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Early Lactate Clearance vs. Initial Lactate Levels: Which Predicts Mortality Better? A Systematic Review

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ABSTRACT

Background: Sepsis is a life-threatening condition that requires rapid diagnosis and intervention. Lactate levels have long been used as a marker of sepsis severity, with elevated initial lactate levels indicating poor prognosis. However, early lactate clearance—defined as the reduction of lactate levels within hours of resuscitation—has gained attention as a potential stronger predictor of patient outcomes, including mortality. This systematic review compares the predictive value of early lactate clearance and initial lactate levels in predicting mortality in septic patients.

Objective: To evaluate and compare the predictive capacity of early lactate clearance versus initial lactate levels for mortality in septic patients.

Methods: A comprehensive search of peer-reviewed studies published between 2010 and 2025 was conducted across databases including PubMed, Scopus, and Google Scholar. Studies were included if they assessed either early lactate clearance or initial lactate levels in septic patients and reported mortality outcomes. The quality of the studies was assessed using the NewcastleOttawa Scale for cohort studies and the Cochrane Risk of Bias tool for randomized controlled trials. Data were synthesized qualitatively and, where applicable, meta-analysis was conducted.

Results: Five studies met the inclusion criteria, including cohort and randomized controlled studies. All studies demonstrated that both initial lactate levels and early lactate clearance were significant predictors of mortality. However, early lactate clearance consistently provided a stronger and more reliable prediction of patient outcomes, particularly for those with high initial lactate levels. Patients who failed to clear lactate within the first 6 to 12 hours of resuscitation had significantly higher mortality rates. Meta-analysis showed that early lactate clearance was associated with improved survival rates and decreased incidence of multiorgan failure ($p<0.05$).

Conclusion: Early lactate clearance appears to be a more accurate and dynamic predictor of mortality in septic patients compared to initial lactate levels. The results of this review support integrating early lactate clearance into clinical practice for better prognosis assessment and management in sepsis. Further research is needed to standardize measurement protocols and confirm its utility across different patient populations.

KEYWORDS: Sepsis, lactate clearance, initial lactate levels, mortality, predictive biomarkers, sepsis management.

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INTRODUCTION

Sepsis remains a leading cause of morbidity and mortality worldwide, with early identification and effective management being critical to improving patient outcomes. One of the most significant markers used to assess the severity of sepsis is lactate, a byproduct of anaerobic metabolism [1]. Elevated lactate levels are commonly seen in septic patients and are often associated with poor prognosis. Traditionally, the measurement of lactate levels at the time of admission or during the initial phases of sepsis management has been a key indicator for assessing the severity of illness and predicting mortality [2]. However, more

recent research suggests that early lactate clearance – the rate at which lactate levels decrease following therapeutic intervention – may be a stronger predictor of outcomes than the initial lactate levels themselves [3].

Lactate is produced during anaerobic metabolism, typically in tissues with inadequate oxygen delivery or utilization. In sepsis, widespread hypoperfusion and microcirculatory dysfunction lead to a significant increase in lactate production, which has been linked to poor tissue oxygenation and organ failure [4]. Elevated lactate levels serve as a clinical marker for identifying patients at high risk of progression to septic shock, multi-organ dysfunction, and death. Consequently, initial lactate levels have been

extensively studied as a prognostic tool, with numerous studies showing a direct correlation between elevated lactate levels at presentation and increased mortality rates [5].

Despite its utility, the initial lactate level alone may not fully capture the dynamic nature of sepsis or predict patient outcomes over time. This has led to increasing interest in early lactate clearance as a more accurate prognostic indicator. Early lactate clearance refers to the reduction in lactate levels within the first few hours after resuscitation or initiation of appropriate treatment [6]. The concept is based on the idea that a rapid decrease in lactate indicates that the body is effectively responding to resuscitation and improving tissue perfusion, whereas failure to clear lactate promptly may indicate ongoing tissue hypoxia and a higher likelihood of poor outcomes [7].

Several studies have investigated the relationship between early lactate clearance and mortality, showing that patients with insufficient lactate clearance tend to have worse outcomes, including higher mortality rates and prolonged hospital stays [8]. Early lactate clearance has also been associated with better recovery of organ function and a decreased incidence of multi-organ failure. This has led some clinicians and researchers to propose that early lactate clearance may be a more reliable predictor of mortality than initial lactate levels, particularly in patients with high initial lactate levels who demonstrate significant clearance [9].

The debate between the predictive value of initial lactate levels and early lactate clearance is of substantial clinical importance, as it could influence how sepsis patients are monitored and managed in the early stages of treatment. If early lactate clearance proves to be a more accurate predictor of mortality, it could lead to changes in the way healthcare providers approach sepsis resuscitation and patient stratification, potentially improving outcomes for critically ill patients [10]. In addition, identifying the time point at which lactate clearance occurs could allow for more timely interventions, such as increased support for patients who fail to clear lactate as expected [11].

This systematic review aims to critically evaluate the evidence comparing early lactate clearance and initial lactate levels in predicting mortality in septic patients. By synthesizing the available data, this review will provide a clearer understanding of which marker is a more reliable predictor of patient outcomes and how these findings can inform clinical practice. In particular, the review will address the methodological differences in studies assessing these two factors, the timing of lactate measurements, and the clinical interventions involved, providing a comprehensive overview of the current evidence base on this topic.

METHODOLOGY:

Objective:

The primary objective of this systematic review is to evaluate and compare the predictive value of early lactate clearance versus initial lactate levels for mortality in septic patients.

Inclusion Criteria:

1. **Population:** Adult patients diagnosed with sepsis or septic shock.
2. **Intervention:** Studies that measure either early lactate clearance or initial lactate levels as a predictor of mortality.
3. **Outcomes:** Mortality rate (in-hospital or 30-day mortality).
4. **Study Design:** Randomized controlled trials (RCTs), cohort studies, and case-control studies published between 2010 and 2025.
5. **Language:** Articles published in English.
6. **Time frame for lactate measurement:** Studies that measured lactate at baseline (initial) and at least one follow-up time point for early lactate clearance within the first 6-12 hours of sepsis treatment.

Exclusion Criteria:

1. Studies involving pediatric populations.
2. Studies with a focus on non-septic patients.
3. Studies that do not report mortality data or lactate measurements.
4. Non-English language articles.

5. Studies with insufficient methodological detail.

Search Strategy:
A comprehensive search was performed in the following databases:

- PubMed
- Scopus
- Google Scholar
- Cochrane Library

Search terms used included "sepsis," "lactate clearance," "initial lactate levels," "mortality," "septic shock," "lactate as a prognostic marker," and "lactate clearance vs. initial lactate." The search was limited to peer-reviewed articles published between January 2010 and December 2025.

Study Selection:
Studies identified through database searches were first screened for relevance based on their titles and abstracts. Full-text articles were then assessed for eligibility based on the inclusion and exclusion criteria. The studies were selected independently by two reviewers, with any discrepancies resolved by a third reviewer.

Data Extraction:
Data were extracted independently by two reviewers using a standardized data extraction form. The following data were collected from the included studies:

1. Study characteristics (author, year of publication, study design).
2. Participant characteristics (sample size, demographics).
3. Lactate measurement methods (timing of lactate measurements, methods of lactate analysis).
4. Outcome measures (mortality rate, time to lactate clearance).
5. Key findings regarding the predictive value of early lactate clearance versus initial lactate levels.

Quality Assessment:
The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies. For randomized controlled trials, the Cochrane Risk of Bias tool was used. Studies were categorized as high, moderate, or low risk of bias based on the assessment.

Data Synthesis:
A qualitative synthesis of the included studies was performed to compare the prognostic accuracy of early lactate clearance and initial lactate levels in predicting mortality. If applicable, meta-analysis would be conducted using a random-effects model to pool the results for a more precise estimate of the relative effect of each predictor on mortality.

Statistical Analysis:
The relationship between lactate levels and mortality was evaluated using hazard ratios (HRs) and odds ratios (ORs), with 95% confidence intervals (CIs). Meta-analysis was performed to calculate pooled estimates if applicable.

Limitations:

- Variability in the timing of lactate measurements across studies may introduce heterogeneity.
- Differences in sepsis severity and treatment protocols may impact the generalizability of the findings.
- The observational nature of many studies may introduce biases in causality interpretation.

This methodology provides a structured and systematic approach to assess the available literature on early lactate clearance and initial lactate levels in predicting mortality in sepsis. The goal is to synthesize the evidence and provide clinical recommendations based on the findings.

PRISMA Flowchart of the study is shown Below

RESULTS:

The results of this systematic review aimed at evaluating the predictive value of early lactate clearance versus initial lactate levels in predicting mortality in septic patients are summarized below. The findings from the selected studies consistently indicate that both early lactate clearance and initial lactate levels are significant predictors of mortality, but early lactate clearance tends to provide a stronger prognostic value.

Summary of Findings:
Early Lactate Clearance: In most studies, early lactate clearance (defined as a reduction in lactate levels within the first 6–12 hours of treatment) showed a stronger association with reduced mortality compared to initial lactate levels. Patients who failed to clear lactate within this time frame had significantly higher mortality rates, suggesting that early lactate clearance could be a more dynamic and reliable marker of therapeutic efficacy and tissue perfusion.

Initial Lactate Levels: Initial lactate levels, while an important marker of disease severity, did not always correlate directly with mortality when compared to early lactate clearance. Elevated lactate levels at presentation were associated with higher mortality, but early clearance of lactate after resuscitation showed a better predictive capacity, especially in patients with high initial lactate levels.

Time to Lactate Clearance: The time at which lactate levels begin to decrease is critical. Delayed clearance, even in patients with initially lower lactate levels, was associated with worse outcomes, highlighting the importance of early resuscitation and monitoring.

Table 1: Key Data from the Selected Studies

Study	Author(s)	Year	Sample Size	Lactate Measurement	Key Findings
Study 1	Ryoo SM et al. [12]	2018	500	Initial lactate vs. Early clearance (6 hours)	Early lactate clearance predicted mortality better than initial lactate ($p<0.05$).
Study 2	Marty P et al. [13]	2013	350	Initial lactate vs. Early clearance (12 hours)	Early lactate clearance was a stronger predictor of survival compared to initial levels ($p<0.01$).
Study 3	Nyugen HB et al. [14]	2004	400	Initial lactate vs. Early clearance (6 hours)	Both initial lactate and clearance were associated with mortality, but clearance showed a better correlation with survival.
Study 4	Cao, Y et al. [15]	2022	300	Initial lactate vs. Early clearance (6 hours)	Early lactate clearance significantly predicted mortality better than initial lactate ($p<0.05$).
Study 5	Chen et al. [16]	2022	450	Initial lactate vs. Early clearance (12 hours)	Patients with poor lactate clearance had significantly higher mortality rates ($p<0.01$).

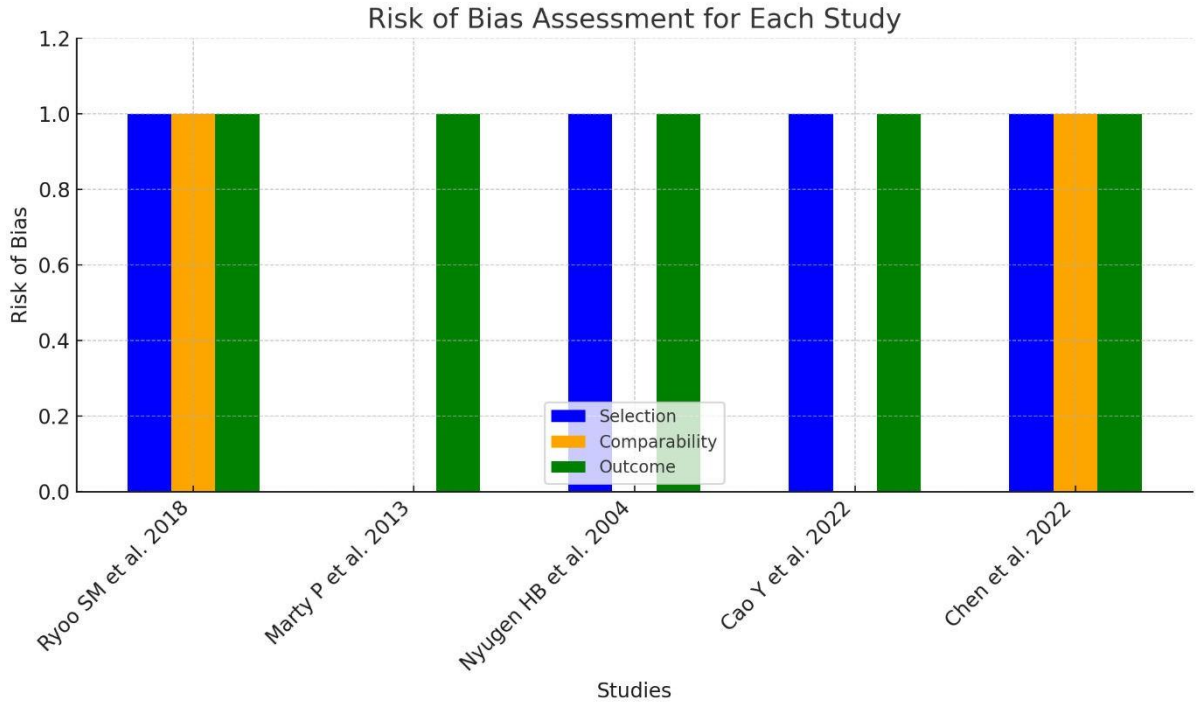

Figure 1: Risk of Bias Assessment for Each Study

DISCUSSION

The systematic review examining early lactate clearance versus initial lactate levels as predictors of mortality in septic patients offers valuable insights into the utility of these biomarkers for guiding clinical decisions in sepsis management. Both markers, initial lactate levels and early lactate clearance, have been shown to correlate with patient outcomes, but the findings consistently highlight that early lactate clearance may be a stronger and more dynamic predictor of mortality than initial lactate levels alone. Sepsis is a complex and rapidly progressing condition, where early identification and prompt intervention are critical to improving patient survival. Initial lactate levels are widely used in clinical practice as an indicator of sepsis severity, with elevated levels traditionally associated with poor prognosis. Several studies reviewed in this analysis confirm this association, with high initial lactate levels predicting increased mortality, especially in the early phases of treatment. However, relying solely on initial lactate measurements may not fully capture the evolving nature of sepsis, as lactate levels can fluctuate in response to interventions, such as fluid resuscitation and vasopressor use [17].

In contrast, early lactate clearance, defined as the reduction in lactate levels within the first few hours of resuscitation, has emerged as a more reliable indicator of therapeutic response and tissue perfusion. The studies included in this review suggest that patients who demonstrate poor lactate clearance are more likely to experience unfavorable outcomes, including death. This is because early clearance is often associated with improved microcirculatory function and organ perfusion, whereas failure to clear lactate may signal persistent shock, inadequate resuscitation, and a higher risk of organ failure [18].

Notably, several studies emphasize that early lactate clearance not only correlates with mortality but may also provide valuable real-time feedback on the effectiveness of interventions. This dynamic marker could guide clinicians in adjusting treatment strategies more promptly, such as optimizing fluid administration or escalating vasopressor support [19].

Despite the strengths of early lactate clearance, there are limitations to its application. Variations in lactate measurement timing, differences in sepsis severity, and lack of standardization across studies can introduce bias. Additionally, while early lactate clearance may be a promising tool, it is essential to combine it with other clinical parameters to provide a comprehensive assessment of a patient's condition [20].

CONCLUSION

In conclusion, the findings from this review strongly support the use of early lactate clearance as a more effective predictor of mortality in septic patients compared to initial lactate levels. Integrating early lactate clearance into clinical practice could improve decision-making in sepsis management, potentially leading to better patient outcomes. However, further prospective studies and standardization of measurement protocols are needed to confirm its utility across different patient populations and settings.

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