Brief Report

Prognostic Value of Incremental Lactate Elevations in Emergency Department Patients With Suspected Infection

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Abstract

Objectives: Previous studies have confirmed the prognostic significance of lactate concentrations categorized into groups (low, intermediate, high) among emergency department (ED) patients with suspected infection. Although the relationship between lactate concentrations categorized into groups and mortality appears to be linear, the relationship between lactate as a continuous measurement and mortality is uncertain. This study sought to evaluate the association between blood lactate concentrations along an incremental continuum up to a maximum value of 20 mmol/L and mortality.

Methods: This was a retrospective cohort analysis of adult ED patients with suspected infection from a large urban ED during 2007–2010. Inclusion criteria were suspected infection evidenced by administration of antibiotics in the ED and measurement of whole blood lactate in the ED. The primary outcome was in-hospital mortality. Logistic and polynomial regression were used to model the relationship between lactate concentration and mortality.

Results: A total of 2,596 patients met inclusion criteria and were analyzed. The initial median lactate concentration was 2.1 mmol/L (interquartile range [IQR] = 1.3 to 3.3 mmol/L) and the overall mortality rate was 14.4%. In the cohort, 459 patients (17.6%) had initial lactate levels >4 mmol/L. Mortality continued to rise across the continuum of incremental elevations, from 6% for lactate <1.0 mmol/L up to 39% for lactate 19–20 mmol/L. Polynomial regression analysis showed a strong curvilinear correlation between lactate and mortality ($R = 0.72$, $p < 0.0001$).

Conclusions: In ED patients with suspected infection, we found a curvilinear relationship between incremental elevations in lactate concentration and mortality. These data support the use of lactate as a continuous variable rather than a categorical variable for prognostic purposes.

Severe sepsis remains a major public health problem, with over 750,000 patients treated annually in U.S. hospitals, representing a significant resource allocation. Elevated serum lactate measurements have been demonstrated to be associated with mortality in both emergency department (ED) and hospitalized patients with suspected infection. The use of lactate to screen for severe sepsis in patients with infection and systemic inflammatory response syndrome criteria is recommended by the Surviving Sepsis Campaign. When investigating lactate, previous investigators have typically categorized patients in groups according to the lactate concentration, such as low and high or low, intermediate, and high. When analyzed as a categorical variable, lactate appears to have a linear relationship with mortality. However, lactate is reported and used clinically as a continuous measurement, and its relationship with mortality in a more continuous fashion is uncertain. We sought to evaluate the association between blood lactate concentrations along an incremental continuum up to a maximum value of 20 mmol/L and mortality.

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continuum and mortality in ED patients with suspected infection.

METHODS

Study Design
We conducted a retrospective cohort analysis of ED patients with suspected infection. The study was reviewed and approved by the institutional review board of Carolinas Healthcare System and waiver of informed consent and authorization were granted.

Study Setting and Population
This study took place from January 2007 to May 2011 at Carolinas Medical Center, Charlotte, North Carolina, which is a large, urban, tertiary care hospital staffed by emergency medicine resident physicians supervised by board-certified emergency physicians. Patients were included in the present study if they 1) were admitted to the hospital from the ED, 2) had suspected infection evidenced by administration of antibiotics in the ED, and 3) had whole blood lactate measurements performed in the ED. Our institution implemented the use of point-of-care (POC) measurement of whole blood lactate (i-STAT, Abbott Point of Care Inc., Princeton, NJ) in January 2007 in the ED only (no other hospital units used i-STAT). The results of these tests are automatically stored in each patient’s electronic medical record (PowerChart, Cerner Corp., Kansas City, MO). At the same time, an institutional guideline was implemented that suggested the measurement of lactate concentration on all ED patients with suspected or confirmed infection who were admitted to the hospital.

Patient identification for inclusion in the study followed a two-step process. First, all patients who were admitted to the hospital from the ED and had POC lactate measurements from January 2007 to May 2011 were identified though a script query of the electronic medical record. If more than one lactate measurement was performed during a single patient encounter, only the first measurement was included. These results were then cross-referenced to all patients during the same time frame who had antibiotics dispensed in the ED from the pharmacy dispensing system (Pyxis, CareFusion Corp., San Diego, CA). All antibiotics on formulary in our hospital during the study period were queried.

The only explicit written treatment guideline of ED patients with infection during the study period was the use of an early quantitative resuscitation protocol for septic shock, as has been previously described. The primary outcome was in-hospital mortality.

Data Analysis
Data were first analyzed using logistic regression, with in-hospital mortality as the dependent variable and lactate as the independent variable. Goodness of fit was assessed by the method of Hosmer and Lemeshow. To further evaluate the possible nonlinear nature of the relationship between lactate and mortality, patients were grouped by initial lactate measurement in 1 mmol/L increments (0 to <1, 1 to <2, 2 to <3 mmol/L, etc.) up to the maximum value reported by the device, 20 mmol/L. In-hospital mortality was calculated for each group. First, a simple linear regression model was constructed, weighted by the number of patients within each lactate increment. Expecting the relationship between lactate and mortality to be nonlinear rather than linear, a polynomial regression model was then constructed and fitted by the method of linear least squares. The two regression models were compared by subjective goodness of fit by visually assessing the plotted data and the fitted curve. An analysis of variance was evaluated as a reflection of the overall fit of the regression model. The final model is presented with 95% confidence intervals (CIs). All statistical tests were two-sided with p < 0.05 considered significant, and the figure of the model is presented with 95% CI. Univariate data are presented as medians with interquartile ranges (IQRs) or proportions with 95% CI. Data were analyzed using commercially available statistical software (StatsDirect 2.7.7, Cheshire, England; and STATA 10.0, StataCorp, College Station, TX).

RESULTS

Over the study period, 2,596 patients met inclusion criteria. The median age was 61 years (IQR = 49 to 74 years), 52% (95% CI = 50% to 53%) were white, the median hospital length of stay was 8 days (IQR = 5 to 14 days), and the overall mortality was 14.4%. The median initial lactate concentration was 2.1 mmol/L (IQR = 1.3 to 3.3 mmol/L), and 459 (17.6%) subjects had an initial lactate > 4 mmol/L.

Logistic regression demonstrated a highly significant association between lactate and in-hospital mortality (p < 0.001), and goodness-of-fit testing demonstrated no overfitting of the model (p = 0.27). A simple, weighted linear regression model demonstrated a significant association between lactate group and mortality (R = 0.70, p < 0.0001), with good model fit (p < 0.001). Visual inspection of the relationship suggested a potential curvilinear relationship, particularly for significantly elevated lactate values. The polynomial regression

Figure 1. Polynomial regression model demonstrating the relationship between lactate and mortality rate, as represented by the center gray line, with 95% CIs represented by the outer black lines. Regression equation: Mortality % = 0.066 + 0.030 (lactate) - 0.001 (lactate)^2.
model showed an improved correlation \((R = 0.72, p < 0.0001)\) with good model fit \((p < 0.0001)\). The final model and regression equation are shown in Figure 1.

**DISCUSSION**

In this study we present the largest cohort reported to date of ED patients with suspected infection evaluating the prognostic value of lactate. We found that the prognostic value of lactate continues to rise across a wide range of values, from 0 to 20 mmol/L, and that the relationship between lactate and mortality may be best described by a curvilinear relationship rather than a simple linear relationship. These data suggest that grouping patients into less granular and larger groups, such as low, intermediate, and high, potentially underutilizes the prognostic value of the test. Furthermore, we did not find any value of lactate, up to a maximum value of 20 mmol/L, where mortality failed to increase with an increase in lactate concentration. These data suggest that clinicians should not view all patients with suspected infection and a high lactate to be at similar risk of death.

The prognostic value of lactate in ED\(^2,3\) and intensive care unit\(^4,5\) patients is well described and remains a significant independent predictor of mortality even after adjusting for confounding variables, including blood pressure\(^2\) and severity of illness.\(^4\) Traditionally, patients have been grouped into low or high\(^5\) or low, intermediate, and high\(^2,4\) levels, with increasing mortality rates between groups. Furthermore, in heterogeneous critically ill patients, a single elevated lactate has been demonstrated to be an independent predictor of mortality\(^3\) and demonstrates a dose–response relationship with increasing odds ratios as lactate values increase above the typical value of “high,” consistent with the findings of this study. Our study enhances the current literature by demonstrating that in ED patients with suspected infection, the risk of death continues to increase beyond lactate concentrations of 4 mmol/L.

The strength of this study is its size, representing the largest analysis of the value of lactate in ED patients with suspected infection. Additionally, more than 17% of our study subjects had lactate concentrations more than 4 mmol/L, allowing more granular evaluation of the relationship between significantly elevated lactate and mortality. Finally, lactate is a simple test available at the bedside, and this study supports the powerful prognostic value of even a single, markedly elevated measurement.

**LIMITATIONS**

First, our findings are from a single center, which may limit their generalizability. Second, our institution has considerable experience with early sepsis resuscitation, which may have affected our results. Third, there were relatively few patients with markedly elevated lactate levels, limiting the analysis at these levels. Fourth, our study is retrospective and is thus potentially affected by the inherent limitations of the design such as workup bias, confounding, and inability to establish cause and effect.

**CONCLUSIONS**

In ED patients with suspected infection, incremental elevations in whole blood lactate values up to 20 mmol/L are associated with progressive increases in mortality. Clinicians should be aware of the prognostic significance of incremental increases in lactate, even in the significantly elevated range, and should avoid considering all patients with a high lactate to be at similar risk of death.

**References**