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RESEARCH

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Preoperative fractional exhaled nitric oxide is a risk and predictive factor of postoperative cough for early-stage non-small cell lung cancer patients: a longitudinal study

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Abstract

Background To determine whether preoperative fractional exhaled nitric oxide (FENO) level is a risk and predictive factor of postoperative cough by using the Leicester Cough Questionnaire in Mandarin-Chinese (LCQ-MC).

Methods 292 early-stage non-small cell lung cancer (NSCLC) patients without preoperative cough were enrolled. 138 patients (47.2%) developed postoperative cough, univariate and multivariate logistic regression analysis were performed to identify the independent risk factors of postoperative cough. For an exploratory analysis, patients with cough were divided into low and high- FENO [≥ 31 parts per billion (ppb)] groups. The LCQ-CM was used to evaluate changes and recovery trajectory of postoperative cough over time between the two groups for 12 months after surgery.

Results The independent factors of postoperative cough included preoperative FENO level [odds ratio (OR) 1.106, 95% confidence interval (CI): 1.076–1.137, $p < 0.001$] and duration of anesthesia (OR 1.008, 95% CI: 1.002–1.013, $p = 0.004$). The low-FENO group reported significantly higher LCQ-MC scores at 1 month after surgery and returned to preoperative physical (28 vs. 91 days), psychological (28 vs. 60 days), social (28 vs. 80 days) and total (28 vs. 91 days) scores faster than the high-FENO group (all $p < 0.05$).

Conclusion Higher preoperative FENO level and longer duration of anesthesia were independent risk factors related to postoperative cough. Additionally, patients with high preoperative FENO level had worse cough-related quality of life and slower recovery from postoperative cough.

Trial Registration This study was approved by the Chinese Clinical Trial Registry (Clinicaltrials.gov number: ChiCTR1900023419) on 26 May 2019 and the first patient was enrolled after pre-registration.

Keywords Lung cancer, Fractional exhaled nitric oxide, Postoperative cough, Leicester cough questionnaire

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Background

Lung cancer is the most common cancer and the leading cause of cancer death in China [1].In general, surgery remains the best option for patients with early-stage non-small cell lung cancer (NSCLC) [2]. Video-assisted thoracic surgery (VATS) has been become the preferred surgical procedure over open thoracotomy for early-stage NSCLC [3]. The postoperative symptom burden of patients is high, particularly in the early postoperative phase, including cough, dyspnea and pain [4].

Regarding postoperative symptoms, cough is a most common symptom, affecting physical, psychological, and social aspects of daily life; contributing to fatigue and insomnia; increases anxiety in patients; and leading to social isolation [5]. Several recent studies have revealed that postoperative cough occurs in 30.0–46.0% of NSCLC patients after VATS, and gender, duration of anesthesia, mediastinal lymph node dissection (related to surgical side), injury of vagus nerve lung branch or bronchial artery were independent risk factors [6–9].However, morbidity and distress levels due to postoperative cough have been underestimated, especially after discharge, representing an unmet clinical need [10].

The discovery of nitric oxide (NO) as an important signalling molecule in human tissues has led many researchers to investigate its role in both systemic and organ-specific physiological and pathological processes, and the measurement of fractional exhaled NO (FENO) was published in 1991 [11, 12]. An accumulating body of published data has illustrated that high FENO level can diagnose or predict acute and chronic cough [13, 14]. The FENO measure, however, is not performed routinely before thoracic surgery. It is unclear which preoperative FENO level would stratify patients for the risk of developing postoperative cough or provides the best prognostication of cough-related quality of life (QOL) and the course of recovery.

Thus, we performed a longitudinal study and followed up early-stage NSCLC patients after VATS with routinely measured FENO to assess its potential significance in predicting the risk of postoperative cough and its changes and recovery trajectory. In additional, we chose the Leicester Cough Questionnaire in Mandarin-Chinese (LCQ-MC) as the instrument for the investigation and follow-up [15]. This longitudinal study was performed in accordance with the STROCSS Reporting Checklist [16].

Methods

Subjects

292 consecutive patients who underwent VATS performed by a single medical team between May 2019 and September 2021 at the Department of Thoracic Surgery, Fujian Provincial Hospital were enrolled. Due to the exploratory nature of the study, we have chosen to analyze data from patients with early-stage NSCLC in the above registry study. There will be some differences in exclusion criteria and sample size.

Patients were included according to the following criteria: (1) aged 18 years or older, (2) no cough symptoms within the 2 weeks prior to surgery, (3) provided a signed informed consent form, (4) underwent VATS, and (5) had postoperative pathological findings indicative of NSCLC and TNM stage I. Patients were excluded according to the following criteria: (1) underwent bilateral pulmonary surgery, (2) underwent conversion to open thoracotomy or experienced bleeding exceeding 1,000 mL, (3) were transferred to the intensive care unit after surgery, or (4) refused to answer the survey or dropped out.

Surgical procedures

Single utility port VATS was performed, and sublobectomy achieved parenchymal resection margins ≥ 2 cm or ≥ the size of the node and sampled the appropriate N1 and N2 lymph node stations. Mediastinal lymphadenectomy included stations 2R, 4R, and 7–9 for right-sided cancer and 4 L and 5–9 for left-sided cancer [17, 18]. Lymph node dissection included the N1 and N2 nodes with a minimum of 3 N2 stations sampled or complete dissection [19]. Patients with adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA) do not need mediastinal lymph node dissection or sampling [20, 21].

For wedge resection, a 22Fr chest tube or 12 Fr pigtail catheter was placed in the observation port for postoperative drainage (7th or 8th intercostal space). For lobectomy or segmental resection, an additional 12 Fr pigtail catheter was placed in the 8th or 9th intercostal posterior axillary line.

Measurement of preoperative FENO

Nitric oxide is a gas that can be measured in the exhaled breath. Measuring the fraction of this gas during a steady-state exhalation, called the FENO, is a standardized and quantitative method for assessing the level of this gas in exhaled breath. FENO (reported as parts per billion, ppb) was measured using a nitric oxide analyzer (Sunvou-CA2122, Sunvou, China), in accordance with the standard procedure recommended by the American Thoracic Society/European Respiratory Society (ATS/ERS) [22]. During the test, subjects breathed quietly for at least 3 cycles, and exhaled fully at the last expiration. With the mouthpiece fitted to avoid leakage, the subjects inhaled nitric oxide-free air maximally via their mouths to total lung capacity and subsequently exhaled at a constant flow rate (50 mL/s) for 10 s.

Assessment measurements and endpoint

The LCQ, which assesses the impact of cough-related QOL, consists of 19 items divided into three domains: physical (8 items), psychological (7 items), and social (4 items). A 7-point Likert scale was used to score the individual domains. The total scores ranged from 3 to 21, with a higher score indicating better cough-related QOL [23]. The LCQ has been translated into a Mandarin version, the LCQ-MC [15]. Our previous study showed that the LCQ-MC is a reliable, valid instrument for assessing postoperative.

cough in NSCLC patients [24]. Patients completed the LCQ-MC before discharge and at multiple timepoints after surgery.

We administered the LCQ-MC to eligible patients before discharge and 1 month after surgery, and we continued follow-up until cough symptom disappeared every 3 months (Fig. 1). The follow-up endpoint was defined as the disappearance of cough symptoms. We defined "recovery from postoperative cough" when the patients reported three domain score or a total LCQ-MC score that had returned to the preoperative (baseline) level, as we did in our previous study [25].

Postoperative diagnoses were determined using the 2015 World Health Organization Classification of Lung Tumors and the eighth edition of the Union for International Cancer Control /American Joint Committee on Cancer lung cancer staging classification guidelines [26, 27]. Regional lymph node classification was based on the International Association for the Study of Lung Cancer lymph node map [28].

Data collection

Our investigators assisted patients with postoperative cough to complete paper questionnaire before discharge. Postoperative follow-up was performed by telephone or out-patient review. Then, we uploaded the baseline and follow-up data to a network database for management and analysis (jinshuju, a data collection and management platform developed by MININGLAMP TECHNOLOGY, Beijing, P.R.China, https://jinshuju.net/).

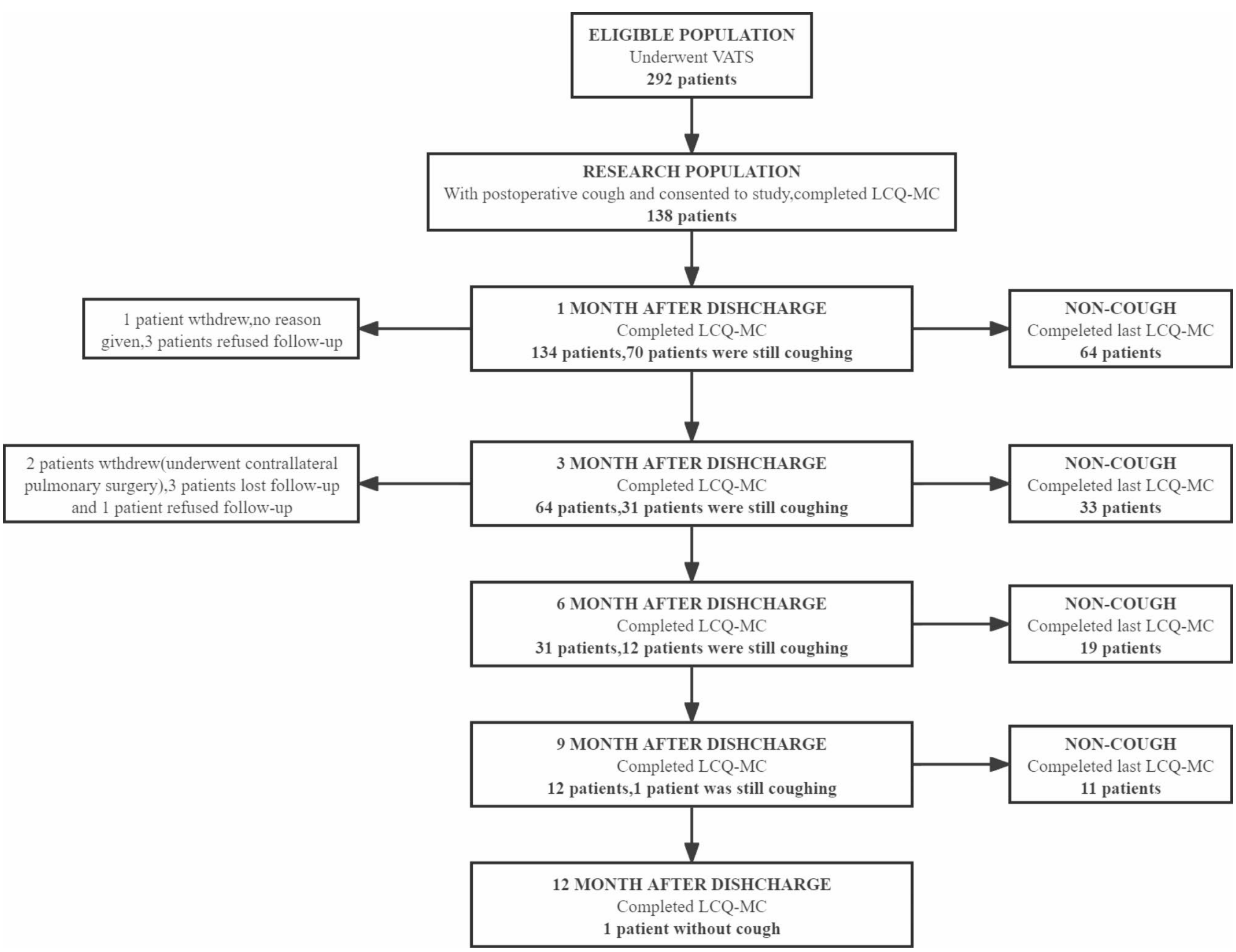

Fig. 1 Flowchart of the study; LCQ-MC, leicester cough questionnaire in mandarin-chinese

Statistical analysis

Comparisons among groups the cough and non-cough groups were performed using the *t* test or Wilcoxon rank sum test (Mann-Whitney U tests) for continuous variables and the Chi-squared for categorical variables. The optimal cut-off points of preoperative FENO and duration of anesthesia were obtained by receiver operating characteristic (ROC) curve.

To identify independent risk and predictive factors of postoperative cough, multivariate logistic regression analyses were performed. Variables with $p<0.10$ in the univariate analysis were entered into the multivariate analysis and only variables with $p<0.05$ were included in a final model using forward and backward stepwise selection methods. For exploratory analysis of changes in LCQ-MC scores and recovery trajectory of postoperative cough, patients were divided into 2 groups (high-FENO and low-FENO groups) based on cut-off points.

The censoring was performed at 1 month and then every 3 months until 12 months after surgery, and the time to event was the time from hospital discharge to cough symptom disappear. The recovery time from postoperative cough between high-FENO and low-FENO groups was compared using Kaplan-Meier curves and log-rank tests.

All comparisons were 2-sided, and differences with $p<0.05$ were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 22.0 (Statistical Package for the Social Sciences, Chicago, IL, USA) and GraphPad Prism, version 9.0 (GraphPad Software, San Diego, CA, USA).

Results

Patient characteristics

There were 292 patients consented to participate in the study, and 138 (47.26%) reported postoperative cough. From these,138 completed study entry data, and 128 patients completed all assessments until postoperative cough symptom disappear (attrition rate 7.25%, 10/138 patients) (shown in Fig. 1). The clinical characteristics of the study population are shown in Table 1.

Table 1 Clinical characteristics and demographic

Variable	Cough(*n* = 138)	Non-cough (*n* = 154)	t/χ2/Z value	*P* value
Age, *n* (%)				
≥ 60 years	85(61.5)	77(50.0)	3.961[a]	0.047
< 60 years	53(38.5)	77(50.0)		
Gender, *n* (%)				
Male	49(35.5)	52(33.8)	0.098[a]	0.755
Female	89(64.5)	102(66.2)		
Preoperative lung function				
FEV1(L)	2.22 ± 0.45	2.24 ± 0.46	-0.160[b]	0.873
FVC(L)	2.79 ± 0.53	2.82 ± 0.49	-0.390[b]	0.697
FENO (ppb)	34(19,40)	18(13,24)	-8.075[c]	< 0.001
Past medical history, *n* (%)				
Hypertension	41(29.7)	43(27.9)	0.114[a]	0.736
Coronary heart disease	6(4.3)	6(3.9)	0.038[a]	0.846
Diabetes mellitus	27(19.6)	19(12.3)	2.705[a]	0.100
COPD	20(14.5)	16(10.4)	1.134[a]	0.287
Smoking history	25(18.1)	24(15.6)	0.334[a]	0.563
Duration of anesthesia (min)	195(160,230)	170(140,200)	-4.253[c]	< 0.001
Surgical side, *n* (%)				
Right	81(58.7)	88(57.1)	0.072[a]	0.788
Left	57(41.3)	66(42.9)		
Extent of surgery, *n* (%)				
Lobectomy	72(52.2)	75(48.7)	0.351[a]	0.554
Sublobectomy	66(47.8)	79(51.3)		
Pathology, *n* (%)				
Adenocarcinoma	133(96.4)	148(96.1)	0.015[a]	0.903
Squamous carcinoma	5(3.6)	6(3.9)	0.015[a]	0.903
AIS or MIA	59(42.8)	85(55.2)	4.507[a]	0.036

[a] Data are presented as No. (%) and *χ2* test. [b] Data are presented as mean ± SD and *t* test .[c] Data are presented as median (IQR) and Mann-Whitney U test

FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FENO, fractional exhaled nitric oxide; COPD, chronic obstructive pulmonary disease; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; SD, standard deviation; IQR, interquartile range

Clinical factors associated with postoperative cough

The analysis was conducted for patients at study entry, and clinical factors associated with postoperative cough were determined by univariate and multivariate analysis. The results of the univariate analysis are shown in Table 1. 61.5% of patients in the cough group were over 60 years old, compared with 50% in the non-cough group ($p=0.047$).

The clinical factors found to be statistically significantly associated with a higher incidence of postoperative cough were preoperative FENO level [34 ppb, interquartile range (IQR), 19–40 in cough group vs. 18 ppb in non-cough group, IQR,13–24; $p<0.001$], duration of anesthesia (195 min, IQR,160–230 in cough group vs. 170 min in non-cough group, IQR,140–200; $p<0.001$) and pathology of AIS or MIA (42.8% in cough group vs. 55.2%; $p=0.036$). Notably, surgical characteristics (i.e. operative type, surgical side) were not associated with postoperative cough; neither were smoking or chronic obstructive pulmonary disease (COPD).

The multivariate logistic regression analysis included all parameters with $p\leq0.01$ in the univariate analysis (age, preoperative FENO, diabetes mellitus, duration of anesthesia and pathology of AIS or MIA), and the results are showed in Table 2. The analysis identified that higher preoperative FENO level (odds ratio [OR]:1.106; 95% confidence interval [CI]: 1.076–1.137) and longer duration of anesthesia (OR: 1.008; 95% CI: 1.002–1.013) were independent risk factors related to postoperative cough.

ROC curve for predicting postoperative cough according to preoperative FENO level and duration of anesthesia

To predict postoperative cough in early-stage NSCLC patients, the optimal cut-off point for preoperative FENO level was 31 ppb with a sensitivity of 63.0% and specificity of 90.9%, and the positive predictive value (PPV) and negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were 87.0% and 73.4%, 6.9 and 0.4, respectively. The sensitivity and specificity of duration of anesthesia for predicting postoperative cough were 73.9% and 48.7% at a cut-off point of 168 min, with the PPV, NPV, PLR and NLR were 56.4% and 67.6%, 1.4 and 0.5 respectively. The ROC curve and area under the ROC curve (AUC) are shown in Fig. 2.

Changes in LCQ-MC scores over time and recovery time from postoperative cough

We examined the cut-off point for preoperative FENO level (≥31 ppb) as the predictor of cough-related QOL and recovery of postoperative cough in early-stage NSCLC patients. Therefore, we stratified patients with postoperative cough into two groups according to the cut-off point. An exploratory analysis of changes in LCQ-MC scores and recovery trajectory over time of the 138 patients who developed postoperative cough was performed to compare those with preoperative FENO level above and below the cut-off points (31 ppb) (high-FENO and low-FENO groups).

Table 3 shows that the individual domain score and total LCQ-MC scores decreased rapidly after surgery and then returned to preoperative level over time. The high-FENO group reported significantly lower physical, psychological, and total LCQ-MC scores than the low-FENO group at 1 month after surgery (all $p<0.05$). There was no significant difference in LCQ-MC scores between the two groups at other timepoints after surgery. The dynamic changes and detailed scores are shown in Fig. 3; Table 3.

Table 4 shows that the physical, social, and total LCQ-MC scores returned to preoperative level for all patients at approximately 2 months. The psychological score of the LCQ-MC took only 1 month to recover. Figure 4 shows the profiles of and significant differences in the physical, psychological, social, and total aspects of recovery from postoperative cough between two groups by Kaplan-Meier analysis, confirming the sensitivity of the LCQ-MC to indicate recovery after surgery. Compared to patients with low-FENO group, high-FENO group required significantly more time to return to baseline levels of the physical aspect (91 vs. 28 days, $p=0.007$), psychological aspect (60 vs. 28 days, $p=0.014$), social aspect (80 vs. 28 days, $p=0.002$) and total aspect (91 vs. 28 days, $p=0.007$) of postoperative cough (Table 4).

Discussion

To our knowledge, this was the first study to explore the clinical significance of preoperative FENO level and postoperative cough in patients with early-stage NSCLC. Higher preoperative FENO level and longer

Table 2 Multivariate logistic regression analysis of postoperative cough

	b	SE	Wald	OR	95%CI	*P*
Age ≥ 60 years	0.391	0.296	1.747	1.478	0.828–2.638	0.189
With diabetes mellitus	0.281	0.395	0.506	1.324	0.611–2.869	0.477
Preoperative FENO (ppb)	0.100	0.014	50.912	1.106	1.076–1.137	< 0.001
Duration of anesthesia (min)	0.008	0.003	7.920	1.008	1.002–1.013	0.004
AIS or MIA	-0.158	0.284	0.311	0.854	0.489–1.489	0.577
Constant	-4.200	0.681	38.019	0.015		< 0.001

FENO, fractional exhaled nitric oxide; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; OR, odds ratio; CI, confidence interval

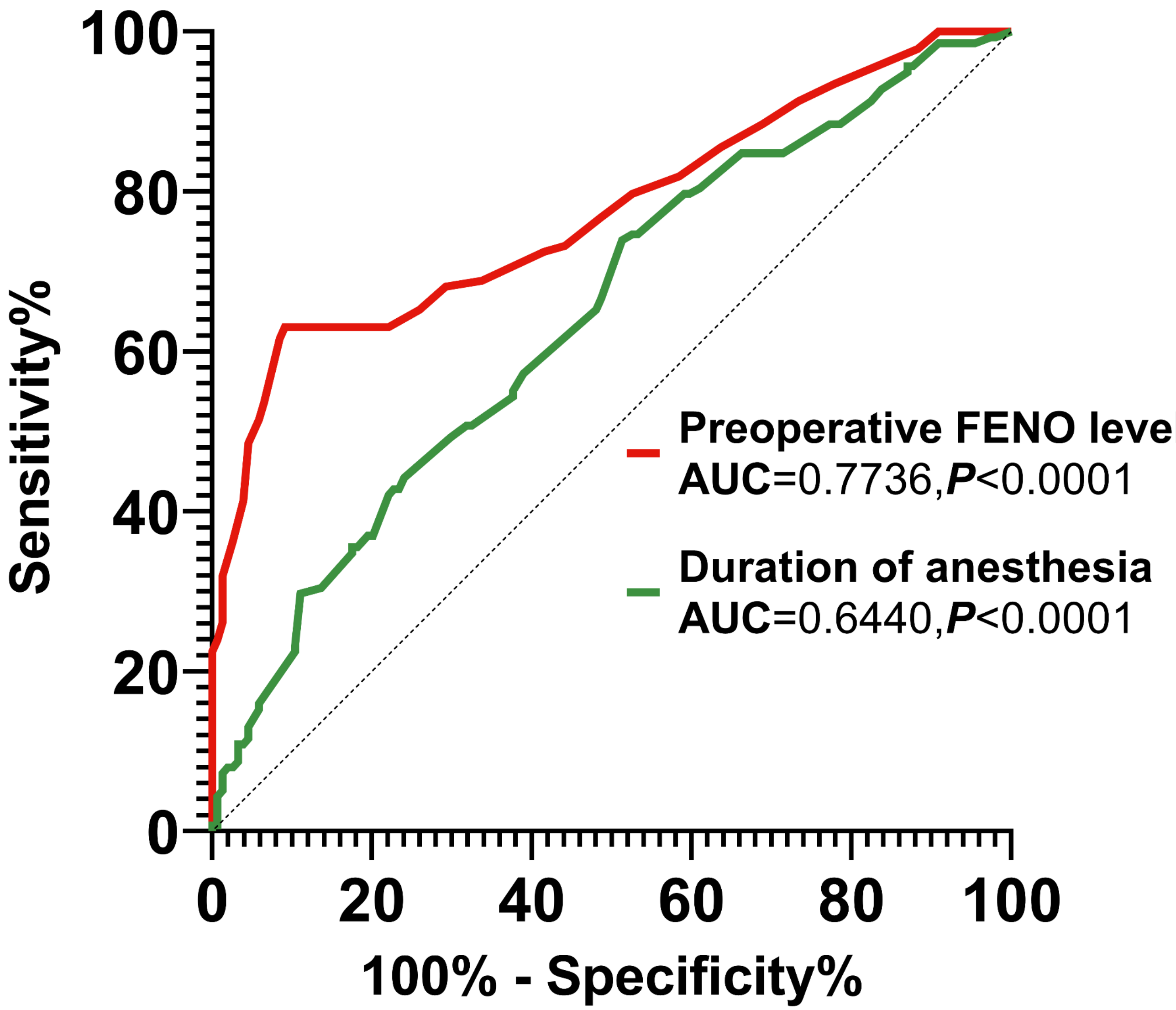

Fig. 2 ROC curve for preoperative FENO level and duration of anesthesia. Data labels show the selected cut-off points of preoperative FENO level and duration of anesthesia. The ideal cut-off point of FENO is 31 ppb and duration of anesthesia 168 min. FENO, fractional exhaled nitric oxide; AUC, area under the ROC curve

duration of anesthesia were significantly associated with high incidence of postoperative cough. And we describe the changes and recovery trajectory in postoperative cough by the LCQ-CM. Furthermore, we performed an exploratory analysis and found that preoperative FENO level is a predictive factor of cough-related QOL and its recovery.

In this study, we found that longer duration of anesthesia was a significant risk factor of postoperative cough, in agreement with many previous studies [7, 9]. It is important to consider factors during anesthesia that may explain this result, such as. exaggerated laryngeal reflexes, awake extubation, the presence of a tracheal tube during emergence from anesthesia and the use of propofol during awake tracheal intubation [29, 30]. Intravenous bolus injections of opioids (e.g., fentanyl, sufentanil, remifentanil and alfentanil), are widely used in the induction and maintenance of anesthesia, have been reported to cause the development of postoperative cough [31, 32].

However, there was no difference in the surgical side (related to mediastinal lymph node dissection) in univariate analysis and pathology of AIS or MIA (do not need mediastinal lymph node dissection or sampling) in multivariate logistic regression analysis between cough and no-cough groups, an observation inconsistent with previous findings, and an alternative explanation is necessary [33–35]. It is possible that some deeply located mediastinal lymph nodes, such as subcarinal nodes, upper paratracheal nodes and lower paratracheal nodes, can also be challenging to sample [36, 37]. As a result, the stimulation and stretching of bronchi or nerve, and operative

Table 3 The LCQ-MC scores after surgery and follow-up

LCQ-MC	High-FENO	Low-FENO	Z value	*P* value
Postoperative scores	≥ 31 ppb(*n* = 87)	< 31 ppb(*n* = 51)		
Physical	5.00(4.71–5.50)	5.29(4.50–5.71)	-1.058	0.290
Psychological	4.71(4.00-5.60)	5.14(4.40–5.40)	-1.524	0.128
Social	5.33(4.67-6.00)	5.33(4.76-6.00)	-0.614	0.540
Total	15.08(13.47–17.50)	15.08(14.27–17.07)	-1.204	0.229
Scores at 1 month	≥ 31 ppb(*n* = 84)	< 31 ppb(*n* = 50)		
Physical	6.14(5.43-7.00)	7.00(5.96-7.00)	-2.118	0.034
Psychological	5.90(4.40-7.00)	7.00(5.60-7.00)	-2.261	0.024
Social	6.33(5.42-7.00)	7.00(6.00–7.00)	-1.890	0.059
Total	18.25(15.78-21.00)	21.00(17.46-21.00)	-2.159	0.031
Scores at 3 months	≥ 31 ppb(*n* = 44)	< 31 ppb(*n* = 20)		
Physical	6.64(5.57-7.00)	7.00(6.00–7.00)	-1.201	0.230
Psychological	6.70(4.80-7.00)	7.00(5.90-7.00)	-1.226	0.220
Social	7.00(5.75-7.00)	7.00(6.50-7.00)	-1.557	0.119
Total	19.73(16.32-21.00)	21.00(18.77-21.00)	-1.263	0.207
Scores at 6 months	≥ 31 ppb(*n* = 23)	< 31 ppb(*n* = 8)		
Physical	7.00(6.57-7.00)	6.64(6.46-7.00)	-1.288	0.275*
Psychological	7.00(6.80-7.00)	6.50(5.85-7.00)	-1.596	0.172*
Social	7.00(6.80-7.00)	6.83(6.42-7.00)	-1.704	0.203*
Total	21.00(20.09-21.00)	19.83(18.87-21.00)	-1.672	0.145*
Scores at 9 months	≥ 31 ppb(*n* = 7)	< 31 ppb(*n* = 5)		
Physical	7.00(7.00–7.00)	7.00(7.00–7.00)	-0.845	0.755*
Psychological	7.00(7.00–7.00)	7.00(7.00–7.00)	-0.845	0.755*
Social	7.00(7.00–7.00)	7.00(7.00–7.00)	-0.845	0.755*
Total	21.00(21.00–21.00)	21.00(21.00–21.00)	-0.845	0.755*
Scores at 12 months	≥ 31 ppb(*n* = 1)	< 31 ppb(*n* = 0)		
Physical	NA	NA	NA	NA
Psychological	NA	NA	NA	NA
Social	NA	NA	NA	NA
Total	NA	NA	NA	NA

Data are presented as median (IQR) and Mann-Whitney U test

*, *P* value is using exact value

LCQ-MC, Leicester Cough Questionnaire in Mandarin-Chinese ; IQR, interquartile range

time for sampling difficult mediastinal lymph nodes is consistent with that of lymph node dissection.

Another important finding is that NSCLC patients with postoperative cough have higher preoperative FENO level than those without postoperative cough (34 ppb, IQR,19–40 vs. 18 ppb, IQR,13–24). And the ROC curve for preoperative FENO level indicated acceptable predictive ability (FENO cut off 31ppb, AUC = 0.7736 > 0.7, $p < 0.0001$) in postoperative cough (Fig. 2) [38].Thus we undertook an exploratory analysis of the optimal cut off (≥31 ppb, based on the ROC curve) of preoperative FENO level for predicting postoperative cough-related QOL and recovery trajectory by LCQ-MC. The LCQ-MC enables real-time reporting of the postoperative cough-related QOL in different domains to surgeon or patients. Postoperative cough peaked immediately after surgery, representing a combined effect from surgical trauma and other perioperative factors. The patients in low-FENO group reported significantly higher physical, psychological, and total LCQ-MC scores at 1 month after surgery than those in the high-FENO group, with no significant difference in LCQ-MC scores at other timepoints after surgery between two groups. Notwithstanding the preoperative FENO level in patients with cough do not correlate well with LCQ-MC scores, our finding suggests that postoperative cough returned to preoperative level after approximately 1 month (median time for the physical, psychological and social score are all 28 days) in low-FENO group. In the high-FENO group, the postoperative cough had a somewhat different pattern of recovery in this study and recovered more slowly (median time for the physical score: 91 days, psychological score: 60 days, and social score: 80 days) (Fig. 4; Table 4).

While much of the literature on FENO in the field of asthma has been thoroughly investigated [12, 39]. In contrast, the impact of FENO on postoperative pulmonary complications (PPCs) (including postoperative cough) after lung resection surgery, has received very little

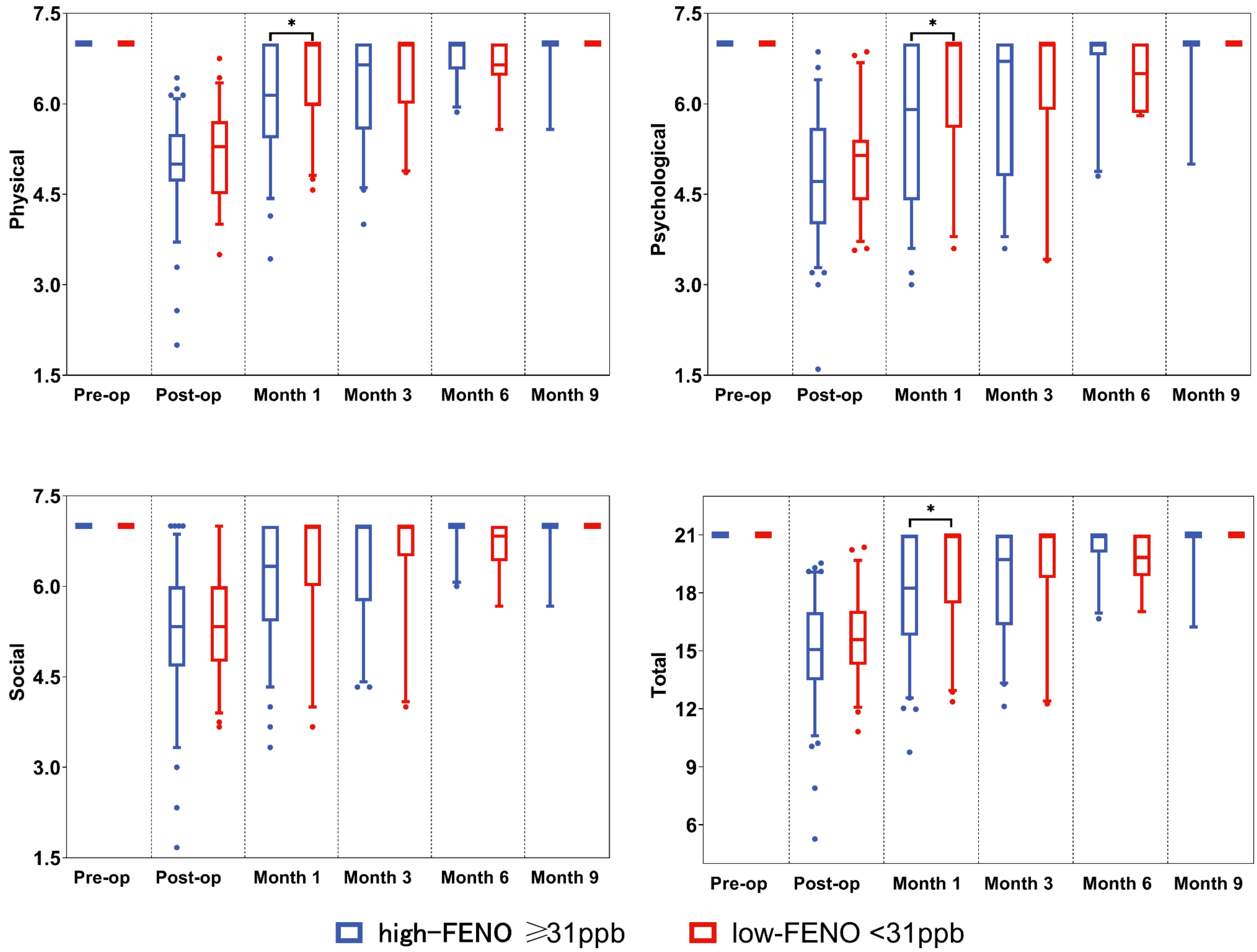

Fig. 3 Change in LCQ-MC scores during the 12 months after surgery, by surgery type. *, $p < 0.05$. FENO, fractional exhaled nitric oxide; LCQ-MC, Leicester Cough Questionnaire in Mandarin-Chinese

Table 4 Kaplan–Meier estimated postoperative cough recovery time (days from surgery)

	Median days to recovery (95% confidence interval) [a]			
LCQ-MC	**Overall**	**FENO ≥ 31 ppb**	**FENO < 31 ppb**	***P* value**
Physical	54(32–76)	91(56–126)	28(26–30)	0.007
Psychological	32(21–43)	60(5-115)	28(26–30)	0.014
Social	47(35–59)	80(43–117)	28(26–30)	0.002
Total	54(32–76)	91(56–126)	28(26–30)	0.007

Data are presented as median(95%CI)

[a]Recovery of postoperative cough was defined as the patient having reported LCQ-MC individual domain or total score at the preoperative (baseline) level

FENO, fractional exhaled nitric oxide; CI, confidence interval; LCQ-MC, Leicester Cough Questionnaire in Mandarin-Chinese

attention [40, 41]. Previous studies did not demonstrate a difference in the incidence of postoperative pneumonia or major complications and preoperative FENO in NSCLC patients after lung resection surgery [40, 41]. Another study analyzed the outcomes of lung resection surgery in patients with primary lung cancer reported fewer PPCs with low preoperative FENO level than with high preoperative FENO level [40]. Our results are consistent with the latter finding, which seems reasonable, because high preoperative FENO level suggests high airway inflammation and airway hyperresponsiveness (AHR). Similar to the exacerbations often experienced by patients with asthma, high airway inflammation can cause postoperative peripheral airway obstruction, prolonged and worsen the postoperative cough [42, 43].

AHR, which is defined as excessive bronchoconstriction of airway smooth muscle in response to nonspecific stimuli, might be another major factor [44]. A recent study found that AHR is one of the potential mechanisms of postoperative cough after right upper lobectomy and ATS guidelines suggest FENO as an alternative indicator of AHR [39, 45].

This is the first longitudinal study focusing on the postoperative cough-related QOL changes and recovery trajectory by preoperative FENO level. Our work

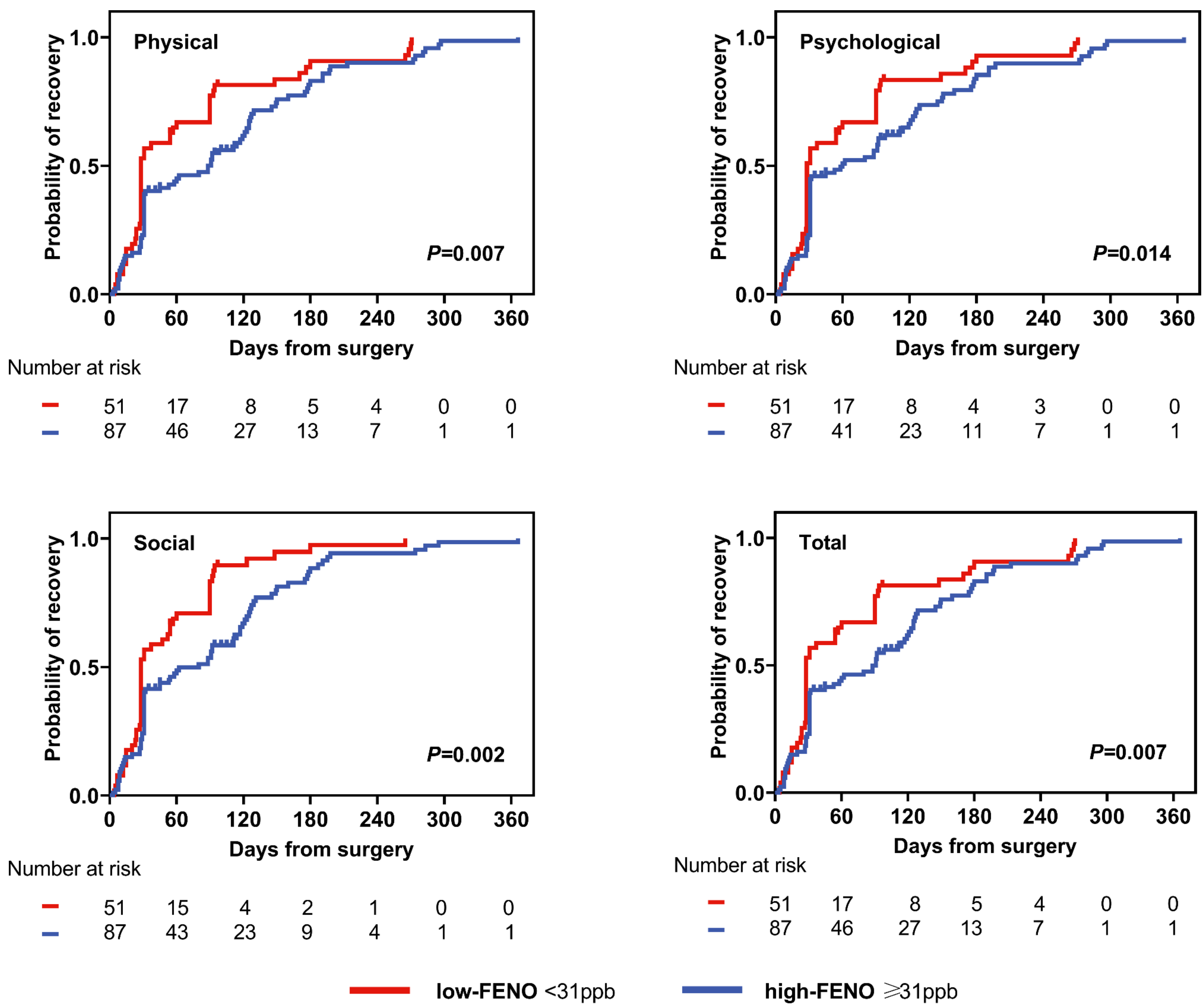

Fig. 4 The recovery trajectories of postoperative cough by surgery type. *P* value by log-rank test. VATS, video-assisted thoracic surgery

has focused more on preoperative FENO level than on postoperative FENO level. Previous retrospective studies found that FENO peaked on postoperative day 1–3 after lung resection surgery [40, 41]. In another study found a tendency for a reduction in FENO and reached significance at 48 h lung resection surgery [46].

In future studies, the investigation and identification of invasive or non-invasive biomarkers is important as it will facilitate the identification of high-risk patients for preoperative, intraoperative and postoperative interventions to reduce the risk of respiratory complications (including postoperative cough) and other major complications. Previous studies have identified some potential biomarkers of lung injury during one-lung ventilation (OLV) in bronchoalveolar lavage fluid (BALF) or blood, including tumor necrosis factor-α (TNF-α) (increased during OLV in BALF and blood analyses), interleukin 6(IL-6) (increased during OLV in BALF and blood analyses) and interleukin 8(IL-8) (increased during OLV in BALF only) [46, 47]. It is not easy to clarify whether preoperative FENO level is a risk or predictive factor for postoperative cough. FENO level was also associated with many surgical, anesthesia-related factors or other confounding factors (lung injury or contusion cause by surgical procedure, lung resection, OLV, postoperative respiratory failure, etc.) [46, 48, 49]. Despite its exploratory nature, our findings suggest that the diagnostic and predictive value of preoperative FENO level could be a potential non-invasive adjunct in postoperative cough. Preoperative FENO is a simple method that can be used to guide effective management of postoperative cough, including perioperative pulmonary rehabilitation and significantly more postoperative expectorants and antitussives [34, 50, 51].

Limitations

This study had several limitations. First, the sequential study sample of a hospital-based registry with inherent selection bias and unmeasured confounding. There is a lack of consistency in the management of the single center design, and the daily workload of our doctors and nurses may affect the enrolment of some eligible patients. Some airway diseases, such as atopy, asthma, and allergic rhinitis may be seasonal and the characteristics of patients attending hospitals in different seasons may influence FENO level [12, 52]. Further investigations with more generalizability required to exploratory subgroup analysis and high-quality multicenter study. Second, the sample size of the exploratory analysis of preoperative FENO level was imbalanced in two groups (high-FENO and low-FENO groups, 87 vs. 51) and insufficient, which may have underpowered significant results. Future studies with a more diverse sample are warranted to identify potential risk and predictive factors by multivariate analysis and ROC curve and define the trajectory of postoperative cough recovery. Third, we only evaluated preoperative FENO once and did not collect postoperative FENO or follow-up, a further study with more focus on the change of perioperative and a long follow-up is therefore suggested. The timing of preoperative FENO measurement was inconsistent, and result could not exclude effects of diurnal variation [53].The differences and impact of FENO in postoperative complications (including postoperative cough) that were observed clinically may have been even more striking if these data had been included in the analysis. Last but not least, univariate and multivariate analyses only enrolled duration of anesthesia, additional anesthesia-related parameters, such as depth of intubation, choice of double-lumen bronchial tube or bronchial occlusive device, dose and type of induction and maintenance drugs, should be included for further research [29, 54, 55]. It is also worth noting that non-endotracheal intubation anesthesia has become more widely used in thoracic surgery, which has several advantages, including easy performance, short time, fewer complications, fast recovery [56, 57]. There is plenty of room for further progress in non-endotracheal anesthesia and postoperative complication. In addition, the COVID-19 (coronavirus disease 2019) pandemic (which started in December 2019) occurred during our study period (May 2019 to September 2021), which was completely unforeseen in the study design/clinical trial registry. Many studies have shown that COVID-19 or long COVID can cause acute or persistent cough, and that patients infected with COVID-19 after discharge may have worsening cough symptoms or prolonged cough recovery [58–60].

Conclusions

In the present study, we aimed to investigate the clinical significance of preoperative FENO level as potential biomarker in early-stage NSCLC patients with postoperative cough. We have demonstrated that higher preoperative FENO level and longer duration of anesthesia may be independent risk factors for postoperative cough. In addition, an exploratory analysis described the nature of and changes in postoperative cough between different preoperative FENO levels, patients with higher preoperative FENO level had generally worse cough-related quality of life and slower recovery from postoperative cough. To date, the preoperative FENO level was first described in our study and few other research mentioned associations between preoperative FENO level and postoperative cough. Future prospective study with adequately controlled is required to clarify our exploratory findings.

Abbreviations

NSCLC	Non-small cell lung cancer
VATS	Video-assisted thoracic surgery
COPD	Chronic obstructive pulmonary disease
FENO	Fractional exhaled nitric oxide
QOL	Quality of life
LCQ-MC	Leicester Cough Questionnaire in Mandarin-Chinese
AIS	Adenocarcinoma in situ
MIA	Minimally invasive adenocarcinoma
ATS	American Thoracic Society
ERS	European Respiratory Society
VAS	Visual Analogue Scale
CSS	Cough Symptom Score
HADS	Hospital Anxiety and Depression Scale
SF-36	36-item Short-Form Health Survey
IQR	Interquartile range
ROC	Receiver operating characteristic
OR	Odds ratio
CI	Confidence interval
PPV	The positive predictive value
NPV	Negative predictive value
PLR	Positive likelihood ratio
NLR	Negative likelihood ratio
AUC	Area under the ROC curve
PPCs	Postoperative pulmonary complications
AHR	Airway hyperresponsiveness
OLV	One-lung ventilation
BALF	Bronchoalveolar lavage fluid
TNF-α	Tumor necrosis factor-α
IL-6 and IL-8	Interleukin 6 and 8
COVID-19	Coronavirus disease 2019

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

RJL, XHT were involved in the research conception. Study was conceptualized by all 3 authors. RJL and XHT was the principal investigator and responsible for the data collection, entry and analysis with RJL, GMY and XHT for manuscript preparation. GMY revised manuscript and all authors read and approved the final manuscript.

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Data availability
This is part of a larger study. The dataset generated and analyzed during the current study is not publicly available but may be obtained from the corresponding author if accompanied by a reasonable request.

Declarations

Ethics approval and consent to participants
This is part of a larger study which was approved by China Ethics Committee of Registering Clinical Trials (approval no. from the ethics committee: ChiECRCT20190084) and was approved by the Chinese Clinical Trial Registry (Clinicaltrials.gov number: ChiCTR1900023419). Due to the exploratory nature of the study, we have chosen to analyze data from patients with early-stage NSCLC in the above registry study. There will be some differences in exclusion criteria and sample size. The decision to respond to the questionnaire was considered as an informed consent. All methods were performed in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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