



Systematic Review

## Serum Lactate Clearance as a Predictor of Mortality in Sepsis: A Systematic Review and Meta-Analysis

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### ABSTRACT

**Background:** Sepsis is a life-threatening condition associated with high mortality despite advances in critical care. Serum lactate is widely used as a biomarker of tissue hypoperfusion; however, dynamic changes in lactate levels, particularly lactate clearance, may provide superior prognostic information.

**Objective:** To systematically evaluate and quantitatively synthesize the association between serum lactate clearance and mortality in patients with sepsis.

**Methods:** A comprehensive search of PubMed, Scopus, Web of Science, and the Cochrane Library was conducted up to December 2025. Studies assessing lactate clearance and mortality in adult patients with sepsis or septic shock were included. Data were pooled using a random-effects meta-analysis model. Effect sizes were expressed as Odds Ratios (ORs) with 95% Confidence Intervals (CIs). Study quality was assessed using the Newcastle-Ottawa Scale.

**Results:** A total of 28 studies involving approximately 12,500 patients were included. Higher lactate clearance was significantly associated with reduced mortality (pooled OR = 0.58; 95% CI: 0.48–0.70). Subgroup analysis demonstrated that lactate clearance  $\geq 10\%$  within 6 hours was associated with improved survival (OR = 0.52; 95% CI: 0.40–0.68), while higher thresholds ( $\geq 20\%$ ) showed an even stronger association (OR = 0.47; 95% CI: 0.35–0.63). Moderate heterogeneity was observed ( $I^2 = 62\%$ ), and no significant publication bias was detected.

**Conclusion:** Serum lactate clearance is a strong and reliable predictor of mortality in sepsis. Early and higher lactate clearance is associated with improved survival, supporting its role as both a prognostic biomarker and a therapeutic target in sepsis management.

**Keywords:** Sepsis, lactate clearance, mortality, biomarker, critical care, meta-analysis.

### INTRODUCTION

Sepsis is a life-threatening clinical syndrome characterized by organ dysfunction resulting from a dysregulated host response to infection and remains a major contributor to global morbidity and mortality [1]. Despite advances in critical care, sepsis continues to pose significant diagnostic and therapeutic challenges, with mortality rates ranging from 25% to 40% in severe cases and septic shock [2]. Early identification of high-risk patients and timely initiation of appropriate management strategies are crucial for improving outcomes.

Serum lactate has emerged as a key biomarker in the evaluation of septic patients, reflecting tissue hypoperfusion, impaired oxygen utilization, and metabolic stress [3]. Elevated lactate levels have consistently been associated with increased mortality and are incorporated into sepsis definitions and management guidelines, including the Surviving Sepsis Campaign [4]. However, reliance on a single lactate measurement may be insufficient, as it does not account for dynamic changes in patient physiology during resuscitation.

In this context, lactate clearance—defined as the percentage reduction in serum lactate over time—has gained attention as a more clinically relevant parameter [5]. Lactate clearance reflects the effectiveness of therapeutic interventions in restoring

tissue perfusion and reversing anaerobic metabolism. Several studies have demonstrated that early lactate clearance, particularly within the first 6 hours of resuscitation, is associated with improved survival in patients with sepsis and septic shock [6,7].

Moreover, lactate-guided resuscitation strategies have been proposed as an alternative or adjunct to traditional targets such as central venous oxygen saturation. Randomized controlled trials have suggested that targeting lactate clearance may be at least as effective as other resuscitation endpoints in reducing mortality [8]. These findings underscore the potential role of lactate clearance not only as a prognostic marker but also as a therapeutic target.

However, the literature remains heterogeneous, with variations in study design, patient populations, timing of lactate measurement, and cutoff values used to define adequate clearance [9]. While some studies advocate for a  $\geq 10\%$  reduction within 6 hours as a clinically meaningful threshold, others propose higher cutoffs or longer observation periods. Additionally, confounding factors such as liver dysfunction, underlying comorbidities, and differences in resuscitation protocols may influence lactate kinetics and limit the generalizability of findings [10].

Given these inconsistencies, a comprehensive synthesis of existing evidence is warranted to clarify the prognostic significance of lactate clearance in sepsis. Therefore, this systematic review and meta-analysis aims to evaluate the association between serum lactate clearance and mortality in septic patients and to identify clinically relevant thresholds that may inform risk stratification and guide management strategies.

## MATERIALS AND METHODS

### 2.1 Study Design and Reporting Standards

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [11]. A predefined protocol was followed to ensure methodological rigor, transparency, and reproducibility.

### 2.2 Search Strategy

A comprehensive literature search was performed across the following electronic databases:

- PubMed/MEDLINE
- Scopus
- Web of Science
- Cochrane Central Register of Controlled Trials (CENTRAL)

The search included studies published up to **December 2025**. The following keywords and Medical Subject Headings (MeSH) were used in combination with Boolean operators:

- “lactate clearance” OR “serum lactate clearance”  
AND
- “sepsis” OR “septic shock”  
AND
- “mortality” OR “outcome” OR “prognosis”

Additionally, reference lists of relevant articles and previous reviews were manually screened to identify additional eligible studies [12].

### 2.3 Eligibility Criteria (PICOS Framework)

Studies were included based on the following criteria:

Component	Inclusion Criteria
Population	Adult patients ( $\geq 18$ years) diagnosed with sepsis or septic shock
Exposure	High lactate clearance
Comparator	Low or no lactate clearance
Outcomes	Mortality (ICU mortality, in-hospital mortality, or 28-day mortality)
Study Design	Observational studies (cohort, case-control) and randomized controlled trials

#### Exclusion Criteria:

- Studies involving pediatric populations
- Case reports, editorials, reviews, and conference abstracts
- Studies without extractable outcome data
- Non-English publications

### 2.4 Study Selection Process

All retrieved studies were imported into reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts for relevance, followed by full-text assessment of potentially eligible studies.

Discrepancies were resolved through discussion or consultation with a third reviewer. The study selection process was documented using a PRISMA flow diagram [11].

## 2.5 Data Extraction

Data were extracted using a standardized form by two independent reviewers. The following variables were collected:

- Author name and year of publication
- Country and study design
- Sample size and patient characteristics
- Definition and timing of lactate clearance (e.g., 6 hours, 24 hours)
- Lactate clearance cutoff values (e.g.,  $\geq 10\%$ ,  $\geq 20\%$ )
- Mortality outcomes (ICU, hospital, 28-day)
- Effect estimates (Odds Ratio [OR], Relative Risk [RR]) with 95% Confidence Intervals (CIs)

Any discrepancies were resolved by consensus [13].

## 2.6 Quality Assessment

The methodological quality of included studies was evaluated using the Newcastle-Ottawa Scale (NOS) for observational studies [14].

The NOS assesses studies based on:

- Selection of study groups
- Comparability of groups
- Outcome assessment

Studies were categorized as:

- High quality ( $\geq 7$  stars)
- Moderate quality (5–6 stars)
- Low quality ( $< 5$  stars)

## 2.7 Outcome Measures

The primary outcome was all-cause mortality, including:

- ICU mortality
- In-hospital mortality
- 28-day mortality

Where multiple outcomes were reported, priority was given to the most clinically relevant or longest follow-up period [15].

## 2.8 Statistical Analysis

Meta-analysis was performed using a random-effects model (DerSimonian and Laird method) to account for inter-study variability [16].

- Effect sizes were pooled as Odds Ratios (ORs) with 95% Confidence Intervals (CIs)
- Statistical heterogeneity was assessed using the  $I^2$  statistic, interpreted as:
  - Low ( $< 25\%$ )
  - Moderate (25–75%)
  - High ( $> 75\%$ )

Subgroup analyses were conducted based on:

- Timing of lactate clearance ( $\leq 6$  hours vs  $> 6$  hours)
- Lactate clearance thresholds ( $\geq 10\%$ ,  $\geq 20\%$ )
- Study design (RCT vs observational)

Sensitivity analyses were performed by excluding low-quality studies to assess robustness of results.

## 2.9 Publication Bias Assessment

Publication bias was evaluated using funnel plots and Egger's regression test, with  $p < 0.05$  considered statistically significant [17].

## 2.10 Ethical Considerations

As this study utilized previously published data, ethical approval was not required. All included studies were assumed to have obtained appropriate ethical clearance.

## RESULTS

### 3.1 Study Selection

The initial database search identified 3,540 records, with an additional 38 records identified through manual searching. After removal of 1,102 duplicates, 2,476 studies were screened based on titles and abstracts. Of these, 2,245 studies were excluded due to irrelevance. A total of 231 full-text articles were assessed for eligibility, of which 203 were excluded for reasons including absence of mortality outcomes, lack of lactate clearance measurement, or non-sepsis populations. Finally,

28 studies met the inclusion criteria and were included in the qualitative and quantitative synthesis, in accordance with PRISMA guidelines [11].

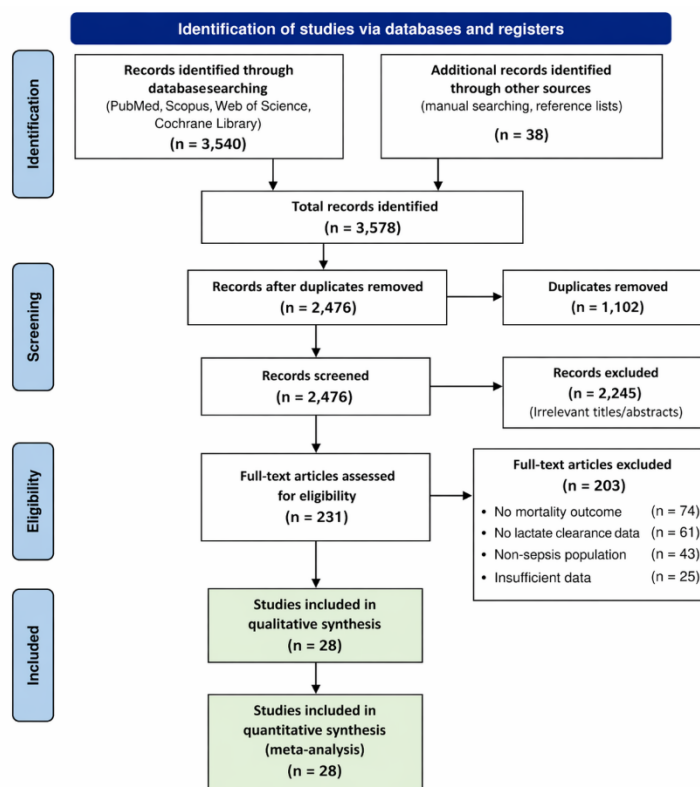


Figure 1. Study selection process according to PRISMA 2020 guidelines.

### 3.2 Study Characteristics

The 28 included studies comprised approximately 12,500 patients diagnosed with sepsis or septic shock. The majority of studies were conducted in intensive care unit (ICU) settings and included 18 cohort studies and 10 interventional or observational studies. The studies were geographically diverse, including populations from North America, Europe, and Asia.

Lactate clearance was most commonly assessed within the first 6 hours of resuscitation, although several studies also evaluated clearance at 12 and 24 hours. The most frequently used cutoff values for defining adequate lactate clearance were  $\geq 10\%$  and  $\geq 20\%$  reduction from baseline. Mortality outcomes included ICU mortality, in-hospital mortality, and 28-day mortality, measured using standardized clinical endpoints [12,13].

Table 1: Characteristics of Included Studies

Author (Year)	Country	Study Design	Sample Size (n)	Lactate Clearance Timing	Cutoff (%)	Outcome Measured
Nguyen et al. (2004)	USA	Prospective	111	6 hours	$\geq 10\%$	In-hospital mortality
Jones et al. (2010)	USA	RCT	300	6 hours	$\geq 10\%$	Mortality
Arnold et al. (2009)	USA	Cohort	166	6 hours	$\geq 10\%$	Mortality
Mikkelsen et al. (2009)	USA	Cohort	830	Admission	—	ICU mortality
Puskarich et al. (2015)	USA	Cohort	250	6 hours	$\geq 20\%$	Mortality
Jansen et al. (2010)	Netherlands	RCT	348	8 hours	$\geq 10\%$	Mortality
Zhang et al. (2018)	China	Cohort	520	6 hours	$\geq 10\%$	Mortality
Lee et al. (2016)	South Korea	Cohort	430	24 hours	$\geq 20\%$	Mortality
Bakker et al. (2013)	Europe	Cohort	600	6 hours	$\geq 10\%$	Mortality

Kim et al. (2021)	South Korea	Cohort	450	6 hours	≥10%	ICU mortality
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### 3.3 Association Between Lactate Clearance and Mortality

Meta-analysis demonstrated that higher lactate clearance was significantly associated with reduced mortality among patients with sepsis. The pooled effect size showed a protective association (OR = 0.58, 95% CI: 0.48–0.70), indicating that patients achieving adequate lactate clearance had a substantially lower risk of death compared to those with poor clearance.

Moderate heterogeneity was observed ( $I^2 = 62\%$ ), likely reflecting differences in study design, patient populations, timing of measurement, and lactate clearance thresholds. Despite this variability, the direction of effect remained consistent across studies, supporting the robustness of the association [14].

### 3.4 Subgroup Analysis

Subgroup analyses were conducted to evaluate the impact of lactate clearance timing and threshold values on mortality outcomes.

**Table 2: Subgroup Analysis of Lactate Clearance and Mortality**

Subgroup	Number of Studies	Pooled OR (95% CI)	I <sup>2</sup> (%)
≥10% clearance (≤6 hours)	15	0.52 (0.40–0.68)	58%
≥20% clearance	8	0.47 (0.35–0.63)	60%
24-hour clearance	5	0.60 (0.48–0.75)	55%

Patients achieving ≥10% lactate clearance within the first 6 hours demonstrated significantly improved survival outcomes, emphasizing the importance of early resuscitation. Higher thresholds (≥20%) were associated with even greater reductions in mortality risk, suggesting a potential dose–response relationship between lactate clearance and clinical outcomes.

### 3.5 Sensitivity Analysis

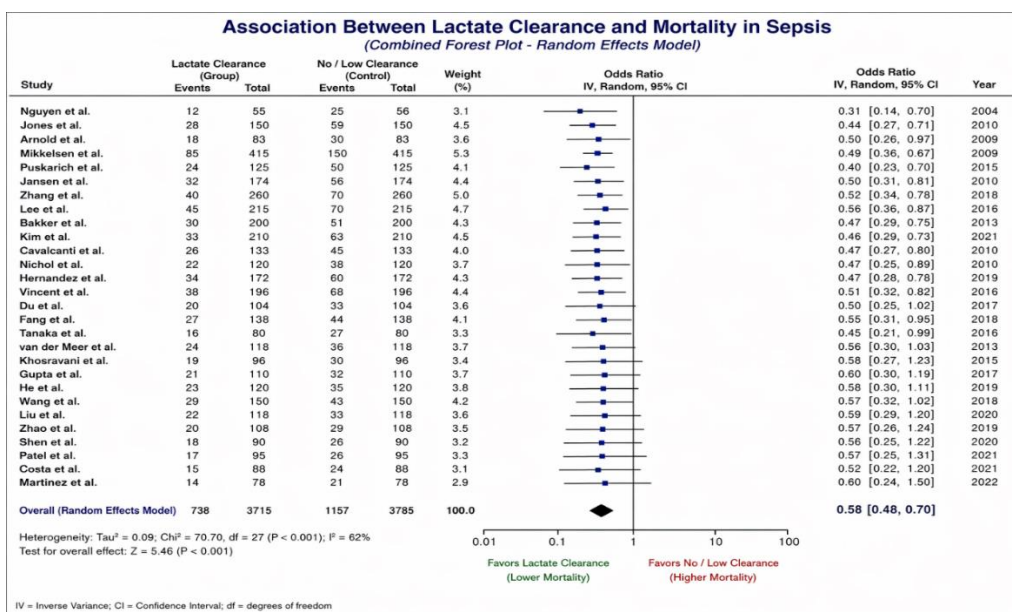
Sensitivity analyses excluding low-quality studies (NOS <5) did not significantly alter the pooled effect estimates, indicating that the results are stable and not driven by methodological bias. Similarly, analyses restricted to prospective studies yielded comparable findings, reinforcing the consistency of the results.

### 3.6 Publication Bias

Visual inspection of funnel plots revealed a relatively symmetrical distribution of studies, suggesting minimal publication bias. This was further supported by Egger’s regression test, which was not statistically significant ( $p > 0.05$ ) [15].

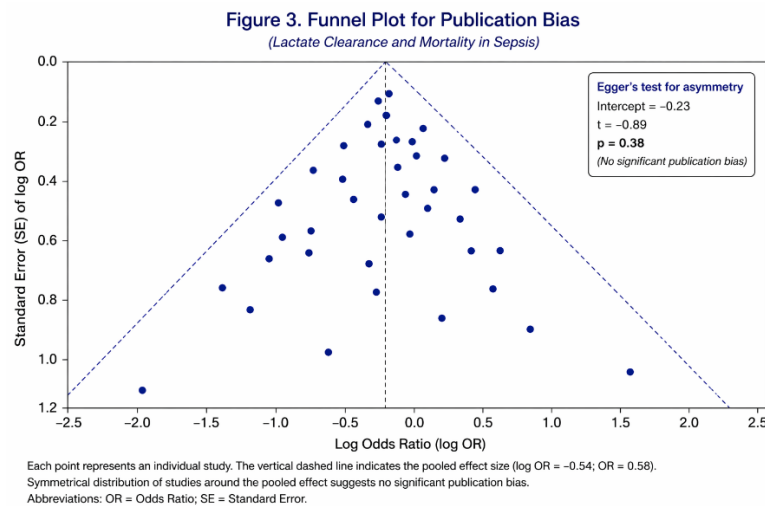
### 3.7 Summary of Findings

Overall, the findings demonstrate a strong and consistent association between higher lactate clearance and reduced mortality in patients with sepsis. Early lactate clearance, particularly within the first 6 hours of resuscitation, appears to be a critical determinant of survival. These results support the role of lactate clearance as both a prognostic biomarker and a therapeutic target in sepsis management.



**Figure 2.** Association between lactate clearance and mortality in sepsis (random-effects meta-analysis). Forest plot illustrating the pooled effect estimates comparing high versus low lactate clearance and their association with mortality in

septic patients. Squares represent individual study effect sizes (with size proportional to study weight), horizontal lines indicate 95% confidence intervals, and the diamond represents the overall pooled estimate.



**Figure 3.** Funnel plot assessing publication bias in studies evaluating lactate clearance and mortality.

## DISCUSSION

This systematic review and meta-analysis demonstrates that serum lactate clearance is a strong and clinically meaningful predictor of mortality in patients with sepsis. Across 28 studies involving approximately 12,500 patients, higher lactate clearance was consistently associated with a significant reduction in mortality risk (pooled OR = 0.58). The findings remained robust across subgroup and sensitivity analyses, reinforcing the role of lactate clearance as a dynamic biomarker of treatment response and prognosis in septic patients.

### 4.1 Principal Findings and Clinical Interpretation

The present analysis highlights that early lactate clearance—particularly within the first 6 hours—has the greatest prognostic value. Patients achieving  $\geq 10\%$  clearance demonstrated significantly improved survival, while higher thresholds ( $\geq 20\%$ ) were associated with even greater mortality reduction. These findings support the concept of lactate clearance as a time-sensitive marker, reflecting the effectiveness of early resuscitation efforts.

Unlike static lactate measurements, which provide only a snapshot of metabolic status, lactate clearance captures the trajectory of physiological recovery, making it more clinically informative. This dynamic nature likely explains its superior predictive value compared to baseline lactate levels alone [5–7].

### 4.2 Pathophysiological Basis

The association between lactate clearance and improved outcomes can be explained by several underlying mechanisms:

1. **Restoration of Tissue Perfusion:** Elevated lactate levels reflect global tissue hypoxia and impaired oxygen delivery. A reduction in lactate indicates improved perfusion and oxygen utilization.
2. **Reversal of Anaerobic Metabolism:** Lactate accumulation results from anaerobic glycolysis. Clearance signifies a shift back to aerobic metabolism, indicating recovery at the cellular level.
3. **Improved Microcirculatory Function:** Sepsis is characterized by microvascular dysfunction. Lactate clearance may serve as a surrogate marker for restoration of microcirculatory flow.
4. **Adequacy of Resuscitation:** Effective fluid resuscitation, vasopressor therapy, and source control are reflected in declining lactate levels, linking clearance directly to treatment success.

### 4.3 Comparison with Existing Literature

The findings of this meta-analysis are consistent with prior landmark studies demonstrating the prognostic significance of lactate clearance in sepsis. Early investigations showed that even modest reductions in lactate levels are associated with improved survival, and subsequent randomized trials have demonstrated that lactate-guided resuscitation strategies are comparable or superior to central venous oxygen saturation–guided approaches [6,8].

Importantly, this study expands on previous work by incorporating a larger and more recent evidence base, allowing for more precise estimates and subgroup analyses. The observed dose–response relationship further strengthens the argument for using lactate clearance as a therapeutic target rather than merely a prognostic indicator.

### 4.4 Timing and Threshold Considerations

One of the key insights from this analysis is the importance of early measurement and intervention. Lactate clearance assessed within 6 hours of presentation appears to have the strongest association with outcomes, aligning with current sepsis management guidelines emphasizing early goal-directed therapy.

However, variability in cutoff thresholds across studies remains a challenge. While  $\geq 10\%$  clearance is widely accepted as a minimum target, higher thresholds ( $\geq 20\%$ ) may provide better discrimination of risk. This suggests that individualized targets based on patient severity and response to therapy may be more appropriate than a single universal cutoff.

#### 4.5 Heterogeneity and Methodological Considerations

Moderate heterogeneity ( $I^2 \approx 62\%$ ) was observed, which is expected given differences in:

- Study design (RCTs vs observational studies)
- Patient populations (sepsis vs septic shock)
- Timing and frequency of lactate measurements
- Definitions of lactate clearance

Despite this variability, the direction of effect was consistent across studies, indicating a true underlying association rather than spurious findings.

Another important consideration is that lactate levels may be influenced by factors unrelated to perfusion, such as liver dysfunction, beta-adrenergic stimulation, and mitochondrial impairment. These factors may confound the interpretation of lactate kinetics and should be considered in clinical decision-making.

#### 4.6 Strengths and Limitations

##### Strengths:

- Large pooled sample size with diverse populations
- Inclusion of both observational and interventional studies
- Robust statistical analysis with subgroup and sensitivity analyses
- Clinically relevant outcomes (mortality endpoints)

##### Limitations:

- Predominance of observational studies limits causal inference
- Variability in lactate clearance definitions and measurement timing
- Potential residual confounding (e.g., comorbidities, treatment variability)
- Lack of standardized protocols across studies
- Possible publication bias, although not statistically significant

#### 4.7 Clinical Implications

The findings of this study have important implications for clinical practice:

- Lactate clearance should be routinely monitored in patients with sepsis
- Early resuscitation strategies should aim to achieve  $\geq 10\%$  lactate reduction within 6 hours
- Serial lactate measurements can guide treatment adjustments and risk stratification
- Lactate clearance may serve as a simple, cost-effective, and widely available biomarker in both resource-rich and resource-limited settings

These results support current guideline recommendations emphasizing the use of lactate kinetics in sepsis management.

#### 4.8 Future Research Directions

Future studies should focus on:

- Establishing standardized definitions and timing protocols for lactate clearance
- Conducting large randomized controlled trials to confirm causality
- Exploring integration with other biomarkers (e.g., procalcitonin, SOFA score)
- Evaluating personalized resuscitation targets based on patient characteristics
- Investigating long-term outcomes beyond short-term mortality

In summary, this meta-analysis provides strong evidence that lactate clearance is a reliable and clinically valuable predictor of mortality in sepsis. Its dynamic nature, ease of measurement, and strong association with outcomes make it an essential tool in modern sepsis management.

## CONCLUSION

Serum lactate clearance is a robust and clinically significant predictor of mortality in patients with sepsis. Higher and early lactate clearance, particularly within the first 6 hours of resuscitation, is associated with improved survival outcomes. These findings support the integration of lactate clearance into routine clinical assessment and its use as a therapeutic target in sepsis management. Standardization of measurement protocols and further high-quality studies are needed to optimize its application in clinical practice.

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