Published in final edited form as:

Acad Emerg Med. 2012 November ; 19(11): 1268–1275. doi:10.1111/acem.12015.

Hyperlactatemia Affects the Association of Hyperglycemia with Mortality in Nondiabetic Adults With Sepsis

Jeffrey P. Green, MD, Tony Berger, MD, MS, Nidhi Garg, MD, Timothy Horeczko, MD, MSCR, Alison Suarez, MD, Michael S. Radeos, MD, MPH, Yolanda Hagar, PhD, and Edward A. Panacek, MD, MPH

Department of Emergency Medicine, UC Davis Health System, UC Davis School of Medicine (JPG, TB, TH, EAP), Sacramento, CA; the Department of Emergency Medicine, New York Hospital Queens, Weill Cornell Medical College (NG, AS, MSR), Flushing, NY; and the Department of Applied Mathematics, University of Colorado, Boulder (YH), Boulder, CO

Abstract

Background—Admission hyperglycemia has been reported as a mortality risk factor for septic nondiabetic patients; however, hyperglycemia's known association with hyperlactatemia was not addressed in these analyses.

Objectives—The objective was to determine whether the association of hyperglycemia with mortality remains significant when adjusted for concurrent hyperlactatemia.

Methods—This was a post hoc, nested analysis of a retrospective cohort study performed at a single center. Providers had identified study subjects during their ED encounters; all data were collected from the electronic medical record (EMR). Nondiabetic adult ED patients hospitalized for suspected infection, two or more systemic inflammatory response syndrome (SIRS) criteria, and simultaneous lactate and glucose testing in the ED were enrolled. The setting was the ED of an urban teaching hospital from 2007 to 2009. To evaluate the association of hyperglycemia (glucose > 200 mg/dL) with hyperlactatemia (lactate ≥ 4.0 mmol/L), a logistic regression model was created. The outcome was a diagnosis of hyperlactatemia, and the primary variable of interest was hyperglycemia. A second model was created to determine if coexisting hyperlactatemia affects hyperglycemia's association with mortality; the main outcome was 28-day mortality, and the primary risk variable was hyperglycemia with an interaction term for simultaneous hyperlactatemia. Both models were adjusted for demographics; comorbidities; presenting infectious source; and objective evidence of renal, respiratory, hematologic, or cardiovascular dysfunction.

Results—A total of 1,236 ED patients were included, and the median age was 77 years (interquartile range [IQR] = 60 to 87 years). A total of 115 (9.3%) subjects were hyperglycemic, 162 (13%) were hyperlactatemic, and 214 (17%) died within 28 days of their initial ED visits. After adjustment, hyperglycemia was significantly associated with simultaneous hyperlactatemia (odds ratio [OR] = 4.14, 95% confidence interval [CI] = 2.65 to 6.45). Hyperglycemia and concurrent hyperlactatemia were associated with increased mortality risk (OR = 3.96, 95% CI = 2.01 to 7.79), but hyperglycemia in the absence of simultaneous hyperlactatemia was not (OR = 0.78, 95% CI = 0.39 to 1.57).

Conclusions—In this cohort of septic adult nondiabetic patients, mortality risk did not increase with hyperglycemia unless associated with simultaneous hyperlactatemia. The previously reported association of hyperglycemia with mortality in nondiabetic sepsis may be due to the association of hyperglycemia with hyperlactatemia.

Sepsis is a significant cause of death and morbidity in the United States, resulting in more than one million annual hospitalizations and over 200,000 deaths.¹ Early identification of patients at high risk for sepsis-related morbidity leads to improved clinical outcomes via targeted, empiric, broad-spectrum antibiotics and rapid resuscitation.^{2–4} For nondiabetic patients, hyperglycemia has been associated with an increased mortality risk in sepsis.^{5–7} Whether hyperglycemia has a causal role in the pathologic process of sepsis has been disputed, but the possibility has led to investigations of intensive insulin therapy to improve outcomes.⁸ Unfortunately, recent evidence indicates that such efforts may not decrease, and may rather increase, mortality risk.⁹ This discrepancy prompted our new look at the relationship of hyperglycemia with mortality risk in nondiabetic sepsis.

Sepsis is a hypermetabolic pathophysiologic state. The inflammatory cascade leads to a catecholamine surge, relative insulin resistance, and hyperglycemia.¹⁰ Recent studies demonstrate that a single episode of hyperglycemia (serum glucose > 200 mg/dL) on initial patient presentation may be associated with increased mortality risk in nondiabetic sepsis.^{5,7} However, these analyses did not account for possible simultaneous hyperlactatemia. Previous research has shown that glucose and lactate levels may correlate in sepsis and that abnormal glucose accumulation could be in part a direct result of hyperlactatemia.¹¹ Accumulated lactate in sepsis can be cleared by oxidation to pyruvate or transformed into glucose by gluconeogenesis or into glycogen via the Cori cycle.¹² Subsequent glycogenolysis can lead to further glucose accumulation, a pathway known to have increased activity in sepsis.¹² Consequently, hyperglycemia in nondiabetic sepsis could be directly linked to lactate metabolism. As hyperlactatemia has a known significant association with mortality risk in sepsis, the association of glucose with lactate levels must be determined prior to assessing the correlation of hyperglycemia with mortality.

If hyperglycemia's association with mortality risk were a direct result of coexisting hyperlactatemia, we would expect several findings. First, hyperglycemia would be significantly correlated with hyperlactatemia in sepsis, even after adjustment for illness severity and comorbidities. Second, hyperlactatemia would be associated with increased mortality risk, regardless of the presence of simultaneous hyperglycemia. Finally, isolated hyperglycemia (in the absence of coexisting hyperlactatemia) would not correlate with increased mortality risk in nondiabetic sepsis. To determine whether hyperglycemia's association with mortality in sepsis was dependent on simultaneous hyperlactatemia, we analyzed a previously identified cohort of nondiabetic, adult ED patients hospitalized for suspected sepsis. The objective of this study was to first determine whether admission hyperglycemia correlated with simultaneous hyperlactatemia after adjustment for demographics and coexisting illness severity. Additionally, we sought to determine whether hyperglycemia on initial ED presentation was associated with an increased 28-day mortality risk in sepsis after adjusting for concurrent hyperlactatemia and other markers of illness severity.

METHODS

Study Design

This was a nested secondary analysis of an existing cohort of adults (>21 years old) presenting to a single ED with probable sepsis. The institutional review board of the study site approved the study with a waiver of informed consent.

Study Setting and Population

The study was performed at New York Hospital Queens, a 450-bed urban teaching hospital with an annual ED census of 95,000–100,000 visits. For the study cohort, providers identified adult patients with suspected acute infections in real time; data were then retrospectively extracted into standardized data collection forms by review of the electronic medical record (EMR), as previously described.¹³ For this analysis, eligible patients were 21 years of age or older (patients less than this age were triaged to a separate pediatric ED), had two or more systemic inflammatory response syndrome (SIRS) criteria on triage or initial ED vital signs and laboratory studies, had both serum lactate and glucose level measurements in the ED, and were hospitalized, with admitting diagnoses of infection. International Classification of Disease, 9th Revision, (ICD-9), ED admitting codes were used to define infection, as previously described in adult patients with sepsis.¹⁴ The SIRS criteria include: body temperature of < 96.8 or $> 100.4^{\circ}\text{F}$; heart rate > 90 beats/min; respiratory rate > 20 breaths/min; and a white blood cell count less than 4×10^9 or greater than 12×10^9 cells/L or greater than 10% immature neutrophils (band forms).¹⁵ For patients with repeat ED visits during the study period, only the initial visit was used. Patients were enrolled from February 1, 2007, to October 31, 2008.

Study Protocol

A protocol was in place throughout the study to test serum lactate and glucose levels, as well as other markers of organ dysfunction, on all adult patients having blood drawn in the ED for suspected infection. This protocol was developed to comply with consensus guidelines for severe sepsis screening.¹⁶

Trained research associates abstracted the medical records of all patients identified by ED providers as having suspected acute infections. Previously published recommendations for quality chart abstraction were followed.¹⁷ Specifically, data abstractors were trained in advance, used standardized data abstraction sheets, were routinely audited, and were blinded to the study hypothesis. Ten percent of subjects had all variables collected by a second blinded abstractor to confirm reliability of the results (Cohen's $\kappa = 0.80$ or greater for all variables). The primary endpoints were the presence of hyperlactatemia (serum lactate ≥ 4.0 mmol/L) on initial ED laboratory studies and mortality 28 days following the initial ED visit. For patients discharged alive prior to 28 days from the initial ED encounter, the Social Security Death Index (SSDI) was queried (more than 1 year following the initial ED evaluation) to confirm whether the patient survived to 28 days.¹⁸

Serum lactate (mmol/L) and glucose levels (mg/dL) were measured using a serum-based immunoassay (Unicel Synchron, Beckman Coulter Inc., Brea, CA). Venous lactate levels were generally tested to improve protocol compliance. Previous studies have shown that venous lactate levels correlate with arterial measurements of lactate as well as with short-term mortality risk in septic adult ED patients.^{19,20} In cases when multiple lactate and glucose levels were tested in the ED, only the initial levels were used for analysis.

Data Analysis

Summary and descriptive statistics (medians and interquartile range [IQR] for continuous variables, frequencies, and percentages for categorical variables) were generated for the study cohort. To determine whether hyperglycemia is associated with an increased likelihood of elevated serum lactate levels, a multiple logistic regression model was developed, with hyperlactatemia (serum lactate ≥ 4.0 mmol/L) as the primary outcome variable and hyperglycemia (serum glucose > 200 mg/dL) as the primary variable of interest. These glucose and lactate parameters have been reported to be associated with increased mortality risk in septic adult patients.^{19,21} Additional covariates with plausible

clinical associations with hyperglycemia and hyperlactatemia were evaluated for inclusion in the model.

Next, we developed a logistic regression model to quantify the effects of glucose and lactate levels on mortality. The primary measure of interest was the interaction between glucose and lactate levels; we created new indicator variables that represented the four possible categories for high or low glucose levels and high or low lactate levels. For this analysis, patients with a glucose < 200 mg/dL and lactate < 4.0 mmol/L were considered the reference group. Additional covariates with plausible associations with hyperglycemia, hyperlactatemia, and mortality were evaluated for inclusion in the model. To assess for potential multicollinearity, we created interaction terms for the hyperglycemia/hyperlactatemia indicator variables and compared model point estimates for the combined hyperglycemia/hyperlactatemia indicator variable with and without the isolated hyperglycemia and hyperlactatemia variables. Continuous covariates were assessed for possible linear associations with model outcome probabilities.

Additional clinical covariates with significant potential associations with the outcome or primary risk variable were considered for inclusion into each model. A priori we required a minimum of 10 outcome events for each covariate evaluated to avoid model overfitting. For both models, patient demographics (age, sex, race) and comorbidities were evaluated for inclusion. The Charlson Comorbidity Index was used to adjust for mortality risk from underlying comorbidities.²² A validated method was used to construct the Charlson Comorbidity Index from medical records.²³ We also evaluated whether a specific presenting infectious illness (i.e., lower respiratory tract infection, skin or soft tissue infection, or nonspecific sepsis) was significant in either model. Previous research demonstrated that the presenting infectious source can significantly affect mortality probability in sepsis.^{24,25}

Finally, presenting evidence of organ dysfunction was evaluated for model inclusion. Due to the retrospective nature of data collection, we were not consistently able to collect all variables needed to calculate a complete organ dysfunction score. However, we used previously validated definitions of organ dysfunction to adjust for abnormalities of the following organ systems: respiratory dysfunction, defined as respiratory rate > 20 breaths/min or hypoxemia (pulse oximetry < 90% on room air or < 95% while breathing supplemental oxygen 4 L/min), or mechanical ventilation; cardiovascular dysfunction, defined as systolic blood pressure < 90 mm Hg after an isotonic fluid bolus; renal dysfunction, defined as blood urea nitrogen > 20 mg/dL; hematologic dysfunction, defined as platelet count < $100 \times 10^9/L$; and hepatic dysfunction, defined as total bilirubin > 2 mg/dL.^{24,26} Previous studies have shown that dysfunction of individual organ systems meaningfully affects short-term mortality risk.²⁷

For each model, the effect of covariates on outcomes was initially evaluated by creating separate logistic regression models for each covariate. These models also included hyperglycemia for the hyperlactatemia model and the glucose/lactate level indicator variable for the model of 28-day mortality. Covariates with significant adjusted associations with model outcomes at the $p = 0.05$ level in these initial models were then simultaneously included in a multivariate logistic regression model. Covariates that remained significant at the $p = 0.05$ level were retained in the final models. The final models were cross-validated using automated selection methods, informed by the Akaike Information Criterion, which compares the fit of different regression models.²⁸ Calculations were performed in R: A Language Environment for Statistical Computing (<http://www.r-project.org/>).

RESULTS

During the study period, 2,375 adult patients were hospitalized from the ED for suspected infections, of whom 1,259 (53%) were nondiabetic and had two or more SIRS criteria. A total of 1,234 (98%) of these patients had simultaneous glucose and lactate testing in the ED and made up the study cohort. Baseline characteristics for the cohort are reported in Table 1 (by the presence of hyperglycemia) and in Table 2 (by 28-day mortality). A total of 115 (9.3%) patients were hyperglycemic (serum glucose > 200 mg/dL). The cohort tended to be elderly (median age = 77 years; IQR = 60–87 years), with a large percentage of severe sepsis or septic shock (80% of the study cohort), and a high mortality risk (214 deaths at 28 days, 17%). As demonstrated in other studies of nondiabetic patients with suspected sepsis,^{5,7} patients with hyperglycemia in this cohort had a significantly higher 28-day mortality risk (29.6%) than did nonhyperglycemic patients (16.1%; $p < 0.001$).

A total of 162 (13%) patients in the study cohort were hyperlactatemic (serum lactate ≥ 4.0 mmol/L). Similar to previous studies of adult patients with suspected sepsis, hyperlactatemic patients had a higher mortality risk (38%) than did nonhyperlactatemic patients (14%; $p < 0.001$).^{29,30} To determine whether coexisting hyperlactatemia affected the association of hyperglycemia with mortality, we first investigated whether hyperglycemia had a significant adjusted association with hyperlactatemia in a logistic regression model. After adjustment for covariates, we found that hyperglycemic patients were significantly more likely to have concurrent hyperlactatemia than were nonhyperglycemic patients (odds ratio [OR] = 4.14, 95% confidence interval [CI] = 2.65 to 6.45; Table 3).

We next sought to determine whether hyperglycemia was associated with an increased mortality risk when adjusted for the presence of simultaneous hyperlactatemia. A multiple logistic regression model was created for the outcome of 28-day mortality. After adjustment for covariates, hyperglycemia with coexisting hyperlactatemia carried an increased risk for 28-day mortality (OR = 3.96, 95% CI = 2.01 to 7.79). Similarly, isolated hyperlactatemia denoted higher odds for mortality (OR = 2.49, 95% CI = 1.59 to 3.92). However, isolated hyperglycemia (i.e., without concurrent hyperlactatemia) did not significantly increase 28-day mortality risk (OR = 0.78, 95% CI = 0.39 to 1.57; Figure 1).

DISCUSSION

In this cohort of adult nondiabetic patients hospitalized for suspected sepsis, we found that in simple univariate analysis, hyperglycemia had a significant association with increased mortality risk. This finding is consistent with previous studies of nondiabetic patients hospitalized with sepsis.^{5–7} We also demonstrated that hyperglycemia is significantly associated with hyperlactatemia in nondiabetic patients with sepsis. However, when adjusted for concurrent hyperlactatemia, hyperglycemia was not significantly associated with increased mortality risk in nondiabetic patients with sepsis.

Hyperglycemia has been linked to hyperlactatemia in sepsis via several mechanisms. Hyperlactatemia appears to inhibit glucose uptake by muscle cells and decrease activity of the GLUT-4 transporters, resulting in hyperglycemia.³¹ Hyperlactatemia has also been shown to increase insulin resistance directly.³² Revelly et al.¹¹ investigated the relationship of lactate and glucose levels in sepsis by measuring baseline levels and then infusing radiolabeled lactate and glucose in critically ill adults with sepsis. They demonstrated that glucose and lactate levels tend to be elevated simultaneously in severe sepsis at baseline. Their experiment also estimated that 45% of infused lactate is either converted into glucose via gluconeogenesis or is transformed into glycogen via the Cori cycle.¹² This represents a higher proportion of glucose formation from lactate than in nonseptic controls.

In sepsis, there is evidence that glucose accumulates due to the sympathomimetic response to a systemic infection.¹² Increased catecholamine levels in sepsis lead to increased activity of the Na^+K^+ -ATPase, resulting in accumulation of adenosine diphosphate (ADP). Increased levels of ADP in turn augment glycogenolysis.³³ This same pathway is considered a likely cause of lactate accumulation in patients with sepsis after volume resuscitation.³⁴ Mitochondrial metabolism cannot meet the increased cellular energy needs of sepsis. The resultant accumulation of ADP leads to cytosolic glycolysis and lactate production, even in an aerobic environment.¹¹ Given this mechanism, septic patients would simultaneously accumulate glucose and lactate as a by-product of increased catecholamine levels.³⁵ Quite possibly, elevated glucose and lactate levels in sepsis both may be measures of the same phenomenon.

Previous cohort studies of sepsis in humans have consistently demonstrated an association between hyperglycemia and mortality in nondiabetic patients. Stegenga et al.⁵ found a univariate association for hyperglycemia with mortality risk that was similar to that shown in this current study. However, the association of hyperglycemia with mortality in nondiabetic patients was a secondary finding of the study by Stegenga et al., and multivariate adjustment was not attempted for this association. Similarly, Schuetz et al.⁷ analyzed a population of adult ED patients hospitalized for suspected sepsis that was similar to that in the current study. They found that among nondiabetic patients, a single episode of hyperglycemia in the ED was significantly associated with increased mortality risk, even after adjustment for demographics, comorbidities, and illness severity. Finally, Egi et al.⁶ evaluated a population of more than 3,500 nondiabetic adults with sepsis and demonstrated that hyperglycemia has an adjusted association with mortality risk. However, none of these studies accounted for concurrent lactate levels. Based on our analysis, it is possible that the mortality association found for hyperglycemia in these studies could be at least partially explained by concurrent hyperlactatemia in sepsis. However, further research is needed to confirm this finding.

The confounding relationship of hyperlactatemia and hyperglycemia in nondiabetic sepsis patients may have significant therapeutic implications. Based on prior observational studies of the mortality risk of hyperglycemia in critically ill nondiabetic patients, it has been postulated that intensive insulin therapy in critically ill patients may decrease mortality risk. Initial trials were promising,⁸ but more recent studies have demonstrated no benefit and a potentially increased risk with intensive insulin therapy.^{36,37} These unsuccessful trials have called into question the utility of tight glucose control and are cause for reexamining the association of hyperglycemia with mortality. If the findings of this study are correct, it could be that intensive insulin therapy may not be the most plausible approach to curtailing mortality risk in sepsis because hyperglycemia is not the primary problem. Instead, further efforts might be focused on understanding and regulating lactate metabolism as the key energy mediator and mortality risk predictor of sepsis.

LIMITATIONS

Although providers in the ED prospectively identified and categorized patients, the data were collected retrospectively from the EMR. This data collection method is prone to misclassification and selection bias. However, we followed previously published and accepted guidelines for medical record abstraction, and the majority of factors studied (including demographics, vital signs, laboratory data, and the outcome of mortality) are objective findings less likely to be subject to misclassification.¹⁷ Due to the retrospective nature of data collection, we were not able to use an illness severity score for mortality adjustment in this study, but we used previously validated definitions to adjust for dysfunction of respiratory, cardiovascular, renal, hematologic, and hepatic organ

systems.^{24,26} An additional limitation is that hyperlactatemia is an enrollment criterion used clinically for early goal-directed therapy. The study site's protocol was to enact early goal-directed therapy for hyperlactatemic patients with suspected or confirmed infection. Enrollment in this clinical intervention was not measured, so we were unable to include it in the analysis. However, the size of the study makes it less likely that early goal-directed therapy use would be significantly imbalanced between groups.

A further limitation is that patients were not followed prospectively after discharge from the hospital. The outcome of 28-day mortality consisted of a combination of in-hospital survival to 28 days and querying the SSDI for patients discharged alive prior to 28 days from the initial ED encounter. The SSDI is a website designed to allow for epidemiologic studies of survival that has previously been validated for use in patients discharged either from the hospital or ED.¹⁸ However, it is possible that some patients who were discharged prior to 28 days from the index encounter may have died but were not entered into the SSDI. Finally, the study was entirely performed at one hospital. The external validity of these results is unknown and further study, in other settings, is warranted.

CONCLUSIONS

We found that although hyperglycemia has a significant univariate association with mortality risk in sepsis, when adjusted for concurrent hyperlactatemia and other markers of organ dysfunction, hyperglycemia was not a significant predictor of mortality risk in nondiabetic adult patients with sepsis. Additionally, in this cohort hyperglycemia was significantly associated with concurrent hyperlactatemia. This relationship may affect the observed association found between hyperglycemia and mortality in multiple prior studies of nondiabetic sepsis that did not account for concurrent hyperlactatemia.

Acknowledgments

This publication was made possible in part by grant 2UL1RR024146 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) and NIH Roadmap for Medical Research.

References

1. Lagu T, Rothberg MB, Shieh MS, Pekow PS, Steingrub JS, Lindenauer PK. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. *Crit Care Med.* 2012; 40:754–761. [PubMed: 21963582]
2. Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med.* 2010; 38:1045–1053. [PubMed: 20048677]
3. Kumar A, Haery C, Paladugu B, et al. The duration of hypotension before the initiation of antibiotic treatment is a critical determinant of survival in a murine model of *Escherichia coli* septic shock: association with serum lactate and inflammatory cytokine levels. *J Infect Dis.* 2006; 193:251–258. [PubMed: 16362889]
4. Jones AE, Brown MD, Trzeciak S, et al. The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: a meta-analysis. *Crit Care Med.* 2008; 36:2734–2739. [PubMed: 18766093]
5. Stegenga ME, Vincent JL, Vail GM, et al. Diabetes does not alter mortality or hemostatic and inflammatory responses in patients with severe sepsis. *Crit Care Med.* 2010; 38:539–545. [PubMed: 19851093]
6. Egi M, Bellomo R, Stachowski E, et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. *Crit Care Med.* 2008; 36:2249–2255. [PubMed: 18664780]

7. Schuetz P, Jones AE, Howell MD, et al. Diabetes is not associated with increased mortality in emergency department patients with sepsis. *Ann Emerg Med.* 2011; 58:438–444. [PubMed: 21683473]
8. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med.* 2001; 345:1359–1367. [PubMed: 11794168]
9. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med.* 2008; 358:125–139. [PubMed: 18184958]
10. Leverve X. Hyperglycemia and oxidative stress: complex relationships with attractive prospects. *Intensive Care Med.* 2003; 29:511–514. [PubMed: 12800829]
11. Revelly JP, Tappy L, Martinez A, et al. Lactate and glucose metabolism in severe sepsis and cardiogenic shock. *Crit Care Med.* 2005; 33:2235–2240. [PubMed: 16215376]
12. Barth E, Albuszies G, Baumgart K, et al. Glucose metabolism and catecholamines. *Crit Care Med.* 2007; 35:S508–S518. [PubMed: 17713401]
13. Green JP, Berger T, Garg N, et al. Impact of metformin use on the prognostic value of lactate in sepsis. *Am J Emerg Med.* 2012 in press.
14. Wang HE, Shapiro NI, Angus DC, Yealy DM. National estimates of severe sepsis in United States emergency departments. *Crit Care Med.* 2007; 35:1928–1936. [PubMed: 17581480]
15. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med.* 2003; 31:1250–1256. [PubMed: 12682500]
16. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med.* 2008; 36:296–327. [PubMed: 18158437]
17. Panacek EA. Performing chart review studies. *Air Med J.* 2007; 26:206–210. [PubMed: 17765825]
18. Quinn J, Kramer N, McDermott D. Validation of the Social Security Death Index (SSDI): an important readily-available outcomes database for researchers. *West J Emerg Med.* 2008; 9:6–8. [PubMed: 19561695]
19. Mikkelsen ME, Miliades AN, Gaieski DF, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med.* 2009; 37:1670–1677. [PubMed: 19325467]
20. Gallagher EJ, Rodriguez K, Touger M. Agreement between peripheral venous and arterial lactate levels. *Ann Emerg Med.* 1997; 29:479–483. [PubMed: 9095008]
21. Nichol AD, Egi M, Pettila V, et al. Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. *Crit Care.* 2010; 14:R25. [PubMed: 20181242]
22. Murray SB, Bates DW, Ngo L, Ufberg JW, Shapiro NI. Charlson Index is associated with one-year mortality in emergency department patients with suspected infection. *Acad Emerg Med.* 2006; 13:530–536. [PubMed: 16551775]
23. Kieszak SM, Flanders WD, Kosinski AS, Shipp CC, Karp H. A comparison of the Charlson comorbidity index derived from medical record data and administrative billing data. *J Clin Epidemiol.* 1999; 52:137–142. [PubMed: 10201654]
24. Howell MD, Talmor D, Schuetz P, Hunziker S, Jones AE, Shapiro NI. Proof of principle: the predisposition, infection, response, organ failure sepsis staging system. *Crit Care Med.* 2011; 39:322–327. [PubMed: 21099424]
25. Rubulotta F, Marshall JC, Ramsay G, Nelson D, Levy M, Williams M. Predisposition, insult/infection, response, and organ dysfunction: a new model for staging severe sepsis. *Crit Care Med.* 2009; 37:1329–1335. [PubMed: 19242329]
26. Shapiro NI, Howell MD, Bates DW, Angus DC, Ngo L, Talmor D. The association of sepsis syndrome and organ dysfunction with mortality in emergency department patients with suspected infection. *Ann Emerg Med.* 2006; 48:583–590. [PubMed: 17052559]
27. Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on “sepsis-related problems” of the European Society of Intensive Care Medicine. *Crit Care Med.* 1998; 26:1793–1800. [PubMed: 9824069]
28. Akaike H. A new look at statistical model identification. *IEEE Trans Inform Theory.* 1974; 19:716–723.

29. Howell MD, Donnino M, Clardy P, Talmor D, Shapiro NI. Occult hypoperfusion and mortality in patients with suspected infection. *Intensive Care Med.* 2007; 33:1892–1899. [PubMed: 17618418]
30. Trzeciak S, Dellinger RP, Chansky ME, et al. Serum lactate as a predictor of mortality in patients with infection. *Intensive Care Med.* 2007; 33:970–977. [PubMed: 17431582]
31. Lombardi AM, Fabris R, Bassetto F, et al. Hyperlactatemia reduces muscle glucose uptake and GLUT-4 mRNA while increasing (E1alpha)PDH gene expression in rat. *Am J Physiol.* 1999; 276:E922–E929. [PubMed: 10329987]
32. Choi CS, Kim YB, Lee FN, Zabolotny JM, Kahn BB, Youn JH. Lactate induces insulin resistance in skeletal muscle by suppressing glycolysis and impairing insulin signaling. *Am J Physiol Endocrinol Metab.* 2002; 283:E233–E240. [PubMed: 12110527]
33. Levy B. Lactate and shock state: the metabolic view. *Curr Opin Crit Care.* 2006; 12:315–321. [PubMed: 16810041]
34. Levy B, Gibot S, Franck P, Cravoisy A, Bollaert PE. Relation between muscle Na+K+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. *Lancet.* 2005; 365:871–875. [PubMed: 15752531]
35. Trager K, DeBacker D, Radermacher P. Metabolic alterations in sepsis and vasoactive drug-related metabolic effects. *Curr Opin Crit Care.* 2003; 9:271–278. [PubMed: 12883281]
36. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009; 360:1283–1297. [PubMed: 19318384]
37. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA.* 2008; 300:933–944. [PubMed: 18728267]

Figure 1.

Adjusted 28-day mortality risk by lactate and glucose stratum. Glucose measured in mg/dL. The model was adjusted for patient age (AOR = 1.04 for every year older than 21 years; $p < 0.01$), Charlson score (AOR = 1.15 for every one-point increase in scoring system; $p < 0.01$), renal dysfunction (AOR = 1.11 for serum blood urea nitrogen > 20 mg/dL; $p < 0.01$), respiratory dysfunction (AOR = 1.15, $p = 0.01$), and cardiovascular dysfunction (AOR = 1.29, $p < 0.01$). Hosmer-Lemeshow goodness-of-fit test $\chi^2 = 11.22$ (DF = 8), $p = 0.19$, which indicates statistically significant “fit.” Reference group: 21-year-old subject with a serum lactate level < 4.0 mmol/L and serum glucose level < 200 mg/dL. AOR = adjusted odds ratio.

Table 1**Baseline Characteristics on Admission by Hyperglycemia**

Variable	Nonhyperglycemic, 200 mg/dL	Hyperglycemic, >200 mg/dL
<i>n</i> (%)	1121 (90.7)	115 (9.3)
Age, years	76 (58–86)	80 (72–88)
Sex (male), %	557 (49.7)	42 (36.5)
Comorbidities		
Coronary artery disease	143 (12.8)	22 (19.1)
Chronic obstructive pulmonary disease	290 (25.9)	31 (27.0)
Chronic renal insufficiency	179 (16.0)	18 (15.7)
Congestive heart failure	251 (22.4)	29 (25.2)
Cerebral vascular disease	32 (2.9)	7 (6.1)
Liver disease	24 (2.1)	2 (1.7)
Vital signs *		
Temperature (°F)	100.7 (99.0–102.0)	100.8 (98.9–101.9)
Heart rate (beats/min)	103 (93–116)	107 (95–118)
Respiratory rate (breaths/min)	20 (18–24)	22 (20–26)
Systolic blood pressure (mm Hg)	122 (102–144)	121 (97–151)
Oxygen saturation (%)	97 (95–99)	97 (94–99)
Sepsis categories		
Suspected sepsis	241 (21.5)	6 (5.2)
Severe sepsis †	761 (67.9)	92 (80.0)
Septic shock ‡	119 (10.6)	17 (14.8)
Laboratory data		
White blood cell count ($\times 10^9/L$), <i>n</i> = 1,234	12.2 (8.0–16.6)	14.4 (9.8–18.8)
Platelet count ($\times 10^9/L$), <i>n</i> = 1,231	230 (168–312)	257 (201–361)
BUN (mg/dL), <i>n</i> = 1,227	20 (13–33)	36 (21–58)
Creatinine (mg/dL), <i>n</i> = 1,227	1.1 (0.8–1.5)	1.4 (0.9–2)
Bilirubin, total (mg/dL), <i>n</i> = 1,193	0.9 (0.7–1.3)	1.0 (0.7–1.4)
Glucose (mg/dL), <i>n</i> = 1,236	121 (104–142)	242 (216–292)
Lactate (mmol/L), <i>n</i> = 1,236	1.8 (1.3–2.7)	2.8 (1.8–4.8)
Categorized lactate (mmol/L)		
0–3.9	1000 (89.2)	74 (64.3)
4.0	121 (10.8)	41 (35.7)
Charlson Comorbidity Index	2 (0–3)	2 (0–3)
28-day mortality	180 (16.1)	34 (29.6)

Data are reported as *n* (%) or median (IQR). Laboratory data were not available on every patient. Therefore, the number of patients for whom laboratory data were available is indicated for each laboratory variable.

BUN = blood urea nitrogen; IQR = interquartile range; SIRS = systemic inflammatory response syndrome.

* Taken at ED triage or first recorded vital sign.

† Severe sepsis defined as infection, two or more SIRS criteria and objective evidence of organ dysfunction, as previously defined.

[‡]Defined as suspected infection, two or more SIRS criteria and persistent hypotension (systolic blood pressure < 90 mm Hg) after an isotonic fluid bolus.

\$watermark-text

\$watermark-text

\$watermark-text

Table 2**Baseline Characteristics on Hospital Admission by 28-Day Mortality**

Variable	Survivors	Nonsurvivors
<i>n</i> (%)	1,022 (82.7)	214 (17.3)
Age (years)	74 (56–85)	85 (76–91)
Sex (male), %	511 (50.0)	89 (41.6)
Comorbidities		
Coronary artery disease	129 (12.6)	36 (16.8)
Chronic obstructive pulmonary disease	261 (25.5)	60 (28.0)
Chronic renal insufficiency	143 (14.0)	54 (25.2)
Congestive heart failure	200 (19.6)	80 (37.4)
Cerebral vascular disease	26 (2.5)	13 (6.1)
Liver disease	24 (2.3)	2 (0.1)
Vital signs *		
Temperature (°F)	100.9 (99.1–102.0)	99.5 (97.6–101.2)
Heart rate (beats/min)	104 (94–117)	103 (89–118)
Respiratory rate (breaths/min)	20 (18–24)	22 (20–26)
Systolic blood pressure (mmHg)	124 (105–146)	109 (91–132)
Oxygen saturation (%)	97 (95–99)	96 (92–99)
Sepsis categories		
Suspected sepsis	231 (22.6)	16 (7.5)
Severe sepsis †	702 (68.7)	151 (70.6)
Septic shock ‡	89 (8.7)	47 (22.0)
Laboratory data		
White blood cell count ($\times 10^9/L$), <i>n</i> = 1,234	12.3 (8.1–16.6)	13.4 (8.5–18.7)
Platelet count ($\times 10^3/L$), <i>n</i> = 1,231	230 (171–308)	244 (174–367)
BUN (mg/dL), <i>n</i> = 1,224	19 (13–31)	36 (22–59)
Creatinine (mg/dL), <i>n</i> = 1,227	1.1 (0.8–1.5)	1.5 (1.0–2.3)
Bilirubin, total (mg/dL), <i>n</i> = 1,193	0.9 (0.7–1.3)	1.1 (0.8–1.5)
Glucose (mg/dL), <i>n</i> = 1,236	124 (106–148)	130 (104–167)
Lactate (mmol/L), <i>n</i> = 1,236	1.8 (1.3–2.6)	2.4 (1.7–4.5)
Categorized lactate (mmol/L)		
0–3.9	922 (90.2)	152 (71.0)
4.0	100 (9.8)	62 (29.0)
Categorized glucose (mg/dL)		
200	941 (92.1)	180 (84.1)
>200	81 (7.9)	34 (15.9)
Charlson Comorbidity Index	1 (0–3)	2 (1–4)

Data are reported as *n* (%) or median (IQR). Laboratory data were not available on every patient. Therefore, the number of patients for whom laboratory data were available is indicated for each laboratory variable.

BUN = blood urea nitrogen; IQR = interquartile range; SIRS = systemic inflammatory response syndrome.

* ED triage or first recorded vital sign.

† Severe sepsis defined as infection, two or more SIRS criteria, and objective evidence of organ dysfunction, as previously defined.

‡ Defined as suspected infection, two or more SIRS criteria, and persistent hypotension (systolic blood pressure < 90 mm Hg) after an isotonic fluid bolus.

Table 3Multiple Logistic Regression Demonstrating AOR for Hyperlactatemia (Serum Lactate ≥ 4.0 mmol/L)

Variable	AOR	95% CI	p-value
Glucose > 200 mg/dL	4.14	2.65–6.45	<0.01
African American or black	0.35	0.16–0.76	<0.01
Lower respiratory tract infection	0.87	0.76–0.97	0.02
BUN > 20	1.36	1.12–1.64	<0.01
Respiratory dysfunction [*]	1.27	1.13–1.44	<0.01
Septic shock [†]	1.49	1.28–1.73	<0.01
Platelets < 100 ($\times 10^9$ /L)	1.29	1.05–1.60	0.02

AOR = adjusted odds ratio; BUN = blood urea nitrogen.

^{*} Respiratory dysfunction defined as respiratory rate > 20 or hypoxemia (defined as pulse oximetry $< 90\%$ on room air or $< 95\%$ while breathing supplemental oxygen ≥ 4 L/min) or mechanical ventilation, as previously defined.²

Hosmer-Lemeshow goodness-of-fit test $\chi^2 = 10.05$ (DF = 8), $p = 0.26$, which indicates statistically significant “fit.”

[†] Septic shock defined as systolic blood pressure < 90 mm Hg after an isotonic fluid bolus.