BMC Infectious Diseases

RESEARCH

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Analysis of the correlation between the group-based trajectory modeling of serum osmolality and prognosis in patients with sepsis-associated encephalopathy at 72 h after admission

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Abstract

Background This study aimed to identify distinct trajectories of serum osmolality within the first 72 h for patients with sepsis-associated encephalopathy (SAE) in the MIMIC-IV and eICU-CRD databases and assess their impact on mortality and adverse clinical outcomes.

Methods In this retrospective cohort study, patients with SAE from the MIMIC-IV database were included. Group-based trajectory modeling (GBTM) was used to categorize distinct patterns of serum osmolality changes over 72 h in ICU patients. Differences in survival across the trajectory groups were compared using Kaplan-Meier (K-M) survival curves.

Results A total of 11,376 patients with SAE were included in the analysis, with a median age of 65.6 ± 16.5 years. The in-hospital mortality rate at 30 days was 12.8%. Based on model-defined criteria, three distinct osmolality trajectory groups were identified: Group 1 (59.6%), Group 2 (36.4%), and Group 3 (4.0%). Kaplan-Meier survival analysis indicated that patients with relatively lower serum osmolality within the normal range (Group 1) had a lower 30-day mortality rate compared to those in the other groups (Group 2 and 3). Subgroup analysis demonstrated significant interactions ($P < 0.05$) between osmolality trajectories and covariates such as the Sequential Organ Failure Assessment (SOFA), vasopressor use and renal replacement therapy (RRT).

Conclusion Identifying distinct serum osmolality trajectories may help recognize SAE patient subgroups with varying risks of adverse outcomes, providing clinically meaningful stratification.

Keywords Sepsis-associated encephalopathy, Dynamic trajectory, MIMIC-IV database, Osmolality

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Introduction

Sepsis-Associated Encephalopathy (SAE) is a serious neurological syndrome marked by diffuse brain dysfunction due to sepsis, a life-threatening condition stemming from an abnormal immune response to infection. SAE is typically defined as acute encephalopathy that arises during sepsis or septic shock, with no other identifiable cause besides sepsis itself. It is the most common form of encephalopathy seen in the Intensive Care Unit (ICU). In a 1996 study involving 50 ICU patients with sepsis, 54% were diagnosed with SAE, defined by a Glasgow Coma Scale (GCS) score < 15 [1]. Currently, SAE is defined by a GCS decline linked specifically to sepsis during ICU admission, excluding other causes for reduced GCS. The incidence of SAE was reported at 53% in a French multicenter ICU study [2] and reached 68% in sepsis cohorts from the MIMIC-IV and eICU databases [3]. A recent large multicenter study found that sepsis-associated delirium typically lasted a median of three days, with SAE independently linked to increased short-term mortality.

Serum osmolality, indicating the balance of solutes and water in the blood, serves as a crucial marker of hydration status. Variations in serum osmolality create osmotic gradients that drive water movement across cell membranes, significantly influencing fluid balance, cellular function, electrolyte stability, and kidney health [4–7]. Serum osmolality is calculated using sodium, glucose, and blood urea nitrogen (BUN) levels. Studies have shown that fluctuations in blood glucose, sodium, and BUN levels during sepsis correlate with mortality risk [8–11].

Group-based trajectory modeling (GBTM) is a well-established analytical approach that captures longitudinal changes in serum osmolality, accounting for its dynamic nature over time [12]. GBTM has been widely used in fields such as medicine and psychology to analyze longitudinal data [13]. This method, a specific application of finite mixture modeling, analyzes patterns of behaviors or outcomes over time or age, categorizing individuals into distinct groups based on similar trajectories [13]. This approach enables the exploration of population heterogeneity. Previous studies have applied GBTM to identify ICU sepsis patients with distinct Sequential Organ Failure Assessment (SOFA) score trajectories, revealing varying risks of adverse outcomes across different trajectory groups [14].

The present study aims to use GBTM to identify distinct longitudinal patterns of serum osmolality in sepsis patients, enabling population clustering and an accurate assessment of the association between serum osmolality changes and mortality risk in SAE patients. These findings could inform clinical practice by identifying high-risk populations for targeted care and early intervention.

Methods

Database

The data for this study were obtained from the MIMIC-IV and eICU-CRD databases. MIMIC-IV, released in 2003, is a multi-parameter, structured, single-center ICU database that includes clinical data for 431,231 patients from 2008 to 2019. No individual patient consent or ethical approval is required as the initiative does not impact clinical care and patients in the database are unidentifiable [15]. Our study also adhered to the principles outlined in the Declaration of Helsinki and followed the transparent reporting guidelines for multivariable prognostic or diagnostic models [16]. The eICU-CRD database includes ICU data from over 300 hospitals in the United States, containing routine data from 200,859 patients between 2014 and 2015 [17]. Since both databases are anonymized, no specific patient consent was required.

Patients

At present, there is no precise diagnostic method for Sepsis-Associated Encephalopathy (SAE). Clinical diagnosis relies on exclusion, and according to the Sepsis-3 criteria [18], sepsis is defined by a Sequential Organ Failure Assessment (SOFA) score ≥ 2. In this study, SAE is defined as sepsis patients who experienced a decline in Glasgow Coma Scale (GCS) score during hospitalization, excluding the following criteria: (1) neurological diseases; (2) organ transplant recipients; (3) patients with intoxication; (4) patients with tumors; (5) patients with missing data; (6) patients who were not admitted to ICU for the first time.

Observational variables

The following basic information of the patients with SAE were extracted: gender, height, weight, use of vasopressors, heart rate, respiratory rate, oxygen saturation (SpO2), mean arterial pressure (MAP), GCS score, SOFA score, renal replacement therapy (RRT), mechanical ventilation, blood urea nitrogen (BUN), serum calcium, creatinine, glucose, bicarbonate levels, hematocrit, hemoglobin, international normalized ratio (INR), partial thromboplastin time (PTT), lactate, platelet count (PLT), potassium, sodium, white blood cell count (WBC), alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), and clinical outcome indicators. We collected and calculated the osmolality data for patients within the first 72 h after ICU admission. The osmolality was calculated using the following formula: sodium × 2 + (glucose / 18) + (BUN / 2.8). Navicat Premium 17.0 software and Structured Query Language (SQL) were used to extract indicators from the MIMIC-IV and eICU-CRD databases.

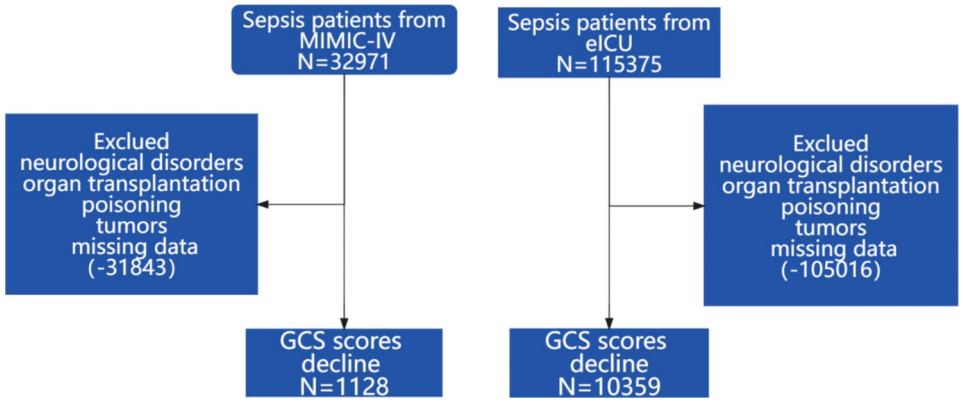

Fig. 1 Flowchart of study patients

Statistical analysis

Statistical analyses were performed using *R* software (version 4.3.3). Continuous variables with normal distribution were presented as mean ± standard deviation and compared using the t-test. Continuous variables with non-normal distribution were presented as median (interquartile range) and compared using the Wilcoxon rank-sum test. Categorical variables were expressed as frequencies or percentages and compared using the $\chi 2$ test or Fisher's exact test. A p-value of < 0.05 was considered statistically significant. Group-based trajectory modeling (GBTM) was used to identify plasma osmolality levels with similar developmental trajectories. The number of trajectory groups was determined using the *traj* package in STATA. To identify the optimal model structure, an initial baseline model was created without including covariates, assessing different polynomial orders (linear, quadratic, and cubic terms). Model selection was based on a combination of Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), entropy, and the proportion of samples in each trajectory group. Participants were assigned to trajectory groups if they had an average posterior probability of at least 70%, with each group representing more than 5% of the total sample. Model simplicity and clinical interpretability were also taken into account. Kaplan-Meier (K-M) curves were used to evaluate survival differences across the different trajectories groups, and subgroup analyses were used to examine survival outcomes among these trajectories groups. All analyses were performed in R (version 4.2.3) and STATA/MP 18.0. Samples with more than 20% missing data were excluded, while missing values in the remaining samples were imputed using package mice.

Results

Baseline characteristics

This study included 11,376 patients with sepsis-associated encephalopathy (SAE) admitted (Fig. 1). Patients were identified to three groups based on serum osmolality levels: normal osmolality (275–295 mmol/L), low osmolality (< 275mmol/L), and high osmolality (> 295 mmol/L). Table S1 presents the baseline characteristics of the patients. The median age was 65.6 ± 16.5 years, with 5,651 (49.7%) males and 5,725 (50.3%) females. Mechanical ventilation was administered to 27.5% ($n = 3,131$) of the patients. The 30-day in-hospital mortality rate was 12.8% ($n = 1,458$), and the incidence of acute kidney injury(AKI) was 24.3% ($n = 2,762$). There were statistically significant differences ($P < 0.05$) among the three osmolality groups in terms of in-hospital mortality, gender, height, weight, vasopressor use, heart rate, respiratory rate, SpO2, MAP, GCS score, SOFA score, RRT, mechanical ventilation, BUN, serum calcium, creatinine, glucose, bicarbonate, hematocrit, hemoglobin, INR, PTT, lactate, PLT, potassium, sodium, WBC, ALT, ALP, AST, diuretic and steroid.

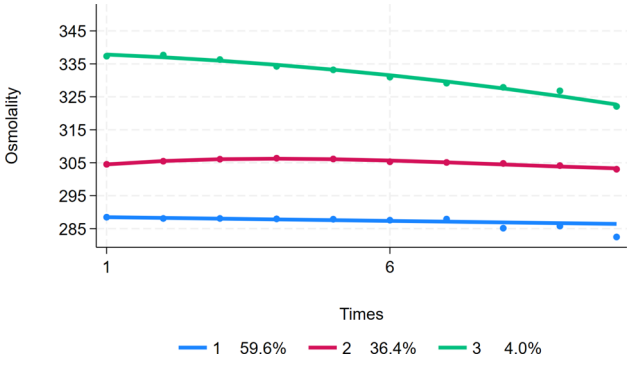

Fig. 2 Three trajectories of serum osmolality based on GBTM

Characteristics of osmolality trajectories

Table S2 presents the model fitting statistics and average posterior probability (AvePP) to identify the best number of serum osmolality trajectories (Fig. 2).Three trajectory groups were identified, each meeting the criteria for satisfactory model fit: Group 1 ($n = 6,970$, 59.6%), Group 2 ($n = 3,967$, 36.4%), and Group 3 ($n = 439$, 4.0%) (Table 1). Each trajectory group had an AvePP exceeding

Table 1 Participants' characteristics of included patients stratified by trajectory grouping for the GBTM analysis of changes in the 72 h serum osmolality

Characters	Levels	Total(*N* = 11376)	Group1 (*N* = 6970)	Group2 (*N* = 3967)	Group3 (*N* = 439)	*P*-value
Age(years)			65.0 (53.0 to 76.9)	71.0 (60.0 to 80.0)	74.0 (64.0 to 82.0)	
Gender						< 0.001*
	Male	5651 (49.7%)	3506 (50.3%)	1969 (49.6%)	176 (40.1%)	
	Female	5725 (50.3%)	3464 (49.7%)	1998 (50.4%)	263 (59.9%)	
LOS(days)		3.5 ± 4.6	1.8 (0.9 to 3.2)	2.7 (1.2 to 5.2)	2.8 (1.3 to 4.9)	< 0.001*
Hospital Mortality		1471 (12.9%)	618 (8.9%)	734 (18.5%)	119 (27.1%)	< 0.001*
Height		168.2 ± 13.8	168.0 (160.0 to 177.8)	167.6 (160.0 to 177.8)	170.2 (162.6 to 177.9)	0.007*
Weight		84.1 ± 31.0	78.6 (65.0 to 97.0)	79.4 (65.0 to 97.7)	75.0 (61.2 to 94.3)	0.004*
Vital Signs						
Heartrate (times/min)		96.6 ± 22.4	96.0 (81.0 to 111.0)	95.0 (80.0 to 110.0)	96.0 (81.0 to 111.0)	0.107
Respiratoryrate (times/min)		22.0 ± 7.0	20.0 (17.0 to 26.0)	21.0 (17.0 to 26.0)	21.0 (17.0 to 27.0)	< 0.001*
SpO_2(%)		95.7 ± 5.4	97.0 (94.0 to 99.0)	97.0 (94.0 to 99.0)	98.0 (95.0 to 100.0)	< 0.001*
Mbp(mmHg)		79.1 ± 29.0	78.0 (66.3 to 93.7)	78.0 (65.0 to 94.0)	76.0 (63.5 to 90.8)	0.051
Glucose(mg/dL)		163.3 ± 108.4	128.0 (104.0 to 172.0)	140.0 (109.0 to 193.0)	163.0 (122.0 to 240.5)	< 0.001*
Severity Score						
GCS		13.1 ± 3.1	15.0 (14.0 to 15.0)	14.0 (11.0 to 15.0)	13.0 (9.0 to 15.0)	< 0.001*
SOFA		4.8 ± 2.3	4.0 (3.0 to 5.0)	4.0 (3.0 to 7.0)	5.0 (3.0 to 7.0)	< 0.001*
Laboratory Tests						
Potassium (mmol/L)		4.3 ± 0.9	4.1 (3.7 to 4.6)	4.3 (3.8 to 4.8)	4.5 (3.9 to 5.2)	< 0.001*
Sodium (mmol/L)		136.3 ± 6.1	135.6 (132.0 to 138.0)	138.0 (135.0 to 141.0)	142.0 (137.0 to 149.0)	< 0.001*
Calcium (mg/dL)		8.0 ± 2.3	8.6 (7.9 to 9.1)	8.7 (8.0 to 9.2)	8.7 (8.0 to 9.4)	< 0.001*
Bicarbonate (mmol/L)		23.6 ± 5.8	24.0 (21.0 to 27.0)	23.0 (20.0 to 27.0)	22.0 (17.9 to 26.0)	< 0.001*
Lactate (mg/dL)		2.9 ± 2.3	2.2 (1.4 to 3.3)	2.4 (1.5 to 3.8)	2.6 (1.6 to 4.2)	< 0.001*
Hematocrit (μmol/L)		35.1 ± 7.4	35.1 (29.8 to 40.2)	35.0 (29.9 to 40.3)	34.3 (28.9 to 40.7)	0.500
Hemoglobin (g/dL)		11.5 ± 2.5	11.5 (9.8 to 13.3)	11.4 (9.7 to 13.2)	11.2 (9.1 to 13.1)	0.002*
INR		1.7 ± 1.2	1.2 (1.1 to 1.6)	1.3 (1.1 to 1.7)	1.3 (1.1 to 2.1)	< 0.001*
PTT(s)		36.4 ± 16.8	32.0 (27.9 to 38.0)	32.1 (27.9 to 39.0)	32.0 (27.0 to 40.1)	0.216
WBC(K/μL)		15.2 ± 9.5	13.4 (9.1 to 18.7)	13.8 (9.4 to 19.4)	15.4 (11.2 to 21.4)	< 0.001*
PLT(K/μL)		238.4 ± 124.8	4.1 (3.7 to 4.6)	4.3 (3.8 to 4.8)	4.5 (3.9 to 5.2)	< 0.001*
BUN(mg/dL)		33.7 ± 25.8	21.0 (14.0 to 32.0)	36.0 (23.0 to 55.0)	75.0 (46.5 to 106.0)	< 0.001*
Creatinine (mg/dL)		2.0 ± 1.9	1.1 (0.8 to 1.8)	1.6 (1.0 to 2.8)	2.5 (1.6 to 4.1)	< 0.001*
ALT(IU/L)		63.4 ± 214.3	25.0 (16.0 to 43.0)	26.0 (17.0 to 48.0)	30.0 (17.0 to 55.5)	< 0.001*
ALP(IU/L)		126.7 ± 115.6	97.0 (72.0 to 137.0)	98.0 (74.0 to 141.0)	101.0 (73.0 to 151.5)	0.019*
AST(IU/L)		92.4 ± 391.5	30.0 (19.0 to 54.0)	31.0 (20.0 to 58.0)	36.0 (21.0 to 72.0)	< 0.001*
Treatment measures						
Mechanical Ventilation						< 0.001*
	No	8245 (72.5%)	5352 (76.8%)	2610 (65.8%)	283 (64.5%)	
	Yes	3131 (27.5%)	1618 (23.2%)	1357 (34.2%)	156 (35.5%)	
RRT						0.462
	No	9866 (86.7%)	6065 (87%)	3419 (86.2%)	382 (87%)	

Table 1 (continued)

Characters	Levels	Total(*N* = 11376)	Group1 (*N* = 6970)	Group2 (*N* = 3967)	Group3 (*N* = 439)	*P*-value
	Yes	1510 (13.3%)	905 (13%)	548 (13.8%)	57 (13%)	
Vasopressor						< 0.001*
	No	4541 (39.9%)	3018 (43.3%)	1381 (34.8%)	142 (32.3%)	
	Yes	6835 (60.1%)	3952 (56.7%)	2586 (65.2%)	297 (67.7%)	
Comorbidity						
AKI						< 0.001*
	No	8697 (76.5%)	5773 (82.8%)	2702 (68.1%)	222 (50.6%)	
	Yes	2679 (23.5%)	1197 (17.2%)	1265 (31.9%)	217 (49.4%)	
HF						< 0.001*
	No	10,314 (90.7%)	6399 (91.8%)	3521 (88.8%)	394 (89.7%)	
	Yes	1062 (9.3%)	571 (8.2%)	446 (11.2%)	45 (10.3%)	
DM						0.012*
	No	9124 (88.1%)	5523 (88.8%)	3240 (87%)	361 (86.2%)	
	Yes	1235 (11.9%)	694 (11.2%)	483 (13%)	58 (13.8%)	
Drug						
Diuretic						
	No	7222 (63.5%)	4396 (63.1%)	2531 (63.8%)	295 (67.2%)	0.192
	Yes	4154 (36.5%)	2574 (36.9%)	1436 (36.2%)	144 (32.8%)	
Steroid						
	No	10,214 (89.8%)	6247 (89.6%)	3576 (90.1%)	391 (89.1%)	0.608
	Yes	1162 (10.2%)	723 (10.4%)	391 (9.9%)	48 (10.9%)	

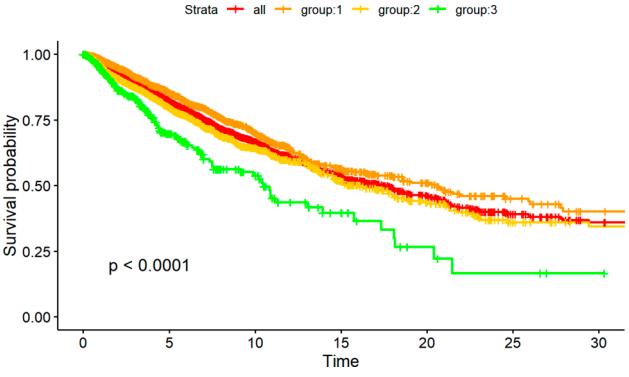

Fig. 3 The Kaplan-Meier survival curves across the different osmolality trajectory groups

0.7, indicating good fit. Table 1 presents clinical characteristics by different serum osmolality trajectories. Statistically significant differences ($P < 0.05^*$) were observed among the three trajectory groups in terms of in-hospital mortality, gender, height, weight, vasopressor use, respiratory rate, oxygen saturation, GCS score, SOFA score, ventilation, BUN, serum calcium, creatinine, glucose, bicarbonate, hemoglobin, INR, lactate, potassium, sodium, WBC count, ALT, ALP, and AST. Violin plots (Figure S1) indicate osmolality distribution in every trajectory group.The distribution of Group 1 and Group 2 is relatively concentrated, while Group 3 is more dispersed. This may also suggest that the osmolality changes in Groups 1 and 2 are smaller, whereas those in Group 3 are larger.

Mortality rates across osmolality trajectories

Figure 3 shows the Kaplan-Meier survival curves across the different osmolality trajectories groups. Significant differences were observed in survival rates among the osmolality groups ($P < 0.001^*$). Group 1 had the lowest 30-day mortality rate, while Group 3 had the highest. Pairwise comparisons revealed significant differences between each group ($P < 0.001^*$) (Fig. 3).

Univariable analysis revealed that the trajectory sub-phenotype was significantly associated with both 30-day mortality compared to Group 1 (Group2:HR = 2.33; 95%CI2.08-2.62, Group3:HR = 3.82; 95%CI3.05-4.79), Other significant factors for 30-day mortality included age, heartrate, mbp, SOFA, GCS, BUN, glucose, creatinine, sodium, wbc, use of mechanical ventilation, RRT, use of vasopressor, use of diuretic, AKI, HF, DM (all $P < 0.05^*$).

Multivariable Cox regression analysis showed that the trajectory sub-phenotype (Group2:HR = 1.45;95%CI1.25-1.69, Group3:HR = 2.42;95%CI1.71-3.41), age (HR = 1.02;95%CI1.00-1.02; $P < 0.001^*$),Mbp(HR = 0.99;95%CI0.99-1.00;$P < 0.001^*$), SOFA(HR = 1.31;95%CI1.27-1.34;$P < 0.001^*$), WBC (HR = 1.01; 95%CI1.01-1.05; $P = 0.008^*$), GCS (HR = 1.03; 95% CI 1.01–1.05; $P = 0.009^*$), DM (HR = 0.79; 95%CI 0.64–0.99;$P = 0.039^*$) and use of mechanical ventilation (HR = 1.26; 95%CI 1.08–1.47;$P = 0.004^*$) were independent risk factors for 30-day mortality (Table 2).

We selected the following as research variables for the stratified subgroup analysis: age, GCS, use of RRT, SOFA,

Table 2 Cox univariate and multivariate regression of 30-day mortality

Variables		Univariable	*P*	Multivariable	*P*
		HR (95% CI)		HR (95% CI)	
Group	1				
	2	2.33 (2.08–2.62)	< 0.001*	1.45 (1.25–1.69)	< 0.001*
	3	3.82 (3.05–4.79)	< 0.001*	2.42 (1.71–3.41)	< 0.001*
Age(years)		1.03 (1.02–1.03)	< 0.001*	1.02 (1.02–1.03)	< 0.001*
Gender	Female	0.94 (0.84–1.05)	0.257		
Heartrate (times/min)		1.01 (1.00-1.01)	< 0.001*	1.00 (1.00-1.01)	0.052
Mbp(mmHg)		0.99 (0.99–0.99)	< 0.001*	0.99 (0.99-1.00)	< 0.001*
SOFA		1.48 (1.44–1.51)	< 0.001*	1.31 (1.27–1.34)	< 0.001*
GCS		0.91 (0.89–0.92)	0.001*	1.03 (1.01–1.05)	0.009*
BUN		1.01 (1.01–1.01)	< 0.001*	1.00 (1.00–1.00)	0.881
Glucose (mg/dL)		1.00 (1.00–1.00)	0.068		
Creatinine (mg/dL)		1.06 (1.03–1.09)	< 0.001*	0.99 (0.95–1.04)	0.660
Sodium (mmol/L)		1.01 (1.00-1.02)	0.179		
WBC(K/μL)		1.01 (1.01–1.02)	< 0.001*	1.01 (1.00-1.02)	0.008*
Mechanical Ventilation		2.28 (2.04–2.56)	< 0.001*	1.26 (1.08–1.47)	0.004*
RRT		1.47 (1.27–1.70)	< 0.001*	1.11 (0.91–1.36)	0.296
Vasopressor		1.92 (1.70–2.17)	< 0.001*	1.04 (0.90–1.20)	0.617
Diuretic		0.79 (0.70–0.88)	< 0.001*	0.87 (0.76-1.00)	0.050
Steroid		1.13 (0.95–1.34)	0.174	1.13 (0.92–1.40)	0.246
AKI		1.84 (1.63–2.07)	< 0.001*	1.12 (0.96–1.29)	0.144
HF		1.32 (1.11–1.57)	0.002*	1.59 (1.30–1.96)	0.071
DM		0.75 (0.62–0.90)	0.002*	0.79 (0.64–0.99)	0.039*

diabetes, AKI, heart failure, use of vasopressor, use of mechanical ventilation(Fig. 4). In our study, for patients in Group 3, those who did not receive vasopressor or RRT treatment had a higher risk of mortality compared to those who did. Additionally, patients with a SOFA score < 6 had a higher risk of death ($P < 0.05^*$).

Discussion

SAE is often defined as an acute encephalopathy that arises during sepsis or septic shock, without any other cause than sepsis itself, typically manifesting as delirium or coma. Serum osmolality could be a useful marker to identify sepsis patients at elevated mortality risk due to its ease of measurement and low cost. Serum osmolality represents the concentration of all solutes in the blood, essential for maintaining cellular volume balance [19]. Changes in osmolality establish gradients that drive water movement; in hypotonic conditions, cells swell from water uptake, while in hypertonic conditions, cells shrink due to water loss, both of which can disrupt physiological function [20]. Previous studies have indicated that low osmolality (≤ 280 mmol/L) correlates with increased all-cause mortality and hospital readmission in heart failure patients, while high osmolality did not show such associations [21]. Additionally, osmolality shifts have been linked to declines in pulmonary function [22], and in critically ill patients, elevated serum osmolality is associated with higher mortality in those admitted for cardiovascular, neurological, gastrointestinal, and other systemic conditions [23]. In neurological disorders, serum osmolality is associated with the prognosis of various conditions, including intracerebral hemorrhage [24, 25], subarachnoid hemorrhage [26], and stroke [27]. Clinically, sodium is often highlighted as the key driver of plasma osmolality, which may lead to an incomplete assessment of total osmolality. Although we stratified patients based on serum sodium trajectories, no significant impact on all-cause mortality was observed (Figure S2, $P = 0.81$), suggesting that serum osmolality influences mortality independently of sodium levels.

While the mechanisms connecting serum osmolality to mortality risk in SAE patients remain uncertain, the current findings offer potential insights. Research indicates that hyperosmolality can elevate intracellular Ca^{2+} and reactive oxygen species (ROS), promoting endoplasmic reticulum stress and resulting in cardiomyocyte apoptosis [28, 29]. The kidneys, crucial in osmoregulation, are particularly susceptible to osmotic stress. Studies have

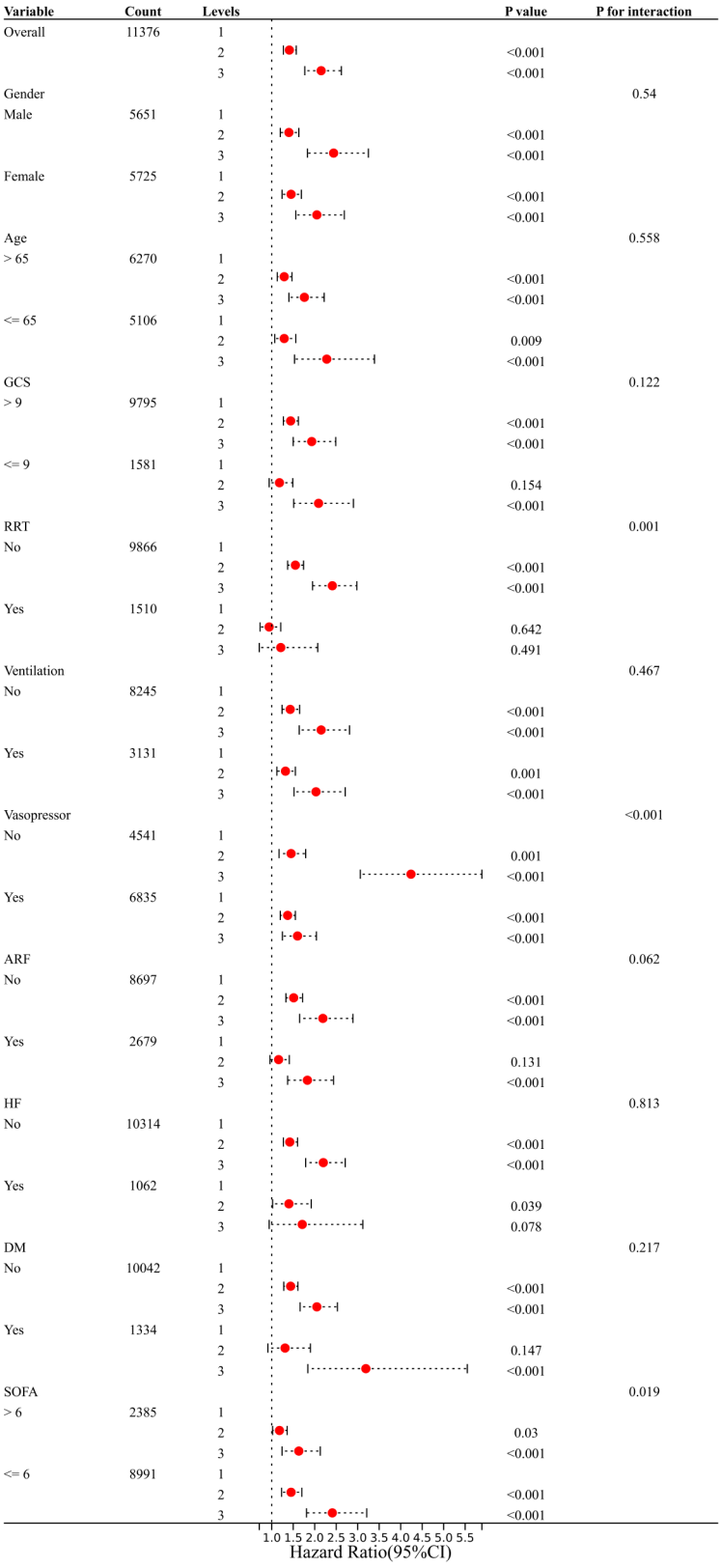

Fig. 4 Subgroup analysis for associations between serum osmolality trajectories and adverse outcomes according to baseline characteristics

shown that hyperosmolality exerts toxic effects on renal tubular epithelial cells by inducing oxidative stress and cytoskeletal damage, ultimately leading to kidney injury [30, 31]. Hyperosmotic conditions may also compromise the blood-brain barrier (BBB), allowing increased levels of cytokines, chemokines, and cell adhesion molecules to circulate [32, 33]. This association between hyperosmolar states and multi-organ damage aligns with the multi-organ dysfunction seen in sepsis.

In this study, group-based trajectory modeling (GBTM) identified three distinct osmolality trajectory groups in SAE patients, showing variations in 72 h osmolality levels and patterns at admission and during hospitalization.

The findings indicate three distinct osmolality trajectories in SAE patients, associated with prognosis and mortality risk. Among the trajectory groups, Group 1 maintained osmolality levels between 285 and 290 mmol/L during the first 72 h of admission, showing relative stability. Plasma osmolality is dynamic; thus, changes over time provide more clinical insights into prognosis than single-point measurements. By analyzing osmolality trajectories within the initial 72 h of SAE patient admission, potential subtypes can be identified to assess how trajectory subtypes impact mortality, disease severity, and associated risk factors, offering clinicians better diagnostic and therapeutic guidance. Patients in Group 1 had the lowest 30-day mortality rate (8.9%), significantly lower than in the other two trajectory groups. Group 2, despite having a generally normal but relatively high osmolality level, exhibited a significantly higher 30-day mortality rate (18.5%) compared to Group 1 ($P < 0.001$). Group 3 had elevated admission osmolality (mean 326.37 mmol/L); although it decreased gradually with treatment, this group still showed a high 30-day mortality rate (27.1%). These results suggest that maintaining a low, stable osmolality within the normal range is associated with better survival, consistent with previous studies linking plasma osmolality at admission within the range of 285.80–296.29 mmol/L to the lowest mortality rates in septic patients [34].The underlying mechanisms linking the trajectories of osmolality changes to mortality risk in SAE patients remain unclear.Several plausible mechanisms may explain how plasma osmolality trajectories contribute to fatal outcomes in SAE patients. First, persistently elevated osmolality can cause electrolyte imbalances [35], leading to cellular shrinkage. Such drastic changes in cell morphology may disrupt critical intracellular components, including the nucleus and mitochondria, resulting in energy production failure and activation of apoptotic signaling pathways, ultimately causing cell death [36, 37]. Additionally, elevated osmolality often triggers the upregulation of inflammatory cytokines such as TNF, IL-1β, IL-6, and IL-8 [38], which are closely associated with SAE progression. Moreover, sustained high osmolality can lead to reduced cerebral blood flow in the internal carotid and middle cerebral arteries without affecting the brain's oxygen metabolic rate [39]. This absolute reduction in cerebral blood flow, coupled with a relative increase in cerebral oxygen metabolism, exacerbates brain injury following SAE, ultimately leading to poor clinical outcomes.

In this study, compared to Group 1, the other two groups were significantly associated with an increased 30-day mortality risk. Furthermore, age, SOFA score, MBP, WBC, mechanical ventilation, and diabetes were identified as independent risk factors for 30-day mortality in SAE patients. Age [40], WBC [41], MBP [18], and diabetes have previously been established as independent predictors of outcomes in patients with infections and sepsis, and their roles in SAE patients are likely similar. Prior research [42] has demonstrated that sepsis patients with diabetes exhibit lower mortality rates, which may be attributed to distinct immune system characteristics in diabetic individuals that influence sepsis outcomes, or to closer medical monitoring and more aggressive management of underlying chronic conditions in diabetic patients. Our findings appear to align with these observations.Mechanical ventilation is commonly utilized for critically ill patients who have a poor baseline prognosis. As such, it may serve as both a marker of disease severity and a direct contributor to outcomes through associated complications (e.g., ventilator-associated pneumonia, barotrauma). The SOFA score, widely used as a tool to assess organ failure, has prognostic value in addition to its diagnostic utility [43, 44].In our study, the hazard ratio of osmolar trajectory subphenotypes was significantly higher than that of the SOFA score. Given that the SOFA score is a known predictor of outcomes in critically ill and septic patients, this finding suggests that osmolar trajectory groups may provide greater value in distinguishing the heterogeneity of sepsis and could serve as a reference for future classification in sepsis management.

Further subgroup analysis revealed that age, gender, and Glasgow Coma Scale (GCS) scores significantly influenced survival outcomes within each group. Previous studies have demonstrated that the incidence and mortality of sepsis increase significantly with age, and GCS scores are strongly associated with mortality in sepsis-associated encephalopathy (SAE). In patients at risk of acute kidney injury (AKI), electrolyte imbalances are frequently observed, and renal replacement therapy (RRT) is the preferred intervention in the ICU for managing severe hyponatremia, hypernatremia, and renal failure. These conditions

may directly impact changes in osmolality.Complications commonly associated with sepsis, such as heart failure, diabetes, and AKI, are also strong predictors of increased mortality risk [45, 46].Although these complications and variables exhibit a strong correlation with mortality outcomes across groups, their effects were consistent within subgroups. However, the use of vasopressors significantly improved the prognosis of patients in osmolality trajectory Group 3. Both vasopressin and vasopressors facilitate water reabsorption and maintain normal osmolality, countering vasodilation in sepsis patients [47]. Studies have reported that vasopressin levels are reduced in septic patients, making them more responsive to exogenous vasopressin, with this effect being independent of catecholamines [48]. Nonetheless, the underlying mechanisms warrant further investigation.In Group 3, patients who did not receive vasopressor or RRT treatment and had a SOFA score < 6 exhibited a higher hazard ratio. This finding suggests that current commonly used ICU assessment methods may fail to accurately identify patients in different serum osmolality trajectory groups, potentially leading to misjudgments of patient conditions by healthcare professionals and contributing to adverse outcomes.

Strengths and limitations

This study aims to explore the relationship between serum osmolality trajectories and poor prognosis in patients with Sepsis-Associated Encephalopathy (SAE), this is the first retrospective study to investigate the effect of longitudinal osmolality data on the outcomes of SAE. We identified distinct serum osmolality trajectories, admission characteristics, and outcomes across three patient groups with SAE. By applying GBTM, we classified different trajectories of serum osmolality in SAE patients. The findings offer valuable insights for clinicians, highlighting the importance of targeted care and early intervention for high-risk patient populations in clinical practice.It also reveals that in clinical practice, there are patients who, despite having a low SOFA score, still face a significantly higher risk of mortality.

We recognize certain limitations in our study. ,Firstly, we only demonstrates statistical associations with all-cause mortality and adverse outcomes, Secondly, its retrospective design with potential for missing data or entry errors in the MIMIC-IV and eICU databases. Finally, because this study only included patients in the USA, the relevance of extrapolating these results to ICU patients in other countries is uncertain.we aim to conduct prospective studies in developing countries to verify whether different conclusions emerge under varying healthcare conditions across regions.

Conclusion

This study explored the relationship between serum osmolality trajectories in SAE patients and their 30-day mortality outcomes. Through GBTM, we found that stable and lower serum osmolality was associated with better survival, with Group 1 patients showing significantly lower 30-day mortality. Additionally, factors like SOFA score, RRT, and vasopressor use influenced mortality risk to varying extents.

Abbreviations

ICU	Intensive care unit
MIMIC	Medical Information Mart for Intensive Care
eICU-CRD	EICU Collaborative Research Database
SAE	Sepsis-associated encephalopathy
GCS	Glasgow Coma Scale
SOFA	Sequential Organ Failure Assessment
RRT	Renal replacement therapy
SpO_2	Oxygen saturation
MAP	Mean arterial pressure
BUN	Blood urea nitrogen
INR	International normalized ratio
PTT	Partial thromboplastin time
PLT	Platelet count
WBC	White blood cell countalanine
ALT	Aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
AKI	Acute kidney injury
HF	Heart failure
DM	Diabetes mellitus
GBTM	Group-based trajectory modeling
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
K-M curves	Kaplan-Meier curves
AvePP	Average posterior probability
HR	Hazard Ratio
AKI	Acute kidney injury
ROS	Reactive oxygen species
BBB	Blood-brain barrier

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10482-9.

Supplementary Material 1

Author contributions

W.W. was instrumental in collecting and analyzing data, as well as drafting the manuscript. W.C. were pivotal in data extraction and played a significant role in the study's design. X.Y.and Z.Y.revised the manuscript for intellectual content. L.X., who oversaw the entire project, contributed by reviewing and designing the study, in addition to providing supervision. W.W. and W.C. contributed equally to this work. All authors actively participated in the development of the article and gave their approval for the final version to be submitted.

Funding

No external funding.

Data availability

Data are available upon reasonable request. The datasets used and/or analysed during the current study are available from MIMIC-IV and eICU-CRD if they completed CITI programme and got permission to access the database.

Declarations

Ethics approval and consent to participate
The model was developed and validated based on public database. After completing the Collaborative Institutional Training Initiative programme, we got permission to access the database. This study used public deidentification databases, so there is no need to obtain the informed consent and approval of the Institutional Review Board. Participants gave informed consent to participate in the study before taking part.

Consent for publication
Not applicable.

Clinical trial
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 15 November 2024 / Accepted: 10 January 2025
Published online: 23 January 2025

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