Time to Lactate Measurement Affects Efficacy of Initial Lactate on Mortality in critically ill patients with sepsis.

Xueying Luo (hjssums@126.com)
Peking University Shenzhen Hospital
Xiaobo Zheng
Anhui University
Xi Rao
Universitats-Herzzentrum Freiburg
Ya Li
Shenzhen University
Sujing Zheng
Shenzhen Second People's Hospital
Weicai Chen
Shenzhen Second People's Hospital
Jinsong He
Peking University Shenzhen Hospital

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Abstract

Background: Evidence regarding the effect of time to lactate measurement on the relationship between the initial lactate level and mortality is limited. We aimed to investigate the relationships between time to lactate measurement, initial lactate level, and in-hospital mortality in critically ill patients with sepsis.

Methods and Results: Of the 14339 eligible adult patients with recognized sepsis upon admission to the ICU based on the MIMIC-III database, the median value of initial lactate was 1.70 mmol/L (interquartile range [IQR] 1.20-2.80), and its detection time was 3.50 hours ([IQR] 1.31-10.24). The results of fully adjusted multivariate analyses demonstrated that lactate was positively associated with in-hospital mortality (odds ratio: 1.126, 95% confidence interval: 1.090 to 1.163, P<0.001), and there was an increase in the odds of death with hourly delays in lactate measurement (OR: 1.006, 95% CI: 1.004 to 1.008, P<0.001). In stratified analyses, delays in lactate measurement significantly interfered with the impact of increased lactate level on mortality (P-value for interaction<0.001). The hospital mortality rate substantially increased by 43.5% for each unit increase in lactate when measurement was delayed by 24 hours (OR: 1.435, 95% CI: 1.260 to 1.635, P<0.001).

Discussion: The association of initial lactate with in-hospital mortality is likely to vary with delays in detection time (grouping based on the “1-hour bundle”) in critically ill patients with recognized sepsis upon admission to the ICU.

Background

As a global health priority, sepsis has received extensive attention because of its high morbidity and mortality[1,2]. There are more than 48.9 million cases of sepsis worldwide each year and 11.0 million related deaths attributed to sepsis, accounting for 19.7% of the global total[3,4]. In the pandemic of the novel coronavirus, the number of cases of septic shock in the intensive care unit(ICU) will increase significantly. To improve the early management of sepsis, the definition of sepsis was updated to infection with organ dysfunction (Sepsis-3)[5,6]. The new Surviving Sepsis Campaign (SSC), merging 3-hour and 6-hour bundles into the “1-hour bundle”, was conducted to begin resuscitation and management immediately[7]. In the new definition of septic shock (sepsis-3.0), elevated serum lactate levels, which are synonymous with abnormal cellular metabolism, are independently associated with mortality[5]. Lactate measurement is an important component of the early management of sepsis, and its optimal execution time is the focus of the current study. Current evidence indicates that delays in the detection time of lactate will lead to an increase in poor prognosis, including death[8–11]. However, whether the delay of lactate measurement will affect the efficacy of initial lactate on mortality has always been neglected.

Therefore, the purpose of this study was to investigate the relationships between initial lactate level, lactate detection time, and in-hospital mortality in critically ill patients with recognized sepsis upon ICU admission in order to clarify whether delays in lactate measurement (in the “1-hour bundle”) interfere with the association of lactate with hospital mortality.

Methods

Study design

Our study was performed to address the relationship between time to lactate measurement, initial lactate level and in-hospital mortality in critically ill patients who have recognized sepsis at the moment of ICU admission (sepsis 3.0). Septic patients in our study were identified from the Medical Information Mart for Intensive Care (MIMIC-III) database. This database included information on 53,423 hospital admissions of patients (16 years or older) in the ICU of Beth Israel Deaconess Medical Center from June 1, 2001 to October 31, 2012 in Boston, Massachusetts[12]. Since the database was provided anonymously and publicly by a third party (the Massachusetts Institute of Technology (MIT) Laboratory for Computational Physiology) with prior approval from the Institutional Review Board (IRB)[13], the requirements for IRB and informed consent approval for the study were waived.

Selection Of Patients

A total of 6888 patients were recruited for this study in accordance with the following inclusion criteria: 1. ICU length of stay exceeds 24 hours; 2. Recorded or suspected infection; 3. SOFA score ≥ 2 points within 24 hours after admission to the ICU; 4. Diagnosis of sepsis was confirmed at admission to the ICU, which means that patients received antibiotic treatment or blood culture within 2 weeks before admission; 5. Patients over 18 years old; and 6. No missing values of initial lactate or time to lactate measurement. PostgreSQL software was conducted in the entire process of screening patients, including calculating the Sequential Organ Failure Assessment [SOFA] score and identifying the start time of interventions. According to the method established by Angus et al., patients with infection or suspected infection were screened in the study[14].

Procedures And Definitions

The covariates included in the analysis were specified a priori as potential confounders in the relationship between time to lactate measurement, initial lactate level and mortality according to clinical experience and previous studies. Details of those covariates used to construct the fully adjusted model are listed as follows: (1) continuous variables: demographics (age and weight), vital signs, lab results (white blood cells [WBCs], haemoglobin, platelet count, creatinine, blood urea nitrogen [BUN]), blood gas analysis (venous sodium, potassium, bicarbonate and lactate), SOFA score (obtained at baseline), and time to balanced crystalloid solutions; (2) categorical variables: demographics (sex), lab results (creatinine kinase), blood gas analysis (arterial PO_2, PCO_2, PH), comorbidities (including congestive heart failure [CHF], atrial fibrillation [AFIB], chronic kidney disease [CKD], liver disease [LD], chronic obstructive pulmonary disease [COPD], coronary artery disease [CAD], and malignancies), interventions(mechanical ventilation, antibiotic use, vasopressin, balanced crystalloid solutions), and time to intervention

(antibiotics). The above information, except comorbidities and interventions, were all obtained as the first documented results after admission to the ICU.

The primary exposure of interest was initial lactate level and time to lactate measurement after admission to the ICU. In the analysis, initial lactate was classified by clinical cut-off point (≤ 2, > 2 and ≤ 4, >4) sepsis management (< 1, ≥ 1 and < 24, ≥24) (hours). The outcome of the study was the survival status of septic patients at the time of hospital discharge (in-hospital mortality) based on the US Social Security Death Index.

Statistical analysis

Continuous data are displayed as the mean ± standard deviation [SD] or median (interquartile range [IQR]). Categorical data are displayed as a number (percentage). Three SD values above or below the average were regarded as outliers. One-way ANOVA, Kruskal-Wallis H (skewed distribution), and chi-square tests (categorical variables) were employed to distinguish the differences in the proportions and means. The missing values of covariates were handled. For the missing values of continuous variables, we supplemented with the median or mean. For categorical variables, we treated missing values as a single group.

To determine the relationship between time to lactate measurement, initial lactate level and hospital mortality as well as the association of initial lactate level with its detection time, multivariate regression analyses were employed. We constructed three models (non-adjusted model, we did not adjust any covariates; minimally-adjusted model: we only adjusted age, sex, weight, respiratory rate, DBP, SBP; and fully-adjusted model, we adjusted all covariates mentioned before, details presented in Table 1).

Table 1
Baseline and Clinical Characteristics of the Study Population.

Time to lactate measurement(hours)	**< 1**	**≥ 1, < 24**	**≥ 24**	**P-value**
N	1364	4659	865	
Lactate	1.40–3.62	1.20–2.70	1.00-1.90	< 0.001
Demographic variables				
Age	66.76 ± 16.35	67.46 ± 16.01	67.31 ± 15.20	0.365
Sex				0.129
Male	776 (56.89%)	2517 (54.02%)	485 (56.07%)	
Female	588 (43.11%)	2142 (45.98%)	380 (43.93%)	
Weight Trisection(kg)				0.259
Low(58.42 ± 8.39)	355 (26.03%)	1364 (29.28%)	237 (27.40%)	
Middle(78.04 ± 5.21)	409 (29.99%)	1332 (28.59%)	247 (28.55%)	
High(105.82 ± 15.92)	390 (28.59%)	1324 (28.42%)	259 (29.94%)	
NA	210 (15.40%)	639 (13.72%)	122 (14.10%)	
Vital signs				
Respiratory Rate (breaths per minute)	20.67 ± 6.62	20.54 ± 6.52	20.68 ± 6.60	0.714
DBP(mmHg)	61.05 ± 18.28	62.05 ± 18.48	61.56 ± 17.09	0.188
SBP(mmHg)	117.17 ± 25.29	116.98 ± 24.31	121.44 ± 25.50	< 0.001
Lab results				
WBC(x10^9/L)	8.00–18.00	7.90–17.10	7.40–15.00	< 0.001
Hemoglobin(g/dl)	10.17 ± 1.91	10.09 ± 1.89	9.99 ± 1.76	0.110

Time to lactate measurement(hours)	< 1	≥ 1, < 24	≥ 24	P-value
Platelet count(x10^9/L)	132.00-276.00	124.00-275.50	122.00-280.00	0.971
Creatinine(mg/dL)	0.90–2.10	0.90–2.10	0.80–2.10	0.880
BUN(mg/dl)	18.00–43.00	18.00–45.00	18.00–49.00	0.071
Creatinine Kinase Trisection(U/L)				0.055
Low(1.00–13.00)	295 (21.63%)	950 (20.39%)	167 (19.31%)	
Middle(14.00–73.00)	268 (19.65%)	946 (20.30%)	199 (23.01%)	
High(≥ 74)	309 (22.65%)	945 (20.28%)	159 (18.38%)	
NA	492 (36.07%)	1818 (39.02%)	340 (39.31%)	
Blood gas analysis				
Sodium(mmol/L)	138.19 ± 5.04	138.38 ± 5.13	138.16 ± 5.09	0.294
Potassium*(mmol/L)	4.12 ± 0.72	4.18 ± 0.75	4.16 ± 0.70	0.065
Bicarbonate(mmol/L)	21.55 ± 5.32	22.14 ± 5.42	23.95 ± 5.14	< 0.001
PO_2 Category(mmHg)				< 0.001
< 60	204 (14.96%)	700 (15.02%)	138 (15.95%)	
≥ 60, < 90	264 (19.35%)	983 (21.10%)	239 (27.63%)	
≥ 90	769 (56.38%)	2415 (51.84%)	438 (50.64%)	
NA	127 (9.31%)	561 (12.04%)	50 (5.78%)	
PCO_2 Category(mmHg)				< 0.001
< 35	313 (22.95%)	1143 (24.53%)	214 (24.74%)	
≥ 35, < 45	505 (37.02%)	1581 (33.93%)	310 (35.84%)	

Time to lactate measurement(hours)	< 1	≥ 1, < 24	≥ 24	P-value
≥ 45	405 (29.69%)	1353 (29.04%)	282 (32.60%)	
NA	141 (10.34%)	582 (12.49%)	59 (6.82%)	
PH-value category				< 0.001
< 7.35	666 (48.83%)	1890 (40.57%)	260 (30.06%)	
≥ 7.35, < 7.45	418 (30.65%)	1669 (35.82%)	387 (44.74%)	
≥ 7.45	163 (11.95%)	687 (14.75%)	180 (20.81%)	
NA	117 (8.58%)	413 (8.86%)	38 (4.39%)	
CHF				0.009
No	1070 (78.45%)	3468 (74.44%)	660 (76.30%)	
Yes	294 (21.55%)	1191 (25.56%)	205 (23.70%)	
AFIB				0.061
No	900 (65.98%)	3117 (66.90%)	543 (62.77%)	
Yes	464 (34.02%)	1542 (33.10%)	322 (37.23%)	
CKD				0.073
No	1089 (79.84%)	3601 (77.29%)	688 (79.54%)	
Yes	275 (20.16%)	1058 (22.71%)	177 (20.46%)	
Liver Disease				0.565
No	1215 (89.08%)	4174 (89.59%)	765 (88.44%)	
Yes	149 (10.92%)	485 (10.41%)	100 (11.56%)	
COPD				0.099

Time to lactate measurement(hours)	< 1	≥ 1, < 24	≥ 24	P-value
No	1305 (95.67%)	4398 (94.40%)	811 (93.76%)	
Yes	59 (4.33%)	261 (5.60%)	54 (6.24%)	
CAD				0.033
No	1082 (79.33%)	3603 (77.33%)	700 (80.92%)	
Yes	282 (20.67%)	1056 (22.67%)	165 (19.08%)	
CVA				< 0.001
No	1292 (94.72%)	4375 (93.90%)	779 (90.06%)	
Yes	72 (5.28%)	284 (6.10%)	86 (9.94%)	
Malignant				0.235
No	1195 (87.61%)	4043 (86.78%)	768 (88.79%)	
Yes	169 (12.39%)	616 (13.22%)	97 (11.21%)	
Risk assessment				
GCS level*				0.354
Mild(13–15)	1094 (80.56%)	3612 (78.33%)	678 (79.21%)	
Moderate(9–12)	136 (10.01%)	505 (10.95%)	98 (11.45%)	
Severe(3–8)	128 (9.43%)	494 (10.71%)	80 (9.35%)	
SOFA score	4.00–9.00	4.00–9.00	3.00–7.00	< 0.001
Interventions				
Mechanical ventilation				< 0.001
No	664 (48.90%)	2673 (57.89%)	567 (65.93%)	
Yes	694 (51.10%)	1944 (42.11%)	293 (34.07%)	

Time to lactate measurement(hours)	< 1	≥ 1, < 24	≥ 24	P-value
Antibiotic Use				0.007
≥ 0,<24	277 (20.31%)	876 (18.80%)	144 (16.65%)	
≥ 24,<48	431 (31.60%)	1524 (32.71%)	248 (28.67%)	
≥ 48	539 (39.52%)	1889 (40.55%)	379 (43.82%)	
NA	117 (8.58%)	370 (7.94%)	94 (10.87%)	
Vasopressin				< 0.001
No	949 (69.57%)	3227 (69.26%)	691 (79.88%)	
Yes	415 (30.43%)	1432 (30.74%)	174 (20.12%)	
Balanced crystalloid solutions(mL)				< 0.001
< 500	905 (66.35%)	3170 (68.04%)	606 (70.06%)	
≥ 500, < 1000	176 (12.90%)	609 (13.07%)	121 (13.99%)	
≥ 1000	217 (15.91%)	653 (14.02%)	76 (8.79%)	
NA	66 (4.84%)	227 (4.87%)	62 (7.17%)	
Time to interventions				
Time to balanced crystalloid solutions (hours)	0.85–3.38	0.99–3.53	0.82–4.35	< 0.001
Time to antibiotic				< 0.001
≤ 0	609 (44.65%)	1971 (42.31%)	298 (34.45%)	
> 0,≤1	46 (3.37%)	156 (3.35%)	16 (1.85%)	
> 1,≤24	440 (32.26%)	1597 (34.28%)	262 (30.29%)	
> 24	139 (10.19%)	504 (10.82%)	169 (19.54%)	

Time to lactate measurement(hours)	< 1	≥ 1, < 24	≥ 24	P-value
NA	130 (9.53%)	431 (9.25%)	120 (13.87%)	
In-hospital mortality				< 0.001
No	1058 (77.57%)	3513 (75.40%)	585 (67.63%)	
Yes	306 (22.43%)	1146 (24.60%)	280 (32.37%)	

Subgroup analyses were performed using stratified regression models. For continuous variables, we first converted time to lactate measurement to a categorical variable as mentioned before and then performed an interaction test. Tests for effect modification for those of subgroup indicators were followed by the likelihood ratio test. Using a generalized additive model, the relationship between initial lactate level (continuous variable) and hospital mortality, stratified by the significant interference factor (time to lactate measurement), was revealed on the smoothing plot.

In addition to verifying the robustness of the data analysis, sensitivity analyses were conducted. Initial lactate and time to lactate measurement were converted into categories, and the P for trend was calculated to verify the results of exposure factors as continuous variables. All analyses were conducted with the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc, Boston, MA). P values less than 0.05 (two-sided) were considered statistically significant.

Results

1. The selection of participants and missed follow-up

After reviewing 52,963 MIMIC-III admissions, we identified 14,339 adult patients who met the sepsis definition within 24 hours after admission to the ICU and who had ICU stays longer than 24 hours (Fig. 1). Based on the inclusion and exclusion criteria, we excluded those cases without recognized sepsis upon admission to the ICU (N = 5158), who lacked data on lactate measurement/time to lactate measurement (N = 2289) and who were under the age of 18 years old (N = 4). A total of 6888 patients (54.85% male) were included in the analysis. The average age of the population was 66.80 ± 15.94 years, the median value of initial serum lactate was 1.70 mmol/L ([IQR] 1.20–2.80), and the median detection time of lactate was 3.50 hours ([IQR] 1.31–10.24).

2. Baseline characteristics of participants

Table 1 depicts the baseline characteristics of the total population. We assigned participants into a subgroup of time to lactate measurement (< 1, ≥ 1, <24, and ≥ 24 hours). This showed that in the < 1 hour

group, participants generally had higher lactate, WBCs, PO_2, and SOFA scores; higher rates of normal PCO_2; lower rates of CHF and CVA; more use of mechanical ventilation and vasopressin; and early action time to interventions (antibiotic and balanced crystalloid solutions) but lower systolic blood pressure [SBP] and bicarbonate and less use of balanced crystalloid solutions and antibiotics. In contrast, there was no statistically significant difference in age, sex, weight, respiratory rate, diastolic blood pressure [DBP], haemoglobin, platelet count, creatinine, BUN, creatinine kinase, sodium, potassium, AFIB, CKD, liver disease, COPD, malignancy status, or Glasgow coma scale [GCS] among different groups.

3. Outcome

Time to lactate measurement and lactate level

The relationship between the initial lactate level and its first detection time is shown in Table 2. Delays in lactate measurement were negatively correlated with lactate level in the non-adjusted (β: -0.005, 95% CI: -0.007 to -0.004) and adjusted models (the fully adjusted model: β:-0.002, 95% CI: -0.003 to -0.000). In the fully adjusted model, the concentration of lactate decreased by 0.685 mmol/L when delays of the lactate test were greater than 24 hours (β:-0.685, 95% CI: -0.840 to -0.529) when compared with the level of the group with a detection time < 1 hour.

Table 2
The association of time to lactate measurement and initial lactate in the entire cohort.

Initial Lactate	Non-adjusted β (95%ci)P-value	Minimally-adjusted model β (95%ci)P-value	Fully-adjusted model β (95%ci)P-value
Time to lactate measurement	-0.005 (-0.007, -0.004) < 0.001	-0.005 (-0.007, -0.004) < 0.001	-0.002 (-0.003, -0.000) 0.010
Time to lactate measurement Category			
<1	Ref.	Ref.	Ref.
≥1, < 24	-0.730 (-0.849, -0.612) < 0.001	-0.722 (-0.840, -0.605) < 0.001	-0.604 (-0.711, -0.497) < 0.001
≥24	-1.207 (-1.374, -1.041) < 0.001	-1.182 (-1.348, -1.016) < 0.001	-0.685 (-0.840, -0.529) < 0.001
P for trend	< 0.001	< 0.001	< 0.001

Table 3
Association of initial lactate,Time to lactate measurement and In-hospital Mortality

In-hospital Mortality	Non-adjusted OR (95%ci)P-value	Minimally-adjusted OR (95%ci)P-value	Fully-adjusted OR (95%ci)P-value
Lactate	1.225 (1.193, 1.258) < 0.001	1.225 (1.192, 1.259) < 0.001	1.126 (1.090, 1.163) < 0.001
Lactate category			
≤2	1.0	1.0	1.0
>2, ≤4	1.477 (1.302, 1.676) < 0.001	1.454 (1.279, 1.653) < 0.001	1.237 (1.070, 1.431) 0.004
>4	2.985 (2.554, 3.488) < 0.001	2.998 (2.556, 3.517) < 0.001	1.805 (1.489, 2.187) < 0.001
P for trend	< 0.001	< 0.001	< 0.001
Time to lactate measurement	1.004 (1.002, 1.005) < 0.001	1.004 (1.002, 1.005) < 0.001	1.006 (1.004, 1.008) < 0.001
Time to lactate measurement category			
<1	1.0	1.0	1.0
≥1, < 24	1.128 (0.977, 1.302) 0.101	1.133 (0.979, 1.310) 0.094	1.362 (1.155, 1.607) < 0.001
≥24	1.655 (1.367, 2.003) < 0.001	1.707 (1.406, 2.073) < 0.001	2.639 (2.107, 3.305) < 0.001
P for trend	< 0.001	< 0.001	< 0.001
OR:odds ratio;CI: Confidence interval			
Non-adjusted model: we did not adjust any covariates.			
Minimally-adjusted model: we only adjusted age,sex,weight,respiratory rate,DBP,SBP.			
Fully-adjusted model : we adjusted age,sex,weight,respiratory rate, DBP,SBP,WBC, hemoglobin, platelet-count,creatinine,BUN,creatinine kinase,sodium,potassium,bicarbonate, PO2, PCO2, PH-value,			
CHF, AFIB,CKD,LD,COPD,CAD,CVA,malignant,SOFA score, GCS,Mechanical ventilation,			
Antibiotic,Vasopressin,Balanced crystalloid solutions,Time to antibiotic,Time to balanced crystalloid solutions,time to lactate measurement(for lactate)/lactate(for time to lactate measurement).			

Time To Lactate Measurement, Lactate Level And In-hospital Mortality

We used a multivariate linear regression model to evaluate the associations between time to lactate measurement, lactate level and in-hospital mortality. We show the non-adjusted and adjusted models in Table 2. In the crude model, lactate and its detection time both showed a positive correlation with the incidence of death (OR = 1.225, 95% CI: 1.193 to 1.258; OR = 1.004, 95% CI: 1.002 to 1.005, respectively). In a minimally adjusted model, the results did not show obvious changes (OR: 1.225, 95% CI: 1.192 to 1.259; OR: 1.004, 95% CI: 1.002 to 1.005; respectively). In the fully adjusted model, we could also detect the connection (OR: 1.126, 95% CI: 1.090 to 1.163; OR: 1.006, 95% CI: 1.004 to 1.008; respectively). For the purpose of sensitivity analysis, we also handled lactate level and time to lactate measurement as categorical variables. In the relationship between lactate and mortality, the high lactate group had a nearly 80.5% increase in death before discharge compared with the mortality rate of the low lactate group in the fully adjusted model (OR = 1.805, 95% CI: 1.489 to 2.187), and we found that the trend across these groups was significant (P for trend < 0.001). In the relationship between time to lactate measurement and mortality, there was a 1.639-fold increased risk of hospital mortality with more than 24 hours of delay in lactate tests (OR = 2.639, 95% CI: 2.107 to 3.305) (P for trend < 0.001).

Time to Lactate Measurement Affects the Efficacy of Initial Lactate on Mortality

We explored the potential risks in the associations between lactate and in-hospital mortality by performing a subgroup analysis to estimate whether detection time would influence the results. After observing the trend of effect sizes, we noticed that the detection time of lactate affected the relationship between lactate and in-hospital mortality (P-value for interaction < 0.001). A stratified analysis of the 1-hour lactate measurement in the fully adjusted model is shown in Fig. 2. When lactate measurement was completed within 1 hour after admission, the hospital mortality rate increased by 10.9% for each unit increase in lactate (OR = 1.109, 95% CI: 1.049 to 1.172). When the time to lactate measurement was between 1 and 24 hours, there was a higher odds of death associated with a one-unit increase in lactate (OR = 1.129, 95% CI: 1.081 to 1.178). The hospital mortality rate substantially increased by 49.7% for each unit increase in lactate when the measurement was delayed to 24 hours later (OR: 1.497, 95% CI: 1.322 to 1.694). To ensure the robustness of the data analysis, the significant differences in hospital mortality according to different levels of lactate (≤ 2, > 2 and ≤ 4, >4 mmol/L) with delays in lactate measurement were revealed by the generalized additive model (Fig. 3).

Discussion

In this study, on the basis of confirming that delays in lactate measurement are slightly related to hospital mortality (OR = 1.006, 95% CI: 1.004 to 1.008), the detection time was a significant interfering factor in the effect of lactate on hospital mortality among critically ill patients with recognized sepsis upon ICU admission (P-value for interaction < 0.001). Completing the lactate measurement within 1 hour after admission to the ICU has a significant advantage in reducing the impact of initial lactate on mortality (OR = 1.109, 95% CI: 1.049 to 1.172) compared with completing the lactate test from 1 to 24 hours after admission (OR = 1.129, 95% CI: 1.081 to 1.178) or more than 24 hours after admission (OR = 1.435, 95%

CI: 1.260 to 1.635). It is worth emphasizing that when the initial serum lactate detection time was delayed over 24 hours, in-hospital mortality was highly increased by 43.5% for each unit increase in lactate.

In the new definition of sepsis and septic shock (Sepsis 3.0), an increase in serum lactate is independently associated with high acute mortality, especially when lactate levels are greater than 2 mmol/L (> 18 mg/dL)[15,5]. Studies highlighting lactate's prognostic potential for mortality and other outcomes are ubiquitous and largely focus on the early stage of sepsis management[16–19]. Based on the International Guidelines for Management of Sepsis and Septic Shock in 2016, a revised "1-hour bundle" was recently developed with the combination of the 3-hour and 6-hour bundles for the purpose of immediately beginning resuscitation and management[20,7]. Lactate measurement, which is an important component of a sepsis bundle, has increased dramatically since 2003 and is performed on patients without overt shock[10]. Current evidence indicates the necessity of early lactate measurement in patients with initial intermediate or elevated lactate levels[21–23,8,24]. This provided the basis for the proposal of the 1-hour bundle. However, this method is weakly recommended due to the low quality of evidence and the potential waste of medical resources in the 1-hour bundle[7]. Sepsis guidelines also suggest the identification of advance directives and treatment goals as early as feasible but no later than within 72 hours of ICU admission (weak recommendation with low-quality evidence)[20]. Currently, research mainly focuses on the independent risk effect of delayed lactate detection on mortality and ignores the effect of delayed lactate measurement on the impact of the initial lactate level on mortality. Our study demonstrated that delays in lactate detection interfere with the relationship between lactate and mortality and confirmed the following: 1. a stronger connection between high initial lactate and increased mortality was detected with the delay of lactate measurement; 2. lactate measurement following the "1-hour bundle" can effectively reduce the impact of lactate on mortality; and 3. lactate management should be performed no later than within 24 hours of ICU admission.

This study had several unique strengths. First, we revealed advantages of reduced mortality associated with lactate measurement in the "1-hour bundle", based on a large sample database. Second, propensity score matching allowed us to minimize the baseline differences between the two groups, thereby limiting the degree of treatment selection bias inherent in a retrospective study. Additionally, we conducted a sensitivity analysis to confirm the reliability of the results. Third, according to previous reports and clinical experience, our study proposed a novel concept—recognized time of sepsis on the combination of the start time of antibiotic treatment or blood culture testing. Patients included in the study were recognized as having sepsis at the moment of ICU admission, which effectively reduced the bias caused by differences in disease recognition time. Moreover, this study further adjusted the interventions and their corresponding start times to reduce the bias in outcomes caused by differences in interventions. As time to interventions was often affected by the exposure groups, an extra-adjusted model was employed in the study. Since the time to intervention was usually affected by the exposure factors, the extra-adjusted model was employed in the study. All the covariates, including time to antibiotic treatment and balanced crystalloid solutions, were adjusted in the model.

Our study has several limitations. First, it is a single-centre investigation and may not be generalizable to other practice settings. Second, the study was based on electronic healthcare records (EHRs) whose data were generated during routine clinical practice. Thus, it is possible that cohort selection is not exactly consistent with the definition of sepsis from the guidelines. As the study was based on screening methods established by Angus et al, there is a risk of potential missed screenings, although the included septic patients were explicitly consistent with the third definition of sepsis. Third, as this was not a randomized controlled trial, our finding of the association of delayed lactate measurements with increased mortality could be due to an unmeasured confounding factor such as immunosuppression status and earlier antibiotic administration. In addition, as the study time span was large, there may have been untimely lactate interventions after lactate testing, which will affect hospital mortality. Finally, the current research population was mainly limited to developed countries. Many developing countries and undeveloped countries still lack relevant evidence.

Conclusion

Delays in lactate detection interfere with the relationship between lactate and mortality in critically ill patients with recognized sepsis upon admission to the ICU. Lactate measurement in the “1-hour bundle” can effectively reduce the impact of lactate on mortality. Furthermore, the measurement should be addressed within 24 hours of ICU admission.

Abbreviations

OR:Odds Ratio;CI:Confidence Interval;MIMIC-III database:Medical Information Mart for Intensive Care -III database; AFIB:atrial fibrillation;CKD:chronic kidney disease;CAD:coronary artery disease; BUN: blood urea nitrogen;SOFA:sequential organ failure assessment score; ICU:Intensive Care Unit; IRB:Institutional Review Board;MIT:Massachusetts Institute of Technology; CHF: congestive heart failure;AFIB:atrial fibrillation;LD:liver disease; CKD:chronic kidney disease;COPD:chronic obstructive pulmonary disease;CAD:coronary artery disease; WBC: white blood cell;IQR:interquartile range;GAM:generalized additive model;BP,blood pressure; EHR:electronic healthcare records;SBP:systolic blood pressure;DBP:diastolic blood pressure.

Declarations

Ethics approval and consent to participate

The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA), and consent was obtained for the original data collection. Therefore, the ethical approval statement and the need for informed consent were waived for this manuscript.

Consent for publication

Not applicable.

Availability of data and materials

The data-sets supporting the conclusions of this article are available in the MIMIC-III database(https://archive.physionet.org/works/MIMICIIIClinicalDatabase/files/).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XYL.: Conceptualization; Data curation; Formal analysis; Investigation; Roles/Writing - original draft;XBZ:Conceptualization; Data curation; Formal analysis;extracted the data from the MIMIC-III database;RX and YL: Data curation; Formal analysis; Investigation; Software; SJZ: Supervision; Validation; Visualization; CWC: Formal analysis;Project administration;Writing - review & editing.JSH: Conceptualization; Data curation; Formal analysis;Funding acquisition; Writing - review & editing.All authors approved the version to be published ,and agree to be accountable for all aspects of the working in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figures

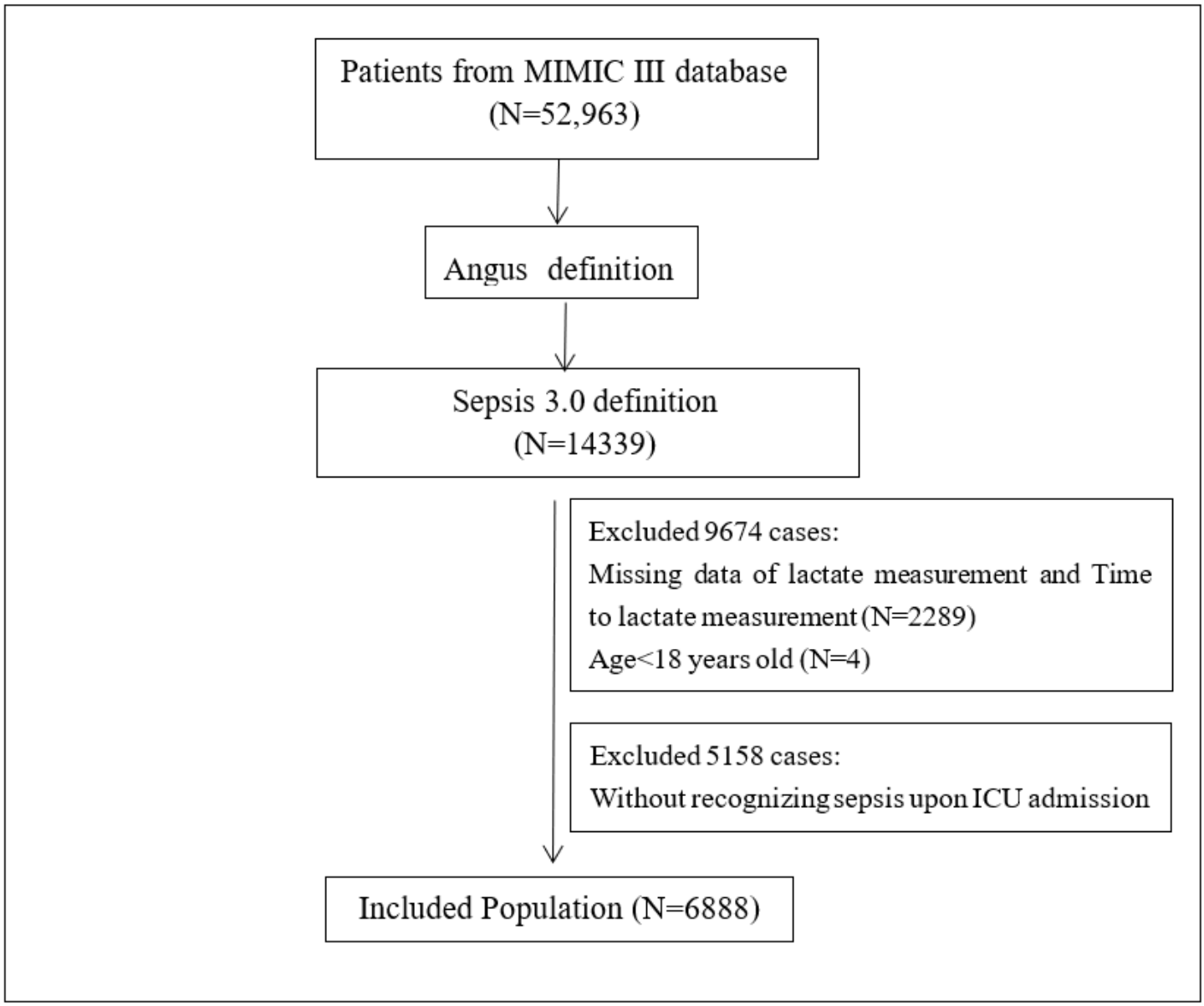

Figure 1

Flowchart of patient selection

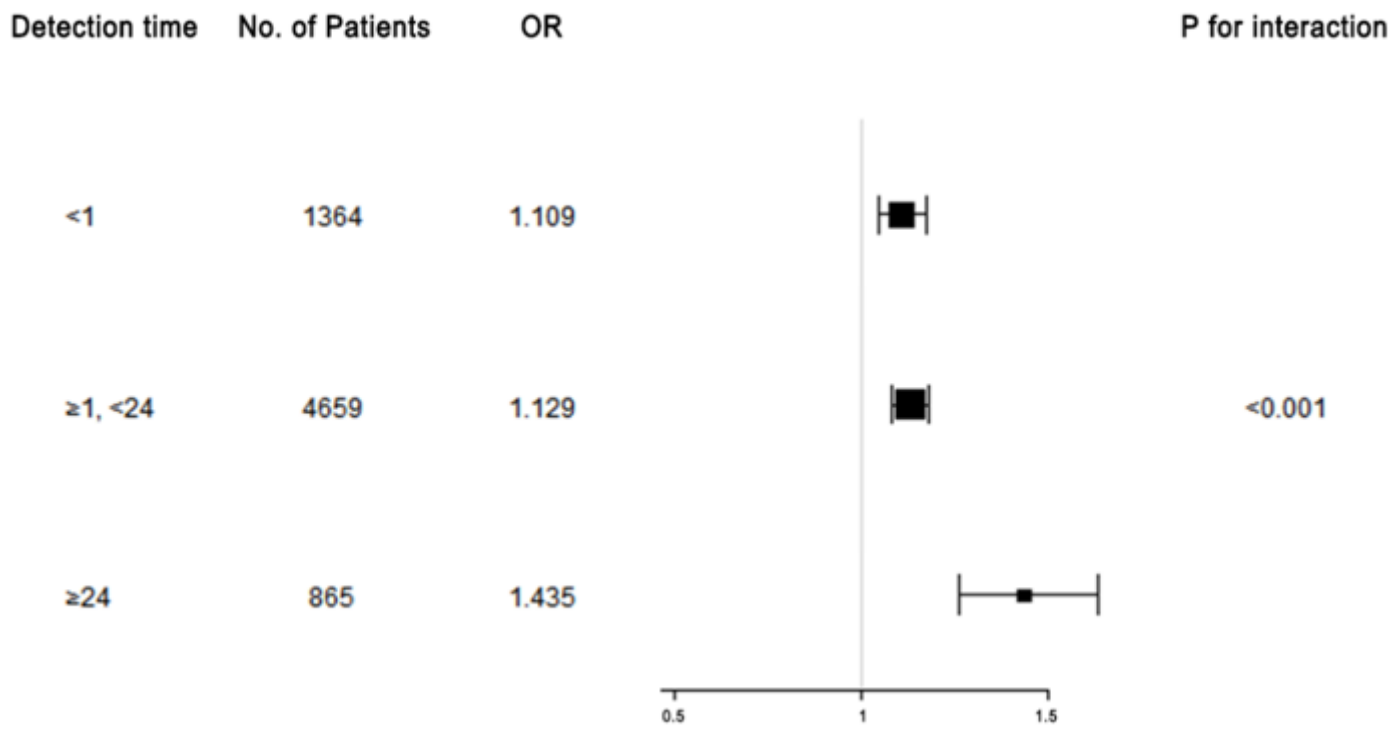

Figure 2

Relationship between initial lactate and in-hospital mortality with different detection time.

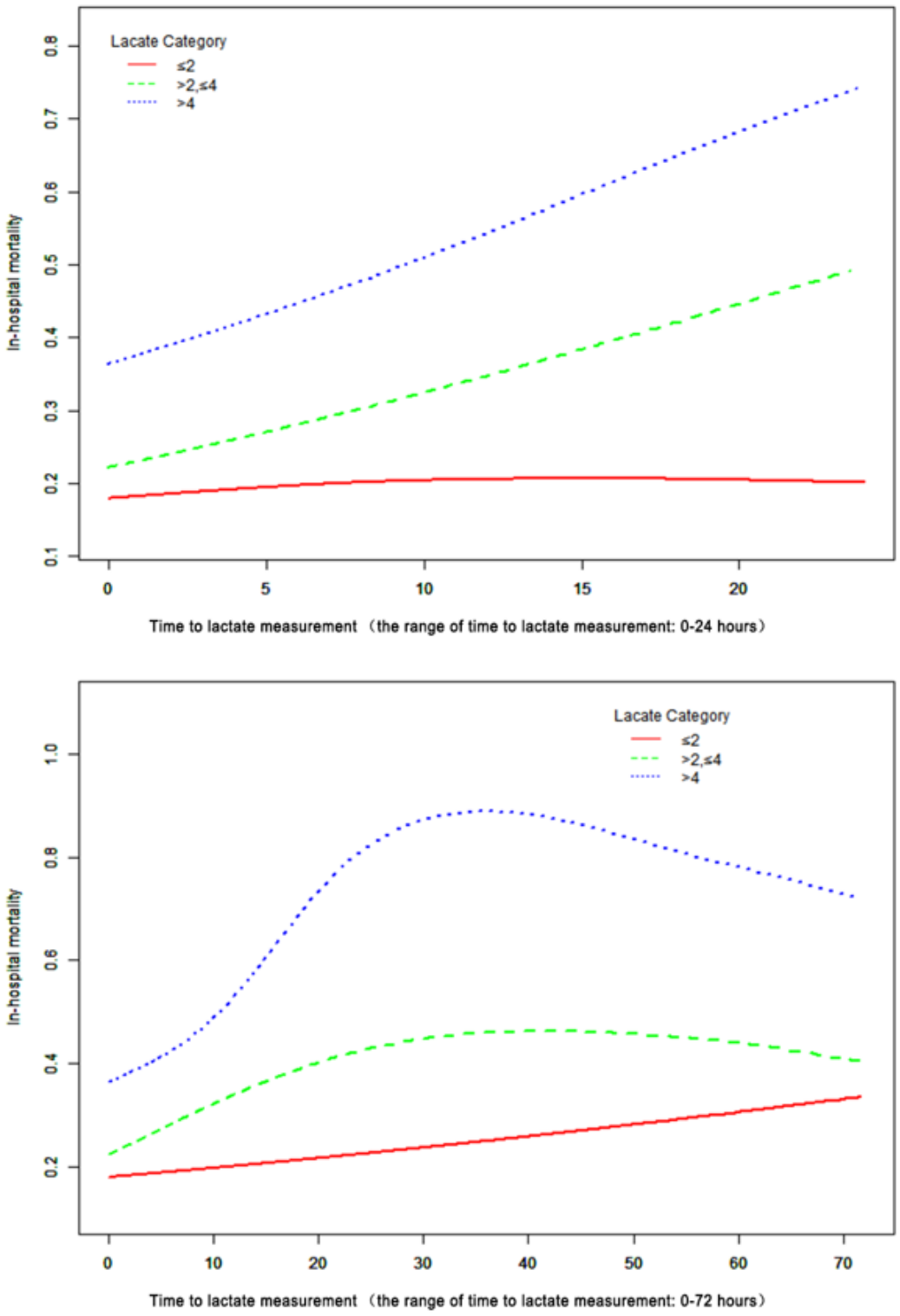

Figure 3

Delays of lactate measurement on mortality with different level of lactate