Int J Clin Exp Med 2017;10(1):37-47
www.ijcem.com /ISSN:1940-5901/IJCEM0037907

Review Article

Early actate levelsfor prediction of mortality in patients with sepsis or septic shock: *a meta-analysis*

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Received August 15, 2016; Accepted October 19, 2016; Epub January 15, 2017; Published January 30, 2017

Abstract: Purpose: Early verification of septic patients at a higher risk of death is still a challenge. There exist several controversies that lactate measurement in septic patients predicted mortality. The present study aimed to explore the diagnostic accuracy of elevated early lactate levels in predicting mortality in septic or septic shock patients. Methods: Three databases including PubMed, Embase and the Cochrane Library were searched from inception to February 2016. We comprehensively performed a systematic review and meta-analysis of all prospective observational studies (POSs) and retrospective observational studies (ROSs) prognosticating mortality. Results: Eight prospective observational studies (POSs) and fourteen retrospective observational studies (ROSs) including a total of 28429 patients were identified. Elevated early lactate levels were significantly associated with increased risk of mortality (odds ratio (OR) 2.92, 95% confidence interval (CI) 2.40 to 3.55, P<0.00001). The association was consistent for cut-off point of about 2 mmol/L (OR 3.21, 95% CI 2.07 to 4.97, P<0.00001) and cut-off point of 4 mmol/L (OR 2.79, 95% CI 2.24 to 3.47, P<0.0001). The overall sensitivity and specificity were 0.56 (95% CI, 0.48-0.64) and 0.70 (95% CI, 0.64-0.75), respectively. Conclusions: Our study demonstrates that an elevated initial lactate level may prove to be a powerful predictor of mortality in septic patients, and its prognostic performance is optimal for clinical utility.Future larger and more adequately powered prospective studies are awaited to clarify the optimal cut-offand the prognostic value of lactate in conjunctionwith other biomarkers.

Keywords: Early lactate levels, sepsis or septic shock, mortality, risk classification

Introduction

Sepsis remains a large challenge to public health, even after years of various aspects progression in medical condition [1-3]. In recent years, the occurrence of sepsis has been increasing and the associated mortality remains high, with great differences between countries and continents [3-6]. The septic response is a vitally complicated chain of events including inflammatory and anti-inflammatory processes, hormonal and cellular reactions, and circulatory disturbance [7, 8]. Early finding, monitoring and intervening risk factors could have an impact on patients' outcome. Therefore, there is a need for a rapid and relatively inexpensive to enhance risk stratification in septic patients.

Human body produces lactate by the reduction of pyruvate that is decomposed by the enzyme lactate dehydrogenase [9]. In normal physiological condition, the reaction is almost irreversible, and this pathway only accounts for one tenth of the total pyruvate metabolism [10]. In a normal adult, altogether 1,500 mmol of lactate is produced daily and blood lactate levels are usually maintained less than 2 mmol/L.

Sepsis is repeatedly complicated by the progression of multiorgan dysfunction syndrome [11]. Tissue perfusion plays an important role in sepsis, which significantly contributes to the development of organ dysfunction [12]. Blood lactate is regarded as an effective biomarker of tissue hypoperfusion and organ dysfunction [13]. To patients with sepsis, elevated lactate has given physicians a quantitative marker of abnormal physiology to support risk stratification and as a treatment end point in sepsis. Nevertheless, initial lactate levels in septic patients while frequently performed have not

been explicitly investigated for use as a prognostic factor [13]. In the present study, we made a systematic review and meta-analysis to evaluate the correlation between early lactate measurement and death in septic patients.

Materials and methods

Methods

This systematic review and meta-analysis was conducted and reported according to the guidelines of Meta-analysis of Observational Studies in Epidemiology [14] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement (PRISMA) [15].

PICO statement

The PICO statement was the following: P-patient, problem or population: Patients with sepsis or septic shock, whatever the cause. Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection. I-intervention or exposure: Early lactate levels, recorded within the first 24 hours after the onset of sepsis. C-comparison, control or comparator: Cut off values of 2 mmol/L and 4 mmol/L was respectively chosen as a termination point of abnormal lactate level and hyperlactatemia. O-outcomes: Hospital mortality was used as assessed value.

Publication searching

We searched databases of PubMed, Embase and the Cochrane Library from inception to February 2016. The following terms were searched in [Title/Abstract]: "Sepsis", "Septic", "Severe sepsis", "septic shock" AND "lactic acid", "lactate", "lactic". There was no language restriction on searching. If multiple studies describing the same population were published, we select the most recent study.

Inclusion and exclusion criteria

Inclusion criteria: all available prospective observational studies (POSs) and retrospective observational studies (ROSs) that initial lactate measurement assess the mortality of patients with sepsis in English without publication category limitation and there is no limitation to lactate range for septic patients selected.

Exclusion criteria: duplicate publication, review articles, case reports, and animal experimental studies, insufficient raw data (data remain cannot be obtained after contacting the author by email), studies only involving the elderly, neonate (perinatal) or nonelderly.

Quality assessment

Given that the eligible studies were POSs and ROSs, reporting quality was assessed according to Newcastle Ottawa Scale [16]. This scale contains eight items evaluating the quality of observational studies in terms of selection, comparability, and outcome. A score of 0-9 (allocated as stars) was allocated to each study.

Study selection and data extraction

Two authors independently screened title and/or abstract produced by the search. Full-text manuscripts that were identified as relevant were obtained and then assessed independently against inclusion and exclusion criteria. Discrepancies were settled by discussion and/or by introducing other reviewers.

Two investigators respectively extracted the following descriptive data from all eligible studies: country, assay manufacturer, publication year, study design, study population and setting, sample size, mean age of study population, male percentage, outcome assessment, mortality of study cohort, marker evaluated (lactate level), timing of lactate measurement, the optimal cut off point. If data needed clarification or were not presented in the publication we directly contacted the corresponding author and/or co-authors via email.

Statistical analysis

RevMan 5.3 software from Cochrance Collaboration and Stata 12.0 software was utilized for the meta-analysis. Odds ratio (OR) was reported to estimate the predictive value of initial lactate measurement on mortality rate. OR and its relevant 95% CI were pooled by using fixed-effect or random-effect models (the DerSimonian and Laird method) [17]. OR more than 1 indicated beneficial effect of the exposure for mortality. Hierarchical summary receiver operating characteristic model (HSROC) was performed to measure diagnostic performance of early lactate levels in predicting mortality.

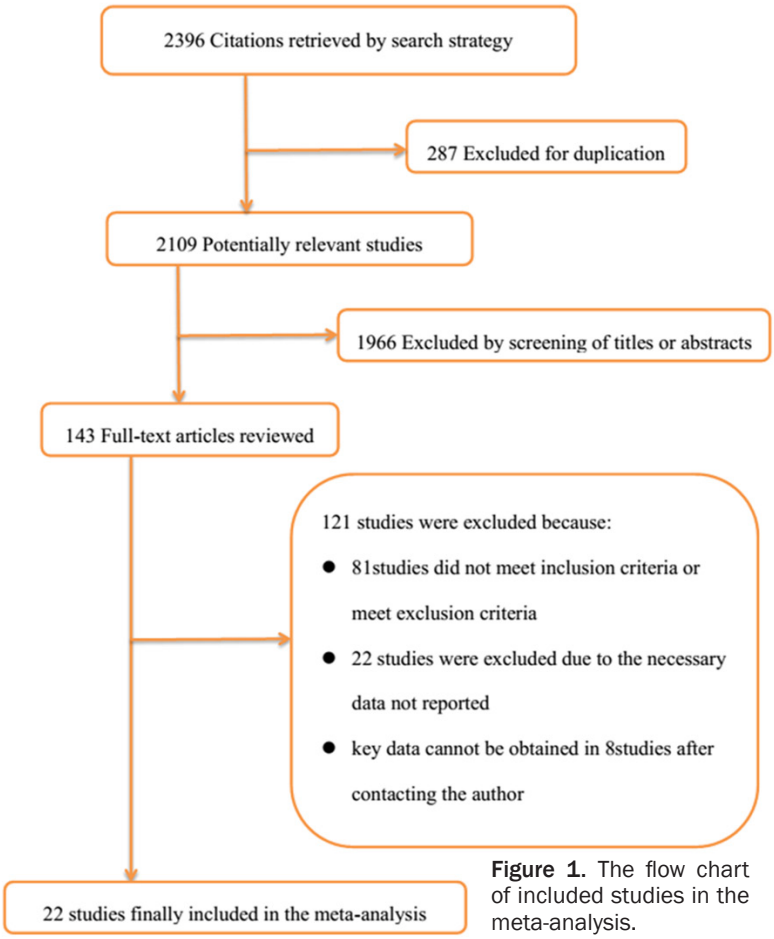

Figure 1. The flow chart of included studies in the meta-analysis.

Heterogeneity was evaluated by using Cochrane's Chi^2 test and I^2 test. The random-effects model was used if there was heterogeneity between studies; otherwise, the fixed-effects model was used. A prior subgroup analyses to explore significant heterogeneity were: Cut off point of about 2 mmol/L (including 1.7, 2.2, 2.4, 2.5 and 3 mmol/L) and 4 mmol/L (including 4.9 mmol/L).

Sensitivity analyses were performed by metainf command in Stata and sequential exclusion of each study in RevMan to explore the heterogeneity observed. Funnel plots were used to screen for potential publication bias.

Results

Study selection and characteristics

The flow chart of study selection procedure is shown in **Figure 1**. Our initial search yielded 2396 citations, of which 2253 were eliminated for inspection of title and/or abstract. After full texts scrutinized according to selection, 22 eligible papers [11, 18-38] which met the inclusion criteria mentioned above were included and 121 were excluded for exclusion criteria, necessary data unreported and key data unobtainable.

Characteristics of included studies are shown in **Table 1**. Eight studies [11, 18, 20, 21, 24, 28, 29, 31] were prospective observational studies (POSs) and fourteen studies [19, 22, 23, 25-27, 30, 32-38] were retrospective observational studies. With respect to clinical setting, eleven studies [11, 18, 21-23, 25, 26, 29-31, 34] were conducted in intensive care medicine (ICU), seven studies [19, 24, 32, 33, 35, 36, 38] accomplished in emergency department (ED), two studies [27, 28] were performed in emergency room (ER) and two studies [20, 37] were not definitely described. The subject population varied across studies: septic shock, severe sepsis or septic shock, severe sepsis, HIV Type 1-Infected and severe sepsis, sepsis and circulatory failure, septic and Non-diabetic, septic shock and hepatic dysfunction, neutropenia and septic shock. The mean age of the patients varied between 35.7 and 76 years. There were more male patients than female patients in most studies, but the study by Ramzi O. T. [37] enrolled equal number of males and females. The overall mortality varied across studies, ranging from 13.3% to 48.9%. Sample sizes of included studies have an extensive range: 20 to 19945. Follow-up periods differed across studies, including 28 days, 30 days and hospital stay. Early serum lactate were tested less than six hours in almost all studies except one recorded within the first 24 hours after the onset of severe sepsis and we only collected initial lactate level for meta-analysis. The optimal cut-off points varied greatly across studies, from to for lactate. Usually, arterial lactate levels were categorised into low: <4 mmol/L, and high: >4 mmol/L [39]. What's

Table 1. Characteristics of included studies

Study	Country	Study population and setting	Study design	No	Male (%)	Mean Age (year)	Outcome	Mortality (%)	Optimal Timing	Cut-off Point (mmol/L)
Ospina 2015 [18]	Columbia	ICU patients with septic shock	POS	135	-	64	28-dayHospitalmortality	42.9	admitted to the ICU	2.0
Shin 2016 [19]	Korea	ED patients with severe sepsis or septic shock	ROS	880	54.7	65	In-Hospital mortality	18.1	arrived at the ED	4.0
Thomas 2015 [11]	Germany	ICU patients with severe sepsis	POS	988	62.4	69	In-Hospital mortality	39.8	the first 24 hours	2.5
Moore 2008 [20]	USA	HIV Type 1-Infected Patient with severe sepsis	POS	70	38.9	35.7	In-Hospital mortality	25.7	ICUadmission	4.0
Jansen 2009 [21]	Netherland	ICU patients with sepsis	POS	138	-	65	In-Hospital mortality	30.0	ICU admission	2.5
Ranzani 2013 [22]	Brazil	ICU patients with severe sepsis/septic shock	ROS	1948	48.3	60	In-Hospital mortality	34.5	Lactate Measured ≤6 h	4.0
Bao 2015 [23]	China	septic patients admitted ICU	ROS	94	76.5	69	In-Hospital mortality	48.9	initial lactate	4.0
Bewersdorf 2015 [24]	Netherland	ED patients with severe sepsis	POS	293	-	61.4	28-dayHospital mortality	32.4	arrived at the ED	2.4
Uvizl 2015 [25]	Czech Republic	ICU patients with severe sepsis	ROS	746	61.9	-	28-dayHospital mortality	40.8	Lactate Measured ≤6 h	4.0
Rech 2015 [26]	USA	ICU patients with severe sepsis	ROS	169	58.6	62.1	30-dayHospital mortality	48.5	initial lactate	4.0
Jasso 2015 [27]	Spanish	ER with diagnosis of septic shock	ROS	67	-	-	In-Hospital mortality	16.4	lactate at admission	4.9
Permpikul 2014 [28]	Thailand	ER with severe sepsis/septic shock	POS	51	-	63.9	In-Hospital mortality	25.5	initial lactate	2.0
Boulain 2014 [29]	France	ICU patients presenting with sepsis and circulatory failure	POS	360	64.2	65.8	28-dayHospital mortality	30.3	lactate at admission	2.2
Diao 2013 [30]	China	ICU patients with severe sepsis/septic shock	ROS	118	69.5	54	In-Hospital mortality	36.0	initial lactate	1.7
Hernandez 2012 [31]	Netherland	ICU patients with septicshock	POS	15	-	67.6	In-Hospital mortality	13.3	initial lactate	4.0
Hermans 2012 [32]	Netherland	ED patients with sepsis	ROS	47	-	63.4	28-dayHospital mortality	36.2	initial lactate	4.0
Green 2012 [33]	USA	septic adult nondiabetic patients in ED	ROS	1236	48.5	76	28-dayHospital mortality	17.3	initial lactate	4.0
Kang 2011 [34]	Korea	ICU septic shock patients with hepatic dysfunction	ROS	118	63	62	In-Hospital mortality	48.0	lactate at admission	4.0
Vorwerk 2009 [35]	UK	ED patients with sepsis	ROS	158	-	71.5	28-dayHospital mortality	33.5	lactate at admission	4.0
Mikkelsen 2009 [36]	Canada	ED patients with severe sepsis	ROS	830	53.1	57	28-dayHospital mortality	22.9	initial lactate	4.0
Ramzi 2007 [37]	Tunisia	neutropenic patients with septic shock	ROS	20	50	41	28-dayHospital mortality	25.0	initial lactate	3.0
Casserly 2015 [38]	USA	ED patients with severe sepsis or septic shock	ROS	19945	-	-	In-Hospital mortality	32.4	Lactate Measured ≤6 h	4.0

ED = emergency department, ER = emergency room, ICU = intensive care unit, POS = prospective observational study, ROS = retrospective observational study.

Table 2. Quality assessment with newcastle ottawa scale

Study	Selection				Comparability	Outcome			
	REC	SNC	AE	AOI	Design and Analysis	Assessment	Enough Follow-up	Adequate Follow-up	Score
Ospina 2015	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Shin 2016	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Thomas 2015	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Moore 2008	☆	☆	☆	☆	☆	☆	☆	☆	8
Jansen 2009	-	☆	☆	☆	☆	☆	☆	☆	7
Ranzani 2013	☆	☆	☆	☆	☆	☆	☆	☆	8
Bao 2015	☆	-	☆	☆	☆	☆	☆	☆	7
Bewersdorf 2015	☆	☆	☆	☆	☆	☆	☆	☆	8
Uvizl 2015	☆	☆	☆	☆	☆	☆	☆	-	7
Rech 2015	☆	☆	☆	☆	☆	☆	☆	☆	8
Jasso 2015	☆	☆	☆	☆	-	☆		☆	6
Permpikul 2014	☆	☆	☆	☆	☆	☆	-	☆	7
Boulain 2014	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Diao 2013	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Hernandez 2012	☆	-	☆	☆	☆	☆	-	☆	6
Hermans 2012	☆	☆	☆	☆	☆	☆	-	☆	7
Green 2012	☆	☆	☆	☆	☆	☆	☆	☆	8
Kang 2011	☆	☆	☆	☆	☆	☆	-	☆	7
Vorwerk 2009	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Mikkelsen 2009	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Ramzi 2007	☆	-	☆	☆	-	☆	☆	☆	6
Casserly 2015	☆	☆	☆	☆	☆	☆	-	☆	7

REC = Representative of Exposed Cohort, SEC = Selection of Nonexposed Cohort AE = Ascertainment of Exposed, AOI = Absence of Outcome of Interest, star (☆) was allocated to a particular item when it was adequately reported and addressed. The item "comparability" could be allocated with a maximum oftwo stars. Dashes indicate this item was not adequately reported or addressed.

more, initial lactate >4 mmol/L is severely compromised in surviving sepsis campaign care bundles [3]. Perhaps blood lactate concentrations >4 mmol/L is an optimal cut-off point. Most studies was chose 4 mmol/L as cut-off point and other studies have own cut-off point.

Study quality

Newcastle Ottawa Scale for observational study was used to assess the reporting quality of included studies. **Table 2** displays the quality assessment for POSs and ROSs. The result showed that seven studies scored 9 points, three scored 6 points, and the remaining scored between 6 and 9 points.

Predictive value of lactates on all-cause mortality

Overall, 3838 (42.8%) of the 8942 patients with elevated high lactate died VS 5156 (26.5%) of the 19482 patients with low lactate. **Figure 2** shows that Elevated lactates were associated with a significantly increased risk of all-cause mortality (OR2.92, 95% confidence interval (CI) 2.40 to 3.55, P<0.00001) with significant heterogeneity (I^2 = 75%, P<0.00001). Subgroup analyses suggested that the association between elevated lactate and increased risk of all-cause mortality was consistent for cut-off point of about 2 mmol/L (OR 3.21, 95% CI 2.07 to 4.97, P<0.00001; I^2 = 70%) [11, 17, 20, 23, 27-29, 36] and cut-off point of 4 mmol/L (OR 2.79, 95% CI 2.24 to 3.47, P<0.0001; I^2 = 73%) [18, 19, 21, 22, 24-26, 30-35, 37], but there is no a notable significant decline about heterogeneity. Because of the significant heterogeneity across studies (I^2 = 75%), random-effects model was used to pool ORs. The overall sensitivity and specificity were 0.56 (95% CI, 0.48-0.64) and 0.70

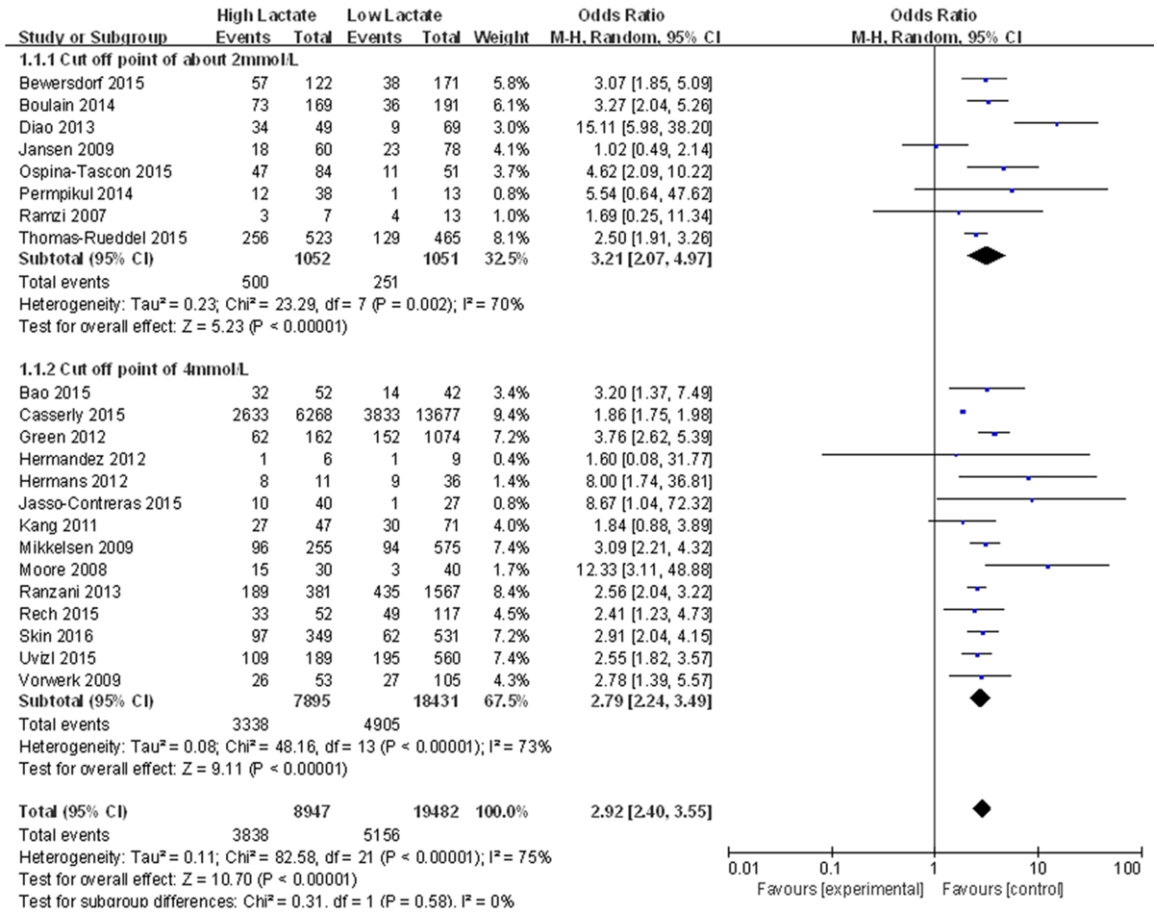

Figure 2. Summary of odds ratio of mortality in septic patients with elevated early lactateSubgroup: Cut off point of about 2 mmol/L and Cut off point of 4 mmol/L.

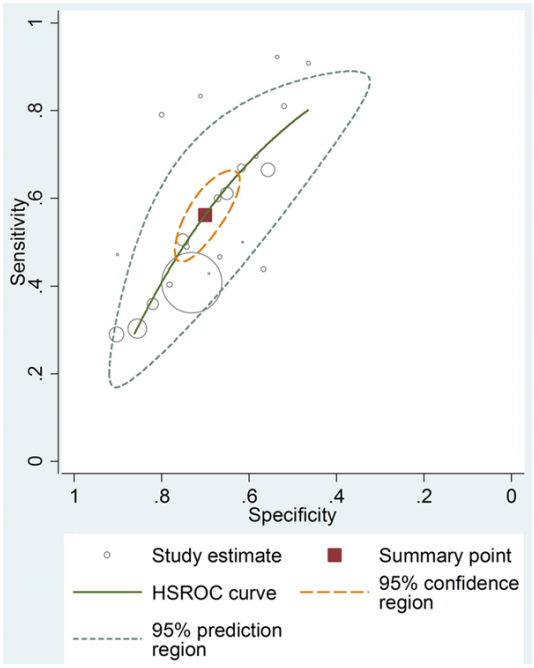

Figure 3. Diagnostic performance of early lactate levels in predicting mortality. Each circle represents acomponent study. The overall sensitivity and specificity were 0.56 (95% CI, 0.48-0.64) and 0.70(95% CI, 0.64-0.75), respectively. HSROC = hierarchical summary receiver operating characteristic.

(95% CI, 0.64-0.75), respectively by hierarchical summary receiver operating characteristic (**Figure 3**).

Sensitivity analysis and publication bias

Sensitivity Analysis (**Figure 4**) indicated that one [38] of all studies had larger deviation relative to other studies. Heterogeneity was seen a great change from I^2 = 75% to I^2 = 44% by remove study by Casserly, B [38] (**Figure 5**). However, by sequential exclusion of remain studies (Casserly, B retained), there was almost no change about heterogeneity. Publication bias was considered to be no obvious by

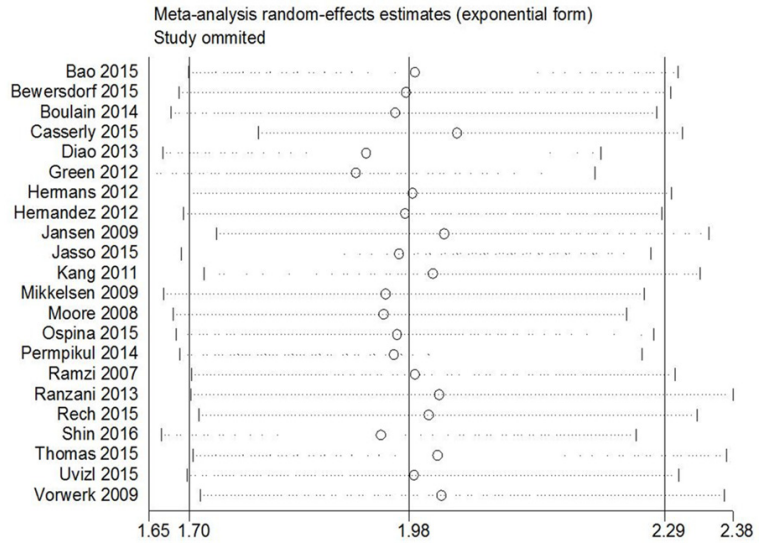

Figure 4. Sensitivity Analysis for the predictive value of elevated early lactate for mortality in patients with sepsis.

inspection of **Figure 6** that displays a funnel plot of the studies included in this meta-analysis.

Discussion

The present meta-analysis of 8 POSs and 14 ROSs studies including 28429 patients by 3838 (42.8%) of the 8942 patients with high lactate died VS 5156 (26.5%) of the 19482 patients with low lactate shown that elevated initial lactates were associated with a significantly increased risk of mortality in patients with sepsis. As such, measurement of lactates may be a simple method of risk stratification in septic patients.

Lactate is thought to be a commendable biomarker of microcirculation, and it is closely related to capillary perfusion independent of hemodynamic variables [40]. Sepsis, regardless of the causes, is easily inclined to imbalance of oxygen delivery and consumption; that is to say the amount of oxygen available for consumption is not able to meet the demand of an organism [41]. Under tissue hypoxia conditions, organism is almost focused on anaerobic glycolysis and mitochondrial oxidative phosphorylation is unable to function [42], lactate concentration continuously increases because of inadequate tissue oxygenation. If not promptly adjusted, sustained impaired oxygen delivery to tissues and organs will lead to multiple organ dysfunction syndrome that is well known to lead to high fatality rate. Lactate is an effective marker of tissue hypoxia and might become an early strategy of quantitative risk to decrease mortality of septic patients. It indicates danger signal is coming toward them when septic patients have high lactates. Maintaining sharp vigilance on hyperlactatemia, continuous monitoring and clearing it can have positive influence on patients' outcome. Normalizing lactate in septic patients with elevated lactate becomes targeting resuscitation in the 2012 sepsis guideline [3]. Our study provides high-grade evidence to confirm the prognostic value of initial lactate measurement in patients with sepsis.

A study [43] performed by Musikatavorn, K. and involving 388 patients eligible for mortality analysis found that there is no association between initial lactate measurement and 30-day mortality. However, included patients diagnosed with sepsis in ED, their hemodynamics is stable without overt organ hypoperfusion and more than 65 years is excluded. Relatively speaking, the patients they investigated had less severe symptoms. So the report suggested that blood lactate is not prediction of mortality in nonelderly sepsis patients' with stable hemodynamic. To date,other biomarkers was also used to predict death rate in the area of sepsis; for instance, procalcitonin [44], brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide [45], leukocyte apoptosis [46]. In this study, pooled sensitivity and specificity for diagnostic performance of early lactate levels in predicting mortality were 0.56 (95% CI, 0.48-0.64) and 0.70 (95% CI, 0.64-0.75), respectively. So, the present prognostic markers have no sufficient (less than 80%) sensitivity and specificity to predict which patients are at greater risk of dying due to sepsis. According to a prospective observational study [18], an initial lactate evaluated showed a better prognostic value in conjunction with other biomarkers (Lactate levels + Cv-aCO_2/Da-vO_2 AUC (0.85) VS Lactate AUC (0.79)), each marker reflects different patho-

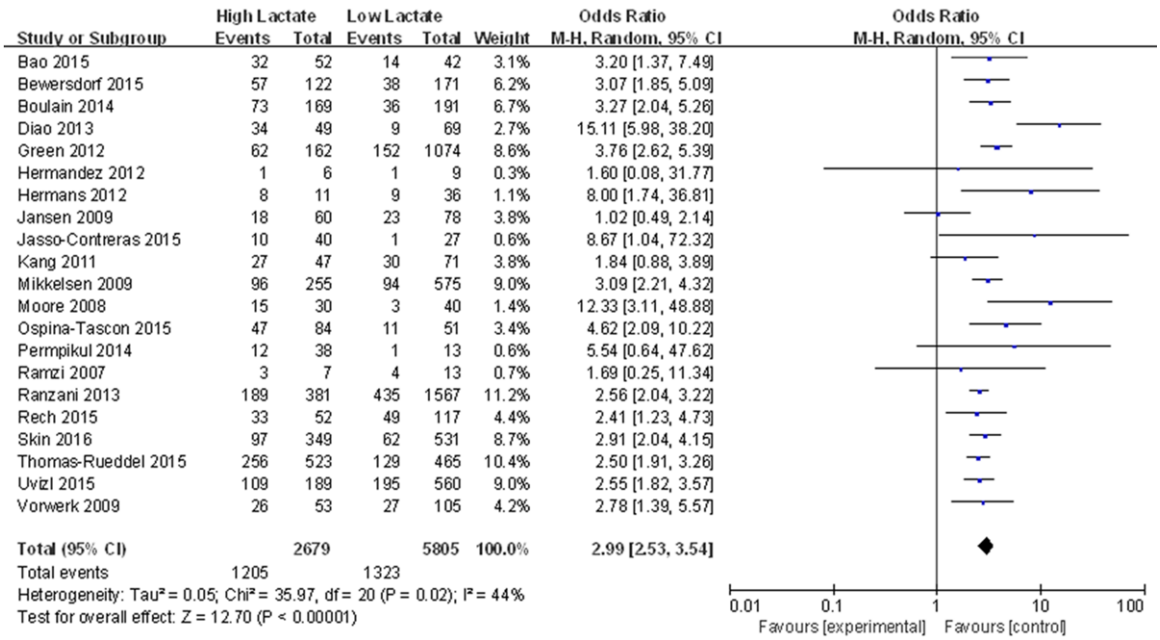

Figure 5. Forest plot of excluding study by study by Casserly, et al.

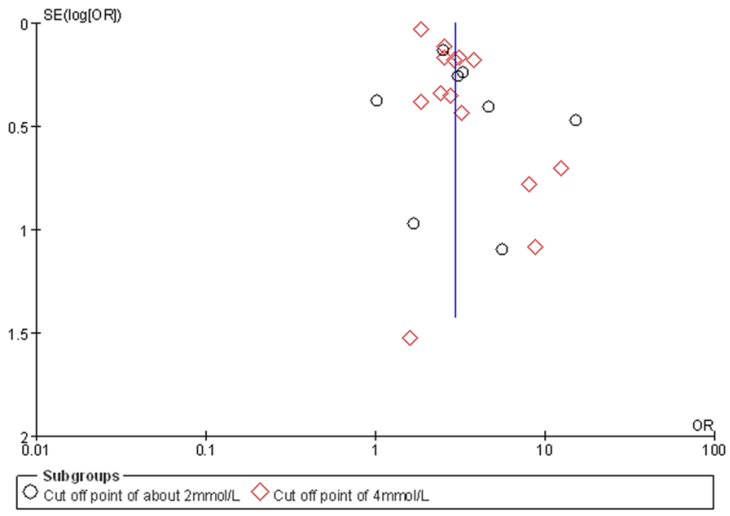

Figure 6. Funnel plot for the predictive value of elevated early lactate for mortality in patients with sepsis.

physiological aspects. Clinical severity scores such as Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores are used to serve as risk classification tools. Lactate may improve the performance of APACHE II, SOFA scores in predicting mortality [47]. A rapid, simple and effective method (biomarker, biomarkers, biomarker combined with severity score systems) with extremely high prognostic performance of severity in septic patient needs to be discovered in further study.

The meta-analysis largely of observational studies has several limitations that must to be taken into account. First, notable heterogeneity existed across the included studies. Casserly, B [38] shows a highly marked influence on heterogeneity of meta-analysis by Sensitivity Analysis and heterogeneity sharply declined without it. In consideration of data from the Surviving Sepsis Campaign Database, it can greatly enhance the reliability of meta-analysis. Second, an ideal cut-off point for lactate tests cannot be able to come to a conclusion on account of the lack of raw data to map out ROC curves. Third, patients with sepsis or septic shock in included studies received treatment in different levels of medical establishment, whether early goal-directed therapy was strictly enforced or not according to Surviving Sepsis Campaign could influence the outcomes. Finally, we have no clear data on causes of high serum lactate in septic patients.

Maybe the circulatory system is relatively steady in a proportion of patients with sepsis. Hyperlactatemia are the result of the other conditions, such as hepatic function deterioration, drug factor (metformin, vasoactive agent), or diabetes mellitus that can interfere with the lactate values. If basic or primary diseases are timely, effectively and pointedly treated in septic patients without evident circulatory failure, the risk of death can be decreased.

Taken together, initial lactate level measurement can be a forceful prognostic marker of mortality in septic patients. The early, fast simple and cost-effective method appears to be optimal for clinical utility. Future larger and more adequately powered prospective studies are awaited to clarify the optimal cut-offand the prognostic value of lactate in conjunctionwith other biomarkers.

Acknowledgements

The authors thank Fundamental Research Funds of the Science and Technology Planning Project of Guangdong's Tianhe district (Grant No. 2013kw028) and Science and Technology Planning Project of Guangdong Province (Grant No. 2014A020211010) for the support.

Disclosure of conflict of interest

None.

Authors' contribution

Study concept and design: GL, HL, YA, XW and XY. Acquisition of data: GL and HL. Analysis and interpretation of data: YA, XW and XY. Drafting of the manuscript: GL and HL. Critical revision of the manuscript for important intellectual content: YA and XW. Statistical analysis: GL and HL. Administrative, technical, and material support: HY, YA, XW and XY. Study supervision: HY and HL. All authors have read and approved the manuscript for publication.

Abbreviations

POSs, prospective observational studies; ROSs, retrospective observational studies; OR, odds ratio; CI, confidence interval; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement; HSROC, hierarchical summary receiver operating characteristic model; ICU, intensive care medicine; ED, emergency department; ER, emergency room; AUC, area under the curve; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; REC, representative of exposed cohort; SEC, selection of non-exposed cohort; AE, ascertainment of exposed; AOI, absence of outcome of interest.

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