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Original Article

Predictive value of lactate levels for mortality in pneumonia: a systematic review and meta-analysis

Ziyun Hu[1 #], Yanfei Qiang[1 #], Xiaolin Yan[1]

[1] Changxing County People's Hospital; Department of Respiratory and Critical Care Medicine, Zhejiang Province, China

# Both authors are co-first authors and contributed equally to this work.

Abstract

Introduction: Lactate levels, a marker of tissue hypoxia and metabolic acidosis, have been suggested as a prognostic indicator for patient outcomes in pneumonia. This systematic review and meta-analysis aim to determine the predictive value of lactate levels for mortality in patients with pneumonia.

Methods: A systematic literature search was done using CINAHL, SCOPUS, EMBASE, MEDLINE, Cochrane, Google Scholar, and ScienceDirect databases. Random-effect models were used to calculate pooled effect estimates, including sensitivity, specificity, and diagnostic odds ratios. Heterogeneity, publication bias, and meta-regression analyses were performed.

Results: A total of 17 studies were included. The pooled diagnostic odds ratio for lactate levels in predicting mortality was 5 (95% CI: 3-8). The sensitivity and specificity were 61% (95% CI: 52 - 69%) and 78% (95% CI: 73 - 82%), respectively. The positive and negative likelihood ratios were 2.7 (95% CI: 2.1-3.4) and 0.51 (95% CI: 0.40-0.64). The area under the receiver operating characteristic curve was 0.77 (95% CI: 0.72-0.82). Subgroup analysis showed that studies with lactate cut-off values between 1.2 and 2 mmol/L had better sensitivity, while studies with cut-off values greater than 2 mmol/L had higher specificity.

Conclusions: Lactate levels have moderate predictive value for mortality in patients with pneumonia. This indicator may potentially aid in risk stratification and clinical decision-making. Further research is needed to determine optimal lactate cut-off values and evaluate the potential benefits of incorporating lactate monitoring into pneumonia management strategies.

Key words: Lactate; meta-analysis; pneumonia; validation studies.

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Introduction

Pneumonia is a significant global health concern. It was responsible for approximately 2.5 million deaths globally in the year 2019 alone, with the highest mortality observed in children under the age of five and elderly populations [1]. Therefore, timely identification of severe cases and appropriate management of pneumonia are crucial in reducing the associated mortality and complications.

Lactate, a byproduct of anaerobic glycolysis, has long been recognized as a valuable biomarker in critical care settings. Elevated lactate levels are indicative of tissue hypoxia, metabolic acidosis, and impaired oxygen delivery, which can be observed in severe infections and sepsis [2]. Previous reports showed the possible value of lactate levels as a prognostic marker for disease severity and patient outcomes in various clinical scenarios, including pneumonia [3–6].

The pathophysiology of pneumonia involves local and systemic inflammatory responses associated with the release of pro-inflammatory cytokines and increased metabolic demand. The resulting tissue hypoxia and anaerobic metabolism may, in turn, lead to the accumulation of lactate [7]. In this context, lactate levels could serve as an indirect marker of the severity of inflammation and tissue damage, thus providing valuable information for risk stratification and guiding clinical decision-making.

The predictive value of lactate levels for mortality in pneumonia is still unclear. While some studies showed a strong association between elevated lactate levels and increased mortality risk, others have found no significant correlation [8–11]. These discrepancies can be attributed to variations in study design, patient populations, and lactate measurement methods.

This systematic review and meta-analysis aim to summarize the existing data to assess the predictive value of lactate levels for mortality in pneumonia. The results will contribute to the current understanding of the prognostic value of lactate levels in pneumonia and

help improve clinical practice guidelines for pneumonia management.

Methods

The protocol was registered at PROSPERO (No. CRD42023420530).

Eligibility criteria

The inclusion criteria were: 1) Eligible observational studies, including cohort (prospective/retrospective), case-control, and cross-sectional studies, were considered for inclusion. 2) Studies done in patients with pneumonia 3) Studies comparing the prognostic role of lactate levels with the real-time occurrence of mortality through the follow-up of patients either through records or in-person were included. 4) Studies reporting the mortality (either in-hospital or out-of-hospital death of pneumonia patients during the follow-up) as outcomes.

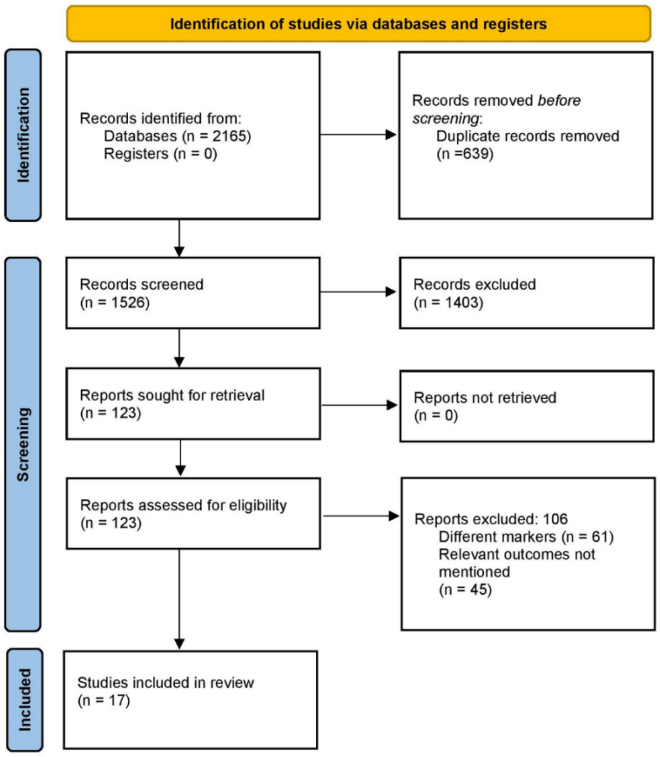
The exclusion criteria were Case reports/series and unpublished grey literature.

Information sources and records retrieval

The search strategy is summarized in the Supplementary Table 1.

The search was conducted in multiple databases, including "CINAHL, SCOPUS, EMBASE, MEDLINE, Cochrane Library, Google Scholar, and ScienceDirect." It incorporated medical subject headings (MeSH) and free-text terms combined with Boolean operators ("AND," "OR," and "NOT"). The search period spanned from January 1964 to March 2023 without language restrictions.

Figure 1. Search Strategy.



Study selection

Titles, keywords, and abstracts of the selected papers were examined independently by two researchers (ZH and YQ). Full texts of the identified relevant studies were then retrieved. The final analysis included studies that met all eligibility criteria. The "Preferred Reporting Items for Systematic Reviews and Meta-Analyses Diagnostic Test Accuracy (PRISMA-DTA) checklist" was employed to report this review [12].

Data management

Two researchers (ZH and YQ) manually extracted data from eligible full-text articles using a predefined semi-structured data collection form. In addition to manual data extraction, the data management process involved verification through cross-checking by an independent reviewer to ensure consistency and accuracy. Furthermore, discrepancies identified during the extraction process were resolved through consensus meetings, and where necessary, a third researcher was consulted.

Risk of bias assessment

A pair of investigators (ZH and XY) evaluated the quality of the included studies using the QUADAS ("Quality Assessment of Diagnostic Accuracy Studies") tool [13]The QUADAS tool encompasses "patient selection, index test, reference standard, and flow of patients and timing of index test domains." Based on the responses, each study was categorized as having good or poor quality.

Statistical analysis

Predictive accuracy was evaluated by calculating the combined sensitivity, specificity, and likelihood ratios for positive and negative outcomes and the overall diagnostic odds ratio (OR) with a 95% confidence interval (CI) for lactate levels. The area under the receiver operation characteristic curve (AUROC) was used to produce "Summary Receiver Operator Characteristic curves (sROC)" [14]. Subgroup analysis was performed to determine the optimal cut-off for lactate levels.

A likelihood ratio (LR) scattergram was generated to determine the clinical value of the lactate test for

mortality prediction. I^2 and chi-square of heterogeneity were used to measure heterogeneity. Meta-regression was done using potential covariates. A publication bias assessment was done using Deek's test and funnel plot. STATA version 14.2 was used for the analysis.

Results

Search results

The initial literature search across the databases identified 2165 papers. Following duplicate removal, 123 full-text articles were retrieved. These studies underwent secondary screening, and a total of 17 eligible studies were finally included (Figure 1) [8–11,15–27].

Characteristics of the included studies

Most studies were from China (n = 9) and Korea (n = 2). Most were conducted as retrospective or retrospective cohort studies (10/17 studies). The sample size in the included studies varied between 101 and 2275. Three studies were conducted in children under five, while the rest were conducted in adults. The cut-off for the lactate levels for mortality prediction ranged from 1.2 to 4.06 mmol/L. Overall, 11 studies had a low risk of bias, and six had a high risk of bias (Table 1).

Mortality

In total, 17 studies have reported the utility of lactate levels for predicting mortality of patients with pneumonia. The predictive accuracy of lactate for mortality is reported in Figure 2. The OR was 5 (95% CI: 3-8), the sensitivity and specificity were 61% (95% CI: 52 - 69%) and 78% (95% CI: 73 - 82%), respectively, and the positive (LR +) and negative (LR-) likelihood ratios were 2.7 (95% CI: 2.1-3.4) and 0.51, respectively (95% CI: 0.40-0.64). Figure 3 shows that LR+ and LR- were in the right lower quadrant of the LR scattergram, indicating that the test is not applicable for confirmation or exclusion.

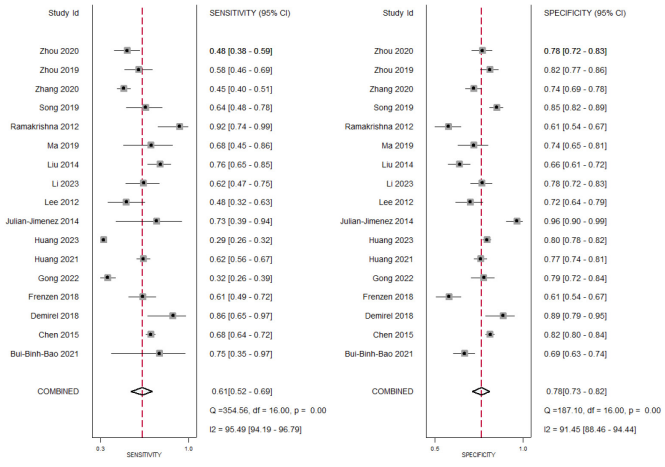
The AUROC was 0.77 (95% CI: 0.72-0.82) (Figure 4). I^2 > 75%, and a chi-square *p* of 0.001 showed significant heterogeneity. As shown in Figure 5, the

Table 1. Included studies.

Author and year	Study design	Country	Inclusion criteria	Sample size	Cut-off for lactate levels	Mean age (in years)	Gender distribution (M: F)	Risk of bias
Bui-Binh-Bao 2021	Prospective cohort	Vietnam	Children aged 2 months to 5 years with pneumonia	281	4.06 mmol/L	NR	169:112	Low
Chen 2015	Prospective cohort	China	Age ≥18 years, new infiltrates on chest radiograph, and two or more symptoms consistent with pneumonia	1641	4 mmol/L	73	968:673	Low
Demirel 2018	Prospective	Turkey	Patients less than 18 years and were admitted to the emergency department and diagnosed as pneumonia	101	3.35 mmol/m3	71	62:39	Low
Frenzen 2018	Retrospective cohort	Germany	patients (aged >17 years) with community acquired pneumonia presenting to the emergency department	303	1.2 mmol/L	73	181:122	High
Gong 2022	Retrospective cohort	China	Patients diagnosed with severe community acquired pneumonia	413	2.1 mmol/L	75.3	263:150	Low
Huang 2021	Retrospective observational	China	Adult Patients diagnosed with severe community acquired pneumonia	883	1.7 mmol/L	66	569:314	High
Huang 2023	Retrospective cohort	China	Adult Patients diagnosed with severe community acquired pneumonia admitted to ICU	2275	2.3 mmol/L	69	1530:745	Low
Julian-Jimenez 2014	Prospective	Spain	Patients diagnosed with community acquired pneumonia in emergency department	127	3.38 mmol/L	65.8	69:58	Low
Lee 2012	Retrospective	Korea	Consecutive adult community acquired pneumonia patients (19 years) admitted to the hospital via the ED	211	2.81 mmol/L	78	123:88	High
Li 2023	Retrospective	China	Patients with Klebseilla Pneumonia associated ICU acquired pneumonia aged 18 years and above	285	2.2 mmol/L	59.4	213:72	High
Liu 2014	Prospective observational	China	Patients suspected of community acquired pneumonia at emergency department	359	2.45 mmol/L	71	221:138	Low
Ma 2019	Prospective cohort	Uganda	Under five children with clinical signs of pneumonia as per WHO IMCI definition	155	3.4 mmol/L	11	90:65	Low
Ramakrishna 2012	Prospective	Malawi	Children with WHO defined pneumonia or severe pneumonia	233	2 mmol/L	NR	123:107	Low
Song 2019	Retrospective observational	Korea	Patients with community acquired pneumonia presenting to the emergency department	443	2 mmol/L	66.5	253:190	High
Zhang 2020	Retrospective	China	Patients (>18 years) with community acquired pneumonia	742	2.3 mmol/L	70.4	462:280	High
Zhou 2019	Retrospective cohort	China	Adult patients diagnosed with community acquired pneumonia	350	1.75 mmol/L	78	217:133	Low
Zhou 2020	Retrospective cohort	China	Adult septic patients with community acquired pneumonia	336	2 mmol/L	76	213:123	Low

NR: Not reported; USA: United States of America; ICU: Intensive Care Unit; WHO: World Health Organization; IMCI: Integrated Management of Childhood Illness.

Figure 2. Forest plot showing sensitivity and specificity of lactate for predicting mortality amongst pneumonia patients.



meta-regression results indicated that the study design was a significant source of heterogeneity in the sensitivity model. At the same time, none of the variables were identified as the source of heterogeneity in the specificity model. However, study design, study region, and risk of bias were identified as a source of heterogeneity in the joint model ($p < 0.001$).

Subgroup analysis based on the cut-off for lactate levels revealed that studies with a cut-off between 1.2 and 2 mmol/L had better sensitivity (63%) than studies with a cut-off of more than 2 mmol/L (59%). However, the specificity was higher in studies with a cut-off of more than 2 mmol/L (79%) compared to studies with a cut-off between 1.2 and 2 mmol/L (75%). Finally, the symmetrically formed funnel plot and non-significant *p* (0.10) of Deek's test (Figure 6) indicated the lack of publication bias.

Figure 4. Summary Receiver Operator Characteristic Curve.

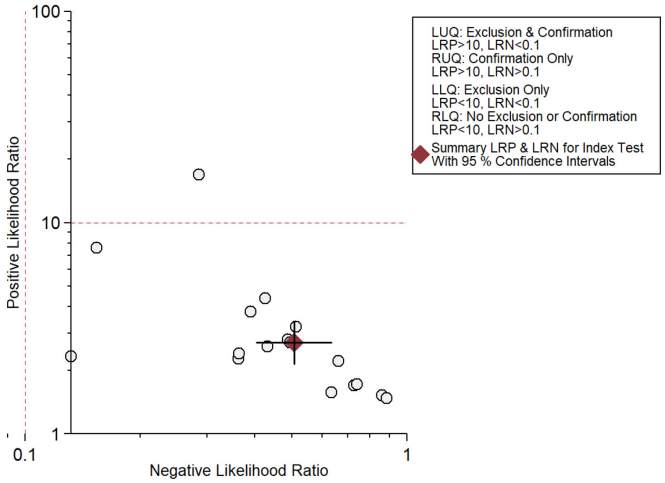
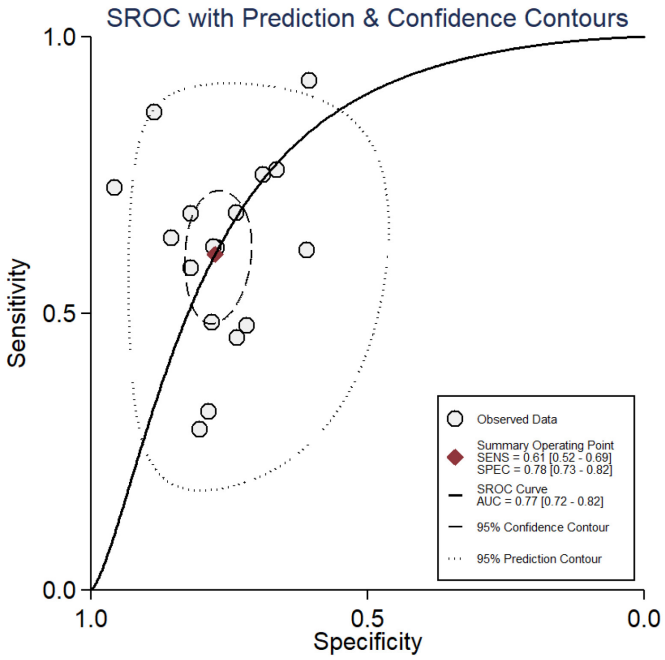


Figure 3. Likelihood ratio scattergram.



Discussion

This study aimed to evaluate the ability of lactate levels to predict mortality in patients with pneumonia. The study included 17 eligible articles, most from China and Korea. The findings reveal that lactate levels have a moderate to high clinical value for predicting mortality, with a pooled diagnostic OR of 5 (95% CI: 3-8), sensitivity of 61% (95% CI: 52-69%), and specificity of 78% (95% CI: 73-82%).

The findings agree with previous reports, highlighting the potential utility of lactate levels in predicting clinical outcomes in patients with variability

Figure 5. Meta-regression results.

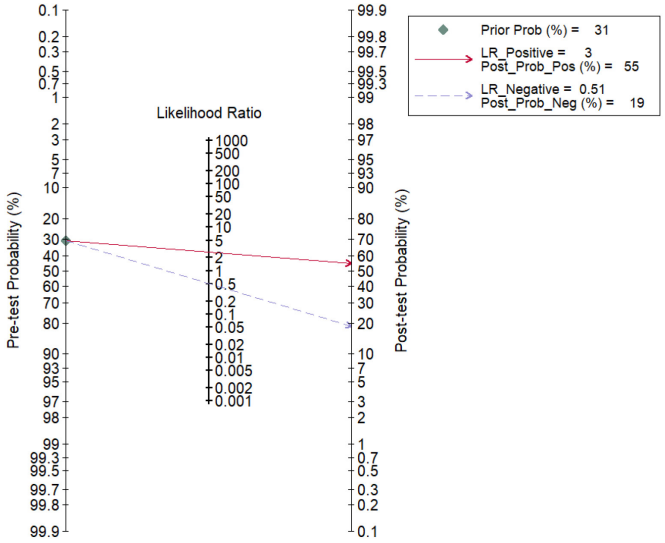
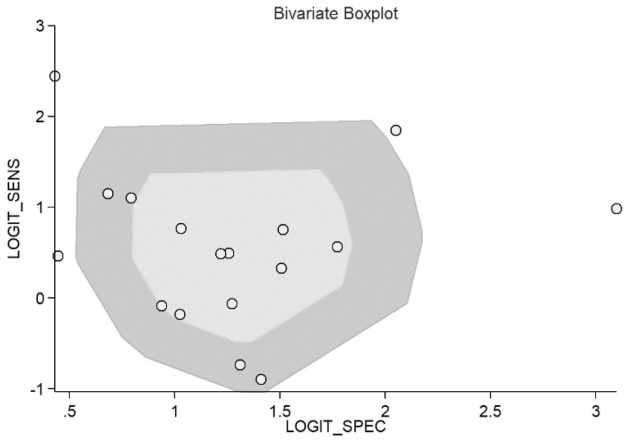


Figure 6. Funnel plot for publication bias assessment.



in comorbidities or emergency settings. [3,5]. Several mechanisms can explain the correlation between increased lactate levels and mortality in pneumonia. Elevated lactate levels indicate tissue hypoxia, impaired oxygen delivery, and anaerobic metabolism, all hallmarks of severe infection and sepsis [7]. Additionally, elevated lactate levels reflect an increased inflammatory response and metabolic demand that may exacerbate tissue damage and further compromise organ function in pneumonia patients [7]. Consequently, lactate levels may serve as a surrogate marker for the severity of inflammation and tissue injury in pneumonia, thereby providing valuable prognostic information. The results suggest that increased lactate levels are associated with higher mortality risk, and lactate monitoring could serve as an additional complementary tool to identify high-risk patients needing more aggressive intervention. Clinicians should consider integrating lactate monitoring into their assessment of pneumonia patients to better identify those at an increased risk of mortality.

However, the study's predictive performance of the lactate levels was lower than that of other tools, such as CURB65, CRB65, or the Pneumonia Severity Index (PSI), used for identifying clinical outcomes. It was also lower than that of certain biomarkers such as pro-adrenomedullin and prohormone forms of atrial natriuretic peptide [28–30]Therefore, lactate alone should not be used as a single parameter to stratify high-risk patients. Incorporating lactate levels into existing risk stratification tools, such as the CURB-65 or PSI scores, may further refine their accuracy in predicting patient outcomes. Ultimately, a more comprehensive understanding of the role of lactate in pneumonia management could lead to more effective treatment strategies and improved patient care.

Interestingly, the subgroup analysis based on lactate cut-off values demonstrated that studies using a cut-off between 1.2 and 2 mmol/L had better sensitivity (63%) than those with a cut-off above 2 mmol/L (59%). Conversely, specificity was higher in studies employing a cut-off greater than 2 mmol/L (79%) than those with a cut-off between 1.2 and 2 mmol/L (75%). Our finding suggests that the optimal lactate cut-off for predicting mortality in pneumonia may depend on the specific clinical context and individual patient characteristics.

The main strengths of this study are the comprehensive literature search and the rigorous methodology used for the analysis. By pooling data from multiple studies, the analysis provides a robust estimate of the value of lactate levels for predicting mortality in pneumonia patients. Furthermore, this study did not find evidence of publication bias, indicating that the results are likely reliable and unbiased.

However, the study has several limitations. The review mainly included retrospective or retrospective cohort studies, which may be associated with a potential selection bias, confounding factors, and limited generalizability of the results. Secondly, the retrospective nature of most studies may introduce biases that could impact the reliability of our results. Furthermore, the significant heterogeneity observed in the analysis may be due to variations in study design, study region, and risk of bias. Lastly, a small number of studies in certain subgroups may have impacted the reliability of the subgroup analysis. The meta-regression results indicated that study design was a significant source of heterogeneity in the sensitivity model. At the same time, no variables were identified as sources of heterogeneity in the specificity model. However, the joint model revealed the study design, study region, and risk of bias as sources of heterogeneity, emphasizing the importance of considering these factors when interpreting the findings.

The findings of this study have important clinical implications for managing pneumonia patients. Increased lactate levels can help identify high-risk patients who may require more aggressive intervention, i.e., early initiation of antibiotics, close monitoring, and appropriate supportive care. Furthermore, the results suggest that the optimal lactate cut-off value for predicting mortality may depend on the specific clinical context and individual patient characteristics. This knowledge could inform the development of tailored management strategies for pneumonia patients based on their lactate levels, ultimately contributing to improved patient outcomes and reduced mortality rates.

Future research should focus on validating our findings in diverse populations and clinical settings and determining the optimal lactate cut-off values for different patient populations. Additionally, further investigations are needed to study the mechanism of the correlation between lactate levels and mortality in pneumonia patients and explore the potential benefits of incorporating lactate monitoring into existing pneumonia management algorithms.

By enhancing our understanding of the prognostic value of lactate levels in pneumonia and informing clinical practice guidelines, this study's findings could contribute to improved patient outcomes and reduced mortality rates in pneumonia. Potential therapeutic approaches may include optimizing oxygen delivery, addressing the underlying causes of tissue hypoxia, and modulating the inflammatory response. Such investigations could provide insights into novel treatment strategies for pneumonia patients with elevated lactate levels.

In conclusion, this study demonstrated that lactate levels have moderate to high clinical value for predicting mortality in patients with pneumonia. Elevated lactate levels are linked to an increased risk of mortality, indicating that lactate monitoring could be beneficial in identifying high-risk patients who may require more aggressive intervention.

Conclusions

This study has demonstrated that elevated lactate levels are moderately predictive of mortality in patients with pneumonia. However, lactate levels alone should not be considered sufficient for risk stratification and should ideally be used in conjunction with established severity assessment tools like CURB-65 or PSI scores. While the meta-analysis highlighted the potential utility of lactate as a supplementary biomarker for identifying high-risk pneumonia patients, significant heterogeneity among the included studies indicates that further research is needed.

Corresponding author

Xiaolin Yan,
Changxing County People's Hospital
Department of Respiratory and Critical Care Medicine,
Changxing County People's Hospital,
66 Taihu Middle Road, Changxing County,
Huzhou City, Zhejiang Province, China
Email: huziyun881788@163.com

Conflict of interests

No conflict of interests is declared.

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Annex – Supplementary Items

Supplementary Table 1. Search strategy of the study.

Search strategy:	("lactat"[All Fields] OR "lactate s"[All Fields] OR "lactates"[MeSH Terms] OR "lactates"[All Fields] OR "lactic acid"[MeSH Terms] OR ("lactic"[All Fields] AND "acid"[All Fields]) OR "lactic acid"[All Fields] OR "lactate"[All Fields]) AND ("pneumonia"[MeSH Terms] OR "pneumonia"[All Fields] OR "pneumonias"[All Fields] OR "pneumoniae"[All Fields] OR "pneumoniae s"[All Fields]) AND ("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading])
Translations	**lactate**: "lactat"[All Fields] OR "lactate's"[All Fields] OR "lactates"[MeSH Terms] OR "lactates"[All Fields] OR "lactic acid"[MeSH Terms] OR ("lactic"[All Fields] AND "acid"[All Fields]) OR "lactic acid"[All Fields] OR "lactate"[All Fields]
	pneumonia: "pneumonia"[MeSH Terms] OR "pneumonia"[All Fields] OR "pneumonias"[All Fields] OR "pneumoniae"[All Fields] OR "pneumoniae's"[All Fields]
	mortality: "mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[Subheading]
SCOPUS	TITLE-ABS-KEY (lactate AND pneumonia AND mortality) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (SRCTYPE, "j")) – 1768 results