

A preliminary study identifies early postoperative lung volume changes in patients with non-small cell lung cancer following video-assisted thoracic surgery using CT volumetry

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Abstract. The present study aimed to investigate the changes in early postoperative lung volume in patients with non-small cell lung cancer (NSCLC) following video-assisted thoracic surgery (VATS) and to analyze the effects of the clinical characteristics on the lung volume of the patients. Therefore, 38 patients with NSCLC, who planned to undergo VATS at the Department of Thoracic Surgery, The Affiliated Hospital of Guizhou Medical University in June 2019, were enrolled into the present study. The clinical and computed tomography (CT) scan data from the patients was prospectively collected within 1 week preoperatively, and at 1, 3 and 6 months following surgery, then subsequently analyzed. A total of 34 patients successfully completed follow-up and were included in the datasets. The results showed that the volume of the right lung was larger compared with that in the left one, at each observational time point. The whole, right and left lung held the same trendline of volume changes, which was sharply decreased during the first postoperative month, increased quickly over the next 3 months, and slowly increased from months 3 to 6. There were 7 patients, whose whole lung volume was increased at 6 months following surgery compared with that preoperatively. In addition, significant differences were observed between males and females in the whole, right and left lung volume. However, the differences on the postoperative

net expansion volume of the whole lung were not significant among sex, age, body mass index (BMI), smoking status and surgical side subgroups. The early changes of the postoperative lung volume were not linear, since the lung volume was significantly reduced during the first postoperative month, quickly increased in the next 3 months, and slowly increased from months 3 to 6. Sex, age, BMI, smoking status and surgical sides was not found to affect the postoperative volume and net expansion of the whole lung following VATS lobectomy.

Introduction

Lung cancer has the second highest incidence and highest mortality rates in both males and females worldwide (1). It is well-known that surgical resection plays an important role in the comprehensive treatment of lung cancer. The preoperative evaluation and postoperative prediction of pulmonary function (PF) is essential for lung resection, as PF can predict the risk of perioperative complications, and long-term disability and mortality following major lung resection (2-4). Furthermore, the prediction of the postoperative PF has been associated with long-term survival following surgery compared with that in preoperative lung function (5). Several methods have been developed to predict the postoperative PF (6-8), such as perfusion scans and segment counting methods; however, it has been suggested that these methods are inaccurate (9-11). The postoperative PF could be theoretically determined by the residual parenchymal volume following lung resection, since the adult lung generally does not have the ability to regenerate new alveolar septal tissues (12). In addition, the compensatory expansion of the remaining lung is not simply a consequence of hyperexpansion of the pre-existing alveolar septal tissue, but is accompanied by compensatory growth of the residual lung in volume and weight (13). Based on this theory, volumetric computed tomography (CT) has been widely used in several studies to observe the perioperative changes in lung volume or for analyzing the correlation between lung volume and PF tests (PFTs) (14-19). Therefore, volumetric CT has been considered

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to be more reliable and accurate in predicting postoperative PF compared with that in the segment-counting method (18-20). However, previous studies have only analyzed the changes in lung volume at two time points, preoperatively and postoperatively. Therefore, the present study aimed to continuously analyze the changes in the early postoperative lung volume in patients with non-small cell lung cancer (NSCLC) following video-assisted thoracic surgery (VATS) using volumetric CT.

Materials and methods

Clinical data collection. A total of 34 patients (58.56 ± 9.00 years) with NSCLC, who planned to undergo VATS lobectomy in June 2019, were enrolled in the present study. The study was approved by the Human Ethics Committee of The Affiliated Hospital of Guizhou Medical University (Guizhou, China; approval no. 2020-244). Written informed consent was provided by all the patients, for the use of their data in scientific research at the beginning of enrollment. The clinical and radiological data of the patients, including sex, age, body mass index (BMI), smoking status, surgical sides and chest CT scans were prospectively collected within 1 week preoperatively (T0), and at 1 (T1), 3 (T2) and 6 months (T3) following surgery.

CT scan. The CT images were acquired using a LightSpeed VCT 64-detector scanner (GE Healthcare), with subjects holding their breath at the end of inspiration without contrast. The following CT parameters were used: 64×0.625 mm detector configuration, 0.969 pitch, 120 kVp tube energy, 250 mA tube current and 0.4 sec gantry rotation (or 100 mAs). The CT scan images were saved as DICOM format.

Surgical procedure. All surgical procedures were performed by the same team using uniportal VATS, as previously described (21).

Lung volume measurement. The CT scan data was loaded into the Chest Imaging Platform and analyzed using the 3D Slicer software (version 4.10.2; macOS; <https://download.slicer.org/>). The Interactive Lobe Segmentation module was used to segment the lung lobes, and the Label Statistics module under the Quantification menu was used to compute the left and right sides, and whole lung volume (Fig. S1).

Statistical analysis. All the data from the recorded measurements was manually entered into the different analyses by the same researcher. Descriptive statistics were used to describe the demographic characteristics. Age and BMI were categorized into two groups (low and high) according to their mean values. Continuous variables were presented as the mean \pm standard deviation, while categorical values were presented as numbers. Net compensatory expansion volume was calculated as the lung volume at the current observation time minus the prior volume. Mixed two-way ANOVA was utilized to compare the differences between subgroups, and χ^2 or Fisher's exact test was used for categorical data. Greenhouse-Geisser was used to adjust the degrees of freedom for the average number of tests of significance if $P < 0.05$ from the Mauchly's Test of Sphericity. A two-tailed $P < 0.05$ was considered to indicate a statistically significant

Table I. Demographic characteristics of the patients in the study.

Variable	Sex		P-value
	Female (n=19)	Male (n=15)	
Age, years			$>0.9999^a$
Low	10	8	
High	9	7	
BMI			0.510 ^a
Low	9	9	
High	10	6	
Smoking status			$<0.001^b$
No	19	7	
Yes	0	8	
Smoking in males			-
No	-	7	
Yes	-	8	
Surgical side			0.491 ^a
Left	11	6	
Right	8	9	

^a χ^2 test. ^bFisher's exact test. -, not applicable. BMI, body mass index.

difference. All statistical analyses were performed using the SPSS v22.0 software (SPSS Inc.).

Results

Demographic characteristics. A total of 38 patients with NSCLC underwent VATS in June 2019 at the Department of Thoracic Surgery, The Affiliated Hospital of Guizhou Medical University, (Guizhou, China). None of the patients were treated with pneumonectomy or complex lobectomy. All the procedures were successfully performed using VATS, without converting to thoracotomy. Among all the patients, two were lost to follow-up at 1 and 3 months following surgery, respectively, and two at 6 months. Finally, there were 34 patients at the end of follow-up and were included in the datasets. The demographic characteristics of the included patients are listed in Table I. A total of 19 male patients were included. Among all the patients, 17 underwent left lateral VATS, while the remaining 17 received right lateral VATS. When the patients were divided by sex, there was no significant difference for the clinicopathological variables, except for smoking status where all eight (23.529%) smokers were males.

Changes on the whole, left and right lung volume over time. The volume of the whole, left and right lung at four observation time points are shown in Table II. The mean T0 volume of the whole, left and right lung was $4,101.884 \pm 1,328.220$, $1,899.614 \pm 646.058$ and $2,202.270 \pm 691.434$, respectively. At T1, T2 and T3 months following surgery the lung volume were $3,030.510 \pm 931.542$, $1,381.809 \pm 670.565$ and $1,648.701 \pm 676.186$; $3,436.707 \pm 1,103.550$, $1,586.401 \pm 739.232$ and

Table II. Volume of the whole, left and right lungs at the 4 different time points.

Variable	Whole lung volume, cm ³				Left lung volume, cm ³				Right lung volume, cm ³			
	T0	T1	T2	T3	T0	T1	T2	T3	T0	T1	T2	T3
Sex												
Female	3,272.759± 810.066	2,477.130± 566.826	2,925.970± 567.092	3,043.140± 654.015	1,497.312± 395.527	1,086.578± 496.934	1,273.863± 475.406	1,317.724± 447.079	1,775.447± 431.080	1,390.552± 467.365	1,652.107± 436.681	1,725.416± 462.275
Male	5,152.108± 1,095.435	3,731.458± 830.874	4,083.640± 1,286.341	4,123.368± 1,036.882	2,409.197± 533.703	1,755.768± 688.682	1,982.282± 834.880	1,948.489± 693.342	2,742.912± 572.334	1,975.691± 769.356	2,101.358± 810.313	2,174.879± 695.152
Age, years												
Low	4,155.538± 1,280.020	3,094.768± 961.623	3,359.832± 1,030.550	3,496.363± 796.523	1,899.322± 618.382	1,151.444± 537.880	1,322.485± 529.842	1,409.095± 467.056	2,256.216± 667.454	1,943.324± 694.713	2,037.347± 710.328	2,087.269± 566.783
High	4,041.522± 1,420.182	2,958.221± 922.255	3,523.191± 1,208.512	3,545.978± 1,203.490	1,899.942± 696.332	1,640.969± 725.281	1,883.306± 840.502	1,806.275± 757.995	2,141.580± 734.480	1,317.251± 487.419	1,639.885± 541.661	1,739.703± 622.942
BMI												
Low	4,481.488± 1,494.895	3,199.363± 1,042.720	3,673.936± 1,321.679	3,689.551± 1,222.608	2,094.263± 722.249	1,333.293± 762.683	1,568.583± 855.659	1,564.583± 757.554	2,387.224± 783.281	1,866.070± 733.236	2,105.353± 764.965	2,124.968± 687.809
High	3,674.829± 990.476	2,840.551± 777.277	3,169.824± 745.623	3,328.643± 633.396	1,680.633± 480.051	1,436.389± 569.210	1,606.445± 609.620	1,631.351± 507.880	1,994.196± 518.858	1,404.162± 525.447	1,563.379± 354.089	1,697.291± 425.326
Smoking status												
No	3,739.141± 1,250.955	2,735.445± 807.939	3,217.146± 879.126	3,244.740± 7,62.950	1,722.129± 604.613	1,199.674± 526.126	1,424.797± 533.893	1,432.506± 468.997	2,017.012± 655.011	1,535.771± 650.131	1,792.349± 666.148	1,812.234± 565.896
Yes	5,280.799± 806.708	3,989.472± 620.692	4,150.280± 1,489.952	4,413.370± 1,172.613	2,476.442± 406.046	1,973.747± 779.455	2,111.612± 1070.479	2,127.369± 862.740	2,804.357± 423.970	2,015.726± 666.815	2,038.668± 638.268	2,286.001± 646.547
Smoking in males												
No	5,005.034± 1,411.875	3,436.586± 985.468	4,007.479± 1,121.726	3,791.939± 814.952	2,332.345± 677.755	1,506.649± 511.953	1,834.476± 491.620	1,744.056± 402.359	2,672.689± 737.446	1,929.937± 926.171	2,173.004± 1,022.533	2,047.883± 777.546
Yes	5,280.799± 806.708	3,989.472± 620.692	4,150.280± 1,489.952	4,413.370± 1,172.613	2,476.442± 406.046	1,973.747± 779.455	2,111.612± 1070.479	2,127.369± 862.740	2,804.357± 423.970	2,015.726± 666.815	2,038.668± 638.268	2,286.001± 646.547
Surgical side												
Left	3,986.829± 1,435.053	2,883.643± 957.540	3,105.051± 1,097.118	3,339.147± 865.230	1,830.101± 677.287	878.966± 276.732	1,045.696± 370.918	1,161.698± 308.242	2,156.729± 762.489	2,004.677± 699.511	2,059.355± 738.477	2,177.449± 570.135
Right	4,216.938± 1,245.427	3,177.378± 909.428	3,768.363± 1,036.508	3,700.276± 1,102.435	1,969.127± 626.006	1,884.652± 559.936	2,127.106± 606.822	2,030.308± 598.418	2,247.810± 632.649	1,292.726± 429.463	1,641.258± 506.538	1,669.968± 554.263
Mean total volume	4,101.884± 1,328.220	3,030.510± 931.542	3,436.707± 1,103.550	3,519.711± 992.888	1,899.614± 646.058	1,381.809± 670.565	1,586.401± 739.232	1,596.003± 643.452	2,202.270± 691.434	1,648.701± 676.186	1,850.306± 658.665	1,923.708± 610.644

T0, preoperative; T1, 1 month following surgery; T2, 3 months following surgery; T3, 6 months following surgery.

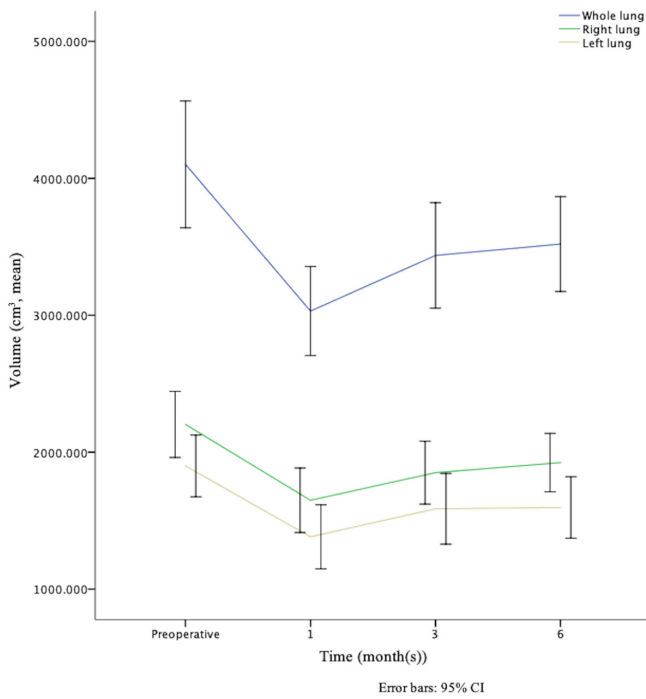


Figure 1. Changes in the whole, left and right lung volume at four different time points.

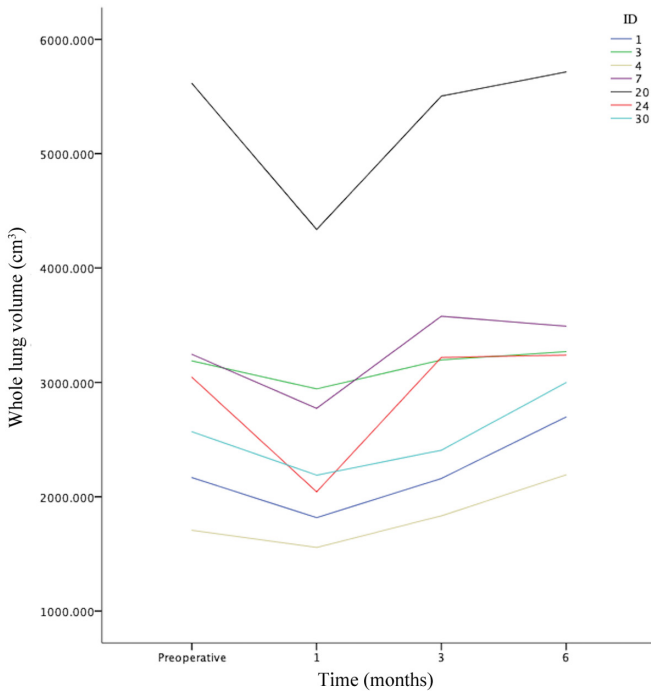


Figure 2. Lung volume changes in patients which had higher whole lung volume at 6 months following surgery compared with that preoperatively.

1,850.306±658.665; and 3,519.711±992.889, 1,596.003±643.452 and 1,923.708±610.644 for whole, left and right lung, respectively. The mean volume of the right lung was larger compared with that in the left one, at each time point. In addition, the trendline of volume changes in the whole, right and left lung were similar; it sharply decreased during the first postoperative month, quickly increased in the following 3 months, and slowly

increased from the 3rd to the 6th month (Fig. 1). In a total of seven patients (20.588%), the whole lung volume at 6 months following surgery was larger compared with that preoperatively (Fig. 2). However, the differences in the distribution of the observational variables were not significant (all $P>0.05$) when the aforementioned seven patients were compared with those whose whole lung volume at 6 months following surgery was similar prior to surgery (Table III).

Changes in lung volume depends on surgical side. When the surgical sides were taken into consideration, the trendline of the ipsilateral lung volume was consistent with the aforementioned results. The postoperative changes on the left lung were consistent (Fig. 3A); however, the right lung rapidly recovered from T1 to T2, and then slightly recovered from T2 to T3 (Fig. 3B). With respect to the contralateral lung, the difference was notable. When the surgery was performed on the right side, the volume of the left lung was increased until T2, and then decreased slightly to just above the baseline (Fig. 3C). On the contrary, when the surgery was performed on the left side, the trendline of the right lung volume was as aforementioned, except that the mean volume at T3 increased to just above baseline (Fig. 3D).

Results of mixed two-way ANOVA

Whole, left and right lung volume. The results of the mixed two-way ANOVA are shown in Table IV. The differences in lung volume for each variable on the whole, left and right lung at the indicated observation time points (all $P<0.05$) were significant compared with that for the main effect for the within-subject effects. This finding indicated that the volume of the whole, left and right lung was significantly changed over the course of time from T0 to T3. However, the differences were not all significant among diverse subgroups compared with the between-subject effects.

Sex. The differences on the whole, left and right lung volume were significant between the sex subgroups compared with the main effect for the between-subject effects (all $P<0.05$). In addition, the whole, left and right lung volume in males was notably increased compared with females among the different observation time points (Table II; Fig. 4A-C). Furthermore, the interactive effects of time and sex on the whole and right lung volume was significant (both $P<0.05$) (interaction with time under within-subject effects; Table IV), but not on that on the left lung volume, indicating that the changing trends on the whole and right lung volume were significantly different between males and females over time (from T0 to T3).

Age. The interactive effects of age and time were significantly different on the volume of the left and right lung (both $P<0.05$) (interaction with time under within-subject effects); however, the differences on the whole, left and right lung volume were not significant between the age subgroups (all $P>0.05$) (main effect under between-subject effects) (Table IV). These findings indicated that the whole, left and right lung volume was similar between the low- and high-age groups at each observation time point, and that the changing trend of the whole lung volume, but not of that of the left and right lung, was the same between the age subgroups.

Table III. Demographic characteristics of 7 patients in which whole lung volume was larger at 6 months postoperatively than preoperatively.

Variable	Whole lung volume larger postoperatively than preoperatively	Whole lung volume preoperatively than postoperatively	P-value
Sex			0.104
Female	6	13	
Male	1	14	
Age, years			0.681
Low	3	15	
High	4	12	
BMI			0.214
Low	2	16	
High	5	11	
Smoking status			>0.9999
No	6	20	
Yes	1	7	
Surgical side			>0.9999
Left	3	14	
Right	4	13	

BMI, body mass index.

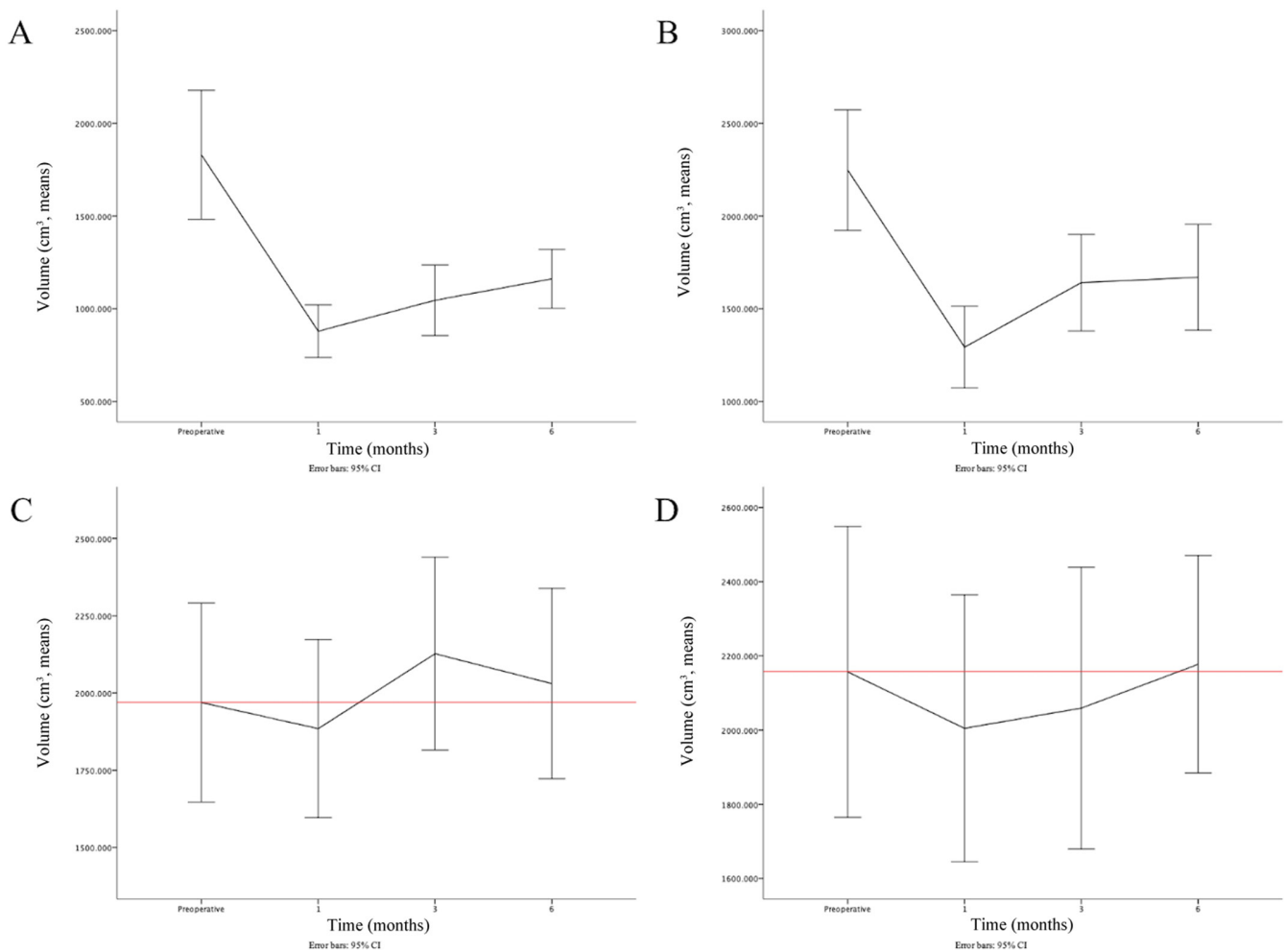


Figure 3. Trendline of the lung volume in association with the surgical side. The change of the (A) left and (B) right mean lung volume in ipsilateral lung surgery. The change of the (C) right and (D) left mean lung volume in contralateral lung surgery. The red line indicates the baseline.

Table IV. Results of whole, right and left lung volume changes analyzed using mixed two-way ANOVA.

A, Whole lung volume								
Variable	Within-subject effects (at different time points)						Between-subject effects (among diverse subgroups)	
	Main effect		Interaction with time		Intercept		Main effect	
	P-value	η^2	P-value	η^2	P-value	η^2	P-value	η^2
Sex	<0.001	0.541	0.001	0.157	<0.001	0.957	<0.001	0.437
Age	<0.001	0.488	0.503	0.024	<0.001	0.924	0.979	<0.001
BMI	<0.001	0.490	0.154	0.053	<0.001	0.928	0.152	0.063
Smoking status	<0.001	0.460	0.144	0.054	<0.001	0.934	0.002	0.265
Smoking in males	<0.001	0.580	0.614	0.045	<0.001	0.956	0.444	0.046
Surgical side	<0.001	0.494	0.226	0.044	<0.001	0.927	0.277	0.037
B, Left lung volume								
Variable	Within-subject effects (at different time points)						Between-subject effects (among diverse subgroups)	
	Main effect		Interaction with time		Intercept		Main effect	
	P-value	η^2	P-value	η^2	P-value	η^2	P-value	η^2
Sex	<0.001 ^a	0.339 ^a	0.269 ^a	0.040 ^a	<0.001	0.919	<0.001	0.345
Age	<0.001 ^a	0.345 ^a	0.005 ^a	0.161 ^a	<0.001	0.876	0.223	0.092
BMI	<0.001 ^a	0.342 ^a	0.007 ^a	0.152 ^a	<0.001	0.875	0.813	0.002
Smoking	<0.001 ^a	0.254 ^a	0.860 ^a	0.003 ^a	<0.001	0.895	0.002	0.257
Smoking in male	0.005 ^a	0.364 ^a	0.597 ^a	0.034 ^a	<0.001	0.926	0.331	0.073
Surgical sides	<0.001 ^a	0.477 ^d	<0.001 ^a	0.484 ^a	<0.001	0.922	<0.001	0.403
C, Right lung volume								
Variable	Within-subject effects (at different time points)						Between-subject effects (among diverse subgroups)	
	Main effect		Interaction with time		Intercept		Main effect	
	P-value	η^2	P-value	η^2	P-value	η^2	P-value	η^2
Sex	<0.001 ^a	0.397 ^a	0.004 ^a	0.147 ^a	<0.001	0.936	0.002	0.267
Age	<0.001	0.380	0.011	0.109	<0.001	0.920	0.070	0.099
BMI	<0.001 ^a	0.346 ^a	0.762 ^a	0.010 ^a	<0.001	0.924	0.024	0.149
Smoking	<0.001 ^a	0.368 ^a	0.043 ^a	0.088 ^a	<0.001	0.908	0.038	0.128
Smoking in male	<0.001	0.478	0.595	0.047	<0.001	0.929	0.819	0.004
Surgical sides	<0.001	0.423	<0.001	0.289	<0.001	0.921	0.058	0.108

^aGreenhouse-Geisser was used to adjust the degrees of freedom for the average number of tests of significance if $P < 0.05$ from the Mauchly's Test of Sphericity. BMI, Body mass index.

BMI. The differences on the right lung volume were significant between the BMI subgroups ($P < 0.05$; main

effect under between-subject effects; Table IV). However, no significant differences were observed in the whole

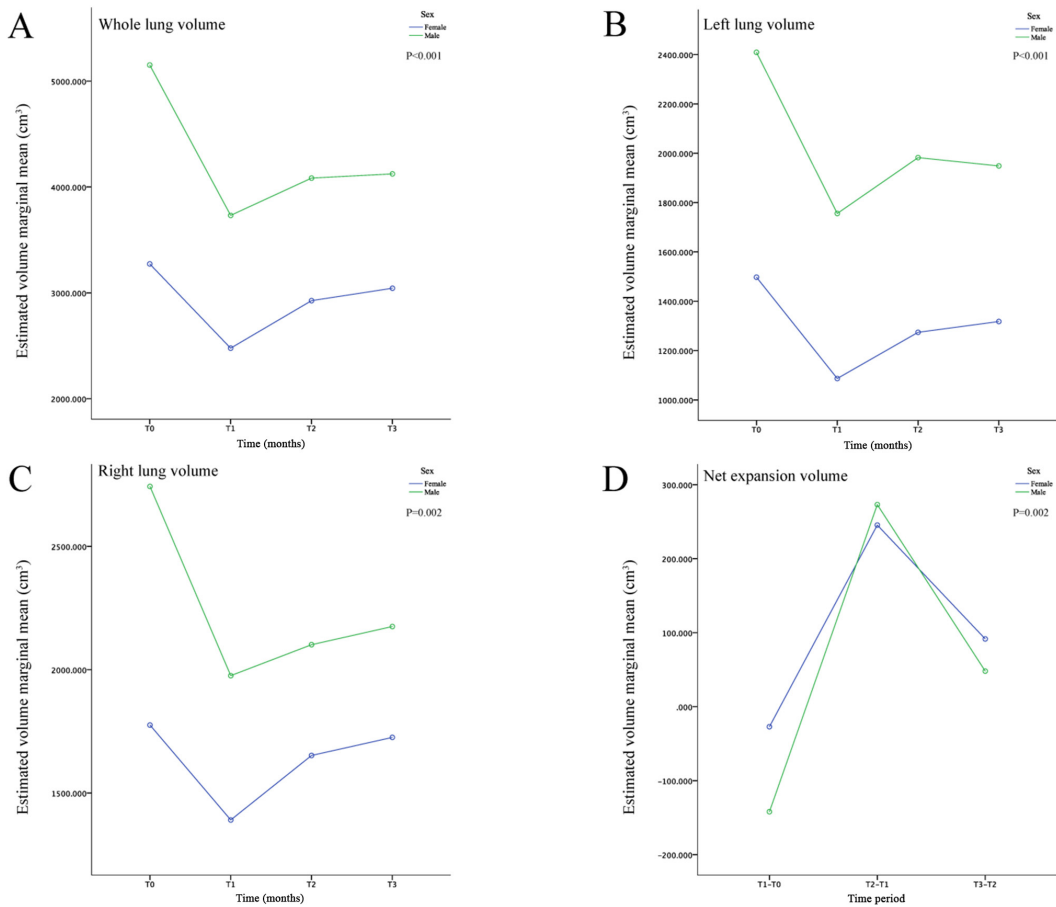


Figure 4. Profile plots of the estimated marginal mean for sex. The profile plots for the (A) whole, (B) left, and (C) right lung, and (D) net expansion.

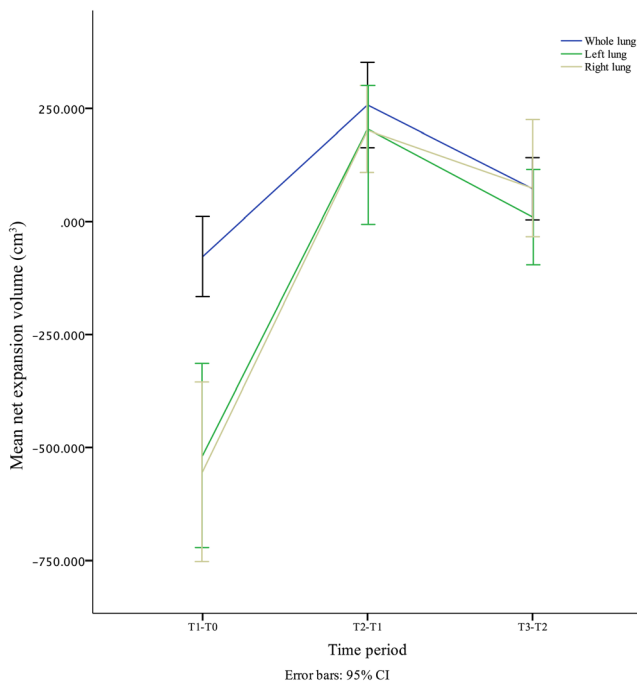


Figure 5. Net expansion changes in the whole, left and right lung volume at the indicated time points.

and left lung volume (both $P>0.05$) (main effect under between-subject effects).

Smoking status. The differences on the whole, left and right lung volume were significant between smoking status and the between-subject effects (all $P<0.05$) (main effect under between-subject effects; Table IV); however, the differences were not significant when compared with the male subgroup (all $P>0.05$) (main effect under between-subjects effects), since all smokers were males. This finding suggested that the whole, left and right lung volume was similar at each time point regardless of the smoking status.

Net expansion volume. The net expansion volume of the whole, left and right lung is presented in Table V. In general, the mean net expansion volume of the whole, left and right lung was sharply decreased during the first postoperative month, quickly increased in the next three months, and slowly decreased from the 3rd to the 6th month (Fig. 5). These changes were in accordance with the volume changes. The differences in age, BMI and surgical side in the left lung, as well as sex and surgical side in the right lung, were significant. However, these observational variables were not significant in the whole lung (Table VI). The combination of the aforementioned results indicated that the differences in the postoperative whole lung volume could be mainly attributed to the differences observed preoperatively regardless of the observational variables. For example, the lung volume in males was larger compared with that in females preoperatively and postoperatively, as the postoperative net expansion volume was similar between males and females (Fig. 4D).

Table V. Net expansion volume changes of whole, left and right lung.

Variable	Whole lung volume, cm ³			Left lung volume, cm ³			Right lung volume, cm ³		
	T1-T0	T2-T1	T3-T2	T1-T0	T2-T1	T3-T2	T1-T0	T2-T1	T3-T2
Sex									
Female	-27.142± 177.701	245.440± 164.166	91.538± 155.426	-410.734± 452.226	187.285± 175.553	43.861± 242.817	-384.895± 429.201	261.556± 217.434	73.309± 240.729
Male	-142.024± 321.508	273.073± 370.911	48.058± 243.555	-653.429± 710.643	226.514± 372.277	-33.793± 369.170	-767.221± 660.695	125.667± 620.850	73.521± 8,499.807
Age, years									
Low	-32.202± 218.993	182.494± 263.741	71.667± 243.561	-747.878± 569.819	171.041± 277.913	86.610± 251.492	-312.892± 418.738	94.024± 527.546	49.921± 487.915
High	-129.151± 286.504	342.160± 260.654	73.1311± 134.823	-258.973± 496.693	242.337± 277.109	-77.031± 338.407	-824.329± 603.099	322.633± 286.154	99.819± 177.439
BMI									
Low	-133.694± 217.425	298.775± 270.518	64.968± 193.242	-760.970± 628.158	235.290± 248.284	-4.00± 305.399	-521.154± 604.786	239.283± 475.435	19.615± 441.113
High	-14.972± 283.210	211.344± 271.875	80.668± 207.242	-244.244± 389.484	170.056± 308.100	24.906± 308.459	-590.034± 541.242	159.217± 408.671	133.913± 273.481
Smoking status									
No	-59.844± 250.658	255.604± 201.136	57.093± 185.427	-522.454± 621.998	225.123± 240.067	7.709± 259.168	-481.241± 457.850	256.578± 263.210	19.885± 349.929
Yes	-136.265± 272.478	264.218± 448.125	121.959± 237.795	-502.695± 473.683	137.866± 381.821	15.756± 437.564	-788.631± 830.976	22.942± 787.057	247.333± 407.546
Smoking in males									
No	-148.605± 393.037	283.193± 294.107	-36.400± 238.403	-825.69± 922.864	327.827± 361.716	-90.420± 295.997	-742.752± 460.026	243.067± 382.808	-125.121± 550.264
Yes	-136.265± 272.478	264.218± 448.125	121.959± 237.795	-502.695± 473.683	137.866± 381.821	15.756± 437.564	-788.631± 830.976	22.942± 787.057	247.333± 407.546
Surgical sides									
Left	-30.281± 186.002	166.730± 248.420	116.001± 217.314	-951.135± 461.452	166.730± 248.420	116.001± 217.314	-152.052± 330.877	54.67± 531.445	118.094± 500.732
Right	-125.370± 305.753	348.532± 268.004	28.710± 169.700	-84.475± 301.425	242.454± 303.290	-96.797± 342.721	-955.085± 462.288	348.532± 268.004	28.710± 169.700
Total volume	-77.825± 253.829	257.631± 270.665	72.356± 197.034	-517.805± 583.746	204.592± 275.675	9.602± 302.507	-553.568± 568.154	201.605± 440.459	73.402± 370.928
BMI, body mass index.									

Table VI. Results of the net expansion volume changes in whole, right and left lung volume analyzed using mixed two-way ANOVA.

A, Whole lung volume

Variable	Within-subject effects (at different time points)						Between-subject effects (among diverse subgroups)	
	Main effect		Interaction with time		Intercept		Main effect	
	P-value	η^2	P-value	η^2	P-value	η^2	P-value	η^2
Sex	<0.001 ^a	0.288 ^a	0.525 ^a	0.017 ^a	<0.001	0.462	0.171	0.058
Age, years	<0.001 ^a	0.298 ^a	0.166 ^a	0.057 ^a	<0.001	0.472	0.504	0.014
BMI	<0.001 ^a	0.277 ^a	0.300 ^a	0.036 ^a	<0.001	0.469	0.625	0.008
Smoking status	0.001 ^a	0.241 ^a	0.605 ^a	0.012 ^a	<0.001	0.384	0.979	<0.001
Smoking in males	0.033 ^a	0.267 ^a	0.703 ^a	0.018 ^a	0.081	0.216	0.424	0.050
Surgical side	<0.001 ^a	0.296 ^a	0.075 ^a	0.085 ^a	<0.001	0.466	0.995	<0.001

B, Left lung volume

Variable	Within-subject effects (at different time points)						Between-subject effects (among diverse subgroups)	
	Main effect		Interaction with time		Intercept		Main effect	
	P-value	η^2	P-value	η^2	P-value	η^2	P-value	η^2
Sex	<0.001	0.424	0.449	0.025	0.001	0.280	0.131	0.070
Age, years	<0.001	0.435	0.009	0.136	0.002	0.262	0.029	0.140
BMI	<0.001	0.430	0.016	0.121	0.001	0.274	0.007	0.206
Smoking status	<0.001	0.321	0.906	0.003	0.007	0.209	0.789	0.002
Smoking in males	0.001	0.431	0.472	0.056	0.020	0.351	0.510	0.034
Surgical side	<0.001	0.534	<0.001	0.390	<0.001	0.387	<0.001	0.477

C, Right lung volume

Variable	Within-subject effects (at different time points)						Between-subject effects (among diverse subgroups)	
	Main effect		Interaction with time		Intercept		Main effect	
	P-value	η^2	P-value	η^2	P-value	η^2	P-value	η^2
Sex	<0.001 ^a	0.386 ^a	0.338 ^a	0.033 ^a	<0.001	0.355	0.001	0.279
Age, years	<0.001 ^a	0.417 ^a	0.015 ^a	0.134 ^a	0.002	0.266	0.174	0.057
BMI	<0.001 ^a	0.373 ^a	0.669 ^a	0.011 ^a	0.003	0.248	0.842	0.001
Smoking status	<0.001 ^a	0.352 ^a	0.176 ^a	0.054 ^a	0.001	0.300	0.118	0.075
Smoking in males	0.009 ^a	0.361 ^a	0.465 ^a	0.050 ^a	0.001	0.593	0.692	0.012
Surgical side	<0.001 ^a	0.449 ^a	<0.001 ^a	0.279 ^a	<0.001	0.345	<0.001	0.378

^aGreenhouse-Geisser was used to adjust the degrees of freedom for the average number of tests of significance if $P < 0.05$ from the Mauchly's test of sphericity. BMI, Body mass index.

Surgical side. The results showed that the changing trend of volume and net expansion volume was significant in the

ipsilateral lung compared with that in the contralateral lung (all $P < 0.05$) (main effect under the between-subjects effects;

Table VII. Volume and net expansion volume changes of the ipsilateral and contralateral lung.

Surgical side	Lung volume, cm ³				Net expansion volume, cm ³		
	T0	T1	T2	T3	T1-T0	T2-T1	T3-T2
Ipsilateral	2,038.956± 679.271	1,085.846± 413.099	1,343.477± 531.478	1,415.832± 511.427	-953.110± 454.823	257.631± 270.665	72.356± 197.034
Contralateral	2,062.928± 693.509	1,944.664± 626.872	2,093.230± 666.431	2,103.879± 580.349	-118.264± 313.543	148.566± 436.599	10.649± 436.361

T0, preoperative; T1, 1 month after surgery; T2, 3 months after surgery; T3, 6 months after surgery.

Table VIII. Differences in volume and net expansion between ipsilateral and contralateral lungs according to surgical sides analyzed using mixed two-way ANOVA.

Variable	Within-subject effects (at different time points)						Between-subject effects (among diverse subgroups)	
	Main effect		Interaction with time		Intercept		Main effect	
	P-value	η^2	P-value	η^2	P-value	η^2	P-value	η^2
Volume	<0.001	0.435	<0.001	0.36	<0.001	0.913	<0.001	0.221
Net expansion	<0.001 ^a	0.427 ^a	<0.001 ^a	0.295 ^a	<0.001	0.364	<0.001	0.427

^aGreenhouse-Geisser was used to adjust the degrees of freedom for the average number of tests of significance if $P < 0.05$ from the Mauchly's test of sphericity.

Tables VII and VIII). It indicated that the ipsilateral lung experienced more dramatic change of volume than contralateral after lobectomy.

Discussion

To the best of our knowledge, the present study reported for the first time the perioperative changes on lung volume. The main finding was that the whole, right and left lung exhibited a similar trendline of volume changes (Figs. 1-3). More specifically, the whole, right and left lung volumes were notably decreased during the first postoperative month (all $P < 0.05$), increased quickly in the next three months (all $P < 0.05$) then increased more slowly from the 3rd to the 6th month (all $P > 0.05$). In addition, the differences in all 3 lung volumes were all significant among the four observational time points (all $P < 0.05$) (Table II). The results indicated that the postoperative compensatory expansion of the bilateral lung, and consequently of the whole lung, occurred before the first month following surgery and lasted ≥ 6 months postoperatively. Furthermore, the results showed that the postoperative lung volume did not change linearly. These findings are consistent with previous studies. For example, Nagamatsu *et al* (22) demonstrated that the forced expiratory volume in 1.0 second (FEV1) per square meter (FEV1/m²), a main parameter of PF, was sharply decreased during the first postoperative month ($P < 0.001$), then quickly increased for the next three months ($P < 0.001$), and increased slowly for the next 3 months. Additional studies also

revealed that FEV1 (23-25), vital capacity (VC) (24), forced vital capacity (FVC) (25) and diffusion capacity of the lung for carbon monoxide (D_{LCO}) (23,24) were decreased in the early postoperative phase, after which they gradually improved, but not linearly. Further studies are required for identifying similar trendlines between the perioperative lung volume observed in the present study and PFTs used in previous studies; however, volumetric CT could be used to analyze perioperative PF or in combination with preoperative PFTs to predict the actual recovery of lung function following surgery. Furthermore, when the postoperative PF was predicted the predictive time points should also be also taken into consideration (22-25).

In addition, the results from the present study demonstrated that there were seven patients (20.588%) with an increased whole lung volume 6th months following surgery compared with that preoperatively (Fig. 2). This could be attributed to preoperative obstructive pneumonia in central lung cancer or an enormous space occupying lesion in peripheral lung cancer. According to widely used algorithms, which were developed to predict postoperative PF based on the preoperative evaluated and resected segment, the postoperative PF should be inferior to the preoperative one (6-8). However, previous studies have already verified that it is imprecise to predict the postoperative function using these algorithms (9-11). This observation is reasonable and inevitable, since all of these algorithms are based on linear regression and ignore the variation of the postoperative lung volume re-expansion over time and the effects of compen-

satory expansion on PF recovery. Furthermore, the PFTs require the effort of the patient, which sometimes vary with time and the patient (24). However, the results of the current study and previous studies confirmed that the postoperative lung volume or PF did not change linearly (22-25).

When the surgical side was taken into consideration, postoperative compensatory expansion was not only observed in the ipsilateral residual lung, but also in the contralateral intact lung (Fig. 3). Ueda *et al* (26) and Choe *et al* (17) used volumetric CT to observe the changes in the regional lung volume after lobectomy or segmentectomy. The authors revealed that not only did the ipsilateral residual lung lobe increase significantly, but also the contralateral lung. Ueda *et al* (26) suggested that the compensatory expansion of the bilateral residual lung following major resection, particularly after lobectomy, could contribute to improved postoperative residual pulmonary function, and that increased postoperative functional lung volume was significantly correlated with improved postoperative PF ($R=0.6$; $P<0.001$).

Unlike previous studies (22-25), which investigated the changes in lung volume at only two different time points, the present study consistently recorded the perioperative changes. In addition, it was also found that the changing trends of the net compensatory expansion volume of the residual lung, which expanded rapidly between the 1st and 3rd postoperative month and then slowly for the next 3 months, were not linear in both the ipsilateral residual and contralateral intact lung (Fig. 5). This trend was similar with that observed in the whole lung, as aforementioned, and could be the root cause of the latter. With respect to the intactness of the contralateral lung, the only interpretation of the compensatory expansion could be the toward shift of the mediastinum ipsilateral chest, due to the ipsilateral chest volume loss attributed to lobectomy. The differences in the net compensatory expansion volume in the left and right lung were significant between the surgical sides ($P<0.001$; Table VI), and the ipsilateral and contralateral lung ($P<0.001$; Table VIII); however, no significant differences were observed in the whole lung ($P=0.995$; Table VI; Fig. 5). This phenomenon could be attributed to the neutralization of the differences in the surgical side by summation when calculating the whole lung volume. Choe *et al* (17) also demonstrated that the differences on the postoperative whole lung volume were not significant between the surgical sides, although a significant difference on the compensatory expansion volume between the contralateral and ipsilateral lung was observed.

Furthermore, the current study showed that sex exerted a significant influence on postoperative early lung volume recovery. The trendline changes of the whole, left and right lung volume were similar between males and females; however, the perioperative mean lung volume in males was significantly larger compared with that in females ($P<0.05$; Tables II and IV; Fig. 4). This finding could be due to the preoperative existing differences on lung volume. This was also in line with the study by Khieya (27) who reported that males were taller and more muscular with respect to body proportions, and not due to sex itself. This finding could also be verified by the absence of a significant difference in the net expansion volume of the whole and left lung between males and females (Table VI), and the fact that the adult

lung does not generally have the ability to regenerate new alveolar septal tissues (12). Kim *et al* (28) showed that the differences on the preservation of FEV1 following VATS were not significant between male and female patients with NSCLC. In addition, Takahashi *et al* (29) confirmed that the sex was not associated with improvement of postoperative PF following lobectomy.

The results of the present study also demonstrated that age, BMI and smoking status had no effect on postoperative lung volume and net expansion of the whole lung following VATS lobectomy. Measuring lung volume alone cannot adequately describe lung function; however, variations on lung volume may reflect changes in its function. It is widely accepted that obesity, old age and smoking increases the risk of postoperative pulmonary complications (30); however, their effect on lung function remains controversial. Matsumoto *et al* (31) suggested that smoking did not affect the decreased volume of VC and FEV1 following pulmonary lobectomy. In addition, Kim *et al* (28) confirmed that the differences on FEV1 preservation following VATS were not significant between smokers and non-smokers, while Takahashi *et al* (29) showed that smoking was negatively correlated with improvement of postoperative PF following lobectomy.

Khieya (27) investigated 317 healthy individuals in the Southern Angami population, and found that BMI was not statistically associated with FEV1, FVC, peak expiratory flow and FEV1/FVC. Furthermore, Kobayashi *et al* (32) retrospectively reviewed the medical records of 445 patients who underwent surgery for lung cancer between 2001 and 2009, and verified that BMI had no effect on PF at years 1 and 5 year following lobectomy. Previous studies also confirmed that BMI had no effect on postoperative PFTs (28,29).

Several studies have demonstrated that age was negatively correlated with PFTs (5,27,28,33). However, a study showed that the differences on PFTs were not significant among the low, medium and high age groups (34). Takahashi *et al* (29) also found that age was not associated with improvement of postoperative PF following lobectomy. However, further studies are required to identify the effect of age, BMI and smoking on postoperative lung function following VATS lobectomy.

There are some limitations in the present preliminary study. Firstly, there was no investigation into the association between lung volume on CT scan and PFTs, since PFTs were not routinely performed following surgery. Secondly, due to the small number of patients, the changes in lung volume, with respect to the resected lobes were not analyzed. Therefore, these analyses will be performed in our future studies. Thirdly, the preoperative PFT was only performed in the patients. As this is a preliminary study, the aim was to investigate perioperative lung volume changes, and the PFT is currently being performed at all the follow-up time points in the ongoing study. Finally, a longer observation time is also required to reveal the lung volume changes one year or more following surgery.

Regardless of these limitations, the current study showed that the early changes on postoperative lung volume were not linear, since the lung volume was significantly decreased during the first postoperative month, rapidly increased in the next 3 months, then slowly increased from 3-6 months. In addition, the results demonstrated that sex, age, BMI, smoking status and surgical sides had no effect on the postoperative

volume and net expansion of the whole lung following VATS lobectomy.

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Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Authors' contributions

XD and HL was involved in the conception and design of the study. CC provided administrative support. LL, MZ, ZT, JZ, PL and HX recruited the patients. LL, MZ, ZT, PL and HX collected and organized the data. XD and HL confirm the authenticity of all the raw data. All authors analyzed and interpreted the data, wrote the manuscript and provided final approval of the manuscript.

Ethics approval and consent to participate

This study was approved the Human Ethics Committee of The Affiliated Hospital of Guizhou Medical University (Guizhou, China; approval no. 2020-244). Medical record review was performed in accordance with the institutional ethics review board guidelines. Informed consent was provided by all individual participants included in the study.

Patient consent for publication

Patients signed informed consent regarding publishing their data and photographs.

Competing interests

The authors declare that they have no competing interests.

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