RESUSCITATION 192 (2023) 109935

Available online at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Serum lactate in refractory out-of-hospital cardiac arrest: Post-hoc analysis of the Prague OHCA study

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Abstract

Background: The severity of tissue hypoxia is routinely assessed by serum lactate. We aimed to determine whether early lactate levels predict outcomes in refractory out-of-hospital cardiac arrest (OHCA) treated by conventional and extracorporeal cardiopulmonary resuscitation (ECPR).

Methods: This study is a post-hoc analysis of a randomized Prague OHCA study (NCT01511666) assessing serum lactate levels in refractory OHCA treated by ECPR (the ECPR group) or conventional resuscitation with prehospital achieved return of spontaneous circulation (the ROSC group). Lactate concentrations measured on admission and every 4 hours (h) during the first 24 h were used to determine their relationship with the neurological outcome (the best Cerebral Performance Category score within 180 days post-cardiac arrest).

Results: In the ECPR group (92 patients, median age 58.5 years, 83% male) 26% attained a favorable neurological outcome. In the ROSC group (82 patients, median age 55 years, 83% male) 59% achieved a favorable neurological outcome. In ECPR patients lactate concentrations could discriminate favorable outcome patients, but not consistently in the ROSC group. On admission, serum lactate >14.0 mmol/L for ECPR (specificity 87.5%, sensitivity 54.4%) and >10.8 mmol/L for the ROSC group (specificity 83%, sensitivity 41.2%) predicted an unfavorable outcome.

Conclusion: In refractory OHCA serum lactate concentrations measured anytime during the first 24 h after admission to the hospital were found to correlate with the outcome in patients treated by ECPR but not in patients with prehospital ROSC. A single lactate measurement is not enough for a reliable outcome prediction and cannot be used alone to guide treatment.

Keywords: Out-of-hospital cardiac arrest, Cardiopulmonary resuscitation, Extracorporeal membrane oxygenation, Lactate

Introduction

The survival rates for out-of-hospital cardiac arrest (OHCA) remain low, with only 8% of patients surviving.[1] The short low-flow duration and early return of spontaneous circulation (ROSC) are crucial for a favorable neurological outcome.[2] Prolonged resuscitation in refractory OHCA leads to more severe ischemia and reperfusion injury, resulting in higher mortality and a worse neurological outcome.[3] The reported survival for patients transported to the hospital without ROSC is <4%.[4,5] Extracorporeal cardiopulmonary resuscitation (ECPR) seems promising to increase the survival of properly selected refractory OHCA patients.[6–12]

Serum lactate level is an easily measured variable[13,14] commonly used for outcome prediction in critically ill patients.[15–18] Considering the devastating metabolic consequences of cardiac arrest, lactate

Abbreviations: ACLS, advanced cardiovascular life support, AUC, area under the curve, AUROC, area under the receiver operating characteristic curve, COPD, chronic obstructive pulmonary disease, CA, cardiac arrest, CPC, Cerebral Performance Category, CPR, cardiopulmonary resuscitation, ECLS, extracorporeal life support, ECMO, extracorporeal membrane oxygenation, ECPR, extracorporeal cardiopulmonary resuscitation, EMS, emergency medical services, h, hours, ICD, implantable cardioverter defibrillator, ICU, intensive care unit, IQR, interquartile range, Lac, serum lactate, OHCA, out-of-hospital cardiac arrest, min, minutes, ROC, receiver operating characteristic, ROSC, return of spontaneous circulation, TTM, target temperature management.

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https://doi.org/10.1016/j.resuscitation.2023.109935

Received 29 May 2023; Received in Revised form 12 July 2023; Accepted 5 August 2023

measurements routinely evaluate the severity of hypoperfusion and tissue hypoxia.[19–21] Still, data on the association between early lactate levels after cardiac arrest and patient outcomes are inconsistent and inconclusive.[22–25] Moreover, the evaluation of lactate in OHCA treated by ECPR has rarely been reported.[26–28]

In this post-hoc analysis of the randomized Prague OHCA study[7] we evaluated the association between early lactate levels and neurological outcomes in refractory OHCA. We hypothesized that lactate serum concentrations might be a prognostically valuable marker in conventionally- and ECPR-managed populations.

Methods

This study is a post-hoc analysis of the prospective open-label randomized clinical trial, the Prague OHCA study (NCT01511666) which compared an invasive approach (early transport to hospital under mechanical cardiopulmonary resuscitation (CPR), ECPR and immediate invasive assessment and therapy) to standard advanced cardiac life support (ACLS) in patients with refractory OHCA. The study was conducted at a single center in Prague, Czech Republic between March 2013 and October 2020. All procedures were followed in accordance with the ethical standards of the institutional review board of the General University Hospital and First Faculty of Medicine, Charles University in Prague (IORG0002175 – General University Hospital in Prague, IRB00002705, 192/11S-IV) and the Helsinki Declaration. Each participant's legal representative and patients who regained normal neurological function were informed of the study enrolment and requested written informed consent.[7]

The main study protocol and results have been published elsewhere.[7,29] In brief, adults aged 18–65 with witnessed OHCA of presumed cardiac etiology were enrolled after a minimum of 5 minutes (min) of ACLS without ROSC. Patients were electronically randomized to invasive or standard treatment arms during the ongoing CPR. In the invasive arm patients were immediately transported directly to the cardiac center catheterization laboratory under continuous mechanical CPR with the intention of proceeding with ECPR if ROSC was not achieved en route or upon hospital admission. Patients allocated to the standard arm were managed by continued ACLS on-site. If ROSC were achieved (defined as a cardiac electrical activity with a palpable pulse), transport to the hospital was initiated for post-CPR care.[7]

The current post-hoc analysis aims to assess the feasibility of predicting the neurological outcome in refractory OHCA patients based on serial serum lactate levels measured during the first 24 hours (h) after hospital admission.

Neurological outcome of patients was assessed blindly by a neurologist at 30 and 180 days after the initial OHCA event. The best Cerebral Performance Category (CPC) score reached anytime within the study period was used to determine the outcome. The CPC score is a five-point scale from 1 (good cerebral performance) to 5 (brain death).[30] CPC scores of 1 and 2 were recognized as favorable and CPC scores 3, 4 and 5 as unfavorable outcomes.

Study population

This post-hoc analysis compares two distinct groups of patients from the original Prague OHCA study population regardless of the initial randomized group assignment. The ECPR group includes patients who presented with the absence of ROSC upon admission to the hospital and had undergone ECPR. The ROSC group comprises patients with standard ACLS therapy who achieved ROSC after randomization. In other words, the ECPR group includes all non-ROSC patients from the original invasive group and those who crossed over from the standard to the invasive group and ultimately received ECPR. The ROSC group contains all patients with ROSC in both the original standard and invasive arms. From the original study population, patients without laboratory data, including those who died on site and patients who presented on admission to the hospital without ROSC and were not treated by ECPR, were excluded from the present analysis.

Study procedures

The serum lactate sampling followed a prespecified protocol, and admission samples were obtained from each patient as soon as possible after admission. In addition, +4-h, +8-h, +12-h, +16-h, +20-h and +24-h samples were collected during the first 24 h at the intensive care unit. In the ECPR group the first blood sample was drawn before or during cannulation, i.e., before ECPR was established. The analyzed blood samples were preferably taken from the femoral artery; if this was not available, then central venous blood was analyzed instead. Lactate concentrations were determined using the blood gas analyzer ABL90 Flex (Radiometer Medical ApS, Brønshøj, Denmark), with values <2.0 mmol/L considered normal.[31–34]

Statistical analysis

The data were analyzed using MedCalc® Statistical Software version 20.211 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023). Continuous variables were expressed as medians with interquartile range (IQR). The Shapiro-Wilk test and a manual check of skewness and kurtosis were used to verify the normality of the distribution of the continuous variables. A non-normal distribution was found for all continuous variables. Therefore, the Mann-Whitney U test was used to evaluate the differences in continuous variables between the favorable and unfavorable subgroups. Categorical variables were expressed as frequencies and percentages. The chi-square and Fisher's exact test (for data in 2×2 pivot tables) were computed to compare categorical variables between subgroups. For Fisher's exact test, a two-tailed p-value was calculated as the doubling of the one-tailed p-value of the Fisher exact test. A two-tailed *p*-value of <0.05 was considered statistically significant. The ECPR and ROSC groups were analyzed separately using identical statistical procedures. Participants from both study groups were divided according to the outcome reached. First, the lactate concentrations of patients with favorable and unfavorable outcomes from each group were directly compared at each time point (i.e., on admission and every 4 h). Second, the area under the curve (AUC) of the lactate concentration in the first 24 h was calculated for each patient. Next, the Mann-Whitney test was again used to compare the AUC values between the subgroups. Using ROC analysis, specific lactate values for each time point were determined to divide the study population based on the outcome. The value with the highest Youden index ($J = \text{sensitivity} + \text{specificity} - 1$) was employed as the cut-off value.

All measured lactate values were used for the direct comparison of lactate concentrations as well as for the ROC analysis. No specific technique was used for the imputation of missing data. However, based on the methods used, the AUC analysis was calculated only for patients with the initial and +24 h lactate values available. If a missing value was found in those patients, the AUC calculation algorithm performed linear interpolation between the closest known values.

Results

Of the 256 participants in the original Prague OHCA study, 174 (68%) were included in this analysis. Some 82 patients did not meet the inclusion criteria for this post-hoc analysis and were excluded. Fig. 1 illustrates the study flow diagram.

ECPR group

Of 92 patients, 24 (26%) achieved a favorable neurological outcome within 180 days. As listed in Table 1, patients with a favorable outcome more often presented with a shockable rhythm, had a shorter time from collapse to emergency medical service arrival and were given lower doses of adrenaline.

Fig. 2 depicts the lactate levels observed in the ECRP group. Generally, lower lactate levels were seen in the favorable outcome patients. The median lactate values for a favorable vs. unfavorable outcome for patients on admission were 11.2 (IQR 9.2–13.8) mmol/L vs. 14.8 (IQR 12.1–17.5) mmol/L, p <0.001, respectively. In both subgroups the lactate values decreased rapidly during the first 4 h after admission, with a continued decrease up to 24 h. Still, the median lactate concentrations after 24 h of hospitalization did not normalize in either group. The difference in serum lactate concentrations between the favorable and unfavorable outcome patients was significant in each measurement during the first 24 h. The median total AUC of lactate levels was 107.8 (IQR 72.8–146.0) in the favorable outcome patients compared to 153.5 (IQR 102.2–207.8) in the unfavorable outcome patients (p = 0.006).

ROSC group

The ROSC group comprised 82 patients, with 48 (59%) reaching a favorable outcome. Baseline characteristics are given in Table 1. Diabetes was more frequent in the unfavorable group. Similar to the ECPR group, favorable outcome patients presented more often with a shockable rhythm and received fewer doses of adrenaline. The median time from collapse to the first emergency medical service crew arrival was equal between favorable and unfavorable patients. However, the favorable patients' total time from collapse to advanced cardiac life support (physician on site) was shorter.

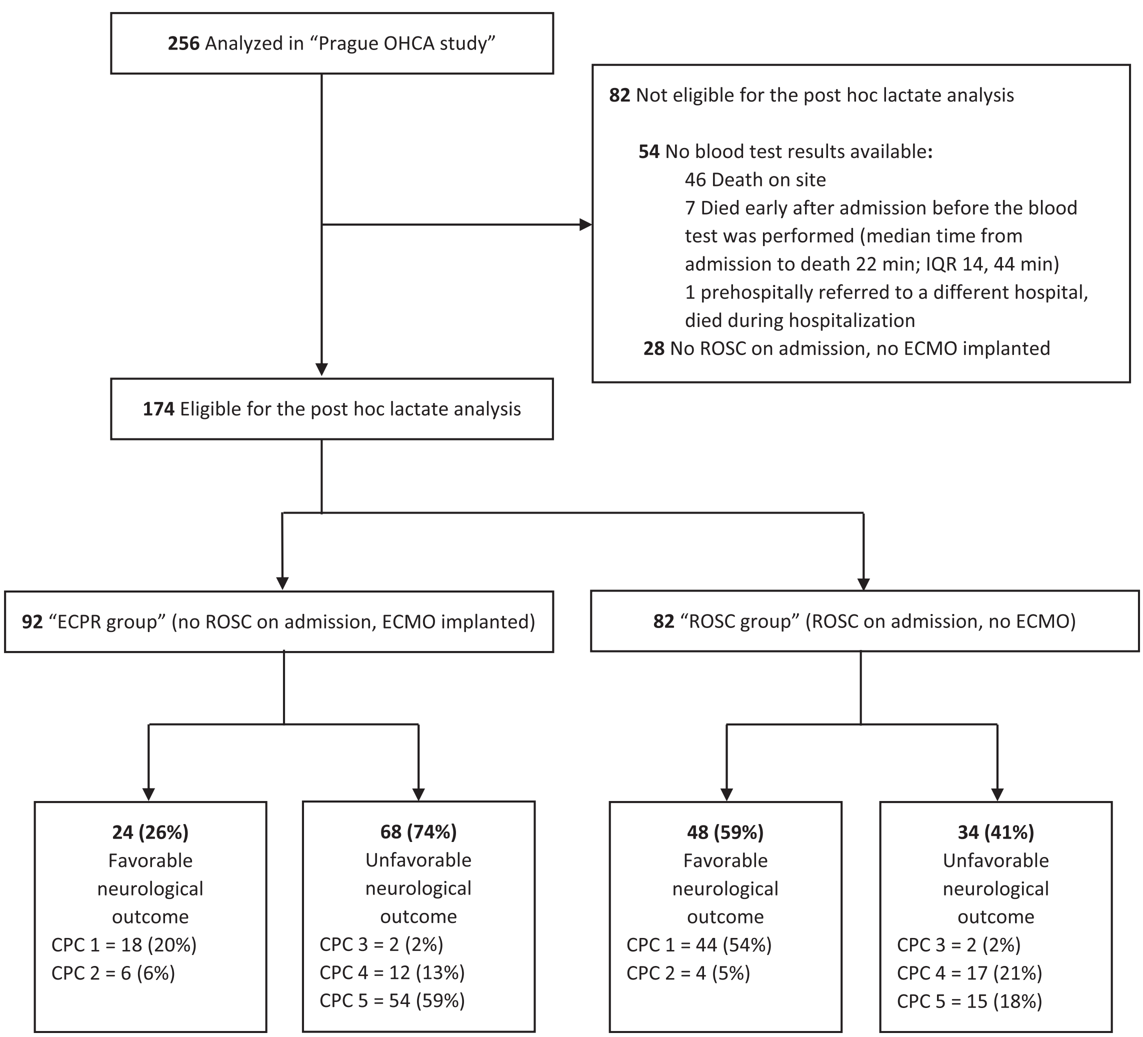


Fig. 1 – Consort flow diagram. Abbreviations: CPC – Cerebral Performance Category; ECMO – extracorporeal membrane oxygenation; ECPR – extracorporeal cardiopulmonary resuscitation; IQR – interquartile range; OHCA – out-of-hospital cardiac arrest; ROSC – return of spontaneous circulation.

Table 1 – Baseline population characteristics according to study group and outcome.

	ECPR group (*N* = 92)			ROSC group (*N* = 82)		
	Favorable (*N* = 24)	Unfavorable (*N* = 68)	*P* value	Favorable (*N* = 48)	Unfavorable (*N* = 34)	*P* value
Age, median (IQR), years	57.5 (40–64.5)	58.5 (47–65.5)	0.25	53.0 (45–61)	58.0 (51–66)	0.32
Sex						
Woman	3 (12.5)	13 (19.1)	0.7	7 (14.6)	7 (20.6)	0.68
Man	21 (87.5)	55 (80.9)		41 (85.4)	27 (79.4)	
Medical history						
Hypertension	9 (37.5)	29 (42.6)	0.44	19 (39.6)	18 (52.9)	0.12
Diabetes	3 (12.5)	10 (14.7)	0.9	4 (8.3)	10 (29.4)	**0.01**
Coronary artery disease	2 (8.3)	13 (19.1)	0.25	9 (18.8)	4 (11.8)	0.82
Chronic heart failure	2 (8.3)	7 (10.3)	1.0	2 (4.2)	1 (2.9)	1.0
COPD	0	2 (3)	1.0	5 (10.4)	2 (5.9)	0.94
Chronic kidney disease	0	2 (3)	1.0	1 (2.1)	2 (5.9)	0.63
ICD implanted	0	2 (3)	1.0	0	0	–
Location of cardiac arrest						
Public place	15 (62.5)	31 (45.6)	0.28	32 (66.7)	20 (58.8)	0.76
Home	4 (16.7)	22 (32.4)		14 (29.2)	12 (35.3)	
EMS	5 (20.8)	15 (22.1)		2 (4.2)	2 (5.9)	
Initial rhythm						
Ventricular fibrillation	23 (95.8)	34 (50)	**<0.001**	44 (91.7)	17 (50)	**<0.001**
Asystole	0	18 (26.5)		2 (4.2)	12 (35.3)	
Pulseless electrical activity	1 (4.2)	16 (23.5)		1 (2.1)	5 (14.7)	
Bystander CPR	23 (95.8)	68 (100)	0.52	48 (100)	32 (94.1)	0.34
Time from collapse to EMS arrival, median (IQR), minutes	6.0 (5.3–8)	9 (7–11)	**0.004**	9 (7–10)	9 (7.5–11.5)	0.34
Time from collapse to ACLS, median (IQR), minutes	8 (6–11)	10.5 (6.5–13)	0.09	10 (8–12)	12 (10–16)	**0.03**
Telephone assisted bystander CPR	18 (75)	47 (69.1)	0.79	44 (91.7)	31 (91.2)	1.0
Time to telephone assisted CPR, median (IQR), minutes	2.5 (2–4)	3 (2–4.8)	0.88	3 (2–4)	3 (2–4)	0.71
Number of adrenalin doses prehospitally, median (IQR), mg	2.5 (1.5–5)	4 (3–6)	**0.03**	2 (1–4)	4 (3–6)	**<0.001**
Number of defibrillations prehospitally, median (IQR)	6 (4–8)	5 (2–7)	0.14	4 (3–5)	3 (1.5–5)	0.17
Time from collapse to hospital arrival, median (IQR), minutes	45.5 (39.5–51)	48 (41.5–57)	0.16	60 (51–66)	63 (55–75)	0.06
Time of CPR (time to death/ROSC or ECLS), median (IQR), minutes	56.5 (52–63)	61 (51–71.5)	0.11	28 (22–36)	33 (25–44)	**0.04**
Target temperature management	24 (100)	66 (97.1)	1.0	48 (100)	30 (88.2)	0.05
Hypothermia initiated prehospitally	4 (16.7)	14 (20.6)	0.93	9 (18.8)	3 (8.8)	0.35

The continuous variables were expressed as medians with interquartile range (IQR). The categorical variables were presented as frequencies and percentages. Statistically significantly different values ($p < 0.05$) are in bold.

Abbreviations: ACLS – advanced cardiovascular life support; COPD – chronic obstructive pulmonary disease; CPR– cardiopulmonary resuscitation; ECLS – extracorporeal life support; EMS – emergency medical services; ICD – implantable cardioverter defibrillator; ROSC – return of spontaneous circulation.

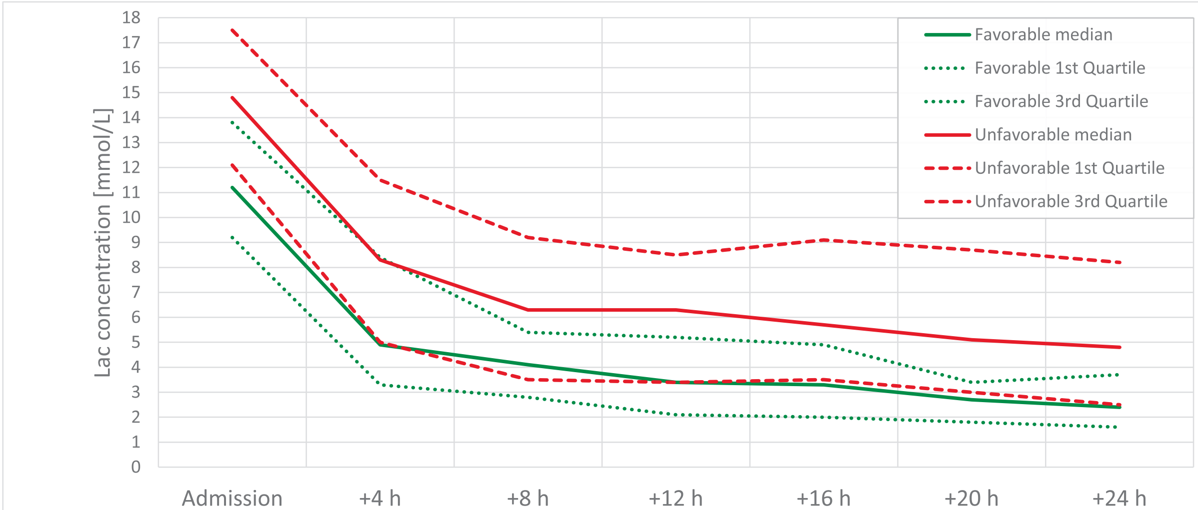
The lactate levels for the ROSC favorable outcome subgroup were generally lower, similar to the ECPR group (Fig. 3). The median serum lactate concentrations on admission were 7.8 (IQR 5.7–10.2) mmol/L in the favorable outcome subgroup compared to 9.7 (IQR 7.1–12.1) mmol/L in the unfavorable outcome subgroup, $p = 0.055$. The median lactate concentration normalized during the first 8 h of hospitalization in the favorable subgroup, which was not the case in the unfavorable outcome patients. We found no difference between the favorable and unfavorable subgroups in serum lactate levels on admission and after 20 and 24 h. For the remaining measurements, differences were present. The total lactate AUC was again lower in favorable patients (57 [IQR 46.7–74.7] vs. 68 [IQR 50.4–143]; $p = 0.04$).

Serum lactate concentration and outcome prediction

Fig. 4 delineates the suggested lactate cut-off values for the outcome prediction. In the ECPR group, a lactate value >14.0 mmol/L on admission predicts an unfavorable outcome with a specificity of 87.5% and a sensitivity of 54.4%. Similarly, a lactate value >10.8 mmol/L (specificity 83.0%, sensitivity 41.2%) predicts an unfavorable outcome for the ROSC group. After 24 h, the suggested cut-off values are 3.9 mmol/L (specificity 81.8%, sensitivity 61.9%) for the ECPR group and 1.6 mmol/L (specificity 61.9%, sensitivity 63%) for the ROSC group.

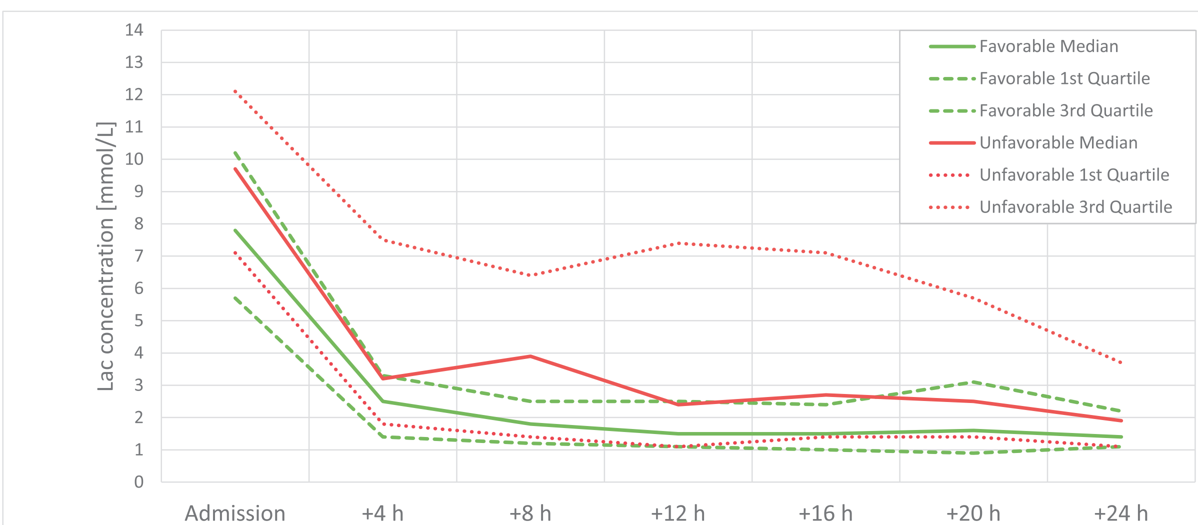
Discussion

This post-hoc analysis of a randomized controlled trial showed the long-term prognostic value of early serum lactate concentrations for neurological outcome prediction in refractory OHCA patients who were treated by ECPR or achieved ROSC with a conventional ACLS.



	Admission	+4 h	+8 h	+12 h	+16 h	+20 h	+24 h
Favorable	**11.2 (9.2-13.8)**	**4.9 (3.3-8.4)**	**4.1 (2.8-5.4)**	**3.4 (2.1-5.2)**	**3.3 (2.0-4.9)**	**2.7 (1.8-3.4)**	**2.4 (1.6-3.7)**
Unfavorable	**14.8 (12.1-17.5)**	**8.3 (5.0-11.5)**	**6.3 (3.5-9.2)**	**6.3 (3.4-8.5)**	**5.7 (3.5-9.1)**	**5.1 (3.0-8.7)**	**4.8 (2.5-8.2)**
p-value	**<0.001**	**0.001**	**0.03**	**<0.001**	**0.005**	**0.002**	**0.001**

Fig. 2 – ECPR group – Serum lactate concentration during the first 24 hours of intensive care according to the outcome. Data are expressed as median (IQR); serum lactate concentration is listed in mmol/L. Abbreviation: Lac – serum lactate.

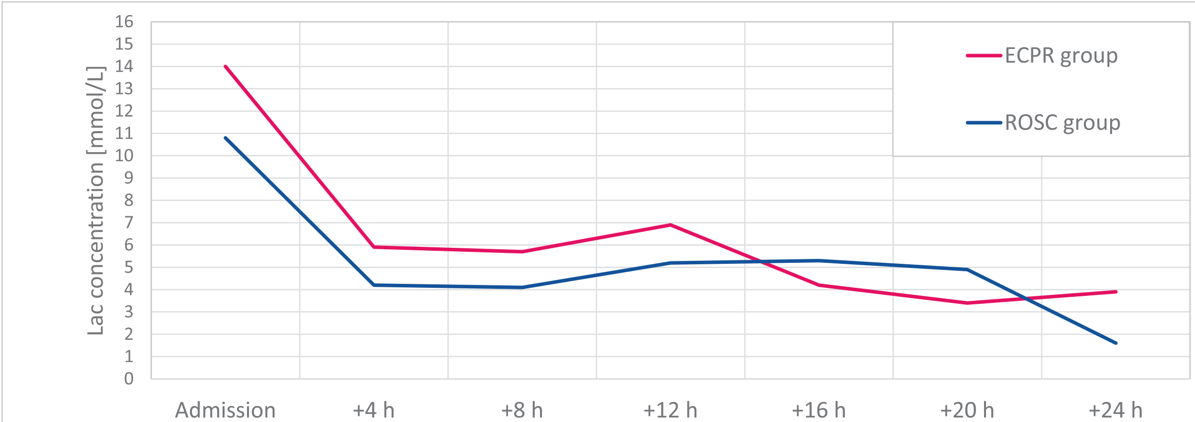


	Admission	+4 h	+8 h	+12 h	+16 h	+20 h	+24 h
Favorable	7.8 (5.7-10.2)	**2.5 (1.4-3.3)**	**1.8 (1.2-2.5)**	**1.5 (1.1-2.5)**	**1.5 (1.0-2.4)**	1.6 (0.9-3.1)	1.4 (1.1-2.2)
Unfavorable	9.7 (7.1-12.1)	**3.2 (1.8-7.5)**	**3.9 (1.4-6.4)**	**2.4 (1.1-7.4)**	**2.7 (1.4-7.1)**	2.5 (1.4-5.7)	1.9 (1.1-3.7)
p-value	0.055	**0.017**	**0.02**	**0.04**	**0.03**	0.07	0.14

Fig. 3 – ROSC group – Serum lactate concentration during the first 24 hours of intensive care according to the outcome. Data are expressed as median (IQR); serum lactate concentration is listed in mmol/L. Abbreviation: Lac – serum lactate.

ECPR patients showed consistently higher lactate values, reflecting a more severe state of organ hypoperfusion. The reasons for these higher lactate values are multiple, with the time sequence of ROSC and the first blood sampling being the most important. ECPR patients were admitted during ongoing CPR and the first blood sample was drawn before the extracorporeal circulation was launched. At the same time, ROSC patients had already restored spontaneous circulation. ROSC achieved prehospital and shorter overall CPR durations are the most likely determinants for the significantly higher number of patients with a favorable outcome in the ROSC group.

Despite the dissimilarities between the main study groups, which were to be expected, higher serum lactate levels in the ECPR and ROSC patients were associated with an unfavorable outcome. For the ECPR group, a significant difference was observed between



ECPR group							
Lac cut-off	**>14.0**	**>5.9**	**>5.7**	**>6.9**	**>4.2**	**>3.4**	**>3.9**
Sensitivity	54.4	70.5	62.3	49.1	68.9	66.7	61.9
Specificity	87.5	70.8	84.2	95.8	72.2	78.9	81.8
AUROC	0.74	0.73	0.67	0.75	0.73	0.76	0.74
ROSC group							
Lac cut-off	**>10.8**	**>4.2**	**>4.1**	**>5.2**	**>5.3**	**>4.9**	**>1.6**
Sensitivity	41.2	48.1	50	35.7	41.2	33.3	63
Specificity	83	89.1	97.6	95.2	96.7	94.4	61.9
AUROC	0.63	0.67	0.67	0.64	0.69	0.64	0.61

Fig. 4 – Cut-off values of serum lactate concentration. Higher values than the cut-off predict an unfavorable outcome. Serum lactate cut-off values are listed in mmol/L. Abbreviations: AUROC – area under the receiver operating characteristic curve; Lac – serum lactate.

the favorable and unfavorable outcome patients in all measurements in the first 24 h of hospitalization. The values continuously decreased after admission in both subgroups. Our results align with a German retrospective cohort study on cardiac arrest patients treated with ECPR, which showed increased serum lactate concentrations associated with higher 30-day mortality.[27] A retrospective study from Japan also proved the high prognostic value of early lactate metabolism after ECPR, despite the different methodologies (lactate clearance calculation).[26]

The significant difference in serum lactate values was proven at 4/7 time points and in the total AUC for the lactate concentrations in the first 24 h for the ROSC patients. The lactate values on admission did not differ significantly. We hypothesize that the initial lactate values are unreliable predictors as different transport times occur from the field to the hospital. The actual time between ROSC and the first lactate measurement differs from patient to patient. Further persistent high lactate levels without clearance may reflect not only the severity of an initial insult but also the severity of reperfusion syndrome or ongoing tissue hypoperfusion and hypoxia. In the ROSC unfavorable outcome subgroup a temporary lactate level increase at +8 h was even observed, possibly suggesting an early phase of postcardiac arrest syndrome.[35] The results indicate the need for serial lactate measurements and careful evaluation of the concentration trend over time, given that a single and randomly measured value can be misleading. This finding is supported by numerous trials showing conflicting data on the prognostic value of the single initial lactate value.[25,36–39]

To translate the results into a parameter that might be used in daily routine we analyzed the ROC curves and calculated the exact lactate values, which might help to separate patients based on the outcome. Of note, the AUROC curves of the measurements made at various times after admission were relatively consistent. Despite the good prognostic performance of lactate levels, no single parameter can currently serve as a decision surrogate to initiate or not the therapy (especially ECPR).[8,40] Even within our study, we identified three patients from the ECPR group and eight from the ROSC group who survived with a favorable neurological outcome despite higher initial lactate levels than the suggested cut-off values.

Several findings make our study valuable and clinically relevant. This study is based on data from a prospectively enrolled and randomized population. Patients were treated both conventionally and with ECPR. The study was focused on true refractory OHCA, documented by long CPR durations with a median time reaching 60 minutes (min) in the ECPR and 30 min in the ROSC group. This excessive length of CPR is also the most probable reason for reported higher on-admission lactate values in our population compared to other analyses with unselected OHCA patients. For example, in Donnino's study the reported median initial lactate level was 4.1 mmol/L for OHCA survivors compared to 7.3 mmol/L for non-survivors.[41] Dadeh and Nuanjaroan performed a retrospective study on lactate in OHCA patients arriving at the hospital with ongoing CPR, which is analogous to the ECRP group from our analysis. However, their suggested initial lactate cut-off of 9.1 mmol/L to predict mortality at 24 h is substantially lower than our proposed value of 14.0 mmol/L.[42] Lastly, we used the outcome assessment during the 180 days after the OHCA event to highlight the predictive value of initial lactate levels in a long-term context.

Limitations

The most important limitations are the single-center design, limited sample size and the post-hoc data analysis. Another limitation is that the medical staff in charge of each patient was not blinded; hence, the actual lactate level could affect the decision-making process. The blood samples were preferably drawn from the artery, but even if some values were taken from the vein, data showed no significant difference in lactate levels between arterial and central venous samples.[43,44]

Conclusion

In refractory OHCA, serum lactate concentrations measured anytime during the first 24 h after admission to the hospital were found to correlate with the outcome in patients treated by ECPR but not consistently in patients with prehospital ROSC. An admission lactate value >14.0 mmol/L for ECPR and >10.8 mmol/L for ROSC patients predicted an unfavorable neurological outcome with a specificity of 87.5% and 83%, respectively. Considering specificity <100%, single lactate values should not be the only parameter in deciding to withdraw or continue the treatment for both ECPR and ROSC patients, but serial lactate measurements as part of a multimodal approach may help to guide the therapy.

Funding

This study has been supported by Ministry of Health, Czech Republic – conceptual development of research organisation (General University Hospital in Prague – VFN, 00064165), and by the Charles University Research program “Cooperatio – Intensive Care Medicine”.

CRediT authorship contribution statement

Milan Dusik: Conceptualization, Methodology, Data Curation, Writing – Original Draft. **Daniel Rob:** Writing – original draft, Methodology, Investigation, Conceptualization. **Jana Smalcova:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Stepan Havranek:** Validation, Investigation, Data curation. **Jiri Karasek:** Writing – review & editing, Validation, Investigation. **Ondrej Smid:** Investigation, Data curation. **Helena Lahoda Brodska:** Investigation, Data curation, Conceptualization. **Petra Kavalkova:** Validation, Project administration, Investigation, Data curation. **Michal Huptych:** Formal analysis, Data curation. **Jan Bakker:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The authors thank Zachary H. K. Kendall, BA and Leslie Shaps, PhD for the language editing.

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