Original Article

Fat-free mass index is superior to body mass index as a novel risk factor for prolonged air leak complicating video-assisted thoracoscopic surgery lobectomy for non-small-cell lung cancer

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Background: To evaluate whether fat-free mass index (FFMI) could be predictive of prolonged air leak (PAL) complicating video-assisted thoracoscopic (VATS) lobectomy for non-small-cell lung cancer (NSCLC).

Methods: A retrospective study was conducted on the prospectively-maintained database in our institution between January 2015 and July 2017. The gender-specific median values of FFMI for males and females were applied as their respective cutoffs to stratify patients into low-FFMI group and high-FFMI group in initial univariable analyses. An effective multivariable logistic-regression analysis was then performed to demonstrate the predictive value of dichotomized FFMI.

Results: There were 1,091 surgical patients with NSCLC included (616 males and 475 females), with a PAL incidence of 14.6%. The median FFMI values among males and females were 17.3 and 14.6 kg/m^2, respectively. PAL cases in both male (16.9±1.5 *vs.* 17.4±1.5 kg/m^2; P=0.002) and female (14.0±0.9 *vs.* 14.6±1.1 kg/m^2; P<0.001) groups had a significantly lower mean FFMI than that of non-PAL cases. The incidence of PAL was significantly increased in male patients with FFMI <17.3 kg/m^2 (23.7% *vs.* 14.3%; P=0.003) and female patients with FFMI <14.6 kg/m^2 (12.7% *vs.* 5.0%; P=0.003). Lower dichotomized FFMI was also significantly associated with prolonged time to air leak cessation and length of stay (LOS). Finally, multivariable logistic-regression analysis indicated that lower dichotomized FFMI [odds ratio (OR) =1.98; 95% confidence interval (CI): 1.33–2.96; P=0.001] could independently predict the occurrence of PAL.

Conclusions: FFMI acts as an excellent categorical risk factor for PAL complicating VATS lobectomy and shows a much superior significance than body mass index (BMI) in terms of the prediction of PAL.

Keywords: Fat-free mass index (FFMI); prolonged air leak (PAL); video-assisted thoracoscopic surgery (VATS); prediction

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Introduction

Rationale

As one of the most frequent complications after pulmonary resections, prolonged air leak (PAL) remains a bothersome problem for thoracic surgeons in their daily practice and draws substantial attention in the thoracic surgery specialty (1-3). In general, 30–50% of patients who undergo lobectomy detect an air leak from the chest drainage system either immediately after operation or on postoperative day (POD) 1 (1,2). Although the presence of air leak progressively ceases several days later, approximately 8–15% of these air leak cases will ultimately develop a PAL, defined by current convention as an air leak that persists beyond 5 PODs, resulting in a dramatically increased rate of adverse morbidity and consequently a higher healthcare cost correlated with more frequent inpatient and outpatient resource utilization (1-3). Therefore, a better understanding of the predisposing factors for PAL will be extremely crucial to assist in adopting a series of prophylactic strategies to prevent the occurrence of this complication (2).

As the most common surrogate measure for obesity in current practice, body mass index (BMI) has been reported to serve as a significant risk factor for PAL in recent large-scale registry-studies (4,5). However, BMI may fail to provide accurate information on subject body composition due to its major limitation in distinguishing between lean body mass (LBM) and fat body mass. Actually, LBM takes up approximately 75–90% of body weight in normal adults (6). Thus, it may be more reasonable to regard BMI as a rough proxy to assess LBM since BMI largely reflects total body weight rather than fat body weight.

Compared to BMI, fat-free mass index (FFMI), which is calculated by the total LBM divided by the square of height, offers a much better discriminatory power for LBM and acts as a superior surrogate for physical fitness (6,7). The clinical significance of FFMI has been explored in cardiac and colorectal surgery, showing a potent predictive value for several major complications (8,9). However, unlike BMI, the impact of FFMI on risk of post-lobectomy PAL has never been elucidated until recently.

Objectives

The primary purpose of our study was to estimate whether FFMI could be predictive of PAL complicating video-assisted thoracoscopic surgery (VATS) lobectomy for operable non-small-cell lung cancer (NSCLC). Our secondary goal was to explore the effects of FFMI on the length of stay (LOS) and time to air leak cessation after surgery.

Methods

Design and protocol

This single-center retrospective study was conducted on the prospectively-maintained database in our institution. We wrote it in compliance with the Strengthening the Reporting of Cohort Studies in Surgery Statement (*Table S1*) (10). The study protocol was approved by our Regional Ethics Committee (ID: 2016-255).

Patient selection

Settings

We retrospectively reviewed the clinical data of consecutive patients undergoing VATS lobectomy for operable NSCLCs at our unit between January 2015 and July 2017. All available data for patient characteristics were extracted from our medical records.

Eligibility criteria

The following eligibility criteria were utilized to determine the appropriateness of patients included:

(I) The target diseases were operable primary NSCLCs;
(II) Only standardized single-lobectomy with systematic mediastinal lymph node dissection (SMLND) operated by a completely VATS procedure would be included. Any additional surgical procedure, such as conversion to thoracotomy or extended resection, was not considered;
(III) Patients who had finished our standardized clinical pathways during the hospitalization were included (11);
(IV) Patients who received neoadjuvant therapy were not considered, in order to avoid any confounding influence from a potential weight loss induced by neoadjuvant therapy, which might complicate the actual roles of baseline FFMI;
(V) Patients with loss of accurate medical records would not be considered.

Outcome data, measures and definitions

We recorded and defined the following characteristics and

outcome data.

Preoperative parameters

Baseline information included age, gender, BMI, FFMI, body fat percentage (BF%), forced expiratory volume in one second (FEV_1), FEV_1 to forced volume capacity ratio (FEV_1/FVC) and smoking history (11-17).

Body composition assessment criteria were as follows:

(I) Body height and weight of included patients were measured by our experienced nurses with standard methods;

(II) BMI (kg/m^2) was calculated by weight (kg)/height (m)^2;

(III) We determined to utilize the Clínica Universidad de Navarra-Body Adiposity Estimator (CUN-BAE) equation to calculate the BF% due to its good validity with remarkable consistency with actual BF% and great accessibility in a large population (7): BF%=−44.988+(0.503×age)+(10.689×gender)+(3.172×BMI)−(0.026×BMI^2)+(0.181×BMI×gender)−(0.02×BMI×age)−(0.005×BMI^2×gender)+(0.00021×BMI^2×age)(1-male;0-female);

(IV) We finally calculated the FFMI (kg/m^2) as: FFMI=(1−BF%)×BMI (7).

Preoperative underlying comorbidities included respiratory comorbidity (comprising of chronic obstructive pulmonary disease, emphysema, lung bullae, tuberculosis, asthma, pneumonia, bronchiectasis, lung abscess and interstitial lung diseases), cardio-cerebrovascular comorbidity (comprising of hypertension, coronary heart diseases, peripheral arterial diseases, stroke, aortic aneurysm and chronic heart failure), diabetes mellitus, renal insufficiency, previous malignancy and steroid use (11-17).

Intraoperative parameters

Estimated intraoperative variables included the tumor location, presence of dense pleural adhesion (15), pulmonary fissure completeness (11,14), estimated intraoperative blood loss (EIBL) (16) and operation time.

Pathological parameters

The following four pathological variables were assessed: histological subtypes, tumor invasion (T-stage), lymph node metastasis (LNM) (N-stage) and pathological TNM-stage, all of which were in compliance with the Union for International Cancer Control Seventh Edition (11-17).

Outcomes of interest

The primary outcome of interest was postoperative PAL. A diagnosis of PAL was determined by an air leak lasting >5 PODs detected from the chest drainage system, which was judged in compliance with the Society of Thoracic Surgeons and the European Society of Thoracic Surgeons joint definition (18).

Our secondary outcomes were the LOS and time to air leak cessation. The LOS was measured from the operation day to the discharge day. The air leak duration was referred to the days that an air leak persists after surgery.

Grouping criteria

Taking account of significant ethnic differences between Chinese and Western populations, our BMI categorization was in compliance with the China's National Health and Family Planning Commission definitions (underweight: <18.5 kg/m^2; normal: 18.5 to <24 kg/m^2; overweight: 24 to <28 kg/m^2; obese: ≥28 kg/m^2) (6).

Many healthy population cross-sectional surveys had been published to describe the body composition classifications, but unfortunately, neither international nor Chinese consensus was thus recommended on the reference values for FFMI (6-9,19). Therefore, we consulted a similar grouping criterion reported by Ekström *et al.* (19) in their body composition analysis. The gender-specific median values of FFMI in male and female patients were determined as the cutoffs to stratify our cohort of patients into the low-FFMI group and the high-FFMI group.

Surgical procedure and chest tube management

Our VATS lobectomy with SMLND was operated through a three-portal access, using a modified 'hilum-first-fissure-last' thoracoscopic technique known as "single-direction lobectomy" (11-17). Mechanical staplers were implemented in all patients to divide the incomplete inter-lobar fissures and close the bronchial stumps. Neither topical sealant nor pleural tenting was utilized in this period. At the end of the operation, we submerged the inflated lung parenchyma (25–30 cmH_2O pressure) in warm sterile saline to examine whether an air leak was present. If air leaks were visually observed, then we would attempt to repair the parenchymal source of bubbles by applying sutures. Finally, one 20 Fr chest tube was placed within the hemithorax and attached to a conventional chest drainage system at −10–20 cmH_2O suction, and then the wounds were stitched.

Chest tube was left on the suction until the morning of POD 1, and then was converted to water seal when minimal

or no air leak was evident. Lung recruitment was shown by chest radiography. The presence of air leak was determined by visualizing the bubbles from the chest drainage system when patients were instructed to perform standardized repeated forced expiratory maneuvers (coughing/blowing) in an upright sitting position. The quantification of air leak was measured according to the Robert-David-Cerfolio Classification System (20). It was documented by our board-certified attending surgeons at least twice daily during the morning and evening rounds. An air leak that ceased until the morning of POD 1 was defined as 'no air leak', but an air leak persisting >5 days was termed as PAL (18). Once PAL was diagnosed, we placed the chest tube on the suction device and began to follow the management algorithm described by Okereke *et al.* (3). Chest tube removal was permitted when air leak cessation was detected from the chest drainage system and 24-hour pleural drainage <200 mL.

Statistical analysis

We employed the Pearson's chi-squared test with Yates correction or Fisher's exact-test, as appropriate, to compare the categorical variables (number with percentage), and the Mann-Whitney U-test to compare the continuous variables [mean ± standard deviation and median with interquartile range (IQR) (25^{th}–75^{th} quartile-interval)] (5,9,19). Effects of dichotomized FFMI on the air leak duration and LOS were estimated by a Kaplan-Meier analysis using the log-rank test.

A receiver operating characteristic (ROC) analysis was conducted to determine the discriminative power of continuous FFMI for the prediction of PAL. Area under curve (AUC) with its 95% confidence interval (CI) was then calculated.

Finally, gender-specific median FFMI and other clinicopathological variables with P<0.10 were included in a multivariable binary logistic-regression model, which utilized the Hosmer-Lemeshow test for goodness-of-fit and the C-statistic for discrimination, to identify the independent risk factors for PAL (5,21). In order to provide concise and informative factors for the prediction of PAL, the continuous variables were dichotomized in accordance with their clinically meaningful cutoffs that were generally accepted for risk stratification in routine clinical practice, including the geriatric state categorized by age >65 years, underweight state defined by BMI <18.5 kg/m^2, impaired lung function categorized by FEV_1% <80 and FEV_1/FVC% <70, larger VATS blood loss categorized by EIBL >100 mL and prolonged operation time >150 min. Odds ratio (OR) with 95% CI was then obtained.

To eliminate potential confounding influence from an inextricable connection between age, gender, BMI and FFMI, we also included the dichotomized data of these baseline characteristics in multivariable logistic-regression model, even though they had no statistical significance in univariable analysis.

We used the IBM SPSS 22.0 software to accomplish above statistical analyses. The statistical significance was indicated by P value <0.05.

Results

Basic information and outcomes

Patient characteristics

During the study period, there were 1,091 patients undergoing VATS lobectomy for operable primary NSCLCs included. Their patient characteristics are presented in *Tables 1,2*. Our cohort were comprised of 616 male (ratio =56.5%) and 475 female patients (ratio =43.5%), with a mean age of 61.4±8.7 years (median =62 years; IQR =55–68 years). The mean BMI, FFMI and BF% of the entire cohort was 23.3±3.0 kg/m^2 (median =23.2 kg/m^2; IQR =21.2–25.2 kg/m^2), 16.1±1.9 kg/m^2 (median =15.9 kg/m^2; IQR =14.7–17.6 kg/m^2) and 30.6±6.6 (median =30.2; IQR =25.5–35.6), respectively. A frequency distribution histogram suggested that our FFMI data could be approximately seen as the normal distribution (*Figure 1*).

The mean FFMI for males and females was 17.3±1.5 kg/m^2 (median =17.3 kg/m^2; IQR =16.3–18.4 kg/m^2) and 14.5±1.1 kg/m^2 (median =14.6 kg/m^2; IQR =13.8–15.3 kg/m^2), respectively. The gender-specific median values of FFMI were further utilized to divide all included patients into the low-FFMI group (male FFMI <17.3 kg/m^2, n=308; female FFMI <14.6 kg/m^2, n=236) and the high-FFMI group (male FFMI ≥17.3 kg/m^2, n=308; female FFMI ≥14.6 kg/m^2, n=239). Patient characteristics between these groups are further summarized in *Table 2*.

Outcomes

An air leak was detected in 58.4% of patients on POD 1 (n=637). Then, the proportion of air leak cases showed a steady decreasing tendency with the increasing LOS (*Figure 2*). Among these cases, 478 of them showed a completely ceased air leak within 5 days, but the remaining

Table 1 Patient characteristics

Characteristics	Total (N=1,091)
Basic information	
Age (years)	
Mean ± SD	61.4±8.7
Median [IQR]	62 [55–68]
Gender (male, %)	616 (56.5%)
Body mass index (kg/m^2)	
Mean ± SD	23.3±3.0
Median (IQR)	23.2 (21.2–25.2)
Fat-free mass index (kg/m^2)	
Mean ± SD	16.1±1.9
Median (IQR)	15.9 (14.7–17.6)
Body fat percentage (%)	
Mean ± SD	30.6±6.6
Median (IQR)	30.2 (25.5–35.6)
FEV_1%	
Mean ± SD	82.2±16.4
Median (IQR)	82.8 (75.0–91.1)
FEV_1/FVC (%)	
Mean ± SD	76.5±9.3
Median (IQR)	77.7 (72.8–82.4)
Smoking history	487 (44.6%)
Respiratory comorbidity	457 (41.9%)
Cardio-cerebrovascular comorbidity	422 (38.7%)
Diabetes mellitus	131 (12.0%)
Renal insufficiency	92 (8.4%)
Previous malignancy	106 (9.7%)
Steroid use	36 (3.3%)
Adjuvant chemotherapy	242 (22.2%)
Intraoperative parameters	
Tumor location	
Right upper lobe	339 (31.1%)
Left upper lobe	263 (24.1%)
Right lower lobe	209 (19.2%)
Left lower lobe	158 (14.5%)
Right middle lobe	122 (11.2%)
Dense pleural adhesion	
Absent	109 (10.0%)
Present	982 (90.0%)
Pulmonary fissure completeness	
Complete	662 (60.7%)
Incomplete	429 (39.3%)
Estimated intraoperative blood loss (mL)	
Mean ± SD	75.5±98.7
Median [IQR]	50 [20–100]
Operation time (min)	
Mean ± SD	113.6±40.3
Median [IQR]	110 [80–130]
Pathological parameters	
Histology	
Adenocarcinoma	831 (76.2%)
Squamous cell carcinoma	165 (15.1%)
Other subtypes of NSCLC	95 (8.7%)
Tumor invasion (T-stage)	
T_1	547 (50.1%)
$T_{2–3}$	544 (49.9%)
Lymph node metastasis (N-stage)	
N_0	903 (82.8%)
$N_{1–2}$	188 (17.2%)
TNM-stage	
I	812 (74.4%)
II–IIIa	279 (25.6%)

FEV_1, forced expiratory volume in one second; FEV_1/FVC, forced expiratory volume in one second to forced volume capacity ratio; IQR, interquartile range; NSCLC, non-small-cell lung cancer; SD, standard deviation.

Table 2 Clinicopathological characteristics between patients divided by gender-specific median values of FFMI in both male and female groups

Characteristics	Male				Female			
	Total (N=616)	FFMI <17.3 kg/m^2 (N=308)	FFMI ≥17.3 kg/m^2 (N=308)	P value	Total (N=475)	FFMI <14.6 kg/m^2 (N=236)	FFMI ≥14.6 kg/m^2 (N=239)	P value
Basic information								
Age (years)								
Mean ± SD	61.4±8.7	64.0±8.1	58.8±8.5	<0.001	61.4±8.8	63.1±8.7	59.8±8.6	<0.001
Median [IQR]	62 [55–68]	64 [60–69]	59 [52–65]		62 [56–67]	63 [58–69]	60 [53–65]	
Body mass index (kg/m^2)								
Mean ± SD	23.6±3.0	21.2±1.8	25.9±2.1	<0.001	23.0±3.0	20.9±1.9	25.2±2.3	<0.001
Median (IQR)	23.5 (21.3–25.6)	21.3 (20.1–22.5)	25.6 (24.5–26.9)		22.9 (20.8–24.8)	20.9 (19.6–22.5)	24.7 (23.8–26.4)	
Fat-free mass index (kg/m^2)								
Mean ± SD	17.3±1.5	16.1±0.9	18.5±0.9	<0.001	14.5±1.1	13.7±0.8	15.4±0.6	<0.001
Median (IQR)	17.3 (16.3–18.4)	16.2 (15.5–16.8)	18.4 (17.8–19.0)		14.6 (13.8–15.3)	13.8 (13.3–14.2)	15.3 (14.9–15.7)	
Body fat percentage (%)								
Mean ± SD	26.2±4.0	24.0±3.3	28.4±3.4	<0.001	36.4±4.5	34.2±3.7	38.6±4.1	<0.001
Median (IQR)	26.1 (23.6–28.9)	24.1 (21.9–26.2)	28.1 (26.1–30.9)		36.2 (33.4–39.1)	34.2 (31.7–37.1)	38.1 (36.0–41.2)	
FEV_1%								
Mean ± SD	77.5±15.0	76.5±15.5	78.5±14.4	0.051	88.3±16.0	88.7±16.4	87.9±15.7	0.78
Median (IQR)	81.5 (68.8–86.5)	80.4 (68.3–85.4)	81.9 (69.4–87.8)		87.1 (78.5–98.0)	87.9 (77.6–98.5)	86.4 (78.6–96.5)	
FEV_1/FVC (%)								
Mean ± SD	74.9±10.1	74.0±11.1	75.9±8.8	0.032	78.5±7.8	78.0±7.7	78.9±7.9	0.085
Median (IQR)	77.0 (72.0–80.9)	76.8 (70.1–80.4)	77.4 (73.5–81.8)		78.9 (73.9–84.0)	78.3 (73.3–83.3)	79.1 (74.6–84.6)	
Smoking history	472 (76.6%)	247 (80.2%)	225 (73.1%)	0.036	15 (3.2%)	5 (2.1%)	10 (4.2%)	0.20
Respiratory comorbidity	313 (50.8%)	187 (60.7%)	126 (40.9%)	<0.001	144 (30.3%)	84 (35.6%)	60 (25.1%)	0.013
Cardio-cerebrovascular comorbidity	250 (40.6%)	114 (37.0%)	136 (44.2%)	0.071	172 (36.2%)	82 (34.7%)	90 (37.7%)	0.51
Diabetes mellitus	88 (14.3%)	39 (12.7%)	49 (15.9%)	0.25	43 (9.1%)	21 (8.9%)	22 (9.2%)	0.91
Renal insufficiency	53 (8.6%)	28 (9.1%)	25 (8.1%)	0.67	39 (8.2%)	24 (10.2%)	15 (6.3%)	0.12
Previous malignancy	56 (9.1%)	27 (8.8%)	29 (9.4%)	0.78	50 (10.5%)	23 (9.7%)	27 (11.3%)	0.58
Steroid use	26 (4.2%)	13 (4.2%)	13 (4.2%)	1.0	10 (2.1%)	7 (3.0%)	3 (1.3%)	0.33
Adjuvant chemotherapy	185 (30.0%)	106 (34.4%)	79 (25.6%)	0.018	57 (12.0%)	21 (8.9%)	36 (15.1%)	0.039

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Male				Female			
	Total (N=616)	FFMI <17.3 kg/m^2 (N=308)	FFMI ≥17.3 kg/m^2 (N=308)	P value	Total (N=475)	FFMI <14.6 kg/m^2 (N=236)	FFMI ≥14.6 kg/m^2 (N=239)	P value
Intraoperative parameters								
Tumor location								
Right upper lobe	186 (30.2%)	100 (32.5%)	86 (27.9%)	0.51	153 (32.2%)	86 (36.4%)	67 (28.0%)	0.22
Left upper lobe	144 (23.4%)	64 (20.8%)	80 (26.0%)		119 (25.1%)	50 (21.2%)	69 (28.9%)	
Right lower lobe	121 (19.6%)	59 (19.2%)	62 (20.1%)		88 (18.5%)	45 (19.1%)	43 (18.0%)	
Left lower lobe	92 (14.9%)	49 (15.9%)	43 (14.0%)		66 (13.9%)	31 (13.1%)	35 (14.6%)	
Right middle lobe	73 (11.9%)	36 (11.7%)	37 (12.0%)		49 (10.3%)	24 (10.2%)	25 (10.5%)	
Dense pleural adhesion								
Absent	549 (89.1%)	271 (88.0%)	278 (90.3%)	0.37	433 (91.2%)	214 (90.7%)	219 (91.6%)	0.13
Present	67 (10.9%)	37 (12.0%)	30 (9.7%)		42 (8.8%)	22 (9.3%)	20 (8.4%)	
Pulmonary fissure completeness								
Complete	354 (57.5%)	181 (58.8%)	173 (56.2%)	0.51	308 (64.8%)	152 (64.4%)	156 (65.3%)	0.71
Incomplete	262 (42.5%)	127 (41.2%)	135 (43.8%)		167 (35.2%)	84 (35.6%)	83 (34.7%)	
Estimated intraoperative blood loss (mL)								
Mean ± SD	91.1±117.9	96.8±127.8	85.2±107.0	0.55	55.1±60.0	54.2±68.2	56.1±50.6	0.065
Median [IQR]	50 [30–100]	50 [30–100]	50 [30–100]		50 [20–50]	40 [20–50]	50 [20–60]	
Operation time (min)								
Mean ± SD	119.0±43.3	118.6±43.8	119.3±42.8	0.44	106.7±34.8	108.4±37.9	104.9±31.5	0.69
Median [IQR]	110 [90–135]	110 [90–140]	115 [90–135]		100 [80–120]	100 [80–120]	100 [80–120]	

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Male				Female			
	Total (N=616)	FFMI <17.3 kg/m^2 (N=308)	FFMI ≥17.3 kg/m^2 (N=308)	P value	Total (N=475)	FFMI <14.6 kg/m^2 (N=236)	FFMI ≥14.6 kg/m^2 (N=239)	P value
Pathological parameters								
Histology								
Adenocarcinoma	418 (67.9%)	190 (61.7%)	228 (74.0%)	0.004	413 (86.9%)	206 (87.3%)	207 (86.6%)	0.97
Squamous cell carcinoma	146 (23.7%)	89 (28.9%)	57 (18.5%)		19 (4.0%)	9 (3.8%)	10 (4.2%)	
Other subtypes of NSCLC	52 (8.4%)	29 (9.4%)	23 (7.5%)		43 (9.1%)	21 (8.9%)	22 (9.2%)	
Tumor invasion (T-stage)								
T_1	255 (41.4%)	113 (36.7%)	142 (46.1%)	0.018	292 (61.5%)	153 (64.8%)	139 (58.2%)	0.14
T_{2-3}	361 (58.6%)	195 (63.3%)	166 (53.9%)		183 (38.5%)	83 (35.2%)	100 (41.8%)	
Lymph node metastasis (N-stage)								
N_0	471 (76.5%)	228 (74.0%)	243 (78.9%)	0.15	432 (90.9%)	218 (92.4%)	214 (89.5%)	0.28
N_{1-2}	145 (23.5%)	80 (26.0%)	65 (21.1%)		43 (9.1%)	18 (7.6%)	25 (10.5%)	
TNM-stage								
I	407 (66.1%)	185 (60.1%)	222 (72.1%)	0.002	405 (85.3%)	213 (90.3%)	192 (80.3%)	0.002
II–IIIa	209 (33.9%)	123 (39.9%)	86 (27.9%)		70 (14.7%)	23 (9.7%)	47 (19.7%)	

FEV_1, forced expiratory volume in one second; FEV_1/FVC, forced expiratory volume in one second to forced volume capacity ratio; FFMI, fat-free mass index; IQR, interquartile range; NSCLC, non-small-cell lung cancer; SD, standard deviation.

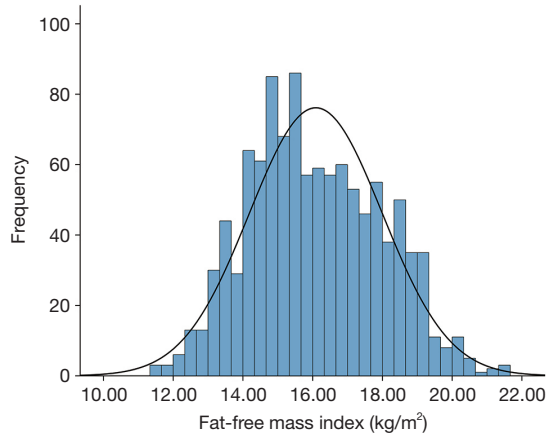

Figure 1 Frequency distribution histogram of FFMI. FFMI, fat-free mass index.

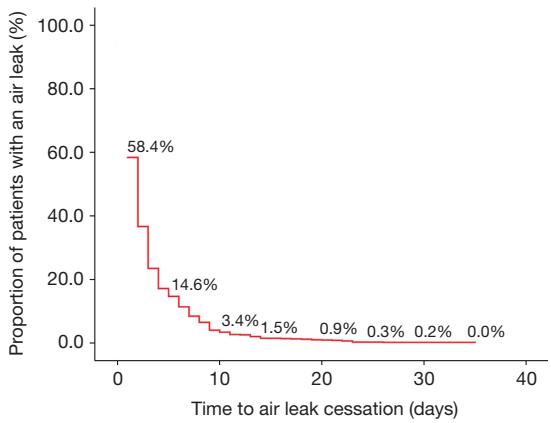

Figure 2 Tendency of proportion of air leak cases with the increasing LOS. LOS, length of stay.

159 patients developed an air leak persisting>5 days. Thus, the overall PAL incidence in our series was 14.6%. There was no in-hospital death. All included patients were discharged without remaining chest tube drainage. In addition, the mean LOS and air leak duration in our series was 6.5±4.3 days (median =6 days; IQR =4–8 days) and 2.8±3.6 days (median =2 days; IQR =0–3 days) respectively.

Comparisons between patients with and without PAL

Male group

Among 616 male patients, a PAL occurred in 117 individuals, with an incidence of 19.0%. PAL cases had significantly higher ratios of respiratory comorbidity (P<0.001), cardio-cerebrovascular comorbidity (P=0.028), incomplete pulmonary fissure (P<0.001), dense pleural adhesion (P=0.016), T_{2-3}-stage tumor invasion (P=0.030), LNM (P=0.006) and II–IIIa-stage cancer (P=0.014) than those of non-PAL cases (*Table 3*).

PAL cases also had significantly higher means of age (P=0.037), EIBL (P<0.001) and operation time (P<0.001) but lower means of FEV_1% (P<0.001) and FEV_1/FVC% (P=0.040) than those of non-PAL cases (*Table 3*). Both mean FFMI (16.9±1.5 *vs.* 17.4±1.5 kg/m^2; P=0.002) and BMI (22.9±3.2 *vs.* 23.7±3.0 kg/m^2; P=0.004) in PAL cases were significantly lower than those in non-PAL cases (*Figure 3A,B,C*). Moreover, the incidence of PAL in patients with FFMI <17.3 kg/m^2 was significantly higher than that in patients with FFMI ≥17.3 kg/m^2 (23.7% *vs.* 14.3%; P=0.003).

Female group

There were 42 of 475 female patients experienced a PAL, with an incidence of 8.8%. Compared to non-PAL cases, PAL cases had a significantly higher mean operation time (P<0.001) and significantly higher ratios of respiratory comorbidity (P=0.011), dense pleural adhesion (P=0.031) and incomplete pulmonary fissure (P=0.014) (*Table 3*). Moreover, both mean FFMI (14.0±0.9 *vs.* 14.6±1.1 kg/m^2; P<0.001) and BMI (21.9±2.9 *vs.* 23.2±3.0 kg/m^2; P=0.003) in PAL cases were significantly lower than those in non-PAL cases (*Figure 3A,B,C*). The incidence of PAL in patients with FFMI <14.6 kg/m^2 was significantly higher than that in patients with FFMI ≥14.6 kg/m^2 (12.7% *vs.* 5.0%; P=0.003).

ROC analysis of continuous FFMI for predicting postoperative PAL

The ROC analysis of continuous FFMI showed an AUC of 0.59 (95% CI: 0.54–0.65; P=0.002) in male group and an AUC of 0.67 (95% CI: 0.59–0.75; P<0.001) in female group for the prediction of PAL (*Figure 4A,B*). The male median FFMI of 17.3 kg/m^2 showed 53.3% sensitivity and 62.4% specificity, while the female median FFMI of 14.6 kg/m^2 showed equal sensitivity at 53.3% but higher specificity at 71.4% with regard to risk of PAL.

Multivariable analysis of risk factors for PAL

A multivariable logistic-regression model was formulated on the clinicopathological parameters with P<0.10 in both male and female patients, as shown in *Table 4*. The

Table 3 Univariable analysis of gender-specific risk factors for PAL

Characteristics	Male				Female			
	Total (N=616)	With PAL (N=117)	Without PAL (N=499)	P value	Total (N=475)	With PAL (N=42)	Without PAL (N=433)	P value
Basic information								
Age (years)								
Mean ± SD	61.4±8.7	63.1±8.1	61.0±8.8	0.037	61.4±8.8	62.8±8.0	61.3±8.9	0.24
Median (IQR)	62 (55–68)	63 (58–69)	62 (54–67)		62 (56–67)	63 (58–67)	62 (56–67)	
Body mass index (kg/m^2)								
Mean ± SD	23.6±3.0	22.9±3.2	23.7±3.0	0.004	23.0±3.0	21.9±2.9	23.2±3.0	0.003
Median (IQR)	23.5 (21.3–25.6)	22.5 (20.7–25.0)	23.7 (21.6–25.8)		22.9 (20.8–24.8)	21.8 (19.8–23.5)	23.1 (21.0–24.9)	
Fat–free mass index (kg/m^2)								
Mean ± SD	17.3±1.5	16.9±1.5	17.4±1.5	0.002	14.5±1.1	14.0±0.9	14.6±1.1	<0.001
Median (IQR)	17.3 (16.3–18.4)	16.9 (15.8–18.2)	17.5 (16.3–18.4)		14.6 (13.8–15.3)	14.0 (13.4–14.8)	14.7 (13.9–15.3)	
Body fat percentage (%)								
Mean ± SD	26.2±4.0	25.8±4.1	26.3±4.0	0.10	36.4±4.5	35.3±4.7	36.5±4.5	0.078
Median (IQR)	26.1 (23.6–28.9)	25.3 (23.2–28.0)	26.2 (23.7–29.2)		36.2 (33.4–39.1)	35.3 (32.6–38.6)	36.4 (33.5–39.2)	
FEV_1%								
Mean ± SD	77.5±15.0	73.1±16.5	78.5±14.4	<0.001	88.3±16.0	86.1±18.0	88.5±15.8	0.39
Median (IQR)	81.5 (68.8–86.5)	78.1 (59.8–84.2)	82.3 (71.5–86.5)		87.1 (78.5–98.0)	85.5 (76.9–98.5)	87.1 (78.5–98.0)	
FEV_1/FVC (%)								
Mean ± SD	74.9±10.1	73.5±11.2	75.3±9.8	0.040	78.5±7.8	77.6±9.5	78.5±7.6	0.39
Median (IQR)	77.0 (72.0–80.9)	75.2 (69.0–80.7)	77.1 (72.5–81.0)		78.9 (73.9–84.0)	75.4 (73.1–83.9)	78.9 (74.0–84.0)	
Smoking history	472 (76.6%)	96 (82.1%)	376 (75.4%)	0.12	15 (3.2%)	0 (0.0%)	15 (3.5%)	0.45
Respiratory comorbidity	313 (50.8%)	80 (68.4%)	233 (46.7%)	<0.001	144 (30.3%)	20 (47.6%)	124 (28.6%)	0.011
Cardio-cerebrovascular comorbidity	250 (40.6%)	58 (49.6%)	192 (38.5%)	0.028	172 (36.2%)	20 (47.6%)	152 (35.1%)	0.11
Diabetes mellitus	88 (14.3%)	13 (11.1%)	75 (15.0%)	0.28	43 (9.1%)	6 (14.3%)	37 (8.5%)	0.34
Renal insufficiency	53 (8.6%)	13 (11.1%)	40 (8.0%)	0.28	39 (8.2%)	5 (11.9%)	34 (7.9%)	0.54
Previous malignancy	56 (9.1%)	15 (12.8%)	41 (8.2%)	0.12	50 (10.5%)	6 (14.3%)	44 (10.2%)	0.57
Steroid use	26 (4.2%)	4 (3.4%)	22 (4.4%)	0.82	10 (2.1%)	2 (4.8%)	8 (1.8%)	0.49
Adjuvant chemotherapy	185 (30.0%)	41 (35.0%)	144 (28.9%)	0.19	57 (12.0%)	2 (4.8%)	55 (12.7%)	0.13

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Male				Female			
	Total (N=616)	With PAL (N=117)	Without PAL (N=499)	P value	Total (N=475)	With PAL (N=42)	Without PAL (N=433)	P value
Intraoperative parameters								
Tumor location								
Right upper lobe	186 (30.2%)	27 (23.1%)	159 (31.9%)	0.24	153 (32.2%)	16 (38.1%)	137 (31.6%)	0.10
Left upper lobe	144 (23.4%)	28 (23.9%)	116 (23.2%)		119 (25.1%)	14 (33.3%)	105 (24.2%)	
Right lower lobe	121 (19.6%)	28 (23.9%)	93 (18.6%)		88 (18.5%)	9 (21.4%)	79 (18.2%)	
Left lower lobe	92 (14.9%)	16 (13.7%)	76 (15.2%)		66 (13.9%)	1 (2.4%)	65 (15.0%)	
Right middle lobe	73 (11.9%)	18 (15.4%)	55 (11.0%)		49 (10.3%)	2 (4.8%)	47 (10.9%)	
Dense pleural adhesion								
Absent	549 (89.1%)	97 (82.9%)	452 (90.6%)	0.016	433 (91.2%)	34 (81.0%)	399 (92.1%)	0.031
Present	67 (10.9%)	20 (17.1%)	47 (9.4%)		42 (8.8%)	8 (19.0%)	34 (7.9%)	
Pulmonary fissure completeness								
Complete	354 (57.5%)	40 (34.2%)	314 (62.9%)	<0.001	308 (64.8%)	20 (47.6%)	288 (66.5%)	0.014
Incomplete	262 (42.5%)	77 (65.8%)	185 (37.1%)		167 (35.2%)	22 (52.4%)	145 (33.5%)	
Estimated intraoperative blood loss (mL)								
Mean ± SD	91.1±117.9	148.1±202.7	77.7±81.8	<0.001	55.1±60.0	67.6±81.1	53.9±57.5	0.13
Median (IQR)	50 (30–100)	90 (43–200)	50 (30–100)		50 (20–50)	50 (30–65)	50 (20–50)	
Operation time (min)								
Mean ± SD	119.0±43.3	140.9±52.4	113.8±39.2	<0.001	106.7±34.8	132.6±43.4	104.2±32.9	<0.001
Median (IQR)	110 (90–135)	125 (110–160)	105 (90–130)		100 (80–120)	120 (100–153)	100 (80–120)	

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Male				Female			
	Total (N=616)	With PAL (N=117)	Without PAL (N=499)	P value	Total (N=475)	With PAL (N=42)	Without PAL (N=433)	P value
Pathological parameters								
Histology								
Adenocarcinoma	418 (67.9%)	73 (62.4%)	345 (69.1%)	0.13	413 (86.9%)	39 (92.9%)	374 (86.4%)	0.44
Squamous cell carcinoma	146 (23.7%)	36 (30.8%)	110 (22.0%)		19 (4.0%)	1 (2.4%)	18 (4.2%)	
Other subtypes of NSCLC	52 (8.4%)	8 (6.8%)	44 (8.8%)		43 (9.1%)	2 (4.8%)	41 (9.5%)	
Tumor invasion (T-stage)								
T_1	255 (41.4%)	38 (32.5%)	217 (43.5%)	0.030	292 (61.5%)	28 (66.7%)	264 (61.0%)	0.47
T_{2-3}	361 (58.6%)	79 (67.5%)	282 (56.5%)		183 (38.5%)	14 (33.3%)	169 (39.0%)	
Lymph node metastasis (N-stage)								
N_0	471 (76.5%)	78 (66.7%)	393 (78.8%)	0.006	432 (90.9%)	39 (92.9%)	393 (90.8%)	0.87
N_{1-2}	145 (23.5%)	39 (33.3%)	106 (21.2%)		43 (9.1%)	3 (7.1%)	40 (9.2%)	
TNM-stage								
I	407 (66.1%)	66 (56.4%)	341 (68.3%)	0.014	405 (85.3%)	36 (85.7%)	369 (85.2%)	0.93
II–IIIa	209 (33.9%)	51 (43.6%)	158 (31.7%)		70 (14.7%)	6 (14.3%)	64 (14.8%)	

FEV_1, forced expiratory volume in one second; FEV_1/FVC, forced expiratory volume in one second to forced volume capacity ratio; IQR, interquartile range; PAL, prolonged air leak; SD, standard deviation.

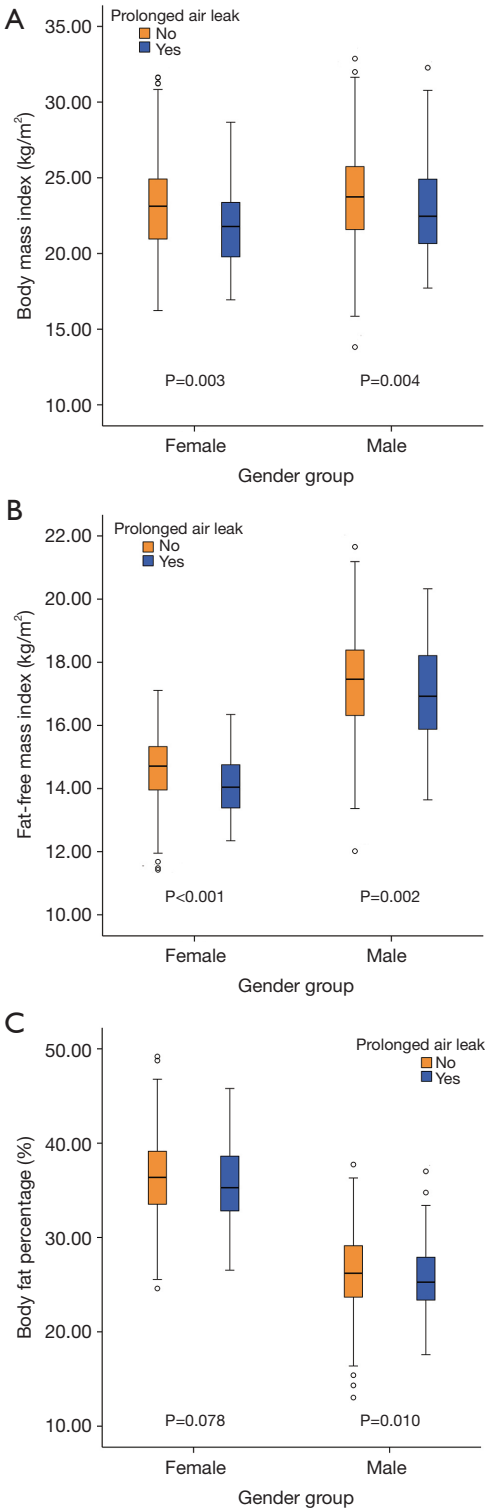

Figure 3 Box-plots revealing mean (A) BMI, (B) FFMI and (C) BF% between patients with and without PAL. BMI, body mass index; FFMI, fat-free mass index; BF%, body fat percentage; PAL, prolonged air leak.

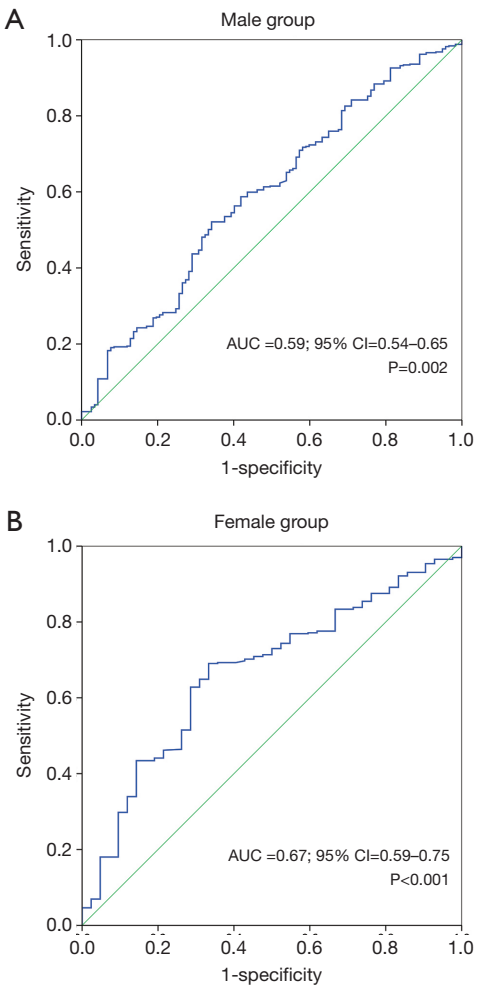

Figure 4 ROC analysis on discriminative power of continuous FFMI for predicting risk of PAL in (A) male and (B) female groups. ROC, receiver operating characteristic; FFMI, fat-free mass index; PAL, prolonged air leak.

multivariable logistic-regression model with Hosmer-Lemeshow P=0.59 and C-statistic =0.77 (95% CI: 0.73–0.81; P<0.001) demonstrated that the male gender (OR =1.58; 95% CI: 1.03–2.41; P=0.035), lower dichotomized FFMI (OR =1.98; 95% CI: 1.33–2.96; P=0.001), FEV_1% <80 (OR =1.76; 95% CI: 1.17–2.65; P=0.007), respiratory comorbidity (OR =1.81; 95% CI: 1.23–2.67; P=0.003), cardio-cerebrovascular comorbidity (OR =1.63; 95% CI: 1.11–2.40; P=0.013), poorly-developed pulmonary fissure (OR =2.60; 95% CI: 1.78–3.77; P<0.001), operation time >150 min (OR =1.93; 95% CI: 1.23–3.05; P=0.005) and EIBL >100 mL (OR =1.76; 95% CI: 1.09–2.85; P=0.020) could independently predict the occurrence of

Table 4 Multivariable analysis of risk factors for PAL

Estimated factors	Odds ratio	95% confidence interval	P value
Gender (male *vs.* female)	1.58	1.03–2.41	0.035
Age (>65 *vs.* ≤65 years)	1.20	0.79–1.81	0.39
Body mass index (<18.5 *vs.* ≥18.5 kg/m^2)	1.54	0.73–3.23	0.26
Fat-free mass index (low *vs.* high)	1.98	1.33–2.96	0.001
FEV_1% (<80 *vs.* ≥80)	1.76	1.17–2.65	0.007
FEV_1/FVC% (<70 *vs.* ≥70)	1.01	0.62–1.66	0.96
Respiratory comorbidity (yes *vs.* no)	1.81	1.23–2.67	0.003
Cardio-cerebrovascular comorbidity (yes *vs.* no)	1.63	1.11–2.40	0.013
Dense pleural adhesion (present *vs.* absent)	1.29	0.75–2.20	0.36
Pulmonary fissure completeness (incomplete *vs.* complete)	2.60	1.78–3.77	<0.001
Estimated intraoperative blood loss (>100 *vs.* ≤100 mL)	1.76	1.09–2.85	0.020
Operation time (>150 *vs.* ≤150 min)	1.93	1.23–3.05	0.005
Tumor invasion (T_{2-3} *vs.* T_1)	1.05	0.69–1.61	0.81
Lymph node metastasis (yes *vs.* no)	1.29	0.63–2.65	0.48
TNM-stage (II–IIIa *vs.* I)	1.03	0.52–2.07	0.93

FEV_1, forced expiratory volume in one second; FEV_1/FVC, forced expiratory volume in one second to forced volume capacity ratio; PAL, prolonged air leak.

PAL. No significant association was found between BMI <18.5 kg/m^2 and postoperative PAL (OR =1.54; 95% CI: 0.73–3.23; P=0.26).

Effects of dichotomized FFMI on air leak duration and LOS

Time to air leak cessation

The Kaplan-Meier curve revealing time to air leak cessation between low-FFMI group and high-FFMI group are presented in *Figure 5A*. The air leak duration in low-FFMI group patients (mean =3.2 days; 95% CI: 2.9–3.6 days) was significantly longer than that in high-FFMI group patients (mean =2.3 days; 95% CI: 2.1–2.5 days) (Log-rank P<0.001).

LOS

Figure 5B shows the LOS between low-FFMI group and high-FFMI group. The Kaplan-Meier analysis indicated that low-FFMI group patients (mean =6.9 days; 95% CI: 6.5–7.4 days) had the significantly prolonged LOS compared with that of high-FFMI group patients (mean =6.0 days; 95% CI: 5.7–6.3 days) (Log-rank P<0.001).

Discussion

Key results and interpretations

Prior prospective studies have demonstrated a significant influence of FFMI on major outcomes complicating cardiac and colorectal surgery (8,9). In these surgical specialties, low FFMI was regarded as one of the most powerful factors for distinguishing undernourished surgical patients and enhanced recovery after surgery (8,9). To the best of our knowledge, the present study was the first to demonstrate the predictive value of FFMI for risk of PAL and time to air leak cessation following VATS lobectomy for NSCLC. We selected a series of widely accepted formulas comprising of BMI, age and gender, rather than a classical dual-energy X-ray absorptiometry (DEXA), to extrapolate the FFMI data of a large cohort consisting of >1,000 cases, as these formulas have been validated with great consistency with the actual FFMI (7). The DEXA scan might not be easily implemented in a large population because of a high cost and a little complex process, although it was considered the gold standard for body composition measurement (6,7,9).

The main finding of our study was that both male and female patients with lower dichotomized FFMI were

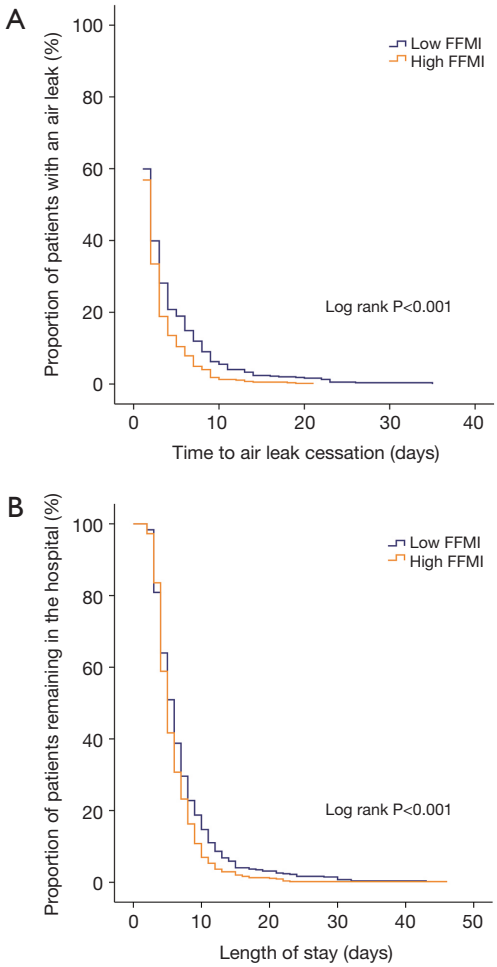

Figure 5 Kaplan-Meier curves revealing (A) time to air leak cessation and (B) LOS between low-FFMI group and high-FFMI group. LOS, length of stay; FFMI, fat-free mass index.

considered to suffer from a significantly higher risk of PAL complicating VATS lobectomy for NSCLC. Furthermore, both air leak duration and LOS were significantly prolonged in the patients with lower dichotomized FFMI. That might be attributed to a higher incidence of PAL among these patients. Finally, an effective multivariable logistic-regression model demonstrated that lower dichotomized FFMI could independently predict the occurrence of PAL in both male and female patients. Low BMI (underweight state) was also identified to predispose to PAL formation but did not reach statistical significance. These findings were consistent with the previous results in other surgical specialties, revealing a superior clinical significance of FFMI compared with BMI (8,9). Although potential mechanisms underlying the association between low FFMI and risk of PAL remain unclear, we hypothesize that the following three explanations may be considered when trying to explain this phenomenon.

First, the LBM, particularly in the form of muscular tissues, contains abundant proteins that maintain every physiological process within somatic cells, including the synthesis of essential enzymes for metabolic responses and active antibodies for immunological reactions, cell signaling, and cell regeneration. As an excellent indicator for LBM, low FFMI may represent an insufficient status of organism nutritional and physiological reserve, implying a large decline of metabolically active somatic cells (8,22). The excessive protein catabolism induced by surgery can further impair the global immunological function and physiological homeostasis. Therefore, patients with lower FFMI are less likely to have an adequate response to operative stress because of their compromised ability to withstand an acute injury, resulting in a dramatically increased risk of adverse events (22). In addition, any operative morbidity in such patients cannot be easily managed and typically requires a prolonged convalescence period after surgery, otherwise, a threshold at which the organism ceases to function will eventually be reached (9,22).

Second, we speculated that a positive correlation between FFMI and major cardiopulmonary function indices might affect the development of PAL. Accumulative evidence demonstrates that each 1 kg/m^2 increase in FFMI is linearly associated with an increasing FEV_1% (23,24). In other words, a lower FFMI can reflect impaired lung function based on a decline of FEV_1%, which represents one of the leading risk factors for PAL (2). This phenomenon suggests that a loss of LBM, particularly of the respiratory muscles within the thorax and upper abdomen, diminishes the capacity of breathing exercises, leading to a downtrend of FEV_1% and tidal volume. Recently, a small cross-sectional study reported that each 1 kg/m^2 decrease in FFMI may be responsible for a decreasing maximal oxygen consumption, which is one of the best measurements reflecting the cardiopulmonary capacity, as the fewer muscular pumps participating in physical activities contribute to a lower venous return to the heart (25). That may be another one predisposing factor for PAL.

Finally, as a powerful risk factor for PAL, COPD is characterized by a range of pathophysiological changes, and one of its main consequences is the progressive wasting of LBM, resulting in the presence of bio-energetic abnormality (26). A decline of physical activities and long-term glucocorticoid administration in COPD patients

further contributes to a loss of muscular mass, which is typically accompanied by an abundance of adiposity. Thus, compared to normal patients, most COPD patients have a lower FFMI and present with a steady downtrend of LBM with the increasing severity of disease, showing a significantly higher probability to experience a PAL (26,27).

Generalizability

Our findings suggest that FFMI may be a more appropriate alternative compared to BMI for the formulation of a novel risk scoring system to help thoracic surgeons stratify the patients at high surgical risk. In addition, we suggest that the present results may help to select the candidates in a teaching program of VATS techniques or in an early learning curve for young surgeons to avoid adverse events and train them more effectively.

Limitations

The following major study limitations must be acknowledged.

First, the present study was subject to inherent limitations of any single-center retrospective analysis. Potential selection bias might complicate our findings, although we included >1,000 patients in accordance with fairly strict eligibility criteria and performed a more appropriate gender-specific risk analysis by multivariable logistic-regression model on the cohort, in order to eliminate potential bias risks from confounding factors, including the application of neoadjuvant therapy, gender heterogeneity, FFMI extrapolation and additional surgical procedures. For example, long-term smoking and consumptive respiratory diseases, such as the COPD, chronic bronchitis and tuberculosis history, could lead to a loss of LBM and impaired lung function before surgery, resulting in a significantly increased probability of PAL. In addition, dissection of the lung parenchyma within the poorly-developed fissure and dense pleural adhesion could significantly prolong the operation time and easily produce a PAL requiring chest suction drainage or even surgical intervention. Given such concerns, we recommend that more prospective validating studies with much better control of potential confounders from patient characteristics are needed to demonstrate the significance of FFMI in lung cancer surgery.

Second, neither FFMI nor BF% in our large series was directly measured by the 'gold-standard' DEXA scan. Nevertheless, we estimated both FFMI and BF% according to the Lavie formula and CUN-BAE equation (7), which have been validated in many large populations and readily employed to assess body composition without any specific equipment or additional cost. However, a further comparison with other calculating formulas of FFMI in a large population is warranted to verify the effectiveness of our findings in the future.

Third, the AUCs of continuous FFMI in both male and female groups were relatively low but with P-values near 0.001 for the prediction of PAL. These results might not provide a strong discriminatory power for the continuous FFMI. Furthermore, the gender-specific median values of FFMI showed fairly low sensitivity and specificity, which might attenuate the practical purpose of our findings in routine clinical practice.

Fourth, some of pulmonary diffusion function indexes, such as the carbon monoxide diffusing capacity, had unfortunately missed from our database maintained during the study period. So these parameters were not evaluated in all included patients.

Finally, the PAL incidence could also depend on the surgeons' expertise and conditions. However, it might be difficult to appropriately perform a quantitative analysis on these artificial factors. Besides, we paid much less attention to the treatment of PAL due to the restriction of primary study objectives.

Conclusions

In conclusion, the present study demonstrates that FFMI can serve as an excellent categorical predictor for PAL complicating VATS lobectomy for NSCLC. Moreover, FFMI was found to be more promising than BMI in terms of the prediction of PAL. It may be extremely helpful to incorporate a FFMI cutoff into perioperative risk assessment models. Owing to several inherent limitations of the retrospective design, more large-scale prospective validating analyses are highly recommended to confirm and modify our findings in the future.

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Footnote

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

Ethical Statement: The study was approved by our Regional Ethics Committee (ID: 2016-255).

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Supplementary

Table S1 The STROCSS guideline

Item No.	Item description	Page number
1	Title. The words "cohort" and the area of focus should appear in the title (e.g., disease, exposure/intervention or outcome). Whether the study is retrospective or prospective should also be stated	1
2a	Abstract—Introduction—What is the background and scientific rationale for the research question	1
2b	Abstract—Methods—Describe the study design (cohort design, retrospective or prospective, single or multi-centre, etc.), what was done to each group, how, when was it done and by whom	1
2c	Abstract—Results—What was found. Give the results for the main outcomes	1
2d	Abstract—Conclusion—What have we learned and what does it mean. Where should future research go	1
3	Explain the scientific background and rationale for the cohort study. What are objectives, research questions and the hypotheses	2
4a	Registration and ethics state the research registry number in accordance with the declaration of Helsinki—Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject (this can be obtained from; ResearchRegistry.com or ClinicalTrials.gov or ISRCTN). Even retrospective studies should be registered prior to submission	2, 13
4b	Ethical Approval—State whether ethical approval was needed and if so, what the relevant judgement reference from the IRB or local ethics committee was? If ethical approval was not needed, state why	2, 17
4c	Protocol—Was a research protocol developed prior? Where can it be accessed. Was it published in a journal e.g., IJS Protocols, BMJ Open, etc., if so, provide the reference	2
5a	Study design—State the research is a cohort study and whether prospective or retrospective in design, whether single or multi-centre	2
5b	Setting—Describe the setting(s) and nature of the institution in which the patient was managed; academic, community or private practice setting? Location(s), and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2
5c	Cohort Groups—State the number of groups in the study. What interventions will each group receive?	3
5d	Sub-group—Analysis. Any planned sub-group analyses are specified/describe any methods used to examine subgroups and interactions	3
6a	Participants—State any eligibility (inclusion/exclusion) criteria and the sources and methods of selection of participants. Describe length and methods of follow-up	2
6b	Recruitment—State the methods of how patients or participants were recruited to each group, over what time periods	2-4
6c	Sample size calculation—Whether there was calculation of margin of error or a prior analysis to determine study population, or mention of how appropriate study sample was determined	2-4
7a	Pre-intervention considerations, e.g., patient optimisation: measures taken prior to surgery or other intervention e.g., treating hypothermia/hypovolaemia/hypotension in burns patients, ICU care for sepsis, dealing with anticoagulation/other medications and so on	3
7b	Types of intervention(s) deployed—To include reasoning behind treatment offered (pharmacological, surgical, physiotherapy, psychological, preventive) and concurrent treatments (antibiotics, analgesia, anti-emetics, nil by mouth, VTE prophylaxis, etc.). Medical devices should have manufacturer and model specifically mentioned	3, 4
7c	Peri-intervention considerations—Administration of intervention (what, where, when and how was it done, including details for surgery; anaesthesia, patient position, use of tourniquet and other relevant equipment, preparation used, sutures, devices, surgical stage (1 or 2 stage, etc.) and operative time. Pharmacological therapies should include formulation, dosage, strength, route and duration). Authors are encouraged to use figures, diagrams, photos, video and other multimedia to explain their intervention	3
7d	Who performed the procedure(s)—Operator experience for each group (position on the learning curve for the technique if established, specialisation and prior relevant training)	3
7e	Quality control—What measures were taken to reduce inter or intra-operator variation. What measures were taken to ensure quality and consistency in the delivery of the intervention e.g., independent observers, lymph node counts, etc.	3, 4
7f	Post-intervention considerations, e.g., post-operative instructions and place of care. Important follow-up measures, diagnostic and other test results. Future surveillance requirements, e.g., imaging surveillance of endovascular aneurysm repair (EVAR) or clinical exam/ultrasound of regional lymph nodes for skin cancer	3, 4
8	Outcomes—What primary and secondary (if any) outcomes will be assessed and how are they defined. Definitions should be clear and precise. Appropriate references to validation of outcome measures used should be provided if they exist	3
9	Statistical methods—Clearly outlined statistical tests used to compare the outcomes between an intervention group and a comparison group, state whether pre-existing differences and known confounders were controlled. The statistical package used should be mentioned	4
10a	Participants recruited with a flow diagram—Report numbers involved in each group and use a flow diagram to show recruitment, non-participation, cross-over, withdrawal from the study with reasons	4
10b	Comparison between groups including a table—Provide a table comparing the demographic, clinical/prognostic features (co-morbidities, tumour staging, smoking status, etc.) and relevant socioeconomic characteristics of each group and whether numerical differences are significant (using P values and/or confidence intervals as appropriate). Were the groups matched and if so, how	4-9, *Tables 1,2*, *Figure 1*
10c	Changes—Any changes in the interventions during the course of the study (how has it evolved, been altered or tinkered with, what learning occurred, etc.) together with rationale and a diagram if appropriate. Degree of novelty for a surgical technique/device should be mentioned and a comment on learning curves should be made for new techniques/devices	4
11a	Outcomes and follow-up—Clinician assessed and patient-reported outcomes (when appropriate) should be stated for each group (size of effect with raw numbers and percentages) with inclusion of the time periods at which assessed. Relevant photographs/radiological images should be provided e.g., 12-month follow-up. Make it clear which confounders were adjusted for and which were not	4, 9-15, *Tables 3,4*, *Figures 2,3,5*
11b	Intervention adherence/compliance and tolerability—How was this assessed. Describe loss to follow-up (express as a percentage and a fraction) or cross-over between group and any explanations for them	4, 9
11c	Complications and adverse or unanticipated events—Described in detail and ideally categorised in accordance with the Clavien-Dindo Classification. How they were prevented, mitigated, diagnosed and managed. Blood loss, wound complications, re-exploration/revision surgery, 30-day post-op and long-term morbidity/mortality may need to be specified	4, 9-14, *Tables 3,4, Figures 3,4*
12	Summarise key results	14
13	Discussion of the relevance of the findings and rationale for conclusions—Relevant literature, implications for clinical practice guidelines, how have the indications for a new technique/device been refined and how do outcomes compare with established therapies and the prevailing gold standard should one exist and any relevant hypothesis generation. The rationale for any conclusions	15, 16
14	Strengths and limitations of the study	16
15	State what needs to be done next, further research with what study design(s)	16
16	State the key conclusions from the study and key directions for future research	16
17a	State any conflicts of interest	17
17b	State any sources of funding	16,17