

# Elevated Lactate as a Mortality Factor in Poly Traumatized Patients: A Systematic Review and Meta-Analysis

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**Abstract:** *Introduction:* According to global health estimates from the World Health Organization (WHO) injuries represent 8% of world deaths. There are systematic reviews that relate lactate and mortality in trauma patients but do not focus on multiple trauma patients.

*Objective:* To determine if elevated lactate is a mortality factor in multiple trauma patients.

*Methodology:* A systematic review and meta-analysis of observational studies were carried out. The search was carried out in 4 databases: PUBMED, Embase, Scopus, and Web of Science.

Data were pooled using a random effects model and summary statistics were calculated using odds ratios (ORs) with their respective 95% confidence intervals (95% CI).

*Results:* Nine studies were included (n=5302). A significant association was found between elevated admission lactate with mortality (OR: 1.80; 95% CI 1.11 to 2.91) and 72-hour mortality (OR: 1.24; 95% CI 1.02 to 1.50). No statistically significant association was found for the analysis of elevated admission lactate and 28-day mortality (OR: 1.24; 95% CI 1.02 to 1.50). Finally, elevated admission lactate is associated with mortality regardless of time (OR: 1.34; 95% CI 1.19 to 1.50).

*Conclusion:* Elevated admission lactate is associated with mortality and 72-hour mortality in multiple trauma patients. No significant association was found between elevated admission lactate and 30-day mortality. Elevated intake of lactate is associated with mortality independent of time.

**Keywords:** Lactic acid, mortality, multiple trauma, Systematic review, Hospital mortality, Patient Admission (Source: MeSH NLM).

## INTRODUCTION

Injuries account for 8% of deaths worldwide, according to global estimates from the World Health Organization (WHO) [1]. The leading causes of death for these are considered to be: traffic accidents (24%), suicide (16%), falls (14%), and homicides (10%) [2]. In Peru, death from injuries is mainly due to traffic accidents, occupying the eighth place of causes of death in 2019 with a rate of 13.6 deaths per 100,000 inhabitants [3].

Because the deaths caused by these significantly impact the families and communities whose lives are altered both economically, socially, psychologically, and spiritually are affected, [4]. Therefore, it is necessary to know the evaluation and prevention of trauma and laboratory markers that can predict which

patients would be more likely to present fatal outcomes compared to others.

In recent years, although lactate has been associated with an important indicator of mortality for trauma patients [5,6], research associated with multiple trauma patients is controversial [7,8]. Lactate levels may be elevated due to the physiological response through a metabolic pathway, independent of the effects of shock and organ hypoperfusion [9]. For this reason, it is proposed to conduct a systematic review with a meta-analysis of the literature to determine if lactate is a factor of mortality in multiple trauma patients.

## METHODS

### Design

A systematic review (SR) with meta-analysis of observational studies. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for reporting systematic reviews

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and meta-analyses was used to guide this study [10]. This is available in Supplementary Annex 1.

### **Search Strategy**

This work was carried out using search strategies in four databases: Pubmed/Medline, SCOPUS, Web of Science, and EMBASE. The main information search strategy included the following words: multiple trauma, lactic acid, and mortality. Within-domain search terms were combined with 'OR' and cross-domain terms with 'AND'. No temporal delimitation of the studies or language filter was applied, but they were excluded if they did not meet the selection criteria. First, a search strategy was developed for PubMed and later it was adapted to other databases. The database search strategy is available in Supplementary Material 2.

### **Selection Criteria**

The inclusion criteria were: 1) studies that evaluated the association between lactate and mortality; 2) an adult population aged 18 years and over; 3) Spanish and English language. The exclusion criteria were 1) if they did not use any comparison group; 2) patients with a history of pathologies that increase lactate levels; 3) reviews, systematic reviews, pooled analyzes, and meta-analyses; 5) articles that did not provide the odds ratio (OR) or relative risk (RR) values and the 95% confidence interval; and 6) articles that did not adjust for other variables.

### **Selection of Studies**

The Rayyan online software (<https://rayyan.qcri.org>) was used. Three researchers independently (BMGC, OGC, and GG) conducted a review of the titles and abstracts of all the citations found to determine if they are studies on the topic. In this way, they classified the records as "included", "excluded" or "doubtful". If there were discrepancies, the final decision was given by a fourth reviewer (VJVP).

After the initial review, a full-text review of all included citations was performed. Then, in an Excel sheet, it was placed whether the study should be included. If it was not included, the reasons were placed. This procedure was also carried out by three researchers (BMGC, OGC, and GG), and if there were discrepancies it was resolved by a third one (VJVP).

### **Data Extraction and Qualitative Analysis**

The articles selected at the end went to the data extraction, they were placed in a file prepared in Microsoft Excel 2016. The following information was

extracted from each selected article: author, year, country, study design, follow-up time, sample size, sex (% men), mean with standard deviation (SD) or median with the interquartile range (IQR) of age, population (selection criteria), mean with SD or median with IRC of lactation, cut-off point to define lactate high, the measure of association used, the outcome that was assessed (mortality overall, at 72 hours or 28 days), and the adjustment variables.

### **Risk of Bias Assessment**

The Newcastle-Ottawa Scale (NOS) was used to assess the level of bias of the studies [11]. The NOS evaluates each manuscript based on selection, comparability, and outcome. A total of 9 points can be obtained. The NOS classification is as follows:  $\geq 7$  indicates low risk, and  $< 7$  indicates high risk. Each investigator did the assessment independently and then compared their results. If there were discrepancies, they were resolved by the fourth investigator.

### **Quantitative Analysis**

A random effects meta-analysis was performed in the Review Manager 5.4 program for statistical analysis to measure the association between elevated lactate and mortality. The independent variable was blood lactate, categorized as normal and elevated. The dependent variable was mortality. DerSimonian and Laird random effects models and the inverse variance method were used to generate the forest plot. The association measure used was the odds ratio (OR), with its respective 95% confidence interval (95% CI). An analysis was made globally and one by subgroups, according to the type of result.

Heterogeneity was identified by the I squared ( $I^2$ ) [12]. This was interpreted according to the Cochrane manual: 0 to 40% = might not be important; 30 to 60% = may represent moderate heterogeneity; 50 to 90% = may represent substantial heterogeneity; 75 to 100% = considerable heterogeneity [13]. Due to heterogeneity, a randomized model analysis was performed.

### **Ethical Aspects**

This study is a secondary analysis of primary studies published in scientific journals, so the risks to people who were part of the studies are minimal. In addition, this was approved by the Research Ethics Committee of the Facultad de Medicina de la Universidad Ricardo Palma.

## RESULTS

### Eligible Studies

Nine hundred forty-two publications were identified. After removing 276 duplicates, 666 manuscripts were evaluated by title and abstract. After excluding 591 studies, a total of 75 full-text articles were obtained. Finally, after applying the selection criteria, 9 articles (Figure 1) were left. The reasons for the exclusion of this last group are listed in the supplementary material.

### Study Characteristics

Table 1 shows the main characteristics of the nine included studies (n=5302). Samples ranged from 106 to 2441 participants in each study. The studies detail is as follows: The measurement of lactate on admission to the care center, (elevation with a cut-off point is not specified in 7 studies), one study used a cut-off point  $\geq 2.5$  mmol/L and another study one of  $\geq 4$  mmol/L. The male sex was the most prevalent in the studies with percentages from 70.3% to 91.84%, meanwhile, the

average age in the studies is between 30 to 45 years [8,14-21].

For a better analysis, they were divided into three subgroups, according to the result, by mortality (absolute count in non-specific time), mortality in 72 hours, and mortality in 28 days with 3 studies in each subgroup. The mean lactate in people who died in the mortality subgroup ranged from  $5.7 \pm 3.8$  mmol/L (mean  $\pm$  SD) to  $29.30 \pm 6.60$  mmol/L (mean  $\pm$  SD) [16,18,19]. The mean lactate in people who died in the 72-hour mortality subgroup ranged from  $3.4 \pm 4.2$  mmol/L (mean  $\pm$  SD) to  $43 \pm 22$  mg/dL (mean  $\pm$  SD) [15,17,20]. The mean lactate in deceased persons in the 28-day mortality subgroup ranged from  $2.8 \pm 8.6$  mmol/L (mean  $\pm$  SD) to  $7.04 \pm 3.92$  mmol/L (mean  $\pm$  SD) [8,14,21].

### Risk of Bias Assessment

The nine selected studies were assessed using the New Castle Ottawa risk of bias tool. Selection scores

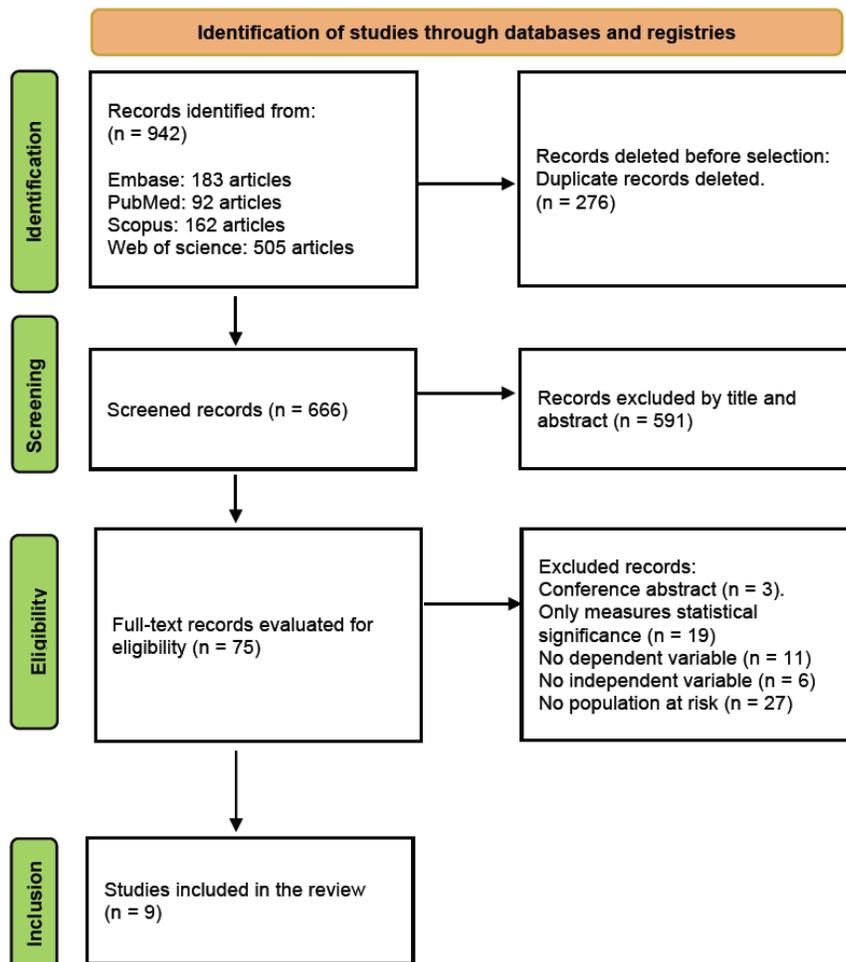


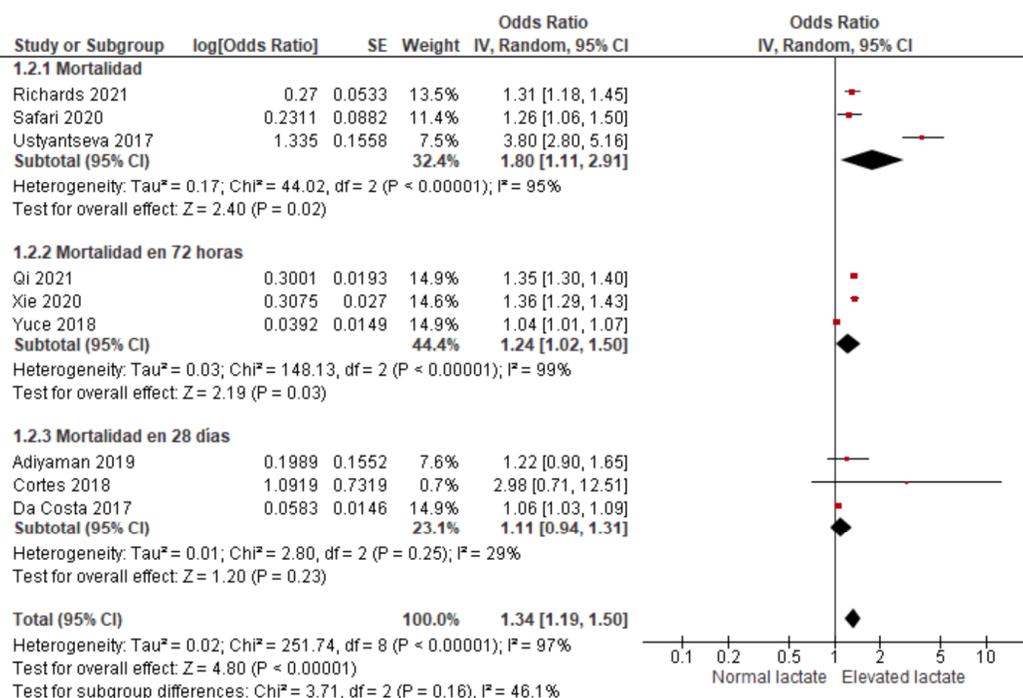
Figure 1: PRISMA 2020 flowchart for new systematic reviews involving database and registry searches.

Table 1: Characteristics of the Studies Included in the Review

Author	Year	Country	Study Design	Time of follow-up	Sample size	Sex (% Men)	Mean (SD) or Median (IQR) Age	Population (selection criteria)	Mean (SD) or Median (IQR) Lactate	Lactate cutoff point	Measure of association	Results	Adjustment variables
Safari et al.													
Ustyantseva et al.													
Richards et al.	2021	USA	Retrospective cohort	January 2010 - December 2016 (7 years)	1439	71.23%	43 (38-55)	18 to 89 years, blunt trauma, (ISS) $\geq 15$ and transfer from the site of injury.	3.59 $\pm$ 2.21 (Mean $\pm$ SD)	-	OR: 1.31 (1.18-1.46) p<0.001	Mortality	Age ISS Admission shock index
Qi et al.	2021	Switzerland	Retrospective cohort	January 1996 - January 2013 (17 years)	2441	74.85%	42	Adults, with polytrauma in a Level 1 trauma center and an admission time of less than 24 h after trauma	2.30 (Median)	-	OR: 1.353 (1.296-1.413) p<0.001	Mortality in 72 hours	Gender Age ISS
Xie et al.	2020	China	Cohort	January 1996 - January 2013 (17 years)	2 315	77.40%	38.7 $\pm$ 13.8	Patients from 18 to 65 years old with polytrauma, admitted within 24 hours of the trauma	4 (2-4-7.0) (Deceased) 2.1 (1.3-3.2) (Alive)	-	OR: 1.36 (1.29-1.42) p<0.001	Mortality in 72 hours	-
Yucel et al.	2018	Turkey	Prospective cohort	May 2015 - May 2016 (1 year)	195	73%	45 $\pm$ 19	18 years of age or older, ISS greater than or equal to 16 years of age	30 $\pm$ 19 (Mean $\pm$ SD)	-	OR: 1.041 (1.01-1.07) p = 0.014	Mortality in 72 hours	-
Cortes et al.	2018	Colombia	Prospective cohort	April 2016 - July 2017 (15 months)	196	91.84%	30	Emergency surgical procedures, arterial blood gases, serum lactate, vital signs, use of blood products, and vasopressors.	7.43 (Median)	4	RR: 2.98 (0.71-12.49) p = 0.10	Mortality in 28 days	-
Adiyaman et al.	2019	Turkey	Retrospective cohort	January 2014 - January 2016 (2 years)	106	82.10%	43 $\pm$ 21	Trauma patients	2.6 $\pm$ 1.9 (Mean $\pm$ SD)	-	OR: 1.22 (0.90-1.64) p = 0.20	Mortality in 28 days	-
Da Costa et al.	2017	Brazil	Prospective cohort	2010-2013 (4 years)	200	82%	37.3 $\pm$ 14.3	18 years of age or older, high energy trauma, ISS greater than or equal to 16	7.04 $\pm$ 3.92 (Deceased) 4.42 $\pm$ 3.25 (Alive)	-	OR: 1.060 (1.029-1.093) p<0.001	Mortality in 30 days	Gender Age ISS Presence of ECT

Table 2: Risk Assessment of the Studies Included in the Review

Authors, year	Selection				Comparability		Outcome			Score	Overall Judgment
	Representativeness of exposed cohort	Selection of unexposed cohort	Determination of exposure	Outcome not present at baseline	Study controls for sex and age	Study controls for any additional important factors	Outcome assessment	Duration of follow-up	Adequacy of follow-up		
Safari <i>et al.</i> 2020	★	★	★	★	-	★	★	-	★	7	Low risk
Ustyantseva <i>et al.</i> 2017	★	★	★	★	-	★	★	★	★	8	Low risk
Richards <i>et al.</i> 2021	★	★	★	★	★	★	★	★	★	8	Low risk
Qi <i>et al.</i> 2021	★	★	★	★	★	★	★	★	★	9	Low risk
Yucel <i>et al.</i> 2018	★	★	★	★	-	★	★	-	★	7	Low risk
XIE <i>et al.</i> 2020	★	★	★	★	-	-	★	★	★	7	Low risk
Cortes <i>et al.</i> 2018	★	★	★	★	-	★	★	-	★	7	Low risk
Adiyaman <i>et al.</i> 2019	★	★	★	★	-	-	★	★	★	7	Low risk
Da Costa <i>et al.</i> 2017	★	★	★	★	★	★	-	★	★	8	Low risk



**Figure 2:** Forest plot of random effects of elevated lactate on mortality, 72-hour mortality, and 28-day mortality.

were homogeneous across studies. In the overall score and judgment, all had high quality and a low level of bias. Publication bias due to the small number of articles was not assessed (Table 2).

### Meta-Analysis of Lactate and Mortality in Multiple Trauma Patients

In the case of the analysis of elevated admission lactate and mortality, the studies that independently presented a statistically significant association were the study by Safari *et al.* [16] (OR: 1.26, IC 95% 1.06-1.51), Ustyantseva *et al.* [18] (OR: 3.8; IC 95% 2.8-5.3) and Richards *et al.* [19] (OR: 1.31; IC 95% 1.18-1.46). Finally, a statistically significant association was found between the variables of interest. (OR: 1.80; IC 95% 1.11 a 2.91) Figure 2.

In the case of the analysis of elevated lactate at admission and mortality at 72 hours, the studies that independently presented a statistically significant association were the ones conducted by Qi *et al.* [17] (OR: 1.35, IC 95% 1.30-1.40), Xie *et al.* [20] (OR: 1.36; IC 95% 1.29-1.43) and Yucel *et al.* [15] (OR: 1.04; IC 95% 1.01-1.07). Finally, a statistically significant association was found between the variables of interest (OR: 1.24; 95% CI 1.02 to 1.50) Figure 2.

In the case of the analysis of elevated admission lactate and 28-day mortality, the study by Da Costa *et al.* [14] (OR: 1.06, IC 95% 1.03-1.09) presented a

statistically significant association, while those of Adiyaman *et al.* [8] (OR: 1.22; IC 95% 0.90-1.65) and Cortes *et al.* [21] (OR: 2.98; IC 95% 0.71-12.51). Finally, no statistically significant association was found between the variables of interest (OR: 1.11; IC 95% 0.94 a 1.31) Figure 2.

Lastly, elevated admission lactate is associated with mortality independent of time. The studies of the first and second subgroups presented considerable heterogeneity, in the first group: I squared (95%), as for the second: I squared (99%). On the other hand, the third subgroup presented insignificant heterogeneity with an I square of 29%.

### DISCUSSION

There are systematic review studies of the association of lactate and mortality in patients with trauma [5,6] but the focus on the polytraumatized patient is essential due to the presence of a series of pathophysiological mechanisms and responses of the organism that make a high mortality susceptible [22].

The highest prevalence of polytraumatized patients in this study would correspond to men and the age group of 30 to 45 years, not distancing from the reality mentioned in WHO reports in which men have twice the risk of dying from trauma and where three of the top ten causes of death in adults are related to trauma [23].

Despite the significant association, the definition of elevated lactate and the precision of the lactate cutoff need to be made more specific in most of the included studies. For Ustyantseva *et al* the cut-off point is 2 mmol/L and for Cortes *et al* the cut-off point is 4 mmol/L. Likewise, during the review, different measurements associated with the time of lactate intake were found, such as lactate in 6 hours, lactate in 24 hours or lactate clearance, which did not find more articles related to it, but they are significant and could be used for future studies [19,21,24].

Mortality times is another topic of discussion when performing a search for articles. Although the trimodal distribution of death in trauma is known, it is very unspecific when it openly points to early mortality from hours to days and late mortality from days to weeks, creating diversity in the studies regarding the result. Furthermore, this concept is changing to a bimodal distribution of death (less than 4 hours and after 1 week) due to current interventions [25,26]. In the included studies, there are two subgroups according to the time of death from admission: mortality within 72 hours [15,17,20] and 30-day mortality [8,14,21]. These subgroups by mortality time serve as standards for the classification of the trimodal distribution. However, other times should be considered to observe a change in the current pattern or continue according to surgical intervention times (24 hours, 1 week) [22].

Studies associate elevated lactate with mortality and 72-hour mortality, which may be due to the pathophysiological mechanism of lactate in trauma, which is elevated by different means, such as that produced by skeletal muscle after trauma, that produced by recruited leukocytes and alveolar macrophages after acute lung injury or SARDS or splanchnic lactate from MODS or acute liver failure. Mortality in 72 hours coincides with the therapeutic times where life support procedures and damage control surgery are necessary, as well as pathophysiological changes due to tissue damage and hyperinflammation [22,27,28]. However, the studies where elevated lactate and 30-day mortality are not significantly associated can be explained due to the new paradigm of early interventions that are currently being presented, managing to avoid the development of complications such as multi-organ failure syndrome or sepsis [22,29].

Primary brain injuries or significant blood loss (hemorrhagic shock) determine immediate and early trauma deaths, while secondary brain injuries and host defense failures cause late mortality. The post-

traumatic response of the host is also influenced by neuroendocrine and metabolic disorders. Primary (bleeding) and secondary (capillary leak) hypovolemia trigger, through aortic or carotid baroreceptors, a sympathoadrenal response. Catecholamines influence post-traumatic metabolism with increased energy expenditure, hepatic glycogenolysis, and gluconeogenesis. Natural post-traumatic insulin secretion is too low to cope with this post-traumatic hyperglycemia. Increased intracellular glucose is oxidized to pyruvate and ultimately reduced to lactate (stress lactate acidosis), contributing to elevated lactate levels caused primarily by metabolic lactic acidosis (cellular hypoxia) [27].

The following limitations must be considered: the studies associated with mortality and mortality in 72 hours present a high heterogeneity due to the lactate cut-off points and population variability. Being the first systematic review to address this issue, lactate measurement times and mortality times are relatively new variables and were obtained based on availability.

## CONCLUSIONS

The present systematic review and meta-analysis found that elevated admission lactate is associated with mortality and 72-hour mortality in multiple trauma patients. No significant association was found between elevated admission lactate and 30-day mortality. Lastly, elevated admission lactate is associated with mortality independent of time. Few studies demonstrate the association found, however, these presented a high heterogeneity that can be explained by the diversity of the population and the heterogeneous cut-off points.

A consensus on lactate measurement times and cut-off points is recommended to facilitate the future development of cohort studies and meta-analyses. In turn, it should be considered that from now on future studies should consider mortality times according to the new patterns of the bimodal theory of death from trauma or the time of interventions. Finally, the measurement of admission lactate is recommended for preventive purposes to complement the therapeutic decision of critical polytraumatized patients.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHORSHIP CONTRIBUTIONS

The authors participated in the genesis of the idea, project design, data collection and interpretation,

analysis of results, and preparation of the manuscript of this research paper.

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## SUPPLEMENTAL MATERIALS

The supplemental materials can be downloaded from the journal website along with the article.

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