Analysis of risk factors for perioperative mortality in adults with small bowel perforation:a case controlled study

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Abstract

Background: Convincing evidence on the risk factors for perioperative death of small bowel perforation is lacking. This study aimed to investigate the etiologies of small bowel perforation and risk factors for perioperative mortality.

Methods: Consecutive patients with small bowel perforation confirmed by emergency surgery at Zhongshan Hospital, Fudan University from January 2015 to December 2019 were analyzed retrospectively.

Results: Of the 85 patients included in this study, ingestion of foreign bodies (19, 22.4%), lymphoma (17, 20.0%) and metastatic cancer (13, 15.3%) were the most common causes for small bowel perforation. Of them, 23 patients underwent perforation repair, 46 underwent segmental resection with primary anastomosis, and the other 16 underwent small-bowel ostomy. The operation time was the shortest for the perforation repair procedure ($P < 0.001$), and the hospital stay was the longest for patients undergoing ostomy ($P = 0.010$). Altogether 11 patients died postoperatively with a perioperative mortality rate of 12.9%. Serum procalcitonin ($P = 0.037$), blood lactate ($P < 0.001$) and APACHE II score ($P = 0.0032$) were higher in the dead than those in survivors.

Conclusions: Foreign body ingestion, lymphoma and metastatic neoplasm were the most common causes for small bowel perforation. Serum precalcitonin, blood lactate and APACHE II score seem to be risk factors of perioperative mortality.

†These authors contributed equally to this work

Background

Gastrointestinal (GI) perforation is a common surgical emergency and usually requires urgent operation. With the ligament of Treitz as an anatomical landmark, the digestive tract is divided into the upper and lower portions. The main etiologies of upper GI perforation are peptic ulcers and gastric malignant tumors. The clinical manifestations are obvious with signs of peritonitis. Compared with upper GI perforation, causes for the lower GI perforation are more complex. As peritoneal irritation in the lower abdominal and pelvic cavities is relatively weak, the clinical manifestations of lower GI tract perforation are often atypical, making early diagnosis and treatment more difficult, while severe or even life-threatening infections are more likely to occur because of the higher content of bacteria and toxins in the lower digestive tract.

There have been many reports about colonic perforation. The most common causes for colonic perforation include diverticulum, malignant tumors and iatrogenic injuries, causing a perioperative mortality rate of 11–30%[1–5]. Given the different spectrum of diseases between the small and large bowels, the etiologies of perforation and perioperative mortalities are not all the same. Although small

bowel perforation is more commonly reported in individual case reports, there is a lack of convincing evidence reported in clinical studies with a large cohort of patients.

In this article, we retrospectively analyzed small bowel perforation cases treated in our center from January 2015 to December 2019 with the aim to provide more evidence-based clues for the clinical diagnosis and management of this disease.

Methods

A total of 85 consecutive GI perforation cases admitted in Zhongshan Hospital, Fudan University (Shanghai, China) from January 1, 2015 to December 31, 2019 were retrospectively analyzed. Clinical features, surgical procedures and pathological findings were reviewed based on the medical records. The eligible criteria were: (1) patients who underwent urgent surgery with GI perforation precisely identified during operation; and (2) patients whose perforation site was located in the small intestine below the ligament of Treitz (i.e. jejunum and ileum). Patients with anastomotic leakage after gastrointestinal surgery and with perforation in the appendix due to acute inflammation were excluded from the study.

The etiologies of perforation were determined by clinical, surgical and pathological findings. Risk variables included general, pathological, surgical and laboratory factors. To accurately reflect the preoperative conditions of the patients, preoperative laboratory data including white blood cell (WBC) count, the neutrophil ratio and procalcitonin (PCT) level were collected from the most recent blood tests before surgery. Postoperative data including arterial blood lactate (LAC) and APACHE II score were obtained immediately after surgery to minimize the impact of treatment on the results.

Observational parameters were perioperative mortality and related risk factors. Perioperative mortality was defined as death after a single admission or within 30 days of surgery. The patients were divided into survival group and non-survival group according to their treatment outcomes, and risk factors related to perioperative mortality were compared and analyzed between the two groups.

Statistical analysis was performed using SPSS 20.0. The t-test and ANOVA were used for quantitative data, and the chi-square test or Fisher exact test was used for classified data. The α level was set at 0.05 for statistical significance.

Results

Etiologies of perforation

Of the 85 patients included in this study, 55 were male and 30 were female (1.83:1) with a mean age of 62.3 ± 16.0 years. Eighty-three (97.6%) of them had a precise diagnosis and the etiologies of perforation were ranked by the number of cases in Fig. 1. The most common causes for small bowel perforation were foreign body ingestion in 19 cases, lymphoma in 17 cases and metastatic tumors in 13 cases.

In the 19 cases of foreign body ingestion causing perforation, 12 cases were caused by jujube nuclei (Fig. 2), 5 cases by fish and chicken bones, and the other two cases by sharp metal objects. Most of the 17 lymphoma perforation cases were aggressive histopathologic types, including 8 cases of B-cell type and 9 cases of T-cell lymphoma (Table 1). Ki-67 was highly expressed in most of these perforated lymphoma cases, suggesting that they had a high proliferation index (Fig. 3). Among the 13 perforation cases from metastasis, 5 were secondary to lung cancer as the primary tumor site, 4 to colorectal cancer, 2 to pancreatic cancer and 1 to gallbladder cancer. The remaining one was related to the uterus. Totally, 34 (40%) of the 85 patients enrolled in present study presented with malignancies, including one with primary carcinomas, 13 with metastatic lesions, 17 with lymphoma, one with stromal tumor, and 2 with bowel obstruction secondary to ileocecal cancer.

Table 1
Histopathologic distribution of lymphoma with perforation

Histopathologic types	**Number (%)**
B-cell type	**8 (47.1%)**
MALT lymphoma	1 (5.88%)
Follicular, grade 1	1 (5.88%)
Diffuse large B-cell	6 (35.3%)
T-cell type	**9 (52.9%)**
Peripheral T-cell	4 (23.5%)
MEITL	4 (23.5%)
EBV + T-cell	1 (5.88%)

MALT lymphoma: Mucosa-associated lymphoid tissue lymphoma; **MEITL**: Monomorphic epitheliotropic intestinal T-cell lyphomas; **EBV**: Epstein-Barr virus

Surgical Outcomes

Of the 85 included patients, 23 underwent perforation repair, including repair of the bowel wall defect after wedge resection of the diverticulum with perforation; 46 underwent segmental bowel resection with primary anastomosis; and 16 underwent small intestine ostomy. The mean operation time was 134 ± 56.1 minutes and the mean hospital stay was 13.5 ± 9.30 days. The operation time for perforation repair was significantly shorter than the other procedures, and the duration of postoperative hospitalization was the longest in those who underwent small intestine ostomy (Table 2). Fifty-two patients were transferred to the intensive care unit (ICU) immediately after surgery, of whom 10 (21.2%) patients died due to the subsequent complications of perforation and multiple organ failure, with a median survival time of 12.5 (range: 3–39) days after surgery. Among the 33 patients who returned to the ward after surgery, only one

death (3.03%) occurred. Totally, 11 patients died postoperatively with a perioperative mortality rate of 12.9%.

Table 2
Comparison of different surgical procedures for small bowel perforation

	Repair	Anastomosis	Ostomy	*P*-value
Operation time (min)	86.2 ± 43.7	142.7 ± 45.6	174.1 ± 56.2	< 0.001
*Hospitalization (day)	10.5 ± 8.30	13.0 ± 6.88	19.4 ± 14.1	0.010
*Duration of hospitalization after surgery				

Risk Factors For Perioperative Mortality

Lymphoma was the most common cause of death (5/11, 45.5%). Other causes were intestinal obstruction (3/11, 27.3%), metastatic tumor (2/11, 18.2%) and primary carcinoma (1/11, 9.09%). Totally, 81.8% (9/11) of the motality were caused by malignant diseases. Although foreign bodies ingestion was the most common cause of perforation, no deaths occurred. The etiologies of mortality were shown in Fig. 4.

Considering that the clinical data of the patients transferred to the ICU were more accurate and homogeneous, we only included patients transferred to the ICU for analysis of death-related factors. The results showed that compared with the 42 surviving patients, the 10 non-survival cases had a significantly higher preoperative PCT level (38.1 ± 35 vs. 16.2 ± 26.3, $P = 0.037$). The postoperative arterial blood lactate level and APACHE II score in non-survival cases were also higher than those in the survivors (4.58 ± 4.17 *vs*. 1.91 ± 0.87, $P < 0.001$; 24.5 ± 11.5 *vs*. 14.4 ± 8.41, $P = 0.0032$). However, there was no significant difference in WBC count and neutrophil percentage between survival and non-survival cases (Table 3).

Table 3
Risk factors of perioperative mortality in patients with small bowel perforation

Factors	Survival group (n = 42)	Non-survival group (n = 10)	*P*-Value
Gender (Male/ Female)	27/15	8/2	0.56
Age(year)	67.8 ± 12.9	67.1 ± 14.8	0.89
Opration time(min)	142.3 ± 52.4	144.7 ± 54.86	0.93
Malignant diesase	19	8	0.048*
PCT (ng/L)	16.2 ± 26.3	38.1 ± 35.9	0.037*
Blood LAC (mmol/L)	1.91 ± 0.87	4.58 ± 4.17	< 0.001*
WBC count (< 4/>12)*10^9/L	19	5	1.00
Neutrophil ratio > 90%	17	6	0.45
APACHE II score	14.4 ± 8.41	24.5 ± 11.5	0.0032*

Discussion

Various etiologies of small bowel perforation seem to be geographically and economically related. For instance, foreign body ingestion, intestinal ischemia, diverticulum and Crohn disease are reported to be the leading causes of small bowel perforation in Western countries[6], while small bowel perforation in developing countries are mainly related to infectious diseases such as typhoid and tuberculosis[7]. However, data from this study suggest that there is a wide spectrum of etiologies responsible for small bowel perforation. In our study, foreign body ingestion, lymphoma and metastatic neoplasm were found to be the most common causes for small boewl perforation. The most common foreign body causing perforation was the jujube nucleus (12/19, 63.2%), which seems to be closely related to the Chinese eating habits. No perforation secondary to typhoid fever was discovered in this study. Only one case of perforation was found to be related to tuberculosis, which is usually the most common cause in most developing countries. The possible reason is that the patients admitted in our center were from the economically developed areas in eastern China and therefore the spectrum of etiologies responsible for small bowel perforation are more similar to those in developed countries.

Although lymphoma only accounts for 17% of all primary tumors in the small bowel, it is the most common type that caused perforation in our series. It was reported that perforation was the most common complication in lymphoma cases with a proportion exceeding 25%[8].. Most lymphomas originating from the small bowel are B-cell type, and only 10–25% are T-cell type with a poorer prognosis. However, the present study showed that the number of small bowel perforation cases from lymphoma is similar in B-cell type (n = 8) and T-cell type (n = 9). Besides, perforation was more likely to occur in

aggressive lymphoma cases (n = 15) as compared with the indolent type (n = 2, one with MALT lymphoma and the other with follicular lymphoma) (Table 1).

Metastatic tumors are more common than primary malignant tumors in the small bowel, and the primary sites of these metastatic tumors are thought of as being mostly from other organs in the abdominal cavity. However, our study demonstrated that the lung was the most common primary site of metastatic tumors causing small bowel perforation. Some researchers suspected that the perforation might be be related to the target therapy for lung cancer. In this study, three of the five metastatic cases secondary to lung cancer developed perforation just after target therapy, including two with bevacizumab and one with afatinib. These target drugs could inhibit angiogenesis of the tumor, subsequently leading to tumor necrosis. They also could regulate the signaling pathways of tumor cells and then cause their apoptosis. These effects would make the lesions prone to perforation. Recently, target therapy has also been reported to cause bowel perforation in metastatic lesions from different primary sites[9, 10].

The overall perioperative mortality rate of small bowel perforation is 12.9% in the present study. The presence of large amounts of Gram-negative bacteria in the colon was thought of as a reason for the higher perforation-related mortality rate as compared with the small bowel. However, the perioperative mortality of colonic perforation reported in the literature[1, 2] is not higher than that in this study, probably because the etiologies of perforation in the colon and small intestine are different. It was reported that most colonic perforation cases were caused by benign diseases, and malignant tumors only accounted for about 20%[1, 2]. In the present study, 40% (34/85) were malignant cases and malignant tumor in deaths was account for 81.8% (9/11). Among the 52 patients who were admitted to the ICU after surgery, the perioperative mortality of patients with malignant etiology was higher than that of benign lesions (P = 0.048) (Table 3). Five (29.4%) of the 17 patients with lymphoma died after surgery. Of the 92 patients with perforated lymphoma reported by Vaidya *et al*.[11], 28 died directly from perforation or subsequent complications with a mortality rate of 30.4%, which is very close to the present study.

The high mortality of GI perforation is mainly due to sepsis caused by severe intra-abdominal infections. Sepsis is thought to be the systemic inflammatory response syndrome (SIRS) of the body against infection which is the so-called sepsis 1.0. The SIRS criteria include four indicators: body temperature, heart rate, respiratory status, and WBC count. As our study was of retrospective nature, it was difficult for us to trace clinical indicators accurately, and therefore we only grouped the WBC count according to the SIRS criteria. However, the result did not show WBC count as a significant factor related to the perioperative mortality in patients with small bowel perforation (Table 3). Clinical practice has shown that the SIRS criteria are too sensitive, and the diagnosis of sepsis 1.0 is very heterogeneous. So sepsis 3.0 has abandoned the SIRS criteria and adopted the SOFA and qSOFA score systems to define sepsis by laying emphasis on organ functions and host response to infection. The accuracy of the prognosis of SOFA scores for patients, especially ICU patients, is higher than that of SIRS[5]. Regretfully, some patients did not have SOFA score in this retrospective study. However, all patients in the ICU routinely received APACHE II score. APACHE II is currently the most commonly used scoring system for classification and prognostic prediction of critically ill patients. Some of the score indicators are overlapped with SOFA

system. Horiuchi et al.[12] found that APACHE II score was closely related to the prognosis, and the mortality rate would significantly increase if APACHE II score was ≥ 20. However, Nakamura et al.[2] failed to find a significant correlation between APACHE II score and prognosis in a study of 76 patients with colon perforation. In this study, the mean APACHE II score of patients in the non-survival group was significantly higher than that of the survival group (24.5 ± 11.5 *vs*. 14.4 ± 8.41, $P = 0.0032$) in the patients who entered the ICU after surgery. Sepsis 3.0 defines septic shock as requiring vasopressor therapy to maintain mean arterial pressure (MAP) > 65 mmHg and blood LAC level > 2 mmol/L after appropriate fluid replacement. Blood LAC level reflects the state of tissue oxygenation and metabolism. Studies have shown that postoperative arterial blood lactate levels are associated with mortality in colorectal patients[1]. In this study, arterial blood LAC level in the survival group was significantly lower than in the Non-survival group (1.91 ± 0.87 *vs*. 4.58 ± 4.17, $P < 0.001$).

Serum PCT levels increase with the severity of infection and organ dysfunction[13, 14]. Multiple studies have shown that PCT is a prognostic indicator[13, 15, 16] and PCT-guided therapy may predict treatment response and reduce length of antibiotic treatment in patients with severe intra-abdominal infection[17, 18]. This study found that the mean serum PCT concentration was much higher in the deaths than that in the survivors (38.1 ± 35 *vs*. 16.2 ± 26.3). PCT may be one of the molecules of the central node in sepsis and play an important role in the interaction between cytokine networks and other molecular interactions[19]. In addition, PCT has been proven to be a potential marker for the diagnosis of sepsis, although the serum PCT concentration is not applied as a diagnostic basis in sepsis 3.0[20].

As the cases and data included in this study are from a single center, the included population may be different from the overall population in terms of the clinical characteristics. Selection and information bias seems unavoidable for a retrospective study, which may affect the statistical results. Some important clinical indicators such as SOFA and qSOFA scores were incomplete or missing, which also made analysis impossible. As case-control studies are usually unable to identify perioperative mortality associated with risk factors, prospective multi-center randomized controlled trails or registry studies are required to provide more reliable and accurate evidence-based medical evidence.

Conclusions

The present study demonstrated that ingestion of foreign bodies, lymphoma and metastatic neoplasm were the leading causes for small bowel perforation. Serum precalcitonin, blood lactate and APACHE II score seem to be risk factors of perioperative mortality in patients with small bowel perforation after urgent surgery.

Abbreviations

DLBCL:Diffuse large B-cell lymphoma; EBV:Epstein-Barr virus; GI:Gastrointestinal; ICU:Intensive care unit; LAC:lactate; MALT lymphoma:Mucosa-associated lymphoid tissue lymphoma; MEITL:Monomorphic

epitheliotropic intestinal T-cell lyphomas; MAP:Mean arterial pressure; PCT:Procalcitonin; SIRS:systemic inflammatory response syndrome; WBC:white blood cell

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of our hospital and the need for informed consent was waived.

Consent for publication
Not applicable

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests

Funding
Not applicable

Authors' contributions
PS and KTS contributed to the design of the study. PS and ZZC contributed to the acquisition of data, the analysis, and interpretation. XDG, and YF provided critical revisions. PS and HL conducted the statistical analysis of the data. KTS and YHS provided the final approval of the version to publish. All the authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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Figures

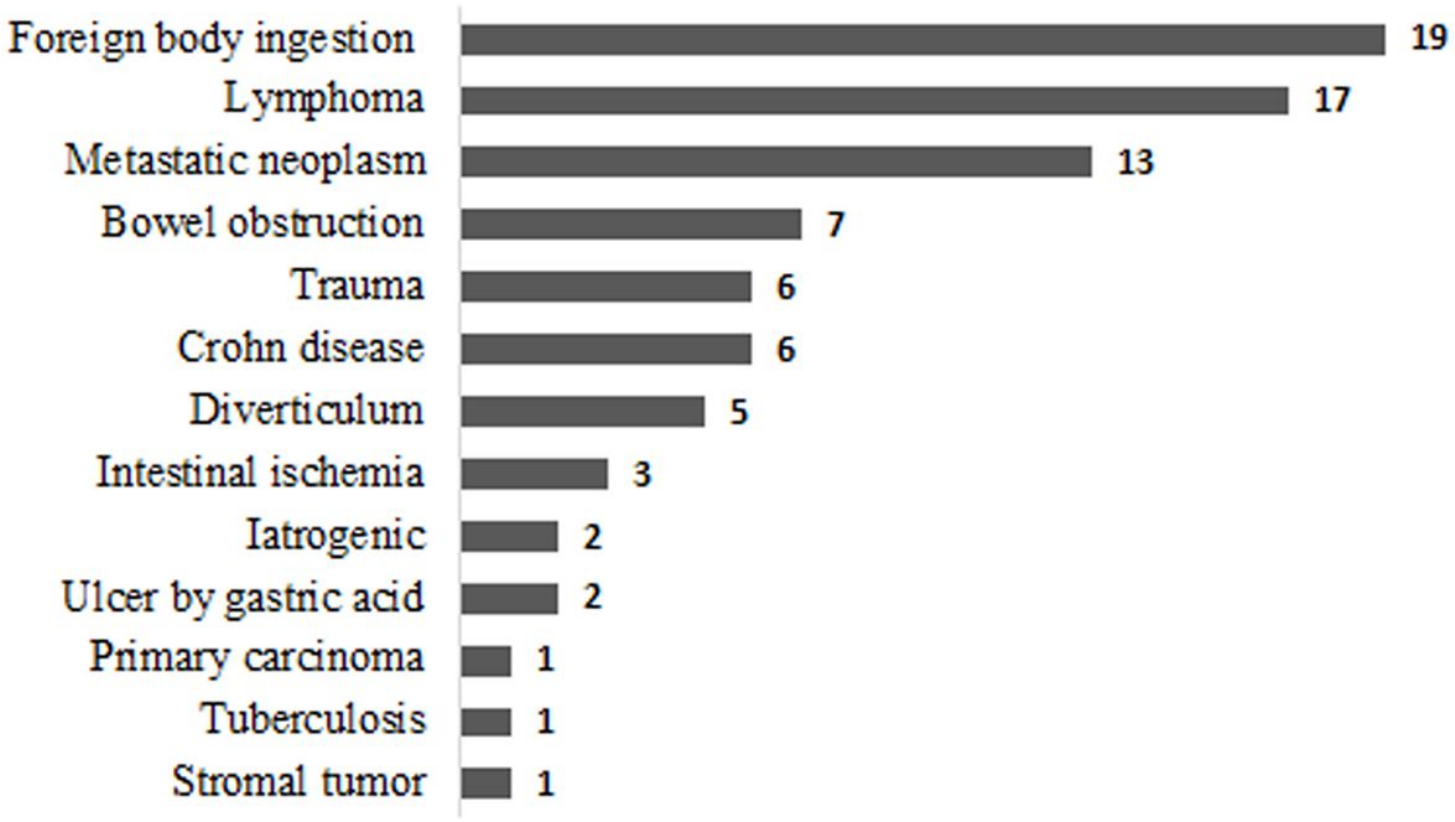

Figure 1

The spectrum of pathologies responsible for the small bowel perforation ranking by number of cases.

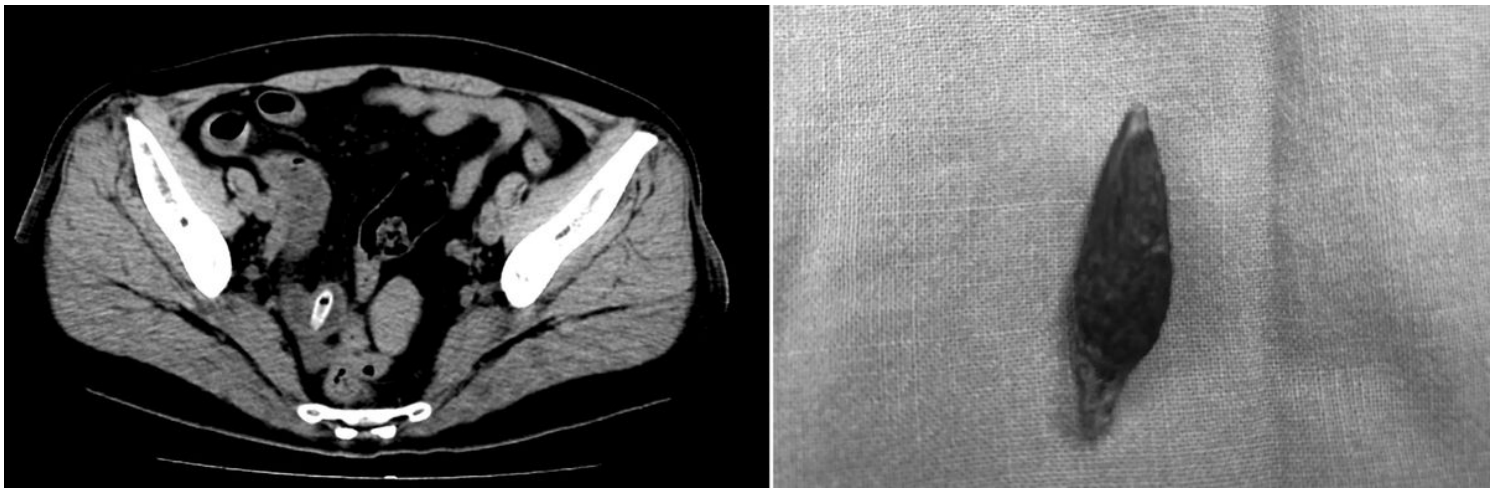

Figure 2

Left: Abdominal CT shows a foreign body in the distal ileum with local inflammatory exudation Right: The foreign body was confirmed to be a jujube nucleus by surgery.

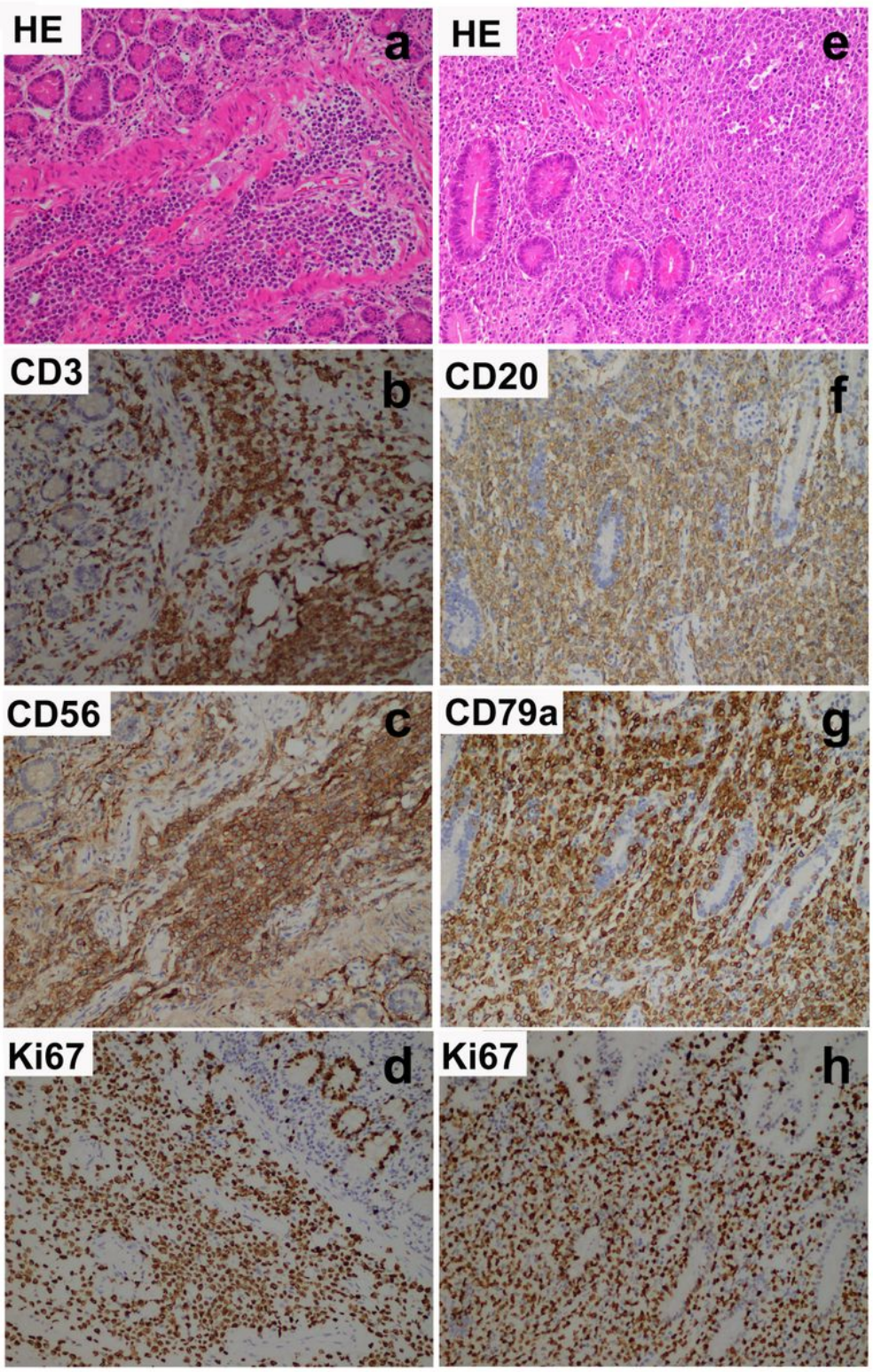

Figure 3

Left (a,b,c,d; 200X): Monomorphic epithelial intestinal T-cell lymphoma (MEITL); Right (e,f,g,h; 200X): Diffuse large B-cell lymphoma (DLBCL)

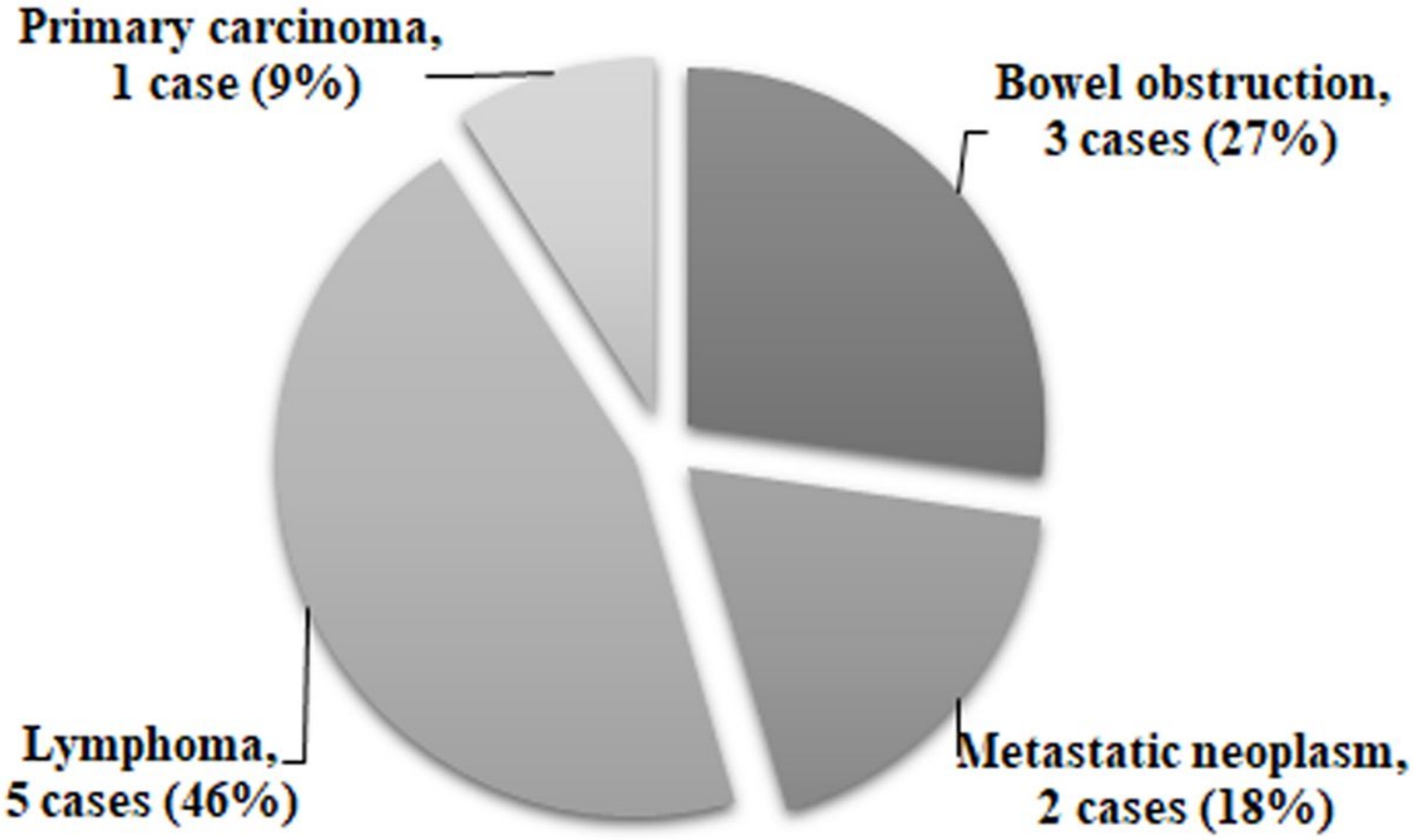

Figure 4

The etiologies of perioperative mortality in small bowel perforation