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Examination of prognostic factors in patients undergoing surgery for colorectal perforation: A case controlled study

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ABSTRACT

Objective: To determine if the POSSUM, SOFA, MPI, and SAS scores provide a better measure of severity for patients with prognostic factors undergoing surgery for colorectal perforation.
Subjects: Fifty-nine patients who underwent surgery between 1996 and 2012.
Methods: We retrospectively reviewed background factors, blood and physiological test results, and intraoperative findings of patients who survived and those who died. We also compared the POSSUM, SOFA, MPI, and SAS scores. Multivariate analysis was performed for factors that were significant by univariate analysis, and selected factors were used to produce a predictive prognostic model.
Results: Univariate analysis revealed significant differences in age, anticoagulant/steroid administration, serum creatinine level, PF ratio, base excess (BE), chest radiography, pulse rate, and severity of peritoneal soiling. Age, serum creatinine level, pulse rate, and severity of peritoneal soiling were selected for multivariate analysis; only pulse rate was significantly different. There were significant differences between the two groups in POSSUM PS, OSS, SOFA, and MPI scores, and a comparison in terms of the ROC curve showed that our model had the highest peak; the area under the curve was 94.8% compared with 70–80% for the other systems, suggesting that our model is better than those systems.
Conclusions: POSSUM and SOFA are valid methods of evaluating risk from colorectal perforation, but our study revealed addition risk factors: (1) the PF ratio and BE, which are not included in POSSUM; (2) the pulse rate and severity of peritonitis, which are not included in SOFA; and (3) anticoagulant/steroid hormone administration.

1. Introduction

Colorectal perforation has a high mortality rate and may easily lead to bacterial peritonitis and progress to sepsis, disseminated intravascular coagulation (DIC), and multiple-organ failure [1]. To improve the survival rate, it is important to accurately assess patients' general condition, appropriately apply surgical indications and choices of procedure, and subsequently provide intensive care. In many cases, however, treatment is ineffective and leads to death. Obtaining informed consent from patients and their families before and immediately following surgery is therefore critical to avoid problems. Therefore, a simple method of risk evaluation is required to provide an adequate explanation for the necessity of surgery and the patient's subsequent anticipated condition. A range of methods for evaluating severity and predicting prognosis have been previously reported, including the Physiological and Operative Severity Score (OSS) for the quantification of mortality and morbidity (POSSUM) [2], the Sepsis-related Organ Failure Assessment (SOFA) [3] the Mannheim Peritonitis Index (MPI) [4], and the Surgical Apgar Score (SAS) [5].

The objective of this study was to investigate preoperative and intraoperative factors affecting the prognosis of patients undergoing surgery for colorectal perforation; compare their prognostic value with that of POSSUM, SOFA, MPI, and SAS; and investigate whether they provided a more accurate severity score.

2. Methods

The study subjects comprised 59 patients with colorectal perforation who underwent emergency surgery in our hospital between 1996 and 2012. The parameters investigated were all the

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items included in POSSUM, SOFA, MPI, and SAS as well as body mass index (BMI), presence of underlying conditions (conditions requiring treatment were judged as present), presence of anticoagulant therapy or steroid therapy, site of perforation, cause of perforation, and surgical method. Patients were divided into 2 groups: surviving patients (Group A) and dead patients (Group D) (all deaths occurred in the hospital). Physiological tests included all the tests covered by the POSSUM; the central nervous system was evaluated using the Glasgow Coma Scale (GCS); chest radiography findings for chronic obstructive pulmonary disease (COPD) were evaluated according to a 4-point scale (normal, mild, moderate, and fibrosis); and electrocardiogram findings were categorized as normal or atrial fibrillation or other arrhythmias. The severity of peritoneal soiling was scored according to POSSUM as follows: no soiling, minor soiling, local pus, and free bowel content with pus or blood.

For statistical analysis, we first performed univariate analysis of individual factors to isolate significant factors. Subsequently, we performed logistic multivariate analysis via the stepdown procedure and the likelihood ratio test using the significant factors from the univariate analysis as inputs. The selected factors were used to develop a predictive prognostic model based on our experience with the current cases. This model was used to evaluate the fit of the model and the cutoff point was set at 50%. Following this, the POSSUM, SOFA, MPI, and SAS scores for our cases were calculated, and the values of individual factors and total scores as predictive prognostic methods for patients undergoing surgery for colorectal perforation were calculated and compared with the value of our model. The χ^2 test, Fisher's direct method, Mann–Whitney test, logistic multivariate analysis by the stepdown method, likelihood ratio, and ROC curve were used for statistical analysis, with values of $p < 0.05$ considered significant. The statistical software used was SPSS II for Windows.

3. Results

3.1. Background factors

The median age of the patients was 65 years in Group A and 75 years in Group D, and the elderly patients had a significantly poorer prognosis ($p = 0.011$). Group A included 25 men and 20 women; Group D included 7 men and 7 women, with no significant difference ($p = 0.766$). A comparison of perforations of the right and left colon showed that perforations of the left colon had a tendency for higher mortality, but that this difference was not significant ($p = 0.084$). The most common causes of perforation were ischemia and diverticulitis, but their effect on prognosis was not significantly different. There were no significant differences in the time from onset to surgery, time from presentation at hospital to surgery, BMI, and the presence of underlying disease. In the presence of anticoagulant/steroids administration, mortality was greater among patients administered anticoagulants or steroids ($p = 0.046$) (Table 1).

3.2. Blood and physiological test findings

The blood tests showed that the white blood cell count tended to be higher in survivors, but this difference was not significant ($p = 0.055$). Among all factors, serum creatinine level in Group A ($p = 0.001$), $PaO_2/PaCO_2$ oxygenation index (PF ratio) in Group A ($p = 0.009$), and BE in Group A ($p = 0.025$) showed significant differences. There were no significant differences in other factors.

There was no significant difference in the GCS score. Chest radiography findings showed that COPD was significantly more common in Group D ($p = 0.048$), and there were no significant differences in electrocardiographic findings. In terms of circulatory tests, there was no significant difference in mean arterial pressure (MAP). The pulse rate was significantly lower in Group A (93/min) than in Group D (111/min) ($p = 0.001$). Median body temperature was 37.6 °C in Group A and 37.0 °C in Group D; however, this difference was not significant ($p = 0.082$) (Table 2).

3.3. Surgical factors

There was no significant difference in terms of the history of laparotomic surgery, intraoperative hemorrhage, minimum intraoperative MAP, minimum intraoperative pulse rate, or surgical procedure. In terms of peritoneal soiling, a significantly higher number of patients in Group A had local pus or serous fluid ($p = 0.016$) (Table 3).S

3.4. Multivariate analysis

Univariate analysis showed that there were significant differences in age, presence of anticoagulant/steroid administration, serum creatinine, PF ratio, BE, severity of COPD, pulse rate, and severity of peritoneal soiling. Using these factors, logistic

Table 1
Patient background.

	A Group			D Group			*p*-value
Age Median minimum maximum	65	36	90	75	55	89	0.011
Gender (cases) Man:Woman	25:20			7:07			0.766
Site (cases) Right:Left	15:30			1:13			0.084
Course (Cases) UC:Cancer:Ischemia:Diveruticulum:Ideopasic:Trauma:Iatrogenic	2:7:4:13:12:4:3			0:4:1:4:5:0:0			0.464
Course2 (cases) Malignant:Benign	7:38			4:10			0.432
Time from onset to surgery (hours) Median minimum maximum	10.0	2.0	124.0	10.8	4.0	79.0	0.743
Time from presentation at hospital to surgery (hours) Median minimum maximum	4.0	2.0	120.0	4.5	2.0	24.0	0.755
BMI Median minimum maximum	21.4	14.5	29.4	19.7	15.6	26.4	0.256
Underlying condition (cases) Yes:No	20:25			4:10			0.361
Anticoagulants/steroids (cases)	11:34			8:06			0.046

Table 2
Blood and physiological test results.

Factors	A Group			D Group			*p*-value
	Median	Minimum	Maximum	Median	Minimum	Maximum	
WBC (/μL)	8500	1070	27,100	4750	1610	17,400	0.055
Hb (g/dL)	12.9	3.4	17.3	12.3	8.4	17.9	0.845
Platelet ($\times 10^4$/μL)	25.2	5	70	18.9	7	56	0.144
Cre (mg/dL)	0.75	0.3	4	1.46	0.6	9.3	0.001
T-Bil (mg/dL)	0.81	0.3	3.5	0.7	0.	1.6	0.884
P/F rate (mmHg)	373	106	515	274	63	439	0.009
$PaCO_2$ (mmHg)	32.6	18.9	46.4	29.4	16.	67.1	0.156
BE (mmol/L)	−1.2	−10.2	9.9	−3.4	−20.6	0.9	0.025
Na (mmol/L)	138	126	155	138.5	134	148	0.241
K (mmol/L)	3.84	3.1	5.2	4.0	2.7	6.3	0.224
GCS	15	8	15	14.5	8	15	0.74
MAP (mmHg)	85.3	43	120	75.5	35	113	0.167
HR (beats/min)	93	46	140	111	76	160	0.001
KT (°C)	37.6	34.8	39.6	37.0	34.6	38.5	0.082

Factors	A Group (cases)	D Group (cases)	*p*-value
Chest radiograph None:mild:moderate: fibrosis	41:2:1:1	9:3:2:0	0.048
ECG Normal:AF:any other abnormal rhythm	33:1:11	8:1:5	0.435

multivariate analysis by the stepdown method and likelihood ratio showed that the combination of age, serum creatinine level, pulse rate, and severity of peritoneal soiling provided the model with the best fit. The only factor for which a statistically significant difference was evident was pulse rate ($p = 0.009$); the odds ratio and lower confidence interval value were both ≥1 (Table 4). From these findings, the probability of death (y%) can be calculated according to the regression formula $\log y/1 - y = 0.138 \times \text{age} + 1752 \times \text{serum creatinine} + 0.098 \times \text{pulse rate} - 1.048 \times \text{minor peritoneal soiling} + 5.449 \times \text{local pus peritoneal soiling}; 9.778 \times \text{free bowel content peritoneal soiling} - 31.796$. When the cutoff point was set at 50%, the sensitivity was 97.6%, specificity was 85.7%, positive predictive value was 95.3%, false negative value was 4.7%, negative predictive value was 92.3%, false positive value was 7.7%, and predictive accuracy was 96.4% (Table 5)

3.5. Comparison of predictive prognostic models

Factors in the POSSUM Physiological Score (PS) that showed significant differences were age ($p = 0.001$), respiratory signs ($p = 0.004$), chest radiographic findings ($p = 0.019$), urea level ($p = 0.001$), pulse ($p = 0.001$), systolic blood pressure ($p = 0.002$), and total score ($p = 0.001$). For the OSS, these factors were peritoneal soiling ($p = 0.002$) and total score ($p = 0.001$). The total score, when the OSS and PS scores were added, was lower in Group A ($p = 0.001$)S (Table 6). The factors in the SOFA score with significant differences were PF ratio ($p = 0.006$), serum creatinine level ($p = 0.001$), and total score ($p = 0.001$). The factors in MPI with significant differences were organ failure ($p = 0.008$), diffuse generalized peritonitis ($p = 0.001$), presence of exudate ($p = 0.001$), and total score ($p = 0.001$). In SAS, the total score tended to be higher in Group A, but this difference was not significant ($p = 0.056$) (Table 7). A comparison of these factors with those selected from our cases (age, serum creatinine, pulse rate, and severity of peritoneal soiling in terms of the ROC curve) showed that ourS model exhibited the highest peak (Fig. 1). The area under the curve was 94.8% for our model using factors suggested by multivariate analysis, as compared to 70–80% for the other systems, suggesting that our model compares favorably with those systems (Table 8).

4. Discussion

In this study, we aimed at investigating the preoperative and intraoperative factors affecting the prognosis of patients undergoing surgery for colorectal perforation. We compared the prognosis through POSSUM, SOFA, MPI, and SAS to find out which of these are most accurate. Colorectal perforation has a poor prognosis, with a mortality rate of 9.1–22.4% and a mortality of 23.7% in our study. We believe the mortality rate in our patients depended on the severity of intestinal perforation and conditions present prior to surgery. Mado et al. [6] hypothesized that the publication of

Table 3
Factors associated with surgery.

	A Group			D Group			*p*-value
Multiple procedure 1:2:>2	34:8:3			9:5:0			0.262
Total blood loss (mL) Median minimum maximum	10	258	4343	10	518	6900	0.432
Peritoneal soiling None:minor:local pus:free bowel content	3:6:16:20			0:0:1:13			0.016
Lowest mean arterial pressure (mmHg) Median minimum maximum	36	58.1	80	43	50.5	77	0.392
Lowest heart rate (beats/min) Median minimum maximum	54	79.3	115	10	91	120	0.159
Methods Hartmann:exteriosation:resection:others	29:5:5:6			10:2:2:0			0.546

Table 4
Results of multivariate analysis.

Factor	Odds rate	95% C.I.	*p*-value
Age	1.148	0.995–1.324	0.059
Creatinine	5.767	0.504–65.94	0.159
Heart rate	1.104	1.025–1.189	0.009
Peritoneal soiling			0.219
Minor	2.849	0.00–2.284	
Local pus	232.5	0.00–1.097	
Free bowel content	17,643	0.00–8.053	

Table 5
Evaluation of fit of model.

	Determined as survivors	Determined as dead	
Actual survivors	40	1	97.60%
Actual deaths	1	13	85.70%
	95.30%	92.30%	96.40%

$\text{Log } y/1 - y = 0.138 \times \text{age} + 1.752 \times \text{Cre} + 0.098 \times \text{HR} - 1.047 \times \text{SOL1} + 5.449 \times \text{SOL2} + 9.778 \times \text{SOL3} - 31.796.$

mortality rates due to colorectal perforation and POSSUM scores for different hospitals would increase the choices of hospitals for patients. This would also be beneficial for medical institutions as they would be able to choose whether to transfer patients to other institutions capable of treating more severe cases. Mado et al. [6] also reported that mortality from colorectal perforation was 14.9% and the scores predicting 50% survival were 21 for APACHE II, 43 for POSSUM PS, and 7 for SOFA [6]. In our study, the scores predicting 50% survival were 40 for POSSUM PS and 7 for SOFA, which are almost the same values as that reported by Mado et al.

Numerous previous studies have compared systems including POSSUM, SOFA, MPI, SAS, APACHE II, and ASA for predicting the prognosis of patients undergoing surgery for colorectal perforation. However, these studies have shown inconsistent results. Horiuchi et al. [7] excluded that APACHE II was of greater value than MPI, and Delibegovic et al. [8] concluded the same while comparing the APACHE II with MPI, MOF, and others. In contrast, Sawayama et al. [9] reported MPI as the most useful as compared to POSSUM, SOFA, and APACHE II; Ishizuka [10] reported POSSUM as the most useful as compared to APACHE II and SOFA; and Ochiai [11] reported SOFA as the most useful as compared to APACHE II. Additionally Bindo et al., who described their own PSS system comprising age, severity of peritonitis, ASA, presence of immunodeficiency, and presence of ischemia, reported that ASA was the most useful method [12]. Muzaffar reported as per multivariate analysis, ASA and CR POSSUM were associated with in-hospital death [13], and Madoo et al. [6] reported APACHE II and POSSUM PS were both equivalent methods for preoperative evaluation. In our study, the area under the ROC curve was $\geq$80% for POSSUM, SOFA, and MPI, with all of these methods providing excellent risk analyses.

With regard to patient background factors, age was significantly associated with prognosis in both our model and POSSUM, but there was no significant difference in the MPI. This difference may have resulted from the fact that the median ages of Group A and Group D in our study were 65 and 75 years, respectively. In addition, in POSSUM, 60 and 70 years were the limits for the youngest and oldest subjects, respectively, but MPI divided the patients into 2 groups aged above and below 50 years. Other studies have also reported age as an important prognostic factor, and this may be because the organ function generally declines in elderly patients.

In terms of sex differences, MPI seems the female gender a poor prognostic factor, but in our study, we found no significant difference and no other reports have indicated that sex is a risk factor. Additionally, no association between prognosis and time from onset or presentation at the hospital to surgery was evident, but in general, the longer the time between the onset and treatment, the worse is the systemic condition of the patient with colorectal perforation. However, there is no method for determining the time of onset other than asking the patient. Symptoms of peritoneal irritation may be unclear in elderly patients and are dependent on the disease; therefore, the initial symptoms may be mild and the exact time of onset of symptoms may be difficult to determine. In our study, over 24 h elapsed from presentation at the hospital until surgery in 4 patients; the cause was ischemia in 2 patients, diverticulitis in 1 patient, and cancer in 1 patient. In 3 of these patients, the condition deteriorated while they were undergoing conservative treatment and colorectal perforation was diagnosed and emergency surgery was performed. Only 1 patient died due to diverticulitis. With respect to the association between time from

Table 6
POSSUM.

	A Group			D Group			*p*-value
	Median	Minimum	Maximum	Median	Minimum	Maximum	
Age	1.9	1	4	3.57	1	4	0.001
GCS	1.07	1	8	1.5	1	8	0.919
Respiratory sign	1.43	1	8	3.0	1	8	0.004
Chest radiograph	1.09	1	8	1.42	1	4	0.019
Urea	1.2	1	8	3.43	1	8	0.001
Pulse	2.13	1	8	5.09	1	8	0.001
Cardiac sign	1.38	1	4	1.70	1	8	0.177
Hb	1.89	1	8	3.33	1	8	0.205
WBC	1.71	1	4	1.62	1	4	0.647
ECG	2.06	1	8	3	1	8	0.287
Na	1.33	1	4	1.21	1	2	0.421
K	1.30	1	4	1.67	1	8	0.107
Systolic BP	1.83	1	8	4.0	2	8	0.002
PS total score	25	14	46	34.67	21	59	0.001
Multiple procedure	1.79	1	8	2.07	1	4	0.52
Total blood loss	1.85	1	8	2.67	1	8	0.375
Presence of malignancy	1.30	1	8	1.31	1	4	0.973
Peritoneal soiling	5.22	1	8	7.71	4	8	0.002
Mode of operation	3.86	1	8	4.0	4	4	0.567
OSS Total score	18.89	13	32	22.25	16	29	0.001
PS + OSS Total score	45	30	67	58	41	81	0.001

Table 7
SOFA, MPI, SAS.

	A Group			D Group			*p*-value
	Median	Minimum	Maximum	Median	Minimum	Maximum	
SOFA							
P/*F* rate	0.81	0	3	2	0	4	0.006
Plate	0.14	0	3	0.25	0	2	0.433
T-Bil	0.32	0	2	0.29	0	1	0.837
MAP	0.23	0	2	0.55	0	3	0.078
G.C.S	0.07	0	3	0.21	0	3	0.919
Cre	0.17	0	3	1.00	0	4	0.001
Total	1.43	0	11	4.50	1	12	0.001
MPI							
Age	4.44	0	5	5.00	5	5	0.196
Gender	2.22	0	5	2.50	0	5	0.718
Organ failure	0.78	0	7	3.0	0	7	0.008
Presence of malignancy	0.98	0	4	1.14	0	4	0.759
Preoperative duration	1.07	0	4	0.57	0	4	0.346
Origin of sepsis		0			0		1
Diffuse generalized peritonitis	3.07	0	6	6.0	6	6	0.001
Exudate	7.83	0	12	12	12	12	0.001
Total	19.5	5	36	30.7	23	38	0.001
SAS							
Blood loss	2.15	0	3	1.83	0	3	0.506
Lowest mean arterial pressure	1.74	0	3	1.40	1	3	0.202
Lowest heart rate	1.17	0	4	0.44	0	4	0.11
Total	4.95	1	9	3.86	1	8	0.056

onset to surgery and prognosis, Pisanu et al. reported an association with age, time until surgery, and MPI [6]. They stated that this association may have resulted from the delayed appearance of symptoms of diverticulitis in elderly patients.

In our study, patients treated with anticoagulants or steroid hormones had poor prognoses.

Anticoagulants are mainly used to treat ischemic heart disease, cerebrovascular disease, and thrombosis, while steroid hormones are used to treat connective tissue disease and COPD; these conditions, rather than the severity of colorectal perforation, may constitute preoperative risk factors. Steroid hormones are a risk factor for immunodeficiency, and as such, are also included in APACHE II, but a search of PubMed and Ichushi for papers from 2002 to 2012 containing the key words “colonic perforation” and “prognostic factor” found no reports of anticoagulants as a risk factor.

Thus, this issue needs to be studied more extensively to determine if steroid hormones are a risk factor for immunodeficiency.

In terms of blood test results, there were significant differences in serum creatinine levels, PF ratio, and BE. Abnormal test results indicated the presence of peritonitis or sepsis due to colorectal perforation. Similar to the previous reports, patients with abnormal kidney or respiratory function are believed to have poor prognoses [14]. Physiological function tests showed that patients who exhibited COPD had poor prognoses, probably due to patient background factors rather than the colorectal perforation. The median value of PF, which reflects oxygenation function, was below 300 in Group D, which may have reflected the fact that acute pulmonary injury was already present.

Because COPD causes hypoxemia, respiratory function worsens further in patients with COPD. Patients with a rapid pulse rate had a poor prognosis; this may be attributed to the colorectal perforation. Colorectal perforation causes respiratory damage via the activation of neutrophils and their accumulation in the lungs, with the release of elastase and consequent permeability of pulmonary vessels [15,16]. Pulse rate, a structural factor in systemic inflammatory response syndrome, signals the risk of organ failure. It is also regarded as a risk factor in POSSUM and APACHE II, wherein it is

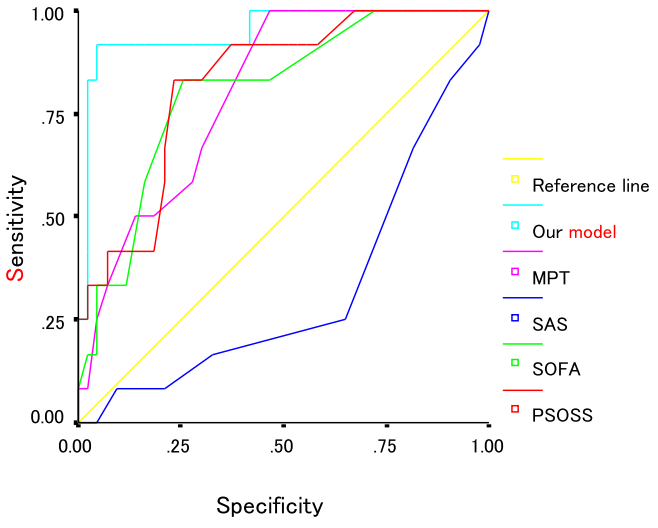

Fig. 1. ROC curves.

Table 8
ROC curves.

Factor	Area	SD	*p*-value
Our Model	0.948	0.037	0.001
POSSUM	0.825	0.063	0.001
SOFA	0.805	0.068	0.001
MPI	0.8	0.062	0.002
SAS	0.322	0.088	0.061

believed to be a sensitive indicator of patients' systemic condition. Although we did not measure blood endotoxins in our study, it is known that tachycardia occurs when endotoxins enter the blood in patients with colorectal perforation and cause septic shock.

The severity of peritoneal soiling was a significant surgical factor. Since it is also an important factor in POSSUM and MPI. Age, serum creatinine level, pulse rate, and severity of peritoneal soiling were selected in multivariate analysis. However, a significant difference was evident only for pulse rate. Both the odds ratio and 95% confidence interval for pulse rate were $\geq$1.0, indicating that it is an important factor for predicting the prognosis of patients undergoing surgery for colorectal perforation. When the cutoff point for the fit of this model was set at 50%, the model had a good fit with predictive accuracy of 96.4%.

When we examined individual factors separately, significant differences were evident for respiratory, kidney, and circulatory function in POSSUM and SOFA; these models take these differences into account. A significant difference was evident in POSSUM, which simply investigated systolic blood pressure, whereas no significant difference was evident for MAP in SOFA and minimum intraoperative MAP in SAS, since these consider vasopressor administration. This should be studied further in the future.

There was a significant difference in the preoperative pulse rate in POSSUM, but no significant difference for intraoperative minimum pulse rate in SAS. This could be because patients were given fluid replacement therapy after presenting at the hospital and before surgery; this therapy alleviated dehydration. In terms of surgical factors, the severity of peritonitis and leakage of bowel contents had a major effect on prognosis, which was reflected in POSSUM and MPI. There was also a significant difference in total scores for POSSUM, SOFA, and MPI, suggesting that these prognostic methods accurately reflect the prognosis of patients undergoing surgery for colorectal perforation. Although there was no significant difference in SAS, the probability of significance was 0.062. We believe this is a simple method that can be effectively used for different conditions.

An investigation of the ROC curves for these predictive prognostic methods and the results of our multivariate analysis showed that the highest peak was shown by the curve derived from our multivariate analysis, for which the area under the curve was 94.8%. The areas under the curve for the other methods were 70–80%, suggesting that these are also excellent predictive prognostic methods. However, as our study was performed as a retrospective investigation, prospective studies will be required in future to further identify the best method.

POSSUM and SOFA, which are currently widely used worldwide, are valid methods of evaluating risk from colorectal perforation. However, our study revealed addition risk factors: (1) PF ratio and BE, which are not included in POSSUM; (2) the pulse rate and severity of peritonitis, which are not included in SOFA, and (3) and anticoagulant/steroid hormone administration. It is more important to assess patients' overall condition than to settle on a single evaluation method.

Such thorough assessments that assess patient's overall condition, has the potential for improving treatment results and acquiring patients' informed consent.

Conflict of interest

The authors have no conflicts of interest to declare.

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