Lactate/Pyruvate Serum Ratio as a Clinical Prognostic Marker for Severe Septic Patients Evolution

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Abstract

Introduction

Various studies have shown that an increase in the lactate/pyruvate (L/P) ratio is associated with higher mortality. In some patients, despite the development of hyperlactatemia, the L/P ratio remains preserved. We determined the impact of variations in lactate, pyruvate, and the L/P ratio on mortality.

Material and methods

We recruited patients above 18 years with sepsis without shock. On admission, we measure lactate, C-reactive protein, lactate, pyruvate. All tests were performed 0, 4, and 8 hours after admission. The SOFA score, APACHE-II, and Shock Index were measured in all participants. All patients had a 30-day follow-up.

Results

Eighteen patients in our cohort died, with an overall mortality of 21.6%. The most prevalent post-mortem diagnosis was pneumonia (50%), followed by sepsis of abdominal origin (38.9%), being statistical relevant ($p = 0.002$). An improvement of at least 30% in the L/P ratio in the next 4 hrs upon arrival at the emergency room confers a protective effect on short term in patients with severe sepsis.

Conclusion

The L/P ratio appears to be a good and earlier predictor regarding hyperlactatemia and/or hypopyruvatemia. The evaluation of L/P over time is more important, with its ratio > 25 on 4 hrs posterior to hospital admission as the cut-off point associated with higher mortality.

Background

Despite medical advancements, sepsis remains a formidable enemy. The most recent estimates indicate that sepsis-related mortality is currently around 10 million patients per year worldwide. [1] To effectively combat it, many potential prognostic markers have been proposed; one is lactate. [2]

It is assumed that lactate elevation in severe sepsis is secondary to tissue hypoperfusion; however, this mechanism is not the only one involved. [3, 4] There are several cases in which lactate elevation is not associated with hypoperfusion-hypoxemia. For this reason, only using lactate as a predictor could be insufficient, especially when there is no clinical evidence of hypoxemia. [5] Previous studies have proposed measuring pyruvate levels and the lactate/pyruvate ratio (L/P) in serum as the best predictors for managing severe sepsis. [6] The increase of lactate levels in patients with severe sepsis has also been recorded as a consequence of elevated pyruvate production, which can increase up to 450% [5, 7].

Various studies have shown that the increase in the L/P is associated with higher mortality. However, in up to 80% of patients with severe sepsis, it has been found that despite hyperlactatemia, the L/P ratio

remains preserved. [8] Several authors agree that as long as pyruvate production is maintained, it can be taken as a benchmark of adequate mitochondrial function, explaining how the L/P ratio can remain at normal levels. [9] When present with a patient with hyperlactatemia, the binomial sepsis + hypotension bases initial efforts on aggressive resuscitation with intravenous fluids and/or vasopressors, making us forget that tissue hypoperfusion may be a consequence (severe mitochondrial damage) and not the very cause of elevated lactate. [10]

Although some studies have described the lactate/pyruvate ratio in emergency and intensive care patients (all with already established shock) [11, 12], no study has specifically focused on studying this relationship in septic patients of any origin without evidence of shock. We conducted this research to determine how variations in lactate, pyruvate, and the L/P ratio, impact mortality.

Materials And Methods

STUDY DESIGN AND APPROACH

This prospective study was conducted in a 18 months period of time and approved by the Ethics Committee of the "Hospital Universitario Dr. José E. González". According to current clinical guidelines, *informed consent was waived by the Ethics Committee of the "Hospital Universitario Dr. José E. González"* because the described procedures are currently considered part of a necessary evaluation in all patients with sepsis. Also, no sensitive information was recorded. *This original research was performed in accordance with local and international relevant guidelines/regulations.*

During the mentioned period, all patients older than 18 years admitted to the emergency room with suspected severe sepsis of any type were included (survival sepsis criteria). Patients with a history of underlying mitochondrial and/or enzymatic diseases and those who reported alcohol consumption in the last 24 hours were excluded. Patients in whom sampling was not performed within the period stipulated by the protocol or with an inflammatory response of non-infectious origin were eliminated.

On admission, venous blood samples were taken to measure lactate, C-reactive protein, a complete biochemical profile, and other tests requested by the attending physician. An additional sample was taken to isolate the serum and was later frozen at -70°C for pyruvate measurement. The tests (lactate, pyruvate, and C-reactive protein) were performed at 0, 4, and 8 hours after each patient admission. The SOFA score, APACHE-II, and Shock Index were measured in all participants. All patients had a 30-day follow-up.

SAMPLING AND MEASUREMENT

Cayman Chemical Item No. 700470 Assay Kit was used for serum pyruvate determination. Samples were drawn in a vacutainer tube without anticoagulant, waiting 30 minutes for clot formation at 25°C. Subsequently, the samples were centrifuged at 2,000 g for 15 minutes at 25°C, extracting the supernatant without contact with the layer of leukocytes. For every 500 uL of serum, 500 uL of MPA was added,

vortexed, and placed on ice for 5 minutes. The samples were centrifuged again at 10,000 g for 5 minutes at 4°C. The resulting supernatant was removed before adding 50 uL of potassium carbonate. Centrifugation was again carried out at 10,000 g for 5 minutes, and the supernatant was frozen at − 80°C. The samples were preserved for an average of 42 days and were analyzed simultaneously after thawing. The Pyruvate Assay Kit No. 700470 (Cayman Chemical Co., Ann Arbor, MI) was used.

STATISTICAL ANALYSIS

The variables lactate, pyruvate, and the L/P ratio were analyzed using two-tailed, non-parametric tests. Parametric or non-parametric tests determined the means and proportions of each contrasted variable according to the Shapiro-Wilk test. Multivariate logistic regression was performed to determine the odds ratio in relation to mortality. The adjusted Kaplan-Meier test with log-rank coefficient was used to determine mortality in relation to time. All confidence intervals were calculated at 95%, considering a p-value < 0.05 statistically significant. The statistical software used for the analysis was SPSS version 20.0

Results

Eighty-three patients were included, of which 43 were women (52%) and 40 men (48%) with a mean age of 47 years (range from 19 to 87). There was no difference regarding the distribution of patients with regard to age or gender in both groups. The causes of sepsis were "mixed" (50.6%), pneumonia (14.4%), abdominal (14.4%), and others.

In our cohort, 18 patients died, with an overall mortality of 21.6%. The primary diagnoses of these patients were pneumonia (50%), followed by sepsis of abdominal origin (38.9%), with a relevant statistical difference (p = 0.002).

The APACHE-II and SOFA clinical scores were evaluated in all patients. In the surviving patients, both scores were lower than those who died. It was observed that non-surviving patients had higher lactate levels on admission to the emergency room. This finding also occurred with the L/P ratio, with a mean of 81.79 in non-surviving patients, compared to 21.93 in patients alive by day 30 (Table 1).

Table 1
Comparison of patient variables between survivors and non-survivors.

	Survivors	Non-survivors	p-value
Age, years	48.4 ± 18.99	45.4 ± 12.95	0.533
Clinical SCORES			
SOFA score	7.2 ± 4.53	12.27 ± 5.61	< 0.001
APACHE-II score	12.02 ± 6.19	16.1 ± 6.32	0.018
Lactate mg/dL	2.13 ± 2.05	4.98 ± 3.33	< 0.001
Pyruvate mmol/L	150.7 ± 82.47	105.07 ± 86.35	0.028
L/P ratio	21.93 ± 31.9	81.79 ± 73.01	0.003
Sepsis origin, n (%)			
Pneumonia	3 (6.0)	9 (50.0)	0.002
Abdominal	5 (10)	7 (38.9)	
Others	42 (84)	2 (11.1)	
Other variables, n (%)			
Shock on admission	13 (26.0)	14 (77.8)	< 0.001
Hemodialysis	17 (34)	8 (44.4)	0.570
Cirrhosis	10 (20.0)	7 (38.9)	0.126
Cancer	11 (22)	8 (44.4)	0.123

L/P, lactate/pyruvate ratio; APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

It is important to note that aside from the higher mean initial serum lactate of non-surviving patients, marked hypopyruvatemia was found with a mean of 105.07 ummol/L, which is associated with the disproportionately high L/P ratio in this group. In comparison, normal levels of pyruvate between 120–150 mmol/L were found in the literature.

Also, patients with hemodynamic variables compatible with septic shock on admission to the emergency room had higher mortality, conferring statistical relevance to the univariate analysis (Table 1).

Although serum lactate and pyruvate showed independently different means in both groups, it is evident that when determining the L/P ratio, the statistical difference becomes more pronounced if it is monitored every 4 hours after arrival at the emergency room.

Notably, all patients who developed an L/P ratio > 25 over 4 hours or more died. Likewise, it should be noted that two patients from the group of non-survivors had an L/P ratio < 25 on admission, which increased to > 25 after 4 hours. (Fig. 1)

It is also interesting that when contrasting mortality through survival curves (log-rank), an improvement of at least 30% in the L/P ratio in the next 4 hours on arrival to the emergency room confers a statistically significant protective effect in the short-term in patients with severe sepsis. (Fig. 2)

Last, we performed a binary logistic regression to determine the variables with the greatest impact on mortality. It was found that the most important variable is the L/P ratio > 25 with an OR of 4.73, conferring higher mortality in these patients. Likewise, a reduction of at least 30% in the L/P ratio in our study conferred a protective effect, with an OR of 0.78. The SOFA and APACHE-II scores did not show statistical differences. (Table 2.)

Table 2
Clinical variables with greater relevance regarding mortality.

Variables	OR (95% CI)	p-value
Initial L/P ratio > 25	4.73 (1.63–7.83)	< 0.001
Reduction of L/P ratio > 30%	0.78 (0.61–0.95)	0.047
APACHE II > 10	3.1 (0.8–5.4)	0.073
SOFA ≥ 6	3.92 (0.42–7.42)	0.097

OR, odds ratio; L/P, lactate/pyruvate ratio; APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

Discussion

The data reported in this study are consistent with previous medical literature on the ominous significance of sustained blood lactate elevation during the first hours of a patient with severe sepsis. The lactate serum level is an important independent predictor for mortality; however, tracking pyruvate levels in patients with sepsis and determining the L/P ratio seems to predict earlier the behavior of patients who will inevitably deteriorate. [1, 7]

Likewise, we were able to document that lactate elevation is not always proportional to the increase of pyruvate, reinforcing the idea that hyperlactatemia in patients with sepsis is of multifactorial origin. In agreement with published evidence and our data, we believe that the concordant elevation of lactate and pyruvate is a sign of cell function preservation that encourages better resistance to the underlying infectious process. [2, 4]

In patients who developed septic shock, mortality was notably high; however, it was higher when patients remained with an L/P ratio > 25 for more than 4 hours. This finding is subject to an apparent

hypopyruvatemia that could be observed in the group of non-survivors, which maintained a mean L/P ratio of 81.79; this, coupled with the initial hyperlactatemia in this same group, differed greatly in survivors. [9, 13]

Two patients had an L/P ratio < 25 at admission, which increased and was sustained during two subsequent tests. These patients eventually died. These patients were the only ones who were HIV-positive by ELISA. It is known that HIV is a virus that can affect the cells at the mitochondrial level. [14.15] Hence, this could explain these two patients' aggressive and fatal deterioration; however, this observation should be studied independently.[16] The severe mitochondrial damage in these patients requires basic science to demonstrate it. Despite this, we believe that cell damage can be severe due to the underlying infection that conditions a poor prognosis in these patients. [5, 9]

Although the SOFA and APACHE-II scores did not show statistical significance in any of the performed logistic models, it does not mean that they should be relegated to the use of the L/P ratio. Rather, biochemical markers, such as the L/P ratio, can probably determine a prognosis earlier and should be considered in the future for the predictive diagnosis of patients with sepsis. [17]

Finally, we had many patients with diabetes mellitus, systemic arterial hypertension, chronic kidney disease, and cirrhosis. None of these pathological entities conferred a greater risk to patients with severe sepsis. [11, 13] Cancer patients' mortality rate was virtually increased, but no statistical relevance was observed when developing the statistical models. This finding may be due to the sample size, so studies that evaluate the body's response to sepsis should be carried out.

Conclusions

The L/P ratio appears to be a good and slightly earlier predictor of hyperlactatemia and hypopyruvatemia. According to our results, the evaluation of L/P over time is more important. A level > 25 4 hrs after hospital admission is the cut-off point associated with higher mortality. We consider that the evidence from this research aimed to consider quantifying pyruvate serum levels in patients with sepsis to determine its importance in the critical management of these patients and seek alternative measures to simplify its measurement and reduce costs.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the "Dr. José E. González" University Hospital, without the need for informed consent.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

O.G.C.R Concept &, Methodology.

J.A.H.Z Concept, design of the study & Supervision

R.M.L. Writing - Review & Editing.

D.H.B. Writing - Review & Editing.

L.E.V.G. Data acquisition & formal analysis

J.C.J.P. Writing - Review & Editing.

C.M.G. Writing - Review & Editing.

O.G.L. Major contributions to final manuscript.

G.A.G.C. Major contributions to final manuscript.

D.G.A. Major contributions to final manuscript.

C.H.G.A. Supervision & major contributions to final manuscript.

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Figures

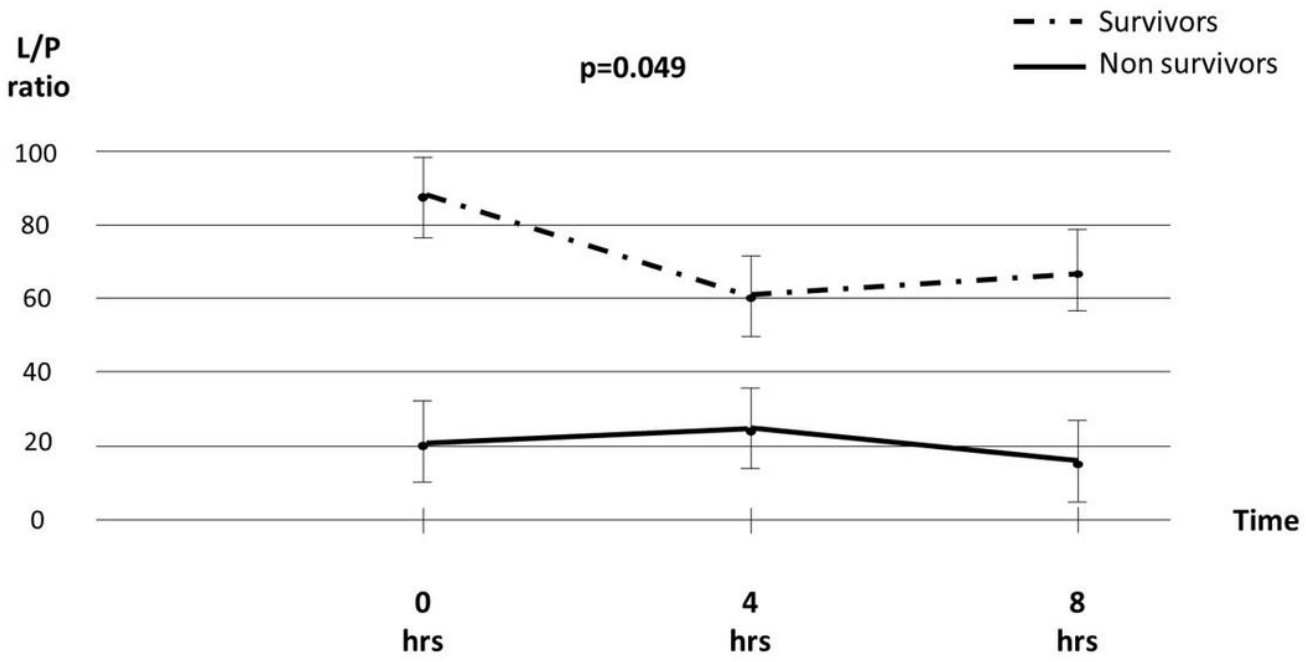

Figure 1

Mean changes in the lactate/pyruvate ratio throughout the study and a comparison between groups (L/P, lactate/pyruvate ratio).

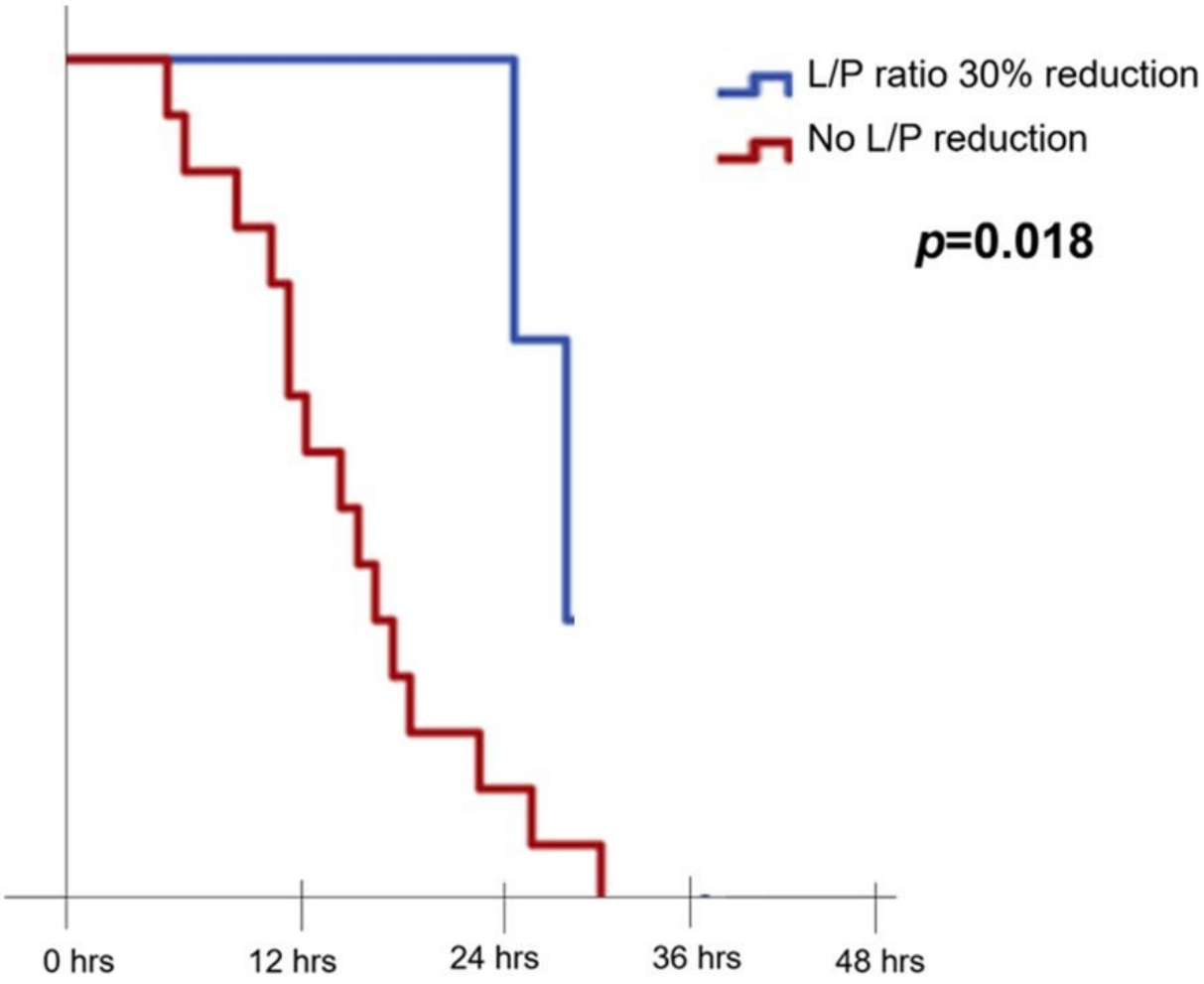

Figure 2

Survival curve. Patients whose lactate/pyruvate (L/P) ratio decreased at least 30% during their stay in the emergency room had a higher survival rate.