Surgical Outcomes in Adults with Acute Small Bowel Perforation and Risk Factors for Mortality: A Single-Center Retrospective Cohort Study.

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Research article

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Abstract

Background Small bowel perforation is a life-threatening surgical emergency even after immediate surgical intervention, while the surgical outcomes are rarely discussed in the literature due to relatively low incidence. This study aimed to investigate the surgical outcomes of small bowel perforation and risk factors for mortality.

Methods Consecutive patients with small bowel perforation confirmed by emergency surgery at Zhongshan Hospital, Fudan University from February 2011 to May 2020 were analyzed retrospectively. Clinical features, laboratory indicators, surgical findings and pathology were reviewed based on the medical records.

Results 199 patients were included in this study, of which 50 patients underwent perforation repair, 117 underwent primary anastomosis, and the other 32 underwent small bowel ostomy. 52.3% (104/199) patients transferred to ICU just after surgery and malignant tumor was the leading cause responsible for perforation in these patients (40.4%, 42/104), although foreign bodies ingestion (27.1%, 54/199) were most common for all cases in this study. The overall postoperative morbidity and mortality rate were 54.3% (108/199) and 10.6% (21/199) respectively, which were higher in the ICU group (74.0% (77/104) and 19.2% (20/104), respectively). Malignant tumor related perforation (OR, 3.567; 95%CI, 1.175-10.823; P=0.025) and high postoperative arterial blood lactate (LAC) level (OR,1.583; 95%CI, 1.127-2.225; P=0.008) were independent risk factors for post-operative mortality for patients transferred to ICU.

Conclusion Small bowel perforation is associated with significant morbidity and mortality rates after emergency surgery, especially for patients transferred to ICU. Malignant tumor related perforation, as well as higher postoperative blood lactate had increased risk of postoperative mortality.

Background

Gastrointestinal (GI) perforation is a common surgical emergency with obvious signs of peritonitis. Compared with other sites of the GI tract[1, 2], small bowel perforation is uncommon and the clinical manifestations are often atypical. However, severe or even life-threatening infections are more likely to occur with small bowel perforation.

The precise causes responsible for small bowel perforation are usually difficult to be identified before surgery. The etiology spectrum of small bowel perforation seems to be geographically and economically related. For instance, foreign body ingestion, intestinal ischemia, diverticulum and Crohn's disease are reported to be leading causes in Western countries[3, 4], while in developing countries, it is mainly related to infectious diseases such as typhoid and tuberculosis[5–7].

Previous literatures had reported a considerable morbidity and mortality in small bowel perforation [8, 9]. The higher content of bacteria and toxins in small bowel would cause more serious intra-abdominal infections with free perforation than that in upper GI tract. Besides, failure to prompt surgical treatment

due to delayed diagnosis would worsen the prognosis of the patients with small bowel perforation. However, the identification of risk factors related to morbidity and mortality following emergency surgery is still lacking large sample clinical studies with higher levels of evidence and remains to be further explored.

In this article, we retrospectively analyzed consecutive small bowel perforation cases treated in our center from February 2011 to May 2020, and explored the surgical outcomes and the risk factors of postoperative mortality in order to provide more evidence-based medical evidences for the optimum clinical diagnosis and treatment of small bowel perforation.

Patients And Methods

From February 1, 2011 to May 30, 2020, Consecutive GC patients who underwent emergency operations for GI perforation in Zhongshan Hospital, Fudan University (Shanghai, China) were retrospectively screened. The eligible criteria were: (1) patients who underwent urgent surgery with GI perforation precisely identified during operation; and (2) perforation site was located in the small intestine below the ligament of Treitz (jejunum and ileum). The exclusion criteria were: (1) anastomotic leakage after gastrointestinal surgery; (2) simultaneous upper gastrointestinal or colorectal perforation; and (3) perforation of the appendix.

Clinical features, laboratory indexes, surgical findings and pathology were reviewed based on the medical records. For patients transferred to ICU after surgery, SOFA and APACHE-II scores were collected as well. Laboratory data were collected from the most recent blood tests before/after surgery to minimize the impact of treatment on the results. Surgical records and postoperative pathology were used to identify the etiology of the small bowel perforation.

Observational parameters included surgical outcomes and the risk factors of death after surgery. Postoperative complications were classified and graded according to the Clavien-Dindo classification of surgical complications. Mortality was defined as death after a single admission or within 30 days of surgery. The use of patients' clinical data was approved by the ethics committee of Zhongshan Hospital, Fudan University(Approval No. : B2020-350), and the study was performed in accordance with the ethical standards presented in the 1964 Declaration of Helsinki and its later amendments.

Statistical analysis was performed using SPSS 25.0. The t-test was used for quantitative data with normal distribution and the Mann-Whitney U test for non-normal distribution; Pearson's Chi-Squared test or Fisher's exact test were performed on classified data. Multivariate analysis of risk factors for postoperative mortality was conducted by the logistic regression model. The α level was set at 0.05 for statistical significance.

Results

Clinical and surgical characteristics

A total of 1061 consecutive patients with GI perforation who underwent emergency surgery in Zhongshan Hospital, Fudan University (Shanghai, China) from February 1, 2011 to May 30, 2020 were identified and filtrated based on the eligible criteria (Fig. 1). Finally, a total of 199 small bowel perforation cases were enrolled and analyzed.

Of the 199 patients included in this study, 127 were male and 72 were female (1.76:1) with a mean age of 61.0 ± 16.3 years. Before surgery, 126 cases had 1–2 ASA grade (n = 127, 63.8%) and the other 73 cases had an equal to or greater than 3 ASA grade. 50 patients underwent perforation repair (including repair of the bowel wall defect after wedge resection of the diverticulum with perforation), 117 underwent segmental resection with primary anastomosis and the other 32 underwent small-bowel ostomy. 95 patients were transferred back to general wards after surgery, while 104 patients with critical conditions required postoperative ICU care. The median (IQR) length of hospital stay was 9.8 (8.2) days. Compared with the non-ICU care group, patients transferring to ICU were older (64.7 ± 15.6 *v.s.* 56.9 ± 16.2, year) with high grade of ASA and longer length of hospital stay (12.3(8.7, 20.5) *v.s.* 7.8(6.6, 11.0). Patients with enterostomy were prone to ICU care than intestinal repair or resection (Table.1).

Table.1 Comparison of clinical characteristics and surgery in non-ICU and ICU groups

	Total (n = 199)	Non-ICU(n = 95)	ICU (n = 104)	*P*-Value
Age (year)	61.0 ± 16.3	56.9 ± 16.2	64.7 ± 15.6	0.001
Gender				0.631
Male	127	59	68	
Female	72	36	36	
ASA grade				< 0.001
Low (1–2)	126	82	44	
High (≥ 3)	73	13	60	
Procedure				< 0.001
Repair	50	32	18	
Anastomosis	117	58	59	
Ostomy	32	5	27	
Hospital stay (day)* Median (Q1,Q3)	9.8(7.3, 15.5)	7.8(6.6, 11.0)	12.3(8.7, 20.5)	< 0.001
Hospital stay *: Duration of hospitalization after surgery.				

Etiologies responsible for perforation

The etiologies of perforation were determined by surgical and postoperative pathological findings. Except for 8 cases of spontaneous perforation with pathologic indications of inflammatory ulcer perforation, all the other cases had a precise etiological diagnosis and the etiologies of perforation were ranked by the number of cases in Fig. 2.

The most common cause for small bowel perforation was foreign body ingestion (54 cases), in which 38 cases were caused by jujube nuclei (Fig. 3), 13 cases by fish and other animal bones and the other three cases by sharp metal objects. Malignant tumor-related perforation was the most common cause in patients who were transferred to ICU. Lymphoma (28/52,53.85%) was the most common subtype of malignant tumor and most of them were aggressive histopathologic types with highly Ki-67 expression. Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)[10] and diffuse large B-cell lymphoma were the two most common pathologic types in lymphoma patients (Table 2). Secondary cancer (21/52, 40.38%，16 from other organs in the abdomen and 5 from the lungs) and stromal tumor (3/52，5.77%) were the other two subtypes of malignant tumors responsible for perforations.

Table 2
Histopathologic distribution of lymphoma with perforation.

Histopathologic types	Number (%)
B-cell type	**11 (39.3%)**
Follicular, grade 1	1 (3.57%)
Diffuse large B-cell	10(35.7%)
T-cell type	**17 (60.7%)**
MEITL	14 (50.0%)
EATL	1 (3.57%)
NK /T-cell	1 (3.57%)
Systemic EBV^{+}T-cell lymphoma	1 (3.57%)

MEITL: Monomorphic epitheliotropic intestinal T-cell lymphoma; **EATL**: Enteropathytype T-cell lymphoma;**NK**: Natural killer

Morbidity and Mortality

Among the 199 patients, 108 (54.3%) had at least one postoperative complication. Gastrointestinal complications (47/199,23.6%), respiratory complications (46/199,23.1%) and incision complications (39/199, 19.6%) were the three most common postoperative complications. Gastrointestinal complications included 36 cases of abdominal residual infection, 13 cases of postoperative intestinal leakage, 9 cases of gastrointestinal motility deficiency, 2 cases of anastomotic stenosis, 1 case of gastrointestinal bleeding and 1 case of diarrhea.

Postoperative complications were classified according to the Clavien-Dindo classification of surgical complications[11, 12]. For patients with multiple complications, the highest Clavien-Dindo grade was identified as the final complication grade. There were 20 cases of grade 1, 35 cases of grade 2, 22 cases of grade 3, 10 cases of grade 4, and 21 cases of grade 5 (death).

The overall mortality rate was 10.6% (21/199). Malignant tumor-related perforations accounted for 66.7% (14/21) in death, other etiologies of perforation were intestinal obstruction (4/21, 19.0%), intestinal ischemia (1/21, 4.8%), foreign body ingestion (1/21, 4.8%) and iatrogenic (1/21, 4.8%) (Fig. 4a). Septic shock, respiratory failure and pulmonary embolism were the direct causes of death(Fig. 4b). As expected, SICU patients had higher morbidity (74.0% v.s. 32.6%,p□0.001) and mortality (19.2% v.s. 1.1%,p□0.001).

Risk factors for mortality

As mentioned above, almost all deaths (20/21, 95.2%) occurred in patients who needed to be transferred to ICU after surgery. We included patients transferred to ICU for analysis of death-related factors. The results showed that compared with the 84 surviving patients, the 20 death cases had significantly higher postoperative arterial blood lactate levels (3.63 ± 3.33 v.s. 2.10 ± 1.26, $P = 0.005$) and APACHE II score (19.14 ± 8.62 v.s. 13.48 ± 7.53, $P = 0.012$). The mortality risk for patients with malignant tumor associated perforations were significantly higher than those with non-malignant tumors (P = 0.013) (Table 3). Furthermore, multivariate regression analysis showed that malignant tumor and blood lactate level (> 1.920mmol/L)(Fig. 4c) were independent risk factors for postoperative death(Table 3).

Table 3
Univariate and Multivariate analysis of clinical and laboratory data between death and survivor groups.

			Univariate analysis		Multivariate analysis	
Factors	**Survival (n = 84)**	**Death(n = 20)**	**P-value**	**Odd Ratio(CI)**	**P-value**	**Odd Ratio(CI)**
Gender			0.126	0.406(0.125–1.323)		
Male	52	16				
Female	32	4				
Age (year)	64.2 ± 16.2	66.60 ± 12.7	0.541	-0.613(-10.106-5.334)		
ASA			0.081	2.6(0.866–7.805)		
Low (1–2)	39	5				
High (≥ 3)	45	15				
WBC count (×109/L)			0.329	0.615(0.231–1.641)		
> 12 or < 4.0	52	10				
≤ 12 and ≥ 4.0	32	10				
Malignant tumor(Y/N)	29/55	13/7	0.013	3.522(1.266–9.797)	0.025	3.567 (1.175–10.823)
Blood LAC (mmol/L)	2.10 ± 1.26	3.63 ± 3.33	0.005[a]		0.008	1.583 (1.127–2.225)
APACHE II score	13.48 ± 7.53	19.14 ± 8.62	0.012[a]		0.207	1.047 (0.975–1.126)
SOFA score	4.98 ± 3.43	6.85 ± 4.11	0.097[a]			
Procedure			0.131			
Repair	17	1				
Anastomosis	48	11				
Ostomy	19	8				
PCT(ng/L)	14.03 ± 3.69	23.73 ± 9.45	0.105[a,b]			

a: the P value of Mann-Whitney Test; b: with a missing proportion of 28.8% (30/104).

Discussion

The small bowel perforation was a critical surgical emergency and the overall morbidity and mortality rates were reported to be 76.5% and 19.1%, respectively[8]. In this study, the overall morbidity and mortality rates were 54.3% and 10.6% respectively, lower than reported in the literature. However, 52.3% (104/199) of patients with small bowel perforation were transferred to ICU after surgery due to critical conditions. For these patients, morbidity and mortality rates were much higher (74.0% and 19.2%).

Data from this study suggest that there is a wide spectrum of etiologies responsible for small bowel perforation. The leading cause was foreign body ingestion and the jujube nucleus (38/54, 70.3%) was the most common kind, which seems to be closely related to Chinese personal eating habits. No perforation secondary to typhoid fever was discovered and only two patients were diagnosed with tuberculosis infection, which are the most common causes in developing countries. According to the medical information database, we found the vast majority of study population were from economically developed areas in eastern China.

There is a gap of etiologies responsible for perforations between non-ICU and ICU groups. Although foreign body ingestion was found to be the most common cause for small bowel perforation, malignant tumor was the leading cause for those in the ICU group and was an independent risk factor for ICU death ($P = 0.025$). On the one hand, it is related to immune disorder caused by tumor itself; on the other hand, anti-tumor therapy aggravates immunodeficiency when organism confronting with perforation and subsequent infection. According to previous domestic statistics in China, adenocarcinoma (52.9%) and stromal tumor (33.6%) are the most common primary tumors in small bowel[13]. However, there was no case of adenocarcinoma related perforation was found and only 3 cases (3/31) with stromal tumors. Lymphoma was the most common subtype of malignant diseases for small bowel perforation (28/31) in this study. Previous studies reported that perforation was the most common complication in lymphoma cases with a proportion exceeding 25%[14]. Most lymphomas originating from the small bowel are B-cell type, and only 10–25% are T-cell type with a poorer prognosis[15]. On the contrary, T cell lymphoma (17/28,60.7%) was more common than B cell lymphoma (11/28,39.3%) in those patients with perforated small intestinal lymphoma in this study. Furthermore, 35.7% (10/28) of the patients with lymphoma died after surgery, which is similar to the mortality rate (30.4%) of Vaidya's study.[15].Therefore, it is reasonable to assume that patients with small intestinal lymphoma have a greater risk of perforation with a worse prognosis, especially those with T-cell lymphoma.

In addition, our study demonstrated that the lung was the most common primary site of metastatic tumors causing small bowel perforation. Some researchers suspected that perforations might be related to the target therapies 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 tumors, subsequently leading to tumor necrosis[16]. They also could regulate the signaling pathways of tumor cells and then cause their

apoptosis[17]. 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[18].

In this study, the mortality was mainly due to sepsis caused by severe intra-abdominal infections (Fig. 4b), which had been verified in other studies.[9, 19]. Sepsis was thought to be the systemic inflammatory response syndrome (SIRS) of the body against infection which is the so-called sepsis version 1.0. The SIRS criteria include four indicators: body temperature, heart rate, respiratory status, and WBC count. We grouped the WBC count according to the SIRS criteria. However, the result did not show WBC count as a significant factor related to the postoperative 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 highly heterogeneous. Sepsis 3.0 adopted the SOFA score systems to define sepsis by laying emphasis on organ functions and host response to infection[20]. The accuracy of the prognosis of SOFA scores for patients, especially ICU patients, is higher than that of SIRS[21]. APACHE II has been applied in clinical practice earlier than SOFA scoring system, and is currently commonly used for classification and prognostic prediction of critically ill patients. Horiuchi et al. found that APACHE II scores were closely related to the prognosis, and the mortality rate would significantly increase if APACHE II scores were ≥ 20[22]. In this study, the mean APACHE II score of patients in the non-survival group was significantly higher than that of the survival group (19.14 ± 8.62 *v.s.* 13.48 ± 7.53, $P = 0.012$) in the patients who entered the ICU after surgery; while there was no significant difference in SOFA score (6.85 ± 4.11 *v.s.* 4.98 ± 3.43,$P = 0.097$). Unfortunately, multivariate regression analysis did not indicate that APACHE-II score was independently risk predictor for mortality.

As an excellent indicator reflecting the state of tissue oxygenation and metabolism, blood LAC level has attracted increasing attention. Sepsis 3.0 defines septic shock as requiring vasopressor therapy to maintain mean arterial pressure (MAP) > 65mmHg and blood lactate (LAC) level > 2mmol/L after appropriate fluid replacement[20]. Previous studies have shown that postoperative arterial blood lactate levels are associated with mortality in colorectal perforation patients[23]. In this study, arterial blood LAC level in the survival group was significantly lower than in the non-survival group (2.10 ± 1.26 v.s.3.63 ± 3.33, $P = 0.005$). Furthermore, lactic acid was analyzed as an independent risk factor of SICU mortality, with cut-off value of ROC 1.920mmol/L(Fig. 4c).

Recent years have witnessed extensive clinical application of serum PCT. Serum PCT level increases with the severity of infection and organ dysfunction[24, 25]. Multiple studies have shown that PCT is a prognostic indicator[26] and PCT-guided therapies may predict treatment response and reduce the length of antibiotic treatments in patients with severe intra-abdominal infection[27, 28]. 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[29]. Unfortunately, univariate analysis did not suggest a significant correlation between PCT level and mortality in this study. Considering the high missing proportion of 28.8% (30/104) in the ICU group, the clinical application value of serum PCT needs further study.

As the cases and data included in this study are from a single center with a limited sample size, the included population may be different from the overall population in terms of clinical characteristics. Selection and information bias are unavoidable for a retrospective study, which may affect the statistical results. Some important clinical indicators (such as PCT) were incomplete or missing. To provide more reliable and accurate evidence-based medical evidence, prospective multi-center studies are required.

Conclusion

In conclusion, the present study demonstrated that small bowel perforation is associated with significant morbidity and mortality rates after emergency surgery, especially for patients transferred to ICU. Although foreign body ingestion was found to be the most common cause for small bowel perforation, malignant tumor was the leading cause for those in the ICU group and was an independent risk factor of postoperative mortality ($P = 0.025$). Since lactic acid is another independent risk factor, patients transferred to ICU with a postoperative lactic acid level above 1.920mmol/L required special attention and medical care.

Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation**; SOFA:** Sequential Organ Failure Assessment**; ASA:** American Society of Anesthesiologists; **LAC:** Lactic acid**; PCT:** Procalcitonin; **MAP:** Mean Arterial Pressure; **SIRS:** systemic inflammatory response syndrome; **MEITL:** Monomorphic epitheliotropic intestinal T-cell lymphoma; **EATL:** Enteropathytype T-cell lymphoma; **NK:** Natural killer

Declarations

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of Zhongshan Hospital, Fudan University(Approval No.: B2020-350).

Consent for publication

All patients enrolled in the current study signed the consent form of our institution to donate health information of biological samples.

Data Availability

The datasets used and analyzed during the current study are available from the

corresponding author on reasonable request.

Conflict of Interest

The authors declare that they have no competing interests.

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No funding was received in support of this work.

Authors' Contributions

Fenglin Liu, Yihong Sun had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Ping Shu, Hongyong He and Fenglin Liu designed the study plan of experimental flow. Jianzhang Wu and Ping Shu were major contributors in drafting the manuscript and contributed to this work equally. Jianzhang Wu, Ping Shu and Haojie Li analyzed and interpreted the patient data. Zhaoqing Tang, Yihong Sun and Fenglin Liu revised the manuscript.

All authors read and approved the final manuscript.

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Figures

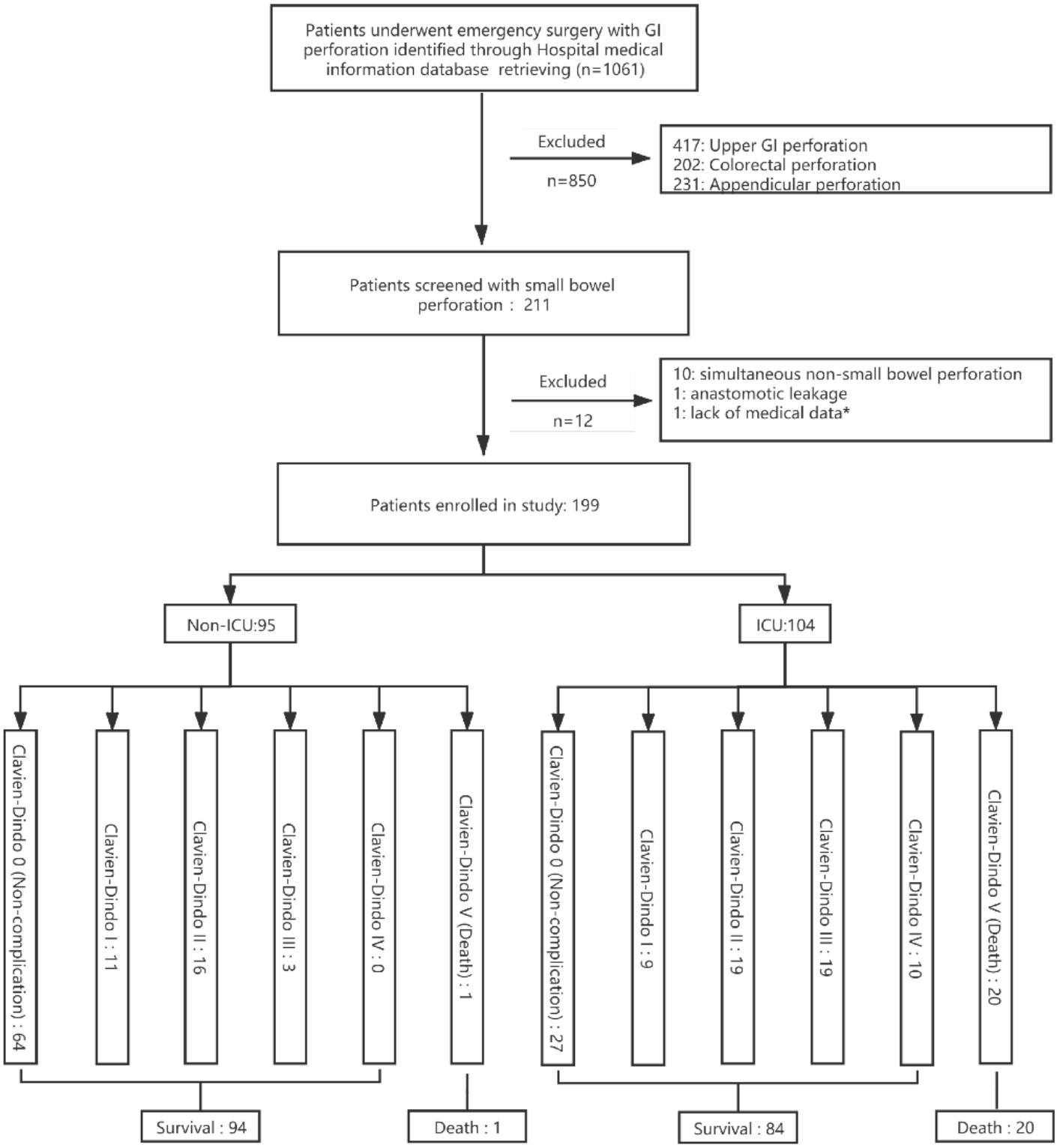

Figure 1

The flow chart of the study. * The medical information was sealed up due to medical dispute.

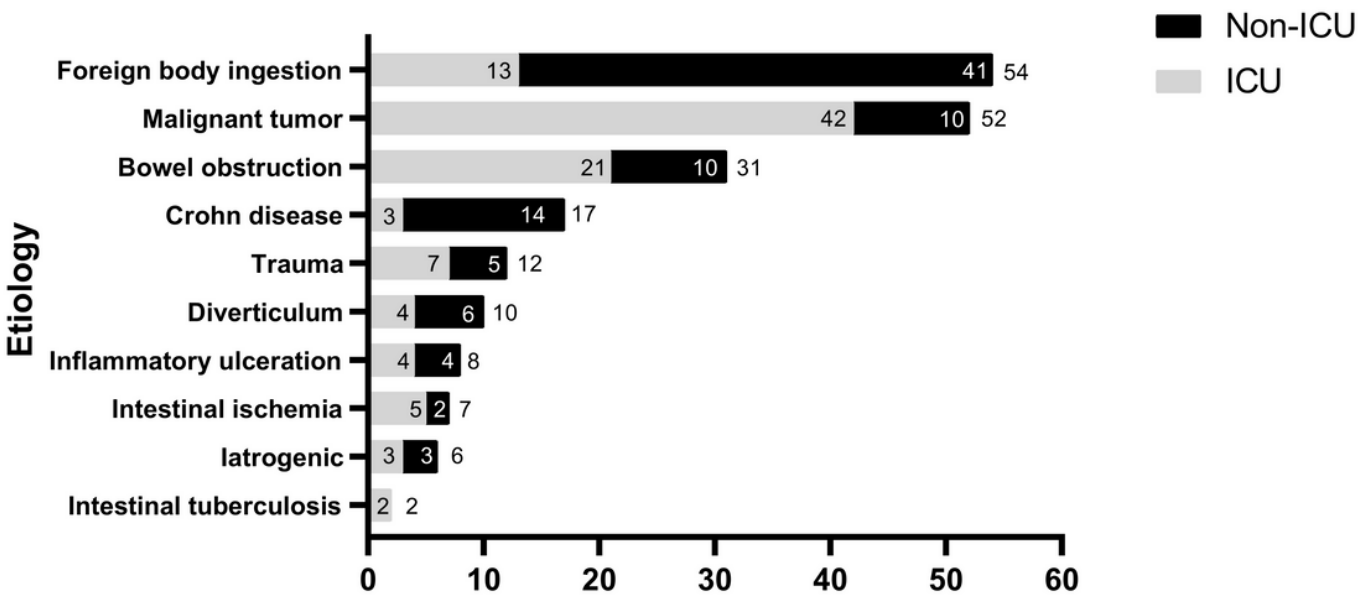

Figure 2

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

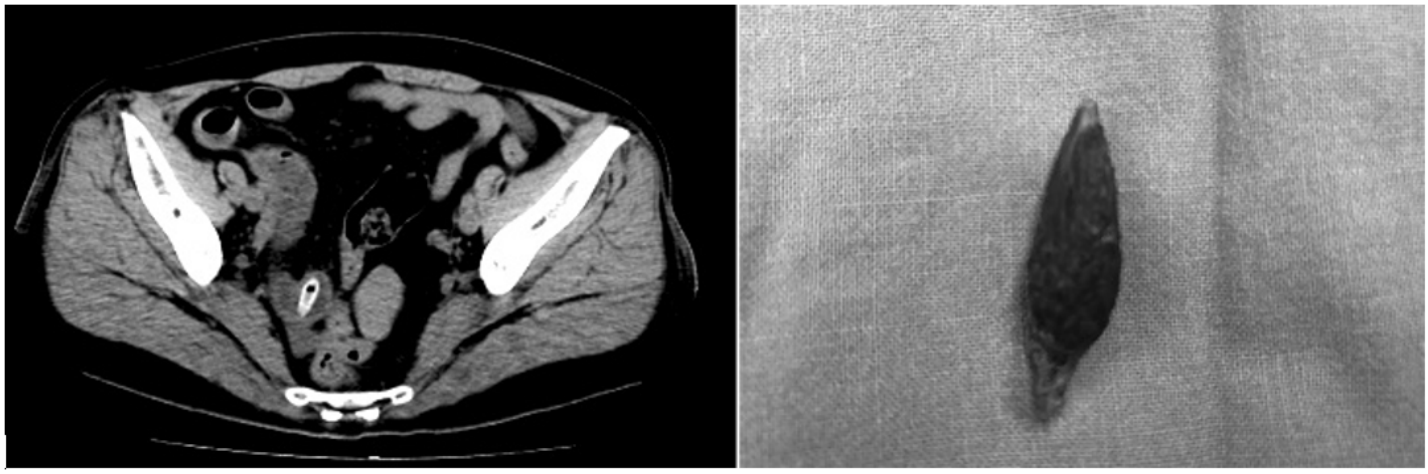

Figure 3

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.

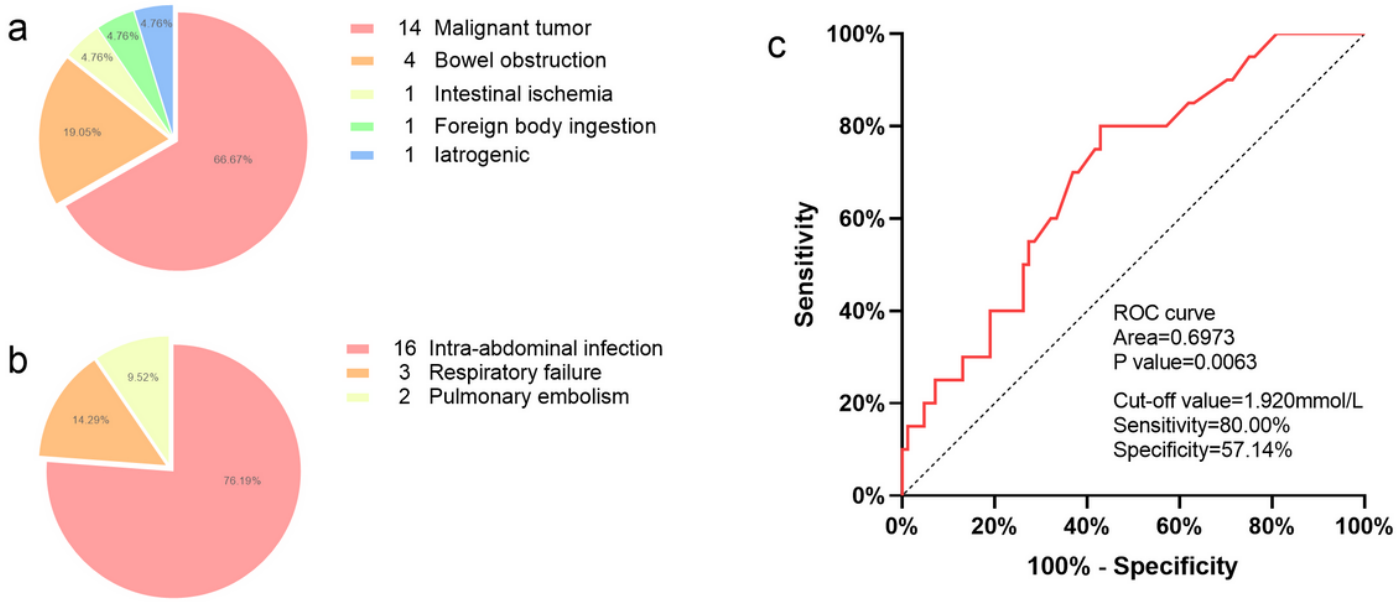

Figure 4

a. Primary causes of perforation in death group, the the subgroup of malignant tumor include 10 patients with lymphoma and 4 patients with secondary tumors. b. Distribution of direct causes of death. c. The ROC curve of postoperative blood lactate, lactic acid was an independent risk factor of SICU mortality, with cut-off value of ROC 1.920mmol/L.