The Incidence and Outcome Differences in Severe Sepsis with and without Lactic Acidosis

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Abstract

Introduction: To compare the incidence, characteristics, and outcomes of lactate expressors and nonexpressors in patients with severe sepsis and septic shock. Methods: This is a retrospective cohort study of patients with severe sepsis and septic shock who presented over a 40-month period to an academic tertiary care center. Primary outcome of interest was in-hospital mortality. Secondary outcomes were hospital length of stay (LOS), Intensive Care Unit (ICU) LOS, and escalation of care. Results: Three hundred and thirty-eight patients met inclusion criteria and were divided into a lactate expressor group (n = 197; initial lactate ≥2.5 mmol/L) and a nonexpressor group (n = 141; lactate <2.5 mmol/L). The mortality rate was 46.2% for lactate expressors and 24.8% for nonexpressors. There were no significant differences in hospital or ICU LOS. The escalation-of-care rate in the severe sepsis nonexpressor group was more than double that found in the expressor group: 16.5% versus 6.2% (P = 0.040). The two groups had baseline differences: expressor group had a higher median Acute Physiology and Chronic Health Evaluation II (APACHE II) illness severity score, and nonexpressors had an increased prevalence of comorbid conditions. APACHE II score (odds ratio [OR] 1.10 [1.07–1.14], P < 0.001) and being in the expressor group (OR 1.72 [1.03–2.89], P = 0.039) increased the odds of mortality. Conclusions: In patients with severe sepsis and septic shock, lactate nonexpressors are common. Although the mortality in this cohort is less than its counterparts who present with lactate elevation, it is still significant which warrants vigilance in their care.

Keywords: Lactate, mortality, sepsis

INTRODUCTION

Severe sepsis and septic shock have been among the leading causes of death in the United States. An estimated 750,000 cases occur each year, with a documented annual increase of 13% within the past decade.1,2 The systemic inflammatory response syndrome (SIRS) and its more severe manifestations affect patients of all demographics. Improvements in patient outcomes have been achieved by establishing a greater focus on early recognition and aggressive management.1,2 However, despite these advancements, patients with severe sepsis and septic shock still have an estimated in-hospital mortality rate of 25% and 50%, respectively.3

Evaluation of disease severity in septic patients is essential for proper diagnosis and optimal management. Progression from sepsis to severe sepsis and septic shock follows established criteria, but there is variability in the treatment of individual patients based on clinical presentation. Serum lactate level is used to stratify patients for heightened vigilance and time-sensitive interventions since hyperlactatemia has been associated with a worse prognosis in numerous studies.4-8 Some suggest that elevated serum lactate should be used as a criterion for the diagnosis of septic shock.9,10 However, hyperlactatemia is not always present in critically ill patients.8,11

The Surviving Sepsis Campaign’s updated treatment bundles recommend obtaining a serum lactate level within 3 h of presentation in those with suspected severe sepsis or septic shock.12,13 For patients with an initial serum
lactate level $\geq 4$ mmol/L, aggressive resuscitation and serial evaluations of volume status and hemodynamics are recommended. However, some evidence suggests that there is increased mortality from lactate values starting as low as 1.4 mmol/L.\(^7\) In addition, a recent retrospective study showed that 8.9% of “stable” severely septic patients with presenting lactate levels between 2 and 4 mmol/L decompensated within 48 h.\(^14\) These findings suggest that the guidelines of 2 SIRS criteria with lactate $\geq 4$ mmol/L and/or hypotension to identify high-risk septic patients may not be rigorous enough.

With the publication of the Sepsis-3 definition, which requires the presence of both lactic acidosis and hypotension for the diagnosis of septic shock, it is even more important to identify the incidence of lactate nonexpression and the associated outcomes in patients with sepsis. Sepsis-3 sets the lactate threshold for septic shock at 2 mmol/L; however, the design of our study preceded the publication of the Third International Consensus Definitions. When choosing the level for lactate expression for our study, we selected a threshold used by a tiered lactate study on patients with vasopressor-dependent septic shock, wherein lactate levels 0–2.4 mmol/L was considered lactate nonexpression.\(^11\)

Previous studies have attempted to address this topic; however, they have focused on only septic shock patients,\(^11\) or they have attempted to address the patients with severe sepsis with intermediate elevations in lactate levels.\(^{15,16}\) The question that is still important to answer is whether lactate nonexpression is a significant concern in the setting of severe sepsis in addition to septic shock. From Dugas’s work, approximately 45% of the patients with septic shock were lactate nonexpressors, however, carried a mortality that was 20%, which although lower than lactate expressors, is still greater than many other disease processes such as ST-elevation myocardial infarction or stroke.\(^11\)

The objective of this study was to compare two groups of patients with severe sepsis and septic shock: those who presented with lactic acidosis and those who did not. Baseline characteristics of the groups were of interest, including comorbidities, illness severity, and level of organ dysfunction. The primary outcome of interest was in-hospital mortality. The secondary outcomes were hospital length of stay (LOS), Intensive Care Unit (ICU) LOS, and escalation of care (for severe sepsis patients not initially admitted to the ICU).

**METHODS**

This was a retrospective cohort study of adult patients with severe sepsis and septic shock who presented to an urban academic tertiary care hospital between October 2010 and December 2013. The population included those admitted from the emergency department (ED), directly admitted patients who did not come through the ED, and patients transferred from outside hospitals.

Infection- or sepsis-based ICD-9 billing codes within the discharge diagnoses were used to identify potentially eligible patients. Based on the billing codes, the electronic medical records of 1004 patients were flagged for review. Following this query, patients were included in the study if (1) they had two or more SIRS criteria at initial presentation; (2) they were at least 18 years old; (3) there was evidence of organ dysfunction, as described below in the study definitions; (4) the initial lactate value was obtained within 24 h of presentation; and (5) sepsis did not occur during a hospitalization that resulted primarily from major trauma, cardiac arrest, or cardiogenic shock.

Septic patients with organ dysfunction were diagnosed with severe sepsis per international consensus panel guidelines.\(^17\) Organ dysfunction was defined as one of the following: acute respiratory failure, with a ratio of partial pressure arterial oxygen and fraction of inspired oxygen $<300$; acute renal failure, with urine output $<0.5$ mL/kg/h or a creatinine increase $>0.5$ mg/dL; acute liver injury, with an international normalized ratio $>1.5$ or alanine aminotransferase or aspartate aminotransferase levels greater than three times the normal value (120 U/L); or thrombocytopenia, with platelets $<100,000$/$\mu$L. Patients were classified as having septic shock when there were severe sepsis and hypotension (systolic blood pressure $<90$ mm Hg) despite adequate fluid resuscitation.\(^12\)

In addition to collecting data on vital signs, SIRS criteria, infection source, and laboratory values, chart reviewers also obtained data on gender, age, race, comorbid conditions, vasopressor support, and hospital course. Included in the information gathered on patients’ hospital course were hospital and ICU admission and discharge times, whether escalation of care occurred, and whether patients were discharged alive. Severity of illness scores for each patient record was calculated using the Acute Physiology and Chronic Health Evaluation II (APACHE II) classification system.

The primary outcome of interest was in-hospital mortality rate. The secondary outcomes of interest were hospital LOS, ICU LOS, and escalation-of-care rate for patients with severe sepsis not initially admitted to the Intensive Care Unit.

For demographic and outcome variables, continuous variables were summarized by their median values and interquartile range (IQR), with differences between groups evaluated based on the Wilcoxon rank-sum test. Categorical variables were reported as counts with associated percentages. Comparison of categorical variables between groups was performed by the Chi-square test. In-hospital mortality was analyzed by multivariable logistic regression and goodness-of-fit assessed using the Hosmer–Lemeshow test. Hospital LOS and ICU LOS were analyzed by multiple linear regression. To mitigate the collinearity of initial lactate and APACHE II, initial lactate was log transformed and APACHE II was centered at its mean.

Multicollinearity between age, APACHE II score, and initial lactate was formally assessed using variance inflation factor (VIF), in which the resulting VIFs ranged from 1.02 to 1.28, indicating very low collinearity. Age, gender, Caucasian race, expressor status, and APACHE II scores were included as...
covariates in all models. Statistical analyses were carried out in SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

The institutional review board of the institution approved the study protocol and provided a waiver of informed consent.

Results

Of the 1004 patients screened for this study, 338 met the definition of severe sepsis or septic shock and had an initial lactate level drawn within 24 h of presentation. Among these, 197 (58%) were categorized as “lactate expressors” (initial serum lactate ≥2.5 mmol/L) and 141 (42%) were categorized as “nonexpressors” (initial serum lactate <2.5 mmol/L) [Figure 1].

The lactate expressor group had higher mortality than the nonexpressor group: 46.2% vs. 24.8%, respectively (P < 0.001). Also notable, the lactate expressor group had a higher median APACHE II score than the nonexpressor group: 27 IQR = (20–35) versus 21 IQR = (15–27), respectively, (P < 0.001) [Table 1]. The other major difference between the cohorts was an increased incidence of comorbidities in the lactate nonexpressor group. Specifically, more lactate nonexpressors had chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, diabetes mellitus, and chronic renal insufficiency.

In the univariate analysis of mortality, APACHE II score and expressor status were associated with increased odds of mortality. APACHE II score increased the odds of mortality by 1.11, 95% confidence interval (CI) = 1.08–1.14, (P < 0.001), while expressor status increased the odds by 2.60, 95% CI = 1.62–4.18, (P < 0.001) [Table 2].

In the multivariable logistic model, with covariates age, gender, Caucasian race, expressor status, and APACHE II scores, the odds or mortality increased with APACHE II score and lactate expressor status, with APACHE II score remaining statistically significant (P < 0.001) [Table 2]. Lactate expression was not independently associated with hospital LOS (P = 0.110) or ICU LOS (P = 0.340) after correcting for baseline differences in age, gender, Caucasian race, and APACHE II scores.

When evaluating the hospital course of the severe sepsis patients, we found that 18 patients who were admitted to an inpatient floor or intermediate unit became unstable and were upgraded to the ICU. Escalation-of-care rates between the expressor groups were compared, and the rate of delayed admission to the ICU was more than twice as high in the nonexpressor cohort compared with the expressor cohort: 16.5% versus 6.2% (P = 0.037).

Discussion

The most important finding of this study is the incidence of lactate nonexpressors in a cohort of patients with severe sepsis and septic shock. This is especially important to recognize given the increased attention being paid to the utilization of lactic acid levels in identifying high-risk patients with sepsis. The recent revision of the sepsis definition published in JAMA adds to this concern, as early identification of septic shock is based on the initial lactic acid levels being elevated. [10] This study further adds information regarding this cohort which has not been previously described. Multiple studies have attempted to describe the prognosis for patients with various lactate thresholds within this population, [15,16] however, none have described how frequently these patients present without lactate elevation. Previous work in a cohort of septic shock patients showed the incidence of lactate nonexpression to be 45% with a mortality rate of 20%. [11] Our study further corroborates this finding by reporting a similar finding in a more broad cohort of patients with severe sepsis and septic shock, again with a mortality that is in excess of 20%.

Another interesting finding of this study is the difference in baseline comorbidities between lactate expressors and nonexpressors, with the nonexpressors having a greater number of baseline comorbidities. It is possible that patients with multiple comorbidities are “metabolic hibernators,” meaning that they have changes in their normal metabolism preventing them from developing lactic acidosis in response to tissue hypoperfusion. This population would be at highest risk for delayed recognition as critically ill in a paradigm utilizing lactate level as a key component of identification.

In addition, evaluation of the outcomes of the 141 nonexpressor patients raises concerns. Almost half of the 338 septic patients in the study had a serum lactate <2.5 mmol/L, but despite their lack of significant serum lactate elevation, nonexpressors were more than twice as likely to have an escalation of care within 24 h of admission and had a mortality burden of almost 25%. Thus, for septic patients with organ dysfunction, the absence of lactate elevation cannot be used as a surrogate for stability.

Of note, the mortality of both cohorts was higher than rates reported in recent large prospective trials. Some of the difference may be accounted for by the Hawthorne effect, [18] in which all patients included in a clinical trial have greater
vigilance of their care and better outcomes regardless of the intervention studied. In addition, based on mean APACHE II scores (21 in nonexpressors and 27 in expressors), the patients in this retrospective study were more severely ill than the patients studied in the PROMISE, ARISE, or ProCESS trials of septic shock patients, in which the mean APACHE II scores were 18, 15.6, and 20.5, respectively.¹⁹⁻²¹

Limitations

The primary limitation of this study is that it is a retrospective review of medical records, and therefore, it is possible that some eligible patients with severe sepsis and septic shock who did not have an infection-related or sepsis-related discharge diagnosis recorded were missed. However, given the severity of illness of the patient population sought, it is unlikely that this would have been the case for a large number of patients. In an attempt to minimize the possibility of mistakes in assessing eligibility or in assigning patients to their respective cohort, two study investigators independently reviewed each patient’s electronic medical records.

As with any observational study, the association between cohort assignment and outcomes of interest may have been confounded by other factors. Although a multivariate model was used to adjust for known confounders, there may have been other unknown or unmeasured factors present that affected outcomes. For example, data on mechanical ventilation status and time to initiation of therapy were not captured. Since patient management was not monitored, practice variation among providers with respect to the timeliness of interventions may have been a factor that contributed to mortality differences. The institution’s standard of care for

Table 1: Demographics and outcome variables by lactate expressor status

| Characteristic                                      | Lactate expressor (n=197) | Lactate nonexpressor (n=141) | P     |
|----------------------------------------------------|---------------------------|-------------------------------|-------|
| Age, median (IQR)                                   | 62 (51.76)                | 63 (53.74)                    | 0.566 |
| Male gender, n (%)                                  | 102 (51.8)                | 80 (56.7)                     | 0.367 |
| Caucasian race, n (%)                               | 88 (44.7)                 | 63 (44.7)                     | 0.998 |
| Comorbid conditions                                 |                           |                               |       |
| Hypertension, n (%)                                 | 113 (57.4)                | 93 (66.0)                     | 0.11  |
| Diabetes mellitus, n (%)                            | 49 (24.9)                 | 49 (34.8)                     | 0.048 |
| Coronary artery disease, n (%)                      | 23 (11.7)                 | 28 (19.9)                     | 0.038 |
| Congestive heart failure, n (%)                     | 24 (12.2)                 | 28 (19.9)                     | 0.054 |
| Chronic kidney disease or end-stage renal failure, n (%) | 27 (13.7)               | 32 (22.7)                     | 0.032 |
| Chronic obstructive pulmonary disease, n (%)        | 21 (10.7)                 | 28 (19.9)                     | 0.018 |
| Liver disease, n (%)                                | 16 (8.1)                  | 6 (4.3)                       | 0.155 |
| Comorbidities present, n (%)                        | 154 (78.2)                | 121 (85.8)                    | 0.075 |
| Temperature (°F), median (IQR)                      | 98.8 (96.8-100.6)         | 99.1 (97.7-100.26)            | 0.17  |
| Heart rate (BPM), median (IQR)                      | 110 (93-122)              | 98 (84-108)                   | <0.001|
| Mean arterial pressure (mmHg), median (IQR)         | 61 (40-85)                | 73 (40-87.5)                  | 0.07  |
| White blood count (per mm³), median (IQR)           | 13.45 (8.9-19.2)          | 14.4 (7.7-19.2)               | 0.26  |
| Vasopressor administered, n (%)                     | 100 (50.8)                | 49 (34.8)                     | 0.003 |
| APACHE II score, median (IQR)                       | 27 (20-35)                | 21 (15-27)                    | <0.001|
| Pneumonia as infection source, n (%)                | 113 (57.4)                | 92 (65.2)                     | 0.143 |
| Initial lactate, median (IQR)                       | 4.7 (3.3-7.3)             | 1.4 (1.1-1.8)                 |       |
| Mortality outcomes, n (%)                           | 91 (46.2%)                | 35 (24.8%)                    | <0.001|
| Hospital length of stay, median (IQR)               | 8.8 (4.1-15.7)            | 9.9 (5.6-16.9)                | 0.105 |
| ICU length of stay, median (IQR)                    | 5.4 (2.4-10.6)            | 6 (2.8-11.8)                  | 0.342 |

BPM: Beats per minute, APACHE: Acute Physiology and Chronic Health Evaluation, ICU: Intensive Care Unit, IQR: Interquartile range, °F: Fahrenheit

Table 2: Univariate and multivariable logistic regression models (mortality outcome)

| Variable                                           | Crude analysis | Adjusted analysis |
|----------------------------------------------------|----------------|-------------------|
| Age                                                | 1.00 (0.99-1.02) | 1.00 (0.98-1.01)  |
| Male gender                                        | 1.42 (0.91-2.21) | 1.44 (0.88-2.36)  |
| Caucasian race                                     | 1.07 (0.69-1.67) | 1.20 (0.73-1.97)  |
| APACHE II score, (mean-centered)                   | 1.11 (1.08-1.14) | 1.10 (1.07-1.14)  |
| Expressor status                                   | 2.60 (1.62-4.18) | 1.72 (1.03-2.89)  |

APACHE II: Acute Physiology and Chronic Health Evaluation, II: Expressor status: Whether patients were designated as expressor (initial lactate levels ≥2.5) or nonexpressor, whose initial lactates were <2.5; OR: Odds ratio, CI: Confidence interval; mean-centered subtracting the average APACHE II Score from its value.
Sepsis management followed the Surviving Sepsis Campaign’s treatment bundles and providers were 45%–50% compliant during the study period. Finally, as with any single-center study, our results may not be generalizable to other institutions.

**Conclusions**

Patients presenting with severe sepsis and septic shock had a high incidence of lactate nonexpression. Although the mortality in this cohort is less than in its counterpart who present with lactate elevation, it is still significant, which suggests that vigilance in their care is warranted. Further study is required to determine optimal interventions to improve care in this subset of patients with sepsis.

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**Conflicts of interest**

There are no conflicts of interest.

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