RESEARCH ARTICLE

Editorial Process: Submission:02/02/2022 Acceptance:05/23/2022

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

Takuya Yanagisawa[1,2]*, Noriatsu Tatematsu[3], Mioko Horiuchi[1], Saki Migitaka[1], Shotaro Yasuda[1], Keita Itatsu[4], Tomoyuki Kubota[5], Hideshi Sugiura[3]

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

Asian Pac J Cancer Prev, **23 (5)**, 1753-1759

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 Y 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

*[1]Department of Rehabilitation, Kamiiida Daiichi General Hospital, 2-70 Kamiiida-kitamachi, Kita-ku, Nagoya, Aichi 462-0802, Japan. [2]Program in Physical and Occupational Therapy, Nagoya University Graduate School of Medicine, 1-1-20 Daiko-minami, Higashi-ku, Nagoya, Aichi 461-8673, Japan. [3]Department of Integrated Health Sciences, Nagoya University Graduate School of Medicine, 1-1-20 Daiko-minami, Higashi-ku, Nagoya, Aichi 461-8673, Japan. [4]Department of surgery, Kamiiida Daiichi General Hospital, 2-70 Kamiiida-kitamachi, Kita-ku, Nagoya, Aichi 462-0802, Japan. [5]Department of breast surgery, Kamiiida Daiichi General Hospital, 2-70 Kamiiida-kitamachi, Kita-ku, Nagoya, Aichi 462-0802, Japan. *For Correspondence: yanagisawa1204@gmail.com*

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 laparotomy, (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, 1098). 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 lymphocyte count (Kanda et al., 2016).

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 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

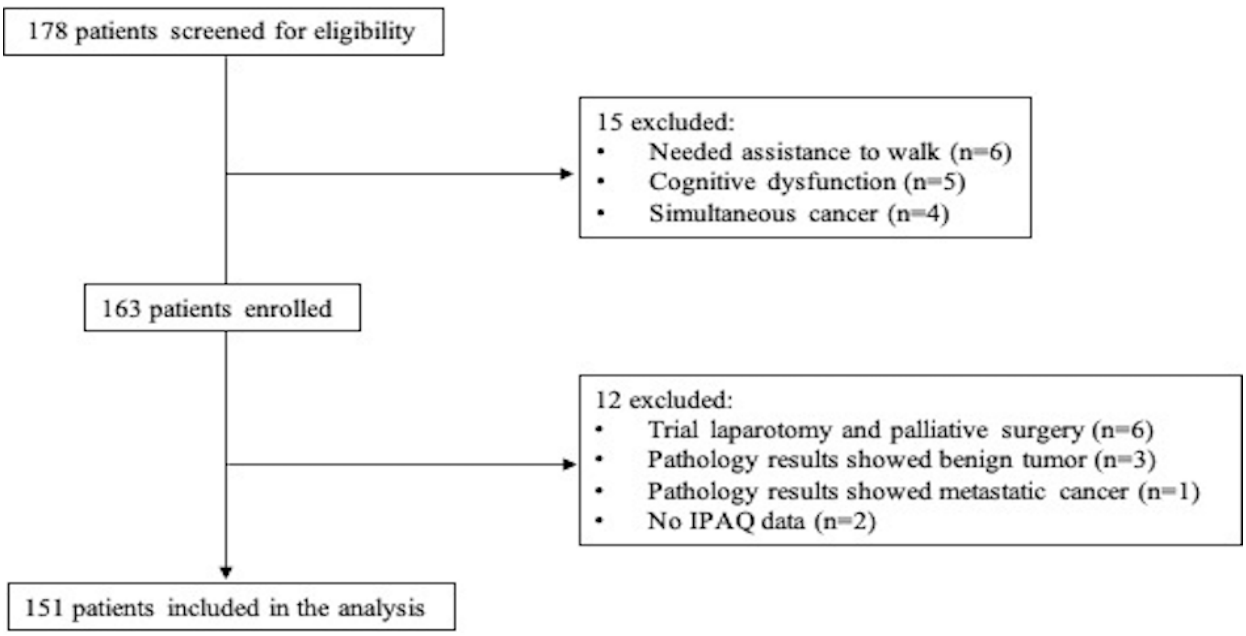

Figure 1. Flow Chart of Patient Selection

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/m^2	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[a]	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]	<0.01
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 (%); a, 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.

Table 2. Multivariate Logistic Regression Analysis to Investigate the Association between Preoperative PA and POD

	Univariate		Multivariate	
	OR (95% CI)	p value	OR (95% CI)	p value
PA, 0=active 1=inactive	2.80 (1.16−6.74)	0.02	2.83 (1.06−7.58)	0.03
DM, 0=no 1=yes	–	–	0.47 (0.15−1.48)	0.20
Sedentary time, per 1 h/day	–	–	0.91 (0.79−1.06)	0.22
Usual gait speed, per 1 m/s	–	–	0.14 (0.03−0.72)	0.01

DM, sedentary time, and usual gait speed were entered into the multiple logistic regression analysis as confounding factors; OR, odds ratio; CI, confidence interval; PA, physical activity; DM, diabetes mellitus

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.

Acknowledgements

We thank all the patients who participated in this study. We also thank the collaborating surgeons and other medical staff for their important contributions to our study. We would like to thank Editage (www.editage.com) for English language editing. The use of short CAM in this study was approved by the Hospital Elder Life Program, 2021.

Funding statement

This work was supported in part by JSPS KAKENHI (Grant Number 18H03127 to H. Sugiura) from the Japan Society for the Promotion of Science.

Ethical approval

The present study was approved by the Ethics Committee of Kamiiida 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.

References

Aune D, Norat T, Leitzmann M, Tonstad S, Vatten LJ (2015). Physical activity and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis. *Eur J Epidemiol*, **30**, 529-42.

Austin CA, O'Gorman T, Stern E, et al (2019). Association Between Postoperative Delirium and Long-term Cognitive Function After Major Nonemergent Surgery. *JAMA Surg*, **154**, 328-34.

Chaiwat O, Chanidnuan M, Pancharoen W, et al (2019). Postoperative delirium in critically ill surgical patients: incidence, risk factors, and predictive scores. *BMC Anesthesiol*, **19**, 39.

Chen BP, Awasthi R, Sweet SN, et al (2017). Four-week prehabilitation program is sufficient to modify exercise behaviors and improve preoperative functional walking capacity in patients with colorectal cancer. *Support Care Cancer*, **25**, 33-40.

Chen LK, Woo J, Assantachai P, et al (2020). Asian Working Group for Sarcopenia: 2019 Consensus Updata on Sarcopenia Diagnosis and Treatment. *J Am Med Dir Assoc*, **21**, 300-7.

Chen Y, Qin J (2021). Modified Frailty Index Independently Predicts Postoperative Delirium and Delayed Neurocognitive Recovery After Elective Total Joint Arthroplasty. *J Arthroplasty*, **36**, 449-53.

Clavien PA, Barkun J, de Oliveira ML, et al (2009). The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*, **250**, 187-96.

Craig CL, Marshall AL, Sjöström M, et al (2003). International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*, **35**, 1381-95.

Dindo D, Demartines N, Clavien PA (2004). Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*, **240**, 205-13.

Engeroff T, Füzéki E, Vogt L, et al (2018). Is Objectively Assessed Sedentary Behavior, Physical Activity and Cardiorespiratory Fitness Linked to Brain Plasticity Outcomes in Old Age?. *Neuroscience*, **388**, 384-92.

Erickson KI, Hillman C, Stillman CM, et al (2019). Physical Activity, Cognition, and Brain Outcomes: A Review of the 2018 Physical Activity Guidelines. *Med Sci Sports Exerc*, **51**, 1242−51.

Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK (2015). The interface between delirium and dementia in elderly adults. *Lancet Neurol*, **14**, 823-32.

Fried LP, Tangen CM, Walston J, et al (2001). Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*, **56**, 146−56.

Gunstad J, Benitez A, Smith J, et al (2008). Serum brain-derived neurotrophic factor is associated with cognitive function in health older adults. *J Geriatr Psychiatry Neurol*, **21**, 166-70.

Huang EJ, Reichardt LF (2001). Neurotrophins: roles in neuronal development and function. *Annu Rev Neurosci*, **24**, 677-736.

Inouye SK, van Dyck CH, Alessi CA, et al (1990). Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*, **113**, 941-8.

Inouye SK (2014). The Short Confusion Assessment Method (Short CAM): Training Manual and Coding Guide. Boston: Hospital Elder Life Program.

Janssen TL, Steyerberg EW, Langenberg JCM, et al (2019). Multimodal prehabilitation to reduce the incidence of delirium and other adverse events in elderly patients undergoing elective major abdominal surgery: An uncontrolled before-and-after study. *PLoS One*, **14**, e0218152.

Jung P, Pereira MA, Hiebert B, et al (2015). The impact of frailty on postoperative delirium in cardiac surgery patients. *J Thorac Cardiovasc Surg*, **149**, 869-75.

Kanda M, Mizuno A, Tanaka C, et al (2016). Nutritional predictors for postoperative short-term and long-term outcomes of patients with gastric cancer. *Medicine (Baltimore)*, **95**, e3781.

Kanda Y (2013). Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant*, **48**, 452-8.

Kassie GM, Nguyen TA, Kalisch Ellett LM, et al (2017). Preoperative medication use and postoperative delirium: a systematic review. *BMC Geriatr*, **17**, 298.

Kirk-Sanchez NJ, McGough EL (2014). Physical exercise and cognitive performance in the elderly: current perspectives. *Clin Interv Aging*, **9**, 51-62.

Kugaya A, Akechi T, Okuyama T, Okamura H, Uchitomi Y (1998). Screening for Psychological Distress in Japanese Cancer Patients. *Jpn J Clin Oncol*, **28**, 333-8.

Lee SH, Lim SW (2020). Risk factors for postoperative delirium after colorectal surgery: a systematic review and meta-analysis. *Int J Colorectal Dis*, **35**, 433-44.

Lee SS, Lo Y, Verghese J (2019). Physical Activity and Risk of Postoperative Delirium. *J Am Geriatr Soc*, **67**, 2260-6.

Lipowski ZJ (1983). Transient cognitive disorders (delirium, acute confusional states) in the elderly. *Am J Psychiatry*, **140**, 1426-36.

Maekawa Y, Sugimoto K, Yamasaki M, et al (2016). Comprehensive Geriatric Assessment is a useful predictive tool for postoperative delirium after gastrointestinal surgery in old-old adults. *Geriatr Gerontol Int*, **16**, 1036-42.

Mosk CA, van Vugt JLA, de Jonge H, et al (2018). Low skeletal muscle mass as a risk factor for postoperative delirium in elderly patients undergoing colorectal cancer surgery. *Clin Interv Aging*, **13**, 2097-106.

Ogawa M, Izawa KP, Kitamura A, et al (2015). Preoperative physical activity in relation to postoperative delirium in elective cardiac surgery patients. *Int J Cardiol*, **201**, 154-6.

Osuka Y, Kim H, Kawai H, et al (2020). Sarcoscore: A Novel Approach for Assessing Sarcopenia and Functional Disability in Older Adults. *J Clin Med*, **9**, 692.

Raats JW, van Eijsden WA, Crolla RM, Steyerberg EW, van der Laan L (2015). Risk Factors and Outcomes for Postoperative Delirium after Major Surgery in Elderly Patients. *PLoS One*, **10**, e0136071.

Rengel KF, Pandharipande PP, Hughes CG (2018). Postoperative delirium. *Presse Med*, **47**, e53-64.

Sato T, Hatakeyama S, Okamoto T, et al (2016). Slow Gait Speed and Rapid Renal Function Decline Are Risk Factors for Postoperative Delirium after Urological Surgery. *PLoS One*, **11**, e0153961.

Scholz AF, Oldroyd C, McCarthy K, Quinn TJ, Hewitt J (2016). Systematic review and meta-analysis of risk factors for postoperative delirium among older patients undergoing gastrointestinal surgery. *Br J Surg*, **103**, e21-8.

Shi Z, Mei X, Li C, et al (2019). Postoperative Delirium Is Associated with Long-term Decline in Activities of Daily

Living. *Anesthesiology*, **131**, 492-500.
Sjostrom M, Ainsworth B, Bauman A, et al (2005). Guidelines for data processing analysis of the International Physical Activity Questionnaire (IPAQ) – Short and long forms. https://docs.google.com/r?a=v&pid=sites&srcid=ZGVmYXVsdGRvbWFpbnx0aGVpcGFxfGd4OjE0NDgxMDk3NDU1YWRlZTM. Accessed 20 May 2021.
Soh S, Shim JK, Song JW, Choi N, Kwak YL (2020). Preoperative transcranial Doppler and cerebral oximetry as predictors of delirium following valvular heart surgery: a case–control study. *J Clin Monit Comput*, **34**, 715-23.
Toriumi T, Yamashita H, Kawasaki K, et al (2020). Preoperative Exercise Habits are Associated with Post-gastrectomy Complications. *World J Surg*, **44**, 2736-42.
Volakis KA, Thorand B, Peters A, et al (2018). Physical Activity, Muscular Strength, and Polypharmacy Among Older Multimorbid Persons: Results From the KORA-Age Study. *Scand J Med Sci Sports*, **28**, 604-12.
Wada S, Inoguchi H, Sadahiro R, et al (2019). Preoperative Anxiety as a Predictor of Delirium in Cancer Patients: A Prospective Observational Cohort Study. *World J Surg*, **43**, 134-42.
Yamamoto M, Yamasaki M, Sugimoto K, et al (2016). Risk Evaluation of Postoperative Delirium Using Comprehensive Geriatric Assessment in Elderly Patients with Esophageal Cancer. *World J Surg*, **40**, 2705-12.
Yang Z, Wang XF, Yang LF, et al (2020). Prevalence and risk factors for postoperative delirium in patients with colorectal carcinoma: a systematic review and meta-analysis. *Int J Colorectal Dis*, **35**, 547-57.
Yasunaga A, Shibata A, Ishii K, et al (2017). Associations of sedentary behavior and physical activity with older adults' physical function: an isotemporal substitution approach. *BMC Geriatr*, **17**, 280.
Yoshimura N, Oka H, Murai S, et al (2011). Reference values for hand grip strength, muscle mass, walking time, and one-leg standing time as indices for locomotive syndrome and associated disability: the second survey of the ROAD study. *J Orthop Sci*, **16**, 768-77.
Zigmond AS, Snaith RP (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*, **67**, 361-70.
Zlatar ZZ, Hays CC, Mestre Z, et al (2019). Dose-dependent association of accelerometer-measured physical activity and sedentary time with brain perfusion in aging. *Exp Gerontol*, **125**, 110679.