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## Retrospective Study

## Prognostic predictors in patients with sepsis after gastrointestinal tumor surgery: A retrospective study

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**Abstract****BACKGROUND**

There have been different reports on mortality of sepsis; however, few focus on the prognosis of patients with sepsis after surgery.

**AIM**

To study the clinical features and prognostic predictors in patients with sepsis after gastrointestinal tumor surgery in intensive care unit (ICU).

**METHODS**

We retrospectively screened patients who underwent gastrointestinal tumor surgery at Peking University Cancer Hospital from January 2015 to December 2019. Among them, 181 patients who were diagnosed with sepsis in ICU were included in our study. Survival was analysed by the Kaplan-Meier method. Univariate and multivariate adjusted analyses were performed to identify predictors of prognosis.

**RESULTS**

The 90-d all-cause mortality rate was 11.1% in our study. Univariate analysis showed that body mass index (BMI), shock within 48 h after ICU admission, leukocyte count, lymphocyte to neutrophil ratio, international normalized ratio, creatinine, procalcitonin, lactic acid, oxygenation index, and sequential organ failure assessment (SOFA) score within 24 h after ICU admission might be all significantly associated with the prognosis of sepsis after gastrointestinal tumor surgery. In multiple analysis, we found that  $BMI \leq 20 \text{ kg/m}^2$ , lactic acid after ICU

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admission, and SOFA score within 24 h after ICU admission might be independent risk predictors of the prognosis of sepsis after gastrointestinal tumor surgery. Compared with SOFA score, SOFA score combined with BMI and lactic acid might have higher predictive ability (area under the receiver operating characteristic curve, 0.859; 95% confidence interval, 0.789-0.929).

## CONCLUSION

Lactic acid and SOFA score within 24 h after ICU admission are independent risk predictors of the prognosis of sepsis after gastrointestinal tumor surgery. SOFA score combined with BMI and lactic acid might have good predictive value.

**Key Words:** Surgery; Sepsis; Gastrointestinal; Prognosis; Post-operative

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**Core Tip:** There have been different reports on mortality of sepsis, but few focus on the prognosis of patients with sepsis after surgery. The purpose of this study was to investigate the prognostic factors of patients with sepsis who were admitted to intensive care unit (ICU) after gastrointestinal surgery. This study retrospectively screened patients who underwent the gastrointestinal tumor surgery at the Peking University Cancer Hospital from January 2015 to December 2019. Among them, 181 patients who were diagnosed with sepsis in ICU were enrolled in our study. In multiple analysis, we found that body mass index  $\leq 20$  kg/m<sup>2</sup>, lactic acid after ICU admission, and sequential organ failure assessment (SOFA) score within 24 h after ICU admission might be independent risk predictors of the prognosis of sepsis after gastrointestinal tumor surgery in ICU. Compared with SOFA score, SOFA score combined with body mass index and lactic acid might have higher predictive ability (area under the receiver operating characteristic curve, 0.859; 95% confidence interval, 0.789-0.929).

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## INTRODUCTION

Sepsis is a worldwide problem, and it is estimated that there are 31.5 million sepsis patients in the world every year, causing about 5.3 million deaths each year<sup>[1]</sup>. It is associated with a high mortality and can be caused by any type of infection. Pathogenic microorganisms include bacteria, fungi, viruses, and parasites. Since previous definition of sepsis (infection plus systemic inflammatory response syndrome) is too sensitive, its new definition is life-threatening organ dysfunction resulting from the host's dysfunctional response to infection. Organ dysfunction is characterized by the sequential organ failure assessment (SOFA) score of not less than two points<sup>[2]</sup>.

Early identification of infection, control of infection source, proper use of antibiotics, and rapid resuscitation of critical patients are the cornerstone of abdominal infection management<sup>[3-6]</sup>. There are many factors affecting the prognosis of sepsis. It has been reported that the prognosis of sepsis is related to lactic acid, interleukin-6, procalcitonin (PCT), C-reactive protein, and heart-fatty acid binding protein<sup>[7-11]</sup>. However, as described by definition, sepsis is a syndrome with extreme heterogeneity. In the past, there were many reports of sepsis mortality; however, few focused on the prognosis of patients with sepsis after gastrointestinal surgery. The purpose of this cohort study was to explore the prognostic predictors of sepsis patients admitted to intensive care unit after gastrointestinal tumor surgery.

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## MATERIALS AND METHODS

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### **Study population**

From January 2015 to December 2019, a total of 1636 patients were admitted to the intensive care unit (ICU) after elective and emergency surgery at the Gastrointestinal Cancer Center of Peking University Cancer Hospital. According to the new definition of sepsis, 181 patients diagnosed with sepsis were included in this cohort study. The exclusion criteria were: (1) Patients were admitted to ICU for other reasons or did not have sepsis during the ICU stay; and (2) Patients' sepsis occurred out of the ICU stay. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Peking University Cancer Hospital and informed consent was obtained from all the patients or their next of kin.

### **Data collection and follow-up**

We followed the guidelines of sepsis treatment strategy<sup>[5,6]</sup>. The clinical data and laboratory tests of the patients were collected as follows: Age, body mass index (BMI), underlying diseases, length of the first operation, culture and sensitivity tests, antibiotics used, whether shock occurred within 48 h after ICU admission, leukocyte count, lymphocyte to neutrophil ratio, international standardized ratio (INR), activated partial thromboplastin time (APTT), albumin, creatinine, cardiac troponin I (TNI), PCT, lactic acid, oxygenation index ( $\text{PaO}_2/\text{FiO}_2$ ) after ICU admission, and SOFA score. Unless otherwise stated, the first test after ICU admission was used for analysis. They were followed in a clinic or by telephone for 90 d.

### **Statistical analyses**

Continuous variables are statistically described as the mean  $\pm$  SD. Non-continuous variables are described as medians [quartile 1 (Q1), quartile 3 (Q3)]. Counting variables are described as numerical values (percentages). The survival rate was calculated by the Kaplan-Meier method, and the log-rank test was used for univariate analysis. Multivariate adjustment analysis was performed using Cox regression and forward LR method. The predictive ability of the factors was assessed using the area under the receiver operating characteristic (AUROC) curve. Statistical analyses were performed using SPSS version 24.0 and *P* values less than 0.05 (two-tailed) were considered significant.

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## RESULTS

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### **Patient characteristics**

According to the new definition of sepsis, a total of 181 patients were diagnosed with sepsis, of whom 86 were diagnosed with septic shock within 48 h after ICU admission. The most common postoperative infection for gastrointestinal tumor was abdominal infection. There were 13 cases with abdominal or gastrointestinal bleeding, 16 with deep vein thrombosis, 1 with cerebral infarction, and 1 with myocardial infarction. The baseline characteristics of the patients are shown in [Table 1](#).

### **Univariate and multiple survival analyses**

Univariate analysis is shown in [Table 2](#). All the sepsis patients were followed for 90 d; 20 patients died (19 died of sepsis related organ failure and 1 died of hemorrhagic shock), and the 90-d all-cause mortality rate was 11.1%. Univariate analysis showed that there were statistically significant differences in BMI, shock within 48 h after ICU admission, leukocyte count, lymphocyte to neutrophil ratio, INR, creatinine, PCT, lactic acid, oxygenation index after ICU admission, and SOFA score within 24 h after ICU admission. Especially, the *P* values of shock within 48 h after ICU admission, INR, creatinine, lactic acid, oxygenation index, and SOFA score within 24 h after ICU admission were all less than 0.01.

The multiple analysis is presented in [Table 3](#). Those factors with a *P* value less than 0.05 were enrolled in the Cox regression analysis. The results showed that BMI  $\leq$  20 kg/m<sup>2</sup>, lactic acid after ICU admission, and SOFA score within 24 h after ICU admission might be independent prognostic predictors. However, there was no significant difference between those with 20 < BMI  $\leq$  28 kg/m<sup>2</sup> and BMI > 28 kg/m<sup>2</sup>. The survival curves of these three predictors are shown in [Figures 1-3](#).

BMI had a mild ability to predict mortality of these patients (AUROC, 0.569); lactic

**Table 1** Baseline characteristics of sepsis patients

Baseline characteristic	n (%)
Age, median (Q1, Q3)	65 (59.71)
Sex	
Male	145 (80.1)
Female	36 (19.9)
BMI, mean (SD), kg/m <sup>2</sup>	23.5 (0.3)
Tumor type	
Gastric cancer	91 (50.3)
Colorectal cancer	84 (46.4)
Other abdominal tumors	6 (3.3)
Coexisting condition <sup>1</sup>	
Hypertension	64 (35.4)
Diabetes	32 (17.7)
Coronary heart disease	17 (9.4)
Chronic obstructive pulmonary disease	11 (6.1)
Arrhythmia	9 (5.0)
Chronic renal insufficiency	2 (1.1)
Location of infection <sup>2</sup>	
Abdominal infection	134 (74.0)
Enterogenous infection	12 (6.6)
Intrathoracic infection	17 (9.4)
Pulmonary infection	31 (17.1)
Skin and soft tissue infection	6 (3.3)
Surgical wound infection	4 (2.2)
Central line-associated bloodstream infection	3 (1.7)
Urinary tract infection	2 (1.1)
Length of first operation, median (Q1, Q3), min	195 (140, 246)

<sup>1</sup>Twenty-seven patients had two or more chronic diseases.

<sup>2</sup>Thirty-one patients were infected in two or more locations.

Q1: Quartile 1; Q3: Quartile 3; BMI: Body mass index.

acid had a mild ability to predict mortality (AUROC, 0.673); SOFA score had a modest ability to predict mortality (AUROC, 0.773). Compared with SOFA score, SOFA score combined with BMI and lactic acid might have higher predictive ability (AUROC, 0.859; 95% confidence interval, 0.789-0.929). The ROC curve of the SOFA score combined with BMI and lactic acid is shown in [Figure 4](#).

## DISCUSSION

Sepsis is one of the most common causes of death in critically ill patients. Until now, there have been few studies on postoperative sepsis. In this study, postoperative sepsis after gastrointestinal tumor surgery was investigated. The mortality rate was lower than that of sepsis reported in the literature<sup>[12]</sup>, which might be related to the fact that the most common source of infection in our patients was abdominal infection. Hence, by a multidisciplinary team, we could control the infection source actively through minimally invasive drainage or surgical debridement. There are many factors that might influence the prognosis in patients with sepsis. In our study, 181 patients with

Table 2 Univariate analysis of sepsis patients

Parameter	n (%)	Survival rate at 90-d	P value
Age, yr			0.840
≤ 65	96 (53.0)	0.885	
> 65	85 (47.0)	0.894	
Sex			0.254
Male	145 (80.1)	0.876	
Female	36 (19.9)	0.944	
BMI, kg/m <sup>2</sup>			0.028
≤ 20	37 (20.4)	0.784	
20 < BMI ≤ 28	118 (65.2)	0.932	
> 28	26 (14.4)	0.846	
Length of first operation, min			0.361
≤ 240	129 (71.3)	0.876	
> 240	52 (28.7)	0.923	
Empirical anti infection evaluation			0.729
Sensitive	132 (72.9)	0.894	
Resistance	18 (10.0)	0.833	
No pathogen detected	31 (17.1)	0.903	
Shock within 48 h after ICU admission			0.001
No	95 (52.5)	0.979	
Yes	86 (47.5)	0.791	
Leukocyte count, 10 <sup>9</sup> /L			0.010
≤ 4	31 (17.1)	0.774	
4 < WBC ≤ 12	77 (42.6)	0.963	
> 12	73 (40.3)	0.863	
Lymphocyte to neutrophil ratio			0.035
≤ 0.15	148 (81.8)	0.912	
> 0.15	33 (18.2)	0.788	
International standardized ratio			0.001
≤ 1.5	127 (70.2)	0.937	
> 1.5	54 (29.8)	0.778	
Activated partial thromboplastin time, s			0.064
≤ 50	138 (76.2)	0.913	
> 50	43 (23.8)	0.814	
Albumin, g/L			0.058
≤ 30	99 (54.7)	0.848	
> 30	82 (45.3)	0.939	
Creatinine, μmol/L			0.001
≤ 120	150 (82.9)	0.927	
> 120	31 (17.1)	0.710	
Cardiac troponin I, ng/mL			0.063
≤ 0.05	138 (76.2)	0.913	

> 0.05	43 (23.8)	0.814	
Procalcitonin, ng/mL			0.011
≤ 5	93 (51.4)	0.946	
> 5	88 (48.6)	0.830	
Lactic acid, mmol/L			0.001
≤ 3	128 (70.7)	0.938	
> 3	53 (29.3)	0.774	
Oxygenation index, mmHg			0.003
≤ 200	97 (53.6)	0.825	
> 200	84 (46.4)	0.964	
SOFA score			0.001
≤ 8	124 (68.5)	0.968	
> 8	57 (31.5)	0.719	

BMI: Body mass index; ICU: Intensive care unit; WBC: White blood cell; SOFA: Sequential organ failure assessment.

**Table 3 Multiple analysis of sepsis patients**

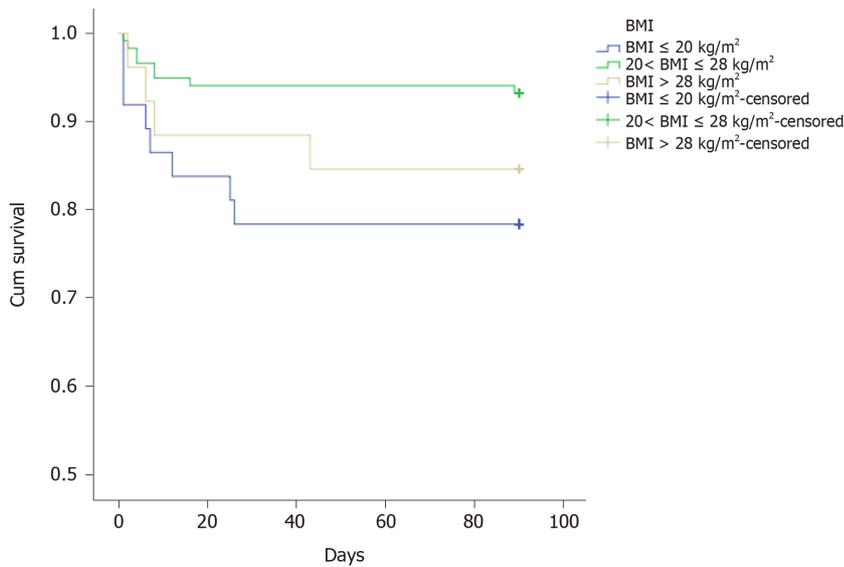
Factor	RR	95%CI		P value
		Lower limit	Upper limit	
BMI (Ref)				0.011
BMI (1)	1.778	0.532	5.942	0.350
BMI (2)	0.377	0.113	1.262	0.114
Lactic acid	2.950	1.168	7.450	0.022
SOFA score	8.359	2.741	25.496	0.001

BMI: Body mass index; SOFA: Sequential organ failure assessment; RR: Risk ratio; CI: Confidence interval

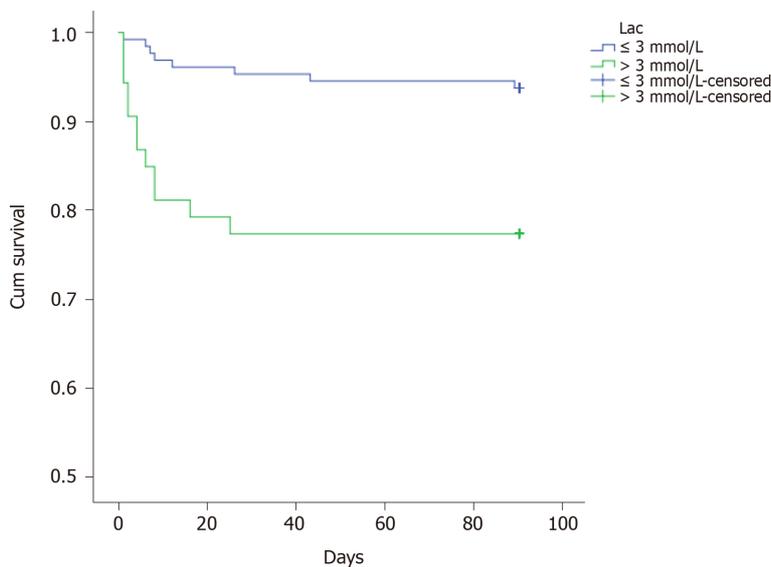
sepsis admitted to intensive care unit after gastrointestinal tumor surgery were analyzed retrospectively and we found that BMI, lactic acid after ICU admission, and SOFA score within 24 h after ICU admission were independent prognostic predictors.

First, we found that patients with BMI  $\leq 20$  kg/m<sup>2</sup> had a worse prognosis than those with  $20 < \text{BMI} \leq 28$  kg/m<sup>2</sup> and BMI  $> 28$  kg/m<sup>2</sup>, so we guessed that BMI  $\leq 20$  kg/m<sup>2</sup> might be a risk predictor. However, the number of patients in this study was limited. The relationship between BMI and the prognosis of sepsis had been widely reported, but the results remained controversial<sup>[13,14]</sup>. Papadimitriou-Olivgeris *et al*<sup>[15]</sup> found that the mortality of obese patients with sepsis increased significantly. Nevertheless, one recent meta-analysis divided sepsis patients into three groups: Overweight ( $25 < \text{BMI} \leq 30$  kg/m<sup>2</sup>), obesity ( $30 < \text{BMI} \leq 40$  kg/m<sup>2</sup>), and morbid obesity (BMI  $> 40$  kg/m<sup>2</sup>). The results showed that the death risk of overweight patients with sepsis was reduced, while obesity and morbid obesity patients with sepsis did not increase the death risk. The reason for this controversy might be linked to the distribution of adipose tissue. It was pointed out that the visceral fat (VAT) accumulation detected by CT scan was a risk factor for poor prognosis of sepsis. Sepsis patients with a high ratio of visceral fat area to the subcutaneous fat area had an increased risk of death and organ damage<sup>[16]</sup>. In the future, more detailed and rigorous studies should aim to elucidate the relationship between sepsis and BMI.

Generally speaking, when the energy of the tissue could not be satisfied by aerobic respiration, the tissue could not get enough oxygen or could not deal with oxygen fast enough, the concentration of lactic acid would rise. Hence, sepsis and septic shock guidelines used lactic acid as an indicator of tissue hypoperfusion and as a target for fluid resuscitation<sup>[5,6]</sup>. Many studies have shown that lactic acid was an independent risk factor for sepsis prognosis<sup>[17-19]</sup>. In our study, it was further confirmed that lactic



**Figure 1** Kaplan-Meier survival curves of body mass index on overall survival at 90 d. BMI: Body mass index.

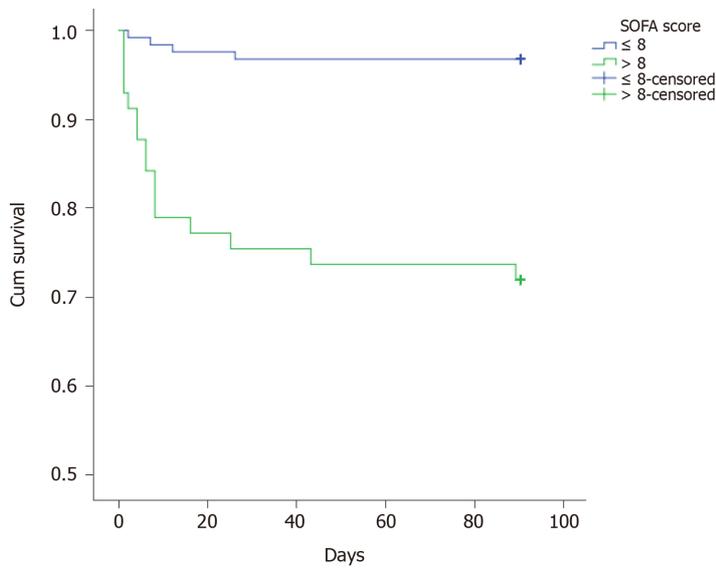


**Figure 2** Kaplan-Meier survival curves of lactic acid on overall survival at 90 d. Lac: Lactic acid.

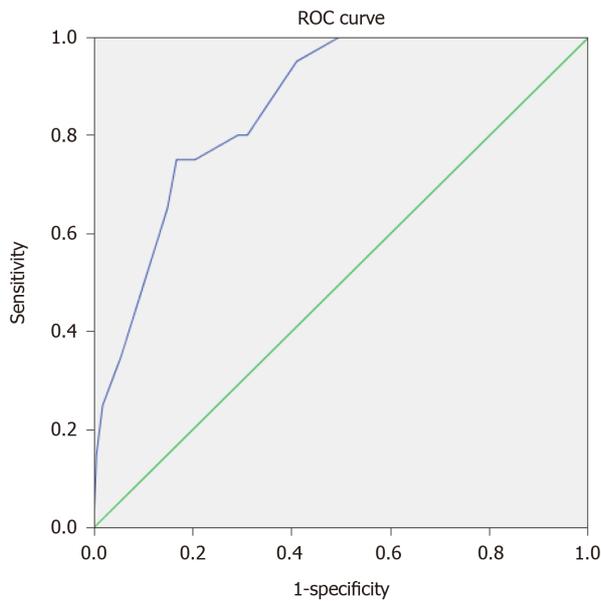
acid > 3 mmol/L after ICU admission was an independent risk predictor of patients with sepsis after gastrointestinal tumor surgery.

There have been many scoring systems for evaluating the severity of critical patients, such as SOFA score and acute physiology and chronic health evaluation II score<sup>[20-22]</sup>. Several studies confirmed that the SOFA score was an independent risk predictor of the prognosis of patients with sepsis<sup>[23,24]</sup>. In our study, we found that the SOFA score within 24 h after ICU admission was statistically significant in the univariate and multivariate analysis. Compared with SOFA score, SOFA score combined with BMI and lactic acid might have better predictive value.

The limitations of this study should be referred. First, this study is a retrospective cohort study and the subjects of this study are sepsis patients admitted to ICU after gastrointestinal tumor surgery. Whether the results can be extended to all sepsis patients remains to be confirmed. Second, patients with sepsis in the general wards were not included in this study, and most of these patients improved in our hospital. Therefore, the mortality of patients with sepsis after gastrointestinal tumor surgery might be overestimated in our study. In the future, we will design prospective studies to elucidate it. Third, there were several missing data, especially brain natriuretic peptide, echocardiography, *etc.* Thus, we could not accurately evaluate their impact on the prognosis of sepsis patients. Finally, the sample size of this study was limited.



**Figure 3** Kaplan-Meier survival curves of sequential organ failure assessment score on overall survival at 90 d. SOFA: Sequential organ failure assessment.



**Figure 4** Receiver operating characteristic curve of sequential organ failure assessment score combined with body mass index and lactic acid. ROC: Receiver operating characteristic.

Many factors were significantly different in univariate analysis, but not in multivariate analysis. We hope that there will be more large-scale studies in the future to confirm these results.

## CONCLUSION

Lactic acid and SOFA score within 24 h after ICU admission are independent risk predictors of the prognosis of sepsis after gastrointestinal tumor surgery. SOFA score combined with BMI and lactic acid might have good predictive value.

## ARTICLE HIGHLIGHTS

**Research background**

There have been different reports on mortality of sepsis, but few focus on the prognosis of patients with sepsis after surgery.

**Research motivation**

To explore the prognostic predictors in patients with sepsis after gastrointestinal tumor surgery.

**Research objectives**

We studied the clinical features and prognostic predictors in patients with sepsis after gastrointestinal tumor surgery in intensive care unit (ICU).

**Research methods**

We retrospectively screened patients who underwent gastrointestinal tumor surgery at Peking University Cancer Hospital from January 2015 to December 2019. Among them, 181 patients who were diagnosed with sepsis in ICU were included in our study. Survival was analysed by the Kaplan-Meier method. Univariate and multivariate adjusted analyses were performed to identify predictors of prognosis.

**Research results**

The 90-d all-cause mortality rate was 11.1% in our study. In multiple analysis, we found that body mass index (BMI)  $\leq 20$  kg/m<sup>2</sup>, lactic acid after ICU admission, and sequential organ failure assessment (SOFA) score within 24 h after ICU admission might be independent risk predictors of the prognosis of sepsis after gastrointestinal tumor surgery. Compared with SOFA score, SOFA score combined with BMI and lactic acid might have higher predictive ability (area under the receiver operating characteristic curve, 0.859; 95% confidence interval, 0.789-0.929).

**Research conclusions**

Lactic acid and SOFA score within 24 h after ICU admission are independent risk predictors of the prognosis of sepsis after gastrointestinal tumor surgery. SOFA score combined with BMI and lactic acid might have good predictive value.

**Research perspectives**

More large-scale studies are needed in the future to confirm these results.

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