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Utilization of lactate trajectory models for predicting acute kidney injury and mortality in patients with hyperlactatemia: insights across three independent cohorts

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ABSTRACT

This study aims to investigate the association between lactate trajectories and the risk of acute kidney injury (AKI) and hospital mortality in patients with hyperlactatemia. We conducted a multicenter retrospective study using data from three independent cohorts. By the lactate levels during the first 48 h of ICU admission, patients were classified into distinct lactate trajectories using group-based trajectory modeling (GBTM) method. The primary outcomes were AKI incidence and hospital mortality. Logistic regression analysis assessed the association between lactate trajectories and clinical outcomes, with adjusting potential confounders. Patients were divided into three trajectories: mild hyperlactatemia with rapid recovery (Traj-1), severe hyperlactatemia with gradual recovery (Traj-2), and severe hyperlactatemia with persistence (Traj-3). Traj-3 was an independent risk factor of both hospital mortality (all $p<0.001$) and AKI development (all $p<0.001$). Notably, Traj-2 was also associated with increased risk of mortality and AKI development (all $p<0.05$) using Traj-1 as reference, except for the result in the Tianjin Medical University General Hospital (TMUGH) cohort for mortality in adjusted model ($p=0.123$). Our finding was still robust in subgroup and sensitivity analysis. In the combination cohort, both Traj-2 and Traj-3 were considered as independent risk factor for hospital mortality and AKI development (all $p<0.001$). When compared with the Traj-3, Traj-2 was only significantly associated with the decreased risk of hospital mortality (OR 0.17, 95% CI 0.14–0.20, $p<0.001$), but no with the likelihood of AKI development (OR 0.90, 95% CI 0.77–1.05, $p=0.172$). Lactate trajectories provide valuable information for predicting AKI and mortality in critically ill patients.

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Lactate; trajectory; group-based trajectory modeling; hyperlactatemia; mortality; acute kidney injury

1. Introduction

Lactate, a byproduct of anaerobic glycolysis, reflects the extent of tissue and intracellular anaerobic metabolism and is widely recognized as a prognostic biomarker for tissue hypoperfusion, including abnormal peripheral perfusion [1–3]. Elevated lactate levels, typically resulting from tissue hypoxia, have been strongly associated with increased mortality in various clinical settings, including pre-hospital, emergency, and hospital environments [4–7]. Numerous studies have confirmed its prognostic value in conditions like sepsis [8], cardiogenic shock [9], cardiac arrest [10] and poisoning [11]. Hyperlactatemia is particularly prevalent in critically ill patients due to the complexity of their conditions, with an incidence exceeding 35% in ICU populations and severe hyperlactatemia occurring in more than 2% of cases [12,13]. Lactate has long been used to evaluate resuscitation efficacy [3], and with the discovery of Lactylation [14], a novel post-translational modification, lactate has drawn renewed attention.

Recent studies have established that elevated lactate levels exhibit significant associations with both heightened risks of AKI progression and increased mortality rates [15,16]. Furthermore, the emergence of advanced predictive modeling and machine learning methodologies has driven a paradigm shift in clinical research, with contemporary investigations

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increasingly focusing on the integration of multiple critical biomarkers to enhance the precision of outcome prediction systems [17]. While traditional prognostic models rely on static biomarker measurements, trajectory-based models that assess dynamic biomarker changes over time offer a more comprehensive view of a patient's physiological state [18]. Among these, group-based trajectory modeling (GBTM) has emerged as a particularly valuable tool. As a finite mixture modeling approach, GBTM identifies distinct clusters of individuals following similar longitudinal patterns in clinical measures, including symptoms, behaviors, or biomarkers. This categorical framework is especially suited for clinical research where discrete patient classifications are crucial [18]. GBTM enhances precision in understanding developmental pathways and informing targeted interventions by capturing heterogeneity in disease progression, enabling real-time outcome prediction, and addressing complexities like nonrandom attrition. Recent studies indicate that trajectories are more predictive of adverse outcomes, including mortality and organ dysfunction, compared to single-time-point measurements [19–22].

The kidneys play a crucial role in lactate metabolism, acting as both a site of production and clearance [23]. However, acute kidney injury (AKI), a complication in up to 60% of critically ill patients, disrupts renal lactate metabolism, which influences both lactate levels and the severity of AKI through alternating in renal glycolysis and gluconeogenesis [24,25]. Lactate-mediated pathways involved in immune regulation and barrier function also contribute to AKI pathogenesis [26,27]. Elevated lactate levels are strongly associated with increased AKI risk and short-term mortality in AKI patients [5,28]. Lactate clearance rates are also commonly used prognostic biomarkers in clinic.

Despite these findings, the relationship between lactate trajectories and outcomes like AKI and mortality in critically ill patients remains underexplored. Our previous research demonstrated that lactate trajectory, determined by temporal changes in lactate levels, serves as a critical biomarker for risk stratification in acute respiratory distress syndrome (ARDS) patients, with several advantages over single-point measurements [19]. By incorporating both initial lactate levels and post-treatment trends, lactate trajectory offers a more robust predictive tool compared to isolated measurements. Given the unclear association between lactate trajectories and AKI, we aim to investigate this relationship using data from three independent cohorts. These findings may provide novel insights that enhance clinical decision-making and improve ICU outcomes.

2. Materials and methods

2.1. Study design and setting

This study is a multicenter retrospective cohort analysis utilizing data from three independent cohorts: Tianjin Medical University General Hospital (TMUGH), the Medical Information Mart for Intensive Care IV (MIMIC IV) [29], and the eICU Collaborative Research Database (eICU-CRD) [30]. TMUGH is a tertiary care academic hospital located in Tianjin, China. The data were collected from patients admitted to the intensive care unit (ICU) department between November 2021 and June 2023. MIMIC IV Database is a publicly available critical care database includes de-identified health data from the Beth Israel Deaconess Medical Center (BIDMC, Boston, USA) covering the period from 2008 to 2019 [29]. The eICU-CRD database comprises data from multiple ICUs across the United States, including admissions between 2014 and 2015 [30]. Author Yipeng Fang obtained authorized access to MIMIC IV and eICU-CRD databases and was responsible for data extraction in present study (ID: 43025968). We have prepared the current manuscript in accordance with the format required by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [31]. Clinical trial number: Not applicable.

2.2. Ethical approval

As a retrospective study, informed consent was waived. All data were anonymized for protecting the privacy of patients. The MIMIC IV and eICU-CRD datasets have received ethical approval from the Institutional Review Board of the Massachusetts Institute of Technology [29,30]. The overall study protocol was approved by the Ethics Committee of TMUGH (Approval No: IRB2024-YX-431-01).

2.3. Eligibility criteria and participant selection

All patients admitted to the ICU during the study periods from the three datasets (TMUGH, MIMIC IV, and eICU-CRD) were considered as candidates. The eligibility criteria were as follows: (1) Inclusion of all adult patients admitted to the ICU during the study periods; (2) Exclusion of repeated admissions to avoid duplicate records; (3) Exclusion of pediatric patients (under 18 years of age); (4) Exclusion of patients who did not have hyperlactatemia (defined as lactate > 2.0 mmol/L) or lacked lactate measurements within the first 8 h of ICU admission; (5) Exclusion of patients who had only one lactate measurement during their entire ICU stay.

2.4. Outcomes and follow-up

This study did not conduct active follow-up after discharge. Outcomes were assessed based on the patient's condition during their hospital stay and at discharge. The primary outcomes measured were hospital mortality and the development of AKI during their ICU stay. AKI was diagnosed according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, using only the serum creatinine criteria as standard [32]. In short, patients with an increase in serum creatinine by ≥ 0.3 mg/dL within 48 h, or an increase in serum creatinine to ≥ 1.5 times baseline within the prior 7 days was diagnosed as AKI [32]. For patients lacking a baseline serum creatinine level, the first available serum creatinine measurement upon hospital admission was used as the baseline creatinine.

2.5. Variables

In this retrospective study, we included a range of variables such as demographic parameters (age, gender and body weight), comorbidities (hypertension, diabetes, coronary artery disease, acute or chronic heart failure, chronic kidney disease, and chronic liver disease), laboratory parameters (white blood cell count, hemoglobin, platelet count, creatinine, serum sodium, and serum potassium, using the extreme values within the first 48 h of ICU admission), specific interventions (invasive mechanical ventilation and vasopressors exposure within the first 48 h of ICU admission), and severity scores (Acute Physiology and Chronic Health Evaluation II Score [APACHE II] and Acute Physiology Score III [APS III] on the first day of ICU admission, and the highest Sequential Organ Failure Assessment (SOFA) score within the first 48 h of ICU admission).

2.6. Data cleaning

Outliers were defined according to the following standards and treated as missing value: 1) values exceeding three times the standard deviation (SD) from the mean for normally distributed variables; 2) values exceeding 1.5 times the interquartile range (IQR) from the 25th or 75th percentiles for skewed variables. For variables with less than 5% missing, mean and median were used to imputed. For variables with missing percentage between 5% and 20%, random forest imputation was planned; however, no variables in this study fell into this category. Variables with missing data exceeding 20%, such as bilirubin and INR, were excluded from the final analysis.

2.7. Group-based trajectory models analysis

GBTM is a statistical method used to identify distinct groups of individuals following similar developmental trajectories over time, allowing for the classification of patients into subgroups based on their lactate level trends during the ICU stay. In this study, we used GBTM to categorize patients into different trajectory groups based on serial lactate measurements taken during the first 48 h of ICU admission. In this study, lactate measurements were collected at 8-h interval, reflecting the standard ICU practice of performing arterial blood gas analysis every 8 h in our department. To minimize the influence of extreme values, we used the average lactate level within each 8-h interval as the exposure variable. We determined the optimal number of trajectory groups by comparing models with varying numbers of groups using the Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC). In addition to statistical fit, consistency across cohorts and the interpretability of the results were crucial factors in selecting the final model. Patients were assigned to the trajectory groups based on their highest posterior probability, with an average posterior probability of assignment (AvePP) greater than 0.7 considered indicative of robust classification. We aimed to ensure that each trajectory group comprised at least 5% of the patient population to maintain clinical relevance and statistical power [33].

2.8. Statistical methods

We conducted a normality test for continuous data using the Shapiro–Wilk test (Additional file Table S1). Continuous variables were expressed as mean ± SD or median (IQR) and compared using the Student's *t*-test or Mann–Whitney U-test, depending on the distribution. ANOVA or Kruskal–Wallis tests were used for comparing continuous variables across multiple groups. Categorical variables were shown as number (percentage) and further compared using chi-square or Fisher's exact test.

Logistic regression was used to assess the association between different lactate trajectories and the occurrence of AKI and mortality. In multivariate logistic regression analysis, demographic information and comorbidities were adjusted. Subgroup analyses were conducted by stratifying patients based on demographic characteristics and the use of vasopressors. Patients were divided into older and younger groups according to the mean value of age, and also divided into obesity and thinness according to the medium value of body weight.

Since death and chronic kidney disease (CKD) may influence the association between lactate and AKI development, we excluded non-survival patients and those with chronic kidney disease CKD for sensitivity analysis to further validate the association between different lactate trajectories and the odds of developing AKI. To further eliminate effect of confounders on the results, propensity score matching (PSM) was performed to balance baseline characteristics, including demographics and comorbidities, between the trajectory groups using a 1:1 nested matching method without replacement with a caliper width of 0.05 [34].

A *P*-value < 0.05 was considered statistically significant. All analyses were performed using Stata 15.0 SE software.

3. Results

3.1. Population selection and trajectory decision

As shown in Figure 1, a total of 3000 patients admitted to the ICU at TMUGH from November 2021 to June 2023 were initially included in the study. After applying exclusion criteria, 943 patients remained for analysis. Similarly, in the MIMIC IV and eICU-CRD cohorts, 7925 and 7477 patients were included in the final analysis after exclusions. We summarized the number of trajectories identified in each cohort (Additional file Figure S1) and the corresponding parameters (Additional file Table S2). Based on these parameters, along with the consistency across cohorts and the interpretability of the results, we determined that a model with three distinct trajectories was optimal (Figure 2 and Additional file Table S3).

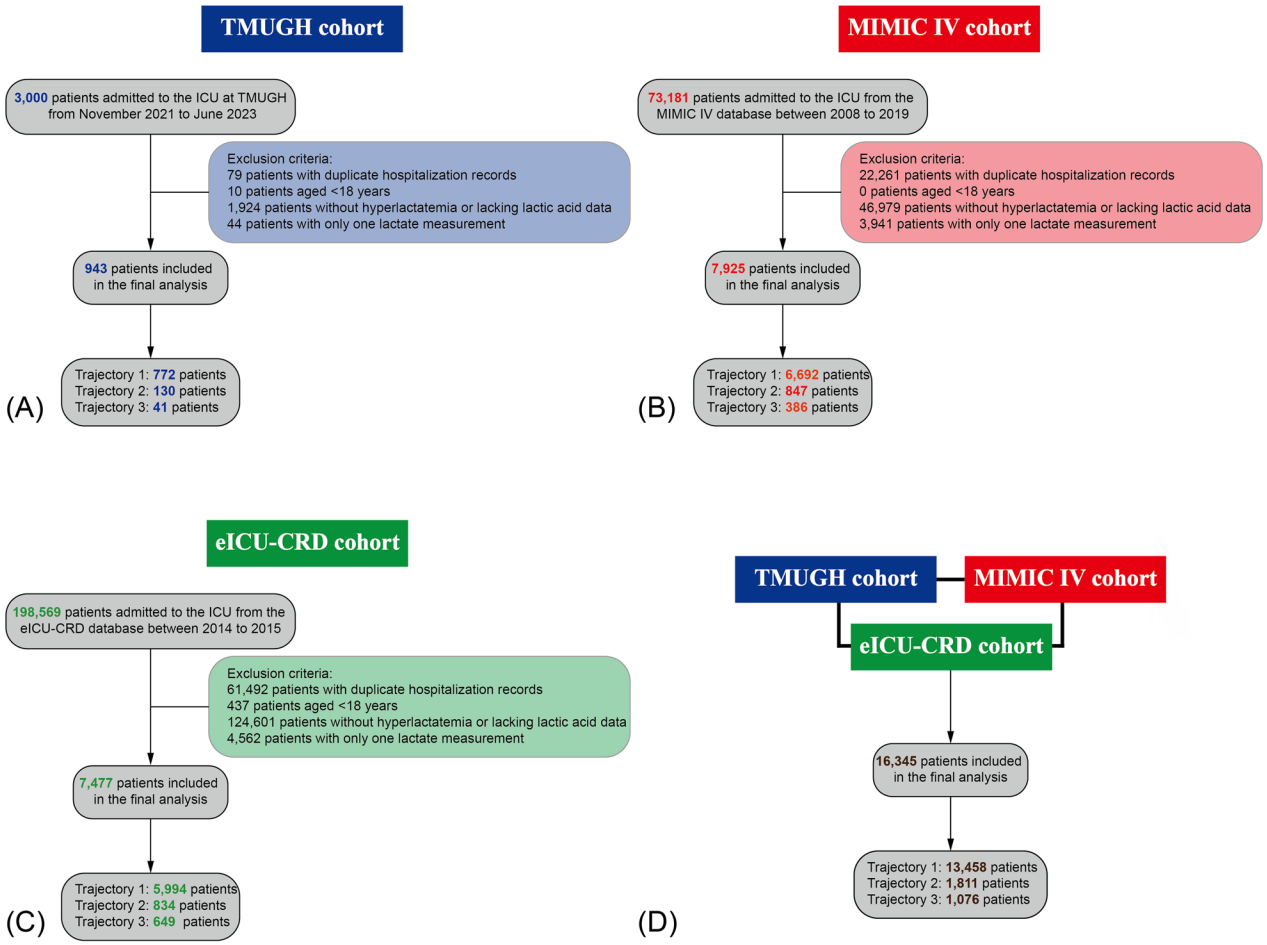

Figure 1. The flow chart of present study.

- Traj-1: Mild hyperlactatemia with rapid recovery– This lactate trajectory exhibited mild hyperlactatemia, with lactate levels returning to the normal range within 24 hours.
- Traj-2: Severe hyperlactatemia with gradual recovery – This lactate trajectory showed severe hyperlactatemia, with lactate levels gradually decreasing to the normal range over 48 hours.
- Traj-3: Severe hyperlactatemia with persistence – This lactate trajectory is characterized by severe hyperlactatemia, with consistently elevated lactate levels persisting for the full 48-hour period.

The patients were categorized into three lactate trajectories in the TMUGH cohort: Traj-1 ($n=772$), Traj-2 ($n=130$) and Traj-3 ($n=41$). The MIMIC IV cohort was divided into Traj-1 ($n=6692$), Traj-2 ($n=847$) and Traj-3 ($n=386$), while the eICU-CRD cohort was categorized into Traj-1 ($n=5994$), Traj-2 ($n=834$) and Traj-3 ($n=649$). A Sankey diagram was utilized to illustrate the relationships between various trajectories and both AKI and hospital mortality (shown in Figure 2D).

3.2. Baseline characteristics and outcomes between AKI and non-AKI patients

As shown in Table 1, the results showed that AKI patients were generally older (all $p<0.001$), had higher incidences of comorbidities such as coronary heart disease, heart failure and chronic kidney disease, and presented with more severe laboratory abnormalities, such as higher white blood cell counts, lower platelet levels, and higher creatinine and lactate levels. Additionally, AKI patients had significantly higher scores on disease severity scales compared to non-AKI patients (all $p<0.001$). Notably, in all three cohorts, patients with AKI had significant higher hospital morality rates than non-AKI patients (21.57% vs. 4.33% in TMUGH, 30.14% vs. 9.48 in MIMIC IV, 35.75% vs. 23.44% in eICU-CRD, all $p<0.001$). Similarly, patients in the AKI subgroups had longer hospital and ICU-LOS compared to non-AKI subgroups (all $p<0.001$).

3.3. Different lactate trajectories and clinical outcomes

As shown in Table 2, the trajectory groups showed significant differences in AKI incidence and hospital mortality across all cohorts. Specifically, in the TMUGH cohort, the overall incidence of AKI was 16.58% in Traj-1, 39.23% in Traj-2 and 60.98% in Traj-3 ($p<0.001$). In both the survival and non-CKD cohorts, patients in Traj-3 had the highest incidence of AKI following by Traj-2 and Traj-1 (all $p<0.001$). Hospital-mortality rates were 4.53%, 12.31% and 60.98% for Traj-1, Traj-2 and Traj-3, respectively ($p<0.001$). These trends were consistent in the MIMIC IV and eICU-CRD cohorts, where higher lactate trajectories were associated with

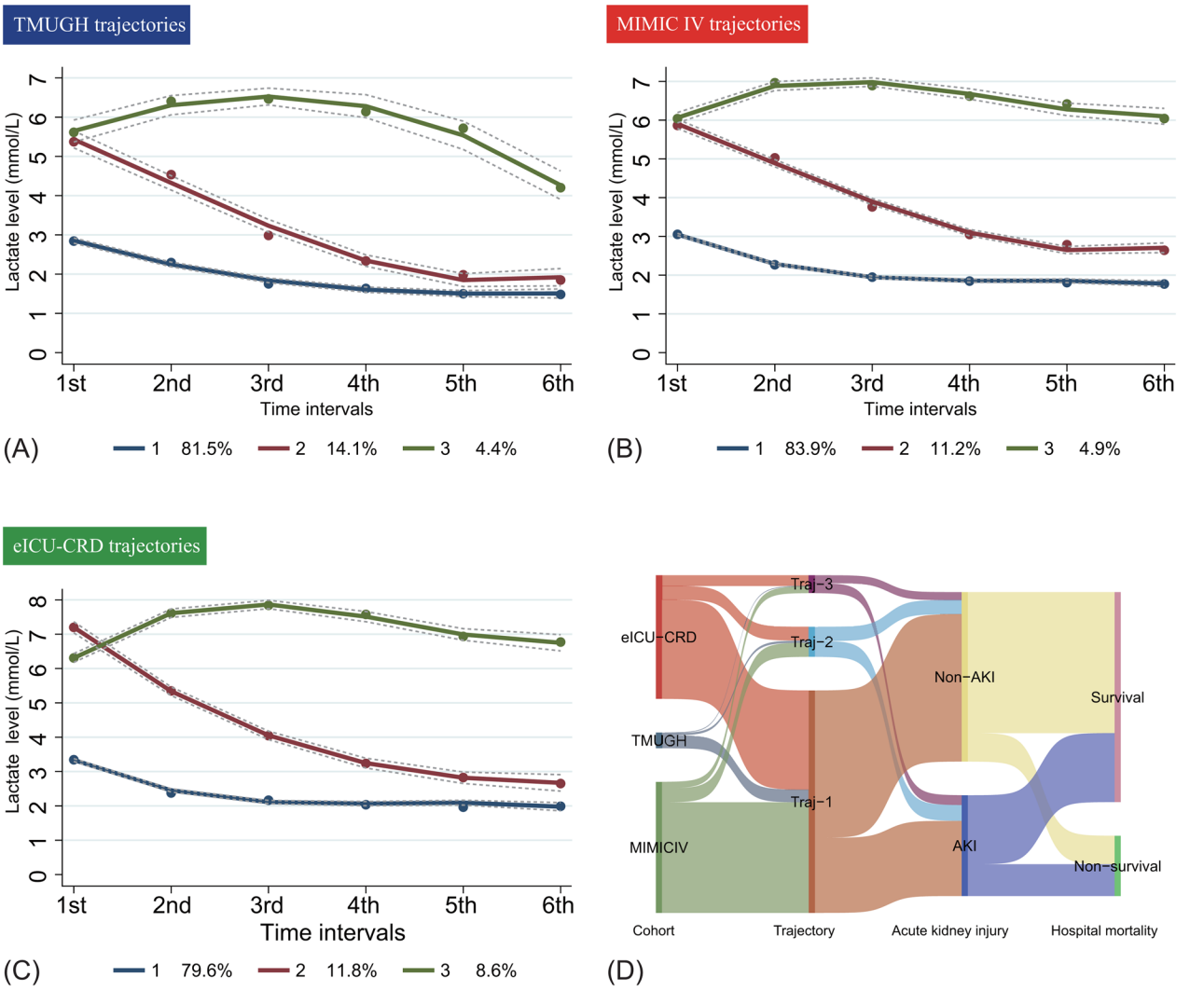

Figure 2. Lactate-based trajectories and Sankey diagram in patients with hyperlactatemia from different cohorts. (A–C) The lactate-based trajectories from the TMUGH, MIMIC IV and eICU-CRD cohorts. (D) The Sankey diagram about the association between different trajectories and the prognosis.

significantly higher incidence of AKI and hospital-mortality ($p < 0.001$ for all comparisons).

3.4. Logistic regression analysis

As shown in Table 3, with Traj-1 as reference, Traj-2 was significantly associated with a higher risk of hospital mortality in univariate logistic regression model (crude OR 2.96, 95% CI 1.58-5.51, $p < 0.001$), but no significance was found in the multivariate model in the TMUGH cohort (adjusted OR 1.74, 95% 0.86-3.50, $p = 0.123$). In both MIMIC IV and eICU-CRD cohorts, Traj-2 was an independent risk factor for hospital mortality in univariate and multivariate models (all OR > 1, all $p < 0.001$). In all three cohorts, Traj-3 was significantly associated with a 1170%-3290% increased risk of mortality compared to Traj-1 (OR 11.70-32.90, all $p < 0.001$). In the terms of AKI, both Traj-2 and Traj-3 was significantly associated with an increased likelihood of AKI (OR 2.50, 95% 1.60-3.91 for Traj-2, OR 5.45, 95% 2.67-11.12 for Traj-3, all $p < 0.001$), taking Traj-1 as reference. Similar findings were observed in the MIMIC IV and eICU-CRD cohorts, with Traj-2 and Traj-3 showing the increased odds for AKI in both univariate and multivariate models (all OR > 1, all $p < 0.001$).

3.5. Sensitivity analysis

As death and the existed CKD might influence the potential association between the trajectories and likelihood of AKI development, we further detected their association in the survival and the non-CKD cohorts. All evidences supported that Traj-2 and Traj-3 significantly associated with the increased odds of AKI development with Traj-1 as reference (all OR > 1, all $p < 0.01$, shown in Additional file Table S4)

We also performed PSM method to eliminate the effect of imbalanced confounders. As shown in Additional file Tables S5–S7, no significant difference was found in baseline information between Traj-1 and Traj-2 (all $p > 0.05$). And similar results were found between Traj-1 and Traj-3 (all $p > 0.05$) in all three cohorts. After balancing confounders, we obtained similar tendency that we observed in the original logistic

Table 1. Baseline characteristics and outcomes between AKI and non-AKI patients.

	TMUGH cohort			MIMIC cohort			eICU-CRD cohort		
Variable	Non-AKI	AKI	*P*-value	Non-AKI	AKI	*P*-value	Non-AKI	AKI	*P*-value
Number	739	204		3,880	4,045		5,631	1,846	
Age (years)	64 (54,70)	67 (57,76)	<0.001	66 (55,77)	68 (57,79)	<0.001	64 (52,76)	66 (55,77)	<0.001
Male (%)	418 (56.56)	135 (66.18)	0.014	2,238 (57.68)	2,434 (60.17)	0.024	3,094 (54.95)	1,032 (55.90)	0.472
Weight (kg)	68 (60,75)	69 (60,75)	0.632	79 (67,93)	81 (69,97)	<0.001	79 (66,96)	82 (68,100)	<0.001
Comorbidity									
Coronary heart disease (%)	163 (22.06)	73 (35.78)	<0.001	1,302 (33.56)	1,460 (36.09)	0.018	763 (13.55)	287 (15.55)	0.032
Heart failure (%)	139 (18.81)	85 (41.67)	<0.001	848 (21.86)	1,324 (32.73)	<0.001	695 (12.34)	257 (13.92)	0.077
Hypertension (%)	357 (48.31)	126 (61.76)	0.001	1,859 (47.91)	1,609 (39.78)	<0.001	2,255 (40.05)	806 (43.66)	0.006
Diabetes mellitus (%)	162 (21.92)	57 (27.94)	0.071	1,227 (31.62)	1,370 (33.87)	0.033	1,649 (29.28)	599 (32.45)	0.010
Chronic kidney disease (%)	60 (8.12)	79 (38.73)	<0.001	458 (11.80)	1,018 (25.17)	<0.001	513 (9.11)	224 (13.13)	<0.001
Liver disease (%)	141 (19.08)	64 (31.37)	<0.001	502 (12.94)	1,027 (25.39)	<0.001	343 (6.09)	169 (9.15)	<0.001
Laboratory parameter									
White blood cell (k/uL)	13.4 (10.8,16.6)	16.2 (12.0,19.8)	<0.001	14.9 (11.2,19.2)	16.0 (12.4,20.5)	<0.001	14.2 (11.0,19.0)	14.6 (11.2,19.4)	<0.001
Hemoglobin (g/dL)	93 (77,109)	71 (62,85)	<0.001	9.3 (8.0,10.8)	8.6 (7.5,10.1)	<0.001	9.8 (8.1,11.4)	9.7 (8.1,11.3)	0.355
Platelets (k/uL)	145 (94,197)	87 (46,132)	<0.001	131 (97,178)	109 (70,159)	<0.001	139 (91,190)	120 (72,175)	<0.001
Creatinine (mg/dl)	0.8 (0.6,1.1)	1.8 (1.1,2.4)	<0.001	1.0 (0.8,1.3)	1.5 (1.1,2.2)	<0.001	1.2 (0.9,1.7)	1.9 (1.2,2.6)	<0.001
Sodium (mmol/L)	140.09 ± 4.08	144.49 ± 5.56	<0.001	141.01 ± 5.04	140.94 ± 5.43	0.542	141.71 ± 5.64	141.79 ± 5.70	0.610
Potassium (mmol/L)	4.47 ± 0.42	4.94 ± 0.35	<0.001	4.63 ± 0.66	5.02 ± 0.84	<0.001	4.50 ± 0.64	4.70 ± 0.68	<0.001
#Lactic acid (mmol/L)	2.8 (2.3,3.6)	3.4 (2.4,4.9)	<0.001	3.2 (2.6,4.3)	3.8 (2.9,5.5)	<0.001	3.4 (2.6,4.7)	3.7 (2.7,5.5)	<0.001
Intervention									
Mechanical ventilation (%)	675 (91.34)	174 (85.29)	0.011	2,189 (56.42)	3,009 (74.39)	<0.001	2,611 (46.37)	879 (47.62)	0.351
Vasoactive drug (%)	206 (27.88)	127 (62.25)	<0.001	1,396 (35.98)	2,443 (60.40)	<0.001	1,848 (32.82)	943 (51.08)	<0.001
Disease severity score									
APACHEII score	13 (10,16)	21 (17,26)	<0.001				17 (13,24)	21 (16,28)	<0.001
SOFA score	4 (3,8)	9 (7,11)	<0.001	6 (4,8)	9 (6,13)	<0.001	5 (2,7)	6 (4,9)	<0.001
APSIII score				43 (32,61)	68 (49,92)	<0.001			
Outcomes									
Hospital mortality (%)	32 (4.33)	44 (21.57)	<0.001	368 (9.48)	1,219 (30.14)	<0.001	1,320 (23.44)	660 (35.75)	<0.001
Hospital LOS (days)	18.9 (12.9,27.0)	20.9 (12.0,33.3)	0.189	7.3 (5.0,11.4)	11.4 (6.5,19.4)	<0.001	7.4 (4.1,13.3)	8.7 (4.3,15.5)	<0.001
ICU LOS (days)	1.5 (0.8,2.8)	6.7 (3.6,12.4)	<0.001	2.2 (1.3,3.7)	4.7 (2.5,9.5)	<0.001	2.9 (1.6,5.6)	3.9 (2.0,7.7)	<0.001

Abbreviation: APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; APS III: Acute Physiology Score III; LOS: Length of Stay.

regression model (shown in Additional file Table S8). Traj-2 and Traj-3 were still associated with the increased odds of mortality and AKI in both three cohorts (all OR > 1, all $p < 0.001$), except for Traj-2 in the TMUGH for hospital mortality ($p = 0.223$).

3.6. Subgroup analysis

Our subgroup analysis explored the impact of patient characteristics, such as age, sex, weight, and use of vasoactive drugs, on the associations between lactate trajectories and patient outcomes (shown in Figure 3). These relationships were robust across all subgroups, consistently showing that both Traj-2 and Traj-3 were associated with a higher likelihood of AKI occurrence and hospital mortality compared to Traj-1 (all OR > 1). We observed a significant interaction between age and lactate trajectory in the TMUGH and MIMIC IV cohorts (all *P* for interaction <0.05). Specifically, in the younger population within the TMUGH cohort, the association between Traj-2 and AKI risk was more pronounced (OR 4.98, 95% CI: 2.38-10.41) compared to older patients (OR 1.67, 95% CI: 0.95-2.95). In contrast, in the MIMIC IV cohort, the association between Traj-3 and AKI risk was stronger in the younger population (OR 8.84, 95% CI: 5.47-14.30) compared to the older population (OR 3.98, 95% CI: 2.79-5.69). In the eICU cohort, we observed an interaction between the use of vasoactive drugs and lactate trajectory (*P* for interaction = 0.041 for Traj-1 vs. Traj-2), where Traj-2 was associated with a higher likelihood of hospital mortality regardless of vasoactive drug use.

3.7. Combined analysis of multiple cohorts

A combined analysis using logistic regression across all cohorts (Table 4) confirmed that both Traj-2 and Traj-3 were strongly predictive of increased risks for both AKI and hospital mortality (all OR> 1, $p < 0.001$), with Traj-1 as reference. The associations between lactate trajectories and AKI persisted even in the survivals and non-CKD cohorts (all OR > 1, $p < 0.001$). After adjusting potential confounders, these association still existed (all adjusted OR > 1, $p < 0.001$). However, when compared with the Traj-3, Traj-2 only significantly associated with the decreased risk of hospital morality (OR 0.17, 95% CI 0.14–0.20, $p < 0.001$), but not with the likelihood of AKI development (OR 0.90, 95% CI 0.77–1.05, $p = 0.172$).

Table 2. Clinical outcomes between different trajectories of lactate.

	Traj-1	Traj-2	Traj-3	*P*-value
TMUGH cohort				
Number	772	130	41	
AKI (%)				
Overall	128 (16.58)	51 (39.23)	25 (60.98)	<0.001
Alive	107 (14.52)	45 (39.47)	8 (50.00)	<0.001
Without CKD	77 (11.32)	32 (32.99)	16 (59.26)	<0.001
Hospital mortality (%)	35 (4.53)	16 (12.31)	25 (60.98)	<0.001
Hospital LOS (days)	19 (13,36)	21 (13,36)	15 (12,26)	0.119
ICU LOS (days)	1.8 (0.8,3.8)	3.4 (1.5,6.9)	6.0 (1.9,12.5)	<0.001
Vasoactive drug (%)	217 (28.11)	83 (63.85)	33 (80.49)	<0.001
SOFA score	5 (3,8)	9 (6,11)	11 (10,15)	<0.001
MIMIC IV cohort				
Number	6692	847	386	
AKI (%)				
Overall	3,096 (46.26)	624 (73.67)	325 (84.20)	<0.001
Alive	2,407 (41.93)	358 (68.32)	61 (82.43)	<0.001
Without CKD	2,281 (41.77)	484 (71.18)	262 (85.06)	<0.001
Hospital mortality (%)	952 (14.23)	323 (38.13)	312 (80.83)	<0.001
Hospital LOS (days)	8.8 (5.6,14.7)	11.4 (5.7,21.2)	4.1 (1.5,14.2)	<0.001
ICU LOS (days)	3.0 (1.8,5.6)	5.3 (2.7,11.3)	2.2 (1.2,6.2)	<0.001
Vasoactive drug (%)	2,886 (42.83)	634 (74.85)	339 (87.82)	<0.001
SOFA score	7 (4,10)	12 (8,14)	14 (11,16)	<0.001
eICU cohort				
Number	5994	834	649	
AKI (%)				
Overall	1,322 (22.06)	279 (33.45)	245 (37.75)	<0.001
Alive	957 (19.93)	169 (31.89)	60 (36.36)	<0.001
Without CKD	1,149 (21.20)	257 (34.22)	216 (38.03)	<0.001
Hospital mortality (%)	1,192 (19.89)	304 (36.45)	484 (74.58)	<0.001
Hospital LOS (days)	7.9 (4.6,13.8)	8.7 (4.2,16.4)	3.2 (1.7,10.5)	<0.001
ICU LOS (days)	3.1 (1.7,5.9)	4.0 (2.1,7.8)	2.2 (1.2,5.7)	<0.001
Vasoactive drug (%)	1,946 (32.47)	418 (50.12)	427 (65.79)	<0.001
SOFA score	4 (2,7)	7 (5,9)	8 (6,11)	<0.001

Abbreviation: AKI: Acute Kidney Injury; CKD: Chronic Kidney Disease; LOS: Length of Stay; SOFA: Sequential.

Table 3. Predictive value of different lactate trajectories for AKI and hospital mortality.

	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
TMUGH cohort				
Hospital mortality				
Traj-2 vs. Traj-1	2.96 (1.58–5.51)	0.001	1.74 (0.86–3.50)	0.123
Traj-3 vs. Traj-1	32.90 (16.12–67.14)	<0.001	28.26 (12.44–64.22)	<0.001
AKI				
Traj-2 vs. Traj-1	3.25 (2.18–4.85)	<0.001	2.50 (1.60–3.91)	<0.001
Traj-3 vs. Traj-1	7.86 (4.08–15.14)	<0.001	5.45 (2.67–11.12)	<0.001
MIMIC IV cohort				
Hospital mortality				
Traj-2 vs. Traj-1	3.72 (3.18–4.34)	<0.001	3.49 (2.98–4.10)	<0.001
Traj-3 vs. Traj-1	25.42 (19.55–33.05)	<0.001	22.50 (17.21–29.42)	<0.001
AKI				
Traj-2 vs. Traj-1	3.25 (2.77–3.82)	<0.001	3.14 (2.66–3.70)	<0.001
Traj-3 vs. Traj-1	6.19 (4.69–8.17)	<0.001	5.45 (4.11–7.24)	<0.001
eICU-CRD cohort				
Hospital mortality				
Traj-2 vs. Traj-1	2.31 (1.98–2.70)	<0.001	2.35 (2.01–2.75)	<0.001
Traj-3 vs. Traj-1	11.82 (9.79–14.26)	<0.001	11.70 (9.68–14.15)	<0.001
AKI				
Traj-2 vs. Traj-1	1.78 (1.52–2.08)	<0.001	1.75 (1.49–2.05)	<0.001
Traj-3 vs. Traj-1	2.14 (1.81–2.54)	<0.001	2.10 (1.77–2.50)	<0.001

Tip: Abbreviation: OR: Odds Ratio; CI: Confidence Interval; AKI: Acute Kidney Injury. Multivariate logistic regression model adjusted for gender, age, body weight, hypertension, coronary heart disease, diabetes mellitus, acute or chronic heart failure, liver disease, and chronic kidney disease.

4. Discussion

This study, which analyzed data from three independent cohorts, underscores the significant prognostic value of lactate trajectory patterns in critically ill patients with hyperlactatemia. Our findings show that specific lactate trajectories, particularly those characterized by persistently elevated levels, are strongly associated with increased risks of hospital mortality and AKI. The association between these adverse outcomes and lactate trajectories was consistent

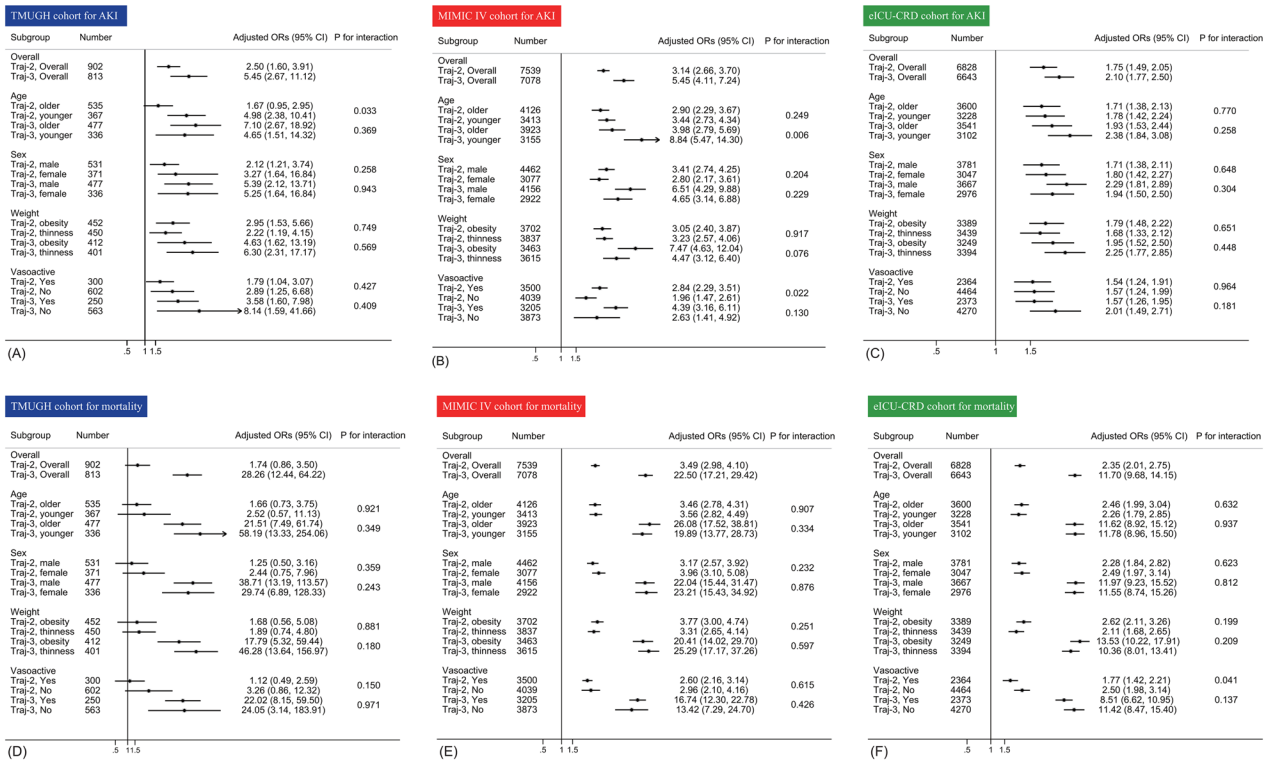

Figure 3. The forest plot of subgroup analysis. (A–C) represent subgroup analyses with AKI as the outcome, while (D-F) present analyses with hospital mortality as the outcome. Data in (A) and (D) are derived from the TMUGH cohort, (B) and (E) from the MIMIC IV cohort, and (C) and (F) from the eICU cohort.

Table 4. Combined analysis of multiple cohorts using logistic regression analysis.

	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
AKI in overall				
Traj-2 vs. Traj-1	2.18 (1.98–2.41)	<0.001	2.13 (1.92–2.36)	<0.001
Traj-3 vs. Traj-1	2.43 (2.14–2.75)	<0.001	2.33 (2.04–2.65)	<0.001
AKI in survivals				
Traj-2 vs. Traj-1	2.16 (1.91–2.44)	<0.001	2.20 (1.94–2.49)	<0.001
Traj-3 vs. Traj-1	2.30 (1.80–2.95)	<0.001	2.40 (1.85–3.10)	<0.001
AKI in non-CKDs				
Traj-2 vs. Traj-1	2.35 (2.11–2.62)	<0.001	2.89 (2.05–2.55)	<0.001
Traj-3 vs. Traj-1	2.77 (2.42–3.18)	<0.001	2.65 (2.30–3.05)	<0.001
Hospital mortality				
Traj-2 vs. Traj-1	2.85 (2.56–3.17)	<0.001	2.79 (2.50–3.11)	<0.001
Traj-3 vs. Traj-1	16.67 (14.38–19.32)	<0.001	16.19 (13.94–18.80)	<0.001

Tip: Abbreviation: OR: Odds Ratio; CI: Confidence Interval; AKI: Acute Kidney Injury. Multivariate logistic regression model adjusted for gender, age, body weight, hypertension, coronary heart disease, diabetes mellitus, acute or chronic heart failure, liver disease, and chronic kidney disease.

across the three cohorts, indicating the robustness and generalizability of our results. Notably, our combined analysis revealed that patients with rapid lactate clearance exhibited the lowest risk of AKI and mortality, while slow clearance reduced mortality risk but had a limited effect on AKI incidence. In contrast, patients with persistently high lactate levels remained at elevated risk for both mortality and AKI. These results highlight the importance of monitoring lactate dynamics in critical care, offering a novel perspective for clinical management and prognostic evaluation in patients with hyperlactatemia.

Hyperlactatemia is common among critically ill patients and is closely associated with increased mortality and higher incidence of complications [13]. The importance of continuous dynamic lactate monitoring has been widely considered as crucial in guiding clinical assessment and treatment [3]. Our findings are consistent with prior researches demonstrating that elevated lactate levels are a reliable marker for poor prognosis in critically ill patients. Severe hyperlactatemia is strongly associated with higher ICU mortality, with maximum lactate levels and 12-h lactate clearance serving as useful prognostic biomarkers [35]. Both elevated lactate levels and low lactate clearance rates are positively correlated with poor prognosis [35]. A previous RCT study by Jansen TC et al. found that lactate-guided intervention, aiming to reduce lactate levels by over 20% every 2 h during the first 8 h of ICU

admission, can effectively improve outcomes in patients with hyperlacticaemia [36]. These results indicate that the tendency of lactate is valuable prognostic indicator. This trajectory-based approach allowed for a more accurate prediction of patient outcomes compared to independent-point measurements. For instance, our results are consistent with those of prior studies linking high lactate levels and low lactate clearance rates to poor outcomes, but we further elucidate the specific lactate trajectory patterns that are most predictive of adverse outcomes. To the best of our knowledge, present study is the first research describing the relationship between lactate trajectories and the prognosis of patients with hyperlactatemia.

The concept of biomarker trajectories is gaining traction in critical care research, and recent studies have explored this approach with other laboratory parameters. Tie X et al. for example, analyzed serum albumin trajectories in critically ill patients, identifying those patients with increasing or consistently high albumin levels had lower mortality and a reduced risk of AKI [20]. Similarly, Zhu S et al. examined hemoglobin trajectories in post-cardiac surgery patients and found that maintaining hemoglobin levels above 10 g/dL through red blood cell transfusion was associated with a higher risk of AKI [37]. Huang S et al. investigated sodium trajectories and found that both increasing and decreasing sodium patterns were linked to higher mortality in AKI patients [38]. These studies emphasize the value of considering both the initial levels of biomarkers and their dynamic changes over time, as trajectory-based models provide more comprehensive prognostic insights compared to single-point measurements. However, the generalizability of these findings was limited by smaller sample sizes and single-cohort designs. Our study, featuring data from three independent cohorts with a larger sample size, improves upon these limitations and provides more generalizable and clinically applicable findings.

Several mechanisms may explain the association between adverse lactate trajectories and poor outcomes such as mortality and AKI. Persistent hyperlactatemia likely reflects ongoing tissue hypoxia and anaerobic metabolism, signaling inadequate oxygen delivery or impaired cellular utilization. Elevated lactate levels are indicative of an active inflammatory response, which may exacerbate organ injury [39]. Additionally, organ dysfunction, particularly in the liver or kidneys, reduces lactate clearance, sustaining elevated levels. A decrease in lactate is often associated with hemodynamic improvement and restored tissue perfusion, signaling effective resuscitation and treatment strategies [40]. Our findings suggest that persistently high lactate levels reflect ongoing hypoxic stress or severe organ dysfunction, leading to increased mortality and AKI risk. Interestingly, although patients in the Traj-2 group had lower mortality compared to the Traj-3 group, the risk of AKI was similar. This suggests that while lactate reduction can lower mortality, it may not always prevent AKI, possibly due to rapid organ damage caused by elevated lactate levels.

Previous research suggests that lactate is not merely a byproduct of anaerobic metabolism but may also act as a signaling molecule contributing to organ injury [41]. Lactate is increasingly recognized as a regulator of energy metabolism and signal transduction [42]. As Tan C et al. reported, lactate exacerbates sepsis associated AKI by negatively influencing metabolic reprogramming, inhibiting autophagy and promoting cell apoptosis through the SIRT3/AMPK pathway [43]. Additionally, the Warburg effect, in which cells produce lactate even under aerobic conditions, may further increase lactate levels and contribute to AKI [44]. The latest theories regarding lactate's role include the lactate shuttle hypothesis, lactate homeostasis, and lactate's interaction with the microenvironment in various diseases [42,45]. Lactylation, a recently discovered post-translational modification where lactate conjugates with proteins, has been implicated in inflammation and tissue damage, potentially worsening organ dysfunction [14]. The classical pathway of lactylation involves the modification of lysine residues on histones through lactyl-CoA, thereby regulating gene expression and cellular functions [46]. This lactate-induced modification could exacerbate tissue damage and organ dysfunction in critically ill patients, potentially contributing to the development of conditions, including AKI. For instance, lactylation of histone H3K18 has been shown to exacerbate renal dysfunction in AKI [47]. Meanwhile, non-histone lactylation has also garnered increasing attention. Research by S. An et al. revealed that PDHA1 hyperacetylation-driven lactate overproduction exacerbates SAKI injury through Fis1 lactylation [48]. The persistent elevation of lactate, therefore, represents not only a biomarker of hypoxia but also an active participant in pathophysiological processes leading to poor outcomes.

Our study also highlights the importance of understanding lactate not only as a biomarker but as a potential mediator of organ injury. Although the recovery of hyperlactatemia is often viewed as a biomarker of better cellular metabolism, the direct benefits of interventions targeting lactate remain unclear. K Yang et al. discovered that lactate can lead to increased vascular permeability and organ dysfunction [27]. Their study showed that lactate induces ERK-dependent calpain 1/2-mediated cleavage of VE-cadherin, enhancing VE-cadherin endocytosis in endothelial cells, thereby disrupting adherens junctions and leading to hyper-permeability [27]. Inhibiting lactate production or blocking lactate receptors, such as GPR81, may reduce vascular permeability, prevent organ damage, and improve patient outcomes [27]. From an immunological perspective, lactate has been shown to suppress both innate and adaptive immune responses, potentially exacerbating tissue damage in critically ill patient [49]. Targeted interventions aimed at reducing lactate levels, such as the use of PKM2 inhibitors like Shikonin, have shown promise in improving survival in sepsis models [50].

Our study provides valuable insights into the management of clinical hyperlactatemia and possesses several notable strengths. First, the use of a multicenter, large-scale cohort design significantly enhances the generalizability of our findings, ensuring that the results are applicable across diverse clinical settings. Second, by incorporating data from three independent cohorts, we were able to provide robust

evidence, which strengthens the consistency and reliability of our results while minimizing the risk of bias commonly associated with single-center studies. Third, the application of GBTM allowed us to perform a comprehensive analysis of lactate dynamics, leading to more precise risk stratification for critically ill patients with hyperlactatemia. This approach goes beyond traditional single-point measurements, offering deeper insights into the temporal patterns of lactate changes and their clinical implications. Our findings are highly generalizable and hold significant clinical guidance value, supported by rigorous validation across three independent cohorts. It is well established that hyperlactatemia is typically detrimental, with excessively high lactate levels being strongly associated with an increased risk of developing AKI and mortality. While correcting hyperlactatemia has efficacy in mortality reduction, its impact on AKI prevention remains inconclusive. These results underscore the critical importance of implementing proactive strategies in clinical practice, including: (1) early prevention of hyperlactatemia, (2) timely management of elevated lactate levels, and (3) continuous monitoring of lactate dynamics, rather than relying on isolated measurements.

Despite these strengths, several limitations of our study should be acknowledged. First, as a retrospective analysis, our study is inherently subject to potential biases related to data collection and missing data, especially regarding the causes of hyperlactatemia and the specific intervention to reduce lactate levels. Although we employed multiple logistic regression and PSM methods to adjust for confounders, the possibility of residual confounding due to unmeasured variables remains. Second, the observational nature of our study limits our ability to establish definitive causal relationships between lactate trajectories and clinical outcomes. Third, while the inclusion of multiple cohorts strengthens our findings, the exclusive focus on ICU patients with hyperlactatemia may restrict the generalizability of our results to other populations and clinical settings. Four, this study focused only on in-hospital mortality, and the lack of long-term follow-up data prevents us from determining whether different trajectory models have an impact on long-term patient outcomes. As such, further prospective studies are needed to validate our findings and explore the potential benefits of lactate-targeted interventions across a broader patient population.

5. Conclusions

The present study underscores the significant prognostic value of lactate trajectories in critically ill patients, particularly those with hyperlactatemia. Our findings suggest that rapid lactate clearance is strongly associated with improved outcomes, while persistently elevated lactate levels reflect ongoing hypoxic or metabolic stress, leading to a higher risk of mortality and AKI. The use of a multicenter study design enhances the generalizability of these findings, and the application of GBTM enables more precise risk stratification, allowing clinicians to better predict patient outcomes based on dynamic lactate trends. Future prospective studies are necessary to validate these findings and explore targeted interventions aimed at reducing lactate levels more effectively, which may help mitigate the risk of organ dysfunction and improve overall survival in critically ill patients with hyperlactatemia.

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Authors' contributions

Yipeng Fang: Writing – original draft, Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Software, Validation, Visualization. Ying Zhang: Writing – review & editing, Data curation. Xuejun Shen: Writing – review & editing, Formal Analysis, Methodology, Software, Validation. Yunfei Zhang: Writing – review & editing, Formal Analysis, Visualization. Aizhen Dou and Hui Xie: Writing – review & editing. Keliang Xie: Writing – review & editing, Conceptualization, Funding acquisition, Project administration, Supervision. All contributing authors have carefully examined and approved the final version of the manuscript, ensuring the integrity and taking responsibility for all aspects of the research presented.

Ethics approval and consent to participate

The MIMIC IV and eICU-CRD datasets have received ethical approval from the Institutional Review Board of the Massachusetts Institute of Technology, and the overall study protocol was approved by the Ethics Committee of TMUGH (Approval No: IRB2024-YX-431-01). Informed consent was waived due to the anonymization of all data, which protected the privacy of patients.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The datasets analyzed during the current study are available in the MIMIC-IV (Version 2.2, accessible at https://physionet.org/content/mimiciv/2.2/) and eICU-CRD databases (Version 2.0, accessible at https://physionet.org/content/eicu-crd/2.0). The date for the TMUGH cohort and all raw data can be obtained through the corresponding author upon reasonable request.

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