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# Emergency Department Lactate Is Associated with Mortality in Older Adults Admitted With and Without Infections

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## Abstract

**Objectives:** Serum lactate values in the emergency department (ED) have been associated with mortality in diverse populations of critically ill patients. This study investigates whether serum lactate values measured in the ED are associated with mortality in older patients admitted to the hospital, both with and without infections.

**Methods:** This is a retrospective cohort study performed at two urban teaching hospitals. The study population includes 1,655 older ED patients (age  $\geq 65$  years) over a 3-year period (2004–2006) who had serum lactate measured prior to admission. The presence or absence of infection was determined by review of International Classification of Diseases Ninth Revision (ICD-9) admission diagnosis codes. Mortality during hospitalization was determined by review of inpatient records. Mortality at 30 and at 60 days was determined using a state death registry.

**Results:** In patients with infections, increasing serum lactate values of  $\geq 2.0$  mmol/L were linearly associated with relative risk (RR) of mortality during hospitalization (RR = 1.9 to 3.6 with increasing lactate), at 30 days (RR = 1.7 to 2.6), and at 60 days (RR = 1.4 to 2.3) when compared to patients with serum lactate levels of  $< 2.0$  mmol/L. In patients without infections, a similar association was observed (RR = 1.1 to 3.9 during hospitalization, RR = 1.2 to 2.6 at 30 days, RR = 1.1 to 2.4 at 60 days). In both groups of patients, serum lactate had a greater magnitude of association with mortality than either of two other commonly ordered laboratory tests, leukocyte count and serum creatinine.

**Conclusions:** Higher ED lactate values are associated with greater mortality in a broad cohort of admitted patients over age 65 years, regardless of the presence or absence of infection.

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**Keywords:** lactic acid, infection, mortality, elderly, older patients, geriatric, emergency

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As emergency department (ED) visitors, older adults have the highest admission rate, longest length of stay, and greatest degree of resource utilization of any age group.<sup>1</sup> The U.S. population over

the age of 65 years is growing, and ED visits for people aged 65–74 years are projected to double from 6.4 million visits to 11.7 million visits per year by 2013.<sup>2,3</sup> Compared to all other age groups, patients over the age of

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65 years also have a greater risk of mortality during their hospitalization.<sup>4</sup>

Atypical presentations and attenuated physiologic responses are common in older patients.<sup>5</sup> These patients often have complex medical histories, and chronic conditions may mask acute illness. Identifying factors associated with in-hospital and postdischarge mortality would be useful in the triage of older adults at the time of hospital admission. Triage scores such as the Emergency Severity Index are associated with mortality at 1 year in older adults, but such tools depend on subjective parameters.<sup>6</sup> The Identification of Seniors at Risk tool relies on a self-report screening assessment that includes assessment of functional status, support systems, and prehospitalization risk factors, but does not take into account physiologic parameters on presentation.<sup>7</sup> Other tools use objective data gathered during hospitalization to predict 1-year mortality in older adults, but offer no short-term prognostic information and require more data than are available to the emergency physician or to the accepting physician at the time of admission.<sup>8</sup>

Laboratory biomarkers provide an objective measure of abnormal physiology. Random leukocyte count and serum creatinine values have been associated with long-term mortality risk.<sup>9</sup> Serum lactate has robust associations with mortality in patients with circulatory shock, after cardiac arrest, in trauma patients, and in patients with clinically suspected infection.<sup>10-13</sup> However, the ability of serum lactate and other laboratory markers to predict mortality specifically in older hospitalized patients has not been studied.

This study aims to investigate whether serum lactate is associated with mortality in a broad cohort of older patients admitted to the hospital from the ED. We hypothesized that lactate values in the ED would be associated with in-hospital, 30-day, and 60-day mortality in patients with infection-related as well as non-infection-related diagnoses. We further hypothesized that serum lactate would have a greater magnitude of association with mortality than would leukocyte count or serum creatinine.

## METHODS

### Study Design

This was a retrospective cohort analysis of a database of ED admissions of patients aged 65 years and older over a period of 3 years at two urban hospitals. The study was approved with exemption from informed consent by the institutional review board of the University of Pennsylvania.

### Study Setting and Population

The data were gathered from two centers: a tertiary care university hospital with an annual ED census of 56,000 (the Hospital of the University of Pennsylvania) and a community teaching hospital with an annual ED census of approximately 30,000 (Penn Presbyterian Medical Center). The population sample included all adults 65 years or older admitted to either of the two urban teaching hospitals through the ED for any cause between January 2004 and December 2006. Excluded

from the study were patients seen for any seizure-related condition; patients in whom a serum lactate measurement was not obtained; patients transferred to other hospitals from the ED for continued care; and patients who left without being seen, left against medical advice, or died in the ED. Trauma patients whose presentations were deemed critical enough in the pre-hospital setting to be evaluated in the trauma bay were excluded because those patient encounters are systematically recorded in a separate charting system from that of the main ED.

### Study Protocol

Study subjects were identified for inclusion via EM-TRAC (University of Pennsylvania Philadelphia, PA), the electronic medical record (EMR) for the ED. If a patient was admitted more than once, only data for the last admission during the study period were analyzed. Demographic, clinical, and laboratory variables (age, sex, race, vital signs, serum lactate, leukocyte count, and serum creatinine) were obtained from the EMR. Initial serum lactate levels were measured using a serum-based assay catalyzed by lactate oxidase (Vitros, Ortho Clinical Diagnostics, Rochester, NY). Patient and hospital-level admission and discharge data were obtained by record linkage analysis of ED medical records with information extracted from the McKesson Horizon Performance Management System (HPM, Alpharetta, GA). The presence or absence of infection was determined by chart review of International Classification of Diseases Ninth Revision (ICD-9) diagnoses coded in the ED, in accordance with recognized standards for retrospective chart review in ED research.<sup>14</sup>

Two chart abstractors, a physician and a fourth-year medical student, were provided lists of all ICD-9 diagnoses charted in the ED for the population sample that met inclusion criteria. Both abstractors were made aware of the study hypothesis but were blinded to all clinical data, including serum lactate value, leukocyte count, creatinine, and mortality outcomes. Each abstractor was instructed to categorize each listed diagnosis as "infection-related," "non-infection-related," "seizure-related," or "not enough information available to categorize." Any diagnosis in which the presence of seizures was suspected was categorized as "seizure-related," regardless of whether the diagnosis implied the presence of infection. "Infection-related" was defined as "implying the presence of any (bacterial, viral, or fungal) infection" in the absence of seizure. As in-depth extraction from charts was not performed, no further specialized training was required for the two abstractors.

Any patient with one or more "infection-related" diagnosis code was placed into the "infection-related" group. Where abstractors felt there was not enough information or did not agree, a second database was created that included all coded ED ICD-9 diagnosis codes (up to five) for each patient record, as well as the diagnosis-related group (DRG) code entered upon patient discharge or death. Based only on this information, and blinded to other clinical data as stated, the two data abstractors then categorized each of those 647 patient records as "infection present," "infection

absent," or "seizure present." For a patient record to be considered in the "non-infection-related" group, none of the coded diagnoses for that record could be infection-related nor imply seizure. The standardized abstraction forms were computerized spreadsheet lists of diagnoses as described. Overall interrater reliability was 88%. To minimize misclassification bias, 192 records where the two abstractors were discordant were excluded from primary analysis and instead were subjected to subgroup analysis.

Patients with a seizure-related diagnosis were excluded from analysis, as seizures may cause elevations in lactate,<sup>15</sup> and a seizure disorder may not portend the same prognosis as elevations in lactate due to non-seizure-related illness. The remaining patients in each group were stratified based on initial serum lactate values (Figure 1). For purposes of comparison, we also calculated mortality rates for 8,376 admitted patients over the age of 65 years who did not have lactate measured in the ED.

**Measures**

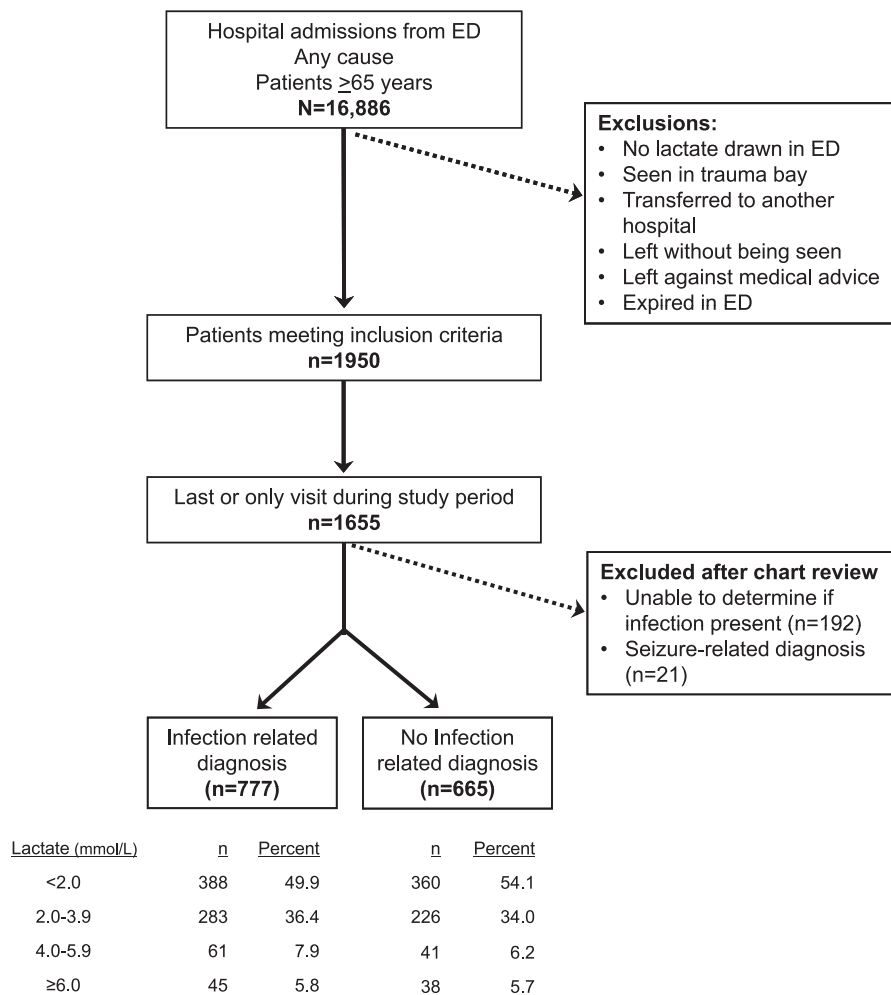
The outcomes measured were mortality during hospitalization, at 30 days, and at 60 days. Postdischarge sur-

vival data were obtained by application for protected mortality data files on patients deceased in Pennsylvania during years 2004–2007. These data were supplied by the Bureau of Health Statistics and Research at the Pennsylvania Department of Health. The majority (90%, 15,301 of 16,886) of study participants were residents of Pennsylvania at the time of admission. The next most frequent state of residence was New Jersey (7.8%, 1,322 of 16,886).

**Data Analysis**

Lactate levels were stratified into four groups (0–1.9, 2.0–3.9, 4.0–5.9, and ≥6.0 mmol/L). To examine mortality by lactate level, the chi-square test for trend was used. To determine differences between patients with infection compared to those without, the chi-square or Fisher’s exact test was used for categorical data, and the t-test was used for continuous data. For these comparisons, data are presented as frequencies and percents or as means and standard deviations (SDs).

To assess whether lactate was independently associated with mortality while simultaneously adjusting for confounders (age, sex, race, hospital, presence or absence of two or more systemic inflammatory



**Figure 1.** Study profile. Patients meeting all inclusion and no exclusion criteria were divided into those with at least one infection-related diagnosis and those without. They were further stratified by lactate value.

response syndrome [SIRS] criteria, and hypotension), relative risk (RR) was estimated using a generalized linear model with a log link, Gaussian error, and robust estimates of the standard errors of the model coefficients.<sup>16</sup> These analyses were performed using STATA (Version 9.2, StataCorp, College Station, TX). Data for these analyses were presented as RRs with 95% confidence intervals (CIs). SIRS criteria were defined as: heart rate of >90 beats/min, respiratory rate of >20 breaths/min, or pCO<sub>2</sub> of <32 mm Hg, temperature of >100.4°F or <96.8°F, and leukocyte count of <4 × 10<sup>3</sup> or >12 × 10<sup>3</sup> cells/μL.<sup>17</sup> Hypotension was defined as a systolic blood pressure (sBP) of ≤90 mm Hg at triage.

Separate regression models were built to assess the association between leukocyte count or serum creatinine and mortality. The categories used for leukocyte count were low (<4.0 × 10<sup>3</sup>/μL), normal (4 × 10<sup>3</sup>–10 × 10<sup>3</sup>/μL), elevated (10.1 × 10<sup>3</sup>–20.0 × 10<sup>3</sup>/μL), and very elevated (>20.0 × 10<sup>3</sup>/μL). Serum creatinine was categorized as normal (≤1.0 mg/dL), mildly elevated (1.1–1.4 mg/dL), elevated (1.5–3.0 mg/dL), and very elevated (>3.0 mg/dL).<sup>18</sup> The normal reference range for serum lactate was 0–1.9 mmol/L, consistent with ranges used in other studies.<sup>19</sup> Unless otherwise noted, all analyses were performed using SAS statistical software (Version 9.1, SAS Institute, Cary, NC).

## RESULTS

A total of 1,950 ED visits met inclusion criteria before chart review. Of these, 295 were excluded as repeat visits, leaving 1,655 unique patient visits. After chart review, 192 records were excluded because they could not be categorized as infection-related or non-infection-related visits, and another 21 records were excluded because the ED visits were thought to be seizure-related. Of the remaining 1,442 records, 777 were deemed infection-related and 665 were deemed non-infection-related.

The mean age of our population was 77.2 (±7.8) years. The majority of patients (49.9% in infection-related

diagnosis group and 54.1% in non-infection-related group) had initial serum lactate values of less than 2.0 mmol/L (Figure 1). Fewer than 6% of patients had lactate values in the extreme range (≥6.0 mmol/L).

The mortality of admitted patients who did not have lactate measured was 5.1% during hospitalization, 10.2% at 30 days, and 12.9% at 60 days. In patients who had lactate measured, mortality during hospitalization was 12.8% in patients without infections and 16.9% in patients with at least one infection-related diagnosis (p = 0.03; Table 1). Mortality at 30 days was 20.2% in uninfected patients and 24.7% in the infected patients (p = 0.04). There was no significant difference between groups in mortality at 60 days (24.4% in the uninfected compared to 28.2% in the infected group, p = 0.1).

Patients with infections were similar to those without infections with respect to sex, race, and admission to the intensive care unit (Table 1). Infected patients as a group were older and had higher leukocyte counts and lower serum creatinine values than patients without infections. A greater proportion of infected patients (80.7% compared to 56.2% in uninfected group) met at least two SIRS criteria, but there was no difference between groups in the proportion of patients who were hypotensive (sBP ≤ 90 mmHg). Notably, mean serum lactate value (2.5 mmol/L) was not different between groups.

Figure 2 shows that in both infection-related and non-infection-related groups, serum lactate showed an approximately linear association with 30-day, 60-day, and in-hospital mortality. In both groups, the chi-square test for trend demonstrated a significant association between increasing serum lactate levels and mortality at each time point (p < 0.001).

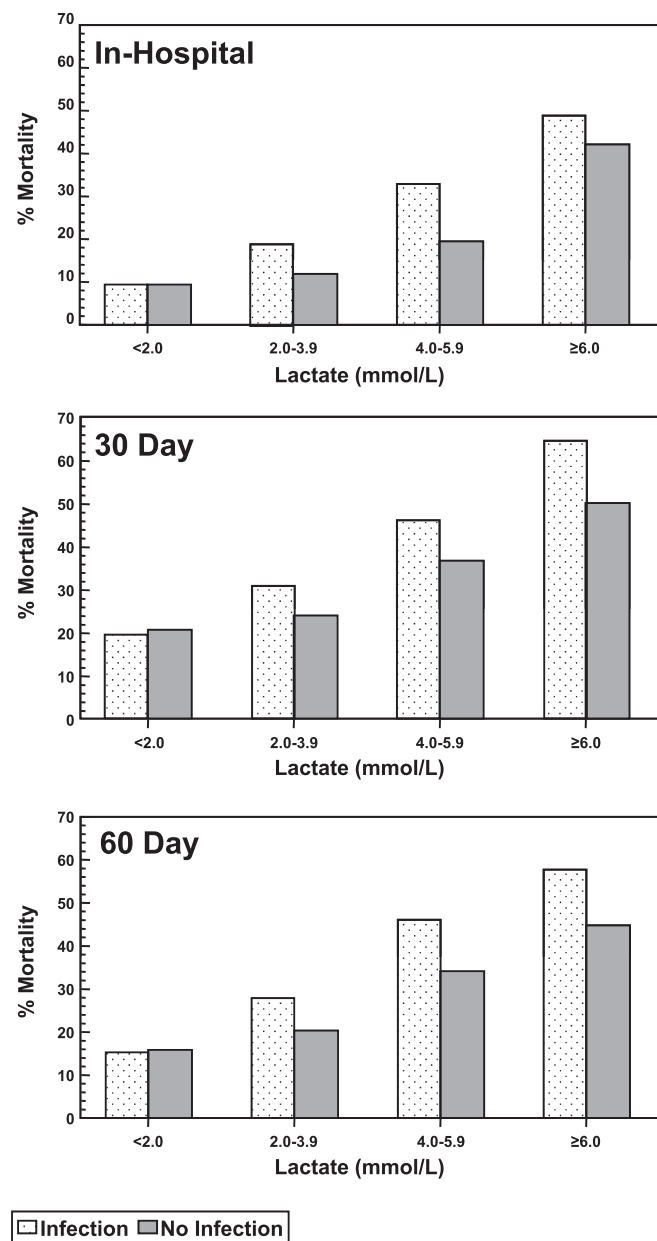
Figure 3 demonstrates that elevated serum lactate levels remain strongly associated with mortality after adjusting for potential confounders (age, sex, race, hospital, hypotension, and SIRS). Furthermore, the strength of association was greater with initial serum lactate levels (RR = 1.1 to 3.9) than with either of the two other laboratory markers tested (leukocyte count,

Table 1  
Population Characteristics of Adults Age 65 Years and Older Admitted to the Hospital From the ED with Serum Lactate Ordered

Characteristic	Infection (n = 777)	No Infection (n = 665)	p-value
Male, n (%)	357 (46.0)	287 (43.2)	0.3
Caucasian, n (%)	197 (25.7)	178 (27.0)	0.8
Age (yr), n (%)			
65–74	313 (40.3)	312 (46.9)	0.009*
75–84	285 (36.7)	238 (35.8)	
≥85	179 (23.0)	115 (17.3)	
Two or more SIRS criteria, n (%)	627 (80.7)	374 (56.2)	<0.0001*
sBP ≤ 90 mm Hg, n (%)	113 (14.5)	102 (15.3)	0.05
Admitted to intensive care unit, n (%)	233 (30.0)	204 (30.7)	0.8
Mean (±SD) leukocyte count (×10 <sup>3</sup> /μL)	13.4 (±9.0)	11.1 (±11.7)	<0.0001*
Mean (±SD) creatinine (mg/dL)	1.9 (±1.8)	2.2 (±2.4)	0.02*
Mean (±SD) lactate (mmol/L)	2.5 (±2.0)	2.5 (±2.2)	0.5
Mortality			
In-hospital	131 (16.9)	85 (12.8)	0.03*
30-day	192 (24.7)	134 (20.2)	0.04*
60-day	219 (28.2)	162 (24.4)	0.1

sBP = systolic blood pressure; SIRS = systemic inflammatory response syndrome.

\*Statistically significant (p < 0.05).



**Figure 2.** Association between serum lactate and mortality in older patients. There is an association between serum lactate and mortality in older patients with ( $n = 777$ ) and without ( $n = 665$ ) infection-related diagnosis. Percentage of mortality is measured during hospitalization and also at 30 and 60 days.

RR = 0.96 to 2.5; and serum creatinine, RR = 1.1 to 1.7). The association between lactate and mortality in both the infection-related and the non-infection-related groups was strongest during hospitalization, with diminishing strength of association at 30 and 60 days.

The association between lactate and mortality was also supported in adjusted multivariate analysis of lactate as a continuous, rather than categorical, variable. In patients with infections, the adjusted RR of death per 0.1 mmol/L increase in lactate was 1.11 (95% CI = 1.09 to 1.14) during hospitalization, 1.10 (95% CI = 1.07 to 1.12) at 30 days, and 1.08 (95% CI = 1.06 to 1.10) at 60 days. In patients without infections, the adjusted RR

of death per 0.1 mmol/L increase in lactate was 1.13 (95% CI = 1.09 to 1.17) during hospitalization, 1.09 (95% CI = 1.06 to 1.13) at 30 days, and 1.08 (95% CI = 1.05 to 1.11) at 60 days. All of these associations were statistically significant ( $p < 0.001$ ).

The association between serum lactate and mortality was robust in the overall analysis of all 1,442 patients meeting our final inclusion criteria. Analyzed as both a continuous and a categorical variable and adjusted for confounders, lactate was associated with a significantly increased risk of mortality at 30 days, at 60 days, and during hospitalization (RR = 1.04–1.05 per 0.1 mmol/L,  $p < 0.01$ ).

The area under the receiver operating curve (AUC) was calculated for lactate as a test for mortality. The strongest association noted was between lactate and in-hospital death, with the predictive ability of lactate decreasing at later time points (AUC<sub>in-hospital</sub> = 0.756, AUC<sub>30-day</sub> = 0.728, AUC<sub>60-day</sub> = 0.709 in patients with infections; AUC<sub>in-hospital</sub> = 0.662, AUC<sub>30-day</sub> = 0.647, AUC<sub>60-day</sub> = 0.626 in patients without infections).

Subgroup analysis of the 192 patients who could not be categorized clearly as infection-related or non-infection-related failed to demonstrate any significant association. Sixteen patients (8.3%) in this subgroup died during hospitalization, 25 (13.0%) died within 30 days, and 33 (17.2%) died within 60 days.

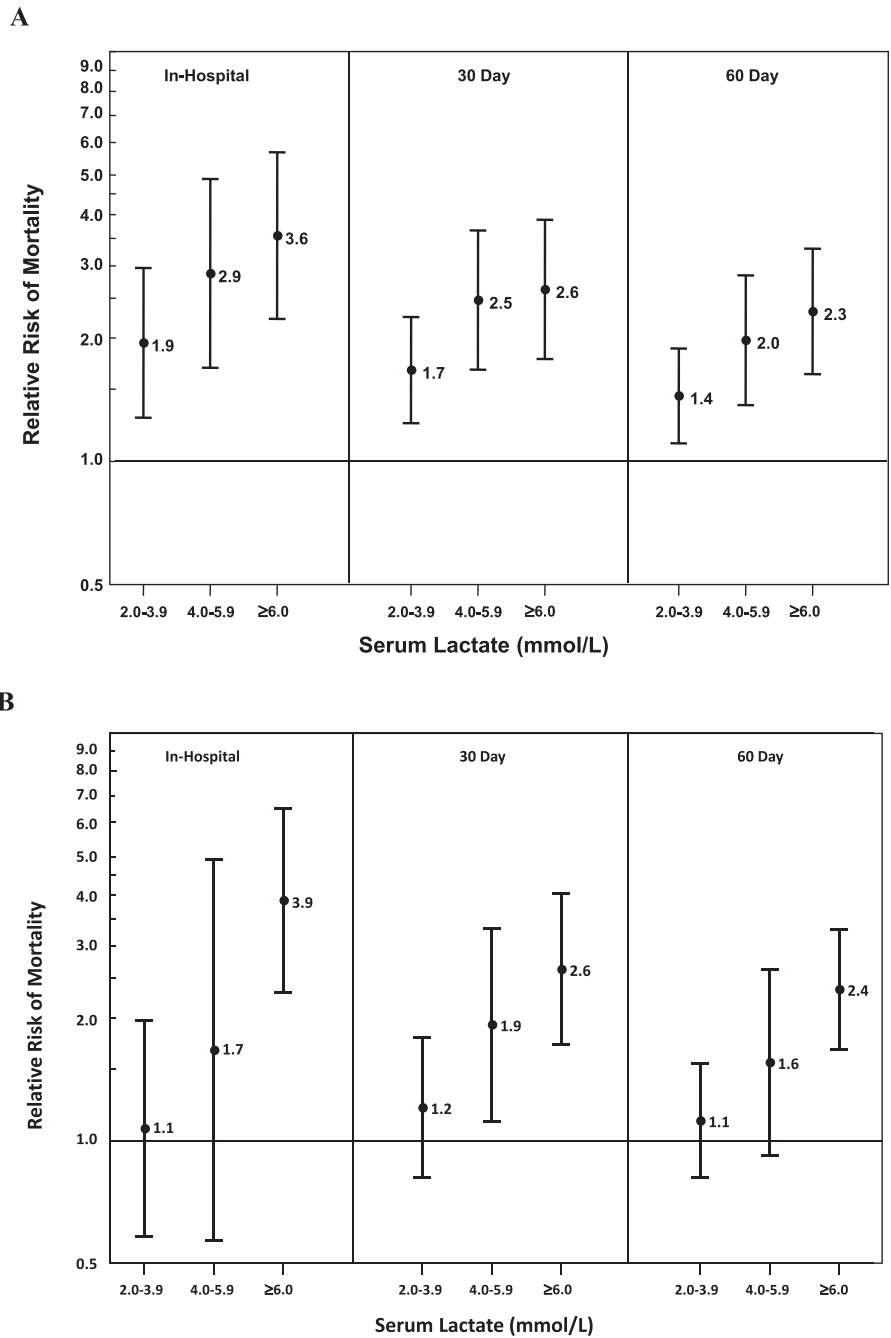
## DISCUSSION

We found that elevated ED lactate values in a broad cohort of older adults admitted to the hospital are associated with increased risk of mortality during hospitalization, at 30 days, and at 60 days. When analyzed separately, a similar association is observed both in patients with infections and in those without infections. Furthermore, we found that serum lactate had a greater magnitude of association with mortality than two other commonly ordered laboratory tests, leukocyte count and serum creatinine.

Our principal finding, that serum lactate is associated with mortality in older patients, adds to the growing body of work that has examined the prognostic value of lactate in a variety of critically ill populations.<sup>13,20–22</sup> Previous studies have shown that lactate elevations portend mortality in groups of patients with circulatory shock, after cardiac arrest, in trauma patients, and in patients with clinically suspected infection.<sup>10–13</sup> Most recent work has focused on patients with infections. Shapiro et al.<sup>13</sup> showed that in ED patients with suspected infection, lactate elevations predicted 3- and 28-day in-hospital mortality. In a post hoc analysis of the same patients, Howell et al.<sup>22</sup> demonstrated that lactate was associated with 28-day mortality, independent of hypotension or comorbidities.

Our study, which is to our knowledge the largest multicenter study of lactate and mortality, further supports the notion that early lactate measurements provide prognostic information. It is the first study to examine the association between lactate and mortality in a population restricted to adults aged 65 years and older. Our results suggest that lactate is a useful risk-stratification tool in this age group independent of





**Figure 3.** (A) Adjusted relative mortality risk of lactate in patients with one or more infection-related diagnoses (95% CI shown). (B) Adjusted relative mortality risk of lactate in patients without any infection-related diagnosis (95% CI shown).

sociodemographics and hemodynamics. Furthermore, as we separately examined patients with and without infections, it appears that the association between elevated serum lactate levels and mortality in older patients is not restricted to those presenting to the ED with infection. In our patients without infections, the most common diagnoses were “other lower respiratory disease,” nausea and vomiting, fluid and electrolyte disorders, and “other injuries and conditions due to external causes,” suggesting a broad range of noninfectious pathology for which lactate is prognostic. It is worth noting that the majority of patients without infections (374 of 665, 56.2%) met two or more SIRS criteria, indi-

cating that in many of these cases, an inflammatory state was present.

Lactate is classically described as a biomarker of tissue hypoperfusion.<sup>23</sup> By controlling for hypotension in our analysis, we have validated findings by others that lactate is independently predictive of mortality.<sup>19,22,24</sup> By controlling for the presence or absence of SIRS criteria, we have shown that lactate is not simply a biomarker for the systemic inflammatory response.<sup>19</sup> Our finding that lactate is associated with mortality even in uninfected patients prompts consideration of whether there are common or divergent mechanisms by which hyperlactatemia arises in these diverse groups. While

inflammation may play some role, there may be micro-circulatory dysfunction from other causes,<sup>25</sup> derangements in metabolism such as those related to ischemia or alteration of pyruvate dehydrogenase activity,<sup>26</sup> catecholamine effects leading to pyruvate overproduction,<sup>27</sup> and ineffective clearance<sup>28</sup> that contribute to hyperlactatemia as well. The etiology of elevations in serum lactate warrants further investigation.

According to 2008 Surviving Sepsis guidelines, elevated lactate is considered to be a marker of tissue hypoperfusion, and a lactate of  $\geq 4$  mmol/L in a septic patient warrants aggressive resuscitation using early goal-directed therapy.<sup>29,30</sup> Recent studies have shown that infected patients with lactate in the 2.0–3.9 mmol/L range have a risk of mortality that is approximately twice that of patients with a lactate level of  $<2.0$  mmol/L.<sup>19,22</sup> It has been suggested that perhaps the threshold of 4.0 mmol/L misses a large at-risk group of patients with intermediate lactate values who may benefit from aggressive resuscitation to reverse the underlying physiologic derangements.<sup>19,31</sup> Our study further challenges the commonly accepted lactate threshold, and we have identified a trend toward increased risk of mortality (statistically significant only in the infected group), even in patients with lactate values between 2.0–3.9 mmol/L compared to those whose lactate level is  $<2.0$  mmol/L. It is unclear from our retrospective approach, especially in the cohort without infections, whether these patients may have benefited from aggressive resuscitation. As patients in this intermediate lactate range comprised a large percentage of our patients (36.4% of infected and 34.0% of uninfected patients), we believe that patients with lactate between 2.0 and 4.0 mmol/L should be included in further study of protocol-based resuscitation. Finally, by demonstrating that serum lactate drawn in the ED has a greater magnitude of association with mortality than two other commonly ordered laboratory tests, we advance the argument for more routine usage of serum lactate as a screening tool.<sup>24</sup>

Our results support the merit of measuring serum lactate in a broader group of older patients beyond those with infections. The selection bias of this retrospective study may further be addressed by performing a prospective study in which lactate is measured on all admitted patients age 65 or older to determine if the same association with mortality persists. Comparison to other prognostic scoring systems should also be ascertained in a prospective fashion. While economic analysis to estimate the cost-benefit ratio of using lactate as a screening tool in any population of elder ED patients falls outside the scope of this study, future studies are suggested to determine feasibility and cost effectiveness of screening specific ED populations using serum lactate.

## LIMITATIONS

The retrospective nature of our study may introduce a selection bias that was difficult to account for, as there was no consistent documentation of clinicians' rationale for ordering a lactate. It may be that the patients in our population raised greater concern for infection or critical illness, in which case the reported mortality rate may overestimate that of the general ED population

over age 65 years. We addressed the issue of selection bias by analyzing mortality rates for a comparison cohort of elder admitted patients who did not have lactate measured in the ED. Indeed, the group of patients in whom lactate was measured had a higher mortality rate than those in whom lactate was not measured.

There is also the potential for misclassification of patients into infected or uninfected groups. The use of ICD-9 codes that are based on ED documentation alone mimics the reality of ED clinical practice; however, this approach may fail to capture important clinical data, such as cultures, that become available only after the decision to admit. By having two chart abstractors independently categorize all records that met inclusion criteria, rather than just a convenience sample, we believe our categorization was as accurate as the available data allowed. To reduce the risk of misclassification, we excluded from primary analysis 192 records on which consensus could not be achieved by two independent chart abstractors.

The decision to use data from only patients' last visits potentially biases the results toward overestimating overall mortality in our study population. However, this approach allowed us to avoid oversampling from repeat ED visitors. Our approach also provided adequate power to include more variables in our multivariate analysis. We did separately conduct an analysis of first patient visits, with similar findings.

The AUC (max AUC = 0.756) demonstrates that lactate alone is not a good diagnostic test for separating patients who will die from those who will live. Interpreted in isolation, serum lactate lacks both the sensitivity and the specificity to prognosticate on an individual patient. It is not our intention to suggest that lactate may replace clinical judgment, nor should it eclipse the overall clinical assessment of any individual patient. Rather, we report that in a broad cohort, lactate is independently associated with mortality. Therefore lactate, while shown to be a simple prognostic tool, may be particularly useful in combination with other risk assessment tools such as the Acute Physiology and Chronic Health Evaluation (APACHE)<sup>32</sup> score or the Simplified Acute Physiology Score (SAPS)<sup>33</sup>. Recognizing that many prognostic scoring systems have limited accuracy or utility in the ED setting,<sup>34</sup> there are also ED-specific prognostic scores to which serum lactate may add value, such as the Rapid Emergency Medicine Score (REMS) in nonsurgical patients<sup>35,36</sup> or the Mortality in Emergency Department Sepsis (MEDS) score in sepsis patients.<sup>37,38</sup> Ideally, our analysis would have assessed whether lactate added prognostic information beyond these commonly used scores. Unfortunately, too much data were missing to retrospectively calculate these scores for all patients, so we elected instead to focus our analysis only on data available at the time of admission.

## CONCLUSIONS

Emergency department lactate values are associated with mortality in a cohort of admitted patients over age 65 years, regardless of the presence or absence of infection.

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