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CLINICAL INVESTIGATION

Hyperosmolar Dehydration in Sepsis: Implications for Initial Fluid Management

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OBJECTIVE: Patients with sepsis are prone to hypovolemia which can lead to hyperosmolar dehydration and result in intracellular volume depletion. This study aimed to assess the effect of hyperosmolar dehydration on the clinical outcomes of patients with sepsis and its potential as an indicator of optimal initial fluid management.

DESIGN: A nationwide propensity score-matched cohort study analyzing data prospectively collected between September 2019 and December 2021.

SETTING: Twenty tertiary- or university-affiliated hospitals in South Korea.

PATIENTS: Adult patients with sepsis or septic shock admitted to the ICU.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Hyperosmolar dehydration was defined as serum osmolarity greater than or equal to 295 mOsm/L. The primary outcome, 30-day mortality, was compared using logistic regression adjusted for key prognostic factors in a 1:1 propensity score-matched cohort. Restricted cubic-spline models were used to analyze the clinical outcomes using the pre-ICU fluid volume as a continuous variable. Of the 4,487 patients, 2,605 (58.1%) had hyperosmolar dehydration. After matching, 1,537 pairs were analyzed. The 30-day mortality was higher in the hyperosmolar dehydration group (29.9%) than in the non-dehydration group (27.3%) (adjusted odds ratio, 1.18; 95% CI, 1.00–1.39). Liberal fluid management (greater than30 mL/kg) before ICU admission was associated with improved lactate levels in the hyperosmolar dehydration group ($p = 0.009$) without increasing sequential organ failure assessment score ($p = 0.111$). Among patients without dehydration, liberal fluid management was associated with an increased Sequential Organ Failure Assessment score ($p = 0.034$) and a higher risk for mechanical ventilation ($p < 0.001$), and without improving lactate levels ($p = 0.388$).

CONCLUSIONS: Hyperosmolar dehydration at the diagnosis of sepsis was associated with increased 30-day mortality. A liberal fluid management benefits patients with hyperosmolar dehydration by improving lactate levels without increasing sequential organ failure assessment score. These findings highlight the importance of individualized fluid management based on the dehydration status in sepsis management.

KEYWORDS: dehydration; fluid therapy; propensity score; Sepsis; treatment outcome

Dehydration, characterized by an excessive loss of body water, is a common but frequently unrecognized and undertreated condition among older and hospitalized patients (1, 2). Notably, 37% of patients 65 years old or older are found to be dehydrated (1), and up to 60% of patients admitted to hospitals develop new-onset hypernatremia (2), underscoring

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KEY POINTS

Question: Does hyperosmolar dehydration affect the mortality of patients with sepsis, and can liberal fluid management improve clinical outcomes based on dehydration status?

Findings: In this nationwide propensity score-matched cohort study, hyperosmolar dehydration at sepsis onset was associated with increased 30-day mortality. Liberal fluid management improved lactate levels without worsening SOFA scores or increasing the risk of mechanical ventilation in patients with hyperosmolar dehydration, whereas worsening SOFA scores and increasing mechanical ventilation risk in non-dehydrated patients.

Meaning: Dehydration status at sepsis onset can serve as an additional guide for optimizing personalized fluid management, potentially improving patient outcomes.

the prevalence of dehydration in clinical settings. However, its diagnosis is challenging because various diagnostic methods may be inaccurate, potentially resulting in misdiagnosis. Nevertheless, plasma osmolality has been recognized for its reliable sensitivity and specificity in identifying dehydration, establishing it as a valuable marker for dehydration assessment (3). In addition, the calculated plasma osmolarity serves as a practical surrogate for plasma osmolality, further facilitating dehydration diagnosis (4, 5).

Previous studies have established an association between hyperosmolar dehydration and AKI (6), heart failure (7), and CNS complications, including neurologic deficits, altered mental status, and cerebrovascular injuries (8, 9). These associations underscore the negative effect of hyperosmolar dehydration on clinical outcomes (10–13). Furthermore, studies on critically ill patients have drawn attention to the severe consequences of hyperosmolar dehydration, including increased 28-day mortality rates among patients with septic shock (14) and higher in-hospital mortality rates among patients with nonpulmonary diseases in ICUs (15). Hyperosmolar dehydration frequently occurs with sepsis (14), a condition that can be exacerbated by factors such as a hypermetabolic state, excessive sweating, insufficient oral fluid intake, hyperventilation, diarrhea, and renal excretion (16). These factors contribute to pure hypovolemia, which is characterized by an absolute reduction in total circulating blood volume, in contrast to relative hypovolemia, which results from inadequate distribution of blood volume between the central and peripheral compartments (e.g., venodilatation) (17). In hyperosmolar dehydration, the loss of extracellular fluid exacerbates osmotic imbalances, leading to intracellular volume depletion, which causes cell shrinkage and subsequent cellular dysfunction (18). The relationship between hyperosmolar dehydration and decreased cellular activity in sepsis highlights the need for refined fluid management strategies.

A recent study showed that major components of plasma osmolality, such as serum glucose and blood urea nitrogen levels, may influence the effectiveness of early goal-directed therapy, which involves more aggressive fluid administration within the first six hours of sepsis diagnosis (19). However, the prognostic significance of hyperosmolar dehydration in patients with sepsis remains unclear. Furthermore, the potential of hyperosmolar dehydration as an indicator of optimal initial fluid management in patients with sepsis remains largely uncharacterized. This study aimed to investigate the effect of hyperosmolar dehydration on the clinical outcomes of patients with sepsis and its potential as an indicator of optimal initial fluid management.

MATERIALS AND METHODS

Study Design and Patient Population

This nationwide, multicenter, prospective cohort study analyzed patients with sepsis or septic shock in the Korean Sepsis Alliance registry between September 1, 2019, and December 31, 2021. Twenty tertiary- or university-affiliated hospitals in South Korea conducting educational programs on sepsis management participated in this study. A detailed description of the Korean Sepsis Alliance registry is provided in **eMethod 1** (https://links.lww.com/CCM/H808). Adult patients aged 19 years old or older who were diagnosed with sepsis or septic shock according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (20) prior to ICU admission and subsequently admitted to the ICU were included in the study. Clinical

outcomes were followed until hospital discharge or death. We excluded patients whose serum osmolarity could not be calculated due to missing values. All data were anonymized to ensure individual privacy. This study was approved by the institutional review board (IRB) of each participating site (see **eTable 1**, https://links.lww.com/CCM/H808, for more information) and conducted in accordance with the ethical standards of the institutional committees and the Helsinki Declaration of 1975. Since this was an observational study, the decision to obtain or waive written informed consent was at the discretion of the participating hospitals' IRBs. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed to ensure proper reporting in this cohort study (21).

Definitions and Outcome Measures

Based on previous studies (5, 22), serum osmolarity was calculated using the Khajuria and Krahn equation (4), with laboratory values obtained at the time of sepsis diagnosis and, in most cases, prior to the initiation of fluid administration. As glucose is already incorporated in the equation, measured (uncorrected) sodium values were used to avoid redundant adjustment. Hyperosmolar dehydration was defined as serum osmolarity greater than or equal to 295 mOsm/L (23). Patients were divided into the hyperosmolar dehydration (serum osmolarity ≥ 295 mOsm/L) and non-dehydration (serum osmolarity less than295 mOsm/L) groups. The primary outcome was 30-day mortality. Secondary outcomes included the requirement of continuous kidney replacement therapy (CKRT) and mechanical ventilation within 3 days of ICU admission, improvement in SOFA score (≤ 0 of SOFA score at 3 d of ICU admission minus SOFA score at sepsis diagnosis), and improvement in lactate level (≤ 0 mmol/L of lactate level at ICU admission minus lactate level at sepsis diagnosis). Additional secondary outcomes are described in **eMethod 2** (https://links.lww.com/CCM/H808). Pre-ICU fluid balance was defined as the net difference between total fluid input—including IV crystalloids, colloids, and blood products—and total fluid output, which comprised urine output, drain losses, and other measurable outputs, from the time of sepsis diagnosis until ICU admission. This value represents the patient's net fluid status during the pre-ICU period. The discharge location was categorized as discharged to home or transferred to another hospital, including a nursing home.

Statistical Analysis

Categorical variables were expressed as counts and percentages, and continuous variables as means with SDs or medians with interquartile ranges (IQRs). Between-group differences were assessed using the Student *t* test or Mann-Whitney *U* test for numerical variables and the chi-square or Fisher exact test for categorical variables. To reduce confounding and approximate causal inference, we used propensity score matching to estimate the probability of hyperosmolar dehydration based on baseline covariates (24, 25). Patients with and without hyperosmolar dehydration were then matched 1:1 using nearest-neighbor matching without replacement. The detailed propensity score methodology is provided in **eMethod 3** (https://links.lww.com/CCM/H808). Mixed-effect logistic regression was used to evaluate outcomes across the unmatched, propensity-matched, and sensitivity cohorts. Models were adjusted for key demographic and clinical factors associated with mortality, and hospital was treated as a random effect (**eMethod 4**, https://links.lww.com/CCM/H808). Kaplan-Meier estimates and mixed-effects Cox proportional hazards models were used to assess differences in cumulative mortality without covariate adjustment. Restricted cubic-spline models, adjusted for key covariates, assessed nonlinear associations between pre-ICU fluid volume and clinical outcomes (**eMethod 5**, https://links.lww.com/CCM/H808). In the restricted cubic-spline model, a pre-ICU fluid volume of 30 mL/kg was used as the clinical reference point, while fluid volume was modeled as a continuous variable. Liberal fluid management was defined as the administration of a total IV fluid volume greater than 30 mL/kg, and restrictive management as less than or equal to 30 mL/kg, measured from sepsis diagnosis to ICU admission. This threshold was based on previous literature (26) distinguishing liberal and restrictive managements. Sensitivity analyses included restriction to patients with serum creatinine less than or equal to 2 mg/dL to reduce potential confounding from renal dysfunction, and a separate propensity score matching using serum sodium (≥ 140 vs. <140 mmol/L) as the exposure variable, reflecting its role as a physiologic and clinical marker of dehydration (27). The results were presented as odds ratios (ORs) with

corresponding 95% CIs. All analyses were two-tailed, and *p* value of less than 0.05 was considered statistically significant. Statistical analyses were performed using the R Statistical Software (Version 4.1.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Participants

Among the 4765 patients with sepsis admitted to the ICU between September 1, 2019, and December 31,

TABLE 1.
Baseline Demographic and Clinical Characteristics of Patients With and Without Dehydration, Before and After Propensity Score Matching

Variable	Before Matching			After Matching		
	Non-dehydration (*n* = 1882)	Dehydration (*n* = 2605)	SMD (%)	Non-dehydration (*n* = 1537)	Dehydration (*n* = 1537)	SMD (%)
Estimated osmolarity, mOsm/L	287 (281–291)	307 (300–318)	183	287 (281–291)	305 (299–315)	182
Age, yr	70 (60–79)	75 (65–82)	33.5	73 (63–80)	72 (62–80)	1.6
Sex, male	1091 (58.0)	1540 (59.1)	1.2	889 (57.8)	880 (57.3)	0.6
Body mass index, kg/m^2	21.9 (19.2–24.8)	22.0 (19.4–24.9)	1.3	21.9 (19.0–24.8)	22.0 (19.4–25.0)	5.1
Comorbidities						
Cardiovascular disease	352 (18.7)	738 (28.3)	9.6	331 (21.5)	340 (22.1)	0.6
Diabetes	539 (28.6)	1163 (44.6)	16.0	517 (33.6)	529 (34.4)	0.8
Chronic lung disease	223 (11.8)	239 (9.2)	1.3	210 (13.7)	213 (13.9)	0.2
Chronic kidney disease	157 (8.3)	543 (20.8)	12.5	155 (10.1)	171 (11.1)	1.0
Chronic liver disease	223 (11.8)	239 (9.2)	2.7	155 (10.1)	177 (11.5)	1.4
Malignancy	760 (40.4)	781 (30.0)	10.4	568 (37.0)	558(36.3)	0.7
Chronic neurologic disease	403 (21.4)	693 (26.6)	5.2	364 (23.7)	350 (22.8)	0.9
Charlson comorbidity index[a]	5 (3–6)	5 (4–7)	24.1	5 (4–7)	5 (4–7)	0.1
Clinical frailty scale[b]	5 (3–7)	6 (4–7)	21.0	5 (3–7)	5 (3–7)	1.2
Sequential Organ Failure Assessment score[c]	6 (4–8)	7 (5–10)	38.5	6 (5–9)	6 (5–9)	1.4
Time zero to ICU admission, min	437 (275–817)	444 (265–837)	1.9	437 (275–817)	444 (265–837)	5.2
Type of fluid administered[d]						
0.9% normal saline	462/726 (63.6)	617/979 (63.0)	0.4	391/604 (64.7)	360/570 (63.2)	1.2
Balanced crystalloid[e]	264/726 (36.4)	362/979 (37.0)	0.5	213/604 (35.3)	210/570 (36.8)	1.3

(*Continued*)

TABLE 1. (*Continued*)

Baseline Demographic and Clinical Characteristics of Patients With and Without Dehydration, Before and After Propensity Score Matching

Variable	Before Matching			After Matching		
	Non-dehydration (*n* = 1882)	Dehydration (*n* = 2605)	SMD (%)	Non-dehydration (*n* = 1537)	Dehydration (*n* = 1537)	SMD (%)
Pre-ICU fluid balance, mL[f]	1170 (434–2100)	1200 (450–2157)	6.4	1114 (421–2071)	1236 (460–2241)	10.9
Liberal fluid management	882/1625 (54.3)	1149/2256 (50.9)	3.4	719/1337 (53.8)	714/1337 (53.4)	0.4
Pre-ICU fluid volume, mL/kg	32.6 (18.3–51.1)	31.0 (17.1–48.8)	1.1	31.9 (18.5–49.7)	32.3 (17.7–49.4)	2.5
Pre-ICU fluid volume, mL	1896 (1040–2800)	1759 (1000–2700)	1.7	1850 (1030–2750)	1818 (1019–2760)	3.7
Pre-ICU output, mL/kg	7.9 (2.6–17.8)	6.4 (1.9–14.5)	8.5	7.9 (2.6–18.0)	6.7 (2.0–15.1)	8.0
Pre-ICU output, mL	450 (150–1000)	360 (100–844)	8.2	460 (150–1025)	390 (110–850)	7.0
Vasopressor within ICU day 1	1497 (79.5)	1989 (76.4)	3.2	1232 (80.2)	1164 (75.7)	4.4
Norepinephrine	1488 (79.1)	1967 (75.5)	0.7	1225 (79.7)	1150 (74.8)	4.3
Vasopressin	481 (25.6)	653 (25.1)	6.7	380 (24.7)	405 (26.4)	6.1
Dopamine	44 (2.3)	138 (5.3)	15.0	35 (2.3)	68 (4.4)	9.5
Epinephrine	190 (10.1)	252 (9.7)	5.8	147 (9.6)	156 (10.1)	4.7

SMD = standardized mean difference.

[a]The charlson comorbidity index ranges from 0 to 37, with higher score indicating greater comorbidity and increased mortality risk.

[b]The clinical frailty scale ranges from 1 to 9, with higher scores indicating increased frailty.

[c]Sequential organ failure assessment score ranges from 0 to 24, with higher scores indicating more severe organ dysfunction.

[d]Data shown for patients with available records; the fluid listed is the most commonly administered.

[e]This category includes Hartmann's solution, Ringer's lactate, Plasma-Lyte, and Plasma Solution.

[f]Only in patients who had complete pre-ICU fluid volume data. Liberal fluid management was defined as the administration of a total IV fluid volume exceeding 30 mL/kg between the time of sepsis diagnosis and ICU admission.

Data are reported as *n* (%), *n*/total (%), or median (first–third quartiles).

2021, we excluded 278 patients whose serum osmolarity could not be calculated due to missing values. Consequently, this study included 4487 patients. The patients were divided into two groups based on the calculated serum osmolarity: 1882 (41.9%) in the non-dehydration group and 2605 (58.1%) in the hyperosmolar dehydration group. The two groups showed difference in several baseline demographic and clinical characteristics (**Table 1**; and **eTable 2**, https://links.lww.com/CCM/H808). After propensity score estimation and matching in a 1:1 ratio, 1537 matched patient pairs were generated (**eFig. 1**, https://links.lww.com/CCM/H808). Standardized mean differences were less than 0.1 for all matched variables, and the propensity score distributions shared common support for the covariates in the model, indicating a balance between the two groups.

The baseline demographic and clinical characteristics of the study population before and after propensity score matching are presented in Table 1 and eTable 2 (https://links.lww.com/CCM/H808). In the matched cohort, the median calculated serum osmolarity was 287 mOsm/L (281–291) in the non-dehydration group and 305 mOsm/L (299–315) in the hyperosmolar

TABLE 2.
Primary and Secondary Outcomes of Patients With and Without Dehydration in the Propensity-Matched Cohort

Outcome	Non-dehydration (*n* = 1537)	Dehydration (*n* = 1537)	*p*	Adjusted OR (95% CI)
Primary outcome				
30-d mortality	419 (27.3)	459 (29.9)	0.046	1.180 (1.003 to 1.388)
Secondary outcomes				
In-hospital mortality	494 (32.1)	528 (34.4)	0.115	1.133 (0.970 to 1.323)
ICU mortality	337 (21.9)	389 (25.3)	0.011	1.253 (1.053 to 1.491)
Requirement for continuous kidney replacement therapy[a]	282 (18.3)	435 (28.3)	< 0.001	1.804 (1.507 to 2.160)
Requirement for mechanical ventilation[a]	688 (44.8)	828 (53.9)	< 0.001	1.432 (1.225 to 1.673)
Delta SOFA[b]	1 (−1 to 4)	1 (−1 to 5)	< 0.001	
Delta SOFA ≤ 0	533/1197 (44.5)	519/1265 (41.0)	0.084	0.863 (0.730 to 1.020)
Delta lactate, mmol/L[c]	0 (−1.0 to 0.5)	0 (−1.1 to 0.7)	0.533	
Delta lactate ≤ 0 mmol/L	662/1462 (45.3)	670/1469 (45.6)	0.790	1.020 (0.880 to 1.184)
Length of ICU stay, d				
ICU survivors	4.0 (2.1 to 8.7)	5.0 (2.8 to 10.5)	0.003	
ICU nonsurvivors	3.1 (1.0 to 11.7)	2.9 (1.1 to 10.6)	0.668	
Length of hospital stay, d				
In-hospital survivors	17.8 (11.4 to 30.8)	18.9 (12.2 to 32.2)	0.168	
In-hospital nonsurvivors	8.0 (2.0 to 20.8)	6.6 (2.1 to 18.9)	0.588	
Discharge[d]			0.037	0.815 (0.672 to 0.988)
To home	645/1043 (61.8)	591/1009 (58.6)		
To other hospital[e]	409/1043 (38.2)	418/1009 (41.4)		

OR = odds ratio, SOFA = Sequential Organ Failure Assessment.
[a]Within 3 days of ICU admission.
[b]Only in patients who had complete pre-ICU and ICU day 3 SOFA score information. Delta SOFA was defined as the SOFA score at day 3 of ICU admission minus SOFA score at sepsis diagnosis. Delta SOFA ≤ 0 was interpreted as an improvement in SOFA score.
[c]Only in patients who had complete pre-ICU and ICU day 1 lactate level information. Delta lactate was defined as the lactate level at ICU admission minus lactate level at sepsis diagnosis. Delta lactate ≤ 0 mmol/L was interpreted as an improvement in lactate level.
[d]Only in patients who survived to hospital discharge.
[e]Including nursing home.
Data are reported as *n* (%), *n*/total (%), or median (first–third quartiles).

dehydration group. The median age of the participants was 72 years (62–80) and 57.5% were men, with a median body mass index of 22.0 kg/m^2 (19.3–24.9). Their median SOFA score was 6 (5–9). The most common comorbidity was malignancy (36.6%), and the most common primary site of infection was the lungs (43.2%). Furthermore, 64.4% of the patients were treated with combination antibiotics, and 86.9% received appropriate initial empirical antibiotic therapy (**eTable 3**, https://links.lww.com/CCM/H808).

Primary and Secondary Outcomes Among Propensity-Matched Patients

We analyzed primary and secondary outcomes in the propensity-matched cohort using mixed-effect logistic regression. The 30-day mortality was significantly higher in the hyperosmolar dehydration group than in the non-dehydration group: 29.9% (459 of 1537 patients) vs. 27.3% (419 of 1,537 patients) (adjusted OR [aOR], 1.18; 95% CI, 1.00–1.39) (**Table 2**). The

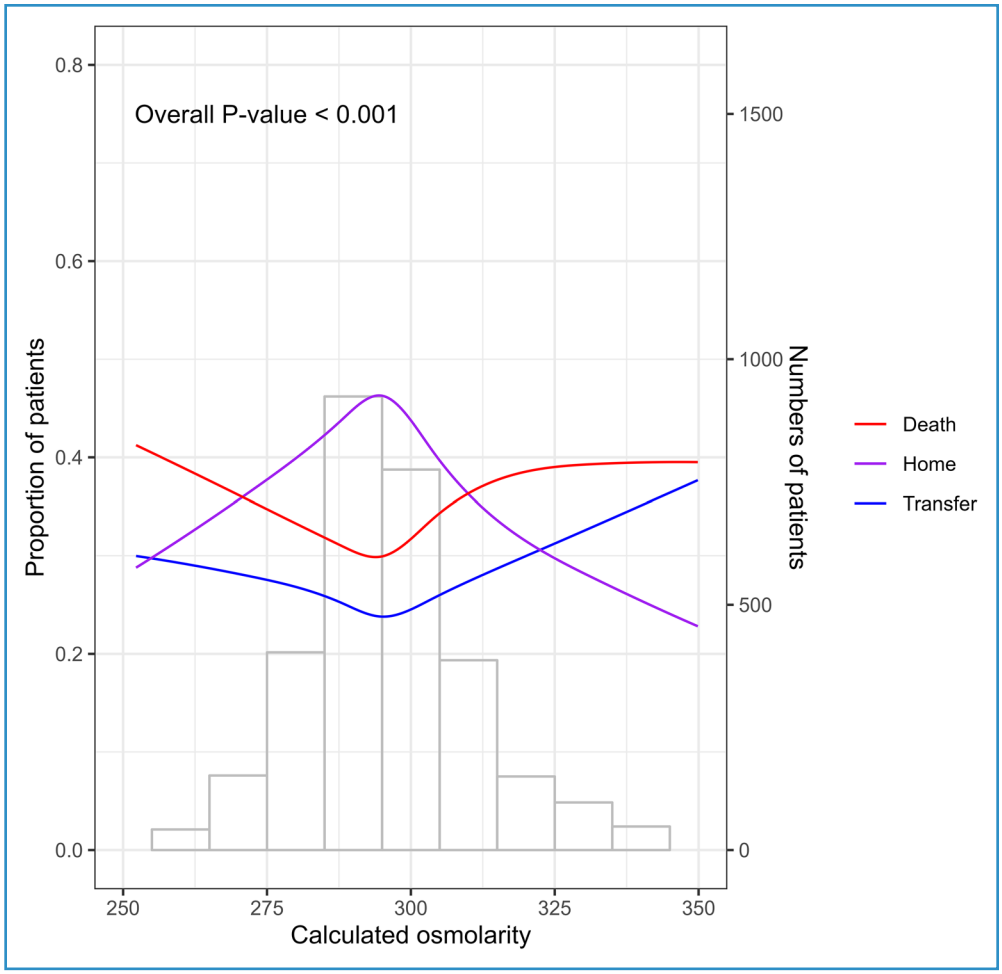

Figure 1. Association between calculated osmolarity and in-hospital mortality, transfer to other hospitals, and discharge to home after propensity score matching. The left *y*-axis represents the proportion of patients with each outcome (in-hospital mortality, transfer to another hospital, or discharge). The right *y*-axis represents the number of patients in each osmolarity category.

Kaplan-Meier estimates of 30-day mortality are shown in **eFigure 2** (https://links.lww.com/CCM/H808). The curves diverged significantly during the study period, showing a significant difference in mortality between the two groups (p = 0.026). The hyperosmolar dehydration group had a significantly higher requirement for CKRT (aOR, 1.80; 95% CI, 1.51–2.16) and mechanical ventilation (aOR, 1.43; 95% CI, 1.23–1.67) within 3 days of ICU admission than the non-dehydration group. Among the patients who survived to ICU discharge, the ICU length of stay was significantly longer in the hyperosmolar dehydration group (5.0; [2.8–10.5] d) than that in the non-dehydration group (4.0; [2.1–8.7] d) (p = 0.003). **Figure 1** shows that the rate of discharge to home was highest when the calculated osmolarity was 290–300 mOsm/L. Concurrently, the rates of transfer to other facilities and in-hospital mortality were lowest at 290–300 mOsm/L. Mixed-effects logistic regression analyses of our primary and secondary outcomes in both the unmatched and creatinine-restricted sensitivity cohort demonstrated consistent findings, similar to those observed in the propensity-matched cohort. However, in a separate sodium-based sensitivity analysis, no significant association was observed for 30-day mortality (aOR, 0.93; 95% CI, 0.78–1.12) (**eTables 4–8**, https://links.lww.com/CCM/H808).

Effects of Pre-ICU Fluid Volume Among Propensity-Matched Patients

Among the propensity-matched cohorts, data on pre-ICU fluid balance and fluid volume were available for 2674 patients. The pre-ICU fluid volume was not significantly different between the non-dehydration and dehydration groups (1850 mL; IQR, 1030–2750 mL vs. 1,818 mL; IQR, 1019–2,760 mL; p = 0.144) (Table 1). Restricted cubic-spline curves showed that a pre-ICU fluid volume of greater than 30 mL/kg (liberal fluid management) was associated with improved lactate levels from sepsis diagnosis to ICU admission in patients with hyperosmolar dehydration (p for overall = 0.009; p for nonlinearity = 0.011), whereas no association was observed in those without dehydration (p for overall = 0.388; p for nonlinearity = 0.221) (**Fig. 2**). Among the 2674 patients, SOFA scores at 3 days of ICU admission were available for 2147 patients. Liberal fluid management was not associated with changes in SOFA scores in hyperosmolar dehydration (p for overall = 0.111; p for nonlinearity = 0.264). However, in patients without dehydration, liberal fluid management significantly

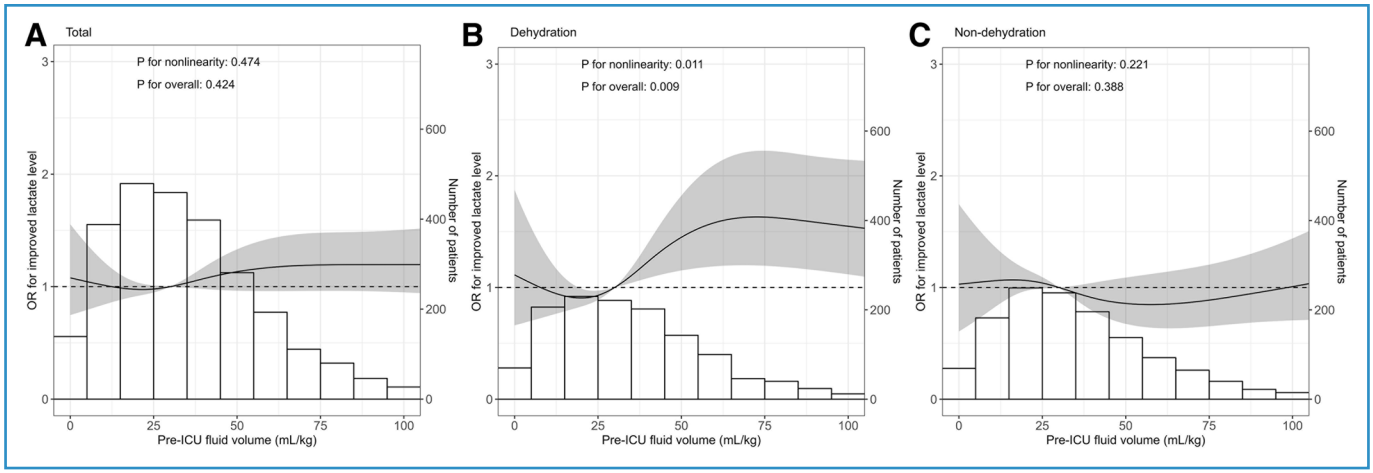

Figure 2. Association between pre-ICU fluid volume and the improvement of lactate levels at ICU admission. **A**, **B**, and **C,** Restricted cubic-spline plots of the association between pre-ICU fluid volume and improved lactate levels upon ICU admission for the entire matched cohort, patients with dehydration, and patients without dehydration, respectively. *Shaded areas* represent 95% CIs. A 30-mL/kg pre-ICU fluid volume was used as the clinical reference point, as indicated by the *dashed line*. Improvement of lactate levels at ICU admission is defined as a lactate level at ICU admission that is less than or equal to the lactate level at sepsis diagnosis (≤ 0 mmol/L difference). OR = odds ratio.

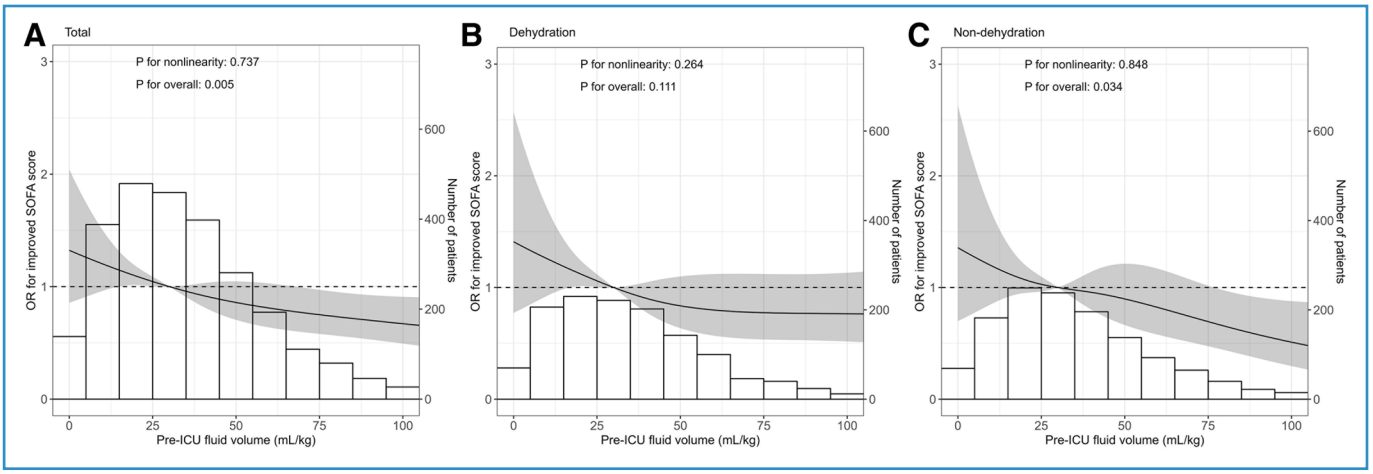

Figure 3. Association between pre-ICU fluid volume and the improvement of SOFA scores at 3 days of ICU admission. **A**, **B**, and **C**, Restricted cubic-spline plots of the association between pre-ICU fluid volume and improved SOFA scores upon 3 days of ICU admission for the entire matched cohort, patients with dehydration, and patients without dehydration, respectively. *Shaded areas* represent 95% CIs. A 30 mL/kg pre-ICU fluid volume was used as the clinical reference point, as indicated by the *dashed line*. Improvement of SOFA scores at 3 days of ICU admission is defined as a SOFA score at 3 days of ICU admission that is less than or equal to the SOFA score at sepsis diagnosis (≤ 0 difference). OR = odds ratio, SOFA = Sequential Organ Failure Assessment.

worsened SOFA scores (p for overall = 0.034; p for nonlinearity = 0.848) (**Fig. 3**). In addition, pre-ICU fluid volume was associated with an increased risk of mechanical ventilation within 3 days of ICU admission in patients without dehydration (p for overall < 0.001; p for nonlinearity < 0.001), whereas no association was observed in those with hyperosmolar dehydration (p for overall = 0.458; p for nonlinearity = 0.328) (**Fig. 4**). However, there was no significant association between the pre-ICU fluid volume and CKRT risk within 3 days of ICU admission in either group (**eFig. 3**, https://links.lww.com/CCM/H808). Furthermore, there was no significant association between pre-ICU fluid volume and 30-day mortality in either group (**eFig. 4**, https://links.lww.com/CCM/H808). These findings remained consistent in both the creatinine-restricted sensitivity analysis and the separate sodium-based sensitivity analysis using propensity score matching by hypernatremia status (**eFigs. 5–14**, https://links.lww.com/CCM/H808).

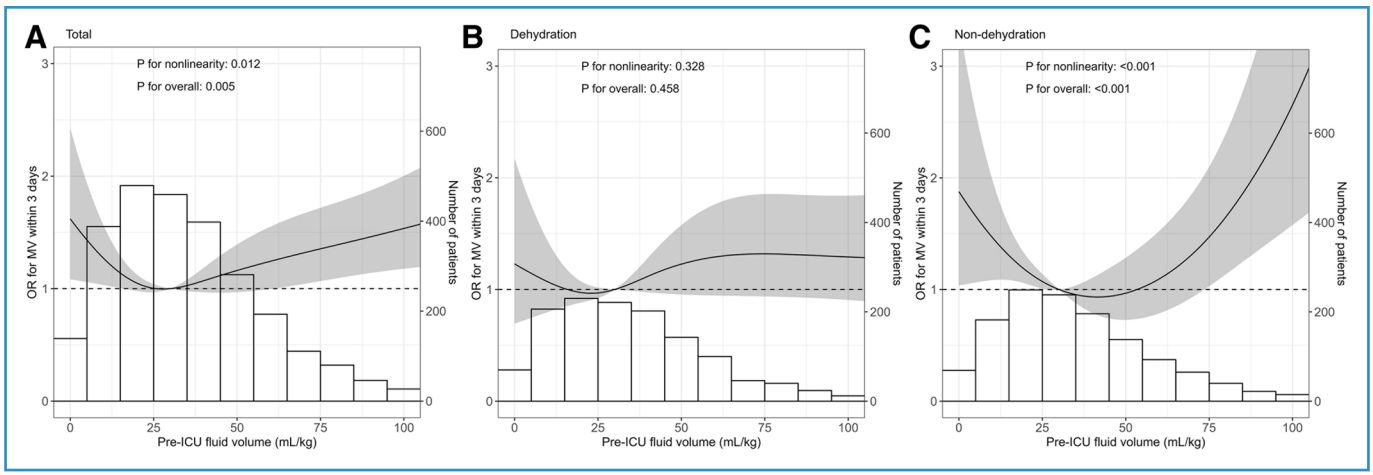

Figure 4. Association between pre-ICU fluid volume and the requirement for mechanical ventilation (MV) within 3 days of ICU admission. **A**, **B**, and **C**, Restricted cubic-spline plots of the association between the pre-ICU fluid volume and the requirement for mechanical ventilation within 3 days of ICU admission for the entire matched cohort, patients with dehydration, and patients without dehydration, respectively. *Shaded areas* represent 95% CIs. A 30-mL/kg pre-ICU fluid volume was used as the clinical reference point, as indicated by the *dashed line*. OR = odds ratio.

DISCUSSION

This nationwide multicenter prospective cohort study of patients with sepsis showed that hyperosmolar dehydration at sepsis diagnosis was significantly associated with an increased risk of 30-day mortality. Among patients with hyperosmolar dehydration, liberal fluid management, defined as greater than30 mL/kg of IV fluid before ICU admission, was associated with improved lactate levels and did not increase SOFA scores, the risk of mechanical ventilation, CKRT, or 30-day mortality. Conversely, in patients without dehydration, liberal fluid management was associated with an increased SOFA score and a higher risk for mechanical ventilation, and without improving lactate levels. Accordingly, patients with hyperosmolar dehydration may benefit from a liberal fluid management, whereas those without dehydration may require more cautious fluid administration. To our knowledge, this is the first study to evaluate the effect of hyperosmolar dehydration on clinical outcomes and its potential as an additional indicator of optimal initial fluid management in patients with sepsis.

Previous studies have demonstrated that hyperosmolar dehydration can precipitate AKI (6). Hypernatremia, a significant component of the hyperosmolar state, exacerbates AKI risk (28). The activation of the polyol-fructokinase and vasopressin pathways by hyperosmolality can lead to kidney injury (29). Furthermore, hyperosmolar dehydration has been associated with an increased risk of hyperventilation (30). In patients with COVID-19 2019, it has been linked to a greater need for mechanical ventilation (31, 32). Furthermore, neurologic impairment caused by hypernatremia may prolong the duration of mechanical ventilation in critically ill patients (33). Similarly, patients with hyperosmolar dehydration in the present study had an increased risk requiring mechanical ventilation and CKRT within 3 days of ICU admission. Impaired pulmonary and kidney functions may increase mortality in patients with hyperosmolar dehydration. However, since the present and previous studies were observational and non-randomized, whether these associations reflect causal relationships or they are due to the increased severity of illness necessitating these interventions remain unclear.

Our findings showed no association between the initial fluid volume and mechanical ventilation risk in patients with dehydration, whereas patients without dehydration had an increased risk of mechanical ventilation with higher initial fluid administration. Previous studies have suggested that a hyperosmolar status can mitigate pulmonary edema, thereby preventing the need for mechanical ventilation, even with a liberal fluid strategy (34, 35). Furthermore, liberal fluid management was associated with improved lactate levels only in patients with dehydration. In contrast, in patients without dehydration, liberal fluid management was associated with increased SOFA scores. This finding is consistent with

a previous observational study that showed fluid overadministration was associated with worsened SOFA scores (36). Our findings support the adoption of a liberal fluid management in patients with hyperosmolar dehydration. However, when implementing liberal fluid management, it is crucial to consider the potentially harmful consequences of fluid accumulation on end-organ function (37). Future research is necessary to elucidate the mechanisms underlying these effects and to optimize fluid management protocols according to the hyperosmolar dehydration status.

Our results unequivocally indicate that hyperosmolar dehydration at the time of sepsis diagnosis is associated with worse clinical outcomes, providing valuable insights into the potential clinical trajectory of patients with sepsis who experience hyperosmolar dehydration. Furthermore, this study suggested hyperosmolar dehydration as an additional indicator of optimal initial fluid management in patients with sepsis. Fluid responsiveness tests such as the passive leg raising test (38) and mini-fluid challenge (39) are recommended for non-intubated patients with early septic shock or hypotension. However, these tests may not be suitable for some patients with sepsis, and advanced hemodynamic monitoring may not be feasible in all clinical settings or hospitals. Furthermore, these tests assess cardiac output in response to preload, focusing primarily on intravascular volume status without considering extravascular volume status. Therefore, incorporating hyperosmolar dehydration, which can be easily calculated from daily clinical practice, as a complementary parameter for preload responsiveness could enable a more individualized approach to initial fluid management.

Calculated osmolarity is commonly used as a surrogate for serum osmolality in assessing dehydration; however, its reliability in patients with sepsis may be limited due to potential confounding factors such as elevated blood urea nitrogen (BUN); urea, as a permeable solute, does not contribute to effective tonicity. In sepsis, BUN may rise in the absence of true volume depletion—for example, in the setting of increased catabolism or acute kidney injury (AKI) not associated with circulatory impairment. Nonetheless, dehydration is frequently encountered in early sepsis, and BUN elevation and dehydration are not mutually exclusive; rather, they often coexist. This is further supported by the fact that early sepsis-associated AKI is commonly driven by hemodynamic disturbances, such as hypovolemia and reduced perfusion. Given this potential overlap, to minimize the confounding effect of elevated BUN in patients with AKI, we conducted a sensitivity analysis restricted to patients with serum creatinine less than or equal to 2 mg/dL. The results remained consistent with our main findings: 30-day mortality was higher in patients with hyperosmolar dehydration, and liberal fluid administration in this group was significantly associated with improved lactate clearance. These findings support the clinical utility of calculated osmolarity in identifying dehydration in patients with early sepsis. This is in line with the European Society for Clinical Nutrition and Metabolism guideline, which recommend using serum osmolality or calculated osmolarity to guide fluid administration in geriatric patients with hyperosmolar dehydration (40).

Our study had some limitations. First, this study is observational study in nature. Although we adjusted for numerous potential confounders using rigorous propensity score matching and regression analyses, the risk of unmeasured confounders may have been present in the non-randomized study. In addition, the fluid management strategy was not protocolized, raising concerns that some patients may not have received appropriate fluid management. However, in the present study, patients' fluid resuscitation compliance for both the 1-hour (84.0%) and 3-hour bundles (90.8%) was similar to, or even higher than, that reported in previous research (41, 42). Although this observational study provides valuable real-world data across diverse clinical scenarios and treatment strategies, a randomized controlled trial is necessary to clarify the direct causal effects of liberal fluid management in patients with hyperosmolar dehydration. Second, plasma osmolarity trajectory could not be calculated due to insufficient data. Further investigation into the trajectory of plasma osmolarity in sepsis patients is warranted. Third, calculated osmolarity may overestimate dehydration when BUN is elevated due to non-volume-related factors such as catabolism or impaired renal clearance. To address this, we performed sensitivity analyses limited to patients with creatinine less than or equal to 2 mg/dL and those stratified by serum sodium. These findings suggest that calculated osmolarity may capture aspects of osmotic and metabolic stress that are not solely reflected by serum sodium. Fourth, our analysis of pre-ICU fluid volume and balance did not differentiate fluid types, and potential differences in osmolality were not explicitly considered. Although recent studies have shown that fluid type can influence renal function and mortality in critically ill patients (43, 44), they did

not directly evaluate serum osmolality. Future studies should consider fluid type as a standalone covariate to better assess its clinical impact.

CONCLUSIONS

In this cohort study of patients with sepsis, hyperosmolar dehydration at the time of sepsis diagnosis was associated with an increased risk of 30-day mortality. Although liberal fluid management was associated with improved lactate levels without worsening SOFA scores and increasing the risk of mechanical ventilation in patients with hyperosmolar dehydration, it was associated with worsening SOFA scores and an increased risk of mechanical ventilation without improving lactate levels in patients without dehydration. Our findings underscore the potential for using dehydration status as an additional tool in guiding personalized fluid management for patients with sepsis and highlight the need for future research on optimal fluid management strategies tailored to individual dehydration status.

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