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Original Contributions

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EARLY LACTATE DYNAMICS IN CRITICALLY ILL NON-TRAUMATIC PATIENTS IN A RESUSCITATION ROOM OF A GERMAN EMERGENCY DEPARTMENT (OBSERVE-LACTATE-STUDY)

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☐ **Abstract—Background: Management of critically ill non-trauma patients in the resuscitation room of an emergency department (ED) is very challenging, and it is difficult to identify patients with a higher risk of death. Previous studies have shown that lactate indices can predict survival for selected diseases and syndromes. Objective: As reported for other patient populations, we set out to determine whether admission lactate or lactate dynamics (LD) within 24 h can predict 30-day mortality in unselected critically ill non-traumatic patients. Methods: In this retrospective study over a 1-year period, admission lactate, time weighted average lactate (Lac_{TW}) and LD of all critically ill adult patients admitted from ED to intensive care unit were analyzed. A linear regression model was implemented to estimate lactate data 1 h after admission. Results: The admission lactate, Lac_{TW}, and LD within 24 h were analyzed from 392 critically ill patients. The overall 30-day mortality rate was around 29%. Admission lactate (4.1 ± 4.0 mmol/L vs. 6.6 ± 6.1 mmol/L; $p < 0.01$) and Lac_{TW} (1.8 ± 1.7 mmol/L vs. 4.1 ± 4.8 mmol/L; $p < 0.01$) were different between survivors and non-survivors. LD between survivors and non-survivors did not differ at 1 h, 6 h, 12 h, or 24 h. After excluding patients with out-of-hospital or in-hospital cardiac arrest during resuscitation room management, admission lactate and LD between survivors and non-survivors did not differ at 1 h, 12 h, and 24 h. LD at 6 h (44% ± 42% vs. 33% ± 58%; $p = 0.042$) and Lac_{TW} (1.7 ± 1.6 mmol/L vs. 2.6 ± 3.0 mmol/L; $p < 0.01$) did differ. Conclusions: In critically ill ED patients initially requiring treatment in a resuscitation room setting, LD at 6 h and Lac_{TW} may predict their survival beyond 30 days. These findings need to be confirmed in a prospective study design.** © **2018 Elsevier Inc. All rights reserved.**

☐ **Keywords—emergency department; resuscitation room; lactate; lactate-clearance; lactate-dynamics; non-traumatic critically ill patients; mortality**

INTRODUCTION

The challenges in treatment of critically ill patients admitted to the resuscitation room of an emergency department (ED) were recently demonstrated by our group (1). Early identification of the underlying problems and appropriate management after ED arrival improves the outcome of critically ill patients.

After initial stabilization of their vital functions in the ED, these patients are evaluated based on their symptoms, and appropriate critical care interventions are initiated (2).

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Blood lactate and its dynamics have been the subject of many studies that included patient groups with specific diagnoses (e.g., trauma, sepsis, surgical, cardiogenic shock, cardiac arrest, general intensive care unit [ICU] patients) (3–27). These studies have shown that initial high lactate levels and high lactate levels during the in-hospital course as well as slow lactate decrease are associated with higher mortality (28). Nichol et al. showed that dynamic lactate indices within the first 24 h after ICU admission have independent and better predictive values compared to static indices (29).

The aim of our study has been to investigate admission lactate and dynamic lactate parameters within the first 24 h after presentation in the ED in a non-selected population of critically ill patients. The goal has been to identify patients with a higher risk of death up to 30 days after admission, and to test the applicability of findings from studies based on highly selective patient subgroups in a general emergency patient population. We wanted to know whether lactate and its early dynamics could be used as a simple tool to help emergency physicians pre-estimate the risk of death of critically ill patients in the ED.

METHODS

Study Design

Data from the OBSERvE study was analyzed retrospectively with regard to lactate levels at admission, time weighted average lactate (Lac_{TW}), and lactate dynamics (LD) during the first 24 h (1). The OBSERvE study was a prospective single-center observational cohort study that described the epidemiology, management, and outcome in non-traumatic critically ill ED patients (1). From September 1, 2014 to August 31, 2015, all non-traumatic patients who were admitted to the resuscitation room of a German university hospital ED were observed. The study documentation did not affect the individual treatment and the decision-making process during the study period. The study protocol was approved by the Institutional Ethical Committee (amendment 478/16-EK, 264-14-25082014).

Study Population

The aim of the investigation was to observe lactate and its course within the first 24 h after admission in a non-selected cohort of adult non-traumatic critically ill patients. Admission criteria for these patients to the resuscitation room were problems in airway, breathing or circulation, unconsciousness or neurologic deficits, and a critical physical state for other reasons. As part of the routine protocol of the resuscitation room, the first blood gas analysis including the admission blood lactate level was done on all patients within 15 min after admission (blood gas analyzer: ABL800 FLEX XQ, Radiometer Medical ApS, Bronshoj, Denmark).

Inclusion Criteria

We included all patients ≥ 18 years of age who underwent further treatment in ICU or intermediate care units, because in our hospital periodically blood gas analyses

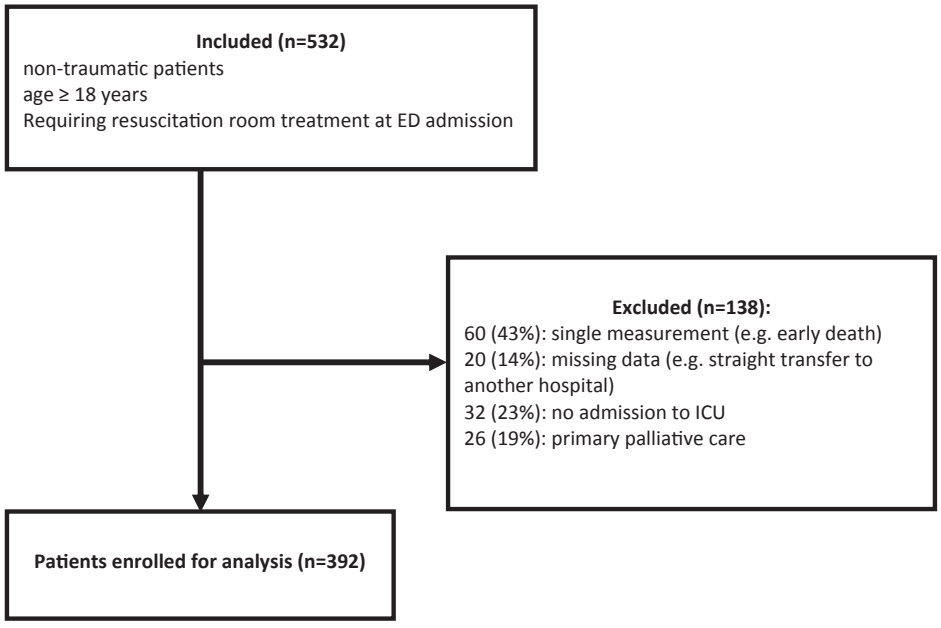

Figure 1. Enrollment flow diagram. ED = emergency department, ICU = intensive care unit.

Table 1. Patients Characteristics and Diagnosis Groups

Variable	Total	Non-Survivor	Survivor
Patients, n	392	113	279
Male sex, n (%)	237 (60.46)	67 (59.29)	170 (60.93)
Age, years			
Mean ± SD	67.18 ± 15.75	71.44 ± 14.21	65.46 ± 16.03
Median (IQR)	71 (58–79)	74 (64–82)	69 (56–78)
Mechanical ventilation rate in RR, n (%)	144 (36.73)	54 (47.79)	90 (32.26)
Catecholamines in resuscitation area, n (%)	49 (12.5)	27 (23.89)	22 (7.89)
Hospital stay, days, median (range)	8 (0–80)	5 (0–28)	10 (1–80)
ICU stay, days, median (range)	4 (0–46)	4 (0–22)	3 (0–46)
Ongoing CPR at admission, n (%)	31 (7.91)	19 (16.81)	12 (4.3)
SBP at admission, mm Hg			
Mean ± SD*	136.39 ± 44.22	130.24 ± 51.0	138.67 ± 41.3
Median (range)*	135 (40–350)	127.5 (40–300)	136.5 (60–350)
No. of lactate measurements, median (range)	8.5 (2–17)	9 (2–17)	8 (2–16)
Cardiovascular problems (including AMI/PE/HF/CD), n (%)	75 (19.13)	14 (12.39)	61 (21.86)
Loss of blood, n (%)	20 (5.1)	2 (1.77)	18 (6.45)
Intracerebral bleedings and coma, n (%)	69 (17.6)	26 (23.01)	43 (15.41)
COPD, n (%)	31 (7.91)	8 (7.08)	23 (8.24)
Cardiac arrest, n (%)	69 (17.6)	39 (34.51)	30 (10.75)
Seizure, n (%)	26 (6.63)	1 (0.88)	25 (8.96)
Toxic exposure or overdose, n (%)	29 (7.4)	1 (0.88)	28 (10.04)
Sepsis, n (%)	55 (14.03)	19 (16.81)	36 (12.9)
Others, n (%)	18 (4.59)	3 (2.56)	15 (5.38)

AMI = acute myocardial infarction; CD = cardiac dysrhythmia; COPD = chronic obstructive pulmonary disease; CPR = cardiopulmonary resuscitation; HF = heart failure; ICU = intensive care unit; IQR = interquartile range; PE = pulmonary embolism; RR = resuscitation room; SBP = systolic blood pressure; SD = standard deviation.
* Patients under ongoing CPR excluded.

are only performed in ICU and intermediate care units, but not in the general wards (Figure 1).

Exclusion Criteria

We excluded patients in palliative care settings at admission, and those lacking lactate data within the first 24 h (e.g., due to transfer to another hospital).

Subgroup Definition

We investigated the whole study population, as well as the following subgroups: patients without cardiopulmonary resuscitation (CPR), patients with CPR, admission lactate ≤ 2.2 vs. > 2.2 mmol/L (according to the upper limit of normal), and < 4.0 vs. ≥ 4.0 mmol/L (according to the Surviving Sepsis Campaign and Casserly et al. (30–32).

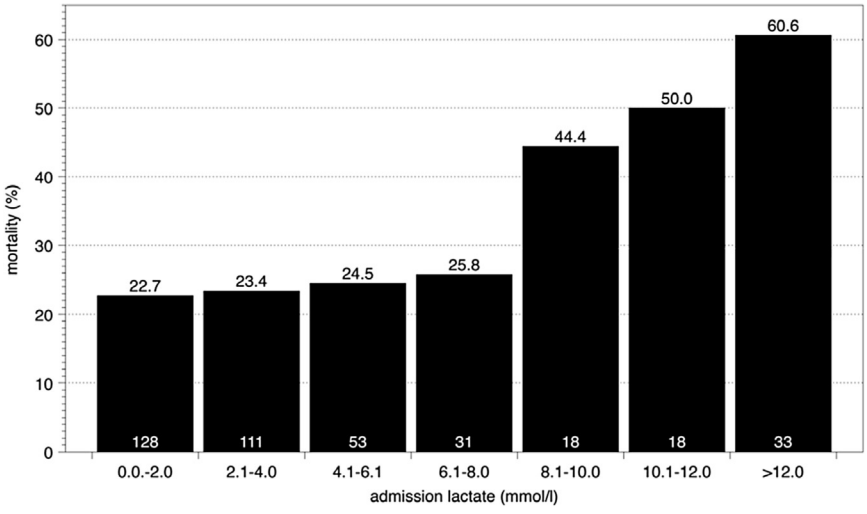

Figure 2. Mean 30-day mortality rate in 392 critically ill non-traumatic patients, depicted for lactate level ranges at admission to the emergency department. White numbers are absolute patient numbers included per lactate range. Roughly, admission lactate > 8.0 mmol/L was associated with a twofold increase in mortality. compared to admission lactate < 8.0 mmol/L.

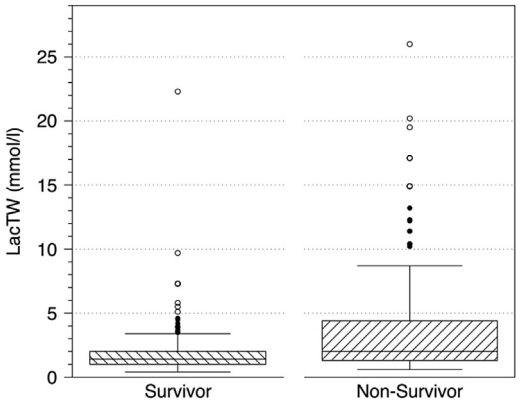

Figure 3. Time weighted average lactate (LacTW) in survivors vs. non-survivors (mean ± SD = 1.8 ± 1.7 mmol/L vs. 4.1 ± 4.8 mmol/L, $p < 0.01$).

Study Definitions and Data Collection

In our hospital, the point of care analyzing devices automatically transmit the results to the clinical information system. The admission lactate levels and the blood lactate levels within the first 24 h from arterial or venous blood gas analyses were collected from this system.

The admission lactate was the earliest available lactate level, usually taken within the first 15 min after arrival in the ED. We defined the LD as the lactate level at 1, 6, 12, and 24 h after admission relative to the admission lactate level. A negative LD thus indicates an increase in lactate. Because there was no special hospital guideline for the frequency of measurement of blood gas levels for critically ill patients, the measurements were made at the discretion of the treating physicians. We developed a software solution to help us offset the different periods between the measurements. Assuming a linear change of lactate levels, a linear regression model was used to interpolate between two measured values from the existing data to estimate a value at the time point of interest (Supplementary Figure S1). We then used these interpolated values for missing data at time points 1, 6, 12, and 24 h after admission.

We also calculated and compared the Lac_{TW}, which is an index of the course of blood lactate levels. Lac_{TW} was calculated according to Nichol et al. by adding the mean lactate value between the measurement time points multiplied with the period of time between these points divided by the total time (Supplementary Figure S2) (29). Other than the LD, the Lac_{TW} was calculated using the actually measured lactate values.

Study Outcomes

The primary outcome was survival within 30 days after hospital admission or survival until discharged from the hospital.

Statistical Analysis

All data were collected anonymously using Microsoft Excel 2016 (Microsoft, Redmond, WA) and were analyzed using XLSTAT Free (Addinsoft, Paris, France) and DataGraph 4.2.1 (Visual Data Tools, Inc.). The descriptive statistics included numbers and percentage, mean value ± standard deviation, median, minimal, and maximal values. The Mann-Whitney U test, χ^2 test,

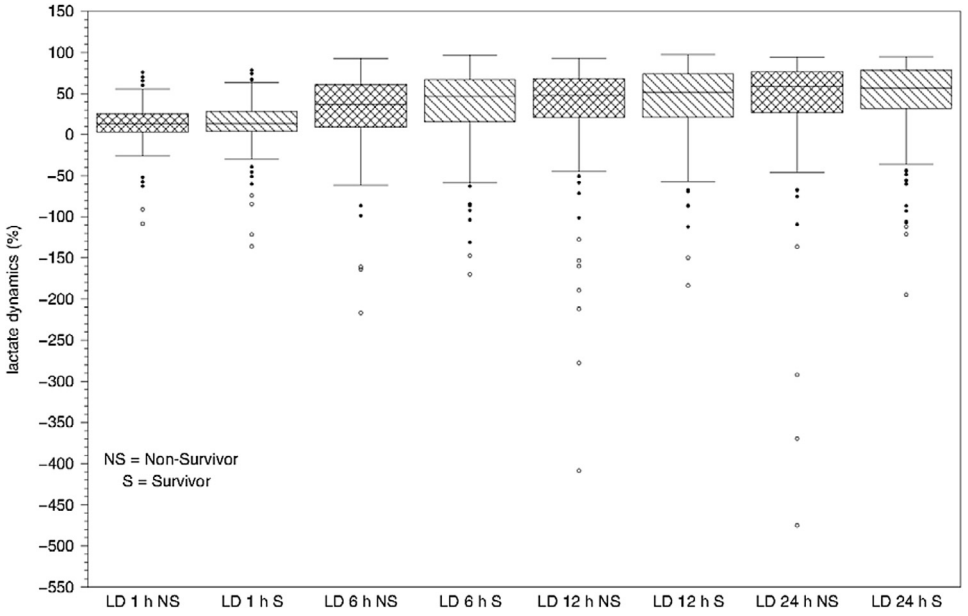

Figure 4. Lactate dynamics (LD) at 1, 6, 12, and 24 h after admission for survivors (S) vs. non-survivors (NS) (entire cohort).

Table 2. Admission Lactate, Time Weighted Average Lactate, and Lactate Dynamics at 1, 6, 12, and 24 h After Admission for All Patients, for All Patients Without Cardiopulmonary Resuscitation, and for All Patients With Out-of-Hospital or In-Hospital Cardiopulmonary Resuscitation

Variable	Total	Non-Survivor	Survivor	*p* Value
All patients				
Patients, n	392	113	279	
Admission lactate, mmol/L				
Mean ± SD	4.84 ± 4.85	6.63 ± 6.13	4.11 ± 4.01	<0.01
Median (range)	2.9 (0.4–27.0)	4.2 (0.5–27.0)	2.6 (0.4–27.0)	
Lac_{TW}, mmol/L				
Mean ± SD	2.4 ± 3.1	4.1 ± 4.8	1.8 ± 1.7	<0.01
Median (range)	1.5 (0.4–26.0)	2.0 (0.6–26.0)	1.4 (0.4–22.3)	
LD, %, mean ± SD				
1 h after admission	14.4 ± 25.1	12.6 ± 26.9	15.1 ± 24.4	0.542
6 h after admission	34.2 ± 46.1	26.8 ± 53.0	37.0 ± 42.8	0.114
12 h after admission	37.4 ± 56.7	23.9 ± 81.8	42.3 ± 43.1	0.257
24 h after admission	42.3 ± 62.2	30.8 ± 92.1	46.8 ± 44.5	0.703
Patients without CPR				
Patients, n	323	74	249	
Admission lactate, mmol/L				
Mean ± SD	3.9 ± 3.9	4.4 ± 4.7	3.8 ± 3.7	0.527
Median (range)	2.5 (0.4–27.0)	2.7 (0.5–24.0)	2.5 (0.4–27.0)	
Lac_{TW}, mmol/L				
Mean ± SD	1.9 ± 2.1	2.6 ± 3.0	1.7 ± 1.6	<0.01
Median (range)	1.4 (0.4–22.3)	1.5 (0.6–17.1)	1.3 (0.4–22.3)	
LD, %, mean ± SD				
1 h after admission	14.1 ± 24.5	10.8 ± 27.7	15.1 ± 23.4	0.258
6 h after admission	32.7 ± 46.8	20.3 ± 58.2	36.4 ± 42.3	0.042
12 h after admission	35.4 ± 57.4	16.4 ± 86.7	40.8 ± 44.0	0.053
24 h after admission	39.5 ± 61.1	24.1 ± 91.4	44.6 ± 46.1	0.205
Only patients with out-of-hospital or in-hospital CPR				
Patients, n	69	39	30	
Admission lactate, mmol/L				
Mean ± SD	9.1 ± 6.3	10.9 ± 6.3	6.7 ± 5.4	<0.01
Median (range)	8.8 (0.7–27.0)	10.8 (1.2–27.0)	4.9 (0.7–20.0)	
Lac_{TW}, mmol/L				
Mean ± SD	5.0 ± 5.2	6.9 ± 6.1	2.5 ± 1.6	<0.01
Median (range)	2.9 (0.6–26.0)	4.1 (1.1–26.0)	2.0 (0.6–7.3)	
LD, %, mean ± SD				
1 h after admission	15.6 ± 27.9	15.9 ± 25.1	15.2 ± 31.2	0.966
6 h after admission	41.7 ± 41.3	41.0 ± 35.5	42.5 ± 46.8	0.667
12 h after admission	48.5 ± 51.9	41.7 ± 65.4	55.3 ± 31.7	0.877
24 h after admission	56.0 ± 65.7	48.6 ± 91.9	62.3 ± 26.7	0.787

CPR = cardiopulmonary resuscitation; Lac_{TW} = time weighted average lactate; LD = lactate dynamics; SD = standard deviation.

or Student's *t*-test were used for statistical comparisons at a significance level of $p < 0.05$. As this study was intended for hypothesis formation, correction for multiple testing was not required.

RESULTS

A total of 34,303 patients were admitted to the ED during the 12-month study period of the OBSERvE study (1). There were 13,229 patients excluded from the OBSERvE study due to trauma as the main diagnosis, including 592 patients treated in the resuscitation area due to major trauma. Of the remaining 21,074 patients, 537 (2.54%) non-trauma critically ill patients were admitted to the ED. Five patients were excluded from the OBSERvE study due to missing data (1). Of the remaining 532 patients, 138 patients were excluded due to having only a single lactate measurement (at hospital admission; n = 60), missing data (n = 20), no ICU admission (n = 32) or due to primary palliative care (n = 26). Finally, the lactate data from 392 patients were analyzed in the OBSERvE-Lactate study (Figure 1). Patient characteristics for all included patients, survivors, and non-survivors are shown in Table 1. There were significant differences in age, mechanical ventilation rate, and catecholamine requirement between survivors and non-survivors, but not in sex, ICU stay, or blood pressure at admission.

Admission Lactate, Lac_{TW}, and LD

Higher admission lactate levels (Figure 2, Supplementary Figure S3) as well as higher Lac_{TW} levels (Figure 3) were

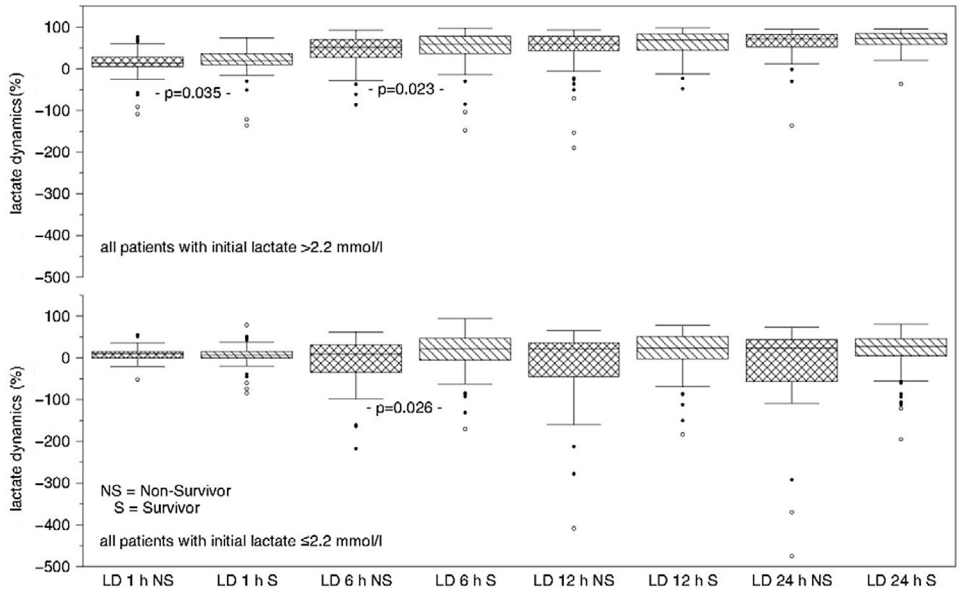

Figure 5. Lactate dynamics (LD) for patients with lactate at admission >2.2 mmol/L and ≤ 2.2 mmol/L at 1, 6, 12, and 24 h after admission for survivors and non-survivors. Statistical differences between survivors and nonsurvivors were observed for admission lactate < 2.2 mmol/L for 1 and 6 h after admission.

associated with a higher 30-day mortality. Especially, admission lactate levels > 8.1 mmol/L were associated with almost a doubling in mortality. Considering all patients, no significant difference for the LD between survivors and non-survivors was found at any time (Figure 4). After excluding patients with out-of-hospital or in-hospital cardiac arrest in the resuscitation room, admission lactate between survivors and non-survivors did not differ. Lac_{TW} did differ between survivors and non-survivors, and LD between survivors and non-survivors differed only 6 h after admission (Table 2).

For patients with admission lactate levels above the upper limit of normal (>2.2 mmol/L), we found significant differences between survivors and non-survivors in the early LD at 1 and 6 h and significant differences in the Lac_{TW}. These findings were different from those of patients with admission lactate levels ≤ 2.2 mmol/L, where we found significant differences between survivors

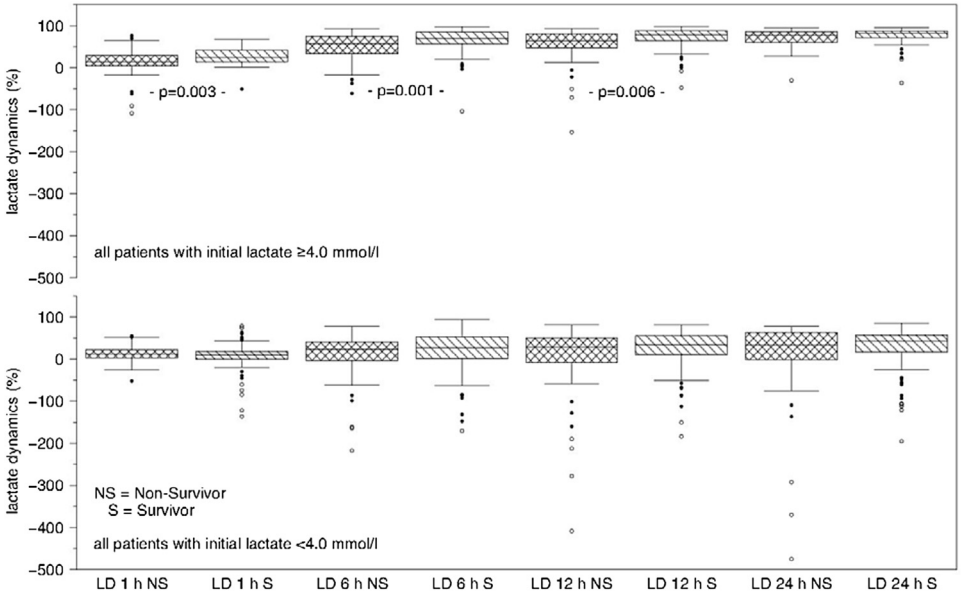

Figure 6. Lactate dynamics (LD) for patients with lactate at admission ≥4.0 mmol/L and <4.0 mmol/L at 1, 6, 12 and 24 h after admission for survivors (S) vs. non-survivors (NS). Statistical differences between survivors and non-survivors were observed for admission lactate ≥4.0 mmol/L at 1, 6, and 12 h after admission.

and non-survivors only at 6 h and in Lac_{TW} (Figure 5). Considering patients with higher lactate levels at admission (≥4.0 mmol/L), we observed significant differences in the LD between survivors and non-survivors at 1, 6, and 12 h but not 24 h after admission as well as in Lac_{TW} (Figure 6).

DISCUSSION

In this retrospective analysis of data from the OBSERvE study, lactate levels at admission as well as a slow LD and a high Lac_{TW} within the first 24 h have been associated with an increased risk of death (1). We wanted to know whether lactate parameters can help clinicians identify critically ill patients with a higher risk of death.

Recently, numerous studies investigated lactate and its dynamic as a potential predictive parameter for mortality focusing on very specific patient populations, for example, patients after cardiac arrest, patients after cardiac surgery, trauma patients, children, or sepsis patients (5–12,15,20,21,23–27,33,34). Vincent et al. systematically reviewed 96 of such studies to evaluate the value of blood lactate kinetics in critically ill patients (28). Most of these studies with highly selected patient cohorts concluded that high admission lactate and high lactate during in-hospital course are consistently associated with poor clinical outcomes. So it was shown that the initial measurement of lactate in the ED can help to stratify risk of death. In unselected patient groups, a limit of 2.7 mmol/L was suggested (35,36). Consecutively, fast decreasing lactate levels were associated with improved outcomes. In line with these studies, our findings have confirmed these results in unselected non-traumatic critically ill patients with initial hyperlactatemia, above the upper level of normal (>2.2 mmol/L) for admission lactate, Lac_{TW} and LD 1 h and 6 h after admission and also for patients with higher hyperlactatemia (≥4.0 mmol/L) for admission lactate, Lac_{TW} and LD 1, 6, and 12 h after admission. Considering the 69 cardiac arrest patients of our study cohort, we saw differences between survivors and non-survivors in admission lactate and Lac_{TW}; however, in contrast to the abovementioned studies, no difference in LD.

Although the term *lactate clearance* is incorrect because the dynamic changes in blood lactate levels are the result of both production and elimination, many studies have used this term to describe decreasing blood lactate levels during the hospital course (28). We avoid the term *clearance* due to aforementioned reasons and use the term *lactate dynamics* instead, as suggested by Vincent et al. (28).

The definition of LD and the time points of measurement vary across the studies. For example, LD has been defined as the percentage change in the first 12 or 24 h or as the normalization of lactate levels within 6 hours, which makes cross-study comparisons difficult (29,37,38).

A point-of-care blood gas analysis including lactate was carried out in every patient in our cohort early after admission, as well as throughout the course of treatment according to medical need. Therefore, evaluating admission lactate, Lac_{TW}, and LD based on available data did not increase costs of medical care. Moreover, the cost-effectiveness of early lactate testing has been shown for patients with suspected sepsis (39).

In contrast to previous studies, we investigated a very heterogeneous population. From our point of view, survival prediction of critically ill patients in the ED is very difficult. The results of the OBSERvE-Lactate study show that higher admission lactate levels were associated with mortality and confirmed the results of Casserly et al. (32). Furthermore, our results in an unselected patient group were in line with other investigations, which suggested that an admission lactate > 4 mmol/L is associated with higher mortality, as suggested by the recommendations of the Surviving Sepsis campaign (31). It should be kept in mind that admission lactate and glucose are major biomarkers according to the recommendation of the Surviving Sepsis Campaign (31). Interestingly, in line with Nichol et al., the Lac_{TW} showed significant differences between survivors and non-survivors over all considered subgroups in the OBSERvE-Lactate study (29). Restrictions were found due to the nature of the emergency setting because we investigated the data of patients with a high variability of diseases in our ED. While studies in selected patient populations found a high association between LD and outcome, we could confirm this only at 1 and 6 h in patients with an admission lactate > 2.2 mmol/L, and additionally at 12 h for patients with an admission lactate of 4.0 mmol/L or higher. The death of patients within the first 24 h may explain the observation that earlier LDs differ more than the late ones.

Limitations

One limitation is the retrospective nature of the study design. To our knowledge, there is no validated institutional guideline for repeated lactate measurements during the in-hospital course. Therefore, a software solution to interpolate the available data sets had to be developed. Indeed, natural processes do not follow linear courses. But in a small pilot study on patients with a high frequency of lactate measurements, we validated our regression model and found the approximations to be sufficiently accurate (data not shown). This method assumes a linear course of the blood lactate between the measured values (Supplementary Figure S1). A prospective evaluation with the measurement of lactate at defined

time points (e.g., every 2 h) would be more valuable. The number of almost 400 individuals gives us the possibility to reduce the weakness of this study design. Yet, obviously, a cohort of 10-fold the number of patients would be more valuable. We included arterial as well as venous blood samples in our analyses because previous investigations showed close agreement between these sampling conditions (40–42). Also, we used univariate analysis throughout this study, a decision made consciously to focus on LD.

CONCLUSIONS

In unselected, non-trauma, critically ill ED patients initially requiring treatment in a resuscitation room setting of an ED, admission lactate and dynamic lactate parameters may predict 30-day mortality; especially in patients with high initial hyperlactatemia. If these findings can be confirmed in a prospective study with a larger patient population, this might give clinicians an additional tool for risk evaluation and therapeutic strategizing.

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SUPPLEMENTARY DATA

Supplementary Data can be found at https://doi.org/10.1016/j.jemermed.2018.10.033.

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ARTICLE SUMMARY

1. Why is this topic important?

Various previous studies showed that blood lactate levels and its dynamics are able to predict survival. But these studies investigated highly selected patient cohorts.

2. What does this study attempt to show?

We wanted to know whether early dynamic lactate parameters are also able to identify a higher risk of death in critically ill non-traumatic patients who presented in the resuscitation room without selecting them by symptoms or diseases. We developed a software solution to handle the differences in the time-points of measurements because the measurements followed no protocol but the clinical course.

3. What are the key findings?

In our non-selected patient cohort, the admission lactate and the time weighted average lactate differed between survivors and non-survivors.

4. How is patient care impacted?

As part of the blood gas analysis, serial lactate values are available for almost every critical ill patient. So the admission lactate level as well as calculated lactate dynamics can be used to evaluate critical ill non-traumatic patients who presented in the resuscitation room.