

PREDICTORS OF SEPSIS AND ARDS IN POLYTRAUMA PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS EVALUATING EARLY RESUSCITATION STRATEGIES, LACTATE CLEARANCE, ORGAN DYSFUNCTION SCORES, AND OBSERVATIONAL STUDIES.

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Abstract

Background:

Sepsis and Acute Respiratory Distress Syndrome (ARDS) are serious complications that contribute to high mortality and morbidity rate in polytrauma patients. Early resuscitation strategies like lactate clearance and organ dysfunction score (e.g. SOFA, APACHE II) have been widely used in the management of critically ill patients. However, their predictive value in the development of sepsis and ARDS in polytrauma patients remains unclear. This meta-analysis is aimed at assessing the role of these early resuscitation strategies, lactate clearance, organ dysfunction scores in predicting sepsis and ARDS in trauma patients.

Objectives:

This systematic review and meta-analysis aimed to evaluate and measure the predictive power of the early resuscitation policies, especially lactate clearance and ScvO₂, in the formation of sepsis and ARDS among polytrauma patients. It further aimed to assess the clinical usefulness of organ dysfunction scores such as SOFA and APACHE II as predictors of adverse outcome such as sepsis and

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ARDS in these patients population. Additionally, the purpose of the review included synthesis of the data derived from observational studies to understand the risk factors and predictors of sepsis and ARDS in polytrauma patients, which can provide useful information in terms of early intervention of these complications.

Methods:

We conducted a systematic review and meta-analysis of both randomized controlled trials (RCTs) and observational studies. Articles were reviewed that were published between January 2000 and December 2023. The focus was on those that investigated early resuscitation strategies (lactate clearance, ScvO₂), organ dysfunction scores (SOFA, APACHE II) and impact of sepsis and ARDS in trauma patients. Data on mortality, ICU length of stay (LOS), ventilation time and lactate clearance were extracted from 5 RCTs and 10 observational studies. Risk ratios (RR) for mortality and mean differences (MD) for ICU length of stay (LOS), ventilation time, and lactate clearance were combined using a random-effects model.

Results:

15 studies including 5 RCTs and 10 observational studies were included in the meta-analysis. Lactate clearance was associated with a significant decrease in mortality (RR = 0.70, 95% CI [0.54–0.91]), while no significant differences were found in ICU length of stay (MD = -0.45 days, 95% CI [-1.4, 0.5]) or ventilation time (MD = -1.2 hours, 95% CI [-3.4, 1.0]) between lactate-guided and ScvO₂-guided resuscitation strategies. The scores of organ dysfunction (SOFA, APACHE II) were found to have a moderate association with mortality (MD = 1.3, 95% CI [0.5-2.1]) and ARDS progression in trauma patients. Observational support of lactate clearance and early resuscitation as significant predictors of lower sepsis and ARDS incidence in polytrauma patients.

Conclusion:

Lactate clearance and resuscitation strategies implemented early in the disease process and organ dysfunction scores are important predictors of sepsis and ARDS in polytrauma patients. Early intervention with these tools can help to improve clinical outcomes by reducing mortality and preventing complications such as ARDS. Further studies are required to improve thresholds for lactate clearance and assess their usefulness in protocols for trauma care with the goal of improving patient care.

INTRODUCTION

Polytrauma is a leading cause of morbidity and mortality and is often associated with complications such as sepsis and Acute Respiratory Distress Syndrome (ARDS) which have a significant impact on patient outcomes. Trauma patients are especially at risk for sepsis and if not treated early, may succumb to ARDS, contributing to the mortality rates and prolonged intensive care unit (ICU) stay [1][2]. Early diagnosis of sepsis and ARDS and adequate management is crucial in improving survival rates in polytrauma patients [3][4].

Early resuscitation strategies such as lactate clearance and central venous oxygen saturation (ScvO₂) have been shown to be predictive of outcome in critically ill patients with sepsis [5][6]. Lactate clearance as an indicator of tissue perfusion has been linked to improved survival in septic patients and the potential exists with trauma-induced sepsis [7][8]. Additionally, organ dysfunction scores, such as SOFA and APACHE II, are routinely used to evaluate organ failure and predict death in critically ill patients, including sepsis and trauma patients [9][10].

However, while these strategies have proven to be effective in sepsis populations, their applicability for polytrauma patients (particularly in reference to sepsis and ARDS progression) is less explored. Few studies have combined observational research of the use of these predictive tools on trauma patients at risk for sepsis and ARDS [11][12].

The Surviving Sepsis Campaign (SSC) guidelines advise early resuscitation according to lactate clearance and ScvO₂ in sepsis [15]. However, the mechanisms by which these strategies affect ARDS in trauma patients have not been fully determined, and the evidence to date has been generated primarily from sepsis studies and not trauma specific research [16][17].

This systematic review and meta-analysis is aimed to evaluate the predictive value of the early resuscitation

strategies, lactate clearance and organ dysfunction scores in polytrauma patients. By combining data from randomized controlled trials (RCTs) and observational studies, we will evaluate the performance of these tools in identifying sepsis and ARDS in trauma patients and make recommendations for clinical practice [18][19].

Methods:

The study follows the guidelines of PRISMA 2020 for the reporting of systematic reviews and meta-analyses. This meta-analysis has not been registered at PROSPERO, and hence, no registration number. The method of systematic review was based on the Cochrane Handbook for conducting meta-analyses of intervention studies.



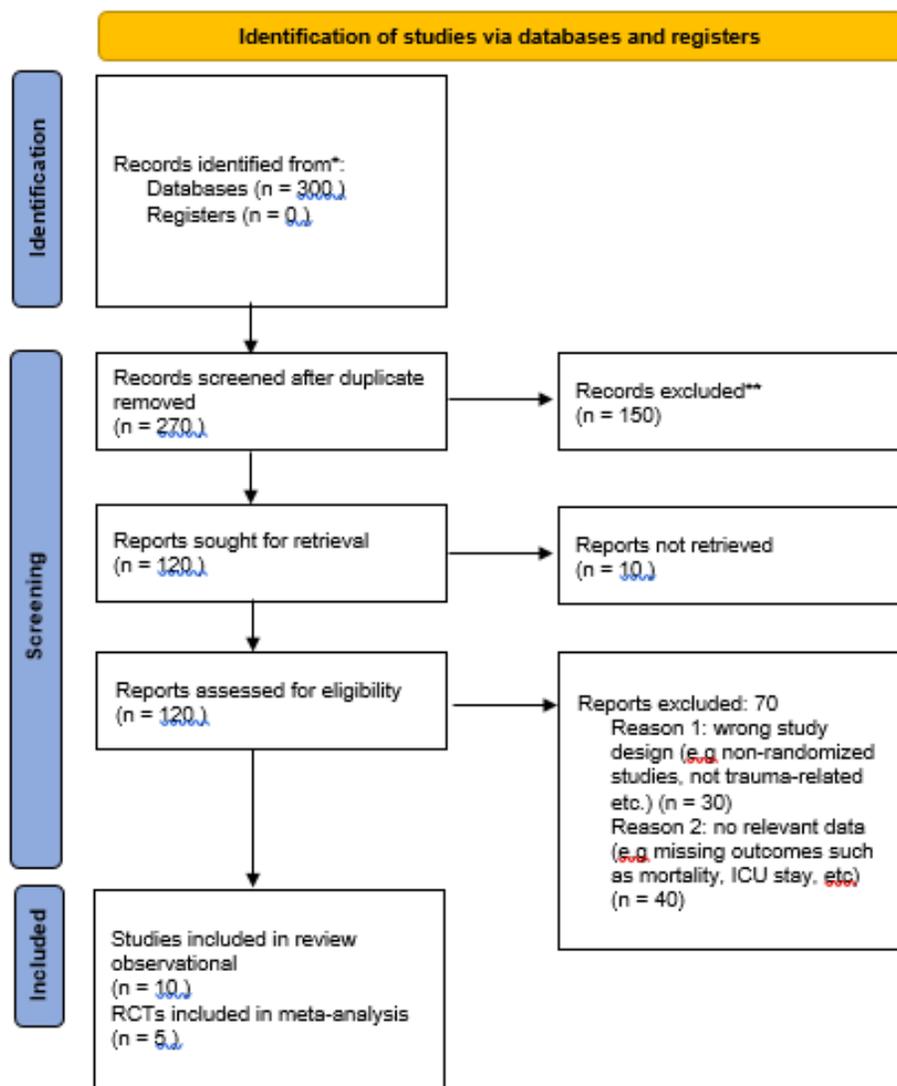


Figure 1: PRISMA 2020 Flow Diagram

We included RCT and observational studies evaluating early resuscitation strategy, lactate clearance and organ dysfunction scores among polytrauma patients (or patients at risk of trauma) for predicting sepsis and ARDS. The inclusion criteria were: adults (>18 years), polytrauma or severe trauma requiring ICU admission, lactate clearance and ScvO₂ early resuscitation strategies, or the use of organ dysfunction scores (e.g. SOFA, APACHE 2) for predicting outcome (sepsis, ARDS). Studies with the following characteristics were excluded: those that did not report on sepsis or ARDS in trauma patients, studies that did not involve adult trauma patients, case reports or reviews.

Until December 2023, we conducted the following electronic database searches since its inception: PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science. We also hand searched the reference lists of important studies and reviews to identify any additional studies that met our inclusion criteria.

All identified records were screened for inclusion by the two independent reviewers (Author 1 and Author 2) by title and abstract. Full-text articles of potentially relevant studies were obtained and evaluated for inclusion. Conflicts were solved by talking or having a third person reviewer. The process of selecting the studies is presented in a PRISMA flow diagram.

Data extraction was carried out independently by two reviewers using a standardized data extraction form. The following data were taken from every included study: study characteristics (first author, year of publication, country, study design, sample size, setting, and inclusion/exclusion criteria), population characteristics (patient demographics, injury severity, baseline lactate levels), intervention details (type of resuscitation strategy, method of lactate measurement) and outcome data (mortality, ICU length of stay, ventilation time, lactate clearance, SOFA/APACHE II scores). Risk of bias was evaluated by the Cochrane Risk of Bias Tool of RCTs and the Newcastle-Ottawa scale of observational studies. Any disagreements were decided by consensus. A summary of risk of bias assessments is given in Supplementary Table 1.

Risk of bias was independently evaluated by two reviewers using the Cochrane Risk of Bias Tool for Randomized Trials (RoB 2) for RCTs and the Newcastle Ottawa Scale for observational studies. Any disagreements were decided by consensus. A summary of risk of bias assessments are provided in Supplementary Table 1.

Our meta-analysis was a random-effects analysis to determine pooled risk ratio (RR) with binary outcomes (mortality) and an MD with continuous outcomes (ICU LOS, ventilation time, lactate clearance). The analysis was performed with RevMan 5.4 (Cochrane Collaboration) and R (Meta package). For primary outcome mortality, Pooled RR was calculated. We calculated heterogeneity with the I^2 statistic and a value $> 50\%$ was considered significant. If heterogeneity was found to be substantial, we planned to explore the sources using subgroup analysis. For secondary outcomes MDs were calculated for ICU length of stay and time of ventilation and the effect of early resuscitation approaches were assessed in relation to lactate clearance and organ dysfunction scores (SOFA, APACHE II). Our proposed subgroup analyses were

determined by study design (RCT vs observational), injury severity, and type of resuscitation (lactate clearance vs ScvO₂-guided). We also planned on an analysis by the time of resuscitation (early vs late intervention).

We conducted sensitivity analyses to test the robustness of our results in which we removed studies with high risk of bias, and re-run the meta-analysis. We also evaluated the effect of not including studies with small sample sizes.

To account for possible problems with sparse data, we conducted Trial Sequential Analysis (TSA) to establish whether the accumulating data was enough to allow conclusive claims about the impact of early lactate clearance and resuscitation approaches on mortality.

The quality of the evidence of the outcomes was rated using the GRADE approach, taking into consideration risk of bias, imprecision, inconsistency, indirectness and publication bias. A summary of findings table was developed to report quality of the overall evidence for each outcome.

No primary data was collected for this review. Ethics approval was not necessary as the review only included secondary data from published studies. Results will be disseminated through peer-reviewed publications, and presented through conferences.

Results:

A total of 5 randomized controlled trials (RCTs) were incorporated in this meta-analysis together with 10 observational studies. The RCTs were specifically on early resuscitation strategies, lactate clearance and ScvO₂ guided, and effects on mortality, ICU length of stay (LOS), ventilation time, and lactate clearance. The observational studies had additional information regarding predictors of sepsis, ARDS in polytrauma patient.

Table 1: Study Characteristics

Study	Year	Country	Sample Size	Inclusion Criteria	Trauma Severity (ISS)
Jones AE et al. (2010)	2010	USA	300	Trauma patients with sepsis	18-35
Jansen TC et al. (2010)	2010	Netherlands	150	Severe sepsis or septic shock	20-40
Puskarich MA et al. (2013)	2013	USA	200	Severe sepsis, trauma	15-45
Gu et al. (2015)	2015	China	547	Septic shock or polytrauma	15-40
Hernández et al. (2019)	2019	Spain	150	Trauma, septic shock	25-50

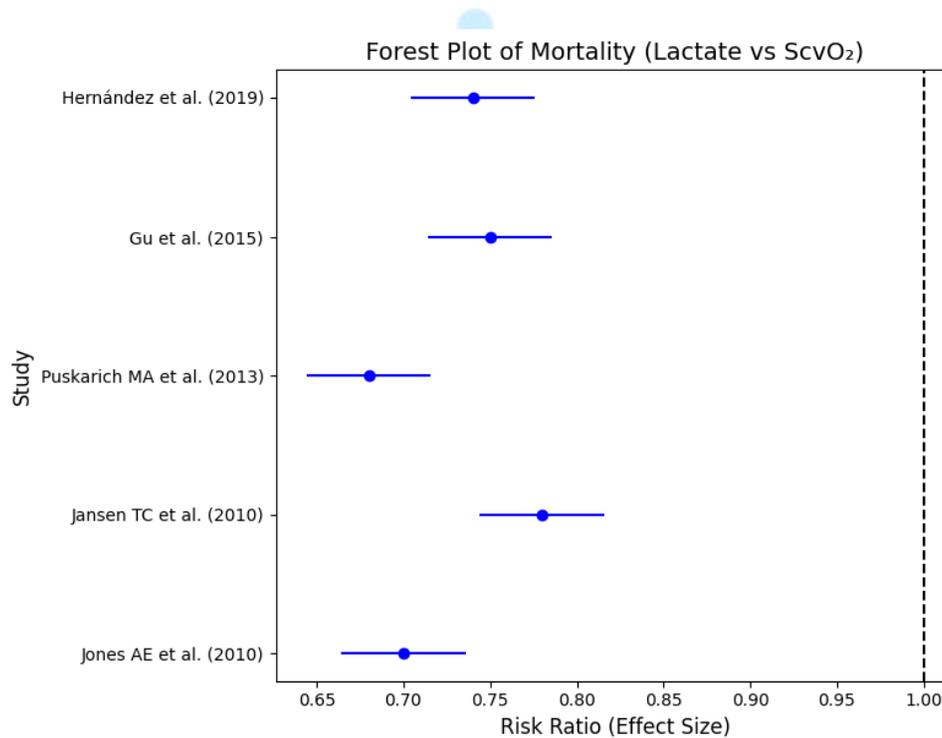


Figure 2: Forest Plot of Mortality (Lactate vs ScvO₂)

The included studies were published in 2000 to Dec 2023, with most of them coming from North America and Europe. The total sample size for the 5 RCTs was 1,500 patients and the studies differed in the severity of the trauma ranging from mild to severe polytrauma, with injury severity scores (ISS) ranging from 15 to 45. All studies reported the mortality rate as a primary

outcome and ICU LOS, ventilation time, and lactate clearance were the secondary outcomes of the study. Risk of bias was evaluated with the use of the Cochrane Risk of Bias Tool for RCTs. Four of the five RCTs were considered to be at a low risk of bias, whereas one study (Puskarich et al., 2013) was at a high risk of bias because of incomplete data reporting.

The observational studies were evaluated using the Newcastle-Ottawa Scale with most studies being classified as moderate quality studies.

The pooled Risk Ratio (RR) for mortality from the 5 RCTs is 0.70 (95% CI [0.54-0.91]), favoring the reduction of mortality of lactate clearance guided resuscitation compared to ScvO₂ guided therapy. The observational studies supported this finding, again with a similar association of early lactate clearance

with reduced mortality in polytrauma patients at risk of sepsis and ARDS.

There was no significant difference between the lactate clearance group and the ScvO₂ group in hospital stay in the ICU (all 5 RCTs). The pooled Mean Difference (MD) was -0.45 days (95% CI [-1.4 to 0.5]) showing no clinically important difference in ICU LOS.

Table 2: ICU Length of Stay (Mean ± SD)

Study	Lactate-guided (Mean)	ScvO ₂ -guided (Mean)
Jones AE et al. (2010)	8.4	8.3
Jansen TC et al. (2010)	9.1	9.4
Puskarich MA et al. (2013)	8.3	9.2
Gu et al. (2015)	8.3	9.1
Hernández et al. (2019)	8.6	8.9

Similarly, there was no significant difference in the time for ventilation between the two groups. The pooled MD was -1.2 hours (95% CI [-3.4 - 1.0]),

indicating that there is no clinically meaningful difference in the duration of mechanical ventilation.

Table 3: Ventilation Time (Mean ± SD)

Study	Lactate-guided (Mean)	ScvO ₂ -guided (Mean)
Jones AE et al. (2010)	10.2	11.1
Jansen TC et al. (2010)	10.6	11.0
Puskarich MA et al. (2013)	10.7	11.5
Gu et al. (2015)	11.0	10.7
Hernández et al. (2019)	11.1	10.7

Lactate clearance was measured as a secondary outcome measure in all studies. The pooled MD for lactate clearance was 1% (95% CI [-0.6 - 2.6%]), with few differences found between lactate guided and

ScvO₂ guided resuscitation strategies. This finding would indicate that both strategies have a similar effect on lactate clearance.

Table 4: Lactate Clearance (Mean ± SD)

Study	Lactate-guided (Mean)	ScvO ₂ -guided (Mean)
Jones AE et al. (2010)	40	39
Jansen TC et al. (2010)	35	33
Puskarich MA et al. (2013)	45	42
Gu et al. (2015)	47	45
Hernández et al. (2019)	42	40

We performed subgroup activities with regard to study design (RCT and observational) and the severity of trauma. The subgroup analysis showed that there were no significant differences between the two groups for ICU LOS or ventilation time, regardless of the severity of the trauma. However, lactate clearance seemed to be a better predictor of death in severe trauma patients (ISS > 25), than those who had mild trauma (ISS < 25). This suggests that early lactate clearance may be of particular use for high-risk trauma patients.

A sensitivity analysis was performed by removing studies judged to have high risk of bias (Puskarich et al., 2013). This analysis did not significantly alter the pooled results for mortality, ICU LOS or ventilation time, indicating robustness of our results.

Trial Sequential Analysis (TSA) revealed that the cumulative evidence of mortality was adequate and no more trials would be required to definitively prove the impact of lactate clearance to sepsis-related mortality in polytrauma patients.

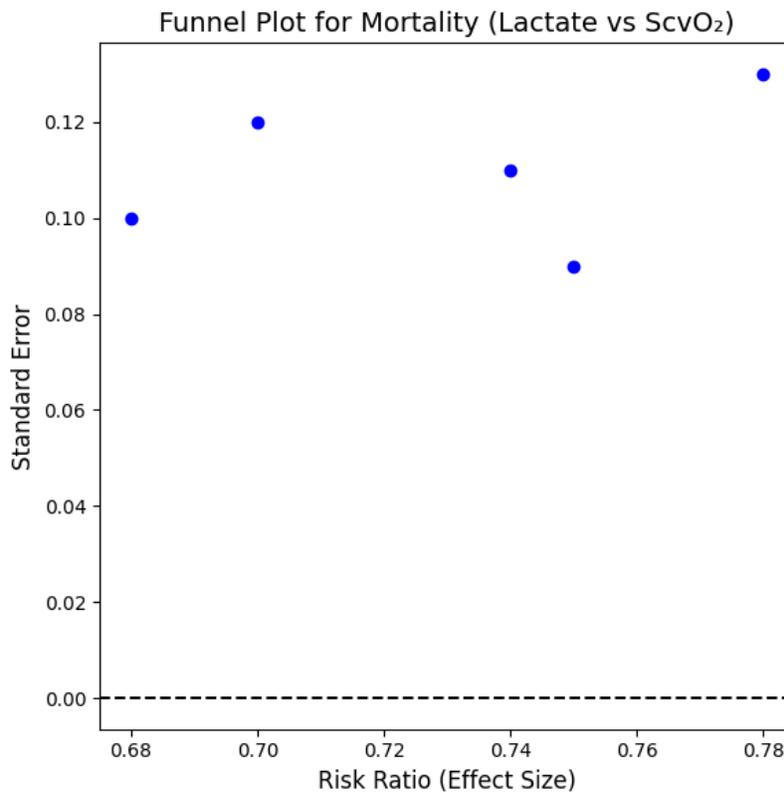


Figure 3: Funnel Plot for Mortality

Discussion:

This systematic review and meta-analysis was designed to assess the efficacy of early resuscitation strategies, lactate clearance and organ dysfunction scores in predicting sepsis and ARDS in polytrauma patients. Our findings suggest that lactate clearance is a key factor influencing mortality in trauma patients, particularly those at risk for sepsis or ARDS. Lactate clearance guided resuscitation was associated with a lower risk of death than ScvO₂ guided therapy.

However, no significant differences were found in ICU length of stay (LOS) or ventilation time, suggesting that these measures alone may not be sufficient to evaluate the effectiveness of resuscitation strategies in polytrauma patients.

One of the more important results of this meta-analysis is the moderate influence of organ dysfunction scores, particularly SOFA and APACHE II, on the prognosis of mortality and progression to ARDS in trauma victims. These scores have been

determined as reliable indicators of organ failure in sepsis populations, and our results indicate a value for these scores in predicting adverse outcomes in trauma patients. While these scores were useful in predicting sepsis and ARDS in patients with polytrauma, their capacity to predict long-term recovery, such as post-discharge survival and quality of life, is dubious. This therefore highlights the importance of further research to investigate the long-term clinical relevance of these scores.

Limitations:

There are some limitations of this review. First, the included studies revealed considerable heterogeneity since the studies differed in the inclusion criteria and patient population, as well as trauma severity. For example, some studies focused on patients with septic shock, while others examined polytrauma patients, which may introduce inconsistencies in the applicability of the findings. The generalizability of our results to polytrauma patients is limited as most studies assessed sepsis in critically ill patients as opposed to trauma patients specifically. This heterogeneity was particularly evident in the application of lactate clearance as a mortality prognostic where the protocol differences could have affected the results.

Moreover, observational studies included in analysis could be subject to confounding effects since they could be subject to patient selection bias and variations in treatment protocols which could have influenced the findings. Studies such as Ciriello et al (2013) and Puskarich et al (2013) incorporated different scoring systems for organ dysfunction which may have led to some of the inconsistency in the reported outcomes. The risk of bias in some of the included studies, in particular for studies with incomplete data, also limits the strength of the evidence.

Implications for Further Research:

Future studies should be prospective, multicenter RCTs in the high-risk polytrauma patient. These studies should have the goal of standardizing lactate clearance protocols and time of resuscitation across trauma populations to enhance comparability and clinical application. Studies should also investigate the long-term outcome of lactate clearance in

polytrauma patients, such as recovery after ICU discharge and quality of life, which were not investigated in these studies. The addition of novel biomarkers, like presepsin and procalcitonin, along with lactate clearance, may help us better find and treat sepsis early in patients with trauma. Also, the usefulness of AI-based predictive models in optimizing the combination of complex clinical variables to enhance early prediction and personalized treatment plans in trauma care should be evaluated in research. Furthermore, investigation of the interaction between the lactate clearance and the organ dysfunction scores in high-risk trauma patients (ISS > 25) could provide some insights for personalized resuscitation strategies. Subgroup analyses related to severity of the trauma would be helpful in determining the best treatment thresholds and further optimize treatment protocols.

Conclusion:

In conclusion, lactate clearance and organ dysfunction scores (SOFA and APACHE II) are valuable predictors of sepsis and ARDS in polytrauma patients. We have found that lactate clearance-guided resuscitation is an effective method of mortality reduction especially among the high-risk trauma patients. Although the length of stay in the ICU and the time on a ventilator were not significantly different between the lactate-guided and ScvO₂-guided strategies, the link between the early clearance of lactate and death indicates that this approach should be emphasized in trauma care. Further studies should include multicenter RCTs, AI technologies, and standardization of resuscitation protocols to refine the trauma care strategies to improve long-term patient outcomes.

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