

An Examination of the Predictive Factors of Perioperative Mortality in Patients with Colorectal Perforation

Udaka T^{1*}, Taniguchi A¹, Kouzai J¹, Ootsuka T¹, Watanabe N¹, Endou I¹, Yoshida O¹, Asano H¹ and Kubo M¹

¹Department of Surgery, Mitoyo General Hospital, Japan

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2. Key words

Colorectal perforation; Predictive factors; Preoperative shock; history of hemodialysis; SOFA score

1. Abstract

1.1. Purpose: Even after surgery and intensive postoperative treatment, the mortality rate associated with colorectal perforation is high. In this retrospective study, we assessed the preoperative predictive factors of perioperative mortality in patients with colorectal perforation.

1.2. Methods: We enrolled a total of 131 patients with colorectal perforation who underwent emergency surgery at our hospital between January 2008 and December 2019. They were divided into two groups: patients who died during the perioperative period (mortality group) and those who survived (survivor group). The clinical findings, blood test results, blood gas analysis results, and sequential organ failure assessment (SOFA) scores of the patients were examined and compared between the two groups.

1.3. Results: The total mortality rate was 9.9%. A univariate analysis indicated the significant predictive factors of perioperative mortality to be the platelet (PLT) count, SOFA scores, history of hemodialysis (HD), and preoperative shock. A multivariate analysis showed that the preoperative shock, history of HD, and SOFA scores were independent predictive factors of the perioperative mortality.

1.4. Conclusions: Colorectal perforation is often associated with poor outcomes. Patients with preoperative shock, a history of HD, or a SOFA score had a high risk of perioperative mortality associated with colorectal perforation. For such patients, surgical operation and postoperative intensive treatment should be performed very carefully.

3. Abbreviation: **ALB:** Albumin; **ASA:** American Society of Anesthesiologist; **CRP:** C-reactive protein; **CT:** Computed tomography; **HD:** hemodialysis; **OR:** Odds ratio; **PF:** PaO₂/FiO₂; **PLT:** platelet; **ROC:** Receiver operating-characteristic; **SIRS:** Systemic inflammatory response syndrome; **SOFA:** Sequential organ failure assessment; **SPSS:** Statistical Package for Social Science; **WBC:** white blood cell

4. Introduction

Because colorectal perforation causes widespread dissemination of bacteria throughout the intra-abdominal space, severe bacterial infection can easily lead to septic shock, and the disease is likely to become severe rapidly. Once the disease becomes severe, it leads to Disseminated Intravascular Coagulation (DIC) and Multiple Organ Failure (MOF), making it one of the most deadly diseases in modern medicine [1, 2]. To improve the survival rate, it is important to accurately assess patients' general condition and preoperative risk factors for mortality and appropriately apply surgical indications and procedure selection with subsequent intensive care.

A number of studies have reported several risk factors for mortality associated with colorectal perforation, such as age, sex, the serum protein level, and the serum creatinine level [1-4]. However, most such studies involve small samples or were performed many years ago. Therefore, we analyzed the mortality markers in consecutive patients with colorectal perforation who underwent surgical operations in our hospital.

5. Methods

5.1. Patients and study Design

The study protocol was approved by the Institutional Review Board of Mitoyo General Hospital, and it conformed to the concepts of the Declaration of Helsinki and its amendments. We enrolled a total of 131 patients who were diagnosed with colorectal perforation and underwent emergency surgery from January 2008 to December 2019.

We excluded cases of perforation of the appendix and cases of perforation due to suture failure of colorectal surgery. The patients

*Corresponding Author (s): Tetsunobu Udaka, Department of Surgery, Mitoyo General Hospital, Japan, Tel: 0875-52-3366; Fax: 0875-52-4936, E-mail: udaka@abeam.ocn.ne.jp

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were divided into two groups: the mortality group for those who died during the perioperative period and the survivor group for those who remained alive.

The preoperative data gathered were the age, sex, time from the symptom onset to surgery, body temperature, presence of Systemic Inflammatory Response Syndrome (SIRS) [5], presence of preoperative shock (systolic pressure <80 mmHg), history of Hemodialysis (HD), perforation site and etiology, Hinchey' stage, duration of surgery, and amount of blood loss, and preoperative laboratory study findings including hematologic, blood gas. The preoperative white blood cell (WBC) counts were dichotomized into <4,000/ μ L, 4,000/ μ L to 12,000/ μ L and >12,000/ μ L, and the preoperative body temperature was dichotomized into $\leq 36^{\circ}\text{C}$, 36°C to 38°C , and $>38^{\circ}\text{C}$, which reflect the criteria for SIRS criteria. Other variables were evaluated as continuous variables.

The severity of illness was assessed according to the Sequential Organ Failure Assessment (SOFA) scoring systems [6]. The SOFA score was based on the following six variables: PaO₂/FiO₂ (PF) for the respiratory function, bilirubin for the hepatic function, hypotension for the cardiovascular function, creatinine or urine output for the renal function, and the Glasgow coma scale for the central nervous system status.

5.2. Outcome measures

The primary outcome was mortality after surgery. The main outcome examined was the preoperative predictive factors of perioperative mortality in patients with colorectal perforation.

5.3. Statistical analyses

Statistical analyses were performed using the Statistical Package for Social Science (SPSS) version 24 (Chicago, IL, USA) software program. The chi-square and Fisher's exact tests were used to compare categorical variables, and Student's *t*-test or the Mann-Whitney test was used to compare continuous variables. Subsequently, Receiver Operating-Characteristic (ROC) curves were constructed to illustrate the sensitivity and false positive rate (1-specificity) of SOFA scores for the prediction of mortality. A multiple logistic regression analysis was performed to identify significant predictors associated with the need for bowel resection. All tests were two-sided and *P* values lower than 0.05 were considered significant.

6. Results

6.1. Clinical Characteristics of Patients

The mean age was 74.7 years old, and there were 70 males and 61 females.

The most common perforation site was the sigmoid colon (82 cases: 62.6%), followed by the rectum (24 cases), transverse colon (8 cases), ascending colon (7 cases), descending colon (7 cases), and cecum (3 cases).

The most common cause of perforation was diverticula (44 cases:

33.6%)), followed by malignancy (30 cases), constipation (16 cases), iatrogenic perforation (7 cases), intestinal ischemia (6 cases), barium (4 cases), trauma (3 cases), fishbone (2 cases), and idiopathic perforation (19 cases) (Table 1).

Table 1: Clinical characteristics of patients

Variables	
Cases	131
Age (years)	74.7 \pm 14.0*
Sex	Male 70 (53.4%), Female 61 (46.6%)
Perforation site	
Cecum	3 (2.3%)
Ascending colon	7 (5.3%)
Transverse colon	8 (6.1%)
Descending colon	7 (5.3%)
Sigmoid colon	82 (62.6%)
Rectum	24 (18.3%)
Perforation etiology	
Diverticulum	44 (33.6%)
Cancer	30 (22.9%)
Fecal impaction	16 (12.2%)
Iatrogenic	7 (5.3%)
Ischemic disease	6 (4.6%)
Barium	4 (3.1%)
Trauma	3 (2.3%)
Fishbone	2 (1.5%)
Idiopathic	19 (14.5%)

*Mean \pm standard deviation

6.2. Surgical operation

Hartmann's operation was performed the most frequently in 101 cases (77.1%). Anastomosis was performed in 14 cases, colostomy in 5 cases, direct closure in 4 cases, anastomosis plus covering ileostomy in 4 cases, and direct closure plus covering ileostomy in 3 cases (Table 2).

Table 2: Surgical operation

Surgical operation	
Hartmann's operation	101 (77.1%)
Anastomosis	14 (10.7%)
Colostomy	5 (3.8%)
Direct closure	4 (3.1%)
Anastomosis + covering ileostomy	4 (3.1%)
Direct closure + covering ileostomy	3 (2.3%)

6.3. Clinical characteristics

There were 13 cases in the mortality group and 118 cases in the survivor group. The total mortality rate was 9.9%. A univariate analysis showed that preoperative shock (*P*<0.001) and a history of HD (*P*=0.0026) were significant prognostic factors (Table 3).

Table 3: The comparison of the clinical characteristics

	Mortality (n=13)	Survivor (n=118)	<i>P</i> -value
Age (years) (mean \pm SD)	80.69 \pm 8.11	74.01 \pm 14.36	0.114
Sex	Male	57	0.885
	Female	61	
Time from the symptom onset to surgery (hour)	<24	9	0.861
	≥ 24	4	
		34	
Body temperature ($^{\circ}\text{C}$)	$38^{\circ}\text{C} >, 36^{\circ}\text{C} <$	10	0.72
	$38^{\circ}\text{C} \leq, 36^{\circ}\text{C} \geq$	3	
		38	
SIRS	None	57	0.702
	Positive	61	
Shock (Systolic blood pressure < 80mmHg)	None	111	<0.001
	Positive	7	
History of hemodialysis	None	113	0.0026
	Positive	5	
Perforation site	Right	17	0.889
	Left	101	
Perforation etiology	Benign	92	0.843
	Malignant	26	
Hinchey' stage (mean \pm SD)	2.77 \pm 1.36	2.48 \pm 1.31	0.482
Operation time (min) (mean \pm SD)	147.23 \pm 43.56	138.35 \pm 46.16	0.498
Bleeding (ml) (mean \pm SD)	253.85 \pm 407.46	193.94 \pm 257.51	0.613

SIRS: systemic inflammatory response syndrome

6.4. Blood Test and Blood Gas Analysis Results

A univariate analysis showed that the platelet (PLT) count was significantly lower in the mortality group ($P<0.001$) (Table 4).

Table 4: The comparison of the blood tests and arterial blood gas analysis findings

	Mortality (n=13)	Survivor (n=118)	p-value
WBC (/ μ L)			0.781
4,000 \leq \leq 12,000	5	45	
<4,000, >12,000	8	73	
CRP (mg/dl) mean \pm SD	10.36 \pm 10.64	10.78 \pm 11.51	0.895
PLT (/ μ L)	145,620 \pm 6,776	235,180 \pm 100,874	<0.001
PT-INR	1.19 \pm 0.38	1.15 \pm 0.43	0.739
BE (mmol/L)	-4.46 \pm 5.84	-2.20 \pm 4.09	0.197

WBC: white blood cell, CRP: C-reactive protein, PLT: platelets, PT-INR: prothrombin time-international normalized ratio, BE: base excess

6.5. SOFA Score

A univariate analysis showed that the preoperative SOFA score was significantly higher in the mortality group than in the survivor group (4.15 \pm 2.03 vs. 1.89 \pm 1.47; $P<0.001$). The mortality group also showed significantly higher rates of coagulation, cardiovascular, and renal function when compared for each parameter (Table 5).

Table 5: The comparison of the SOFA score factors

	Mortality (n=13)	Survivor (n=118)	P-value
SOFA score	4.15 \pm 2.03	1.89 \pm 1.47	<0.001
Respiration	1.15 \pm 1.34	0.62 \pm 0.64	0.196
Coagulation	0.85 \pm 0.90	0.21 \pm 0.47	0.0086
Liver function	0.33 \pm 0.38	0.32 \pm 0.60	0.857
Cardiovascular	0.54 \pm 0.52	0.08 \pm 0.27	0.0064
Central nerve	0.00 \pm 0.0	0.00 \pm 0.0	1
Renal function	1.62 \pm 1.71	0.55 \pm 1.08	0.002
mean \pm SD			

SOFA: sequential organ failure assessment

6.6. Multivariate Analysis Results

The cut-off value of the SOFA score for mortality was 2.5 (sensitivity: 0.692 and specificity: 0.280 according to the examination of the ROC curve (Figure 1). Nearly every variable proved insignificant in the logistic regression analysis, with the exception of preoperative shock which had an odds ratio (OR) of 25.25 ($P<0.001$), history of HD which had an OR of 11.37 ($P=0.031$), and the SOFA scores which had an OR of 4.95 ($P=0.042$) (Table 6).

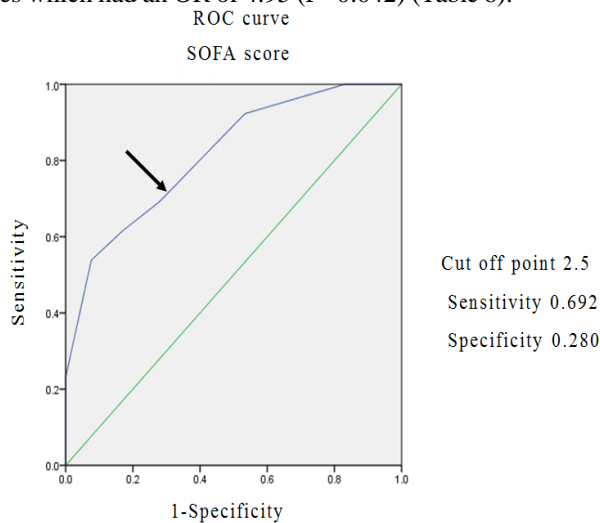


Figure 1: Discriminatory power of the maximum SOFA score. The ROC curve summarizes the relationship between the sensitivity (number of true positives) and 1-specificity (number of false positives) for all possible scores.

Table 6: The results of a multivariate logistic regression analysis of the risk factors for mortality due to colorectal perforation

	Odds ratio	95% confidence interval	P value
Shock	25.25	4.76-133.97	<0.001
History of hemodialysis	11.37	1.25-103.52	0.031
SOFA scores	4.95	1.06-23.14	0.042
PLT	2.75	0.55-13.63	0.216

SOFA: sequential organ failure assessment, PLT: platelet

7. Discussion

Severe colorectal perforation has a poor prognosis and can easily lead to sepsis, DIC, and MOF due to generalized peritonitis. In the past, the mortality and morbidity rates have been reported to be 15%-33.3%, even after immediate treatment with emergency surgery [3, 4, 7-10]. The results of intensive treatment for sepsis have improved, and in recent years, the mortality rate has been reported to be 10.6% to 18.6%. The prediction of mortality using routinely and easily available preoperative parameters is important to provide adequate information about the likelihood of postoperative death to patients and their families and to prepare for intensive postoperative management should the need for rescue arise.

Our study showed that preoperative shock, a history of HD, and a high SOFA score were independent risk factors for mortality in patients with colorectal perforation. As in our study, Shinkawa et al. [9] similarly showed that associated septic shock, diffuse peritonitis, and concurrent end-stage renal failure were all significantly related to early postoperative mortality in cases of colorectal perforation. These factors present a combination of the patients' severe underlying conditions and the consequences of diffuse peritonitis. Yamamoto et al. [11] also found that a higher age and a lower preoperative systolic blood pressure were independent risk factors for mortality in patients with colorectal perforation. Han et al. [12] reported that an older age, high American Society of Anesthesiologist (ASA) grade, systemic hypotension, preoperative presence of renal failure, and requirement for intraoperative transfusion significantly increased the mortality rate.

Onishi et al. [13] showed that a history of HD was a risk factors for the prognosis of colorectal perforation. An estimated 13% of the adult population suffers from chronic kidney disease, which is treated with HD; this percentage is expected to rise [14]. Infection is a leading cause of morbidity and mortality among dialysis patients [15] possibly due to their often

immunocompromised state, though to be based on abnormality of cellular, humoral and phagocytic immunity malfunctions [16-18].

Ochiai et al. [19] concluded that the SOFA score is predictive of the outcome in postoperative cases of colorectal perforation. Patients with a SOFA score higher than 7 had a greater risk of hospital death than those with lower values. Sumi et al. [20] reported that the POSSUM and SOFA scores, which are currently used worldwide, were useful for evaluating the additional risk associated with colorectal perforation. However, their study identified additional risk factors in the PF ratio and base excess, which are not included in

the POSSUM score [21] and the pulse rate and severity of peritonitis, which are not included in the SOFA, along with anticoagulant/steroid hormone administration. It is thus deemed more important to assess a patient's condition than to settle on a single evaluation method.

Shimazaki et al. [4] indicated in their retrospective analysis that the postoperative arterial blood lactate level could be a predictive marker for mortality in patients with colorectal perforation. The lactate level is an easily measurable marker of decreased peripheral perfusion.

We performed Hartmann's procedure in all patients who died. In their retrospective observational nationwide study, Tsuchiya A et al. [22] reported a significant difference in the 30-day mortality between cases of Hartmann's procedure and primary anastomosis without a diverting stoma among adult patients with various underlying etiologies. Physicians should be advised to select Hartmann's procedure for patients with shock, an immunosuppressed conditions, or advanced age.

In the present study, the mortality of colorectal perforation was 9.9%, which is considerably lower than that previously reported [3, 4, 7-10]. This was considered to be the result of a proper assessment of the patient condition using our predictive factors of mortality coupled with intensive postoperative treatment whenever possible.

Several limitations associated with the present study warrant mention. First, the operative and postoperative management was performed by different doctors and was thus inconsistent in its quality. Second, this study was conducted at a single center and the number of patients was small. A large-scale multicenter study should be performed to confirm our findings.

8. Conclusions

To reduce the high mortality of colorectal perforation, it is essential to make an early diagnosis and to perform surgery as soon as possible. Preoperative shock, a history of HD, and the SOFA score were independent prognostic factors in patients with colorectal perforation. It is important to identify patients with prognostic factors of mortality, select an appropriate surgical procedure, and provide the intensive treatment in order to improve the mortality rate.

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