# Prognostic Value of Blood Lactate Levels: Does the Clinical Diagnosis at Admission Matter?

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***Background:*** **Hyperlactatemia and its reduction after admission in the intensive care unit (ICU) have been related to survival. Because it is unknown whether this equally applies to different groups of critically ill patients, we compared the prognostic value of repeated lactate levels (a) in septic patients versus patients with hemorrhage or other conditions generally associated with low-oxygen transport (LT) (b) in hemodynamically stable versus unstable patients.**

***Methods:*** **In this prospective observational two-center study (n = 394 patients), blood lactate levels at admission to the ICU ($Lac_{T0}$) and the reduction of lactate levels from T = 0 to T = 12 hours ($\Delta Lac_{T0-12}$) and from T = 12 to T = 24 hours ($\Delta Lac_{T12-24}$), were related to in-hospital mortality.**

***Results:*** **Reduction of lactate was associated with a lower mortality only in the sepsis group ($\Delta Lac_{T0-12}$: hazard ratio [HR] 0.34, $p = 0.004$ and $\Delta Lac_{T12-24}$: HR 0.24, $p = 0.003$), but not in the LT group ($\Delta Lac_{T0-12}$; HR 0.78, $p = 0.52$ and $\Delta Lac_{T12-24}$; HR 1.30, $p = 0.61$). The prognostic values of $Lac_{T0}$, $\Delta Lac_{T0-12}$, and $\Delta Lac_{T12-24}$ were similar in hemodynamically stable and unstable patients ($p = 0.43$).**

***Conclusions:*** **Regardless of the hemodynamic status, lactate reduction during the first 24 hours of ICU stay is associated with improved outcome only in septic patients, but not in patients with hemorrhage or other conditions generally associated with LT. We hypothesize that in this particular group a reduction in lactate is not associated with improved outcome due to irreversible damage at ICU admission.**

***Key Words:*** **Lactate, Hyperlactatemia, Hemorrhage, Sepsis, Prognosis, Intensive care.**

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Blood lactate levels are often determined in critically ill patients, because repeated measurements identify those patients who are at risk for multiple organ failure and death.[1–3] In these patients, hyperlactatemia is thought to be predominantly caused by impaired organ perfusion. Although this condition is often associated with hemodynamic instability, hyperlactatemia can also occur during stable hemodynamic conditions, in which case it is considered to be due to occult hypoperfusion.[4–6] Treatment aims at correction of tissue perfusion, resulting in decreased lactate levels and improved patient outcome.[7]

With this purpose, monitoring of lactate levels is used in a broad range of patients, including trauma as well as sepsis patients.[8,9] The generalized use of lactate in critically ill patients has given rise to a universal concept that a high lactate level is bad and that a decrease in lactate levels is good, despite considerable differences in underlying disease (e.g., hemorrhage vs. sepsis) and hemodynamic status within the patient population. In fact, it is unknown whether these factors, which can be clinically evaluated at admission, influence the risk of death associated with initial lactate levels and their course during therapy. Therefore, it was our objective to compare the prognostic value of repeated lactate levels after intensive care unit (ICU) admission in different categories of patients: (a) in septic patients versus patients with hemorrhage and other conditions generally associated with low-oxygen transport (LT) and (b) in hemodynamically stable versus unstable patients.

## PATIENTS AND METHODS

### Study Design and Patients

In this prospective observational two-center study, we enrolled all consecutive unscheduled patients admitted to the general ICU of two Dutch university-affiliated hospitals from May 2000 to April 2002. In patients, who were readmitted during the study period only data of the first admission were used. This study was approved by the Medical Ethical Committees of both hospitals and informed consent was waived.

### Patient Classification

To categorize patients according to their disease at admission to the ICU, we used prespecified admission diagnoses derived from the Acute Physiology and Chronic Health Evaluation (APACHE) III scoring system.[10] In this way, patients were classified as SEPSIS (all conditions associated

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with infectious disease), LT (hemorrhage and other conditions generally associated with LT: low cardiac output, hemoglobin level, or oxygen saturation) or OTHERS. The SEPSIS group comprised the following admission diagnoses: bacterial/viral pneumonia, aspiration pneumonia, meningitis/encephalitis, sepsis, septic shock, intestinal perforation, and cholecystitis/cholangitis. The LT group comprised the following admission diagnoses: trauma with or without traumatic brain injury, gastrointestinal bleeding, ruptured aortic aneurysm, cardiogenic shock, congestive heart failure, arrhythmia, acute myocardial infarction, pulmonary embolism with circulatory failure, and cardiac arrest. Patients who could not be classified as either SEPSIS or LT were classified as OTHERS because we were not able to determine whether these patients should be regarded as either SEPSIS or LT according to their disease at admission. As a result, the OTHERS group of admission diagnoses became heterogeneous, including patients with completely different mechanisms of hyperlactatemia (e.g., liver failure). Therefore, we focused on the SEPSIS and LT groups in the first analysis.

In a second analysis, patients were classified as hemodynamically stable ($HD_{stable}$) or hemodynamically instable ($HD_{instable}$), which was defined as a mean arterial pressure (MAP) $<$60 mm Hg or the requirement of catecholamines or both (dopamine $\geq$3 mcg/kg/min, dobutamine any dose, norepinephrine any dose, or epinephrine any dose) during the first 24 hours after ICU admission.

## Data Collection

For each patient, baseline characteristics were recorded including APACHE III[10] (for admission diagnosis), APACHE II[11] (for disease severity) and hospital and ICU length of stay and mortality. Predicted hospital death rate was calculated as $e^{-3.517 + (APACHE\ II) \times 0.146}/(1 + e^{-3.517 + (APACHE\ II) \times 0.146})$.[11] Blood lactate levels were collected at the time of ICU admission ($Lac_{T0}$) and after 12 and 24 hours after admission. The reduction in lactate was calculated from 0 to 12 hours ($\Delta Lac_{T0-12}$) and from 12 to 24 hours ($\Delta Lac_{T12-24}$). For lactate measurement, arterial blood samples were drawn from an arterial catheter and analyzed in the central hospital laboratory. Renal, respiratory, and circulatory organ function were assessed on the basis of serum creatinine levels (creat), requirement of mechanical ventilation (MV), and a MAP $<$60 mm Hg/requirement of catecholamines ($\downarrow$ MAP/catechol).

## Treatment

Normalization of blood lactate levels was a treatment target in both hospitals. This was primarily performed by increasing $DO_2$ (fluids guided by fluid challenges, dobutamine or other inotropic agents, red blood cell transfusion, MV/optimization of oxygenation) or decreasing $VO_2$ or both (e.g., analgosedation).

## Statistical Analysis

Because blood lactate levels were not normally distributed, they were logarithmically transformed before analysis. To compare lactate levels of survivors and nonsurvivors, the Student's $t$ test was used. Mortality rates of patients with hyperlactatemia ($\geq$2.5 mmol/L[5,7,12]) were compared with those of patients with normal levels by using $\chi^2$ testing or Fisher's exact test if necessary, based on sample size. To evaluate the prognostic values of lactate levels at T = 0, T = 12, and T = 24, receiver operating characteristic (ROC) curves for in-hospital death (primary outcome measure) were constructed with corresponding area under the ROC values (AUROC).

To evaluate whether the prognostic values of lactate at admission ($Lac_{T0}$) and of the reduction over time ($\Delta Lac_{T0-12}$ and $\Delta Lac_{T12-24}$) were dependent on admission diagnosis (SEPSIS or LT) or hemodynamic status ($HD_{stable}$ or $HD_{instable}$), multivariable Cox proportional hazards models were constructed. These models excluded patients who died within 24 hours and those with missing lactate levels. Two multivariable analyses were constructed: (a) for the comparison between SEPSIS and LT and (b) for the comparison between $HD_{stable}$ and $HD_{instable}$ patients:

a. The following variables were entered in the model: $Lac_{T0}$, $\Delta Lac_{T0-12}$, $\Delta Lac_{T12-24}$ and diagnosis (SEPSIS or LT) and subsequently, interaction terms were added (diagnosis $\cdot$ $Lac_{T0}$, diagnosis $\cdot$ $\Delta Lac_{T0-12}$, and diagnosis $\cdot$ $\Delta Lac_{T12-24}$). For this analysis, patients classified as OTHERS were excluded.
b. The following variables were entered in the model: $Lac_{T0}$, $\Delta Lac_{T0-12}$, $\Delta Lac_{T12-24}$ and HD status ($HD_{stable}$ or $HD_{instable}$) and again, interaction terms were added (HD status $\cdot$ $Lac_{T0}$, HD status $\cdot$ $\Delta Lac_{T0-12}$, and HD status $\cdot$ $\Delta Lac_{T12-24}$).

To correct for the hemodynamic status within the SEPSIS versus LT comparison, an additional subgroup analysis was performed:

c. The following variables were entered in this model: $Lac_{T0}$, $\Delta Lac_{T0-12}$, $\Delta Lac_{T12-24}$, diagnosis, HD status, diagnosis $\cdot$ $Lac_{T0}$, diagnosis $\cdot$ $\Delta Lac_{T0-12}$, and diagnosis $\cdot$ $\Delta Lac_{T12-24}$. Subsequently, additional interaction terms were added: HD status $\cdot$ diagnosis, HD status $\cdot$ $Lac_{T0}$, HD status $\cdot$ $\Delta Lac_{T0-12}$, HD status $\cdot$ $\Delta Lac_{T12-24}$, diagnosis $\cdot$ $Lac_{T0}$ $\cdot$ HD status, diagnosis $\cdot$ $\Delta Lac_{T0-12}$ $\cdot$ HD status, and diagnosis $\cdot$ $\Delta Lac_{T12-24}$ $\cdot$ HD status.

Values are provided as mean $\pm$ SEM (SE) (with exception of the baseline characteristics where the values represent mean $\pm$ SD). Statistical analyses were performed using SPSS version 11.0.1/12.0.1 (SPSS, Chicago, IL).

# RESULTS

## Patient Characteristics

Four hundred twenty-one patients were enrolled during the study period, of which 27 patients were excluded because data were recorded during readmissions. The flow chart of

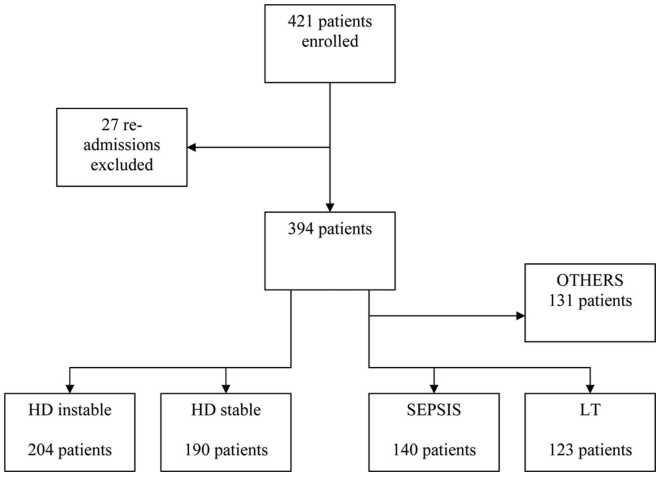


**Fig. 1.** *Flow-chart of enrolled patients.*

patient enrollment is shown in Figure 1. Table 1 provides an overview of the distribution of admission diagnoses in the SEPSIS, LT, and OTHERS groups. Table 2 describes the baseline characteristics and clinical variables of the total population and more specifically for the SEPSIS and LT groups and the $HD_{stable}$ and $HD_{instable}$ groups.

## SEPSIS Versus LT

Sepsis compared with LT patients had a higher APACHE II score, longer length of ICU stay but an equal length of hospital stay and mortality (Table 2). The proportion of patients with hyperlactatemia at admission was equal.

In the SEPSIS group, the mean lactate level was significantly higher in nonsurvivors than in survivors at T = 12 and T = 24, but not at admission (Fig. 2). In contrast, in the LT group, it was higher in nonsurvivors at admission and T = 12, but not at T = 24. When looking at patients with normal or elevated levels, a similar difference between the SEPSIS and LT groups was found (Fig. 3, A and B). In the SEPSIS group, mortality was not significantly higher in those with elevated levels at admission, but those with normalized levels after 24 hours did have a lower risk of dying. In the LT group, outcome was worse in patients with abnormal levels directly

**Table 1** The Groups Classified on the Basis of APACHE III Admission Diagnoses

| Group | Admission Diagnosis | N | Percentage of Subtotal |
|---|---|---|---|
| SEPSIS group | Sepsis respiratory tract | 64 | 46 |
| | Sepsis urinary tract | 9 | 6 |
| | Abdominal sepsis | 35 | 25 |
| | Cholecystitis/cholangitis | 8 | 6 |
| | Meningitis/encephalitis | 3 | 2 |
| | Others | 21 | 15 |
| | *Subtotal group* | *140* | *100* |
| LT group | Trauma without traumatic brain injury | 15 | 12 |
| | Trauma with traumatic brain injury | 13 | 11 |
| | Ruptured abdominal aortic aneurysm | 28 | 23 |
| | Gastrointestinal bleeding | 35 | 29 |
| | Arrhythmia | 5 | 4 |
| | Acute myocardial infarction | 3 | 2 |
| | Pulmonary embolism with circulatory failure | 2 | 2 |
| | Congestive heart failure | 9 | 7 |
| | Cardiogenic shock | 4 | 3 |
| | Cardiac arrest | 9 | 7 |
| | *Subtotal group* | *123* | *100* |
| OTHERS group | Non-infectious respiratory disease (e.g., COPD) | 19 | 15 |
| | Liver failure | 1 | 1 |
| | Pancreatitis | 4 | 3 |
| | Intestinal obstruction (nonsurgical) | 2 | 2 |
| | GI surgery: obstruction | 19 | 15 |
| | GI surgery: inflammatory bowel disease | 4 | 3 |
| | GI surgery: intestinal ischemia | 3 | 2 |
| | SAH/intracerebral hemorrhage/CVA | 9 | 7 |
| | Epileptic seizure | 5 | 4 |
| | Metabolic disease (e.g., diabetic ketoacidosis) | 8 | 6 |
| | Autointoxication | 8 | 6 |
| | Hematological disorder | 7 | 5 |
| | Renal insufficiency | 13 | 10 |
| | Others | 29 | 22 |
| | *Subtotal group* | *131* | *100* |
| | Total | 394 | |

GI surgery, gastrointestinal surgery; SAH, subarachnoid hemorrhage; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident.

**Table 2** Baseline Characteristics and Clinical Variables of the Total Population and More Specifically for the SEPSIS and LT Groups and the $HD_{stable}$ and $HD_{instable}$ Groups

| | Total (n = 394) | $HD_{instable}$ (n = 204) | $HD_{stable}$ (n = 190) | *p* value $HD_{instable}$ vs. $HD_{stable}$ | SEPSIS (n = 140) | LT (n=123) | *p* value SEPSIS vs. LT |
|---|---|---|---|---|---|---|---|
| Age (yrs) | 65 ± 16 | 69 ± 13 | 61 ± 18 | <0.001 | 67 ± 14 | 65 ± 17 | 0.76 |
| Sex: male/female (%) | 56/44 | 54/46 | 58/42 | 0.48 | 56/44 | 66/34 | 0.10 |
| In-hospital mortality (%) | 27 | 31 | 22 | 0.041 | 30 | 29 | 0.89 |
| Predicted hospital mortality (%) | 29 | 39 | 24 | 0.001 | 36 | 26 | 0.09 |
| ICU mortality (%) | 16 | 22 | 10 | 0.001 | 16 | 19 | 0.62 |
| Hospital LOS (d) | 25 ± 26 | 28 ± 28 | 21 ± 22 | 0.005 | 28 ± 30 | 21 ± 18 | 0.13 |
| ICU LOS (d) | 97 ± 13 | 10 ± 16 | 5 ± 8 | <0.001 | 10 ± 17 | 7 ± 11 | 0.004 |
| APACHE II | 18 ± 8 | 21 ± 7 | 16 ± 7 | <0.001 | 20 ± 7 | 17 ± 8 | 0.001 |
| Hospital: I/II (%) | 45/55 | 45/55 | 46/54 | 0.76 | 45/55 | 43/57 | 0.80 |
| Referring department | | | | 0.07 | | | <0.001 |
| ED (%) | 34 | 29 | 38 | | 24 | 42 | |
| Ward (%) | 45 | 48 | 41 | | 59 | 33 | |
| OT (%) | 10 | 13 | 7 | | 5 | 15 | |
| Others (%) | 11 | 10 | 13 | | 11 | 10 | |
| MV at admission (%) | 52 | 66 | 37 | <0.001 | 47 | 63 | 0.013 |
| RRT first 24 h (%) | 8 | 13 | 4 | 0.002 | 9 | 1 | 0.002 |
| Surgery 7 d before ICU (%) | 31 | 35 | 26 | 0.06 | 23 | 35 | 0.040 |
| Lactate, T = 0 (mmol/L) | 3.2 ± 3.1 | 3.7 ± 3.5 | 2.5 ± 2.4 | <0.001 | 2.9 ± 2.3 | 3.5 ± 3.1 | 0.10 |
| Lactate, T = 12 (mmol/L) | 2.2 ± 2.1 | 2.5 ± 2.3 | 1.8 ± 1.7 | <0.001 | 2.5 ± 2.6 | 92.2 ± 1.8 | 0.17 |
| Lactate, T = 24 (mmol/L) | 2.0 ± 1.8 | 2.3 ± 2.2 | 1.6 ± 0.9 | <0.001 | 2.2 ± 2.1 | 1.9 ± 1.2 | 0.26 |
| Lactate ≥2.5 mmol/L, T = 0 (%) | 169/391 (43) | 106/203 (52) | 63/188 (34) | <0.001 | 60/138 (44) | 65/123 (53) | 0.13 |
| Lactate ≥2.5 mmol/L, T = 12 (%) | 93/362 (26) | 63/198 (32) | 30/164 (18) | 0.003 | 42/136 (31) | 29/110 (26) | 0.44 |
| Lactate ≥2.5 mmol/L, T = 24 (%) | 60/305 (20) | 48/176 (27) | 12/129 (9) | <0.001 | 30/114 (26) | 18/97 (19) | 0.19 |
| Heart rate, T = 0 (beats/min) | 100 | 103 | 97 | 0.015 | 106 | 97 | 0.001 |
| Heart rate, T = 12 (beats/min) | 96 | 99 | 93 | 0.002 | 97 | 94 | 0.22 |
| Heart rate, T = 24 (beats/min) | 96 | 97 | 94 | 0.21 | 97 | 94 | 0.35 |
| MAP, T = 0 (mm Hg) | 84 | 76 | 92 | <0.001 | 79 | 85 | 0.022 |
| MAP, T = 12 (mm Hg) | 78 | 74 | 84 | <0.001 | 75 | 79 | 0.022 |
| MAP, T = 24 (mm Hg) | 81 | 77 | 87 | <0.001 | 79 | 82 | 0.34 |
| Vasopressor/inotropics, T =0 (%) | 27 | 52 | 0 | <0.001 | 30 | 29 | 0.89 |
| Vasopressor/inotropics, T = 12 (%) | 39 | 76 | 0 | <0.001 | 50 | 37 | 0.040 |
| Vasopressor/inotropics, T = 24 (%) | 35 | 67 | 0 | <0.001 | 46 | 32 | 0.020 |
| pH at admission | 7.36 ± 0.11 | 7.34 ± 0.11 | 7.38 ± 0.10 | 0.001 | 7.37 ± 0.09 | 7.35 ± 0.10 | 0.09 |
| BE at admission (mmol/l) | −4.2 ± 5.9 | −5.3 ± 5.9 | −3.0 ± 5.7 | <0.001 | −3.9 ± 5.3 | −4.4 ± 4.7 | 0.66 |

Values represent means ± SD. Student's *t* test, $\chi^2$ test, ANOVA or nonparametric Kruskall-Wallis were used when appropriate.

LOS, length of stay; Hospital I, Isala Clinics Zwolle; Hospital II, Gelre Hospitals Apeldoorn; ED, emergency department; OT, operation theatre; RRT, renal replacement therapy; BE, base excess; MAP, mean arterial pressure; vasopressor/inotropics, dopamine ≥3 mcg/kg/min, dobutamine any dose, norepinephrine any dose or epinephrine any dose.

at admission, whereas after 24 hours, mortality in those with abnormal levels was not higher anymore than in those with levels in the normal range. In the subgroup of LT patients with initial hyperlactatemia who succeeded to normalize lactate during 24 hours of treatment, still 45% died compared with 36% in those who did not.

The accuracy to predict mortality also differed when focusing on the ROC curves. AUROC values increased from T = 0 to T = 24 in the SEPSIS group whereas they decreased in the LT group (Fig. 4).

Multivariable analysis confirmed the impact of admission diagnosis on the ability of lactate levels to predict outcome: the prognostic values of $Lac_{T0}$, $\Delta Lac_{0-12}$, and $\Delta Lac_{12-24}$ were significantly different between SEPSIS and LT ($p = 0.043$ for the interaction term). In the SEPSIS group, reductions in lactate level were associated with significantly lower mortality, whereas in the LT group this was not the case (Table 3).

To evaluate whether the LT group would be a valid comparison group for trauma patients only, we have separated out the 23% trauma patients and compared these to the entire LT group. Although the results are not significant, as expected due to the low number of patients (n = 28), they trended toward the same direction as in the LT group. Similar to the LT group, mortality seemed to be higher in trauma patients with an abnormal (27%, 4 of 15) versus a normal lactate at admission (15%, 2 of 13). Also in agreement with the LT group, mortality in trauma patients who normalized their lactate within 24 hours (35%, 6 of 17) did not seem to be lower compared with those who failed to normalize lactate (0%, 0 of 5).

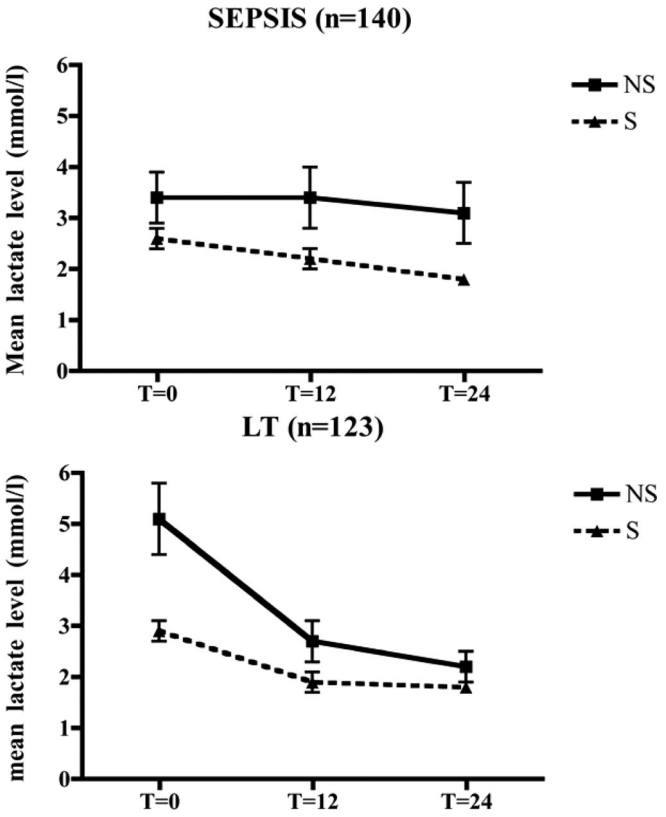


**Fig. 2.** *Mean lactate levels in survivors (S) and nonsurvivors (NS) in SEPSIS and LT groups.* Error bars *represent ±1 SEM.* *p < *0.05,* **p < *0.01 for comparison between survivors and nonsurvivors at the different time points (T = 0, T = 12, and T = 24 hours).*

Administered catecholamines could possibly confound lactate levels and their prognostic values. However, epinephrine, mostly associated with increased production of lactate, was hardly used (n = 2) and additional correction for catecholamine use in general (any infusion of norepinephrine, dopamine, dobutamine, or epinephrine) did not affect the difference in prognostic value between the SEPSIS and LT groups ($p = 0.13$ for the interaction term).

When looking at organ function, we found that in the LT group renal, respiratory, and circulatory organ function were similar in nonsurvivors and survivors at T = 0 (creat 122 vs. 106, $p = 0.26$; MV 71% vs. 59%, $p = 0.22$; ↓MAP/catechol 28% vs. 37%, $p = 0.39$). However, at T = 24 LT nonsurvivors on average had more severe organ dysfunction (creat 141 vs. 94, $p < 0.001$; MV 70% vs. 46%, $p = 0.030$; ↓MAP/catechol 49% vs. 25%, $p = 0.017$).

On the other hand, in the SEPSIS group nonsurvivors had more severe renal and circulatory organ dysfunction at T = 0 (creat 245 vs. 154, $p = 0.009$; MV 39% vs. 50%, $p = 0.27$; ↓MAP/catechol 55% vs. 29%, $p = 0.004$), whereas at T = 24 organ function was comparable (creat 172 vs. 140, $p = 0.24$, MV 75.8% vs. 62.2%, $p = 0.200$, ↓MAP/catechol 55% vs. 42%, $p = 0.20$). The use of renal replacement therapy was similar at all times, both in the LT (T = 0: 0 vs. 0%, T = 24: 3 vs. 0%, $p = 0.30$) and in the SEPSIS groups (T = 0: 5 vs. 1%, $p = 0.21$, T = 24: 9 vs. 8%, $p = 0.73$).

### Hemodynamic Status

Patients in the $HD_{instable}$ group (n = 204) had a higher APACHE II score, longer length of stay, and a higher mortality than patients in the $HD_{stable}$ group (n = 190) (Table 2). The proportion of patients with hyperlactatemia at admission was higher in $HD_{instable}$ patients. Nevertheless, multivariable analysis showed that the prognostic value of $Lac_{T0}$, $\Delta Lac_{0-12}$, and $\Delta Lac_{12-24}$ was similar in $HD_{instable}$ and $HD_{stable}$ patients ($p = 0.43$ for the interaction term).

### Sepsis Versus LT According to Hemodynamic Status

The effect of SEPSIS or LT on the relationship between serial lactate levels and outcome persisted after subdivision by hemodynamic status (Fig. 5). This can be illustrated by the dichotomous analyses (Table 4): both in the hemodynamically instable and stable patients of the SEPSIS group, mortality was equal in those with abnormal and normal levels at admission, but after 24 hours, mortality became higher in patients with elevated levels. In the LT group, patients with high and normal levels after 24 hours had equal mortality rates, also irrespective of their hemodynamic status.

This could be confirmed in the Cox PH model, in which additional correction for hemodynamic status within the Sepsis-LT model did not change the found differences in prognostic value between SEPSIS and LT ($p = 0.16$ for the interaction term). Similarly, when looking at ROC curve analysis, both in the hemodynamically instable and stable patients of the SEPSIS group, AUROC was lowest at admission and highest after 24 hours. In both hemodynamic subgroups of the LT group, AUROC was highest at admission and decreased over time (data not shown). Thus, the impact of admission diagnosis (SEPSIS or LT) on the prognostic value was really independent of the hemodynamic status.

## DISCUSSION

This study shows that a reduction in lactate concentration during the first 24 hours after ICU admission is associated with improved outcome in septic patients, but not in patients presenting with hemorrhage or other conditions frequently associated with LT.

Surprisingly, the lactate levels at admission, but not the reduction over time, predicted mortality in the LT group. This is illustrated by the high mortality (45%) in LT patients with initial hyperlactatemia despite the normalization of lactate levels during the first 24 hours. We hypothesize that the nonsurvivors, who had significantly higher admission lactate levels, experienced a more severe insult in the time before ICU admission that could have led to irreversible organ damage. During the first 24 hours in the ICU, the conditions leading to increased lactate levels (e.g., tissue oxygen delivery demand mismatch) could have been resolved, leading to a reduction in lactate levels, but not to a recovery of tissue

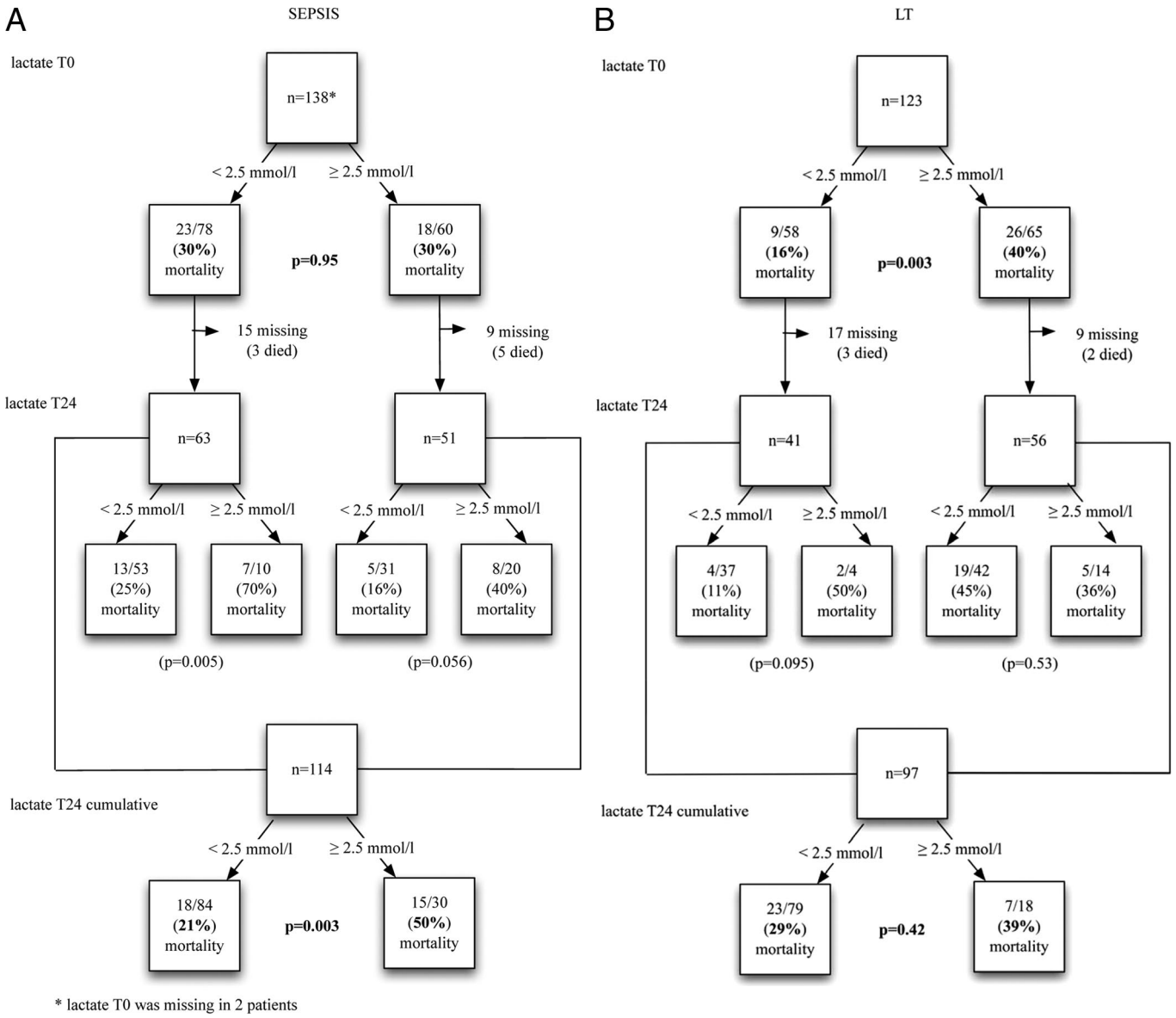


**Fig. 3.** (A) *Mortality rates of SEPSIS patients with high (≥2.5 mmol/L) or normal (<2.5 mmol/L) blood lactate levels at admission or after 24 hours of ICU therapy.* (B) *Mortality rates of LT patients with high (≥2.5 mmol/L) or normal (<2.5 mmol/L) blood lactate levels at admission or after 24 hours of ICU therapy.*

damage.[13] As a result, only the lactate levels at admission and not after 24 hours were related to patient survival.

Such a phenomenon is probably best illustrated by the recovery from cardiac arrest, in which the extent of (neurologic) organ damage determines prognosis,[14] rather than the ability to reduce lactate levels in 24 hours after return of spontaneous circulation.[15,16] Possibly a likewise mechanism is present in other LT conditions, such as trauma and hemorrhage. After hemorrhage control and restoration of circulation, severe and irreversible organ damage might already have occurred despite a normalization of lactate levels at a later stage. This explanation is supported by our observation that the LT nonsurvivors developed more severe organ dysfunction after 24 hours, while the mean lactate concentration was equal to survivors at that time point.

In the SEPSIS group, we found opposite results. Lactate levels in the SEPSIS nonsurvivors remained elevated over 24 hours, which is in agreement with previous studies.[3,17] Several explanations exist for the hyperlactatemia in this group of patients other than impaired tissue oxygen delivery.[18,19] First, cytokine-mediated uptake of glucose[20] or catecholamine-stimulated increased Na-K-pump activity[21] might have increased aerobic glycolysis. Second, pyruvate dehydrogenase dysfunction may have limited the conversion of pyruvate to acetyl coenzyme A[22,23] and last, microcirculatory derangement[24,25] or mitochondrial dysfunction[26] may have

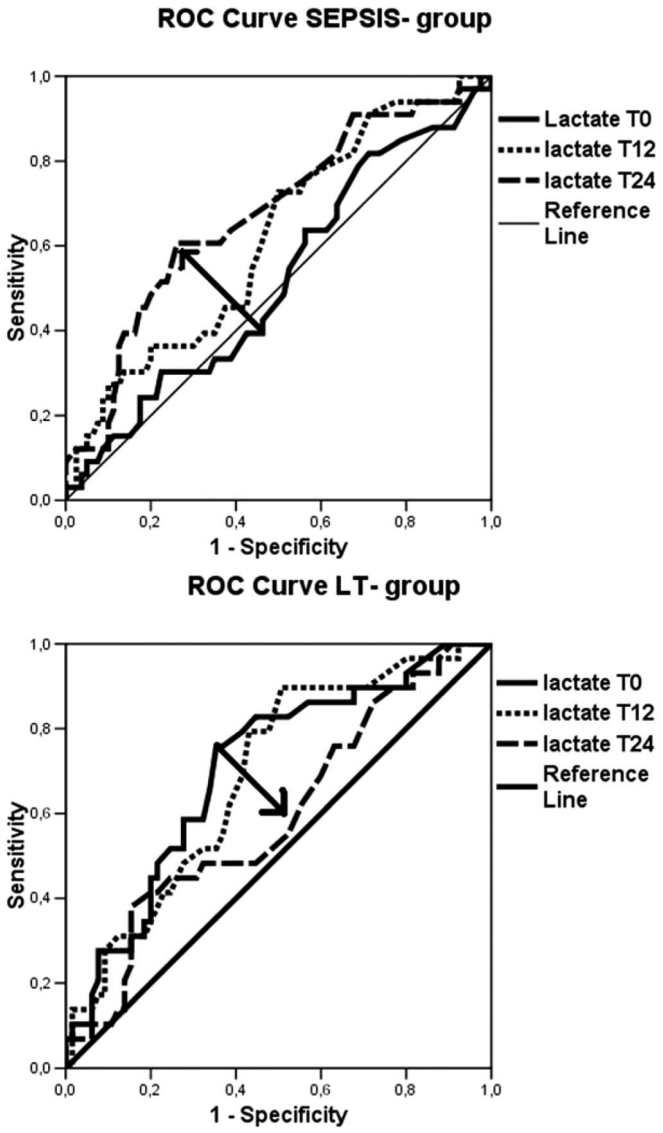


**Fig. 4.** *Receiver operating characteristic (ROC) curves of lactate levels at the different time points to predict in-hospital death. The* arrows *depict the progression of the prognostic value of lactate during the first 24 hours of ICU admission. The area under the ROC value increased from T = 0 to T = 24 in the SEPSIS group (T = 0, 0.52,* p = *0.73; T = 12, 0.62,* p = *0.049; T = 24, 0.68,* p = *0.004) whereas it decreased in the LT group (T = 0, 0.71,* p = *0.002; T = 12, 0.69,* p = *0.004; T = 24, 0.59,* p = *0.15).*

hampered oxygen utilization at the tissue level. On the basis of our results, we can only conclude that if these processes can somehow be resolved within the first 24 hours of ICU admission, thereby leading to decreased lactate levels, patient survival in this group is improved.

The different time course of lactate levels in the SEPSIS and LT nonsurvivors could possibly be explained by differences in the pathogenesis of hyperlactatemia, although mechanisms such as catecholamine-stimulated Na-K-ATP-ase activation have been described in hemorrhage as well.[27–29]

**Table 3** **Cox Proportional Hazard Model: Hazard Ratios (95% CI) for In-Hospital Death for the Lactate Level at ICU Admission ($Lac_{T0}$) and the Reduction From 0 to 12 h ($\delta Lac_{T0-12}$) and 12 to 24 h ($\delta Lac_{T12-24}$)**

| | Sepsis | Low $TO_2$ |
|---|---|---|
| $Lac_{T0}$ | 2.72 (1.42–5.20), $p = 0.003$ | 2.43 (1.14–5.16), $p = 0.021$ |
| $\delta Lac_{T0-12}$ | 0.34 (0.16–0.71), $p = 0.004$ | 0.78 (0.36–1.67), $p = 0.52$ |
| $\delta Lac_{T12-24}$ | 0.24 (0.10–0.61), $p = 0.003$ | 1.30 (0.48–3.49), $p = 0.61$ |

Because of logarithmic transformation, interpretation of the hazard ratios is as follows: in the SEPSIS group, each decrement specified as a 10% increase of the 0 to 12 h lactate ratio ($\delta Lac_{T0-12}$) causes a −10% (−16 to −3%) change of the mortality hazard. Each 10% increase of $\delta Lac_{T12-24}$ causes a −13% (−20 to −5%) change. In the LT group, the corresponding (nonsignificant) changes in mortality are −2% (−9 to +5%) for $\delta Lac_{T0-12}$ and +3% (−7 to +13%) for $\delta Lac_{T12-24}$. Each 10% reduction in $Lac_{T0}$ causes a −10% (−16 to −4%) change of the mortality hazard in SEPSIS and −9% (−16 to −1%) in LT.

Another hypothesis could be that the SEPSIS patients suffered a less severe and more continuous insult from their disease compared with the LT patients. As a result organ damage and dysfunction might be more reversible and less related to patient survival. This is supported by our observation that the extent of organ dysfunction in SEPSIS survivors and nonsurvivors became similar after 24 hours (i.e., survivors had similar organ dysfunction but somehow this was reversible), whereas the exact opposite happened in LT patients. Reversal of organ dysfunction in septic patients has been suggested to be part of a protective regulatory process, which induces a temporary hypometabolic state resembling hibernation that may protect the cells from dying and allow the possibility of functional recovery.[30]

With regard to the patients' hemodynamic status, we found that the prognostic value of hyperlactatemia was similar in hemodynamically stable and instable patients, also within the SEPSIS and LT groups. This means that, regardless of hemodynamics, reduction or normalization of lactate was not associated with improved outcome in LT patients. This finding might be in contradiction with previous studies in trauma patients with occult hypoperfusion,[5,7] in which a long time to normalization was associated with a higher mortality. Besides potential variation in time before ICU admission, this discrepancy could perhaps be explained by the higher mortality in our LT patients (29% vs. 3–11%[5,7]), possibly corresponding with more irreversible organ damage at admission.

Our study has several limitations. First, the group classification might have changed during the 24 hours. For instance, a trauma patient with a hemorrhagic shock at admission could have developed ischemia-reperfusion damage or sepsis within 24 hours. However, for clinical relevance we were interested in the course of lactate concentration in different categories of patients who can be easily identified immediately at admission. Although this classification might

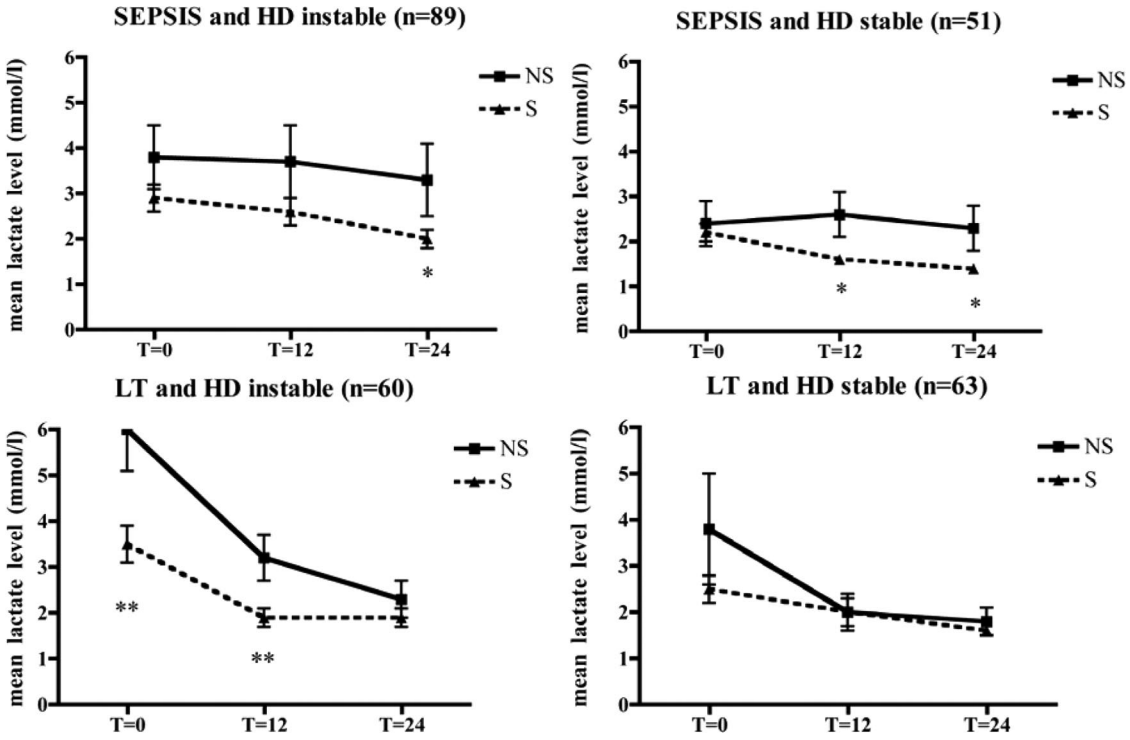


**Fig. 5.** *Mean lactate levels in survivors (S) and nonsurvivors (NS) of the SEPSIS and LT groups according to hemodynamic status.* Error bars *represent ±1 SEM.* *p $<$ *0.05,* **p $<$ *0.01 for comparison between survivors and nonsurvivors at the different time points (T = 0, T = 12, and T = 24).* Solid line*, nonsurvivors;* Dashed line*, survivors.*

**Table 4 Mortality Rates of SEPSIS and LT Patients With Normal and High Blood Lactate levels According to Hemodynamic Status**

| | Hemodynamically Instable | | | Hemodynamically Stable | | |
|---|---|---|---|---|---|---|
| | Lactate <2.5 | Lactate ≥2.5 | *p* | Lactate <2.5 | Lactate ≥2.5 | *p* |
| Sepsis | | | | | | |
| T = 0 | 31% (13/42) | 35% (16/46) | 0.70 | 28% (10/36) | 14% (2/14) | 0.32 |
| T = 24 | 24% (12/50) | 46% (12/26) | 0.049 | 18% (6/34) | 75% (3/4) | 0.035 |
| LT | | | | | | |
| T = 0 | 14% (3/22) | 48% (18/38) | 0.008 | 17% (6/36) | 30% (8/27) | 0.22 |
| T = 24 | 38% (15/40) | 39% (5/13) | 0.95 | 21% (8/39) | 40% (2/5) | 0.32 |

have introduced some inaccuracy, it does resemble daily clinical practice where the prognosis needs to be estimated at the bedside as soon as patients are admitted. Second, we did not collect indices to examine anaerobic or aerobic pathogenesis of hyperlactatemia (e.g., lactate to pyruvate ratio, liver function test, serum catecholamine concentration, or microcirculation imaging). We felt that it was beyond the scope of this study to speculate on the exact causes of hyperlactatemia in our patients. Third, we did not register any form of advanced hemodynamic monitoring, such as cardiac output or $SvO_2$, nor measured oxygen transport. This might be considered a disadvantage because septic patients can be hypodynamic in the early phase[19] and trauma or aortic aneurysm surgery patients can be hyperdynamic in a later phase due to sepsis or ischemia-reperfusion. However, as mentioned before we categorized our patients according to their admission diagnosis, before invasive monitoring. In this way, we tried to make an early classification based on underlying disease rather than on hemodynamic profile. Last, although treating clinicians generally aimed at normalization of lactate levels by increasing $DO_2$ and reducing $VO_2$, we did not collect data on actual provided treatment. Different clinicians might have responded differently to patients with increased lactate levels, in ways we did not capture in our documentation. We don't know in which way this might have influenced the study results. However, because the same trained intensivists were primarily responsible for the treatment of both SEPSIS and LT patients, it seems unlikely that the difference between SEPSIS and LT is systematically biased by a difference in compliance with resuscitation protocols.

In conclusion, we found that lactate reduction during the first 24 hours of ICU stay is associated with improved out-

come only in septic patients, but not in patients with hemorrhage or other conditions generally associated with LT, regardless of the hemodynamic status. Therefore, lactate-directed therapy might not be as beneficial in this particular group of patients, or should be started in an earlier phase in the emergency department.

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