The prognostic factors in sepsis patients after operation of gastrointestinal tumors in ICU

CURRENT STATUS: UNDER REVIEW

World Journal of Surgical Oncology • BMC

Ren-Xiong Chen
Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute

ORCiD: https://orcid.org/0000-0003-0471-3449

Zhou-Qiao Wu
Beijing Cancer Hospital

Zi-Yu Li
Beijing Cancer Hospital

Hong-Zhi Wang

Corresponding Author
ORCiD: https://orcid.org/0000-0003-0985-2157

Jia-Fu Ji
Beijing Cancer Hospital

DOI: 10.21203/rs.3.rs-24716/v1

SUBJECT AREAS
Oncology

KEYWORDS
prognostic factors, sepsis, gastrointestinal tumor
Abstract
Background: We studied the clinical profiles and the prognostic factors in patients with sepsis after the gastrointestinal tumor surgery in ICU.

Methods: We 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. Cox regression was performed for multivariate adjusted factor analyses.

Results: The 90-day all-cause mortality rate was 11.1% in our study. The univariate analysis showed that BMI, shock within 48 h after entering ICU, number of blood leukocytes, ratio of lymphocytes to neutrophils, INR, creatinine, procalcitonin, lactic acid, oxygenation index, SOFA score within 24 h after entering ICU, APACHE II score within 24 h after entering ICU were statistically significant. In multiple analysis, we found that BMI $\geq 20$ kg/m$^2$ was a protective factor, while lactic acid $\geq 3$ mmol/L after entering ICU and APACHE II score $\geq 20$ within 24 h after entering ICU were independent risk factors for the prognosis of sepsis after the gastrointestinal tumor surgery in ICU.

Conclusions: BMI $\geq 20$ kg/m$^2$ was a protective factor, while lactic acid $\geq 3$ mmol/L after entering ICU and APACHE II score $\geq 20$ within 24 h after entering ICU were independent risk factors for the prognosis of sepsis after the gastrointestinal tumor surgery in ICU.

Background
Sepsis was a worldwide problem. It is estimated that there are 31.5 million patients with sepsis every year in the world, which causes about 5.3 million deaths every year [1]. Sepsis is very dangerous and associated with high mortality. About 14000 people died of its complications every day in the world.

Sepsis can be caused by any part of the infection. Pathogenic microorganisms include bacteria, fungi, viruses and parasites. As the previous definition of sepsis (infection + SIRS) is too sensitive, the new definition of sepsis is the life-threatening organ dysfunction caused by the host's maladjusted response to infection. Organ dysfunction manifests that sepsis related organ failure score was no less than two points [2]. About 9% of sepsis patients will have septic shock and multiple organ dysfunction.

The most common postoperative infection of gastrointestinal tumor is abdominal infection. Early
identification of infection, control of infection source, proper use of antibiotics and rapid resuscitation of critical patients are the cornerstones of abdominal infection management \(^{[3-6]}\). 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, PCT, CRP, HFABP and so on \(^{[7-11]}\). However, as the definition describes, sepsis is a syndrome with high heterogeneity. In the past, there were different reports on mortality of sepsis, and few studies on the prognosis of patients with sepsis after operation. The purpose of this study is to investigate the prognostic factors of patients with sepsis who were admitted to ICU after gastrointestinal operation.

**Patients And Methods**

**Patients**
From January, 2015 to December, 2019, a total of 1636 patients were admitted to ICU after surgery from the gastrointestinal tumor center of Peking University Cancer Hospital. According to the new definition of sepsis, 181 patients diagnosed sepsis were enrolled in this study. Exclusion criteria: patients were admitted to ICU for other reasons or did not have sepsis during the period of ICU stay, or patients’ sepsis occurred out of ICU stay.

**Therapeutic method**
For sepsis patients, we gave active anti infection treatment, sent etiology examination and tried to find the source of infection. For the patients with septic shock, we took the following measures: First, gave broad-spectrum antibiotics within 1 hour, and took the etiological examination before giving antibiotics. Second, 30 ml/kg of crystalloid fluids was used for rapid volume resuscitation within 3 hours, and the initial target of mean arterial pressure (MAP) was 65 mmHg. If the MAP was not achieved the target within 1 hour, noradrenaline was used for increasing the blood pressure. Third, we looked for and controlled the source of infection actively. For patients with a definite source of infection, we controlled the source of infection by minimally invasive drainage, surgical debridement, removal of a central venous catheter and sputum aspiration by bronchoscope, etc. To emphasize, we follow the guidelines for other treatment strategies \(^{[5, 6]}\).

**Data collection and follow-up**
The clinical data and laboratory examination of the patients were collected as follows: age, body mass
index (BMI), underlying diseases, the length of the first operation, pathogen susceptibility test, antibiotics used, whether shock occurred within 48 hours after entering ICU, the number of blood leukocytes, lymphocyte percentage, neutrophil percentage, international standardized ratio (INR), activated partial thromboplastin time (APTT), albumin, creatinine, cardiac troponin I (TNI), procalcitonin (PCT), lactic acid (Lac), base excess (BE), oxygenation index (PaO2 / FiO2) after entering ICU, sequential organ failure (SOFA) score and acute physiological function and chronic health evaluation (APACHE) II score within 24 h after entering ICU. Unless otherwise stated, the first test after entering ICU was used for analysis. They were followed up to 90 days in clinic or by phone call.

Statistical analyses
The data of continuous variables were statistically described by mean ± standard deviation. The non-continuous variables were described by median (quartile 1 [Q1], quartile 3 [Q3]). The counting variables were described by numerical value (percentage). The Kaplan-Meier method was used to calculate the survival rate of patients and log-rank test was used for the univariate analysis. Cox regression was used for the multivariate adjusted analyses with forward LR method. Statistical analyses were carried out using SPSS version 24.0 and *P* values less than 0.05 (two-tailed) were considered significant.

Results
Patient characteristics
According to the new definition of sepsis, a total of 181 patients were diagnosed with sepsis and 86 of them were diagnosed with septic shock within 48 hours after entering ICU. There were 13 patients complicated by abdominal bleeding or gastrointestinal bleeding, 16 cases by deep vein thrombosis, 1 case by cerebral infarction and 1 case by myocardial infarction. See Table 1 for baseline characteristics of patients.
Table 1
Baseline characteristics of sepsis patients

| Baseline characteristics | Number (%) |
|--------------------------|------------|
| Age, median (Q1, Q3)     | 65 (59, 71) |
| Sex                      |            |
| Male                     | 145 (80.1) |
| Female                   | 36 (19.9)  |
| BMI, Mean (SD), kg/m²    | 23.5 (0.3) |
| Tumor type               |            |
| Gastric cancer           | 91 (50.3)  |
| Colorectal cancer        | 84 (46.4)  |
| Other abdominal tumors   | 6 (3.3)    |
| Coexisting conditions^a  |            |
| 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^b  |            |
| 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) |

^a 27 patients had two or more chronic diseases.

^b 31 patients were infected with two or more locations.

The Univariate and multiple survival analyses

The univariate analysis is shown in Table 2. All the sepsis patients were followed up for 90 days, 20 patients died and the 90-day all-cause mortality rate was 11.1%. Univariate analysis showed that there were statistically significant differences in BMI, shock within 48 h after entering ICU, the number of blood leukocytes, the ratio of lymphocyte to neutrophil, INR, creatinine, PCT, Lac, BE, oxygenation index after entering ICU, SOFA score and APACHE II score within 24 h after entering ICU. Among them, BMI more than 20 kg/m² was a protective factor, the others were risk factors. Especially, shock within 48 h after entering ICU, INR, creatinine, Lac, oxygenation index after entering ICU, SOFA score and APACHE II score within 24 h after entering ICU had P values less than 0.01.

Table 2
The univariate analysis of sepsis patients

| Items                        | Number (%) | Survival rate at 90-day | P value |
|-----------------------------|------------|-------------------------|---------|
| Age, years                  |            |                         |         |
| ≤ 65                        | 96 (53.0)  | 0.885                   | 0.840   |
| >65                         | 85 (47.0)  | 0.894                   |         |
| Sex                         |            |                         | 0.254   |
| Male                        | 145 (80.1) | 0.876                   |         |
| Female                      | 36 (19.9)  | 0.944                   |         |
| BMI, kg/m²                  |            |                         | 0.018   |
| ≤ 20                        | 37 (20.4)  | 0.784                   |         |
| >20                         | 144 (79.6) | 0.917                   |         |
| Charlson score              |            |                         | 0.356   |
| Charson score | \(\leq 3\) | 142 (78.5) | 0.901 |
|---------|---------|------------|--------|
| \(\leq 3\) | 39 (21.5) | 0.846 |
| Length of first operation, min | \(\leq 240\) | 129 (71.3) | 0.876 |
| \(> 240\) | 52 (28.7) | 0.923 |
| Empirical anti infection evaluation | 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 entering ICU | No | 95 (52.5) | 0.979 |
| | Yes | 86 (47.5) | 0.791 |
| Number of blood leukocytes, \(10^9/L\) | \(\leq 4\) | 31 (17.1) | 0.774 |
| | WBC \(\leq 12\) | 77 (42.6) | 0.963 |
| | WBC \(> 12\) | 73 (40.3) | 0.863 |
| Ratio of lymphocyte to neutrophil | \(\leq 0.15\) | 148 (81.8) | 0.912 |
| | \(> 0.15\) | 34 (18.2) | 0.788 |
| International standardized ratio | \(\leq 1.5\) | 127 (70.2) | 0.937 |
| | \(> 1.5\) | 54 (29.8) | 0.778 |
| Activated partial thromboplastin time, S | \(\leq 50\) | 138 (76.2) | 0.913 |
| | \(> 50\) | 43 (23.8) | 0.814 |
| Albumin, g/L | \(\leq 30\) | 99 (54.7) | 0.848 |
| | \(> 30\) | 82 (45.3) | 0.939 |
| Creatinine, umol/L | \(\leq 120\) | 150 (82.9) | 0.927 |
| | \(> 120\) | 31 (17.1) | 0.710 |
| Cardiac troponin I, ng/ml | \(\leq 0.05\) | 138 (76.2) | 0.913 |
| | \(> 0.05\) | 43 (23.8) | 0.814 |
| Procalcitonin, ng/ml | \(\leq 5\) | 93 (51.4) | 0.946 |
| | \(> 5\) | 88 (48.6) | 0.830 |
| Lactic acid, mmol/L | \(\leq 3\) | 128 (70.7) | 0.938 |
| | \(> 3\) | 53 (29.3) | 0.774 |
| Base excess, mmol/L | \(\leq -3\) | 101 (55.8) | 0.941 |
| | \(> -3\) | 80 (44.2) | 0.825 |
| Oxygenation index, mmHg | \(\leq 200\) | 97 (53.6) | 0.825 |
| | \(> 200\) | 84 (46.4) | 0.964 |
| SOFA score | \(\leq 8\) | 124 (68.5) | 0.968 |
| | \(> 8\) | 57 (31.5) | 0.719 |
| APACHE II score | \(\leq 20\) | 124 (68.5) | 0.976 |
| | \(> 20\) | 57 (31.5) | 0.702 |

See Table 3 for multiple analysis. Those factors with P values less than 0.05 were enrolled in cox regression analysis. The results showed that BMI, lactic acid after entering ICU and APACHE II score within 24 h after entering ICU were independent prognostic factors. The BMI \(\geq 20\) kg/m\(^2\) was a protective factor, while lactic acid \(\geq 3\) mmol/L after entering ICU and APACHE II score \(\leq 20\) within 24
hours after entering ICU were risk factors. The survival curves of these three factors are shown in Fig. 1, Fig. 2 and Fig. 3.

Table 3
Multiple analysis of sepsis patients

| Factors       | RR  | 95% interval | P value |
|---------------|-----|--------------|---------|
| BMI           | 0.199 | 0.076 - 0.522 | 0.001   |
| Lactic acid   | 3.333 | 1.290 - 8.610 | 0.013   |
| APACHE II score | 14.479 | 4.145 - 50.580 | 0.001   |

Discussion

Sepsis is one of the most common causes of death in critically ill patients. At present, there are only a few studies focused on postoperative sepsis. This study focuses on sepsis after operation of gastrointestinal tumor. In this study, the mortality rate is lower than that of sepsis reported in the literature [12], which may be related to the fact that most of the infection sources of the patients we selected are abdominal infection and we can actively control the infection sources by multidisciplinary cooperation. In this study, 181 patients with sepsis who were admitted to ICU after operation of gastrointestinal tumor were analyzed retrospectively and we found that BMI ≥ 20 kg/m², lactic acid ≥ 3 mmol/L after entering ICU and APACHE II score ≥ 20 within 24 h after entering ICU were independent prognostic factors.

The World Health Organization classified BMI: BMI < 18.5 kg/m² was underweight, 18.5 ≤ BMI ≤ 25 kg/m² was normal weight, 25 ≤ BMI ≤ 30 kg/m² was overweight and BMI ≥ 30 kg/m² was obesity [13]. In this study, we found that patients with BMI ≥ 20 kg/m² had a better prognosis than those with BMI ≤ 20 kg/m², so we guessed that BMI ≥ 20 kg/m² might be a protective factor. However, the number of patients in this study was limited, and we did not conduct a more detailed stratified study. There were many reports about the relationship between BMI and the prognosis of sepsis, though the results were still controversial [14, 15]. Matthaios PO et al. [16] found that the mortality of obese patients with sepsis increased significantly. But one recent meta-analysis divided sepsis patients into three groups: overweight (25 ≤ BMI ≤ 30 kg/m²), obesity (30 ≤ BMI ≤ 40 kg/m²) and morbid obesity (BMI ≥ 40 kg/m²). 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 related to the distribution of adipose tissue. It was reported 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 VAT area to subcutaneous fat (SAT) area had an increased risk of death and organ damage [17]. In future, more detailed and rigorous studies should be designed to clarify the relationship between sepsis and BMI.

Lactic acid was constantly produced in metabolism and exercise, but its concentration generally did not rise. Only when the production of lactic acid was accelerated and lactate could not be removed in time, its concentration would increase. 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 [5, 6]. Many studies had shown that lactate was an independent risk factor for sepsis prognosis [18-20]. In our study, it was also confirmed that the lactic acid ≥3 mmol/L after entering ICU was an independent risk factor for sepsis patients after the gastrointestinal tumor surgery.

There were many scoring systems for evaluating the severity of critical patients, such as SOFA score and APACHE II score [21-23]. APACHE II score had been considered as the gold standard for risk assessment of critical patients in the past. Several studies had confirmed that APACHE II score is an independent risk factor for the prognosis of sepsis patients [24, 25]. In our study, we found that the SOFA score and APACHE II score within 24 hours after entering ICU were statistically significant in the univariate analysis, while the multivariate analysis showed that only APACHE II score ≥20 was an independent risk factor in this group. However, there was evidence that APACHE II score might provide inaccurate information in some patients, for example, in patients with unconsciousness, the score might be too high [26]. Therefore, we need to increase the sample size to confirm this result in future.

The limitations of this study should be referred. First, this study was a retrospective study and the subjects of this study were patients with sepsis who were admitted to ICU after operation of
gastrointestinal tumor, so, whether the results could be extended to all sepsis populations remains to be confirmed. Second, patients with sepsis in the general ward were not included in this study, and most of these patients improved in our hospital. Therefore, the mortality of patients with sepsis after gastrointestinal surgery might be overestimated in our study. In the future, we will design prospective research to verify it. Third, there were several missing data, especially BNP, echocardiography etc. So we could not accurately evaluate their impact on the prognosis of sepsis patients. Finally, the small sample size of this study increased the risk of type two error which made the study power limited. We hope that there will be more large-scale researches to confirm these results in the future.

Conclusions

BMI \( > 20 \text{ kg/m}^2 \) was a protective factor, while lactic acid \( > 3 \) mmol/L after entering ICU and APACHE II score \( > 20 \) within 24 hours after entering ICU were independent risk factors for the prognosis of sepsis after the gastrointestinal tumor surgery in ICU.

Abbreviations

BMI: body mass index; INR: International standardized ratio; APTT: activated partial thromboplastin time; TNI: cardiac troponin I; PCT: procalcitonin ; Lac: lactic acid; BE: base excess; SOFA score: sequential organ failure and acute score; APACHE II score: Acute Physiology and Chronic Health Evaluation II score.

Declarations

Ethics approval and consent to participate

We received the approval of the Medical Ethical Committee of Peking University Cancer Hospital. All patients or their near kin in our study provided informed consent.

Consent for publication

Not applicable.

Availability of data and materials

Data will be shared after this study is published.

Funding

The authors received no specific funding for this work.

Conflict of interest
The authors declare no conflicts of interest.

**Authors' contributions**

Ren-Xiong Chen designed the study and drafted the manuscript. Hong-Zhi Wang and Jia-Fu Ji critically revised the manuscript. Zhou-Qiao Wu participated in the study design and helped to perform statistical analysis. Zhou-Qiao Wu and Zi-Yu Li helped draft the manuscript. All authors read and approved the final manuscript.

**Acknowledgements**

Not applicable.

**Authors' information**

Ren-Xiong Chen was attending Doctor of ICU and doctoral candidate of Department of Gastrointestinal Surgery at Peking University Cancer Hospital & Institute

Professor Hong-Zhi Wang was the chief of ICU.

Professor Jia-Fu Ji was the chief of Department of Gastrointestinal Surgery.

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Figures
Figure 1

Kaplan-Meier survival curves of BMI on overall survival at 90 days
Figure 2

Kaplan-Meier survival curves of Lac on overall survival at 90 days
Figure 3

Kaplan-Meier survival curves of APACHE II score on overall survival at 90 days