Original Article

Risk factors of cough in non-small cell lung cancer patients after video-assisted thoracoscopic surgery

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Background: Cough is a common respiratory complication in non-small cell lung cancer (NSCLC) patients after surgery. Previous studies have proposed a number of risk factors for postoperative cough; however, these studies are mainly based on traditional thoracotomies and tend to lack adequate objective assessment methods. The purpose of this study was to identify the risk factors of cough in NSCLC patients after video-assisted thoracoscopic surgery (VATS) using the Leicester Cough Questionnaire in Mandarin Chinese (LCQ-MC) to evaluate postoperative cough.

Methods: A total of 198 NSCLC patients were enrolled. Overall, 91 patients (46.0%) developed cough after VATS, and 73 patients remained cough after 1 month. Univariate and multivariate logistic regression analyses were performed to identify the independent risk factors of postoperative cough.

Results: The independent factors of postoperative cough included female sex [odds ratio (OR) 2.399, 95% confidence interval (CI): 1.260–4.565, P=0.008], duration of anesthesia (over 164 minutes; OR 2.810, 95% CI: 1.368–5.771, P=0.005), resection of the lower paratracheal nodes (OR 3.697, 95% CI: 1.439–9.499, P=0.007), and resection of the subcarinal nodes (OR 4.175, 95% CI: 1.203–14.495, P=0.024). The follow-up LCQ-MC total score after 1 month (18.00±1.80) was significantly higher than the postoperative total score (16.35±2.26; P=0.004).

Conclusions: Female sex, duration of anesthesia over 164 minutes, lower paratracheal node resection and subcarinal node resection were independent risk factors related to cough in NSCLC patients after VATS. In addition, the LCQ-MC performed satisfactorily in describing the longitudinal changes in cough symptoms.

Keywords: Cough; Leicester Cough Questionnaire (LCQ); lung cancer; risk factor; video-assisted thoracoscopic surgery (VATS)

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Introduction

Lung cancer is the most common cancer and is the leading cause of cancer-related death in China (1). With the increase in widespread general health examinations and the development of medical imaging techniques, more and more patients have been diagnosed with early-stage lung cancer and have undergone pulmonary resection (1). Cough is a common complication in patients with non-small cell lung cancer (NSCLC) who have received surgery, and the incidence ranges from 24.7% to 50.0% (2-4). In severe cough, patients experience disrupted sleep and difficulty talking, which increases their psychological burden and worsens their quality of life (4-7).

Postoperative cough has been hypothesized to be related to pulmonary C-fiber activation, extraction of the vagus nerve, acid regurgitation, endobronchial sutures and

mediastinal lymph node resection as well as other anatomical reasons (3,8-11). However, the mechanism and characteristics of cough after pulmonary resection remain controversial.

Previous research has mainly focused on traditional thoracotomy rather than video-assisted thoracoscopic surgery (VATS) and has lacked adequate standardized methods for assessing postoperative cough. VATS is a widespread technique linked to improved postoperative respiratory function and reduced length of hospital stay (12-15).

In our study, we investigated postoperative cough in NSCLC patients via the Leicester Cough Questionnaire in Mandarin Chinese (LCQ-MC) and followed up with the patients at 1-month post-surgery. Meanwhile, we analyzed data to find potential risk factors that could be altered by medical intervention with the hope of reducing the incidence of postoperative cough.

Methods

This study was part of a validation of the LCQ-MC in patients undergoing lung resection for lung disease (Clinicaltrials.gov, number ChiCTR-DDD-17014237). The West China Hospital of Sichuan University in Sichuan, China, approved the study. All the participants provided written informed consent.

Subjects

A total of 198 patients who underwent thoracic surgery performed by a single medical team between September 2016 and October 2017 at the Thoracic Surgery Department of West China Hospital of Sichuan University were enrolled.

The inclusion criteria were (I) patients ≥18 years old; (II) patients with no cough symptoms experienced within 2 weeks prior to surgery; (III) patients who provided written informed consent; (IV) patients who underwent surgery performed via VATS; and (V) postoperative pathological findings indicative of NSCLC.

The exclusion criteria were (I) VATS was converted to thoracotomy or bleeding was >1,000 mL; (II) a pneumonectomy was performed; (III) the patient rejected the survey or dropped out; and (IV) the patient was diagnosed with lung cancer tumor node metastasis (TNM) stage pT4, pN3, and/or M1.

Surgical procedures

The surgery performed was a single-direction thoracoscopic lobectomy or sublobar resection, which included a segmentectomy and wedge resection of the lung (16,17). A systematic mediastinal lymphadenectomy was conducted in accordance with the Chinese Guidelines for the Diagnosis and Treatment of Primary Lung Cancer (2015 Version) (18). Double 16-French chest tubes were placed in the surgical holes in the 3rd or 4th, 7th intercostal spaces for postoperative drainage (19).

The duration of anesthesia refers to the time from the beginning of endotracheal intubation to the point of extubation. All the patients were extubated at the end of the operation and transferred to the ward after a brief stay in the recovery area.

Postoperative management

The patients were encouraged to ambulation early, and a chest X-ray was arranged on the first postoperative day. The chest tube withdrawal criteria were the absence of air leakage through the chest tube, pleural fluid drainage under 200 mL in 24 hours, and postoperative chest X-ray showing no pneumothorax. The chest tubes were removed on the secondary postoperative day if the above criteria were met.

Postoperative pain management was performed with an analgesic pump (5 mg loading dose followed by 1.0–1.5 mg/h) or using non-steroidal anti-inflammatory drugs (NSAIDs) (Tallinn or Fenbid) only when necessary. The analgesia pump is also stopped when the drainage tube is removed.

Assessment measurements

The LCQ-MC, which assesses the cough-related quality of life, consists of 19 items divided into three domains: the physical (8 items), psychological (7 items) and social (4 items) domains. A 7-point Likert scale was used to score individual domains. The total scores ranged from 3 to 21, with a higher score indicative of a better health status (20,21). In a recent study, the LCQ-MC was validated in the patients with NSCLC (22).

The minimal clinically important difference (MCID) is the smallest change in the quality-of-life score considered to be clinically meaningful (23). The MCID is 1.3 for the LCQ-MC total score relating to chronic cough (24).

The postoperative diagnoses were determined using the 2015 World Health Organization (WHO) Classification of Lung Tumors and the Eighth Edition of the Lung Cancer Stage Classification guidelines from the Union

Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) (25,26). Regional lymph node classification was based on the International Association for the Study of Lung Cancer (IASLC) lymph node map (27,28).

Data collection

Our investigators assisted the in-patients in completing paper questionnaires in the ward. Postoperative follow-up was performed by telephone or out-patient review at one month after surgery. Then, we uploaded the data to a network database for management and analysis.

Statistical analysis

Patient characteristics are presented as the mean ± SD for continuous variables and as relative frequencies for categorical variables.

A univariate analysis was performed to identify the differences between the cough and no cough groups, using *t*-tests, Pearson's χ^2 tests and Yates's correction for continuity, as appropriate.

Multivariate predictors were evaluated using logistic regression analysis, and the odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. For the logistic regression analysis, the conventional receiver operating characteristic (ROC) curve was used to determine the cutoff value of each variable that gave maximal sensitivity and specificity

All comparisons were two-sided, and differences with P≤0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS software version 19.0 (Statistical Package for the Social Sciences, Chicago, IL, USA) and GraphPad Prism version 7.0 (GraphPad Software, San Diego, CA, USA).

Results

Patient characteristics and univariate analysis

Table 1 presents the characteristic of 198 patients diagnosed with NSCLC. Overall, 91 patients (46.0%) developed cough after surgery. These patients had a mean age of 58.33±9.69 years, and 53 of the patients were female (58.2%). The total scores of the LCQ-MC were 17.17±2.62, physical scores were 5.36±1.03, psychological scores were 5.57±1.14 and social scores were 6.23±0.87. Other baseline characteristics are indicated in *Table 1*.

A univariate analysis was performed to determine the potential risk factors for postoperative cough. Compared to the cough group, the no cough group demonstrated significant differences in gender (P=0.032), the duration of anesthesia (P=0.001), pulmonary resection type (P=0.003), operated side (P=0.009), upper paratracheal node resection (P=0.044), lower paratracheal node resection (P<0.001), and subcarinal node resection (P=0.017), while there were no discrepancies among the other variables (*Table 1*).

Multivariate logistic regression analyses

After the univariate logistic regression analysis, the potential risk factors were entered into a multivariable analysis. The cutoff of anesthetic duration was 164 minutes, which was determined based on the ROC curve. In the logistic regression analysis, gender (female; OR 2.399, 95% CI: 1.260–4.565, P=0.008), duration of anesthesia (≥164 minutes; OR 2.810, 95% CI: 1.368–5.771, P=0.005), lower paratracheal node resection (OR 3.697, 95% CI: 1.439–9.499, P=0.007), and subcarinal node resection (OR 4.175, 95% CI: 1.203–14.495, P=0.024) were independent factors related to postoperative cough (*Table 2*). These results indicate that apart from gender, surgery-related factors were the only factors for postoperative cough.

LCQ-MC scores after surgery and follow-up

In total, 91 patients developed cough after surgery. The follow-up after 1 month demonstrated that 73 patients (80.2%) maintained their cough, 17 patients were no longer coughing (18.7%), and 1 patient (1.1%) was lost to follow-up.

The follow-up total score after 1 month (18.00±1.80) was significantly higher than the postoperative total score (16.35±2.26; P=0.004). The mean difference between the 1-month follow-up score and the postoperative score was 1.51, which was greater than the reference MCID related to chronic cough of 1.3. Meanwhile, the follow-up scores of the psychological and social domains (6.07±0.58 and 6.58±0.60, respectively) were both significantly higher than the postoperative scores (5.25±1.05 and 6.05±0.88; P<0.001 and P=0.016, respectively). However, there were no significant differences in the physical domain of the LCQ-MC between the postoperative and follow-up time points (P=0.227; *Table 3*). These results indicate that the postoperative cough symptoms improved after one month, especially in the psychological and social domains.

Table 1 Clinical characteristics and univariate analysis in NSCLC patients after VATS

Characteristic	Category	Cough (n=91)	No cough (n=107)	P value
Age (years)		58.33±9.69	57.43±9.05	0.505
Gender	Male	38	61	0.032
	Female	53	46	
Anesthesia duration (min)		191.01±53.66	164.20±51.29	0.001
Smoking history	Yes	28	43	0.168
	No	63	64	
Pulmonary resection type	Lobectomy	40	26	0.003
	Sublobar resection	51	81	
Histology	Adenocarcinoma	81	94	0.800
	Squamous cell	10	13	
Pathological staging	I	74	90	0.603
	II and IIIa	17	17	
Operated side	Left lung	35	61	0.009
	Right lung	56	46	
Lymphadenectomy				
Upper paratracheal	Yes	47	40	0.044
	No	44	67	
Pre-vascular and retrotracheal	Yes	12	10	0.391
	No	79	97	
Lower paratracheal	Yes	67	50	<0.001
	No	24	57	
Subaortic	Yes	36	57	0.054
	No	55	50	
Para-aortic	Yes	28	36	0.666
	No	63	71	
Subcarinal	Yes	87	90	0.017
	No	4	17	
Paraesophageal	Yes	18	32	0.102
	No	73	75	
Pulmonary ligament	Yes	61	77	0.452
	No	30	30	
LCQ-MC scores	Physical	5.36±1.03		
	Psychological	5.57±1.14		
	Social	6.23±0.87		
	Total	17.17±2.62		

NSCLC, non-small cell lung cancer; VATS, video-assisted thoracoscopic surgery; LCQ-MC, Leicester Cough Questionnaire in Mandarin Chinese.

Table 2 Multivariate logistic regression analysis in NSCLC patients after VATS

Variable	β	S.E.	Wald	OR	95% CI	P value
Gender (female)	0.875	0.328	7.102	2.399	1.260–4.565	0.008
Anesthesia duration (≥164 min)	1.033	0.367	7.921	2.810	1.368–5.771	0.005
Operation (lobectomy)	0.150	0.375	0.160	1.162	0.557–2.424	0.689
Operated side (left lung)	0.744	0.557	1.783	2.105	0.706–6.274	0.182
Upper paratracheal node resection	0.985	0.621	2.514	0.373	0.110–1.262	0.113
Lower paratracheal node resection	1.307	0.481	7.375	3.697	1.439–9.499	0.007
Subcarinal node resection	1.429	0.635	5.064	4.175	1.203–14.495	0.024

NSCLC, non-small cell lung cancer; VATS, video-assisted thoracoscopic surgery; OR, odds ratios; CI, confidence interval.

Table 3 LCQ-MC scores after surgery and follow-up [patients still have cough 1 month (n=73)]

LCQ-MC	After surgery	Follow-up after 1 month	P value	Δ scores
Physical	5.05±0.92	5.35±1.12	0.227	0.48±0.38
Psychological	5.25±1.05	6.07±0.58	<0.001	0.79±0.75
Social	6.05±0.88	6.58±0.60	0.016	0.63±0.46
Total	16.35±2.26	18.00±1.80	0.004	1.51±0.80

LCQ-MC, Leicester Cough Questionnaire in Mandarin Chinese; Δ scores: mean difference between two scores.

Discussion

To our knowledge, this is the first study to determine the potential risk factors of cough in NSCLC patients after VATS. Our study appears to indicate that gender (female), the duration of anesthesia, lower paratracheal node resection and subcarinal node resection were independent factors related to postoperative cough. Furthermore, we also assessed and followed up postoperative cough via the LCQ-MC, which performed satisfactorily.

Our main objective was to identify the risk factors for the development of postoperative cough following VATS in NSCLC patients. The non-surgical factor associated with an increased risk of postoperative cough was female gender, which was identified as an independent risk factors in the multivariate analysis. A recent review indicated that there was a significant gender difference in the proportion of chronic cough patients, with a preponderance of females (29). Another study demonstrated an association between the health-related quality of life (HRQOL) and women, where the HRQOL of women with chronic cough is more adversely affected than that in men, the longer a cough lasts (30). The reasons for this phenomenon may be related to hormonal influences and high visceral sensitivity in females, along with a hypersensitivity of airway afferents to the somatosensory cortex (29,31-34).

Coughing is a physiological response to airway stimulation and is associated with increases in arterial blood pressure, venous pressure and heart rate (35,36). Therefore, coughing during the induction and recovery of general anesthesia is a common phenomenon because of the tracheal stimulation during intubation and extubation (36-38). Opioids, such as fentanyl, sufentanil, and remifentanil, are widely used in the induction and maintenance of general anesthesia (39). Opioid-induced cough has been reported in many studies (40-42). In addition, the noxious effects of an anesthetic gas or of uncleared secretions are all thought to increase the incidence of coughing (43,44). Our results demonstrated that the duration of anesthesia is another important independent risk factor for postoperative cough in NSCLC patients, which is an observation consistent with previous findings.

There is a relationship between the surgical procedures and a postoperative cough. In our study, resection of the lower paratracheal nodes and resection of the subcarinal nodes were considered the most important independent risk factors indicating the development of a postoperative cough. It is possible that cough receptors are mainly located

in the larynx, trachea, carina and the larger lung bronchi (45,46). Consistent with the anatomical location of cough receptors, we did find that there were significant differences in upper paratracheal node resection, lower paratracheal node resection, and subcarinal node resection between the cough group and the no cough group in the univariate analysis. Our data agree with previous studies; for example, Sawabata *et al.* speculated that mediastinal lymph node resection may contribute to a postoperative cough (3,10).

We administered the LCQ-MC to describe the longitudinal changes in cough symptoms. It is a useful tool that is used in clinical trials and longitudinal studies of chronic cough (11,20,21). However, there were no reports about assessing cough with the LCQ-MC in NSCLC patients after VATS. Our study suggested that the LCQ-MC was well employed to assess cough after surgery and at the one-month follow-up in NSCLC patients after VATS. The LCQ-MC can provide important additional information concerning the impact of postoperative cough (22).

Our study has several limitations that should be considered. First, our study was limited by the number of patients and parameters, and there were a few published studies that could be consulted. Second, lack of preoperative cough symptom assessment, we assessed patient whether cough before surgery by asking case history. Third, our research did not examine a long follow-up period in postoperative cough patients. Additional anesthesia-related parameters, such as anesthetic drug and dose, should be included for further research.

In conclusion, female sex, the duration of anesthesia over 164 minutes, lower paratracheal node resection and subcarinal node resection were independent risk factors related to cough in NSCLC patients after VATS. In addition, the LCQ-MC performed satisfactorily in describing the longitudinal changes in cough symptoms. The mechanisms and characteristics of cough after pulmonary resection require further clarification.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The West China Hospital of Sichuan University in Sichuan, China, approved the study. All the participants provided written informed consent.

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