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Novel prehospital lactate cut-off estimation for mortality: a multicentre observational study

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ABSTRACT

Objectives Point-of-care testing available in prehospital settings requires the establishment of new medical decision points. The aim of the present work was to determine the cut-off of the lactate threshold that activates alert triggers for all-cause 2-day mortality.

Design Multicentre, prospective, ambulance-based, observational study.

Setting Patients treated via emergency medical services (EMSs) and delivered to the emergency department between 2019 and 2023 were selected in Spain.

Participants Adults with any acute disease.

Primary and secondary outcome measures Epidemiological data, vital signs and prehospital point-of-care glucose and lactate levels were obtained. The outcome was all-cause 2-day in-hospital mortality. The cut-offs were obtained via three different methods: (i) indirect (which considers survivors and non-survivors), direct (which considers only survivors) assessment and lactate quartile. Additionally, the quartile approach was used to determine the differences in lactate distribution between survivors and non-survivors. Three different back-to-back studies with the same methodology were used.

Results A total of 11 713 patients fulfilled the inclusion criteria. The mortality rate was 4.6% (542 patients). The difference in the median prehospital lactate concentration (mmol/L) between survivors and non-survivors was statistically significant (p<0.001): 2.29 (95% CI 1.43 to 3.38) and 7.14 (95% CI 5.11 to 9.71), respectively. Globally, the cut-off for all the studies combined was estimated by the direct method to be 3.71 mmol/L (95% CI 2.92 to 3.91), which was similar to the indirect value of 3.07 (95% CI 2.95 to 5.49) and the third quartile of 4.00. The mortality rate in patients who were less than 3.71 mmol/L was 0.004%, and that above that cut-off was 18%.

Conclusions This study established a real-world lactate cut-off for 2-day in-hospital mortality of 3.71 mmol/L (95% CI 2.92 to 3.91) on the basis of data from the EMS. Considering this cut-off point could improve patient management via EMS services, allowing quick identification of patients at high risk of clinical worsening.

Trial registration number ISRCTN Registry (ISRCTN17676798, ISRCTN48326533, ISRCTN49321933).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study proposed a novel lactate cut-off for mortality based on multicentre, prospective, ambulance-based, real-time data from primary emergency medical service (EMS) patients.
⇒ This work was performed by using both classical methodologies and approaches recommended by the International Federation of Clinical Chemistry and Laboratory Medicine Committee on Reference Intervals and Decision Limits.
⇒ Lactate was measured at different points in the care system.
⇒ The direct technique requires healthy patients, which are difficult to obtain in a sample from the EMS.
⇒ Indirect methods are less suitable for establishing the cut-off by mixing healthy and unhealthy subjects.

INTRODUCTION

Point-of-care testing (POCT) in emergency medical services (EMSs) is a fast-growing trend, providing on-scene analytical data on a regular basis. These devices are reliable, fast, user friendly, and ultraportable and are ideal for regular implementation in workflows by EMS providers.[1] Among other available biomarkers, the prognostic ability of bedside lactate levels for predicting poor outcomes and short-term mortality is well documented,[2 3] and this parameter is uncontroversially used in diverse clinical conditions in prehospital critical care, for example, sepsis, major trauma, cardiac arrest and seizures.[4–7]

Until recently, blood tests were hospital-only practices; however, owing to recent advances, it was possible to perform colorimetric and/or immunoassay analysis techniques on-scenes. As a result of this change, EMS providers, in order to start interpreting the analytical values, have adopted reference intervals (RIs) validated in hospitals. Recently, prehospital lactate risk thresholds

have become available, and lactate levels >4 mmol/L are considered to indicate hyperlactataemia, whereas those >6 mmol/L indicate severe hyperlactataemia.[8] The correlation between unplanned intensive care unit (ICU) admission and short-term mortality with high prehospital lactate levels is clear.[9]

During the ultra-acute stage of acute life-threatening illness in prehospital care, potential physiopathological disorders (eg, hypoperfusion, hypoxia, coagulopathy, ischemia, acidosis and tissue inflammation) may appear, leading to significant alterations in the standard analytical parameters.[10] As a result, a cascade of response pathways is triggered to compensate for these mismatches, and EMS providers provide life-saving interventions[11] so that the analytical values of lactate determined in the emergency department (ED) do not necessarily match the analytical values measured on-scene.[12] In acute stages of the disease, biomarkers suggesting tissue hypoperfusion, for example, lactate, pH, bicarbonate and excess bases, are drastically disturbed, showing evidence of oxygen deprivation, so that the values taken on-scene may be substantially different from those obtained in the hospital. Consequently, the aim of this study was to determine the lactate threshold that activates alert triggers, that is, tagging patients at high risk of short-term mortality and therefore in need of early escalation, with real-world data collected at the bedside and considered a key benchmark in prehospital critical care.

METHODS

Study design

We conducted a multicentre, prospective, ambulance-based study of unselected adults with acute disease managed by the EMS system and delivered to the ED.

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (online supplemental file 1, p3).[13] The study was approved by the institutional review boards of the comité de ética de la investigación con medicamentos de las areas de salud de valladolid (references: PI-010–18, PI-049–19 and PI-217–20).

Cases were prospectively included from three back-to-back studies based on an identical methodology and running concurrently in time in the same location: 'Use of early warning scales in the prehospital scope as a diagnostic and prognostic tool (preNEWS-L)' (doi.org/10.1186/ISRCTN17676798) (cohort #1), 'Prehospital identification of prognostic biomarkers in time-dependent diseases (HITS study)' (doi.org/10.1186/ISRCTN48326533) (cohort #2) and 'Identification of biomarkers of clinical-risk deterioration in prehospital care (preBIO study)' (doi.org/10.1186/ISRCTN49321933) (cohort #3).

Study setting

Between 1 January 2019 and 1 November 2023, one emergency dispatch centre (1-1-2 phone number), eight advanced life support (ALS) units, 54 basic life support (BLS) units and five hospitals from four Spanish provinces (Burgos, Salamanca, Segovia and Valladolid), with a reference target of 1 364 952 inhabitants (in urban and rural areas), in the Community of Castilla y León (Spain) participated in the study. Resources were fully pooled and managed by the Public Health System (SACYL).

Typically, BLS units are staffed by two emergency medical technicians (EMTs), while the ALS units comprise two EMTs, an emergency registered nurse (ERN) and a physician. On-scene and EMS providers work with pre-established workflows, following international guidelines appropriate for each pathology (details about the EMS system in supplementary data p5).

Population

Patients (≥18 years old) with any acute disease were included. All the patients analysed in the present study were evaluated for ALS and then evacuated to the ED, either for ALS or BLS.

Minors, out-of-hospital cardiac arrest without recovery from spontaneous circulation, pregnant women (evident or probable), end-stage patients (with a specialist medical report and who, in addition, must receive palliative care), patients with no prehospital lactate results (eg, improper vascular access, malfunction of lactate monitoring devices) or patients without informed consent were excluded.

Written informed consent was obtained during prehospital care by ALS ERN and was obtained throughout the entire study, including during the follow-up duration. In cases of particularly critical conditions or in cases where the level of consciousness did not permit sufficient clear understanding, the document was signed by a relative or legal guardian. If, despite the two previous attempts, authorisation was not granted, an associate investigator from each ED was responsible for a third effort to obtain the document. Patients who did not provide informed consent were excluded.

The informed consent obtained did not delay healthcare. In case of doubt about the patient's cognitive capacity to understand and sign the document, as indicated above, consent was always obtained with a second intention, either by a family member or legal guardian or in the ED, with the ultimate aim of not delaying care. A copy of the informed consent can be found in the online supplemental data

Outcome

The principal outcome was 2-day in-hospital mortality (all-cause).

At the 30-day follow-up from the index event (prehospital assistance), an associate investigator assigned mortality dates to each hospital. This time frame was adopted to directly relate EMS care to the direct cause of death, in line with the findings of similar studies.[9 11] For longer-term mortality, patients could have died from complications not stemming from the primary disease.

Data acquisition

The EMS providers involved in the study attended mandatory face-to-face training to learn how to handle, calibrate, log and clean up the POCTs, as well as how to correctly use the data collection notebook.

Epidemiological data (age, sex and whether patients were from nursing home origin) and a full vital signs panel (respiratory rate, oxygen saturation, blood pressure, heart rate, temperature and Glasgow Coma Scale) were collected via the ALS ERN during the first contact with the patient. Prospectively, prehospital point-of-care glucose and lactate levels were measured. Prehospital lactate results were not considered for any on-scene or *en route* intervention. Oxygen saturation, blood pressure, heart rate and temperature were measured with a LifePAK 15 monitor-defibrillator (Physio-Control, Inc., Redmond, USA). Lactate and glucose analyses were performed in cohort #1 with Accutrend Plus (Roche Diagnostics, Mannheim, Germany), with the device operating by reflectance photometry (measuring range 0.8–21.7 mmol/L) and in cohorts #2 and #3 with the Epoc Blood Analysis System (Siemens Healthcare GmbH, Erlangen Germany), with the device processed by immunochromatography (measurement range of 0.2–22 mmol/L). Arterial, venous and capillary blood can be processed with both systems; however, only venous blood samples were tested in this study.

The ALS physician subsequently recorded the suspected prehospital diagnoses (29 different subcategories) (see supplementary material p6). At the 30-day follow-up from the index event, an associate investigator assigned to each hospital collected the 17 comorbidities needed to calculate the age-adjusted Charlson comorbidity index (aCCI)[14] (see supplementary material p6) and hospital outcomes (hospital admission and ICU admission).

Statistical methods

Absolute values and percentages were used for categorical variable representations, and means and SD or medians and interquartile ranges were used for continuous variables. The sample characteristics were presented by the descriptive results and by the associations between variables and the outcome with the following hypothesis tests: the Mann–Whitney U test or the χ^2 test, when appropriate. The Shapiro–Wilk test was used for normal distribution assessment. Details regarding the data collection, missing values, sample size calculations, software and RI calculation procedures can be found in supplementary data p8.

The analysis of the data was divided into three steps (note that three cohorts were used in the present work; therefore, the analysis was adapted to this fact):

1. To demonstrate the effects of confounding factors on lactate levels, a logistic regression for 2-day mortality analysis including all the variables described above was performed. The reference value for the calculation of ORs corresponds to the category with the lowest number of events.
2. To calculate the cut-off for each cohort and for the whole sample (using both direct and indirect methods), we developed two parallel analyses, one for the direct method and the other for the indirect method. This procedure is recommended by the members of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Committee on Reference Intervals and Decision Limits (C-RIDL)[15 16] (supplementary data p8), since it allows the cut-off from both methods to be obtained and the results to be compared. The direct method is performed using only survivors, and indirect methods are performed using large datasets from survivors and non-survivors. This last method requires statistical techniques, that is, the Box–Cox technique, to separate both cohorts' distributions of values. In particular, for the indirect method, we followed the method described here.[17–19] In particular, we use the pipeline described in online supplemental figure S1 but do not transform the data or use the final step described in[19] because the refineR package allows skewed distributions. For the direct method, we use the same pipeline used for the indirect method. The CIs associated with the cut-off were obtained by bootstrapping.
3. To study of both distributions (survivors and non-survivors) and calculation of ranges via the classical approach of quartiles, the study of both cohorts was performed by considering the overlapping coefficient (OC) of two distributions and the Cohen standardised mean difference (SMD). The OC allows us to quantify the overlap between two distributions. An OC of 0 means no overlap, and 1 assumes a complete overlap. The SMD is a measure of the distance between two means. This approach allows calculation of the effect size. An SMD close to 0 reflects no difference between means; the scientific community assumes that SMD <0.2, SMD between 0.2 and 0.8, and SMD >0.8 are small, moderate and large effect sizes, respectively. Note that the SMD can reach positive and negative values, and the aforementioned ranges of SMDs are based on the absolute value.

The data were analysed via R, V.4.2.2 (http://www.R-project.org; the R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among the 17 916 participants, 12 027 were eligible, and the final analysis cohort included 11 713 patients who met no exclusion criteria (see figure 1).

Survivors (95.4%, 11 171 patients) were typically 68 years old (IQR 52–80; range 18–104), and 41.7% (4657 patients) were females. There were statistically significant differences in age (p<0.0001) but not sex (p=0.554) between survivors and non-survivors. In general, vital signs were reported to be within the normal limits, with a median prehospital lactate level of 2.29 mmol/L (IQR 1.43–3.38; range 0.21–21). One-half of the suspected

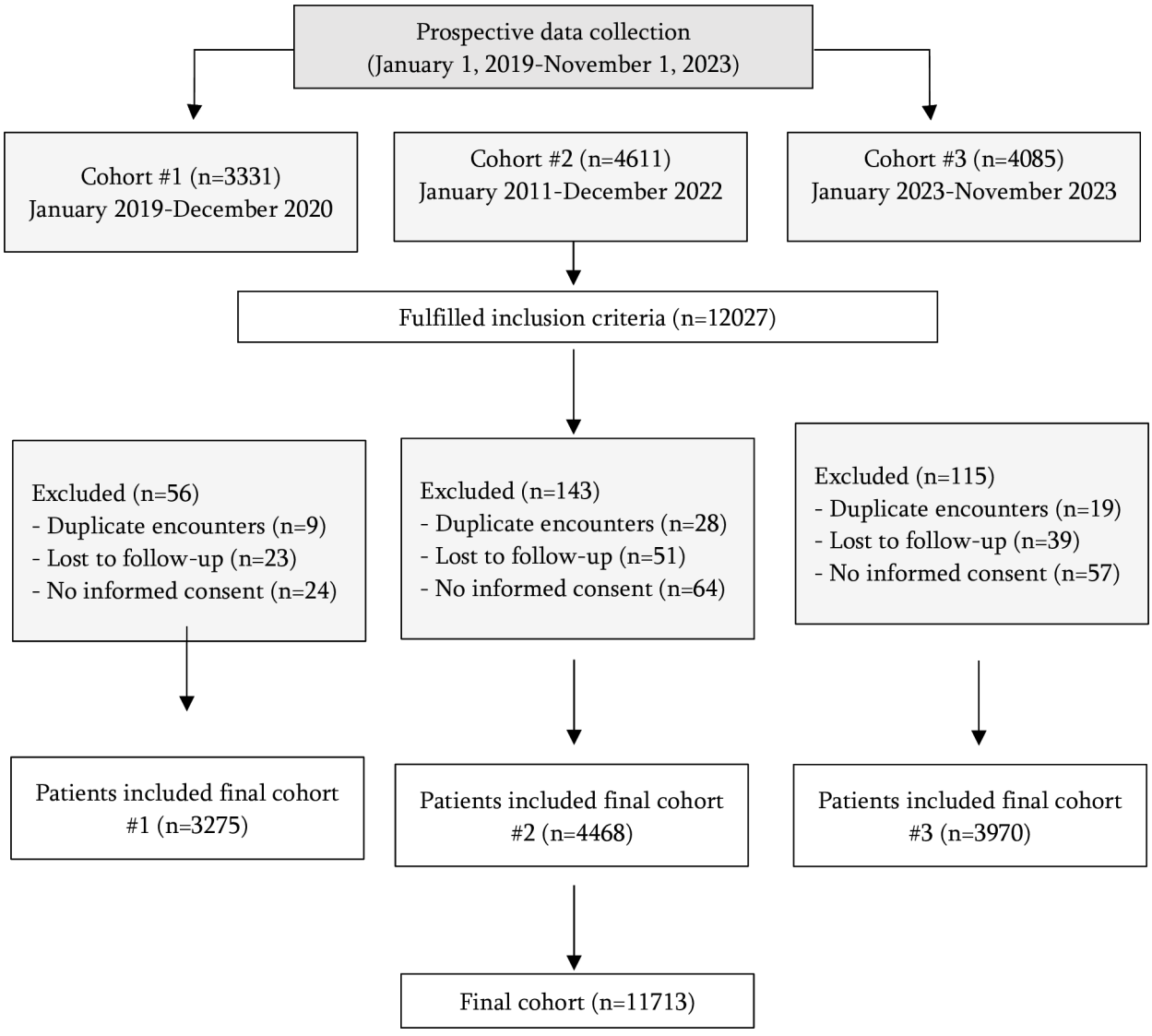

Figure 1 Study flowchart. Cohort #1: 'Use of early warning scales in the prehospital scope as a diagnoatic and prognostic tool-preNEWS-L_'; Cohort #2: 'Prehospital identification of prognostic biomarkers in time-dependent diseas - HITS study_'; Cohort #3: 'Identification of biomarkers of clinical-risk deterioration in prehospital care - PreBIO study'.

prehospital diagnoses were acute chest pain, syncope, stroke, intoxication, convulsion or dyspnoea (tables 1 and 2). Conversely, among the non-survivors (4.6%, 542 patients), the median age was 77 years (IQR 62–85; range 18–100), and 40.4% (219 patients) were females. As expected, vital signs were clearly impaired, with a median prehospital lactate level of 7.14 mmol/L (IQR 5.11–9.71; range 0.98–21) (p<0.001); similarly, on-scene advanced life support interventions (advanced airway management and intravenous medication (medications named in supplementary material p6)) were significantly more common. Among the non-survivors, 61.2% had suspected prehospital diagnoses of out-of-hospital cardiac arrest with recovery from spontaneous circulation, stroke, sepsis, polytrauma, dyspnoea or congestive heart failure. Not surprisingly, ICU admission rates increased in non-survivors versus survivors (47.8% vs 8.8%; p<0.001); however, acute cardiac care unit admission and stroke unit admission rates seemed consistent (tables 1 and 2).

The differences among the three studies were assessed for different subsets of patients. All the variables evaluated showed statistically significant differences between studies for the survivor subset, except for sex (online supplemental table S1). For the non-survivor subset, all variables presented statistically significant differences, except sex, type of transport, heart rate, temperature and use of non-invasive mechanical ventilation (online supplemental table S2). Finally, for the whole sample, the only non-significant factor was sex (online supplemental table S3).

After all confounding factors (study, age, sex, advanced life support, basic life support, rural or urban origin, nursing home, respiratory rate, oxygen saturation, fraction of inspired oxygen, systolic blood pressure, diastolic blood pressure, heart rate, temperature, Glasgow Coma Scale Ocular, Glasgow Coma Scale verbal, Glasgow Coma Scale motor, glucose, lactate, non-invasive mechanical ventilation, invasive mechanical

Table 1 Baseline patient characteristics based on 2-day mortality

	Total	Survivors	Non-survivors	P value*
No. (%) with data†	11 713 (100)	11 171 (95.4)	542 (4.6)	N.A.
Epidemiological variables				
Sex at birth, female	4876 (41.6)	4657 (41.7)	219 (40.4)	0.554
Age, year	68 (52–80)	68 (52–80)	77 (62–85)	<0.001
Age groups, year				
18–49	2522 (21.5)	2451 (21.9)	71 (13.1)	<0.001
50–74	4708 (40.2)	4541 (40.6)	167 (30.8)	
>75	4483 (38.3)	4179 (37.4)	304 (56.1)	
Transfer, ALS	7341 (62.7)	6866 (61.5)	475 (87.6)	<0.001
Nursing homes	1046 (8.9)	945 (8.5)	101 (18.6)	<0.001
On-scene vital signs				
Respiratory rate, breaths/min	18 (14–23)	18 (14–22)	23 (12–32)	<0.001
Oxygen saturation, %	96 (93–98)	96 (94–98)	87 (70–94)	<0.001
SBP, mm Hg	135 8115–153)	135 (117–154)	110 (80–145)	<0.001
DBP, mm Hg	79 (66–90)	80 (67–91)	61 (43–87)	<0.001
Heart rate, beats/min	85 (70–104)	84 (70–103)	101 (71–126)	<0.001
Temperature, °C	36.1 (35.9–36.7)	36.1 (36–36.7)	36 (35.1–36.7)	0.009
Glasgow coma scale, points	15 (15–15)	15 (15–15)	8 (3-14)	<0.001
Prehospital POCT				
Glucose, mg/dL	126 (104–160)	125 (104–156)	177 (129–241)	<0.001
Lactate, mmol/L	2.35 (1.47–3.61)	2.29 (1.43–3.38)	7.14 (5.11–9.71)	<0.001
Support on-scene				
NIMV	399 (3.4)	317 (2.8)	82 (15.1)	<0.001
IMV	783 (6.7)	509 (4.6)	274 (50.6)	<0.001
Intravenous medication, quantity				
No medication	1923 (16.4)	1916 (17.2)	7 (1.3)	<0.001
1	3719 (31.8)	3656 (32.7)	63 (11.6)	
2	2232 (19.1)	2173 (19.5)	59 (10.9)	
3	1547 (13.2)	1466 (13.1)	81 (14.9)	
4	1085 (9.3)	978 (8.8)	107 (19.7)	
5	660 (5.6)	580 (5.2)	80 (14.8)	
6	321 (2.7)	250 (2.2)	71 (13.1)	
7 or more	226 (1.9)	152 (1.4)	74 (13.9)	

*The Mann–Whitney U test or χ^2 test was used as appropriate.
†Values are expressed as the total number (percentage) and median (25th percentile–75th percentile), as appropriate.
ALS, advanced life support; DBP, diastolic blood pressure; IMV, invasive mechanical ventilation; NIMV, non-invasive mechanical ventilation; POCT, point-of-care testing; SBP, systolic blood pressure.

ventilation, aCCI calculation and medication number) were included, we determined the adjusted ORs and p values for all the variables. As shown in table 3 and in online supplemental table S4, lactate presented the lowest p value (p<2.2e-16, which is the minimum p value reported by R by default) and the highest Z value (15.7) compared with the other variables. The OR for lactate was 1.23 (95% CI 1.20 to 1.25), and the other statistically significant factors were as follows: being a patient from study #3 0.45 (95% CI 0.34 to 0.58), age 1.03 (95% CI 1.02 to 1.04), being from a rural origin 1.37 (95% CI 1.09 to 1.71), being from a nursing home 1.42 (95% CI 1.08 to 1.85), respiratory rate 1.03 (95% CI 1.02 to 1.04), oxygen saturation 0.98 (95% CI 0.98 to 0.99), systolic blood pressure 0.99 (95% CI 0.98 to 0.99), Glasgow Coma Scale Ocular 0.78 (95% CI 0.67 to 0.90), Glasgow Coma Scale verbal 0.84 (95% CI 0.76 to 0.94), use of non-invasive mechanical ventilation 1.97 (95% CI 1.46 to 2.66), use of invasive mechanical ventilation 2.45 (95% CI 1.85 to 3.24), aCCI 1.06 (95% CI

Table 2 Other determinants based on 2-day mortality

	Total	Survivors	Non-survivors	P value*
No. (%) with data†	11 713 (100)	11 171 (95.4)	542 (4.6)	N.A.
Suspected prehospital diagnoses				
Abdominal pain/GB	522 (4.5)	499 (4.5)	23 (4.2)	<0.001
Abdominal trauma	54 (0.5)	53 (0.5)	1 (0.2)	
Acute chest pain	1210 (10.3)	1205 (10.8)	5 (0.9)	
Acute myocardial infarction	702 (6)	679 (6.1)	23 (4.2)	
Anaphylaxis	124 (1.1)	124 (1.1)	0 (0)	
Bradycardia	137 (1.2)	131 (1.2)	6 (1.1)	
Burns	57 (0.5)	52 (0.5)	5 (0.9)	
Cardiac arrest	216 (1.8)	110 (1)	109 (19.6)	
Confusional syndrome	87 (0.7)	83 (0.7)	4 (0.7)	
Congestive heart failure	197 (1.7)	164 (1.5)	33 (6.1)	
COPD/dyspnoea	759 (6.5)	719 (6.4)	40 (7.4)	
Headache	58 (0.5)	58 (0.5)	0 (0)	
Heart failure	384 (3.3)	359 (3.2)	25 (4.6)	
Hypertensive crisis	174 (1.5)	173 (1.5)	1 (0.2)	
Infection/febrile syndrome	518 (4.4)	497 (4.4)	21 (3.9)	
Metabolic disease	206 (1.8)	193 (1.7)	13 (2.4)	
Orthopaedic trauma	522 (4.5)	522 (4.7)	0 (0)	
Poisoning‡	850 (7.3)	835 (7.5)	15 (2.8)	
Polytraumatised	221 (1.9)	176 (1.6)	45 (8.3)	
SARS-CoV-2	162 (1.4)	154 (1.4)	8 (1.5)	
Seizures	777 (6.6)	772 (6.9)	5 (0.9)	
Sepsis	193 (1.6)	146 (1.3)	47 (8.7)	
Status epilepticus	61 (0.5)	57 (0.5)	4 (0.7)	
Stroke	951 (8.1)	891 (8)	60 (11.1)	
Syncope	1211 (10.3)	1199 (10.7)	12 (2.2)	
Tachyarrhythmia	528 (4.5)	525 (4.7)	3 (0.6)	
Thoracic trauma	122 (1)	118 (1.1)	4 (0.7)	
Transient ischaemic attack	235 (2)	234 (2.1)	1 (0.2)	
Trauma brain injury	475 (4.1)	443 (4)	32 (5.9)	
Hospital outcomes				
aCCI, points	4 (1–6)	4 (1–6)	6 (4–8)	0.001
Inpatient	6355 (54.3)	5813 (52)	542 (100)	<0.001
ICU admission	1239 (10.6)	980 (8.8)	259 (47.8)	<0.001
ACCU admission	1006 (8.6)	950 (8.5)	56 (10.3)	0.138
Stroke unit admission	486 (4.1)	473 (4.2)	13 (2.4)	0.033

*The Mann–Whitney U test or χ^2 test was used as appropriate.
†Values are expressed as the total number (percentage) and median (25th percentile–75th percentile), as appropriate.
‡Smoke inhalation syndrome is included in the section on poisoning.
aCCI, age-adjusted Charlson comorbidity index; ACCU, acute cardiac care unit; COPD, chronic obstructive pulmonary disease; GB, gastrointestinal bleeding; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1.02 to 1.10) and medication number 1.255 (95% CI 1.18 to 1.33).

Online supplemental figure S2 shows the difference in lactate levels versus the probability of death according to two approaches: logistic regression (online supplemental figure S2A) and lowess smoothing (online supplemental figure S2B). Both figures show that the survival rate decreases as the lactate concentration increases.

Table 3 Logistic regression for mortality

Variable	OR	5 CI	95 CI	P value
Study 2	0.792	0.621	1.010	0.114
Study 3	0.450	0.345	0.586	<0.001
Age	1.034	1.026	1.041	<0.001
Sex	1.084	0.897	1.309	0.484
Advanced life support	1.354	1.038	1.777	0.064
Basic life support	0.000	NA	NA	0.979
Zone: rural	1.370	1.092	1.713	0.021
Nursing homes: Yes	1.425	1.088	1.857	0.029
Respiratory rate	1.034	1.024	1.045	<0.001
Oxygen saturation	0.989	0.981	0.997	0.021
Fraction of inspired oxygen	1.782	0.964	3.270	0.119
Systolic blood pressure	0.990	0.986	0.995	<0.001
Diastolic blood pressure	1.004	0.997	1.012	0.341
Heart rate	0.999	0.997	1.002	0.698
Temperature	0.940	0.867	1.019	0.208
Glasgow Coma Scale Ocular	0.782	0.677	0.903	0.005
Glasgow Coma Scale verbal	0.847	0.763	0.943	0.01
Glasgow Coma Scale motor	0.891	0.806	0.984	0.057
Glucose	1.001	1.000	1.002	0.066
Lactate	1.231	1.205	1.258	<0.001
Non-invasive mechanical ventilation: yes	1.977	1.465	2.660	<0.001
Invasive mechanical ventilation: yes	2.454	1.855	3.245	<0.001
Age-adjusted Charlson Comorbidity Index calculation	1.064	1.028	1.100	0.003
Medication number	1.255	1.180	1.334	<0.001

Table 4 Reference interval estimation

Reference	Cohort	Method
5.24 (4.41–5.71)	1	Direct
3.30 (1.66–4.32)	2	Direct
3.18 (1.87–3.46)	3	Direct
3.71 (2.92–3.92)	All	Direct
4.89 (4.20–6.44)	1	Indirect
2.79 (1.64–3.58)	2	Indirect
3.48 (1.77–6.21)	3	Indirect
3.07 (2.95–5.49)	All	Indirect
4.00	1	Q3
3.21	2	Q3
3.48	3	Q3
3.61	All	Q3
Statistics value		
0.34	1	OC
0.30	2	OC
0.25	3	OC
0.29	All	OC
−1.40	1	SMD
−1.46	2	SMD
−1.51	3	SMD
−1.44	All	SMD

The 95% CIs are shown in parentheses
OC, overlapping coefficient; Q3, 3rd quartile; SMD, Cohen standardised mean difference.

The cut-off calculations (table 4) yielded similar results for all the methods, except for the indirect method, which resulted in a lower RI. Among the cohorts, only cohort 1 presented the highest RI, but these differences were not found in the OC or SMD. Globally, the cut-off for all the cohorts was directly estimated to be 3.71 mmol/L (95% CI 2.92 to 3.91), which was similar for the indirect value of 3.07 mmol/L (95% CI 2.95 to 5.49) and the third quartile of 4.00. The OC for all studies reached 0.29, which reflects a low overlap between the survivor and non-survivor lactate distributions. The SMD was −1.44, reflecting a large effect size, that is, difference between means.

Finally, if the resulting RI, for instance, 3.71, was applied to our cohort, the mortality rate below this point was 0.004%, and above that point, the mortality rate reached 18% (figure 2 and online supplemental figure S2).

DISCUSSION

This study considered unselected adults with acute disease and derived a novel lactate cut-off (3.71 mmol/L; 95% CI 2.92 to 3.91) on the basis of real-time data from primary EMS patients to target prehospital care. The proposed novel lactate cut-off is supported by both classical methodologies and approaches recommended by the IFCC C-RIDL.[15 16]

As anticipated, a gap appeared between the hospital cut-off and the novel lactate prehospital cut-off (3.71 mmol/L vs 4 mmol/L).[20 21] EMS systems provide support in the subacute stage of acute life-threatening illness, with subsequent physiological and analytical changes.[22] Specifically, standardised advanced life support interventions

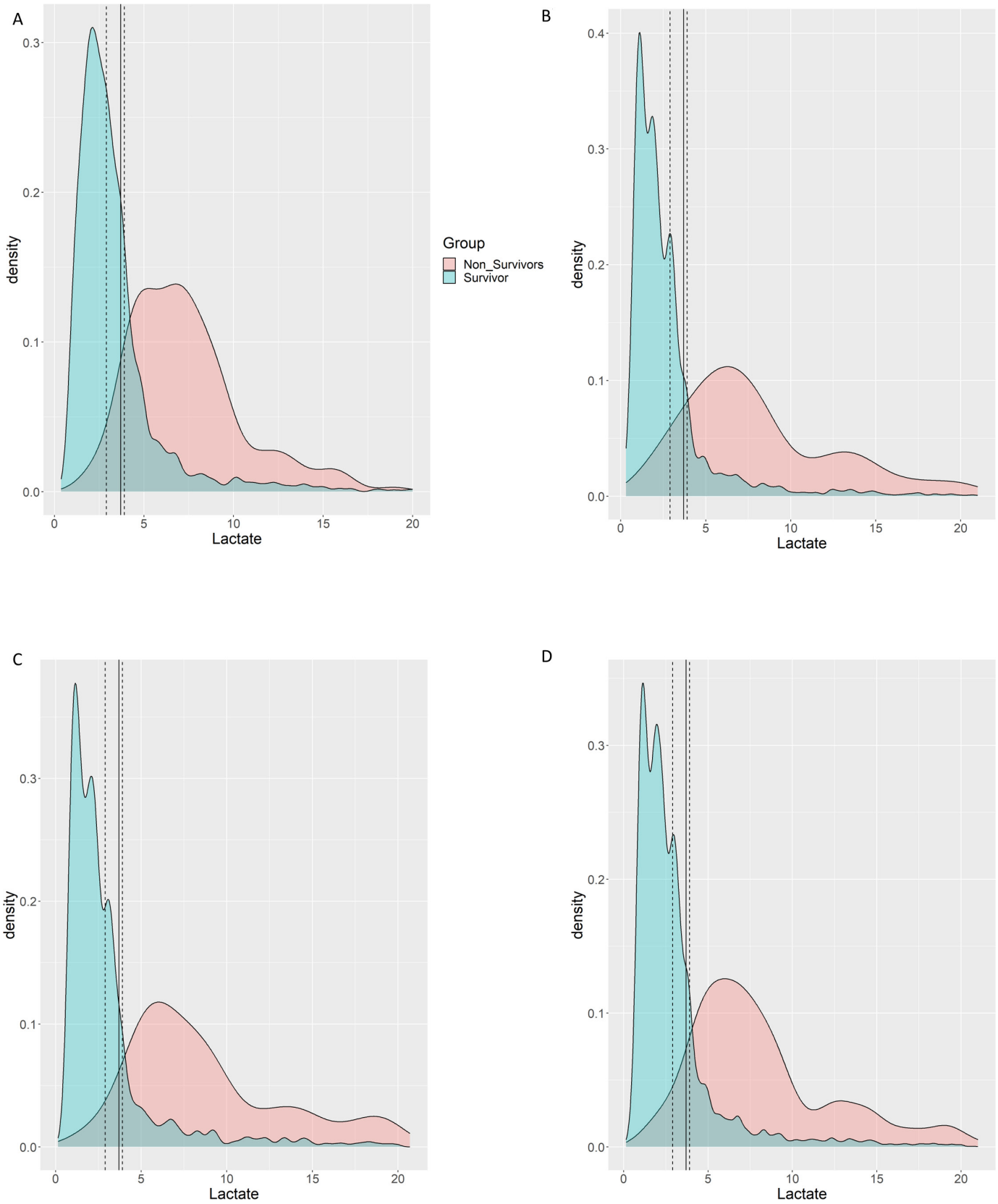

Figure 2 Distribution of patients in cohort 1 (A), cohort 2 (B), cohort 3 (C) and the whole cohort (D). Non-survivors (red area) and survivors (blue area). The solid line represents the reference interval, and the dashed lines represent the confidence intervals obtained by bootstrapping.

are performed by the EMS; therefore, the patient's condition can be expected to improve or at least not worsen, so by the time the ED is reached, patients in the ultra-acute phase may have subsided or diminished.[5 23]

The prehospital lactate level, an indicator of short-term mortality and clinical worsening, is well established.[3 5 24 25] The next appropriate step was to identify lactate thresholds, which were performed on the basis of data collected at the in-hospital point.[26 27] Recently, several attempts have been made to establish an on-scene cut-off point to guide the decision-making process in prehospital care. Swan *et al*[9] (retrospective study with 253 cases) reported that a lactate concentration above 2.5 mmol/L was associated with in-hospital mortality. Martín-Rodríguez *et al*[28] reported in a prospective study with 2997 patients who 1.9 mmol/L and 4 mmol/L were the cut-off points for low and high mortality, respectively. Galvagno *et al*[11] (a prospective study with 261 trauma patients) reported that a lactate level >4 mmol/L was significantly associated with greater sensitivity and specificity for predicting the need for a lifesaving intervention. Gaessler *et al*,[29] in a prospective study of 130 trauma patients, identified a cut-off point of 4 mmol/L (together with less than 2.5 mmol/L of excess base) as an indicator of the need for early transfusion. Walter *et al*.[30] (a prospective study with 745 patients), in line with previous reports, reported that a lactate >4 mmol/L was associated with 7-day mortality.

In brief, a prehospital lactate concentration of 4 mmol/L appears to be a well-established cut-off. By using both direct and indirect methods, the novel cut-off was 3.71 mmol/L (95% CI 2.92 to 3.91), a value that slightly deviated from the information provided by previous references. However, all the studies analysed thus far have been carried out with restricted sample sizes, providing the current study with an advantage over all previous studies, which also updated the cut-off calculation method. As a result, following the implementation of direct methods and the availability of a large cohort, a more accurate characterisation of the novel prehospital lactate cut-off was obtained, emphasising not only the divergence in the value but also the excellent CI delivered, delimiting in an optimal way the critical threshold starting from an alert triggering point. On the other hand, despite all the confounding factors analysed, lactate is the most consistent variable, regardless of the type of patient or clinical condition.[6 31] For example, the example of glucose did not show statistically significant differences in the logistic regression (p=0.066), despite the statistically significant differences found in the univariate analysis.

Novel lactate intervals could help to determine the origin of certain alterations in prehospital care, for example, syncope versus seizures. Elevated lactate levels (above even 6 mmol/L) correlate with seizures but are not associated with worse short-term outcomes.[32] Similarly, lactate values greater than 4 mmol/L in patients with traumatic brain injury and a Glasgow Coma Scale score greater than 9 points (non-severe trauma) correlate with an elevated risk of clinical impairment, suggesting that this may serve as a red flag for labelling these patients as severe in principle.[33] Similarly, on-scene use of prehospital point-of-care lactate may decisively help in the timely recognition of high-risk patients who are going to require more intensive advanced life support interventions, leading to a strategy to be followed and facilitating the transfer and continuity of care in the ED.[11]

Our study has several strengths. This was a multicentre, prospective, ambulance-based study with a relevant sizeable sample collected non-stop (including the COVID-19 pandemic period), in urban and rural areas, by distinct ambulance stations, and with the use of various POCTs from different manufacturers. Indeed, the value of prehospital lactate may be corroborated by not being dependent on the POCT employed,[1 34 35] and our findings should also be transferable to other scenarios involving free-for-all medical care, including nursing homes and primary care centres. Moreover, the present study included three back-to-back substudies conducted with different POCTs. Discrepancies among cohorts were reported in terms of mortality, age and lactate concentration; however, despite these differences, the cut-off were considered similar. The data suggested that the novel cut-off derivative was consistent.

Nonetheless, the study has certain limitations. First, the data extractors were unblinded. To minimise biases, the EMS providers lacked access to hospital follow-up data; vice versa, the hospital research associates were unaware of the prehospital variables. Only the data manager and the principal investigator could access the master database. However, the EMS providers were aware of the lactate concentrations, which may have influenced the decision-making process on-scene or en route. Second, the use of a variety of POCT systems is common in EDs; however, EMS systems have rapidly started to implement these devices. Currently, there are hand-held, ultraportable, rugged, reliable and inexpensive lactometers, with operations identical to those of standardised implanted glucometers; therefore, the routine use of prehospital lactate could become a standard technique. To operate correctly, the POCTs used must run between 10 and 32°C. Outside these limits, measurements are not possible, and for clinical safety reasons, the device is inoperative. To overcome this limitation, the POCTs were placed in isothermal rugged suitcases, ensuring a stable temperature between 15 and 25°C at all times and in all weather conditions. Third, direct analysis techniques discriminate the total cohort into two subcohorts: healthy and unhealthy. Deeming healthy patients as having demanded assistance from the EMS and having been seen by an on-scene ALS may not be correct. However, to overcome this limitation, our patients were dichotomously split into survivors (healthy) and non-survivors (2-day mortality), a distinction critical for prehospital care, to identify patients at high risk of ultrafast clinical worsening. Fourth, indirect methods are less suitable for establishing the cut-off by mixing healthy and unhealthy subjects. In populations in which establishing this nuance is complex, this method

may be useful; however, in the present study, the principal outcome was well defined so that standard methodologies, and direct techniques appeared to be more suitable for the intended scope. Finally, it should be noted that both direct and indirect methods are one-dimensional approaches; therefore, no covariates can be included in the analysis.

In summary, the ability of prehospital lactate levels to predict impairment risk and associated short-term mortality in a timely manner should not be underestimated; thus, the availability of dedicated and tailor-made cut-off s for prehospital care is an overriding demand. This study, performed with real-world data gained by EMS systems, has derived a novel lactate cut-off (3.71 mmol/L; 95% CI 2.92 to 3.91), a cut-off point like that of previous studies but with a reduced CI, yielding a fine on-scene alert trigger, thus helping in a decisive way in the decision-making process in prehospital critical care.

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Contributors FM-R and CdPV conceptualised the project, managed and coordinated the project, assisted with the design of the methodology, analysed the data and prepared the initial and final drafts of the manuscript. AS-G, SGV and LADL took responsibility for the data and their analysis. DZS, PÁdSC, ESA, SAO and RCI contributed to the management and coordination of the project, assisted with the design of the methodology and helped review the manuscript. RLI and FM-R conceptualised the project and helped review and comment on the initial and final drafts of the manuscript. Guarantor is FM-R. All the authors performed a critical review and approved the final manuscript for interpretation of the data and important intellectual input.

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Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by the institutional review boards of the comité de ética de la investigación con medicamentos de las areas de salud de valladolid (references: PI-010-18, PI-049-19 and PI-217-20). The study is registered in the WHO International Clinical Trials Registry Platform with the numbers ISRCTN17676798, ISRCTN48326533 and ISRCTN49321933. Details of the study design, statistical analysis plan and raw data are available online. Participants gave informed consent to participate in the study before taking part.

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REFERENCES

1 Nadim G, Laursen CB, Pietersen PI, *et al*. Prehospital emergency medical technicians can perform ultrasonography and blood analysis in prehospital evaluation of patients with chronic obstructive pulmonary disease: a feasibility study. *BMC Health Serv Res* 2021;21:290.
2 Corral Torres E, Hernández-Tejedor A, Millán Estañ P, *et al*. Prognostic value of metabolic parameters measured by first responders attending patients with severe trauma: associations with the New Injury Severity Score and mortality. *Emerg* 2023;35:90–6.
3 Martín-Rodríguez F, López-Izquierdo R, Castro Villamor MA, *et al*. Prognostic value of lactate in prehospital care as a predictor of early mortality. *Am J Emerg Med* 2019;37:1627–32.
4 Olander A, Magnusson C, Sundler AJ, *et al*. Prediction of the Risk of Sepsis by Using Analysis of Plasma Glucose and Serum Lactate in Ambulance Services: A Prospective Study. *Prehosp Disaster Med* 2023;38:160–7.
5 Stojek L, Bieler D, Neubert A, *et al*. The potential of point-of-care diagnostics to optimise prehospital trauma triage: a systematic review of literature. *Eur J Trauma Emerg Surg* 2023;49:1727–39.
6 Dusik M, Rob D, Smalcova J, *et al*. Serum lactate in refractory out-of-hospital cardiac arrest: Post-hoc analysis of the Prague OHCA study. *Resuscitation* 2023;192:109935.
7 Patel J, Tran QK, Martinez S, *et al*. Utility of serum lactate on differential diagnosis of seizure-like activity: A systematic review and meta-analysis. *Seizure* 2022;102:134–42.
8 Martín-Rodríguez F, Sanz-García A, Martínez Fernández FT, *et al*. Association between prehospital lactate categories with short- and long-term mortality: a prospective, observational multicenter study. *QJM* 2023;116:835–44.
9 Swan KL, Avard BJ, Keene T. The relationship between elevated prehospital point-of-care lactate measurements, intensive care unit admission, and mortality: A retrospective review of adult patients. *Aust Crit Care* 2019;32:100–5.
10 Pape H-C, Moore EE, McKinley T, *et al*. Pathophysiology in patients with polytrauma. *Injury* 2022;53:2400–12.
11 Galvagno SM Jr, Sikorski RA, Floccare DJ, *et al*. Prehospital Point of Care Testing for the Early Detection of Shock and Prediction of Lifesaving Interventions. *Shock* 2020;54:710–6.
12 Shinada K, Koami H, Matsuoka A, *et al*. Prediction of return of spontaneous circulation in out-of-hospital cardiac arrest with non-shockable initial rhythm using point-of-care testing: a retrospective observational study. *World J Emerg Med* 2023;14:89–95.
13 Vandenbroucke JP, von Elm E, Altman DG, *et al*. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med* 2007;4:e297.
14 Charlson M, Szatrowski TP, Peterson J, *et al*. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;47:1245–51.
15 Jones GRD, Haeckel R, Loh TP, *et al*. Indirect methods for reference interval determination - review and recommendations. *Clin Chem Lab Med* 2018;57:20–9.
16 Ozarda Y, Ichihara K, Jones G, *et al*. Comparison of reference intervals derived by direct and indirect methods based on compatible datasets obtained in Turkey. *Clin Chim Acta* 2021;520:186–95.
17 Ichihara K, Boyd JC, IFCC Committee on Reference Intervals and Decision Limits (C-RIDL). An appraisal of statistical procedures

used in derivation of reference intervals. *Clin Chem Lab Med* 2010;48:1537–51.
18 Crutchfield CA, Thomas SN, Sokoll LJ, *et al*. Advances in mass spectrometry-based clinical biomarker discovery. *Clin Proteomics* 2016;13:1.
19 Ammer T, Schützenmeister A, Prokosch H-U, *et al*. refineR: A Novel Algorithm for Reference Interval Estimation from Real-World Data. *Sci Rep* 2021;11:16023.
20 Ress KL, Koerbin G, Li L, *et al*. Reference intervals for venous blood gas measurement in adults. *Clin Chem Lab Med* 2021;59:947–54.
21 Tyler PD, Du H, Feng M, *et al*. Assessment of Intensive Care Unit Laboratory Values That Differ From Reference Ranges and Association With Patient Mortality and Length of Stay. *JAMA Netw Open* 2018;1:e184521.
22 Drumheller BC, Tuffy E, Gibney F, *et al*. Severe bradycardia from severe hyperkalemia: Patient characteristics, outcomes and factors associated with hemodynamic support. *Am J Emerg Med* 2022;55:117–25.
23 Collopy KT, Westmoreland A, Powers WF. Patient Care Alterations After Point-of-Care Laboratory Testing During Critical Care Transport. *Air Med J* 2022;41:370–5.
24 Boland LL, Hokanson JS, Fernstrom KM, *et al*. Prehospital Lactate Measurement by Emergency Medical Services in Patients Meeting Sepsis Criteria. *West J Emerg Med* 2016;17:648–55.
25 Abuzer Ö. Evaluation of Short-Term Mortality Prediction Using Initial Lactate and NEWS+L at Admission in COVID-19 Patients. *Disaster Med Public Health Prep* 2023;17:e333.
26 Tehrani BN, Truesdell AG, Sherwood MW, *et al*. Standardized Team-Based Care for Cardiogenic Shock. *J Am Coll Cardiol* 2019;73:1659–69.
27 Cannon CM, Miller RT, Grow KL, *et al*. Age-adjusted and Expanded Lactate Thresholds as Predictors of All-Cause Mortality in the Emergency Department. *West J Emerg Med* 2020;21:1249–57.
28 Martín-Rodríguez F, López-Izquierdo R, Medina-Lozano E, *et al*. Accuracy of prehospital point-of-care lactate in early in-hospital mortality. *Eur J Clin Invest* 2020;50:e13341.
29 Gaessler H, Helm M, Kulla M, *et al*. Prehospital predictors of the need for transfusion in patients with major trauma. *Eur J Trauma Emerg Surg* 2023;49:803–12.
30 Walther LH, Zegers F, Nybo M, *et al*. Accuracy of a point-of-care blood lactate measurement device in a prehospital setting. *J Clin Monit Comput* 2022;36:1679–87.
31 Graham CA, Leung LY, Lo RS, *et al*. Agreement between capillary and venous lactate in emergency department patients: prospective observational study. *BMJ Open* 2019;9:e026109.
32 Magnusson C, Herlitz J, Höglind R, *et al*. Prehospital lactate levels in blood as a seizure biomarker: A multi-center observational study. *Epilepsia* 2021;62:408–15.
33 Martin-Rodriguez F, Sanz-Garcia A, Lopez-Izquierdo R, *et al*. Prehospital Lactate Levels Obtained in the Ambulance and Prediction of 2-Day In-Hospital Mortality in Patients With Traumatic Brain Injury. *Neurol*2024;103:e209692.
34 Füzéry AK, Elian FA, Kost GJ. A review of temperature-related challenges and solutions for the Abbott i-STAT and Siemens Healthineers epoc devices. *Clin Biochem* 2023;115:49–66.
35 Blanchard IE, Kozicky R, Dalgarno D, *et al*. Community paramedic point of care testing: validity and usability of two commercially available devices. *BMC Emerg Med* 2019;19:30.