Postoperative delayed ambulation after thymectomy is associated with preoperative six-minute walk distance

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This study was approved by the Ethics Committee of Nagoya University Hospital.

Keywords: thymectomy; thoracic surgery; rehabilitation, physical therapy, delayed ambulation, six-minute walk distance

Abstract

Objective: Delayed postoperative ambulation is a risk of postoperative complications and increases overall healthcare costs. We investigated preoperative and intraoperative variables associated with delayed ambulation in patients who underwent thymectomy.

Methods: A total of 57 consecutive patients undergoing thymectomy were included in this study. Preoperative functional exercise capacity was evaluated by six-minute walk distance. Ambulation was considered to be delayed if the patient could not walk the ward on postoperative day 1. Binary logistic regression analysis was performed to clarify the factors associated with delayed ambulation.

Results: Preoperative six-minute walk distance was the only significant variable which was associated with delayed ambulation. The area under the receiver operating characteristic curve for predicting delayed ambulation was 0.684 (95% confidential interval: 0.546–0.823, p=0.017), and the optimal discriminatory preoperative six-minute walk distance value was 498 m. Postoperative hospital stay was significantly longer in patients with low six-minute walk distance (<498 m) than those with high six-minute walk distance (≥498 m). In contrast, the presence of myasthenia gravis or adjuvant chemo-radiotherapy was not associated with delayed ambulation.

Conclusions: Our results suggest that low preoperative six-minute walk distance is

associated with delayed postoperative ambulation and longer postoperative hospital stay in patients who underwent thymectomy.

Introduction

Surgical resection including thymectomy is the mainstay of treatment for thymic epithelial tumors such as thymoma and thymic cancer [1]. One-third of patients with thymoma are accompanied with myasthenia gravis (MG) [2]. MG is an autoimmune disorder in the neuromuscular transmission with characteristic fatigability and muscular weakness. Even in patients with MG without thymoma, thymectomy is considered as one of the choice for treatment. Association with the presence of MG and postoperative course after thymectomy has been reported [3–7]. It has been reported that the presence of MG is associated with increased perioperative mortality, typically secondary to severe aggravation of muscle weakness with respiratory failure after thymectomy [3]. On the other hand, several reports have indicated that the presence of MG has no adverse effects on long term outcome after thymectomy [4–7]. Thus, it has not been fully clarified the effects of the presence of MG on physical fitness after thymectomy.

Delayed postoperative ambulation is a risk of postoperative complications and increases overall healthcare costs [8,9]. Moreover, prolonged bed rest leads to muscle loss and weakness, impairs pulmonary function, and predisposes patients to venous stasis, thromboembolism, urinary tract infection, delirium, and pressure sores [10].

Delayed ambulation after thoracic surgery is often caused by postoperative pain, dizziness, nausea, vomiting, feeling hot, blurred vision, and eventual syncope [9,11]. The higher age [12], physical activity [13], intraoperative complications [14], and increased blood loss [15] have been reported to predict delayed postoperative recovery such as ambulation. In addition, recently previous reports showed low preoperative six-minute walk distance (6MWD) associated with postoperative complications and prolonged hospital stay in patients undergoing lobectomy [16]. The 6MWD has been used to assess functional exercise capacity [17], which has also a potential to predict delayed postoperative recovery. However, in patients who underwent thymectomy, the preoperative and intraoperative variables associated with delayed ambulation are not fully investigated.

The purpose of the present study was to determine the preoperative and intraoperative factors for predicting delayed ambulation after thymectomy.

Methods

Participants

A total of 57 consecutive patients undergoing thymectomy from April 2013 to June 2015 at Nagoya University Hospital were included in this study. Patients who underwent combined resection of phrenic nerve (n=2) or pneumonectomy (n=1) were excluded. Demographic characteristics, comorbidities, preoperative functional exercise capacity, operative time, anesthesia time, blood loss, intraoperative fluid balance, operative procedure, epidural anesthesia, time until the try to ambulation, and length of postoperative hospital stay were extracted from the patients' medical records.

The perioperative rehabilitation, including orientation and measurements, was performed by specialized physical therapists. The preoperative rehabilitation protocol included orientation for postoperative rehabilitation program and encouragement of early ambulation. The postoperative rehabilitation included positioning, stretching of respiratory muscles, deep diaphragmatic breathing, coughing and huffing, mobilization, and ambulation. The patients were asked to try to ambulate in the postoperative day (POD) 1 by a physical therapist. Epidural anesthesia or para-vertebral block were used for postoperative pain control for 48 to 96 hours. Non-steroidal anti-inflammatory drugs, or acetaminophen were also administrated. Information about the patients was collected through a review of electronic medical records.

Preoperative and postoperative assessment

The newly proposed tumour–node–metastasis (TNM) staging system criteria for thymic malignancies by the International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancy Interest Group (ITMIG) are used [18]. MG was diagnosed by neurologist, based on the values of serum antiacetylcholine receptor antibody and physical symptoms. All MG patients were classified according to the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification [19].

Preoperative pulmonary functions were routinely evaluated using computerized equipment (Fudak77, Fukuda Sangyo, Tokyo, Japan) at the clinical laboratory within 30 days before surgery. As for spirometric parameters, vital capacity (VC), forced vital capacity (FVC), and forced expiratory volume in 1 s (FEV_1) were measured. The predicted values for spirometry and lung volumes were calculated according to the method proposed by Japanese Respiratory Society [20].

Preoperative functional exercise capacity was evaluated by six minute walk test (6MWT). The six minute walk distance (6MWD) was measured by following a standardized procedure [17]. Briefly, patients were instructed to walk the predetermined course at their own pace for 6 minutes. Standardized encouragement was given for patients in every minute during the 6MWT. At 6 minutes, patients were instructed to stop walking and the walked distance was measured.

The outcome of interest was defined as delayed ambulation. Ambulation was considered to be delayed if the patient could not walk the ward on POD1 [11]. For patients with delayed ambulation, data on reasons for delayed ambulation were also collected.

Statistical analysis

The chi-squared test and Mann–Whitney U tests were used for the comparison of variables between two groups, as appropriate. Stepwise binary logistic regression analysis was used to investigate the effect of the pre- and intraoperative variables on delayed ambulation, and odds ratios (ORs) were calculated for each variable. The factors showing $P < 0.2$ in the intergroup comparison analysis were included in the multivariate logistic regression analysis. The statistical analyses were conducted using SPSS software (version 23.0 for Microsoft Windows, SPSS Inc, Chicago, IL, USA). P values less than 0.05 were considered to be statistically significant. This study was approved by the institutional review board of Nagoya University Hospital (Approval number: 2015-0413).

Results

Patient baseline characteristics are shown in Table 1. The median of age was 61, ranging from 21 to 79. The study cohort consisted of 33 male and 27 female. Thirteen patients had MG and two of them were without thymoma. The patients with MG were well-controlled. The number of patients according to the MGFA Clinical Classification was 10 in Class I, 1 in Class IIa, and 2 in Class IIb (Table 1). Neither MG patient experienced dysautonomia, fatigue nor gait hypokinesia related to MG.

After surgery, 31 patients (54%), 22 patients (38%), and 4 patients (7%) started to ambulate on POD1, POD2, and POD3, respectively. The reasons for delayed ambulation were nausea or vomiting (n=14, 53%), dizziness (n=7, 26%), and wound pain (n=5, 19%). No postoperative myasthenic crisis was observed during hospital stay. Data of pre-, intra-, and postoperative variables between patients with MG and those without MG are compared in Table 2. There was no significant difference in the delayed ambulation between the MG and non-MG groups. Preoperative 6MWD in MG patients was marginally higher than patients without MG, although the difference was not statistically significant. Percent VC in the MG group was significantly less than that in the non- MG group. Intraoperative fluid balance in the MG group was more than that in the non-MG group. Only one patient without MG developed postoperative pneumonia. Of 13 patients with MG, the number of patients with delayed ambulation was 4 of 10 in MGFA Class I, 1 of 1 in MGFA Class IIa, and 1 of 2 in MGFA Class IIb. There was no significant difference in the MGFA class between the groups with and without delayed ambulation (Table 3).

Next, data of pre-, intra-, and postoperative variables between patients with delayed ambulation and those without were compared (Table 3). Preoperative 6MWD of the patients without delayed ambulation (519.9±99.4 m) was significantly longer than that with delayed ambulation (460.0±96.7 m). Preoperative %VC and %FEV_1 of the patients without delayed ambulation were significantly less than those with delayed ambulation. There was no significant difference in other parameters such as age, comorbidities, operative time, anesthesia time, blood loss, intraoperative fluid balance, operative procedure, epidural anesthesia between the groups.

The results of the binary logistic regression analysis with delayed ambulation are shown in Table 4. Six preoperative and intraoperative variables with $p<0.2$ (comorbidity of hypertension, preoperative chemo-radiation, %VC, %FEV_1, and preoperative 6MWD) and the presence of MG were included into the binary logistic regression multivariate analysis. Preoperative low 6MWD was the only independent risk factor for delayed ambulation (OR: 1.0066, 95% confidential interval (CI): 1.0005–1.0127, p = 0.035).

Figure 1 shows the receiver operating characteristic (ROC) curve for predicting delayed ambulation. The optimal cut-off level of preoperative 6MWD was 498 m. The area under the ROC curve for preoperative 6MWD was 0.684 (95% CI: 0.546–0.823, $p = 0.017$).

We classified all patients into two groups, namely low 6MWD (<498 m) group (n=27, 47%) and high 6MWD (≥498 m) group (n=30, 52%). As shown in Figure 2, postoperative hospital stay was significantly longer in patients with low 6MWD (8.1±4.8 days) than that in patients with high 6MWD (6.1±1.4 days).

Discussion

The present study firstly showed that patients with low preoperative 6MWD (<498 m) were associated with delayed postoperative ambulation and longer postoperative hospital stay after thymectomy. Marjanski et al. reported that patients with 6MWD <500 m before lobectomy have an increased risk of postoperative complications and prolonged hospital stay in patients with lung cancer [16]. Moreover, Hayashi et al. reported low preoperative 6MWD is associated with postoperative delayed ambulation and prolonged hospital stay after open abdominal aortic aneurysm surgery [13]. To date, the investigation in perioperative rehabilitation undergoing thymectomy has not been reported. Early ambulation has one of the key roles for enhanced recovery programs

[14,21,22] and early discharge [13,23].

In patients with MG, one of the serious complications after thymectomy is muscular weakness specifically due to myasthenic crisis [3]. However, the presence of MG was not associated with postoperative delayed ambulation in our study. Most of our patients with MG were well-controlled by medication with prednisolone and/or immunosupressant. Unexpectedly, preoperative 6MWD in MG patients was marginally higher than patients without MG, although the difference was not statistically significant (Table 2). From our findings, the well-controlled MG is unlikely a risk for postoperative delayed ambulation. Further investigation is required in patients with more serious MG symptoms than those in the present study.

It was reported that postoperative delayed ambulation is associated with postoperative orthostatic intolerance symptoms such as nausea, vomiting, and dizziness after thoracic surgery [11]. Indeed, our patients with delayed ambulation mostly experienced nausea, vomiting, and dizziness when they tried ambulation after surgery. Orthostatic intolerance is induced by reduced functional exercise capacity, functional deterioration of cardiovascular system, inadequate blood volume, and loss of intact physical pumps comprising the skeletal muscle pump [24]. In the present study, postoperative delayed ambulation was associated with preoperative 6MWD. In contrast, perioperative variables such as operative time, anesthesia time, blood loss, intraoperative fluid balance, operative procedure, and epidural anesthesia were not associated with delayed ambulation. Because the 6MWD reflects the functional exercise capacity, it has been extensively assessed in patients with pulmonary and cardiovascular diseases [25,26] and who underwent surgery [13,17,27]. The present results demonstrated that poor functional exercise capacity leads to postoperative orthostatic intolerance, delayed ambulation, and increased postoperative hospital stay in patients undergoing thymectomy, consistent with findings in other diseases. Moreover, it is not known how preoperative 6MWD affects occurrence of symptoms such as nausea and dizziness which lead to orthostatic intolerance. Therefore, further investigation of the mechanisms is required.

A recent systematic review described that preoperative rehabilitation, called "prehabilitation", may reduce length of stay and possibly provide postoperative physical benefits [28]. Prehabilitation and optimized perioperative care could allow a greater proportion of high-risk patients to undergo surgery. It is expected that preoperative 6MWD would be a predictive factor for identifying not only high-risk patients who may not be able to complete treatment, but also those who will benefit from prehabilitation.

The present study has several limitations. Firstly, this was limited by its retrospective nature. We included only a small number of patients from a single medical center. Secondly, most of our patients with MG were well-controlled. The predictive factors for delayed ambulation in patients with serious MG symptoms might differ from the results in the present study. Moreover, preoperative pulmonary functions were well in most patients. Unexpectedly, preoperative pulmonary functions such as %VC and %FEV_1 were better in the patients without delayed ambulation than that with delayed ambulation. Thus, preoperative pulmonary functions were not restriction factors for postoperative ambulation. Further investigation with a large cohort is required.

Conclusions

The lower preoperative 6MWD was associated with the delayed postoperative ambulation and longer postoperative hospital stay in patients who underwent thymectomy. Assessment of preoperative 6MWD might be useful for estimating the postoperative course in patients undergoing thymectomy with perioperative rehabilitation.

Conflict of interest statement

The authors certify that no affiliation or financial involvement exists between them and any organization with a direct interest in the subject matter or materials discussed in the article.

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Figure Legends

Figure 1. Receiver operating characteristic (ROC) curves for estimating delayed ambulation using preoperative 6-minute walk distance (6MWD)

The discriminatory 6-minute walk distance (6MWD) value of 498 m determined from ROC curve was statistically defined as the optimal compromise between sensitivity and specificity.

Figure 2. Postoperative hospital stay

Data are shown with mean ± standard deviation. Postoperative hospital stay was significantly longer in patients with low 6MWD (< 498 m) than patients with high 6MWD (≥ 498 m).

Table 1. Patient characteristics

Age, median (range)	61 (21-79)
Male / female, n	33 / 24
Diagnosis, total (stage I, II, IIIA, IIIB, IVA, IVB), n	
Thymoma without MG	34 (28, 1, 4, 0, 1, 0)
Thymoma with MG	11 (10, 1, 0, 0, 0, 0)
Thymic cancer	6 (3, 0, 3, 0, 0, 0)
Thymic cyst	4
MG without thymoma	2
MG related data (n=13)	
MGFA Clinical Classification, total (Class I, IIa, IIb), n	13 (10, 1, 2)
Serum antiacetylcholine receptor antibody, nmol/l, median (range)	26.0 (5.2-170.0)
Treated with prednisolone, n (%)	5 (38%)
Treated with immunosuppressant, n (%)	1 (7%), Tacrolimus

MG, myasthenia gravis; MGFA, myasthenia gravis foundation in America.

Table 2. Comparison of data of patients with and without myasthenia gravis

	Without MG (n=44)	With MG (n=13)	P value
Age, years old	59.2±13.1	58.6±11.7	0.783
Male/Female, n	27 / 17	6 / 7	0.329
Height, cm	161.0±7.3	162.2±7.6	0.628
Body mass index, kg/m^2	23.3±3.7	22.1±3.9	0.287
%VC <80%, n (%)	1 (2%)	2 (15%)	0.063
%VC	107.3±14.8	96.4±14.8	0.046*
FEV_1/FVC <70%, n (%)	6 (13%)	2 (15%)	0.873
%FEV_1	104.5±20.6	95.1±18.2	0.074
Hypertension, n (%)	10 (22%)	6 (46%)	0.099
Diabetes mellitus, n (%)	5 (11%)	0	0.203
Dyslipidemia, n (%)	7 (15%)	2 (15%)	0.964
Coronary artery disease, n (%)	3 (6%)	0	0.333
Chronic kidney disease, n (%)	1 (2%)	0	0.583
Cerebrovascular disease, n (%)	0	1 (7%)	0.063
Sleeping disorder, n (%)	1 (2%)	1 (7%)	0.351
Taking anti-anxiety drug, n (%)	1 (2%)	0	0.583
Preoperative chemoradiotherapy, n (%)	3 (6%)	0	0.333
Six-minute walk distance, m	480.1±105.1	534.8±79.4	0.051
Perioperative data			
Median sternotomy / robotic, n	40 / 4	11 / 2	0.516
Operative time, min	168.6±64.1	189.4±58.2	0.209

Anesthesia time, min	242.0±70.3	271.8±67.6	0.174
Blood loss, ml	170.8±158.0	91.5±90.8	0.058
Intraoperative fluid balance, ml	1183±583	1536±585	0.017*
Extended thymectomy, n (%)	4 (9%)	13 (100%)	<0.001*
Combined resection of lung, pericardial, or pleural, n (%)	10 (22%)	2 (15%)	0.568
Epidural anesthesia, n (%)	31 (70%)	11 (84%)	0.308
Time from surgery until the first try to ambulation, hour	19.9±2.7	19.1±2.2	0.234
Delayed ambulation, n (%)	20 (45%)	6 (46%)	0.975
Postoperative pneumonia, n (%)	1 (2%)	0	0.583
Time to hospital discharge, ≤6days / >6days, n	26 / 18	7 / 6	0.736

MG, myasthenia gravis. Data are mean ± standard deviation (SD) or otherwise indicated. The data were analyzed by chi-squared test or Mann–Whitney U test. *Significantly different between patients with MG and those without ($P<0.05$).

Table 3. Comparison of data of patients with and without delayed ambulation after the surgery

	Without delayed ambulation (n=31)	Delayed ambulation (n=26)	P value
Age, years old	60.0±13.1	58.0±12.3	0.496
Male/Female, n	18 / 13	15 / 11	0.977
Height, cm	161.6±7.4	160.9±7.4	0.898
Body mass index, kg/m^2	23.7±4.2	22.2±3.2	0.249
%VC <80%, n (%)	2 (6%)	1 (3%)	0.661
%VC	101.3±15.1	109.0±14.9	0.016*
FEV_1/FVC <70%, n (%)	6 (19%)	2 (7%)	0.207
%FEV_1	98.3±23.5	107.2±14.5	0.047*
Myasthenia gravis, n (%)	7 (22%)	6 (23%)	0.965
MGFA Clinical Classification (Class I / IIa / IIb), n	6 / 0 / 1	4 / 1 / 1	0.514
Hypertension, n (%)	11 (35%)	5 (19%)	0.174
Diabetes mellitus, n (%)	3 (9%)	2 (7%)	0.792
Dyslipidemia, n (%)	5 (16%)	4 (15%)	0.939
Coronary artery disease, n (%)	1 (3%)	2 (7%)	0.452
Chronic kidney disease, n (%)	0	1 (3%)	0.271
Cerebrovascular disease, n (%)	0	1 (3%)	0.271
Sleeping disorder, n (%)	1 (3%)	1 (3%)	0.899
Taking anti-anxiety drug, n (%)	1 (3%)	0	0.356
Preoperative chemoradiotherapy, n (%)	0	3 (11%)	0.052

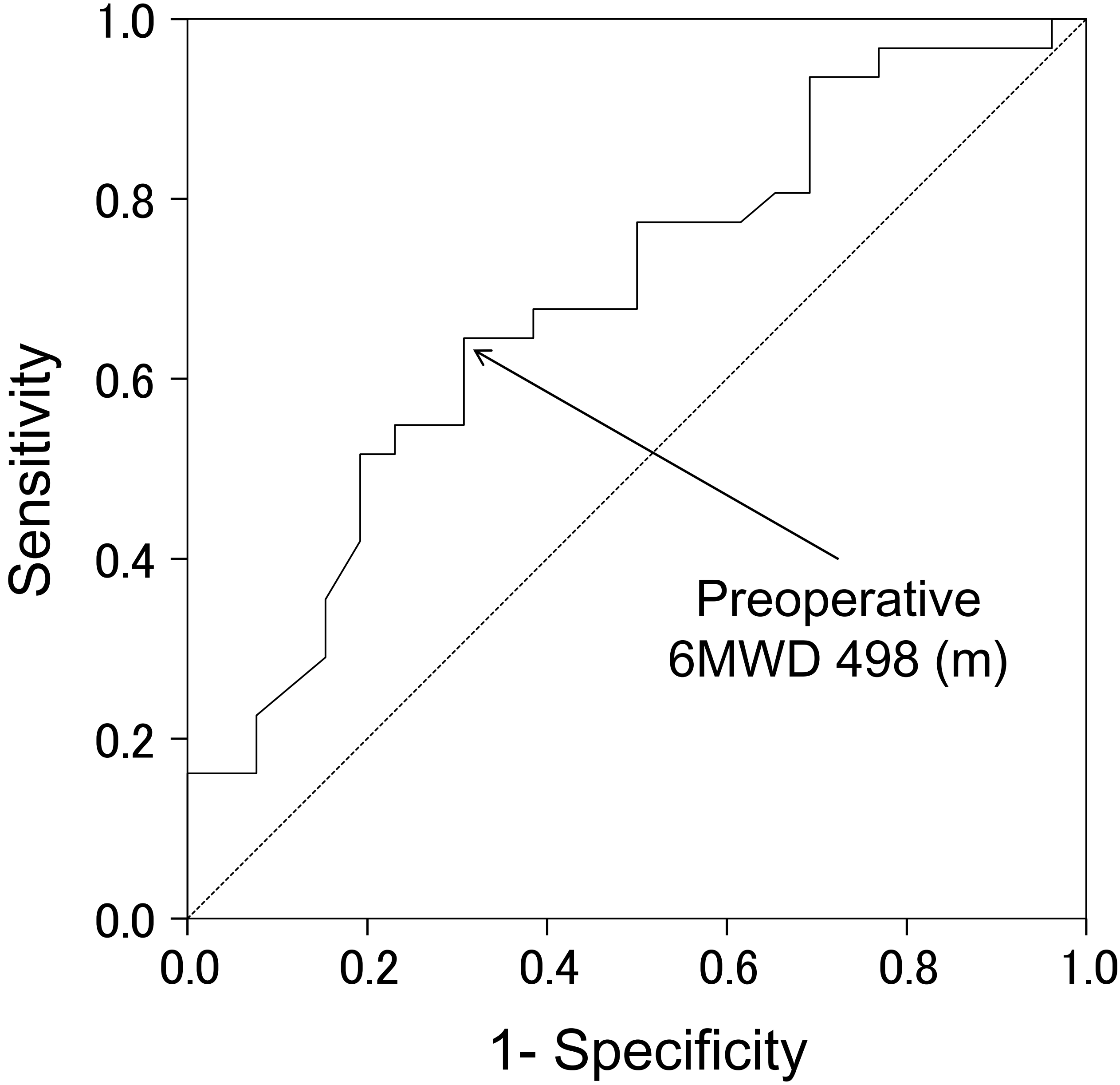
Six-minute walk distance, m	519.9±99.4	460.0±96.7	0.017*
Perioperative data			
Median sternotomy / robotic, n	28 / 3	23 / 3	0.820
Operative time, min	168.2±61.9	179.6±64.8	0.501
Anesthesia time, min	240.9±69.0	258.1±71.8	0.456
Blood loss, ml	126.6±111.7	183.8±180.6	0.321
Intraoperative fluid balance, ml	1321±668	1196±503	0.575
Extended thymectomy, n (%)	9 (29%)	8 (30%)	0.886
Combined resection of lung, pericardial, or pleural, n (%)	6 (19%)	6 (23%)	0.731
Epidural anesthesia, n (%)	23 (74%)	19 (73%)	0.924
Time from surgery until the first try to ambulation, hour	20.0±2.7	19.3±2.5	0.340
Postoperative pneumonia, n (%)	1 (3%)	0	0.356
Time to hospital discharge, ≤6days / >6days, n	21 / 10	12 / 14	0.100

Data are mean ± standard deviation (SD) or otherwise indicated. The data were analyzed by chi-squared test or Mann–Whitney U test.*Significantly different between patients with delayed ambulation and those without (P<0.05).

Table 4. Binary logistic regression analysis for delayed ambulation

	Odds ratio	95% CI		P value
		lower limit	upper limit	
Preoperative 6MWD	1.0066	1.0005	1.0127	0.035*
Preoperative %VC				0.104
Preoperative %FEV_1				0.130
Hypertension				0.201
Preoperative chemo-radiation				0.216
MG				0.536

Six preoperative and intraoperative variables with $P<0.2$, preoperative six-minute walk distance (6MWD), %VC, %FEV_1, hypertension, preoperative chemo-radiation, and the presence of MG were entered into the binary logistic regression models. *Preoperative 6MWD was a statistically significant variable.


1.0
0.8
0.6
0.4
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Sensitivity
Preoperative
6MWD 498 (m)
0.0
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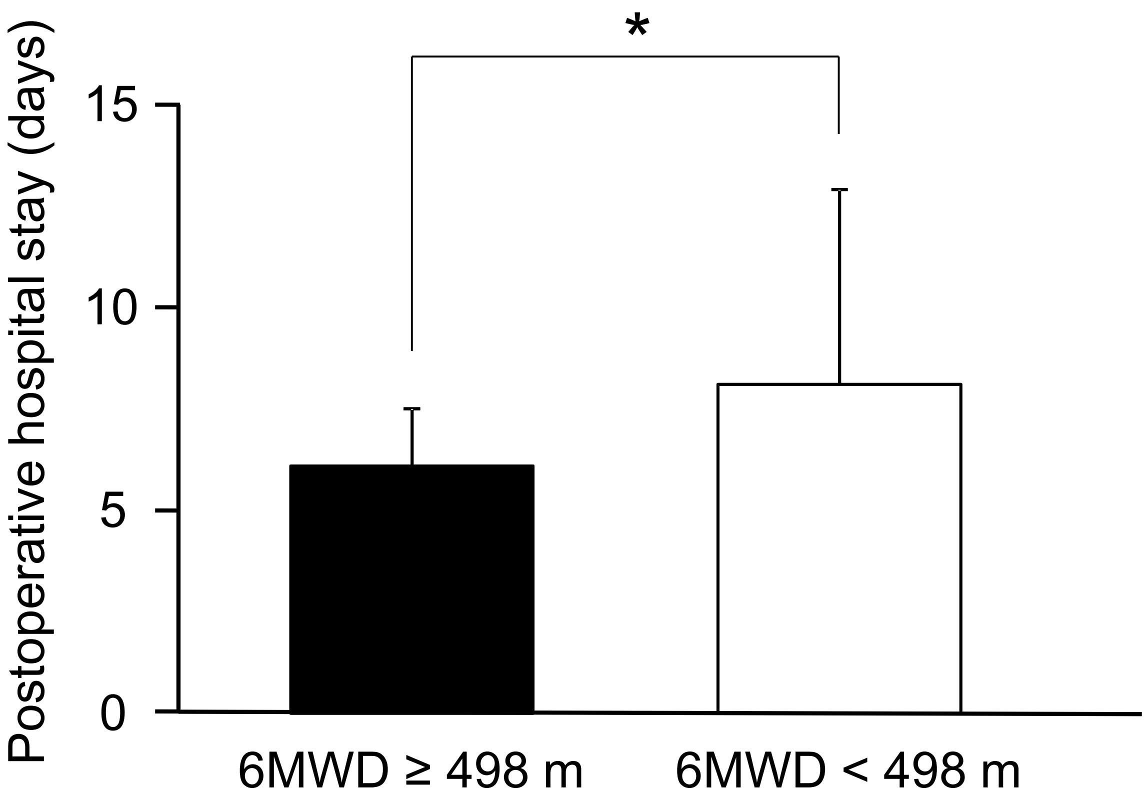
0.6
0.8
1.0
1- Specificity

Fig 1



*
15
10
5
0
Postoperative hospital stay (days)
6MWD ≥ 498 m
6MWD < 498 m

Fig 2