ORIGINAL RESEARCH

Normal lung attenuation distribution and lung volume on computed tomography in a Chinese population

Ting Cheng[1,2],*
Yong Li[1,2],*
Shuai Pang[1,2]
HuanYing Wan[1,2]
GuoChao Shi[2,3]
QiJian Cheng[1,2]
QingYun Li[2,3]
ZiLai Pan[4]
ShaoGuang Huang[2,3]

[1]Department of Respiratory Medicine, Ruijin Hospital North, Shanghai Jiaotong University School of Medicine, Shanghai, People's Republic of China; [2]Institute of Respiratory Diseases, Shanghai Jiaotong University School of Medicine, Shanghai, People's Republic of China; [3]Department of Respiratory Medicine, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, People's Republic of China; [4]Department of Radiology, Ruijin Hospital North, Shanghai Jiaotong University School of Medicine, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: HuanYing Wan;
QiJian Cheng
Department of Respiratory Medicine, Ruijin Hospital North, Shanghai Jiaotong University School of Medicine, No. 999, Xiwang Road, Malu Town, Jiading District, Shanghai 201801, People's Republic of China
Tel +861 812 126 3363;
+861 812 126 3118
Fax +860 216 788 8855
Email hy_wan_2013@126.com;
chengqijian@aliyun.com

Background and objectives: Although lung attenuation distribution and lung volume on computed tomography (CT) have been widely used in evaluating COPD and interstitial lung disease, there are only a few studies regarding the normal range of these indices, especially in Chinese subjects. We aimed to describe the normal range of lung attenuation distribution and lung volume based on CT.

Methods: Subjects with normal lung function and basically normal chest CT findings (derivation group) at Ruijin Hospital, Shanghai (from January 2010 to June 2014) were included according to inclusion and exclusion criteria. The range of the percentage of lung volume occupied by low attenuation areas (LAA%), percentile of the histogram of attenuation values (Perc n), and total lung volume were analyzed. Relationships of these measures with demographic variables were evaluated. Participants who underwent chest CT examination for disease screening and had basically normal CT findings served as an external validation group.

Results: The number of subjects in the derivation group and external validation groups were 564 and 1,787, respectively. Mean total lung volumes were $4,468\pm1,271$ mL and $4,668\pm1,192$ mL, and median LAA%(-950 HU) was 0.19 (0.03–0.43) and 0.17 (0.01–0.41), in the derivation and external validation groups, respectively. Reference equations for lung volume and attenuation distribution (LAA% using -1,000–210 HU, Perc 1 to Perc 98) were generated: Lung volume (mL) = $-1.015*10^4+605.3*$Sex (1= male, 0= female)$+92.61*$Height (cm) $-12.99*$Weight (kg) ±1766; LAA% (-950 HU)=$[0.2027+0.05926*$Sex (1= male, 0= female) $-4.111*10^{-3}*$Weight (kg) $+4.924*10^{-3}*$Height (cm) $+8.504*10^{-4}*$Age]$^{7.341}-0.05$; Upper limit of normal range: $[0.2027+0.05926*$Sex$-4.111*10^{-3}*$Weight$+4.924*10^{-3}*$Height$+8.504*10^{-4}*$Age$+0.1993]^{7.341}-0.05$.

Conclusion: This large population-based retrospective study demonstrated the normal range of LAA%, Perc n, and total lung volume measured on CT scans among subjects with normal lung function and CT findings. Reference equations are provided.

Keywords: lung attenuation, emphysema, lung volumes, quantitative computed tomography, reference equations, normal range, densitometry

Introduction

Lung computed tomography (CT) examination has been widely used to provide indices reflecting regional density.[1–3] Two main indices of emphysema visualized on CT – the percentage of lung volume occupied by low attenuation areas (LAA%) and percentile of the histogram of attenuation values (Perc n),[4] have been correlated with the presence and extent of emphysema on macroscopic or microscopic morphometry,[1,3,5,6] and are helpful for evaluating prognosis and lung function in patients with COPD,[7–10] among smokers,[11] and even in the general population.[12]

Lung attenuation distribution based on CT, such as measurement of the percentage of high attenuation areas (HAA%), which is generally calculated by 100%-LAA%, can be used to quantitatively evaluate interstitial lung disease (ILD),[13–16] pulmonary infection,[17] and acute respiratory distress syndrome (ARDS).[18] For ILD, these quantitative indices show good correlation with visual scores, severity of dyspnea, lung function, and prognosis.[13,14] Indices of extent of fibrosis include mean and median lung attenuation,[19] and the proportion of the lung volume with attenuation of -700–200 HU, ie, HAA% (HAA% =100%-LAA%) using a threshold of -700 HU.14 Functional lung volume (FLV) can be measured as lung volume with attenuation from -950–700 HU. The ILD volume (ILDV) can be measured as lung volume with attenuation from -700–500 HU.[15] The extent of ground-glass opacity can be measured as lung volume with attenuation from -800–500 HU.[16] For ARDS, lung proportion with attenuation from -1,000–900 HU is defined as overdistended, lung proportion with attenuation from -900–500 HU is defined as normally aerated, and lung proportion with attenuation above -500 HU is defined as poorly aerated or non-aerated.[18]

CT examination can also provide indices regarding lung volume[20] which makes it useful in differentiating among types of ventilatory defects. When FEV1 and FVC are concomitantly decreased, total lung capacity (TLC) in pulmonary function tests (PFT) is very important in differentiation of obstructive, restrictive, and mixed abnormalities.[21,22] However, a single-breath (SB) test may systematically underestimate TLC, especially in the presence of severe airflow obstruction, which may increase the risk of misclassification of PFT abnormalities.[22,23] Plethysmographic lung volume testing is expensive, and is ordinarily only available at specialized referral centers.[24] A strong correlation has been reported between TLC measured by plethysmography and CT measurement of total lung volume.[25,26] Therefore, lung volume from CT scans can be used in differential diagnosis of ventilatory defects.

To distinguish disease manifestations, the normal range of lung attenuation distribution and lung volume on CT is helpful. In a normal population, LAA% may vary due to altered stretch or compression of the lung related to gravity, height of the lung and support of the heart,[2,27] variation in residual peripheral airway structures, and scatter effects.[28] Several studies[29–38] have reported the normal range of LAA%, Perc n, and lung volume for both smokers and non-smokers. However, only two studies with comparatively small sample sizes (22,436 and 8,033) included Asian participants, and neither of these studies is from People's Republic of China. Only the normal range of LAA%(-960 HU),[29] LAA%(-950 HU),[29–31,34–39] LAA%(-912 HU),[33] LAA%(-910 HU),[36] Perc 15,[29,35] and mean lung attenuation[30,32,33,35,37] have been reported, and these indices are inadequate for differentiating ILD from poorly aerated normal lungs.

In this article, we described the normal range of lung attenuation distribution, and lung volume on CT based on a large sample of subjects with normal lung function and CT findings, and provided normal reference equations for the Chinese population.

Methods and materials
Study design
This retrospective study was performed in Ruijin Hospital, Shanghai, People's Republic of China. Subjects who underwent chest CT examination with or without lung function tests in this hospital from January 2010 to June 2014 were retrospectively analyzed. The study was approved by the Institution Ethics Committee of Ruijin Hospital, and patient consent requirement was waived due to the retrospective nature of the study and the waiver of informed consent would not affect the health and rights of the subjects. Patient data confidentially was protected and complied with the declaration of Helsinki.

Study population
The derivation group consisted of subjects who had normal lung function and basically normal chest CT findings. The normal reference value of lung function was calculated by the default equation for Chinese in Jaeger® MasterScreen Body/Diff system (CareFusion Corporation, San Diego, CA, USA). Subjects in the derivation group needed to meet all inclusion criteria and none of the exclusion criteria. Participants in the external validation group were those who underwent chest CT examination for disease screening and had basically normal CT findings, and met second inclusion criterion and neither of the first two exclusion criteria.

Inclusion criteria were: i) subjects with normal spirometric values; ii) subjects underwent a chest CT examination that was reconstructed using a standard (or B26, I31, I41) algorithm and section thickness and intervals of 5 mm as described in the previous report.[40] Exclusion criteria were: i) subjects who had undergone thoracic surgery; ii) subjects who had a CT finding of pneumothorax, pleural effusion, pneumonia, emphysema, ILD, chronic bronchitis, bronchiectasis, lung bullae, lung abscess, or lung mass, lung neoplasm; and iii) patients who had an abnormal rate of carbon monoxide (CO) uptake in the lungs.

CT scanning and analysis

Chest CT examination was performed following the standardized breathing instructions using one of five CT scanners: Discovery CT750 HD (GE Medical Systems, Milwaukee, WI, USA), LightSpeed VCT (GE Medical Systems), LightSpeed[16] (GE Medical Systems), Perspective (Siemens Medical Solutions, Forchheim, Germany), and SOMATOM Definition Flash (Siemens Medical Solutions). In the derivation group, the following technical parameters were used: tube voltage, 100–140 kVp; tube current, 100–250 mA; and tube rotation time, 0.8 s. The algorithm and section thickness of reconstruction were described in the previous paragraph. In the external validation group, parameters were the same as those in the derivation group except for the tube current which was 28–120 mA. Scans were acquired at suspended full inspiration following coaching to inhale to TLC.

Lung volume and LAA% were calculated automatically using commercial software, Myrian® (Intrasense, Montpellier, France), under every threshold from -1,000–210 HU with an interval of 10 HU. Every Perc n was subsequently calculated (Perc 1 to Perc 98 with an interval of 1%). The volume with attenuation of -950–700 HU, expressed as V (-950–700 HU), and its ratio to lung volume, expressed as V% (-950–700 HU) were calculated as FLV and proportion. V (-700–500 HU) and V% (-700–500 HU) were calculated as ILDV and proportion.15 V (-800–500 HU) and V% (-800–500 HU) were calculated as ground-glass opacity volume and proportion.16 V (-1,000–900 HU) and V% (-1,000–900 HU) were calculated as overdistended lung. V (-900–500 HU) and V% (-900–500 HU) were calculated as normally aerated lung. V (above -500 HU) and V% (above -500 HU) were calculated as poorly aerated or non-aerated lung.18.

Lung function test

Lung function tests, including spirometry and SB determination of CO uptake, were performed using Jaeger® MasterScreen Body/Diff system according to the American Thoracic Society/European Respiratory guidelines.[41,42]

Statistical analysis

LAA%, Perc n, and lung volume were expressed as median, interquartile range, and 2.5th and 97.5th percentiles. BOXCOX transformation is proposed as a parametric power transformation technique, which deals with data that do not confirm normality and/or homogeneity of variance.[43] Since LAA% and Perc n did not show a normal distribution, uniform distribution, or exponential distribution, the BOXCOX

transformation and the optimal λ value (with three digits after the decimal point) were used (Figures S1 and S2).

Relationships between CT-based measures and demographic variables such as sex, age, height, and weight were examined using linear regression models. Variables were selected stepwise, with an entry criterion of $p<0.05$, and a removal criterion of $p>0.10$. Reference equations for CT-based measures were developed from the results of linear regressions. The normal range was calculated as follows: predicted value ±1.96* RSD, where RSD is the residual standard deviation. For indices for which 0 was in the normal range (shown as 2.5th percentile =0), the normal range was calculated as predicted value +1.645*RSD.

BOXCOX transformations were completed with STATA 11.0 (StataCorp LP, College Station, TX, USA). Descriptive statistics and linear regressions were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 5,139 chest CT scans with corresponding lung function tests were initially screened for the derivation group, and 564 subjects were included for analyses (Figure 1A). Similarly, 4,816 chest CT scans for the external validation group were screened and reviewed, and 1,787 subjects were regarded as eligible (Figure 1B).

The demographic characteristics of participants are provided in Table 1. Subjects in the derivation group had a median age of 58 years with an interquartile range of 48–64. Participants in the external validation group had a median age of 60 years with a range of 53–67.

Mean and median volume were 4,468±1,271 mL and 4,423 mL (3,614–5,294), respectively in the derivation group, and 4,668±1,192 mL and 4,586 mL (3,873–5,524) in the external validation group. Median LAA%(-950 HU) was 0.19 (0.03–0.43) in the derivation group and 0.17 (0.01–0.41) in the external validation group. Distributions of lung volume and main indices of LAA% and Perc n are shown in Table 2. The distributions of other indices are shown in Figure 2 and Table S1.

No emphysema index (LAA% using -1,000–210 HU, Perc 1 to Perc 98) except for Perc 96 and Perc 97 followed a normal distribution. Normality obviously improved after BOXCOX transformation (Table S2). The scatter graph of LAA%(-950 HU) and lung volume vs demographic characteristics are shown in Figure S3. Reference equations and normal ranges were derived for lung volume, every LAA%, and Perc n and included terms of age, sex, height, weight and only age and sex. Main indices are shown in Table 3, and others are shown in Table S3.
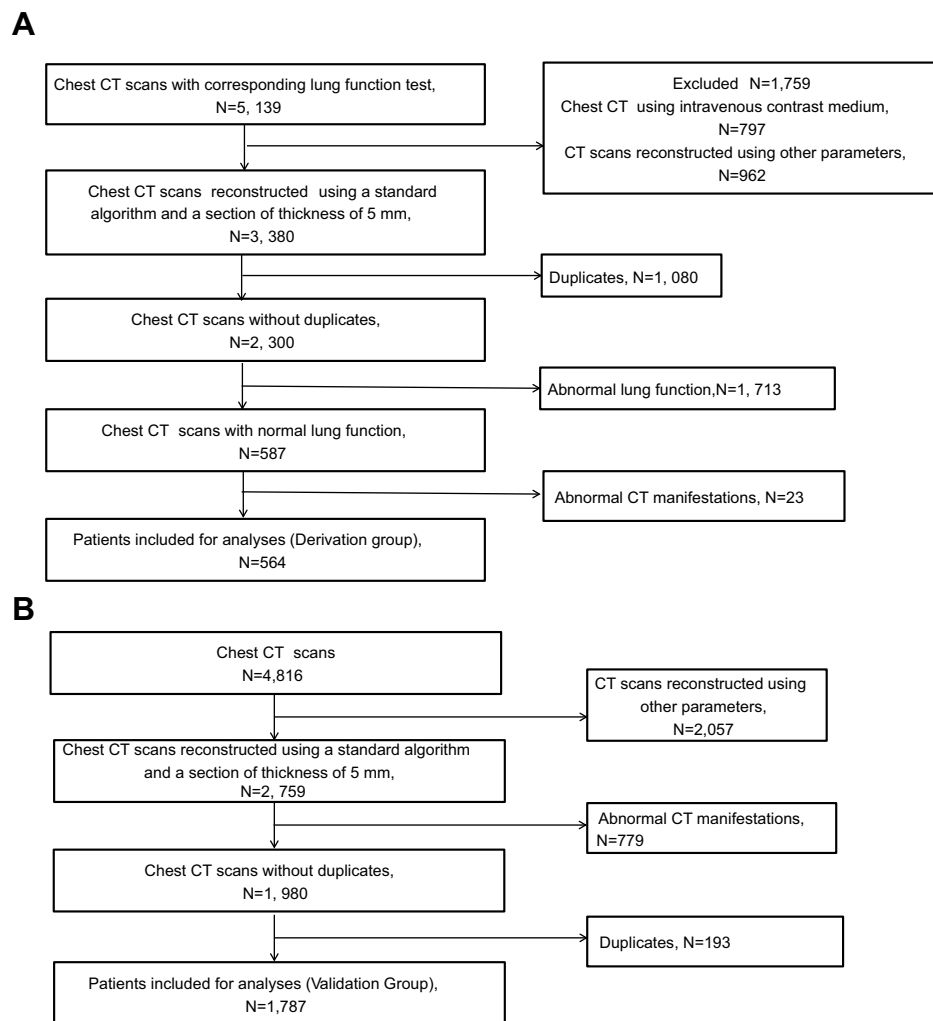
A

B

Figure 1 Flow chart for subject screening in the derivation group (**A**) and external validation group (**B**).

Lung volume (mL) =-1.015*10^4+605.3 * Sex (1= male, 0= female) +92.61 * Height (cm) - 12.99 * Weight (kg) ±1,766

LAA%(-950 HU) =[0.2027+0.05926 * Sex (1= male, 0= female) - 4.111*10^-3 * Weight (kg) +4.924*10^-3 * Height (cm) +8.504*10^-4 * Age] ^7.341–0.05

Upper limit of normal range: [0.2027+0.05926 * Sex - 4.111*10^-3* Weight +4.924*10^-3 * Height +8.504*10^-4 * Age +0.1993] ^7.341–0.05

We also found small but significant differences in LAA %(-950 HU), LAA%(-930 HU), and Perc 15 among different CT scanners even with similar reconstruction kernels and the same section thickness. Significant differences were not seen for total lung volume (Table 4).

Table 5 shows differences between the observed values measured in the study subjects and values calculated from several available prediction equations. Aside from our equations, lung volumes were most closely consistent with the reference equation by Come et al[31] for African Americans. Using a previous equation, Hoffman et al[36] underestimated lung volume and overestimated LAA% (-950 HU), and Come et al[31] overestimated lung volume. The differences between observed values and predicted values calculated from the present reference were similar in the derivation and external validation groups (Table S4).

The median lung volume measured by SB gas dilution method (TLC-SB) in derivation group was 5.12 L (4.345–5.92). The lung volume measured on CT was closely correlated with TLC-SB (r=0.814, p<0.001) (Figure 3A). However, there were still some differences between CT lung volume and SB lung volume. The mean difference was -339±777 mL. The difference seems to confirm normal distribution and was not

Table 1 Demographic characteristics of participants in the derivation and external validation groups

Characteristics	Median [IQR]	
Groups	Derivation group	External validation group
Male/total	240/564	1066/1787
Height (cm)	163 [158–170]	-
Age (years)	58 [48–64]	60 [53–67]
Lung volume (mL)	4,423 [3,614–5,294]	4586 [3873–5524]
Weight (kg)	64. [57.-71.]	
Body mass index (kg/m^2)	24 [22–26]	
FEV1 (L)	2.56 [2.13–3.19]	
FEV1% FVC	86.5 [81.29–92.49]	
FVC (L)	2.95 [2.49–3.65]	
TLC-SB (L)	5.12 [4.345–5.92]	
RV%TLC-SB	40.54 [35.97–45.29]	
DLCO SB (mmol/min/kPa)	7.43 [6.605–8.435]	
DLCO/VA (mmol/min/kPa/L)	1.5 [1.405–1.66]	
FVC%pred	94.3 [88.-101.2]	
FEV1%pred	99.2 [92.4–106.9]	
TLC-SB%pred	90.75 [85.1–97.]	
DLCO SB%pred	88.05 [83.8–94.45]	
DLCO/VA%pred	99.7 [93.58–109.5]	

Abbreviations: IQR, interquartile range; RV, residual volume; TLC, total lung capacity; SB, single-breath; DLCO, diffusing capacity of the lung for carbon monoxide; pred, predicted.

correlated to other factors (eg, SB lung volume, age, sex, height, weight) (Figure 3B–F). However, the absolute deviations from mean of the difference between CT lung volume and SB lung volume seem positively correlated with age (r=0.150, p=0.061) (Figure 3D).

Spearman's correlation showed that LAA%(-950 HU), LAA%(-910 HU), and Perc 15 were not significantly correlated to X-ray tube current (r=0.017, -0.021, 0.030, respectively). Although there was a positive correlation between lung volume and tube current (r=0.115, p=0.006), the tube current was more closely correlated to height (r=0.676, p<0.001) and weight (r=0.360, p<0.001). Tube current was not an independent influencing factor of lung volume when other demographic characteristics (ie, height, weight, sex, age) were included in the multivariate regression.

Discussion

Results of the present study demonstrate significant variation in LAA%, Perc n, and total lung volume on CT scans due to demographic factors among Chinese subjects with normal lung function. We provided reference equations to account for normal variation and to more accurately define abnormal values of LAA%, Perc n, and total lung volume on CT scans.

Although CT characteristics in a normal population have been previously described in several studies,[29,30,37,38] to the

best of our knowledge, this study is the first to explore whole lung attenuation distribution from LAA%(-1,000 HU) to LAA%(-210 HU), and from Perc 1 to Perc 98, with a comparatively large sample size among Chinese subjects with normal lung function, using routine chest CT images reconstructed with 5 mm section thickness and the standard algorithm. Acquisition protocols were the same as protocols used in routine clinical practice. Reference equations were validated with an independent cohort, which strengthens the reliability of the study. Since routine CT scans do not include information about patients' height and weight, we also generated reference equations using only age and sex. Hence, reference equations developed in our study are likely to be directly applicable to clinical practice.

Mean and median lung volumes were consistent with values reported in previous studies.[32,35–37] Median LAA% (-950 HU) were lower than values in most previous studies.[29–31,34–38] These results may be due to differences among races as well as differences in section thickness and reconstruction kernels. Previous studies showed that LAA%(-950 HU) in normal Asian participants was lower than LAA% for Caucasians.[32] Median LAA%(-950 HU) in normal participants were 1%–2.5% with thin slice thickness and standard reconstruction,[31,34,36,37] and 7.5%–15% with thin slice thickness and high resolution reconstruction.[30,34,35] However, LAA%(-950 HU) was

Table 2 Description of lung attenuation distribution and lung volume from computed tomography (CT) in the derivation and external validation groups

Percentile	Group	2.5	25	50	75	95	97.5	99
Lung volume (mL)	Derivation	2169	3614	4423	5294	6680	6973	7845
	Validation	2344	3873	4586	5524	6649	7121	7494
LAA%(-960 HU)	Derivation	0	0	0.09	0.26	0.85	1.28	2.10
	Validation	0	0	0.07	0.25	0.69	1.05	1.84
LAA%(-950 HU)	derivation	0	0.03	0.19	0.43	1.2	2.17	3.05
	Validation	0	0.01	0.17	0.41	1.12	1.52	2.73
LAA%(-930 HU)	Derivation	0	0.22	0.56	1.42	5.22	7.59	13.32
	Validation	0	0.2	0.54	1.39	5.21	7.83	11.8
LAA%(-910 HU)	Derivation	0	0.81	2.41	7.84	22.84	29.87	38.79
	Validation	0	0.76	2.67	8.21	22.46	28.37	35.01
LAA%(-850 HU)	Derivation	0.82	25.66	46.86	62.72	73.86	76.61	78.93
	Validation	1.86	30.61	50.57	63.71	73.64	75.91	78.5
Perc 15 (HU)	Derivation	-921	-899	-884	-863	-810	-784	-768
	Validation	-921	-901	-887	-868	-829	-806	-783
V%(-950-700 HU)	Derivation	47.44	81.5	85.67	87.68	89.25	89.71	90.01
	Validation	59.66	82.94	86.06	87.68	89.25	89.62	90.06
V%(-800-500 HU)	Derivation	10.22	14.45	20.14	32.75	64.59	73.19	77.5
	Validation	10.41	14.01	18.39	28.1	55.13	66.51	75.37
V%(-700-500 HU)	Derivation	4.71	6.01	7.34	10.18	25.1	34.19	37.69
	Validation	4.81	5.87	7.01	8.98	18.91	25.76	34.05
V%(-1,000-900 HU)	Derivation	0.07	1.53	5.26	15.06	34.49	42.6	50.3
	Validation	0.04	1.63	6.33	16.14	34.46	40.79	48.18
V%(-900-500 HU)	Derivation	51.57	77.96	86.04	89.41	91.62	91.9	92.44
	Validation	53.71	77.46	85.96	89.81	91.96	92.44	92.79
V%(above-500 HU)	Derivation	4.91	6	6.75	8.23	13.62	18.1	23.05
	Validation	5.06	5.99	6.63	7.74	11.5	13.9	16.72
V(-950-700 HU)(mL)	Derivation	1066	2957	3798	4588	5938	6189	6939
	Validation	1462	3233	3937	4796	5880	6319	6628
V(-700-500 HU)(mL)	Derivation	246	292	348	417	648	746	833
	Validation	231	295	340	398	583	715	874

Abbreviations: LAA%, percentage of lung volume occupied by low attenuation areas; Perc 15, the 15th percentile of the histogram of attenuation values; V (given range), volume of lung with the CT attenuation within the given range; V% (given range), the ratio of V (given range) to the lung volume.
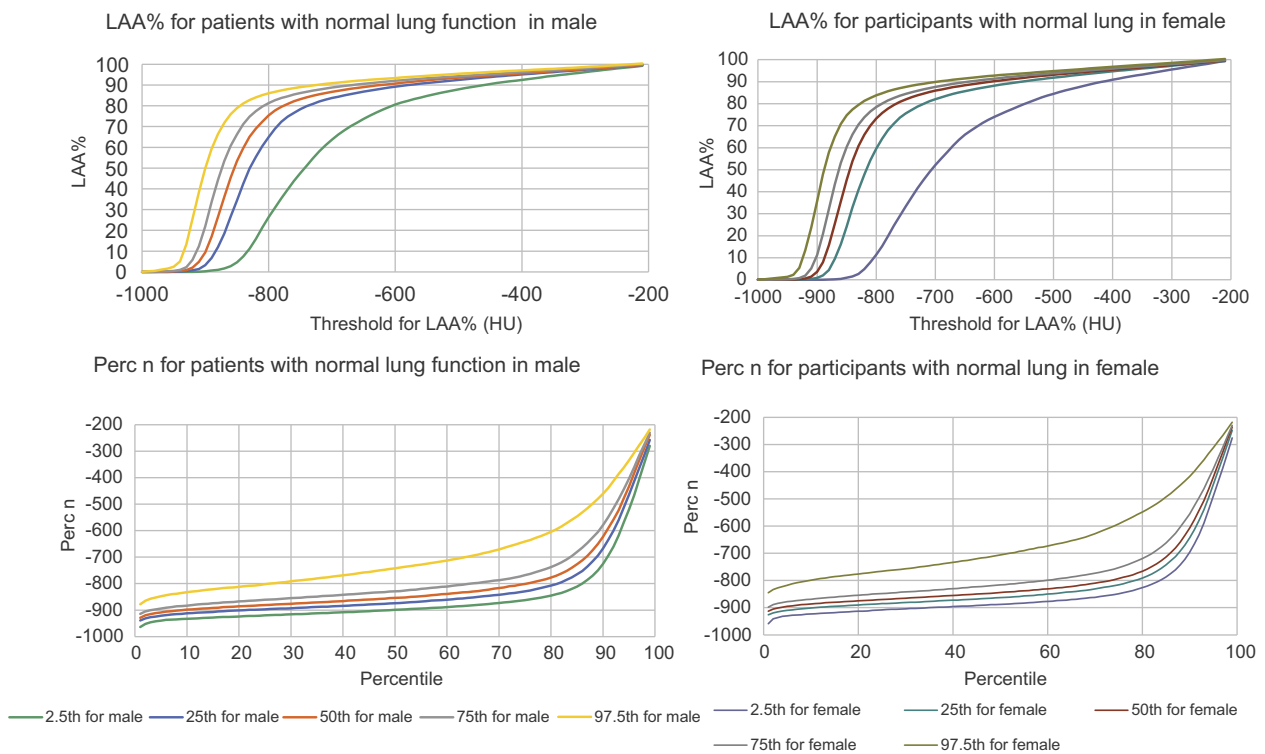
Figures titled: "LAA% for patients with normal lung function in male", "LAA% for participants with normal lung in female", "Perc n for patients with normal lung function in male", "Perc n for participants with normal lung in female".

Legend: 2.5th for male, 25th for male, 50th for male, 75th for male, 97.5th for male; 2.5th for female, 25th for female, 50th for female, 75th for female, 97.5th for female.

Figure 2 Distributions of LAA% and Perc n in subjects with normal lung function in males and females.
Abbreviations: LAA%, percentage of lung volume occupied by low attenuation areas; Perc n, percentile of the histogram of attenuation values.

low (0.19%–0.59%) in young participants, even when reconstructed using high-frequency and 2 mm slice thickness.[29,38]

Median FLV, its ratio to lung volume (FLV%), ILDV, and ILDV% of patients with normal function and CT finding in previous studies fall between the 25th to 75th percentiles in the present study.[15] Median FLV, FLV%, ILDV, ILDV% of patients with ILD in previous studies fall[14,15] between the 2.5th and 25th or 75th and 97.5th percentiles in the present study. Overlaps of these indices are seen with ILD patients and normal participants.

In the present study, lung volume was found to be higher in males and tall and comparatively thin individuals, and was negatively related to age in the absence of height and weight information. This finding is consistent with most previous studies that also show higher lung volume in males[31,36,37] and taller individuals.[31,32,36] One study reported that lung volume was negatively correlated with body mass index,[36] while another showed that lung volume was positively correlated with weight.[32] Only one study[36] indicated a negative correlation between age and lung volume; in other studies the correlations were not

significant.[31,37] The present study shows that LAA% (-950 HU) was higher in male, tall, thin, and elderly subjects. Previous studies reported that LAA% is higher in males.[36,37] One study indicated that LAA% was higher in tall, thin, and elderly individuals,[36] while another did not.[37] Besides, we found that the lung volume measured on CT was lower than lung volume measured by SB gas dilution method. The differences between CT lung volume and SB lung volume may be caused by several factors. 1), the CT was performed at spine position and lung function test was performed at sitting position, while the lung volume at spine position was lower than that at sitting position. Therefore, the mean difference between CT lung volume and SB lung volume was negative. 2) The random error exists in every exam. 3) Some subjects, especially elders, may not cooperate with exams well. Therefore, the random error was larger in elders.

There are some limitations in this study. 1) The target population of this study was Chinese, healthy individuals. However, it is unethical to enroll healthy individuals to undergo chest CT. Therefore, we chose two different sample groups to ensure the representativeness. The derivation group included the patients with

Table 3 Reference equations and normal ranges for lung attenuation distribution and lung volume from computed tomography (CT) scans based on data from the derivation group

Indices	Normality of residual error	Reference equations and normal range
With height and weight		
Lung volume (mL)	0.392	−1.015*10^4+605.3*Sex+92.61*Height-12.99*Weight±1766
LAA%(-950 HU)	0.098	[0.2027+0.05926 *Sex-4.111*10^-3*Weight+4.924*10^-3*Height+8.504*10^-4*Age]^7.341−0.05
LAA%(-930 HU)	0.694	ULN: [0.2027 +0.05926 *Sex-4.111*10^-3*Weight+4.924*10^-3*Height+8.504*10^-4*Age+0.1993]^7.341−0.05 [0.1477 +0.06335 *Sex-3.957*10^-3*Weight+6.011*10^-3*Height+9.405*10^-4*Age]^10.63−0.05
LAA%(-910 HU)	0.740	ULN: [0.1477 +0.06335 *Sex-3.957*10^-3*Weight+6.011*10^-3*Height+9.405*10^-4*Age+0.1741]^10.63−0.05 [-0.2288 +0.01058 *Height-6.500*10^-3*Weight+0.08544 *Sex]^8.201−0.05
LAA%(-850 HU)	0.080	ULN: [-0.2288 +0.01058 *Height-6.500*10^-3*Weight+0.08544 *Sex+0.2991]^8.201−0.05 100-[4.436−0.01473 *Height+6.992*10^-3*Weight±0.1846]^4.405
Perc 15 (HU)	0.996	[-1.564*10^-3+1.391*10^-4*Sex+2.703*10^-5*Height-1.450*10^-5*Weight±8.607*10^-4]^-0.796−1024
V% (-950-700 HU)	0.079	100−(-0.02572−7.282*10^-5*Age+2.925*10^-3*Height-1.534*10^-4*Weight±9.114*10^-3)^-0.602
V% (-800-500 HU)	0.087	(-0.1977−3.777*10^-4*Age+2.925*10^-3*Height-1.345*10^-3*Weight±0.09071)^-1.742
V% (-700-500 HU)	0.101	(-0.1875−4.183*10^-4*Age+2.144*10^-3*Height-9.551*10^-4*Weight±0.06203)^-0.799
V% (-1,000-900 HU)	0.514	(-1.761+0.1724*Sex+0.02511*Height-0.01514*Weight±0.8356)^4.464
V% (-900 HU to -500 HU)	0.217	95-(1.145−0.03139*Sex-8.776*10^-4*Age-3.642*10^-3*Height+2.293*10^-3*Weight±0.168)^-4.878
V% (above -500 HU)	0.295	(-0.08562−2.522*10^-4*Age+1.059*10^-3*Height-5.596*10^-4*Weight±0.02495)^-0.59
V (-950-700 HU) (mL)	0.062	−9641+546.7*Sex-7.432*Age+89.43*Height-17.15*Weight±1911
V (-700 -500 HU) (mL)	0.022	(2.551*10^-4−1.441*10^-5*Sex-7.157*10^-7*Age-1.340*10^-6*Weight±8.117*10^-5)^-0.649
Without height and weight		
Lung volume (mL)	0.566	4612+1495*Sex-13.99*Age±1960
LAA%(-950 HU)	0.283	[0.7894+0.06981*Sex]^7.341−0.05
LAA%(-930 HU)	0.481	ULN: [0.7894+0.06981*Sex+0.2077]^7.341−0.05 [0.9218+0.08791*Sex]^10.63−0.05
LAA%(-910 HU)	0.490	ULN: [0.9218+0.08791*Sex+0.1843]^10.63−0.05 [1.066+0.1406*Sex]^8.201−0.05
LAA%(-850 HU)	0.048	ULN: [1.066+0.1406*Sex+0.3168]^8.201−0.05 100-[2.383−0.106*Sex+2.335*10^-3*Age±0.4393]^4.405
Perc 15 (HU)	0.836	[2.065*10^-3+2.882*10^-4*Sex-3.370*10^-6*Age±9.078*10^-4]^-0.796−1024
V% (-950-700 HU)	0.058	100−(0.01633+2.051*10^-3*Sex-1.033*10^-4*Age±9.647*10^-3)^-0.602
V% (-800-500 HU)	0.087	(0.2019+0.02202*Sex-6.541*10^-4*Age±0.09483)^-1.742
V% (-700-500 HU)	0.226	(0.1076+0.01595*Sex-6.243*10^-4*Age±0.06529)^-0.799
V% (-1,000-900 HU)	0.268	(1.33+0.3065*Sex±0.8855)^4.464
V% (-900-500 HU)	0.129	95-(0.6523−0.04607*Sex±0.1735)^-4.878
V% (above -500 HU)	0.629	(0.05517+6.497*10^-3*Sex-3.562*10^-4*Age±0.02734)^-0.59
V (-950-700 HU) (mL)	0.130	4094+1376*Sex-16.62*Age±2086
V (-700 -500 HU) (mL)	0.060	(1.746*10^-4−2.861*10^-5*Sex-7.082*10^-7*Age±8.483*10^-5)^-0.649

Notes: For all equations, age was measured in years; height was measured in cm; weight was measured in kg; and sex was coded as 1= male, 0= female.

Abbreviations: LAA%, percentage of lung volume occupied by low attenuation areas; Perc 15, the 15th percentile of the histogram of attenuation values; V (given range), volume of lung with the CT attenuation within the given range; V % (given range), the ratio of V (given range) to the lung volume; ULN, upper limit of normal range.

Table 4 Lung volume and attenuation distribution from different scanners and reconstruction kernels

Manufacturer	Scanner	Kernel	n	Lung volume (mL)	LAA% (-950 HU)	LAA% (-910 HU)	Perc 15 (HU)
GE	Discovery CT750 HD	STANDARD	24	4105±1254	0.07 [0~0.21]	0.47 [0.22~2.47]	−857 [−885~−837]
GE	LightSpeed VCT	STANDARD	62	4220± 1302	0.20 [0.05~0.39]	1.11 [0.47~3.37]	−870 [−889~−844]
GE	LightSpeed16	STANDARD	281	4504 ±1331	0.23 [0.06~0.47]	2.90 [0.94~8.64]	−886 [−901~−868]
SIEMENS	Perspective	I31	101	4540 ± 1137	0.09 [0~0.29]	2.45 [0.79~9.16]	−886 [−903~−867]
SIEMENS	Perspective	I41	69	4444 ± 1169	0.12 [0~0.38]	2.13 [0.82~8.25]	−884 [−899~−863]
SIEMENS	SOMATOM Definition Flash	B26f	27	4779 ± 1253	0.36 [0.01~0.80]	3.44 [1.59~11.85]	−891 [−905~−877]

Abbreviations: LAA%, percentage of lung volume occupied by low attenuation areas; Perc 15, the 15th percentile of the histogram of attenuation values.

Table 5 Comparison between observed value of derivation group and the predicted value from different reference equations for lung volume and extent of emphysema

Indices	Mean difference	Mean absolute difference	% Observed values over the ULN	% Observed values below the LLN
Lung volume (mL)				
Present 1	−4	709	1.42%	3.01%
Present 2	0	792	1.77%	2.30%
Hoffman 1	298	783	NA	4.43%
Come 1	−1010	1101	NA	NA
Come 2	−246	736	NA	NA
LAA%(-950 HU)				
Present 1	−0.05	0.26	5.32%	NA
Present 2	0.15	0.28	5.85%	NA
Hoffman 2	−0.98	1.07	0.35%	NA
Hoffman 3	−0.76	0.87	6.56%	NA
Hoffman 4	−0.61	0.74	0.71%	NA

Notes: Present 1: the reference equations of the present study including sex, age, height, and weight. Present 2: the reference equations of the present study including only sex and age. Come 1: the reference equation for the lung volume of NHW. Come 2: the reference equation for the lung volume of African American. Hoffman 1: the reference equation for the lung volume. Hoffman 2: the reference equation for LAA%(-950 HU) for former smokers and never-smokers. Hoffman 3: the reference equation for LAA%(-950 HU) for current smokers (about five cigarettes per day). Hoffman 4: the reference equation for LAA%(-950 HU) for current smokers (about 20 cigarettes per day).
Abbreviations: LAA%, percentage of lung volume occupied by low attenuation areas; ULN, upper limit of normal range; LLN, lower limit of normal range.

normal lung function and basically normal chest CT. The external validation group included the subjects who underwent chest CT examination for disease screening and had basically normal CT manifestations. In the derivation group, the patients underwent these examinations mainly as preoperative examination, or to find the causes of cough or chest tightness. 2) The information on symptoms and smoking status were not available. Smokers, asthmatic patients were not excluded. However, only individuals with normal lung function and chest CT were included. Currently, no evidence proves the differences in the lung volume and lung density distribution between asthmatic patients with normal spirometry results and healthy individuals. The healthy smokers without lung disease can also be regarded as a part of the normal, healthy population. Therefore, we considered that this group is at least representative of the population that presents to a hospital with a variety of conditions, but with normal lung structure and function. 3) The normal range and reference equation was not validated in an internal validation group with the same acceptance criteria. However, the comprehensive effect of the bias from overfitting and sample selection was evaluated by the external validation group. 4) In the present study, the tube current of external validation group was lower than the derivation group. Although some studies showed that CT scan measurements of low density lung structures were affected by radiation dose but are less sensitive to the lung volume,[44] others showed there was no significant
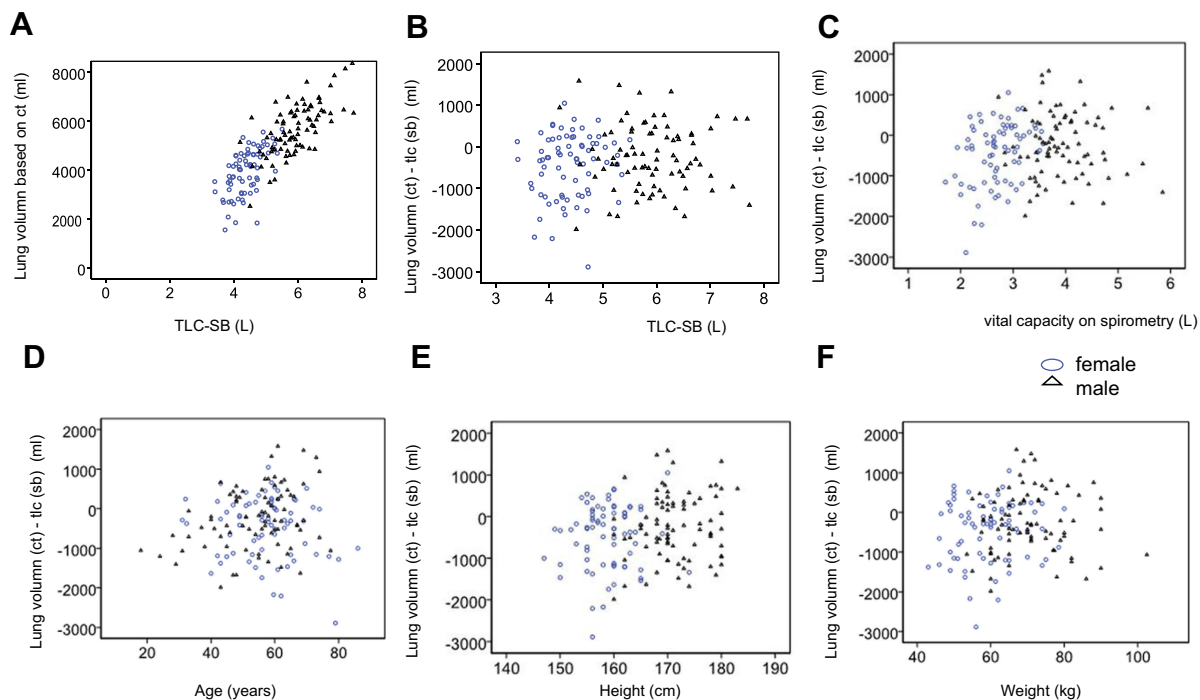
Figure 3 Consistency and difference between computed tomography (CT) lung volume vs single-breath (SB) lung volume. (**A**) Scatter plot between lung volume measured on CT and lung volume measured by SB gas dilution method (total lung capacity [TLC]-SB). (**B**) Scatter plot between lung volume (CT) - TLC (SB) and TLC (SB). (**C**) Scatter plot between lung volume (CT) - TLC (SB) and vital capacity on spirometry. (**D**) Scatter plot between lung volume (CT) - TLC (SB) and age. (**E**) Scatter plot between lung volume (CT) - TLC (SB) and height. (**F**) Scatter plot between lung volume (CT) - TLC (SB) and weight.

effect of tube current on emphysema extent measured on chest CT.[5] In the present study, the X-ray tube current was not an independent influencing factor of LAA% (-950 HU), LAA%(-910 HU), Perc 15, and lung volume. Thus, we believed that this difference will not influence the results in this study.

In conclusion, herein we present a large population-based assessment of LAA%, Perc n, and total lung volume measured using CT scans from subjects with normal lung function and CT findings. We demonstrated significant differences in these measures based on sex, age, height, and weight, and we provided reference equations to account for these differences.

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Disclosure

The authors report no conflicts of interest in this work.

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