Postoperative Severe Lung Failure and Functional Variations in Lung Cancer Patients with Different Extent of Resection: A Pilot Study .

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Abstract

BACKGROUND

Lung cancer is recognized to be the main cause of cancer death worldwide and it is closely associated with cigarette smoking and chronic obstructive pulmonary disease (COPD). Only about 15% of patients affected by lung cancer are suitable for surgery and the clinical postoperative outcomes are variable.

We aim to investigate the variables that affect post-surgery complications .

METHODS

A sample of 75 patients who underwent surgery for lung cancer was retrospectively studied about respiratory function and arterial gasanalysis .Data were collected before and after surgery.

A subgroups comparative analysis was performed between group who underwent lobectomy vs group who underwent sub-lobar resection represented by either wedge or segmentectomy. Lung failure was categorized as severe for PaO2< 50 mmHg or non severe for PaO2 >50 mmHg.

RESULTS

The overall data were: mean age 71.5, hospitalization time 7.8 days, pack-year 34, body mass index (BMI) 25.4, chronic obstructive pulmonary disease(COPD) assessment test (CAT) mean value was 16.5, forced expiratory one second volume (FEV1) at baseline 1.6 l corresponding to 73.6% of predicted.

The mean age was 71.5, males/females rate 35/30

The prevalent stage was IA and prevalent histotype was adenocarcinoma.

Among the variables affecting lung failure development only the type of surgery along with presence of COPD showed a significant impact.

Comparing the groups about the risk of severe lung failure development the treatment with lobectomy is associated with an increased risk compared with sub-lobar resection ($p<0.0005$). A CAT questionnaire > 10 was also associated with greater risk of lung failure with oxygen therapy need($p<0.04$).

The subgroups were comparable for age and pack-year , and for PaO2, FEV 1 and FVC at baseline. A significant difference was observed in terms of hospitalization time ($p<0.03$) that was longer in group of lobectomy and PaO2 15 days after surgery ($p<0.03$). The COPD percentage was higher in the group treated by lobectomy ($p<0.01$). The PaO2 level increased at 3 month check in patients treated with sub-lobar resection that was slightly increased compared with patients treated with lobar resection ($p<0.04$)post-surgery ($p<0.04$).

The variations of the main functional parameters FEV1 and FVC in terms of a reduction the main functional parameters FEV1 and FVC were more evident in patients who underwent lobectomy compared

with group treated with sub-lobar resection($p<0.001$).

CONCLUSIONS

All patients affected by lung cancer who undergo surgery report lung failure of different intensity depending on the type of surgery.

COPD itself could influence the outcome, too. A greater negative variations of functional parameters after surgery is found in group who undergo lobectomy.

Introduction

Lung cancer it is the leading cause of cancer death worldwide. It is classified as non small cell that includes squamous, adenocarcinoma, large cell and small cell lung cancer. All histotypes are often associated with COPD .

The latter is defined as an inflammatory bronchial chronic condition characterized by airflow limitation that is not fully reversible and it is usually caused by exposure to noxious particles or gases predominantly cigarette smoking, though other exposures such as biomass fuels are an important cause. It is the major cause of morbidity and mortality worldwide. It is frequently a comorbidity in lung cancer patients.

The relationships between inflammation, airflow limitation, and lung cancer are known but not fully clarified(1)

By far the main avoidable cause of both COPD and lung cancer is tobacco smoke which contains several chemicals more than 5,000 identified, including tobacco-specific carcinogens such as nitrosamines, nitric oxide, benzopyrene.

By contrast smoking cessation is recognized to be the main tool to improve by itself the prognosis of the diseases and lung function(2).

Lung failure is a possible complication of both diseases and it often occurs after surgery(3)

Lung cancer and COPD are often associated share the same initial pathogenesis (4)

Lung cancer survival has reached partial improvements in the last few decades. Poor outcomes are linked to late clinical presentation, yet early diagnosis can be challenging as lung cancer symptoms are common and non-specific.

Furthermore it is vital in assessing lung cancer risk to look carefully at lifestyle factors and past medical history

The aim of our study is to investigate the effects of the type of surgery in lung cancer patients on lung failure development to determine the variables influencing severe lung failure development and to detect the functional and respiratory changes after surgery comparing the two subgroups.

Methods

From 2019 to 2020, 65 patients were retrospectively analyzed who underwent thoracic surgery for lung cancer. This is a monocentric study based on the collaborations between thoracic surgeons and pulmonologists.

The age and demographic data were recorded as well as functional data, types of surgery, tumor staging, hospitalization time.

Patients underwent different lung resection by mini-thoracotomy approach meaning and incision of 3-4 inch between the ribs, some had lobectomy by thoracotomy and some others underwent sub-lobar resection by mini-thoracotomy .

All patients performed spirometry before and after surgery with detection of post-bronhodilator values, an arterial blood sample was also done with hemogasanalysis that was performed at baseline, 15 days after surgery and at three month check(GEM 3000 device,USA). The COPD assessment test was also applied and it was considered positive in case of score>10 according to GOLD guidelines.

The spirometry was performed by body plethysmography (Jaeger system masterscreen, Germany) as follows: briefly, flow sand dynamic volumes were measured by the pneumotacographic method and volumes and resistances by the plethysmographic method. Data recorded were post-bronchodilator Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV1), recorded as liters and percentage of predicted. The time for post-bronchodilation was 25 minutes obtained by salbutamol 400 µg. The techniques followed the American Thoracic Society and European Respiratory Society task force guidelines(5). Lung failure is categorized as severe ($PaO_2 < 50$ mmHg) or non severe.

The sub-analysis included a group who underwent lobectomy(35) and group with sub-lobar resection (40).The study was approved by S.Andrea-Sapienza Ethic Committee, and a consent form was obtained by each patient.

STATISTICAL METHOD AND ANALYSIS

The normality of the data was assessed by the Kolmogorov-Smirnov test and values were expressed as mean and standard deviation (SD) or median and interquartile range, as appropriate. A sub-analysis was performed to compare subgroup of patients as described previously.

For this purpose Mann-Whitney test or Fisher’s test was applied as appropriate and significance p level was set at <0.05

A logistic regression analysis was performed to correlate functional data and type of surgery with severe lung failure. Subsets of patients depending on type of surgery and their association with different grade of lung failure was detected by contingency table test and odds ratio calculation.

ANOVA test one way was eventually performed for repeated measurements to compare the changes in respiratory function before and after surgery between groups.

All data were acquired by SPSS version 24.0(USA)

Results

Overall data revealed 40 wedge resections and 25 lobectomies.

The prevalent stage was IA2 and prevalent hystotype was adenocarcinoma At baseline table 1 displays the following

Table 1

Demographic data

	Mean	SD
Age	71.5	7
Males/females	35/30	
Hospitalization	7.8	2.5
Pack-year	34.0	11.3
mMRC	1.3	0.70
BMI	25.4	3.3
CAT	16.5	7.1
FEV1 l	1.6	0.77
FEV1 perc	73.6	27.5

Baseline data

The mean age was 71.5±7 , males/females rate 35/30

Mean pack- year 34±11.3

The hospitalization time was 7.8±2.5, mMRC 1.3±0.7, BMI 25.4±3.3, CAT 16.5±7.1

Concerning the functional parameters: FEV1 l mean was 1.68±0.77 and FEV1 percentage 73.6±27.5, FVC 2.5±0.9, TLC 5.1±1.3.

No significant bleeding or complications due to surgery technique were observed.

Patients are still alive except for 4 patients who died of whom 3 underwent lobectomy and 1 underwent wedge resection.

In Table 2 a logistic regression analysis revealed the following data:

Table 2

Dependent variable: severe lung failure

	OR	CI	p
Age	0.9	0.83-1.1	0.9
FEV1	1.0	0.9-1.0	0.9
FEV1 %	0.9	0.94-1.0	0.9
FVC	1.1	0.9-1.08	0.1
Lobectomy	2.8	0.7-3.2	0.04
TLC	1.0	0.9-1.0	0.6
Smoke history	0.7	0.1-4.9	0.7
COPD	2.1	0.6-2.9	0.03

Logistic multi-regression analysis
Odds ratio and confidence interval

Only the type of resection and COPD affected significantly the dependent variable that was severe lung failure. The OR was 2.8 about lobectomy and 2.1 about COPD influence($p<0.04$ and $p<0.03$ respectively).

Table 3 contingency table with determination of odds ratio of the relationship between patients treated with sub-lobar resection(group 0) versus patients treated with lobectomy (group 1) with the risk of severe lung failure development and showed a significant increased risk in patients treated by lobectomy lobectomy with higher risk of long lasting oxygen supply($p<0.005$) .

Table 3

Realationship : type of surgery and CAT>10 vs severe lung failure

Sub-lobar vs lobectomy	OR 0.1 (95%CI 0.03-0.38)		p <0.0005
Sublobar resection	12/40	oxygen >1400 l 24/30	<1,400l
Lobectomy	20/25	oxygen >1,400 l 5/25	<1,400l
CAT questionnaire>10	OR 2.8 (0.51-9.5)		p<0.04

Contingency tables with Odds ratio determination

An increased risk was also found associated with a positive CAT score with an OR 2.8 (p<0.04).

Table 4

Difference between group 0 (sub-lobar resection) and 1(lobectomy)

	Group 0	Group 1	p
Age	73(68-75)	74(67-76)	0.8
Hospitalization	6(4.5-8)	9(7-12)	0.03
Pack-year	35.0(30-40)	40(35-40)	0.07
FEV 1 basal liters	1.7(1.62-1.85)	1.7(1.60-1.81) 0.10	
COPD perc patien	56	62	0.01
PaO2 pre mmHg	65.7(61-70.5)	62.58(58.1-61.2)	0.12
PaO2 post	60.6(58.1-62.3)	48.6 (51.5-59.5)	0.03
PaO2 3 month	62.2(56.7-65.8)	49.0(50.8-60.3)	0.04

Baseline data
Median and interquartile range
Mann Whitney test

Differences between group 0 and group 1 were significant about hospitalization time(p<0.03) with a longer time in patients treated by lobectomy. The groups were comparable for COPD ,age and pack-year. A significant difference in PaO2 value was also found(p<0.03)at 15 days post-surgery and after three months from surgery (p<0.04) showing an improvement only in the group treated with a limited resection .

In group 0 (sub-lobar resection) 60% of patients gave up oxygen after 3 months from surgery, compared with 45% in group 1.

Table 5

Changes of FEV1 and FVC before and after surgery: comparison between group treated by sub-lobar resection G0 and group treated by lobectomy

	Mean differences G1	G0	Mean square	F	p
FEV1 l	-0.20	-0.10	0.39	86.7	<0.001
FVC l	-0.35	-0.15	0.33	31.39	<0.001

One way ANOVA test for repeated measures

Differences were observed abut the variations of of changes of the main functional parameters before and after surgery comparing the two subgroups ,group 0 sub-lobar resection and group 1 lobectomy. A greater lost of functional values was observed in the second group and the difference was significant for both FEV 1 and FVC ($p<0.001$).

Figure 1 and 2 depict the differences in variations among groups highlighting a higher reduction post-surgery of values in group 1 who underwent lobectomy.

Discussion

Patients are often concerned about the prospect of using oxygen therapy postoperatively, and this factor may affect their choice about lung cancer treatment.

Our study showed important findings concerning the need of oxygen therapy after surgery and pointed out which variables are associated with the clinical outcome

Notably a higher percentage of patients who recovered from lung failure was found at post-surgery check in the group who underwent wedge sub-lobar resection. The CAT questionnaire major than 10 was also associated with a higher risk of severe lung failure meaning that concurrent COPD exacerbation may influence post-surgery complications. The development of respiratory failure after surgery is a frequent occurrence with a long-lasting need of oxygen therapy but after three months from surgery patients treated with sub-lobar resection returned to acceptable PaO_2 values without oxygen supply. The presence of COPD was indeed a factor affecting lung failure development and was more present in group high oxygen intensity.

Smoking habit is the main avoidable cause of both COPD and lung cancer as we know from previous studies (4).

COPD and lung cancer have a common origin sharing inflammation as main associated feature(4).

For NSCLC, surgical resection is the standard treatment for stage I-II disease; patients with IB or II disease are being offered adjuvant chemotherapy. Some patients with a stage IIIA tumor are suitable for surgery but often receive pre- or post-operative radiation and/or chemotherapy(6). Depending on their extent, pulmonary resections lead to permanent loss of pulmonary function. In healthy people, resections up to a pneumonectomy are remarkably well tolerated.

Consistenly with the literature our findings suggest that COPD could influence the respiratory failure development but the extension of the removed parenchyma influence even more the functional values decrease and as a consequence it influences the outcome(7).

Indeed, we found a major change in FEV1 and FVC in patients who underwent lobectomy as well as a worse hospitalization time. The risk of respiratory failure precludes lung surgery in many patients with severe chronic obstructive pulmonary disease. It is generally agreed that a minimum value of forced expiratory volume in 1 second (FEV1) is required preoperatively (2 l before pneumonectomy and 1.5 l in case of lobectomy, respectively). Variable cutoff values of FEV1(ranging from 35–80%) have been arbitrarily chosen to assess the severity of COPD and to predict the risk for pulmonary complications. By using receiver-operating characteristic analysis, Licker et coll confirmed that the best cutoff value of FEV1 for predicting respiratory complications was 60% (7, 8).

The risk of respiratory failure in COPD may preclude lung surgery in many patients with severe chronic obstructive pulmonary disease may be a drawback in patients who undergo thoracic surgery for lung cancer .

We found that COPD irrespective of FEV1 value itself influences the post-operative outcome(9).

The presence of COPD is not an absolute contraindication to surgery as we know from the literature since lobectomy for cancer can be performed successfully also in selected patients with chronic obstructive pulmonary disease(10). However the grade of airflow limitation and concurrent cardiovascular abnormalities are associated with an increased morbidity (11, 12). A PaCO2 alteration along with FEV1 early decrease may be observed ,mainly among patients who died after surgery(13, 14, 15). In the present study a worse arterial oxygenation level was observed in the group undergoing more extensive resection. Previous studies compared lobectomy with pneumonectomy but not lobectomy with sub-lobar resection(16, 17). Predictors of complications may include age ,gender, history of smoking, type of resection aside from FEV1 value (18, 19, 20). Our population was mainly former smokers and pack-year did not affect significantly lung failure occurence.

The results show us that COPD is the main comorbidity affecting the quality of life and the possibility of complications that could be partially reversed by bronchodilators and smoking cessation (21, 22, 23). As far as surgery techniques is concerned one possible approach in lung cancer surgery treatment is the video assisted thoracoscopy (VATS) approach that has a significantly lower rate of complications compared with thoracotomy (28% vs 45%, $p = 0.04$) (24).Other valid approaches that we used are mini-thoracotomy or lateral muscle sparing thoracotomy suitable for different extent of resection. Our study is the result of an interdisciplinary cooperation notably between pulmonologist and thoracic surgeon allows to better manage the patient undergoing lung cancer treatment consistently with previous studies (25)Greater loss of function in the sense of a decrease of FEV1 and FVC was observed in patients treated with lobectomy leading to a greater lung failure percentage and longer hospitalization time. A recovery from lung failure after three months along with a lower hospitalization time was observed notably in patients treated with sub-lobar resection.

Conclusions

Our study highligths the influence of COPD and extent of lung parenchyma resection on respiratory failure development. The majority of patients treated with a more conservative surgery recovered more easily from lung failure .COPD was the main comorbidity able to affect the outcome along with the type of surgery.

The greater changes of functional parameters was notably observed in cases treated with lobectomy. Considering the results we advise a screening of high risk patients to find an early diagnosis in order to promote a sparing parenchyma resection considering equal oncological radicality to reduce post-operative complications. Moreover being a pilot study more patients will be recruited in early future.

Abbreviations

FEV1 Forced one second expiratory Volume

FVC Forced Vital Capacity

COPD Chronic Obstructive Pulmonary Disease

VATS Video-assisted thoracoscopy

CAT COPD Assessment Test

mMRC modified medical Research Council dyspnea test

NSCLC Non small cell lung cancer

Declarations

Conflict of Interest

Nothing to declare

Ethics Approval and Consent

The study was approved by the S.Andrea Hospital-Sapienza University Ethic Committee and a consent form was provided by each patient.

Consent form for publication

A consent form approved by our Institution was provided by each patient.

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Authors' contributions

All authors contributed to the drafting and conception of the manuscript.

Aldo Pezzuto, Massimo Ciccozzi and Beatrice Trabalza Marinucci in addition performed the analysis of data.

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The datasets generated during and/or analyzed during the current study are available

from the corresponding author on reasonable request.

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Figures

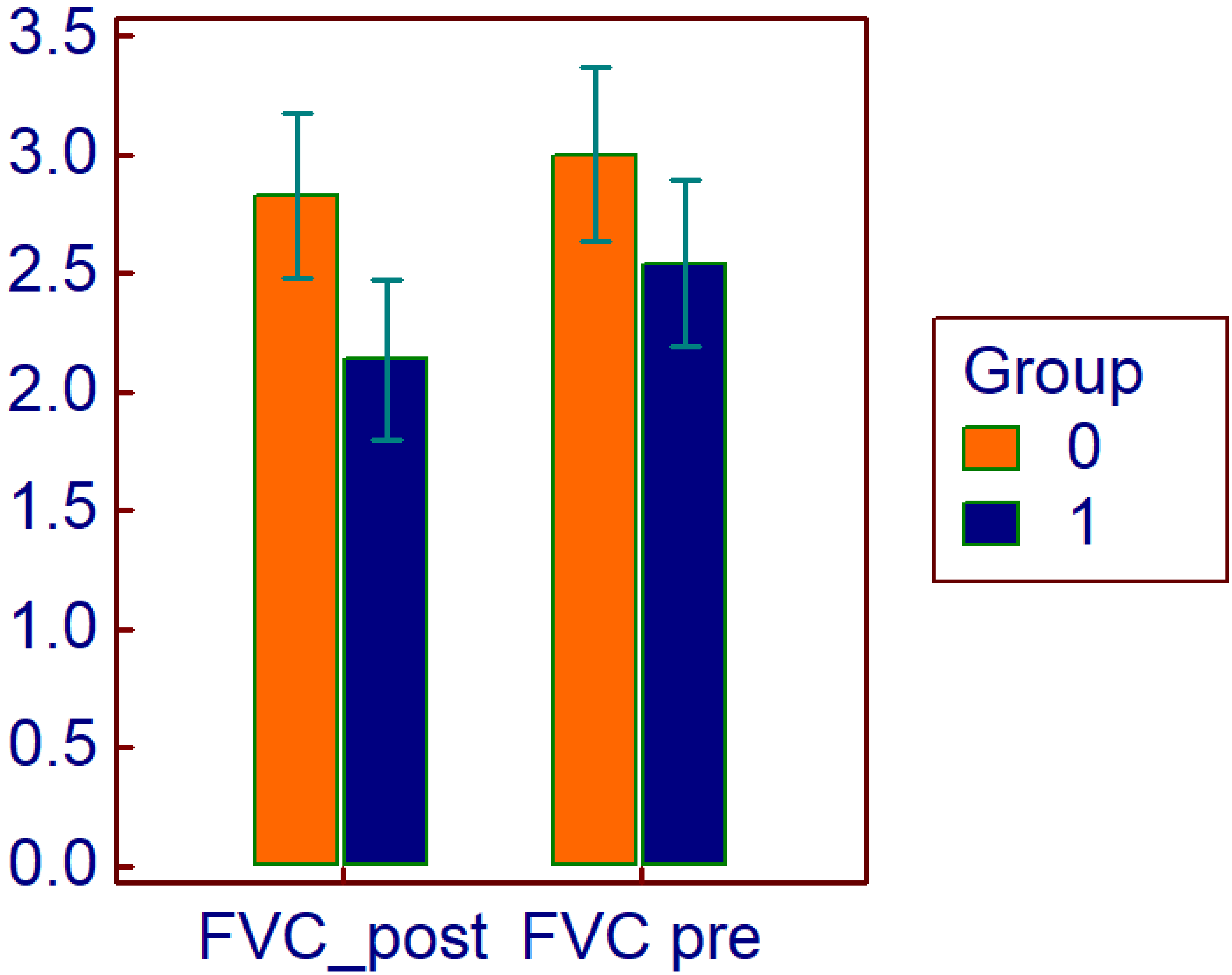

Figure 1

Changes of FVC before and after surgery

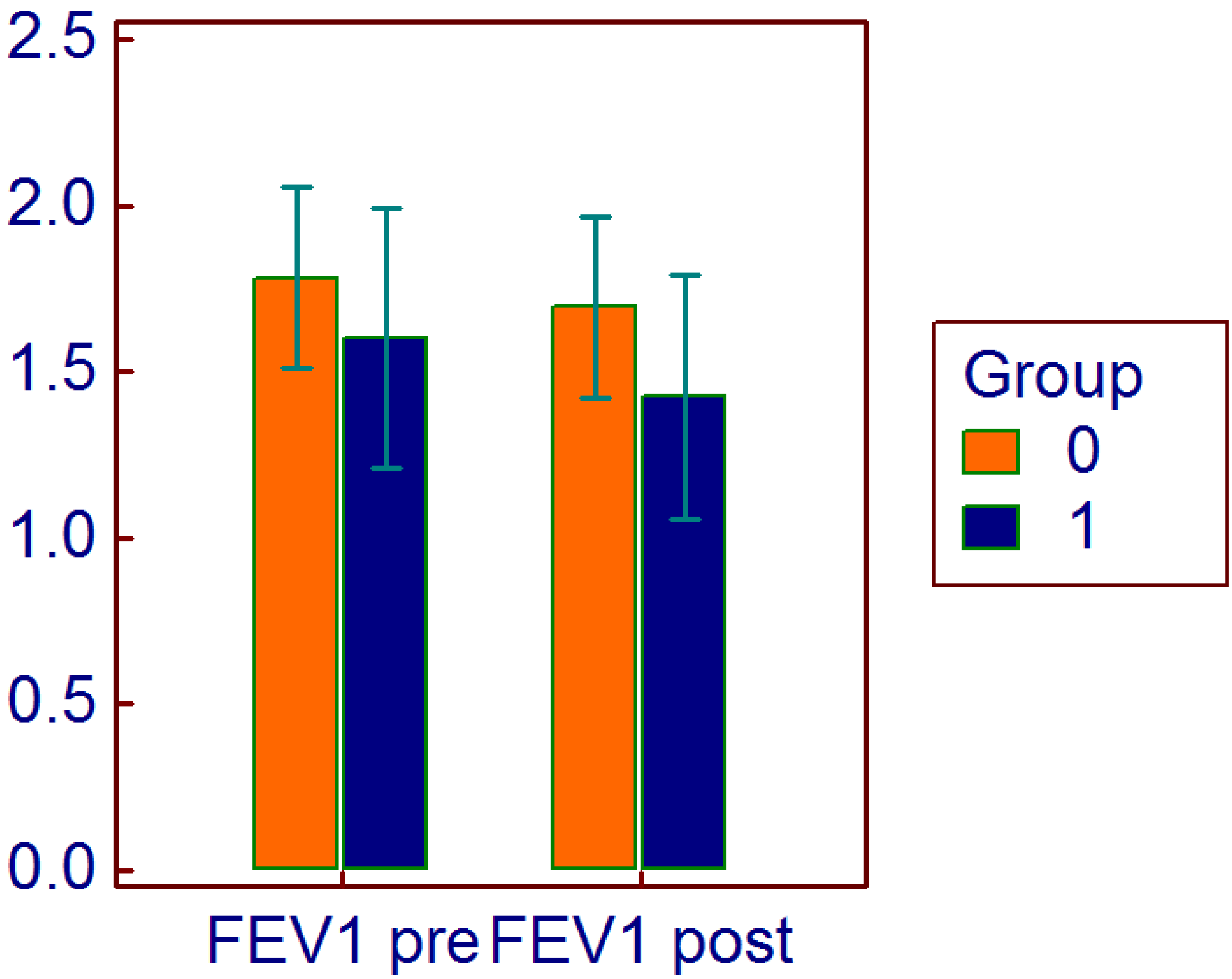

Figure 2

Changes of FEV1 before and after surgery