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Pre-resuscitation Lactate and Hospital Mortality in Prehospital Patients

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Abstract

Objective—Serum lactate elevations are associated with morbidity and mortality in trauma patients, but their value in prehospital medical patients prior to resuscitation is unknown. We sought to assess the distribution of blood lactate concentrations prior to intravenous (IV) resuscitation and examine the association of elevation on in-hospital death.

Methods—A convenience sample of adult patients over 14 months who received an IV line by eight EMS agencies in Western Pennsylvania had lactate measurement prior to any IV treatment. We assessed the lactate values and any relationship between these and hospital mortality (our primary outcome) and admission to the intensive care unit (ICU). We also compared the ability of lactate to discriminate outcomes with a prehospital critical illness score using age, Glasgow Coma Score, and initial vital signs.

Results—We included 673 patients, among whom 71 (11%) were admitted to the ICU and 21 (3.1%) died in-hospital. Elevated lactate (≥ 2 mmol/L) occurred in 307 (46%) patients and was strongly associated with hospital death after adjustment for known covariates (odds ratio = 3.57, 95% confidence interval [CI]: 1.10, 11.6). Lactate ≥ 2 mmol/L had a modest sensitivity (76%) and specificity (55%), and discrimination for hospital death (area under the curve [AUC] = 0.66, 95%CI: 0.56, 0.75). Compared to the prehospital critical illness score alone (AUC = 0.69, 95% CI: 0.59, 0.80), adding lactate to the score offered modest improvement (net reclassification improvement = 0.63, 95%CI: 0.23, 1.01, $p < 0.05$).

Conclusions—Initial lactate concentration in our prehospital medical patient population was associated with hospital mortality. However, it is a modest predictor of outcome, offering similar discrimination to a prehospital critical illness score.

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Keywords

emergency medical services; critical illness; lactic acid; prehospital; pre-resuscitation

Introduction

Many critically ill patients, including those with time-sensitive conditions, such as myocardial infarction, stroke, and trauma, access the health-care system through emergency medical services (EMS).^{1–3} EMS personnel often use an unstructured approach to guide initial care, risk stratify, and choose transport destinations.⁴ This approach can compromise accurate prediction of those who will benefit from emergency care⁵ and admission to the hospital.⁶ Current medical priority dispatch codes and tools perform poorly in identifying critical illness or predicting need for advanced interventions,^{7–11} and direct physician oversight may not be routinely available.¹² As a result, acutely ill medical patients may not be optimally matched to critical care resources in a coordinated system of emergency care.¹³

Two prospective trials evaluated prehospital point-of-care serum lactate (“lactate”) measurement as a biomarker in trauma patients and in patients with abnormal prehospital vital signs.^{14,15} In these studies, elevated prehospital lactate levels improved prediction of in-hospital mortality, surgery, and organ dysfunction over vital signs alone. This is consistent with broad literature supporting lactate for critical illness prognostication during hospital care in patients with septic shock, myocardial infarction, cardiac arrest, trauma, and invasive surgical procedures.^{16–27} However, few studies evaluate lactate prior to intravenous (IV) resuscitation or intervention by emergency clinicians, and any biomarker performance may be confounded by ongoing treatments.

We sought to determine the association between pre-resuscitation lactate measured during prehospital care with hospital mortality. Second, we sought to determine if prehospital lactate measurement improves discrimination of outcomes among medical patients compared to a prehospital critical illness score.²⁸

Methods

Study Design and Setting

We conducted a prospective observational cohort study in a convenience sample of adult, nontrauma patients transported by EMS between April 2010 and July 2011. Eight EMS agencies in western Pennsylvania with a combined annual response volume of 100,000 cases participated. The participating EMS agencies serve both urban and rural areas, and are all staffed with paramedic-level providers who have advanced life support (ALS) capabilities. These agencies receive medical command and continuing education through a single academic tertiary-level institution. The University of Pittsburgh institutional review board granted a waiver of the requirement for patient informed consent for this minimal risk study.

Selection of Participants

We enrolled a convenience sample of subjects transported to any of four hospitals and who received ALS care, as defined by placement of a peripheral IV catheter, during prehospital care. For this study, we did not modify the indications or protocols for IV catheter insertion. The statewide EMS protocols used in this EMS system specify that a peripheral IV should be initiated for specific complaints and indications, including suspected acute coronary syndrome, severe respiratory distress, allergic reaction, altered mental status, and suspected shock, among others. Our prior quality improvement data reveals an IV placement rate of approximately 20% in this EMS system. Each of the receiving hospitals is an urban, tertiary-care facility with advanced critical care capability. We excluded those patients less than 18 years old, pregnant, imprisoned, or with a prehospital seizure. We also excluded trauma patients because the prehospital critical illness score was developed for nontrauma patients²⁸ and the performance of prehospital lactate assessment is already described for this group.¹⁴

Study Protocol and Outcome Measures

Prior to study initiation, all paramedics participated in a 1-hour training session reviewing the entry criteria and operating procedures for use of a Food and Drug Administration-approved, Clinical Laboratory Improvement Amendments-waived point-of-care whole-blood lactate meter (LactatePro, FACT, Canada).^{29–31} EMS personnel obtained a lactate value on patients meeting the entry criteria using blood obtained during IV catheter insertion, prior to the administration of IV fluid. Receiving hospital staff and online medical command physicians were blinded to the lactate values. EMS personnel recorded the lactate value in the prehospital electronic medical record after the completion of patient care. In Pennsylvania, prehospital electronic medical records are forwarded to the hospitals within 48 hours of patient transfer, but are not available to physicians in the emergency department concurrent with patient care. We instructed EMS personnel not to alter their treatment based on the lactate value, and existing treatment protocols do not dictate any specific care based on lactate measurements.

From the EMS medical record, we abstracted lactate values and other clinical data, including age; sex; initial vital signs that included systolic blood pressure (mmHg), heart rate (beats per minute), oxygen saturation via pulse oximetry (%), and respiratory rate (breaths per minute); and Glasgow Coma Scale score.²⁸ We linked prehospital charts to hospital records using patient demographic information. From the hospital medical record, we abstracted intensive care unit (ICU) admission and hospital mortality. Data were abstracted by physician investigators and undergraduate research assistants. Data abstractors received standardized training, all data were entered using a standard data form, and we assessed accuracy of all extracted data points in a random sample of 10% of the population by the primary author.

Prehospital Critical Illness Score Calculation

We calculated the prehospital critical illness score using previously described methods.²⁸ We assigned point values to demographics and vital signs in the following categories: age 45years (1 point); initial systolic blood pressure ≥ 90 mmHg (1 point), initial heart rate ≥ 120 /min (1 point); initial respiratory rate <12 or $24\text{--}35$ (1 point), or ≥ 36 /min (2 points);

initial Glasgow Coma Scale score 8–14 (1 point), or <8 (2 points); initial pulse oximetry <87% (1 point).

Statistical Analysis

We analyzed hospital mortality as the primary outcome, and pre-resuscitation lactate (mmol/L) as the primary exposure. We dichotomized lactate at 2 mmol/L based on published cutoffs from multiple professional societies.³² We performed bivariate comparisons of demographics and prehospital data between those subjects with pre-resuscitation lactate above and below 2 mmol/L using the chi-square test for proportions, Student *t*-tests for normally distributed outcomes, and, otherwise, Wilcoxon rank sum tests. Our analysis consisted of three steps: 1) determine the independent association between pre-resuscitation lactate and hospital mortality, 2) assess the discrimination of pre-resuscitation lactate using traditional operating characteristics (e.g., sensitivity, specificity) and the area under the receiver operating characteristic curve, and 3) determine if pre-resuscitation lactate improved discrimination beyond the specified prehospital critical illness score.

First, we sought to determine the independent association between pre-resuscitation lactate and hospital mortality. We developed multivariable logistic regression models of hospital mortality on pre-resuscitation lactate (> 2 mmol/L) and a priori confounders known to be associated with hospital outcomes.²⁸ Confounders included age, sex, and initial prehospital vital signs measured by the responding paramedic (e.g., heart rate, respiratory rate, systolic blood pressure, Glasgow Coma Scale score, and oxygen saturation). We used Huber White standard errors, and report the odds of hospital death, on average, comparing subjects above and below 2 mmol/L lactate. We assessed the robustness of our model in three sensitivity analyses: 1) alternate outcome of intensive care unit admission,²⁸ 2) alternate parameterization of pre-resuscitation lactate as a log-transformed continuous variable, and 3) alternate confounders using worst (not initial) prehospital vital signs.

Second, we determined the discrimination of pre-resuscitation lactate for hospital mortality using the area under the receiver operating characteristic curve (AUC) from bivariate logistic regression model of hospital death on continuous lactate alone. We then explored traditional operating characteristics (e.g., sensitivity, specificity, positive and negative likelihood ratios) at different dichotomizing thresholds around 2.0 mmol/L.

Finally, we determined if pre-resuscitation lactate improved discrimination beyond the prehospital clinical risk score using two methods: 1) the change in AUC comparing the clinical risk score and the clinical risk score plus lactate, and 2) the net reclassification improvement (NRI) statistic.³³ The NRI summarizes risk reclassification of patients when lactate is added to the clinical model by summing of the net proportion of deaths reclassified to a higher risk category and the net proportion of survivors reclassified to a lower risk category. In our case, we calculated the NRI over a continuous risk of death, avoiding the need to define a priori risk categories. As such, should lactate improve classification beyond the clinical model, it will have a positive NRI, while the NRI for a null effect is zero. Bootstrapped confidence intervals for the NRI that do not include zero are considered significant evidence of improvement in prediction.³⁴

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA) and STATA 11.0 (College Station, TX). We set two-sided per-comparison alpha error at 0.05.

Results

Of 876 patients who received an IV catheter and were transported to a study hospital, we excluded 160 (18%) with trauma and 43 (4.9%) with missing data. The final sample included 673 subjects (77%), with 21 (3.1%) not surviving to discharge from the hospital (Figure 1). Median pre-resuscitation lactate was 1.8 mmol/L (interquartile range [IQR]: 1.3–2.6 mmol/L), and greater among those who died (2.8 mmol/L, IQR: 2.2–3.5 mmol/L) compared to survivors (1.8 mmol/L, IQR: 1.3–2.4 mmol/L) (Figure 2). We observed that 307 patients (46%) had pre-resuscitation lactate ≥ 2.0 mmol/L. Compared to those with lactate < 2.0 mmol/L, patients with high lactate were more likely to be admitted to intensive care (14 vs. 7.4%, $p < 0.01$) and more likely to die in the hospital (5.2 vs. 1.4%, $p < 0.01$) (Table 1).

In unadjusted logistic regression models, pre-resuscitation lactate ≥ 2.0 mmol/L was associated with hospital mortality (odds ratio [OR] = 3.97, 95% confidence interval [CI]: 1.44, 11.0, $p < 0.01$). After adjusting for covariates, lactate elevation retained an association with mortality, albeit slightly lessened in magnitude (Table 2). In sensitivity analyses, even the worst prehospital physiology or re-parameterizing lactate as a continuous variable did not unseat the lactate association with in-hospital mortality (Table 3).

Despite a strong association with outcome, pre-resuscitation lactate ≥ 2.0 mmol/L alone was a modest discriminator of hospital mortality (area under the receiver operating characteristic curve (AUC) = 0.66, 95% CI: 0.56, 0.75). Pre-resuscitation lactate ≥ 2.0 mmol/L also had a modest sensitivity (76%) and low specificity (55%). Higher lactate thresholds were more specific, but resulted in substantially lower sensitivity (Table 4). In comparison, we observed that the prehospital clinical risk score had similar discrimination for hospital mortality (AUC = 0.69, 95% CI: 0.59, 0.80). When lactate ≥ 2.0 mmol/L was added to the prehospital clinical risk score, the AUC increased to 0.73 (95% CI: 0.62, 0.84) (Figure 3), and the continuous net reclassification improvement statistic revealed significant improvement (NRI = 0.63, 95% CI: 0.23, 1.01).

Discussion

The association of elevated lactate with worse outcomes is well known in hospitalized critically ill patients.^{16–27} Our data suggest that lactate measured in the prehospital setting prior to IV resuscitation similarly has value for risk stratification and is also associated with in-hospital death. If this relationship holds in an independent dataset, it may be an additional tool that could be utilized to risk stratify patients at risk of critical illness during the initial encounter in the field. Risk stratification adds substantial value to the prehospital encounter, which is characterized by an opportunity to provide limited interventions and transport for further medical care. Better risk stratification may allow a more defined role for initiating specific therapies in the prehospital setting.^{35,36} For example, at present, prehospital patients with severe sepsis receive a low rate of interventions and fluid before hospital arrival,³⁷ and

lactate-guided therapy may improve outcomes in severe sepsis, as has been demonstrated in the in-hospital setting.³⁸ A better detection tool that identifies critical illness might accelerate treatment or alter selection of destination.³⁹

Few studies have evaluated the incremental utility of blood lactate measurement over readily available clinical data.¹⁵ In a pilot study, Jansen et al. found that in a high-risk group, prehospital blood lactate levels predicted in-hospital mortality with greater sensitivity than vital signs alone. Our findings build on this work with a larger sample that included patients with a broader set of chief complaints. We noted that pre-resuscitation lactate, when added to a prehospital critical illness score, modestly improves discrimination of patients with poor outcome in this prehospital population. This improvement may be useful for particular clinical situations.^{14, 40–44}

Blood lactate measurement in the field, either alone or in combination with risk stratification tools derived from clinical data, may be of greatest value in higher risk subsets of patients. Prior work by Seymour et al. on the use of biomarkers for risk stratification demonstrated that even weak biomarkers reclassified cases at higher risk of critical illness, whereas only strong biomarkers can reclassify controls as lower risk.⁴⁵

Our findings support this prior work by suggesting that lactate measurements may have more value in a higher risk subset of prehospital patients, instead of using it as a tool for every prehospital patient receiving ALS-level care. Additionally, it may be only through combination of lactate measurement with clinical data or other biomarkers that we can achieve a tool that is sufficiently robust to differentiate patients with critical illness from an otherwise undifferentiated prehospital population.

While prehospital lactate measurement alone provides similar discrimination to a prehospital critical illness score using already available clinical data, it may be easier to implement the use of lactate measurement in the prehospital setting. A provider may find it preferable to obtain a single reading after placing an IV rather than calculating a score requiring multiple variables. Lactate measurement is a simple, reliable, and reproducible measure that may actually be less susceptible to measurement error than other clinical data.^{29–31} Similarly, medical command physicians who assist in treatment and destination decisions based on an online report may be better informed by reporting of a single clinical value in addition to a patient vignette than having to calculate a clinical risk score themselves. Future studies should explore the value of lactate measurements in discrimination of higher risk subsets of patients and as part of algorithms for prehospital treatment, such as early goal-directed therapy for suspected sepsis. The value of serial lactate measurements in the field should also be explored.

Limitations

Our study is limited by the use of a convenience sample of subjects with intravenous access, transported to select tertiary-care centers. This group may be more severely ill than the general population transported by an ambulance. The association between pre-resuscitation lactate among those without peripheral IV catheters was not assessed and may be less robust. At the same time, some of the most severely ill patients may not have been enrolled

because IV access was unsuccessful, due to factors such as hypotension and peripheral vasoconstriction, or because the patients received intraosseous access. However, this subset of patients would typically be more easily identified as critically ill through conventional means and therefore lactate levels and prehospital critical illness scores might be less useful. We acknowledge that, with more than 100,000 patients transported during the study period, not all eligible patients were enrolled, but our enrollment rate is comparable to that of other prehospital cohort studies.^{46–47} Furthermore, EMS personnel were not blinded to lactate values, and measurement may have altered patient care. However, our EMS providers follow state protocols that do not incorporate lactate into prehospital management. Finally, we acknowledge that the association between pre-resuscitation lactate and intensive care admission may be subject to practice variation, ICU census, and bed availability.⁴⁸ These factors should not affect the primary outcome of hospital mortality.

Conclusion

Pre-resuscitation lactate measured in our prehospital medical patient population is associated with hospital mortality. A modest predictor of outcome, pre-resuscitation lactate provides similar discrimination to a prehospital clinical risk score. Additional tools are needed to identify prehospital patients at risk of critical illness.

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Figure 1.
Patient accrual among advanced life support (ALS) prehospital encounters.

Figure 2.
Distribution of pre-resuscitation lactate across hospital mortality.

Figure 3.

Receiver operating characteristic curve for hospital mortality of pre-resuscitation lactate alone (*black curve*) compared to pre-resuscitation lactate and a prehospital clinical risk score (*dashed gray curve*). Pre-resuscitation lactate included in the model as dichotomous variable (≥ 2 mmol/L).

Table 1

Prehospital characteristics and outcomes comparing those above and below pre-resuscitation lactate of 2.0 mmol/L

Variable	Lactate 2.0 mmol/L (N = 307)	Lactate <2.0 mmol/L (N = 366)
Age, years, mean (SD)	64 (19)	62 (21)
Male gender, <i>n</i> (%)	131 (44)	147 (43)
Medical category, <i>n</i> (%)		
Infection	46 (15)	34 (9)
Altered mental status	110 (36)	82 (22)
Shortness of breath or chest pain	141 (46)	223 (61)
Other	10 (3)	27 (7)
Scene arrival to hospital arrival time, mean (SD), min	35 (11)	32 (9)
Time from arrival to lactate measurement, mean (SD), min	20 (9)	19 (8)
Prehospital vital signs		
Systolic blood pressure, mean (SD), mmHg	141 (34)	144 (31)
Systolic blood pressure < 90 mmHg, <i>n</i> (%)	25 (8)	9 (2)
Respiratory rate, mean (SD), breaths per minute	21 (5)	20 (4)
Heart rate, mean (SD), beats per min.	96 (25)	88 (22)
Oxygen saturation, mean (SD), %	96 (10)	96 (4)
Glasgow Coma Scale score, mean (SD)	14 (2)	14 (2)
Prehospital critical illness score, mean (SD)	1.72 (1.0)	1.31 (0.93)
Resource utilization		
Discharge from emergency department, <i>n</i> (%)	88 (29)	125 (34)
Mechanical ventilation, <i>n</i> (%)	25 (8)	16 (4)
ICU admission, <i>n</i> (%)	44 (14)	27 (7)
Hospital death, <i>n</i> (%)	16 (5)	5 (2)

ICU, intensive care unit; SD, standard deviation.

Table 2

Regression estimates of the association between pre-resuscitation lactate and hospital mortality in unadjusted and adjusted logistic regression models and sensitivity analyses

Model	Odds ratio of pre-resuscitation lactate (95%CI)	p-Value
Bivariate model	3.97 (1.44, 11.0)	<0.01
Final multivariable model	3.57 (1.10, 11.60)	0.03
Sensitivity analysis		
Outcome: intensive care admission	1.60 (0.91, 2.81)	0.10
Adjustment variables: worst prehospital vital signs ^a	3.71 (1.14, 12.06)	0.03
Exposure: log-transformed, continuous lactate	2.29 (1.00, 5.24)	0.05

All models include $N = 673$ subjects with lactate dichotomized at 2.0 mmol/L, except for final sensitivity analysis where lactate is a continuous, normally distributed variable.

^aVital signs reparameterized as worst rather than initial includes respiratory rate, heart rate, and systolic blood pressure.

Table 3

Regression estimates from final multivariable logistic regression model

Variable	Odds ratio	95% confidence interval	p-Value
Pre-resuscitation lactate, 2.0 mmol/L	3.57	1.01, 11.59	0.03
Initial prehospital vital signs ^a			
Systolic blood pressure, mmHg	0.99	0.98, 1.00	0.17
Respiratory rate, breaths per minute	1.07	1.0, 1.15	0.06
Heart rate, beats per minute	1.00	0.98, 1.02	0.81
Glasgow Coma Scale score	0.87	0.73, 1.04	0.12
Oxygen saturation, %	1.01	0.88, 1.16	0.88
Age, years	1.02	1.00, 1.06	0.05
Male gender	1.29	0.49, 3.41	0.60

^aPrehospital vital signs parameterized as continuous variables, odds ratio (OR) derives from exponentiated regression coefficient, where a one unit increase in the parameter is associated with an (OR – 1)% increase in the odds of hospital mortality.

Table 4

Operating characteristics of pre-resuscitation lactate at different thresholds

Operating characteristics	Dichotomizing threshold			
	1.0	2.0	3.0	4.0
True positive (<i>n</i>)	20	16	9	2
False positive (<i>n</i>)	606	291	108	44
True negative (<i>n</i>)	46	361	544	608
False negative (<i>n</i>)	1	5	12	19
Sensitivity (95%CI)	95.2 (76.2, 99.9)	76.2 (52.8, 91.8)	42.9 (21.8, 66.0)	9.52 (1.2, 38.4)
Specificity (95%CI)	7.1 (5.2, 9.3)	55.4 (51.5, 59.2)	91.4 (91, 91.8)	93.3 (91.0, 95.1)
Positive likelihood ratio (95%CI)	1.02 (0.93, 1.13)	1.7 (1.3, 2.2)	2.6 (1.5, 4.4)	1.4 (0.4, 5.4)
Negative likelihood ratio (95%CI)	0.67 (0.10, 4.7)	0.43 (0.20, 0.93)	0.69 (0.47, 0.99)	0.97 (0.84, 1.1)