Evaluation of the Prognostic Value of Lactate and Acid-base Status in Patients Presenting to the Emergency Department

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Abstract

Introduction

Point-of-care metabolic screens are frequently used in the assessment of critical illness. Lactate levels predict mortality in a wide range of patients presenting to the Emergency Department but the effect of co-existing acidosis is unknown. We investigated the effect that acidosis has on in-hospital mortality for patients with hyperlactataemia.

Methods

This is a retrospective cohort study. The inclusion criteria were patients over 17 years of age who received a metabolic panel on arrival to the resuscitation area of the Emergency Department. The primary outcome was in-hospital mortality. The groups were normal lactate (0.0-2.0 mmol/L), intermediate lactate (2.1-4.0 mmol/L) and high lactate (>4.0 mmol/L), with and without acidosis. Odds ratios (OR) were calculated to assess the differences in mortality rates between groups stratified by lactate and acid-base status.

Results

4107 metabolic panels were collected and 3238 were assessed. 510 (15.8%) & 784 (24.2%) patients had a normal lactate and acidosis or no acidosis respectively. 587 (18.1%) & 842 (26.0%) patients had intermediate lactate and acidosis or no acidosis respectively. 388 (12.0%) & 127 (3.9%) patients had high lactate and acidosis or no acidosis respectively. The overall mortality was 5%. In normal lactate group mortality was 4.3% and 0.6%, intermediate lactate mortality was 5.6% and 2.6%, and high lactate group mortality was 19.3% and 3.9%, with and without acidosis respectively. Combining base excess < -6 and lactate >4 mmol/L had a sensitivity of 39%, specificity of 96%, positive predictive value of 32% and a negative predictive value of 98% for in-hospital mortality, OR 14.0 (95% CI 9.77 – 20.11).

Conclusion

In an undifferentiated cohort of Emergency Department patients presenting to the resuscitation area lactaemia associated with acidosis is a more accurate predictor of in-hospital mortality than hyperlactataemia.

Introduction

Early recognition of critical illness in the Emergency Department (ED) is associated with improved outcomes. Physiological scores and biochemical measurements (creatinine, acid-base status and serum lactate) are widely used to identify high-risk patients requiring urgent intervention. Point of care metabolic panels, most commonly based on blood gas analysis, provide these parameters to clinicians within minutes of venepuncture.
Lactate levels are widely used to identify critical illness. Three recent international trials and the surviving sepsis campaign have used lactate levels to identify patients in septic shock\textsuperscript{7,8} with no differentiating for venous, central venous or arterial sampling. There is no universally accepted value to define hyperlactataemia, with the upper limit of normal ranging from 1.0 and 2.5 mmol/L\textsuperscript{9-13}. Hyperlactataemia is associated with adverse outcomes in undifferentiated ED patients and in a diverse range of illnesses; including sepsis, trauma and regional ischaemia\textsuperscript{9,14-21}. Recent studies suggest the prognostic value of hyperlactataemia is also aetiology dependent\textsuperscript{22,23}. Hyperlactataemia is common in patients presenting with shock and is attributed to tissue hypoperfusion (type A lactic acidosis), with subsequent treatment focussing on increasing oxygen delivery with fluid, blood transfusion and inopressor therapy\textsuperscript{24,25}. There are many causes of hyperlactataemia that are not consequent upon anaerobic metabolism (type B lactic acidosis), including hepatic dysfunction, sympathetic stimulation, inadequate tissue oxygen extraction, thiamine deficiency and medications\textsuperscript{24-26}. In these cases, administering fluids and vasoactive medications may not benefit the patients and risks harm from fluid overload\textsuperscript{27-31}.

An ED based study identified different mortalities for type A and B hyperlactataemia, with type A associated with a higher mortality than type B (45.8% vs. 12.5%)\textsuperscript{32}. No analysis for the presence or absence of acidosis was performed. We were able to identify only one paper that explored the effects of lactate levels with or without acidosis on outcomes in an ED population\textsuperscript{33}. This study suggested that the presence of acidosis as opposed to hyperlactataemia predicted mortality in sepsis.

The primary objective of our study was to investigate the effect of concurrent acidosis and hyperlactataemia on in-hospital mortality in undifferentiated adult patients presenting to the Emergency Department (ED) resuscitation area.

**Methods**

**Study design and setting**

This was a single centre, retrospective observational cohort study carried out in an inner-city university teaching hospital. We analysed metabolic panel results from adult (\(\geq 17\)) patients who presented to the Emergency Department resuscitation area between February - May 2016 and September 2016 - March 2017. These patients received a venous or arterial blood gas (ABL 700 FLEX, Radiometer, Denmark) on arrival as a routine part of their initial assessment, alongside recording basic physiology and a 12 lead ECG. Blood gas data was downloaded directly and stored on a secure Microsoft Excel spread sheet. In the case of multiple samples drawn during the same admission, only the first blood gas drawn was included in analysis. Samples from patients with >1 presentation were included at each attendance. Unidentifiable data due to missing patient ID number, name and/or date of birth, and incomplete blood gas samples were excluded.

**Variables**
Lactate, pH, base excess (BE) and bicarbonate values were recorded. The medical record was inspected by the study team for in-hospital mortality and demographic data including age, sex and ethnicity. Data was anonymised in accordance with local data protection guidelines.

For this study, we selected a value of 2 mmol/L to define abnormality, based on the Sepsis-3 consensus published in February 2016. Acidosis was defined as one or more of: pH < 7.35, base deficit < -3 mEq/L or HCO3 < 20 mmol/L.

**Groups**

Results were stratified into six groups according to lactate value and the presence or absence of acidosis: normal lactate (0.0-2.0 mmol/L), intermediate lactate (2.1-4.0 mmol/L) and high lactate (>4.0 mmol/L), with and without acidosis. The primary outcome was in-hospital mortality. As a secondary outcome, we subdivided acidic patients according to BE value to assess any correlation with in-hospital mortality. Additionally, we combined BE and lactate to assess their role in predicting mortality.

**Statistical methods**

Continuous data is represented as means (standard deviation, SD) for normally distributed data or median (interquartile range) for non-normally distributed data. Categorical data is reported as number (percentage). Normality was checked using the Shapiro-Wilk test and by visually assessing the frequency distribution. Significance was set at p < 0.05. The difference in mortality between groups was calculated using OR and are expressed with 95% confidence intervals (CI).

**Ethics**

The study was deemed as research that did not require formal REC review by the Trust research and clinical governance departments (in line with the UK Health Research Authority guidance) as there were no interventions, no deviations from usual care and no identifiable data stored. The study was registered along local guidelines.

**Results**

We collected 4107 metabolic panel results and analysed 3238 (Figure 1). The mean age was 51 years and 59% were male.

There was an overall in-hospital mortality of 5%. The ICU admission rate was 3.1% (data available on 1882 patients for ward, ED or ICU admission). Hyperlactataemia with acidosis was associated with increased mortality compared to hyperlactataemia without acidosis. In patients with hyperlactataemia (>2.0 mmol/L), the presence of concurrent acidosis had a more significant effect on mortality in patients with high lactate (>4.0 mmol/L) than in patients with intermediate lactate (2.1-4.0 mmol/L) (Table 1, Figure 2). In the 2.1 - 4.0 mmol/L lactate group mortality was 5.6% and 2.6% with and without acidosis respectively, OR 2.22 (95% CI 1.28 – 3.85) (Table 1, Figure 2). In those with lactate > 4.0 mmol/L,
mortality was 19.3% and 3.9% in the groups with and without acidosis respectively, OR 5.85 (95% CI 2.31 – 14.81).

Irrespective of lactate level, in-patient mortality was 8.7% and 1.8% in the groups with and without acidosis respectively, OR 5.16 (95% CI 3.48 – 7.65). Stratifying patients by lactate level, mortality was 6.9% and 2.1% in the patient groups with and without hyperlactataemia (>2.0) respectively, OR 3.50 (95% CI 2.32 – 5.33).

We combined BE and lactate to assess their role in predicting in-hospital mortality. Table 2 shows the results of these analyses. Combining lactate >4 with BE < -6 gave a mortality rate of 31.9% in our cohort, 63 out of 197 patients died, OR 14.0 (95% CI 9.77 – 20.11). Using a combination of BE and lactate is the most specific indicator for in-hospital mortality. It conveys the highest positive-predictive and negative-predictive values of the 4 combinations analysed.

Table 1. Groups stratified by lactate and acidosis showing numbers and mortality figures with percentages shown in brackets.

| Lactate (mmol/L) | Acidosis | Number of patients | Mortality (%) |
|------------------|----------|--------------------|---------------|
| 0.0 - 2.0        | Yes or no| 1294 (40.0%)       | 27 (2.1)      |
| 0.0 - 2.0        | No       | 784                | 5 (0.6)       |
| 0.0 - 2.0        | Yes      | 510                | 22 (4.3)      |
| 2.1 - 4.0        | Yes or no| 1429 (44.1%)       | 55 (3.8)      |
| 2.1 - 4.0        | No       | 842                | 22 (2.6)      |
| 2.1 - 4.0        | Yes      | 587                | 33 (5.6)      |
| > 4.0            | Yes or no| 515 (15.9%)        | 80 (15.5)     |
| > 4.0            | No       | 127                | 5 (3.9)       |
| > 4.0            | Yes      | 388                | 75 (19.3)     |

Table 2. Statistical analyses of base excess (BE), Lactate (Lac), acidosis and systolic blood pressure (BP) as prognostic indicators for in-hospital mortality. Blood pressure data only available on 1395 patients. Sens- Sensitivity. Spec- Specificity. PPV- Positive predictive value. NPV- Negative predictive value.
|                | Sens % | Spec % | PPV | NPV |
|----------------|--------|--------|-----|-----|
| BE <-3         | 63     | 82     | 16  | 98  |
| BE <-6         | 48     | 92     | 25  | 97  |
| Lac >4 BE <-6  | 39     | 96     | 32  | 98  |
| Lac >4 acidotic | 46     | 90     | 19  | 97  |
| Systolic BP ≤ 90mmHg | 18       | 96     | 19  |     |

### Discussion

We found that in an undifferentiated cohort of adult ED patients treated in the resuscitation area hyperlactataemia with co-existing acidosis conferred a higher risk of in-hospital death than elevated lactate levels alone (no acidosis). The margin was greater at higher lactate levels (> 4 as compared to 2.1-4.0 mmol/L).

In keeping with previous studies, we found that the mortality rate of individuals with a lactate >= 2 mmol/L was higher than those with lactate < 2.0 mmol/L ⁴,²¹,²³,³⁴. However, we found the risk of in-hospital mortality to be higher in those patients with acidosis, regardless of lactate level, than patients with no acidosis.

We reported a mortality of 2.1% for patients with a lactate of <=2.0 mmol/L, 3.8% for patients with a lactate of 2.0–3.9 mmol/L and 15.5% if lactate was > 4.0 mmol/L. The OR death for a lactate 2.0 - 3.9 mmol/L was 2.2 and for > 4 mmol/L was 5.9. Our blood gas samples were drawn during the initial assessment of adult patients treated in the resuscitation area prior to in-ED treatment within minutes of arrival. Previous ED based studies have targeted populations selected by clinician concern or by diagnosis. Previous studies also involved blood samples drawn at variable times in the patients’ ED journey. In 2015 Datta et al ²¹ reported a cohort of 747 undifferentiated (Scottish) ED patients (15% admitted to critical care, median age 67, 27500 patients attended in study period, 2.7% had blood gas sampled, samples drawn < 4 hours of ED arrival) with arterial lactate values of <2, 2.0-3.9, and ≥ 4.0 mmol/L associated with 30-day mortalities of 10.1%, 19% and 50%, respectively. Blood gas analysis was performed at the discretion of the treating clinician, suggesting that sicker patients may have been targeted. Contenti et al ³⁵ reported (94% venous) lactate measurement in 11% (13089/118737 adults, median age 52, time of lactate sample not reported) of attendees at a French ED (increasing to around half if the diagnosis was infection). The authors did not report mortality stratified by lactate level.

Nouland ³² reported lactate related mortality in 5.8% (1144/19822) patients admitted to (Dutch) medical wards, (median age 67, time of blood sampling not stated). The authors found that lactate levels of <4 mmol/L and > 4 mmol/L were associated with mortalities of 18.5% and 40.6% respectively. Patients who did not have a lactate measured had a 28-day mortality of 9.5%. Our patients had a median age of 51 and samples were drawn prior to treatment, which may explain why our reported mortality rates were
lower than in these clinician selected groups. Our resuscitation area admits all patients requiring invasive or non-invasive ventilation, trauma calls, stroke calls, high risk chest pain, tachyarrhythmias (ventricular tachycardia, atrial fibrillation > 120 betas per minute, supraventricular tachycardia), sepsis, patients with systolic blood pressure < 90 mmHg, electrolyte abnormalities, suspected aortic emergency and patients for procedural sedation. However clinicians may identify patients they believe will benefit from treatment in the resuscitation area and transfer them. The ambulance service transports patients with STEMI and ventricular tachycardia directly to a specialised cardiac hospital, bypassing the ED. Clinicians initially draw a venous sample on all patients unless the patient is mechanically ventilated or has severe trauma, when arterial blood sampling is used.

Nouland and Datta21 reported arterial lactate levels whereas our study and Contenti’s35 included predominantly venous samples. This may alter the reported risk associated with lactaemia as venous samples overestimate lactate levels as compared to arterial samples in the ED setting36, with the discrepancy more marked at higher levels. High levels of correlation between venous and arterial lactate levels have been reported, but in these studies the majority of samples were in the normal range.

Bloom et al investigated agreement between venous and arterial samples at pathological lactate levels and noted increasing disagreement with increasingly elevated lactate levels. This work suggests around 17% of the patients with a lactate > 4.0 mmol/L by venous sampling would have arterial levels below this and 36% of patients with a venous lactate > 2.0 would have an arterial lactate < 2.0 mmol/L. This would see a higher proportion of low risk patients identified by venous as opposed to arterial samples.

Pedersen et al23 studied a cohort of 5360 adult undifferentiated ED patients who received an ABG or VBG (proportion not reported) within 4 hours of admission (exact times not reported). In this study 77.2% patients had a lactate < 2mmol/L, 16.2% 2.0-3.9 mmol/L and 6.6% > 4 mmol/L. In our study we identified 40.0% patients to have a lactate of <= 2.0 mol/L, 44.1% 2.1-4.0 mol/L and 15.9% > 4.0 mmol/L. Samples in our study were drawn on arrival prior to any treatment being delivered, which may account for the increased proportion of elevated lactate levels reported as compared to Pedersen et al. Pedersen et al23 reported (7 day) mortality rates of 2.9%, 7.8% (OR death 3.0) and 23.9% (OR death 11.5) for patients with low (0-1.9 mmol/L), intermediate (2-3.9 mmol/L) and high lactate (≥ 4 mmol/L) respectively, slightly higher than our work. The authors investigated various diagnostic subgroups and reported lactate to be a useful prognostic biomarker for patients with a diagnosis of infection, trauma, cardiac and gastrointestinal disease but not (or of uncertain value) for patients with neurological, non-infective respiratory, endocrine diseases, alcohol intoxication or malignancy. Our study did not set out to look at subgroups which would be too small for meaningful comparison and as we had no means to assess for the diagnostic accuracy reported in the medical records.

We are aware of only one small study that previously described the effect of acidosis on lactataemia and mortality. Lee SW et al33 investigated 126 patients with severe sepsis or septic shock with similar aims to our study and similar findings that acidosis was associated with a higher risk of death than lactataemia in isolation. Patients with hyperlactataemia alone (lactate ≥ 2 mmol/L, no acidosis) had similar mortality
rates as compared to patients with normal pH and lactate levels. However, in-hospital mortality was significantly higher in patients with lactic acidosis as compared to those with normal pH and lactate. The authors concluded that the acid-base status of patients should be considered when using tests such as lactate to predict outcomes in patients with sepsis.

The combination of a lactate > 4 mmol/L and acidosis had a sensitivity of 46% and specificity of 90% for in-patient mortality, while lactate > 4 mmol/L combined with BE <-6 was associated with a sensitivity of 39% and specificity of 96%. Figures for BE <-6 alone were 48% and 92% respectively. In an ICU based study, Smith et al reported that the combination of a BE <-4 mmol/L and a lactate > 1.5 mmol/L was more sensitive and specific for mortality than either alone, with a sensitivity of 80.3% and specificity of 58.7% for mortality. Husain et al retrospectively investigated the prognostic individual value of lactate and base deficit in a surgical intensive care unit setting. The authors reported initial and 24-hour lactate (≥ 2 mmol/L) correlated well with mortality. Base deficit (< -2) only correlated with mortality in trauma patients at 24 hours and not on admission. These data suggest each of these is useful in identifying patients with a high mortality. No acid base / lactate combination was found to be sensitive enough to use a screen for critical illness.

Limitations

As with all retrospective studies the authors were dependent on data entered to the patients’ clinical record by clinicians prior to the study being performed and thus over which no quality assurance was possible. This study depended on the accurate inputting of patient identifying data into the blood gas machine in order to link results to patient's records. 360 (9%) samples were excluded from analysis as they did not have correct patient identifiable data (name, hospital number, date of birth). These blood gases were commonly very abnormal, presumably as these samples were taken from critically ill patients on their arrival in the ED and prior to booking them onto the computer system. Missing data is a common problem in retrospective studies on this topic, for example Contenti reported 10% data missing. Our primary outcome was in-hospital mortality, defined as whether or not the patient survived to discharge. This could be considered a less clinically valuable endpoint than 7-day or 30-day mortality as it did not take into account patients transferred from our institution to another, in which they could have died. Our study was performed on a single site and may not be generalizable to other areas of practice, in particular the mean patient age was younger than similar studies. We did not report our findings for different diagnostic groups and work published since we designed this study have identified that lactate levels offer different prognostic information for different patient groups. Future work should include a large enough sample to assess different patient groups by diagnosis, treatment and disposition. Our ED has two blood gas machines and while one is placed next to the resuscitation area staff may bring samples from other areas of the ED if the second machine is in use or undergoing maintenance or calibrating. Finally we did not adjust our findings for confounding variables such as blood pressure or age or the presence of chronic illnesses associated with increased mortality.
Conclusion

The results of this study suggest blood gas results obtained in the ED are a useful prognostic marker. Lactataemia associated with acidosis is a more accurate predictor of in-hospital mortality than elevated lactate alone. The effect of coexisting acidaemia varies with the severity of hyperlactataemia. The marked differences in mortality associated with hyperlactataemia with and without acidosis have significant implications for the role of lactataemia in identifying critical illness and as a resuscitation end point. A combination of BE < -6 and lactate > 4 were associated with the highest specificity for mortality.

The majority of studies which have previously analysed the relationship between elevated lactate and mortality have not reported the effect of acid-base disturbance. Further studies examining the effect of lactate and various measures of acid base disturbance in different subgroups of ED patients are required.

List Of Abbreviations

ED: Emergency Department
BE: Base Excess
SD: Standard Deviation

Declarations

Ethics approval and consent to participate.

The need for patient consent was waived by the ethical review committee as there were no interventions, no deviations from usual care and no identifiable data stored. The study was registered along local guidelines.

Consent for publication: Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions
RD: Study concept and design, acquisition of data, analysis and interpretation of the data, drafting of the manuscript.

LD: Study concept and design, acquisition of data, analysis and interpretation of the data, drafting of the manuscript, statistical expertise.

TM: Study concept and design, acquisition of data.

BC: Acquisition of data.

BB: Critical revision of the manuscript.

TH: Study concept and design, critical revision of the manuscript.

All authors read and approved the final manuscript.

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