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Outcomes of patients with severe sepsis after the first 6 hours of resuscitation at a regional referral hospital in Uganda

Abdallah Amir, MBChB, MMed [a], Kacie J. Saulters, MD [b,1], Sam Olum, MBChB, MMed [a], Kelly Pitts, MD [b], Andrew Parsons, MD, MPH [b], Cristina Churchill, MD [b], Kabanda Taseera, MBChB, MMed [a], Rose Muhindo, MBChB, MMed [a], Christopher C. Moore, MD [a,b,*]

[a] Department of Medicine, Mbarara University of Science and Technology, Mbarara, Uganda
[b] Division of Infectious Diseases and International Health, University of Virginia, Charlottesville, VA

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ABSTRACT

Introduction: The optimal resuscitation strategy for patients with severe sepsis in resource-limited settings is unknown. Therefore, we determined the association between intravenous fluids, changes in vital signs and lactate after the first 6 hours of resuscitation from severe sepsis, and in-hospital mortality at a hospital in Uganda.
Materials and methods: We enrolled patients admitted with severe sepsis to Mbarara Regional Referral Hospital and obtained vital signs and point-of-care blood lactate concentration at admission and after 6 hours of resuscitation. We used logistic regression to determine predictors of in-hospital mortality.
Results: We enrolled 218 patients and had 6 hour postresuscitation data for 202 patients. The median (interquartile range) age was 35 (26-50) years, 49% of patients were female, and 57% were HIV infected. The in-hospital mortality was 32% and was associated with admission Glasgow Coma Score (adjusted odds ratio [aOR], 0.749; 95% confidence interval [CI], 0.642-0.875; $P < .001$), mid-upper arm circumference (aOR, 0.876; 95% CI, 0.797-0.964; $P = .007$), and 6-hour systolic blood pressure (aOR, 0.979; 95% CI, 0.963-0.995; $P = .009$) but not lactate clearance of 10% or greater (aOR, 1.2; 95% CI, 0.46-3.10; $P = .73$).
Conclusions: In patients with severe sepsis in Uganda, obtundation and wasting were more closely associated with in-hospital mortality than lactate clearance of 10% or greater.

1. Introduction

Severe sepsis and septic shock are leading causes of mortality in hospitalized patients in resource-limited settings (RLSs) such as sub-Saharan Africa. Although the true incidence of sepsis in sub-Saharan Africa is not known, it is estimated that there are 1.2 to 2.2 million cases of sepsis and 6.5 million deaths due to infection annually [1]. In a recent study at Mbarara Regional Referral Hospital (MRRH) in southwestern Uganda, the in-hospital mortality rate was 10% for patients with sepsis, 34% for patients with severe sepsis, and 59% for patients with septic shock [2].

Resuscitation and monitoring of patients with severe sepsis during the critical first 6 hours of resuscitation remains a significant challenge in RLS. Recent guidelines from the Surviving Sepsis Campaign (SSC) recommend many interventions and monitoring strategies that are impractical in most RLS [3–5]. The World Health Organization has also provided recommendations for management of septic shock and severe respiratory distress in RLS, but these guidelines also require intensive clinical monitoring and have not been validated [6,7]. However, point-of-care blood lactate concentration predicts mortality in patients with severe sepsis in Africa [8,9]. Lactate clearance of at least 10% is associated with improved outcomes in resource-rich settings and is a targeted end point in the SSC guidelines [4,10]. Accordingly, although monitoring SSC-recommended end points such as central venous pressures and mixed venous oxygen saturation may not be possible in RLS, serial assessment of vital signs and lactate may be a more feasible method of monitoring patients being resuscitated from severe sepsis [8,9,11].

Therefore, the objective of this study was to describe the current management strategies used during the first 6 hours of resuscitation of patients with severe sepsis in a regional referral hospital in Uganda. We aimed to determine whether improvements in measurable physiological parameters were associated with improved in-hospital mortality. We were particularly interested to know whether lactate clearance of at least 10% was associated with improved in-hospital mortality.

* Corresponding author at: Division of Infectious Diseases and International Health, Department of Medicine, University of Virginia, PO Box 801337, Charlottesville, VA 22908.
E-mail addresses: dr.amir83@yahoo.com (A. Amir), kaciesaulters@gmail.com (K.J. Saulters), soketokeny@gmail.com (S. Olum), kp7dq@virginia.edu (K. Pitts), asp5c@virginia.edu (A. Parsons), cc8qg@virginia.edu (C. Churchill), kabtash@yahoo.com (K. Taseera), drmuhindo@gmail.com (R. Muhindo), ccm5u@virginia.edu (C.C. Moore).
[1] Present address: Department of Medicine, Division of Hospital Medicine, Georgetown University, Washington, DC.

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2. Materials and methods

2.1. Description of the study site

This study was conducted at the medical emergency department (ED) and the adult general medical ward of MRRH. MRRH has 600 beds and serves as the main referral center for all the districts in southwestern Uganda as well as neighboring parts of Rwanda and the Democratic Republic of Congo. It is also the teaching hospital for the Mbarara University of Science and Technology Faculty of Medicine. Patients 14 years or older with sepsis and other nonsurgical emergencies are initially resuscitated and stabilized in the ED before being transferred to the adult general medical ward. The ED has 8 monitored beds and is staffed by 1 nurse.

2.2. Patient recruitment process

We consecutively enrolled patients at least 14 years of age with severe sepsis presenting to the ED between October 2014 and May 2015. Severe sepsis was defined by: (1) a clinically suspected infection; (2) at least 2 systemic inflammatory response syndrome criteria including an axillary temperature of at least 38°C or less than 36°C, heart rate higher than 90 beats/min, respiratory rate higher than 20 breaths/min, or white blood cell concentration greater than 12 000 cells/μL or less than 4000 cells/μL; and (3) signs of end-organ dysfunction including a systolic blood pressure (SBP) of 90 mm Hg or lower, thrombocytopenia (<100 000 cells/μL), or a Glasgow Coma Scale (GCS) score lower than 15 [2]. Patients were excluded if they required triage to a surgical or obstetrics and gynecology ward, had received any antibiotics or intravenous fluids prior to recruitment, or had a history suggestive of other diagnoses associated with lactic acidosis such as diabetic ketoacidosis, acute coronary syndrome, or chronic liver disease.

2.3. Data collection

At enrollment, each patient underwent a physical examination including measurement of their vital signs and mid-upper arm circumference (MUAC), which was obtained at the midway point between the olecranon and acromion processes as previously described [12,13]. We obtained blood for laboratory testing including random glucose concentration, complete blood cell concentration, HIV serostatus, CD4 + T-cell concentration (if HIV infected), peripheral blood bacterial cultures, and point-of-care lactate as previously described [2,13]. We obtained lactate concentration in duplicate and recorded the mean value. Six hours after the admission lactate measurement, we repeated vital signs and lactate measurements. The study team provided all vital signs and laboratory data to the admitting clinicians but was not directly involved in the management of the patients. We defined the initial time point of resuscitation as the time of initial lactate acquisition. We recorded the antibiotics, blood products, and volume of intravenous fluids administered to each patient during the first 6 hours of resuscitation. We followed up each patient throughout their hospital stay until discharge or death.

2.4. Statistical analysis

To calculate our sample size, we set α at .05 or less and power at 80%. Based on previously published data, we assumed that 30% of patients would clear lactate by at least 10% and that the in-hospital mortality for patients that cleared or did not clear lactate by at least 10% would be 25% and 45%, respectively [2,10]. Using these parameters, we determined that 199 patients would provide enough power to determine a statistically significant difference in in-hospital mortality between the 2 groups (PASS 13 Power Analysis and Sample Size Software; NCSS, LLC, Kaysville, Utah, 2014). Factoring in a dropout rate of 10% gave us an additional 19 patients for a total sample size of 218 patients. Data were recorded using Epi-Info (Centers for Disease Control, Atlanta, Ga, 2011) and analyzed using SPSS software (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp, Armonk, New York). We summarized patient characteristics as frequency with percentage for categorical variables and median with interquartile range (IQR) for continuous variables. We determined relationships between clinical and laboratory variables and outcomes using logistic and linear regression with significance set at $P < .05$. For the multivariable logistic regression models, we required that there be at least 10 outcome events for every included predictor variable [14]. In addition, we did not include predictor variables that were correlated with each other either clinically (eg, GCS and ambulatory status) or statistically as defined by a Pearson correlation P value < .05, or if the associated P value in the univariate analysis was .2 or greater. However, given our a priori hypothesis that lactate clearance of at least 10% would predict in-hospital mortality, this variable was included in the final multivariable in-hospital mortality model even if the P value in the univariate analysis was .2 or greater.

2.5. Ethical considerations

The study was approved by the Faculty Ethics Review Committee and the Institutional Ethical Review Committee at Mbarara University of Science and Technology as well as the institutional review board at the University of Virginia. All patients provided informed consent prior to enrollment in the study. If a patient could not provide informed consent, then an accompanying family member or friend provided it for them.

3. Results

3.1. Patient characteristics and resuscitation

We enrolled 218 patients and had data after 6 hours of resuscitation for 202 patients. The median (IQR) age was 35 (26-50) years, 49% of patients were female, and 57% were HIV infected, of whom 73% were receiving antiretroviral therapy (Table 1). The median (IQR) duration of illness preceding hospitalization was 14 (4-53) days and was highly correlated with low MUAC (Pearson correlation < .001). The most common presenting focus of infection was the chest (44%) followed by the gastrointestinal tract (30%) and the central nervous system (20%). MUAC was a strong predictor of HIV infection (odds ratio [OR], 0.931; 95% confidence interval [CI], 0.870-0.995; $P = .035$). Patients spent a median (IQR) of 8 (5-16) hours in the ED. The median (IQR) volume of intravenous fluids administered to patients was during the first 6 hours of resuscitation was 1.5 (1-2) liters and 89% of patients received antibiotics with a median (IQR) time to administration of 30 (14-60) minutes. For every unit increase in admission lactate, the patients received an increase of 73 mL in administered intravenous fluid (95% CI, 28-117; $P = .002$). For every unit decrease in admission oxygen saturation and mean arterial pressure (MAP), the patients received an increase of 170 mL (95% CI, 100-240; $P < .001$) and 130 mL (95% CI, 80-180; $P < .001$), respectively, in administered intravenous fluid. For every liter of administered intravenous fluid, lactate clearance increased by 10% (95% CI, 2-18; $P = .014$) and MAP increased by 5 mm Hg (95% CI, 2-9; $P = .002$). Blood pressure, heart rate, respiratory rate, and lactate were improved after 6 hours of resuscitation, but there were no improvements in temperature or oxygen saturation (Table 2). The median (IQR) lactate clearance was 24% (7%-41%), and 72% of patients achieved lactate clearance of at least 10%. In the univariate analysis, duration of illness, admission MUAC, and the total volume of administered fluids were all associated with lactate clearance of at least 10% (Table 3). In the multivariable analysis, the total volume of administered fluids remained an independent predictor of lactate clearance of at least 10% (Table 3).

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Table 1
Characteristics of the population studied

Patient characteristics (n = 218)	
Variable	Values
Demographics	
Age (y), median (IQR)	35 (26-50)
Female, n (%)	108 (49)
Clinical parameters	
HIV-infected, n (%)	125 (57)
CD4+ T-cell concentration (cells/μL), median (IQR)	78 (20-202)
Receiving antiretroviral therapy, n (%)	73 (66)
Focus of infection	
Chest, n (%)	81 (44)
Gastrointestinal, n (%)	56 (30)
Central nervous system, n (%)	36 (20)
Days of illness, median (IQR)	14 (4-53)
SBP (mm Hg), median (IQR)	85 (76-91)
DBP (mm Hg), median (IQR)	53 (40-60)
MAP (mm Hg), median (IQR)	65 (53-70)
Temperature (°C), median (IQR)	38 (37-39)
Heart rate (beats/min), median (IQR)	120 (106-136)
Respiratory rate (breaths/min), median (IQR)	34 (28-42)
O_2 saturation (%), median (IQR)	93 (86-96)
GCS, median (IQR)	15 (14-15)
MUAC (cm), median (IQR)	22 (19-25)
WBC (thousand cells/μL), median (IQR)	6.5 (4-11)
Hemoglobin (g/dL), median (IQR)	11 (8-13)
Platelets (thousand cells/μL), median (IQR)	159 (95-260)
Resuscitation	
Received antibiotics, n (%)	178 (89)
Time to antibiotics (min), median (IQR)	30 (14-60)
Supplemental oxygen, n (%)	15 (7)
Total intravenous fluids (L), median (IQR)	1.5 (1.0-2.0)
Time in ED (h), median (IQR)	8 (6-10)
Admission lactate (mmol/L), median (IQR)	3.4 (2.2-5.2)

DBP indicates diastolic blood pressure; WBC, white blood cell count.

3.2. Mortality

The in-hospital mortality rate was 32%, and the median (IQR) survival time was 4 (1-8) days. There was no statistically significant difference in mortality between patients younger than 18 years (n = 8) and patients a least 18 years of age (29% vs 32%; 2-tailed Fisher exact test, $P = 1.0$). Lactate clearance of at least 10% after 6 hours of resuscitation was not associated with improvement in in-hospital mortality (OR, 0.980; 95% CI, 0.468-2.052; $P = .956$). There were 35 patients (16%) who received therapy for *Mycobacterium tuberculosis* (MTb) infection, but this was not associated with in-hospital mortality (OR, 1.330; 95% CI, 0.603-2.930; $P = .480$). Changes in vital signs and lactate over 6 hours were not associated with in-hospital mortality. However, in a subgroup analysis of patients in the lowest quartile of admission SBP, there was an association between the change in SBP for 6 hours and in-hospital mortality (OR, 1.004; 95% CI, 1.004-1.038; $P = .018$). In the univariate analysis, duration of illness, admission GCS and MUAC, inability to walk, receipt of supplemental oxygen, and 6-hour SBP and oxygen saturation were all associated with in-hospital mortality (Table 4). In the multivariable analysis, admission GCS and MUAC, and 6-hour SBP remained independent predictors of in-hospital mortality.

Table 2
Physiological measurements at admission and 6 hours after admission

	$T = 0$ h	$T = 6$ h	P
SBP (mm Hg), median (IQR)	85 (76-90)	96 (90-100)	<.001
DBP (mm Hg), median (IQR)	55 (40-60)	60 (50-70)	<.001
MAP (mm Hg), median (IQR)	65 (53-70)	71 (63-80)	<.001
Temperature (°C), median (IQR)	38 (37-39)	38 (37-38)	.871
Heart rate (beats/min), median (IQR)	120 (106-136)	110 (96-120)	<.001
Respiratory rate (breaths/min), median (IQR)	33 (28-42)	28 (22-32)	<.001
O_2 saturation (%), median (IQR)	92 (86-96)	94 (89-96)	.234
Lactate (mmol/L), median (IQR)	3.4 (2.2-5.2)	2.5 (1.7-4.0)	<.001

DBP indicates diastolic blood pressure.

4. Discussion

Deaths from severe sepsis in RLS are increasingly recognized as a global public health crisis, and improved strategies for management of critically ill patients with severe sepsis in RLS are urgently needed [1]. For the first time, we have reported the outcomes of patients with severe sepsis after the critical first 6 hours of resuscitation in a regional referral hospital in Uganda. We found that although physiological parameters including blood lactate concentrations were improved after resuscitation, this had no bearing on in-hospital mortality. Instead, obtundation as measured by a low GCS and wasting as measured by MUAC were independently associated with in-hospital mortality.

This finding differs from several studies performed in resource-rich settings where lactate clearance of at least 10% was associated with improved outcomes from severe sepsis [4,10]. However, these studies were performed in EDs and intensive care units with the capacity for sophisticated monitoring and advanced life support which generally does not exist in RLS [11]. In addition, unlike our study, these studies did not include predominantly HIV-infected patients who are the most likely to die of severe sepsis in sub-Saharan Africa [2]. These patients are often wasted as measured by MUAC which was closely associated with HIV infection in our study, and wasting is a known risk factor for in-hospital and 30-day mortality [13,15].

Despite most of our study patients achieving lactate clearance of at least 10%, the median lactate concentration at 6 hours remained abnormally high at 2.5 mmol/L [4,16,17]. In addition, although heart rate and respiratory rate improved with resuscitation, they too remained elevated at 6 hours. This suggests that either resuscitation was not adequate or improvement in physiologic parameters during treatment of severe sepsis did not reflect correction of underlying pathology [18–20]. Once patients were transferred to the medical ward, it is likely that they received much less frequent monitoring due to limited human and material resources, and consequently, physiological trends in the wrong direction may have been missed [11,21]. Even if worrying trends were noted on the ward after initial resuscitation in the ED, like many hospitals in RLS, there is currently no automated rapid response mechanism at MRRH that could provide further early diagnostic and therapeutic interventions [21].

The optimal fluid resuscitation strategy for patients with severe sepsis is not known, and it is likely that overresuscitation is just as harmful as underresuscitation particularly when mechanical ventilation is not available [22,23]. In 2 randomized studies performed in African settings, fluid resuscitation was associated with harm particularly in those with hypoxemic respiratory failure [24,25]. In contrast, a prior study from Uganda showed that targeted fluid resuscitation with a median volume of 3 L of fluid improved outcomes compared with historical controls that received a median of 0.5 L of fluid [6]. In our study, increased lactate, low MAP, and low oxygen saturation at admission were associated with increased fluid administration and the total volume of administered fluid was associated with improved lactate clearance. This suggests that clinicians based resuscitation decisions on the perceived severity of patient illness. Given the increased volume of intravenous fluids administered to the most severely ill patients and the finding that low oxygen saturation at 6 hours was associated with in-hospital mortality in the univariate analysis, it is possible that fluid resuscitation caused harm to our patients despite improvements in measurable physiological parameters.

Even when resuscitation improves physiological parameters and tissue perfusion, patients may ultimately die of infection if they receive inadequate source control or inappropriate antibiotics, or if they are

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Table 3
Predictors of ≥10% lactate clearance after 6 hours of resuscitation

	OR	95% CI	*P*	aOR	95% CI	*P*
Baseline variables						
Days of illness	0.994	0.988-0.999	.022	0.995	0.988-1.001	.105
Admitted between 8 PM and 8 AM	0.744	0.264-2.094	.576			
Age	1.019	0.999-1.039	.065	1.012	0.989-1.035	.307
Female	0.894	0.483-1.655	.721			
HIV-infected	0.971	0.519-1.816	.927			
CD4 + T-cell concentration (cells/μL)	1.000	0.997-1.002	.775			
WHO HIV stage	1.525	0.779-2.987	.218			
Receiving antiretroviral therapy	0.911	0.375-2.214	.836			
SBP (mm Hg)	0.997	0.988-1.006	.529			
DBP (mm Hg)	1.000	0.987-1.014	.952			
Temperature (°C)	1.031	0.884-1.204	.694			
Heart rate (beats/min)	1.005	0.993-1.017	.411			
Respiratory rate (breaths/min)	1.005	0.980-1.030	.715			
O_2 saturation (%)	0.980	0.954-1.006	.127	0.988	0.960-1.017	.407
Glasgow Coma Scale score	1.047	0.921-1.189	.484			
MUAC (cm)	1.088	1.004-1.179	.040	1.084	0.982-1.196	.110
Ambulatory	0.811	0.420-1.563	.531			
WBC concentration (thousand cells/μL)	1.048	0.995-1.103	.074	1.032	0.983-1.083	.200
Platelet concentration (thousand cells/μL)	0.999	0.997-1.001	.383			
6-h variables						
SBP (mm Hg)	1.001	0.988-1.015	.844			
DBP (mm Hg)	1.000	0.982-1.019	.974			
Temperature (°C)	0.911	0.744-1.115	.366			
Heart rate (beats/min)	1.007	0.989-1.024	.466			
Respiratory rate (breaths/min)	0.985	0.955-1.016	.340			
O_2 saturation (%)	0.999	0.980-1.019	.914			
Received antibiotics	1.496	0.595-3.759	.392			
Received oxygen	1.159	0.302-4.453	.830			
Received blood	1.054	0.438-2.536	.906			
Total fluids received (L)	1.837	1.217-2.773	.004	1.901	1.190-3.039	.007
Delta variables measuring change from baseline to 6 h						
SBP (mm Hg)	0.994	0.985-1.005	.279			
DBP (mm Hg)	0.999	0.985-1.013	.915			
MAP (mm Hg)	0.997	0.983-1.011	.676			
Temperature (°C)	1.076	0.902-1.284	.418			
Heart rate (beats/min)	1.007	0.992-1.023	.365			
Respiratory rate (breaths/min)	1.029	0.993-1.065	.112			
O_2 saturation (%)	0.990	0.974-1.006	.208			

aOR indicates adjusted odds ratio; WBC, white blood cell count; WHO, World Health Organization.

immune compromised. The benefits of source control in RLS were recently demonstrated in a provincial hospital in northeastern Thailand, where source control substantially reduced mortality from *Staphylococcus aureus* infection [26]. Unfortunately, like many regional referral hospitals in sub-Saharan Africa, MRRH has limited diagnostic ability to identify deep space infections that would be amenable to source control. *M tuberculosis* was the predominant cause of bloodstream infections in a recent study of patients admitted with severe sepsis in Uganda, but only 15% of these patients received anti-MTb therapy [27]. It is known that delays in MTb therapy in patients with shock leads to excess mortality, and this lack of appropriate therapy may explain increased mortality in our patients despite initial resuscitation [28]. Other undiagnosed infections such as malaria and dengue virus may contribute to poor outcomes in high-prevalence settings, but a prior study from MRRH showed that malaria is an infrequent cause of sepsis and dengue virus seroprevalence in the region is low [29–31]. Finally, many of our study patients were HIV infected with low CD4 + T-cell concentrations. Accordingly, they had limited ability to overcome severe sepsis despite resuscitation due to immune compromise and wasting [13,15].

Our study was limited in several ways. We were only able to obtain clinical and laboratory measurements at admission and at 6 hours. Data at additional time points may have allowed us to better understand the clinical trajectory of the patients. There may have been interobserver variations in some measurements such as MUAC, although we lessened variability by only using trained study personnel to obtain the values [12]. It is possible that usually unavailable 6-hour vital sign and lactate data which were provided to clinicians biased patient outcomes. We were unable to obtain additional laboratory testing such as blood gases and metabolic panels which may have provided further information about the severity of illness. Our information about underlying microbiological causes of sepsis was limited, and therefore, we cannot make comment about appropriateness of antimicrobial administration. Finally, we do not have detailed information about what transpired with patients once they left the ED and were admitted to the general medical ward. Nonetheless, our data provide a real-world example of the outcomes of patients with severe sepsis in a regional referral hospital in sub-Saharan Africa after the critical first 6 hours of resuscitation.

5. Conclusions

Although patients with severe sepsis at a regional referral hospital in southwestern Uganda had improvement in vital signs and lactate values after 6 hours of resuscitation, this was not associated with decreased in-hospital mortality. Instead, obtundation and wasting were the strongest predictors of in-hospital mortality. The volume of intravenous fluids administered during the first 6 hours of resuscitation was associated

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Table 4
Predictors of in-hospital mortality after 6 hours of resuscitation

	OR	95% CI	*P*	aOR	95% CI	*P*
Baseline variables						
Days of illness	1.005	1.000-1.011	.048			
Admitted between 8 PM and 8 AM	1.063	0.352-3.211	.913			
Age	1.007	0.991-1.024	.386			
Female	1.117	0.616-2.024	.715			
HIV-infected	1.326	0.722-2.435	.363			
CD4 + T-cell concentration (cells/μL)	1.000	0.997-1.003	.842			
WHO HIV stage	2.193	0.886-5.431	.090			
SBP (mm Hg)	0.997	0.989-1.006	.541			
DBP (mm Hg)	0.993	0.981-1.006	.302			
Temperature (°C)	0.993	0.981-1.006	.302			
Heart rate (beats/min)	0.998	0.987-1.010	.783			
Respiratory rate (breaths/min)	1.007	0.984-1.030	.545			
O_2 saturation (%)	0.992	0.977-1.006	.262			
Glasgow Coma Scale score	0.811	0.711-0926	.002	0.749	0.642-0.875	<.001
MUAC (cm)	0.914	0.846-0.988	.023	0.876	0.797-0.964	.007
Ambulatory, n (%)	0.271	0.135-0.543	<.001			
WBC concentration (thousand cells/μL)	1.000	0.995-1.005	.866			
Platelet concentration (thousand cells/μL)	1.001	0.999-1.003	.428			
Lactate (mmol/L)	1.072	0.977-1.176	.142			
6-h variables						
SBP (mm Hg)	0.983	0.969-0.997	.016	0.979	0.963-0.995	.009
DBP (mm Hg)	0.990	0.973-1.008	.288			
Temperature (°C)	0.987	0.969-1.005	.145	1.003	0.982-1.024	.807
Heart rate (beats/min)	1.009	0.990-1.028	.369			
Respiratory rate (breaths/min)	1.017	0.987-1.049	.261			
O_2 saturation (%)	0.977	0.957-0.998	.029	0.987	0.966-1.009	.241
Lactate clearance (%)	1.000	0.995-1.005	.994			
Lactate clearance >10%	0.980	0.468-2.052	.956	1.390	0.640-3.018	.406
Received antibiotics	0.890	0.356-2.222	.803			
Received oxygen	4.2	1.345-13.116	.014			
Received blood	1.047	0.458-2.393	.913			
Total fluids received (L)	1.020	0.755-1.377	.897			
Delta variables measuring change from baseline to 6 h						
SBP (mm Hg)	1.009	0.997-1.020	.153			
DBP (mm Hg)	0.999	0.985-1.012	.847			
MAP (mm Hg)	1.002	0.988-1.016	.761			
Temperature (°C)	0.991	0.972-1.011	.372			
Heart rate (beats/min)	0.997	0.982-1.012	.695			
Respiratory rate (breaths/min)	0.994	0.966-1.023	.663			
O_2 saturation (%)	1.006	0.991-1.020	.459			
Lactate	1.058	0.943-1.188	0.336			

aOR indicates adjusted odds ratio; WBC, white blood cell count; WHO, World Health Organization.

with the severity of illness of patients and the ability to clear lactate by at least 10%. Further studies are needed to better delineate optimal early management and monitoring of patients with severe sepsis in RLS.

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