Published in final edited form as:

Respir Med. 2023 January ; 206: 107062. doi:10.1016/j.rmed.2022.107062.

Lower Respiratory Illnesses in Childhood are Associated with The Presence of Air Trapping in Early Adulthood.

Francesca Polverino[1,2], **Debra A. Stern**[1], **Eric M. Snyder**[3], **Courtney Wheatley-Guy**[4], **Surya P. Bhatt**[5], **Fernando D. Martinez**[1], **Stefano Guerra**[1], **Wayne J Morgan**[1]

[1]Asthma and Airway Disease Research Center, University of Arizona, Tucson, AZ 85719

[2]Baylor College of Medicine, Houston, TX 77030

[3]Geneticure, Rochester, MN 55902

[4]Cardiovascular Diseases, Mayo Clinic Scottsdale, Scottsdale AZ 85259

[5]Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL, 35924

Abstract

Several factors occurring in early life, including lower respiratory tract illnesses (LRIs), are involved in determining lung structure and function in adulthood, but effects of these factors on lung development remain largely unknown. Hereby, we evaluated the parameters from computed tomography (CT) scans performed at the age of 26 years in 39 subjects from the birth cohort of the Tucson Children's Respiratory Study (TCRS) in order to determine the relationship between early childhood factors and lung structural changes in young adult life. We found that participants with LRIs in childhood had increased air trapping at the age of 26 suggesting an association between childhood infections and lung development.

Introduction:

Large longitudinal cohorts have shown that about half of the individuals who will develop COPD in their adult life do not reach their expected maximal lung function in early adulthood[1], but the etiology of the various lung function trajectories is unclear. Structural studies using computed tomography (CT) carry complementary information that is not captured by spirometry, offering the opportunity to elucidate the structure-function relationships underpinning the trajectories of lung function development.

Multiple factors are involved in determining lung structure and function in adulthood, including genetics, pre- and peri-natal smoke exposure, preterm birth, and lower respiratory tract illnesses (LRIs) in early life[2]. We, and others, have previously shown that individuals sustaining childhood respiratory infections[3] are at increased risk of reduced adult lung function.

Corresponding author: Francesca Polverino, MD PhD, Asthma and Airway Disease Research Center, University of Arizona, Tucson, AZ 85719; Pulmonary and Critical Care Medicine, Baylor College of Medicine, Houston, TX, 77030, fpolverino@copdnet.org. Telephone: +1- 617-306-8999.

So far, the effect of pre- and peri-natal factors on lung structural development remains largely unknown because no prospective study has determined whether early-life risk factors are associated with structural alterations in adult life. In the current study, we used the data from the Tucson Children's Respiratory Study (TCRS) cohort to determine the relation between early childhood factors and imaging-based lung structural changes in young adult life.

Methods

Between 1980 and 1984, 1,246 healthy infants were enrolled in the TCRS Study, a non-selected birth cohort study of the early origins of respiratory diseases followed to date[4]. At age 26 years, 39 non-selected participants, prioritized based upon whether they had lung function testing during infancy, completed post-bronchodilator high-resolution chest CT scans. Lung masks were used to segment the lungs and the percentage of gas trapping[5]. The percentage of gas trapping was calculated as the percentage of lung voxels with attenuation less than −856 Hounsfield Units ($\%LAA_{-856}$) at end-expiratory lung volume (EELV)[5]. Respiratory symptoms during the past year, lung function, total lung capacity (TLC) by nitrogen washout at the time of the CT scan, and lung clearance index (LCI) were assessed. Physician diagnosed asthma with symptoms during the past year was ascertained by parent completed questionnaire at ages 6, 8, 11, 13, and 16. Lung function parameters S_{cond} and $S_{acin,}$ indices of peripheral airway function sensitive to the conduction-diffusion wavefront in the terminal bronchioles, were also measured and multiplied by tidal volume (*Vt) to adjust for lung volume and breathing pattern[6,7]. LRI from birth to age 3 years, and smoking history from adolescence to age 26 were determined prospectively. The occurrence of respiratory syncytial virus (RSV)-LRI was determined by viral culture[6,7]. Analysis of variance, multiple linear regression, contingency tables with Fisher exact test, and Spearman correlation with 95%CI calculated using the bootstrap method were used for data analysis. P-values <0.05 were considered significant. Data were analyzed using STATA 16.

Results

See Table 1 for participant characteristics.

The demographic composition (sex, race/ethnicity, parental smoking at enrollment, history of parental asthma), as well as the frequency of current symptoms, smoking and lung function of the group of participants with CT data, were similar to the participants without CT at age 26. CT-assessed $\%LAA_{-856}$ values ranged from 0.2% to 38.0% (median=14.3%, IQR: 3.2% - 22.3%). Thirty-three participants had complete LRI data from birth through age 3 years, of whom 18 (54.6%) had at least one LRI. A history of LRI was associated with greater $\%LAA_{-856}$ (Table 1 and Figure 1). Mean $\%LAA_{-856}$ was 18.8% (95%CI: 13.7, 23.9) for those with a history of LRI and 9.5% (95%CI: 3.2, 15.7) for those without a history of LRI (p=0.018).

After adjusting for sex and body mass index (BMI), participants with a history of LRI had significantly greater $\%LAA_{-856}$ compared to participants without a history of LRI (adjusted beta coefficient: 7.4%, [95%CI: 0.35%, 14.5%], p=0.040). The relation between

LRI and %LAA-$_{856}$ was not appreciably changed by adjustment for smoking at age 26 as 'never smoker' and 'ever smoker' categories (adjusted beta coefficient: 7.3% [95%CI: 0.1%, 14.6%] p=0.047) or respiratory symptoms during the past year (adjusted beta coefficient: 8.3%, [95%CI: 1.2%, 15.3%], p=0.023). The %LAA$_{-856}$ was similar for those with RSV compared to those with non-RSV LRIs (p=0.848). There was no significant interaction between sex and LRI on %LAA$_{-856}$ (interaction p=0.710) after adjusting for BMI.

There was an inverse correlation between %LAA$_{-856}$ and % predicted post-bronchodilator $FEF_{25–75}$ (Table 1). We also found a moderate association between height-, weight- and sex-adjusted values of S_{cond}*VT and %LAA$_{-856}$ (rho=0.57, p=0.018; n=17) (Figure 2). Physician-diagnosed asthma, found in 11 of the 39 participants, did not affect the relation between LRI and %LAA$_{-856}$.

In an additional analysis of the relation between the factors shown in Table 1 to LRI, we found no significant differences in the prevalence of LRI by sex, race/ethnicity, maternal smoking or maternal asthma. Additionally, LRI was not related to ever smoking, BMI, FEV_1/FVC ratio, $FEF_{25–75}$, CT airway measures, ppRV, or symptom score at age 26. However, those with LRI had a trend towards lower FEV_1 (p=0.05), FVC (p=0.06), and ppTLC (p=0.07) compared to those without LRI.

Discussion

The TCRS cohort is the only existing long-term birth cohort followed into the fourth decade of life with HRCT scans performed in young adulthood. We recently showed, in this same population, that a lower time to peak tidal expiratory flow / expiratory time ratio (T_{PTEF}/T_E) compatible with longer respiratory system time constants at birth is associated with reduced airway caliber at EELV at age 26[8]. We now show an association between LRIs in the first three years of life and increased lung lucency as %LAA$_{856}$, commonly interpreted as gas trapping[9]. Accordingly, Scond*Vt was moderately correlated with increased lung lucency. Increases in Scond*Vt is believed to be related to increased convection-dependent inhomogeneity in the conducting airway zone and have shown to be increased in airway obstructive diseases such as asthma. This suggests that subtle gas trapping may have contributed to the increased %LAA-$_{856}$[10] due to local peripheral conducting airway obstruction and/or reduced local elastance.

Previous studies have found lung structure derangements, such as air trapping and emphysema, to be common in the general elderly population[11]. However, these studies did not address potential effects by pre- and peri-natal exposures. Our findings provide evidence that LRI in childhood is associated with changes in lung structure.

This study has some limitations. First, it is not possible to determine whether the association between LRI and structural changes on CT is due to lung structural damage caused by the respiratory infection itself or to preexisting deficits in lung structure in young children in whom LRI develops. Nonetheless, air trapping on CT is associated with further lung function decline, and hence is an important finding[12]. Also, it is difficult to extrapolate whether the observed increase in %LAA$_{-856}$ in subjects who had LRI in childhood was

associated with parenchymal structural changes since none of the subjects had a clear emphysematous pattern. However, it is plausible that alveolar simplification could be a consequence of RSV-LRI or a risk factor for symptomatic LRI due to less recoil maintaining small airway patency.

These observations provide the first evidence of structural lung abnormalities associated with LRIs earlier in life. Further studies are needed in order to clarify the prognostic significance of these findings on CT in a population-based sample, and to shed light onto the physiology of lung structural changes over the course of life.

Acknowledgments

This study was supported by awards AI135108 from National Institute of Allergy and Infectious Diseases and HL132523 from National Heart, Lung, and Blood Institute, US National Institutes of Health. We gratefully acknowledge the contributions of Lynn M. Taussig who started the Tucson Children's Respiratory Study in 1980. We thank Per M. Gustafsson for assistance with MBW measurements, and our study nurses and technicians for data collection and participant follow-up. We would like to thank the TCRS study participants and their parents for their continued support and enthusiasm.

References

1. Lange P, Celli B, Agusti A, et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. N Engl J Med 2015;373(2):111–122. DOI: 10.1056/NEJMoa1411532 [doi]. [PubMed: 26154786]
2. Polverino F, Sam A, Guerra S. COPD: To Be or Not to Be, That is the Question. Am J Med 2019;132(11):1271–1278. DOI: 10.1016/j.amjmed.2019.04.047. [PubMed: 31152719]
3. Voraphani N, Stern DA, Wright AL, Guerra S, Morgan WJ, Martinez FD. Risk of current asthma among adult smokers with respiratory syncytial virus illnesses in early life. Am J Respir Crit Care Med 2014;190(4):392–8. DOI: 10.1164/rccm.201311-2095OC. [PubMed: 24927374]
4. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. N Engl J Med 1988;319(17):1112–7. DOI: 10.1056/NEJM198810273191702. [PubMed: 3173442]
5. Ukil S, Reinhardt JM. Anatomy-guided lung lobe segmentation in X-ray CT images. IEEE Trans Med Imaging 2009;28(2):202–14. DOI: 10.1109/TMI.2008.929101. [PubMed: 19188109]
6. Robinson PD, Latzin P, Verbanck S, et al. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. Eur Respir J 2013;41(3):507–22. DOI: 10.1183/09031936.00069712. [PubMed: 23397305]
7. Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to present. J Allergy Clin Immunol 2003;111(4):661–75; quiz 676. DOI: 10.1067/mai.2003.162. [PubMed: 12704342]
8. Guerra S, Lombardi E, Stern DA, et al. Fetal Origins of Asthma: A Longitudinal Study from Birth to Age 36 Years. Am J Respir Crit Care Med 2020;202(12):1646–1655. DOI: 10.1164/rccm.202001-0194OC. [PubMed: 32649838]
9. Bhatt SP, Kim YI, Wells JM, et al. FEV(1)/FEV(6) to diagnose airflow obstruction. Comparisons with computed tomography and morbidity indices. Ann Am Thorac Soc 2014;11(3):335–41. DOI: 10.1513/AnnalsATS.201308-251OC. [PubMed: 24450777]
10. Kjellberg S, Houltz BK, Zetterstrom O, Robinson PD, Gustafsson PM. Clinical characteristics of adult asthma associated with small airway dysfunction. Respir Med 2016;117:92–102. DOI: 10.1016/j.rmed.2016.05.028. [PubMed: 27492518]
11. Oelsner EC, Hoffman EA, Folsom AR, et al. Association between emphysema-like lung on cardiac computed tomography and mortality in persons without airflow obstruction: a cohort study. Ann Intern Med 2014;161(12):863–873. DOI: 2023010 [pii];10.7326/M13-2570 [doi]. [PubMed: 25506855]

12. Bhatt SP, Soler X, Wang X, et al. Association between Functional Small Airway Disease and FEV1 Decline in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2016;194(2):178–84. DOI: 10.1164/rccm.201511-2219OC. [PubMed: 26808615]

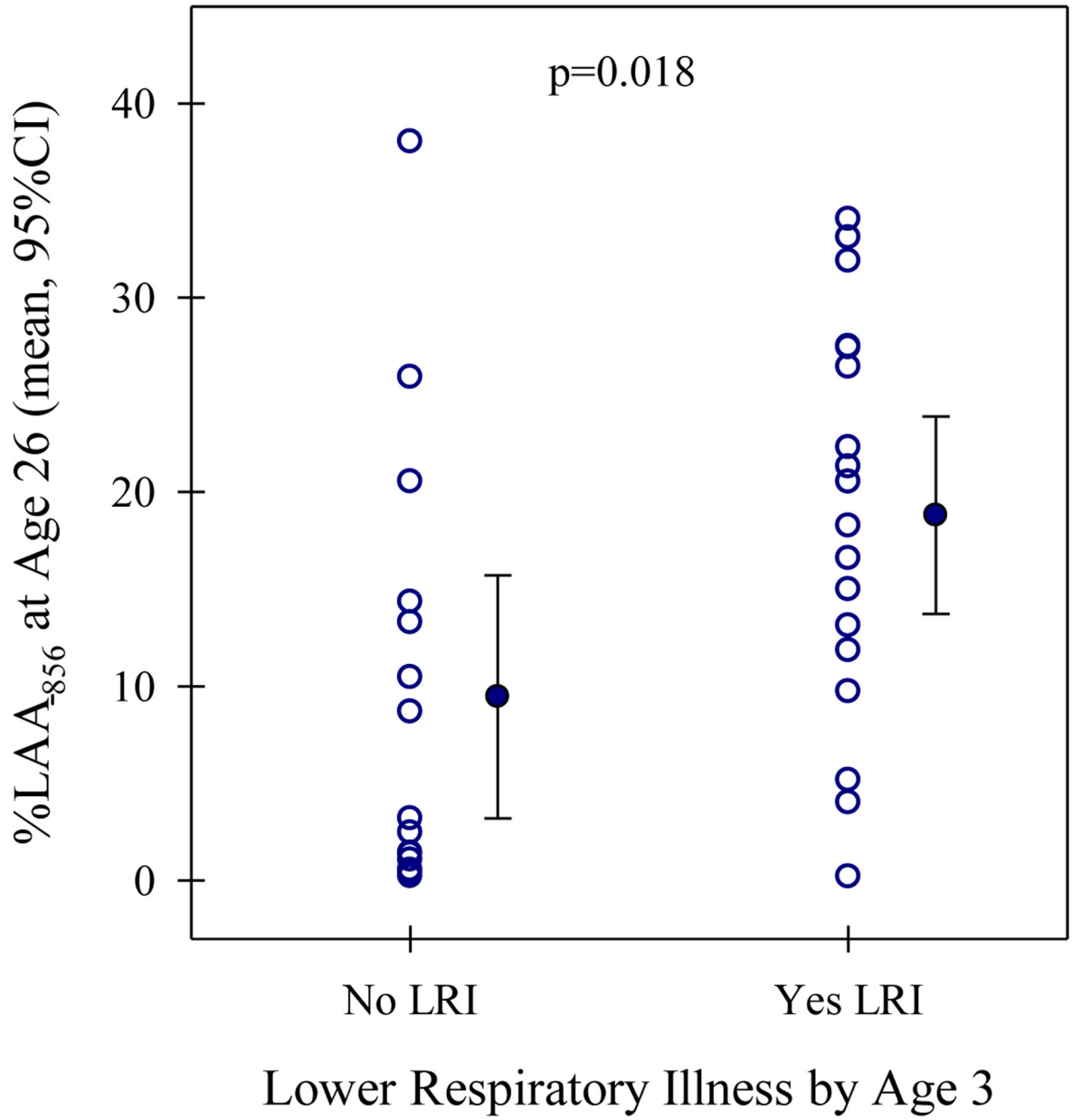

Figure 1.
Comparison of %LAA$_{-856}$ levels by early life lower respiratory illness (LRI)

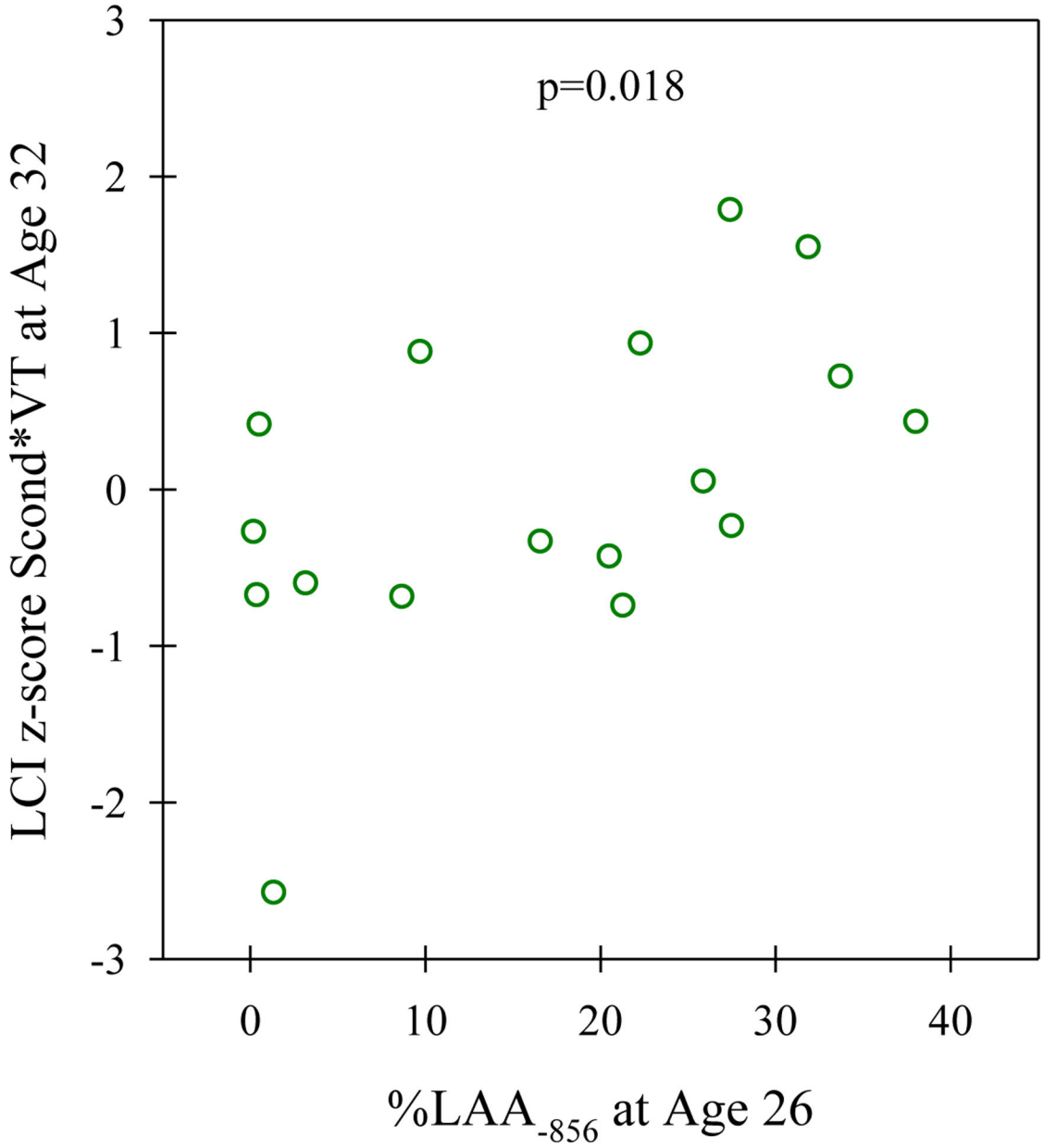

Figure 2.
Association between LCI Scond*VT and $\%LAA_{-856}$. The association persisted after removing the outlier with LCI z-score below −2.

Table 1.

Bivariate relation of participant characteristics to %LAA-$_{856}$. Participants were enrolled in the study at birth and HRCT was performed at age 26 years.

Characteristics	Group/Type	n	Mean %LAA$_{-856}$	95%CI	p-value
Early life factors:					
Sex	Male	18	18.5	12.9, 29.1	
	Female	21	12.0	7.1, 16.8	0.071
Race/Ethnicity	NHW	27	15.8	11.1, 20.5	
	HW	7	12.4	2.8, 21.9	
	Other	5	14.3	1.5, 27.0	0.773
Maternal Smoking	No	32	15.1	10.8, 19.2	
(at enrollment)	Yes	7	14.6	5.8, 23.5	0.928
Maternal Asthma	No	34	15.2	11.2, 19.2	
(at enrollment)	Yes	5	13.6	0.7, 26.5	0.774
LRI by age 3 years	No	15	9.5	3.2, 15.7	**0.018**
	Yes	18	18.8	13.7, 23.9	
RSV-LRI by age 3 years	No	15	9.5	3.2, 15.7	
	RSV	9	16.8	10.1, 23.5	
	Non-RSV	9	20.8	11.8, 29.8	**0.047**
At age 26:					
Smoking	Never	19	15.4	10.1, 20.6	
	Ever	20	14.6	9.0, 20.2	0.831
Respiratory Symptoms	No	22	17.0	11.7, 22.3	
(during the past year)	Yes	17	12.4	7.2, 17.5	0.205
		n	**rho with %LAA$_{-856}$**	**95%CI**	**p**
BMI	interval	39	−0.38	−0.67, −0.09	**0.017**
TLC, percent predicted	interval	38	0.22	−0.13, 0.56	0.191
RV, percent predicted	interval	38	0.10	−0.23, 0.44	0.566
Percent predicted (GLI), post-bronchodilator:					
FEV1	interval	39	−0.24	−0.57, 0.09	0.141
FVC	interval	39	−0.02	−0.36, 0.32	0.910
FEV$_1$/FVC	interval	39	−0.28	−0.62, 0.05	0.080
FEF$_{25–75}$	interval	39	−0.33	−0.67, −0.003	**0.037**
CT Airway Measures at EELV[*]:					
Wall Thickness	interval	39	−0.18	−0.49, 0.13	0.283
Inner Area	interval	39	0.03	−0.28, 0.33	0.871

[*]Average-average wall thickness and average inner area at end expiratory volume for generation 3

Abbreviations: HRCT - high-resolution computed tomography; LRI - lower respiratory illness; RSV - respiratory syncytial virus; FEV_1 - forced expiratory volume in 1 second; FVC - forced vital capacity; $FEF_{25-75\%}$ - forced expiratory flow; BMI - body mass index; EELV - end expiratory volume; TLC - total lung capacity; GLI - global lung initiative