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### OPINION REVIEW

- 652 Fear can be more harmful than the severe acute respiratory syndrome coronavirus 2 in controlling the corona virus disease 2019 epidemic  
*Ren SY, Gao RD, Chen YL*

### ORIGINAL ARTICLE

#### Clinical and Translational Research

- 658 Identification of key genes and pathways in gastric signet ring cell carcinoma based on transcriptome analysis  
*Zhao ZT, Li Y, Yuan HY, Ma FH, Song YM, Tian YT*

#### Case Control Study

- 670 Risk factors for postoperative sepsis in patients with gastrointestinal perforation  
*Xu X, Dong HC, Yao Z, Zhao YZ*
- 679 Clinical observation of soft palate-pharyngoplasty in the treatment of obstructive sleep apnea hypopnea syndrome in children  
*Ding XX, Zhao LQ, Cui XG, Yin Y, Yang HA*
- 689 Application of positive behavior management in patients after breast cancer surgery  
*Hao YJ, Sun HB, Li HW, Chen BJ, Chen XL, Ma L, Li YL*

#### Retrospective Study

- 700 Breast non-mass-like lesions on contrast-enhanced ultrasonography: Feature analysis, breast image reporting and data system classification assessment  
*Xu P, Yang M, Liu Y, Li YP, Zhang H, Shao GR*
- 713 Risk factors for long-term prognosis of hepatocellular carcinoma patients after anatomic hepatectomy  
*Tian YL, Ji JJ, Chen LN, Cui XL, Liu ST, Mao L, Qiu YD, Li BB*
- 723 Upper esophageal sphincter abnormalities on high-resolution esophageal manometry and treatment response of type II achalasia  
*Huang CZ, Huang ZW, Liang HM, Wang ZJ, Guo TT, Chen YP*
- 736 Effectiveness of surgical resection for complicated liver cancer and its influencing factors: A retrospective study  
*Yu J, Wu ZZ, Li T, Xu Y, Zhao YC, Zhang BL, Tian H*

**Observational Study**

- 743** Effectiveness of a microabrasion technique using 16% HCL with manual application on fluorotic teeth: A series of studies  
*Nevárez-Rascón M, Molina-Frechero N, Edith Adame, Almeida E, Soto-Barreras U, Gaona E, Nevárez-Rascón A*
- 757** Prevalence and associated factors of suicide among hospitalized schizophrenic patients  
*Woottituk P, Maneeton B, Jaiyen N, Khemawichanurat W, Kawilapat S, Maneeton N*

**SYSTEMATIC REVIEW**

- 771** Lymphoepithelioma-like carcinoma of the upper urinary tract: A systematic review of case reports  
*Lai SC, Seery S, Zhang W, Liu M, Zhang G, Wang JY*

**CASE REPORT**

- 782** Extrapleural solitary fibrous tumor of the thyroid gland: A case report and review of literature  
*Suh YJ, Park JH, Jeon JH, Bilegsaikhan SE*
- 790** Must pilots permanently quit flying career after treatment for colorectal cancer? - Medical waiver for Air Force pilots with colorectal cancer: Three case reports  
*Gu GL, Duan FX, Zhang Z, Wei XM, Cui L, Zhang B*
- 798** Mesenteric phleboscrosis with amyloidosis in association with the long-term use of medicinal liquor: A case report  
*Hu YB, Hu ML, Ding J, Wang QY, Yang XY*
- 806** Using Materialise's interactive medical image control system to reconstruct a model of a patient with rectal cancer and situs inversus totalis: A case report  
*Chen T, Que YT, Zhang YH, Long FY, Li Y, Huang X, Wang YN, Hu YF, Yu J, Li GX*
- 815** Delayed right coronary ostial obstruction after J-valve deployment in transcatheter aortic valve implantation: A case report  
*Xu Z, Yu H, Liang P*
- 820** Diverticulum of the buccal mucosa: A case report  
*Zhang Y, Wang L, Liu K*
- 825** Borderline form of empty follicle syndrome treated with a novel dual trigger method combined with delayed oocyte retrieval: A case report  
*Cao XL, Sun ZG*
- 831** Ligament augmentation reconstruction system artificial ligaments in patellar tendon reconstruction - a chronic patellar tendon rupture after multiple operations: A case report  
*Yang F, Wang GD, Huang R, Ma H, Zhao XW*

- 838** Thyroid metastasis from breast cancer presenting with enlarged lateral cervical lymph nodes: A case report  
*Zhang YY, Xue S, Wang ZM, Jin MS, Chen ZP, Chen G, Zhang Q*
- 848** Rescue treatment and follow-up intervention of a left main acute myocardial infarction with typical carina shift under 3D optical coherence tomography: A case report  
*Du BB, Tong YL, Wang XT, Liu GH, Liu K, Yang P, He YQ*

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## Case Control Study

# Risk factors for postoperative sepsis in patients with gastrointestinal perforation

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## Abstract

### BACKGROUND

Sepsis is fatal in patients with gastrointestinal perforation (GIP). However, few studies have focused on this issue.

### AIM

To investigate the risk factors for postoperative sepsis in patients with GIP.

### METHODS

This was a retrospective study performed at the Department of General Surgery in our treatment center. From January 2016 to December 2018, the medical records of patients with GIP who underwent emergency surgery were reviewed. Patients younger than 17 years or who did not undergo surgical treatment were excluded. The patients were divided into the postoperative sepsis group and the non-postoperative sepsis group. Clinical data for both groups were collected and compared, and the risk factors for postoperative sepsis were investigated. The institutional ethical committee of our hospital approved the study.

### RESULTS

Two hundred twenty-six patients were admitted to our department with GIP. Fourteen patients were excluded: Four were under 17 years old, and 10 did not undergo emergency surgery due to high surgical risk and/or disagreement with the patients and their family members. Two hundred twelve patients were finally enrolled in the study; 161 were men, and 51 were women. The average age was  $62.98 \pm 15.65$  years. Postoperative sepsis occurred in 48 cases. The prevalence of postoperative sepsis was 22.6% [95% confidence interval (CI): 17.0%-28.3%]. Twenty-eight patients (13.21%) died after emergency surgery. Multiple logistic regression analysis confirmed that the time interval from abdominal pain to emergency surgery [odds ratio (OR) = 1.021, 95%CI: 1.005-1.038,  $P = 0.006$ ], colonic perforation (OR = 2.761, CI: 1.821-14.776,  $P = 0.007$ ), perforation diameter (OR = 1.062, 95%CI: 1.007-1.121,  $P = 0.027$ ), and incidence of malignant tumor-

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related perforation (OR = 5.384, 95%CI: 1.762-32.844,  $P = 0.021$ ) were associated with postoperative sepsis.

## CONCLUSION

The time interval from abdominal pain to surgery, colonic perforation, diameter of perforation, and the incidence of malignant tumor-related perforation were risk factors for postoperative sepsis in patients with GIP.

**Key words:** Risk factor; Sepsis; Gastrointestinal perforation; Prevalence; Postoperative period

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**Core tip:** Postoperative sepsis is fatal in patients with gastrointestinal perforation (GIP). The definition of sepsis was revised in 2016. Few studies have focused on the risk factors for postoperative sepsis (revision 2016). In this study, the medical records of patients with GIP who underwent emergency surgery from January 2016 to December 2018 were reviewed. It was found that the time interval from abdominal pain to emergency surgery, colonic perforation, diameter of perforation, and the incidence of malignant tumor-related perforation were risk factors for postoperative sepsis in patients with GIP.

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## INTRODUCTION

Gastrointestinal perforation (GIP) is a common acute abdominal injury. It usually requires active rescue in the intensive care unit with an emergency laparotomy<sup>[1]</sup>. The risk factors for GIP vary and include older age, diabetes, antecedent diverticulitis, glucocorticoid therapy, and use of nonsteroidal anti-inflammatory drugs<sup>[2-4]</sup>. GIP is an indication for emergency surgery. Laparotomy and laparoscopic surgery are the most effective and important treatment methods<sup>[5,6]</sup> despite reports regarding therapeutic endoscopy and conservative treatment for GIP<sup>[7-9]</sup>.

Previous studies have shown that GIP is the most common cause of sepsis in the intensive care unit<sup>[10,11]</sup>. Wickel *et al*<sup>[12]</sup> reported that the incidence of postoperative sepsis was > 70% in patients with GIP, thus leading to severe peritonitis. Despite advances in intensive care and antibiotic treatment, the hospital mortality rate due to abdominal sepsis remains high, and the mortality due to a postoperative septic abdomen in patients with GIP can reach 50%<sup>[12-16]</sup>. The definition of sepsis was revised in 2016 (sepsis 3.0) to better reflect the prognosis and organ function damage rather than being defined as infection-induced systemic inflammatory response syndrome<sup>[17]</sup>. Once sepsis occurs, the prognosis worsens, and few studies have focused on the risk factors for postoperative sepsis in patients with GIP. The present study was conducted to investigate these risk factors.

## MATERIALS AND METHODS

### Study design

This was a retrospective study performed at the Department of General Surgery in our treatment center. From January 2016 to December 2018, the medical records of patients with GIP who underwent emergency surgery were reviewed. Patients younger than 17 years or who did not undergo surgical treatment were excluded. Patients were divided into the postoperative sepsis group and the non-postoperative sepsis group. Clinical data for both groups were collected and compared, and the risk factors for postoperative sepsis were investigated. The institutional ethical committee of our hospital approved the study (No. 2019110). All study participants provided informed written consent during treatment. The statistical methods used in this study



were reviewed by Doctor Ren from Henan University.

### Data collection

Following admission, each patient underwent routine blood and biochemical tests. A computed tomography scan was also performed for a detailed diagnosis. After GIP was diagnosed, emergency surgery (either laparotomy or laparoscopic surgery) was performed. All patients received third-generation cephalosporins to treat the infection after admission. Data for each patient, including demographic characteristics (*e.g.*, age, sex, and body mass index), laboratory examination results at admission, perforation location, etiology (*i.e.*, trauma, malignant tumor, or benign ulcer), time interval from abdominal pain to surgery, perforation diameter, surgical procedure, and whether postoperative sepsis occurred were collected. In the present study, sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction was represented by an increase of  $\geq 2$  points on the Sepsis-related Organ Failure Assessment score<sup>[17]</sup>. Sepsis was evaluated daily after surgery, until the patients were discharged.

### Statistical analysis

All statistical analyses were performed using the SPSS, version 20.0 for Windows (IBM, Analytics, Armonk, NY, United States). A Kolmogorov-Smirnov test was performed to determine whether continuous variables conformed to a normal distribution, and then the Student's *t*-test (for normally distributed data) or the Mann-Whitney U test (for data that were not normally distributed) were performed. Fisher's exact test was used to compare categorical variables. Multiple logistic regression analysis was performed to evaluate the risk factors for GIP. Odds ratios (ORs) are expressed with 95% confidence intervals (CIs). Kaplan-Meier estimates followed by a log-rank test were used to evaluate the prognoses between different groups. *P* values  $< 0.05$  were considered statistically significant.

## RESULTS

### Population and prevalence of postoperative sepsis

Two hundred twenty-six patients were admitted to our department due to GIP. Fourteen patients were excluded: Four were under 17 years old, and 10 did not undergo emergency surgery because of high surgical risk and/or disagreement with the patients and their family members. Two hundred twelve patients were finally enrolled in the study; 161 were men, and 51 were women. The average age was  $62.98 \pm 15.65$  years. Postoperative sepsis occurred in 48 cases. The prevalence of postoperative sepsis was 22.6% (95% CI: 17.0%-28.3%). Twenty-eight patients (13.21%) died after emergency surgery. Table 1 shows the characteristics of the 212 patients.

### Emergency surgical procedures

Table 2 shows the emergency surgical procedures. Of the 212 enrolled patients, 169 underwent perforation repair: Seventy one of those underwent laparoscopic gastrointestinal repair, and 98 underwent standard surgical repair. Of the remaining 43 patients, 11 underwent repair + ostomy (colonic repair + enterostomy), 6 underwent resection and anastomosis, 12 underwent resection + ostomy, and 14 underwent subtotal gastrectomy + gastrojejunostomy due to gastric malignant perforation.

### Risk factors for postoperative sepsis in patients with GIP

Patients were divided into either the postoperative sepsis group ( $n = 48$ ) or the non-postoperative sepsis group ( $n = 164$ ). Following univariate analysis (Table 1), 16 factors differed between the two groups: Age, temperature, heart rate, mean arterial pressure, ascites incidence, serum creatinine, white blood cell counts, C-reactive protein, colonic perforation, gastric perforation, time interval from abdominal pain to emergency surgery, preoperative American Society of Anesthesiologists score, incidence of malignant tumor-related perforation, perforation diameter, perforation repair, and digestive tract reconstruction.

Multiple logistic regression analysis confirmed that the time interval from abdominal pain to emergency surgery (OR = 1.021, 95% CI: 1.005-1.038,  $P = 0.006$ ), colonic perforation (OR = 2.761, CI: 1.821-14.776,  $P = 0.007$ ), perforation diameter (OR = 1.062, 95% CI: 1.007-1.121,  $P = 0.027$ ), and incidence of malignant tumor-related perforation (OR = 5.384, 95% CI: 1.762-32.844,  $P = 0.021$ ) were associated with postoperative sepsis (Table 3).



**Table 1** The characteristics of the 212 patients with gastrointestinal perforation and univariate analysis for postoperative sepsis

Clinical variables	Enrolled patients (n = 212)	Univariate analysis		
		Postoperative sepsis group (n = 48)	Non-postoperative sepsis group (n = 164)	P value
Age, (yr; mean $\pm$ SD)	62.98 $\pm$ 15.65	72.58 $\pm$ 14.89	60.17 $\pm$ 14.77	< 0.001
Female, n (%)	51 (24.06)	16 (33.33)	35 (21.34)	0.123
BMI (kg/m <sup>2</sup> ; mean $\pm$ SD)	22.40 $\pm$ 2.95	22.10 $\pm$ 2.67	22.48 $\pm$ 3.02	0.441
Temperature [°C, mean (IQR)]	36.75 (36.50-37.00)	36.80 (36.63-38.80)	36.65 (36.50-37.00)	0.001
Heart rate [beats/min, mean (IQR)]	80 (77-88)	87 (80-99)	80 (78-84)	< 0.001
Mean arterial pressure (mmHg; mean $\pm$ SD)	90.75 $\pm$ 13.80	84.97 $\pm$ 12.11	92.45 $\pm$ 13.84	0.001
Breathing rate [times/min, mean (IQR)]	20 (19-21)	20 (20-22)	20 (10-21)	0.12
Hemoglobin (g/L, mean $\pm$ SD)	135.33 $\pm$ 19.85	130.73 $\pm$ 19.32	136.67 $\pm$ 19.86	0.068
Serum creatinine ( $\mu$ mol/L, mean $\pm$ SD)	84.38 $\pm$ 49.89	106.38 $\pm$ 79.37	77.94 $\pm$ 40.12	< 0.001
Total bilirubin ( $\mu$ mol/L, mean $\pm$ SD)	15.99 $\pm$ 12.36	13.75 $\pm$ 6.48	16.65 $\pm$ 13.56	0.152
White blood cells ( $\times 10^9$ /L) [mean (IQR)]	10.74 (7.20-15.00)	7.50 (4.48-13.21)	11.42 (7.83-15.20)	0.003
C-reactive protein (mg/L, mean $\pm$ SD)	128.67 $\pm$ 77.42	157.08 $\pm$ 77.26	120.35 $\pm$ 75.70	0.004
Preoperative ASA score [mean (IQR)]	2 (1-3)	3 (2-4)	2 (1-2)	< 0.001
Ascites, n (%)	156 (73.58)	48 (100)	108 (65.85)	< 0.001
Diameter of perforation, (mm, mean $\pm$ SD)	12.69 $\pm$ 10.63	15.93 $\pm$ 10.11	11.75 $\pm$ 10.61	0.015
Time interval from abdominal pain to emergency surgery (h, mean $\pm$ SD)	23.49 $\pm$ 35.63	42.21 $\pm$ 44.62	18.01 $\pm$ 30.59	0.001
Operation duration, [h, mean (IQR)]	2 (1.5-2.5)	2 (15-3)	2 (1.3-2)	0.061
Anatomy of GIP, n (%)				
Stomach	118 (55.66)	12 (25)	106 (64.63)	0.001
Duodenum	33 (15.57)	10 (20.83)	23 (14.02)	0.262
Jejunum/Ileum	19 (8.96)	6 (12.5)	13 (7.93)	0.388
Colon	42 (19.81)	16 (33.33)	26 (20.12)	0.008
Etiology, n (%)				
Trauma	80 (37.74)	18 (37.5)	62 (37.80)	1.000
Malignant tumor	30 (14.15)	14 (29.17)	16 (9.76)	0.002
Benign ulcer	102 (48.11)	16 (33.33)	86 (52.44)	0.220
Surgical procedure, n (%)				
Repair	169 (79.71)	30 (62.5)	139 (84.76)	0.002
Repair + Ostomy <sup>1</sup>	11 (5.19)	3 (6.25)	8 (4.88)	0.751
Resection and anastomosis <sup>2</sup>	6 (2.83)	2 (4.17)	4 (2.44)	0.623
Resection + ostomy <sup>3</sup>	12 (5.66)	4 (8.33)	8 (4.88)	0.451
Digestive tract reconstruction <sup>4</sup>	14 (6.60)	9 (18.75)	5 (3.05)	0.001
Laparoscopic surgery, n (%)	71 (33.50)	19 (39.58)	52 (31.71)	0.385
Co-morbidities, n (%)				
Hypertension	33 (15.57)	6 (12.5)	27 (16.46)	0.652
Diabetes mellitus	19 (8.96)	7 (14.58)	12 (7.32)	0.149
Coronary disease	27 (12.74)	6 (12.5)	21 (12.81)	1.000
Sepsis, n (%)	48 (23.11)	N/A	N/A	N/A

<sup>1</sup>Eleven patients received a repair + ostomy (colon repair + enterostomy), due to trauma-related colonic perforation.

<sup>2</sup>Two patients with a jejunal/ileal perforation, and 4 with a gastric tumor received tumor resection.

<sup>3</sup>Twelve patients with a colonic malignant perforation received resection + ostomy (9 patients with partial colectomy + colostomy, 3 patients with colectomy and anastomosis + enterostomy).

<sup>4</sup>Fourteen patients received a subtotal gastrectomy + gastrojejunostomy, due to gastric cancer. ASA score: American Society of Anesthesiologists score; BMI: Body mass index; GIP: Gastrointestinal perforation; SD: Standard deviation; IQR: Interquartile range.  $P < 0.001$ , *vs* the non-postoperative sepsis group.

### Prognosis of patients with postoperative sepsis

The time interval from emergency surgery to sepsis was 1 d (range, 1-2 d). Twenty-four patients (50%) died in the postoperative sepsis group, whereas only 4 died (2.44%) in the non-postoperative sepsis group (Table 4). Mortality was higher in the postoperative sepsis group than in the non-postoperative sepsis group (Figure 1;  $P < 0.001$ ). Length of stay in survivors was longer in the postoperative sepsis group than in the non-postoperative sepsis group ( $20.96 \pm 4.97$  d *vs*  $11.69 \pm 2.8$  d;  $P < 0.001$ ).

## DISCUSSION

GIP is a common but fatal acute abdominal injury. The primary method for treating GIP is emergency surgery<sup>[8,9]</sup>. Prior studies showed that the incidence of sepsis due to GIP reached 20%-73%<sup>[12,14-16]</sup>, and mortality due to GIP-induced sepsis was 30%-50%<sup>[12,14-16]</sup>. In the present study, the incidence of sepsis was 22.6%, and the mortality due to sepsis was 50%. Although a new definition of sepsis has been introduced, mortality was not significantly increased, possibly because of the differences between participants in our study and those in previous studies.

The present study included 161 men and 51 women with GIP, with a male/female ratio of approximately 3:1. The male/female ratio was also high in other studies of GIP<sup>[16,18]</sup>. Recent research on peptic ulcer perforation found an even higher male/female ratio of 10:1<sup>[14]</sup>. Sivaram *et al*<sup>[14]</sup> found that being female was a risk factor for mortality in patients with peptic ulcer perforations. However, Sivaram's research was focused on upper gastrointestinal ulcer perforations. Our study included jejunal/ileal and colonic perforations as well as trauma and tumor-related perforations; this may have caused the difference in the male/female ratio.

In our study, colonic perforation was associated with postoperative sepsis. The colon contains more bacteria; thus, these patients will absorb more toxins<sup>[19,20]</sup>, resulting in a higher risk for postoperative complications, which has been demonstrated in many studies. The time interval from abdominal pain to emergency surgery was a risk factor for postoperative sepsis in our study. A longer interval may have caused more intestinal fluid to spill and be absorbed into the blood, possibly leading to postoperative sepsis. The occurrence of sepsis would lead to high mortality<sup>[14,15]</sup>. Some studies found that a delay of more than 24 h is associated with mortality and morbidity due to GIP<sup>[15,21]</sup>, thus illustrating the importance of the time interval from abdominal pain to emergency surgery. Perforation diameter is also associated with prognosis. Sivaram *et al*<sup>[14]</sup> revealed that perforation diameters  $> 1.0$  cm led to poor outcomes. Taş *et al*<sup>[21]</sup> reported that patients with perforation diameters  $> 0.5$  cm were at high risk for postoperative morbidity. Our research showed that the perforation diameter may be associated with postoperative sepsis, which was consistent with previous studies.

The present study also revealed that malignant tumor-related perforations may be associated with postoperative sepsis. The edges of malignant gastrointestinal ulcers are more irregular or asymmetric; folds appear more disrupted and "moth-eaten" near the crater edge and/or are clubbed or fused and more crisp or tough than benign ulcers<sup>[22]</sup>. Consequently, malignant tumor-related perforations are more difficult to treat than benign ulcer-related perforations<sup>[22]</sup>. In our study, 30 patients had malignancy-related perforations. The operation duration was longer for patients with malignancy-related tumor perforations (3 h<sup>[3,4]</sup> *vs* 2 h<sup>[1,2]</sup>;  $P < 0.001$ ). In addition, no patients with malignant tumor-related perforations underwent repair procedures. The surgical procedures included digestive tract reconstruction (gastrectomy + gastrojejunostomy,  $n = 14$ ), gastrectomy ( $n = 4$  patients with malignant gastric tumors), and resection + ostomy ( $n = 12$  patients, 9 with a partial colectomy + colostomy and 3 with a partial colectomy and anastomosis + enterostomy). Studies of damage control<sup>[23]</sup> have shown that complex surgical procedures can lead to poor prognoses. In summary, patients with malignant tumor-related perforations are more likely to experience postoperative sepsis with higher mortality rates.

Our study had some limitations. First, because the study was retrospective, some selection bias existed. Second, procalcitonin was not analyzed, which might be

**Table 2** Emergency surgical procedures

Emergency surgical procedure	Location of the perforation	n (%)
Laparoscopic surgery		
Laparoscopic gastric repair	Stomach <sup>1</sup>	52 (24.52)
Laparoscopic duodenal repair	Duodenum	10 (4.72)
Laparoscopic jejunal/ileal repair	Jejunum/Ileum	9 (4.25)
Open abdominal surgery		
Repair		
Gastric repair	Stomach <sup>1</sup>	48 (22.64)
Duodenal repair	Duodenum	23 (10.85)
Jejunal/ileal repair	Jejunum/Ileum	8 (3.77)
Colonic repair	Colon <sup>2</sup>	19 (8.96)
Repair + ostomy		
Colonic repair + enterostomy	Colon <sup>2</sup>	11 (5.019)
Resection and anastomosis		
Partial gastrectomy	Stomach <sup>3</sup>	4 (1.87)
Jejunal/ileal resection and anastomosis	Jejunum/Ileum	2(0.94)
Resection + ostomy		
Partial colectomy + colostomy	Colon <sup>4</sup>	9 (4.24)
Partial colectomy and anastomosis + enterostomy	Colon <sup>4</sup>	3 (1.42)
Digestive tract reconstruction		
Subtotal gastrectomy + gastrojejunostomy	Stomach <sup>3</sup>	14 (6.60)

<sup>1</sup>Non-tumor-related gastric perforation.<sup>2</sup>Non-tumor-related colonic perforation.<sup>3</sup>Malignant tumor-related gastric perforation.<sup>4</sup>Malignant tumor-related colonic perforation.

regarded as an infection index. Third, the number of patients in the group with postoperative sepsis was very different from that in the non-postoperative sepsis group. In addition, the causes of the perforation would partially influence the surgical procedure, which may make some factors less prominent. Subgroup studies should be performed in the future.

In conclusion, the time interval from abdominal pain to emergency surgery, colonic perforation, perforation diameter, and malignant tumor-related perforation incidence were risk factors for postoperative sepsis in patients with GIP.

**Table 3 Risk factors for postoperative sepsis in patients with gastrointestinal perforation**

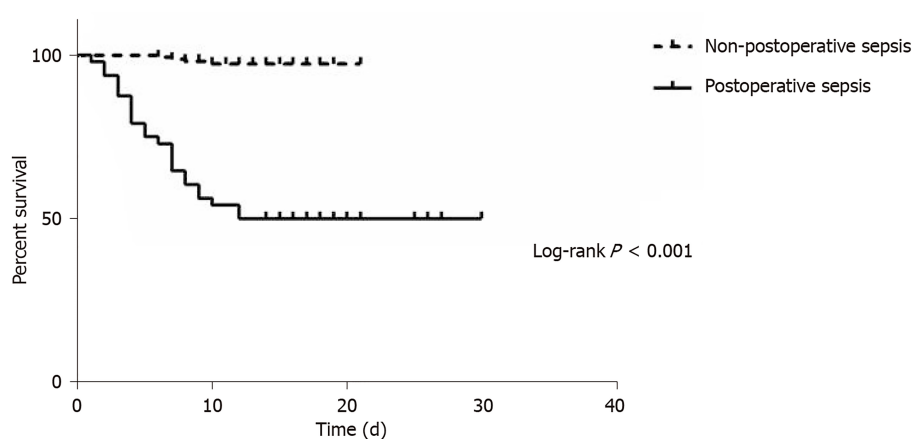
Clinical variables	OR	95%CI	P value
Age	1.019	0.966-1.042	0.234
Temperature	2.160	0.998-4.147	0.053
Heart rate	1.047	0.996-1.104	0.071
Mean arterial pressure	0.946	0.349-1.108	0.171
Serum creatinine	0.997	0.987-1.006	0.527
White blood cells	1.037	0.938-1.147	0.479
C-reactive protein	1.006	0.997-1.014	0.245
Ascites	1.316	0.102-14.982	0.996
Diameter of perforation	1.062	1.007-1.121	0.027
Gastric perforation	0.897	0.854-1.175	0.089
Colonic perforation	2.761	1.821-14.776	0.007
Preoperative ASA score	1.273	0.637-2.542	0.494
Time interval from abdominal pain to emergency surgery	1.021	1.055-1.038	0.006
Repair of perforation	0.961	0.247-3.739	0.954
Digestive tract reconstruction <sup>1</sup>	6.460	0.907-46.007	0.063
Malignant tumor-related perforation	5.384	1.762-32.844	0.021

<sup>1</sup>Subtotal gastrectomy + gastrojejunostomy. ASA score: American Society of Anesthesiologists score; GIP: Gastrointestinal perforation; OR: Odds ratio; CI: Confidence interval.

**Table 4 Prognosis of patients**

Clinical variables	Postoperative sepsis group	Non-postoperative sepsis group	P value
Death, <i>n</i> (%)	24 (50)	4 (2.44)	< 0.001
Septic shock	22 (45.83)	0 (0)	< 0.001
Pulmonary embolism	0 (0)	3 (1.83)	1.000
Heart failure	2 (4.17%)	1 (0.610%)	0.129
LOS of survivors (mean ± SD, d)	20.96 ± 4.97	11.69 ± 2.8	< 0.001

LOS: Length of stay. *P* < 0.001, *vs* the non-postoperative sepsis group.



**Figure 1 Kaplan-Meier estimates of survival between the postoperative sepsis group and the non-postoperative sepsis group.** <sup>c</sup>*P* < 0.001 *vs* the non-postoperative sepsis group.

## ARTICLE HIGHLIGHTS

### Research background

Gastrointestinal perforation (GIP) is a common acute abdominal injury. It usually requires active

rescue in the intensive care unit with an emergency laparotomy. The definition of sepsis was revised in 2016 (sepsis 3.0) to better reflect the prognosis and organ function damage rather than being defined as infection-induced systemic inflammatory response syndrome. Once sepsis occurs, the prognosis worsens, and few studies have focused on the risk factors for postoperative sepsis in patients with GIP.

### Research motivation

In 2016, the definition of sepsis was revised. According to the revision, patients with postoperative sepsis would be at a higher risk for death. As a result, we thought an investigation of the risk factors for postoperative sepsis was very necessary.

### Research objectives

This study aimed to investigate the risk factors for postoperative sepsis in patients with GIP.

### Research methods

From January 2016 to December 2018, the medical records of patients with GIP, receiving emergency surgery, were retrospectively reviewed and analyzed. Risk factors for postoperative sepsis in patients with GIP were evaluated.

### Research results

A total of 212 patients were eligible. The prevalence of postoperative sepsis was 22.6% [95% confidence interval (CI): 17.0%-28.3%,  $n = 48$ ]. The time interval from abdominal pain to emergency surgery [odds ratio (OR) = 1.021, 95% CI: 1.005-1.038,  $P = 0.006$ ], colonic perforation (OR = 2.761, CI: 1.821-14.776,  $P = 0.007$ ), diameter of perforation (OR = 1.062, 95% CI: 1.007-1.121,  $P = 0.027$ ), and the incidence of malignant tumor-related perforation (OR = 5.384, 95% CI: 1.762-32.844,  $P = 0.021$ ) were associated with postoperative sepsis.

### Research conclusions

The time interval from abdominal pain to emergency surgery, colonic perforation, diameter of perforation, and the incidence of malignant tumor-related perforation were risk factors for postoperative sepsis in patients with GIP.

### Research perspectives

A further study plans to include more subjects and the development of a prediction model for postoperative sepsis, in order to identify a truly accurate diagnostic method suitable for clinical use.

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