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Early body temperature trajectories and short term prognosis in sepsis associated acute kidney injury

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To explore the associations between temperature trajectories and in-hospital mortality and renal replacement therapy in patients with sepsis-associated acute kidney injury (SA-AKI). By using data from the Medical Information Mart for Intensive Care (MIMIC)-IV, participants were divided into three groups (≤ 36 °C, 36–38 °C, ≥ 38 °C). We identified body temperature trajectories by a latent class mixed model and explored the associations of these trajectories with in-hospital mortality using Cox hazard proportional regression models, further exploring the associations with renal replacement therapy using logistic regression models. Total 1,831 in-hospital deaths during 9,760 person-years of follow-up were documented. In the hypothermia group, five different temperature trajectory classes were identified: L1, L2, L3, L4, and L5. Similarly, four trajectory classes (M1, M2, M3, and M4) emerged in the normal temperature group, whereas the hyperthermia group presented four distinct trajectory classes (H1, H2, H3, and H4). Compared with patients with the M3 trajectory, those with the L1 (hazard ratio [HR]: 2.41, 95% confidence interval [CI]: 1.58–3.66), L2 (HR: 1.48, 95% CI 1.11–1.97), L3 (HR: 1.27, 95% CI 1.01–1.59), L4 (HR: 1.29, 95% CI 1.08–1.54), and M1 (HR: 1.29, 95% CI 1.06–1.57) trajectories were at greater risk of in-hospital mortality. For patients with different baseline temperatures, the L1 (HR: 1.95, 95% CI 1.19–3.18), M1 (HR: 1.28, 95% CI 1.05–1.56), and H4 (HR: 2.37, 95% CI 1.05–5.36) trajectories were related to an elevated risk of in-hospital mortality. The study suggests that early body temperature trajectories are linked to increased in-hospital mortality risk in patients with SA-AKI.

Keywords Sepsis-associated acute kidney injury, Temperature trajectories, In-hospital mortality, Renal replacement therapy, Latent class mixed model

Sepsis-associated acute kidney injury (SA-AKI) is a severe and life-threatening complication in critically ill patients that significantly contributes to morbidity and mortality[1,2]. This multifactorial condition is characterized by a rapid decline in kidney function, often accompanied by systemic inflammation, organ dysfunction, and poor outcomes[3,4]. Between 41% and 62.3% of sepsis patients in intensive care units (ICUs) develop AKI, with the rate of mortality in patients with SA-AKI exceeding 50%[5–8]. Furthermore, the presence of both AKI and sepsis notably elevates the risk of ICU and in-hospital mortality[9]. Compared with patients with nonseptic AKI, patients with SA-AKI in the ICU are at greater risk for severe illness, increased mortality, and increased dialysis requirements[9]. Therefore, early identification of SA-AKI is vital for preventing complications, reducing mortality, and improving clinical outcomes.

The kidneys play a crucial role in thermoregulation, and their dysfunction may directly affect the ability to regulate body temperature. Studies have shown that the integrated response of the kidneys under heat stress contributes to thermoregulation, cardiovascular control, and the regulation of water and electrolytes[10]. However, the risk of pathological events in the kidneys increases during heat stress, especially in cases of dehydration and exercise, which may lead to AKI and potentially progress to chronic kidney disease (CKD). This risk is particularly significant in older adults due to changes in renal structure and physiological function that may make them more susceptible to injury during heat stress. Furthermore, hospitalization rates during fever are significantly higher in patients with chronic kidney disease, closely related to renal dysfunction under heat stress. Research indicates that during fever, water and electrolyte imbalance and acute kidney injury are the primary reasons for hospitalization in older adults[11]. Under conditions of heat stress, renal dysfunction can lead to a decline in the ability to regulate body temperature. Studies show that the response of the kidneys to heat stress involves not

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only thermoregulation but also cardiovascular and water-electrolyte regulation[12]. Renal dysfunction can disrupt these regulatory mechanisms, affecting the stability of body temperature. Therefore, maintaining renal function is crucial for normal thermoregulation, especially when facing extreme environmental conditions.

The pathophysiology of SA-AKI is complex and involves a combination of hemodynamic instability, inflammatory mediators, and renal tubular damage[13,14]. Emerging evidence suggests that body temperature may serve as a potential indicator of clinical severity and disease progression[4,15–18]. Early temperature abnormalities may reflect a dysregulated response to infection; fever is often observed as part of the body's inflammatory cascade and associated with lower mortality in sepsis patients[16,19]. In contrast, hypothermia is commonly linked to a higher incidence of AKI[20]. The dynamic fluctuations in body temperature may represent a heterogeneous immune response in patients with sepsis. Several temperature trajectory phenotypes have been identified in sepsis, with varying immune profiles across these phenotypes. Patients with persistently low temperatures have the highest mortality rates, whereas those with initially elevated temperatures followed by rapidly decreasing temperatures have relatively low mortality rates[21,22]. Prognostic models indicate that a higher baseline body temperature is also associated with reduced mortality in ICU patients with SA-AKI[23,24]. Hypothermia has been reported to enhance renal function, potentially preventing or minimizing injury and assisting in renal recovery by reducing metabolic demand, decreasing free radical production, promoting cellular integrity, limiting apoptosis, and exerting anti-inflammatory effects[25,26]. In renal ischemia–reperfusion injury models, sustained hypothermia has been shown to mitigate renal damage[27].

The precise relationship between early temperature trajectories and clinical outcomes in patients with SA-AKI remains adequately defined. This study aimed to address this gap by exploring these associations, thereby contributing to the refinement of prognostic models and development of targeted interventions for patients with SA-AKI.

Methods

Study participants

The present retrospective study utilized the Medical Information Mart for Intensive Care (MIMIC)-IV-ICU-v2.0 database, which includes ICU admission data from critically ill patients at the Beth Israel Deaconess Medical Center (BIDMC) collected between 2008 and 2022. The deidentified data, which were collected during routine clinical care, were processed and made available to qualified researchers who completed the necessary human research ethics training and signed a data use agreement. The Institutional Review Board at BIDMC waived the requirement for informed consent and authorized the sharing of research resources. All the data can be accessed publicly at https://mimic.mit.edu/docs/iv/.

Patients diagnosed with SA-AKI upon their first ICU admission were included in the analysis. Sepsis was identified on the basis of the Sepsis-3 criteria, where patients with a documented or suspected infection and a ≥ 2-point increase in the Sequential Organ Failure Assessment (SOFA) score are classified as septic[1]. Acute kidney injury was diagnosed according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, defined as an increase of 0.3 mg/dl in the serum creatinine (Scr) level within 48 h, a 1.5-fold increase in the Scr level from baseline within the previous 7 days, or a urine output < 0.5 mL/kg/h for 6 h[28]. The exclusion criteria were as follows: (1) an age < 18 years, (2) an ICU stay < 24 h, (3) missing creatinine data, (4) a history of kidney transplant, (5) the presence of end-stage renal disease at ICU admission, (6) the use of renal replacement therapy (RRT) within 24 h of ICU admission, (7) a lack of AKI assessment during follow-up, (8) fewer than three temperature measurements within 24 h of ICU admission, and (9) missing survival information. The detailed selection process is depicted in Fig. 1.

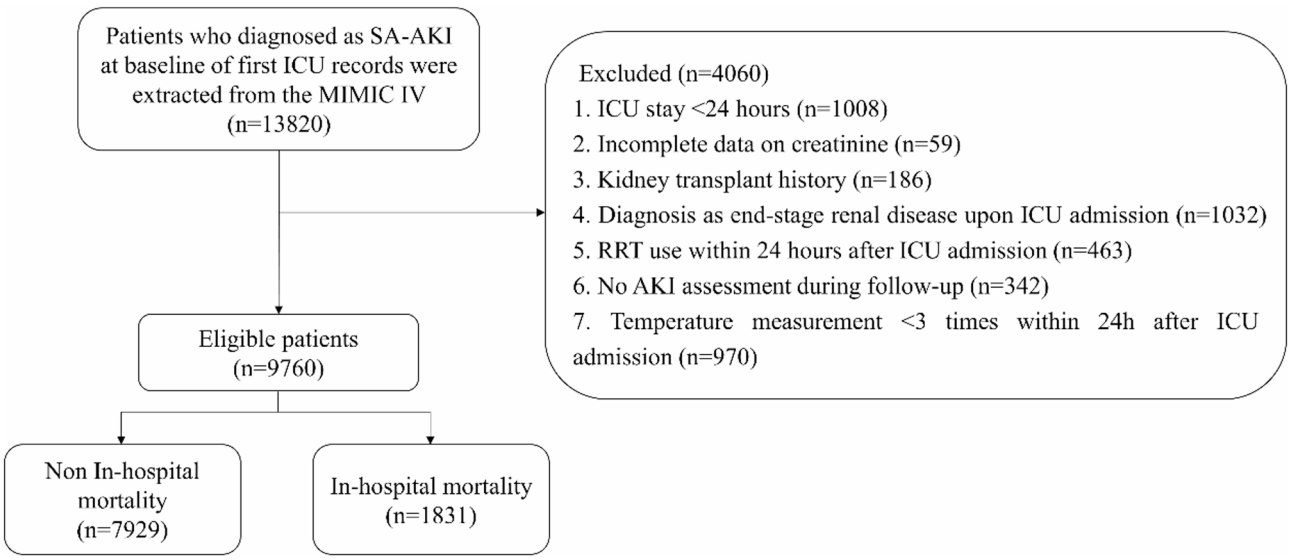

Fig. 1. Selection process for patients with SA-AKI.

Variables	Total ($n=9760$)	Non in-hospital mortality ($n=7929$)	In-hospital mortality ($n=1831$)	Statistics	*P*
Age, years, Mean (± SD)	66.79 (± 15.50)	66.09 (± 15.57)	69.79 (± 14.81)	t′ = − 9.545	< 0.001
Sex, n (%)				$\chi^2 = 9.076$	0.003
Female	4121 (42.22)	3290 (41.49)	831 (45.39)		
Male	5639 (57.78)	4639 (58.51)	1000 (54.61)		
Race, n (%)				$\chi^2 = 88.010$	< 0.001
White	6631 (67.94)	5505 (69.43)	1126 (61.50)		
Black	723 (7.41)	595 (7.50)	128 (6.99)		
Others	1201 (12.31)	966 (12.18)	235 (12.83)		
Unknown	1205 (12.35)	863 (10.88)	342 (18.68)		
Insurance, n (%)				$\chi^2 = 66.543$	< 0.001
Medicare	5863 (60.07)	4654 (58.70)	1209 (66.03)		
Private	2273 (23.29)	1960 (24.72)	313 (17.09)		
Medicaid	1238 (12.68)	1012 (12.76)	226 (12.34)		
Others	237 (2.43)	200 (2.52)	37 (2.02)		
Unknown	149 (1.53)	103 (1.30)	46 (2.51)		
Marital status, n (%)				$\chi^2 = 153.128$	< 0.001
Married	4316 (44.22)	3615 (45.59)	701 (38.29)		
No married	4358 (44.65)	3580 (45.15)	778 (42.49)		
Unknown	1086 (11.13)	734 (9.26)	352 (19.22)		
First care unit, n (%)				$\chi^2 = 489.807$	< 0.001
MICU	4002 (41.00)	2953 (37.24)	1049 (57.29)		
SICU	2551 (26.14)	2074 (26.16)	477 (26.05)		
CVICU	2107 (21.59)	2041 (25.74)	66 (3.60)		
Others	1100 (11.27)	861 (10.86)	239 (13.05)		
Severity AKI stage, n (%)				$\chi^2 = 936.324$	< 0.001
1	1580 (16.19)	1452 (18.31)	128 (6.99)		
2	4960 (50.82)	4414 (55.67)	546 (29.82)		
3	3220 (32.99)	2063 (26.02)	1157 (63.19)		
Urine output 24 h, mL, M (Q_1, Q_3)	857.50 (506.50, 1365.00)	915.00 (557.00, 1438.00)	597.00 (319.50, 1043.50)	W = 9428219.500	< 0.001
SOFA, score, Mean (± SD)	6.20 (± 3.13)	5.76 (± 2.82)	8.11 (± 3.65)	t′ = − 25.840	< 0.001
CCI, score, Mean (± SD)	2.99 (± 2.40)	2.76 (± 2.30)	3.99 (± 2.58)	t′ = − 18.785	< 0.001
Weight, kg, M (Q_1, Q_3)	84.27 (71.30, 98.40)	85.00 (72.44, 99.70)	81.01 (68.00, 93.80)	W = 8235412.000	< 0.001
Heart rate, bpm, Mean (± SD)	91.12 (± 20.81)	89.90 (± 20.29)	96.38 (± 22.16)	t′ = − 11.462	< 0.001
MAP, mmHg, Mean (± SD)	84.18 (± 18.13)	84.24 (± 17.90)	83.91 (± 19.11)	t′ = 0.678	0.498
Respiratory rate, bpm, Mean (± SD)	19.58 (± 6.37)	19.12 (± 6.25)	21.56 (± 6.49)	t′ = − 14.595	< 0.001
SPO_2, %, M (Q_1, Q_3)	98.00 (95.00, 100.00)	99.00 (96.00, 100.00)	97.00 (94.00, 100.00)	W = 8482879.000	< 0.001
WBC, K/uL, M (Q_1, Q_3)	12.30 (8.60, 17.00)	12.10 (8.60, 16.50)	13.30 (8.60, 19.10)	W = 6655917.000	< 0.001
Platelet, K/uL, Mean (± SD)	199.03 (± 113.16)	199.53 (± 109.35)	196.89 (± 128.39)	t′ = 0.812	0.417
RBC, m/uL, Mean (± SD)	3.53 (± 0.78)	3.54 (± 0.76)	3.45 (± 0.86)	t′ = 4.009	< 0.001
Hemoglobin, g/dL, Mean (± SD)	10.58 (± 2.28)	10.64 (± 2.24)	10.35 (± 2.42)	t′ = 4.686	< 0.001
Hematocrit, %, Mean (± SD)	32.30 (± 6.87)	32.38 (± 6.75)	31.93 (± 7.34)	t′ = 2.411	0.016
RDW, %, Mean (± SD)	15.21 (± 2.37)	14.95 (± 2.19)	16.33 (± 2.76)	t′ = − 19.916	< 0.001
eGFR, Mean (± SD)	69.66 (± 30.18)	72.32 (± 29.57)	58.16 (± 30.10)	t = 18.400	< 0.001
INR, ratio, M (Q_1, Q_3)	1.37 (1.20, 1.60)	1.35 (1.20, 1.50)	1.40 (1.20, 1.90)	W = 5766042.500	< 0.001
PT, seconds, M (Q_1, Q_3)	15.20 (13.30, 17.50)	15.08 (13.20, 16.80)	15.80 (13.80, 21.10)	W = 5805875.500	< 0.001
BUN, mg/dL, Mean (± SD)	27.69 (± 19.59)	25.59 (± 17.71)	36.78 (± 24.20)	t′ = − 18.659	< 0.001
Glucose, mg/dL, M (Q_1, Q_3)	138.00 (112.00, 177.00)	137.00 (113.00, 176.00)	138.00 (106.00, 184.00)	W = 7390621.000	0.226
Lactate, mmol/L, M (Q_1, Q_3)	2.00 (1.50, 2.83)	1.93 (1.42, 2.70)	2.30 (1.60, 3.80)	W = 5765148.500	< 0.001
Anion gap, mEq/L, M (Q_1, Q_3)	14.40 (± 4.02)	14.01 (± 3.85)	16.08 (± 4.30)	t′ = − 18.938	< 0.001
Calcium, mg/dL, Mean (± SD)	8.16 (± 0.85)	8.17 (± 0.81)	8.11 (± 0.99)	t′ = 2.156	0.031
Antibiotics, n (%)				$\chi^2 = 5.506$	0.019
No	1896 (19.43)	1504 (18.97)	392 (21.41)		
Yes	7864 (80.57)	6425 (81.03)	1439 (78.59)		
Ventilation, n (%)				$\chi^2 = 0.376$	0.540
No	957 (9.81)	785 (9.90)	172 (9.39)		
Continued					

Variables	Total ($n=9760$)	Non in-hospital mortality ($n=7929$)	In-hospital mortality ($n=1831$)	Statistics	*P*
Yes	8803 (90.19)	7144 (90.10)	1659 (90.61)		
Vasopressor, n (%)				$\chi^2 = 35.338$	< 0.001
No	4926 (50.47)	4117 (51.92)	809 (44.18)		
Yes	4834 (49.53)	3812 (48.08)	1022 (55.82)		
Ibuprofen, n (%)				$\chi^2 = 2.995$	0.084
No	9690 (99.28)	7866 (99.21)	1824 (99.62)		
Yes	70 (0.72)	63 (0.79)	7 (0.38)		
Aspirin, n (%)				$\chi^2 = 147.270$	< 0.001
No	5944 (60.90)	4600 (58.01)	1344 (73.40)		
Yes	3816 (39.10)	3329 (41.99)	487 (26.60)		
Acetaminophen, n (%)				$\chi^2 = 64.299$	< 0.001
No	7590 (77.77)	6037 (76.14)	1553 (84.82)		
Yes	2170 (22.23)	1892 (23.86)	278 (15.18)		
Diuretic, n (%)				$\chi^2 = 13.629$	< 0.001
No	7368 (75.49)	5924 (74.71)	1444 (78.86)		
Yes	2392 (24.51)	2005 (25.29)	387 (21.14)		
Hospital follow time, days, M (Q_1, Q_3)	8.25 (5.15, 14.73)	8.57 (5.28, 15.13)	7.12 (3.60, 13.10)	W = 8648375.500	< 0.001
RRT, n (%)				$\chi^2 = 439.514$	< 0.001
No	9239 (94.66)	7688 (96.96)	1551 (84.71)		
Yes	521 (5.34)	241 (3.04)	280 (15.29)		
Class Kind, n (%)				–	< 0.001
M3	5077 (52.02)	4146 (52.29)	931 (50.85)		
L1	45 (0.46)	21 (0.26)	24 (1.31)		
L2	265 (2.72)	212 (2.67)	53 (2.89)		
L3	564 (5.78)	480 (6.05)	84 (4.59)		
L4	660 (6.76)	516 (6.51)	144 (7.86)		
L5	31 (0.32)	23 (0.29)	8 (0.44)		
M1	394 (4.04)	282 (3.56)	112 (6.12)		
M2	1765 (18.08)	1448 (18.26)	317 (17.31)		
M4	437 (4.48)	372 (4.69)	65 (3.55)		
H1	18 (0.18)	14 (0.18)	4 (0.22)		
H2	188 (1.93)	154 (1.94)	34 (1.86)		
H3	302 (3.09)	254 (3.20)	48 (2.62)		
H4	14 (0.14)	7 (0.09)	7 (0.38)		
Temperature, °C, Mean (± SD)	36.65 (± 0.94)	36.67 (± 0.91)	36.58 (± 1.07)	t′ = 3.075	0.002
Temperature, n (%)				$\chi^2 = 2.063$	0.357
36–38	7673 (78.62)	6248 (78.80)	1425 (77.83)		
< 36	1565 (16.03)	1252 (15.79)	313 (17.09)		
> 38	522 (5.35)	429 (5.41)	93 (5.08)		

Table 1. Characteristics of patients with AS-AKI. *SD* standard deviation; *M* median; Q_1 1st quartile; Q_3 3st quartile. t: Student's t test; t′: Satterthwaite t test; W: Wilcoxon rank sum test; χ^2: Chi-square test; -: Fisher's exact test. SA-AKI: sepsis-associated acute kidney injury, *RRT* renal replacement therapy, *MICU* medical intensive care unit, *SICU* surgical intensive care unit, *CVICU* cardiovascular intensive care unit, *SOFA* sequential organ failure assessment, *CCI* Charlson comorbidity index, *MAP* mean arterial pressure, *WBC* white blood cell count, *RBC* red blood cell count, *RDW* red cell distribution width, *eGFR* estimated glomerular filtration rate, *INR* international normalized ratio, *PT* prothrombin time, *BUN* blood urea nitrogen. Severity AKI stage: the most severe AKI grade during the, Urine output 24h: total urine output within 24 hours after ICU admission.

Measurement of body temperature

Body temperature was measured within the first 24 h of ICU admission. According to many scoring systems (e.g., APACHE II, PIRO, SAPS II, SIRS), body temperature below 36.0 °C or above 38.0 °C are considered equally pathological[1], which values are in accordance with the criteria of the systemic inflammatory response syndrome. In present study, patients were categorized into three groups on the basis of their maximum body temperature during the first 24 h: the hypothermia group (< 36 °C), the normal temperature group (36–38 °C), and the hyperthermia group (> 38 °C)[19]. Body temperature trajectories were determined using a latent class mixed

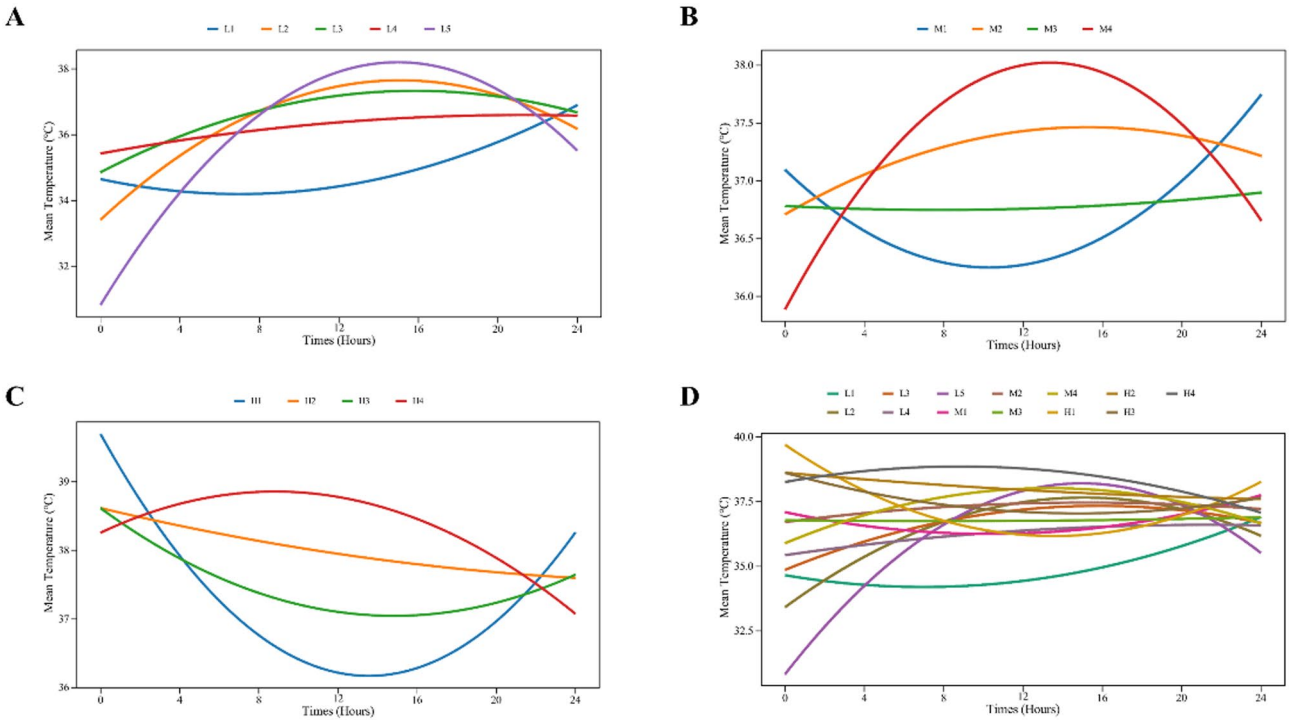

Fig. 2. Body temperature trajectories of patients with SA-AKI. (**A**) for the hypothermia group, (**B**) for the normal temperature group, (**C**) for the hyperthermia group, and (**D**) for the overall dynamic temperature changes.

model (LCMM), which analyzes individual developmental patterns from repeated longitudinal measurements and defines population heterogeneity as a finite number of latent classes[29]. Individuals with similar trajectories are assigned to the same latent class on the basis of the calculated probabilities. These latent classes represent distinct trajectory groups.

Outcomes and follow-up

The primary outcome was in-hospital mortality, whereas the secondary outcome was the receipt of RRT from 24 h after ICU admission to ICU discharge. Follow-up was conducted from admission to the ICU until discharge or death.

Data collection

Structured Query Language (SQL) was used to extract data recorded on the first day of ICU admission. The extracted data included sociodemographic data, vital signs data, first care unit data, laboratory data, pretreatment scoring system data, and data on drugs used during the ICU stay. Sociodemographic data included age, sex, race, insurance status, marital status, and weight. Vital signs data included data on temperature, heart rate, mean arterial pressure (MAP), and respiratory rate. For patients, the first care unit data (Medical Intensive Care Unit [MICU], Surgical Intensive Care Unit [SICU], Cardiac Vascular Intensive Care Unit [CVICU], and others) were also documented. The laboratory data included the white blood cell (WBC) count, platelet count, red blood cell (RBC) count, hemoglobin level, hematocrit level, red cell distribution width (RDW), estimated glomerular filtration rate (eGFR), international normalized ratio (INR), prothrombin time (PT), blood urea nitrogen (BUN) level, glucose level, lactate level, anion gap, and calcium level. The pretreatment scoring systems included the SOFA score and the Charlson Comorbidity Index (CCI). Drugs used during the ICU stay, including antibiotics, vasopressors, ibuprofen, aspirin, acetaminophen, and diuretics, were also recorded. Additionally, SpO_2, AKI severity, 24-hour urine output, RRT use, and first-day ventilation use were included.

Statistical analysis

An LCMM was employed to identify subgroups of patients with SA-AKI exhibiting similar longitudinal temperature trajectories. LCMMs divide heterogeneous populations by estimating latent classes and model individual trajectories using linear mixed models[30,31]. This model calculated the probability of each individual's longitudinal body temperature trend belonging to each potential class, assigning the class with the highest probability. Separate models for Groups 1–3 were fitted in each functional form, with optimal models selected on the basis of the following criteria: (1) the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC); (2) an entropy value > 0.7; (3) group membership > 1% for each class; (4) a posteriori probability > 0.7 for each class; and (5) the clinical significance of the classification.

Variables	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Class kind						
M3	Ref		Ref		Ref	
L1	3.37 (2.25–5.06)	< 0.001	2.43 (1.60–3.69)	< 0.001	2.41 (1.58–3.66)	< 0.001
L2	1.23 (0.93–1.62)	0.144	1.47 (1.11–1.96)	0.008	1.48 (1.11–1.97)	0.007
L3	0.96 (0.77–1.20)	0.710	1.27 (1.01–1.60)	0.042	1.27 (1.01–1.59)	0.043
L4	1.30 (1.09–1.55)	0.003	1.30 (1.08–1.55)	0.005	1.29 (1.08–1.54)	0.005
L5	1.38 (0.69–2.78)	0.360	0.78 (0.38–1.61)	0.505	0.78 (0.38–1.59)	0.488
M1	1.45 (1.19–1.76)	< 0.001	1.29 (1.06–1.57)	0.012	1.29 (1.06–1.57)	0.012
M2	0.86 (0.76–0.98)	0.023	1.04 (0.91–1.19)	0.541	1.05 (0.92–1.19)	0.495
M4	0.85 (0.66–1.09)	0.200	1.27 (0.99–1.64)	0.064	1.28 (0.99–1.66)	0.056
H1	0.86 (0.32–2.30)	0.764	0.71 (0.26–1.90)	0.494	0.72 (0.27–1.93)	0.512
H2	0.72 (0.51–1.02)	0.061	0.93 (0.66–1.32)	0.692	0.94 (0.67–1.34)	0.739
H3	0.75 (0.56-1.00)	0.053	0.81 (0.60–1.09)	0.158	0.81 (0.61–1.09)	0.171
H4	1.91 (0.91–4.03)	0.088	1.71 (0.80–3.64)	0.164	1.73 (0.81–3.68)	0.158
Temperature	0.87 (0.83–0.90)	< 0.001	0.89 (0.85–0.93)	< 0.001	0.89 (0.85–0.93)	< 0.001
Temperature						
36–38	Ref		Ref		Ref	
< 36	1.26 (1.11–1.42)	< 0.001	1.29 (1.14–1.48)	< 0.001	1.29 (1.13–1.47)	< 0.001
> 38	0.79 (0.64–0.98)	0.031	0.84 (0.68–1.04)	0.113	0.84 (0.68–1.05)	0.124

Table 2. Associations of temperature trajectories with in-hospital mortality in all patients with SA-AKI. *HR* hazard ratio; *CI* confidence intervals; *Ref* reference. Model 1was crude model, Model 2 adjusting RRT, age, insurance, marital status, first care unit, severity KAI stage, urine output 24h, SOFA, CCI, weight, heart rate, respiratory rate, SPO2, RBC, hematocrit, RDW, eGFR, PT, BUN, lactate, and anion gap. Model 3 adjusting RRT, age, insurance, marital status, first care unit, severity KAI stage, urine output 24h, SOFA, CCI, weight, heart rate, respiratory rate, SPO2, RBC, hematocrit, RDW, eGFR, PT, BUN, lactate, anion gap, buprofen, aspirin, and acetaminophen.

The normality of continuous data was detected using skewness and kurtosis, whereas homogeneity was detected by the Levene test. Continuous data are presented as the means ± standard deviations (SDs) for normally distributed data and as medians with interquartile ranges (IQRs) for nonnormally distributed data. Categorical data are reported as numbers and percentages (%). For continuous data, Student's t tests, Satterthwaite t tests, and Wilcoxon rank sum tests were performed to evaluate the differences between two groups. Chi-square tests and Fisher's exact tests were used for categorical data comparisons. Missing data were addressed through multiple imputations, followed by a sensitivity analysis before and after imputation. Covariates with a P value < 0.05 in the univariate Cox and logistic regression models were identified as potential confounders. Both univariate and multivariate Cox and logistic regression models incorporating bidirectional stepwise regression were used to examine the relationships between temperature trajectories and in-hospital mortality and RRT use in patients with SA-AKI. Hazard ratios (HRs), odds ratios (ORs), and confidence intervals (CIs) were computed to assess these relationships. Latent class analysis was performed using the R package 'lcmm' in R V.4.3.1, with additional analyses also conducted via R software. A two-tailed P value < 0.05 was considered to indicate statistical significance.

Results

Characteristics of patients with SA-AKI

Among the 9760 individuals included, the median age was 66.79 years (IQR: 51.29–82.29 years), with 5639 (57.78%) male participants. During the 8.25-day (IQR: 3.10-22.98 days) follow-up, 1831 (18.76%) individuals died in the hospital, and 521 (5.34%) participants received RRT during their ICU stay. The mean body temperature was 36.65 (0.94)°C. Compared with patients with SA-AKI without in-hospital mortality, those with in-hospital mortality were more likely to be older, have Medicare insurance, have more severe AKI, use vasopressors, and use RRT. Compared with patients with SA-AKI without in-hospital mortality, those with in-hospital mortality had higher SOFA scores, CCIs, heart rates, WBC counts, and BUN levels and lower 24-hour urine output, SPO_2 levels, and eGFRs (all $P < 0.05$). Table 1 shows more detailed characteristics of the patients with SA-AKI. No significant differences were observed before and after the imputation of data for the missing variables (see Supplementary Tables S1 and S2).

Body temperature trajectories of patients with SA-AKI in the first 24 h after ICU admission

We selected models with latent classes contained in the hypothermia, normal temperature, and hyperthermia groups on the basis of the lowest AIC and BIC values and an entropy value > 0.7. Additionally, the model had mean posterior class membership probabilities ranging between 0.7 and 0.81 and the highest relative entropy

Variables	Model 1		Model 2	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Hypothermia group				
Class kind				
M3	Ref		Ref	
L1	3.56 (2.26–5.61)	< 0.001	1.95 (1.19–3.18)	0.008
L2	1.31 (0.93–1.85)	0.124	1.22 (0.86–1.74)	0.266
L4	1.38 (1.05–1.80)	0.021	1.04 (0.78–1.38)	0.795
L5	1.51 (0.73–3.11)	0.269	0.67 (0.32–1.44)	0.310
Temperature	0.84 (0.77–0.91)	< 0.001	0.93 (0.84–1.02)	0.130
Normal temperature group				
M3	Ref		Ref	
M1	1.45 (1.19–1.76)	< 0.001	1.28 (1.05–1.56)	0.015
M2	0.86 (0.76–0.98)	0.021	1.05 (0.92–1.20)	0.471
M4	0.85 (0.66–1.09)	0.203	1.29 (1.00-1.66)	0.051
Temperature	0.89 (0.85–0.94)	< 0.001	0.92 (0.87–0.97)	0.004
Hyperthermia group				
H3	Ref		Ref	
H1	1.22 (0.44–3.39)	0.700	1.13 (0.40–3.17)	0.814
H2	0.97 (0.62–1.51)	0.892	1.05 (0.67–1.65)	0.824
H4	2.54 (1.13–5.74)	0.024	2.37 (1.05–5.36)	0.039
Temperature	1.16 (0.95–1.41)	0.145	1.20 (0.98–1.47)	0.085

Table 3. Associations of temperature trajectories with in-hospital mortality in SA-AKI patients with different temperature groups. *HR* hazard ratio; *CI* confidence intervals; *Ref* reference. Model 1was crude model, Model 2 covariates were adjusted for three groups: Hypothermia group: Age, race, insurance, marital status, first care unit, severity AKI stage, SOFA, CCI, weight, heart rate, RBC, RDW, PT, BUN, anion gap, acetaminophen. Normal temperature group: RRT, age, insurance, marital status, first care unit, severity KAI stage, SOFA, CCI, weight, heart rate, respiratory rate, SPO2, platelet, RBC, hematocrit, RDW, eGFR, INR, BUN, lactate, anion gap. Hyperthermia group: Age, severity AKI stage, SOFA, acetaminophen.

among the models with different classes, suggesting that this model provided better discrimination. The estimation of the models for a varying number of latent classes is summarized in Supplementary Tables S3 and S4. The different body temperature trajectories of each class are depicted in Fig. 2. In the hypothermia group, five different temperature trajectory classes were identified: L1, L2, L3, L4, and L5. Similarly, four trajectory classes (M1, M2, M3, and M4) emerged in the normal temperature group, whereas the hyperthermia group presented four distinct trajectory classes (H1, H2, H3, and H4). Each trajectory class represented unique patterns of temperature variations within the first 24 h of ICU admission. The overall distribution of trajectory classes varied, with some patients showing rapid temperature increases and others showing gradual decreases or maintaining relatively stable temperature levels.

Associations between body temperature trajectories and in-hospital mortality

Covariates, including RRT use, age, insurance status, marital status, first care unit, AKI severity, 24-hour urine output, SOFA score, CCI, weight, heart rate, respiratory rate, SPO_2 level, RBC count, hematocrit level, RDW, eGFR, PT, BUN level, lactate level, anion gap, ibuprofen use, aspirin use, and acetaminophen use (Supplementary Table S5), were adjusted for. Compared with patients with the M3 trajectory, those with the L1 (HR: 2.41, 95% CI 1.58–3.66), L2 (HR: 1.48, 95% CI 1.11–1.97), L3 (HR: 1.27, 95% CI 1.01–1.59), L4 (HR: 1.29, 95% CI 1.08–1.54), and M1 (HR: 1.29, 95% CI 1.06–1.57) trajectories were at greater risk of in-hospital mortality. Compared with patients with a body temperature between 36 °C and 38 °C, those with a temperature < 36 °C (HR: 1.29, 95% CI 1.13–1.47) had an increased risk of in-hospital mortality (Table 2). This association was further analyzed in patients with SA-AKI with varying baseline temperatures. In the hypothermia group, the L1 (HR: 1.95, 95% CI 1.19–3.18) trajectory was associated with increased in-hospital mortality risk. In the normal temperature group, the M1 (HR: 1.28, 95% CI 1.05–1.56) trajectory was related to elevated in-hospital mortality risk. In the hyperthermia group, the H4 (HR: 2.37, 95% CI 1.05–5.36) trajectory was associated with increased in-hospital mortality risk (Table 3).

Associations between body temperature trajectories and RRT use

Additionally, we examined the links between body temperature trajectories and RRT use. Covariates, including age, marital status, 24-hour urine output, SOFA score, respiratory rate, eGFR, glucose, antibiotics, ventilation, vasopressors, diuretics, ibuprofen use, aspirin use, and acetaminophen use, were adjusted for (Supplementary Table S6). Among all patients with SA-AKI, the M2 (HR: 1.32, 95% CI 1.01–1.73), M4 (HR: 1.65, 95% CI 1.03–2.66), H1 (HR: 4.96, 95% CI 1.38–17.77), and H4 (HR: 6.52, 95% CI 1.74–24.42) trajectories were linked

Variables	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Class kind						
M3	Ref		Ref		Ref	
L1	3.37 (2.25–5.06)	< 0.001	2.43 (1.60–3.69)	< 0.001	2.41 (1.58–3.66)	< 0.001
L2	1.23 (0.93–1.62)	0.144	1.47 (1.11–1.96)	0.008	1.48 (1.11–1.97)	0.007
L3	0.96 (0.77–1.20)	0.710	1.27 (1.01–1.60)	0.042	1.27 (1.01–1.59)	0.043
L4	1.30 (1.09–1.55)	0.003	1.30 (1.08–1.55)	0.005	1.29 (1.08–1.54)	0.005
L5	1.38 (0.69–2.78)	0.360	0.78 (0.38–1.61)	0.505	0.78 (0.38–1.59)	0.488
M1	1.45 (1.19–1.76)	< 0.001	1.29 (1.06–1.57)	0.012	1.29 (1.06–1.57)	0.012
M2	0.86 (0.76–0.98)	0.023	1.04 (0.91–1.19)	0.541	1.05 (0.92–1.19)	0.495
M4	0.85 (0.66–1.09)	0.200	1.27 (0.99–1.64)	0.064	1.28 (0.99–1.66)	0.056
H1	0.86 (0.32–2.30)	0.764	0.71 (0.26–1.90)	0.494	0.72 (0.27–1.93)	0.512
H2	0.72 (0.51–1.02)	0.061	0.93 (0.66–1.32)	0.692	0.94 (0.67–1.34)	0.739
H3	0.75 (0.56-1.00)	0.053	0.81 (0.60–1.09)	0.158	0.81 (0.61–1.09)	0.171
H4	1.91 (0.91–4.03)	0.088	1.71 (0.80–3.64)	0.164	1.73 (0.81–3.68)	0.158
Temperature	0.87 (0.83–0.90)	< 0.001	0.89 (0.85–0.93)	< 0.001	0.89 (0.85–0.93)	< 0.001
Temperature						
36–38	Ref		Ref		Ref	
< 36	1.26 (1.11–1.42)	< 0.001	1.29 (1.14–1.48)	< 0.001	1.29 (1.13–1.47)	< 0.001
> 38	0.79 (0.64–0.98)	0.031	0.84 (0.68–1.04)	0.113	0.84 (0.68–1.05)	0.124

Table 4. Associations of temperature trajectories with receiving RRT in all patients with SA-AKI. *HR* hazard ratio; *CI* confidence intervals; *Ref* reference. Model 1was crude model, Model 2 adjusting age, marital status, urine output 24h, SOFA, respiratory rate, eGFR, glucose, antibiotics, ventilation, vasopressor, and diuretic. Model 3 adjusting age, marital status, urine output 24h, SOFA, respiratory rate, eGFR, glucose, antibiotics, ventilation, vasopressor, diuretic, buprofen, aspirin, and acetaminophen.

to increased odds of receiving RRT (Table 4). In the normal temperature group, the M4 (HR: 1.66, 95% CI 1.03–2.68) trajectory was associated with increased odds of receiving RRT. For the hyperthermia group, the H1 (HR: 5.19, 95% CI 1.04–25.75) and H4 (HR: 5.45, 95% CI 1.03–28.76) trajectories were correlated with a higher incidence of RRT use (Table 5).

Discussion

We found that in patients with SA-AKI, a gradual increase in the hypothermia trajectory (L1), a decrease followed by an increase in the normal trajectory (M1) and an increase followed by a gradual decrease in the hyperthermia trajectory (H4) were both associated with an increased in-hospital mortality risk compared with a stable normal temperature trajectory (M3). With respect to RRT use, the M4, H1, and H4 trajectories, characterized by substantial fluctuations in body temperature, were significantly associated with a higher incidence of RRT use. Our findings agree with those of previous studies that have suggested a link between body temperature abnormalities and adverse outcomes in patients with sepsis.

Our findings align with and build upon previous studies investigating the relationship between body temperature fluctuations and outcomes in patients with sepsis. Research has indicated that both fever and hypothermia can contribute to poor prognosis in sepsis patients, as they are markers of systemic inflammation and underlying physiological dysfunction[32]. Bhavani SV et al.[22] found that hypothermic patients, who had the highest mortality rate, also presented the lowest levels of most pro- and anti-inflammatory cytokines. Similar findings were also reported by Zhao et al.[16], Yang et al.[17], and Doman et al.[18]. Han et al.[33] reported that in hypothermic sepsis patients, an increase of 1 °C or more in body temperature after the initial 6 h was associated with a reduced risk of 28-day mortality, which is similar to our findings. Unlike previous studies that focused primarily on peak or nadir temperature values, our findings underscore the importance of monitoring temperature trends, particularly in the early stage of SA-AKI, to predict patient prognosis more accurately.

The mechanisms underlying the observed associations between temperature trajectories and clinical outcomes in patients with SA-AKI are likely multifactorial and reflect underlying pathophysiological processes in sepsis. Body temperature-related markers, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α levels, is increased in response to infection and inflammation[4,34,35]. Our study indicates that both gradual increases in hypothermic temperature trajectories and fluctuations within the normal range are associated with poorer outcomes, likely due to disrupted thermoregulation and systemic inflammation.

The gradual increase in the hypothermic trajectory (L1) observed in our study may reflect a progressive collapse of the thermoregulatory and immune systems, potentially due to a systemic inflammatory response or inadequate compensatory mechanisms in the context of SA-AKI. In sepsis, hypothermia is often associated with impaired peripheral vasoconstriction and reduced metabolic activity, both of which can contribute to poor organ perfusion and worsening kidney function[33,36]. The increase in temperature following a decrease in the normal trajectory (M1) could signify a dysregulated immune response or an inadequate compensatory mechanism

Variables	Model 1		Model 2	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Hypothermia group				
Class kind				
M3	Ref		Ref	
L1	2.69 (0.98–7.42)	0.055	0.78 (0.25–2.45)	0.668
L2	1.57 (0.84–2.93)	0.156	1.12 (0.55–2.28)	0.751
L4	1.28 (0.76–2.15)	0.352	1.29 (0.73–2.28)	0.390
L5	2.31 (0.66–8.11)	0.192	1.03 (0.24–4.41)	0.973
Temperature	0.82 (0.69–0.96)	0.013	1.10 (0.89–1.37)	0.373
Normal temperature group				
M3	Ref		Ref	
M1	1.90 (1.31–2.77)	0.001	1.39 (0.91–2.12)	0.131
M2	1.20 (0.94–1.52)	0.142	1.29 (0.98–1.70)	0.066
M4	1.22 (0.80–1.87)	0.352	1.66 (1.03–2.68)	0.036
Temperature	1.05 (0.95–1.16)	0.315	1.00 (0.89–1.12)	0.964
Hyperthermia group				
H3	Ref		Ref	
H1	10.17 (3.08–33.59)	< 0.001	5.19 (1.04–25.75)	0.044
H2	2.29 (1.03–5.11)	0.042	1.72 (0.64–4.65)	0.283
H4	10.58 (2.87–39.08)	< 0.001	5.45 (1.03–28.76)	0.046
Temperature	1.37 (1.02–1.83)	0.034	1.21 (0.82–1.78)	0.328

Table 5. Associations of temperature trajectories with receiving RRT in SA-AKI patients with different temperature groups. *HR* hazard ratio; *CI* confidence intervals; Ref: reference. Model 1was crude model, Model 2 covariates were adjusted for three groups: Hypothermia group: Age, urine output 24h, SOFA, platelet, RDW, eGFR, BUN, glucose, anion gap. Normal temperature group: Age, race, marital status, urine output 24h, SOFA, respiratory rate, WBC, eGFR, INR, PT, antibiotics, ventilation, vasopressor, diuretic. Hyperthermia group: Urine output 24h, SOFA, SPO2, eGFR, lactate, calcium

in response to infection, possibly leading to endothelial dysfunction and increased risk for organ failure. Temperature fluctuations, particularly rapid increases or decreases in body temperature, suggest a disturbed immune response and metabolic disturbance, both of which contribute to increased mortality risk in patients with SA-AKI[37,38]. An increase followed by a gradual decrease in the hyperthermia trajectory (H4) showed body temperature trajectory remained above 38 °C for an extended period, indicating persistent high inflammation or hyperdynamic state post-admission. Studies have shown that high temperatures can directly damage renal tubules[39,40], and excessive inflammatory responses can further exacerbate renal ischemia and hypoxia, leading to AKI[39]. Although some believe that fever-induced renal function decline may be a self-protective mechanism to reduce water loss[10], sustained elevation in body temperature still negatively impacts renal function more than positively. In contrast, a stable normal temperature trajectory appears to reflect better immune regulation and organ function, as patients with stable temperatures are less likely to experience drastic alterations in clinical status.

Our findings provide new insights into the utility of temperature monitoring in patients with SA-AKI. Current management strategies for septic patients often focus on addressing the underlying infection and supporting organ function, with temperature monitoring being a routine part of patient assessment. However, our study suggests that early, dynamic changes in temperature, rather than just static temperature measurements, can be critical for identifying patients at high risk for in-hospital mortality and those who need RRT. By integrating temperature trajectory monitoring into routine clinical practice, health care providers may be able to identify high-risk patients earlier, allowing timely interventions to mitigate further organ damage and improve outcomes. Moreover, these findings suggest that interventions aimed at stabilizing body temperature, such as targeted temperature management, might hold promise for improving the prognosis of SA-AKI, although further research is needed to assess the effectiveness of such approaches in this specific cohort.

Several limitations must be acknowledged. First, our study was observational, and while our findings were statistically significant, we cannot draw definitive causal conclusions. The observed associations between temperature trajectories and outcomes may be influenced by unmeasured confounding variables (such as antipyretics or ECMO), which could affect both body temperature and clinical outcomes. Additionally, recent researches indicate that the prognostic significance of temperature patterns may vary significantly across different ICU subgroups[41,42], our findings are based on a specific cohort of patients with SA-AKI, which limits the generalizability of the results to other patient populations or those with different underlying conditions. Further studies examining a broader range of patients and conditions are needed to determine whether body temperature trajectories can serve as universal prognostic markers for other forms of acute kidney injury or sepsis.

In summary, our study suggested that early body temperature trajectories, including a gradual increase in the hypothermia trajectory, a decrease followed by an increase in the normal trajectory and an increase followed by a gradual decrease in the hyperthermia trajectory, were both associated with increased in-hospital mortality risk in patients with SA-AKI. Large fluctuations in temperature, particularly in the normal temperature and hyperthermia trajectories, were associated with the receipt of RRT. These findings highlight the potential role of body temperature trajectories as early indicators of clinical deterioration and emphasize the importance of early monitoring and intervention for patients with SA-AKI. However, further research is needed to validate these associations and explore the underlying mechanisms by which temperature dysregulation influences clinical outcomes in patients with SA-AKI.

Data availability

All data generated or analyzed during this study are available from the MIMIC-Ⅳ.

Received: 8 March 2025; Accepted: 21 August 2025
Published online: 29 August 2025

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Acknowledgements

We would like to thank the Medical Information Mart for Intensive Care IV (MIMIC-Ⅳ) for the offering the related data regarding the paper. Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Author contributions

N.F. and M.Z. designed this study. N.F., Z.S.,T.G. and L.G. analyzed data. Z.S. and N.F. wrote the paper. N.F. and M.Z. revised the manuscript. Z.S., T. G. and L. G. contributed equally as first author in this work.All authors have read and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Consent for publication

Not applicable.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-17170-3.

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