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ORIGINAL ARTICLE

# Persistent hyperlactataemia is related to high rates of in-hospital adverse events and poor outcome in acute heart failure

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## Abstract

**Background:** Although lactate is a well-established marker in intensive care, our understanding of its utility in acute heart failure (AHF) is modest and based on studies with a single measurement of this marker.

**Aim:** We aimed to investigate whether persistent elevation of lactate during hospitalisation is related to a higher risk of adverse events.

**Methods:** We conducted a prospective study to assess AHF patients hospitalised in one cardiac centre. The diagnosis of persistent hyperlactataemia was based on two measurements of the marker (on admission and at 24 h of hospitalisation) and it was defined as lactate elevation (≥ 2 mmol/L) at both time points.

**Results:** The population consisted of 222 patients at a mean age of 70 ± 13 years. Mean ejection fraction and creatinine level on admission were 37% ± 16% and 1.36 ± 0.51 mg/dL, respectively. The percentage of patients with elevated lactates on admission, at 24 h of hospitalisation, and persistent hyperlactataemia were 47%, 35%, and 24%, respectively. The group with persistent hyperlactataemia did not differ in most clinical and laboratory variables from the rest of the population. Patients with persistent hyperlactataemia had higher rate of adverse events during hospitalisation: worsening of heart failure (22.6% vs. 6.5%, $p < 0.05$), inotrope use (22.6% vs. 5.3%, $p < 0.05$), and increase of N-terminal pro–B-type natriuretic peptide at 48 h of hospitalisation (30% vs. 18%, $p < 0.05$). Persistent hyperlactataemia was an independent predictor of one-year mortality (hazard ratio 2.5, 95% confidence interval 1.5–4.3, $p < 0.001$).

**Conclusions:** Persistent hyperlactataemia within the first 24 h of hospitalisation is a predictor of a worse outcome in AHF and is related to higher rates of in-hospital adverse events and one-year mortality.

**Key words:** acute heart failure, hyperlactataemia, lactate, outcome

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## INTRODUCTION

Lactate is an end-product of the anaerobic pathway of energy production [1–3]. In humans, the anaerobic metabolism is mainly used to maintain the production of energy despite the lack of adequate oxygen supply [2]. This process is inefficient, but it is critical to survive stress conditions and to adapt to this transient, unfavourable situation [4]. Under normal steady conditions, lactate is continuously produced (at low levels) and cleared to maintain its low concentration [3]. Thus, lactate is a metabolic marker widely used in many different clinical scenarios, mainly in intensive care medicine [2, 5–10]. The physiological information it carries is also used in endurance sports because intense exercise leads to lactate accumulation even in the absence of any overt pathology [11]. Unlike other widely used markers in heart failure (HF), lactate is unique because it reflects the dynamic energetic/metabolic status of the patient [12–16]. It does not reflect the severity of heart dysfunction itself, but rather the metabolic consequences of the insult driven by the decompensation and its severity in each patient.

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However, the data on lactate utility in HF remain limited [4, 17–20]. Only recently, we showed that a single lactate measurement on admission in acute HF (AHF) patients without overt clinical signs of hypoperfusion may help identify individuals with end-organ dysfunction and worse prognosis [19]. It remains unknown whether AHF patients who are able to clear lactate accumulated on admission during the first hours of hospitalisation have different clinical course and prognosis than those with persistent hyperlactataemia.

Therefore, we aimed to extend our knowledge and investigate whether dynamic changes in lactate levels during the first 24 h of hospitalisation can help identify a high-risk AHF subpopulation.

## METHODS

### Study population

This was a single-centre, prospective, observational study. The study population consisted of patients admitted to the Centre of Heart Diseases, Fourth Military Hospital, Wroclaw, Poland, enrolled between 2016 and 2017. Inclusion criteria comprised AHF as the primary cause of hospitalisation (AHF was diagnosed according to guideline criteria of the European Society of Cardiology [ESC]) and written consent of the patient to participate in the study [21]. Exclusion criteria included cardiogenic shock, the need for intra-aortic balloon pump implantation, clinical diagnosis of concurrent acute coronary syndrome or infection, and known severe liver disease or renal disease requiring or with planned renal replacement therapy. After inclusion, information on demographics, clinical history, comorbidities, previous therapies, and physical examination findings was recorded. Clinical and laboratory assessments including (but not limited to) an evaluation of the clinical sings of HF, as well as assessment of dyspnoea and HF worsening, were performed by attending clinicians on admission, at 24 h, at 48 h, and at discharge.

According to the protocol, lactate levels were measured on admission and at 24 h of hospitalisation as part of standard blood testing to assess capillary blood oxygen saturation and acid-base balance.

Patients were treated in accordance with the recommendations of the attending physicians, which are in line with the ESC guidelines [21], rather than by protocol. The research was approved by the local Ethics Committee, and all participants gave written, informed consent. The study was conducted in compliance with the Declaration of Helsinki.

### Laboratory measurements

At the predefined time points, the following laboratory measurements were recorded using standard methods:

- capillary blood for oxygen saturation, carbon dioxide concentration, pH, bicarbonate, and lactate (direct method, ABL 800 Flex analyser, Radiometer, Copenhagen, Denmark) (on admission and at 24 h);
- haematology: haemoglobin, white blood cell count, and platelet count (on admission and at 48 h);
- serum electrolytes: sodium ($Na^+$) and potassium ($K^+$) (on admission, at 24 h, and at 48 h);
- renal function tests: creatinine and blood urea nitrogen (on admission, at 24 h, and at 48 h);
- liver function tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and albumin (on admission);
- plasma N-terminal pro–B-type natriuretic peptide (NT-proBNP; immunoenzymatic assay, Siemens, Marburg, Germany) (on admission and at 48 h).

### Definitions

On the basis of previous reports, for the purposes of this analysis, elevated lactate was defined as lactate ≥ 2 mmol/L [19, 21]. Persistent hyperlactataemia was defined as elevated lactate at both timepoints: on admission and at 24 h of hospitalisation. Patients in whom elevation of lactate was found only at one time point did not fulfil the definition of persistent hyperlactataemia and were classified to the non-persistent hyperlactataemia group. Persistent tachycardia was defined as heart rate > 100 bpm on admission and at 24 h, persistent hypotension was defined as systolic blood pressure (SBP) < 100 mmHg on admission and at 24 h, and persistent pulmonary congestion was defined as the presence of any congestion on admission and at 24 h assessed by auscultation.

### Clinical follow-up

Surviving patients were followed in the Heart Failure Clinic for at least 365 days. Information was either obtained directly from patients or their relatives (telephone contact) or from the Heart Failure Clinic, the hospital system database, or the central authority census. No patient was lost to follow-up. All-cause mortality at one year was the primary endpoint of interest.

### Statistical analysis

Continuous variables with normal distribution were described using means ± standard deviation, variables with skewed distribution were described by medians with upper and lower quartiles, and categorical variables were given as numbers and percentages. The statistical significance of differences between the groups was assessed using: Student t test, Mann-Whitney U-test, or $\chi^2$ test where appropriate. The Cox proportional hazards model was used to calculate the hazard ratio (HR) with corresponding 95% confidence interval (CI) for all-cause mortality. The multivariate analyses were adjusted for age, serum creatinine, serum $Na^+$, SBP, and NT-proBNP. Kaplan-Meier survival curves were constructed to demonstrate the survival. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using the STATISTICA 13 software (StatSoft Poland, Krakow, Poland).

Table 1. Baseline characteristics of patients with acute heart failure

| Parameter | Population (n = 222) |
|---|---|
| Male sex | 164 (74) |
| Age [years] | 70 ± 13 |
| Heart rate [bpm] | 90 ± 24 |
| SBP on admission [mmHg] | 134 ± 31 |
| DBP on admission [mmHg] | 79 ± 16 |
| LVEF [%] | 37 ± 16 |
| Acute HF (*de novo*) | 88 (39) |
| Ischaemic aetiology of HF | 115 (52) |
| Blood count: | |
| Haemoglobin [g/dL] | 13.3 ± 1.9 |
| WBC [g/L] | 9.2 ± 4.5 |
| Platelets [g/L] | 209 ± 88 |
| AST [IU/L] | 28 [21–40] |
| ALT [IU/L] | 31 [22–56] |
| Bilirubin [mg/dL] | 1.02 [0.72–1.71] |
| Serum sodium [mmol/L] | 139 ± 4 |
| Creatinine [mg/dL] | 1.36 ± 0.51 |
| BUN [mg/dL] | 28 ± 14.4 |
| CRP [mg/L] | 7.7 [4.2–18] |
| NT-proBNP [pg/mL] | 5654 [3365–12081] |
| Troponin I [ng/mL] | 0.06 [0.03–0.17] |
| SBP at 24 h [mmHg] | 122 ± 23 |
| Creatinine at 24 h [mg/dL] | 1.3 ± 0.5 |
| Length of hospitalisation [days] | 8 ± 6 |
| Lactate on admission [mmol/L] | 2.2 ± 1.2<br>2.0 [1.5–2.6] |
| Lactate at 24 h [mmol/L] | 2.1 ± 1.2<br>1.8 [1.5–2.4] |

Data shown as number (percentage), mean ± standard deviation or median [25th–75th quartiles]. ALT — alanine aminotransferase; AST — aspartate aminotransferase; BUN — blood urea nitrogen, CRP — C-reactive protein; DBP — diastolic blood pressure; HF — heart failure; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal pro–B-type natriuretic peptide; SBP — systolic blood pressure; WBC — white blood cell count
Conversion factor to SI units: for haemoglobin [g/dL] — 10 [g/L], for leukocytes [G/L] — 1, for platelets [G/L] — 1; for creatinine [mg/dL] — 88.4 [μmol/L]; for CRP — 9.52 [nmol/L]; for plasma NT-proBNP levels [pg/mL] — 0.1182 [pmol/L]

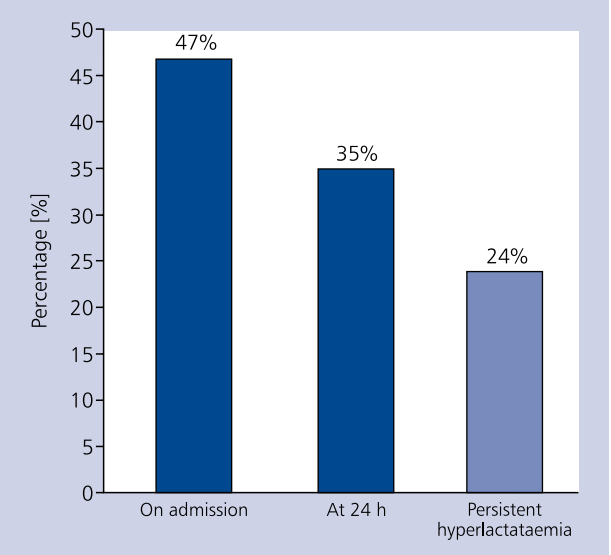


Figure 1. Percentage of patients (n = 222) with elevated lactate (≥ 2 mmol/L)

## RESULTS

### Baseline characteristics

The study population consisted of 222 patients (164 [74%] men) at a mean age of 70 ± 13 years. A total of 88 (39%) patients had *de novo* AHF. The median (25th–75th quartiles) plasma levels of NT-proBNP and troponin I were 5654 pg/mL (3365–12081 pg/mL) and 0.06 pg/mL (0.03–0.17 ng/mL), respectively. Mean lactate levels on admission and at 24 h of hospitalisation were 2.2 ± 1.2 mmol/L and 2.1 ± 1.2 mmol/L, respectively. The detailed baseline characteristics of the patients are shown in Table 1.

### Percentage of patients with elevated lactate during hospitalisation

There were 47% of patients with lactate levels ≥ 2 mmol/L on admission. During the first 24 h of hospitalisation, the percentage of patients with lactate levels above the cut-off value dropped to 35% (Fig. 1). There were 53 (24%) patients with persistent hyperlactataemia (Fig. 1).

### Comparison of patients with and without persistent hyperlactataemia

There were no differences between patients with and without persistent hyperlactataemia in terms of SBP (127 ± 32 mmHg vs. 136 ± 31 mmHg, $p > 0.05$), creatinine (1.3 ± 0.5 mg/dL vs. 1.4 ± 0.5 mg/dL, $p > 0.05$), and serum $Na^+$ (138 ± 5 mmol/L vs. 139 ± 4 mmol/L, $p > 0.05$) on admission. However, patients with persistent hyperlactataemia had higher heart rate (102 ± 27 bpm vs. 86 ± 21 bpm, $p < 0.05$), haemoglobin (13.9 ± 1.9 g/dL vs. 13.1 ± 1.9 g/dL, $p < 0.05$), and bilirubin (1.99 ± 2.1 mg/dL vs. 1.26 ± 1.0 mg/dL, $p < 0.05$) on admission. The group with persistent hyperlactataemia had significantly higher lactate levels at both time points (Table 2). There was no difference in the percentage of patients with in-hospital treatment as well as clinical manifestations of HF (oedema, pulmonary congestion, ascites, elevated jugular venous pressure, or hepatomegaly) between the two groups on admission (Table 2).

Table 2. Comparison of patients with and without persistent hyperlactataemia

| Variables | No persistent hyperlactataemia (n = 169) | Persistent hyperlactataemia* (n = 53) | p |
|---|---|---|---|
| Male sex | 124 (73) | 40 (75) | 0.76 |
| Age [years] | 71 ± 13 | 66 ± 12 | 0.23 |
| Heart rate [bpm] | 86 ± 21 | 102 ± 27 | < 0.0001 |
| SBP on admission [mmHg] | 136 ± 31 | 127 ± 32 | 0.10 |
| DBP on admission [mmHg] | 79 ± 16 | 77 ± 17 | 0.55 |
| LVEF [%] | 38 ± 14 | 34 ± 13 | 0.06 |
| Acute HF (*de novo*) | 94 (57) | 36 (68) | 0.15 |
| Ischemic aetiology of HF | 84 (50) | 31 (58) | 0.23 |
| Blood count: | | | |
| Haemoglobin [g/dL] | 13.1 ± 1.9 | 13.9 ± 1.9 | < 0.005 |
| WBC [g/L] | 8.6 ± 4.0 | 10.6 ± 5.3 | 0.004 |
| Platelets [G/L] | 203 ± 87 | 216 ± 86 | 0.35 |
| AST [IU/L] | 27 [20–38] | 33 [25–70] | 0.004 |
| ALT [IU/L] | 30 [21–53] | 33 [25–109] | 0.02 |
| Bilirubin [mg/dL] | 1.26 ± 1.0 | 1.99 ± 2.1 | 0.001 |
| Serum sodium [mmol/L] | 139 ± 4 | 138 ± 5 | 0.09 |
| Creatinine [mg/dL] | 1.4 ± 0.5 | 1.3 ± 0.5 | 0.68 |
| BUN [mg/dL] | 25 [18–35] | 24 [18–32] | 0.78 |
| CRP [mg/L] | 7 [3–17] | 10 [6-29] | 0.02 |
| NT-proBNP [pg/mL] | 5581 [3476–12118] | 5664 [3129–12081] | 0.92 |
| Troponin I [ng/mL] | 0.05 [0.03–0.11] | 0.09 [0.04–0.62] | 0.007 |
| SBP at 24 h [mmHg] | 123 ± 31 | 113 ± 22 | < 0.005 |
| Creatinine at 24 h [mg/dL] | 1.3 ± 0.5 | 1.2 ± 0.4 | 0.12 |
| Length of hospitalisation [days] | 8 ± 5 | 10 ± 7 | 0.02 |
| Lactate on admission [mmol/L] | 1.9 ± 0.8<br>1.7 [1.3–2.1] | 3.3 ± 1.5<br>2.8 [2.3–3.4] | < 0.0001 |
| Lactate at 24 h [mmol/L] | 1.7 ± 0.5<br>1.7 [1.5–1.9] | 3.2 ± 1.9<br>2.7 [2.3–3.2] | < 0.0001 |
| Treatment during hospitalisation: | | | |
| Furosemide (yes) | 169 (100) | 53 (100) | 1.0 |
| Nitroglycerine (yes) | 90 (53) | 26 (49) | 0.59 |
| ACEI/ARB (yes) | 139 (82) | 47 (89) | 0.25 |
| $\beta$-blocker (yes) | 164 (97) | 50 (94) | 0.35 |
| MRA (yes) | 66 (39) | 16 (30) | 0.24 |
| Oedema on admission: | | | 0.5 |
| No | 45 (27) | 19 (36) | |
| 1+ | 42 (25) | 8 (15) | |
| 2+ | 47 (28) | 14 (26) | |
| 3+ | 35 (21) | 12 (23) | |
| Pulmonary congestion on admission: | | | 0.2 |
| No | 15 (9) | 8 (15) | |
| < 1/3 lungs | 96 (57) | 28 (53) | |
| > 1/3 lungs | 57 (34) | 17 (32) | |
| Ascites (yes) | 23 (14) | 5 (9) | 0.4 |
| JVP > 6 cm (yes) | 52 (31) | 16 (30) | 0.2 |
| Hepatomegaly (yes) | 26 (15) | 9 (17) | 0.7 |

Data shown as number (percentage), mean ± standard deviation or median [25$^{th}$–75$^{th}$ quartiles]. ACEI/ARB — angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; JVP — jugular venous pressure; MRA — mineralocorticoid receptor antagonist; other abbreviations — see Table 1

*Defined as elevated lactate (≥ 2 mmol/L) on admission and at 24 h of hospitalisation.

Table 3. Comparison of in-hospital adverse events in patients with and without persistent hyperlactataemia

| Variables | $\chi^2$ | No persistent hyperlactataemia | Persistent hyperlactataemia* | p |
|---|---|---|---|---|
| Initial admission to CICU | 14 | 30 (18) | 23 (43) | 0.0002 |
| Need for readmission to CICU | 3.1 | 13 (7.6) | 9 (16.9) | 0.07 |
| Worsening of HF during hospitalisation** | 9.7 | 11 (6.5) | 12 (22.6) | 0.002 |
| Inotrope use during hospitalisation | 10.9 | 9 (5.3) | 12 (22.6) | 0.001 |
| In-hospital death | 11.1 | 3 (1.8) | 7 (13.2) | 0.0008 |
| Increase in NT-proBNP level at 48 h | 4.2 | 31 (18) | 16 (30) | 0.04 |
| JVP > 6 cm on day 2 | 3.5 | 18 (11) | 11 (21) | 0.07 |
| Pulmonary congestion on day 2 | 1.7 | 48 (29) | 20 (38) | 0.19 |

Data are shown as number (percentage). CICU — cardiac intensive care unit; other abbreviations — see Tables 1 and 2
*Defined as lactate ≥ 2 mmol/L on admission and at 24 h of hospitalisation; **Assessed by attending cardiologist's clinical judgment

### *In-hospital clinical course of patients with and without persistent hyperlactataemia*

A higher percentage of patients from the group with persistent hyperlactataemia were initially admitted to the cardiac intensive care unit (CICU) (43% vs. 18%, $p < 0.005$) and needed to be readmitted to the CICU during hospitalisation (16.9% vs. 7.6%, $p = 0.07$). Moreover, a higher percentage of patients in this group had worsening of HF during hospitalisation (22.6% vs. 6.5%, $p = 0.002$), increased NT-proBNP level on the second day of hospitalisation (30% vs. 18%, $p = 0.04$), and needed inotropic support (22.6% vs. 5.3%, $p = 0.001$). In-hospital mortality (13.2% vs. 1.8%, $p < 0.001$) and the length of hospital stay (10 ± 7 days vs. 8 ± 5 days, $p = 0.02$) were also higher in the group of persistent hyperlactataemia (Tables 2 and 3).

### *Predictive value of serial lactate assessment in AHF*

There were 62 (28%) deaths during 365 days of follow-up, including 10 (4.5%) deaths during hospitalisation. Lactate level, which was assessed at two time points (on admission and at 24 h of hospitalisation), was a strong prognosticator of one-year mortality (HR 1.5, 95% CI 1.2–1.8, $p < 0.01$ and HR 1.5, 95% CI 1.2–1.8, $p < 0.01$, respectively). Moreover, after dichotomisation of lactate at a cut-off value of 2 mmol/L, it remained significant at both time points (Table 4). Patients with persistent hyperlactataemia had significantly higher risk of death during the one-year follow up (HR 2.4, 95% CI 1.4–3.4, $p = 0.002$). The risk was independent of other well-established prognosticators, such as age, serum creatinine, serum $Na^+$, SBP, or NT-proBNP (HR 2.5, 95% CI 1.5–4.3, $p < 0.001$) as well as of clinical markers of adverse clinical course, such as persistent tachycardia (defined as heart rate > 100 bpm on admission and at 24 h), persistent hypotension (defined as SBP < 100 mmHg on admission and at 24 h), persistent pulmonary congestion (on admission and at 24 h), and worsening of HF during hospitalisation (HR 2.0, 95% CI 1.2–3.4, $p < 0.01$). During the follow-up period, there were 24 (45%) deaths in the hyperlactataemia group vs. 38 (22%) deaths in the rest of the population; the Kaplan-Meier curves demonstrating the survival are shown in Figure 2A ($p = 0.001$).

In order to clarify whether the difference in mortality risk between patients with and without persistent hyperlactataemia was not biased by patients without any elevation of lactate, we performed an additional analysis. The population was divided into three groups: patients with persistent hyperlactataemia (lactate ≥ 2 mmol/L at both timepoints; n = 53) vs. patients with lactate ≥ 2 mmol/L only at one time point (either on admission or at 24 h; n = 77) vs. patients without elevation of lactate (lactate < 2 mmol/L at both timepoints; n = 92). The percentage of patients who died during follow-up was: 45.3% vs. 25% vs. 21%, respectively ($p < 0.05$). Kaplan-Meier curves demonstrating the survival in those groups are shown in Figure 2B ($p = 0.004$).

## DISCUSSION

There are at least four major novel findings of our analyses. To the best of our knowledge, we have shown for the first time that persistent hyperlactataemia, which was defined as elevated lactate level (≥ 2 mmol/L) on admission and at 24 h of hospitalisation, is related to higher rates of in-hospital adverse events and higher one-year mortality in AHF patients. Our data support the hypothesis that AHF patients with insufficient lactate clearance have poor prognosis. It remains unknown whether persistent hyperlactataemia is caused by excessive lactate production or its low elimination, but most likely both factors contribute to this result. A simple, physiological explanation of our observation is that patients who are able to clear the lactate (during the first 24 h of treatment) should have better prognosis despite the initial lactate accumulation because they are able to restore the aerobic metabolism more efficiently [9]. Thus, the decrease of lactate may be an early marker of microcirculatory restoration and better global energy metabolism [2, 8, 22]. Coherent results have already been reported

Table 4. Predictors of one-year mortality — univariate and multivariate analyses

| Variables | $\chi^2$ | HR (95% CI) | p |
|---|---|---|---|
| Lactate on admission (per 1 mmol/L) | 11.6 | 1.5 [1.2–1.8] | 0.0002 |
| Lactate at 24 h (per 1 mmol/L) | 17.3 | 1.5 [1.2–1.8] | < 0.0001 |
| Lactate ≥ 2 mmol/L on admission | 4.6 | 1.7 [1.0–2.9] | 0.03 |
| Lactate ≥ 2 mmol/L at 24 h | 5.7 | 1.8 [1.1–3.1] | 0.02 |
| Persistent hyperlactataemia* | 8.8 | 2.4 [1.4–3.9] | 0.002 |
| Baseline values on admission: | | | |
| SBP (per 1 mmHg) | 5.4 | 0.9 [0.9–0.9] | 0.03 |
| DBP (per 1 mmHg) | 9.1 | 0.9 [0.9–.0.9] | < 0.004 |
| Heart rate (per 1 bpm) | 1.8 | 0.9 [0.9–1.0] | 0.2 |
| Serum sodium (per 1 mmol/L) | 10.8 | 0.9 [0.9–0.9] | < 0.0005 |
| BUN (per 1 mg/dL) | 7.2 | 1.0 [1.0–1.0] | 0.003 |
| Creatinine (per 1 mg/dL) | 7.6 | 1.8 [1.2–2.5] | 0.002 |
| Haemoglobin (per 1 g/dL) | 1.1 | 0.9 [0.8–1.0] | 0.2 |
| NT-proBNP (log) [pg/mL] | 11.7 | 1.0 [1.0–1.0] | 0.0002 |
| Multivariate analyses: | | | |
| Persistent hyperlactataemia*# | 37.7 | 2.5 [1.5–4.3] | < 0.001 |
| Persistent hyperlactataemia*## | 20.9 | 2.0 [1.2–3.4] | 0.007 |

*Defined as elevated lactate (≥ 2 mmol/L) on admission and at 24 h of hospitalisation; #Adjusted for age, serum creatinine, serum sodium, SBP, NT-proBNP; ##Adjusted for persistent tachycardia (defined as heart rate > 100 bpm on admission and at 24 h), persistent hypotension (defined as SBP < 100 mmHg on admission and at 24 h), persistent pulmonary congestion (on admission and at 24 h) and worsening of HF during hospitalisation. CI — confidence interval; HR — hazard ratio; other abbreviations — see Table 1

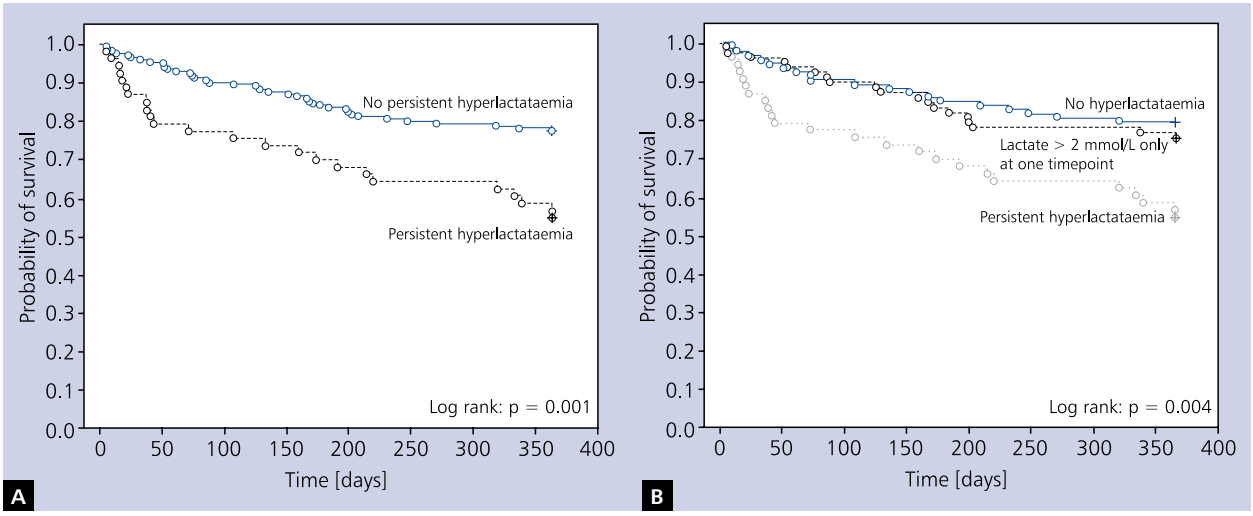


Figure 2. Kaplan-Meier curves; **A.** Comparison of patients with and without persistent hyperlactataemia; **B.** Comparison of patients with persistent hyperlactataemia vs. patients with lactate ≥ 2 mmol/L only at one time point vs. patients without hyperlactataemia

in critical care populations [9]. Although we provide the data on lactate assessed early during the hospitalisation (within the first 24 h), it would also be very interesting to examine its utility as a maker measured at discharge. In this context we may only speculate that it might be a decision-making variable; however, this needs further prospective research.

The pathophysiology of lactate accumulation in HF is complex [1, 4, 7]. Only recently, we have shown in a cohort of HF patients who had undergone haemodynamic monitoring that lactate was moderately correlated with central haemodynamics (cardiac index) and that the strongest determinants of lactate included mixed venous oxygen saturation, systemic

vascular resistance, and heart rate [18]. Indeed, the present analysis seems to confirm our previous observation because significantly higher heart rate on admission was reported for the group with persistent hyperlactataemia. The question of whether hyperlactataemia is a result of more extensive insult (decompensation) or reduced compensatory capabilities of AHF patients remains unanswered. Furthermore, the group with persistent hyperlactataemia showed signs of liver dysfunction (higher AST, ALT, and bilirubin), which may lead to limited clearance abilities of the organism. On the other hand, the observed liver injury may be a result of higher metabolic stress driven by the decompensation itself. Interestingly, the group with persistent hyperlactataemia had significantly higher levels of haemoglobin when compared to the rest of the population. This phenomenon has already been noted in our previous paper and is difficult to explain. We may only conclude that the hyperlactataemia is definitely not a maker of hypoxia that is driven by "simple" anaemia [18]. Thus, this observation supports the hypothesis that the pathophysiology of lactate accumulation is beyond simple tissue hypoxia.

Secondly, there were no obvious signs indicating worse clinical course in the group of persistent hyperlactataemia on admission because there were no differences in most clinical signs of HF and laboratory variables on admission (e.g. SBP, $Na^+$, renal function, and NT-proBNP) [16, 23]. However, it should be stressed that higher heart rate and worse liver function on admission, which are known prognosticators in HF, were observed in the hyperlactataemia group [12, 24–27]. But most importantly, patients who were not able to clear lactate within 24 h were more likely to experience in-hospital adverse events, such as worsening of HF, need for inotropes, increased NT-proBNP level at 48 h, and in-hospital death. To explain this observation, we may only speculate that the hyperlactataemia group included patients with ongoing, clinically undetected energetic debt that led to in-hospital complications and poor outcome. Moreover, this also shows that lactate is a unique HF marker because it reflects the dynamic metabolic status of the patient rather than the static degree of myocardial damage or dysfunction (such as NT-proBNP, troponin I). For the first time, we have linked the metabolic/energetic status of AHF patients during hospitalisation with adverse clinical scenarios.

Thirdly, we have shown that lactate measured during hospitalisation has prognostic importance. Previous papers have shown clinical utility of a single (admission) lactate measurement in AHF populations [17, 19, 20]. Thus, we have demonstrated that serial assessment of lactate during hospitalisation may help to identify patients with higher one-year mortality. The multivariate analyses confirmed that persistent hyperlactataemia was an independent prognosticator of one-year mortality. The persistent elevation of lactate remained an independent prognosticator after adjustment for other factors associated with unfavourable clinical course, such as persistent hypotension, tachycardia, and congestion (present on admission and at 24 h of hospitalisation). Moreover, there was no difference in prognostic significance between lactate measured on admission and at 24 h of hospitalisation (data not shown). Interestingly, the visual analysis of Kaplan-Meier curves revealed that the group with persistent hyperlactataemia were at risk of significantly higher mortality mainly during the first 60 days of follow-up.

The additional analyses (Fig. 2B) revealed that the difference between the groups with vs. without persistent hyperlactataemia was not biased by a relatively low risk related to patients without any elevation of lactate levels. Moreover, the curves rather suggest that the mortality risk assessed only at a single time point may actually be influenced by the patients who have persistent hyperlactataemia in both time points.

Fourthly, there were a significant number of patients with elevated lactate during hospitalisation because approximately one-third of the study population still had lactate levels ≥ 2 mmol/L after 24 h of treatment. Although a decrease in lactate levels was observed during the first day of treatment, much lower levels would be expected. Moreover, almost one-fourth of patients had persistent hyperlactataemia, which indicated an ongoing energy deficit that is usually not identified based on a simple clinical assessment.

The arbitrary cut-off value used for the analyses (2 mmol/L) is based on previous reports and our understanding of lactate physiology [19, 21]. However, we need to stress that each patient population (e.g. patients with sepsis, cardiogenic shock, previous cardiac arrest, etc.) as well as each individual patient may have their own lactate cut-off value for prognosis. Thus, it is likely that higher values of lactate may overperform the value we used in HF patients.

We can conclude that persistent hyperlactataemia within the first 24 h of hospitalisation for AHF is an ominous sign and is related to higher rates of adverse events and higher one-year mortality.

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## WHAT IS NEW?

Lactate is an end-product of anaerobic metabolism. It is used as a marker in many different clinical scenarios, mainly in intensive care medicine. Unlike other markers widely used in heart failure (HF), lactate is unique because it reflects the dynamic energetic/metabolic status of the patient rather than the severity of heart dysfunction. The data on lactate utility in acute HF remain limited. Herein we have shown that elevated lactate level (≥ 2 mmol/L) is common in acute HF patients on admission and during the first day of hospitalisation. For the first time we have demonstrated that acute HF patients with persistent hyperlactataemia, defined as elevated lactate on admission and at 24 h of hospitalisation, have worse outcome. These patients are more likely to experience adverse events during hospital stay (HF worsening or the need for more intensive treatment) and significantly higher one-year mortality.