Impact of postoperative physical activity on the development of pneumonia in the subacute phase after esophagectomy in patients with esophageal cancer: a retrospective cohort study

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ABSTRACT

Background: Physical activity is important to improve recovery following surgery. This study investigated the impact of physical activity on the development of pneumonia after radical esophagectomy in patients with thoracic esophageal cancer in the subacute phase from postoperative day 11 to hospital discharge.

Methods: This retrospective cohort study included 83 patients who underwent radical esophagectomy for esophageal cancer between 2016 and 2022. Physical activity was measured using an activity tracker, and the average number of steps between postoperative days 8 and 10 was examined. The primary outcome was pneumonia (Clavien-Dindo classification 2 or higher) developing between postoperative day 11 and hospital discharge. We used the receiver operating characteristic (ROC) curve analysis to calculate the optimal cutoff value of physical activity that can predict the development of pneumonia and define low physical activity. We used logistic regression analysis to investigate the impact of low physical activity on postoperative pneumonia.

Results: Pneumonia developed in 10 patients (12.0%) during the observation period. The optimal cutoff value of physical activity for predicting pneumonia was 1,494 steps per day (sensitivity: 60.0%, specificity: 89.0%, area under the curve: 0.743). In multivariate analysis, low physical activity was an independent predictor of incident pneumonia [odds ratio: 12.10, 95% confidence interval: 2.21–65.90, p=0.004], with adjustment for age, gastric tube reconstruction route, and postoperative recurrent nerve palsy.

Conclusions: Physical activity following radical esophagectomy in patients with thoracic esophageal cancer was an independent predictor of the development of pneumonia in the subacute phase after radical esophagectomy.

Keywords: physical activity, surgery, pneumonia, esophageal cancer, rehabilitation

INTRODUCTION

Esophageal cancer is the sixth leading cause of cancer-related death worldwide (Global Burden of Disease Cancer Collaboration et al., 2019), and esophagectomy is a curative treatment option. Although advances in surgical techniques have improved early postoperative mortality, postoperative complications remain high (Griffin et al., 2020). In particular, postoperative pneumonia is one of esophagectomy's most frequent complications, with an incidence of approximately 12% (Kikuchi et al., 2022; Soutome et al., 2020). Postoperative pneumonia has also been reported to have a negative impact on overall survival (Tamagawa et al., 2019); thus, prevention of pneumonia is critical in the perioperative management of patients with esophageal cancer.

The enhanced recovery after surgery (ERAS) protocol is a strategy for preventing postoperative complications and has been widely adopted in surgery for use on various gastrointestinal cancers (Ljungqvist et al., 2017). In patients with esophageal cancer, several systematic reviews and meta-analyses have reported that ERAS reduces the incidence of respiratory complications, including pneumonia (Pisarska et al., 2017; Puccetti et al., 2022). The impact of a multidisciplinary plan for patients with esophageal cancer surgery is broadly clear, but the evidence for each individual component of ERAS is varied (Low et al., 2019), hence more specific intervention details are warranted.

Promotion of postoperative physical activity with early mobilization is strongly

recommended by the ERAS protocol (Low et al., 2019). Prolonged postoperative bedrest leads to systemic inflammation and respiratory dysfunction (Brower, 2009), indicating the need to promote physical activity during the early postoperative period. Several studies have reported the use of activity trackers to promote perioperative physical activity in patients with gastrointestinal cancer (Honke et al., 2022; Low et al., 2018; Nakajima et al., 2020; Nevo et al., 2022). In patients with esophageal cancer, the preoperative use of activity trackers has been reported to reduce the incidence of postoperative pneumonia (Honke et al., 2022). However, the authors of the study did not investigate the quantity of postoperative physical activity or the activity level needed to prevent postoperative pneumonia. Investigation of the quantity of postoperative physical activity necessary to prevent pneumonia could present as a useful guide for early mobilization.

Therefore, this study focused on the quantity of postoperative physical activity and examined the amount of physical activity required to prevent pneumonia after esophageal cancer surgery. Furthermore, we investigated the impact of low physical activity on the development of postoperative pneumonia.

METHODS

Study population

This retrospective cohort study included patients who underwent radical esophagectomy for

thoracic esophageal cancer at Tokushima University Hospital from October 2016 to June 2022.

Exclusion criteria were as follows: refusal to use wearable activity trackers; inability to walk independently at postoperative day (POD) 8 due to oxygen supplementation or intravenous infusion; clinical evidence of pneumonia before POD 10 or evidence of pneumonia on radiographs or computed tomography images at POD 8; missing patient data.

In patients treated with neoadjuvant chemotherapy, the regimen was typically weekly docetaxel plus low-dose cisplatin and 5-fluorouracil therapy (Yoshida et al., 2010). The standard surgical procedure was subtotal esophagectomy with 2- or 3- field lymphadenectomy and reconstruction using a gastric tube through the posterior mediastinum, retrosternally, or subcutaneously. The standard nutritional management was tube feeding starting on the day after surgery, and initiation of oral intake approximately 8 days post-surgery. Perioperative oral care was provided to all patients by dentists and dental hygienists. All patients received rehabilitation by a physical therapist 1–4 days before surgery and from the day after surgery until discharge. Details of rehabilitation interventions are described elsewhere (Kondo et al., 2022).

This study was approved by the Ethics Committee of the University of Tokushima Hospital (approval number 3108-3) and was conducted in accordance with the 1964 Declaration of Helsinki (as revised in Edinburgh 2000). Written informed consent was obtained from all patients prior to the study.

Data collection

We collected the following information from the patients' medical records: age, sex, body mass index (BMI), performance status, preoperative nutritional status, prevalence of sarcopenia, Brinkman index, and comorbidities (such as hypertension, diabetes, cardiovascular disease, pulmonary disease). In addition, the following were obtained: respiratory function (percentage of vital capacity [%VC] and percentage of forced expiratory volume in 1 s [FEV1 %]); tumor location, histology, and clinical stage (cStage); type of neoadjuvant therapy. Other clinical data collected included: surgical information (surgical approaches, lymph node dissection, gastric tube reconstruction route, operation time, blood loss); postoperative course (postoperative oxygenation, initiation of oral intake, initiation of ambulation, chest tube removal, total energy intake at POD 8 [kcal/day]); serum chemical data at POD 8 (serum albumin and C-reactive protein levels); duration of postoperative hospital stay. Preoperative nutritional status was assessed using the Mini Nutritional Assessment-Short Form (MNA-SF). Sarcopenia was assessed based on the Asian Working Group for Sarcopenia 2019 (Chen et al., 2020). The clinical stage was defined according to the Union for International Cancer Control, 8th edition (Rice et al., 2017).

Physical activity

Physical activity was measured using a wearable activity tracker (Kenz LifecoderGS, Suzuken

Co., Ltd., Nagoya, Japan). Patients were instructed to wear the activity tracker on their waist from the moment they wake up until bedtime, except while bathing (Nakajima et al., 2020). Every day, the physical therapist checked the number of steps completed from the previous day and encouraged the patient to walk more. Following esophagectomy, physical activity is often limited by environmental factors, such as oxygenation and chest drain tube placement. Therefore, the number of steps taken during the three-day period (Huisingh-Scheetz et al., 2018) from POD 8 to POD 10, when oxygen or drain tubes are removed in most patients, was averaged and used for analysis as physical activity.

Outcomes

Pneumonia was defined as the development of Grade II or higher complication (Takeuchi et al., 2020) according to the Clavien-Dindo classification (Dindo et al., 2004). In this study, the average number of steps completed during PODs 8–10 was defined as physical activity. Therefore, to clarify the causal relationship, development of pneumonia from POD 11 to discharge was defined as postoperative pneumonia, and patients who developed pneumonia prior to POD 10 were excluded. Other complications, including recurrent nerve palsy, surgical site infections, and anastomotic leakage, were also defined as postoperative complications if they were Grade II or higher according to the Clavien-Dindo classification (Dindo et al., 2004).

Statistical analysis

Comparison of patients categorized by the presence or absence of pneumonia was performed using Fisher's exact test for categorical variables and Student's *t*-test or Mann−Whitney U test for continuous variables. Continuous variables are expressed as median and interquartile range (IQR) for nonparametric variables and as mean ± standard deviation (SD) for parametric variables. We used receiver operating characteristic (ROC) curve analysis to identify the optimal cutoff value of physical activity required to predict the development of pneumonia (Sato et al., 2018). Physical activity was categorized into low physical activity and normal physical activity based on the results of the ROC curve analysis. We performed univariate and multivariate analyses using logistic regression models to determine the impact of low physical activity on PODs 8–10 on the development of pneumonia from POD 11 to discharge. Multivariate analysis was adjusted for factors previously reported to influence the development of pneumonia: age (<70 years vs. ≥70 years) (Sato et al., 2018) , gastric tube reconstruction route (retrosternal vs. subcutaneous or posterior mediastinal) (Kikuchi et al., 2022), and postoperative recurrent nerve palsy (Koyanagi et al., 2015) as confounding factors.

All statistical analyses were two-sided, and p-values <0.05 were considered statistically significant. All statistical analyses were performed using EZR version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among the 123 patients included, 83 met this study's inclusion criteria (18 females and 65 male, median age 67.5 years). Forty patients were excluded for the following reasons: clinical evidence of pneumonia before POD 10 or evidence of pneumonia on radiography or computed tomography images at POD 8 (n=4), inability to walk independently at POD 8 (n=12), refusal to use wearable activity tracker (n=11), and missing data (n=13).

The median observation period was 25 days (19–40 days). Pneumonia developed in 10 of the 83 patients (12.0%) during the observation period. The cumulative incidence of pneumonia and the number of postoperative days are shown in Figure 1. The median days to the development of pneumonia was 19.5 days (16.5–23.5 days).

Table 1 shows patient characteristics categorized by the presence or absence of pneumonia. No significant differences were observed between the groups with and without pneumonia in age, sex, BMI, nutritional status, prevalence of sarcopenia, smoking history, comorbidities, respiratory function tests, tumor site, histology, clinical stage, type of neoadjuvant therapy or surgical procedures. During the postoperative course, patients with pneumonia showed delayed initiation of oral intake (12.0 days vs. 8.0 days, p=0.037) and less physical activity (1,479.5 steps/day vs. 2,848.0 steps/day, p=0.013) compared to patients without pneumonia, respectively. Conversely, no significant difference was noted in the

incidence of postoperative complications, but patients with pneumonia had a significantly longer length of hospital stay (45.5 days vs. 24.0 days, p=0.002).

The ROC curve analysis demonstrated that the optimal cutoff value for physical activity between PODs 8–10 to predict pneumonia was 1,494 steps/day (sensitivity: 60.0%, specificity: 89.0%, area under the curve [AUC]: 0.743) (Figure 2). We defined 1,494 steps or less as low physical activity and 1495 steps or more as normal physical activity.

To investigate the impact of postoperative low physical activity on the development of pneumonia, logistic regression analysis was performed (Table 2). In univariate analysis, low physical activity was a significant predictor of pneumonia (odds ratio [OR]: 12.20, 95% confidence interval [CI]: 2.82–52.60, p=0.001). Similarly, multivariate analysis (adjusted for age, reconstruction route, and postoperative recurrent nerve palsy) indicated that low physical activity was an independent predictor of pneumonia (OR: 12.10, 95% CI: 2.21–65.90, p=0.004).

DISCUSSION

To the best of our knowledge, this is the first study to investigate the impact of physical activity after radical esophagectomy for thoracic esophageal cancer on the development of postoperative pneumonia. The incidence of pneumonia during the observation period was 12% (10 cases), similar to previous findings (Kikuchi et al., 2022; Soutome et al., 2020). The optimal cutoff value of physical activity used to predict the development of postoperative pneumonia

was 1,494 steps/day, with a sensitivity of 60.0%, specificity of 89.0%, and AUC of 0.743. Low physical activity, defined as 1,494 steps/day or less, was an independent predictor of the development of postoperative pneumonia, after adjusting for age, gastric tube reconstruction route, and postoperative recurrent nerve palsy complications.

Postoperative low physical activity was an independent factor predicting the development of pneumonia following radical esophageal cancer surgery. Physical activity and oral care have been previously recommended for the prevention of non-ventilator-associated hospital-acquired pneumonia (Mitchell et al., 2019; Quinn et al., 2020). In a randomized controlled trial, perioperative physical therapy interventions, including early ambulation, reportedly reduced the incidence of pneumonia in patients undergoing upper abdominal surgery (Boden et al., 2018). In an observational study, Honke et al. have reported a reduction in the incidence of pneumonia in patients undergoing radical esophagectomy who wore activity trackers and were encouraged to engage in physical activity during the perioperative period (Honke et al., 2022). In these studies, various preoperative interventions were provided, and the incidence of pneumonia was reduced by comprehensive interventions, including early ambulation. The results of our study focused on postoperative walking, suggesting the importance of early ambulation. The outcome was pneumonia developing in the subacute phase after POD 11. Pneumonia after POD 11 may result from aspiration (Okamura et al., 2016), which is more common among older patient populations (Soutome et al., 2020). As the number

of older adult patients increases, it will be necessary to pay attention to the risk of aspiration after surgery, and the importance of promoting early ambulation will further grow.

The mechanism of postoperative physical activity involved in the prevention of pneumonia has not been sufficiently elucidated. Respiratory function declines with low physical activity (Bédard et al., 2020), and poor respiratory function is associated with the development of pneumonia after esophagectomy (Okamura et al., 2016). Low postoperative physical activity reduces the ability to expel airway secretions. Physical activity influences immune function and is associated with higher concentrations of CD4 T cells and salivary immunoglobulin IgA (Chastin et al., 2021). Physical activity has been reported to reduce the development of infectious diseases, including pneumonia, through activation of these immune functions (Chastin et al., 2021). The effects of low physical activity on respiratory and immune function may be associated with the development of pneumonia after esophagectomy.

In this study, the optimal cutoff value for predicting the development of postoperative pneumonia was 1,494 steps/day, providing a quantitative target for early mobilization. The use of activity trackers reduced the risk of postoperative pneumonia during the perioperative period following radical esophagectomy (Honke et al., 2022); however, specific postoperative activities were not described. The strength of our study is that it focused on the postoperative period, in which activity levels often decline due to pain or environmental factors. Walking at least 1,495 steps/day during PODs 8–10 may be a common goal for both patients and clinicians.

A study of community-dwelling older adult subjects reported an association between the number of steps and immune function and found that subjects with fewer steps had significantly lower levels of salivary antimicrobial peptides (Shimizu et al., 2017). Although the number of steps defined as low physical activity was different, the results suggest that the lack of physical activity may be associated with infection. As a strategy for postoperative rehabilitation, it is important to remove the chest tube and supplemental oxygenation to promote physical activity. In addition, postoperative physical therapy promotes physical activity, especially walking.

Due to a higher incidence of anastomotic leakage, initiation of oral intake was significantly delayed in patients with pneumonia. Delayed oral intake could adversely affect swallowing, resulting in aspiration. In patients with delayed oral intake, indirect swallowing exercises may be necessary.

This study has several limitations. First, the sample size is small as this is a cohort study from a single institution. Second, some patients refused to wear the activity tracker or forgot to wear the device. In the future, the use of devices wearable at the wrist or ankle is warranted, as these may be less stressful for patients. Third, patients with pneumonia showed higher C-reactive protein (CRP) levels at POD 8, although we found no evidence of pneumonia on radiologic images at POD 8. Therefore, the reason for the higher CRP may be attributed to other complications such as anastomotic leakage. Finally, the study outcome was development of pneumonia after POD 11; therefore, the results cannot be applied to all postoperative

pneumonia. In the future, the measurement of physical activity should begin immediately post-surgery.

CONCLUSION

Physical activity following radical esophagectomy in patients with thoracic esophageal cancer was an independent predictor for the development of pneumonia in the subacute phase after POD 10.

The optimal cutoff value for physical activity to predict the development of pneumonia was 1,494 steps per day during PODs 8–10. This study suggests that promoting physical activity in the early postoperative period may prevent the development of postoperative pneumonia following radical esophagectomy.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

The authors declare no conflict of interest.

Ethical approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent, or a substitute for it, was obtained from all patients for inclusion in the study.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Shin Kondo, Tatsuro Inoue, Takashi Saito, Takashi Fujikawa, Motomu Kamada, Seiya Inoue, Satoshi Fujiwara, Masakazu Goto, Nori Sato, Rei Ono, Toshihiro Akisue and Shinsuke Katoh. The first draft of the manuscript was written by Shin Kondo and all authors commented on previous versions of the manuscript. Hiromitsu Takizawa and Tetsuya Matsuura supervised the project. All authors read and approved the final

manuscript.

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FIGURE LEGENDS

Figure 1. Cumulative incidence of subacute pneumonia after radical esophagectomy.

Figure 2. Receiver operating characteristic curves for physical activity (steps/day) to predict the development of pneumonia.

TABLES

Table 1. Patients characteristics

	Pneumonia (+)	Pneumonia (-)	*p*-value
	n = 10	n = 73	
Age (years)			
Median (IQR)	72.5 (62.0–76.0)	67.0 (60.0–71.0)	0.310
Sex			
Female	2 (20.0)	16 (21.9)	1.000
Male	8 (80.0)	57 (78.1)	
Body mass index (kg/m^2)			
Mean ± SD	21.9 ± 2.6	22.1 ± 2.6	0.842
Performance status			
≥ 2	0 (0.0%)	0 (0.0%)	1.000
Nutrition status			
Normal	7 (70.0)	44 (60.3)	0.824
Risk for undernutrition	3 (30.0)	26 (35.6)	
Undernutrition	0 (0.0)	3 (4.1)	
Sarcopenia			
yes	2 (20.0)	9 (12.3)	0.615
Brinkman Index			
0	1 (10.0)	15 (20.5)	0.376
1–399	0 (0.0)	10 (13.7)	
≥ 400	9 (90.0)	48 (65.8)	
Comorbidity			
Hypertension	4 (40.0)	34 (46.6)	0.748

Diabetes	1 (10.0)	13 (17.8)	1.000
Cardiovascular disease	0 (0.0)	8 (11.0)	0.587
Pulmonary disease	1 (10.0)	4 (5.5)	0.483
Pulmonary Function Test			
%VC	98.0 ± 16.6	104.6 ± 13.2	0.216
FEV1%	72.1 ± 3.5	75.7 ± 7.3	0.172
Location of tumor			
Upper thoracic	1 (10.0)	7 (9.6)	0.526
Middle thoracic	7 (70.0)	33 (45.2)	
Lower thoracic	2 (20.0)	26 (35.6)	
Abdominal esophagus	0 (0.0)	7 (9.6)	
Histology			
Squamous cell carcinoma	10 (100.0)	65 (89.0)	0.587
Adenocarcinoma	0 (0.0)	8 (11.0)	
Clinical stage			
1-2	4 (40.0)	35 (47.9)	0.743
3-4	6 (60.0)	38 (52.1)	
Neoadjuvant therapy			
Not administered	1 (10.0)	14 (19.2)	0.495
Chemotherapy	7 (70.0)	52 (71.2)	
Chemoradiotherapy	2 (20.0)	7 (9.6)	
Intraoperative variables			
Surgical approach			
Thoracoscopy-assisted	6 (60.0)	53 (72.6)	0.465

Mediastinoscopy-assisted	4 (40.0)	20 (27.4)	
Lymph node dissection			
Two-field	2 (20.0)	21 (28.8)	0.719
Three-field	8 (80.0)	52 (71.2)	
Reconstruction route			
subcutaneous	2 (20.0)	3 (4.1)	0.164
retrosternal	7 (70.0)	57 (76.1)	
posterior mediastinal	1 (10.0)	13 (17.8)	
Operative time (min)			
Median (IQR)	638.0 (501.0–712.0)	582.0 (512.0–672.0)	0.611
Blood loss (ml)			
Median (IQR)	93.5 (77.0–208.5)	150.0 (74.0–310.5)	0.471
Postoperative outcomes			
Postoperative oxygenation (days)	2.0 (2.0–5.5)	2.0 (2.0–4.0)	0.695
Initiation of oral intake (days)	12.0 (9.0–23.8)	8.0 (8.0–9.0)	0.037
Initiation of Ambulation (days)	2.0 (2.0–2.0)	2.0 (2.0–2.0)	0.221
Chest tube removal (days)	4.5 (3.0–8.5)	4.0 (4.0–6.0)	0.858
Total energy intake (kcal/day)	1,384.6 ± 318.8	1,406.6 ± 311.4	0.835
Physical activity	1,479.5 (1,173.0–	2,848.0 (2,234.0–	0.013

(steps/day)	2,518.5)	4,268.0)	
Albumin level (g/dl)	2.8 (2.7-2.9)	3.0 (2.7–3.10)	0.333
CRP level (mg/dl)	5.1 (2.6-9.0)	2.34 (1.1–4.9)	0.066
Recurrent nerve paralysis	3 (30.0)	21 (28.8)	1.000
Anastomotic leakage	3 (30.0)	14 (19.2)	0.420
Surgical site infection	2 (20.0)	17 (23.3)	1.000
Length of stay (days)	45.5 (31.0–60.5)	24.0 (18.0–36.0)	0.002

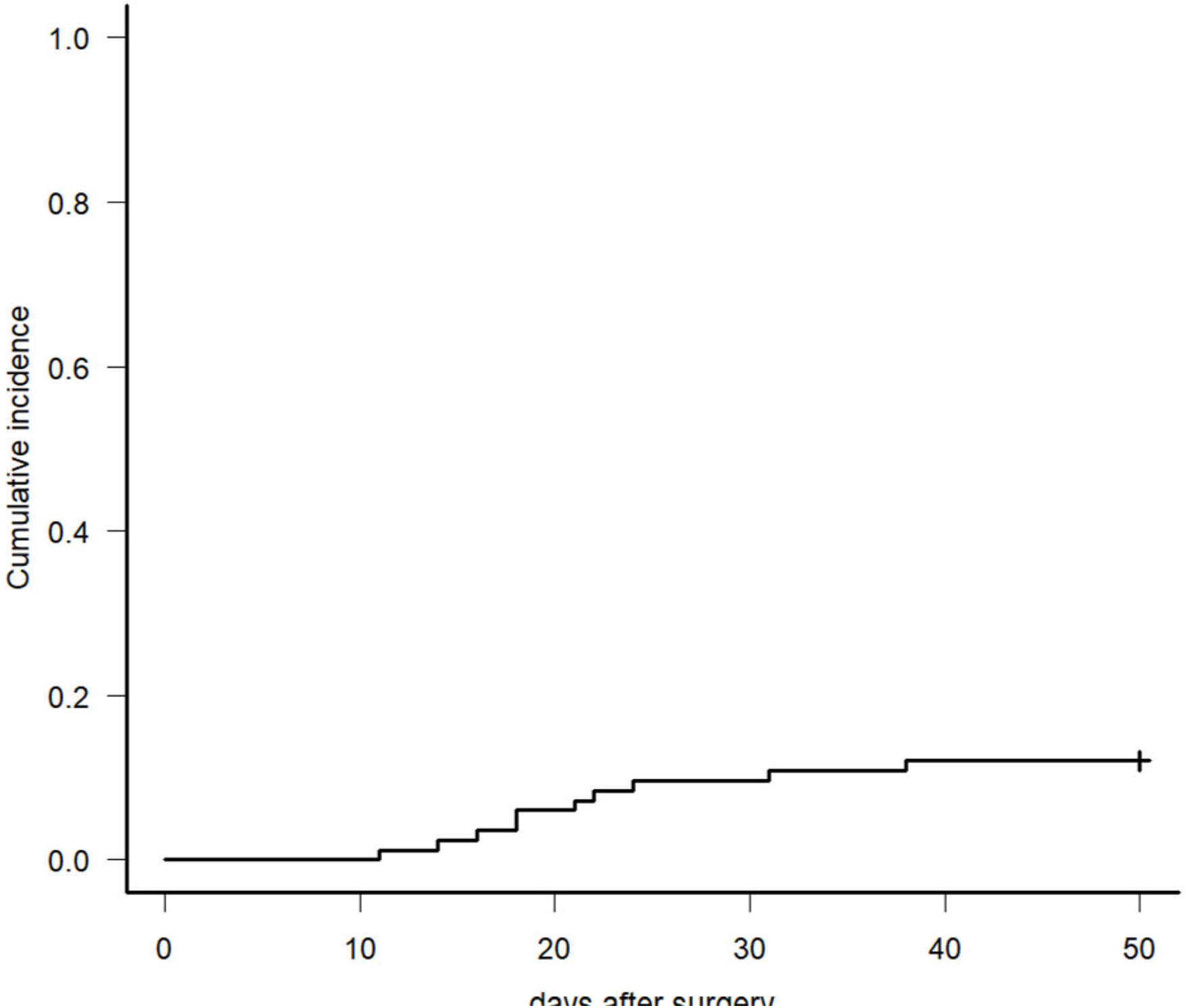
Data are expressed as n (%) unless otherwise specified. *IQR*, interquartile range; *SD*, standard deviation; *%VC*, percentage of vital capacity; *FEV1%*, forced expiratory volume ％ in 1 s.

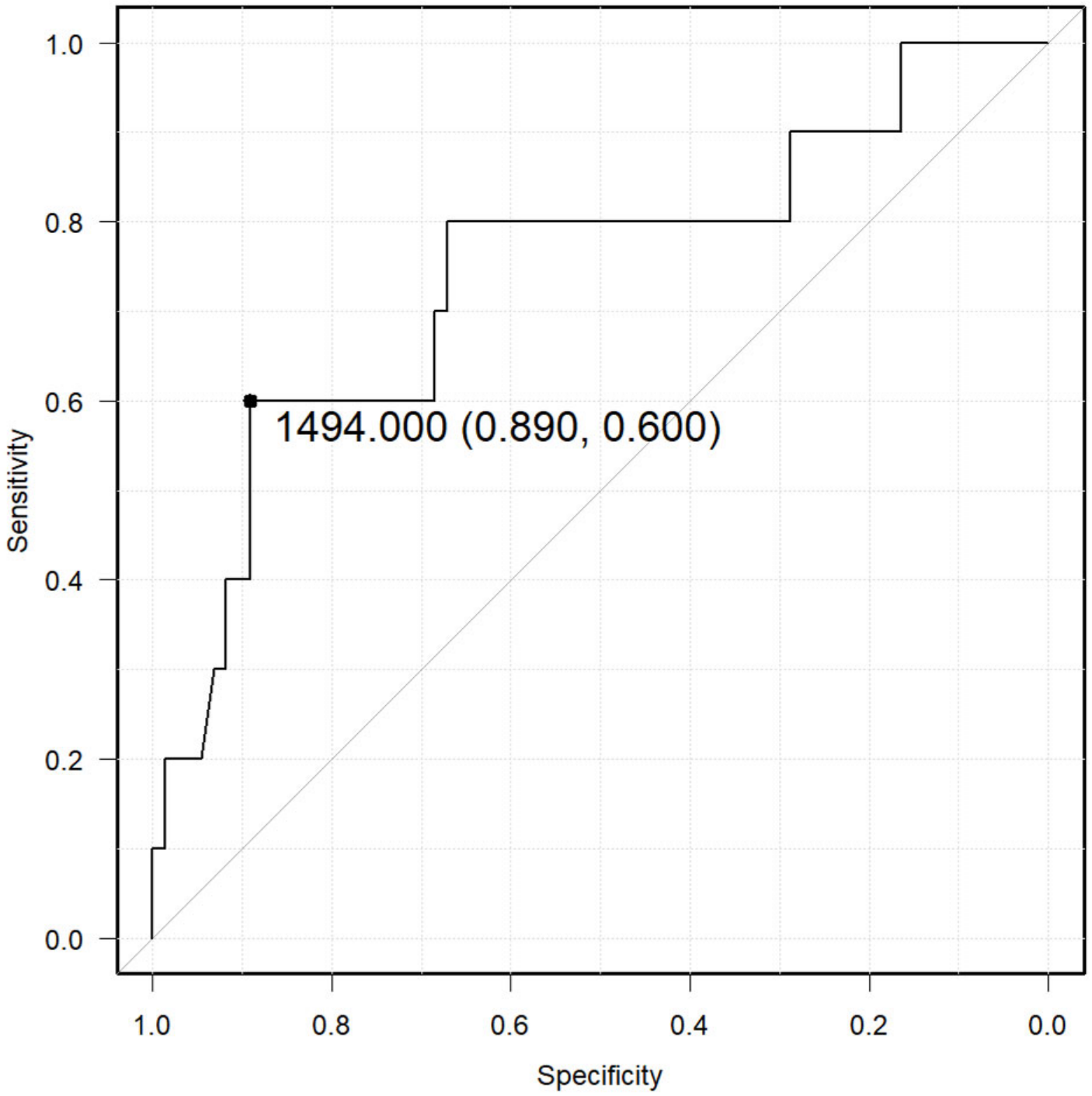
Table 2. Univariate and multivariate analyses on the impact of physical activity on postoperative pneumonia

Variable (reference)	Univariate analysis			multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Physical activity (NPA)						
LPA	12.20	2.82–52.60	0.001	12.10	2.21–65.90	0.004
Age (<70 years)						
≥70 years	3.06	0.79–11.90	0.106	1.37	0.28–6.81	0.698
Reconstruction route (retrosternal)						
subcutaneous	5.43	0.77–38.30	0.090	3.92	0.36–42.20	0.260
posterior mediastinal	0.63	0.07–5.54	0.674	0.75	0.07–7.87	0.808
Recurrent nerve paralysis						

(no)						
yes	1.06	0.25–4.50	0.936	0.54	0.09–3.35	0.504

CI, confidence interval; *OR*, odds ratio; *NPA*, normal physical activity; *LPA*, low physical activity


1.0
0.8
0.6
0.4
0.2
0.0
Cumulative incidence
0
10
20
30
40
50
days after surgery


1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
1494.000 (0.890, 0.600)
1.0
0.8
0.6
0.4
0.2
0.0
Specificity