, interpretation of results and write up of the manuscript. SLM and HM: Conception of project, literature review, interpretation of results and write up of the manuscript. DM, TK, SY, TS, MR, KC and AY: Interpretation of results and write up of the manuscript. MA: Conception of project, interpretation of results and write up of the manuscript. All authors have given final approval for this manuscript to be submitted to Transplant International.

Funding

The authors have declared no funding.

Conflicts of interest

None of the authors have any conflicts of interest to disclose as described by *Transplant International*. UNOS and the centers participating in the OPTN are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis of the conclusions derived by the authors.

Acknowledgements

The data reported here have been supplied by the UNOS as the contractor for the OPTN. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the U.S. Government.

Data availability statement

The data that support the findings of this study are available from Organ Procurement and Transplantation Network (OPTN). Restrictions apply to the availability of these data, which were used under license for this study. Data are available OPTN at https://optn.transplant.hrsa.gov/data/request-data/ with the permission of OPTN and United Network of Organ Sharing (UNOS).

SUPPORTING INFORMATION

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

Figure S1. (a) Extreme hyponatremia 90-day waitlist dropout due to death or too sick. (b) Extreme hyponatremia 90-day waitlist probability of transplantation.

Figure S2. (a) Patients without extreme hyponatremia 90-day waitlist dropout due to death or too sick. (b) Patients without extreme hyponatremia 90-day waitlist probability of transplantation.

Figure S3. Effect on post-MELD-Na era on waitlist mortality and transplant probability (ref: pre-MELD-Na). Adjusted for age at listing, INR at listing, bilirubin at listing, creatinine at listing, BMI at registration, sex, diabetes, functional status, sodium concentration at listing, life support at listing, liverkidney listing, dialysis at registration, ascites at listing, encephalopathy at listing, diagnosis of HCC, diagnosis of ALD, diagnosis of NASH, and a diagnosis of HCV.

Figure S4. (a) Fine-Gray multivariable model for 90-day waitlist mortality (subdistribution Hazard ratio for 90-day waitlist mortality for extreme hyponatremic patients (ref: 135–145). Adjusted for age at listing, INR at listing, bilirubin at listing, creatinine at listing, BMI at registration, sex, diabetes, functional status, sodium concentration at listing, life support at listing, liver-kidney listing, dialysis at registration, ascites at listing, encephalopathy at listing, diagnosis of HCC, diagnosis of ALD, diagnosis of NASH, and a diagnosis of HCV. (b) Fine-Gray multivariable model for 90-day likelihood of transplant (subdistribution Hazard ratio for 90-day waitlist mortality for extreme hyponatremic patients (ref: 135–145) Adjusted for age at listing, INR at listing, bilirubin at listing, creatinine at listing, BMI at registration, sex, diabetes, functional status, sodium concentration at listing, life support at listing, liver-kidney listing, dialysis at registration, ascites at listing, encephalopathy at listing, diagnosis of HCC, diagnosis of ALD, diagnosis of NASH, and a diagnosis of HCV.

Figure S5. (a) 365-day post-LT survival stratified by serum sodium at LT (pre-MELD-Na era). (b) 365-day post-LT survival stratified by serum sodium at LT (post-MELD-Na era).

Figure S6. (a) 90-day post-LT survival in patients with extreme hyponatremia stratified by era. (b) 365-day post-LT survival in patients with extreme hyponatremia stratified by era.

Figure S7. (a) Mixed effects Cox proportional hazard model forest plot for post-LT 365-day mortality in pre-MELD-Na era by serum sodium concentration (ref: serum sodium concentration 135–145 mEq/l). Adjusted for recipient factors (sodium level at LT, age, encephalopathy, ascites, liver disease etiology [ALD, HCV, NASH, HCC], life support, diabetes, bilirubin, INR, creatinine, dialysis requirement, BMI, functional status, exception points, liver kidney listing), and donor factors (DCD, CIT, age, BMI), and era. (b) Cox proportional hazard model forest plot for post-LT 365-day mortality in post-MELD-Na era by serum sodium concentration (ref: serum sodium concentration 135–145 mEq/l). Adjusted for recipient factors (sodium level at LT, age, encephalopathy, ascites, liver disease etiology [ALD, HCV, NASH, HCC], life support, diabetes, bilirubin, INR, creatinine, dialysis requirement, BMI, functional status, exception points, liver kidney listing), and donor factors (DCD, CIT, age, BMI), and era.

Figure S8. (a) Mixed effects Cox proportional hazard model with a penalized spline fit of sodium concentration for post-LT 90-day survival in the pre-MELD-Na era (adjusted for bilirubin at transplant, INR at transplant, creatinine at transplant, recipient age, encephalopathy, ascites, recipient diabetes, dialysis before LT, etiology of liver disease, recipient BMI, functional status, life support, exception points, liver-kidney listing, DCD, CIT, donor age, and donor BMI). (b) Mixed effects Cox proportional hazard model with a penalized spline fit of sodium concentration for post-LT 90-day survival in the post-MELD-Na era (adjusted for bilirubin at transplant, INR at transplant, creatinine at transplant, recipient age, encephalopathy, ascites, recipient diabetes, dialysis before LT, etiology of liver disease, recipient BMI, functional status, life support, exception points, liver-kidney listing, DCD, CIT, donor age, and donor BMI).

Table S1. Dialysis status by sodium group (pre-MELD-Na and post-MELD-Na).

Table S2. Patient characteristics by sodium group (pre-MELD-Na).

Table S3. Patient characteristics by sodium group (post-MELD-Na).

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