Preoperative Low Physical Activity is a Predictor of Postoperative Delirium in Patients with Gastrointestinal Cancer: A Retrospective Study

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Abstract

**Background:** Postoperative delirium (POD) is one of the most common postoperative complications in gastrointestinal surgery patients. POD has been reported to affect long-term activities of daily living, cognitive function decline, and mortality. Previous studies have indicated that preoperative physical activity (PA) predicted POD in patients with other diseases, but we have not found any reports in patients with gastrointestinal cancer. In this retrospective study, we investigated the relationship between preoperative PA and POD in gastrointestinal cancer patients. **Methods:** POD was diagnosed based on the short confusion assessment method. We divided patients into active and inactive groups based on their preoperative PA assessed by the International Physical Activity Questionnaire (Japanese version). Multivariate logistic analysis was conducted to investigate the association between preoperative PA and POD. **Results:** POD occurred in 25 of the 151 patients (16.6%). Preoperative low PA was associated with POD after adjusting for confounders, namely, diabetes mellitus, sedentary time, and usual gait speed (odds ratio, 2.83; 95% confidence interval: 1.06–7.58; p=0.03). **Conclusion:** Preoperative low PA was a predictor of POD independent of the confounding factors in patients with gastrointestinal cancer.

**Keywords:** Physical activity- postoperative delirium- gastrointestinal cancer

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Introduction

Postoperative delirium (POD) is characterized by acute episodes of inattention, confusion in thinking, and changes in consciousness levels (Fong et al., 2015). POD is one of the most common postoperative complications, with an incidence of 8.2–54.4% and a median rate of 23.9% in gastrointestinal surgery patients (Scholz et al., 2016). It has been reported that POD affects long-term activities of daily living, cognitive function decline, and mortality in patients who undergo surgery (Raats et al., 2015; Shi et al., 2019; Austin et al., 2019).

In gastrointestinal disease and cancer patients, several risk factors for POD, including age, male, body mass index (BMI), comorbidities such as diabetes mellitus (DM) and cerebrovascular disease (CVD), American Society of Anesthesiologists physical status (ASA-PS), number of medications, serum albumin level, anxiety, depression, and blood transfusion, have been reported (Scholz et al., 2016; Yamamoto et al., 2016; Wada et al., 2019; Yang et al., 2020). In general, risk factors of delirium are classified into three categories: preparatory, precipitating, and direct (Lipowski, 1983). In recent years, low skeletal muscle mass has been reported to be a risk factor of POD in gastrointestinal cancer patients (Mosk et al., 2018). In patients who undergo surgery for other diseases, slow gait speed and frailty have also been reported to be risk factors for POD (Jung et al., 2015; Sato et al., 2016; Chen et al., 2021). Low skeletal muscle mass, low gait speed, and frailty can be viewed as preparatory factors for POD, suggesting that factors related to sarcopenia and frailty may also affect POD in patients who undergo surgery.

Low physical activity (PA) is a risk factors for sarcopenia and frailty (Fried et al., 2001; Chen et al., 2020), and preoperative PA can also be considered as a preparatory factor for POD. PA has been reported to modify...
the metabolic, structural, and functional dimensions of the brain and preserve cognitive performance in older adults (Kirk-Sanchez, and McGough, 2014). In addition, an association between preoperative PA and POD has been reported in patients who underwent cardiac or orthopedic surgery (Ogawa et al., 2015; Lee et al., 2019). These results suggest that preoperative PA may be associated with POD. However, no study has investigated this association in patients with gastrointestinal cancer. Since it has been reported that prehabilitation can reduce the incidence of POD after abdominal surgery (Janssen et al., 2019), clarification of the association between preoperative PA and POD may help to examine intervention methods in prehabilitation.

Therefore, the purpose of our study was to investigate the relationship between preoperative PA and POD in gastrointestinal cancer patients.

### Materials and Methods

#### Patients

This retrospective study enrolled 178 patients who underwent surgery (open or laparoscopic) for primary gastrointestinal cancer (colorectal, gastric, or esophagogastric junction) between October 2016 and April 2021 at our hospital. Exclusion criteria were as follows: (1) had simultaneous cancer, (2) needed assistance to walk alone preoperatively, (3) had difficulty in understanding instructions preoperatively, (4) underwent palliative surgery or trial laparatomy, (5) had benign tumor or no primary cancer revealed by pathological examination, and (6) had missing data. All patients underwent rehabilitation from the day after surgery (twice a day on weekdays and once on Saturdays), including mobilization, ambulation, and breathing, aerobic, and muscle strength exercises.

The present study was approved by the Ethics Committee of Kamiiida Daiichi General Hospital and Nagoya University School of Medicine. Prior to participation, all patients were fully informed about this study and provided written consent in accordance with the Declaration of Helsinki.

#### Diagnosis of POD

The study outcome was POD, which was diagnosed based on the Japanese version of the short confusion assessment method (short CAM). The short CAM consists of items for acute onset, fluctuation, inattention, disorganized thinking, and/or altered level of consciousness (Inoue et al., 1990; Inoue, 2014). Delirium observed from the day after surgery to the day before discharge was defined as POD (Maekawa et al., 2016). POD was evaluated by physical therapists during the rehabilitation period.

#### Preoperative PA

Preoperative PA was assessed within 1 week before surgery using the Japanese version of the usual 7-day short version of the International Physical Activity Questionnaire (IPAQ). This questionnaire is used to evaluate vigorous- to moderate-intensity PA and walking activity during the usual 7 days and sedentary time during a usual weekday (Craig et al., 2003). Each intensity scores were assigned a metabolic equivalent (MET) value (e.g., METs for vigorous intensity = 8.0, moderate intensity = 4.0, and walking = 3.3), and patients were classified into three groups (e.g., high, moderate, and low) based on the IPAQ scoring protocol (Sjostrom et al., 2005). We then defined high and moderate as “active” and low as “inactive,” according to a previous study (Toriumi et al., 2020).

#### Preoperative muscle strength and physical function

Grip strength and usual gait speed were evaluated as muscle strength and physical function, respectively. We measured grip strength once on each side using a dynamometer (Grip-D, TKK 5401; Takei Scientific Instruments Co., Niigata, Japan), and the average of the left and right sides was obtained (Yoshimura et al., 2011). Also, usual gait speed was evaluated over a 10-m distance between the 3- and 13-m marks of a 16-m walkway (Osuka et al., 2020). These measurements were obtained within a week before surgery.

#### Anxiety and depression

The Japanese version of the Hospital Anxiety and Depression Scale (HAD) was used to assessed anxiety and depression within a week before surgery. The HAD consists of each 7 items for anxiety and depression subscales, respectively. A four-point response scale was used, each subscale ranging from 0 to 21. A score of 11 or higher on the subscale was determined as anxiety or depression, respectively (Zigmond and Snaith, 1998). The reliability and validity of the Japanese version of the HAD were confirmed (Kugaya et al., 1998).

#### Characteristics of patients, surgery-related variables, and laboratory data

Age, sex, BMI, Brinkman index, presence or absence of polypharmacy, presence or absence of DM and CVD, ASA-PS, cancer site (colorectal, gastric, or esophagogastric junction), and pathological TNM stage were obtained from electronic medical record as characteristics of patients. We defined polypharmacy as the intake of five or more daily medications based on previous study (Volakis et al., 2018).

Surgical approach (open or laparoscopic), presence or absence of combined resection and transfusion, operative time, anesthesia time, blood loss, and postoperative complications were recorded as surgery-related variables. We used Clavien–Dindo (CD) classification to grade postoperative complications (grades 1–5) (Dindo et al., 2004; Clavien et al., 2009). We excluded grade 1 complications, and considered above grade 2 complications except for delirium as postoperative complications to eliminate the possibility of description bias in patient records.

Preoperative laboratory data including albumin, C-reactive protein (CRP), hemoglobin, white blood cells, and total lymphocyte counts were recorded. As a nutritional status indicator, prognostic nutrition index (PNI) was calculated using the following equation: PNI = 10 μ serum albumin (mg/dL) + 0.005 μ total
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analysis as confounding factors. The association between preoperative PA and POD remained significant after adjusting for confounding factors (odds ratio, 2.83; 95% confidence interval: 1.06–7.58; p=0.03).

Discussion

The present study indicates that preoperative low PA is a predictor of POD, independent of the confounding factors, namely DM, sedentary time, and gait speed, in patients with gastrointestinal cancer.

POD occurred in 25 of 151 patients (16.6%) in our study. The incidence of POD in our study was lower than that in a previous meta-analysis study, which indicated that median incidence of POD was 23.9% in gastrointestinal disease surgery patients (Scholz et al., 2016). Advanced age is well-known risk factor of POD in patients undergoing gastrointestinal cancer surgery (Lee and Lim, 2020). Thus, inclusion of younger patients (aged 60 years and below), who are at a lower risk for POD, in the present study might have resulted in a relatively lower incidence of POD. In addition, POD in the present study was evaluated only by physical therapists during the rehabilitation period. Hence, it is possible that the number of patients who developed POD was small, which might have resulted in a lower incidence of POD in our study than in the previous study (Scholz et al., 2016).

The association between preoperative PA and POD, independent of DM, sedentary time, and usual gait speed was an important finding in our study. In previous studies, preoperative physical function assessed by gait speed, and DM have been related to POD in patients who underwent surgery (Sato et al., 2016; Chaiwat et al., 2019). While PA was related to physical function and DM (Aune et al., 2015; Yasunaga et al., 2017), our results suggest that PA was directly associated with POD, and not only through physical function or DM in patients who underwent gastrointestinal cancer surgery. Although our study also reported that preoperative PA was associated

Statistical analysis

All continuous variables and categorical variables were expressed as medians (interquartile ranges) and numbers (%), respectively. We divided patients into active and inactive groups based on their preoperative PA. χ2 test or Fisher’s exact test for categorical and the Mann–Whitney U test for continuous variables were used to analysis differences between two groups. Variables with p<0.05 in the univariate analysis were entered as confounding factors in the multivariate logistic analysis. Multivariate logistic regression analysis adjusted for confounding factors was performed to clarify the relationship between preoperative PA and POD. EZR version 1.40 (Saitama Medical Center, Jichi Medical University, Tochigi, Japan) was used for statistical analysis (Kanda, 2013).

Results

Of the 178 patients, 27 were excluded from this study based on the exclusion criteria. Thus, we included 151 patients in the analysis (Figure 1). POD occurred in 25 of the 151 patients (16.6%). The study patients divided into two groups based on preoperative PA level: active group (n=92) and inactive group (n=59).

Table 1 showed a comparison of patient characteristics between the two groups. We found no significant differences between the two groups, except for DM, sedentary time, and usual gait speed. The number of patients with DM was significantly higher in the inactive group than in the active group (p=0.02). Sedentary time was significantly longer and usual gait speed was significantly slower in the inactive group than in the active group (p=0.03 and p<0.01, respectively).

Table 2 showed the results of the multiple logistic regression analysis. We entered DM, sedentary time, and usual gait speed into the multiple logistic regression
Table 1. Comparison of Patient Characteristics between Active and Inactive Patients

| Variable                        | Total (n=151) | Active group (n=92) | Inactive group (n=59) | p value |
|---------------------------------|---------------|---------------------|-----------------------|---------|
| **Preoperative characteristics**|               |                     |                       |         |
| Age, years                      | 70 [63−77]    | 69 [60−77]          | 73 [64−77.5]          | 0.13    |
| <60                             | 27            | 22 (23.9)           | 5 (8.5)               |         |
| ≥60                             | 124           | 70 (76.1)           | 54 (91.5)             |         |
| Female, n (%)                   | 54 (35.8)     | 32 (34.8)           | 22 (37.3)             | 0.86    |
| BMI, kg/m²                      | 22.7 [20.0−25.0] | 22.8 [19.8−25.0] | 22.4 [20.2−25.1]      | 0.92    |
| Brinkman index                  | 360 [0−700]   | 320 [0−600]         | 400 [0−820]           | 0.16    |
| Polypharmacy, n (%)             | 64 (42.4)     | 35 (38.0)           | 29 (49.2)             | 0.18    |
| ASA-PS, n (%)                   | 0.66          |                     |                       |         |
| 1                               | 39 (25.8)     | 25 (27.2)           | 14 (23.7)             |         |
| 2                               | 109 (72.2)    | 66 (71.7)           | 43 (72.9)             |         |
| 3                               | 3 (2.0)       | 1 (1.1)             | 2 (3.4)               |         |
| **Comorbidities**               |               |                     |                       |         |
| DM, n (%)                       | 41 (27.2)     | 19 (20.7)           | 22 (37.3)             | 0.03    |
| CVD, n (%)                      | 13 (8.6)      | 6 (6.5)             | 7 (11.9)              | 0.37    |
| Cancer site, n (%)              |               |                     |                       | 0.33    |
| Colorectal                      | 112 (74.2)    | 69 (75.0)           | 43 (72.9)             |         |
| Gastric                         | 37 (24.5)     | 21 (22.8)           | 16 (27.1)             |         |
| Esophagogastric junction        | 2 (1.3)       | 2 (2.2)             | 0 (0)                 |         |
| Stage, n (%)                    |               |                     |                       | 0.20    |
| 0                               | 9 (6.0)       | 6 (6.5)             | 3 (5.1)               |         |
| 1                               | 37 (24.5)     | 19 (20.7)           | 18 (30.5)             |         |
| 2                               | 49 (32.5)     | 35 (38.0)           | 14 (23.7)             |         |
| 3                               | 50 (33.1)     | 27 (29.3)           | 23 (39.0)             |         |
| 4                               | 6 (4.0)       | 5 (5.4)             | 1 (1.7)               |         |
| PNI                             | 49.4 [44.6−53.0] | 49.1 [44.5−52.8] | 49.5 [45.0−53.3]      | 0.87    |
| Albumin, g/dL                   | 4.0 [3.8−4.3] | 4.0 [3.8−4.3]       | 4.1 [3.7−4.3]         | 0.98    |
| CRP, mg/dL                      | 0.17 [0.07−0.36] | 0.15 [0.06−0.32] | 0.24 [0.10−0.49]      | 0.05    |
| Hemoglobin, g/dL                | 13.1 [11.4−14.7] | 13.1 [11.4−14.5] | 13.1 [11.3−14.8]      | 0.81    |
| WBC, ×10^3/μL                   | 6.4 [5.4−7.5] | 6.5 [5.4−7.3]       | 6.3 [5.3−7.9]         | 0.80    |
| TLC, ×10^3/μL                   | 1.6 [1.3−2.0] | 1.6 [1.3−2.0]       | 1.6 [1.2−2.0]         | 0.93    |
| Sedentary time, h/day           | 5 [3−7]       | 4 [3−6]             | 6 [4−8]               | <.01    |
| Grip strength, kg               | 26.9 [20.1−33.3] | 28.5 [21.0−34.4] | 25.5 [18.4−32.6]      | 0.08    |
| Usual gait speed, m/s           | 1.25 [1.06−1.44] | 1.29 [1.17−1.46] | 1.13 [0.92−1.35]      | <0.01   |
| Anxiety, n (%)                  | 42 (27.8)     | 29 (31.5)           | 13 (22.0)             | 0.26    |
| Depression, n (%)               | 52 (34.4)     | 26 (28.3)           | 26 (44.1)             | 0.05    |
| **Intraoperative characteristics**|               |                     |                       |         |
| Surgical approach, n (%)        |               |                     |                       | 0.50    |
| Open                            | 69 (45.7)     | 40 (43.5)           | 29 (49.2)             |         |
| Laparoscopy                     | 82 (54.3)     | 52 (56.5)           | 30 (50.8)             |         |
| Combined resection, n (%)        | 32 (21.2)     | 20 (21.7)           | 12 (20.3)             | 0.99~    |
| Operative time, min             | 274 [207.5−348.5] | 279 [211−356] | 264 [206−341]         | 0.81    |
| Anesthesia time, min            | 341 [265−419] | 342 [275−421]       | 333 [258−414]         | 0.88    |
| Blood loss, mL                  | 88 [20−331.5] | 61 [24−301]         | 100 [18−357]          | 0.59    |
| Transfusion, n (%)              | 7 (4.6)       | 5 (5.4)             | 2 (3.4)               | 0.70    |
| **Postoperative characteristics**|               |                     |                       |         |
| Postoperative complications, n (%)| 63 (41.7)   | 39 (42.4)           | 24 (40.7)             | 0.86    |
| POD, n (%)                      | 25 (16.6)     | 10 (10.9)           | 15 (25.4)             | 0.02    |
| Postoperative hospital stay, day | 12 [10−20]   | 12 [10−19]          | 12 [10−22]            | 0.81    |

Continuous variables are shown as median [interquartile range] and categorical variables as number (%); n, colorectal cancer only; BMI, body mass index; ASA-PS, American Society of Anesthesiologists physical status; DM, diabetes mellitus; CVD, cerebrovascular disease; PNI, prognostic nutrition index; CRP, C-reactive protein; WBC, white blood cell count; TLC, total lymphocyte count; POD, postoperative delirium.
with POD independently of sedentary time, no study has investigated the relationship between the intensity of PA and POD. Janssen (2019) have reported, although not in a randomized controlled trial, that about one-month of a prehabilitation program reduced the incidence of POD in major abdominal surgery patients. In addition, moderate- to vigorous-intensity PA was reported to improve the cognitive function in another review (Erickson et al., 2019). These results implicate that lower PA intensity, rather than sedentary behavior, may be associated with the incidence of POD.

The pathophysiology of delirium has been indicated to be multifactorial, and several mechanisms have been reported in a previous review (Rengel et al., 2018). In previous reports, brain-derived neurotrophic factor (BDNF), which influences neuroplasticity and neurotransmission and plays a important role in learning, memory, and cognition (Huang and Reichardt, 2001), was positively related to cognitive function (Gunstad et al., 2008), and PA was positively associated with BDNF levels in older adults (Engeroff et al., 2018). Moreover, the relationships between PA and cerebral blood flow in older adults and between preoperative cerebral oximetry and POD in patients who underwent surgery have also been reported (Zlatar et al., 2019; Soh et al., 2020). Therefore, it is speculated that patients with low preoperative PA may be more susceptible to POD because they have lower BDNF levels and cerebral blood flow, which affect brain function. However, the detailed mechanism of POD is not sufficiently clear, and the results of our study do not suggest a mechanism; thus, future studies to clarify the mechanism of POD are needed.

Our study has several limitations. First, although patients with clinically evident cognitive decline (inability to understand the meaning of instructions or questionnaires) were excluded, preoperative cognitive function, which was revealed to be a risk factor for POD, was not evaluated using objective indicators such as the Mini Mental State Examination in our study. This was because of its retrospective design. Further, it cannot be denied that our study may have included patients below the cutoff value for objective cognitive function assessment used in a previous study (Chen et al., 2017). Second, since POD in the present study was assessed by only physical therapists during rehabilitation time, the number of patients who developed POD may have been underestimated. Therefore, it is possible that we overestimated the magnitude of the association between the preoperative PA and POD. Third, due to the small sample size, we were not able to adequately adjust for confounding factors, especially age. Thus, the results of our study should be interpreted with caution. Fourth, the mechanism by which preoperative PA influences POD is not clear in the present study because we did not measure neurophysiological factors that affect POD. Fifth, we were not able to assess the duration and severity of POD due to the retrospective design. Therefore, the relationship between preoperative PA and the duration and severity of POD is unknown. Finally, the present study did not investigate the effects of dose or type of preoperative medications, although a previous study reviewed the association between preoperative medication type and POD (Kassie et al., 2017). Future study is needed to take into account the effects of these medications.

In conclusion, low preoperative PA was a predictor of POD in gastrointestinal cancer patients, independent of confounding factors such as DM, gait speed, and sedentary time. Thus, our results suggest that preoperative PA plays a key role in predicting and preventing POD in these patients.

**Author Contribution Statement**

T.Y., K.I., T.K., and H.S. conceived and designed the project. T.Y., M.H., S.M., and S.Y. acquired the data. T.Y., N.T., and H.S. analyzed and interpreted the data and wrote the paper.

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**Ethical approval**

The present study was approved by the Ethics Committee of Kamiida Daiichi General Hospital and Nagoya University School of Medicine.
Availability of data
The dataset is available from the corresponding author on reasonable request.

Conflict of Interest
The authors declare no conflicts of interest associated with this study.

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