

Original Research Article

Machine Learning-based Model for Predicting Postoperative Complications among Patients with Colonic Perforation: A Retrospective study

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Abstract

Objectives: Surgery for colonic perforation has high morbidity and mortality rates. Predicting complications preoperatively would help improve short-term outcomes; however, no predictive risk stratification model exists to date. Therefore, the current study aimed to determine risk factors for complications after colonic perforation surgery and use machine learning to construct a predictive model.

Methods: This retrospective study included 51 patients who underwent emergency surgery for colorectal perforation. We investigated the connection between overall complications and several preoperative indicators, such as lactate and the Glasgow Prognostic Score. Moreover, we used the classification and regression tree (CART), a machine-learning method, to establish an optimal prediction model for complications.

Results: Overall complications occurred in 32 patients (62.7%). Multivariate logistic regression analysis identified high lactate levels [odds ratio (OR), 1.86; 95% confidence interval (CI), 1.07-3.22; $p = 0.027$] and hypoalbuminemia (OR, 2.56; 95% CI, 1.06-6.25; $p = 0.036$) as predictors of overall complications. According to the CART analysis, the albumin level was the most important parameter, followed by the lactate level. This prediction model had an area under the curve (AUC) of 0.830.

Conclusions: Our results determined that both preoperative albumin and lactate levels were valuable predictors of postoperative complications among patients who underwent colonic perforation surgery. The CART analysis determined optimal cutoff levels with high AUC values to predict complications, making both indicators clinically easier to use for decision making.

Keywords

colonic perforation, postoperative complication, albumin, lactate

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Introduction

Colonic perforation, a well-known disease requiring urgent treatment, is caused by diverticulum, carcinoma, ischemia, and trauma, including iatrogenic causes[1-4]. Patients with colonic perforation frequently require emergency surgery and intensive care support. Despite improved surgical

techniques and perioperative management, colonic perforation surgery still has high morbidity and mortality rates[1]. Some single-center studies reported that over 50% of patients who underwent colonic perforation surgery developed postoperative complications[1,5-7], resulting in perioperative mortality and prolonged hospitalization, delaying postoperative therapy among those with cancer, and increasing medi-

cal costs. Therefore, predicting complications preoperatively would improve short-term outcomes after colonic perforation.

Several studies identified risk factors for complications following surgery for colonic perforation, such as the Mannheim peritonitis Index (MPI)[1,7] and sarcopenia[5]. However, given the complexity of their calculations, they may not be clinically usable in emergencies. Several MPI factors are subjective and may promote evaluative inconsistencies among surgeons. Moreover, considering the absence of a predictive model for risk stratification, an objective and straightforward predictive model for postoperative complications is urgently needed.

The current study aimed to determine risk factors for complications after colonic perforation surgery and establish a predictive model using classification and regression tree (CART) analysis, a machine-learning method. We mainly focused on factors from routine blood tests and inflammation-based indicators of postoperative complications, such as lactate, neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), Glasgow Prognostic Score (GPS), and C-reactive protein-to-albumin ratio (CAR).

Methods

Patients and methods

This single-center, retrospective cohort study included 51 patients who underwent emergency surgery for colorectal perforation at Tokyo Saiseikai Central Hospital between 2012 and 2020. Emergency surgery means surgery performed on the day of the patient's arrival at the hospital. The study excluded patients who underwent elective surgeries and those who could not undergo surgery due to poor systemic status. Hospital records were then retrospectively evaluated for clinical characteristics, including age, sex, clinical findings, preoperative laboratory results, and surgical procedures. We also evaluated several inflammation-based markers, such as NLR, LMR, GPS, and CAR, determined from routine preoperative blood test results. Patients with C-reactive protein (CRP) levels greater than 1.0 mg/dL, and albumin levels lower than 3.5 g/dL were given a GPS of 2. Those with only one laboratory abnormality were given a GPS of 1. Those with normal values in both tests were given a GPS of 0.

Patients underwent the Hartmann procedure, resection, and primary anastomosis, or simple closure according to intra-abdominal findings during surgery. We performed intraoperative colonic lavages in cases requiring primary anastomosis. Hartmann procedure patients tended to have severe intra-abdominal inflammation (e.g., those with diffuse peritonitis or pericolic/distant intra-abdominal abscesses), be at high risk for anastomotic leakage due to poor systemic

status, and have perforations in areas with poor visibility, such as in the rectum. Patients without considerable intra-abdominal inflammation or those with perforations in areas where a wide range of procedures is possible primarily underwent resection and primary anastomosis. Moreover, those with small perforations without considerable inflammation received simple closure. While intra-abdominal drains were routinely inserted, subcutaneous drains were inserted according to the surgeon's preference. Patients received broad-spectrum antibiotics before surgery. We routinely administer antibiotics for approximately seven days after surgery; however, this protocol may need to change if postoperative complications occur. If infectious complications occur postoperatively, we postpone antibiotic administration.

The Clavien-Dindo classification assessed postoperative complications[8]. Accordingly, a Grade I complication was any deviation from the normal postoperative course without the need for treatment. Grade II complications were those requiring pharmacological treatment. Grade III complications were those requiring surgical, endoscopic, or radiological intervention. Grade IV complications were life-threatening complications requiring intensive care unit management, and Grade V complications were patient death. Overall complications were defined as all postoperative complications of Clavien-Dindo Grade I or higher. Pneumonia was defined as high fever with abnormal chest radiography findings and positive sputum culture. Anastomotic leakage was diagnosed based on computed tomography (CT) findings and/or anastomotic drain characteristics. Wound infections were categorized as superficial and deep incisional surgical site infections. Abscesses were diagnosed using CT findings and/or a positive aspirate culture.

The ethics committee approved this study of Tokyo Saiseikai Central Hospital, and all patients provided written consent.

Statistical analysis

We conducted statistical analyses using Stata/IC 16 for Mac (StataCorp, College Station, TX, USA) and R version 3.1.2 (R Foundation Statistical Computing, Vienna, Austria). Categorical variables were analyzed using the chi-square test for univariate analysis, whereas continuous variables were analyzed using the Mann-Whitney U test. A p-value < 0.05 was considered statistically significant. We entered variables with p-values < 0.05 during univariate analysis into a logistic regression model for multivariate analysis. Moreover, CART analysis, a machine-learning method used to construct prediction models simulating the clinical decision process[9-11], was conducted to determine the optimal cut-off values of each blood examination to predict complications. This type of analysis, using a generalization of the binomial variance called the Gini index, has some advantages, including quick prediction and easy visual recognition of

Table 1. Patient Characteristics.

	All (n = 51)	Complication (+) (n = 32)	Complication (-) (n = 19)	p-value
Sex (male/female)	29/22	17/15	12/7	0.484
Age	73 (36–93)	74 (36–93)	72 (54–91)	0.858
ASA score (I/II/III/IV)	20/20/24/5	2/8/17/5	0/12/7/0	0.026
Body mass index (kg/m ²)	22.0 (13.3–30.8)	22.2 (15.0–30.8)	21.5 (13.3–24.7)	0.337
Perforated site (sigmoid/rectum/other)	40/4/7	26/1/5	14/3/2	0.253
Etiology of perforation (carcinoma/diverticulum/others)	10/12/29	7/5/20	3/7/9	0.225
Cardiac history	11 (21.6%)	8 (25%)	3 (27.3%)	0.439
Pulmonary history	5 (9.8%)	3 (9.4%)	2 (10.5%)	0.894
Renal history	12 (23.5%)	8 (25%)	4 (21.1%)	0.748
Diabetes mellitus	8 (15.7%)	3 (9.4%)	5 (26.3%)	0.108
Steroid use	3 (5.9%)	3 (9.4%)	0	0.169
Anticoagulant use	13 (25.5%)	8 (25%)	5 (26.3%)	0.917
Albumin (g/dL)	3.4 (1.1–4.8)	2.7 (1.1–4.8)	3.7 (2.1–4.3)	0.015
Leucocyte (/μL)	8100 (900–36400)	6450 (900–36400)	8800 (1300–22000)	0.371
C-reactive protein (mg/dL)	5.43 (0.03–49.8)	5.65 (0.30–49.8)	5.43 (0.03–41.1)	0.296
Platelet (×10 ³ /μL)	215 (108–496)	218.5 (108–496)	215 (125–391)	0.689
International normalized ratio of prothrombin time	1.1 (0.91–2.28)	1.13 (0.91–2.28)	1.05 (0.94–2.23)	0.089
Lactate (mmol/L)	2.21 (0.65–21.97)	2.38 (0.92–21.97)	1.46 (0.65–5.02)	0.011
NLR	9.9 (1.1–97)	9.7 (1.1–97)	11 (2.4–23)	0.422
LMR	2.7 (0.5–22)	5.8 (0.5–22)	2.5 (1.1–14.5)	0.411
GPS (0/1/2)	15/13/23	8/6/18	7/7/5	0.107
CAR	1.3 (0.01–33.2)	2.1 (0.08–33.2)	1.3 (0.01–14.2)	0.105
Surgical procedure (Hartmann procedure/resection and primary anastomosis/simple closure/others)	34/10/5/2	22/6/2/2	12/4/3/0	0.497
Operative time (min)	189 (82–348)	194 (82–348)	175 (103–308)	0.612
Bleeding (ml)	150 (0–1600)	150 (0–1600)	150 (0–750)	0.602
Time to surgery from first symptom (≤24 h/>24 h)	34/17	22/10	12/7	0.682
The duration of postoperative antibiotics administration (day)	14 (1–43)	22 (1–43)	7 (4–26)	<0.001

Data are presented in n (%) or median (minimum–maximum). ASA, American Society of Anesthesiologists; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; GPS, Glasgow Prognostic Score; CAR, C-reactive protein-to-albumin ratio.

important variables. We started with a single node and subsequently assessed binary distinctions that provided the most information regarding the class until a stop criterion was satisfied. The algorithm stopped when there was no dependence between predictor variables and the outcome variable. The p-value indicates the relationship between predictor and outcome variables. At the beginning of the analysis, the first decision node was most strongly associated with outcome and was extracted as the first node. Finally, the accuracy of the results for predicting complications was confirmed using the area under the receiver operating characteristic curve (AUC). The R package “party” was used.

Results

Patient characteristics and morbidity

The study included 51 patients [29 males and 22 females; median age, 73 years (range 36-93 years)], among whom 40

(78.4%) had a perforation in the sigmoid colon, four in the rectum, three in the ascending colon, two in the transverse colon, and one in the cecum and descending colon. Perforations resulted from a diverticulum in 12 patients (23.5%) and cancer in 10 patients (19.6%). Other causes of colonic perforation were stool (in 14 patients), iatrogenic factors (in 6 patients), idiopathic factors (in 4 patients), ischemic enteritis (in 2 patients), foreign body (in 2 patients), and ulcerative colitis (in 1 patient). The Hartmann procedure was performed in 34 patients (66.7%), while 10 (19.6%) patients underwent partial colorectal resection with primary anastomosis. Table 1 summarizes the patients’ clinical characteristics.

In this study, 32 patients (62.7%) developed overall complications. Wound infection was the most common (n = 13; 25.4%), followed by abdominal abscess (n = 9; 17.6%), pneumonia (n = 6; 11.8%), anastomotic leakage, and gastrointestinal hemorrhage (n = 2; 3.9%). Among the included patients, 3 (5.9%) died following surgery (Table 2).

Table 2. Postoperative Complications.

	All (n = 51)	CD Grades 1 and 2	CD Grades 3 and higher
Postoperative complication	32 (62.7%)	16 (31.4%)	16 (31.4%)
Wound infection	13 (25.4%)	9 (17.6%)	4 (7.8%)
Abdominal abscess	9 (17.6%)	4 (7.8%)	5 (9.8%)
Pneumonia	6 (11.8%)	4 (7.8%)	2 (3.9%)
Anastomotic leakage	2 (3.9%)	0	2 (3.9%)
Gastrointestinal hemorrhage	2 (3.9%)	0	2 (3.9%)
Other	4 (7.8%)	2 (3.9%)	2 (3.9%)
Death	3 (5.9%)		

Data are presented as n (%). CD, Clavien–Dindo classification.

Table 3. Multivariate Logistic Regression Analysis for Predicting Overall Complications.

	Multivariable analysis	
	Odds ratio (95% CI)	p-value
Hypoalbuminemia	2.56 (1.06–6.25)	0.036
High ASA score	1.47 (0.49–4.36)	0.491
High lactate levels	1.86 (1.07–3.22)	0.027

ASA, American Society of Anesthesiologists; CI, confidence interval.

Risk factors for overall complications

Table 1 shows univariate analyses for overall complication factors. Accordingly, significant intergroup differences were observed in American Society of Anesthesiologists scores ($p = 0.026$), albumin levels ($p = 0.015$), and lactate levels ($p = 0.011$). Other inflammation-based indicators, such as NLR, LMR, and GPS, were not identified as significant factors. Because we postponed the administration of antibiotics in patients who had infectious complications postoperatively, the intergroup differences in postoperative antibiotic therapy duration were also significant ($p < 0.001$). However, antibiotic therapy duration is a postoperative factor. Therefore, we did not include it in multivariable analysis for predicting overall complications. Multivariate logistic regression analysis of the three aforementioned factors identified high lactate levels [odds ratio (OR), 1.86; 95% confidence interval (CI), 1.07–3.22; $p = 0.027$] and hypoalbuminemia (OR, 2.56; 95% CI, 1.06–6.25; $p = 0.036$) as predictors of overall complications (Table 3). We found a similar tendency after excluding the three patients who suffered mortality (lactate: OR, 1.85; 95% CI, 1.06–3.22; $p = 0.030$ and albumin: OR, 2.58; 95% CI, 1.06–6.25; $p = 0.036$).

CART-based prediction model for overall complications

To establish a prediction model for overall complications after surgery, we used significant variables in multivariable analyses (i.e., albumin and lactate levels). Accordingly, albu-

min level was the most critical parameter for overall complication (Figure 1), with an optimal cutoff value of 2.8 g/dL. As such, patients with albumin levels below the cutoff had significantly higher complication rates than those with levels over the cutoff (high-risk group: 18/20 patients; $p = 0.02$). The second most important parameter was lactate level, with an optimal cutoff value of 1.56 mmol/L. Despite having albumin levels above the cutoff, patients with lactate levels above the cutoff had significantly higher complication rates than those below the cutoff (middle-risk group: 13/20 patients, low-risk group: 1/11 patients; $p = 0.027$). The CART decision tree had an AUC of 0.830 (95% CI, 0.717–0.942). Table 4 shows the relationship between risk groups established by the predictive model and the Clavien–Dindo Grade. This model could stratify risk groups and predict Grade 1 complications ($p = 0.005$) and Grade 3 or higher complications ($p = 0.016$).

Discussion

The present study demonstrated that both preoperative albumin and lactate levels were valuable indicators for predicting complications among patients who had undergone surgery for colonic perforation. Additionally, we used CART analysis to determine the optimal cutoff levels with high AUC values for predicting complications, making both indicators clinically easier to use and facilitated decision making. Our report is the first to establish a prediction model for postoperative complications among patients with colonic perforation to the best of our knowledge.

Several studies have suggested that objective laboratory results are associated with postoperative complications after surgery for colonic perforation. Accordingly, Shin et al. reported CRP and estimated glomerular filtration rate were significant risk factors for postoperative complications after multivariable analysis[12]. Kubo et al. showed that age and renal dysfunction were significant predictive factors for severe complications, together with sarcopenia[5]. Despite the utility of the aforementioned objective factors for predicting complications preoperatively, none of the previous studies

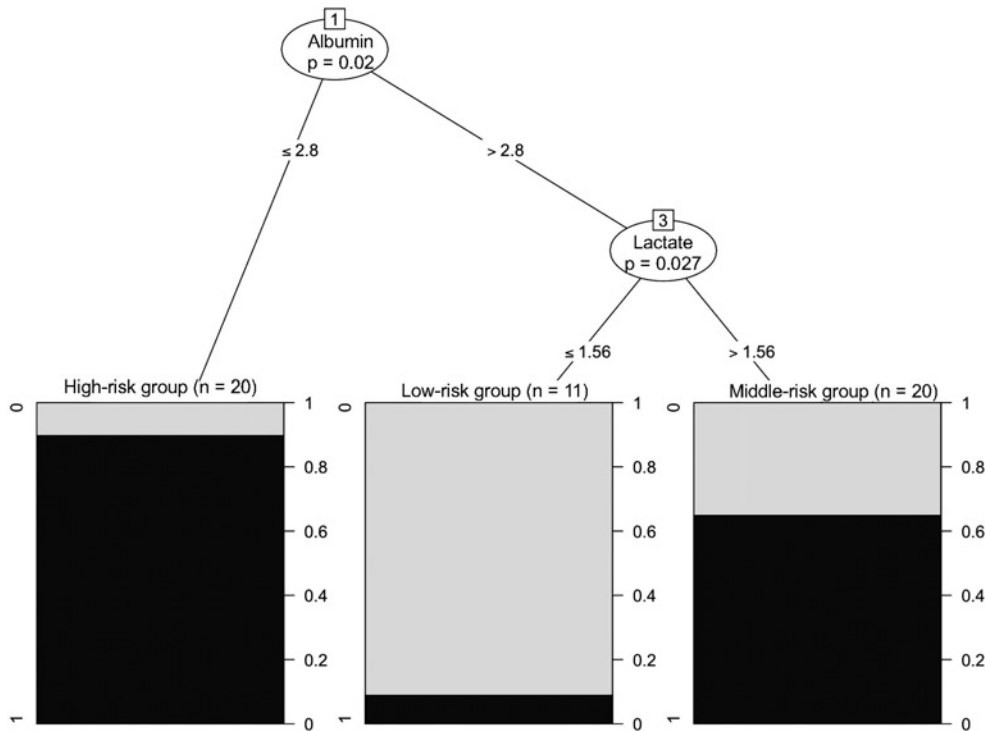


Figure 1. Prediction model for overall complication using classification and regression tree analysis.

Classification and regression tree analysis determined albumin level as the most important parameter for overall complication, with an optimal cutoff value of 2.8 g/dL. Accordingly, patients with albumin levels below the cutoff had significantly higher complication rates than those below the cutoff. The second most important parameter was lactate, with an optimal cutoff value of 1.56 mmol/l. Accordingly, complication rates were 90% (18/20 patients), 65% (13/20 patients), and 9.1% (1/11 patients) among patients in the high-, middle-, and low-risk group, respectively.

Table 4. Relationship between Risk Group Established by Predicting Model and Complications.

Complication	High-risk group (n = 20)	Middle-risk group (n = 20)	Low-risk group (n = 11)	p-value
All complications				<0.001
Yes (n = 32)	18 (90%)	13 (65%)	1 (9.1%)	
No (n = 19)	2 (10%)	7 (35%)	10 (90.9%)	
CD Grades 1 and 2*				0.005
Yes (n = 16)	8 (80%)	7 (50%)	1 (9.1%)	
No (n = 19)	2 (20%)	7 (50%)	10 (90.9%)	
CD Grades 3 and higher				0.016
Yes (n = 16)	10 (50%)	6 (30%)	0 (0%)	
No (n = 35)	10 (50%)	14 (70%)	11 (100%)	

Data are presented as n (%). CD, Clavien–Dindo classification.

*The 16 patients who have Clavien–Dindo Grades 3 and higher complications were excluded in the analyses for relationship between risk groups and Grade 1 and 2 complications.

had created a predictive risk stratification model. Therefore, the present study established a model composed of albumin and lactate levels for predicting postoperative complications using CART analysis. In patients with colonic perforation,

we selected surgical treatment for each patient intraoperatively based on the severity of inflammation. Therefore, this predictive model can help determine the optimal surgical approach, including whether primary anastomosis is possible.

The present study found that preoperative albumin and lactate levels were significant predictors of complications. Numerous studies have revealed that hypoalbuminemia was a strong prognostic indicator of morbidity and mortality following colorectal surgery[13-17]. Moreover, albumin is a negative acute-phase inflammatory reactant[18]. Patients with considerable inflammation, such as those with low preoperative albumin levels, may have increased risk for postoperative complications due to lymphopenia, leading to compromised cell-mediated immunity[19,20]. Furthermore, hypoalbuminemia-induced malnutrition can also lead to impaired healing and impaired immune response[19,20], which may cause complications, particularly infectious ones. Although clinical hypoalbuminemia has been typically defined as albumin levels less than 3.0 g/dL, our study suggested that 2.8 g/dL was the optimal cutoff value. Since our patients had considerable inflammation, the optimal cutoff value estimated herein may have been low. Studies have shown that lactate levels can be elevated in two ways: (1) increased production or (2) reduced liver or kidney clearance[21]. Accordingly, excess lactate production may occur due to inflammatory mediators, whereas reduced lactate clearance may occur due to microcirculatory disorder. Jobin et al. associated preoperative lactate levels with postoperative mortality among patients undergoing emergency laparotomy for perforation peritonitis[22]. Therefore, we also considered that lactate levels could reflect perforation severity and that complications may occur among patients with serious systemic conditions that raise lactate levels.

Recent studies have shown that systemic inflammatory response indicators, such as GPS and NLR, correlated with long-term prognoses and postoperative morbidities[23,24]. As such, the current study also investigated the association between several indicators of a systemic inflammatory response, including NLR, LMR, CAR, and GPS, and short-term outcomes. However, there was no significant association between these indicators and short-term outcomes despite them reflecting immune response and systemic nutritional status similar to albumin, a risk factor in the present study. The insufficient number of patients included in this study is the main reason why we found no difference regarding these inflammatory markers. Further analysis with a larger cohort might reveal a different result. However, another reason may be that noninfectious complications, such as gastrointestinal hemorrhage, were included as outcomes.

Several limitations of the current study are worth noting. First, this single-center study included only a small number of Japanese patients, which may have resulted in selection bias. Second, this study did not consider colonic perforation severity, which we believed had been indicated by albumin and lactate levels. Therefore, more research is needed to clarify the relationship between albumin and lactate levels and colonic perforation severity.

In conclusion, the findings presented herein suggest that both preoperative albumin and lactate levels were valuable indicators for predicting complications among patients who had undergone surgery for colonic perforation. Additionally, CART analysis determined the optimal cutoff levels with high AUC values for predicting complications, which made both indicators clinically easier to use and facilitated decision making.

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Conflicts of Interest

There are no conflicts of interest.

Author Contributions

HHo and MT contributed equally to this work. All authors give final approval of the manuscript and agree to be accountable for all aspects of the work.

HHo-literature search, study design, analysis plan, data analysis and interpretation, drafting of the manuscript.

MT-literature search, study design, analysis plan, data analysis and interpretation, drafting of manuscript

TI-data interpretation and analysis, manuscript revision

HY-data interpretation and analysis, manuscript revision

AY-data interpretation and analysis, manuscript revision

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YKo-study design, data interpretation and analysis

YKa-study design, data interpretation and analysis

MO-study design, data analysis, manuscript revision

FT-study design, data interpretation and analysis

TE-study design, data interpretation and analysis

HHa-study design, manuscript revision

Approval by Institutional Review Board (IRB)

Our study protocol was approved by the Institutional Review Board of Tokyo Saiseikai Central Hospital. (Registration No: 2019037).

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