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Systemic Inflammatory Response Syndrome (SIRS) and the Pattern and Risk of Sepsis Following Gastrointestinal Perforation

Authors' Contribution:
Study Design A
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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Background: Systemic inflammatory response syndrome (SIRS) is characterized by systemic inflammation and tissue injury. Secondary sepsis is a common critical illness associated with poor clinical outcome. The aim of this study was to investigate the risk of SIRS-positive and SIRS-negative sepsis following gastrointestinal (GI) perforation.

Material/Methods: A retrospective study included 51 patients with GI perforation who had clinical evidence of sepsis, with or without SIRS. Clinical outcome was assessed at day 30 using the Glasgow Outcome Scale (GOS) (score, 1–5) and the sequential organ failure assessment (SOFA) (score, 1–6) to determine organ function.

Results: Fifty-one patients were included in the study (median age, 74 years; 37 male patients); 20 patients (39.2%) developed secondary sepsis; 16 patients (80%) had SIRS-negative sepsis; four patients had SIRS-positive sepsis. An increased SOFA score was a significant independent predictor of GI perforation with sepsis (5.4±3.1 *vs.* 1.5±2.8) (P<0.0001). Patients with GI perforation with SIRS-negative sepsis had a significantly less favorable outcome (5/16 *vs.* 2/35) (P=0.03). The risk of SIRS-negative sepsis following GI perforation was 39.2%, and the risk of mortality for SIRS-negative sepsis was 31.3%. In the Cox regression analysis, septic shock and septic encephalopathy were associated with a worse clinical outcome.

Conclusions: The findings of this study support the recognition of SIRS-negative sepsis following GI perforation as an important condition to recognize clinically, given its association with increased patient morbidity and mortality.

MeSH Keywords: Gastrointestinal Diseases • Risk Assessment • Sepsis

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Background

In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) introduced definitions for systemic inflammatory response syndrome (SIRS) as well as sepsis, severe sepsis, and septic shock [1]. SIRS is a clinical syndrome characterized by systemic inflammation and widespread tissue injury [1]. Ten years later, the Second International Consensus further established SIRS and multiple organ dysfunction syndrome (MODS) in the diagnosis of sepsis [2].

During the past decade, the definition of SIRS has evolved in clinical practice also to include patients with a diagnosis of sepsis, but few clinicians may be aware that patients may suffer from sepsis without SIRS. However, in 2015, Kaukonen et al. divided sepsis into two clinical patterns, SIRS-positive sepsis (with ≥ two SIRS criteria) and SIRS-negative sepsis (with < two SIRS criteria) [3]. However, many clinicians remain unfamiliar with this pattern of SIRS.

Gastrointestinal (GI) perforation presents as an acute surgical emergency, and the aim of this study was to test the hypothesis that the pattern of sepsis following GI perforation was predictive of patient morbidity and mortality. To test this hypothesis, the patient outcome with SIRS-positive and SIRS-negative sepsis following GI perforation was evaluated in a single center in China.

Material and Methods

Study design

A retrospective cohort of consecutive patients was selected for the study. The Ethical Committee on Clinical Research of the Shuyang Peoples' Hospital, China approved the study, which was in full compliance with the Helsinki Declaration. Written informed consent to participate in the study was obtained from the patients or their families.

Patient identification

Patients with an admission diagnosis of gastrointestinal (GI) perforation who were admitted to the Department of General Surgery of Shuyang County Peoples' Hospital between January 2014 and December 2016 were evaluated. All patients underwent an initial abdominal computed tomography (CT) scan or a plain abdominal radiograph on admission. Eligible patients who had a GI perforation, diagnosed by a history of sudden abdominal pain on admission and abnormal imaging findings, were included in this study.

In this study, the 2015 criteria were used for systemic inflammatory response syndrome (SIRS) in defining severe sepsis as described by Kaukonen et al. [3]. The diagnostic criteria for sepsis were as follows: suspected or confirmed infection, and signs of two or more SIRS criteria (SIRS-positive sepsis) or less than two SIRS criteria (SIRS-negative sepsis); one or more organs with organ failure for the sepsis-related sequential organ failure assessment (SOFA) score (1–6); and a time from the onset of GI symptoms to sepsis of <72 hours.

The exclusion criteria for screening for sepsis included: a patient without infection; noninfection-associated organ failure; time from the onset of GI symptoms to hospital admission of >96 hours.

Clinical assessment

The following criteria were used to define SIRS: a body temperature >38°C or <36°C; a heart rate >90 beats per minute; a tachypnea >20 respirations per minute or a PCO_2 <32 mmHg; and a white blood cell (WBC) count >12.0×10^9/L, <4.0×10^9/L, or >10% band forms [2]. Organ failure was defined as a SOFA score ≥2 for a particular organ, after the onset of infection [4].

The following indicators were considered to be equivalent to a SOFA score ≥2 for a particular organ (on a scale from 0-4), with higher scores indicating more severe organ failure: sepsis-associated encephalopathy, with a Glasgow Coma Scale (GCS) score <13; respiratory failure, with bilateral infiltrates on chest radiography, and the arterial oxygen pressure and arterial oxygen fraction of inspired oxygen ratio (PaO_2/FiO_2) ≤300, or a need for supplemental oxygen to maintain >90% oxygen saturation; circulation failure, with hypotension and systolic blood pressure (SBP) <90 mmHg, mean arterial pressure <65 mmHg or decrease of >40 mmHg in systolic pressure; hepatic failure, with a total serum bilirubin >33 μmol/L; kidney failure, with a creatinine of 171 μml/L; GI failure, with a loss of abdominal sounds, or a high degree of abdominal distention; and thrombocytopenia, with a platelet count ≤100×10^9/L.

All data were extracted from electronic medical records. The data recorded, included patient age, gender, time from onset of symptoms to hospital admission, body temperature, blood pressure, heart rate, respiratory rate, general characteristics of GI perforation, the GCS score, creatinine, bilirubin, serum glucose, WBC count, platelet count, bacteriological findings, and signs of sepsis-related organ failure. The findings of abdominal radiography, computed tomography (CT) or other imaging were noted. According to their different clinical presentations, the patients with GI perforation were divided into two groups, those with and without SIRS-negative sepsis. Patients were followed for 30 days, or until death.

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Table 1. Baseline characteristics of patients with gastrointestinal GI perforation (n=51).

Baseline characteristics	Value (N, %, range)
Male	N=37 (72.5%)
Age, median (IQR)	74 yrs (range, 11–95 yrs)
Acute abdominal pain Fever	N=47 (92.1%) N=3 (5.9%)
Diarrhea or vomiting	N=1 (2.0%)
Signs of peritoneal irritation	N=51 (100%)
Location and cause of GI perforation	
Distal gastric ulcer	N=13 (25.5%)
Duodenal bulb ulcer	N=21 (42.2%)
Small intestine and colon	N=7 (13.7%)
Appendix	N=1 (2.0%)
Unknown	N=9 (17.6%)
Operation treatment	N=37 (72.5%)
Conservative treatment	N=14 (27.5%)
Hospital length of stay, median (IQR)	N=10 (8,13%)

GI – gastrointestinal; IQR – interquartile range.

Statistical analysis

The results in each group were expressed as the mean ± standard deviation (SD) or median interquartile range (IQR), and n (%) for qualitative values. Continuous variables were compared using the t-test. The Chi-squared test and Pearson's correlation coefficients were used to explore the relationships between baseline variables. Cumulative survival event curves were constructed for the secondary outcomes with the use of the Kaplan-Meier method. Multivariate-adjusted risk ratios (RR) and the 95% confidence intervals (CI) were estimated using a Cox proportional hazards model to examine sepsis baseline status and to determine whether the variables played a role in the risk of death events. Differences between patients were considered significant if a two-sided p-value was <0.05. Statistical calculations were performed using a proprietary, computerized statistics package (SPSS version 10.0).

Results

A total of 56 patients who were admitted with gastrointestinal (GI) perforation to the department of general surgery were initially recruited to the study. Of these patients, five patients were excluded due to missing data in the medical record, including two patients because of death within the first hour, two patients with incomplete clinical data, and one patient who was later transported out of the ward. Finally, 51 patients with GI perforation were included in the study, accounting for 1.7% of hospitalized patients during the same period. The median age of the 51 patients was 74 years (range, 11-95 years), and 72.5% were male patients. The baseline characteristics of patients with GI perforation are shown in Table 1.

Table 2. Clinical characteristics of systemic inflammatory response syndrome (SIRS)-negative sepsis.

Clinical manifestation	SIRS-negative sepsis (mean ±SD; range, N, %) (N=16)
Male,	N=13 (81.3%)
Age, years (mean ±SD)	68.7±15.9
Onset to sepsis time, median (IQR)	6 (1–72)
Suspected infection	N=3 (18.8%)
Confirmed infection	N=13 (81.2%)
Body temperature (°C)	36.5±3.1
Heart rate (beats/min)	82±10
Respiratory (breaths/min)	19±1.0
WBC (mm3)	11.4±5.4
SBP (mm Hg)	110±27.1
DBP (mm Hg)	63.2±16.0
Blood glucose (mmol/l)	7.2±2.5
Sepsis-related organ failure	
GI failure	N=8 (50.0%)
Brain	N=6 (37.5%)
Septic shock	N=8 (50.0%)
Lungs	N=1 (6.2%)
Kidney	N=3 (18.8%)
Hepatic	N=6 (37.5%)
Platelet	N=1 (6.2%)
SOFA score	5.9±3.2
Mortality at 30 days	N=5 (31.3%)

SIRS – systemic inflammatory response syndrome;
SOFA – sequential organ failure assessment.

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Table 3. Univariate analysis of patients with gastrointestinal (GI) perforation with and without secondary systemic inflammatory response syndrome (SIRS)-negative sepsis.

Variables	SIRS-negative (n=16)	Non-SIRS-negative sepsis (n=35)	P
Male	N=12 (75.0%)	N=25 (71.4%)	1.000
Age (years)	68.5±15.7	58.4±18.4	0.080
Time from onset to admission (hrs)	13.8±12.9	13.6±28.7	0.986
Confirmed infection	N=11 (68.8%)	N=2 (5.7%)	0.000
Suspected infection	N=5 (31.2%)	N=32 (91.4%)	0.000
Body temperature (°C)	36.7±1.0	36.9±0.7	0.392
Heart rate(beat/min)	82.6±1.9	86.0±16.5	0.449
Respiratory (times/min)	19.5±1.3	21.0±10.0	0.443
WBC	10.9±4.5	11.6±4.6	0.637
C-reactive protein, (mg/L)	128.5±77.5	108.8±77.1	0.375
Blood glucose (mmol/l)	7.1±2.6	5.9±1.2	0.035
SBP (mmHg)	113.6±28.6	134.9±21.7	0.021
DBP (mmHg)	66.4±16.9	85±12.9	0.001
Sepsis-related organ failure			
Sepsis-related encephalopathy	N=6 (37.5%)	N=3 (8.6%)	0.020
Sepsic shock	N=8 (50.0%)	N=2 (5.7%)	0.001
Lungs	N=1 (6.2%)	N=1 (2.9%)	0.533
Kidney	N=3 (18.8%)	N=1 (2.9%)	0.086
Hepatic	N=6 (37.5%)	N= 2 (5.7%)	0.008
GI failure	N=6 (37.5%)	N=2 (5.7%)	0.008
Platelets	N=1 (6.2%)	N=0(0)	0.314
SOFA score	5.4±3.1	1.5±2.8	0.000
GCS score	12.6±3.9	14.6±1.5	0.014
Surgical treatment	N=10 (62.5%)	N=27 (77.1%)	0.322
Length of ICU stay (days)	1.1±1.4	0.3±1.0	0.052
Length of hospital stay (days)	10.0±6.7	12.0±9.5	0.473
GOS score	3.4±1.9	4.7±1.0	0.005
Mortality at 30 days (%)	N=5 (31.3%)	N=2 (5.7%)	0.000

GI – gastrointestinal; SIRS – systemic inflammatory response syndrome; SOFA – sequential organ failure assessment; GCS – Glasgow Coma Scale; GOS – Glasgow Outcome Scale.

Characteristics of SIRS-negative sepsis following GI perforation

Of the GI perforation cases during the study period, 20 patients (39.2%) developed sepsis according to the inclusion and exclusion criteria, including for systemic inflammatory response syndrome (SIRS). SIRS-negative sepsis was the most common type of case in 80% (16/20), and SIRS-positive sepsis was present in 20% (4/20) cases. All patients had intra-abdominal infection, including peritonitis and retroperitoneal abscess near

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Table 4. Multivariate logistic risk ratios for secondary systemic inflammatory response syndrome (SIRS)-negative sepsis in patients with gastrointestinal (GI) perforation.

Variable	RR	95% CI	P-value
SOFA score >2	1.647	1.218–1.226	0.001

GI – gastrointestinal; SI SIRS – systemic inflammatory response syndrome; RR – risk radio; CI – confidence intervals.

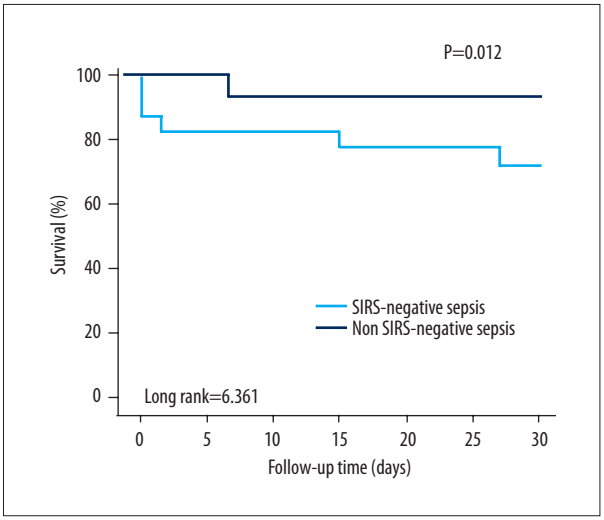

Figure 1. Kaplan-Meier survival curves for patients with gastrointestinal (GI) perforation and sepsis show that patients with systemic inflammatory response syndrome (SIRS)-negative sepsis had significantly worse survival compared with patients with GI perforation and non SIRS-negative sepsis.

the GI perforation, and sepsis-related organ failure. Of the 16 SIRS-negative sepsis patients, five patients (31.3%) died within 30 days, and eight patients (50.0%) with secondary sepsis, who almost all had single organ failure rather than septic shock. The clinical manifestations of patients with GI perforation are shown in Table 2.

The results of univariate analysis are shown in Table 3. There was no difference in gender, patient age, body temperature, heart rate, respiratory rate, white blood cell (WBC) count, C-reactive protein (CRP), SIRS criteria, acute renal failure, and sepsis-related hepatic failure in subjects with SIRS-negative sepsis and non-SIRS-negative septic subjects (P>0.05). The presence of SIRS-negative sepsis was significantly associated with infection, acute sepsis-associated encephalopathy, septic shock, hepatic failure, GI failure, increased blood pressure, elevated blood glucose, a lower Glasgow Coma Scale (GCS) score, and elevated sequential organ failure assessment (SOFA) score, and lower Glasgow Outcome Scale (GOS) score (all P<0.05). However, the only independent predictor of GI perforation with secondary SIRS-negative sepsis was an increased SOFA score (5.4±3.1 versus 1.5±2.8; P<0.0001) (Table 4).

Outcome of SIRS-negative sepsis following GI perforation

The data from this study were useful during the 30-day follow-up period. Of the 20 patients with GI perforation associated with sepsis, seven patients died (35.0%), including three deaths in the intensive care unit (ICU), and four deaths within between one to four weeks after hospital discharge. Patients with SIRS-negative sepsis had a significantly greater incidence of mortality compared with non SIRS-negative sepsis (31.3% versus 5.7%; P<0.0001). Based on Kaplan-Meier survival curves that included patients with GI perforation, with and without SIRS-negative sepsis events, during the 30-day follow-up period, the risk of reduced survival was significantly associated with GI perforation with SIRS-negative sepsis events (Figure 1).

Using Cox proportional analysis, the risk of reduced survival in patients with GI perforation with SIRS-negative sepsis was significantly associated with septic encephalopathy (RR, 0.5; 95% CI, 0.304–0.842; P<0.0001), and septic shock (RR, 8.6; 95% CI, 1.420–4.803; P<0.05) (Table 5).

Table 5. Multivariate Cox risk ratios for secondary systemic inflammatory response syndrome (SIRS)-negative sepsis in patients with gastrointestinal (GI) perforation.

Variable	RR	95% CI	P-value
SAE	0.5	0.304–0.842	0.009
Septic shock	8.6	1.420–4.803	0.026

GI – gastrointestinal; SIRS – systemic inflammatory response syndrome; SAE – sepsis-associated encephalopathy; RR – risk radio; CI – confidence intervals.

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Discussion

Because systemic inflammatory response syndrome (SIRS) is characterized by systemic inflammation and tissue injury, this study investigated the risk of SIRS-positive and SIRS-negative sepsis following gastrointestinal (GI) perforation. The findings were that the risk of SIRS-negative sepsis following GI perforation was 39.2% and the risk of mortality for SIRS-negative sepsis was 31.3%, and septic shock and septic encephalopathy were associated with a worse clinical outcome. Previous studies have reported that the mortality rate for sepsis is between 30% and 45% [5,6].

Clinically, the most common source of sepsis is from chest infections [6–9]. The second most common source of sepsis is from the GI system [6,7,9], and the most common cause is GI perforation [9]. GI perforation can cause deep retroperitoneal abscess and sepsis associated with GI perforation has been reported to occur in up to 43.5% of cases [10].

In the present study, SIRS-negative sepsis accounted for 80% of cases of sepsis, which was contrary to a previous study in patients with sepsis [3]. In the present study, patients did not have specific underlying comorbidities that could lead to an immunosuppressed state, such as liver cirrhosis, chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), and underlying malignancy, or the use of any immunosuppressive medications. However, the GI tract is the largest immune organ in the body [11,12], and patients with GI perforation with SIRS-negative sepsis have previously been reported to be more likely to be immunosuppressed [5,13].

Univariate analysis of the data from the current study indicated that the SIRS definition standards do not necessarily predict sepsis, indicating in SIRS-negative patients, a diagnosis of sepsis cannot be excluded. In this study, the univariate analysis of in-hospital conditions, including suspected and confirmed infection, sepsis-associated encephalopathy, septic shock, liver or intestinal failure, blood sugar, blood pressure, Glasgow Coma Scale (GCS) score, the Glasgow Outcome Scale (GOS) score, and the sequential organ failure assessment (SOFA) score in patients with GI perforation who developed SIRS-negative sepsis were analyzed. The multivariate regression analysis, after adjustment for other confounders, showed that only an increased SOFA score was an independent predictor of sepsis after GI perforation. These study findings are similar to the 2016 Third International Consensus on the New Definition of Sepsis, defined as sepsis that is a life-threatening organ dysfunction caused by the host's response to infection [7]. However, this study also showed that septic shock and sepsis-associated encephalopathy were two independent risk factors for reduced patient survival following GI perforation with SIRS-negative sepsis.

Also, in this patient series with GI perforation, five out of six patients (83.3%) with SIRS-negative sepsis-associated encephalopathy patients died from septic shock.

Although previous studies have shown that infection can increase the risk of acute cerebral ischemia [14,15], the most common cause of global ischemia was severe hypotension [16], and microcirculatory disturbance is the main pathogenesis in experimental models of sepsis [17]. The mechanism underlying the higher rate of adverse outcomes in patients with septic shock and septic encephalopathy may be associated with global cerebral ischemia, which can cause extensive subcortical white matter damage, or lead to multifocal necrotizing white matter encephalopathy [18,19]. This white matter encephalopathy is essentially a kind of sepsis-associated encephalopathy, with a mortality as high as 51.0–71.9% [20]. However, previously published data also showed that patients with secondary sepsis-associated encephalopathy who met two or more SIRS criteria and were without septic shock were more likely to have vasogenic brain edema on brain imaging [21,22]. A previous animal model also showed that sepsis leads to cerebrovascular permeability changes in the blood-brain barrier [23]. Therefore, in some cases, the pathological mechanism of SIRS-negative sepsis-associated encephalopathy may differ from that of SIRS-positive sepsis-associated encephalopathy, but this possible difference requires further study..

To our knowledge, few previous studies have reported a higher prevalence of SIRS-negative sepsis associated with and reduced outcomes in patients with GI perforation. Published guidelines indicate that if there is no delay in the diagnosis and antibiotic treatment is commenced at an early stage, with the majority of patients having microbiology cultures being sent after initiation of antibiotics therapy, the mortality in patients with sepsis may be reduced to less than 30% [24]. A recent study has found that modulation of the gene for triggering receptor expression on myeloid cells 1 (*TREM-1*) by a synthetic peptide might be a potential therapeutic option for polymicrobial sepsis [25]. Therefore, such treatment approaches may be recommended in future for patients with GI perforation with sepsis.

This study had several limitations, including the fact that this was a small retrospective study in a single center that included a relatively small study size. Also, the majority of patients had specimens for microbiology investigation taken following the start of antibiotic treatment, which may be the reason for the low rate of positive microbial culture. Brain imaging for diagnosis of sepsis-associated encephalopathy would be an important component of future studies. Also, because this was a single-center study, and the sample size is not large, there may have been some bias in the data interpretation. Further large-scale, multi-center, prospective, controlled clinical studies are required.

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Conclusions

In this retrospective clinical study, the prevalence of sepsis without systemic inflammatory response syndrome (SIRS) following gastrointestinal (GI) perforation in patients was 39.2% and the risk of death was 31.3%. The findings of this study support the recognition of SIRS-negative sepsis following GI perforation as an important condition to recognize clinically, given its association with increased patient morbidity and mortality.

Conflicts of interests

None.

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