

## PROGNOSIS AND RISK FACTORS OF SEPSIS PATIENTS IN CHINESE ICUS: A RETROSPECTIVE ANALYSIS OF A COHORT DATABASE

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**ABSTRACT—Background:** Sepsis-3 proposed a new definition of septic shock that excluded patients without hyperlactacidemia. The data from China might help to elucidate the prognosis of this special patient group. **Objective:** To study the clinical prognosis and factors affecting patients with sepsis based on data from Chinese intensive care units (ICUs). **Methods:** We conducted a retrospective, multicentre observational study in a larger Chinese cohort from January 1, 2014 to August 31, 2015. The patients were divided into four groups according to the presence or absence of hypotension/vasopressor delivery and hyperlactacidemia after fluid resuscitation. Descriptive statistics for the clinical characteristics were presented. The differences between groups were assessed. A survival curve was then plotted using the Kaplan-Meier method. Finally, to better understand the risk factors for the 28-day hospital mortality rates, Cox regression analysis was performed. **Results:** In total, 1,194 patients with sepsis were included: 282 with hypotension and hyperlactacidemia, 250 with hypotension but without hyperlactacidemia, 161 with hyperlactacidemia but without hypotension, and 501 without hypotension and hyperlactacidemia. The 28-day mortality rates of the four groups were 48.2%, 43.2%, 26.1%, and 24.8%, respectively. Age, the Acute Physiology And Chronic Health Evaluation (APACHE) II score, hyperlactacidemia, hypotension, intra-abdominal infection, and cancer increased the risk of the 28-day mortality, while soft tissue infection and coming from the operating room were associated with a decreased risk of mortality. **Conclusions:** Patients with hypotension but without hyperlactacidemia in the ICU also show a high 28-day mortality, and some clinical factors may affect their prognosis and must be treated carefully in the future.

**KEYWORDS—**Hyperlactacidemia, hypotension, lactate, mortality, septic shock

### INTRODUCTION

Sepsis is the body's response to an infection and may cause severe organ dysfunction or even death. Septic shock, as the most life-threatening condition of sepsis, is associated with a higher mortality. Therefore, early recognition and timely treatment can substantially improve the prognosis. In 2016, the European Society of Intensive Care Medicine (ESICM) and Society of Critical Care Medicine (SCCM) developed a new definition for sepsis and septic shock known as Sepsis-3 (1). In contrast to previous studies on Sepsis-1 (2) and Sepsis-2 (3), Sepsis-3 excluded the concept of systemic inflammatory response syndrome (SIRS) and introduced sequential organ failure assessment (SOFA) as part of the diagnostic criteria of

sepsis. Serum lactate was added to the diagnostic criteria of septic shock.

Although the new definition was formulated using a big data-driven approach (4, 5), studies still reported inconsistent results, particularly regarding lactate levels (6, 7). Engoren et al. showed that patients with normal lactate levels have similar mortality to patients with elevated lactate levels (8). The prognosis of patients with different lactate levels requires further study. Additionally, Sepsis-3 was based on analysing the Surviving Sepsis Campaign (SSC) database, which included sepsis subjects in 218 hospitals (3). However, the hospitals registered in the SSC database are mainly located in North America, South America, and Europe, indicating a lack of Chinese data. Therefore, we aimed to compare the clinical prognosis of sepsis patients with or without hyperlactacidemia and the influencing factors in a large-scale multicentre Chinese cohort. This information may help to elucidate the effect of hyperlactacidemia on septic shock and improve the diagnostic criteria for sepsis.

### MATERIALS AND METHODS

This was a retrospective observational study. We retrospectively analysed a previously established prospective multicenter cohort database that included patients admitted to ICUs in 16 tertiary hospitals around China between January 1, 2014 and August 31, 2015. All the patients aged older than 18 years admitted to the ICUs for the first time and stayed for more than 24 h during that period

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were enrolled in the database. If a patient refused to participate, withdrew from further therapy within 48 h or had insufficient clinical data, the patient was excluded.

The protocol for the database was approved by the ethics committees of Fuxing Hospital, Capital Medical University (Number 2013FXHEC-KY018). This study was registered with the Chinese Clinical Trial Registry (www.chictr.org.cn); the registry number is ChiCTR-ECH-13003934.

In this study, consecutive adult patients with suspected or documented sepsis at ICU admission were recruited from the database. We excluded patients who met any one of the following conditions: undocumented lactate data or missing other data needed for this study.

In this study, the diagnostic criteria of sepsis were from the definition of sepsis in Sepsis-3. Although the database was created before the publication of Sepsis-3, we reviewed the data from the database and revised the diagnosis of the patients. Patients with sepsis were defined as patients with an acute elevation of SOFA scores  $\geq 2$  points following suspected or confirmed infection.

The data on demographic information, vital signs, infection sites, vasopressor administration and laboratory values were obtained from the database. The hospital course data, including the dates of admission and discharge, and survival information, were also extracted. The severity of illness was evaluated using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and SOFA score.

According to the Sepsis-3 definition, hypotension was defined as a mean arterial pressure (MAP)  $< 65$  mmHg or requiring vasopressor treatment after adequate fluid resuscitation on the day of ICU admission. Hyperlactacidemia was defined as the first documented serum lactate level  $> 2$  mmol/L after fluid resuscitation on the day of ICU admission. Based on the existence of hypotension and/or hyperlactacidemia, we divided the patients into four groups: hypotension with hyperlactacidemia group (Group 1), hypotension without hyperlactacidemia group (Group 2), nonhypotension with hyperlactacidemia group (Group 3) and nonhypotension without hyperlactacidemia group (Group 4).

The primary outcome of interest was the 28-day mortality. We also performed survival analysis based on the 28-day mortality using the Kaplan-Meier curve. To identify the risk factors for the 28-day mortality, we performed univariate analysis using univariate Cox regression and then multivariate Cox regression using the stepwise method.

Nonnormally distributed continuous variables were reported as medians and interquartile ranges (IQRs), and differences between groups were evaluated using the Wilcoxon rank-sum test. Categorical variables were reported as counts

with percentages, and comparisons between groups were performed using chi-squared test. The 28-day mortality and in-hospital mortality rates were compared between groups using chi-squared test. The 28-day survival curve was plotted using the Kaplan-Meier method and evaluated using the log-rank test. Risk factors for the 28-day mortality were analysed by Cox regression. All the tests in this study were two-sided, and a  $p$  value  $< 0.05$  was considered statistically significant. Bonferroni adjustment was used for multiple comparisons because the study comprised four groups. We used 0.01 rather than 0.008 as the  $\alpha$  value of multiple comparisons to avoid increasing the likelihood of type II error. Statistical analyses were performed using SPSS for Windows version 23.0 and R version 3.4.3.

## RESULTS

In total, 4,910 patients were enrolled in the database. Among them, 1,407 patients were diagnosed with suspected or documented sepsis. We excluded 139 patients with undocumented lactate data and 74 patients who were missing other necessary data. (Fig. 1).

Finally, 1,194 eligible patients were identified and divided into four groups. Group 1 included patients with both hypotension and hyperlactacidemia ( $n = 282$ ; 23.6%), while Group 2 patients had only hypotension and no hyperlactacidemia ( $n = 250$ ; 20.9%). Patients in Group 3 had no hypotension but had hyperlactacidemia ( $n = 161$ ; 13.5%). Group 4 comprised patients with normal levels of blood pressure and lactate ( $n = 501$ ; 42.0%).

No significant difference was found in the sex ratios among the four groups ( $P = 0.31$ ), while the ages of the four groups were slightly different ( $P = 0.03$ ). Compared with Groups 3 and 4, Groups 1 and 2 had significantly higher APACHE II scores (Group 1 vs Groups 3 and 4:  $P < 0.05$  and  $P < 0.05$ , respectively; Group 2 vs Groups 3 and 4:  $P < 0.05$  and  $P < 0.05$ ,

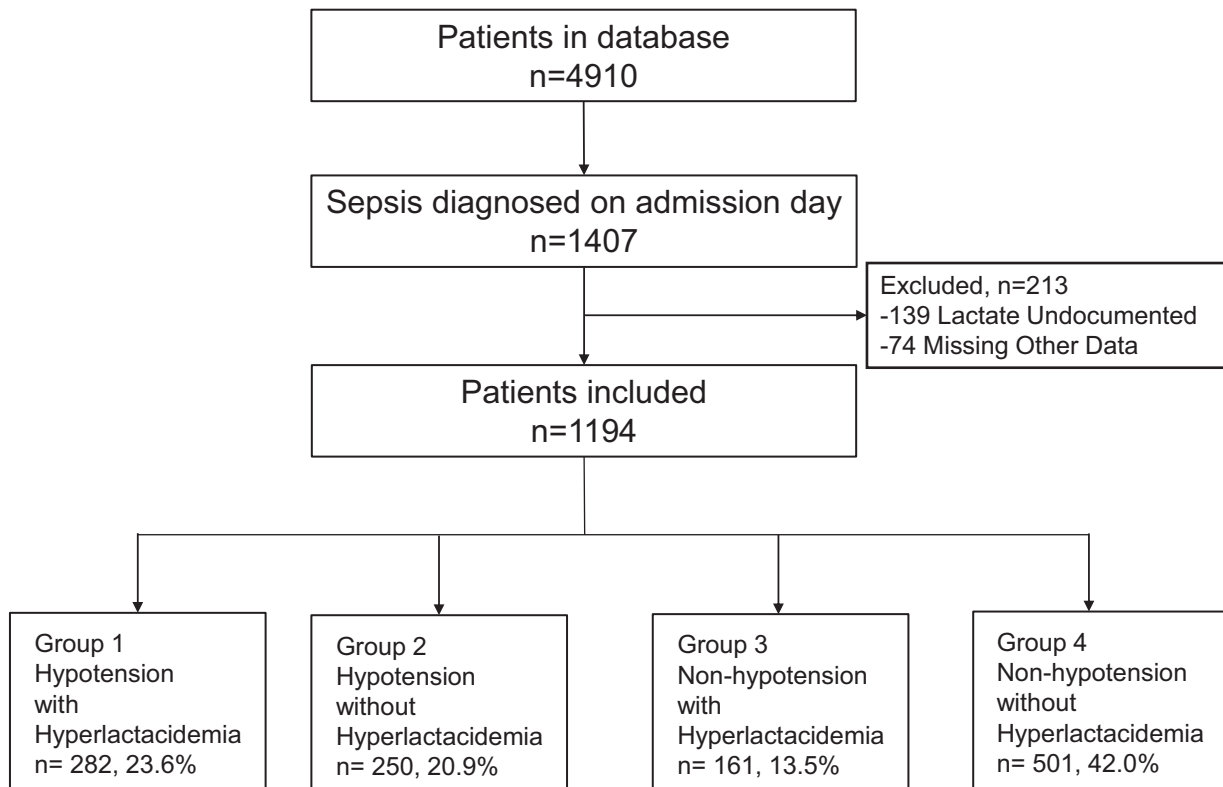


Fig. 1. Enrolment and grouping of patients to evaluate the prognosis between January 2014 and August 2015.

TABLE 1. Baseline characteristics of the study population

	Group 1	Group 2	Group 3	Group 4	<i>P</i>
n	282	250	161	501	
Male	174 (61.7%)	167 (66.8%)	102 (63.4%)	340 (67.9%)	0.31
Age (IQR)	68 (58.79)	72 (60.81)	65 (53.78)	68 (52.80)	0.03
APACHE II (IQR)	22 (17.28)	21 (16.27)	18 (13.24)	18 (14.24)	<0.01
SOFA (IQR)	12 (10.14)	10 (8.12)	7 (5.10)	6 (4.8)	<0.01
Comorbidities					
Cardiac disease	46 (16.3%)	50 (20.0%)	27 (16.8%)	86 (17.2%)	0.70
Hypertension	94 (33.3%)	100 (40.0%)	53 (32.9%)	212 (42.3%)	0.04
Diabetes	53 (18.8%)	63 (25.2%)	31 (19.3%)	117 (23.4%)	0.23
Cancer	33 (11.7%)	25 (10.0%)	20 (12.4%)	31 (6.2%)	0.02
COPD	16 (5.7%)	42 (16.8%)	11 (6.8%)	56 (11.2%)	<0.01
Chronic renal disease	19 (6.7%)	16 (6.4%)	7 (4.4%)	42 (8.4%)	0.36
No comorbidities	125 (44.3%)	82 (32.8%)	59 (36.7%)	178 (35.5%)	0.03
Suspected infection site					
Respiratory system	132 (46.8%)	156 (62.4%)	86 (53.4%)	356 (71.1%)	<0.01
Blood stream	26 (9.2%)	23 (9.2%)	9 (5.6%)	19 (3.8%)	<0.01
Intra-abdominal	111 (39.4%)	75 (30.0%)	52 (32.3%)	99 (19.8%)	<0.01
Urinary system	15 (5.3%)	11 (4.4%)	8 (5.0%)	31 (6.2%)	0.77
Wounds and soft tissues	9 (3.2%)	6 (2.4%)	12 (7.5%)	9 (1.8%)	<0.01
Others	2 (0.7%)	3 (1.2%)	4 (2.5%)	10 (2.0%)	0.38
Uncertain	35 (12.4%)	21 (8.4%)	19 (11.8%)	38 (7.6%)	0.10
Source of patients					
Emergency room*	94 (33.3%)	69 (27.6%)	61 (37.9%)	211 (42.1%)	<0.01
Other departments†	91 (32.3%)	108 (43.2%)	54 (33.5%)	191 (38.1%)	<0.05
Operating room‡	67 (23.8%)	46 (18.4%)	33 (20.5%)	52 (10.4%)	<0.01
Other hospitals§	30 (10.6%)	27 (10.8%)	13 (8.1%)	47 (9.4%)	0.48
Prognosis					
28-day mortality	136 (48.2%)	108 (43.2%)	42 (26.1%)	124 (24.8%)	<0.01
In-hospital mortality	153 (54.3%)	124 (49.6%)	52 (32.3%)	149 (29.7%)	<0.01
ICU LOS (IQR)	8 (4,16)	10 (5,19)	7 (3,16)	10 (5,19)	0.01
Hospital LOS (IQR)	13 (5,23)	16 (8,24.8)	14 (8,24)	17 (10,26)	<0.01

\*Admission from the emergency room refers to community patients who were initially diagnosed and treated in the emergency room and then admitted to the ICUs.

†Admission from other departments refers to hospitalized patients who were transferred to ICUs from other departments in the same hospital.

‡Admission from the operating room refers to post-operation patients transferred to ICUs from the operating room directly.

§Admission from other hospitals refers to patients who had been treated at other hospitals and were transferred to ICUs directly from other hospitals. COPD indicates chronic obstructive pulmonary disease; IQR, interquartile range; SOFA, sequential organ failure assessment.

respectively). A significant difference was found among the SOFA scores of the four groups (each pair of groups,  $P < 0.05$ ). (Table 1).

Patients in the two hypotension groups (Groups 1 and 2) had similar 28-day mortality rates (48.2% vs. 43.2%, respectively;  $P = 0.26$ ), and those in the two nonhypotension groups (Groups 3 and 4) also had similar 28-day mortality rates (26.1% vs. 24.8%, respectively;  $P = 0.75$ ). Compared with Groups 3 and 4, Group 1 had a significantly higher 28-day mortality rate ( $P < 0.01$ ,  $P < 0.01$ , Bonferroni adjusted), as did Group 2 ( $P < 0.01$ ,  $P < 0.01$ , Bonferroni adjusted).

By plotting the 28-day Kaplan-Meier curve, the survival rate of Group 1 was significantly lower than the rates of Group 3 and Group 4 ( $P < 0.01$  and  $P < 0.01$ , respectively, Bonferroni adjusted). Additionally, the survival rate of Group 2 was lower than that of Group 4 ( $P < 0.01$ , Bonferroni adjusted). No significant difference was found between the two hypotension groups (Group 1 vs. Group 2;  $P = 0.042$ , Bonferroni adjusted) or between the two nonhypotension groups (Group 3 vs. Group 4;  $P = 0.279$ , Bonferroni adjusted) (Fig. 2).

We performed Cox regression analysis of the 28-day mortality. First, we introduced twenty-one factors into univariate Cox regression, such as age, sex, the APACHE II score,

hypotension, hyperlactacidemia, the site of infection (including the respiratory system, blood stream, intra-abdominal region, urinary system, or soft tissue), source of patients (from other departments of the same hospital, from an operating room, or

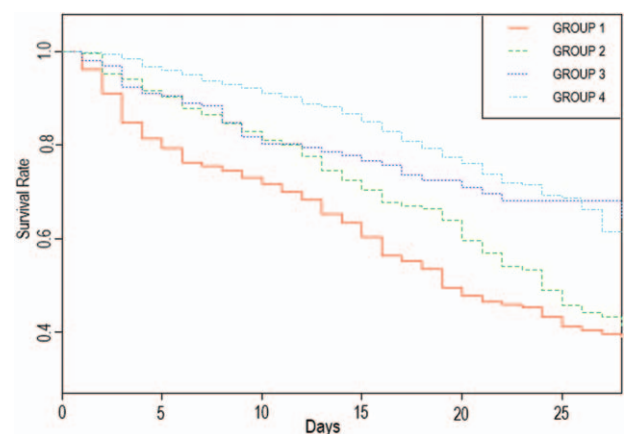


FIG. 2. Twenty-eight-day Kaplan-Meier curve of the four groups. Group 1: Hypotension with hyperlactacidemia; Group 2: Hypotension without hyperlactacidemia; Group 3: Nonhypotension with hyperlactacidemia; Group 4: Nonhypotension without hyperlactacidemia.

TABLE 2. Univariate Cox regression of risk factors

	HR		95% CI	P
Age*	1.020	1.014	1.027	<0.001
Sex	0.965	0.787	1.183	0.729
APACHE II*	1.063	1.050	1.076	<0.001
Hypotension*	2.079	1.707	2.532	<0.001
Hyperlactacidemia*	1.541	1.268	1.874	<0.001
Site of infection				
Respiratory system*	1.273	1.030	1.573	0.025
Blood stream	1.339	0.947	1.893	0.099
Intra-abdominal	1.005	0.802	1.259	0.967
Urinary system	0.770	0.486	1.221	0.267
Soft tissue*	0.350	0.145	0.846	0.020
Source of patient				
Emergency room	Reference			
Other departments*	1.253	1.007	1.559	0.043
Operating room*	0.681	0.478	0.970	0.033
Other hospitals	1.074	0.766	1.505	0.680
Comorbidities				
COPD*	1.396	1.062	1.837	0.017
Asthma	1.527	0.682	3.421	0.304
Cardiac disease	1.264	0.998	1.602	0.052
Hypertension	1.183	0.973	1.438	0.092
Diabetes	1.184	0.949	1.477	0.134
Liver cirrhosis*	2.396	1.237	4.642	0.010
Cancer*	1.554	1.143	2.112	0.005
Chronic renal disease*	1.459	1.057	2.015	0.022

\*Risk factors with statistical significance in univariate Cox regression.

APACHE II indicates Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio.

from other hospitals, compared with patients from the emergency department as a reference), and comorbidities (including chronic obstructive pulmonary diseases [COPD], asthma, coronary heart disease, hypertension, diabetes, liver cirrhosis, cancer, and chronic renal disease). The results of the univariate Cox regression are reported in Table 2. In univariate Cox regression, 12 factors showed statistical significance—age, the APACHE II score, hypotension, hyperlactacidemia, respiratory system infection, soft tissue infection, patients from other departments, patients from the operation room, patients with COPD, liver cirrhosis, cancer, and chronic renal disease. Next, we performed multivariate Cox regression using the stepwise method. After stepwise model selection, seven factors were excluded from the final model—sex, bloodstream infection, urinary system infection, COPD, coronary heart disease, hypertension, and diabetes. The results of the final model showed that age (hazard ratio [HR]: 1.015 [1.009–1.022];  $P < 0.01$ ), the APACHE II score (HR: 1.053 [1.040–1.067];  $P < 0.01$ ), hyperlactacidemia (HR: 1.436 [1.165–1.770];  $P < 0.01$ ), hypotension (HR: 1.595 [1.289–1.974];  $P < 0.01$ ), intra-abdominal infection (HR: 1.409 [1.062–1.869];  $P = 0.02$ ) and cancer (HR: 1.395 [1.021–1.905];  $P = 0.04$ ) were risk factors for the 28-day mortality. Soft tissue infection (HR: 0.372 [0.153–0.904];  $P = 0.02$ ) and coming from the operating room (HR: 0.609 [0.409–0.907];  $P = 0.01$ ) were associated with a lower risk of the 28-day mortality (Fig. 3).

## DISCUSSION

In the present study, we reported the prognosis and factors affecting sepsis patients in Chinese ICUs with or without

hyperlactacidemia based on a large-scale multicentre cohort that might provide a reference for future studies.

Presently, increasing evidence has shown that sepsis patients with hypotension and hyperlactacidemia have a higher mortality (4, 9, 10), which is in line with the conclusion of our study. However, we found that the patients with hypotension but without hyperlactacidemia also showed a higher 28-day mortality, similar to that of the patients with hypotension and hyperlactacidemia (48.2% and 43.2%, respectively;  $P = 0.26$ ). Another cross-sectional survey performed in China reported that patients with hypotension alone had a higher 90-day mortality rates (53.3%) (11). However, in previous studies, patients with hypotension but without hyperlactacidemia usually had lower mortality rates than those patients with septic shock diagnosed according to Sepsis-3 (14.4% vs. 28.5%; 8.2% vs. 25.5%) (9, 10). One possible reason may explain the inconsistency. The development of Sepsis-3 was based on a large database in European and American countries (3–5), and less is known in some developing countries, including China. In China, ICUs usually have fewer hospital beds than in high-income countries. In our study, the participating ICUs accounted for only 1.9% of the total hospital beds, while ICUs in developed countries usually acquired 10% to 20% of the total hospital beds (12, 13). Because of the small proportion of ICU beds in Chinese hospitals, patients admitted to the ICU might be more serious in China than in developed countries, and the mortality rates of these patients might be higher than those of the patients who were retained in the general wards. The SOFA scores of the patients in our study were higher than those of patients in the United States and Korea (10 [8, 12] vs. 5 [3, 8] and 6 [4, 8]) (9, 10), providing supporting evidence. Several

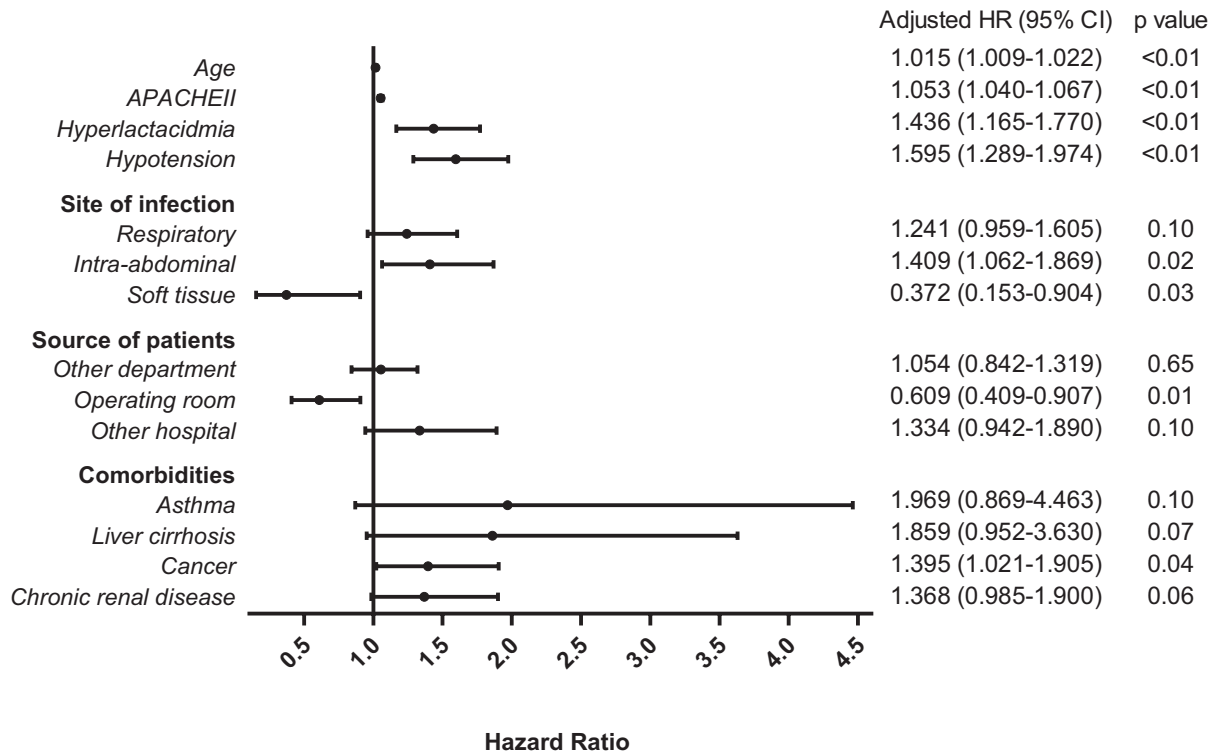


FIG. 3. Cox regression showing that age, the APACHE II score, hyperlactacidemia, hypotension, intra-abdominal infection, and cancer were risk factors for the 28-day mortality; soft tissue infection and coming from the operating room were associated with a lower risk of the 28-day mortality.

studies in low- and middle-income countries reported that the ICU mortality rates of sepsis patients with hypotension were approximately 40%, similar to the mortality rate in our study (14, 15). The relationship between medical resources and mortality of patients with sepsis in ICUs requires further research. This phenomenon may occur in other developing countries with fewer intensive care bed resources or in situations in which the medical system is overloaded.

To determine the risk factors for mortality, Cox regression was performed in our study. Hypotension and hyperlactacidemia were associated with higher hazard ratios than other risk factors for the 28-day mortality, suggesting that hypotension and hyperlactacidemia are the most important indicators of the severity of illness. This finding is consistent with other studies in which patients matching the septic shock criteria in Sepsis-3 had a high mortality (6, 16, 17). The Sepsis-3 septic shock criteria combined two risk factors with high hazard ratios, hypotension and hyperlactacidemia and showed higher specificity and lower sensitivity than prior criteria to identify patients with a relatively higher mortality rate (9, 17). Hypotension showed the highest hazard ratio in Cox regression, indicating that hypotension might still be used to predict the prognosis of patients with sepsis, particularly in developing countries that lack lactate testing devices. Cox regression also showed that age, the APACHE II score, intra-abdominal infection and cancer were risk factors, while soft tissue infection and coming from the operating room were associated with a lower risk. Intra-abdominal infection remains a challenge in infection treatment. It is usually associated with Gram-negative bacterial

infection, intestinal organism translocation, gastrointestinal dysfunction and difficulty in drainage, all of which require complex treatment and may lead to poor prognosis (18). In contrast, in our study, soft tissue infection was associated with a lower risk, and patients with soft tissue infection as the original infection site might have a better prognosis. This reason might be due to the ease of surgical treatment of soft issue infection and less impact on vital organs. Other studies reported similar results: intra-abdominal infection showed higher mortality rates, while soft tissue infection showed lower mortality rates (19, 20). Compared with patients admitted from the emergency department, patients from the operating room were associated with a lower risk, likely because of the preoperative evaluation and surgical treatment of the primary lesions.

The strength of this study includes the following aspects: First, this retrospective study was based on a previously established prospective multicentre cohort database. This database was the first large-scale multicentre cohort focusing on the treatments and prognosis of sepsis patients in intensive care units in China. Second, this study reported the characteristics of sepsis patients in a country like China with limited intensive care resources, providing a reference for other developing countries with limited intensive care resources or countries with overloaded medical systems.

There are several limitations of this study. First, the sample size of this study was smaller than that of some other studies. Considering China's population, this study only occupied a small number of cases in China. Second, although our research units were located in different areas of China, the participating

ICUs were mainly located in the capitals of provinces. The lack of data from rural regions might introduce selection bias.

## CONCLUSION

In ICUs in China, hypotensive patients with hyperlactacidemia showed the highest 28-day mortality and the worst prognosis. However, hypotensive patients without hyperlactacidemia who were excluded by the Sepsis-3 septic shock diagnostic criteria still had a poor prognosis, which should not be ignored. Therefore, in clinical work, these patients must receive adequate attention.

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