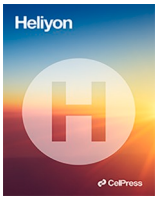
Heliyon 10 (2024) e23608

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Clinical significance of serum lactate and lactate dehydrogenase levels for disease severity and clinical outcomes in patients with colorectal cancer admitted to the intensive care unit

Xin Wang [a,1], Chen Li [b,1], Ming Li [c,1], Xiongfei Zeng [a], Jinsong Mu [a,**], Yan Li [a,d,*]

[a] Department of Critical Care Medicine, 5th Medical Center of Chinese PLA General Hospital, Beijing, China
[b] Department of Urology Surgery, Beijing Rehabilitation Hospital, Capital Medical University, Beijing, China
[c] Department of Clinical Laboratory, First Medical Center of Chinese PLA General Hospital, Beijing, China
[d] Department of Intensive Care Unit, Beijing Huasheng Rehabilitation Hospital, Beijing, China

ARTICLE INFO

Keywords:
Colorectal cancer
Intensive care unit
Lactate
Lactate dehydrogenase
Disease severity
Clinical outcome

ABSTRACT

Objective: Serum lactate (LA) and lactate dehydrogenase (LDH) levels have a major impact on the clinical treatment of malignant tumors and critically ill patients. Nevertheless, the assessment of disease severity in oncology patients admitted to the intensive care unit (ICU) remains incomplete when considering the serum LA and LDH levels. This study aimed to investigate the significance of serum LDH and LA levels in assessing disease severity and predicting clinical outcomes in patients with colorectal cancer (CRC) admitted to the ICU.

Methods: This retrospective study included patients with CRC who were admitted to the ICU between January 2017 and December 2022. The patients were divided into three groups based on the tumor treatment methods they had received within 3 months before ICU admission: post-chemotherapy group, post-surgery group, and palliative treatment group. The association between serum LA and LDH levels and disease severity and clinical outcomes was analyzed.

Results: Of 137 patients with CRC admitted to the ICU were finally studied. Patients in the post-chemotherapy group exhibited higher serum LA and LDH levels compared to those in the other two groups. Additionally, they had higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores, longer ICU length of stay, and a higher 30-day mortality. We found a significant positive correlation between serum LA levels and APACHE II scores as well as ICU length of stay and 30-day mortality. In contrast, we only observed a significant positive correlation between serum LDH levels and disease severity in the post-chemotherapy group, whereas no significant correlation between LDH levels and 30-day mortality in any of the three groups.

Conclusion: Our study concludes that elevated serum LA levels, rather than LDH levels, are more effective in assessing disease severity and could be used as predictors for clinical outcomes in patients with CRC admitted to the ICU.

* Corresponding author. Department of Critical Care Medicine, 5th Medical Center of Chinese PLA General Hospital, Beijing, China.
** Corresponding author.
E-mail addresses: Jinsongmu@126.com (J. Mu), liyanmdhuxi@163.com (Y. Li).
[1] Xin Wang, Chen Li and Ming Li contributed equally to this work and share first authorship.

https://doi.org/10.1016/j.heliyon.2023.e23608
Received 27 August 2023; Received in revised form 6 December 2023; Accepted 7 December 2023
Available online 12 December 2023

1. Introduction

In recent years, there has been a significant increase in the morbidity and mortality of colorectal cancer (CRC), making it the fourth most fatal malignant tumor disease worldwide. According to statistics, approximately 1.2 million people are diagnosed with CRC annually, with 600,000 losing their lives to this disease [1]. Prognosis in CRC is influenced by various factors, including age, physical activity, biological parameters, tumor size, grade, lymph node involvement, and the presence of metastasis. Numerous studies have shown that an increasing number of cancer patients require admission to intensive care units (ICU) for supportive care [2]. Patients with CRC are admitted to the ICU for various reasons, such as post-surgical recovery, management of acute complications arising from cancer or its treatment, risk assessment and monitoring, and administration of antineoplastic therapy [3]. Elderly patients over 80 years old, in particular, may experience early complications like pneumonia, sepsis, and anastomotic leakage following colorectal surgery. Regular monitoring of vital signs in the ICU can help prevent immediate postoperative deterioration in patients, thereby reducing the likelihood of postoperative complications, especially in elderly patients [4]. Patients who receive chemotherapy may have a higher frequency of ICU admissions compared to those who do not, due to increased complications [5]. Additionally, some advanced cancer patients receiving palliative care may be admitted to the ICU to significantly alleviate their pain symptoms [6]. With the growing number of cancer patients worldwide, it is estimated that cancer-related admissions may account for more than 15 % of all ICU admissions. Among these patients, the ICU mortality rates for different solid tumors have been reported to range from 4.6 % to 76.8 % [7]. Higher disease severity scores have been linked to increased mortality within 90 days of admission, and similar effects have been observed on short-term mortality [8]. The duration of ICU stay and the Acute Physiology and Chronic Health Evaluation (APACHE) II score are commonly used as primary assessment indicators for disease severity in ICU patients [9]. Especially APACHE II score, which has also been regarded as the best prognostic score for the outcome of ICU cancer patients [10]. Although there may be some bias in assessing the severity using clinical data within 24 h of admission, it is undeniable that some data still contribute to ICU management and benefit a considerable number of patients [7].

Recent studies have shown that lactate (LA) acts as a trigger to promote the activity and proliferation of cancer stem cells [11]. Excessive LA levels can cause extracellular acidosis, promote invasion, angiogenesis, and metastasis, impair immune response, and worsen prognosis [12]. Since the 1960s, a serum LA level greater than 4 mmol/L was identified as an important criterion for judging irreversible systemic tissue hypoxia in shock patients admitted to the ICU [13]. Recent research findings suggest that lactate-guided resuscitation proves beneficial during the initial phases of shock [14]. Nevertheless, it is important to acknowledge that even with resuscitation efforts, there remains a significant correlation between persistent hyperlactaemia and mortality [15]. In both shock and trauma patients, serum LA levels within 24 h of ICU admission serve as a biomarker of disease severity [16]. A previous study found that high LA levels were significantly linked to lower overall survival in patients with metastatic lung cancer. These patients typically had two metastases, ICU admission, endotracheal intubation, or elevated serum anion gap (AG) and lactate dehydrogenase (LDH) levels [17]. Elevated serum LDH levels during tumor cell transformation might serve as a detrimental prognostic marker for hypoxic and angiogenic carcinomas [18]. It has been reported that serum LDH levels are strongly associated with survival in metastatic breast cancer, metastatic melanoma, esophageal squamous cell carcinoma, renal cell carcinoma, and lung cancer. However, in patients with CRC, serum LDH levels do not seem to be useful in predicting patient outcomes after CRC resection [19].

Previous research has shown that LA and LDH have practical implications for the clinical management of malignant tumor patients and critically ill patients. However, there is a lack of published research specifically focusing on the role of LA and LDH in assessing disease severity in cancer patients admitted to the ICU, particularly those with CRC. This study aims to examine the association of serum LA and LDH levels with disease severity and clinical outcomes in this population.

2. Methods

2.1. Study population and design

This was a retrospective cohort study of critically ill patients with CRC admitted to ICU from January 2017 to December 2022. It was conducted at the Fifth Medical Center of Chinese PLA General Hospital, which specializes in hematology and oncology. The ICU was a 12-bed medical-surgical closed unit that admitted approximately 250 patients with various diagnoses per year. This study included all patients with CRC requiring ICU admission due to infection, shock, and other reasons. Patients were excluded if they met the following criteria: 1) age less than 14 years, 2) presence of other primary tumors, 3) ICU admission of less than 3 days, or 4) excessive antibiotic treatment. In this study, certain ICU patients with elevated infection indicators and fever were initially suspected to have severe infection. However, subsequent examination revealed negative results in their blood culture. In order to ensure comprehensive antibacterial coverage, it had led to either inappropriate durations of antibiotic use for patients or the administration of multiple antibiotics concurrently, potentially giving rise to a bias in the research findings, hence necessitating its exclusion.

All included patients were divided into three groups based on treatment characteristics: a post-surgery group (patients with CRC who underwent radical resection of colorectal carcinoma within 3 months before ICU admission), a post-chemotherapy group (patients with CRC who received chemotherapy within 3 months before ICU admission), and a palliative care group (patients who did not receive anti-tumor therapy or only received palliative surgery within 3 months before ICU admission). Included in the post-chemotherapy group were predominantly patients with severe acquired opportunistic infections or even sepsis resulting from a weakened immune system following chemotherapy. Additionally, a limited number of patients experiencing severe organ dysfunction as a consequence of drug-related factors within a few hours or days post-chemotherapy were also encompassed within this group. Patients in the palliative care group were primarily admitted to the ICU for treatment because they were experiencing severe

complications. They were included in the study as a control group for comparison with the other two groups.

2.2. Data collection

All anonymized data were collected and recorded through retrospective retrieval of the hospital information system (HIS), with full protection of patients' personal information except for age and gender. Baseline characteristics, clinical data, and laboratory data were collected at ICU admission. Baseline characteristics included age, gender, tumor sites, Dukes staging (A-D), distant metastases of tumor, and comorbidities. Clinical data involved disease severity, 24-h urine output, and mean arterial pressure (MAP). Disease severity at ICU admission was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score and ICU length of stay, and clinical outcomes were assessed by 30-day mortality. Laboratory data included inflammatory parameters (serum procalcitonin [PCT] and C-reactive protein [CRP] levels), serum LA, LDH, and N-terminal pro-B-type naturetic peptide (NT-BNP) levels, as well as arterial blood gases. Arterial blood gases in this study mainly referred to arterial blood hydrogen potential (pH), sodium (Na^+), bicarbonate (HCO_3^-), chloride (Cl^-), AG, and base excess (BE) levels, oxygenation index (OI).

Arterial blood AG was calculated using the following formula: [20]. The arterial blood OI was calculated using the formula: [21]. In this formula, PaO_2 represents the arterial blood oxygen pressure, and FiO_2 represents the fraction of inspired oxygen.

Serum LA, LDH, and NT-BNP levels, 24-h urine output, and MAP at 24, 48, and 72 h after ICU admission were included in the analysis. Arterial blood gas data at 24, 48, and 72 h after ICU admission were also examined.

2.3. Statistical analysis

Data analysis was performed using GraphPad Prism 9.0.3 software. Non-parametric data were logarithmically transformed. Categorical variables were presented as counts (percentages), continuous variables were presented as means (standard deviations) for normally distributed data, and visually skewed data were presented as medians (25–75 percentiles). The chi-square test was used to analyze differences between categorical variables, while the two-sample *t*-test or two-tailed Mann-Whitney test was used to analyze differences between continuous variables. Two-way analysis of variance (ANOVA) with Tukey's multiple comparisons test procedure was used to compare the differences in serum LA, LDH, and NT-BNP levels, 24-h urine output, MAP and arterial blood gas data at different time points among the three groups. Spearman's rank correlation test was used to assess the associations between serum LA and LDH levels and disease severity and clinical outcomes. A p value of < 0.05 was considered statistically significant.

Table 1
Characteristics of colorectal cancer patients admitted to the ICU.

Variables	Post-surgery group (n = 50)	Post-chemotherapy group (n = 47)	Palliative care group (n = 40)
Age, (years)	70 (52–86)	68 (55–83)	70 (52–88)
Male gender, n (%)	28/22	26/21	22/18
Tumor sites, n (%)			
Colon	33 (64.0)	32 (68.1)	28 (70.0)
Rectum	17 (34.0)	15 (31.9)	12 (30.0)
Dukes staging, n (%)			
A - B	32 (64.0)	17 (36.2)	25 (62.5)
C - D	18 (36.0)	30 (63.8)*#	15 (37.5)
Distant metastases, n (%)			
No	40 (80.0)	25 (53.2)	31 (77.5)
Yes	10 (20.0)	22 (46.8)*#	9 (22.5)
Comorbid conditions, n (%)			
Respiratory diseases	20 (40.0)	18 (38.3)	16 (40.0)
Cardiovascular disease	31 (62.0)	25 (53.2)	22 (55.0)
Neurological disease	9 (18.0)	7 (14.9)	7 (17.5)
Digestive disease	11 (22.0)	12 (25.5)	8 (20.0)
Diabetes mellitus	15 (30.0)	12 (25.5)	9 (22.5)
Urinary diseases	10 (20.0)	11 (23.4)	11 (22.0)
Disease severity			
APACHE II score	19.8 (4.5)	25.6 (4.7)*#	19.2 (4.2)
ICU stay time, (day)	7 (2)	10 (3)*	8 (3)
Outcome			
30-day mortality	12 (24.0)	20 (40.4)	9 (22.5)

APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit. Data are presented as medians (25th-75th percentile), means (standard deviation) or No. (%). * Significant difference versus the post-surgery group. # Significant difference versus the palliative care group. Colorectal cancer was divided into early (Dukes A or B) and advanced (Dukes C or D) stages using the Dukes staging system. $p < 0.05$ means statistically significant.

3. Results

3.1. Baseline characteristics, disease severity, and clinical outcomes

A total of 137 patients with CRC admitted to ICU that met the inclusion criteria were analyzed, among whom 50 (36.5 %) were post-surgery, 47 (34.3 %) patients were post-chemotherapy, and the remaining 40 (29.2 %) patients received palliative care. The baseline characteristics data are summarised in Table 1. The patients in the three groups were all older (median age over 65 years), and they were mainly male. From the perspective of tumor site, the cases of colon cancer among the three groups of patients were the most, about twice that of rectal cancer. According to Dukes staging, a significant majority of patients (63.8 %) in the post-chemotherapy group were classified as C-D stage, which was significantly higher compared to the other two groups (36.0 %, $p = 0.008$ and 37.5 %, $p = 0.018$, respectively). The distant metastasis rate of patients in the post-chemotherapy group was also significantly higher, reaching 46.8 %, while it was only 20 % in the post-surgery group ($p = 0.009$), and 25 % in the palliative care group ($p = 0.025$). In terms of comorbidities, the three groups of patients were mainly accompanied by cardiovascular and respiratory system diseases.

Table 1 also lists the disease severity and outcomes for all included patients. The APACHE II score in the post-chemotherapy group was significantly higher than that in the post-surgery group (25.6 [4.7] vs. 19.8 [4.5], $p < 0.001$), and the ICU length of stay (in days) was also significantly longer than that in the post-surgery group (10 [3] vs. 7 [2], $p < 0.001$). Besides, there was also a statistically significant difference in APACHE II scores between the post-chemotherapy group and the palliative care group (25.6 [4.7] vs. 19.2 [4.2], $p < 0.001$). Regarding the outcomes, the post-chemotherapy group exhibited a higher 30-day mortality (40.4 %) the other two groups (24.0 % and 22.5 %, respectively). However, these differences did not reach statistical significance (all $p > 0.05$).

3.2. Circulatory parameters at study time points

The dynamic changes of circulatory parameters such as 24-h urine output, MAP and serum NT-BNP levels are presented in Fig. 1. By comparison, it was found that 24-h urine output of the post-chemotherapy group at 24, 48 and 72 h after ICU admission was significantly smaller than that of the post-surgery group ($p = 0.020$, $p = 0.029$ and $p = 0.011$, respectively), and also significantly smaller than that of the palliative care group ($p = 0.005$, $p = 0.038$ and $p = 0.018$, respectively, Fig. 1a). Meanwhile, the MAP of the post-chemotherapy group was also significantly lower than that of the other two groups at 72 h after ICU admission ($p = 0.012$ and $p = 0.026$, respectively, Fig. 1b). Patients in the post-chemotherapy group exhibited the highest serum NT-BNP levels at 72 h after ICU

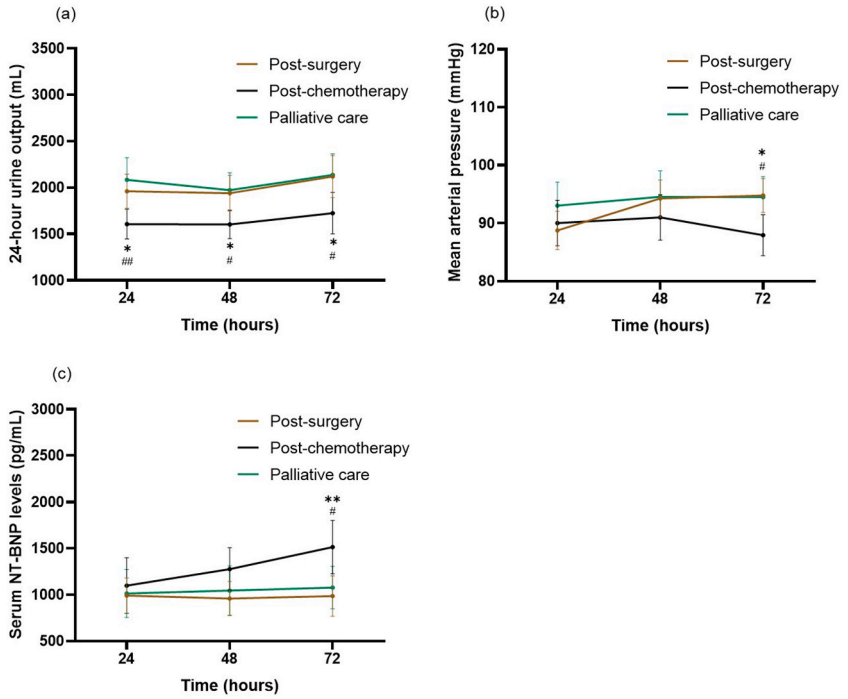


Fig. 1. The dynamic changes of circulatory parameters. Panel (a) represents the 24-h urine output, panel (b) represents the mean arterial pressure (MAP), and panel (c) represents the serum N-terminal pro-B-type naturetic peptide (NT-BNP) levels. In each panel, the brown line represents data of the post-surgery group, the black line represents data of the post-chemotherapy group, and the red line represents data of the palliative care group. * and ** indicate a significant difference compared to the post-surgery group ($p < 0.05$ and $p < 0.01$, respectively), while # and ## indicate a significant difference compared to the palliative care group ($p < 0.05$ and $p < 0.01$, respectively). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

admission, in comparison to the patients in the other two groups ($p = 0.004$ and $p = 0.034$, respectively, Fig. 1c).

3.3. Inflammatory parameters at study time points

The dynamic changes of inflammatory parameters are presented in Fig. 2. Patients in the post-chemotherapy group had higher serum PCT levels than those in the other two group at 24 h after ICU admission ($p = 0.002$ and $p = 0.005$, respectively, Fig. 2a). Likewise, serum CRP levels were relatively higher in the chemotherapy group, but not significantly different from the post-surgery group and palliative care group (all $p > 0.05$, Fig. 2b).

3.4. Arterial blood gas analyses at study time points

The dynamic changes of arterial blood gas data are presented in Fig. 3. Compared with the palliative care group, arterial blood BE levels were higher in the post-chemotherapy group at 24 h after ICU admission ($p = 0.023$), and arterial blood BE levels were also higher in the post-surgery group at 48 and 72 h after ICU admission ($p = 0.030$ and $p = 0.009$, respectively, Fig. 3e). Although there were statistical differences, they were all within the normal range. Meanwhile, there were no signficant differences found in arterial blood pH values (Fig. 3a), HCO_3^- and AG levels (Fig. 3b and c), and OI (Fig. 3d) among the three groups (all $p > 0.05$).

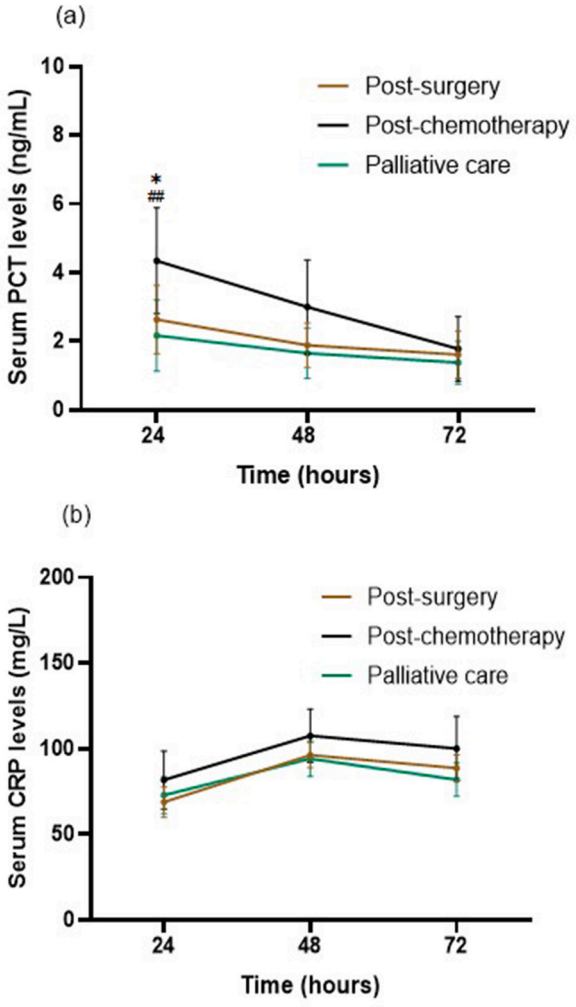


Fig. 2. The dynamic changes of inflammatory parameters. Panel (a) presents the serum procalcitonin (PCT) levels, while panel (b) shows the serum C-reactive protein (CRP) levels. In each panel, the brown line represents data of the post-surgery group, the black line represents data of the post-chemotherapy group, and the red line represents data of the palliative care group. * indicates a significant difference compared to the post-surgery group ($p < 0.05$), while $^{\#\#}$ indicates a significant difference compared to the palliative care group ($p < 0.01$). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

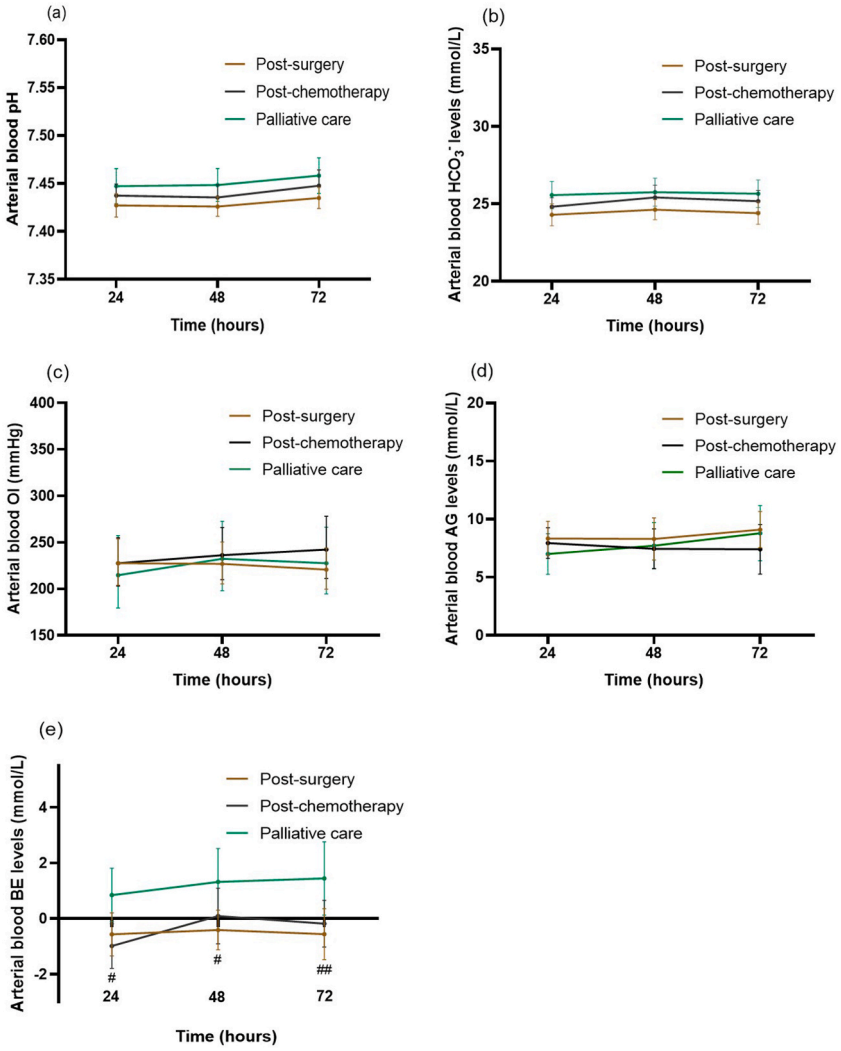


Fig. 3. The dynamic changes of arterial blood gas data. Panel (a) displays the arterial blood hydrogen potential (pH), panel (b) shows presents the arterial blood bicarbonate (HCO_3^-) levels, panel (c) shows the oxygenation index (OI), panel (d) presents the arterial blood anion gap (AG) levels, and panel (e) shows the arterial blood base excess (BE) levels. In each panel, the brown line represents data of the post-surgery group, the black line represents data of the post-chemotherapy group, and the red line represents data of the palliative care group. $^{\#}$ and $^{\#\#}$ indicate a significant difference compared to the palliative care group ($p < 0.05$ and $p < 0.01$, respectively). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.5. Serum LA and LDH levels at study time points

The dynamic changes of serum LA and LDH levels are presented in Fig. 4. In contrast, patients in the post-chemotherapy group had significantly higher serum LA levels than those in the post-surgery group at 24 and 48 h after ICU admission ($p = 0.012$ and $p = 0.005$, respectively), and were significantly higher than those in the palliative care group at both time points ($p = 0.003$ and $p = 0.009$, respectively, Fig. 4a). As for LDH, the serum levels of the post-chemotherapy group was the highest, but only at 72 h after ICU admission, there was a significant difference found between the post-chemotherapy group and the palliative care group ($p = 0.019$, Fig. 4b).

3.6. Associations between serum LA and LDH levels and disease severity

Table 2 summarizes the associations between serum LA and LDH levels and disease severity. Serum LA levels at 24 h after ICU admission showed significant positive correlations with APACHE II scores ([$r = 0.413$, 95 % confidence interval [CI]: 0.144–0.626, $p = 0.003$] and [$r = 0.443$, 95 % CI: 0.170–0.653, $p = 0.002$]) and ICU length of stay ([$r = 0.324$, 95 % CI: 0.042–0.558, $p = 0.022$] and [$r = 0.388$, 95 % CI: 0.105–0.613, $p < 0.001$]) in the post-surgery group and the post-chemotherapy group, respectively. At the same

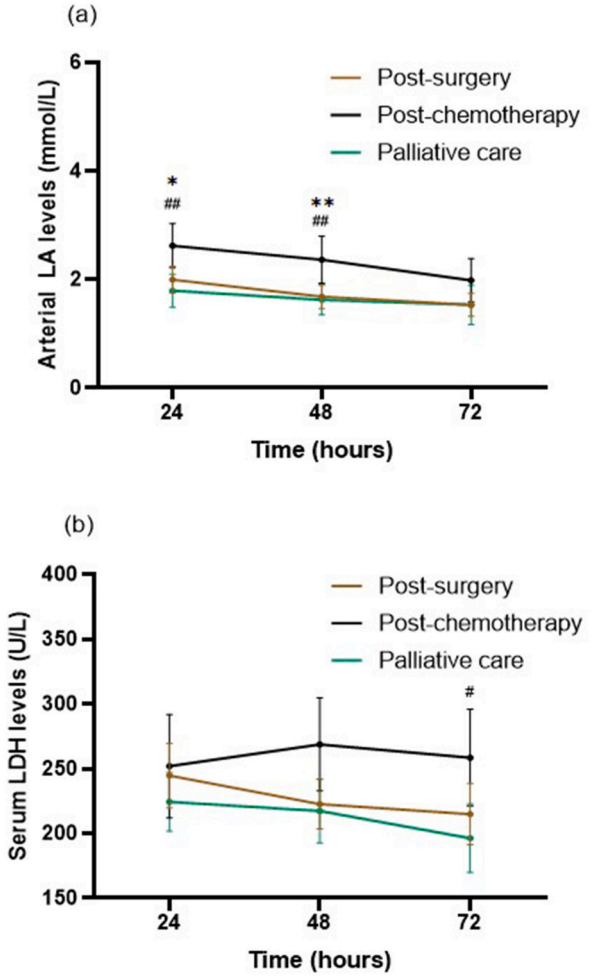


Fig. 4. The dynamic changes of serum lactate (LA) and lactate dehydrogenase (LDH) levels. Panel (a) represents serum LA levels, while panel (b) represents serum LDH levels. In each panel, the brown line, black line, and red line represent the data of the post-surgery group, the post-chemotherapy group, and the palliative care group, respectively. * and ** indicate a significant difference compared to the post-surgery group ($p < 0.05$ and $p < 0.01$, respectively), while $^{\#\#}$ indicates a significant difference compared to the palliative care group ($p < 0.05$ and $p < 0.01$, respectively). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Association between serum LA and LDH levels at 24 h after ICU admission and disease severity.

	APACHE II score		ICU length of stay	
Group	*r* (95 % CI)	*p* - value	*r* (95 % CI)	*p* - value
Post-surgery				
Serum LA levels	0.413 [0.144, 0.626]	0.003	0.324 [0.042, 0.558]	0.022
Serum LDH levels	0.213 [-0.078, 0.471]	0.137	0.190 [-0.101, 0.452]	0.185
Post-chemotherapy				
Serum LA levels	0.443 [0.170, 0.653]	0.002	0.606 [0.379, 0.765]	0.000
Serum LDH levels	0.149 [-0.153, 0.426]	0.317	0.388 [0.105, 0.613]	0.007
Palliative care				
Serum LA levels	0.167 [-0.162, 0.462]	0.304	0.348 [0.032, 0.601]	0.028
Serum LDH levels	0.305 [-0.016, 0.570]	0.055	0.122 [-0.206, 0.425]	0.454

APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; ICU, intensive care unit; LA, lactate; LDH, lactic dehydrogenase; *r*, Spearman's rank correlation coeffcient. $p < 0.05$ means statistically significant.

time, serum LA levels at 24 h after ICU admission were also significantly positively correlated with ICU length of stay in the palliative care group ([$r = 0.348$, 95 % CI: 0.032–0.601, $p = 0.028$]). In contrast, serum LDH levels at 24 h after ICU admission showed a significant positive correlation with ICU length of stay ([$r = 0.388$, 95 % CI: 0.105–0.613, $p = 0.007$]) only in the post-chemotherapy group. Additionally, there were no significant correlations observed between serum LDH levels and APACHE II scores in any of the

three groups (all $p > 0.05$).

3.7. Associations between serum LA and LDH levels and clinical outcomes

Table 3 presents an overview of the associations between serum LA and LDH levels and clinical outcomes. In the post-chemotherapy group, serum LA levels at 24 h after ICU admission were significantly positively correlated with 30-day mortality ([$r = 0.396$, 95 % CI: 0.115–0.620, $p = 0.006$]). This positive correlation was also observed in the post-surgery group ([$r = 0.346$, 95 % CI: 0.067–0.575, $p = 0.014$]) and the palliative care group ([$r = 0.349$, 95 % CI: 0.033–0.602, $p = 0.027$]). However, no significant correlations were identified between serum LDH levels and 30-day mortality in any of the three groups (all $p > 0.05$).

4. Discussion

LA, serves as the primary carbon source for cell metabolism in both normal and cancerous tissues. It tends to accumulate in the tissue microenvironment during inflammatory diseases and the development of cancer [22]. Monitoring blood LA levels can be helpful in assessing the risk of patients admitted to the ICU. Even in the absence of organ dysfunction or shock, the serum LA level at admission has been found to potentially predict mortality [23]. Numerous studies have demonstrated that LA can be utilized to evaluate the severity of disease in ICU patients with specific malignancies. For instance, Gruttadauria et al. discovered a significant association between hyperlactatemia observed during the perioperative period of pancreatic cancer resection and a longer ICU stay [24]. Similarly, Hervás et al. reported that a high LA level was a risk factor for postoperative complications in patients undergoing peritoneal cytoreductive surgery, resulting in an extended ICU length of stay [25]. LDH, which is the final enzyme in the lactate pathway and the end product of anaerobic glucose glycolysis, has also been identified as an independent risk factor in various types of cancer [26]. Regrettably, there is insufficient clinical evidence to confirm the correlation between elevated serum levels of LA and LDH and the severity of disease in ICU patients with CRC. In this study, the researchers compared the serum levels of LA and LDH in ICU patients with CRC and investigated their potential associations with disease severity.

Surgery is the first-line treatment for early-stage CRC (Dukes A and B1), while surgery combined with chemotherapy is the preferred treatment for advanced CRC (Dukes C) [27]. In our study, most of the patients in the post-chemotherapy group were also in the Dukes C-D stage, while most of the patients in the post-surgery group were in the Dukes A-B stage. Additionally, advanced CRC often exhibits distant metastasis. A study conducted by Stewart et al. [28] found that approximately 20–25 % of patients with CRC experienced distant metastasis. Similarly, our study also found that the proportion of distant metastasis in patients with CRC admitted to the ICU, particularly those in the post-surgery group and the palliative care group, did not exceed 25 %. However, the rate of distant metastasis in patients with CRC in the post-chemotherapy group was approximately 43.6 %. In the ICU, the APACHE II scoring system is widely used to classify patients based on disease severity. Clinically, it is often used in conjunction with the ICU length of stay to assess the disease severity of critically ill patients [29]. The main reasons for patients with CRC to require ICU admission are infection, organ dysfunction, or post-surgery care [4]. This study compared the disease severity of the three groups of patients and found that the APACHE II score of the chemotherapy group was higher than that of the other two groups. Additionally, the ICU length of stay for the chemotherapy group was longer than that of the post-surgery group. A recent research conducted by Silva et al. [30] revealed that the ICU mortality rates varied among patients categorized as appropriately admitted, potentially inappropriately admitted, and inappropriately admitted, with percentages of 4.8 %, 32.6 %, and 35.0 % respectively. The latter two categories required longer organ support. In the present study, patients in the post-chemotherapy group were admitted to the ICU primarily due to severe acquired opportunistic infections, requiring unplanned intensive care treatment. These admissions to the ICU were deemed inappropriate. Consequently, this particular patient population exhibited a higher 30-day mortality compared to patients in the other two groups.

Urine output, MAP, and serum NT-BNP level are commonly used parameters for assessing hemodynamics, and their data obtained at 24 h after ICU admission may effectively predict poor prognosis. Sasko et al. found that hypotensive patients had significantly higher serum LA and NT-BNP levels, and decreased urine output, which were strongly associated with a higher 28-day mortality [31]. To investigate potential differences in the circulation function among three patient groups, a comparative analysis was conducted. The

Table 3
Association between serum LA and LDH levels at 24 h after ICU admission and outcome.

	30-day mortality	
Group	*r* (95 % CI)	*p* - value
Post-surgery		
Serum LA levels	0.346 [0.067, 0.575]	0.014
Serum LDH levels	0.138 [-0.154, 0.408]	0.339
Post-chemotherapy		
Serum LA levels	0.396 [0.115, 0.620]	0.006
Serum LDH levels	0.198 [-0.103, 0.466]	0.181
Palliative care		
Serum LA levels	0.349 [0.033, 0.602]	0.027
Serum LDH levels	0.183 [-0.146, 0.475]	0.259

APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; ICU, intensive care unit; LA, lactate; LDH, lactic dehydrogenase; *r*, Spearman's rank correlation coeffcient. $p < 0.05$ means statistically significant.

findings revealed that within 72 h of ICU admission, the post-chemotherapy group exhibited a lower 24-h urine output compared to the other two groups. Additionally, the post-chemotherapy group displayed a lower MAP and higher serum NT-BNP levels at 72 h after ICU admission. These results indicate that patients with CRC who underwent chemotherapy within 3 months before ICU admission were more likely to have compromised circulation.

Infection is a serious complication in cancer patients, and research has shown that serum levels of PCT and CRP are significantly higher in cancer patients with infection compared to those without infection. PCT levels appear to be more accurate than CRP in reflecting the extent of systemic inflammatory response in tumor patients [32]. Additionally, a study by Keramidaris et al. on CRC revealed that patients with distant metastasis had higher serum PCT levels compared to those without distant metastasis [33]. Similarly, higher serum PCT levels were observed in the post-chemotherapy group compared to the other two groups, whereas no significant differences in serum CRP levels were found among the three groups. These findings suggest that patients with CRC who underwent chemotherapy within 3 months before ICU admission were more susceptible to systemic inflammatory reactions, which could be attributed to infection or tumor progression.

Arterial blood gas measures several parameters including pH, PO_2, and HCO_3^- etc. These parameters accurately reflect a patient's oxygenation, ventilation adequacy, and acidity. For many years, baseline blood gas values have been used as important prognostic indicators in critically ill patients [34]. Currently, blood gas analysis in oncology primarily focuses on lung cancer to assess hypoxia induced by anesthesia and chemotherapy in tumor patients [35]. However, there is limited research on patients with gastrointestinal tumors, especially CRC. This study compared arterial blood gas data among three groups of patients but did not yield any significant findings. Apart from some differences in serum BE levels, there was no significant difference in hypoxia among the different groups.

The primary focus of this study was to examine the serum LA and LDH levels of patients with CRC who were admitted to the ICU. Our findings revealed that patients in the post-chemotherapy group had significantly higher serum LA levels compared to the other two groups within 72 h of ICU admission. Elevated serum LA levels are commonly observed in critically ill patients who experience hypoperfusion and tissue hypoxia, including those in a state of shock [36]. Correspondingly, the post-chemotherapy group also exhibited significantly impaired circulation function in our study. However, the arterial blood gas data did not indicate the presence of hypoxemia, indirectly ruling out the possibility of increased oxygen consumption leading to hypoxia. It is important to note that elevated serum LA levels can also be attributed to increased production or decreased clearance, which may not be directly related to hypoxia and hypoperfusion caused by tumors [37]. As for LDH, previous studies have confirmed that tumor progression and elevated LDH levels are independent unfavorable factors for the survival of patients after discharge [38]. Elevated LDH levels are more common in acute complications and are determined by the characteristics of the malignancy, as observed in the general oncology population and in tumor patients requiring invasive mechanical ventilation or dialysis [3]. Our study also found that patients in the post-chemotherapy group had significantly higher LDH levels compared to those in the palliative care group. The serum LDH levels in the post-chemotherapy group were also relatively high compared to the post-surgery group, although the difference was not statistically significant due to sample size limitations. These findings suggest that LDH elevation is more likely to occur in patients with CRC who received chemotherapy within 3 months before ICU admission, although the difference in serum LDH levels among the three groups was not as significant as that in serum LA levels.

In a previous study conducted by Wei et al., it was discovered that serum LA and LDH levels were closely linked to the prognosis of patients with metastatic CRC [38]. Additionally, Alici et al. found that high serum LDH is a predictive factor for lower survival in younger patients with CRC [39]. However, Caputo et al. reported that serum LDH level is not a valid prognostic factor for resected CRC patients [19]. In our study, we examined the associations between serum LA and LDH levels at 24 h after ICU admission and disease severity and clinical outcomes in patients with CRC admitted to the ICU. The results demonstrated that higher serum LA levels were correlated with higher APACHE II scores, longer ICU length of stay and higher 30-day mortality, particularly in the post-chemotherapy group and the post-surgery group. Conversely, a stronger association between serum LDH levels and disease severity was only observed in the post-chemotherapy group. However, it is important to note that serum LDH levels of all three groups of patients were not significantly correlated with clinical outcomes. Therefore, when assessing the disease severity and predicting clinical outcomes in patients with CRC requiring ICU admission, it might be more useful to consider serum LA levels instead of serum LDH. Previous studies have highlighted that serum LA levels are commonly used as a biomarker in ICUs to assess disease severity and predict outcomes in various conditions, including sepsis, septic shock, cardiac arrest, trauma, local ischemia, and liver dysfunction [40]. One possible explanation is that, in the case of patients with CRC admitted to the ICU, the detrimental effects of severe complications and impaired circulatory organ function may outweigh the impact of the tumor itself.

The current study has identified both strengths and limitations. Firstly, it is important to note that this study was conducted at a single center and focused specifically on patients with CRC admitted to the ICU. As a result, the sample size was limited. Secondly, it should be acknowledged that the patients included in this study had varying underlying diseases, which could potentially impact serum LA and LDH levels. Thirdly, the limited sample size of this study hinders a comprehensive examination of the association between changes in serum lactate levels and disease severity and clinical outcomes. Additionally, the chemotherapy regimen or surgical difficulty experienced by patients prior to ICU admission varied, which could also influence the findings. Lastly, it is worth noting that while some patients may not have exhibited a higher disease severity upon ICU admission, their condition may have deteriorated during subsequent treatment. Despite these limitations, our study offers valuable insights into the clinical management of this particular patient population.

5. Conclusion

In summary, patients with CRC who received chemotherapy within 3 months before admission to ICU exhibited advanced tumor

stages, often accompanied by distant metastasis, poor circulatory function, and a more severe inflammatory response. These factors might contribute to elevated serum LA and LDH levels, which could be linked to greater disease severity and higher mortality. However, when assessing disease severity and predicting clinical outcomes in patients with CRC admitted to the ICU, elevated serum LA levels were more effective than LDH levels. In clinical practice, ICU medical staff should closely monitor the dynamic changes in serum LA and LDH levels in these patients and adjust the treatment plan accordingly to optimize prognosis. Nevertheless, further multi-center research is needed to confirm these findings and develop clinically useful strategies in the future.

Ethical statement

This study was approved by the Medical Ethics Committee of 5th Medical Center of Chinese PLA General Hospital [ky-2020-8-18]. The requirement of obtaining informed consent was waived due to the retrospective nature of the study, and the source of data was anonymized.

Data availability statement

Data associated with the study has not been deposited into a publicly available repository and data will be made available on request.

CRediT authorship contribution statement

Xin Wang: Writing – original draft, Investigation, Formal analysis. **Chen Li:** Writing – original draft, Software, Methodology. **Ming Li:** Writing – original draft, Investigation, Data curation. **Xiongfei Zeng:** Software, Formal analysis, Data curation. **Jinsong Mu:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Conceptualization. **Yan Li:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Abbreviations

AG: anion gap; ANOVA: analysis of variance; APACHE: Acute Physiology and Chronic Health Evaluation; CRC; colorectal cancer; BE: base excess; CI: confidence interval; Cl^-: chloride; CRP: C-reactive protein; FiO_2: the fraction of inspired oxygen; HCO_3^-: bicarbonate; HIS: hospital information system; ICU: intensive care unit; LA: lactate; LDH: lactic dehydrogenase; MAP: mean arterial pressure; Na^+: sodium; NT-BNP: N-terminal pro-B-type naturetic peptide; OI: oxygenation index; PaO_2: arterial blood oxygen pressure; PCT: procalcitonin; pH: hydrogen potential.

References

[1] H. Brenner, M. Kloor, C.P. Pox, Colorectal cancer, Lancet 383 (9927) (2014) 1490–1502.
[2] Y. Aksoy, A. Kaydu, O.F. Sahin, C.K. Kacar, Analysis of cancer patients admitted to intensive care unit, North Clin Istanb 3 (3) (2017) 217–221.
[3] M.F. Camus, L. Ameye, T. Berghmans, M. Paesmans, J.P. Sculier, A.P. Meert, Rate and patterns of ICU admission among colorectal cancer patients: a single-center experience, Support. Care Cancer 23 (6) (2015) 1779–1785.
[4] M. Fahim, R.A. Visser, L.M. Dijksman, D.H. Biesma, P.G. Noordzij, A.B. Smits, Routine postoperative intensive care unit admission after colorectal cancer surgery for the elderly patient reduces postoperative morbidity and mortality, Colorectal Dis. 22 (4) (2020) 408–415.
[5] Y. de Man, F. Atsma, M.G. Oosterveld-Vlug, L. Brom, B.D. Onwuteaka-Philipsen, G.P. Westert, et al., The intensity of hospital care utilization by Dutch patients with lung or colorectal cancer in their final months of life, Cancer Control 26 (1) (2019), 1073274819846574.
[6] E.H. Jung, S.W. Lee, Y.J. Kim, B. Kang, K.J. Suh, J.H. Lee, et al., Clinical outcomes of operating an acute palliative care unit at a comprehensive cancer center, JCO Oncol Pract 18 (10) (2022) e1661–e1671.
[7] T. Wigmore, P. Farquhar-Smith, Outcomes for critically ill cancer patients in the ICU: current trends and prediction, Int. Anesthesiol. Clin. 54 (4) (2016) e62–e75.
[8] K. Puxty, P. McLoone, T. Quasim, J. Kinsella, D. Morrison, Survival in solid cancer patients following intensive care unit admission, Intensive Care Med. 40 (10) (2014) 1409–1428.
[9] X. Wang, Q. Zhang, Y. Yan, Y. Yang, X. Shang, Y. Li, Clinical significance of pro-inflammatory cytokines and their correlation with disease severity and blood coagulation in septic patients with bacterial Co-infection, Shock 56 (3) (2021) 396–402.
[10] E. Kostakou, N. Rovina, M. Kyriakopoulou, N.G. Koulouris, A. Koutsoukou, Critically ill cancer patient in intensive care unit: issues that arise, J. Crit. Care 29 (5) (2014) 817–822.

[11] H.C. Zhou, Xin-Yan Yan, W.W. Yu, X.Q. Liang, X.Y. Du, Z.C. Liu, et al., Lactic acid in macrophage polarization: the significant role in inflammation and cancer, Int. Rev. Immunol. 41 (1) (2022) 4–18.
[12] D. Sharma, M. Singh, R. Rani, Role of LDH in tumor glycolysis: regulation of LDHA by small molecules for cancer therapeutics, Semin. Cancer Biol. 87 (2022) 184–195.
[13] G. Broder, M.H. Weil, Excess lactate: an index of reversibility of shock in human patients, Science 143 (1964) 1457–1459.
[14] M.E. Kiyatkin, J. Bakker, Lactate and microcirculation as suitable targets for hemodynamic optimization in resuscitation of circulatory shock, Curr. Opin. Crit. Care 23 (4) (2017) 348–354.
[15] J. Chertoff, M. Chisum, L. Simmons, B. King, M. Walker, J. Lascano, Prognostic utility of plasma lactate measured between 24 and 48 h after initiation of early goal-directed therapy in the management of sepsis, severe sepsis, and septic shock, J Intensive Care 4 (2016) 13.
[16] H.B. Nguyen, Lactate in the critically ill patients: an outcome marker with the times, Crit. Care 15 (6) (2011) 1016.
[17] P.J. Vlachostergios, K.G. Oikonomou, E. Gibilaro, G. Apergis, Elevated lactic acid is a negative prognostic factor in metastatic lung cancer, Cancer Biomarkers 15 (6) (2015) 725–734.
[18] X. Zhang, M. Guo, J. Fan, Z. Lv, Q. Huang, J. Han, et al., Prognostic significance of serum LDH in small cell lung cancer: a systematic review with meta-analysis, Cancer Biomarkers 16 (3) (2016) 415–423.
[19] D. Caputo, M. Caricato, B. Vincenzi, V. La Vaccara, G. Mascianà, R. Coppola, Serum lactate dehydrogenase alone is not a helpful prognostic factor in resected colorectal cancer patients, Updates Surg 66 (3) (2014) 211–215.
[20] J.A. Kraut, N.E. Madias, Metabolic acidosis: pathophysiology, diagnosis and management, Nat. Rev. Nephrol. 6 (5) (2010) 274–285.
[21] X.B. Teng, Y. Shen, M.F. Han, G. Yang, L. Zha, J.F. Shi, The value of high-flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia, Eur. J. Clin. Invest. 51 (3) (2021), e13435.
[22] V. Pucino, M. Certo, V. Bulusu, D. Cucchi, K. Goldmann, E. Pontarini, et al., Lactate buildup at the site of chronic inflammation promotes disease by inducing $CD4^+$ T cell metabolic rewiring, Cell Metabol. 30 (6) (2019) 1055–1074.e8.
[23] O. Kruse, N. Grunnet, C. Barfod, Blood lactate as a predictor for in-hospital mortality in patients admitted acutely to hospital: a systematic review, Scand. J. Trauma Resuscitation Emerg. Med. 19 (2011) 74.
[24] S. Gruttadauria, I.R. Marino, C.H. Vitale, L. Mandala, V.L. Scott, C. Doria, Correlation between peri-operative serum lactate levels and outcome in pancreatic resection for pancreatic cancer, preliminary report, J. Exp. Clin. Cancer Res. 21 (4) (2002) 539–545.
[25] M.S. Hervás, R. Játiva-Porcar, D. Robles-Hernández, A.S. Rubert, B. Segarra, C. Oliva, et al., Evaluation of the relationship between lactacidemia and postoperative complications after surgery for peritoneal carcinomatosis, Korean J Anesthesiol 74 (1) (2021) 45–52.
[26] V. Jurisic, S. Radenkovic, G. Konjevic, The actual role of LDH as tumor marker, biochemical and clinical aspects, Adv. Exp. Med. Biol. 867 (2015) 115–124.
[27] P. Luna-Pérez, A. Reyna Huelga, D.F. Rodríguez Coria, R. Medrano, J. González Macouzet, Cáncer colorrectal [Colorectal cancer], Rev. Gastroenterol. México 62 (3) (1997) 175–183.
[28] C.L. Stewart, S. Warner, K. Ito, M. Raoof, G.X. Wu, J. Kessler, et al., Cytoreduction for colorectal metastases: liver, lung, peritoneum, lymph nodes, bone, brain. When does it palliate, prolong survival, and potentially cure? Curr. Probl. Surg. 55 (9) (2018) 330–379.
[29] S.A. Naved, S. Siddiqui, F.H. Khan, Apache-II score correlation with mortality and length of stay in an intensive care unit, J Coll Physicians Surg Pak 21 (1) (2011) 4–8.
[30] C.M.D. Silva, J.N. Germano, A.K.A. Costa, G.A. Gennari, P. Caruso, A.P. Nassar Jr., Association of appropriateness for ICU admission with resource use, organ support and long-term survival in critically ill cancer patients, Intern Emerg Med 18 (4) (2023) 1191–1201.
[31] B. Sasko, T. Butz, M.W. Prull, J. Liebeton, M. Christ, H.J. Trappe, Earliest bedside assessment of hemodynamic parameters and cardiac biomarkers: their role as predictors of adverse outcome in patients with septic shock, Int. J. Med. Sci. 12 (9) (2015) 680–688.
[32] L. Rao, K. Zhang, H. Luo, S. He, Y. Li, C. Liu, et al., The ability of inflammatory markers to recognize infection in cancer patients with fever at admission, Immunol. Res. 70 (5) (2022) 667–677.
[33] D. Keramidaris, N. Koronakis, E.E. Lagoudianakis, A. Pappas, I. Koukoutsis, I. Chrysikos, et al., Procalcitonin in patients with colorectal cancer, J BUON 18 (3) (2013) 623–628.
[34] M. Gupta, N. Agrawal, S.K. Sharma, A.K. Ansari, T. Mahmood, L. Singh, Study of utility of basic arterial blood gas parameters and lactate as prognostic markers in patients with severe dengue, Cureus 14 (5) (2022), e24682.
[35] F. Venuta, E.A. Rendina, T. De Giacomo, E. Mercadante, F. Francioni, F. Pugliese, et al., Nd:YAG laser resection of lung cancer invading the airway as a bridge to surgery and palliative treatment, Ann. Thorac. Surg. 74 (4) (2002) 995–998.
[36] A.J. Reddy, S.W. Lam, S.R. Bauer, J.A. Guzman, Lactic acidosis: clinical implications and management strategies, Cleve. Clin. J. Med. 82 (9) (2015) 615–624.
[37] L.W. Andersen, J. Mackenhauer, J.C. Roberts, K.M. Berg, M.N. Cocchi, M.W. Donnino, Etiology and therapeutic approach to elevated lactate levels, Mayo Clin. Proc. 88 (10) (2013) 1127–1140.
[38] Y. Wei, H. Xu, J. Dai, J. Peng, W. Wang, L. Xia, et al., Prognostic significance of serum lactic acid, lactate dehydrogenase, and albumin levels in patients with metastatic colorectal cancer, BioMed Res. Int. 2018 (2018), 1804086.
[39] S. Alici, N.F. Aykan, B. Sakar, G. Bulutlar, E. Kaytan, E. Topuz, Colorectal cancer in young patients: characteristics and outcome, Tohoku J. Exp. Med. 199 (2) (2003) 85–93.
[40] M. Bender, K. Haferkorn, J. Nagl, E. Uhl, M. Stein, Serum lactate as serum biomarker for cardiopulmonary parameters within the first 24 hours after a spontaneous intracerebral hemorrhage, Diagnostics 12 (10) (2022) 2414.