

BMJ Open Lactate clearance as a useful biomarker for the prediction of all-cause mortality in critically ill patients: a systematic review study protocol

Zhongheng Zhang, Xiao Xu, Kun Chen

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Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, Zhejiang, People's Republic of China

Correspondence to

Dr Kun Chen;
13957970707@sina.com

ABSTRACT

Introduction: Arterial lactate is a reflection of balance between lactate production and clearance. Accumulating lactate may be a marker of global hypoxia or hypoperfusion. Lactate clearance is the reduction of lactate concentrations with interventional strategies, and it has been associated with increased risk of death in critically ill patients. However, conflicting results exist, which mandates a systematic review to clarify the association between lactate clearance and clinical outcome.

Methods and analysis: Critically ill adult patients will be included in our analysis. This population will include heterogeneous study participants, including patients with sepsis or severe sepsis, trauma, surgical intensive care unit (ICU) patients, and so on. We will search four databases including EBSCO, PubMed, Scopus and ISI Web of knowledge from inception to February 2014. There will be no language restrictions in the electronic search for studies. Newcastle Ottawa Scale for cohort study will be employed to assess the reporting quality of included original studies. We will report pooled relative risk of death for those with lactate clearance and those without. The diagnostic performance of lactate clearance in predicting mortality will be explored by using the hierarchical summary receiver operating characteristic model.

Ethics and dissemination: The protocol for the systematic review has been registered in PROSPERO. The study will be disseminated electronically and in print. It will also be presented to conferences related to critical care medicine.

Trial registration number: CRD42013006511.

INTRODUCTION

Lactate is the end product of anaerobic glycolysis. In situations of hypoperfusion or hypoxia, pyruvate will no longer enter into the mitochondria for aerobic metabolism, but instead, it is preferentially reduced to lactate, resulting in accumulation of lactate in the blood. The process is an adaptive

mechanism to produce energy in situations of low oxygen supply, but at the expense of deteriorating acidosis.^{1 2} Lactate is produced in the majority of tissues in human beings, but the main producers include red blood cells, intestine, brain and muscles. In critically ill patients, the daily production of lactate is approximately 1300 mmol/day and the concentrations of arterial lactate represent the balance between production and clearance. Lactic acidosis or hyperlactatemia occurs when production exceeds clearance, which has been confirmed to be associated with worse clinical outcomes in critically ill patients. Even a mild increase in arterial lactate is associated with higher risk for worse outcome. Such association has been replicated in several patient populations, including trauma, cardiac arrest, severe sepsis and septic shock.^{3–6}

Single measurement of lactate cannot improve clinical outcome, but therapeutic strategies that can potentially decrease arterial lactate may be associated with improved clinical outcomes. The aim of such a strategy is to reverse the global tissue hypoxia. The idea of lactate clearance (LC) is to accommodate this concept. Many clinical studies have demonstrated that patients with LC showed better clinical outcomes as compared with those without LC; furthermore, patients with rapid LC were more likely to survive than those with slow LC.^{7–11} However, the diagnostic performance of LC in predicting mortality has not been well defined and conflicting results exist among studies. For instance, the area under receiver operating characteristic curve (AU-ROC) ranged from 0.67 to 0.87 as reported by different studies. We here presented a study protocol for a systematic review to investigate the association of LC with clinical outcomes.

METHODS

Inclusion criteria of studies

Participants

Critically ill adult patients will be included in our analysis. This population will include heterogeneous study participants, including patients with sepsis or severe sepsis, trauma, surgical intensive care unit (ICU) patients and so on. Children will be excluded because lactate metabolism in children is different.¹²

Exposed group and control group

Patients with LC are used as the exposed group. LC will be defined from two aspects: magnitude and time needed for the clearance. A threshold of 10% reduction from baseline or normalisation is employed, and 24 hour is used as the time frame for LC. The control group is defined as those without LC.

Study endpoints

The primary outcome is mortality. The pooled data will show how the risk of death differs between patients with and without LC. Furthermore, the diagnostic performance of LC in predicting mortality will be reported. Statistics for diagnostic performance including sensitivity, specificity, positive likelihood ratio and negative likelihood ratio will be reported.

Studies to be included

Both observational cohort studies and randomised controlled trials (RCT) will be included for analysis. Observational studies will include both prospective and retrospective studies.

Search methods for identifying studies

We will search four databases including EBSCO, PubMed, Scopus and ISI Web of knowledge from inception to February 2014. There will be no language restrictions in the electronic search for studies.

The searched item will include terms related to critically ill patients (intensive care, ICU, critically ill, intensive care unit, critical care, severely ill and emergency) and terms related to LC (lactate clearance, lactate normalisation, kinetics and lactic clearance). The specific searching strategies for the four databases are shown in table 1. References of all relevant articles will be searched by hand to uncover other potentially eligible studies. If necessary, experts of this field will be contacted for additional studies for our topic.

Data collection

A standardised form will be made for data abstraction. The following data will be extracted from original articles: the name of the first author, publication year, male percentage, subjects (ie, sepsis, major surgery) and setting (ie, medical ICU, surgical ICU, or emergency department), mean age of study population, sample size, mortality, definition of clearance (ie, the percentage reduction and time frame for LC) and the initial lactate level. Data used for meta-analysis will be as follows: the numbers of survivors and non-survivors in the LC group and the non-LC groups; the AU-ROCs curve and the corresponding confidence interval; the cut-off value of LC for the best sensitivity and specificity to predict mortality. Other secondary outcomes will be included if available in original articles. If these data were unavailable in original articles, we tried to contact the corresponding authors for more data.

Table 1 Searching strategy in PubMed, EBSCO, ISI Web of knowledge and Scopus

PubMed	EBSCO	ISI Web of knowledge	Scopus
#1 lactate clearance[Title/Abstract] OR lactate normalization[Title/Abstract] OR lactate kinetics[Title/Abstract] OR lactic clearance[Title/Abstract] OR hyperlactatemia[Title/Abstract]	S1: AB lactate clearance OR AB lactate normalization OR AB lactate kinetics OR AB lactic clearance OR AB hyperlactatemia	#1 Topic=('lactate clearance') OR Topic=('lactate normalization') OR Topic=('lactate kinetics') OR Topic=('lactic clearance') OR Topic=('hyperlactatemia') <i>Timespan=All years Search language=Auto</i>	#1 (TITLE-ABS-KEY('lactate clearance') OR TITLE-ABS-KEY('lactate normalization') OR TITLE-ABS-KEY('lactate kinetics') OR TITLE-ABS-KEY('lactic clearance') OR TITLE-ABS-KEY('hyperlactatemia'))
#2 (intensive care[Title/Abstract] OR ICU[Title/Abstract] OR critically ill [Title/Abstract] OR intensive care unit[Title/Abstract] OR critical care[Title/Abstract] OR severely ill[Title/Abstract] OR emergency [Title/Abstract])	S2: AB intensive care OR AB ICU OR AB critically ill OR AB intensive care unit OR AB critical care OR AB severely ill OR AB emergency	#2 Topic=('intensive care') OR Topic=('ICU') OR Topic=('critically ill') OR Topic=('intensive care unit') OR Topic=('critical care') OR Topic=('severely ill') OR Topic=('emergency') <i>Timespan=All years Search language=Auto</i>	#2 (TITLE-ABS-KEY('intensive care') OR TITLE-ABS-KEY('ICU') OR TITLE-ABS-KEY('critically ill') OR TITLE-ABS-KEY('intensive care unit') OR TITLE-ABS-KEY('critical care') OR TITLE-ABS-KEY('severely ill') OR TITLE-ABS-KEY('emergency'))
#1 AND #2	S1 AND S2	#1 AND #2	#1 AND #2

Quality assessment of included studies

Newcastle Ottawa Scale for cohort study will be employed to assess the reporting quality of included original studies.¹³ This scale comprises eight items evaluating the quality of observational cohort studies in terms of selection, comparability and outcome. If patients were not followed up for the entire length of stay in hospital (eg, ICU mortality), the follow-up was thought to be not long enough for the outcome to occur. Table 2 shows the criteria used for quality assessment adapted from Newcastle Ottawa Scale.

Data synthesis

Mantel-Haenszel methods will be used to combine effect size for fixed-effect model. Otherwise, if there are significant heterogeneity in component studies, the random-effects method will be used by assuming that the different studies are estimating different effects. This method is based on the inverse variance approach, assigning study weights according to variance.¹⁴ We will report relative risk (RR) of death for those with LC and those without, with an RR <1 indicating LC is associated with a lower risk of death and a RR >1 indicating LC is a risk factor for death. For continuous outcome variables, the mean difference will be used to measure effect size. Standard deviations together with sample size will be used to assign weight to each study. For variables in difference scale, standardised mean difference will be used, which standardises the mean difference by SD to a single scale.

The diagnostic performance of LC in predicting mortality will be of interest to clinicians; thus, we will synthesize data regarding diagnostic statistics. Owing to expected substantial between-study heterogeneity, we will employ the hierarchical summary receiver operating characteristic model. This model assumes that there is an underlying ROC curve in each study with parameters α and β that represent the accuracy and asymmetry of the ROC curve.¹⁵ The reported pooled statistics include

sensitivity, specificity, positive likelihood ratio and negative likelihood ratio. Data synthesis will be performed by using the software Stata (College Station, Texas, USA).

Heterogeneity

Heterogeneity will be assessed by using a statistical test. Inconsistency across component studies will be quantified by using the equation:

$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%,$$

where Q is the χ^2 statistic and df is its degree of freedom.^{16 17} I^2 ranges between 0% and 100%, with 0–40% indicating no important heterogeneity, 40–60% indicating moderate heterogeneity, 60–90% indicating substantial heterogeneity, and >90% indicating considerable heterogeneity. Heterogeneity will be explored by using subgroup analysis restricting to sepsis or septic shock. Depending on the number of studies available, other subgroup analyses involving trauma, major operation will be explored. Sensitivity analysis will be performed by excluding retrospective studies.

Publication bias

The contour enhanced funnel plot will be used to detect publication bias. RR from each study is plotted against their variance. Asymmetrical appearance of the plot indicates the presence of publication bias. Contours of statistical significance are overlaid on the funnel plot, which facilitates the assessment of whether the areas where component studies locate are areas of statistical significance and whether the areas where studies are potentially missing are areas of low significance. In situations when studies are missing in areas of low significance, it is possible that the asymmetry is due to publication bias. Otherwise, if the areas where studies are missing are areas of high statistical significance, publication bias is less likely to be present.¹⁸ Egger's test will

Table 2 The Newcastle-Ottawa Scale (NOS) for assessing the quality of included studies

Selection	Representativeness of the exposed cohort	This item will be assigned a '★' when all eligible patients with LC are included in analysis during study period
	Selection of the non-exposed cohort	This item will be assigned a '★' when all eligible patients with non-LC are included in analysis during study period
	Ascertainment of exposure	This item will be assigned a '★' when lactate is directly obtained from medical chart, not by reporting from the patient
Comparability	Outcome of interest is not present at the start of study	This item will be assigned a '★' when death is not occurred within the time frame for determining LC
	Comparability of cohorts on the basis of design or analysis	Baseline characteristics of LC and non-LC patients are comparable. Usually this can be found in table 1
Outcome	Assessment of outcome	This item will be assigned a '★' when mortality is assessed by investigator, not by the report of the patient's family or next-of-kin.
	Is follow-up long enough for outcome to occur	The adequate follow-up is during hospital stay
	Adequacy of follow-up of cohort	This item will be assigned a '★' when follow-up rate >95%

LC, lactate clearance.

be used to test the asymmetry of the funnel plot. It is tested by the linear regression of RR against its standard, weighted by the inverse variance of RR.¹⁹

DISCUSSION

LC has been incorporated into the initial resuscitation target in the 2012 Surviving Sepsis Campaign guideline.²⁰ It is stated “We suggest targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.” This is based on empirical evidence that hyperlactatemia is associated with significantly increased risk of death. Furthermore, two multicentre trials evaluated the resuscitation strategy that included LC as a target. The result showed that quantitative resuscitation based on LC was non-inferior to that based on central venous oxygenation saturation.²¹ The other showed that the resuscitation strategy based on both LC and central venous oxygenation saturation was associated with a 9.6% absolute reduction in mortality.²² The results of these two RCTs are encouraging and inspire more researches on this field. Many studies have been carried out aiming to investigate the association of LC with mortality.^{7–11} These studies reported conflicting results. For instance, the sensitivity of LC in predicting mortality ranged from 0.45 to 0.97; and the specificity ranged from 0.52 to 0.84. Such conflicting results may confuse clinicians on whether LC can be utilised for clinical decision-making, or in what situation can LC provide the most useful information. Therefore, a systematic review is mandatory at this stage to clarify this linkage. Subgroup analysis restricted to patients with sepsis will provide further insights into the clinical usefulness of LC.

Contributors ZZ and KC made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; XX helped in drafting the article and revising it critically for important intellectual content; and all authors gave final approval of the version to be published.

Competing interests None.

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