Serum lactate cut-offs as a risk stratification tool for in-hospital adverse outcomes in emergency department patients screened for suspected sepsis

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ABSTRACT

Objectives We investigated specific lactate thresholds for adverse outcomes in patients presenting to emergency departments (EDs) with suspected sepsis identified based on the performance of a sepsis screening algorithm. Design and setting A standardised sepsis bundle was implemented across public hospitals in New South Wales, Australia, as a quality improvement initiative. A register of all adult ED presentations (≥18 years) meeting predefined criteria for sepsis was created, using a combination of data linkage and direct reporting from 97 participating sites. Participants A total of 12 349 adult ED presentations with suspected sepsis and 8310 (67.3%) having serum lactate analysis on arrival. Analysis of outcomes was based on dataset for 12 349 subjects obtained through multiple imputation for missing data. Interventions A sepsis management bundle including early antibiotic prescribing, fluid therapy and referral to intensive care unit (ICU) services was implemented. Outcome measures A primary composite adverse event (AE) outcome of inhospital mortality (IHM) and/or prolonged ICU stay ≥72 hours (ICU 72 hours) was used for this study. Results There was statistically significant increase both in the ORs of AE and IHM with each integer increase in serum lactate values. After adjusting for the presence of hypotension, the estimated ORs for the combined AE outcome were 2.71 (95% CI 2.05 to 3.57), 2.65 (95% CI 2.29 to 3.08), 3.10 (95% CI 2.71 to 3.53) and 3.89 (95% CI 3.36 to 4.50) for serum lactate levels at or above 1, 2, 3 and 4 mmol/L, respectively. The corresponding ORs for IHM were 2.93 (95% CI 2.08 to 4.13), 2.77 (95% CI 2.34 to 3.29), 3.26 (95% CI 2.80 to 3.80) and 4.01 (95% CI 3.40 to 4.73), respectively (all P<0.0001). More than 10% of patients with suspected sepsis and with serum lactate ≥2 mmol/L experienced a prolonged ICU stay or died in hospital. Conclusions ED sepsis screening algorithms intended to identify patient adverse outcomes should incorporate a serum lactate cut-off of ≥2 mmol/L as a threshold for the initiation of specific interventions and increased monitoring.

INTRODUCTION

Sepsis is the life-threatening condition that results from dysregulated host response to infection and organ dysfunction and is responsible for one-third to one-half of all deaths in hospital. Early recognition and prompt treatment offer the best chance of survival but early diagnosis of sepsis presents a challenge.

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (box) rejected systemic inflammatory response syndrome (SIRS) diagnostic criteria in favour of organ failure assessment criteria. For clinical operationalisation, organ dysfunction has been represented by an increase in the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score of 2 points.

Strengths and limitations of this study

- A retrospective analysis of a large statewide dataset of patients with suspected sepsis based on performance of a specific sepsis screening algorithm across 97 hospital sites in the most populous state in Australia, with outcome data on 12 349 patients.
- Data were reported voluntarily as part of a quality improvement initiative and clinical practices may have varied between sites. The results can therefore be generalised to working emergency departments (EDs) in this state but lack the rigour of a well-controlled research study.
- Glasgow Coma Scale information was not collected and other systemic inflammatory response syndrome (SIRS) data (eg, respiratory rate) were incomplete, preventing full quick Sequential Organ Failure Assessment analysis.
- Lactate levels were available on 67.3% and systolic blood pressure on 92.2% of the cohort. Multiple imputation was used to populate missing data variables to reduce potential bias due to missing data.
- Patients were placed on the sepsis pathway through SIRS-based screening and therefore may not represent the complete cohort of patients with sepsis presenting to the participating EDs.
or more. The Sepsis-3 working group used a combined adverse event (AE) (prolonged intensive care unit (ICU) stay ≥72 hours or death in hospital) as a marker of adverse outcomes that are typical of sepsis rather than uncomplicated infection. An abbreviated quick SOFA (qSOFA) tool has been developed from the SOFA score: 2 or more qSOFA points in patients with suspected infection predict increased risk for this combined adverse outcome (box).

Serum lactate is not part of the SOFA score, but lactate remains part of the septic shock definition, a key resuscitation target in the Surviving Sepsis Campaign (SCC) guidelines and in sepsis management bundles worldwide. A recent Australian study found hyperlactatemia to be a stronger mortality predictor than refractory hypotension and abnormal lactate levels were previously considered in definitions of severe sepsis. An increased risk of death has also been reported in association with elevations in serum lactate in those with suspected sepsis, and this risk rises exponentially with rise in lactate levels.

There is increasing evidence that sepsis-associated hyperlactatemia is driven at least in part by increased aerobic glycolysis secondary to the stress response rather than simple tissue hypoxaemia or hypoperfusion and is indicative of disease severity. Sepsis screening algorithms aim to identify patients at higher risk of adverse outcomes. We hypothesised that raised lactate levels ≥2 mmol/L in the emergency department (ED) would predict higher risk for adverse outcomes (in-hospital mortality (IHM) and/or ICU stay ≥72 hours), independent of the presence of hypotension at ≥100 mm Hg as recently promulgated by the qSOFA tool.

**OUTCOME MEASURES**

In view of the adverse outcome used by Sepsis-3 to differentiate sepsis from uncomplicated infection, we defined a composite combined AE of IHM and/or ICU 72 hours as the primary outcome for the study. We report on IHM as an important secondary outcome for our study.

**STATISTICAL ANALYSIS**

Fully conditional multiple imputation was used to replace missing lactate and SBP measurements using the imputation sequence age, triage category, presumed source, IHM status, ICU 72 hours status, SBP and lactate. Thirty datasets were imputed and pooled imputed estimates were derived for summary statistics and for ORs from the logistic regression models. All covariates and outcomes were included in the imputation model (n=30) as per statistical principles. To address the specific aim of the study to investigate initial serum lactate thresholds, lactate levels were categorised into ranges (<1, 1 to <2, 2 to <3, 3 to <4, ≥4 mmol/L) and the proportion who were prospectively collected from voluntary reporting at participating sites. As part of the SEPSIS KILLS pathway implementation, sites were required to report SIRS variables and investigations (lactate level) at the time of initiation of the sepsis management bundle. However, this was not separately verified and strong inferences regarding the optimal timing of SIRS and lactate investigations cannot be made from these data. Patients were identified at each site based on the sepsis screening tool in the SEPSIS KILLS programme. Management was guided by local protocols with an emphasis on fluid resuscitation and antibiotic administration within 60 minutes. Ethics approval was obtained for the NSW Sepsis Register, developed as a public health and disease register under the Public Health Act 2011.

**METHODS**

We conducted a retrospective analysis of data from the Clinical Excellence Commission (CEC) SEPSIS KILLS initiative, a statewide quality improvement programme implemented in 180 public hospitals in New South Wales (NSW), Australia, which aims to improve recognition and treatment of sepsis in ED and inpatient units across the state (online supplementary appendix). Data were prospectively collected from voluntary reporting at participating sites. As part of the SEPSIS KILLS pathway implementation, sites were required to report SIRS variables and investigations (lactate level) at the time of initiation of the sepsis management bundle. However, this was not separately verified and strong inferences regarding the optimal timing of SIRS and lactate investigations cannot be made from these data. Patients were identified at each site based on the sepsis screening tool in the SEPSIS KILLS programme. Management was guided by local protocols with an emphasis on fluid resuscitation and antibiotic administration within 60 minutes. Ethics approval was obtained for the NSW Sepsis Register, developed as a public health and disease register under the Public Health Act 2011.
suffered either IHM or ICU 72 hours (either or both AE) and the proportion who died in hospital (IHM) were calculated in each lactate category. The multiple imputation and subsequent analyses were performed using IBM SPSS Statistics V.23.0.13

Distributions for age, lactate and SBP were summarised using the median value and IQR. Percentages were used to summarise categorical variables. Exact 95% CIs were computed for percentages.

For both AE and IHM, a test for trend in proportions across lactate categories was conducted. For each category, logistic regression was used to estimate the OR and corresponding 95% CI comparing the odds of the outcome for those above that threshold relative to those below the threshold. These analyses were stratified by (SBP ≤100 mm Hg vs SBP >100 mm Hg) and a test for interaction was used to assess evidence of effect modification between lactate and SBP. We further investigated the lactate threshold of ≥2 mmol/L in both SBP groups stratified by presumed source of infection. A P<0.01 was considered statistically significant. We considered an adverse outcome rate of more than 10% (IHM or ICU 72 hours) to be clinically important in line with similar threshold adopted by recent sepsis definitions working group.1

Reported results are based on the set including imputed data for all 12 349 patients. Results for the subgroup of patients with directly measured lactate and SBP are also presented as online supplementary etables.

RESULTS

Subjects

Between June 2010 and December 2013, the CEC Sepsis Register included 12 349 adult patients. A total of 8310 patients (67.3%) had an initial serum lactate measurement on presenting to ED. Almost all of these patients (97.6%; 8111/8310) were reviewed by a clinician for initial assessment and lactate measured within 3 hours of presentation along with usual laboratory investigations and blood cultures. Participating sites reported initial SIRS criteria (including SBP) value and lactate values at the time of sepsis recognition (online supplementary etables). While the SEPSIS KILLS pathway advocated the repeat measurements of lactate in patients with initial levels ≥1 mmol/L, this information was not specifically collected. Missing data for lactate measurements (32.7%) and SBP (7.8%) were imputed as previously described, allowing all 12 349 patients to be included in risk stratification and logistic modelling to investigate the influence of specific lactate threshold levels.

Patient characteristics are reported in table 1. The median age was 72.4 years (IQR 58.1–82.6); no sex delineation data were available. The estimated median lactate and SBP levels were 2.0 mmol/L and 121 mm Hg, respectively. In the cohort of 8310 patients in whom lactate measurements were available, the combined AE rate (IHM or ICU 72 hours) was 11.8% (983/8310) and IHM was 9.0% (751/8310). The one-third of patients (32.7%) who did not have serum lactate measured on arrival suffered significantly less AE (7.0%, 281/4039, P<0.002) and IHM (6.3%, 254/4039; P<0.002). IHM rate was 7.9% (977/12 349), and combined AE rate was 10.2% (1261/12 349) in overall cohort (table 2).

Table 1 Patient characteristics, location of service and source of infection (reported and imputed estimates shown for lactate)

| Cohort      | Variable                  | Number | Median (IQR)   |
|-------------|---------------------------|--------|----------------|
| Total       | Age (years)               | 12 349 | 72.6 (58.1–82.6) |
| Lactate     | Lactate (measured), mmol/L| 8310 (67.3%) | 1.9 (1.3–2.9) |
|             | Lactate (imputed data), mmol/L| 12 349 | 2.0 (1.2–3.1) |
|             | SBP (reported), mm Hg     | 11 383 (92.2%) | 121 (100–140) |
|             | SBP (imputed data), mm Hg | 12 349 | 121 (102–141) |
| Rural ED    | Age (years)               | 3713   | 72.5 (60.1–82.1) |
| Metropolitan ED | Age (years)         | 3544   | 74.1 (59.1–84.2) |
| Tertiary ED | Age (years)               | 5092   | 70.9 (55.3–81.9) |
| Presumed source | Abdomen                  | 1028   | 8.3 (7.9 to 8.8) |
|             | Lung                      | 5051   | 40.9 (40.1 to 41.8) |
|             | Skin/soft tissue          | 933    | 7.6 (7.1 to 8.0) |
|             | Urinary tract             | 2909   | 23.6 (22.8 to 24.3) |
|             | Unknown                   | 1252   | 10.1 (9.6 to 10.7) |
|             | Other                     | 1176   | 9.5 (9.0 to 10.1) |

ED, emergency department; SBP, systolic blood pressure.
outcomes, the increase took the form of an exponential trend (P<0.0001) (table 2).

**Relationship between AE and IHM and serum lactate level, stratified for hypotension**

When stratified by SBP on presentation (SBP >100 mm Hg and SBP ≤100 mm Hg), the ORs of AE and IHM increased as the lactate threshold increased from 2 to 4 mmol/L (tables 3 and 4). While this study has limited power to detect effect modification between lactate and SBP, logistic regression models revealed no evidence of interaction at any threshold. After removing the interaction term from each model, both main effects for lactate and SBP were highly statistically significant (P<0.0001) at every lactate threshold. For AE, the estimated ORs were 2.71 (95% CI 2.05 to 3.57), 2.65 (95% CI 2.29 to 3.08), 3.10 (95% CI 2.71 to 3.53) and 3.89 (95% CI 3.36 to 4.50) for lactate thresholds of 1, 2, 3 and 4 mmol/L, respectively (all P<0.0001). For IHM, the estimated ORs for lactate (adjusted for SBP) were 2.93 (95% CI 2.08 to 4.13), 2.77 (95% CI 2.34 to 3.29), 3.26 (95% CI 2.80 to 3.80) and 4.01 (95% CI 3.40 to 4.73), respectively.

**Lactate cut-offs in cohort stratified across predicted source in ED**

The respiratory tract (40.9%), followed by urinary tract and abdominal causes were the most common presumed infection sources. A lactate cut-off of ≥2 mmol/L was associated with >10% combined AE rate (ICU 72 hours and/or IHM) for those in whom the presumed source of infection was respiratory or abdominal, with slightly lower AE rates attributed to urinary tract infection at that level (9.4%) (table 5).

| Lactate group (mmol/L) | n   | Age (years), median (IQR) | Lactate (mmol/L), median (IQR) | AE number (% 95% CI) | IHM number (% 95% CI) |
|------------------------|-----|---------------------------|-------------------------------|----------------------|-----------------------|
| 0–<1                   | 1880| 69.1 (48.1–79.4)          | 0.6 (0.0–0.8)                 | 78 (4.2, 3.3 to 5.2) | 55 (2.9, 2.3 to 3.8)  |
| 1 to <2                | 4296| 72.1 (57.0–82.1)          | 1.4 (1.2–1.7)                 | 272 (6.3, 5.6 to 7.1) | 203 (4.7, 4.1 to 5.4) |
| 2 to <3                | 2745| 73.1 (60.3–83.0)          | 2.4 (2.2–2.7)                 | 243 (8.9, 7.8 to 10.0) | 181 (6.6, 5.7 to 7.6) |
| 3 to <4                | 1564| 74.3 (61.9–83.5)          | 3.4 (3.2–3.7)                 | 186 (11.9, 10.4 to 13.6) | 146 (9.3, 8.0 to 10.9) |
| ≥4                     | 1864| 74.1 (60.9–84.0)          | 5.1 (4.4–6.3)                 | 482 (25.9, 23.9 to 27.9) | 392 (21.0, 19.2 to 22.9) |
| Total                  | 12349| 72.6 (58.1–82.6)         | 2 (1.3–3.2)                   | 10.2 (9.7 to 10.8)    | 7.9 (7.5 to 8.4)    |

AE defined as IHM or prolonged ICU length of stay (ICU 72 hours).
ICU, intensive care unit.

| Lactate cut-off (mmol/L) | n   | OR† (95% CI) |
|--------------------------|-----|--------------|
| 0–<1                     | 1880| NA           |
| 1 to <2                  | 4296| 2.47 (1.78 to 3.42) |
| 2 to <3                  | 2745| 2.42 (2.01 to 2.91) |
| 3 to <4                  | 1564| 3.01 (2.53 to 3.58) |
| ≥4                       | 1864| 4.06 (3.34 to 4.94) |

*AE died or ICU length of stay (ICU 72 hours) with no overlap.
†OR and 95% CI calculated at each cut-point conducted on imputed dataset of 12349 patients.
AE, adverse event; ICU, intensive care unit; NA, not applicable; qSOFA, quick Sequential Organ Failure Assessment; SBP, systolic blood pressure.
**DISCUSSION**

In this retrospective cohort analysis of a statewide quality improvement initiative in a representative statewide sample of public hospitals, we found a significantly increased risk for a combined adverse outcome (ICU stay of at least 72 hours or death in hospital) with increasing lactate threshold values. More than 1 in 10 who had an initial serum lactate of ≥2 mmol/L experienced a severe AE, irrespective of hypotension (SBP >100 mm Hg) and for almost all sources. Our dataset was derived from a quality audit tool with results applicable to the specific sepsis screening algorithm employed. Our findings on adverse outcome and sepsis risk therefore need to be demonstrated in other clinical settings, especially in those where different sepsis screening algorithms are used.

Approximately one-third of patients (32.7%) identified as suspected sepsis in the register did not undergo lactate measurement in ED. Our analysis for AEs in this group indicated less AE and mortality risk than for those in whom serum lactate was measured. While a complex multiple imputation using limited available variables was conducted to account for missing data, the lack of true lactate measurements in this group may have impacted our overall study results. It is difficult to predict the direction of such an impact, but our finding of incrementally increased risk for inhospital adverse outcomes with increasing lactate levels is consistent with other reports. Our mortality rates of 21% in patients with suspected sepsis with a lactate level ≥4 mmol/L are lower than previously reported from the USA but are in keeping with past findings for patients treated in Australian ICUs for severe sepsis and septic shock. While previous studies have used SBP <90 mm Hg to define hypotension, we selected a cut-off of SBP ≤100 mm Hg, in line with recommendations under the recently revised sepsis definitions for predicting sepsis, including qSOFA, as these are likely to be widely adopted for identifying patients at risk for adverse outcomes. Our mortality rates of 8.4% in the absence of hypotension (SBP >100 mm Hg) and 19.7% with SBP ≤100 mm Hg and lactate ≥2 mmol/L are in keeping with previous reports. As part of the SEPSIS KILLS pathway implementation, sites were advised to voluntarily report on the SIRS variables and investigations results data (lactate level) at the time of initiation of the sepsis management bundle. While most patients had these done within the first few hours of arrival in ED, it is difficult to decipher the exact timing of these data endpoints in each case. Thus, strong conclusions regarding timing of SIRS and lactate level thresholds cannot be derived or promulgated from our analysis.

AE rates (10.8% and 24.7%) and IHM (8.4% and 19.7%) in patients with initial lactate levels of ≥2 mmol/L and SBP >100 mm Hg and ≤100 mm Hg, respectively, are therefore consistent with previous findings, and suggest that initial serum lactate ≥2 mmol/L is more appropriate than ≥4 mmol/L for entry into sepsis management pathways and for identification of an increased risk of death. We noted a near doubling of AE and IHM rates in patients with initial lactate levels ≥4 mmol/L when compared with those with less than 4 mmol/L, in keeping with findings in a similar ED cohort.

As the health burden of sepsis becomes increasingly apparent, global initiatives such as the SCC have led to the increasing use of screening algorithms in the ED. These algorithms result in the implementation of management bundles which have been shown to improve outcomes in sepsis. One of the key interventions in these bundles is the escalation of clinical supervision...
**Table 5** IHM and adverse outcomes (IHM or ICU 72 hours) in cohorts based on predicted source and lactate cut-off ≥2 mmol/L

| Presumed source | Lactate cut-off (mmol/L) | **Adverse event** | **IHM** |
|-----------------|--------------------------|-------------------|---------|
|                 |                          | Number/total      | Per cent (95% CI) | OR (95% CI) | Number/total | Per cent (95% CI) | OR (95% CI) |
| Lung            | < 2                      | 183/2682          | 6.8 (5.9 to 7.8)  | 2.92 (2.37 to 3.60) | 136/2682 | 5.1 (4.3 to 6.0) | 3.11 (2.46 to 3.92) |
|                 | ≥ 2                      | 418/2369          | 17.6 (16.2 to 19.2) | 344/2369 | 14.5 (13.2 to 16.0) |
| Urinary tract   | < 2                      | 49/1453           | 3.4 (2.6 to 4.4)  | 301/1453 | 2.7 (2.0 to 3.6) | 3.00 (2.00 to 4.45) |
|                 | ≥ 2                      | 137/1456          | 9.4 (8.0 to 11.0) | 109/1456 | 7.5 (6.3 to 9.0) |
| Abdomen         | < 2                      | 22/437            | 5.0 (3.3 to 7.5)  | 4.48 (2.72 to 7.38) | 11/437 | 2.5 (1.4 to 4.5) | 6.92 (3.53 to 13.57) |
|                 | ≥ 2                      | 111/591           | 18.8 (15.8 to 22.1) | 88/591 | 14.9 (12.3 to 18.0) |
| Skin/soft tissue| < 2                      | 26/450            | 5.8 (4.0 to 8.3)  | 206 (1.22 to 3.49) | 24/450 | 5.3 (3.6 to 7.8) | 1.60 (0.91 to 2.81) |
|                 | ≥ 2                      | 54/483            | 11.2 (8.7 to 14.3) | 41/483 | 8.5 (6.3 to 11.3) |
| Unknown         | < 2                      | 39/536            | 7.3 (5.4 to 9.8)  | 246 (1.62 to 3.74) | 27/536 | 5.0 (3.5 to 7.2) | 2.52 (1.52 to 4.18) |
|                 | ≥ 2                      | 117/716           | 16.3 (13.8 to 19.2) | 83/716 | 11.6 (9.5 to 14.1) |
| Other†          | < 2                      | 31/617            | 5.0 (3.6 to 7.0)  | 288 (1.82 to 4.56) | 22/617 | 3.6 (2.4 to 5.3) | 2.89 (1.67 to 5.01) |
|                 | ≥ 2                      | 74/559            | 13.2 (10.7 to 16.3) | 53/559 | 9.5 (7.3 to 12.2) |
| Total           | < 2                      | 350/6176          | 5.7 (5.1 to 6.3)  | 288 (2.49 to 3.34) | 258/6176 | 4.2 (3.7 to 4.7) | 3.03 (2.56 to 3.58) |
|                 | ≥ 2                      | 911/6173          | 14.8 (13.9 to 15.7) | 719/6173 | 11.7 (10.9 to 12.5) |

*OR and 95% CI calculated at lactate cut-off of 2 mmol/L conducted on imputed dataset of 12 349 patients.
†Other includes orthopaedic, central nervous system, vascular device infections.
ICU, intensive care unit; IHM, inhospital mortality.
through referral of care to senior clinicians and ICUs. Our composite AE endpoint is designed to address this directly.

We have previously reported on the performance of various international sepsis screening algorithms using a range of lactate thresholds. Recent statements from the Surviving Sepsis Committee have suggested the need for closer observation of patients who meet the new sepsis criteria with qSOFA ≥2. The recent shift in definitions of sepsis based on SOFA scores, which requires calculations based on investigations’ results is unlikely to uniformly occur in ED patients presenting with suspected infection. Our findings indicate that lactate ≥2 mmol/L should be incorporated as a risk predictor in ED patients with suspected sepsis.

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