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Original Contribution

The prognostic role of non-critical lactate levels for in-hospital survival time among ED patients with sepsis☆,☆☆

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ABSTRACT

Objective: This study describes emergency department (ED) sepsis patients with non-critical serum venous lactate (LAC) levels (LAC <4.0 mmol/L) who suffered in-hospital mortality and examines LAC in relation to survival times.

Methods: An ED based retrospective cohort study accrued September 2010 to August 2014. Inclusion criteria were ED admission, LAC sampling, >2 systemic inflammatory response syndrome criteria with an infectious source (sepsis), and in-hospital mortality. Kaplan-Meier curves were used for survival estimates. An a priori sub-group analysis for patients with repeat LAC within 6 hours of initial sampling was undertaken. The primary outcome was time to in-hospital death evaluated using rank-sum tests and regression models.

Results: One hundred ninety-seven patients met inclusion criteria. Pulmonary infections were the most common (44%) and median LAC was 1.9 mmol/L (1.5, 2.5). Thirteen patients (7%) died within 24 hours and 79% by ≤28 days. Median survival was 11 days (95% CI, 8.0-13). Sixty-two patients had repeat LAC sampling with 14 (23%) and 48 (77%) having decreasing increasing levels, respectively. No significant differences were observed in treatment requirements between the LAC subgroups. Among patients with decreasing LAC, median survival was 24 days (95% CI, 5-32). For patients with increasing LAC median survival was significantly shorter (7 days; 95% CI, 4-11, $P = .04$). Patients with increasing LAC had a non-significant trend toward reduced survival (HR = 1.6 95% CI, 0.90-3.0, $P = .10$).

Conclusions: In septic ED patients experiencing in-hospital death, non-critical serum venous lactate may be utilized as a risk-stratifying tool for early mortality, while increasing LAC levels may identify those in danger of more rapid deterioration.

1. Introduction

Sepsis, defined as a systemic inflammatory response syndrome (SIRS) in the setting of infection, represents a wide spectrum of pathology and is a common emergency department (ED) diagnosis [1,2]. Severe sepsis is defined by the presence of acute organ dysfunction secondary to infection, while the sub-classification of septic shock occurs with concomitant hypotension not reversed by fluid resuscitation therapies. In the United States more than 750,000 patients with severe sepsis are treated in EDs annually [2]. Contemporary trials demonstrate a mortality rate of approximately 20% to 30% among those with septic shock [3–5]. ED patients admitted to hospitals with uncomplicated or non-severe sepsis (having no clinical evidence of shock or acute organ dysfunction) compose a less well-studied population [6]. This clinical sub-group however accounts for a large proportion of the sepsis-related morbidity and mortality per annum [7–10]. Identification of patients with non-severe sepsis who will have poor outcomes is difficult as there is often a lack of early clinical indicators and hemodynamic instability may not manifest until hours or days after the initial ED evaluation [11–13]. Research has shown that ED patients with uncomplicated sepsis have a one in five chance of developing severe sepsis or septic shock within 72 hours of presentation, and with this disease progression there is an associated increased risk of mortality [11].

Serum venous lactate (LAC) is a physiologic marker that has prognostic value for mortality in ED patients with sepsis [13,14]. LAC >4 mmol/L is the most commonly used clinical parameter in defining severe sepsis and levels above this critical value are associated with increased mortality [2,14]. The utility of LAC in relation to morbidity and mortality outcomes among patients with non-severe sepsis is less well defined. In an ED based prospective study enrolling nonelderly patients

Abbreviations: LAC, serum venous lactate; NCLAC, non-critical serum venous lactate; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.

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with stable hemodynamics and elevated LAC >2 mmol/L was associated with increased need for pharmacologic vasopressor support and mechanical ventilation by 72 hours of hospitalization [15]. A systematic review examining patients with intermediate lactate levels (2.0-3.9 mmol/L) found a 28-day mortality rate of 15% for ED patients with uncomplicated sepsis and normotension [14]. Furthermore, a retrospective study of patients admitted with sepsis and initial LAC levels in the intermediate range found that those who had improvement in their LAC on repeat sampling within 12 hours had a 30-day mortality rate of 13.3% as compared to 24.7% among patients who failed to have improvement [16]. Although guidelines do not recommend repeat sampling in non-severe sepsis these findings suggest that serial LAC sampling may provide clinically important information in this subpopulation. While these studies show a significant mortality risk for patients with non-critical serum venous lactate (NCLAC) levels and that LAC clearance may be associated with reduced mortality, they fail to define the utility of LAC levels in prognosticating survival time in such high-risk cohorts. This study aims to describe the characteristics of ED patients with NCLAC levels and sepsis who died during hospitalization and evaluate the role of initial, and trends in LAC in relation to in-hospital survival.

2. Methods

2.1. Study setting and design

This retrospective cohort study was carried out at an urban teaching hospital. The ED has an annual census of approximately 140 000 visits. Documentation in the hospital is done using an electronic medical record (EMR) that allows for comprehensive review of all health information. Institutional review board approval was obtained before the study.

2.2. Inclusions and exclusion criteria and data acquisition

ED patients meeting the following criteria were included in the study: (1) admission through the ED, (2) >2 SIRS criteria at time of triage and a documented infectious source (sepsis) [2], (3) NCLAC on initial ED serologic evaluation, and (4) death during the index hospitalization. The study reviewed all hospital admissions from the ED that occurred between 1 September 2010 (the initiation date of the current EMR system) and 31 August 2014. The hospital's EMR (Quadramed; Quadramed Corporation, Reston, VA) was queried for patients that died during the defined time period. After obtaining the list of all deaths, the medical records were screened for patients meeting all other inclusion criteria. Trained research personnel using a structured data acquisition protocol extracted data from the EMR, which were inputted into a secure database with ten percent double entered and showing an error rate of less than 5%. Information pertaining to patient demographics, past medical history, the index presentation, ED vital signs, initial laboratory results, treatments, cause of death, date and time of ED arrival, and date and time of death were obtained.

2.3. Outcome definition

The primary outcome of in-hospital survival time was derived from the difference in time from ED presentation (ED EMR time-stamped arrival time) to time of in-hospital death. Time of death was based on the time that was recorded in the EMR disposition note. Time variables were extracted to include the hour and minute of the time point of interest. For subjects dying in less than 24 hours fractional days were calculated based on survival hours and minutes.

2.4. Statistical methods

Data were explored using descriptive statistics with frequencies and corresponding percentages for categorical variables and medians with interquartile ranges (25% and 75% quartiles) or 95% confidence intervals (95% CI) for continuous variables. Statistical associations between comparison variables were assessed using Mann-Whitney *U* or Wilcoxon rank-sum tests for continuous variables and Pearson χ^2 or Fisher exact tests for categorical variables. Kaplan-Meier curves were used to define survival estimates with median values and corresponding 95% CI calculated. Based on prior research showing potential prognostic utility of LAC trends among septic patients, an a priori subgroup analysis of patients with repeat LAC within 6 hours of ED presentation was undertaken [16–18]. The subgroups were stratified by increasing versus decreasing repeat LAC levels. The differences in median survival time were assessed using Wilcoxon rank-sum test and Cox proportional hazards models. All analysis was performed using STATA version 11.0 (College Station, TX).

3. Results

3.1. Cohort characteristics

During the study period a total of 440 ED patients with NCLAC levels died during index hospitalizations. Among these, 197 patients (45%) met inclusion criteria and were analyzed. The majority of patients (79%) died ≤28 days of initial presentation. Thirteen patients (7%) died in ≤24 hours from time of ED presentation (Fig. 1).

The median age for the cohort was 67 years (quartiles: 55, 79) with a range from 19 to 99 years. There were slightly more male than female subjects (54% vs 46%). The majority of patients (93%) had documented pre-existing comorbidities. The most frequently observed SIRS parameters were elevated heart rate (84%), elevated band count (72%) and abnormal White Blood Cell count (67%). An Initial systolic blood pressure ≤90 mmHg was found in 13% of subjects at triage, all of which improved to >90 mmHg with ED therapies. The median initial ED LAC level was 1.9 mmol/L (1.5, 2.5). In the cohort ED laboratory evaluations found that electrolytes and creatinine levels were within normal ranges and that the median hemoglobin level was 10 g/dL. The most common infectious sites were pulmonary (44%) and genitourinary (19%). Nearly all patients (99%) had antibiotics administered during ED treatment. Approximately half of the cohort necessitated treatment with endotracheal intubation or pharmacologic vasopressor support and 44% required intensive care unit admission (Table 1).

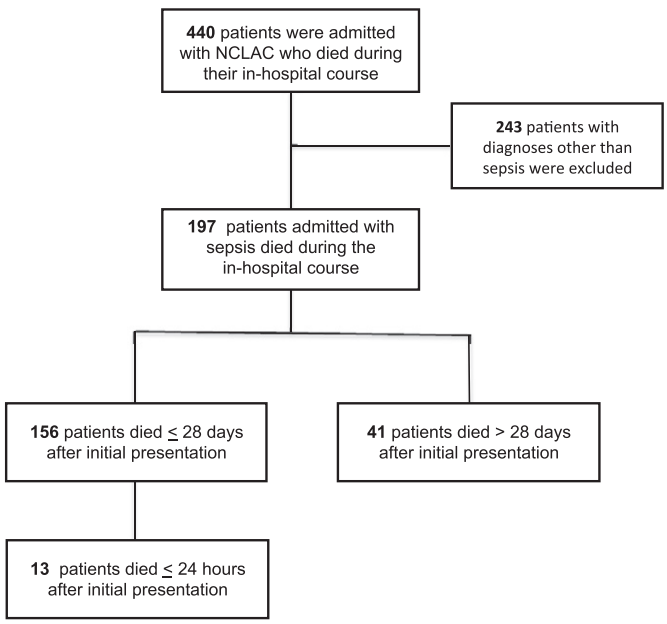

Fig. 1. Study flow diagram.