ORIGINAL ARTICLE

Preoperative Walking Capacity Indirectly Relates to Decreased Postoperative Complications in Patients with Gastrointestinal Cancer

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Objectives: Postoperative complications (PCs) in patients with gastrointestinal cancer (GIC) lead to reduced lifespan and poor quality of life. The aim of this study was to investigate the correlation between preoperative exercise-related factors, together with other contributory factors, and the frequency of PCs in patients with GIC. **Methods:** This was a cross-sectional, three-institution study. We enrolled 299 patients who were scheduled for elective surgery for GIC (182 men and 117 women; age, 65.7 ± 11.0 years). PCs were graded using the Clavien–Dindo classification based on the medical records 1 month postoperatively. Exercise-related factors (the skeletal muscle index, the isometric knee extension torque, and the 6-min walk test [6 MWT] distance) were measured before surgery. Based on previous studies of factors contributing to complications, data on age, sex, clinical cancer stage, comorbidities, neoadjuvant therapy, type of surgery, surgery duration, blood loss, blood transfusion, laboratory data, respiratory function, body mass index, and visceral fat area were collected. **Results:** The frequency of PCs was positively correlated with surgery duration (β=0.427) and C-reactive protein (CRP) level on postoperative day 3 (β=0.189). The 6 MWT was negatively correlated with the frequency of PCs through CRP level on postoperative day 3 (β=–0.035). This model demonstrated an acceptable fit to the data (goodness-of-fit index, 0.979; adjusted goodness-of-fit index, 0.936; comparative fit index, 0.944; and root mean square error of approximation, 0.076). **Conclusions:** Preoperative walking capacity was correlated with PCs in patients undergoing GIC surgery. Prevention of PCs in patients with GIC requires the monitoring of both surgical parameters and postoperative inflammation.

Key Words: preoperative walking capacity; postoperative inflammation; gastrointestinal cancer patients

INTRODUCTION

Postoperative complications (PCs) in patients with gastrointestinal cancer (GIC) not only worsen physical and mental burdens but also lead to a reduced quality of life and lifespan.[1,2] In previous studies, exercise-related factors, including physical function[3,4] and body composition,[5–10] have been linked to PCs in patients with GIC. PCs that are associated with exercise-related factors include anastomotic leakage, pancreatic fistula, bleeding, wound infection, intra-abdominal infection, ileus, postoperative acute respiratory failure, and pneumonia.[3–10] A systematic review of major abdominal surgeries reported that preoperative physical exercise may lead to a reduction in postoperative pulmonary

complications and overall morbidity.[11] These findings suggest that improving exercise-related factors in patients with GIC can reduce PCs.

Patient demographics (age, sex, postoperative clinical cancer stage, comorbidities, and neoadjuvant therapy),[5–8] surgical parameters (type of surgery, surgery duration, blood loss, and blood transfusion),[5–7,12–14] laboratory data (serum albumin, platelet count, white blood cell [WBC] count, and C-reactive protein [CRP] levels before surgery and on postoperative day 3),[15–19] and respiratory function (forced expiratory volume in 1 s [FEV_1])[18] are also important factors reportedly related to PCs in patients with GIC. Therefore, the ability of exercise-related factors to decrease PCs in patients with GIC should be examined in an analysis that equally considers these other factors. Additionally, multicenter studies should be conducted to gain further insight because most of the previous investigations were single-center studies.

The current study aimed to investigate how preoperative exercise-related factors can influence the frequency of PCs in patients with GIC and to compare these factors with other contributory factors. The study was performed at three acute care medical institutions in Japan.

MATERIALS AND METHODS

The study protocol was approved by the Research Ethics Board of the International University of Health and Welfare (Otawara-shi, Tochigi, Japan; registration: 17-Io-202-2), and the procedures were conducted in accordance with ethical standards and the principles of the Declaration of Helsinki. All patients provided written and verbal informed consent.

Patients

The study included all patients who were scheduled for elective surgery for GIC or suspected GIC between March 1, 2016, and March 31, 2020, at the International University of Health and Welfare Mita Hospital, the International University of Health and Welfare Hospital, and the International University of Health and Welfare Ichikawa Hospital, all of which are accredited as designated cancer treatment hospitals. Exclusion criteria included the diagnosis of a non-malignant tumor after surgery or referral to another hospital. Clinical data were collected throughout the hospital stay.

Study Design

This was a cross-sectional study of patients from three acute care medical institutions. Exercise-related factors before surgery in patients with GIC were evaluated by a physical therapist, and the onset of PCs was recorded based on the medical records 1 month postoperatively. Additionally, we recorded the subjects' demographics, surgical data, laboratory data, and respiratory function. Perioperative care for all subjects was managed by the gastrointestinal surgeon based on the clinical protocols of each medical institution. The standard postoperative rehabilitation program for all subjects included aerobic exercises, resistance exercises, and the training of inspiratory muscles based on the clinical protocols of each medical institution. Rehabilitation was provided by a physical therapist and was performed in the intensive care unit, ward, or rehabilitation room for 20−40 min according to the subject's clinical course. PCs were graded using the Clavien–Dindo classification[20] based on the medical records 1 month postoperatively. In this study, Clavien–Dindo classification grade II or higher was defined as a PC.[16]

Evaluation of Exercise-related Factors

The skeletal muscle index (SMI), the isometric knee extension torque (IKET), and the 6-min walk test (6 MWT) distance of each patient were measured. SMI was evaluated on computed tomography (CT) images at the third lumbar vertebra (L3) using thresholds of −29 to +150 Hounsfield units (HU: water is defined as 0, air as 1000).[21] SMI was normalized as the sum of the cross-sectional areas (cm^2) of multiple muscles (namely the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique abdominals, and the rectus abdominis muscles) divided by the square of the height (cm^2 or m^2). SMI analyses were performed using ImageJ (version 1.51; NIH, Bethesda, Maryland; Java 1.8.0_112) by one analyst. The IKET was evaluated using a handheld dynamometer. Patients were instructed to extend their right knee against the pad with maximum effort for 5 s while in the sitting position. The normalized joint torque was calculated as the maximum force multiplied by the distance from the knee joint space to the pad center divided by the body weight. The 6 MWT was evaluated based on the guidelines of the American Thoracic Society.[22] Patients were instructed to walk back and forth along a 30-m hallway for 6-min at a pace that would require maximum effort by the end of the walk. The total distance covered within 6 min was recorded in meters for each evaluation.

Other Factors Related to PCs

Body composition data, including body mass index (BMI) and visceral fat area (VFA), were recorded before surgery.[5–10]

BMI was calculated using the height and weight measured with the patient dressed. VFA was evaluated on a CT image at L3 using thresholds of 150 to 50 HU[21] and recorded as the cross-sectional area (cm^2) of visceral fat. VFA analyses were performed using ImageJ (version 1.51; NIH, Bethesda, Maryland; Java 1.8.0_112) by one analyst.

The following clinical data[5–8,12–19] were collected: age at surgery, sex, postoperative clinical cancer stage, comorbidities (hypertension, hyperlipidemia, diabetes mellitus, cardiac diseases, respiratory diseases, orthopedic diseases, and cerebrovascular diseases), diagnosis, neoadjuvant therapy, type of surgery (laparoscopic, open, or robot-assisted), surgery duration, blood loss, blood transfusion (red cell concentrates and fresh frozen plasma), laboratory data (serum albumin, platelet count, WBC count, and CRP levels before surgery and on postoperative day 3), and FEV$_1$ before surgery.

Statistical Analysis

The unpaired t-test was used to compare clinical characteristics between patients with and without complications. Categorical variables and the frequency of PCs were compared using the chi-squared test. The relationships between the frequency of PCs and the other related factors were analyzed using logistic regression analysis. Patients with and without complications were set as dependent variables, and factors significantly related to the patients with and without complications were set as independent variables. From the logistic regression analysis results, except for the categorical variables, the relationships among the frequency of PCs, other related factors, and exercise-related factors were subsequently analyzed using structural equation modeling path analysis. The initial model tested variables that were significantly associated with PCs. Exercise-related factors were confirmed to be directly and/or indirectly related to PCs.

This study derived a final model by excluding the non-significant variables and factors not related to PCs identified in the initial model. The goodness-of-fit of all models was evaluated using the following parameters: goodness-of-fit index (GFI; values >0.95 indicate good model fit), the adjusted goodness-of-fit index (AGFI; values >0.95 indicate good model fit), the comparative fit index (CFI; values >0.95 indicate good model fit), and the root mean square error of approximation (RMSEA; values <0.07 indicate good model fit).[23] All statistical analyses were performed using SPSS statistics version 24.0, and SPSS Amos version 24.0 (SPSS, Chicago, Il, USA). Statistical significance was set at P <0.05.

RESULTS

In total, 503 patients were approached for consent; 45 patients declined to participate, and 159 patients were excluded (31 according to the exclusion criteria and 128 because of incomplete data). Ultimately, a total of 299 patients were enrolled in the study. All the study participants were of Japanese descent (**Fig. 1**). Patients were classified into two groups based on the presence of complications 1 month postoperatively; finally, 95 and 204 patients were included in the complications and no complications groups, respectively. Based on the Clavien–Dindo classification, the frequency of PCs (including multiple PCs in some patients) observed in the complications group was as follows: grade I, 22.1%; grade II, 75.8%; grade III, 1.1%; grade IIIa, 23.2%; grade IIIb, 9.5%; grade IV, 4.2%; and grade IVa, 2.1%. The most common PCs were infection (n = 33), ileus (n = 11), and anastomotic leakage (n = 11). In the no complications group, only grade I complications were observed (n = 57). The length of hospital stay was significantly higher in the complications group than in the no complications group (37.1 ± 58.6 vs. 16.4 ± 8.7 days, P = 0.000).

Factors Related to PCs

The patient demographics and clinical characteristics of the two groups are shown in **Tables 1 and 2**. The age at surgery, cardiac diseases, diagnosis (esophageal cancer, pancreatic cancer, or colon cancer), neoadjuvant therapy, type of surgery (open, laparoscopic), surgery duration, blood transfusion, laboratory data (platelets and CRP on postoperative day 3), and FEV$_1$ before surgery were significantly different between the two groups. The logistic regression analysis results are presented in **Table 3**. The age at surgery, open surgery, surgery duration, and CRP level on postoperative day 3 were significantly associated with the frequency of PCs (χ^2) = 79.321, P = 0.000; Hosmer–Lemeshow test: P = 0.555).

Factor Structure Model Including Exercise-related Factors Affecting PCs

Our initial model determined that the age at surgery, surgery duration, and CRP level on postoperative day 3 were directly related to PCs and that exercise-related factors (SMI, IKET, and 6 MWT) were directly and indirectly related to PCs. Additionally, the initial model showed that the age at surgery was directly related to exercise-related factors and that surgery duration was directly related to CRP level on postoperative day 3. The surgery duration (standardized β =
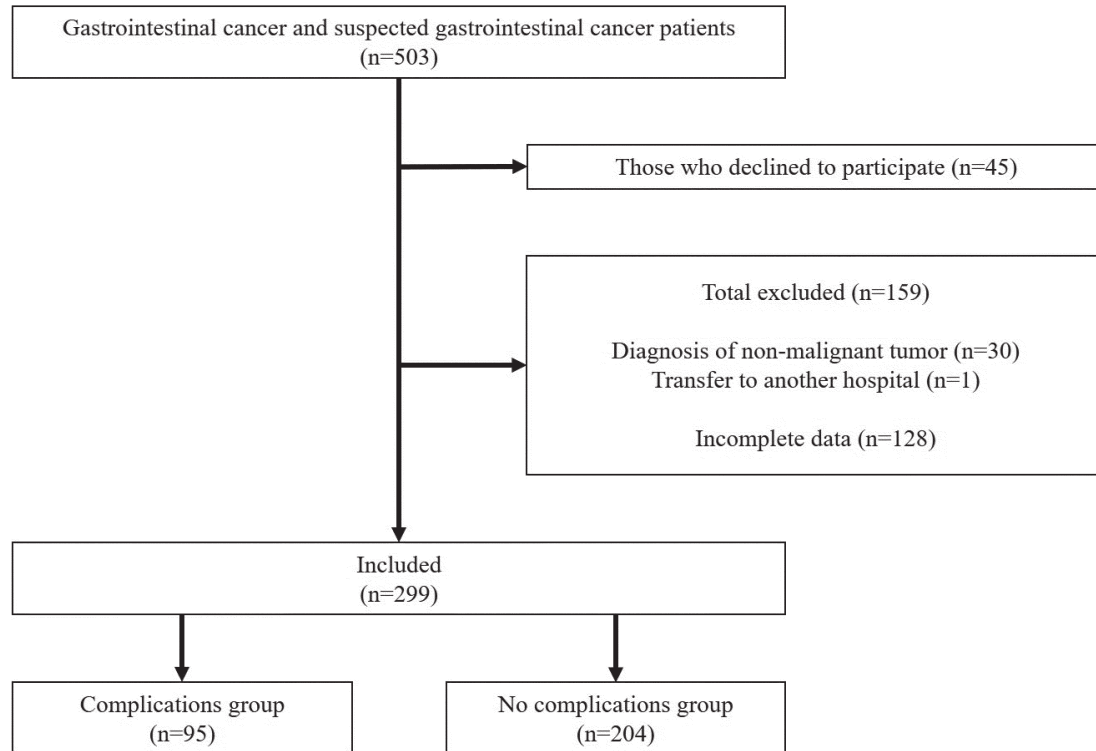
Fig. 1. Subject selection for the study.

0.381, P < 0.05) and the CRP level (standardized β = 0.177, P < 0.05) were significantly and positively correlated with PCs. Among the exercise-related factors, the SMI correlated significantly and positively with both the surgery duration (standardized β = 0.151, P < 0.05) and CRP level on postoperative day 3 (standardized β = 0.181, P < 0.05), whereas the 6 MWT correlated significantly and negatively with CRP level on postoperative day 3 (standardized β= −0.173, P < 0.05). However, neither the SMI nor the 6 MWT correlated significantly with PCs. Additionally, the age at surgery was significantly and negatively correlated with exercise-related factors, and the surgery duration was significantly and positively correlated with the CRP level on postoperative day 3. The fit parameters of the initial model were as follows: GFI = 0.960, AGFI = 0.774, CFI = 0.871, and RMSEA = 0.163 (**Fig. 2**).

In the final analysis, the surgery duration (standardized β = 0.427, P < 0.05) and the CRP level (standardized β = 0.189, P < 0.05) on postoperative day 3 were significantly and positively correlated with PCs (**Table 4**). SMI positively and indirectly correlated with PCs through both surgery duration and CRP level on postoperative day 3 (standardized β = 0.101, P < 0.05), and 6 MWT negatively and indirectly correlated with PCs through CRP level on postoperative day 3

(standardized β = −0.035, P < 0.05) in the final model (**Table 4**). The fit parameters of the final model were as follows: GFI = 0.979, AGFI = 0.936, CFI = 0.944, and RMSEA = 0.076 (**Fig. 3**).

DISCUSSION

We found that PCs in patients with GIC were significantly and positively correlated with surgery duration and CRP level on postoperative day 3 (**Table 4**, **Fig. 3**). Among the exercise-related factors, the SMI was indirectly and positively correlated with PCs through surgery duration and CRP level on postoperative day 3, whereas the 6 MWT indirectly and negatively correlated with PCs through CRP on postoperative day 3 (**Table 4**, **Fig. 3**). Additionally, exercise-related factors before surgery were affected by age in patients with GIC. PCs in patients with GIC may be decreased by exercise-related factors, as suggested by the indirect correlation with 6 MWT and other related factors, such as surgical parameters, postoperative inflammation, and age.

Under severe surgical stress, cardiac output is increased to avoid tissue hypoxia.[24] The ability to secure the tissue oxygen supply is a crucial determinant of postoperative outcomes[25] because the failure to address tissue oxygen debt

Table 1. Patient demographics and baseline characteristics in 299 individuals with gastrointestinal cancer

	Complications group	No complications group	P-value [a]
No. of patients	95	204	–
Age (years)	67.9 ±10.6	64.7 ± 11.1	0.016
Sex			
Female	30 (31.6)	87 (42.6)	0.075
Male	65 (68.4)	117 (57.4)	
Clinical cancer stage			
I	34 (35.8)	69 (33.8)	0.794
II	24 (25.3)	63 (30.9)	0.342
III	21 (22.1)	52 (25.5)	0.566
IV	16 (16.8)	20 (9.8)	0.089
Comorbidities			
Hypertension	29 (30.5)	58 (28.4)	0.785
Hyperlipidemia	13 (13.7)	15 (7.4)	0.090
Diabetes mellitus	17 (17.9)	35 (17.2)	0.871
Cardiac diseases	17 (17.9)	15 (7.4)	0.009
Respiratory diseases	6 (6.3)	13 (6.4)	1.000
Orthopedic diseases	7 (7.4)	21 (10.3)	0.525
Cerebrovascular diseases	6 (6.3)	9 (4.4)	0.571
Diagnosis			
Esophageal cancer	12 (12.6)	3 (1.5)	0.000
Gastric cancer	14 (14.7)	42 (20.6)	0.267
Liver cancer	14 (14.7)	24 (11.8)	0.462
Gallbladder cancer	1 (1.1)	1 (0.5)	0.535
Bile duct cancer	5 (5.3)	4 (2.0)	0.149
Pancreatic cancer	13 (13.7)	10 (4.9)	0.017
Colon cancer	15 (15.8)	74 (36.3)	0.000
Rectal cancer	21 (22.1)	46 (22.5)	1.000
Neoadjuvant therapy	11 (11.6)	5 (2.5)	0.002

Values are expressed as numbers (%) or mean ± standard deviation.
[a] P < 0.05 was considered significant.

and dysfunction in the immediate postoperative period may lead to the development of organ failure complications.[26,27] Additionally, severe blood loss during surgery has been found to increase the postoperative mortality of patients with GIC.[28] In current study, prolonged surgery, which may be related to surgical stress, overwhelmed the body's compensatory responses and may result in complications in patients with GIC.

Increased CRP levels after surgery reflect postoperative inflammatory responses, which may be related to tissue repair and infection prevention.[29] Similarly, CRP levels are associated with decreasing T-lymphocyte function and developing hyperglycemia with protein catabolism.[29,30] Postoperative CRP levels are useful laboratory data for monitoring in-

flammatory reactions to surgical stress[31]; CRP reaches the maximum value 48 h after surgery and fluctuates until 120 h.[32] Additionally, CRP data are reportedly useful in predicting PCs in patients with GIC.[19] In the current study, the CRP level on postoperative day 3 was significantly related to PCs likely because there were high numbers of complications with infection, abscess, and anastomotic leakage (**Table 2**).

SMI was indirectly and positively correlated with PCs through surgery duration and CRP level on postoperative day 3 (**Table 4**, **Fig. 3**). Skeletal muscle mass is an important energy source for immune response activity after surgery[33]; however, it was not directly related to decreased PCs in this study. Generally, SMI improves physical performance and may lead to a reduction in PCs in patients with GIC.[9,10] In

Table 2. Surgical parameters, laboratory data, and postoperative complications in 299 patients with gastrointestinal cancer

	Complications group	No complications group	P-value [a]
No. of patients	95	204	–
Type of surgery			
Open	39 (41.1)	48 (23.5)	0.003
Laparoscopic	55 (57.9)	148 (72.5)	0.016
Robot-assisted	1 (1.1)	8 (3.9)	0.281
Surgery duration (min)	369.4 ± 140.5	254.0 ± 97.5	0.000
Blood loss (mL)	518.8 ± 771.5	268.7 ± 1165.8	0.058
Blood transfusion			
Red cell concentrates (mL)	288.8 ±717.3	97.4 ±701.3	0.030
Fresh frozen plasma (mL)	138.6 ±418.5	92.1 ±951.3	0.648
Laboratory data			
Serum albumin (mg/dL)	4.1 ± 0.5	4.2 ± 0.5	0.159
Platelets (10^3/μL)	20.9 ± 7.4	23.1 ± 7.6	0.020
White blood corpuscles (/μL)	5922.8 ± 2120.6	6053.8 ± 1849.0	0.587
C-reactive protein (mg/dL)	0.6 ± 1.6	0.5 ± 1.7	0.594
C-reactive protein on postoperative day 3 (mg/dL)	14.3 ± 8.0	9.5 ± 6.1	0.000
Preoperative forced expiratory volume in 1 s (%)	76.2 ± 10.5	78.9 ± 8.5	0.017
Body mass index (kg/m^2)	23.2 ± 3.8	23.2 ± 3.7	0.906
Visceral fat area (cm^2)	92.8 ± 68.0	83.6 ± 69.7	0.284
Exercise-related factors			
Skeletal muscle index (cm^2/m^2)	36.2 ± 8.6	36.1 ± 8.7	0.960
Isometric knee extension torque (Nm/kg)	3.34 ± 1.97	3.42 ± 1.95	0.763
6-minute walk test (m)	486.5 ± 96.9	511.7 ± 108.6	0.054
Clavien–Dindo classification [b]			
Grade I	21 (22.1)	57 (27.9)	
Grade II	72 (75.8)	0 (0.0)	
Grade III	1 (1.1)	0 (0.0)	
Grade IIIa	22 (23.2)	0 (0.0)	
Grade IIIb	9 (9.5)	0 (0.0)	
Grade IV	4 (4.2)	0 (0.0)	
Grade Iva	2 (2.1)	0 (0.0)	
Grade IVb	0 (0.0)	0 (0.0)	
Grade V	0 (0.0)	0 (0.0)	
Postoperative complications			
Infection	33 (34.7)	0 (0.0)	
Ileus	11 (11.6)	0 (0.0)	
Abscess	4 (4.2)	0 (0.0)	
Anastomotic stenosis	3 (3.2)	0 (0.0)	
Anastomotic leakage	11 (11.6)	0 (0.0)	
Lymphatic fistula	2 (2.1)	0 (0.0)	
Atelectasis	9 (9.5)	0 (0.0)	
Heart failure	3 (3.2)	0 (0.0)	
Hepatic insufficiency	4 (4.2)	0 (0.0)	
Delirium	3 (3.2)	0 (0.0)	
Others	21 (22.1)	0 (0.0)	
Duration of hospital stay (days)	37.1 ± 58.6	16.4 ± 8.7	0.000

Values are expressed as numbers (%) or mean ± standard deviation.
[a] P < 0.05 was considered significant.
[b] Includes duplicate cases, compared with Grade 0 or I and Grade II or higher.

Table 3. Logistic regression analysis results

Dependent variable	Independent variables	β	Standard error	P-value	Odds ratio	95% confidence interval	Chi-square test χ^2	P-value
Postoperative complications with Clavien–Dindo classification Grade II or higher	Open surgery	0.750	0.305	0.014	2.116	1.163 to 3.851		
	Age	0.031	0.014	0.027	1.031	1.003 to 1.060		
	Surgery duration	0.008	0.001	0.000	1.008	1.005 to 1.010	79.321	0.000
	C-reactive protein of postoperative day 3	0.057	0.021	0.008	1.058	1.015 to 1.104		

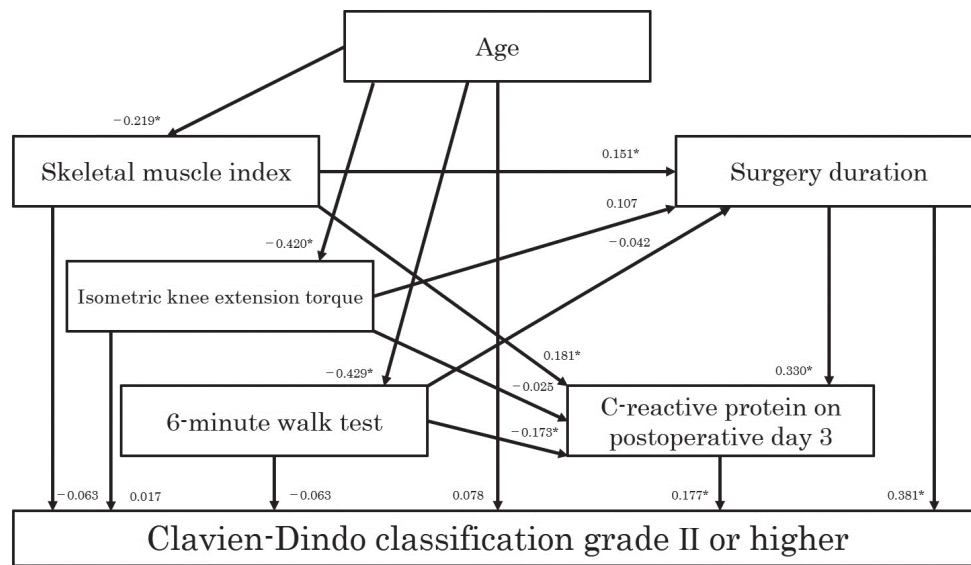Hosmer–Lemeshow test: P = 0.555.

Fig. 2. Initial model of factors affecting postoperative complications in patients with gastrointestinal cancer. Model fit: goodness-of-fit index, 0.960; adjusted goodness-of-fit index, 0.774; comparative fit index, 0.871; root mean square error of approximation, 0.163; *P < 0.05.

Table 4. Correlation of each variable with postoperative complications in the final model

	Standardized direct effect	Standardized indirect effect	Standardized total effect
Age	0.000	−0.007	−0.007
Skeletal muscle index	0.000	0.101	0.101
6-minute walk test	0.000	−0.035	−0.035
Surgery duration	0.365	0.062	0.427
C-reactive protein of postoperative day 3	0.189	0.000	0.189

the current study, enrolled GIC patients received various treatments, including neoadjuvant therapy and surgery. Therefore, the influence of SMI should be interpreted with caution because the surgical site, type of surgery, and other treatments in patients with GIC were not unified. In contrast, IKET was not significantly correlated directly or indirectly with PCs (**Fig. 2**). Generally, muscle strength is not linearly

related to skeletal muscle mass.[34,35] Additionally, IKET was reported to have a low association with immune function compared to lean body mass.[36] This may explain why IKET and PCs were not significantly correlated in this study.

In rehabilitation medicine, the 6 MWT is a simple scale for evaluating cardiopulmonary reserve[22,26]; the test captures increased utilization of oxygen in skeletal muscles and the
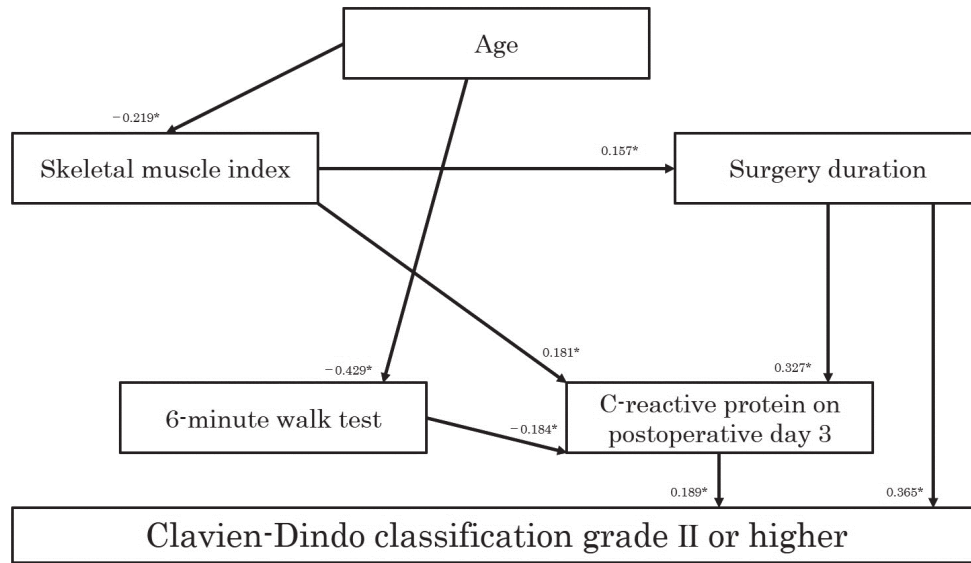
Fig. 3. Final model of factors affecting postoperative complications in patients with gastrointestinal cancer. Model fit: goodness-of-fit index, 0.979; adjusted goodness-of-fit index, 0.936; comparative fit index, 0.944; root mean square error of approximation, 0.076; *$P < 0.05$.

entire interlocking lung–heart–vascular oxygen transport system,[37] reflecting oxygen intake, carbon dioxide excretion, and pulmonary blood flow.[26] In the current study, the 6 MWT was significantly and indirectly correlated with PCs through CRP level on postoperative day 3 (**Table 4**, **Fig. 3**). GIC patients with higher cardiopulmonary reserve before surgery may be able to better adapt to the postoperative inflammatory response and ensure adequate systemic oxygen supply. The preoperative 6 MWT in patients with GIC may be related to the decreased frequency of PCs via the postoperative CRP level. However, in the current study, the preoperative cardiopulmonary reserve could not be accurately evaluated. Therefore, for GIC patients, future studies are warranted that investigate the maximum oxygen consumption during exercise tolerance tests using a gas analysis system.

The age at surgery of patients with GIC was significantly and directly correlated only with exercise-related factors and not with PCs (**Table 4**, **Fig. 3**). GIC patients in this study may have shown results different from those seen in previous studies[6,8] because of the small number of patients and their low average age. Age was negatively correlated with exercise-related factors, as was found in previous studies.[38] The effects of aging may be implicated when focusing on preoperative exercise-related factors in patients with GIC.

This study has some limitations. First, the surgical site and the type of surgery were heterogeneous across the GIC patients. Ideally, a cross-sectional multicenter study of the frequency of PCs should be conducted using the data of GIC patients who underwent the same treatment, such as ductal surgery (i.e., for gastric, colon, and rectal cancers). Second, not all laboratory data related to PCs could be obtained. Specifically, extensive laboratory data, such as testosterone,[39] procalcitonin,[40] and prealbumin levels,[41] should be included in future investigations. Third, the definitive influence of exercise-related factors is unclear because this was a cross-sectional study. In the future, a randomized controlled study of preoperative intervention for exercise-related factors should be conducted.

Conclusions

The preoperative walking capacity, which was affected by patient age at surgery, was related to the occurrence of PCs in patients who underwent GIC surgery. Additionally, decreased frequencies of PCs in GIC patients were also related to the surgery duration and CRP level on postoperative day 3. Consequently, in addition to general acute medical care, comprehensive rehabilitation to improve the preoperative walking capacity of patients with GIC may help prevent PCs.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this article.

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