

# Arterial lactate in predicting mortality after paraquat poisoning

## A meta-analysis

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### Abstract

**Objective:** This study aimed to explore the effects of arterial lactate as a predictor of mortality in patients with paraquat (PQ) poisoning.

**Methods:** The databases PubMed, EMBase, Web of Science, ScienceDirect, Cochrane library, and studies published until 31 February 2018 were searched. The data were extracted to perform pooled analysis, heterogeneity testing, sensitivity analysis, publication bias analysis, and Fagan plot analysis.

**Results:** Pooled analysis showed that a high arterial lactate was significantly correlated with poor mortality (pooled odds ratio = 16.94, 95% confidence interval [CI]: 7.96–36.08,  $P < .001$ ). The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 77% (95% CI: 0.69–0.84), 84% (95% CI: 0.74–0.90), 4.7 (95% CI: 2.9–7.8), 0.28 (95% CI: 0.20–0.39), and 17 (8–36), respectively. An area under the curve of 0.87 (95% CI: 0.83–0.89) means a high ability for prognostic detection.

**Conclusion:** Our findings show that arterial lactate is an effective predictor of mortality in patients with PQ poisoning.

**Abbreviations:** AUC = area under the curve, CI = confidence interval, DOR = diagnostic odds ratio, NLR = negative likelihood ratio, OR = odds ratio, PLR = positive likelihood ratio, PQ = paraquat, QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2 tool, SROC = summary receiver operating characteristic.

**Keywords:** arterial lactate, mortality, paraquat

## 1. Introduction

Paraquat (PQ, 1,1'-dimethyl-4,4'-bipyridinium dichloride) is a fast-acting and non-selective contact herbicide widely used in agricultural and horticultural industries. Although PQ is safe for occupational use, PQ poisoning has been observed in patients who ingested the pesticide either accidentally or intentionally in an attempt to commit suicide.<sup>[1]</sup> PQ poisoning remains a major cause of death among patients with acute poisoning in developing countries, with a mortality rate of 50% to 90%.<sup>[2–4]</sup> Lung damage from acute PQ poisoning is caused by increasing PQ concentrations in lung tissues, resulting in free radical build-up that triggers inflammatory responses, thereby causing lung fibrosis. Thus, the

identification of lesions in the lungs and their severity may be crucial to the evaluation of patient outcomes and to the identification of early treatment and alternative treatment modalities.

Plasma PQ concentration is considered the most relative, sensitive, and accurate index for identifying the degree of PQ toxicity.<sup>[5]</sup> However, extending the plasma PQ concentration technology to district hospitals is difficult because of the high cost of the assay. Several prognostic markers and laboratory tests have been reported, and they indicated poor prognosis. These markers include overt systemic toxicity (e.g., hypotension, severe hypoxia, acidosis, and low Glasgow Coma Scale), renal failure, changes in chest radiograph, and gastrointestinal lesions.<sup>[6–8]</sup>

Additionally, arterial lactate has been indicated as a predictor of mortality in patients with PQ poisoning<sup>[9–14]</sup>; yet small sample size of each study might lack statistical power to draw definitive conclusions. Therefore, we conducted a meta-analysis to evaluate the value of arterial lactate as a predictor of mortality in patients with PQ poisoning.

## 2. Methods

All results and analyses were based on previous ethically approved studies, thus no further ethical approval and patient consent are required. This protocol has been registered in the PROSPERO network (registration number: CRD42018092619).

### 2.1. Search strategy

A systematic literature search was performed in PubMed, EMBase, Web of Science, ScienceDirect, Cochrane library, and studies published until 31 February 2018 for eligible studies to

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assess the prognostic value of the arterial lactate as a predictor of mortality in PQ poisoning cases. The following search terms were used: “arterial lactate” and “paraquat.” Relevant references cited in the retrieved works were also screened when they were considered potentially pertinent. If >1 publication exists on the same study population, only the most recent study was included.

The inclusion criteria were as follows: studies covering arterial lactate among survival and nonsurvival patients with PQ poisoning; studies providing adequate data for extracting and calculating individual predictive accuracy for mortality. Studies were excluded due to the following reasons: duplicated or overlapped studies; abstracts, comments, case reports, reviews, meta-analyses, and conference papers.

## 2.2. Data collection

Two reviewers (LSL and ZDN) independently reviewed all titles and abstracts for eligibility. They then independently evaluated full texts for inclusion, resolving any disagreement by discussion. The extracted data included the following items: first author's name, publication year, study design, country of origin, sample size, sex, mortality percentage, arterial lactate, cutoff values, study period, sensitivity, and specificity. We primarily sought odds ratios (ORs) for mortality. If ORs were not presented in the study, but the raw data were available, we calculated the ORs. In case of ambiguity over the results, we contacted the authors for clarification.

## 2.3. Quality assessment of the selected articles

Two reviewers (LY and GJ) independently assessed the risk of bias of the included studies by using Quality Assessment of Diagnostic Accuracy Studies 2 tool (QUADAS-2).<sup>[15]</sup>

## 2.4. Statistical analysis

We considered hazard ratios (HRs) to approximate the relative estimate expressed in other studies by using ORs in accordance with previous meta-analyses. Stata 12.0 was used to analyze the pooled effects with ORs and 95% confidence intervals (CIs). The potential heterogeneity across studies was evaluated using the Cochran *Q*-test and expressed using the *I*<sup>2</sup> index. The pooled results for OR were calculated by the fixed-effects model (*I*<sup>2</sup> ≤ 50%) or the random-effects model (*I*<sup>2</sup> > 50%). To further analyze the sources of heterogeneity, meta-regression were performed according to country, mortality percentage, sample size, and study design. The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were pooled to estimate the prediction power of arterial lactate on survival. We calculated the summary receiver operating characteristic (SROC) curves and area under the curve of arterial lactate with 95% CI. Publication bias was estimated using Egger test, Begg tests, and a funnel plot with the trim and fill method, which was also utilized to adjust for publication bias from potential unpublished studies. Fagan plot analysis was also performed, which assesses the relationship among an estimated pretest probability of the disease, the likelihood ratio of the diagnostic test, and the post-test probability of the disease. We assumed pretest probabilities of 25%, 50%, and 75%, and the corresponding positive and negative post-test probabilities were calculated. The *P* value of <.05 was considered statistically significant.

## 3. Results

### 3.1. Search strategy

According to our defined searching strategy, 152 references were identified after an initial search (Fig. 1). Four duplicated publications were excluded, and 138 unrelated publications were excluded after reviewing their abstracts. Furthermore, we reviewed the remaining 10 publications carefully and found that 4 studies did not provide enough data for our analysis or the publications were meta-analyses and reviews. Finally, 6 studies encompassing 1022 patients with PQ poisoning were included in this meta-analysis.

### 3.2. Study characteristics

Characteristics of the 6 included studies are summarized in Table 1. The 6 included studies were published between 2011 and 2017, among which 5 were conducted in China and 1 in Republic of Korea. Four studies were published in English, and 2 studies were published in Chinese. The median of sample size was 170 with a wide range from 75 to 272. The mortality ranged from 46.15% to 81.62%, with a total mortality of 57.75%.

### 3.3. Assessment of risk of bias for included studies

The distribution of QUADAS-2 scores of the methodologic quality (i.e., risk of bias and concerns regarding applicability) of every included study is presented in Table 2. The “patient selection” domain in all studies were at unclear risk bias due to lack of detail regarding inconsecutive and the “index test” was labeled as high because the diagnostic threshold was not prespecified.

### 3.4. Association of arterial lactate on survival

A random effects model was utilized to calculate the pooled ORs and 95% CIs because of the significant heterogeneity among studies (*I*<sup>2</sup> = 78.00%, *P* < .001). A high arterial lactate was associated with mortality (pooled OR = 16.94, 95% CI: 7.96–36.08, *P* < .001; Fig. 2). The pooled sensitivity, specificity (Supplemental Figure 1, <http://links.lww.com/MD/C375>), PLR, NLR, and DOR were 77% (95% CI: 0.69–0.84), 84% (95% CI: 0.74–0.90), 4.7 (95% CI: 2.9–7.8), 0.28 (95% CI: 0.20–0.39) and 17 (95% CI: 8–36), respectively. The area under the curve (AUC) of arterial lactate tests was 0.87 (95% CI: 0.83–0.89), thereby implying a relatively high diagnostic accuracy (Fig. 3).

### 3.5. Heterogeneity and publication bias assessment

To identify the possible sources of heterogeneity across these studies, meta regression was performed according to patients' mortality percentage (>50% vs ≤50%), study design (prospective vs retrospective), country (Korea vs China), and sample size (>100 vs ≤100). Meta regression showed that they did not account for the source of heterogeneity.

Publication bias was not found by visual assessment of funnel plots (Supplemental Figures 2 and 3, <http://links.lww.com/MD/C375>), and potential publication bias was confirmed by Egger test (*P* = .175) and by Begg test (*P* = .133).

### 3.6. Sensitivity analysis

All studies were sequentially removed to evaluate the effect of individual study on the pooled ORs (Fig. 4). The pooled ORs of

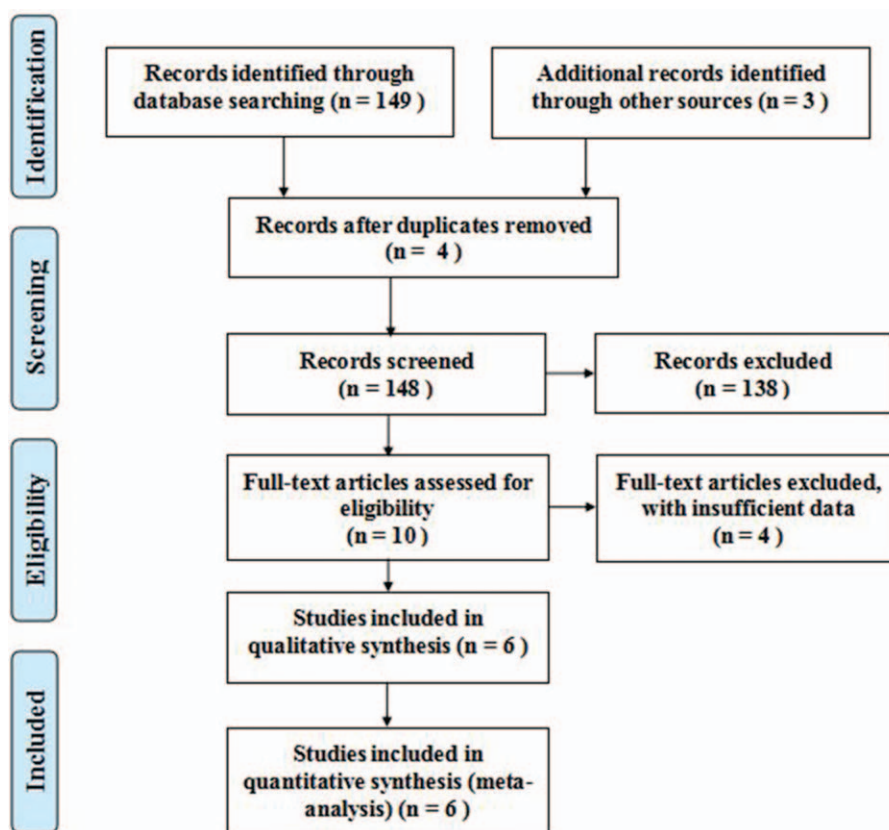


Figure 1. Flow diagram of studies identified in the systematic review.

Table 1

Characteristics of included studies.

Author (Year)	Region	Design	N	Male (%)	Mortality (%)	Serum lactate (mmol/L)		Study period
						Survival	non-survival	
Lu et al <sup>[9]</sup>	China	Retrospective	75	38.67	54.67	2.13 ± 1.24	NA	2009–2012
Jiang et al <sup>[10]</sup>	China	Retrospective	168	39.29	48.21	NA	NA	2010–2013
Xu et al <sup>[11]</sup>	China	Prospective	143	37.76	46.15	2.78 (1.89)	7.63 (2.46)	2011–2012
Sun et al <sup>[12]</sup>	China	Retrospective	170	42.94	57.06	2.00 (1.00, 2.50)	5.00 (2.00, 10.00)	2008–2012
Lee et al <sup>[13]</sup>	Korea	Retrospective	272	63.24	81.62	2.81 ± 1.95	8.30 ± 4.04	2005–2011
Liu et al <sup>[14]</sup>	China	Retrospective	194	37.11	58.76	1.50 ± 0.79	2.90 ± 1.21	2012–2014

NA = not available.

Table 2

Quality assessment of the included studies using QUADAS-2 tool.

Author (Year)	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Xu et al <sup>[11]</sup>	Unclear	Low	Low	Unclear	Low	Low	Low
Sun et al <sup>[12]</sup>	Unclear	High	Low	Low	Low	Low	Low
Liu et al <sup>[14]</sup>	Unclear	High	Low	Low	Low	Low	Low
Lee et al <sup>[13]</sup>	Unclear	High	Low	Unclear	Low	Low	Low
Jiang et al <sup>[10]</sup>	Unclear	High	Low	Low	Low	Low	Low
Lu et al <sup>[9]</sup>	Unclear	High	Low	Low	Low	Low	Low

High indicates high risk of bias; low, low risk of bias; and unclear, unclear risk of bias, which means there was insufficient information to permit judgment.

QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2 tool.

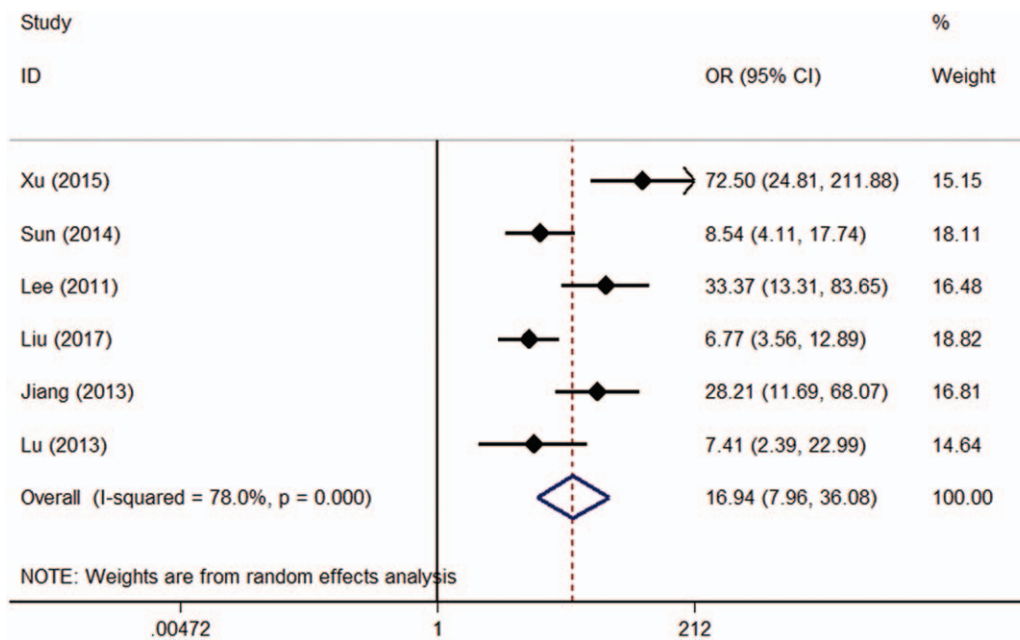


Figure 2. Forest plot of the association between arterial lactate and mortality.

sensitivity analyses varied from 12.18 (95% CI: 8.54–17.39) to 19.29 (95% CI: 12.93–28.77) for the prognostic value of arterial lactate on mortality, suggesting that the pooled ORs were not significantly affected by individual study.

3.7. Translation to clinical practice

The Fagan plot demonstrated that when the pretest probabilities were 25%, 50%, and 75%, the positive post-test probabilities were 61%, 83%, and 93%, and the negative post-test probabilities were 8%, 22%, and 45%, respectively (Fig. 5).

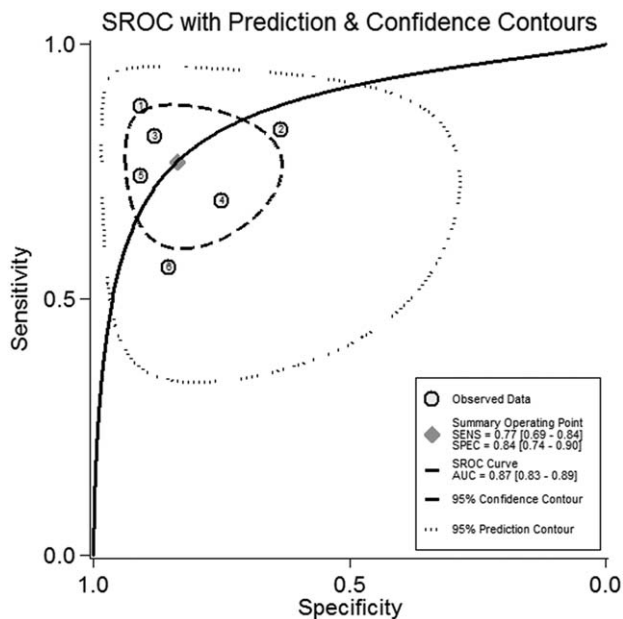


Figure 3. Summary ROC (SROC) curve for the 6 included studies. Numbers in brackets are 95% CIs. AUC=area under ROC curve, CI=confidence interval, SENS=sensitivity, SPEC=specificity.

4. Discussion

PQ ingestion is a major cause of fatal poisoning in many parts of Asia and the Pacific nations. High number of fatality cases due to PQ poisoning is caused by its inherent toxicity and lack of effective treatments. However, optimal prognostic indicators to evaluate patient mortality have not been unequivocally established. Early prognosis of PQ poisoning remains a clinical challenge. A reliable predictor of prognosis would help in finding treatment and in investigating the efficacy of new treatments. For example, early prediction of inevitable death would be important to stop inappropriate treatments in terminal acute PQ poisoning patients. Therefore, prognosis of PQ poisoning based on arterial lactate tests has potential benefits.

In this study, we systematically evaluated the prognostic value of arterial lactate in 1022 PQ poisoning patients from 6 different studies and demonstrated that arterial lactate was an indicator of a favorable prognosis for mortality. The prognostic value of arterial lactate in PQ poisoning reached the same sensitivity in prognosis of PQ poisoning as blood PQ concentration.<sup>[16,17]</sup> When PLR >10 or NLR <0.1, the likelihood of diagnosis or exclusion of a disease increased remarkably. Nevertheless, in our meta-analysis, a pooled PLR of 4.7 (95% CI: 2.9–7.8) and NLR 0.28 (95% CI: 0.20–0.39) suggested that arterial lactate may not be powerful enough to confirm or exclude the potential patient with cancers. However, an AUC of 0.87 (95% CI: 0.83–0.89) means a high ability for prognostic detection. Therefore, arterial lactate was an effective biomarker for prognostic evaluate.

We also utilized meta-regression analysis to identify factors that may have caused the observed heterogeneity among the studies. Although covariates specific to patients and studies were examined, none were found to affect arterial lactate accuracy. We hypothesized that the potential heterogeneity may have been derived from clinical factors, such as treatment strategy and severity of poisoning. Unfortunately, when studies are compared in a meta-analysis, providing definitive conclusions about heterogeneity becomes difficult.<sup>[18]</sup> Therefore, researchers need

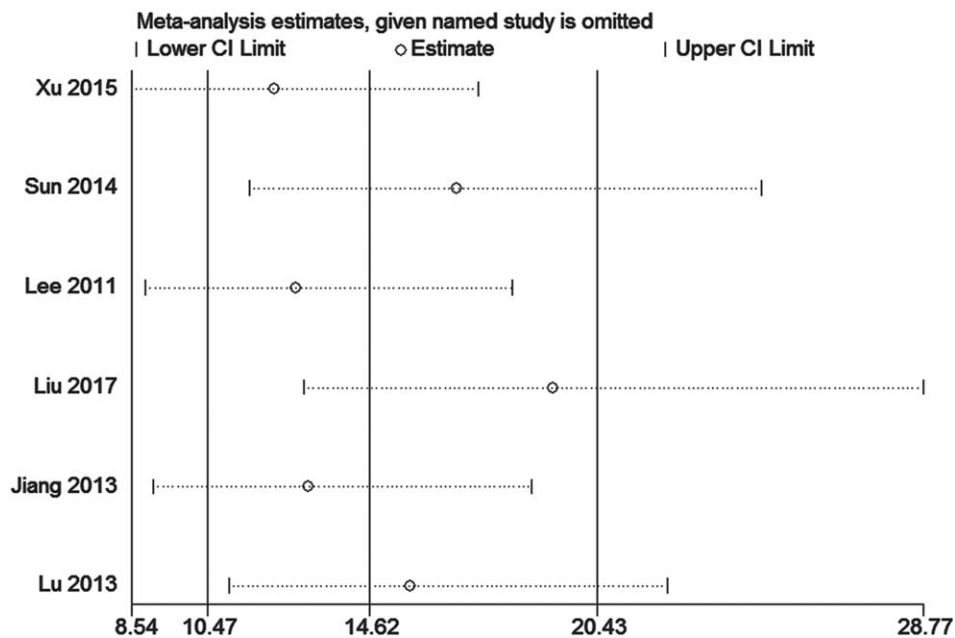


Figure 4. Sensitivity analysis of the relationship between arterial lactate and mortality.

to focus on the development of a perfect experimental design to guarantee the homogeneity of methodology and to offer a scientific theoretical basis for the prevention and treatment of lung injury after PQ poisoning.

A strength of our study was the use of Fagan plot analysis to explore the clinical utility of arterial lactate. At a pretest probability for responses of 25% (low clinical suspicion), the

post-test probability of malignancy with a negative result was 8%; this could be considered sufficient to rule out mortality. At a pretest probability for responses of 75% (high clinical suspicion), the post-test probability of responses, with a positive lactate result, was 93%. This analysis provides further support for the effective predictor of mortality in patients with PQ poisoning.

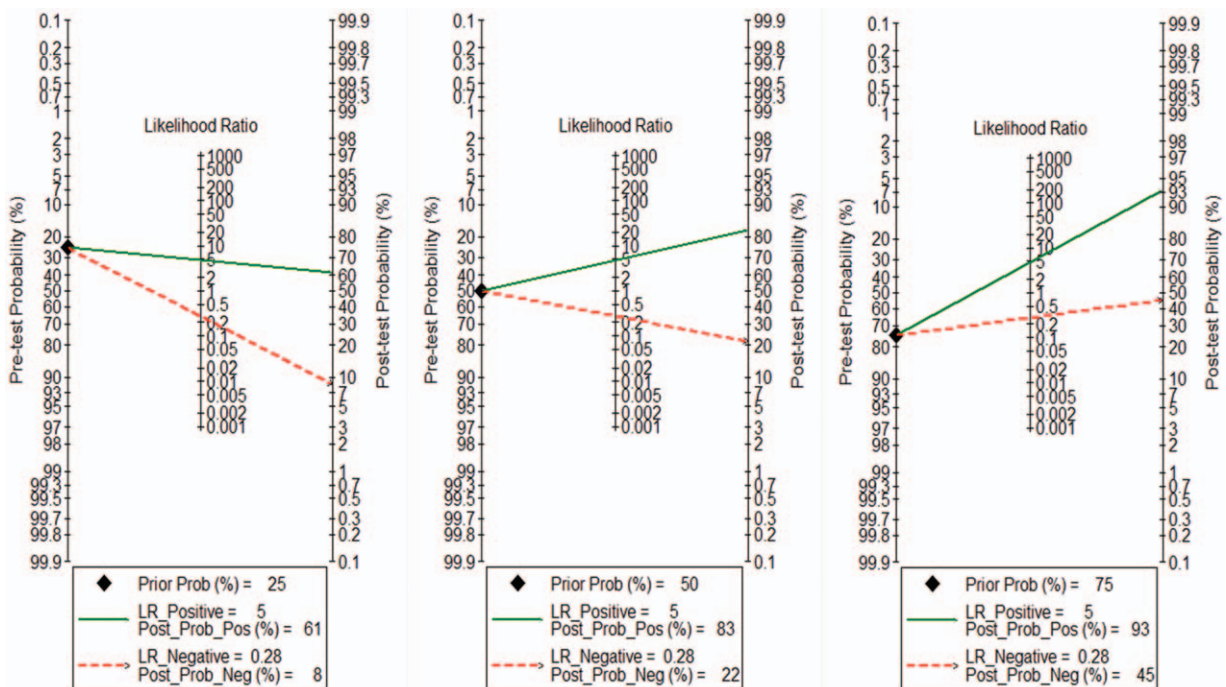


Figure 5. Analysis of the Fagan plot to evaluate the clinical efficacy utility of arterial lactate in predicting mortality. (A) Pre-test probability=25%; (B) pre-test probability=50%; (C) pre-test probability=75%. Each Fagan plot contains a vertical axis on the left for the pre-test probability, an axis in the middle that represents the likelihood ratio, and a vertical axis on the right that represents the post-test probability. NLR=negative likelihood ratio, PLR=positive likelihood ratio.

Our results should be viewed cautiously owing to several limitations. First, most of the included studies were designed retrospectively, which means they unavoidably had a bias risk. Thus, the reliability of our pooled analysis was affected. Second, although strict inclusion criteria were set, patients from different studies may differ in their baseline characteristics (ethnicity, region, disease stage, and treatment regimens), which are also potential confounding factors.

In conclusion, although our study has several limitations and further investigation is needed, these findings may help clinicians evaluate patient outcomes.

### Author contributions

**Conceptualization:** Shilei Li, Danna Zhao, Jie Gao, Yong Li, Shunyi Feng.

**Data curation:** Shilei Li, Danna Zhao.

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**Methodology:** Jie Gao, Yong Li.

**Project administration:** Shilei Li, Danna Zhao.

**Supervision:** Shunyi Feng.

**Writing – original draft:** Jie Gao, Yong Li.

**Writing – review and editing:** Shunyi Feng.

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