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Detection of early cytokine storm in patients with septic shock after abdominal surgery

Jiaojiao Chao[1], Song Cui[1], Chang Liu[2], Shan Liu[1], Sibo Liu[1], Yeye Han[1], Yanyan Gao[2], Dong Ge[1], Aijie Yu[1], Rongli Yang[1]

[1]Department of Critical Care Medicine, Dalian Municipal Central Hospital Affiliated of Dalian Medical University, Dalian, Liaoning Province, China;
[2]Central Laboratory of Dalian Municipal Central Hospital, Dalian Municipal Central Hospital Affiliated of Dalian Medical University, Dalian, Liaoning Province, China

ABSTRACT

Objectives: To explore the characteristics of cytokine storm in patients with septic shock after abdominal surgery, examine its relationship with clinical data, and determine intervention timings. **Materials and Methods:** We prospectively observed a cohort of patients with abdominal infection admitted to the surgical intensive care unit (ICU) after surgery (shock group). A control group of healthy individuals was used for comparison. Plasma samples and clinical data recorded at 0, 12, 24, 48, and 72 h after surgery were collected. Cytokines (tumor necrosis factor-α, interleukin [IL]-6, IL-8, IL-10, monocyte chemotactic protein [MCP]-1, IL-1 β, interferon-γ, IL-12p70, MCP-1α, IL-4, IL-2, and IL-13) were detected using the Luminex® technique. **Results:** Concentrations of most cytokines were significantly higher in the shock group. When a cytokine storm intensity curve was considered with the vasopressor dependency index and a Sequential Organ Failure Assessment (SOFA) score, time point of maximum cytokine storm intensity was earlier than that of the maximum vasopressor dependency index and SOFA score in the shock group. **Conclusions:** Cytokine storm occurred in patients with septic shock shortly after the abdominal surgery and may be a main mechanism leading to septic shock. Cytokine storm interventions should ideally be initiated within 24 h after surgery and be guided by cytokine storm biomarkers.

Key words: sepsis, septic shock, cytokine storm, abdominal infection, vasopressor dependency index, sequential organ failure assessment

Address for Correspondence:
Dr. Rongli Yang, PhD & MD, Department of Critical Care Medicine, Dalian Municipal Central Hospital Affiliated ofDalian Medical University, 826 Southwest Road, Shahekou District, Dalian, Liaoning Province, China.
E-mail: yever3000@yeah.net

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INTRODUCTION

Sepsis, along with its secondary multiple organ dysfunction syndrome, is one of the major causes of death in patients admitted to the intensive care unit (ICU). Epidemiological studies show that sepsis is associated with unacceptably high morbidity and mortality and that the abdomen is the second most common source of sepsis.[1] Despite the developments in medical science, sepsis remains an important global public health concern and a social burden that cannot be ignored.[2] Sepsis-3 defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[3] This essentially describes the pathogenesis of sepsis, which is not only caused directly by a pathogen but also by an overexuberant innate immune response by the host to its presence. The immune system is an important part of the pathophysiological mechanism of sepsis; therefore, in the recent years, immune dysfunction has become a focus of research.[4-6] Cytokine storm, a popular descriptor of the dramatic harmful consequences of the rapid release of cytokines, is triggered by the invasion of pathogens. The sustained high levels of cytokines in a cytokine storm may disrupt the immune homeostasis and cause life-threatening organ dysfunction.[7-9] Determining biomarkers for cytokine storms that meet the needs of early clinical diagnosis, risk stratification, therapeutic response monitoring, and prognosis evaluation has been a continuous goal of

researchers.[10-13] The time course of cytokine storms could, to a certain degree, be used to guide the clinical treatment. This study aimed to explore the characteristics of cytokine storm in patients with septic shock after abdominal surgery, examine its relationship with hemodynamics, and determine appropriate intervention timings for cytokine storms.

MATERIALS AND METHODS

Patients and controls

Twenty patients with abdominal infection who were admitted to the surgical intensive care unit (SICU) after abdominal surgery because of septic shock from April 20, 2018 to January 10, 2019 were enrolled in this study. The inclusion criteria were based on Sepsis-3. Patients who had the following criteria were excluded from the study: other sources of infection before surgery, shock before surgery, other types of shock, autoimmune disease, radiotherapy, and chemotherapy. We also excluded pregnant women and individuals aged <18 years. In addition, 10 healthy individuals of the same race aged between 60 and 90 years who had no evidence of infection and autoimmune disease were enrolled as controls. Written informed consent was obtained from all participants in both the groups.

Therapeutic method

All patients were treated in accordance with the 2016 guidelines for sepsis and septic shock management.[14] The recommended treatments, such as fluid resuscitation, vasoactive medications, and antimicrobial therapy, in addition to other supportive care, were given immediately when patients developed shock. The treatment was not applicable on control group.

Plasma sample collection

Whole blood samples of 1 mL were collected in ethylenediaminetetraacetic acid (EDTA)-containing tubes at 0, 12, 24, 48, and 72 h after surgery. To separate plasma from whole blood, 1 mL of blood was centrifuged at 1000×*g* at 4°C for 15 min. Subsequently, 100 μL of plasma was aliquoted carefully from each sample to avoid contamination by visible blood. The plasma samples of the control individuals were extracted in the same way; one sample was taken from each person. Plasma samples were stored at −80°C until used for cytokine detection; cytokine detection was performed every 3 months.

Cytokine detection

The Luminex® technique was used to detect the cytokine expression profiles in the samples. The Human Magnetic Luminex Assay (R&D Systems®, Inc., Minneapolis, MN, USA) on the Luminex platform (Shanghai Universal Biotech Co., Ltd., Shanghai, China) was used to detect the concentration of 12 cytokines: tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, IL-10, monocyte chemotactic protein (MCP)-1, IL-1 β, interferon-γ, IL-12p70, MCP-1α, IL-4, IL-2, and IL-13. Experiments were conducted according to manufacturer's suggested protocol.

Clinical data collection

In this study, the time of ICU transfer after the surgery was used as the starting point for monitoring cytokine expression. The hemodynamic data and Sequential Organ Failure Assessment (SOFA) score were recorded at 0, 12, 24, 48, and 72 h after the surgery. Hemodynamic data included blood pressure, types and doses of vasopressor, and the vasopressor dependency index,[15] which is calculated as the ratio of inotropic score (IS) to mean arterial pressure (MAP): IS = (dopamine dose × 1) + (dobutamine dose × 1) + (adrenaline dose × 100) + (noradrenaline dose × 100) + (phenylephrine dose × 100), wherein all doses are expressed in μg/kg/min. General characteristics, including age, sex, procalcitonin measures, lactic acid level, mortality rate, ICU residency period, and surgical operation performed, were recorded. This study was approved by the Ethics Committee of Dalian Municipal Central Hospital. The registration number of this study is ChiCTR1800014397 in the China Clinical trial Registry.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 24.0 (IBM Corp, Inc., Armonk, NY, USA). GraphPad Prism 7.0 (GraphPad Software, Inc., La Jolla, CA, USA), and Origin 2017 (OriginLab Corporation, Northampton, MA, USA) were used to draw figurers.

Quantitative data with normal distribution were expressed as the mean ± standard deviation. These were compared, using repeated measures analysis of variance, between the shock and control groups. Non-normally distributed quantitative data were presented as the median (interquartile range) and were compared using the Mann–Whitney U test. Part of the general characteristics of the shock group versus the control group was compared using univariate analysis. Differences with a two-tailed *P* value <0.05 were considered to be statistically significant.

RESULTS

Patient and control characteristics

The mean age of the 20 patients with septic shock (13 men and 7 women) included in the present study was 75.4 ± 11.4 years and that of the 10 control individuals (5 men and 5 women) was 73.6 ± 12.0 years (Table 1). No significant difference in age and sex was observed between the two groups. Patients' general characteristics, data including procalcitonin, lactic acid, mortality rate, ICU residency

Table 1: Patient and Control Characteristics

	Shock group	Control group
Number of patients	20	10
Age* (years)	75.4 ± 11.4	73.6 ± 12.0
Sex* (male/female)	13/7	5/5
Procalcitonin	36.9 ± 30.4	–
lactic acid (mmol/L)	3.6 ± 2.0	–
Length of ICU stay (days)	5.6 ± 5.6	–
Mortality rate (%)	40	–
Surgical operation, *n* (%)		–
Colectomy	6 (30.0)	–
Gastric perforation repair or subtotal gastrectomy	5 (25.0)	–
Duodenal perforation repair	5 (25.0)	–
Appendectomy	2 (10.0)	–
Small intestinal rupture repair or ileostomy	2 (10.0)	–

Quantitative data are expressed as the mean ± SD. Qualitative data are expressed as *n* (%). *There was no significant difference in age and sex between the two groups. ICU: intensive care unit.

period, and surgical operation performed, are summarized in Table 1.

Dynamic changes of cytokines in the shock group and control group

There was a significant difference in the cytokine storm intensity between the shock and control groups. Almost all levels of the 12 cytokines were significantly higher in the shock group compared with the control group at 0, 12, and 24 h (P <0.05). Most of the cytokine concentrations in the septic groups showed a downward trend, and the difference between the two groups gradually narrowed over time. Although the cytokine concentration in the shock group decreased, it was still higher than that in the control group at most time points. The 12 cytokines had different concentration levels. The concentration of IL-6 was more than 500 pg/mL, and it was found to last for more than 72 h in the shock group (Figure 1).

Cytokine storm intensity curve and its clinical significance

We established a cytokine storm intensity curve through PCA to represent the overall trend of 12 cytokines. The normalized weight of 12 cytokines at each time point is summarized in Table 2.

According to the curve, the peak of cytokine storm intensity curve occurred in the early stage after the surgery. The difference in the cytokine levels between the two groups was significant at 0 and 12 h. The cytokine storm declined rapidly from 0 to 24 h and then tended to plateau after 24 h. From 24 to 72 h, the intensity of the cytokine storm in the shock group was close to the normal value of the control group, and there was no significant difference between the two groups (Figure 2).

In the shock group, the time point corresponding to the peak of cytokine storm was 0 h (time of transfer to ICU after operation), whereas the maximum vasopressor dependency index and maximum SOFA score occurred at 24 h (Figure 3). The peaks of these two curves lag behind the peak of the cytokine storm intensity curve.

DISCUSSION

In this study, 12 cytokines with similar differences and trends were analyzed by PCA, and a cytokine storm intensity curve was generated to represent the inflammatory cascade in patients with septic shock. This curve showed that cytokine storms do occur in patients with septic shock after abdominal surgery. The cytokine storm occurred in the early stages of infection and was characterized by proliferation of cytokines in a short period of time. Numerous studies have confirmed that laboratory injections of endotoxin or bacteria in healthy human volunteers or in baboons resulted in plasma concentrations of specific cytokines, such as TNF-α, IL-6, IL-8, and IL-1β, rapidly elevated within hours.[16] Cytokine storms

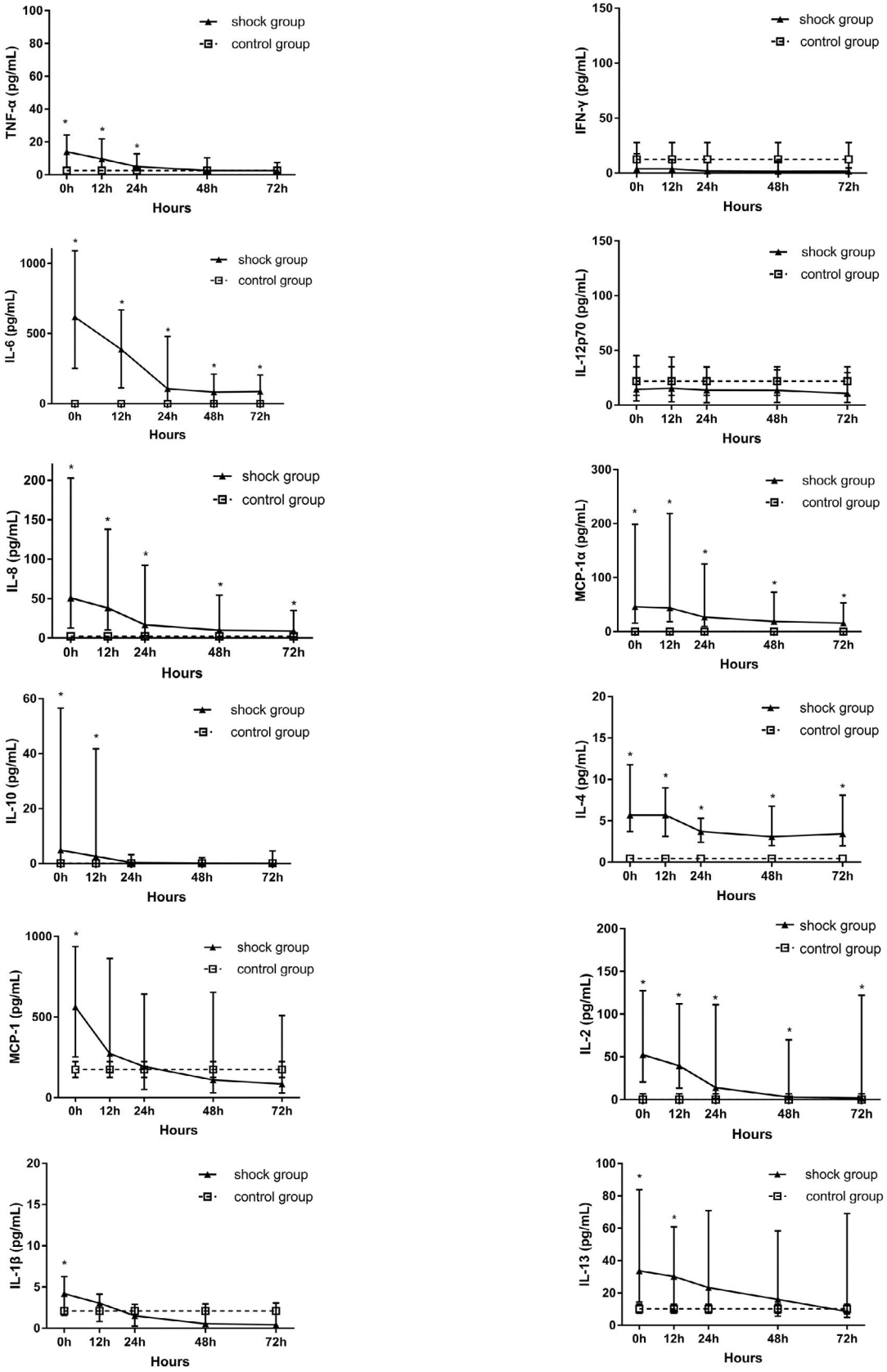

Figure 1: Dynamic changes of 12 cytokines in the shock group and the control group; *Values of $P < 0.05$ were considered statistically significant. TNF: tumor necrosis factor; IL: interleukin; MCP: monocyte chemotactic protein.

Table 2: The normalized weight of 12 cytokines at each time point

Cytokines	0 h	12 h	24 h	48 h	72 h
TNF-α	0.093	0.089	0.083	0.085	0.088
IL-6	0.087	0.082	0.082	0.072	0.075
IL-8	0.077	0.086	0.081	0.068	0.071
IL-10	0.079	0.082	0.047	0.069	0.069
MCP-1	0.090	0.089	0.077	0.092	0.092
IL-1 β	0.059	0.077	0.089	0.094	0.091
IFN-γ	0.082	0.079	0.095	0.069	0.063
IL-12p70	0.072	0.086	0.099	0.080	0.080
MCP-1α	0.088	0.082	0.065	0.094	0.092
IL-4	0.096	0.081	0.096	0.088	0.088
IL-2	0.093	0.087	0.092	0.102	0.100
IL-13	0.086	0.080	0.096	0.086	0.091

TNF: tumor necrosis factor; IL: interleukin; MCP: monocyte chemotactic protein; IFN: interferon.

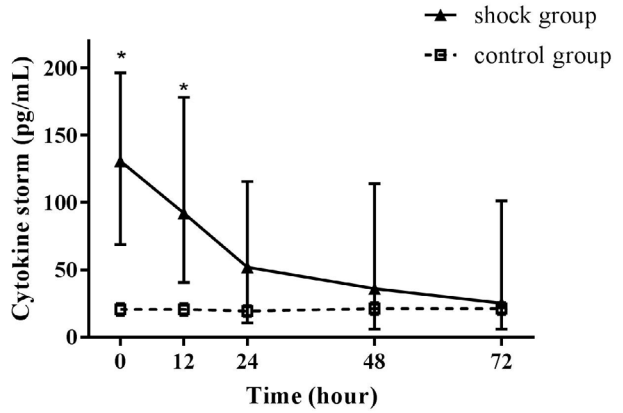

Figure 2: Cytokine storm intensity curve; *Values of $P < 0.05$ were considered statistically significant.

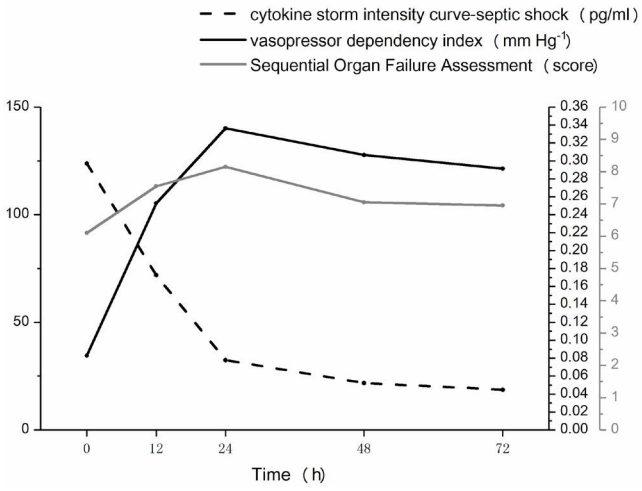

Figure 3: Cytokine storm intensity curve, vasopressor dependency index, and Sequential Organ Failure Assessment score curve in the shock group

begin to decline after reaching their peak in the early stage. It is difficult to detect high levels of cytokine storms in the middle and late stages of many diseases, but systemic inflammatory response continues to develop and eventually results in organ failure.[17]

In clinical practice, because of cost, equipment issues, and other factors, it is limited to synchronously and dynamically monitor various cytokines involved in cytokine storm. As such, it is important to identify cytokines that are representative of cytokine storms. Studies have shown that elevated concentration of IL-6 can lead to injury of vascular endothelial cells, increase in capillary leakage, activate coagulation and inflammatory reaction, and further lead to multiple organ injury, which is closely related to the occurrence, severity, and prognosis of sepsis.[18,19] Our study showed that the concentrations of IL-6 were higher and lasted for a significantly longer period of time than other cytokines. We recommend IL-6 as a crucial representative biomarker for evaluating the intensity and trend change of early cytokine storms.

Diagnostic criteria used for severe cytokine release syndrome (sCRS) secondary to chimeric antigen receptor (CAR)-modified T cells includes either two cytokine max fold changes of at least 75 or one cytokine max fold change of at least 250.[20] The IL-6 measured in this experiment met the diagnostic criteria for sCRS. However, the pathophysiological mechanism of cytokine storm in sepsis is different from that in the sCRS secondary to CAR modified T cells. It is necessary to further develop the criteria for the diagnosis and classification of sepsis cytokine storm.

We found that the intensity of cytokine storm was at a high level within 24 hours after the surgery, and the clinical manifestation of the shock aggravation lagged behind. This suggests that the cytokine storm plays an important role in the pathogenesis of septic shock. If certain interventions are used to remove or antagonize these cytokines, the intensity of a cytokine storm can be reduced and immune homeostasis can be restored. Some hypotheses and studies provide a theoretical basis that targeting the cytokine storm may improve outcome.[19,21-23]

There were many studies on the antagonistic action of cytokine storm in sepsis. Some scholars used TNF or IL-1 inhibitors to treat sepsis, but clinical trials of both TNF and IL-1 inhibitors failed to show effectiveness for the treatment of sepsis.[24,25] The serum levels of TNF-α and IL-1 returned to normal levels within the first few hours and the possibility that the intervention missed its chance was considered a reasonable explanation for this.[26-28]

Blood purification (BP) methods are also be tried to treat sepsis through nonspecific cytokine removing, including high volume hemofiltration, high cut-off hemofiltration, endotoxin adsorption, cytokine adsorption, coupled plasma filtration adsorption, and other different technologies.[29] Several studies have concluded that BP can remove cytokines and treat sepsis.[21,30,31] However, the results of the multicenter study concluded that BP was not beneficial for the treatment of sepsis or septic shock.[14] IVORE studies have shown that there was no evidence that high volume hemofiltration leads to a reduction in 28-day mortality or contributes to early improvements in the hemodynamic profile or organ function. The blood purification in this study lasted 96 hours, during which time the patients may have transited from the peak period of cytokine storm to the immunosuppressive period when the use of BP to remove cytokines may have aggravated the condition.[32]

The timing course of cytokine storms in this study could be used to explain the negative results from other studies that targeted cytokine storms during the treatment of sepsis.[33-38] One possible reason for the failure of BP therapy or immunotherapy in sepsis was that most of these studies did not dynamically monitor cytokine levels, did not accurately understand body's changing immune status, and missed the optimal opportunity for treatment. Cytokines may still be removed or suppressed even during the subsequent immunosuppressive phase.[39-42] Therefore, biomarkers direct therapy should be emphasized.[43] We suggest that interventions targeting cytokine storms should be initiated as soon as possible, preferably within 24 hours after the surgery and that these should be guided by cytokine storm biomarkers.

There are some limitations of this study. First, we have suggested a timeline for the initiation of interventions to prevent cytokine storms based on the time after a surgery. However, this intervention indication is not suitable for patients who have not undergone surgery. Future research could determine the timing of initiation of the intervention based on factors unrelated to surgery such as specific value or change rate of cytokine, indicators of immune system, vasopressor dependency index, SOFA score, or other clinical indicators. Second, in theory, the stronger the cytokine storm in sepsis, the more severe multiple organ damage is. However, hundreds of cytokines, which may do the most damage to the body, were not assessed. The weight given to cytokines by PCA was only a mathematical evaluation of cytokines, whereas it is difficult to evaluate this from a clinical point of view. In the future research, we anticipate that each cytokine will be given a more reasonable and accurate weight coefficient according to its damage during sepsis. There were some other shortcomings, such as a small sample size and limited selection of cytokines. Future studies should expand the sample size and cytokine types to verify the findings of this study.

CONCLUSIONS

In summary, this study monitored the dynamic changes of cytokine storm shortly after abdominal surgery in patients with septic shock. We integrated 12 cytokines into a cytokine intensity curve using PCA analysis to determine which cytokines contributed most to the cytokine storm. Our study found that cytokine storm appears before aggravation of shock and may be one of the main mechanisms leading to septic shock. We suggest that interventions targeting cytokine storms should be initiated as soon as possible, maybe within 24 hours after surgery is the ideal intervention time, which needs further verification and should be guided by cytokine storm biomarkers.

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Conflicts of Interest

Dr. Rongli Yang declared that the funding sources had no role in the design, conduct, or reporting of the study or the decision to submit the manuscript for publication. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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