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Original Conribution

Prognostic value of lactate in prehospital care as a predictor of early mortality☆

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Background: Prehospital Emergency Medical Services must attend to patients with complex physiopathological situations with little data and in the shortest possible time. The objective of this work was to study lactic acid values and their usefulness in the prehospital setting to help in clinical decision-making.

Study design: We conducted a longitudinal prospective, observational study on patients over 18 years of age who, after being evaluated by the Advanced Life Support Unit, were taken to the hospital between April and June 2018. We analyzed demographic variables, prehospital lactic acid values and early mortality (<30 days). The area under the curve of the receiver operating characteristic was calculated for the prehospital value of lactic acid.

Results: A total of 279 patients were included in our study. The median age was 68 years (interquartile range: 54–80 years). Overall 30-day mortality was 9% (25 patients). The area under the curve for lactic acid to predict overall mortality at 30 days of care was 0.82 (95% CI: 0.76–0.89). The lactate value with the best sensitivity and specificity overall was 4.25 mmol/L with a sensitivity of 84% (95% CI: 65.3–93.6) and specificity of 70% (95% CI: 65.0–76.1).

Conclusions: The level of lactic acid can be a complementary tool in the field of prehospital emergencies that will guide us early in the detection of critical patients.

1. Introduction

Prehospital Emergency Medical Services (PhEMS) regularly face critical patients with complex pathophysiological contexts, a high comorbidity and life-threatening situations that require fast and adequate management. However, the early identification of high-risk patients that require specific therapeutic maneuvers or that require close monitoring is not always obvious to the staff of the PhEMS [1].

Diagnostic uncertainty, different levels of experience or the distance to the closest center of care directly influence the clinical decision-making, where point-of-care testing (POCT) reduces the window from the beginning of symptoms to basic analytical certainty of the results [2]. An example of POCT is the determination of capillary glucose, which for years represented an infrequent act but nowadays has extended to the usual medical practice.

Normal amounts of lactic acid are considered to be serum concentrations lower than 2 mmol/L [3-5]. Above this value, tachypnea begins to appear, tachycardia, alteration of mental state, and above 4 mmol/L [6,7], consensus defines a serious situation. Therefore, lactic acid is an early indicator of severity correlating with the severity of the pathology, and predicting mortality and admission to independent critical care [8].

The prognosis of patients in a critical situation is directly related to the time until adequate and timely care is received. In our setting, PhEMS have developed procedures to handle these situations in an

☆ The corresponding author on behalf of the other authors warrants the accuracy, transparency and honesty of the data and information contained in the study, that no relevant information has been omitted and that all discrepancies between authors have been adequately resolved and described.

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optimal way and transfer the patient to the most appropriate center according to their pathology. Nevertheless, in some patients, discerning their true severity -or their prognosis- may prove challenging. This uncertainty influences professionals when deciding on more aggressive stabilization maneuvers, and ultimately, maneuvers that could reduce morbidity and mortality in critically ill patients. Lactic acid has been used as a predictor of early mortality and detection of critically ill patients in very specific situations such as sepsis screening [9], in polytraumatized patients in whom lactic acid levels correlate with admission to intensive care units [10], and in situations of cardiac arrest, where lactic acid clearance is related to short-term prognosis [11]. However, lactate is not used as a routine test.

PhEMS should use this parameter that is easy to obtain, cheap and safe. However, we have not identified any study that evaluates how the routine use of lactic acid levels can improve decision-making in the care for critical patients and time-dependent pathologies.

The main objective of this work was to assess the prognostic value of lactic acid in prehospital emergencies and to identify which lactic acid levels have the highest prognostic value with the goal of facilitating decision-making in situations of diagnostic and prognostic uncertainty.

2. Methods

2.1. Study design

We conducted a longitudinal prospective, observational study in patients above 18 years of age who were treated by the advanced life support unit (ALSU) in the city of Valladolid and transferred to the two public hospitals: Río Hortega University Hospital and University Clinical Hospital of Valladolid between April and June 2018.

The study was conducted in the city of Valladolid (Spain). The PhEMS provides coverage in the metropolitan area to a population of 449,834 inhabitants, distributed over 7210 km^2, with three ALSU, integrated by two paramedics, an emergency nurse and a medical doctor.

The gateway to PhEMS is through the telephone number 1-1-2, operating 24 h a day, 365 days a year. The call is answered by a non-health technician. If the reason for the call is to request medical attention, once the possible data of affiliation and location have been gathered as accurately as possible, the call is immediately transferred to an emergency medical doctor. He or she determines the seriousness of the situation and sends the most appropriate response for that medical emergency.

Participants in the study are treated and transferred by the ALSU to the two public reference hospitals in the city: Río Hortega University Hospital and the University Clinic of Valladolid. Both hospitals have a broad surgical capacity and intensive care unit (ICU), where the door of entry for patients is the Emergency Department (ED).

2.2. Selection of participants

The criteria for including a patient in the study were having been taken by ALSU to the reference hospital, having had as a result of their pathological process a necessary venous line and having signed informed consent (the patient or a relative or legal guardian), and not meeting any exclusion criteria, which were: age under 18 years, cardiorespiratory arrest or death prior to the arrival to the hospital, pregnancy, psychiatric pathology, diagnosis of end-stage disease (in treatment by palliative care units), time of arrival of ALSU >45 min, transfer by other transport vectors or discharge *in situ* (Fig. 1).

2.3. Collection of the parameters

At the time of assistance, demographic variables and time spent during assistance were recorded, as well as the baseline value of venous lactic acid [9,12,13]. We determined blood lactate levels in samples obtained from the venous line. The measuring device we used was Accutrend Plus meter (Roche Diagnostics, Mannheim, Germany), with a measurement range of 0.8–21.7 mmol/L. The entire procedure was performed by the emergency nurse of each ALSU, and consisted of three phases: first, the instrument is turned on and the test strip is inserted; second, the blood drop is deposited (15–40 μL) on the test strip; and third, the lid is closed and a result is obtained within 60 s. Between taking the blood and placing the sample in the device, no >1 min should pass.

Subsequently, a researcher in each hospital monitored the electronic history of the patient 30 days after emergency care to collect the following variables. The patients were classified in relation to their final diagnosis according to the following diagnostic groups: cardiovascular, neurological, respiratory, trauma and injuries by external agents and

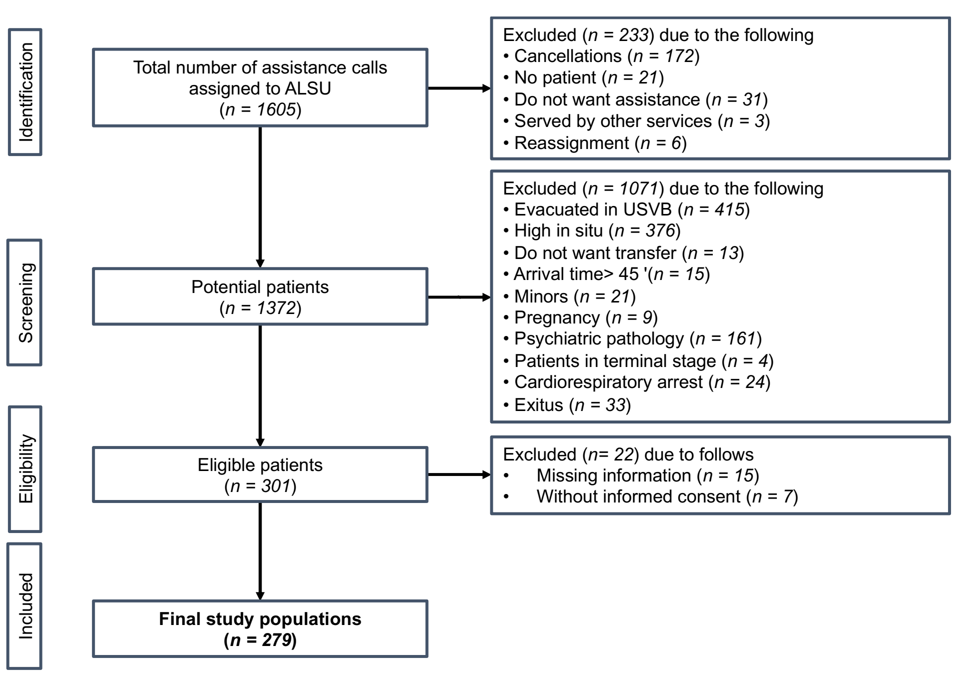

Fig. 1. Flow chart enrolled patients.

other types of pathology (digestive, endocrine, infectious, genitourinary, etc.). In addition, the rest of the variables were collected from the clinical history: destination of the patient, requests for complementary tests, visits by medical specialists and days of admission. Through this same review of the patient's electronic history, it was also known which participants in the study had died outside the hospital but within the timeframe of the 30-day study.

The main outcome variable was mortality from any cause from the index event (prehospital care by the ALSU) until the first 30 days from the index event, accounting for deaths that occurred in the hospital and outside the hospital but within the timeframe 30 days from initial care by the ambulance.

2.4. Statistical analysis

All data were collected and organized in a database designed for that purpose with double data entry to reduce input errors. Prior to applying statistical tests, we cleaned the database by means of logical tests, range tests (for the detection of extreme values) and for data consistency. Subsequently, we checked for the presence and distribution of unknown values ("missing") in all variables.

All data have been collected and organized in a database designed for this purpose in the Microsoft Excel program (version 14.4.0), which after being cleaned was exported to SPSS 20.0 (SPSS Inc.®, Chicago IL, USA).

Continuous quantitative variables are described with median and interquartile range (IQR). The qualitative variables are described by absolute and relative frequencies (%). To compare group, in quantitative variables whose distribution showed no evidence of differing from a normal distribution, Student's *t*-test was used, otherwise the Mann–Whitney *U* test. To compare percentages, the Chi-square test was used for 2×2 contingency tables or, in case of low frequency observed in some cells of the corresponding table, Fisher's exact test.

To evaluate the capacity of lactate to predict 30-day mortality, globally and for each of the groups analyzed, we estimated the sensitivity and specificity of the prognostic tests defined by different cut-off points in the range of observed values for the aforementioned variable. With these estimations, the corresponding ROC curve was obtained and the area under the curve (AUC) was calculated.

The level of lactic acid with best predictive capacity was established according to the Youden index. In addition to the calculated cut-off point, the prognostic test was also performed for cut-off points of 2 and 5 mmol/L. We calculated sensitivity and specificity, the positive and negative predictive values and the positive and negative likelihood ratios. *P* values below 0.05 were considered statistically significant.

3. Results

A total of 279 patients were included in our study: 172 (61.6%) males and 107 (38.4%) females. The median age was 68 years (25th–75th percentile: 54–80 years). The median age of the males was 65 years (25th–75th percentile: 53–79 years) and of the women 73 years (25th–75th percentile: 56–83 years) without statistically significant differences. The 30-day overall mortality was 25 patients (9%).

The main causes of the request for assistance were processes of medical origin in 239 cases (85.7%).

Of the total number of patients analyzed, 121 (43.1%) were diagnosed with processes of cardiovascular origin, followed by neurological problems (21.9%), trauma (deliberate self-harm is classified under overdose or injury as appropriate) and external agents (14.3%), respiratory processes (11.1%), and others (9.3%) (Table 1).

The hospital admission rate was 67% (185 patients) with a median of 3 days of admission (25th–75th percentile: 0–7 days), and a discharge rate in the Emergency Department (ED) of 33% (92 patients) (Table 1). In 187 cases (67%), it was necessary to consult with specialists. In 106 of them (38%), in addition to the standard complementary tests (basic blood tests, electrocardiogram and chest X-ray), it was necessary to perform computerized axial tomography tests and/or ultrasound studies and in 46 of them (16.5%), surgical procedures or other interventions were required.

The median level of lactic acid for all patients was 3.4 mmol/L (25th–75th percentile: 2.4–4.8 mmol/L). The levels of lactic acid were higher in the group of deceased patients, with a median of 5.3 mmol/L (25th–75th percentile: 4.3–7.9 mmol/L) versus a median of 3.2 mmol/L

Table 1
General patient characteristics. Death statistics refer to early mortality rates.

	Total	Survivors	Non-survivors	P-value
Number [*n* (%)]	279 (100)	254 (91)	25 (9)	
Age (years old) [Median (25th–75th percentile)]	68 (54–80)	66 (53–80)	80 (70–86)	0.001
Gender				
Male [*n* (%)]	172 (61.6)	154 (89.5)	18 (10.5)	
Female [*n* (%)]	107 (38.4)	100 (93.5)	7 (6.5)	0.265
Isochronous (minutes) [Median (25th–75th percentile)]				
Arrival time	10 (8–13)	10 (8–13)	10 (8–13)	0.603
Support time	30 (25–36)	30 (24–35)	34 (25–39)	0.200
Transfer time	9 (6–13)	9 (6–13)	9 (7–18)	0.223
Prehospital diagnostic [*n* (%)]				
Cardiac pathology	121(43.1)	109 (90.1)	12 (9.9)	
Neurological pathology	61 (21.9)	55 (90.2)	6 (9.8)	
Respiratory pathology	31 (11.1)	28 (90.3)	3 (9.7)	
Injuries and external agents	40 (14.3)	38 (95)	2 (5)	
Other pathology	26 (9.3)	24 (92.3)	2 (7.7)	0.905
Hospital department [*n* (%)]				
ED/hospitalization	221 (79.2)	212 (95.9)	9 (4.1)	
ICU	58 (20.8)	42 (72.4)	16 (27.6)	<0.001
Lactate ≥2 mmol/L [n (%)]				
Yes	239 (85.7)	214 (89.5)	25 (10.5)	
Not	40 (14.3)	40 (100)	0 (0)	0.0032
Lactate ≥4.25 mmol/L [n (%)]				
Yes	95 (34.1)	74 (77.9)	21 (22.1)	
Not	184 (65.9)	180 (97.8)	4 (2.2)	<0.001
Lactate ≥5 mmol/L [n (%)]				
Yes	58 (20.8)	43 (74.1)	15 (25.9)	
Not	221 (79.2)	211 (95.5)	10 (4.5)	<0.001

ED: Emergency Department; ICU: Intensive Care Unit;

Table 2
Distribution of lactic acid values. Death statistics refer to early mortality rates

	Total	Survivors	Non-survivors	P-value
Total (mmol/L) [Median (25th–75th percentile)]	3.4 (2.4–4.8)	3.2 (2.3–4.4)	5.3 (4.3–7.9)	0.001
Gender (mmol/L) [Median (25th–75th percentile)]				
Male	3.7 (2.4–4.8)	3.3 (2.3–4.5)	5.5 (4.7–7.7)	0.001
Female	3.2 (2.4–4.4)	3.1 (2.3–4.3)	4.4 (4.3–9.8)	0.003
Prehospital diagnostic (mmol/L) [Median (25th–75th percentile)]				
Cardiac pathology	3.2 (2.3–4.3)	3 (2.2–4.1)	5.2 (4.3–8.1)	<0.001
Neurological pathology	3.9 (2.6–5.7)	3.5 (2.5–4.8)	5.9 (4.5–9.8)	0.019
Respiratory pathology	2.9 (2.1–4.1)	2.7 (2.1–3.8)	4.9 (4.1–5.1)	0.024
Injuries and external agents	3.8 (3.2–5.1)	3.8 (3.1–4.8)	11.8 (6.9–16.7)*	0.005
Other pathology	3.4 (1.6–5.2)	3.1 (1.6–5.1)	5.3 (3.8–6.9)*	0.302
Hospital department [Median (25th–75th percentile)]				
ED/hospitalization	3.3 (2.4–5.6)	3.2 (2.4–4.4)	4.9 (4.3–5.7)	0.002
ICU	3.9 (2.4–5.6)	3.1 (2.2–4.3)	6.9 (4.3–9.6)	<0.001
Hospitalization (mmol/L) [Median (25th–75th percentile)]				
1 day or less	3.8 (2.5–4.8)	3.5 (2.4–4.3)	5.1 (4.3–7.5)	0.001
2–10 days	3.1 (2.4–4.8)	3 (2.3–4.5)	6.9 (4.3–13.9)	0.005
>11 days	3.7 (2.3–5.4)	3.2 (2.1–4.5)	6.1 (4.7–9.5)	0.005

ED: Emergency Department; ICU: Intensive Care Unit.
* These statistical summaries have been calculated with only two observations.

(25th–75th percentile: 2.3–4.4 mmol/L) in surviving patients. This difference was statistically significant ($p < 0.001$) (Table 2).

The AUC of lactic acid to predict overall mortality at 30 days of care was 0.82 (95% CI: 0.76–0.89) (Fig. 2). Fig. 1 2 shows the AUC of the different diagnostic groups, reaching statistical significance in the AUC that corresponds to cardiovascular pathology. The lactate value with highest global sensitivity and specificity was 4.25 mmol/L with a sensitivity of 84% (95% CI: 65.3–93.6) and specificity of 70% (95% CI: 65.0–76.1) (Table 3).

4. Discussion

Our data indicate that lactic acid values had a very high capacity to predict early mortality among patients included in the study. Higher lactic acid values corresponded to an increased mortality of patients.

Using lactic acid as an additional parameter can help us identify those patients with life-threatening conditions who should receive early attention. Vital signs routinely collected sometimes do not reflect the state of severity of patients and sometimes only change when the patient's condition is already extremely serious. This justifies the search for new parameters that can guide us towards early action, more so, when certain time-dependent diseases require rapid intervention. However, certain pathologies have a subtle presentation that is difficult to evaluate [8,14]. A delayed identification of the critical pathology of the patient directly impacts the health system, increasing diagnostic procedures and surgical techniques, hospitalizations, stays in intensive care units or unexpected deaths [15].

The early identification of high-risk patients is a priority objective for PhEMS. From the 70s to the present, special interest has focused on finding a biomarker that can guide clinical decision-making. Lactic acid seems ideal as it has been widely demonstrated that the levels of lactic acid and its clearance represent a reliable indicator for severity and prognosis [16-18].

Lactic acid measurement can be compelling as an additional routine test for informing the clinical decision about the transfer to the hospital in the ALSU [3]. Other clear indications are in suspected infection, since lactic acid levels between 3.2 and 3.8 mmol/L [7,8,15] are correlated with a higher incidence of sepsis, or in cases of major trauma [10,14] or patients with cardiorespiratory arrest [11]. However, we believe that patients with nonspecific symptoms and without evident severity criteria would benefit most from this test, because it can guide the emergency team. In the prehospital setting, the levels of lactic acid can inform treatment, but no corrective measures can be taken other than those standardized in the advanced life support protocol depending on the circumstances of each patient. Having this information in the prehospital setting means having a tool supporting decision-making. In contrast, at the time of hospital transfer, lactic acid levels can help establish the possible seriousness of the patient's condition, so we think that they should be used routinely as a fundamental biomarker.

The ease with which a lactic acid measurement can be obtained nowadays both at the patient's collection point and on arrival at an emergency triage makes it the ideal parameter to help the initial assessment of these patients [19,20].

The level of lactic acid that offers us greatest sensitivity and specificity is approximately 4 mmol/L [18,21-23], a figure that can be taken as a reference to identify the most severe patients with greater sensitivity and specificity. Surviving patients always had values below 4 mmol/L, whereas those deceased exhibited values above [16,24,25]. Figures below 2 mmol/L exclude with great reliability the mortality of the patients referred to the hospital, presenting a sensitivity of 100% and a negative predictive value of 100%.

Analyzing by pathologies, we observed that lactate values in cardiovascular pathologies maintain the prognostic capacity, while the rest of

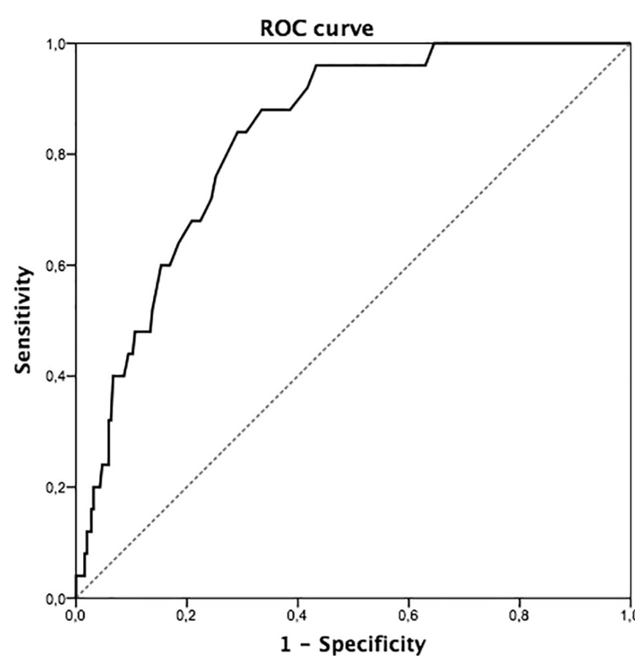

Fig. 2. General area under the curve and for pathology, depending on lactic acid values and early mortality.

Table 3
Sensitivity and specificity analysis and predictive values for each of the cut-off points of lactic acid according to early mortality

	Se [95% CI]	Sp [95% CI]	PPV [95% CI]	NPV [95% CI]	LR (+) [95% CI]	LR (−) [95% CI]
Lactate ≥2 mmol/L	100 (86.7–100)	15.7 (11.8–20.7)	10.5 (7.2–15.0)	100 (91.2–100)	1.19 (1.13–1.25)	0 0
Lactate ≥4.25 mmol/L	84.0 (65.3–93.6)	70.9 (65.0–76.1)	22.1 (14.9–31.4)	97.8 (94.5–99.2)	2.88 (2.23–3.73)	0.23 (0.09–0.56)
Lactate ≥5 mmol/L	60.0 (40.7–76.6)	83.1 (78–87.2)	25.9 (16.3–38.4)	95.5 (91.9–97.5)	3.54 (2.33–5.40)	0.48 (0.29–0.79)

CI: confidence interval; Se: Sensitivity; Sp: Specificity; PPV: positive predictive value: NPV: negative predictive value; LR: Likelihood ratio.

the diagnostic models did not reach statistical significance, although the AUC remained very high. We speculate that this is probably due to the low number of patients who died in the subgroups, which will have to be confirmed in larger studies.

Comparing the data from our study with similar studies, we found the rates of early mortality are similar [21,24]. In our study, the most efficient cut-off point between sensitivity and specificity was 4.25 mmol/L, approaching data obtained in studies on trigger values of lactic acid in sepsis of 4 mmol/L [26,27], presenting our study a prediction capacity superior to that of other studies [16,18,25].

5. Limitations

The sample size was sufficient to obtain results overall, but not to obtain statistically significant results by study subgroups according to pathologies.

One problem that we identified during study design was the lack of specific training of PhEMS professionals for the measurement of lactic acid. This motivated us to carry out a specific training including all professionals participating in the study.

6. Conclusion

Our results show that the level of lactic acid can be the ideal complement to routine tests at prehospital level that can guide us early in the detection of critical patients. Adding the measurement of venous lactic acid to the prehospital assessment of the critical patient can help determine the prognosis up to 30 days after the index event.

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Ethical statement

The study was approved on 9 March 2018, by the Clinical Research Ethics Committee at the Río Hortega University Hospital, and the University Clinic Valladolid (Spain), with registration codes #PI 18-010 & #PI 18-895.

All participants had to provide informed consent. At the time of the initial assistance, the attending physician told the patient of the study. If the patient consented to participate, they were given an informed consent sheet. If the patient was not able to understand the document due to their condition, a relative (or legal guardian) was informed, if possible.

The study was carried out with the highest safety standards, protecting the physical integrity and confidentiality of the participants, complying with national and international regulations for the study in human subjects included in the Declaration of Helsinki (DoH).

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Conflict of interest

None.

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