J Gastrointest Surg (2018) 22:508–515
https://doi.org/10.1007/s11605-017-3622-8

ORIGINAL ARTICLE

Perioperative Factors Predicting Prolonged Postoperative Ileus After Major Abdominal Surgery

Kotaro Sugawara[1,2] · **Yoshikuni Kawaguchi**[1,3] · **Yukihiro Nomura**[1] · **Yusuke Suka**[1] · **Keishi Kawasaki**[1] · **Yukari Uemura**[4] · **Daisuke Koike**[1] · **Motoki Nagai**[1] · **Takatoshi Furuya**[1] · **Nobutaka Tanaka**[1]

Received: 24 August 2017 / Accepted: 26 October 2017 / Published online: 8 November 2017

Abstract

Background Prolonged postoperative ileus (PPOI) is among the common complications adversely affecting postoperative outcomes. Predictors of PPOI after major abdominal surgery remain unclear, although various PPOI predictors have been reported in patients undergoing colorectal surgery. This study aimed to devise a model for stratifying the probability of PPOI in patients undergoing abdominal surgery.

Methods Between 2012 and 2013, 841 patients underwent major abdominal surgery after excluding patients who underwent less-invasive abdominal surgery, ileus-associated surgery, and emergency surgery. Postoperative managements were generally based on enhanced recovery after surgery (ERAS) program. The definition of PPOI was based on nausea, no oral diet, flatus absence, abdominal distension, and radiographic findings. A nomogram was devised by evaluating predictive factors for PPOI.

Results Of the 841 patients, 73 (8.8%) developed PPOI. Multivariable logistic regression analysis revealed smoking history ($P = 0.025$), colorectal surgery ($P = 0.004$), and an open surgical approach ($P = 0.002$) to all be independent predictive factors for PPOI. A nomogram was devised by employing these three significant predictive factors. The prediction model showed relatively good discrimination performance, the concordance index of which was 0.71 (95%CI 0.66–0.77). The probability of PPOI in patients with a smoking history who underwent open colorectal surgery was calculated to be 19.6%.

Conclusions Colorectal surgery, open abdominal surgery, and smoking history were found to be independent predictive factors for PPOI in patients who underwent major abdominal surgery. A nomogram based on these factors was shown to be useful for identifying patients with a high probability of developing PPOI.

Keywords Postoperative prolonged ileus · Nomogram · Colorectal surgery · Upper gastrointestinal surgery · Laparoscopic surgery

Kotaro Sugawara and Yoshikuni Kawaguchi contributed equally to this work.

✉ Yoshikuni Kawaguchi
yokawaguchi-tky@umin.ac.jp

✉ Nobutaka Tanaka
nbtanaka@hospital.asahi.chiba.jp

1 Department of Surgery, Asahi General Hospital, 1326, I, Asahi, Chiba, Japan

2 Department of Gastrointestinal Surgery, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan

3 Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

4 Biostatistics Division, Clinical Research Support Center, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan

Abbreviations

ASA	American Society of Anesthesiologists Physical Status classification system
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
EBL	Estimated blood loss
eGFR	Estimated glomerular filtration rate
ERAS	Enhanced recovery after surgery
IQR	Interquartile range
PNI	Prognostic nutritional index
POD	Postoperative day
PPOI	Postoperative prolonged ileus

PS Performance status
WBC White blood cell count

Introduction

Prolonged postoperative ileus (PPOI) is a common complication, ranging in frequency from 10 to 30% after abdominal surgery[1,2] and 15 to 30% after colorectal surgery.[3,4] PPOI was reported to cause abdominal pain, nausea/vomiting, abdominal distension, and intolerance to oral feeding[5,6] and to increase hospital costs.[7]

Previous studies have identified a variety of predictive factors associated with PPOI, including chronic pulmonary disease, male gender, smoking history, operation history, prolonged operation time, advanced age, an American Society of Anesthesiologists Physical Status classification system (ASA) score ≥ 2, preoperative sepsis, total opioid dose, repeated surgery, the abdominal incision length, using an open surgical approach, preoperative low albumin level, peripheral vascular disease, and perioperative transfusion.[1,3,8,9] However, most of these studies targeted patients who underwent colorectal surgery. Predictors of PPOI in patients undergoing abdominal surgery including gastrointestinal, colorectal, hepato-biliary-pancreatic, and vascular surgeries remain unclear. Selection of a high probability of PPOI is useful for closely monitoring patients and strictly perform evidenced-based postoperative managements. Namely, a laparoscopic surgical approach,[10–12] a non-fasting period,[7,10] optimal fluid management,[10] opioid-sparing analgesia,[10] early mobilization,[7,10,13] and chewing gum use[14] were reported to be effective for the prevention of PPOI. Thus, a model designed to stratify the probability of PPOI in patients undergoing abdominal surgery is useful for preoperatively identifying patients with a high probability of developing PPOI.

The aim of the present study was to devise a model allowing stratification of the probability of PPOI in patients undergoing abdominal surgery, based on evaluating predictive factors for PPOI.

Materials and Methods

Patients

From April 2012 to December 2013, a total of 1666 consecutive patients underwent abdominal surgery under general anesthesia in Asahi General Hospital. The collected data were retrieved from prospectively maintained databases and included baseline patient characteristics (demographic data and comorbidities), operative characteristics, and postoperative outcomes. Patients who underwent less-invasive abdominal surgery (laparoscopic cholecystectomy, appendectomy, stoma construction or closure, and gastrointestinal bypass construction), ileus-related surgery, and emergency surgery for acute panperitonitis were excluded from the analysis. All operations were performed after obtaining informed consent from the individual patients. The local institutional review board approved this study (ID: 2013091712).

Definition of Postoperative Prolonged Ileus

PPOI was defined based on previous studies.[2,15–17] Namely, PPOI was diagnosed when patients developed two or more symptoms among the following five criteria on POD 4 or later:

1. Nausea or vomiting over the preceding 12 h.
2. Inability to tolerate an oral diet over the prior 24 h.
3. Absence of flatus over the prior 24 h.
4. Abdominal distension defined by a clinician as increased abdominal girth with tympany on percussion.
5. Radiologic confirmation such as gastric distension, presence of air–fluid levels, and dilated small or large bowel loops without a transition point.

Preoperative Management for Postoperative Prolonged Ileus

Preoperative counseling was delivered to the patients in the outpatient clinic as recommended in the ERAS program.[18–21] A checklist showing the rehabilitation plan and daily mobilization and nutritional goals were provided.

Anesthesia

All of the patients were given epidural anesthesia and general anesthesia comprised of remifentanil, fentanyl, propofol, O_2–N_2O sevoflurane, rocuronium, vecuronium, and sugammadex without premedication. Nasogastric tubes were routinely removed in the operating room. In case of repeated nausea and/or vomit in the recovery room, nasogastric tubes were inserted to improve patients' symptoms.

Postoperative Management

Postoperative management was generally based on ERAS program[18–21] and partly modified depending on patients' conditions and attending surgeons. A dietary supplementation product enriched with glutamine, dietary fiber, and oligosaccharide[22] was started on postoperative day 1, and a solid diet was started on POD 2 or 3, depending on patients' conditions. Epidural analgesia was generally used until POD 3 or 4. Intravenous opioid administration was initiated when pain was not well-controlled using epidural analgesia, acetaminophen, and/or non-steroidal anti-inflammatory drugs. Patients were encouraged to do mobilization and walk around the ward on postoperative day 1 with physical therapists. The urinary catheter and the abdominal drainage tubes were removed as soon as possible. Complication screening was performed based on clinical symptoms, blood test results, and X-ray imaging on PODs 1, 3, and 5, or later, if needed. Computed tomography was performed to detect complications, if necessary. Postoperative morbidity was graded according to the Clavien-Dindo classification,[23] in which grade III, IV, and V complications were defined as "major."

Studied Criteria

Eastern Cooperative Oncology Group (ECOG) Performance Status was used to assess the functional status of patients.[24] The definitions of comorbidity were as follows. Cardiac disease was defined as having one of following diseases: coronary artery disease, heart failure, severe heart valve disease, myocardial disease, and arrhythmia. Pulmonary diseases included asthma, chronic obstructive pulmonary disease, bronchiectasis, sequelae of pulmonary tuberculosis or tuberculous pleurisy, and interstitial lung disease. Both current smokers and ex-smokers are defined as having "smoking history" in this study. Cerebrovascular diseases included intracerebral hemorrhage and cerebral infarction. All patients were preoperatively referred to anesthesiologists and classified into six grades using the American Society of Anesthesiologists (ASA) Physical Status classification system. The prognostic nutritional index (PNI) was used as an indicator of nutritional status: PNI = 10 × albumin (g/dL) + 0.005 × lymphocyte count (/μL).

Surgical procedures were divided into the following five categories to assess the influence of each surgical procedure on PPOI development: (1) upper gastrointestinal surgery—esophagectomy and gastrectomy; (2) colorectal surgery—colectomy and rectectomy; (3) hepato-biliary-pancreatic surgery—hepatectomy, pancreatectomy, open cholecystectomy, and cholecystolithotomy; (4) vascular surgery—abdominal aortic aneurysm repair; (5) other operations—enterectomy, abdominal wall hernioplasty, splenectomy, and explorative laparotomy.

Statistical Analysis

Categorical variables are expressed in numerical figures and percentages and were compared using Fisher's exact test or the χ^2 test, as appropriate. Continuous variables are expressed as the median (interquartile range (IQR)) and were compared using Wilcoxon's rank-sum test. Multivariable analysis was conducted to identify predictive factors for PPOI, and factors with $P < 0.10$ in the univariable analyses were entered into the logistic regression model for multivariable analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each factor. A P value of less than 0.05 was considered to indicate a statistically significant difference. The logistic regression model and the cross-validation method were used to generate a nomogram to predict the incidence of PPOI. The Harrel's C-statistics of the identified model was estimated. The cutoff level for estimated blood loss (EBL) in our study was set at 500 mL, based on previous reports.[3] Statistical analysis was conducted with JMP software (version 9.0.2; SAS Institute Inc., Cary, NC) and SAS software version 9.4 (SAS Inc., Cary, NC, USA).

Results

Demographic Characteristics

Of the 1666 patients, 841 were selected for this study after exclusion of 825 patients who underwent less-invasive operations such as laparoscopic cholecystectomy ($n = 310$), appendectomy ($n = 204$), stoma construction or closure ($n = 92$), and gastrointestinal bypass construction ($n = 28$) and 191 patients who underwent ileus-associated operations such as emergency surgery for acute panperitonitis ($n = 119$) and procedures for ileus ($n = 72$). There were 577 men and 264 women, with a median age of 71 years (range, 22–94 years). Surgical procedures included upper gastrointestinal surgery in 293 (34.8%) patients, colorectal surgery in 301 (35.8%), hepato-pancreatobiliary surgery in 166 (19.7%), vascular surgery in 62, and other operations ($n = 14$, 1.7%) mainly including intestinal surgeries ($n = 9$, 1.1%). Of the 841 patients, 73 (8.8%) developed PPOI: upper gastrointestinal surgery (7.8%), colorectal surgery (12.4%), hepato-biliary-pancreatic surgery (5.4%), and vascular surgery (4.8%). The remaining 768 (91.2%) did not develop PPOI (the non-PPOI group).

The demographic data were compared between these two groups (Table 1). The rates of male gender and smoking history were significantly higher in the PPOI group than in the non-PPOI group: male, 83.6 vs. 58.4%, $P < 0.001$; smoking history, 83.6 vs. 62.4%, $P < 0.001$. There were no significant differences between the groups in age, BMI, comorbidity, performance status,[25] operation history, or preoperative laboratory data.

Comparison of Intraoperative Outcomes Between the Groups

Intraoperative outcomes are shown in Table 2. The rate of colorectal surgery was significantly higher in the PPOI group than in the non-PPOI group (52.1 vs. 34.9%, $P = 0.004$). The open surgical approach rate was significantly higher in the PPOI group than in the non-PPOI group (93.2 vs. 75.1%, $P < 0.001$). The rates of other types for surgical procedures and emergency surgery were similar in the two groups. The

Table 1 Comparison of demographic characteristics between the groups

Variables	PPOI group (n = 73)	Non-PPOI group (n = 768)	P value
Patient characteristics			
Male/female	61/12	507/261	< 0.001
Age (years)	73 (62–78)	71 (62–77)	0.860
BMI (kg/m^2)	23.6 (21.1–25.9)	22.8 (20.3–25.3)	0.190
Comorbidity			
Hypertension	30 (41.1%)	278 (36.2%)	0.420
Diabetes mellitus	18 (24.7%)	204 (26.5%)	0.710
Cardiac disease	25 (34.2%)	216 (28.1%)	0.39
Pulmonary disease	4 (5.5%)	44 (0.5%)	0.58
Cerebrovascular disease	9 (12.3%)	79 (10.3%)	0.59
Dementia	0 (−)	6 (0.8%)	0.29
Smoking history	61 (83.6%)	479 (62.4%)	< 0.001
PS ≥ 2	6 (8.2%)	28 (3.6%)	0.090
ASA status ≥ 3	9 (12.3%)	113 (14.7%)	0.38
Operation history	27 (37.0%)	271 (35.2%)	0.93
Preoperative laboratory data			
White blood cell count (/μL)	5800 (4700–7200)	5800 (4800–7300)	0.74
Hemoglobin (g/dL)	12.2 (10.6–14.0)	12.4 (10.7–13.8)	0.68
Albumin (g/dL)	3.9 (3.2–4.3)	3.9 (3.4–4.3)	0.82
Total bilirubin (mg/dL)	0.7 (0.58–0.9)	0.7 (0.5–0.9)	0.59
eGFR (mL/min/1.73 m^2)	64.9 (54.0–77.4)	67.0 (55–79.8)	0.63
PNI	45.7 (41.1–52.5)	48 (41.1–52.8)	0.79

ASA the American Society of Anesthesiologists Physical Status classification system, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *PNI* prognostic nutritional index, *PS* performance status

operation time was significantly longer in the PPOI group than in the non-PPOI group: 305 min (IQR, 242–484 min) vs. 270 min (IQR, 211–358 min), P = 0.002. The amounts of EBL did not differ significantly between the groups.

Postoperative Outcomes

The postoperative outcomes are summarized in Table 3. There were no significant differences regarding the postoperative

Table 2 Comparison of operative characteristics between the groups

Variables	PPOI group (n = 73)	Non-PPOI group (n = 768)	P value
Operative procedures			
Surgery type			
Upper gastrointestinal	23 (31.5%)	270 (35.1%)	0.52
Colorectal	38 (52.1%)	268 (34.9%)	0.004
Hepatopancreatobiliary	9 (12.3%)	157 (20.4%)	0.085
Vascular	3 (4.1%)	59 (7.7%)	0.23
Others	0 (−)	14 (1.8%)	
Open abdominal surgery	68 (93.2%)	577 (75.1%)	< 0.001
Emergency surgery	3 (4.1%)	43 (5.6%)	0.58
Malignancy	61 (83.6%)	619 (80.5%)	0.72
Intraoperative variables			
Operation time (min)	305 (242–484)	270 (211–358)	0.002
EBL (mL)	316 (130–737)	218 (50–480)	0.10

EBL estimated blood loss

Table 3 Comparison of postoperative outcomes between the two groups

Variables	PPOI group (*n* = 73)	Non-PPOI group (*n* = 768)	*P* value
Postoperative management			
Use of opioid drugs	29 (39.7%)	264 (34.4%)	0.36
Epidural anesthesia	64 (87.7%)	667 (86.8%)	0.84
Length of hospital stay (days)	19 (12–33)	8 (6–13)	< 0.001
Hospital mortality	2 (2.7%)	21 (2.7%)	0.49
Postoperative morbidity	73 (100%)	249 (32.4%)	< 0.001
Complications except ileus	40 (54.8%)	249 (32.4%)	< 0.001
Minor complications (C-D classification grade I, II)	54 (74.0%)	150 (19.5%)	< 0.001
Ileus	71 (97.3%)	0 (−)	N/A
Others	23 (31.5%)	150 (19.5%)	0.035
Major complications (C-D classification ≥ grade III)	19 (26.0%)	94 (12.2%)	< 0.001
Ileus	2 (%)	0 (−)	N/A
Others	17 (23.3%)	94 (12.2%)	0.003
Abdominal Infection	9 (12.3%)	52 (6.8%)	0.078
Reoperation for abdominal infection	4 (5.5%)	16 (2.1%)	0.07
30-day mortality	2 (2.7%)	6 (0.8%)	0.17
90-day mortality	2 (2.7%)	27 (3.5%)	0.72
180-day mortality	3 (4.1%)	41 (5.3%)	0.32

N/A not available

use of opioid drugs or epidural anesthesia. The median postoperative hospital stay was significantly longer in the PPOI group than in the non-PPOI group: 19 days (IQR, 12–33 days) vs. 8 days (IQR, 6–13 days). The rates of hospital mortality and the 30, 90, and 180-day mortality rates did not differ significantly between the two groups.

The rates of morbidity and major complications other than ileus were significantly higher in the PPOI group than in the non-PPOI group: morbidity, 54.8 vs. 32.4%, $P < 0.001$; major complications, 23.3 vs. 12.2%, $P = 0.003$. The frequencies of abdominal infections more than grade 3 (C-D Classification) did not differ significantly between the groups (PPOI-group, 12.3%; non-PPOI group, 6.8%, $P = 0.08$). Also, the rates of reoperation for abdominal infection did not differ significantly between the PPOI group and the non-PPOI group (5.5 vs. 2.1%, $P = 0.07$).

Factors Associated with PPOI

Univariable analyses showed male gender, smoking history, performance status ≥ 2, colorectal surgery, use of an open surgical approach, operation time > 240 min, and EBL > 500 mL were potential predictors of PPOI. Subsequent multivariable logistic regression analysis revealed that smoking history (OR 2.31, 95% CI 1.11–5.17, $P = 0.025$), colorectal surgery (OR 4.53, 95% CI 1.54–19.4, $P = 0.004$), and use of an open surgical approach (OR 3.74, 95% CI 1.56–11.12, $P = 0.002$) were all independent predictive factors for PPOI (Table 4).

Construction of a Nomogram for PPOI

A nomogram was generated by incorporating the three significant predictive factors: smoking history, operative method, and open surgery (Fig. 1). The performance of the prediction model was assessed using the concordance index, the calculated value of which was 0.71 (95%CI 0.66–0.77), showing relatively good discrimination. Also, the calibration of observed versus predicted outcomes was in good accord with a Hosmer and Lemeshow test *P* value of 0.97. The ability of this model to distinguish patients with a low probability of PPOI from those with a high probability of PPOI can be demonstrated by considering two hypothetical individuals who might be encountered in practice: patient A with smoking history receives open colorectal surgery, whereas patient B without smoking history receives open HPB surgery. Our model predicted that patient A would have a 19.6% probability of developing PPOI whereas patient B would have a 2.5% probability of developing PPOI; that is, the predicted PPOI incidence for patient A was calculated to be 7.8 times greater than that for patient B.

Table 4 Predictive factors associated with postoperative prolonged ileus

Variables	Univariable analysis			Multivariable analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Patient factors						
Sex (male/female)	2.48	1.36–4.90	0.002	1.56	0.74–3.49	0.25
Age (≥ 65/< 65 years)	1.21	0.73–2.10	0.47			
BMI (> 28/< 28)	1.84	0.85–3.63	0.11			
Comorbidity						
Hypertension	1.23	0.75–1.99	0.42			
Diabetes mellitus	0.90	0.50–1.54	0.71			
Cardiac disease	1.25	0.74–2.07	0.39			
Cerebrovascular disease	1.23	0.55–2.45	0.59			
Smoking history	2.88	1.58–5.71	< 0.001	2.31	1.11–5.17	0.025
PS ≥ 2	2.37	0.86–5.57	0.09	2.70	0.94–6.81	0.064
ASA status ≥ 3	1.39	0.68–3.20	0.38			
Operation history	1.02	0.61–1.67	0.93			
Preoperative laboratory data						
Hemoglobin (< 12.0/≥ 12.0 g/dL)	1.11	0.69–1.80	0.66			
Albumin (< 3.8/≥ 3.8 g/dL)	1.00	0.61–1.63	0.99			
eGFR (< 60/ ≥60 mL/min/1.73 m^2)	1.10	0.66–1.81	0.71			
PNI (< 40/≥ 40)	0.85	0.45–1.51	0.59			
Operative procedures						
Surgery type						
Upper gastrointestinal	1.68	0.56–7.22	0.39	2.46	0.80–10.8	0.13
Colorectal	2.79	0.97–11.8	0.059	4.53	1.54–19.4	0.004
Hepatopancreatobiliary	1.13	0.33–5.24	0.85	1.18	0.33–5.56	0.81
Vascular	1.00	Reference		1.00	Reference	
Others	0 (−)	0 (−)	0.25	0 (−)	0 (−)	0.37
Open surgical approach	4.07	1.78–11.7	< 0.001	3.74	1.56–11.12	0.002
Emergency surgery	0.72	0.17–2.05	0.58			
Malignancy	1.12	0.62–2.18	0.72			
Intraoperative variables						
Operation time > 240 min	1.85	1.08–3.34	0.025	1.62	0.86–3.13	0.14
EBL > 500 mL	2.02	1.21–3.30	0.007	1.55	0.85–2.82	0.15
Postoperative management						
Use of opioid drugs	1.19	0.72–1.94	0.49			
Epidural anesthesia	1.06	0.54–2.36	0.86			
Postoperative outcomes						
Intra-abdominal infection (≥ grade IIIa)	1.94	0.86–3.93	0.11			

ASA American Society of Anesthesiologists Physical Status classification system, *eGFR* estimated glomerular filtration rate, *PNI* prognostic nutritional index, *PS* performance status

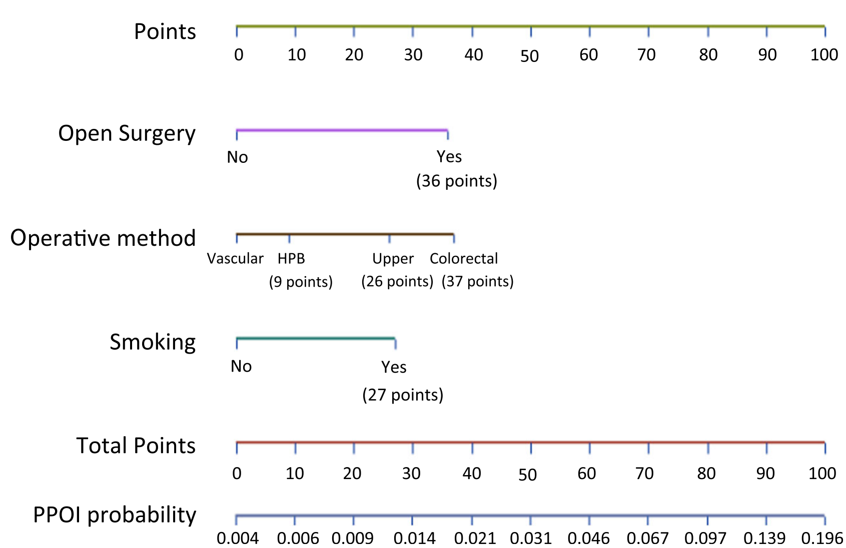

Fig. 1 Nomogram. Three predictive factors were employed for establishing a nomogram; smoking history, operative method, and open surgery. The discrimination concordance index for the predictive model was 0.71 (95%CI 0.66–0.77). A calibration of observed versus predicted outcomes was assessed employing the Homer and Lemeshow test with a *P* value of 0.97

Discussion

Our study identified three independent predictive factors for PPOI in patients who underwent major abdominal surgery: smoking history, colorectal surgery, and employing an open surgical approach. Based on these predictors, a nomogram was constructed to preoperatively select patients with a high probability of PPOI. Thus, a nomogram type of evaluation was found to be useful. The nomogram was found to be capable of distinguishing low-PPOI-probability from high-PPOI-probability patients using variables with a discrimination concordance index of 0.71 (95%CI 0.66–0.77).

The mechanisms of PPOI development are multifactorial.[6,13] Thus, a wide variety of predictors of PPOI have been reported.[1,4,13,26] Operation history was reported to be one of the predictors for postoperative ileus.[16] However, it was not a significant factor to predict PPOI using univariable analysis. The present study demonstrated the three aforementioned independent predictors of PPOI (smoking history, colorectal surgery, open approach) in patients who were mainly managed based on the ERAS program. These factors were in line with those in the previous reports focusing on colorectal surgery. Thus, the nomogram was devised using the three factors. However, few studies have focused on evaluating predictors of PPOI in patients who underwent major abdominal surgery. Our nomogram predicted PPOI development in 13.8% of patients with smoking history undergoing open gastrointestinal surgery, 19.6% of patients with smoking history undergoing open colorectal surgery, and 2.5% of patients without smoking history undergoing open HPB surgery. The nomogram was found to be useful and convenient for nurses and other healthcare professionals as well as doctors by helping them to ascertain the probability of PPOI in each patient before surgery.

A number of studies have shown a lower incidence rate of PPOI in laparoscopic colorectal surgery than open colorectal surgery.[1,15,26] These observations are most likely attributable to the laparoscopic approach reducing the stimulation of bowel inhibitory reflexes, intestinal manipulation, and surgical stress.[13,26] Smoking may reduce arterial blood flow and tissue oxygenation of the alimentary tract, although the mechanism has yet to be fully explained. These results are supported by reports showing respiratory disease and/or chronic obstructive pulmonary disease (COPD) to be predictors for PPOI.[3,4]

Given the higher complication rate, except for ileus, and the longer hospital stay, patients with a high probability of PPOI should have perioperative management different from those with a low probability of PPOI. The ERAS protocols recommended evidence-based managements including preoperative counseling, a non-fasting period, optimal fluid management, decreased use of tubes, enforced early mobilization,[27] gum chewing,[14] and opioid-sparing analgesia[10,17,28] for reducing the PPOI rate. Although the ERAS-based preoperative and postoperative managements were generally used in the study, the PPOI rates remained high. Thus, further studies are needed to address other interventions to reduce PPOI.

The present study has several limitations. First, the retrospective nature and the relatively small patient number in the PPOI group may have weakened the analyses. Second, the present study lacks a robust external validation of the established nomogram. Therefore, these results need to be validated by further analyses of our study results or those of other groups. Third, a regular diet was started depending on each patient condition (mainly on PODs 2 or 3 after major abdominal surgery) although it should be started immediately after elective colorectal surgery according to the ERAS protocols. Nonetheless, this study does highlight a useful probability-classification model for predicting PPOI incidence in patients who undergo general surgery.

In conclusion, colorectal surgery, open abdominal surgery, and smoking history were factors predicting PPOI in patients undergoing major abdominal surgery. A nomogram type classification model based on these factors may be useful for preoperatively predicting patients with a high probability of developing PPOI, and might help doctors and nurses to closely monitor patients and to strictly perform evidence-based preoperative/postoperative managements.

Acknowledgments The authors thank members of the Clinical Research Support Center in Asahi General Hospital for data acquisition and for providing helpful insights.

Authors' Contributions The conception or design of the work: Sugawara, Kawaguchi, Nomura, Tanaka.

The acquisition of data for the work: Sugawara, Suka, Kawasaki.

The analysis of data for the work: Sugawara, Kawaguchi, Uemura, Koike, Nagai, Furuya.

The interpretation of data for the work: Sugawara, Kawaguchi, Nomura, Tanaka.

Compliance with Ethical Standards

Type of Study Retrospective.

Conflict of Interest The authors declare that they have no conflicts of interest.

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