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ORIGINAL REASERCH PERIOPERATIVE MEDICINE

Factors affecting a persistent increase in the perioperative lactate levels in colorectal cancer surgery and its impact on postoperative outcomes

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Abstract

Aim and objectives: High lactate concentration is a sign of tissue hypoxia in the perioperative period. Therefore, close monitoring of blood lactate is essential in cancer patients undergoing surgery. The first aim of this study is to determine the factors affecting the perioperative consistently high lactate levels in patients undergoing colorectal cancer (CRC) surgery. Our second goal was also to investigate the relationship between persistent perioperative hyperlactatemia and postoperative outcomes.

Methodology: Retrospectively enrolled 323 patients who underwent curative resection for colorectal cancer. Lactate values of all patients were examined at the end of the surgery and in ICU-stay at 3rd, 6th, 12th, and 18th hours immediately after surgery. All lactate values above 2 mmol/L were considered elevated. The patients were divided into two groups as those with persistently perioperative increased lactate levels and those without.

Results: Thirty-four out of 323 patients experienced persistent hyperlactatemia during the perioperative period. The multivariate analysis presented that lactate levels were affected by BMI ≥ 30 kg/m^2 (p = 0.005), male sex (p = 0.022), and the TNM stage III (p = 0.045). Major complications were encountered in 45 of 323 patients. Eleven of them were found in the persistent hyperlactatemia group (p = 0.003). Anastomotic leakage was the most common complication among them. The persistent group had a significantly prolonged length of hospital stay (p = 0.050), but there was no survival difference between the two groups (p = 0.797).

Conclusion: In this study, which included patients undergoing elective surgery for colorectal cancer, the risk factors for persistent hyperlactatemia during the perioperative period were BMI ≥ 30 kg/m^2, male gender, and advanced TNM stage. The persistent perioperative hyperlactatemia may predict major complications in the early postoperative period, especially anastomotic leak and also a prolonged hospital stay. On the contrary, it has no prognostic prediction for mortality.

Key words: hyperlactatemia; prognosis; lactate; colorectal cancer; surgery

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1. Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide and the second in terms of cancer-related deaths.[1] In addition to high mortality rates of up to 16.4%, postoperative morbidity with rates as high as 35.1% is also a common problem following colorectal resection.[2] Cancer surgery is a challenging procedure, and therefore postoperative complications have complex causes. The essential part

of all etiological factors is the decreased tissue blood flow and oxygen supply due to the alteration of the microvascular flow.[3] The suitable marker that demonstrates this situation is blood lactate levels. High lactate concentration is a sign of tissue hypoxia in the early phase. Therefore, during the intraoperative and intensive care units (ICU), also in the perioperative period, close monitoring of blood lactate is important for cancer patients.

Hyperlactatemia is a term used for conditions where the serum lactate concentration exceeds 2 mmol/L.[4] Lactate is not only an indicator of tissue hypoxia but also of poor postoperative outcomes and is often used today in the follow-up of critical patients.[5] In contrast, Junior et al.[6] states that intraoperative hyperlactatemia does not have prognostic significance.

Intraoperative lactate measurements are commonly preferred, especially during cardiac surgery, and their predictive importance in this patient group is well known.[7] It has also been well studied as a prognostic marker in ICU and septic shock patients.[8] To the best of our knowledge, the prognosis significance of persistent hyperlactatemia and factors affecting it has not been adequately investigated in the perioperative period in patients undergoing elective colorectal cancer surgery.

The first aim of this study is to determine the factors affecting the perioperative consistently high lactate levels in patients undergoing CRC surgery. Our second goal was also to investigate the relationship between persistent perioperative hyperlactatemia and postoperative outcomes.

2. Methodology

Ethical approval (Ethical Committee No. 2019.4/21-198) was provided by the Institutional Research and Ethics Committee of our hospital. This committee waived the need for informed consent from all eligible patients.

We retrospectively enrolled 323 patients who underwent curative resection in our center for CRC between January 2013 and July 2019. In the present study, exclusion criteria were under 18 years of age, palliative surgery, or emergency surgery. TNM stage IV patients were also excluded from the study. The blood lactate levels of all patients were measured intra-arterially. Initial lactate levels were determined from blood gas analysis before the incision. At the end of the surgery was recorded as the last intraoperative lactate value. The patients were admitted to the ICU immediately after surgery. In the ICU, lactate values of all patients were examined at 3rd, 6th, 12th, and 18th hours. All lactate values above 2 mmol/L in the blood gas analysis were considered increased. Patients, those who had an initial blood lactate level higher than 2 mmol/L, were excluded from the study. The persistent group was defined, serum lactate concentration > 2 mmol/L both at the end of surgery and in all four measurements in the ICU (Figure 1). Finally, according to the lactate analysis, the patients were divided into two groups as the persistent high group and the non-persistent group. If the patient's serum lactate concentration was < 2 mmol/L in any measurement, the patient was excluded from the persistent group.

Patients with chronic liver, kidney, and heart disease that can affect lactate metabolism, where organ function is impaired, and anemia that would require transfusion were also excluded.

The demographic, clinical, and surgical characteristics of the patients were included as variables. Demographic data included age and sex information. As clinical data, Charlson Comorbidity Index (CCI),[9] Diabetes Mellitus (DM) type II, use of Metformin, American Society of Anesthesiologists (ASA) score, Body Mass Index (BMI), and neoadjuvant therapy were recorded. Surgical details included the tumor size, TNM stage, the total volume of administered crystalloids, the volume of urine output, the volume of blood loss, and the operative time, the tumor size, and the TNM stage.

Standard anesthesia induction was applied to all patients with 1-2 mcg/kg fentanyl, 2 mg/kg propofol, and 0.1 mg/kg rocuronium. After orotracheal intubation, mechanical ventilation was performed with 8 ml/kg tidal volume and 12 breaths/minute. Maintenance of the sevoflurane dose was adjusted with the Bispectral Index (BIS) monitoring in the range of 0.8-1 minimum alveolar concentration (MAC).

Complications were carried out according to the Clavien-Dindo classification.[10] Accordingly, those with a score of 3 and above were considered major complications. Postoperative complications within the first 30 days were included in this study.

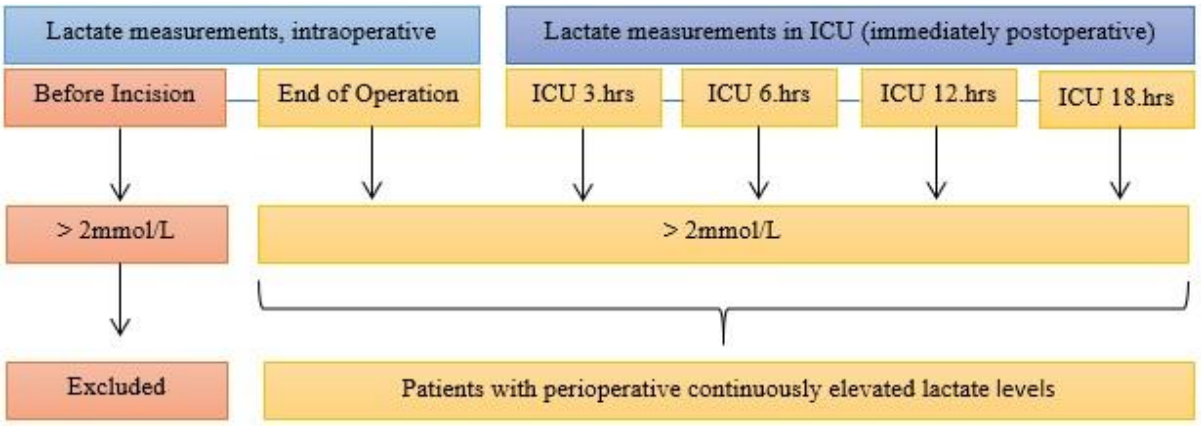

Figure 1: Demonstration of the study groups with the timing of the lactate measurements

All patients were referred to the oncology department for possible adjuvant chemotherapy within the first six weeks after resection. Among these patients, those suitable according to the tumor stage were included in the adjuvant treatment program. Those who accepted treatment were administered 5-fluorouracil-based regimen or capecitabine plus oxaliplatin (XELOX) for 6 to 8 cycles.

Statistical Analysis

The SPSS (Statistical Product and Service Solutions) software version 22 for Windows (SPSS Inc. Chicago, IL, USA) was used for statistical analyses of the study. The normality of the distribution of the data was carried out using the Kolmogorov-Smirnov test. Qualitative data were presented as frequency and percentage. Quantitative data were given as mean ± S.D if the data were normally distributed, and median (Interquartile range-IQR) if not normally distributed. The relationship of elevated lactate levels with categorical variables was analyzed using Chi-square and Fisher's exact tests. The Mann-Whitney-U test was used to examine whether hyperlactatemia was associated with surgery time, blood loss, administered crystalloid volume, urine output, and length of hospital stay. Univariate and multivariate logistic regression analysis was used in patients who underwent CRC surgery to determine the factors that perioperatively affect increased lactate levels. Survival analyzes were performed using the Kaplan-Meier test. A *p*-value lower than 0.05 was accepted as statistically significant.

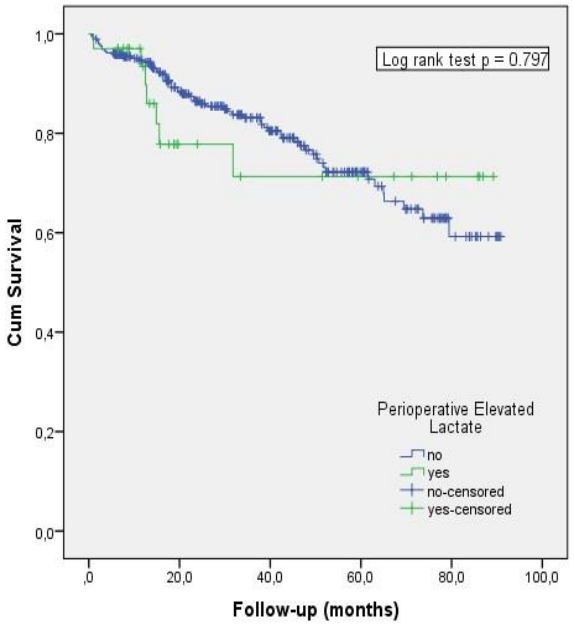

Figure 2: Overall survival analysis with Kaplan-Meier test in patients with perioperative continuously elevated lactate levels

3. Results

In this study, 34 out of 323 patients experienced persistent hyperlactatemia during the perioperative period. Table 1 demonstrates the demographic, clinical, and surgical characteristics of patients. According to the Chi-square test, BMI, and laparotomy were significantly correlated with persistent hyperlactatemia group (p = 0.02 and p = 0.011, respectively). Table 2 shows the risk factors for perioperative persistent lactate elevation by univariate and multivariate regression analysis. In univariate analysis, increased lactate values during intraoperative

and ICU period were observed to be influenced by blood loss, laparotomy, and BMI. The multivariate analysis presented that lactate levels were affected by BMI ≥ 30 kg/m^2 as the most significant parameter (p = 0.005). This variable was followed by the male sex, in which the lactate levels were 2.8 times higher than in females (p = 0.022). The last risk factor was the TNM stage III (p = 0.045). The patients in the TNM stage III had 5.9 times more persistent hyperlactatemia than the stage I. Risk factors such as blood loss and laparotomy were observed to lose their significance in multivariate analysis.

Major complications were encountered in 45 of 323 patients. Eleven of them were found in the persistent hyperlactatemia group (p = 0.003) (Table 1). Table 3 shows the major complications of these 11 patients. Anastomotic leakage was the most common complication among them.

The persistent group had a significantly prolonged length of hospital stay than the other non-persistent group (p = 0.050) (Table 1).

The 5-year overall survival rate of the group with persistently elevated lactate concentrations was 71.3%. The same rate was 72.2% in the other group (p = 0.797). The overall survival analysis of this persistent group was given in Figure 2 with the Kaplan-Meier test.

4. Discussion

In this study, which included a retrospective analysis of 323 patients who had undergone curative colorectal cancer surgery, risk factors that affect perioperatively consistently elevated lactate levels and its impact on postoperative outcomes were investigated. The peculiarity of this study is that, according to our review of the literature, there was no clinical study that directly addresses the risk factors of persistent hyperlactatemia during the perioperative period of planned colorectal cancer surgery and analyzes the postoperative outcomes. The incidence of persistent perioperative elevation of the lactate values was 10.5% of this study. Our findings showed some risk factors affecting lactate metabolism, such as BMI, male sex, and the advanced TNM stage, as a result of multivariate analysis. In addition, no significant association between persistently increased lactate levels and mortality has been shown, while significantly associated with major complications and prolonged hospital stay.

Male patients in this study were more exposed to persistent > 2 mmol/L lactate levels in the perioperative period compared to female patients (25 male vs. 9 female). This result varies between studies. In the study of Naik et al.[11], female patients found a risk factor (p = 0.011) for intraoperative hyperlactatemia, while the research of Wu et al.[12] and also the study of Lawton et al.[13] gender did not have a significant prediction for high lactate.

BMI ≥ 30 kg/m^2 is defined as obesity. According to our study, obesity was an independent risk factor for hyperlactatemia in accordance with the literature.[12] Increased circulating fatty acids released from adipocytes, which are more in obese patients, adversely affect the glucose utilization of the muscles. It also provokes insulin resistance in tumor necrosis factor-α produced by adipocytes.[14] Thus, pyruvate, the end product of increased glycolysis, occurs as a result of triggered hyperglycemia. Lactate is produced from pyruvate so that its level increases in the blood. Lactate is a reliable sepsis marker as an important indicator of tissue hypoxia and has been shown in many other studies where it can predict poor outcomes.[15,16]

In cancer patients, tumor cells convert glucose to lactate in an aerobic environment with the "Warburg effect".[17] This feature for the protection of redox balance in proliferating cells may explain the relationship between the increased tumor stage and lactate, which is another significant result of our study.

According to the univariate analysis of this study, lactate is also a surrogate marker for blood loss.[13] Laparotomy, another significant parameter, is frequently encountered in major abdominal procedures such as cancer surgery. This surgical option can lead to an increase in lactate values for various reasons, e.g., due to increased surgical stress and tissue hypoxia.[18] However, multivariate analysis, which is the final analysis in determining the risk factors of persistent hyperlactatemia, did not show the significance of these two variables in this study. Hyperlactatemia secondary to surgery and associated with the neurohumoral stress response is not uncommon in surgical patients. In operations with prolonged duration, intraoperative

Table 1: Demographic, clinical, and surgical characteristics of the patients

Variables		Perioperative persistent lactate elevation				*p
		No (n = 289)		Yes (n = 34)		
		N (%)	5-year OS	N (%)	5-year OS	
Age, years	<65	166 (57.4%)	75.3%	18 (52.9%)	74.5%	0.616
	≥65	123 (42.6%)	68.4%	16 (47.1%)	69.4%	
Sex	Male	165 (57.1%)	75.5%	25 (73.5%)	79.9%	0.065
	Female	124 (42.9%)	68.2%	9 (26.5%)	47.4%	
BMI (kg/m$^{2)}$	<30	138 (47.8%)	79.5%	15 (44.1%)	93.3%	**0.002**
	≥30	151 (52.2%)	65.3%	19 (55.9%)	59.9%	
CCI	0-2	111 (38.4%)	69.8%	11 (32.4%)	74.1%	0.688
	≥3	178 (61.6%)	73.7%	23 (67.6%)	72.6%	
ASA score	I-II	197 (68.2%)	75.7%	14 (41.2%)	40.9%	0.491
	III-IV	92 (31.8%)	65.9%	20 (58.8%)	95.0%	
Type 2 DM	No	223 (77.2%)	72.1%	26 (76.5%)	74.5%	0.928
	Yes	66 (22.8%)	72.3%	8 (23.5%)	58.3%	
Metformin	No	238 (82.4%)	72.2%	26 (76.5%)	74.5%	0.401
	Yes	51 (17.6%)	72.3%	8 (23.5%)	58.3%	
Neoadjuvant therapy	Not received	225 (77.9%)	74.9%	28 (82.4%)	63.4%	0.547
	Received	64 (22.1%)	63.4%	6 (17.6%)	-	
Tumor size (cm)	< 5 cm	125 (43.3%)	75.3%	13 (38.2%)	80.0%	0.576
	≥ 5 cm	164 (56.7%)	69.5%	21 (61.8%)	63.9%	
Localization	Colon	191 (66.1%)	75.4%	22 (64.7%)	74.2%	0.872
	Rectum	98 (33.9%)	66.5%	12 (35.3%)	71.6%	
Laparoscopy	No (Laparotomy)	216 (74.7%)	64.4%	32 (94.1%)	72.8%	**0.011**
	Yes	73 (25.3%)	94.3%	2 (5.9%)	50.0%	
TNM stage (8^{th} ed. UICC/AJCC)	Stage I	49 (17.0%)	77.1%	2 (5.9%)	-	0.152
	Stage II	111 (38.4%)	67.5%	12 (35.3%)	91.7%	
	Stage III	129 (44.6%)	63.0%	20 (58.8%)	56.6%	
Major Complications	No	255 (88.2%)	75.2%	23 (67.6%)	68.7%	**0.003
	Yes	34 (11.8%)	48.8%	11 (32.4%)	79.5%	
		Median (IQR)				***p
Surgery time (min)		210 (160-260)		240 (150-285)		0.340
Blood loss (mL)		95 (50-175)		150 (100-220)		**0.005**
Administered crystalloid (mL)		2500 (1700-300)		2500 (2000-3200)		0.231
Urine output (mL)		65 (50-90)		65 (45-80)		0.239
Length of hospital stay (days)		8 (7-13)		12 (7-15)		**0.050**

**Chi-squared test; **Fisher's exact test; ***Mann-Whitney U test; BMI: Body Mass Index; CCI: Charlson Comorbidity Index; ASA: American Society of Anesthesiologists; DM: Diabetes Mellitus:* UICC*: Union for International Cancer Control; AJCC: American Joint Committee on Cancer; IQR: Interquartile Range; OS: Overall Survival*

Table 2: The risk factors for perioperative persistent lactate elevation by univariate and multivariate regression analyses

Variables	Univariate		Multivariate	
	OR (95.0% CI)	p	OR (95.0% CI)	p
Age, ≥ 65 y	1.200 (0.588-2.447)	0.617	1.136 (0.481-2.685)	0.771
Sex, Female	0.479 (0.216-1.063)	0.070	0.354 (0.145-0.863)	0.022
CCI, ≥ 3	1.158 (0.566-2.367)	0.688	0.880 (0.342-2.267)	0.514
BMI, ≥ 30 kg/m2	3.059 (1.479-6.325)	0.003	3.334 (1.440-7.718)	0.005
DM Typ II, yes	1.040 (0.449-2.405)	0.928		0.998
Metformin, yes	1.436 (0.615-3.353)	0.403		0.998
Neoadjuvant, yes	0.753 (0.299-1.899)	0.548	0.473 (0.138-1.623)	0.234
Tumor size, ≥ 5 cm	1.231 (0.593-2.554)	0.576	0.965 (0.430-2.167)	0.931
Localization, rectum	1.063 (0.505-2.238)	0.872	1.402 (0.511-3.845)	0.512
Laparoscopy, yes	0.185 (0.043-0.791)	0.023	0.250 (0.053-1.176)	0.079
TNM stage I	1		1	
TNM stage II	2.649 (0.571-12.284)	0.213	3.777 (0.705-20.226)	0.121
TNM stage III	3.798 (0.856-16.859)	0.079	5.329 (1.038-27.345)	0.045
Operative time/min	1.002 (0.997-1.007)	0.376	1.001 (0.995-1.008)	0.728
Blood loss/mL	1.003 (1.000-1.005)	0.021	1.003 (1.000-1.006)	0.071
Administered crystalloid/mL	1.000 (1.000-1.001)	0.127	1.000 (1.000-1.000)	0.985
Urine output/mL	0.990 (0.975-1.006)	0.226	0.997 (0.979-1.014)	0.697

CCI: Charlson Comorbidity Index; *OR: Odds ratio;* CI: Confidence Interval; ASA: *American Society of Anesthesiologists; BMI: Body Mass Index; DM: Diabetes mellitus*

Table 3: Patients with major complications associated with perioperative continuously elevated lactate levels

Major complications	Persistent hyperlactatemia (n = 11)
Leakage of bowel anastomosis	4
Eventration or evisceration	2
Intra-abdominal abscess	2
Ileus-bowel obstruction	1
Pulmonary embolism	1
Severe hematoma in the abdomen	1

hyperlactatemia due to anesthesia and surgery can continue postoperatively. This condition can occurfrom a systemically occult deficit in tissue oxygen utilization.[19] In the follow-up of patients after surgery, lactate monitoring is essential. While changes in blood lactate kinetics are significant between 6 and no more thatablen 12 hours between two lactate measurements, it still does not seem possible to estimate the optimal time between two lactate measurements.[8] The necessity of repetitive lactate measurements in patients followed up in the intensive care unit was emphasized by Godiniak et al.[5], and they found it to be predictive for fatal outcomes of > 2.5 mmol/L at 48 hours. Li et al.[20] reported that the lactate value in the first 24 hours postoperatively has a significant relationship with postoperative complications in patients undergoing major elective abdominal surgery. In the study by De Schryver et al.[21], they performed lactate measurements at the 6th and 12th hours of the patients who underwent pancreatic surgery. They stated that the 6th-hour measures had predictive importance for pancreatic fistula. A contribution was made by Yoshikawa et al.[22] on this topic. However, the lactate value expressed as

the early postoperative measurement in this study is the lactate value taken immediately before the completion of the surgery.

In our study, we observed that persistent hyperlactatemia had a significant relationship with major complications. Anastomotic leak was detected in 4 of 11 patients with persistently increased lactate concentrations and major complications. This condition may be an indirect indicator of tissue hypoxia secondary to regional hypoperfusion in the anastomosis region. In terms of the effect of hyperlactatemia on hospital stay in patients who have undergone abdominal surgery, the literature remains inconsistent with each other. In the literature, studies are showing that there is a relationship between high lactate levels and prolonged stay in the hospital.[18,23] Some studies do not display this result.[13] In our study, the duration of hospitalization was significantly extended in patients with perioperative persistent lactate height. In contrast, the prognostic effect of persistent hyperlactatemia on mortality could not be demonstrated. However, according to many studies in the literature, the common view is that hyperlactatemia is a negative prognostic factor.[17,24] In a few studies, similar to our results, the effect of persistent high lactate levels on survival has not been demonstrated.[6,25]

One of the strengths of the study is that the research included repetitive measurements in lactate measurement instead of just a single blood sample. The lactate values measured before completion of the surgery were supported by four following measures in the early postoperative period, and the relationship between different variables and persistent elevations was investigated. In addition to the analysis of risk factors affecting persistent hyperlactatemia, the effects of this condition on postoperative hospital stay, morbidity, and mortality were also evaluated. Finally, we have not encountered a similar study in the literature investigating patients diagnosed with CRC in this way.

This presented study had some limitations. The first of these limitations was the retrospective design. Second, it did not include catecholamine administration data, which was rarely needed in our patients undergoing elective surgery. Catecholamine administration can influence lactate values.

5. Conclusion

In this study, which included patients undergoing elective surgery for colorectal cancer, the risk factors for persistent hyperlactatemia during the perioperative period were BMI ≥ 30 kg/m2, male gender, and advanced TNM stage. The persistent perioperative hyperlactatemia may predict major complications in the early postoperative period, especially anastomotic leak and also a prolonged hospital stay. On the contrary, according to the results of this study, it has no prognostic prediction for mortality.

6. Conflict of interest

None declareed by the authors

7. Authors' contribution

SG: Study design, manuscript writing

OU, ASS, ZZK, SO, HB: dat collection

DA: Anesthesia dministrator

UD: Statistical analysis

EP, MD: Manuscript editing, review

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