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Clinical predictors of early death from sepsis

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ABSTRACT

Purpose: Patients with severe sepsis who experience rapid, early deterioration and death are of particular concern. Our objective was to identify predictors of early death in Emergency Department (ED) patients with severe sepsis.
Methods: Secondary analysis of two prospective studies of adult ED patients with severe sepsis. The primary outcome was early death, defined as death within 24 h of triage.
Results: Out of 410 severe sepsis admissions, 20 patients experienced early death. These patients demonstrated significantly higher initial lactate (7.3 versus 3.3 mmol/L, $p < 0.001$) and modified SOFA (mSOFA) scores (10 vs 6, $p < 0.001$), were less likely to normalize their lactate ($p < 0.001$), had lower initial pH ($p < 0.001$), and more frequently had early positive blood cultures ($p = 0.021$). Multivariable logistic regression identified initial serum lactate level (OR 1.19, 95% CI 1.06–1.35) and mSOFA score (OR 1.17, 95% CI 1.00–1.36) as independent predictors of early death. A repeat lactate ≥ 5 mmol/L had a sensitivity of 55% and specificity of 89% for early death. There were no significant treatment differences between groups.
Conclusion: Initial serum lactate and mSOFA score were independent predictors of mortality within 24 h of ED admission in patients with severe sepsis.

1. Introduction

Approximately 570,000 patients with sepsis present to Emergency Departments (ED) in the United States each year [1]. Research suggests outcomes in sepsis are improved with timely recognition and early resuscitation initiated in the ED [2]. However, given the broad spectrum of clinical presentations and variable rates of disease progression, the early identification of septic patients at increased risk for clinical deterioration remains challenging. The need for rapid risk stratification of these patients in the ED has fueled a large body of research on biomarkers and clinical prediction tools [3,4,5]. Several studies have demonstrated the role for these clinical indicators in independently predicting in-hospital mortality in patients with sepsis [6,7].

Despite this, there remains a paucity of data on predictors of early death, or death within the first 24 h, in septic patients. Identifying a subset of patients with severe sepsis or septic shock who are at increased risk of early death could aid in the prioritization of care for these patients and assist in predicting which patients are most likely to benefit from higher levels of care. Additionally, this information could help direct future clinical trials investigating novel therapeutic interventions. To our knowledge, no study has specifically evaluated this cohort of septic patients. The objective of this study was to identify independent predictors of mortality within 24 h of ED arrival in patients with severe sepsis or septic shock. Our secondary objective was to test the hypothesis that early therapeutic interventions decreased the risk of early death.

2. Methods

2.1. Study design

We conducted a secondary analysis of two completed studies of adult ED patients with severe sepsis or septic shock, one single-center study and one multi-center study. The single center study was a prospective, observational cohort study evaluating end-tidal carbon dioxide as a resuscitative end point for sepsis [8]. The study was conducted from 2012 to 2014 in the adult ED and intensive care unit at a tertiary care academic medical center in the United States. The multi-center study was a randomized, clinical trial evaluating the non-inferiority of lactate compared with central venous oxygen saturation during early resuscitation in sepsis which took place from January 2007 to January 2009 in the EDs of 3 large, urban, tertiary care centers [9]. Briefly, both

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studies included only adult patients (age > 17 years) with severe sepsis (2 of 4 systemic inflammatory response syndrome criteria, infection, and lactate > 4 mmol/L) or septic shock (systolic blood pressure < 90 mm Hg despite at least 20 mL/kg intravenous fluids) within the first 6 h of sepsis recognition. Patients enrolled in both studies were treated with early, protocolized resuscitation bundles which included early broad-spectrum antibiotics, intravenous fluids, lactate monitoring, and blood cultures within the first 6 h. The institutional review boards at each institution approved the enrollment protocols.

2.2. Study protocol & measures

Prospectively collected data for both original studies included patient demographics, suspected source of infection, patient comorbidities, vital signs, and laboratory values for markers of organ dysfunction, including initial and repeat serum lactate concentrations. Lactate normalization was defined as an initial lactate >2 mmol/L followed by a subsequent measurement <2 mmol/L within 6 h [10]. Additionally, treatment interventions were available for both cohorts, including the total quantity of intravenous fluids administered during the initial 24 h and vasopressor usage. For this secondary analysis, two of the authors (AJ and TR) performed a chart review to retrospectively calculate modified Sequential Organ Failure Assessment (mSOFA) scores, an adjustment of the SOFA score that removes the Glasgow Coma Scale (GCS) component as this data was not prospectively collected for all patients. mSOFA has been studied and has been shown to have similar predictive ability as SOFA for predicting organ failure [11,12]. Both ED and inpatient records were reviewed to adjudicate sepsis diagnosis, and systematically collect comorbidities, source of infection, culture results, presence of shock, vasopressor or inotrope use, respiratory failure requiring mechanical ventilation, time to initial antibiotics, time to initial vasopressors, quantity of fluid resuscitation and blood product administration.

2.3. Data analysis

The primary outcome for this study was all-cause mortality within 24 h of ED presentation. Student's *t*-test, Wilcoxon rank-sum test, and chi-square or Fisher's exact tests were used as appropriate to analyze the differences in baseline demographic characteristics, comorbidities, source of infection, treatment data and physiologic parameters between the early death and early survival groups.

Univariate analyses of multiple covariates, which included patient comorbidities, clinical characteristics and interventions were used to derive a multivariate logistic regression model predictive of composite adverse outcome. Candidate variables were chosen from the univariate analyses, and all variables with p-values of 0.1 or less were used to inform the choice of potential predictor variables for the final regression model. To avoid over-fitting, given the relatively low number of primary outcomes (early mortality) in the sample, we limited the number of independent variables to the three most significant, which is based upon a commonly used method to increase the accuracy of regression models in epidemiology [13]. When univariate comparisons revealed significance for collinear variables, the more clinically useful of the two was chosen for inclusion in the regression model. For example, repeat lactate and lactate normalization are collinear, as lactate normalization is derived from repeat lactate. Therefore lactate normalization was included in the model and repeat lactate value was not. All statistical tests were two-tailed and p-values of <0.05 were considered significant. Graphical and statistical analyses were performed using Stata Version 12 (StataCorp LP, College Station, Texas).

3. Results

A total of 410 patients with severe sepsis or septic shock met the inclusion criteria and were included in the final analysis (Table 1). Of these, 270 (66%) were older than 55 years, 188 (46%) were female. 219 (53%) were white and 158 (39%) were African American. Diabetes mellitus was the most common comorbidity (37%), followed by active cancer (21%), and COPD (20%).The most common sources of infection were pulmonary (49%), followed by urinary tract (28%), and intra-abdominal (15%).

Table 1
Demographic, source of sepsis and comorbidities for patients meeting the primary outcome (death within 24 h) versus survival at 24 h.

Variable	Total (N = 410)	Alive at 24 h (N = 390)	Deceased at 24 h (N = 20)	p-Value
Age > 55	270 (66%)	254 (64%)	16 (80%)	0.172
Sex, female, n (%)	188 (46%)	175 (45%)	13 (65%)	0.078
African American, n (%)	160 (39%)	150 (38%)	10 (50%)	<0.001
Source of sepsis, n (%)				
Pulmonary	158 (49%)	147 (38%)	11 (55%)	0.121
Urinary	112 (28%)	108 (28%)	5 (25%)	0.793
Intra-abdominal	62 (15%)	59 (15%)	4 (20%)	0.556
Bacteremia	16 (4%)	16 (4%)	0 (0%)	0.356
CNS	4 (1%)	4(1%)	0 (0%)	0.649
Comorbidities, n (%)				
Diabetes mellitus	152 (37%)	147 (38%)	5 (25%)	0.252
End stage renal disease	40 (10%)	38 (12%)	1 (5%)	0.481
COPD	80 (20%)	73 (19%)	7 (35%)	0.074
Human immunodeficiency virus	39 (10%)	30 (8%)	1 (5%)	0.657
Malignancy	85 (21%)	77 (20%)	8 (40%)	0.030
Transplant	14 (3%)	14 (4%)	0 (0%)	0.389

Comorbidities were defined by presence as documented in the medical record. HIV = human immunodeficiency virus, COPD = chronic obstructive pulmonary disease, CNS = central nervous system.

Of the 410 patients in the study, 20 (4.9%) patients experienced the primary outcome of death within 24 h of ED arrival. Table 2 compares demographics, physiologic parameters, suspected source of infection, patient comorbidities, and treatment data between the early survival and early death groups. Compared to the early survival group, the early death group had statistically significant higher initial lactate values (7.3 vs. 3.3 mmol/L, p < 0.001), repeat lactates (6.1 vs 1.8 mmol/L, p < 0.001), mSOFA scores (10 (IQR 6,11) vs. 6 (IQR 4,8), p < 0.001), lower mean arterial or venous pH (7.20 vs 7.31, p < 0.001 N = 271) and were more likely to have positive blood cultures (65% vs. 39%, p = 0.021) or active cancer (40% vs 20%, p = 0.030). Figs. 1–3 contain boxplots illustrating median initial lactate levels, repeat lactate levels, and mSOFA scores across the groups.

Lactate normalization differed significantly between groups, with 95% of patients failing to achieve lactate normalization in the early death group, compared to only 48% of patients in the early survivors group (p < 0.001). However, lactate clearance [(initial lactate–subsequent lactate)/initial lactate] did not differ significantly between the groups (−1.3 vs −1.8, p = 0.223). There were no significant differences in age (age > 55 years) (80% vs 64%, p = 0.172), sex (65% vs 45%, p = 0.078), comorbidities, or source of infection among patients with early death. (Table 2).

With regards to early interventions for sepsis, patients with early death had no significant differences for rates of vasopressor use (70% vs 53%, p = 0.145), time to initiating vasopressors (457 min vs 293 min, p = 0.264), time to antibiotics (152 min vs 171 min, p = 0.638), need for mechanical ventilation (80% vs 84%, p = 0.651), IVF administration at 6 h (2484 mL vs 2248 mL, p = 0.507), IVF administration at 24 h (5419 vs 5028, p = 0.507), need for PRBC infusion (15% vs 9.2%, p = 0.391) or quantity of PRBCs administered (2.0 units vs 2.7 units, p = 0.373).

Predictor variables included in the final model were initial serum lactate, lactate normalization, and mSOFA score. The multivariable logistic regression model identified initial serum lactate (OR 1.19, 95% CI 1.05–1.35, p = 0.004) and initial mSOFA score (OR 1.17, 95% CI 1.00–