

# The association of early postoperative lactate levels with morbidity after elective major abdominal surgery

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## ABSTRACT

Lactate levels are widely used as an indicator of outcome in critically ill patients. We investigated the prognostic value of postoperative lactate levels for postoperative complications (POCs), mortality and length of hospital stay after elective major abdominal surgery. A total of 195 patients were prospectively evaluated. Lactate levels were assessed on admission to the intensive care unit (ICU) [ $L_0$ ], at 4 hours ( $L_4$ ), 12 hours ( $L_{12}$ ), and 24 hours ( $L_{24}$ ) after the operation. Demographic and perioperative clinical data were collected. Patients were monitored for complications until discharge or death. Receiver operating characteristic (ROC) curves were used to determine the predictive value of lactate levels for postoperative outcomes. The best cut-off lactate values were calculated to differentiate between patients with and without complications, and outcomes in patients with lactate levels above and below the cut-off thresholds were compared. Univariate and multivariate analyses were used to identify variables associated with POCs and mortality. Seventy-six patients developed 184 complications (18 deaths), while 119 had no complications. Serum lactate levels were higher in patients with complications at all time points compared to those without complications ( $p < 0.001$ ).  $L_{12}$  had the highest predictive value for complications (AUROC<sub>12</sub> = 0.787; 95% CI: 0.719–0.854;  $p < 0.001$ ) and mortality (AUROC<sub>12</sub> = 0.872; 95% CI: 0.794–0.950;  $p < 0.001$ ). The best  $L_{12}$  cut-off value for complications and mortality was 1.35 mmol/l and 1.85 mmol/l, respectively. Multivariate analysis revealed that  $L_{12} \geq 1.35$  mmol/l was an independent predictor of postoperative morbidity (OR 2.58; 95% CI 1.27–5.24,  $p = 0.001$ ).  $L_{24}$  was predictive of POCs after major abdominal surgery.  $L_{12}$  had the best power to discriminate between patients with and without POCs and was associated with a longer hospital stay.

KEY WORDS: Elective surgery; major abdominal surgery; lactate; postoperative complications; in-hospital mortality; surgical intensive care

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## INTRODUCTION

The number of major surgeries undertaken worldwide is estimated to be hundreds of millions per year [1]. Despite the progress in surgical and anesthetic techniques, as well as the advancement in perioperative patient care, postoperative complications (POCs) remain a leading cause of postoperative morbidity and mortality and a serious economic burden to healthcare system [2,3]. To reduce the morbidity and improve short-term and long-term survival of patients, early recognition of POCs is crucial [4]. It has been demonstrated that the impairment of microvascular blood flow both before

and after major abdominal surgery results in a higher rate of POCs [5]. Furthermore, the effect of major surgery on tissue perfusion can be indirectly assessed by measuring lactate levels at the end of surgery [6].

Elevated lactate levels are frequently found in critically ill patients and often correlate with the disease severity. Because of its prognostic role, lactate has been widely used as a biomarker for screening, diagnosis, risk stratification, and monitoring in critically ill patients. Moreover, lactate levels can be used for outcome prediction and as a surrogate endpoint to guide treatment [7]. The rationale for lactate monitoring in critically ill patients is based on the fact that hyperlactatemia is most often caused by tissue hypoperfusion and increased anaerobic glycolysis. Elevated lactate might also be due to an increased aerobic glycolysis, i.e., pyruvate production is higher than the capacity of pyruvate dehydrogenases, which occurs as a response to cytokine release, increased circulating catecholamines, or the

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accumulation of leukocytes at the site of inflammation [7]. Whatever the underlying cause, early detection of hyperlactatemia has shown to be beneficial, since lactate levels were strongly related to the Sequential Organ Failure Assessment (SOFA) scores and outcomes in critically ill patients [8,9].

Multiple studies have evaluated the prognostic value of lactate in heterogeneous groups of critically ill patients, in the intensive care unit (ICU) and emergency department settings [10-12]. Most of those studies involved patients with sepsis, trauma, shock, or severe respiratory failure. On the other hand, data on the significance of lactate monitoring in a relatively homogeneous population of patients undergoing elective major abdominal surgery is scarce.

The aim of our study was to evaluate the ability of early postoperative lactate levels, measured at different time points after elective major abdominal surgery, to predict various POCs. The secondary objectives were to determine the association of static and dynamic measures of lactate homeostasis with in-hospital mortality, length of ICU and hospital stay, and duration of mechanical ventilation after abdominal surgery.

## MATERIALS AND METHODS

### Study design and settings

A prospective, observational cohort study was conducted in the period January–May 2015 at the tertiary care teaching hospital in Belgrade with a semi-closed 14-bed surgical ICU (SICU). This is a model of ICU in which an intensivist-led team is directly responsible for the patient's care. In addition, the surgeon who admitted and operated the patient makes rounds with the ICU team contributing to the patient management. Patients are admitted to the ICU for monitoring and recovery after major abdominal surgery and for the treatment of POCs when indicated.

The study was approved by the Ethics Committee of the School of Medicine, University of Belgrade (reference number 29/XI-13).

### Patient selection

This study enrolled all consecutive adult patients (older than 18 years) who underwent major abdominal surgery, with the expected length of postoperative ICU stay of at least 24 hours. Major surgery was defined as a laparotomy with the operative time of more than 2 hours. Patients were excluded if they had an emergency surgery or if they were reoperated within the same hospitalization.

### Clinical management, data collection, and outcomes

All patients were operated under balanced general anesthesia. Anesthetic drugs and techniques, intraoperative

monitoring, and fluid management were selected at the discretion of the attending anesthesiologist. The patients were transferred to the ICU immediately after the end of surgery. On ICU admission, they were monitored and resuscitated to achieve predefined hemodynamic goals and the target values were as follows: mean arterial pressure (MAP) of 65 mmHg; central venous oxygen saturation ( $S_{cv}O_2$ ) of 70%; urine output of 0.5–1.0 mL/kg/h; and hematocrit (Hct) of 25%. No specific algorithm was used for achieving these hemodynamic goals and laboratory values, and the use of intravenous fluids, vasopressors, inotropes, diuretics, antihypertensive drugs and packed red blood cells (PRBC) was guided by the assessment of the attending intensivist. Lactate levels were not directly used to guide patient management at the ICU.

For each patient, the following preoperative data were obtained: age, sex, body mass index (BMI), history of diabetes, hypertension and heart failure, severe renal or liver disease, American Society of Anesthesiologists (ASA) risk score, and smoking status. Recorded intraoperative variables were type of surgery (esophagogastric, hepatic, pancreaticobiliary, colorectal, or other); hemodynamic instability defined as MAP <65 mmHg or a decrease in MAP for more than 20% of the initial value for a period longer than 30 minutes; significant bleeding, defined as one requiring transfusion of PRBC, or Hct lower than 25%; use of warming devices, such as warming blankets or fluid warmers; and duration of surgery from the induction of anesthesia until the skin closure. Variables assessed during the first 24 hours of ICU stay were: hypotension, defined as MAP <65 mmHg for a period longer than 30 minutes; use of vasopressors;  $S_{cv}O_2$ ; hyperglycemia, defined as blood glucose level >11 mmol/L; 24 hour-fluid balance; urine output; Hct; and the Simplified Acute Physiology Score II (SAPS II) determined 24 hours after the ICU admission.

Arterial blood gas values and lactate levels were obtained on admission ( $L_0$ ), at 4 ( $L_4$ ), 12 ( $L_{12}$ ), and 24 ( $L_{24}$ ) hours after the operation. The measurements were performed using a commercial point-of-care blood gas analyzer (Gem Premier 3000 Instrumentation Laboratory, USA). In addition to these static measures, we also determined dynamic indices of lactate homeostasis. For each patient, lactate area (LA; mmol×h/L) representing cumulative lactate and reflecting the severity and duration of hyperlactatemia was calculated using the method described by Jansen *et al.* [8]. We also calculated the difference between the  $L_{12}$  and  $L_0$  and the  $L_{24}$  and  $L_0$  as the measure of lactate change at 12 and 24 hours, respectively.

Patients were screened for complications and followed up until discharge from the hospital or until death. Complications were defined as “any deviation from the ideal postoperative course that is not inherent in the procedure and does not comprise a failure to cure” [13]. We used the European Perioperative Clinical Outcome (EPCO) definitions

of perioperative outcome measures, issued by the European Society of Anaesthesiology-European Society of Intensive Care Medicine (ESA-ESICM) joint taskforce, to define each POC [14]. The complications were further divided into cardiovascular, respiratory, renal, neurological, infectious (including surgical wound infection), metabolic, and surgical (defined as complications arising as a direct result of a previous surgery, such as bleeding or anastomotic leakage). Secondary outcomes were the length of hospital stay, duration of mechanical ventilation, and duration of ICU stay.

## Statistical analysis

Continuous data, analyzed using the Student's *t*-test or Mann–Whitney U test, were expressed as the mean  $\pm$  standard deviation (SD) or median (interquartile range [IQR]) depending on normality of data distribution. Normality was tested using the Kolmogorov–Smirnov test. Categorical data were tested with  $\chi^2$  and Fisher's exact test as appropriate. Receiver operating characteristic (ROC) curves were constructed to evaluate the ability of different lactate levels to predict POCs and mortality. The best cut-off lactate values to differentiate between patients with and without complications were determined by the Youden's index. According to these cut-off values, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated and the clinical outcomes of patients with lactate levels above and below the thresholds were compared. Factors that showed statistically significant results with regard to POCs and mortality in the univariate analysis were entered in a multivariate regression model. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated subsequently. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp., Armonk, NY). The value of  $p < 0.05$  was considered statistically significant.

## RESULTS

### Patient's characteristics and outcomes

During the study period, a total of 212 patients were admitted to the ICU following major abdominal surgery. Out of 212 patients, 17 were excluded from the study due to the following reasons: 6 were admitted after an emergency surgery, 3 underwent reoperation, and in 8 patients there was a protocol violation and missing lactate values at more than one time point. Finally, 195 patients were evaluated for the purpose of this study, of whom 76 (38.97%) developed a total of 184 complications, including death in 18 patients. The remaining 119 patients had no complications. Characteristics of patients with and without complications are summarized in Table 1.

The predefined hemodynamic goals and laboratory parameters (i.e.,  $S_{cv}O_2 > 70\%$ , MAP  $> 65$  mmHg, urine output 0.5–1.0 mL/kg/h, and Hct  $> 25\%$ ) were not achieved on admission to the ICU in 63/195 patients (32.3%). Among these patients, 56/195 (28.6%) had  $S_{cv}O_2 < 70\%$ ; 14 (7.18%) had Hct  $< 25\%$ ; 6 (3.1%) had a low urine output; and 16 patients (8.2%) had MAP  $< 65$  mmHg. At 12 hours of the admission, in 18/195 patients (9.2%) at least one the hemodynamic goals was still not achieved, as follows:  $S_{cv}O_2$  was low in 10 (5.1%), Hct was  $< 25\%$  in 7 (3.6%), urine output was low in 4 (2.1%), and MAP was  $< 65$  mmHg in 12 patients (6.1%). Nevertheless, the mean  $S_{cv}O_2$  at 12 hours after ICU admission was within the normal range in the entire cohort and did not differ between patients with and without complications (71.94% vs. 72.33%,  $p = 0.663$ ).

Compared to patients without complications, patients with complications were significantly older, had higher ASA and SAPS II scores, were more likely to be treated with vasopressors, and they less frequently received intraoperative warming. As expected, patients with complications had a longer duration of mechanical ventilation, ICU, and hospital stay. The most common complication was infection, 59/76 of patients with complications (77.63%). The median duration of ICU and hospital stay was 1.0 (1.0–1.8) and 12.0 (12.0–16.0) days, respectively.

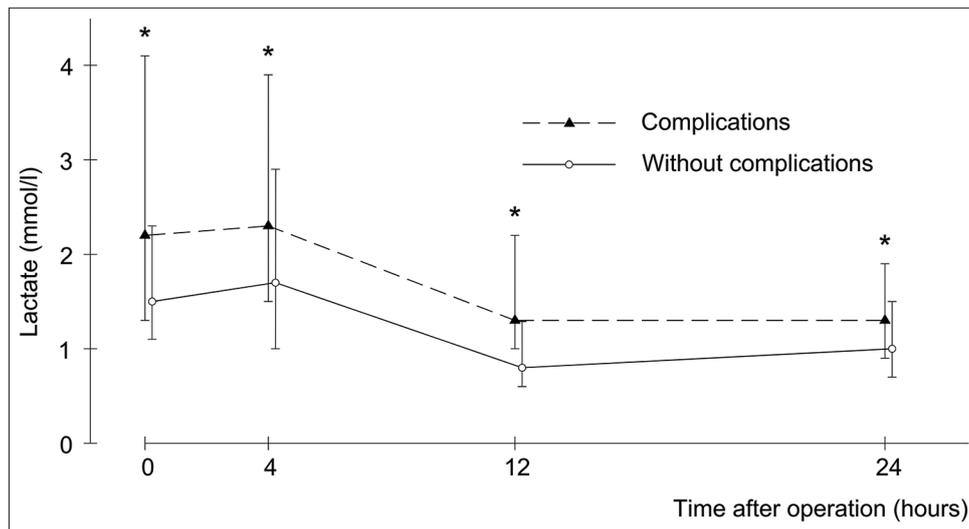
### Lactate levels

The median lactate level on ICU admission ( $L_0$ ) was 1.70 (1.20–2.70) mmol/L,  $L_4$  was 1.90 (1.10–2.90) mmol/L,  $L_{12}$  was 1.10 (0.70–1.625) mmol/L, and median  $L_{24}$  was 1.20 (0.80–1.60) mmol/L. The median LA was 35.0 (24.4–53.0) mmol $\times$ h/L. Lactate levels were significantly higher in patients with complications at all time points, and the same was demonstrated for the LA [ $p < 0.001$ ] (Figure 1). However, lactate levels varied significantly between patients (from both groups) in relation to the types of surgery they underwent (Figure 2). This difference was observed at all time points of lactate measurement (Kruskal–Wallis;  $p = 0.023$ ,  $p < 0.001$ ,  $p < 0.001$ , and  $p = 0.003$  for  $L_0$ ,  $L_4$ ,  $L_{12}$ , and  $L_{24}$ , respectively). Particularly high serum lactate levels were noted in patients who underwent pancreaticobiliary surgery, i.e., lactate did not reach the reference level during the entire 24-hour period resulting in the highest LA (44.4 mmol $\times$ h/L [31.8–86.1]). The difference in lactate levels at 12 hours after the operation ( $L_{12} - L_0$ ) was 0.6 (0.2–1.3) mmol/L and it did not differ significantly between patients with and without complications (0.6 [0.1–1.1] mmol/L vs. 0.6 [0.2–1.4] mmol/L;  $p = 0.682$ ). Similarly, the difference in lactate levels at 24 hours after the operation ( $L_{24} - L_0$ ) was 0.5 (0.0–1.4) mmol/L, without a significant difference between patients with and without complications (0.5 [0.0–1.4] mmol/L vs. 0.6 [0.1–1.8] mmol/L;  $p = 0.391$ ).

**TABLE 1.** Characteristics of ICU patients with and without complications following major abdominal surgery

| Characteristic  | Total (n=195)       | Complications (n=76) | No complications (n=119) | <i>p</i> |
|---|---------------------|----------------------|--------------------------|----------|
| Male (%)  | 132 (67.7)          | 53 (69.7)            | 79 (66.4)                | 0.626    |
| Age (years)   | 62.2±12.9           | 65.4±12.3            | 60.2±12.9                | 0.005    |
| Cigarette smoker (%)  | 58 (29.7)           | 23 (30.3)            | 35 (29.4)                | 0.874    |
| BMI   | 25.4±4.5            | 25.3±3.9             | 25.4±4.8                 | 0.905    |
| ASA >2  | 55 (28.5)           | 27 (35.5)            | 28 (23.5)                | <0.001   |
| Intraoperative warming  | 92 (47.2)           | 17 (18.5)            | 75 (81.5)                | <0.001   |
| Bleeding  | 33 (16.9)           | 15 (19.7)            | 18 (15.1)                | 0.437    |
| Hemodynamic instability   | 77 (39.5)           | 35 (46.1)            | 42 (35.3)                | 0.176    |
| Duration of surgery (minutes)                                   | 165.0 (120.0-240.0) | 165.0 (120.0-240.0)  | 165.0 (108.7-300.0)      | 0.319    |
| S <sub>cv</sub> O <sub>2</sub> 12 hours after ICU admission (%) | 72.1±7.3            | 72.3±8.2             | 71.9±5.0                 | 0.663    |
| Vasopressor   | 15 (7.7)            | 14 (18.4)            | 1 (0.8)                  | <0.001   |
| Hyperglycemia   | 80 (41.0)           | 33 (43.4)            | 47 (39.5)                | 0.655    |
| Fluid balance (mL/kg)   | +56.5±35.6          | +59.9±36.4           | +54.4±35.1               | 0.298    |
| SAPS II score   | 28 (26-31)          | 30 (27-34)           | 22 (19-26)               | <0.001   |
| Type of surgery   |                     |                      |                          |          |
| Esophagogastric   | 26 (13.3)           | 14 (18.4)            | 12 (10.1)                | 0.095    |
| Hepatic   | 19 (9.7)            | 5 (6.6)              | 14 (11.8)                | 0.234    |
| Pancreaticobiliary  | 33 (16.9)           | 23 (30.3)            | 10 (8.4)                 | <0.001   |
| Colorectal  | 96 (49.2)           | 25 (32.9)            | 71 (59.7)                | <0.001   |
| Other   | 21 (10.9)           | 9 (11.8)             | 12 (10.0)                | 0.729    |
| ICU stay (days)   | 1.0 (1.0-1.0)       | 1.0 (1.0-4.0)        | 1.0 (1.0-1.0)            | <0.001   |
| Hospital stay (days after operation)                            | 12.0 (8.0-16.0)     | 15.0 (11.0-19.0)     | 9.0 (8.0-14.0)           | <0.001   |
| Mechanical ventilation (hours)                                  | 0.0 (0.0-0.0)       | 0.0 (0.0-5.0)        | 0.0 (0.0-0.0)            | 0.003    |

Data are presented as mean±standard deviation, number (%), or median (IQR). BMI: Body mass index; ASA: American Society of Anesthesiologists; S<sub>cv</sub>O<sub>2</sub>: Central venous oxygen saturation; SAPS II: Simplified acute physiology score; ICU: Intensive care unit; IQR: Interquartile range



**FIGURE 1.** Lactate levels in patients with and without complications following major abdominal surgery. Data are presented as median (interquartile range [IQR]). Serum lactate levels were significantly higher in patients with complications at all time points compared to those without complications (\**p* < 0.001).

### Predictive value of postoperative lactate levels

ROC curve analysis showed that lactate levels measured at 12 hours after the operation had the highest predictive ability for overall POCs (the area under the ROC [AUROC] 0.787; 95% CI 0.719-0.854; *p* < 0.001; Figure 3A) and postoperative in-hospital mortality (0.872; 0.794-0.950; *p* < 0.001; Figure 3B).

L<sub>12</sub> had the best discriminative power for the majority of POC types, with the highest AUROC for neurological

(0.829; 0.723-0.935) and cardiovascular complications (0.801; 0.683-0.920; *p* = 0.001), as shown in Table 2.

A ROC curve was also used to determine the best cut-off value of L<sub>12</sub> which could discriminate between patients with and without complications. The L<sub>12</sub> value of 1.35 mmol/L corresponded to the AUROC of 0.796, sensitivity of 72.0%, specificity of 60.8%, PPV of 53.5%, and NPV of 76.4% for overall complications. Similarly, 1.85 mmol/L was the optimal cut-off L<sub>12</sub> value that discriminated between patients who survived and those who did not, with AUROC of 0.881,

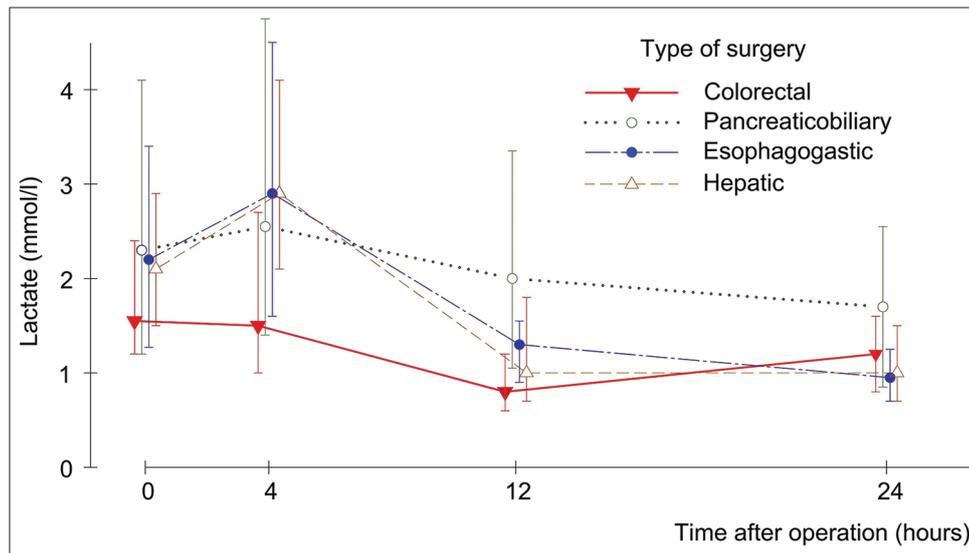
sensitivity of 70.6%, specificity of 81.5%, PPV of 32.2%, and NPV of 96.6% (Table 3).

Patients whose  $L_{12}$  levels were above the defined cut-off value were considered to have a relative hyperlactatemia and were compared regarding the main outcomes with the patients whose  $L_{12}$  levels were under the threshold. A significantly higher number of patients with relative hyperlactatemia developed complications (55 vs. 21 patients without relative hyperlactatemia,  $p < 0.001$ ). Moreover, the length of hospital stay was significantly longer in patients with relative

hyperlactatemia (14.0 days [8.0–18.0] vs. 10.0 days [8.0–14.0],  $p < 0.001$ ; Table 4).

### Factors associated with complications and mortality

According to the univariate logistic regression analysis, risk factors for complications were as follows: patient age [in years] (OR 1.052, 95% CI 1.017–1.089,  $p = 0.007$ ), history of heart failure (OR 3.862, 95% CI 1.145–13.052,  $p = 0.029$ ), ASA  $>2$  (OR 2.068, 95% CI 1.367–3.128,  $p = 0.001$ ),  $L_{12} \geq 1.35$  mmol/L (OR



**FIGURE 2.** Serum lactate levels during the first 24 postoperative hours in relation to different types of major abdominal surgery.

**TABLE 2.** Prognostic value of serum lactate for different postoperative complications following major abdominal surgery

| Type of complication | Number of patients | Best predictive lactate value | AUC   | 95% CI      | <i>p</i> |
|----------------------|--------------------|-------------------------------|-------|-------------|----------|
| Cardiovascular       | 18                 | $L_{12}$                      | 0.818 | 0.698–0.939 | 0.001    |
| Respiratory          | 21                 | $L_{12}$                      | 0.760 | 0.645–0.874 | <0.001   |
| Neurological         | 13                 | $L_{12}$                      | 0.829 | 0.723–0.935 | <0.001   |
| Infectious           | 59                 | $L_{12}$                      | 0.783 | 0.712–0.854 | <0.001   |
| Renal                | 17                 | $L_{12}$                      | 0.786 | 0.682–0.889 | <0.001   |
| Surgical             | 44                 | $L_{24}$                      | 0.809 | 0.733–0.884 | <0.000   |
| Metabolic            | 12                 | $L_{12}$                      | 0.802 | 0.724–0.873 | <0.001   |

AUC: Area under the curve; 95% CI: 95% confidence interval;  $L_{12}$ : Lactate levels 12 hours postoperatively;  $L_{24}$ : Lactate levels 24 hours postoperatively

**TABLE 3.** Prognostic value of  $L_{12}$  for complications and mortality following major abdominal surgery

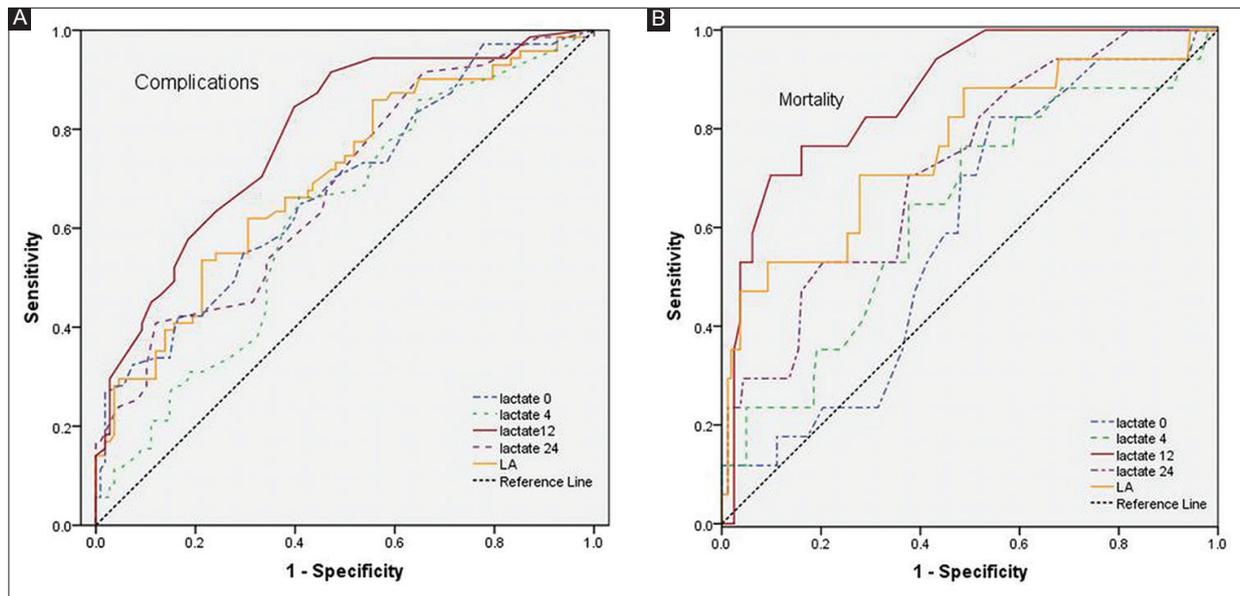
| Variable                   | Cut-off value (mmol/L) | AUC (95% CI)        | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|----------------------------|------------------------|---------------------|-----------------|-----------------|---------|---------|
| $L_{12}$ for complications | 1.35                   | 0.796 (0.688–0.815) | 72.0            | 60.8            | 53.5    | 76.4    |
| $L_{12}$ for mortality     | 1.85                   | 0.881 (0.779–0.901) | 70.6            | 81.5            | 32.2    | 96.6    |

PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under the curve; 95% CI: 95% confidence interval;  $L_{12}$ : Lactate levels 12 hours postoperatively

**TABLE 4.** Outcomes of ICU patients with and without relative hyperlactatemia following major abdominal surgery

| Outcome                                    | $L_{12} \geq 1.35$ mmol/L | $L_{12} < 1.35$ mmol/L | <i>p</i>            |
|--|---------------------------|------------------------|---------------------|
| Complications, n                           | 55                        | 21                     | <0.001 <sup>a</sup> |
| Duration of mechanical ventilation (hours) | 19.2 (10.1–27.2)          | 15.6 (8.3–26.5)        | 0.696 <sup>b</sup>  |
| Length of ICU stay (days)                  | 2.4 (1.0–3.9)             | 1.6 (0.8–3.3)          | 0.052 <sup>b</sup>  |
| Length of hospital stay (days)             | 14.0 (10.0–18.0)          | 10.0 (8.0–14.0)        | <0.001 <sup>b</sup> |

Data are expressed as median (IQR). n: number of patients; <sup>a</sup> $\chi^2$  test; <sup>b</sup>Mann–Whitney U test; ICU: Intensive care unit;  $L_{12}$ : Lactate levels 12 hours postoperatively; IQR: Interquartile range



**FIGURE 3.** ROC curves of serum lactate levels at four time points following major abdominal surgery and lactate area (LA) to predict postoperative complications (A) and mortality (B). AUC for  $L_{12}$  was the highest both for complications (0.722; 95% CI 0.647–0.798;  $p < 0.001$ ) and mortality (0.821; 0.706–0.937;  $p < 0.001$ ). ROC: Receiver operating characteristic; AUC: Area under the curve;  $L_{12}$ : Lactate levels 12 hours postoperatively; CI: Confidence interval.

**TABLE 5.** Factors associated with postoperative complications following major abdominal surgery according to univariate and multivariate regression analysis

| Variable                       | Univariate        |          | Multivariate      |          |
|--------------------------------|-------------------|----------|-------------------|----------|
|                                | OR (95% CI)       | <i>p</i> | OR (95% CI)       | <i>p</i> |
| Age (years)                    | 1.05 (1.02–1.09)  | 0.007    | 1.04 (0.88–1.06)  | 0.082    |
| History of heart failure       | 3.86 (1.14–13.05) | 0.029    | 2.43 (0.55–10.69) | 0.240    |
| ASA >2                         | 2.07 (1.37–3.13)  | 0.001    | 0.91 (0.52–1.59)  | 0.730    |
| $L_{12} \geq 1.35$ mmol/L      | 3.72 (1.99–6.96)  | <0.001   | 2.58 (1.27–5.24)  | 0.001    |
| Pancreatic surgery             | 4.73 (2.10–10.65) | <0.001   | 2.19 (0.83–5.83)  | 0.115    |
| Colorectal surgery             | 0.33 (0.18–0.60)  | <0.001   | 0.39 (0.18–0.86)  | 0.061    |
| Lack of intraoperative warming | 1.86 (1.03–2.99)  | 0.008    | 1.23 (0.65–2.36)  | 0.542    |
| SAPS II score                  | 3.44 (1.24–9.75)  | <0.001   | 2.05 (1.35–6.04)  | <0.001   |

ASA: American Society of Anesthesiologists risk score; SAPS II: Simplified Acute Physiology Score II;  $L_{12}$ : Lactate levels 12 hours postoperatively; OR: Odds ratio; 95% CI: 95% confidence interval

3.720, 95% CI 1.989–6.960,  $p < 0.001$ ), pancreatic surgery (OR 4.730, 95% CI 2.101–10.651,  $p < 0.001$ ), colorectal surgery (OR 0.331, 95% CI 0.181–0.605,  $p < 0.001$ ), not receiving intraoperative warming (OR 1.862, 95% CI 1.035–2.997,  $p = 0.008$ ), and SAPS II score (OR 3.445, 95% CI 1.244–9.752,  $p < 0.001$ ). Multivariate logistic regression analysis revealed that  $L_{12} \geq 1.35$  mmol/L was an independent predictor of POCs (OR 2.58; 95% CI 1.27–5.24,  $p = 0.001$ ), along with the SAPS II score [OR 2.05; 95% CI 1.35–6.04,  $p < 0.001$ ] (Table 5).

Variables independently associated with mortality were ASA >2 (OR 3.41; 95% CI 1.06–10.94,  $p < 0.001$ ),  $L_{12} > 1.85$  mmol/L (OR 3.82; 95% CI 2.46–5.91,  $p < 0.001$ ), and patient age (OR 1.05; 95% CI 1.02–1.09,  $p = 0.004$ ).

## DISCUSSION

Lactate levels are often elevated in critically ill patients and can be used as an indicator of clinical outcome. In this

study, higher serum lactate levels in the early postoperative period after the elective major abdominal surgery were associated with an increased risk of POCs and mortality. Higher lactate was also associated with a longer duration of hospital stay, despite similar postoperative care in all patients. We demonstrated that the lactate levels assessed at 12 hours following the operation had the highest predictive value of the adverse outcomes. The cut-off  $L_{12}$  value for complications was 1.35 mmol/L and for mortality 1.85 mmol/L, both values are commonly considered to be within the normal range in critically ill patients.

Hyperlactatemia following major surgery has been observed in many studies [15–19]. It is usually attributed to an oxygen debt, resulting from a tissue hypoxia [20]. However, there are a number of other causes of hyperlactatemia, and some of them, such as the derangement of glucose metabolism and the effect of circulating catecholamines, may play a vital role during and after a major surgery [21]. A recent study showed

that microcirculatory changes following major abdominal surgery appear to be insignificant and not associated with lactate levels or clinical outcomes [22]. However, abdominal surgery can be accompanied by an increased surgical stress; therefore, it is not surprising that we observed postoperative hyperlactatemia regardless of the surgical site. The study by Xiaojuan *et al.* indicated the significant effect of the site of gastrointestinal surgery on postoperative lactate levels [23]. Similar to our results, they found the lowest rate of hyperlactatemia after colorectal surgery. Although not directly investigated in our study, we can assume that an elective colorectal surgery, routinely performed and with many available perioperative fast-track protocols, is associated with a lower surgical stress compared to a complex pancreaticobiliary surgery (which caused the highest postoperative lactate levels according to our results).

Creagh-Brown *et al.* [24] evaluated the effect of the peak serum lactate, in the first 24 hours of ICU admission after major gastrointestinal surgery, in a very large cohort of more than a hundred thousand patients from 249 hospitals in the United Kingdom. They found that increased in-hospital mortality was associated with elevated lactate levels, with no difference between elective and emergency surgery. Moreover, the positive linear relationship between the lactate levels and risk of mortality continued down into the normal range of lactate (<2 mmol/L). However, due to the retrospective design of their study, the authors took into account only the peak lactate level during the first 24 hours following ICU admission, which may not accurately reflect the clinical outcomes observed in that period. Generally, in-hospital mortality as an outcome is a relatively rare event after elective surgeries and only a crude indicator of the quality of care. In the current study, we determined that lactate levels measured at 12 hours after an elective major abdominal surgery have the best predictive value for both, complications and mortality. Consistently, similar results were obtained when the analysis was restricted to different types of complications. Our results also indicated the importance of monitoring lactate trend over time as a predictor of postoperative outcomes. However, we found no association between the lactate clearance within 12 and 24 hours after the ICU admission and the overall complication rate. This may be due to the fact that there was no significant difference in the lactate clearance between the observed time points. These results are in agreement with other studies, suggesting that the duration of hyperlactatemia, rather than its extent, is associated with poor outcomes in critically ill patients following major surgery [25,26]. Meregalli *et al.* [27] found that lactate levels measured 12 hours after ICU admission could discriminate between survivors and nonsurvivors in a group of high-risk, hemodynamically stable, surgical patients [27]. Moreover, persistent hyperlactatemia in the nonsurvivors at 48 hours correlated with a poor clinical outcome. The authors attributed these findings

to a continuous and inadequate resuscitation that resulted in occult hypoperfusion. The assumption that hyperlactatemia results from oxygen debt is the ground for “lactate-guided” resuscitation protocols. However, not all studies showed good results with these protocols [28,29]. Postoperative hyperlactatemia can be due to different etiologies and measures that only target tissue hypoxia to resolve hyperlactatemia may yield unsatisfactory results. For example, hyperlactatemia that arises in response to an increased surgical stress, postoperative pain, or hypothermia is unlikely to be resolved by an increased oxygen delivery. Whatever the underlying cause, elevated serum lactate levels on ICU admission following surgery should prompt clinicians to analyze all the possible etiologies and undertake various measures to control hyperlactatemia early, preferably in the first half of day. Although not directly investigated, we assume that failure of pain control and persistent hypothermia during the first 12 hours postoperatively could have contributed to the results of our study.

The two cut-off  $L_{12}$  values 1.35 and 1.85 mmol/L, that were able to predict morbidity and mortality, respectively in our study, are considered to be within the normal range in critically ill patients. However, a relative hyperlactatemia has already been identified as a bad prognostic factor in septic patients, suggesting that the serum lactate within the reference range should be interpreted cautiously [30]. A number of studies showed that hyperlactatemia (lactate levels between 2 and 4 mmol/L) is associated with a worse clinical outcome in patients with septic shock. The lower threshold has been proposed according to the new evidence [31]. Since the patients undergoing an elective abdominal surgery are considerably different compared to septic patients, in our opinion, the upper limit of lactate levels associated with worse outcomes in this population should be different as well. The results from this and other studies indicate the need for re-defining the cut-off values of serum lactate to predict outcomes in critically ill patients in the perioperative setting. Nevertheless, additional studies are required to elucidate which of the lactate-guided therapies can improve perioperative outcomes. Overall clinical context should be considered when treating postoperative hyperlactatemia. For example, the attempts to normalize lactate levels through resuscitation with fluids or inotropes, in the absence of other signs of tissue hypoperfusion, may expose patients to overhydration and high doses of inotropes without any obvious benefit [29]. Thus, it is important to take into account other potential aerobic mechanisms of hyperlactatemia and to treat the underlying causes accordingly. With this regard, recognition of signs of hepatic dysfunction is essential as it is related to lactate clearance. Moreover, reduction of increased muscle work arising from shivering, or increased work of breathing can decrease serum lactate levels. The study by Berg *et al.* demonstrated that the administration of

thiamine may increase the aerobic metabolism in critically ill patients with stable hemodynamics, by enabling pyruvate to enter the Krebs cycle [32]. However, the role of thiamine in decreasing serum lactate and thus affecting the postoperative course remains unclear and requires additional studies.

Our study has several limitations. First, it was an observational study and we did not control for possible confounding factors, such as the type and quality of anesthesia and surgical techniques, postoperative pain control, and temperature monitoring. We also did not use advanced techniques for the estimation of tissue perfusion, i.e., monitoring of  $S_{cv}O_2$  and microcirculation, as these are not routinely used at our ICU. Second, the morbidity and mortality were not estimated preoperatively since the frequently used Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) scoring system has never been validated in our population. Instead, we estimated the effect of patient comorbidities, ASA, and SAPS II score on POCs and mortality. Finally, the drawback of our study is that we did not collect the data on interventions and therapies that could have altered the lactate levels.

The strength of our study is its prospective design and the fact that all measurements were done on a single point-of-care blood gas analyzer, thus minimizing the variation in readings. Also separate teams of investigators measured lactate levels and assessed postoperative outcomes, which probably reduced the investigator bias.

## CONCLUSION

This study shows that lactate levels during the first 24 hours postoperatively have a predictive value for POCs and mortality after an elective major abdominal surgery. Serum lactate levels obtained 12 hours postoperatively had the best predictive value to discriminate between patients with and without complications and also between survivors and nonsurvivors. Although not explanatory by its design, our study demonstrates that elevated postoperative lactate is an ominous sign that should to be addressed by the intensivist. However, further studies are required to indicate which strategies aimed at resolving hyperlactatemia improve postoperative outcomes.

## DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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