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Group-based Trajectory Modeling of Serum Sodium and Survival in Sepsis Patients with Lactic Acidosis: Results from MIMIC-IV Database

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The purpose of this project was to characterize the longitudinal dynamic serum sodium trajectory of sepsis patients with lactic acidosis (LA) admitted to the intensive care unit (ICU), and to explore the association between these trajectories and the 30-day mortality rate of patients. Data on patients admitted to the ICU with a diagnosis of LA combined with sepsis from 2008-2019 were collected from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database. Patients admitted to the ICU for > 24 hours and for the first time were sorted into 3 groups based on their serum sodium levels at admission. The Group-based Trajectory Modeling (GBTM) method was applied to analyze the trajectory changes of serum sodium in each group of patients over 72 hours. Patients' survival differences between different trajectory groups were compared using Kaplan-Meier (K-M) survival curves. Subgroup analysis was carried out to determine the influencing factors of the relationship between dynamic changes in serum sodium and patient survival. This study included 514 patients with LA complicated by sepsis, who were clustered into three groups based on their admission serum sodium levels, with 378 patients in the normal blood sodium (135-145 mEq/L) group, 116 patients in the hyponatremia (< 135 mEq/L) group, and 20 patients in the hypernatremia (> 145 mEq/L) group. GBTM analysis generated three different serum sodium trajectories. The K-M curve results demonstrated that patients with relatively stable serum sodium levels within the normal range (Class 2) had lower 30-day mortality compared to groups with larger fluctuations in sodium levels (Class 1, Class 3). Subgroup analysis uncovered notable interactions ($P < 0.05$) between different trajectories of serum sodium and covariates such as race, marital status, Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA), renal replacement therapy (RRT), congestive heart failure, kidney disease, liver disease, and diabetes. Among patients with LA complicated by sepsis, those with stable and normal fluctuations in serum sodium levels had better 30-day survival rates. GBTM is a refined method to describe the evolution of serum sodium and its association with clinical outcomes, which may enhance the current understanding of blood sodium level regulation.

Keywords: Group-based Trajectory Modeling; lactic acidosis; Medical Information Mart for Intensive Care-IV; sepsis; serum sodium
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Introduction

Sepsis is a life-threatening organ dysfunction induced by a dysregulated host response to infection, with septic shock being its most severe form, featuring low blood pressure and changes in peripheral tissue perfusion (Singer et al. 2016; Evans et al. 2021). Sepsis is a major culprit of death in critically ill patients in the Intensive Care Unit

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(ICU). Statistical data reports that there were 48.9 million cases of sepsis globally in 2017, with 11 million related deaths, accounting for nearly 20% of all deaths worldwide (Rudd et al. 2020). Furthermore, sepsis is linked with a considerable economic burden on healthcare systems and society. According to the estimation, healthcare costs related to sepsis treatment in the United States exceeded 24 billion (Paoli et al. 2018). In most cases, sepsis and septic shock present in the form of metabolic acidosis, a common acid-base imbalance characterized by decreased bicarbonate levels. Sepsis patients with concomitant metabolic acidosis have a higher risk of long-term clinical deterioration after discharge (Stumpff-Niggemann and Feldkamp 2020; Sarmin et al. 2021; Yang et al. 2023). Lactic acidosis (LA) is one of the common types of metabolic acidosis in critically ill patients and is also the most common cause of metabolic acidosis in sepsis patients (Ganesh et al. 2016; Achanti and Szerlip 2023). The treatment of LA is very difficult. Compared to patients without LA, patients with LA and sepsis have nearly doubled mortality rates (46.2% vs. 24.8%) (Doshi et al. 2018).

As the main cations in the extracellular fluid of the human body, sodium ions are very crucial for maintaining extracellular fluid volume, regulating acid-base balance, and maintaining normal osmotic pressure and cell physiological functions (Shrimanker and Bhattarai 2024). Abnormal sodium concentration is a common electrolyte disorder, which is linked with the severity of patients' disease, adverse clinical outcomes, and increased in-hospital mortality rates. A previous analysis of the relationship between serum sodium levels and clinical outcomes in septic patients demonstrated that the higher serum sodium level indicates the higher mortality rate of ICU septic patients (Han et al. 2023). Meanwhile, another study discussing the relationship between sepsis and serum sodium put forward that moderate to severe hyponatremia at admission can independently predict the mortality rate of septic patients (Castello et al. 2021). However, all analyses of sodium serum are based on statistical results from specific time points. We currently do not know the changes in sodium serum levels during hospitalization and their relationship with the outcome of sepsis combined with LA.

Group-based Trajectory Modeling (GBTM) is a mature analysis method that can summarize the long-term changes in sodium serum values while considering the dynamic nature of this variable over time (Nagin 2014). Former studies have applied GBTM to identify ICU septic patients with different Sequential Organ Failure Assessment (SOFA) score trajectory groups, where patients in different trajectory groups may be at different levels of risk for adverse outcomes (Yang et al. 2022). Therefore, this project aims to utilize GBTM to reveal the different patterns of longitudinal development of sodium serum, achieve population clustering, and accurately assess the relationship between changes in sodium serum levels after the occurrence of LA in septic patients and the mortality rate of patients' prognosis, thus providing a reference basis for clinical doctors to focus on nursing and taking early interventive measures for key populations in practice.

Materials and Methods

Data source

The Medical Information Mart for Intensive Care (MIMIC) database was funded by the Beth Israel Deaconess Medical Center (BIDMC), the National Institutes of Health, Massachusetts General Hospital, emergency physicians, intensivists, computer science experts, and other professional critical care medicine databases in 2003 (Yang et al. 2020). MIMIC is an intensive care hospital system based on BIDMC and also the largest open-source and free clinical database for ICUs and emergency departments. As the latest version, MIMIC-IV records detailed information of over 70,000 de-identified patients from BIDMC between 2008 and 2019, including demographic data, vital signs, comorbidity, and laboratory tests, proffering reliable data resources for epidemiological research by clinical physicians (https://mimic.physionet.org/about/mimic/). The database provides the patient's time of death inside and outside the hospital from hospital databases or social security databases. As all data has been de-identified, the Institutional Review Board of BIDMC has waived informed consent and permitted the sharing of research resources (Johnson et al. 2023).

Patient selection

This project selected clinical data of 299,712 subjects from the MIMIC-IV database between 2008 and 2019 to investigate the relationship between *in vivo* serum sodium changes and survival of sepsis patients with LA. All data in the MIMIC-IV have undergone de-identification processing and cannot identify specific patients. Therefore, our investigation did not require written informed consent from patients or approval from the institutional ethics review board.

To ensure the integrity of the sample information in this investigation, the following criteria were applied to identify eligible patients: (a) age > 18 years, < 90 years; (b) admitted to the ICU for > 24 hours, with the first admission; (c) patients meeting the sepsis-3 criteria; (d) LA defined as blood pH < 7.35 and lactate level ≥ 4 mmol/L (first measurement within 48 hours of ICU admission). All included patients had serum sodium levels measured more than 4 times within the first 72 hours of admission.

The following patients were excluded: (a) patients who lack survival information; (b) patients who lack laboratory measurements and baseline data of serum sodium within the first 3 days of ICU admission; (c) patients who died within 24 hours of admission. Finally, 514 eligible subjects were included in the project. The detailed selection process of subjects for this study is shown in Fig. 1.

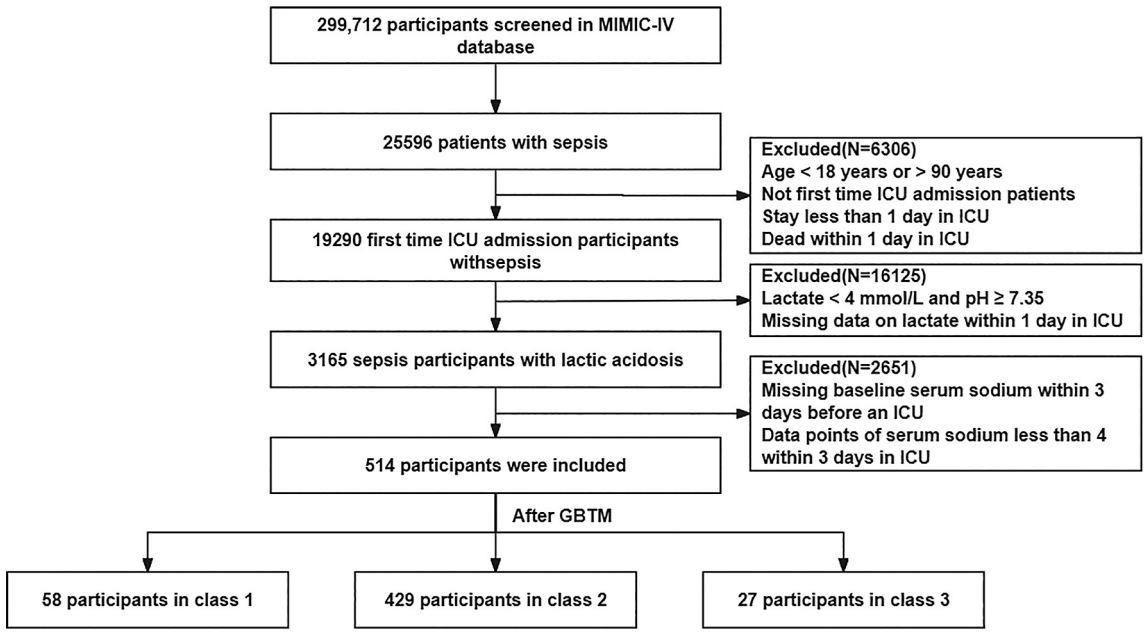

Fig. 1. Study cohort selection workflow of the MIMIC-IV database.

Variable collection

This project collected patients' demographic data, laboratory measurements, severity scores, medication use, positive microbiological culture results, and medical history. The data include age, gender, race, marital status, heart rate, mean blood pressure (MBP), breath rate, temperature, peripheral blood oxygen saturation (SpO_2), glucose, anion gap, bicarbonate, chloride, hematocrit, hemoglobin, lactate, platelets, potassium, partial thromboplastin time (PTT), white blood cell (WBC) count, international normalized ratio (INR), prothrombin time (PT), sodium, blood urea nitrogen (BUN), partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (pCO_2), mean corpuscular volume (MCV), pH, base excess, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), creatinine, Glasgow coma scale (GCS), SOFA, Charlson comorbidity index, Simplified acute physiology score II (SAPSII), vasopressor use (yes or no), mechanical ventilation (yes or no), renal replacement therapy (RRT), microbiological culture (blood, urine, sputum, and others), congestive heart failure (yes or no), kidney disease (yes or no), chronic lung disease (yes or no), diabetes (yes or no), and liver disease (yes or no).

Note: Severity scores, vital signs, and laboratory measurements within 24 hours of admission were collected. The most severe value was utilized when there were multiple results for measurement.

Trajectory grouping of serum sodium content

The GBTM approach was employed to identify serum sodium levels with similar developmental trajectories. The *l cmm* package was applied to identify and determine their trajectories. Patients were sorted into three groups based on their serum sodium levels after admission. The number of trajectories for each group of patients was determined using the GBTM method. The specific process is as follows: by setting up a baseline model without covariate, the number and order of the measured polynomial functions (linear, quadratic, and cubic terms) were determined. The best-fit model was determined by Akaike information criterion (AIC), Bayesian information criterion (BIC), sample-size adjusted BIC (SABIC), entropy, and the proportion of samples in each trajectory group. In addition, each participant was assigned to a model with an average posterior probability of 70% or higher as well as a sample proportion of each trajectory group greater than 5%.

Statistical analysis

Continuous variables in the statistical analysis were expressed as median (IQR), and comparisons between groups were made using the Mann-Whitney U test. Categorical data were expressed as percentages (%), and the chi-square test was utilized for comparison. Baseline serum sodium concentrations were clustered into three groups: < 135 mEq/L, 135-145 mEq/L, and > 145 mEq/L. The association of serum sodium level with demographic and clinical variables in patients with septic shock and LA was compared. A two-sided P value < 0.05 was considered statistically significant for characteristic comparisons between groups. By constructing the baseline characteristics of the best-fitting model for sodium serum using GBTM, Kaplan-Meier (K-M) curves were plotted to compare the survival differences between groups. Subgroup analysis was carried out to compare the survival status among different groups. Data statistical analysis in this experiment was conducted using R (4.2.3) statistical software. R packages utilized in this investigation included

Table 1. Baseline characteristics of patients with hypernatremia, hyponatremia, and normal sodium levels at the time of ICU admission.

Characters	Total (N = 514)	hyponatremia (< 135 mEq/L) (N = 116)	normal sodium levels (135-145 mEq/L) (N = 378)	hypernatremia (> 145 mEq/L) (N = 20)	P-Value
Gender					**0.017**
Female	186 (36.2)	37 (31.9)	136 (36.0)	13 (65.0)	
Male	328 (63.8)	79 (68.1)	242 (64.0)	7 (35.0)	
Age (years)	69.50 [59.00, 78.00]	64.00 [56.00, 72.50]	71.00 [60.00, 79.00]	70.00 [57.00, 80.75]	**0.001**
Race					**0.001**
White	316 (61.5)	73 (62.9)	233 (61.6)	10 (50.0)	
Black	35 (6.8)	5 (4.3)	24 (6.3)	6 (30.0)	
Other race	163 (31.7)	38 (32.8)	121 (32.0)	4 (20.0)	
Marital status					0.120
Married	244 (47.5)	62 (53.4)	176 (46.6)	6 (30.0)	
Unmarried	270 (52.5)	54 (46.6)	202 (53.4)	14 (70.0)	
LOS (day)	4.00 [2.17, 8.68]	4.10 [2.22, 9.03]	3.97 [2.14, 8.56]	4.36 [2.62, 8.52]	0.800
Hospital mortality	258 (50.2)	82 (70.7)	167 (44.2)	9 (45.0)	**< 0.001**
Vital signs					
Heart rate (times/min)	90.20 [81.22, 101.89]	96.16 [84.44, 106.49]	88.38 [80.19, 99.97]	97.13 [84.55, 111.99]	**0.001**
MBP (mmHg)	72.40 [67.30, 77.35]	72.16 [66.60, 76.52]	72.59 [68.09, 77.41]	71.95 [64.30, 77.75]	0.348
Breath rate (times/min)	19.65 [17.52, 22.99]	20.35 [18.10, 23.93]	19.36 [17.34, 22.42]	21.52 [18.71, 23.90]	**0.042**
Temperature (℃)	36.82 [36.49, 37.16]	36.75 [36.46, 37.10]	36.82 [36.49, 37.14]	36.89 [36.81, 37.14]	0.595
SpO_2	97.67 [96.19, 98.76]	97.01 [94.89, 98.64]	97.76 [96.39, 98.83]	97.86 [96.92, 98.54]	**0.006**
Glucose (mg/dL)	145.72 [125.10, 176.31]	145.17 [118.00, 191.33]	144.50 [125.61, 172.44]	153.78 [133.73, 187.17]	0.614
Severity score					
GCS					
≥ 13	425 (82.7)	97 (83.6)	317 (83.9)	11 (55.0)	**< 0.001**
9-12	37 (7.2)	6 (5.2)	24 (6.3)	7 (35.0)	
< 9	52 (10.1)	13 (11.2)	37 (9.8)	2 (10.0)	
SAPSII	48.00 [39.00, 59.00]	51.00 [43.00, 61.50]	47.00 [38.00, 59.00]	53.00 [44.75, 62.75]	**0.010**
SOFA	9.00 [6.00, 11.75]	10.00 [6.00, 13.00]	9.00 [6.00, 11.00]	9.00 [7.75, 12.00]	**0.028**
Charlson comorbidity index	6.00 [4.00, 8.00]	7.00 [5.00, 8.00]	6.00 [4.00, 8.00]	5.00 [4.00, 6.25]	**0.018**
Laboratory tests					
Anion gap (mmol/L)	19.00 [15.00, 23.00]	21.00 [17.00, 24.25]	18.00 [14.00, 22.00]	21.00 [15.00, 31.25]	**< 0.001**
Bicarbonate (mmol/L)	19.00 [15.00, 21.00]	17.00 [13.00, 19.00]	19.00 [16.00, 22.00]	16.50 [11.75, 19.50]	**< 0.001**
Chloride (mmol/L)	107.00 [103.00, 110.00]	102.00 [98.00, 106.00]	108.00 [105.00, 110.00]	113.50 [110.50, 120.00]	**< 0.001**
Hematocrit (µmol/L)	25.80 [22.60, 29.87]	26.85 [23.10, 31.05]	25.70 [22.33, 29.50]	24.05 [22.03, 27.00]	0.127
Hemoglobin (g/dL)	8.60 [7.40, 10.00]	9.05 [7.57, 10.22]	8.55 [7.40, 9.88]	7.70 [7.33, 9.23]	0.098
Lactate (mg/dL)	5.70 [4.60, 7.77]	5.90 [4.57, 8.50]	5.70 [4.70, 7.47]	5.55 [4.38, 10.32]	0.942
Platelet (K/µL)	117.00 [73.00, 172.00]	119.00 [56.50, 192.00]	117.00 [77.00, 164.75]	122.50 [74.50, 177.25]	0.997
Potassium (K/µL)	4.70 [4.40, 5.30]	5.00 [4.38, 5.82]	4.70 [4.40, 5.20]	4.50 [4.20, 5.05]	**0.030**
PTT (s)	44.05 [31.13, 65.97]	50.35 [32.00, 78.12]	42.60 [31.02, 62.68]	39.85 [30.28, 59.85]	0.125
INR	1.60 [1.40, 2.20]	1.90 [1.40, 2.62]	1.60 [1.40, 2.00]	2.20 [1.58, 2.62]	**0.002**
PT (s)	18.15 [15.50, 23.65]	20.00 [15.78, 29.10]	17.75 [15.40, 20.98]	24.00 [16.02, 29.05]	**0.004**
Sodium (mEq/L)	136.00 [133.00, 139.00]	130.50 [127.00, 133.00]	137.00 [135.00, 139.00]	143.50 [141.00, 146.50]	**< 0.001**
BUN (mg/dL)	26.00 [17.00, 43.00]	36.50 [19.00, 54.00]	24.00 [16.00, 39.00]	37.50 [19.75, 57.25]	**< 0.001**
WBC (K/µL)	18.40 [13.15, 24.98]	18.30 [12.47, 24.72]	18.45 [13.33, 25.00]	18.10 [13.65, 24.68]	0.978
pO_2 (mmHg)	65.00 [40.00, 86.00]	56.00 [39.00, 81.25]	68.50 [41.00, 89.00]	41.00 [35.75, 72.50]	**0.020**
pCO_2 (mmHg)	48.00 [42.25, 55.00]	46.00 [36.00, 54.00]	48.00 [44.00, 56.00]	44.50 [42.00, 49.00]	**0.004**
pH	7.25 [7.17, 7.31]	7.24 [7.16, 7.31]	7.25 [7.17, 7.31]	7.25 [7.17, 7.30]	0.885
Base excess (mEq/L)	–7.00 [–12.00, –4.00]	–8.00 [–13.00, –6.00]	–7.00 [–11.00, –4.00]	–10.00 [–15.25, –5.00]	**0.019**
MCH (pg)	30.00 [28.60, 31.40]	30.20 [28.67, 31.50]	29.90 [28.60, 31.20]	29.40 [27.35, 30.95]	0.189
MCHC (g/L)	32.40 [31.10, 33.40]	32.60 [30.90, 33.70]	32.30 [31.30, 33.30]	31.90 [30.42, 32.92]	0.114

MCV (fL)	89.00 [85.25, 94.00]	91.00 [86.00, 95.25]	89.00 [85.00, 94.00]	89.50 [84.50, 93.50]	0.218
RDW	15.50 [14.30, 17.50]	16.40 [14.75, 18.70]	15.30 [14.20, 17.10]	16.65 [15.33, 17.52]	**< 0.001**
Creatinine (mg/dL)	1.40 [1.00, 2.20]	1.75 [1.17, 3.00]	1.30 [1.00, 2.00]	1.65 [1.10, 2.40]	**< 0.001**
Treatment measures					
Vasopressor					0.602
No	342 (66.5)	74 (63.8)	256 (67.7)	12 (60.0)	
Yes	172 (33.5)	42 (36.2)	122 (32.3)	8 (40.0)	
Mechanical ventilation					0.618
No	337 (65.6)	80 (69.0)	245 (64.8)	12 (60.0)	
Yes	177 (34.4)	36 (31.0)	133 (35.2)	8 (40.0)	
RRT					0.102
No	479 (93.2)	103 (88.8)	357 (94.4)	19 (95.0)	
Yes	35 (6.8)	13 (11.2)	21 (5.6)	1 (5.0)	
Culture					
Blood	43 (8.4)	10 (8.6)	31 (8.2)	2 (10.0)	0.955
Urine	37 (7.2)	9 (7.8)	27 (7.1)	1 (5.0)	0.904
Sputum	51 (9.9)	15 (12.9)	33 (8.7)	3 (15.0)	0.308
Other	53 (10.3)	17 (14.7)	34 (9.0)	2 (10.0)	0.215
Comorbidity					
Congestive heart failure					0.692
No	340 (66.1)	80 (69.0)	246 (65.1)	14 (70.0)	
Yes	174 (33.9)	36 (31.0)	132 (34.9)	6 (30.0)	
Chronic pulmonary disease					0.701
No	386 (75.1)	90 (77.6)	282 (74.6)	14 (70.0)	
Yes	128 (24.9)	26 (22.4)	96 (25.4)	6 (30.0)	
Renal disease					0.162
No	398 (77.4)	84 (72.4)	296 (78.3)	18 (90.0)	
Yes	116 (22.6)	32 (27.6)	82 (21.7)	2 (10.0)	
Liver disease					**< 0.001**
No	363 (70.6)	61 (52.6)	290 (76.7)	12 (60.0)	
Yes	151 (29.4)	55 (47.4)	88 (23.3)	8 (40.0)	
Diabetes					0.368
No	339 (66.0)	74 (63.8)	249 (65.9)	16 (80.0)	
Yes	175 (34.0)	42 (36.2)	129 (34.1)	4 (20.0)	

LOS, length of stay; MBP, mean blood pressure; GCS, Glasgow Coma Scale; SAPSII, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell; RBC, red blood cell; RDW, red cell distribution width; PTT, partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; BUN, blood urea nitrogen; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RRT, renal replacement therapy. Forms the bold part of the representative data are statistically significant.

tableone (Panos and Mavridis 2020), *mice* (van Buuren and Groothuis-Oudshoorn 2011), *rms* (https://cran.r-project.org/web/packages/rms/index.html), and *survival* (https://github.com/therneau/survival).

Samples in this investigation with missing variable proportions exceeding 20% were excluded, and other missing variables were handled using the Random Forest (RF) method in the *mice* package.

Results

Baseline characteristics

This project included a total of 514 patients with LA complicated by sepsis between 2008 and 2019. Patients were clustered into three groups based on their serum sodium levels upon admission: normal blood sodium (135-145 mEq/L), hyponatremia (< 135 mEq/L), and hypernatremia (> 145 mEq/L). Table 1 displays characteristics. Baseline characteristics uncovered that the median age of patients with LA complicated by sepsis was 69.50 years, with a majority of males (63.8%) and white race (61.5%). Most patients had a GCS score ≥ 13 (82.7%) and no liver disease (70.6%). Three groups of patients with different serum sodium levels exhibited great differences in gender, age, race, hospital mortality, heart rate, breath rate, SpO_2, SAPSII, GCS, SOFA, Charlson comorbidity index, anion gap, bicarbonate level, serum chloride level, serum potas-

Table 2. Participants' characteristics of included patients stratified by trajectory grouping for the GBTM analysis of changes in the 72-h serum sodium.

Characters	Total (N=514)	Class 1 (N=58)	Class 2 (N=429)	Class 3 (N=27)	P-Value
Gender					0.951
Female	186 (36.2)	22 (37.9)	154 (35.9)	10 (37.0)	
Male	328 (63.8)	36 (62.1)	275 (64.1)	17 (63.0)	
Age (years)	69.50 [59.00, 78.00]	**62.50 [56.00, 73.50]**	70.00 [60.00, 78.00]	65.00 [57.50, 77.50]	**0.010**
Race					0.338
White	316 (61.5)	34 (58.6)	267 (62.2)	15 (55.6)	
Black	35 (6.8)	6 (10.3)	25 (5.8)	4 (14.8)	
Otherrace	163 (31.7)	18 (31.0)	137 (31.9)	8 (29.6)	
Marital status					0.308
Married	244 (47.5)	30 (51.7)	202 (47.1)	12 (44.4)	0.761
Unmarried	270 (52.5)	28 (48.3)	227 (52.9)	15 (55.6)	
LOS (day)	4.00 [2.17, 8.68]	5.01 [2.27, 9.74]	3.93 [2.13, 8.57]	4.10 [2.89, 8.44]	0.556
Hospital mortality	258 (50.2)	41 (70.7)	201 (46.9)	16 (59.3)	0.917
Vital signs					
Heart rate (times/min)	90.20 [81.22, 101.89]	**98.61 [85.78, 109.15]**	89.37 [80.72, 100.45]	89.08 [81.46, 106.77]	**0.013**
MBP (mmHg)	72.40 [67.30, 77.35]	72.51 [66.00, 77.56]	72.40 [68.01, 77.04]	71.62 [65.11, 81.44]	0.962
Breath rate (times/min)	19.65 [17.52, 22.99]	21.21 [17.86, 24.83]	**19.39 [17.35, 22.35]**	21.39 [19.31, 23.42]	**0.014**
Temperature (℃)	36.82 [36.49, 37.16]	36.79 [36.36, 37.11]	36.82 [36.50, 37.16]	36.80 [36.46, 37.11]	0.778
SpO_2	97.67 [96.19, 98.76]	97.56 [95.10, 98.59]	97.72 [96.21, 98.78]	96.66 [96.28, 98.21]	0.202
Glucose (mg/dL)	145.72 [125.10, 176.31]	159.24 [120.42, 208.75]	144.40 [126.23, 172.93]	146.75 [120.19, 181.50]	0.774
Severity score					
GCS					**0.019**
≥ 13	425 (82.7)	41 (70.7)	**362 (84.4)**	22 (81.5)	
9-12	37 (7.2)	10 (17.2)	**24 (5.6)**	3 (11.1)	
< 9	52 (10.1)	7 (12.1)	**43 (10.0)**	2 (7.4)	
SAPSII	48.00 [39.00, 59.00]	**54.00 [43.00, 61.00]**	47.00 [38.00, 59.00]	52.00 [44.00, 58.50]	**0.026**
SOFA	9.00 [6.00, 11.75]	**11.00 [7.00, 13.75]**	9.00 [6.00, 11.00]	9.00 [7.50, 11.00]	**0.003**
Charlson comorbidity index	6.00 [4.00, 8.00]	6.00 [5.00, 8.00]	6.00 [4.00, 8.00]	6.00 [3.00, 7.50]	0.437
Laboratory tests					
Initial odium (mEq/L)	138.00 [135.00, 141.00]	**132.00 [126.25, 138.00]**	138.00 [135.00, 141.00]	138.00 [135.50, 140.50]	**< 0.001**
Anion gap (mmol/L)	19.00 [15.00, 23.00]	**21.00 [18.25, 27.75]**	18.00 [14.00, 23.00]	19.00 [16.00, 23.00]	**< 0.001**
Bicarbonate (mmol/L)	19.00 [15.00, 21.00]	**16.00 [11.00, 18.75]**	19.00 [16.00, 22.00]	18.00 [15.00, 21.00]	**< 0.001**
Chloride (mmol/L)	107.00 [103.00, 110.00]	106.50 [101.00, 111.00]	107.00 [103.00, 110.00]	107.00 [100.00, 114.00]	0.993
Hematocrit (μmol/L)	25.80 [22.60, 29.87]	25.25 [21.18, 30.25]	25.80 [22.80, 29.80]	26.40 [23.55, 30.60]	0.530
Hemoglobin (g/dL)	8.60 [7.40, 10.00]	8.55 [6.75, 9.97]	8.60 [7.50, 10.00]	8.60 [7.45, 10.20]	0.554
Lactate (mg/dL)	5.70 [4.60, 7.77]	6.40 [4.73, 11.70]	5.70 [4.60, 7.40]	5.40 [4.90, 6.85]	0.132
Platelet (K/μL)	117.00 [73.00, 172.00]	90.50 [54.00, 161.75]	117.00 [75.00, 173.00]	131.00 [90.50, 160.00]	0.115
Potassium (K/μL)	4.70 [4.40, 5.30]	5.05 [4.50, 5.88]	4.70 [4.40, 5.20]	4.90 [4.45, 5.25]	0.065
PTT (s)	44.05 [31.13, 65.97]	49.35 [32.00, 79.52]	43.60 [31.20, 63.10]	39.40 [30.75, 67.35]	0.513
INR	1.60 [1.40, 2.20]	**1.95 [1.50, 3.05]**	1.60 [1.40, 2.10]	1.60 [1.40, 2.20]	**0.016**
PT (s)	18.15 [15.50, 23.65]	**20.95 [15.90, 31.68]**	17.80 [15.40, 22.30]	17.20 [15.20, 22.70]	**0.022**
Sodium within 72h in ICU (mEq/L)	138.00 [135.00, 141.00]	139.00 [132.00, 144.00]	138.00 [135.00, 140.00]	135.00 [129.50, 141.00]	**< 0.001**
BUN (mg/dL)	26.00 [17.00, 43.00]	36.50 [16.75, 51.00]	25.00 [17.00, 41.00]	29.00 [17.50, 42.50]	0.179
WBC (K/μL)	18.40 [13.15, 24.98]	19.40 [11.95, 25.80]	18.20 [13.10, 24.90]	19.20 [15.90, 23.30]	0.807
pO_2 (mmHg)	65.00 [40.00, 86.00]	49.00 [37.00, 80.50]	67.00 [40.00, 88.00]	58.00 [42.50, 73.50]	0.065
pCO_2 (mmHg)	48.00 [42.25, 55.00]	46.00 [38.25, 53.75]	48.00 [43.00, 55.00]	46.00 [43.00, 56.00]	0.159
pH	7.25 [7.17, 7.31]	7.22 [7.12, 7.30]	7.25 [7.18, 7.31]	7.23 [7.16, 7.33]	0.378
Base excess (mEq/L)	–7.00 [–12.00, –4.00]	**–10.50 [–15.75, –6.00]**	–7.00 [–11.00, –4.00]	–7.00 [–12.00, –3.00]	**0.010**

MCH (pg)	30.00 [28.60, 31.40]	29.95 [28.65, 31.98]	30.00 [28.60, 31.30]	29.20 [27.95, 31.30]	0.619
MCHC (g/L)	32.40 [31.10, 33.40]	32.50 [30.83, 33.77]	32.40 [31.20, 33.30]	31.80 [30.65, 32.75]	0.398
MCV (fL)	89.00 [85.25, 94.00]	89.00 [85.00, 95.00]	89.00 [86.00, 94.00]	90.00 [85.00, 94.00]	0.998
RDW	15.50 [14.30, 17.50]	**17.25 [15.55, 18.85]**	15.30 [14.20, 17.20]	16.20 [14.00, 17.85]	**< 0.001**
Creatinine (mg/dL)	1.40 [1.00, 2.20]	1.65 [1.02, 2.72]	1.30 [1.00, 2.10]	1.50 [0.90, 2.95]	0.203
Treatment measures					
Vasopressor					0.252
No	342 (66.5)	39 (67.2)	289 (67.4)	14 (51.9)	
Yes	172 (33.5)	19 (32.8)	140 (32.6)	13 (48.1)	
Mechanical ventilation					0.491
No	337 (65.6)	37 (63.8)	285 (66.4)	15 (55.6)	
Yes	177 (34.4)	21 (36.2)	144 (33.6)	12 (44.4)	
RRT					0.210
No	479 (93.2)	51 (87.9)	402 (93.7)	26 (96.3)	
Yes	35 (6.8)	7 (12.1)	27 (6.3)	1 (3.7)	
Culture					
Blood	43 (8.4)	5 (8.6)	34 (7.9)	4 (14.8)	0.454
Urine	37 (7.2)	5 (8.6)	31 (7.2)	1 (3.7)	0.715
Sputum	51 (9.9)	8 (13.8)	39 (9.1)	4 (14.8)	0.363
Other	53 (10.3)	6 (10.3)	45 (10.5)	2 (7.4)	0.878
Comorbidity					
Congestive heart failure					0.145
No	340 (66.1)	45 (77.6)	278 (64.8)	17 (63.0)	
Yes	174 (33.9)	13 (22.4)	151 (35.2)	10 (37.0)	
Chronic pulmonary disease					0.773
No	386 (75.1)	45 (77.6)	322 (75.1)	19 (70.4)	
Yes	128 (24.9)	13 (22.4)	107 (24.9)	8 (29.6)	
Renal disease					0.864
No	398 (77.4)	46 (79.3)	332 (77.4)	20 (74.1)	
Yes	116 (22.6)	12 (20.7)	97 (22.6)	7 (25.9)	
Liver disease					**< 0.001**
No	363 (70.6)	20 (34.5)	**323 (75.3)**	20 (74.1)	
Yes	151 (29.4)	38 (65.5)	**106 (24.7)**	7 (25.9)	
Diabetes					0.552
No	339 (66.0)	40 (69.0)	279 (65.0)	20 (74.1)	
Yes	175 (34.0)	18 (31.0)	150 (35.0)	7 (25.9)	

LOS, length of stay; MBP, mean blood pressure; GCS, Glasgow Coma Scale; SAPSII, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell; RBC, red blood cell; RDW, red cell distribution width; PTT, partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; BUN, blood urea nitrogen; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RRT, renal replacement therapy. Forms the bold part of the representative data are statistically significant.

sium level, INR, PT, serum sodium level, BUN, PO_2, PCO_2, base excess, RDW, creatinine and liver disease ($P < 0.05$; Table 1).

Characterization of the serum sodium trajectory

In Supplementary Table S1, the model fit statistics and average posterior probability (AvePP) were provided to determine the optimal number of serum sodium percentile trajectory groups. Finally, three different trajectory groups were identified to meet our criteria: Class 1 (N = 58, 11.3%), Class 2 (N = 429, 83.5%), and Class 3 (N = 27, 5.3%) (Table 2), with AvePP > 0.7 for each trajectory group, indicating good fit.

Demographic and clinical characteristics stratified by serum sodium trajectory group are shown in Table 2. There were notable differences in heart rate, breath rate, age, GCS, SAPSII, initial sodium level, SOFA, anion gap, INR, bicarbonate level, PT, sodium level, base excess, RDW, and liver disease among the 3 trajectory groups ($P < 0.05$). Overall, age, initial sodium level, bicarbonate level, and base excess in Class 1 were considerably lower than the other two groups ($P < 0.05$), while heart rate, SAPSII, SOFA, anion gap, INR, PT, and RDW were considerably higher ($P < 0.05$). In addition, the respiratory rate in Class

2 was remarkably lower. Regarding GCS and liver disease, the number and proportion of patients with GCS ≥ 13 and without liver disease in Class 2 were higher, with 362 (84.4%) and 323 (75.3%) respectively (Table 2). The 72-hour serum sodium trajectories for the three patient groups are shown in Fig. 2, where the serum sodium levels in the Class 2 group remained relatively stable with minimal fluctuations. The violin plots for each class are displayed in Supplementary Fig. S1, and the results also indicated that the serum sodium levels in the Class 2 group were more concentrated.

Serum sodium trajectory and mortality rate

The survival status of patients with different serum sodium trajectories is shown in the K-M survival curve in Fig. 3. Notable differences in survival rates among patients in different serum sodium groups were observed (P = 0.0015), with Class 2 exhibiting the highest 30-day survival rate. Further analysis unearthed that, except for Class 1 and Class 2 ($P < 0.001$), there were no obvious differences in comparisons between any other two groups ($P > 0.05$) (Fig. 3).

In subgroup analysis, the change in Class 2 serum sodium trajectory was consistently associated with a reduced risk of 30-day mortality in patients (Fig. 4, HR: 0.56, 95% CI: 0.40-0.78). Moreover, factors such as race, marital status, GCS, SOFA, RRT, congestive heart failure, kidney disease, liver disease, and diabetes demonstrated great interactions between patients in different serum sodium trajectory groups ($P < 0.05$).

Discussion

LA is common in patients with septic shock or severe sepsis, being implicated in potential pathophysiological changes, drug therapy, and complications (Sendil et al. 2020; Nunnally et al. 2021). Herein, we focused on specific patients with LA complicated by sepsis. In this cohort, using GBTM, we identified three trajectory groups of sodium changes in patients with LA complicated by sepsis, with significant differences observed in the stability of sodium levels at admission and during hospitalization. To our knowledge, this is the first retrospective cohort study on the impact of longitudinal sodium patterns on sepsis patients with LA.

This project revealed three different longitudinal trajectory changes in serum sodium levels and their relationship with the prognosis and mortality risk of sepsis patients with LA. We unearthed many interesting insights through the GBTM model. The results demonstrated that in Class 2, patients had a stable trajectory of blood sodium levels after admission, and their 30-day mortality rate was remarkably better than the other two trajectory groups. Specifically, the relatively stable trajectory of serum sodium levels within the normal range was linked to the favorable prognosis of septic patients. A recent relationship study on serum sodium level trajectory and survival rate in heart failure patients uncovered that patients with normal steady-state changes in serum sodium levels have the highest survival rate (Xia et al. 2023), which is in line with our conclusion. Previous experiments on the association of serum sodium

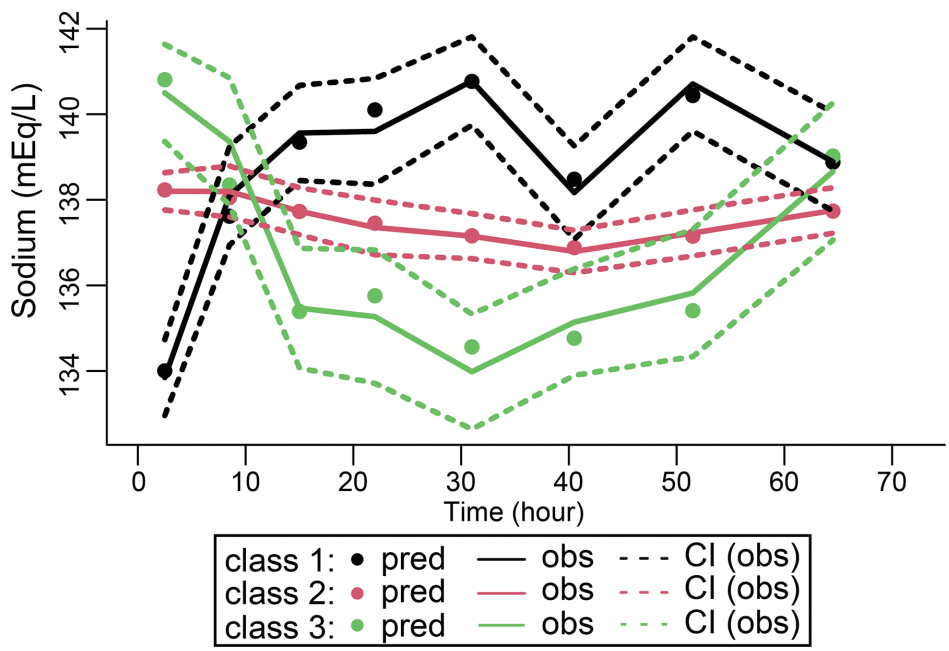

Fig. 2. Three trajectories of the serum sodium based on GBTM.
This graph shows the predicted and observed serum sodium levels over time, divided into three classes: Class 1: Black dots for predictions, solid line for observations, dashed line for CI. Class 2: Pink dots for predictions, solid line for observations, dash-dot line for CI. Class 3: Green dots for predictions, solid line for observations, dash-dot line for CI. Y-axis: Sodium concentration (mEq/L), X-axis: Time (hours).

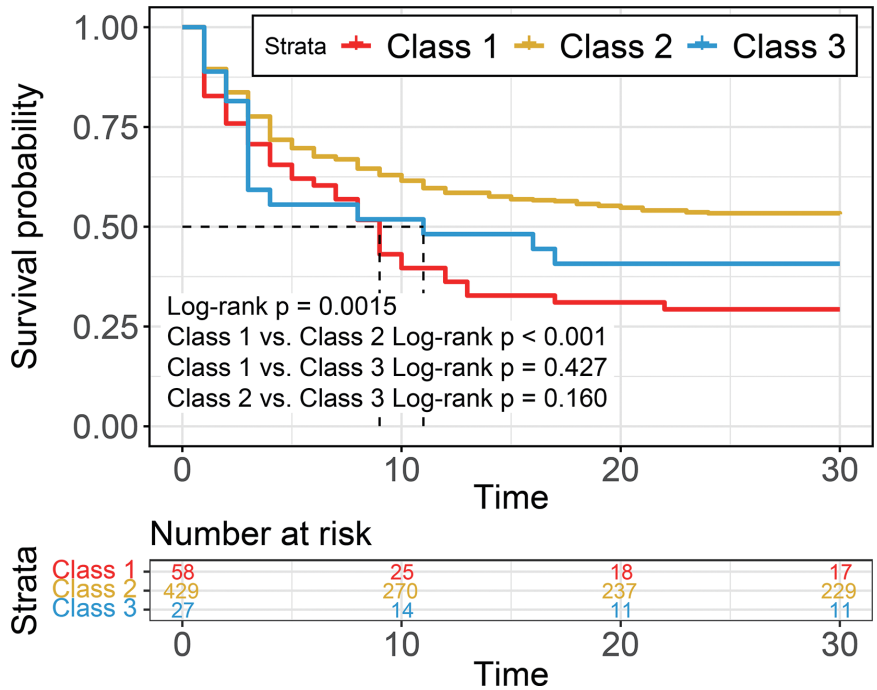

Fig. 3. Survival curves showing the association between the classes and 30-day mortality.
This graph displays survival probability curves over time for differentiating classes and 30-day mortality risk. Class 1: Red line for survival probability.
Class 2: Yellow line for survival probability. Class 3: Blue line for survival probability. The graph also includes Log-rank p-values between classes to assess statistical significance of survival differences. Y-axis: Survival probability (0 to 1). X-axis: Time in days. "Number at risk" shows the number of individuals at risk over time for each class.

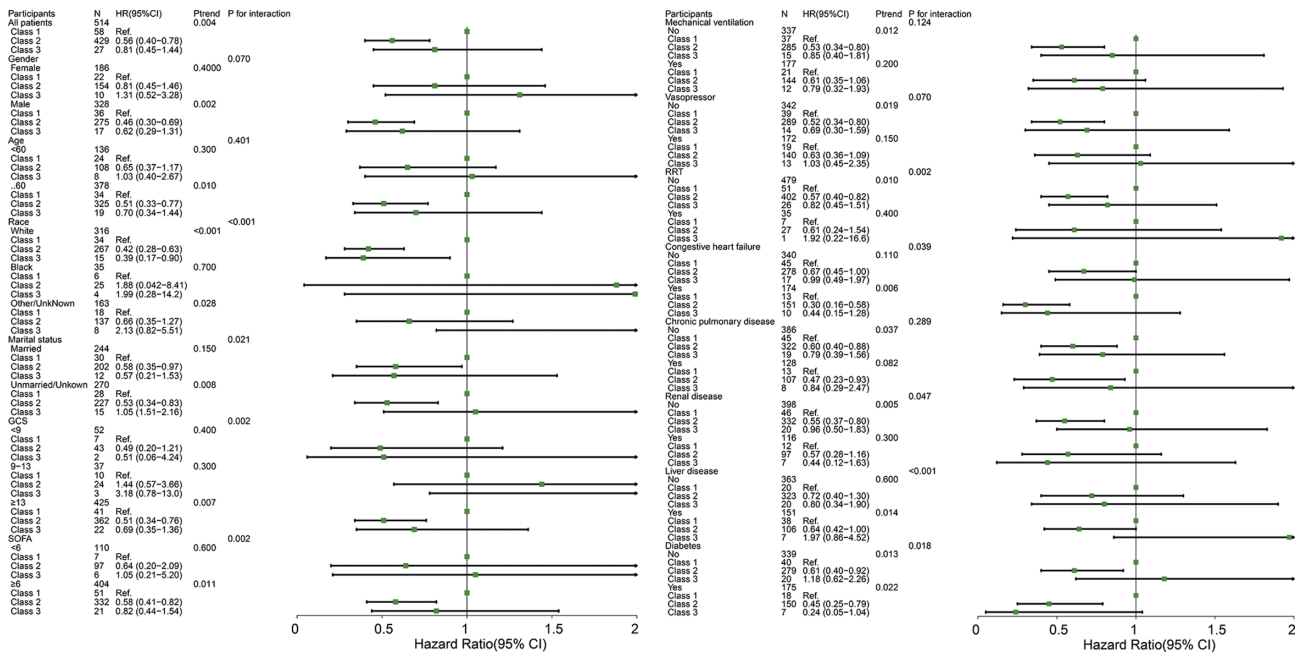

Fig. 4. Subgroup analysis for the association of classes with 30-day mortality.
This figure shows subgroup analysis results linking different classes to 30-day mortality risk. Each forest plot corresponds to an association between a covariate and the classes. In each plot, the x-axis shows the Hazard Ratio (HR) and its 95% CI. Green squares represent HR estimates for each class, with lines indicating the confidence intervals. The plots also show p-values for interactions between covariates and classes. The reference class (Ref.) serves as the baseline for comparing HR estimates of other classes.

levels at admission and discharge with mortality rates of patients have also proven that patients with serum sodium levels between 138-142 mmol/L have the lowest mortality rates (Thongprayoon et al. 2020a, b). In our dynamic serum sodium trajectory changes, we unearthed that in Class 2, the level of serum sodium fluctuated slightly around 138 mmol/L during the first 72 hours of hospitalization, and the 30-day mortality rate was the lowest. The electrolyte levels in the human body are a dynamic process. The dynamic changes seem to be more instrumental in the impact on patient prognosis compared to focusing on the changes in blood sodium levels at a specific time point. By selecting the trajectory of serum sodium changes in septic patients within 72 hours of admission, analyzing possible trajectory subtypes, and determining the impact of different trajectory subtypes on patient mortality, the severity of disease and related risk factors in septic patients with LA were identified, which can proffer a basis and guidance for clinical doctors to diagnose and treatment of such patients.

We further carried out the subgroup analysis based on covariates, finding that ethnicity was a relevant factor affecting the mortality rate of septic patients with LA. The risk of death in white patients was considerably lower than that in black patients. A former study that simultaneously included socioeconomic status and race in sepsis confirmed our results, that is, compared with non-Hispanic white people, the incidence and mortality of sepsis in black people are considerably increased (Minejima and Wong-Beringer 2021), all of which may be attributed to multiple factors such as education, insurance, and income, indicating that in people with lower education, lack of insurance, and lower income, race alone cannot fully explain the differences related to sepsis (Galiatsatos et al. 2019; Minejima and Wong-Beringer 2021). SOFA and GCS scores are well-known scoring models in the ICU, with higher SOFA scores and lower GCS scores before ICU admission associated with increased mortality (Kari et al. 2023). Acute kidney injury is one of the most common organ dysfunctions in sepsis, increasing the risk of adverse outcomes (Kamei et al. 2023). Sodium concentration disorders are common in critically ill patients with possible AKI, many of whom may require dialysis for serum sodium management, with continuous RRT being the preferred dialysis method for patients with severe hyponatremia, hypernatremia, and respiratory distress (Tinawi and Bastani 2021; Yessayan et al. 2021).

Complications have also been studied as predictors of 30-day mortality. Among all trajectory groups, we observed a great interactive correlation of mortality in sepsis patients with congestive heart failure, kidney disease, liver disease, and diabetes. Congestive heart failure, diabetes, kidney disease, and liver disease are the most common comorbidities in sepsis patients, exhibiting an association with increased risk of mortality (Kim and Choi 2020; Bou Chebl et al. 2021; Lindstrom et al. 2021). Previous studies have pointed out that for congestive heart failure patients, high or low levels of serum sodium are linked with increased risk of short-term, medium-term, and long-term all-cause mortality (Peng et al. 2022). Furthermore, this risk relationship has also been detected in other diseases (Lopes-Secundo et al. 2018; Gao et al. 2019; Woyesa et al. 2019).

This project aims to determine the relationship between serum sodium trajectories and adverse prognosis in septic patients with LA, involving GBTM analysis of data obtained from the MIMIC-IV database. We identified the trajectories of serum sodium, characteristics in admission, and outcomes in three different groups of septic patients. Herein, the GBTM was utilized to determine different trajectories of serum sodium in septic patients with LA in the ICU, cluster the population, identify high-risk trajectory populations for adverse outcomes, and determine the characteristic trajectories of adverse serum sodium development trends. This evidence forms a reference basis for clinical doctors to focus on nursing and implementing early intervention measures for key populations in clinical practice. Certain limitations still existed in this project. First, being consistent with the inherent limitations of many large administrative database studies, this project is an observational investigation, only revealing statistical associations with mortality and adverse outcomes. Moreover, based on electronic records of routine clinical practice, since missing data and outliers are common, many pieces of information that could potentially affect the model may not have been collected, which could impact clinical approaches and drug therapies. Therefore, further research is necessary to validate these results. Thirdly, MIMIC-IV is a statistical database with a relatively long period. Catheters for monitoring and treatment methods for serum sodium may have changed over decades, leading to potential biases in the results. Lastly, since this project only included patients from the United States, the relevance of extrapolating these results to ICU patients in other countries remains uncertain.

Conclusion

This study explored the relationship between serum sodium trajectories and prognosis, as well as 30-day mortality, in patients with lactic acidosis complicated by sepsis. By applying the GBTM model, we found that the stability of serum sodium levels was significantly associated with patient outcomes. Specifically, in the Class 2 group, patients maintained relatively stable serum sodium levels after admission, and their 30-day mortality was significantly lower than in the other groups, suggesting that stable serum sodium levels within the normal range are linked to better prognoses. Additionally, we found that factors such as race, SOFA score, GCS score, and acute kidney injury also influenced the risk of death to varying degrees.

Although this study highlights the potential impact of dynamic changes in serum sodium on prognosis and provides important references for early intervention and care in clinical practice, it also has limitations. These include the

limitations of data sources, the inherent drawbacks of observational studies, and the applicability of the results to patients in other countries. Therefore, further research is needed to validate these findings and to explore the management of serum sodium levels in patients of different races and backgrounds.

Author Contributions

Hangyang Li: Conception and design, Data analysis and interpretation, Manuscript writing. Qiongli Zhou: Conception and design, Manuscript writing. Yun Zhang: Administrative support, Data analysis and interpretation. Yuyu Nan and Chengwei Liu: Provision of study materials or patients, Collection and assembly of data. All authors have read and approved the final version of this manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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Supplementary Files

Please find supplementary file(s);
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