

Effect of combination of pre- and
postoperative pulmonary rehabilitation on
onset of postoperative pneumonia: a
retrospective cohort study based on data
from the diagnosis procedure combination
database in Japan

（肺がん術前後のリハビリテーションが
術後の肺炎発症に与える影響：日本における
Diagnosis Procedure Combination データを用い
た 過去起点コホート研究）

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Original Research

Title: Effect of combination of pre and postoperative pulmonary rehabilitation on onset of postoperative pneumonia: A retrospective cohort study based on data from the Diagnosis Procedure Combination database in Japan

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Abstract

Background: To examine the effect of rehabilitation on postoperative pulmonary complication when it is conducted in combination of both before and after lung cancer surgery, as compared with either before or after surgery and no rehabilitation. **Methods:** A retrospective cohort study was conducted to examine the effect of rehabilitation before and after lung cancer surgery on the causes of postoperative pneumonia. Data collected from the Diagnosis Procedure Combination (DPC) database. Patients admitted who received operative treatment for a new primary (ICD codes: C34) were selected. The inclusion criteria were patients who had pneumonectomy, malignant tumor surgery for the lung (thoracotomy), or thoracoscopic surgery (endoscopic; treatment code: K511-00, K513-00~03, and K514-00, 02). The exclusion criteria were patients who had a lung transplantation (treatment code: K514-03~06), suspected diagnosis, and a pneumonia within three months before being diagnosed as having lung cancer. Main Outcome was onset of postoperative pneumonia. **Results:** Among 76,739 lung cancer patients, 15,146 who underwent lung cancer surgery were included in the analysis. In the combination of pre and postoperative group, as compared with the preoperative (odds ratio [OR], 95% confidence interval [CI]: 2.8, 1.8–4.4), postoperative (1.9, 1.6–2.3), and no rehabilitation group (2.5, 2.1–2.8), the onset of pneumonia was less frequent. **Conclusions:** Combination of preoperative and postoperative rehabilitations significantly prevent postoperative pneumonia as compared with having preoperative, postoperative, or no rehabilitation.

Key words: Cancer rehabilitation, Postoperative complication, Lung cancer

Introduction

Malignant neoplasm is the leading cause of death in Japan [1]; lung cancer is the most frequent among them [2].

Although surgical operation is a typical approach for lung cancer, several researchers reported that the incidence of pulmonary complications involving pneumonia range from 7.5% to 20% postoperatively [3,4], with a mortality rate of >60% [5-7].

The effectiveness of rehabilitation has been examined for preventing pulmonary complications and protecting respiratory function after lung surgery [8-10]. Postoperative breathing training such as exhalation practice to stimulate expectorant and deep breaths in improving ventilation are performed with treadmill walking and ergometer exercise [11] to maintain motor function.

A study by Algar et al [12] and a systematic review by Cavalhery [13] proved that preoperative rehabilitation decreases the risk of pulmonary complications. Its effectiveness for improving peak rate of oxygen consumption [14] and forced expiratory volume [15], and for shortening hospitalization duration [16] has been suggested. On the other hand, the effectiveness of postoperative rehabilitation in reducing the risk of postoperative complications was reported by Thomas et al [17] and Hall et al. [18] Based on the existing evidence, rehabilitation before and after lung cancer surgery is recommended by cancer rehabilitation guideline [19-21].

However, the following three points are still unreported. First, it has not been examined the effect of combined rehabilitation both before and after surgery. Second, most prior studies are controlled trials that limited to experimental situations and rigorously conducted; therefore, the effect confirmed in the trials have not been verified in real-world situations. Third, the implementation status of rehabilitation in clinical practice is unknown.

The aim of this study was to examine the effect of rehabilitation on postoperative pulmonary complication when it is conducted both before and after lung cancer surgery, as compared with either before or after surgery and no rehabilitation practice. Moreover, we aimed to determine the implementation status of rehabilitation conducted before/after lung cancer surgery on the basis of large-scale administrative data in Japan.

Patients and methods

This report was based on the Reporting Studies Conducted Using Observational Routinely Collected Health Data (RECORD) Statement [22]. A retrospective cohort study was conducted to examine the effect of rehabilitation before and after lung cancer surgery on the causes of postoperative pneumonia. Data collected from the Diagnosis Procedure Combination (DPC) database and constructed from electronic prescriptions, and DPC data collected by Medical Data Vision Co., Ltd. (MDV), from an accumulated 18.2 million people, were used.

DPC is one of the medical claims database that collects administrative data. DPC data are collected from target hospitals that subscribe to MDV [23]. Data include the basic attributes of the patients, detailed statement of medical practice, characteristics of the medical institution, existence of data related to medical care other than those provided by healthcare claims data [23].

Medical doctors input basic attributes of the patients, such as sex, birthdate, date of hospitalization, main illness, the disease that triggered the admission, the disease that caused the most consumption of medical resources, preoperative comorbidities, and complications after admission. It is a distinctive feature of DPC data that diagnosis names are recorded both on admission and after hospitalization [24]. Individual medical practice details (e.g., surgery, anesthesia, rehabilitation, and medication history), along with the date of operation, number of practice, quantity used, and reference unit, are recorded. Institutional data include the number of hospitals, number of hospital beds, and the basic charge for admission. Information on “how much medical practice of how many medical remuneration points were carried out” could be obtained for claims data. We have guaranteed an opportunity to refuse to participate in this research by directly notifying all research participants from each facility; additionally, information on the usage in the research were released on the facility’s internet homepage or its notice board. Moreover, data used in the present study have been converted into unlinkable anonymization by the MDV. This prevents the researcher from handling the correspondence table, thereby making the data used in this study impossible to link to the personal information of the patients.

1. Participants and data extraction

The target disease name was selected according to the code of the International Statistical Classification of Diseases and Related Health Problems Version 10 [25] (ICD code) and the Medical intervention classification master code [26] (treatment code).

By using the ICD codes of a previous study [27] as reference, hospitalized patients who received operative treatment for a new primary lung cancer (ICD codes: C34) were selected. The inclusion criteria were patients who had pneumonectomy, malignant tumor surgery for the lung (thoracotomy), or thoracoscopic surgery (endoscopic; treatment code: K511-00, K513-00~03, and K514-00, 02). The exclusion criteria included death from lung cancer before the surgery, a lung transplantation (treatment code: K514-03~06), suspected diagnosis, and a pneumonia within three months before being diagnosed with lung cancer. Respiratory disease was defined as pneumonia.

Data from January 2018 to March 2018 that were anonymized by the MDV were accessed. Data that can potentially identify individual patients were not verified. A single database, which was not linked with external data, was used for this study.

2. Measurement variable

The cofounding variables, effect modifier, and prognostic factor of the relevance between having both preoperative and postoperative rehabilitations and onset of pneumonia were extracted. The extracted items were sex, age, smoking index, respiratory function on admission (Hugh-Jones classification), height, weight, cancer stage classification (TNM staging),

comorbidities on admission (chronic respiratory illness, interstitial pneumonia, chronic cardiac failure, hepatic disorder, chronic renal failure, and cerebrovascular accident), performance in activities of daily living on admission (Barthel Index), operative procedure (endoscopic or thoracotomy), and number of days and units of rehabilitation. Lung cancer patients with comorbid chronic respiratory disease, has a higher rate of postoperative pneumonia than those who do not [28]. Also, interstitial pneumonia co-morbid with lung cancer are likely to exacerbate postoperatively [29]. In addition, patients with chronic cardiac failure [30], hepatic disorder [31], chronic renal failure [32], and cerebrovascular accident [33] have a higher risk of pneumonia than those who do not; thus, co-morbidity status of these three diseases were included.

The implementation pattern of pre and postoperative rehabilitation was classified into four groups as follows:

combination of both preoperative and postoperative rehabilitation groups (combination group), preoperative rehabilitation group (preoperative group), postoperative rehabilitation group (postoperative group), and no rehabilitation group.

Preoperative period was defined as 1) seven days before surgery, when medical remuneration points for respiratory rehabilitation as a preoperative rehabilitation was obtainable; 2) patients were hospitalized for cancer treatment, because patient's rehabilitation fee could be assessed. Postoperative rehabilitation is defined on the day of surgery and after surgery.

In the previous study, as postoperative pneumonia occurs immediately after surgery [34], rehabilitation after the onset of pneumonia was omitted from the postoperative rehabilitation. Cancer stage was sorted according to seven levels based on the TNM staging as follows: stage IA, IB, IIA, IIB, IIIA, IIIB, and IV [35]. The Hugh-Jones classification [35] was used to sort respiratory function on admission in I to V stage levels.

3. Outcome

Primary outcome was determined on the basis of postoperative onset of pneumonia. Postoperative is defined as from the day of surgery to the day of discharge. Pneumonia is a representative disease for which the effect of rehabilitation could be anticipated in the attempt of preventing postoperative pulmonary complications [36].

4. Statistical Analysis

1) Descriptive statistics

First, the implementation rates of rehabilitation in the combination, preoperative, postoperative, and no rehabilitation groups were determined. Second, the implementation patterns of rehabilitation and operative procedure were sorted, and then the incidence rate of pneumonia was determined.

2) Multiple logistic regression analysis

To determine the independent effect of rehabilitation patterns, a multiple logistic regression analysis was conducted. The following predictor variables were selected: lung cancer stages (seven levels), sex, age, height, weight, number of days of rehabilitation, Barthel Index, comorbidities on admission (chronic respiratory illness, interstitial pneumonia, chronic cardiac failure, hepatic disorder, chronic renal failure, and cerebrovascular accident), respiratory function on admission (Hugh-

Jones classification), smoking index, and whether rehabilitation fee was assessed. Following this, the relevance between the implementation pattern of preoperative and postoperative rehabilitations and onset of pneumonia was analyzed.

The variance inflation factor (VIF) was used to admit multicollinearity when VIF was ≥ 10 . The analysis was performed for all the subjects and adopted for each surgical procedure group, namely the endoscopic and thoracotomy groups.

For missing values, the situation and pattern of the missing data were confirmed. Among the subjects included in the analysis, $\geq 5\%$ had missing values. Multiple logistic regression analysis using the multiple imputation method was performed [37].

For the variables subjected to the multiple imputation method, even the condition of normal distribution has not met or be in the case of categorical variables, the effect on the analysis was reported to be small [38]. Therefore, variables with the assumption of normal distribution was equally treated. Even if the substituted value of the categorical variable did not collide with the category of a particular variable, the assigned value was not rounded on the basis of the study of Alison [38]. Twenty sets of substitute models were generated, and then integrated using Rubin's rules [39].

In this study, onset of pneumonia was defined as an outcome and was considered to be that rehabilitation prevented pneumonia when the odds ratio was >1 . For the data processing, Stata 15 (StataCorp LCC., USA) and JMPpro.ver13 (SAS Institute Inc., USA) were used.

This study was conducted with the approval of the ethics committee of Kyoto University Graduate School and Faculty of Medicine, Kyoto University Hospital (Authorization No. R1376).

Results

1) Patient attribution

Among 76,739 lung cancer patients, 15,146 who underwent lung cancer surgery and free from pneumonia three month prior to the development of cancer were included in the analysis (Figure1).

The patients' attributes are shown in Table 1, 2 and 3. Of the patients, 8,724 (57.6%) were male and 6,622 (42.4%) were female, with a mean (Standard deviation; SD) age of 69.1 (9.4) years. For the operative procedure, 12,505 patients (82.6%) underwent endoscopic surgery and 2,771 (18.3%) had a thoracotomy. Of these patients, 2,483 (16.4%) developed pneumonia. As comorbidities, chronic respiratory illness, interstitial pneumonia, and hepatic disorder were found in 4,455 (29.4%), 3,646 (24.0%), and 2,188 patients (14.4%), respectively. The mean (SD) Barthel Index score on admission was 96.1 (18.0). The cancer stages were as follows: IA, 7,113 patients (46.9%); IB, 2,298 (15.2%); IIA, 801 (5.3%); IIB, 448 (3.0%); IIIA, 792 (5.2%); IIIB, 31 (0.2%); and IV, 303 (2.0%). No significant difference was found between other attributes such as operative procedure and each intervention group.

2) Descriptive Statistics

The implementation pattern for rehabilitation in the combination, preoperative, postoperative, and no rehabilitation groups was as follows: 4,729 (33.4%), 269 (1.8%), 2,105 (13.9%), and 8,043 (53.1%), respectively (Table4). Postoperative pneumonia occurred in 478 (10.0%), 61 (22.3%), 366 (17.2%), and 1621 patients (19.8%) in the combination, preoperative,

postoperative, and no rehabilitation groups, respectively. According to operational procedure, in the order of endoscopy and thoracotomy, pneumonia was found 402 (10.7%) and 76 (7.6%), 55 (22.2%) and 6 (25.0%), 300 (17.1%) and 66 (18.3%), and 1291 (19.2%) and 330 patients (23.9%), respectively.

3) Multiple logistic regression analysis

The results of the analysis are shown in Table 5. VIF did not exceed ≥ 10 in any model.

In the combination group, as compared with the preoperative (odds ratio [OR], 95% confidence interval [CI]: 2.8, 1.8-4.4), postoperative (1.9, 1.6-2.3), and no rehabilitation (2.5, 2.1-2.8) group, the onset of pneumonia was less frequent. The postoperative group had a significantly lower incidence of pneumonia than the no rehabilitation group (OR: 1.3, 95% CI: 1.1-1.5). No significant difference in the onset of pneumonia was found between the preoperative and no rehabilitation groups, and between the postoperative and preoperative groups.

Among the patients who underwent endoscopic surgery, those in the combination group had a lower incidence of pneumonia than the preoperative (OR, 95% CI: 2.8, 1.8-4.4), postoperative (1.9, 1.6-2.2), and no rehabilitation (2.5, 2.1-2.8) group. The postoperative group had a significantly lower incidence of pneumonia than the no rehabilitation group (OR: 1.3, 95% CI: 1.1-1.5). No significant difference was found between the preoperative and no rehabilitation groups, and between the postoperative and preoperative groups.

Among the patients who underwent thoracotomy, those in the combination group had a lower incidence of pneumonia than the preoperative (OR, 95% CI: 4.2, 2.9-6.3), postoperative (1.9, 1.6-2.3), and no rehabilitation (2.4, 2.1-2.7) group. The

postoperative group had significantly less onset of pneumonia than the preoperative (OR, 95% CI: 2.2, 1.5-3.3) and no rehabilitation (OR: 1.2, 95% CI: 1.1-1.4) group. No significant difference in the onset of pneumonia was found between the preoperative and no rehabilitation groups

With the multiple imputation, the analysis results remained the same (refer to Supplement).

Discussion

From the claims data of 15,146 postoperative lung cancer patients, the combination of both preoperative and postoperative rehabilitations decreased the risk of postoperative pneumonia compared with preoperative alone, postoperative alone, and no rehabilitation. Comparing with no rehabilitation group, postoperative rehabilitation alone was significantly related with less postoperative pneumonia. It should be emphasized that, despite such an effectiveness, rehabilitation was not prescribed for more than half of the study patients.

Analysis of the administrative data, which reflect real-world practice, has shown that combination of preoperative and postoperative pulmonary rehabilitations were the most effective in preventing postoperative pneumonia. For the effect of preoperative rehabilitation, the following has been reported: improvements in postoperative respiration function [40,41], motor function [42], and gait durability [43], and shortened length of hospital stay [44,45]. In addition, the effect of postoperative rehabilitation includes improvement of 1-second forced expiratory volume, which represents respiratory

function [46,47], and improvement of quality of life [48]. As pulmonary complications including pneumonia is caused by retained respiratory secretion invoked by a decreased postoperative ventilation [49], both preoperative and postoperative rehabilitations may prevent pneumonia through improvement of postoperative respiratory function. Compared with preoperative rehabilitation, the direct effect of postoperative rehabilitation toward limited range of motion due to the pain of operative wounds [50] and decrease in pulmonary blood flow in the resected region [51,52] on the prevention of postoperative complication looks promising.

The present study did not confirm the effect of preoperative rehabilitation supported by previous studies. This can be explained by the difference in features between real-world and experimental research data. In randomized controlled trials (RCTs), the subjects are strictly selected and detailed rules on intervention are established [53], whereas in real-world clinical situations, the subjects and methods of intervention are diverse. For example, in a RCT that verified the effects of respiratory rehabilitation on patients with chronic obstructive pulmonary disease (COPD) [54], the rehabilitation group had a lower re-hospitalization rate than the control group. On the other hand, the retrospective cohort study [55] that used data from a database showed no significant difference between the two groups. In addition, it was reported that in a RCT that targeted COPD patients, the inclusion criteria only fit 20% of the actual patients [56]. As with differences in subjects, differences in methods of intervention between real-world and experimental research data are pointed out too. In the field of rehabilitation, the method of intervention is usually difficult to control, especially that only a small number of patients undergo preoperative rehabilitation. Considering the variation in subjects and intervention method, like the difference

between the experimental study and the real world, the difference in the effect was observed between this research and the previous studies.

The present results showed that approximately 30% of the study patients underwent combination of both preoperative and postoperative rehabilitations, and approximately 14% underwent postoperative rehabilitation alone. The previous study investigating the evidence practice gap (EPG) in the field of Japanese rehabilitation reported that, among indicative patients, only 23.7% inpatients and 4.2% outpatients received cardiac rehabilitation [57]. Although the implementation rates were slightly higher in this study, the recommended treatment by the Japanese cancer rehabilitation guideline [19] was only implemented for 1 of 3 patients who require the treatment. These gaps may be due to that clinicians are not fully aware of the guideline recommendations [58] or there are barriers for clinicians to implement evidence-based practice [59,60]. There are also the patient-related factor (comorbidities status [57,58]) and the environmental factor. In addition, effect of rehabilitation, particularly pulmonary rehabilitation that is examined in the present study, has been undermined and not been recognized well among clinicians in general. To conduct a pulmonary rehabilitation in Japan, the cancer or respiratory rehabilitation fee are part of the medical fee system. Only 384 facilities [61] in Japan could conduct cancer rehabilitation under medical insurance, which met the facility criteria and charge cancer rehabilitation fee. Sato et al [62] reported that there is a wide gap between hospitals that perform cancer rehabilitation 100% and hospitals that do not perform it at all.

This study has some limitations. First, because it is a retrospective cohort study based on a database, available data were limited. For example, medical practice (a surgical volume and experience of rehabilitation), institutional data (the size of

hospital and medical remuneration points) and patients' medical conditions, socioeconomic factors. Therefore, the confounding factors, apart from the data acquired in the present study, could not be adjusted. Second, this study did not include outpatient rehabilitation before admission. As the aim of this study was to examine the effect of rehabilitation conducted in combination of both before and after lung cancer surgery on postoperative pulmonary complication, the analysis was limited to patients hospitalized to meet the criteria for charging the cancer patient rehabilitation fee. Therefore, those who received rehabilitation before admission were not included in the preoperative rehabilitation group; thus, the effect on the prevention of the complication in the preoperative rehabilitation group may have been relatively underestimated. Third, the DPC data used in this study represents a part of all hospitals in Japan. DPC data used in this study is a Japan's large-scale administrative data. It is unlikely that the data are seriously biased on a certain portion of hospital, however, generalization should be made with caution. Fourth, factor on a facility level could not be taken into account since IDs for each hospital were unknown.

In conclusions, the combination of both preoperative and postoperative rehabilitations to decrease the risk of postoperative pneumonia compared with preoperative alone, postoperative alone, and no rehabilitation. However, cancer rehabilitation was prescribed to only one third of the patients in need.

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Reference

1. Statistic Japan:

<http://www.e-stat.go.jp/SG1/estat/List.do?lid=000001191145>. Accessed March 2018

2. National Cancer Center Japan

http://ganjoho.jp/reg_stat/statistics/stat/summary.html. Accessed March 2018

3. Sekine Y, Suzuki H, Nakajima T, et al (2010) Risk quantification for pulmonary complications after lung cancer surgery. *Surg Today* 40: 1027-1033.
4. Takenaka T, Katsura M, Shikada Y, et al (2013) The impact of cardiovascular comorbidities on the outcome of surgery for non-small-cell lung cancer. *Interact Cardiovasc Thorac Surg* 16: 270-274.
5. Kearney DJ, Lee TH, Reilly JJ, et al (1994) Assessment of operative risk in patients undergoing lung resection. Importance of predicted pulmonary function. *Chest* 105: 753-759.
6. Busch E, Verazin G, Antkowiak JG, et al (1994) Pulmonary complications in patients undergoing thoracotomy for lung carcinoma. *Chest* 105: 760-766.

7. Deslauriers J, Ginsberg RJ, Piantadosi S, et al (1994) Prospective assessment of 30-day operative morbidity for surgical resections in lung cancer. *Chest* 106: 329S-330S.
8. Algar FJ, Antonio A, Salvatierra A, et al (2003) Predicting pulmonary complications after pneumonectomy for lung cancer. *Eur J Cardiothorac Surg* 23: 201-208.
9. Wang JS (2003) Relationship of carbon monoxide pulmonary diffusing capacity to postoperative cardiopulmonary complications in patients undergoing pneumonectomy. *Kaohsiung J Med Sci* 19: 437-446.
10. Schuurmans MM, Diacon AH, Bolliger CT (2002) Functional evaluation before lung resection. *Clin Chest Med* 23:159-172.
11. Varela G, Ballesteros E, Jiménez MF, et al (2006) Cost-effectiveness analysis of prophylactic respiratory physiotherapy in pulmonary lobectomy. *Eur J Cardiothorac Surg* 29: 216-220.
12. Algar FJ, Alvarez A, Salvatierra A, et al (2003) Predicting pulmonary complications after pneumonectomy for lung cancer. *Eur J Cardiothorac Surg* 23: 201-208.
13. Cavalheri V, Granger C (2017) Preoperative exercise training for patients with non-small cell lung cancer. *Cochrane Database Syst Rev* 7;6:CD012020. doi: 10.1002/14651858.CD012020.pub2.
14. Cavalheri V, Jenkins S, Cecins N, et al (2017) Exercise training for people following curative intent treatment for non-small cell lung cancer: a randomized controlled trial. *Braz J Phys Ther* 21: 58-68.

15. Pehlivan E, Turna A, Gurses A, et al (2011) The effects of preoperative short-term intense physical therapy in lung cancer patients: a randomized controlled trial. *Ann Thorac Cardiovasc Surg* 17: 461-468.
16. Sekine Y, Chiyo M, Iwata T, et al (2005) Perioperative rehabilitation and physiotherapy for lung cancer patients with chronic obstructive pulmonary disease. *Jpn J Thorac Cardiovasc Surg* 53: 237-423.
17. Thomas JA, McIntosh JM (1994) Are incentive spirometry, intermittent positive pressure breathing, and deep breathing exercise effective in the prevention of postoperative pulmonary complications after upper abdominal surgery? A systematic overview and meta-analysis. *Phys Ther* 74: 3-10.
18. Hall JC, Tarala RA, Tap per J, et al (1996) Prevention of respiratory complications after abdominal surgery: a randomised clinical trial. *BMJ* 312: 148-152.
19. The Japanese Association of Rehabilitation Medicine. Guidelines for Cancer Rehabilitation:
http://www.cancer-reha-wg.com/pdf/1404_cancerreha_guidelines.pdf

Accessed March 2018
20. Brunelli A, Charloux A, Bolliger CT, et al (2009) European Respiratory Society and European Society of Thoracic Surgeons joint task force on fitness for radical therapy. ERS/ ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo- radiotherapy), *Eur Respir J* 34: 17-41.

21. Brunelli A, Kim AW, Berger KI, et al (2013) Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 143: e166S-e190S.
22. Benchimol EI, Smeeth L, Guttman A, et al ; RECORD Working Committee (2015) The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med 12: e1001885.
23. Yasunaga H, Matsui H, Horiguchi H, et al (2014) Application of the diagnosis procedure combination (DPC) data to clinical studies (in Japanese) J UOEH 36:191-197.
24. Hideo Y (2016) Clinical epidemiological Studies Using the DPC Data: Challenges for the Future (in Japanese). Iryo To Shakai 26: 7-14
25. World Health Organization. <http://www.who.int/classifications/icd/en/> (15/Dec/2017)
26. Ministry of Health, Labour and Welfare. [http://www.iryohoken.go.jp/shinryohoshu/\(15/Dec/2017\)](http://www.iryohoken.go.jp/shinryohoshu/(15/Dec/2017))
27. McGuire A, Martin M, Lenz C, et al (2015) Treatment cost of non-small cell lung cancer in three European countries: comparisons across France, Germany, and England using administrative databases. J Med Econ 18: 525-532.
28. Sekine Y, Yamada Y, Chiyo M, et al (2007) Association of chronic obstructive pulmonary disease and tumor recurrence in patients with stage IA lung cancer after complete resection. Ann Thorac Surg 84: 946-950.
29. Kobayashi S, Karube Y, Nishihira M, et al (2016) Postoperative pyothorax a risk factor for acute exacerbation of idiopathic interstitial pneumonia following lung cancer resection. Gen Thorac Cardiovasc Surg. 64: 476-480.

30. Bornheimer R, Shea KM, Sato R, et al (2017) Risk of exacerbation following pneumonia in adults with heart failure or chronic obstructive pulmonary disease. *PLoS One*. 12: e0184877.
31. Di Pasquale M, Esperatti M, Crisafulli E, et al (2013) Impact of chronic liver disease in intensive care unit acquired pneumonia: a prospective study *Intensive Care Med* 39: 1776-1784.
32. Chou CY, Wang SM, Liang CC, et al (2014) Risk of pneumonia among patients with chronic kidney disease in outpatient and inpatient settings: a nationwide population-based study. *Medicine (Baltimore)* 93: e174.
33. Lanspa MJ, Peyrani P, Wiemken T, et al (2015) Characteristics associated with clinician diagnosis of aspiration pneumonia: a descriptive study of afflicted patients and their outcomes. *J Hosp Med* 10: 90-96.
34. Radu DM, Jauréguy F, Seguin A et al (2007) Postoperative pneumonia after major pulmonary resections: an unsolved problem in thoracic surgery. *Ann Thorac Surg* 84:1669–1673
35. Hugh-Jones P, Lambert AV (1951). A simple standard exercise test and its use for measuring exertion dyspnoea. *Brit Med J* 1: 65-71.
36. Varela G, Novoa NM, Agostini P, et al (2011) Chest physiotherapy in lung resection patients: state of the art. *Semin Thorac Cardiovasc Surg* 23: 297-306.
37. Bennett, D.A(2001) How can I deal with missing data in my study? *Aust. N. Z. J. Public Health* 25, 464-469.
38. Allison, P.D(2005) Imputation of categorical variables with PROC MI. In: Presented at 30th Meeting of SAS User Group International, Philadelphia, PA, pp10-13

39. Rubin, D. B (1987) Multiple Imputation for Nonresponse in Surveys. Wiley Classics Library, New York
40. Fang Y, Zhao Q, Huang D(2013). The impact of exercise training on surgery tolerance in lung cancer patients with impaired pulmonary function. *Chin J Rehabil* 28: 619–623.
41. Divisi D, Di Francesco C, Di Leonardo G(2013) Preoperative pulmonary rehabilitation in patients with lung cancer and chronic obstructive pulmonary disease. *Eur J Cardiothorac Surg* 43: 293–296.
42. Bobbio A, Chetta A, Ampollini L, et al (2008) Preoperative pulmonary rehabilitation in patients undergoing lung resection for non-small cell lung cancer. *Eur J Cardiothorac Surg*. 33: 95-98.
43. Vagvolgyi A, Rozgonyi Z, Kerti M, et al (2017) Effectiveness of perioperative pulmonary rehabilitation in thoracic surgery. *J Thorac Dis*. 9: 1584-1591.
44. Benzo R, Wigle D, Novotny P, et al (2011) Preoperative pulmonary rehabilitation before lung cancer resection: results from two randomized studies. *Lung Cancer* 74: 441-445.
45. Morano MT, Araújo AS, Nascimento FB, et al (2013) Preoperative pulmonary rehabilitation versus chest physical therapy in patients undergoing lung cancer resection: a pilot randomized controlled trial. *Arch Phys Med Rehabil* 94:53-58.
46. Hattori K, Matsuda T, Takagi Y, et al (2017) Preoperative six-minute walk distance is associated with pneumonia after lung resection. *Interact Cardiovasc Thorac Surg* doi: 10.1093/icvts/ivx310.

47. Saito H, Hatakeyama K, Konno H, et al (2017) Impact of pulmonary rehabilitation on postoperative complications in patients with lung cancer and chronic obstructive pulmonary disease. *Thorac Cancer* 8: 451-460.
48. Liu W, Pan YL, Gao CX et al (2013) Breathing exercises improve post- operative pulmonary function and quality of life in patients with lung cancer: A meta-analysis. *Exp Ther Med*. 5:1194–1200
49. Mujovic N, Mujovic N, Subotic D, et al (2015) Influence of Pulmonary Rehabilitation on Lung Function Changes After the Lung Resection for Primary Lung Cancer in Patients with Chronic Obstructive Pulmonary Disease. *Aging Dis*. 6: 466-477.
50. Bautmans I, Njemini R, De Backer J, et al (2010) Surgery-induced inflammation in relation to age, muscle endurance, and self-perceived fatigue. *J Gerontol A Biol Sci Med Sci* 65: 266-273.
51. Welvaart WN, Paul MA, Stienen GJ, et al (2011) Selective diaphragm muscle weakness after contractile inactivity during thoracic surgery. *Ann Surg* 254: 1044-1049.
52. Juhl B, Frost N (1975) A comparison between measured and calculated changes in the lung function after operation for pulmonary cancer. *Acta Anaesthesiol Scand Suppl* 57:39-45.
53. Price D, Chisholm A, van der Molen T, et al (2011) Reassessing the evidence hierarchy in asthma: evaluating comparative effectiveness. *Curr Allergy Asthma Rep* 11: 526-538.
54. Seymour JM, Moore L, Jolley CJ, et al (2010) Outpatient pulmonary rehabilitation following acute exacerbations of COPD. *Thorax*. 65: 423-428.

55. Adamson SL, Burns J, Camp PG, et al (2016) Effects of Pulmonary Rehabilitation on Exacerbation Number and Severity in People With COPD: An Historical Cohort Study Using Electronic Health Records. *Int J Chron Obstruct Pulmon Dis* 11:61-71.
56. Herland K, Akselsen JP, Skjøsberg OH, et al (2005) How representative are clinical study patients with asthma or COPD for a larger “real life” population of patients with obstructive lung disease? *Respir Med* 99: 11-19.
57. Kanazawa N, Ueshima K, Tominari S, et al (2017) Underuse of Cardiac Rehabilitation in Workers With Coronary Artery Disease - Claims Database Survey in Japan. *Circ J* 81: 1424-1431.
58. Yokoyama Y, Kakudate N, Sumida F, et al (2016) Evidence-practice gap for dental sealant application: results from a dental practice-based research network in Japan. *Int Dent J* 66: 330-336.
59. Glasgow RE, Vinson C, Chambers D, et al (2012) National Institutes of Health approaches to dissemination and implementation science: current and future directions. *Am J Public Health* 102: 1274-1281.
60. Santarius T, Lawton R, Kirkpatrick PJ, et al (2008) The management of primary chronic subdural haematoma: a question- naire survey of practice in the United Kingdom and the Republic of Ireland. *Br J Neurosurg* 22: 529-534.
61. National Cancer Center, Center for Cancer Control and information services.

<https://hospdb.ganjoho.jp/kyotendb.nsf/xpTopPage.xsp>. Accessed Dec 2017

62. Masako S, Noriko S, Susumu K, et al (2017) Association between perioperative pulmonary rehabilitation and postoperative pneumonia in lung cancer resection patients — An analysis using Japanese administrative database —
Journal of the Japan Society for Healthcare Administration 54; 55-63

Fig1 Patients Inclusion

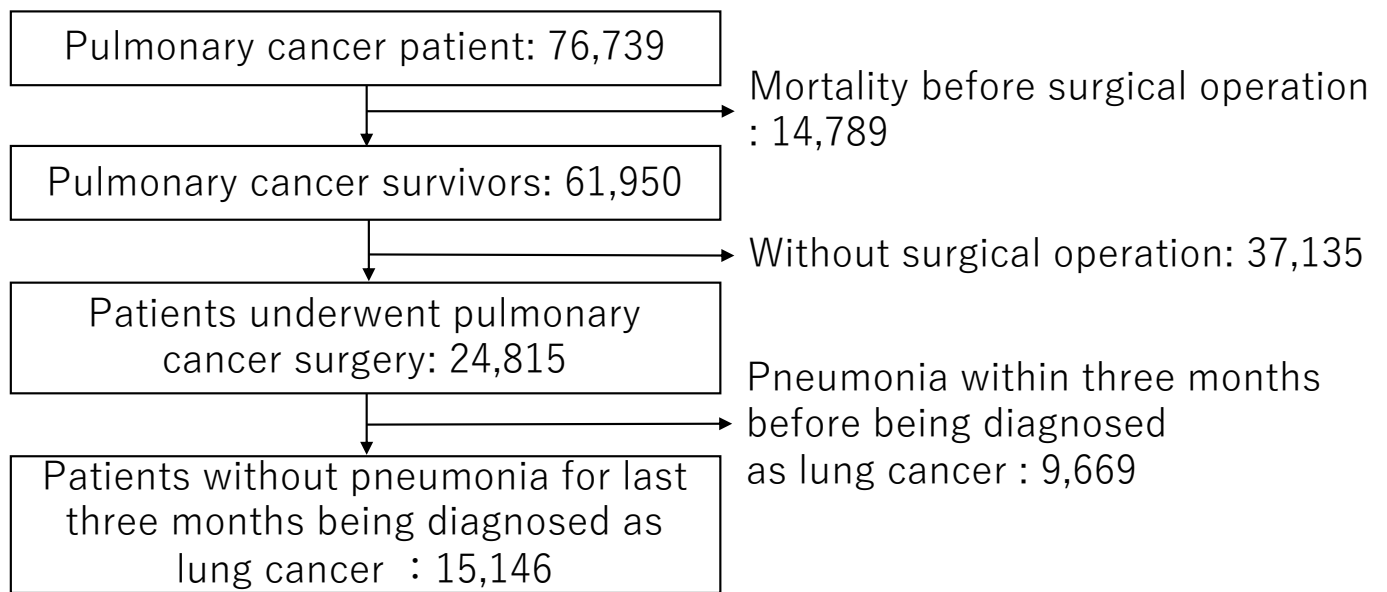


Table 1. Patient attribution (All Patients)

		Operative procedure	All patients				
		Rehabilitation patterns	All patients	Combination group	Preoperative group	Postoperative group	No rehabilitation group
N			15146	4729	269	2105	8043
Sex	N (%)						
		Male	8724 (57.6)	2686(56.8)	153(56.9)	1247(59.2)	4638(57.7)
		Female	6622 (42.4)	2043(43.2)	116(43.1)	858(40.8)	3405(42.3)
		Missing; N (%)	0(0)	0(0)	0(0)	0(0)	0(0)
Age	(Mean±SD)		69.1±9.4	69.4±9.3	70.3±9.4	70.0±9.2	68.6±9.6
		Missing; N (%)	0(0)	0(0)	0(0)	0(0)	0(0)
BMI (kg/m²)	(Mean±SD)		22.7±4.2	22.8±3.7	22.4±4.4	22.8±3.6	22.6±4.6
		Missing; N (%)	137(0.9)	25(0.2)	4(0.02)	7(0.05)	101(0.6)
Onset of pneumonia	N (%)		2483 (16.4)	473(10.0)	60(22.3)	361(17.2)	1589(19.8)
		Missing; N (%)	0(0)	0(0)	0(0)	0(0)	0(0)
Comorbidities on admission	N (%)						
		chronic respiratory illness	4455 (29.4)	1269(26.8)	136(50.6)	540(25.7)	2510(31.2)

BI	(Mean±SD)	interstitial pneumonia	3646 (24.0)	1244(26.3)	35(13.0)	651(30.9)	1716(21.3)
		chronic cardiac failure	1620 (10.7)	611(13.0)	26(9.7)	162(7.7)	821(10.2)
		hepatic disorder	2188 (14.4)	745(15.8)	43(16.0)	293(13.9)	1107(13.8)
		chronic renal failure	867 (5.7)	271(5.7)	21(7.8)	147(7.0)	428(5.3)
		cerebrovascular accident	402 (2.7)	144(3.0)	13(4.8)	56(2.7)	189(2.4)
			96.1±18.0	98.7±8.0	99.2±6.3	98.1±10.3	94.0±23.1
		Missing; N (%)		0(0)	0(0)	0(0)	0(0)
Cancer stage	N (%)						
	I A	7113 (46.9)	2084(44.1)	75(27.9)	928(44.1)	4026(50.1)	
	I B	2298 (15.2)	746(15.8)	25(9.3)	395(18.8)	1132(14.1)	
	II A	801 (5.3)	249(5.3)	8(3.0)	120(5.7)	424(5.3)	
	II B	448 (3.0)	126(2.7)	9(3.3)	100(4.8)	213(2.6)	
	III A	792 (5.2)	239(5.1)	10(3.7)	143(6.8)	400(5.0)	
	III B	31 (0.2)	6(0.1)	0(0)	5(0.2)	20(0.2)	
	IV	303 (2.0)	81(1.7)	4(1.5)	38(1.8)	180(2.2)	
	Missing; N (%)	3360 (22.2)	1198(25.3)	138(51.3)	376(17.9)	1648(20.5)	

Hugh-Jones classification N (%)

I	11867 (78.4)	3479(73.6)	216(80.3)	1681(80.1)	6491(80.9)
II	2044 (13.5)	780(16.5)	29(10.8)	233(11.0)	1002(12.5)
III	510 (3.4)	200(4.2)	10(3.7)	98(4.8)	202(2.5)
IV	157 (1.0)	55(1.1)	5(1.8)	28(1.3)	69(0.9)
V	60 (0.4)	40(0.8)	1(0.3)	4(0.2)	15(0.1)
Missing; N (%)	508(3.4)	175(3.7)	8(3.0)	61(2.9)	264(3.3)

Number of units of
rehabilitation in hospital (Mean±SD)

	3.6±9.2	8.0±10.5	2.1±9.9	7.7±15.2	0.0±0.0
Missing; N (%)	0(0)	0(0)	0(0)	0(0)	0(0)

Number of days of
rehabilitation in hospital (Mean±SD)

	3.4±8.9	7.2±9.7	1.8±9.8	7.9±15.3	0.0±0.0
Missing; N (%)	0(0)	0(0)	0(0)	0(0)	0(0)

N=15146

BMI : Body Mass Index

BI : Barthel Index

Comorbidities on admission is calculated total number

Table2 Patient attribution (Endoscopic)

		Operative procedure	Endoscopic				
		Rehabilitation patterns	All patients	Combination group	Preoperative group	Postoperative group	No rehabilitation group
N			12505	3760	248	1756	6741
Sex	N (%)						
		Male	6966(55.7)	2032(54.0)	139(56.0)	1000(57.0)	3795(56.3)
		Female	5539(44.3)	1728(46.0)	109(44.0)	756(43.0)	2946(43.7)
		Missing; N (%)	0(0)	0(0)	0(0)	0(0)	0(0)
Age	(Mean±SD)		69.3±9.5	69.7±9.2	70.2±9.6	70.0±9.2	68.7±9.7
		Missing; N (%)	0(0)	0(0)	0(0)	0(0)	0(0)
BMI (kg/m²)	(Mean±SD)		22.7±4.3	22.9±3.7	22.4±4.5	22.8±3.6	22.6±4.7
		Missing; N (%)	20(0.16)	7(0.2)	0(0)	2(0.1)	11(0.2)
Onset of pneumonia		N (%)	2048(16.4)	402(10.7)	55(22.2)	300(17.1)	1291(19.2)
		Missing; N (%)	0(0)	0(0)	0(0)	0(0)	0(0)

Comorbidities on admission N (%)

chronic respiratory illness	3560(28.5)	969(25.8)	129(52.0)	435(24.8)	2027(30.1)
interstitial pneumonia	2967(23.7)	920(24.5)	29(11.7)	567(32.3)	1451(21.5)
chronic cardiac failure	1335(10.7)	519(13.8)	23(9.3)	123(7.0)	670(9.9)
hepatic disorder	1819(14.5)	583(15.5)	41(16.5)	244(13.9)	951(14.1)
chronic renal failure	738(5.9)	221(5.9)	20(8.1)	128(7.3)	369(5.5)
cerebrovascular accident	344(2.6)	117(3.1)	12(4.8)	46(2.6)	169(2.5)

BI (Mean±SD)

96.2±17.9 98.7±8.1 99.0±6.6 98.3±10.1 94.1±22.8

Missing; N
(%)

0(0) 0(0) 0(0) 0(0) 0(0)

Cancer stage N (%)

I A	6370(50.9)	1872(49.8)	67(27.0)	839(47.8)	3636(53.9)
I B	1877(15.0)	621(16.5)	23(9.3)	367(20.9)	906(13.4)
II A	521(4.2)	153(4.1)	6(2.4)	91(5.2)	281(4.2)
II B	274(2.2)	76(2.0)	8(3.2)	67(3.8)	128(1.9)
III A	456(3.6)	110(2.9)	4(1.6)	100(5.7)	252(3.7)

IIIB	16(0.1)	2(0.1)	0(0)	3(0.2)	11(0.2)
IV	239(1.9)	71(1.9)	4(1.6)	33(1.9)	147(2.2)
Missing; N (%)	2752(22.0)	936(24.9)	136(54.8)	300(17.1)	1380(20.5)

Hugh-Jones classification N (%)

I	9853(78.8)	2801(74.5)	201(81.0)	1422(81.0)	5429(80.5)
II	1644(13.1)	583(15.5)	28(11.3)	185(10.5)	848(12.6)
III	416(3.3)	156(4.1)	9(3.6)	75(4.3)	176(2.6)
IV	123(1.0)	39(1.0)	5(2.0)	20(1.1)	59(0.9)
V	59(0.4)	35(0.5)	0(0)	2(0.1)	13(0.2)
Missing; N (%)	419(3.4)	146(3.9)	5(2.0)	52(3.0)	216(3.2)

Number of units of
rehabilitation in hospital (Mean±SD)

3.3±7.4 7.5±10.1 1.2±5.0 7.2±8.4 0.0±0.0

Missing; N (%)	0(0)	0(0)	0(0)	0(0)	0(0)
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Number of days of
rehabilitation in hospital (Mean±SD)

3.1±7.7 6.7±8.6 1.3±9.3 7.4±13.6 0.0±0.0

Missing; N (%)	0(0)	0(0)	0(0)	0(0)	0(0)
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N=15146

BMI : Body Mass Index

BI : Barthel Index

Comorbidities on admission is calculated total number

Table3 Patient attribution (Thoracotomy)

		Operative procedure	Thoracotomy				No rehabilitation group
		Rehabilitation patterns	All patients	Combination group	Preoperative group	Postoperative group	
N			2771	1006	24	360	1381
Sex	N (%)						
		Male	1848(66.7)	680(67.6)	17(70.8)	253(70.3)	898(65.0)
		Female	923(33.3)	326(32.4)	7(29.2)	107(29.7)	483(35.0)
		Missing; N (%)	0(0)	0(0)	0(0)	0(0)	0(0)
Age	(Mean±SD)		68.5±9.2	68.4±9.6	70.8±7.7	70.3±9.1	68.1±8.9
		Missing; N (%)	0(0)	0(0)	0(0)	0(0)	0(0)
BMI (kg/m ²)	(Mean±SD)		22.7±3.8	22.8±3.8	22.7±3.0	22.7±3.8	22.6±3.9
		Missing; N (%)	20(0.7)	7(0.1)	0(0)	2(0.5)	11(0.8)
Onset of pneumonia	N (%)		478(17.3)	76(7.6)	6(25.0)	66(18.3)	330(23.9)
		Missing; N (%)	0(0)	0(0)	0(0)	0(0)	0(0)

Comorbidities on admission N (%)

chronic respiratory illness	933(33.7)	310(30.8)	8(33.3)	107(29.7)	508(36.8)
interstitial pneumonia	702(25.3)	332(33.0)	7(29.2)	86(23.9)	277(20.1)
chronic cardiac failure	303(10.9)	97(9.6)	3(12.5)	39(10.8)	164(11.9)
hepatic disorder	384(14.1)	169(16.8)	2(8.3)	51(14.2)	162(11.7)
chronic renal failure	135(4.8)	52(5.2)	2(8.3)	20(5.6)	61(4.4)
cerebrovascular accident	60(2.2)	28(2.8)	1(4.2)	10(2.8)	21(1.5)

BI (Mean±SD)

95.4±19.5 98.7±7.7 100.0±0.0 97.6±10.8 92.4±25.9

Missing; N
(%)

0(0) 0(0) 0(0) 0(0) 0(0)

Cancer stage N (%)

I A	790(28.5)	272(27.0)	8(33.3)	92(25.6)	418(30.3)
I B	449(16.2)	149(14.8)	2(8.3)	53(14.7)	245(17.7)
II A	293(10.6)	102(10.1)	3(12.5)	36(10.0)	152(11.0)
II B	178(6.4)	55(5.5)	1(4.2)	34(9.4)	88(6.4)
III A	346(12.5)	135(13.4)	6(25.0)	50(13.9)	155(11.2)

IIIB	15(0.5)	4(0.4)	0(0)	2(0.6)	9(0.7)
IV	67(2.4)	20(2.0)	1(4.2)	12(3.3)	34(2.5)
Missing; N (%)	633(22.8)	269(26.7)	3(12.5)	81(22.5)	280(20.3)

Hugh-Jones classification N (%)

I	2108(76.1)	702(69.8)	17(70.8)	265(73.6)	1124(81.4)
II	424(15.3)	208(20.7)	1(4.2)	50(13.9)	165(11.9)
III	98(3.5)	45(4.5)	1(4.2)	24(6.7)	28(2.0)
IV	38(1.4)	16(1.6)	1(4.2)	9(2.5)	12(0.9)
V	10(0.4)	5(0.5)	1(4.2)	2(0.6)	2(0.1)
Missing; N (%)	93(3.4)	30(3.0)	3(12.5)	10(2.8)	50(3.6)

Number of units of
rehabilitation in hospital (Mean±SD)

5.1±14.7 9.8±11.7 11.1±27.8 10.6±31.5 0.0±0.0

Missing; N (%)	0(0)	0(0)	0(0)	0(0)	0(0)
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Number of days of
rehabilitation in hospital (Mean±SD)

4.9±13.2 9.0±12.6 6.4±12.9 10.9±24.3 0.0±0.0

Missing; N (%)	0(0)	0(0)	0(0)	0(0)	0(0)
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N=15146

BMI : Body Mass Index

BI : Barthel Index

Comorbidities on admission is calculated total number

Table4 The implementation pattern for rehabilitation and onset pneumonia

	All patients				Endoscopic				Thoracotomy			
	Onset		Offset		Onset		Offset		Onset		Offset	
	n	%	n	%	n	%	n	%	n	%	n	%
Combination group(n=4729)	478	10.0	4256	90.0	402	10.7	3358	89.3	76	7.6	930	92.5
Preoperative group(n=269)	61	22.3	209	77.7	55	22.2	193	77.8	6	25.0	18	75.0
Postoperative group(n=2105)	366	17.2	1744	82.9	300	17.1	1456	82.9	66	18.3	294	81.7
No rehabilitation group (n=8043)	1621	19.8	6454	80.2	1291	19.2	5450	80.9	330	23.9	1051	76.1

n (%)

N=15146

Table5 Multiple logistic regression analysis (Complete case)

	All patients				Endoscopic				Thoracotomy			
	OR	p value	95%CI lower	95%CI upper	OR	p value	95%CI lower	95%CI upper	OR	p value	95%CI lower	95%CI upper
Combination group												
vs Preoperative group	2.8	<0.0001*	1.8	4.4	2.8	<0.0001*	1.8	4.4	4.2	<0.0001*	2.9	6.3
vs Postoperative group	1.9	<0.0001*	1.6	2.3	1.9	<0.0001*	1.6	2.2	1.9	<0.0001*	1.6	2.3
vs No rehabilitation group	2.5	<0.0001*	2.1	2.8	2.5	<0.0001*	2.1	2.8	2.4	<0.0001*	2.1	2.7
Postoperative group												
vs Preoperative group	1.5	0.08	1.0	2.3	1.5	0.08	1.0	2.4	2.2	<0.0001*	1.5	3.3
vs No rehabilitation group	1.3	0.0015*	1.1	1.5	1.3	0.0011*	1.1	1.5	1.2	0.0025*	1.1	1.4
Preoperative group												
vs No rehabilitation group	0.9	0.52	0.6	1.3	0.9	0.53	0.6	1.3	0.6	0.0035*	0.4	0.8

OR=odds ratio

CI= confidence interval

Appendix Multiple logistic regression analysis (Multiple Imputation)

	All patients				Endoscopic				Thoracotomy			
	OR	p value	95%CI lower	95%CI upper	OR	p value	95%CI lower	95%CI upper	OR	p value	95%CI lower	95%CI upper
Combination group												
vs Preoperative group	2.1	<0.0001*	1.5	2.9	2.0	<0.0001*	1.4	1.5	2.7	<0.0001*	2.0	3.7
vs Postoperative group	1.9	<0.0001*	1.7	2.2	1.9	<0.0001*	1.6	2.2	1.9	<0.0001*	1.7	2.3
vs No rehabilitation group	2.3	<0.0001*	2.0	2.6	2.2	<0.0001*	2.0	2.5	2.3	<0.0001*	2.1	2.6
Postoperative group												
vs Preoperative group	1.1	0.66	0.8	1.5	1.1	0.6200	0.8	1.5	1.4	0.0406*	1.0	1.9
vs No rehabilitation group	1.2	0.0196*	1.0	1.3	1.2	0.0106*	1.0	1.4	1.2	0.0073*	1.0	1.4
Preoperative group												
vs No rehabilitation group	1.1	0.56	0.8	1.5	1.1	0.53	0.8	1.5	0.9	0.31	0.6	1.2

OR=odds ratio

CI= confidence interval