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Risk factors for persistent elevation of perioperative lactate levels in gastric cancer surgery

Selcuk Gulmez[1], Orhan Uzun[2], Aziz Serkan Senger[3], Zehra Zeynep Keklikkiran[4], Hilmi Bozkurt[5], Sinan Omeroglu[6], Emre Bozdag[7], Deniz Avan[8], Erdal Polat[9], Mustafa Duman[10]

[1,2,3,4,6]Medical Doctor, [9]Assistant Professor, [10]Professor of Surgery, Department of Gastrointestinal Surgery, University of Health Sciences, Kartal Kosuyolu Higher Specialty Training and Research Hospital, Istanbul, Turkey, [5]Medical Doctor, Department of General Surgery, University of Health Sciences, Haseki Training and Research Hospital, Istanbul, Turkey, [7]Medical Doctor, Department of General Surgery, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey [8]Medical Doctor, Department of Anesthesia, University of Health Sciences, Kartal Kosuyolu Higher Specialty Training and Research Hospital, Istanbul, Turkey

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ABSTRACT

Background: The impact of high-risk surgery on tissue perfusion can be indirectly assessed by measuring lactate levels during surgery and intensive care unit (ICU) stay. While consistently high values are associated with poor prognosis, transient elevations do not mean poor clinical outcomes. Therefore, intraoperative and early postoperative blood lactate monitoring is essential for cancer patients. **Aims and Objective:** This study aimed to determine the risk factors of persistently elevated lactate levels in the intraoperative and postoperative period in patients with elective gastric cancer surgery. **Materials and Methods:** We retrospectively enrolled 293 patients who underwent curative resection for gastric cancer. Lactate values of all patients were examined during surgery and ICU-stay at 3rd, 6th, 12th, and 18th hours. All lactate values above 2 mmol/L were considered elevated. The patients were divided into two groups as those with perioperative persistently increased lactate levels and those without. **Results:** Of the 293 patients, 60 (20.5%) had higher lactate levels in the perioperative period. According to multivariate logistic regression analysis, the operative time had the highest significance rate (p = 0.020) out of two significant variables, followed by the BMI ≥ 30 kg/m^2 (p = 0.048). Besides, patients with perioperative hyperlactatemia had prolonged hospital stays (p = 0.034). **Conclusions:** Operative time and obesity (BMI ≥ 30 kg/m^2) were independent risk factors for persistent lactate elevation in the perioperative period. Also, perioperative hyperlactatemia extended the length of hospital stay.

Key words: Lactate; Hyperlactatemia; Surgery

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INTRODUCTION

Gastric cancer is the fifth most frequently diagnosed cancer globally, which is ranked third in terms of cancer-related mortalities.[1] Postoperative complications in cancer surgery have complex etiology. Many factors related to the patient, cancer disease, anesthesia, and surgery play an essential role in the etiology. Among these reasons, the most substantial proportion is reduced tissue perfusion and oxygenation due to the disruption of the microvascular flow. This condition causes organ dysfunction and has adverse effects on postoperative results.[2]

The organism increases lactate production by anaerobic glycolysis to survive in tissue hypoxia caused by hypoperfusion.[3] The impact of high-risk surgery on tissue perfusion can be indirectly assessed by measuring lactate levels during surgery and intensive care unit (ICU) stay.[4] While consistently

Address for Correspondence:
Selcuk Gulmez, Kartal Kosuyolu Egitim ve Arastırma Hastanesi, Gastrointestinal Cerrahi Klinigi, Denizer cad. No:2. Kartal-Istanbul-Turkey.
Phone: 0090 5530846215. **E-mail:** selcukgulmez54@hotmail.com

high values are associated with poor prognosis, transient elevations do not mean poor clinical outcomes.[5] Therefore, intraoperative and early postoperative blood lactate monitoring is essential for cancer patients. Some studies are showing that increased intraoperative lactate values are associated with poor clinical prognosis.[6] It is possible to find opposing views in the literature.[7] Besides, microvascular flow changes are mostly observed within the first 24 hours postoperatively, and the degree of these alterations determines the course of the outcomes.[8] Many studies are available in the literature, including intraoperative and postoperative lactate measurements and prognostic effects, but the evaluation of risk factors is not sufficiently investigated.

This study aimed to determine the risk factors that play a role in the development of persistent hyperlactatemia in the perioperative period in patients with elective gastric cancer surgery.

MATERIALS AND METHODS

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 293 patients who underwent curative resection in our center for gastric cancer between January 2007 and July 2019. In this study, exclusion criteria were palliative or emergency surgery, and laparoscopic surgery. Patients with TNM stage IV, and also chronic liver, kidney, and heart disease, in which impaired organ functions 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. The last operative lactate value was noted at the end of the surgery. The patients were then admitted to the ICU. In the ICU, lactate values of all patients were examined at 3rd, 6th, 12th, and 18th hours. Normolactatemia defined as lactate levels were ≤ 2 mmol/L. All lactate values above 2 mmol/L were considered as elevated.[9] Patients, those who had an initial (before incision) intra-arterial blood lactate level higher than 2 mmol/L, were excluded from the study. The patients were divided into two groups as those with persistently elevated lactate levels in the perioperative duration and those without persistent perioperative blood lactate concentrations. The persistent group was required to have a serum lactate concentration > 2 mmol/L both at the end of the operation and in the ICU (Figure 1).

All lactate measurements at the end of the operation and in ICU had to be > 2 mmol/L for the persistent group.

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),[10] Diabetes Mellitus (DM) type II, use of Metformin, American Society of Anesthesiologists (ASA) score, body mass index (BMI), and neoadjuvant therapy were noted. Surgical details included the type of surgery, tumor size, TNM stage, the total volume of administered crystalloids, the volume of urine output, the volume of blood loss, and the operative time.

Standard anesthesia induction was applied to all patients with 1-2 mcg/kg fentanyl, 2 mg/kg propofol, and 0.1 mg/kg rocuronium. Maintenance of the sevoflurane dose was adjusted with the Bispectral Index (BIS) monitoring in the range of 0.8-1 minimum alveolar concentration (MAC).

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 (min-max) if not normally distributed. The association of increased perioperative lactate measurements with categorical variables were analyzed using the Chi-square test. The Mann-Whitney-U test was used to evaluate the relationship between numerical data and lactate elevations. Firstly, univariate logistic regression analysis was used to determine the factors affecting perioperative lactate values. The significant variables here were included in the multivariate logistic regression analysis. A p-value lower than 0.05 was accepted as statistically significant.

RESULTS

Of the 293 patients, 60 (20.5%) had higher lactate levels in the perioperative period. Table 1 demonstrates the demographic, clinical, and surgical characteristics of patients.

Male patients of the study represented the majority with a rate of 71.3%. The Chi-square test showed a significant relationship between elevated lactate concentrations and gender ($p = 0.047$). Besides, a statistically significant relationship was found between increased BMI ≥ 30 kg/m^2 and elevated lactate levels ($p = 0.040$). Another significant variable were CCI ≥ 3 ($p = 0.050$) and neoadjuvant therapy ($p = 0.022$).

The most important operative parameter in persistently increased lactate concentrations was the duration of the

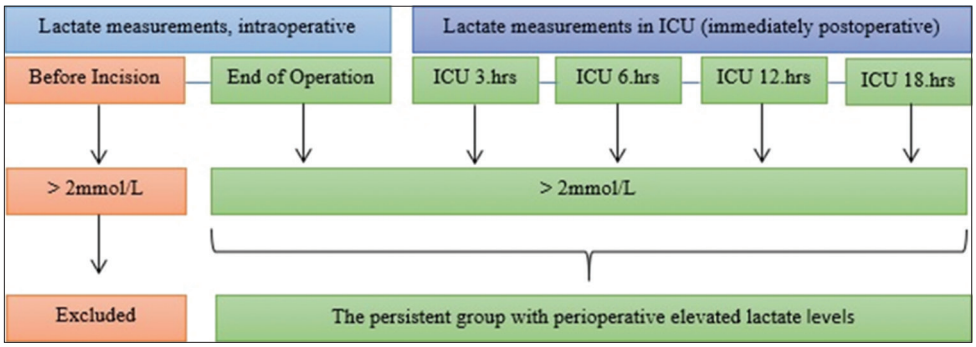

Figure 1: Demonstration of the study groups with the timing of the lactate measurements

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

Variables		Perioperative Hyperlactatemia				*p
		No (n = 233)		Yes (n = 60)		
		n	(%)	n	(%)	
Age, years	<65	145	62.2	38	63.3	0.875
	≥65	88	37.8	22	36.7	
Sex	Male	160	68.7	49	81.7	**0.047**
	Female	73	31.3	11	18.3	
BMI, kg/m^2	<30	191	82.0	42	70.0	**0.040**
	≥30	42	18.0	18	30.0	
CCI	0-2	170	73.0	36	60.0	**0.050**
	≥3	63	27.0	24	40.0	
ASA score	I-II	115	49.4	28	46.7	0.710
	III-IV	118	50.6	32	53.3	
DM type II	No	203	87.1	52	86.7	0.925
	Yes	30	12.9	8	13.3	
Metformin	No	204	87.6	53	88.3	0.870
	Yes	29	12.4	7	11.7	
Neoadjuvant therapy	Not received	161	69.1	32	53.3	**0.022**
	Received	72	30.9	28	46.7	
Tumor size, cm	< 5cm	111	47.6	31	51.7	0.578
	≥ 5cm	122	52.4	29	48.3	
TNM stage (8th ed. UICC/AJCC)	Stage I	45	19.3	10	16.7	0.533
	Stage II	48	20.6	9	15.0	
	Stage III	123	52.8	34	56.7	
	Stage IV	17	7.3	7	11.7	
		Median (IQR)				**p
Operative time/min		270 (215-300)		290 (230-340)		**0.010**
Blood loss/mL		75 (45-200)		100 (63-600)		0.189
Administered crystalloid/mL		3000 (2000-3600)		3000 (2000-3600)		0.644
Urine output/mL		65 (50-90)		65 (50-85)		0.951
Length of hospital stay/day		8 (7-12)		9 (7-15)		**0.034**

*Chi-squared 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

operation ($p = 0.010$). The persistent group stayed in the hospital significantly longer ($p = 0.034$).

All variables were subjected to univariate logistic regression analysis in terms of independent risk factors of persistent lactate elevation in the perioperative period (Table 2a). Gender, BMI, neoadjuvant treatment, and operative time were prominent variables affecting perioperative lactate levels. Finally, all significant parameters were examined with multivariate logistic regression analysis (Table 2b). Accordingly, the operative time had the highest rate of significance with a *p*-value of 0.020. The second and last significant variable was BMI ≥ 30 kg/m^2 ($p = 0.048$). The remaining parameters lost their significance in multivariate analysis.

DISCUSSION

This study includes a retrospective analysis of 293 patients undergoing elective gastric cancer surgery. Lactate levels were followed in the early postoperative period in the intensive care unit since the end of the operation. Furthermore, situations contributing to elevations of the lactate values were

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

Table 2a	Perioperative lactate elevation		Table 2b	Perioperative lactate elevation	
Variables	Univariate		Variables	Multivariate	
	OR (95.0% CI)	*p*		OR (95.0% CI)	*p*
Age, ≥ 65 years	0.954 (0.530-1.718)	0.875	Sex, Female	0.527 (0.253-1.097)	0.087
Sex, Female	0.492 (0.242-1.001)	**0.050**	BMI, ≥ 30 kg/m²	1.979 (1.007-3.891)	**0.048**
BMI, ≥ 30 kg/m²	1.949 (1.022-3.716)	**0.043**	Neoadjuvant, Yes	1.671 (0.896-3.116)	0.106
CCI, ≥ 3	1.799 (0.995-3.251)	0.052	Operative time/min	1.005 (1.001-1.009)	**0.020**
ASA score, III-IV	1.114 (0.631-1.967)	0.710			
DM type II, Yes	1.041 (0.451-2.405)	0.925			
Metformin, Yes	0.929 (0.386-2.238)	0.870			
Neoadjuvant, Yes	1.957 (1.097-3.489)	**0.023**			
Tumor size, ≥ 5cm	0.851 (0.482-1.502)	0.578			
TNM stage I	1				
TNM stage II	0.844 (0.314-2.266)	0.736			
TNM stage III	1.244 (0.568-2.223)	0.585			
TNM stage IV	1.853 (0.607-5.653)	0.278			
Operative time/min	1.004 (1.001-1.008)	**0.024**			
Blood loss/mL	1.001 (0.999-1.002)	0.598			
Administered crystalloid/mL	1.000 (1.000-1.000)	0.955			
Urin output/mL	1.001 (0.989-1.012)	0.912			

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

investigated at the same time. Persistent perioperative lactate elevations and the risk factors affecting them have not been adequately studied in this patients population. Our findings showed that surgery time and BMI ≥ 30 kg/m² were risk factors that affect lactate levels in the perioperative period. In addition, it was observed that perioperative hyperlactatemia significantly extended the hospital stay.

The final risk factors analysis of this study was performed with a multivariant logistic regression test, and the operative time was an independent determinant for both intraoperative and postoperative increased lactate concentrations. Lactate studies in surgical patients usually appear in cardiac procedures. In the analysis of the risk factors for lactate elevation in this patient group of Hoshino et al.,[11] operative time was not significant ($p = 0.439$. In contrast, in the study of Wu et al.[12] the operative time was closely related to severe hyperlactatemia ($p = 0.016$). In their multivariate analysis, it was seen that the surgery time lost its significance while ours continued this feature. Hyperlactatemia can be seen depending on the neurohumoral response secondary to surgery. Microcirculatory alterations in the gut mucosa due to prolonged surgery causes an imbalance between oxygen delivery and consumption. This situation may lead to hyperlactatemia. In addition to surgery, tissue hypoperfusion conditions, which may be related to anesthesia in the intraoperative period, are also associated with increased lactate values. Hyperlactatemia caused by prolonged surgery may also persist in the ICU. Therefore, serial lactate measurements are essential in the perioperative period.[13]

According to our results, the second independent risk factor predicts perioperative lactate elevation was BMI ≥ 30 kg/m². Increased production of circulating fatty acids in obese patients inhibits glucose uptake and leads to hyperlactatemia.[14] In accordance with the literature, in the present study, BMI was observed to have a predictive role for lactate increases during the perioperative period.[15]

This study showed that hyperlactatemia lengthens hospital stay. The results in the literature generally confirm this[16,17] unlike Lawton et al.[18]

This presented study had some strengths. Repeat lactate measurements were used instead of a single blood sample. The measurements were performed during surgery and continued at the ICU. In addition to the analysis of risk factors affecting persistent hyperlactatemia, the effect of this condition on hospital stay was also evaluated. In addition to the analysis of risk factors affecting persistent hyperlactatemia, the impact of this condition on hospital stay was also assessed. Finally, in the literature, we have not encountered sufficient studies investigating patients undergoing gastric cancer surgery for the same purposes.

The limitations of the study were the details of the anesthetic data not included and the retrospective design.

CONCLUSION

According to our study, operative time and obesity (BMI ≥ 30 kg/m²) were independent risk factors for persistent lactate elevation in the perioperative period. Also, perioperative hyperlactatemia extended the length of hospital stay. For validation of this subject, studies including detailed anesthesia data are needed.

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Author's contribution:
SG- Concept and design; interpreted the results,writing of the manuscript; **OU-** Statistically analyzed and interpreted of the results; **ASS-** Critical revision of the manuscript; **EB-** Critical revision of the manuscript; **DA-** Critical revision of the manuscript; **ZZK-** Literature review, data collection for the study; **HB-** Literature review, data collection for the study; **SO-** Literature review, data collection for the study; **EP-** Final review of the manuscript; **MD-** Final review of the manuscript.

Work Attributed to:
University of Health Sciences, Kartal Kosuyolu Higher Specialty Training and Research Hospital, Department of Gastrointestinal Surgery Istanbul, Turkey.

Orcid ID:
Selcuk Gülmez - http://orcid.org/0000-0001-9719-1904
Orhan Uzun - http://orcid.org/0000-0001-6550-0936
Aziz Serkan Senger - http://orcid.org/0000-0003-0981-0141
Zehra Zeynep Keklikkiran - https://orcid.org/0000-0001-6544-7418
Hilmi Bozkurt - https://orcid.org/0000-0003-0389-0523
Sinan Omeroglu - https://orcid.org/0000-0001-7992-5943
Emre Bozdag - https://orcid.org/0000-0002-2729-1667
Deniz Avan - https://orcid.org/0000-0002-1650-7522
Erdal Polat - https://orcid.org/0000-0002-9463-9846
Mustafa Duman - https://orcid.org/0000-0002-0276-0543

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