Assessing the applicability of the new global lung function initiative reference values for the diffusing capacity of the lung for carbon monoxide in a large population set

Pierre-Marie Wardyn, Virginie de Broucker, Cecile Chenivesse, Annie Sobaszek, Richard van Bulck, Thierry Perez, Jean-Louis Edme, Sebastien Hulo

▶ **To cite this version:**

Pierre-Marie Wardyn, Virginie de Broucker, Cecile Chenivesse, Annie Sobaszek, Richard van Bulck, et al.. Assessing the applicability of the new global lung function initiative reference values for the diffusing capacity of the lung for carbon monoxide in a large population set. PLoS ONE, 2021, 16, pp.e0245434. 10.1371/journal.pone.0245434 . hal-03759589

HAL Id: hal-03759589
https://hal.univ-lille.fr/hal-03759589

Submitted on 24 Aug 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution 4.0 International License

PLOS ONE

RESEARCH ARTICLE

Assessing the applicability of the new Global Lung Function Initiative reference values for the diffusing capacity of the lung for carbon monoxide in a large population set

Pierre-Marie Wardyn[1☯], Virginie de Broucker[1,2☯], Cécile Chenivesse[3,4,5‡], Annie Sobaszek[2,6‡], Richard Van Bulck[1‡], Thierry Perez[1,4‡], Jean-Louis Edmé[1,2☯], Sébastien Hulo[1,2☯*]

1 Service des Explorations Fonctionnelles Respiratoires, CHU Lille, Lille, France, **2** EA 4483—IMPECS—IMPact de l'Environnement Chimique sur la Santé humaine, Univ. Lille, Lille, France, **3** Service de Pneumologie et Immuno-Allergologie, Centre de Référence Constitutif des Maladies Pulmonaires Rares, CHU Lille, Lille, France, **4** INSERM U1019—CNRS UMR 8204, Institut Pasteur de Lille—CIIL—Center for Infection and Immunity of Lille, Lille, France, **5** Univ. Lille, Lille, France, **6** Service de Médecine du Travail, CHU Lille, Lille, France

☯ These authors contributed equally to this work.
‡ These authors also contributed equally to this work.
* sebastien.hulo@univ-lille.fr

Check for updates

OPEN ACCESS

Citation: Wardyn P-M, de Broucker V, Chenivesse C, Sobaszek A, Van Bulck R, Perez T, et al. (2021) Assessing the applicability of the new Global Lung Function Initiative reference values for the diffusing capacity of the lung for carbon monoxide in a large population set. PLoS ONE 16(1): e0245434. https://doi.org/10.1371/journal.pone.0245434

Editor: Davor Plavec, Srebrnjak Children's Hospital, CROATIA

Received: August 4, 2020

Accepted: January 3, 2021

Published: January 14, 2021

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0245434

Copyright: © 2021 Wardyn et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: Please note that we cannot share the de-identified data set for legal reasons on the Research Ethics Board of the

Abstract

Background

The single-breath diffusing capacity of the lung for carbon monoxide (D_{LCO}) interpretation needs the comparison of measured values to reference values. In 2017, the Global Lung Function Initiative published new reference values (GLI-2017) for D_{LCO}, alveolar volume (V_A) and transfer coefficient of the lung for carbon monoxide (K_{CO}). We aimed to assess the applicability of GLI-2017 reference values for D_{LCO} on a large population by comparing them to the European Community of Steel and Coal equations of 1993 (ECSC-93) widely used.

Methods

In this retrospective study, spirometric indices, total lung capacity, D_{LCO}, V_A and K_{CO} were measured in adults classified in 5 groups (controls, asthma, chronic bronchitis, cystic fibrosis, and interstitial lung diseases (ILD)). Statistical analysis comparing the 2 equations sets were stratified by sex.

Results

4180 tests were included. GLI-2017 z-scores of the 3 D_{LCO} indices of the controls (n = 150) are nearer to 0 (expected value in a normal population) than ECSC-93 z-scores. All groups combined, in both genders, D_{LCO} GLI-2017 z-scores and %predicted are significantly higher than ECSC z-scores and %predicted. In the ILD group, differences between the 2 equation sets depend on the D_{LCO} impairment severity: GLI-2017 z-scores are higher than ECSC z-

University Hospital of Lille demand. The data set includes sensitive medical information about included patients as medical history and PFT results. Sex, age, height and weight are also included in the data set, which can potentially allow the patients' identification. Data requests may be sent to the Research Ethics Board of the University Hospital of Lille (contact: +33 3.20.44.41.65 / cppnordouestiv@univ-lille2.fr).

Funding: The authors received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

scores in patients with no or "mild" decrease in D_{LCO}, but are lower in "moderate" or "severe" decrease.

Conclusion

GLI-2017 reference values for D_{LCO} are more suitable to our population and influence the diagnostic criteria and severity definition of several lung diseases.

Introduction

The single-breath diffusing capacity of the lung for carbon monoxide (D_{LCO}) is a simple non-invasive way to evaluate the alveolar-capillary gas exchanges [1]. D_{LCO} is a key element in the diagnosis and follow-up of diseases in which lung gas transfer is altered by an alveolar-capillary membrane damage, as seen in interstitial lung diseases.

D_{LCO} measured values need to be compared to reference values calculated with equations based on age, sex and height. Nowadays, in Europe, the European Community of Steel and Coal (ECSC) reference values for D_{LCO} parameters, published in 1983 [2] (ECSC-83) and updated in 1993 [3,4] (ECSC-93), are the most commonly used. They are linear regression equations based on regression equations collation published before 1983. They are suitable for European women and men from 25 to 70 years old. Between 18 and 25 years old, predicted values are based on an age fixed at 25 years old. Before 18 years old, several equations sets can be applied including those of Polgar and Promadhat published in 1971 [5]. Besides the discontinuity problem between adults and children, the methods employed to produce those equations are far from current standards.

In 2017, the Global Lung Function Initiative (GLI) published new reference values for D_{LCO}, alveolar volume (V_A) and transfer coefficient of the lung for carbon monoxide (K_{CO}) for Caucasians aged from 5 to 85 years old (GLI-2017) [6]. Data derived from measured values in 9170 subjects from 14 countries excluding France due to French ethical laws.

Before using a set of equations on daily basis, the most appropriate should be chosen after comparison to the different available options [7,8]. To date, two articles have been published with this aim for GLI-2017 D_{LCO} equations. The first on 145 patients with idiopathic pulmonary fibrosis evaluating the impact of GLI-2017 on clinical trial eligibility for those patients [9], and the second evaluating the effect of GLI-2017 on the normal/abnormal classification of D_{LCO} results [10]. Even if they both concluded that the GLI-2017 should be adopted in laboratories, the need for a study including controls and multiple categories of patients with several degrees of decrease in D_{LCO} still remains.

In our study, we aimed to assess the applicability of the GLI-2017 reference values for D_{LCO} in adults by comparing them to the ECSC-93 equations currently used.

Materials and methods

Study population

We selected data of a control group and patients with symptoms compatible with one of four diseases (asthma, chronic bronchitis, cystic fibrosis, and interstitial lung diseases (ILD)) from pulmonary function tests (PFT) performed on daily basis between November 15th 2012 and May 30th 2016 in the PFT laboratory of the university hospital of Lille, France. PFTs providing all the following indices were selected: forced vital capacity (FVC), forced expiratory volume

in 1 second (FEV_1), FEV_1 to FVC ratio (FEV_1/FVC), total lung capacity (TLC), D_{LCO}, V_A and K_{CO}. Only measurements performed before bronchodilation were included.

Exclusion criteria were: patients under 18 years old; patients classified in more than one group; missing data or outliers for sex, weight or height; any PFT other than spirometry with D_{LCO} measurement; D_{LCO}<1mmol.min^{-1}.kPa^{-1} (minimal value for the D_{LCO} predicted value calculation [6,11]).

For each test, patient's characteristics (sex, age, height, weight), PFTs indices values and patient's medical history were recorded in the laboratory database. For the tests' inclusion, data from the PFT performed between November 15th 2012 and May 30th 2016, and including the indices mentioned above, were extracted to a Microsoft Excel® spreadsheet by the laboratory engineer. Then tests meeting exclusion criteria were excluded using the statistical software SAS® (version 9.4; Statistical Analysis System).

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by the Research Ethics Board of the University Hospital of Lille (Comité de Protection des Personnes Nord Ouest IV)—approval: HP20/02. All adult participants provided written informed consent for the use of their data in the research field. Included patients were addressed to our department for routine functional evaluation.

PFT measurements and results reports

Spirometry and lung volumes measured by body plethysmography and/or helium dilution were performed on a JAEGER® MasterScreen Body device (CareFusion, Hoechberg, Germany). Helium dilution was used for lung volumes measurements when body plethysmography was not feasible. D_{LCO}, V_A and K_{CO} measurements were performed on a JAEGER® MasterScreen PFT device (CareFusion, Hoechberg, Germany). Only test results meeting criteria for acceptability and reproducibility of the 2005 American Thoracic Society/European Respiratory Society recommendations (ATS/ERS-2005) [12–14] were included. In addition to the daily calibrations and verifications recommended by the manufacturer, the laboratory engineer (healthy and non-smoker) carried out a CO uptake measurement (biological calibration) every week. A D_{LCO} variability above 10% led to a device verification.

ECSC-93 were applied to all concerned indices (FVC, FEV_1, FEV_1/FVC and TLC) [2], the 2012 GLI equations for spirometry (GLI-2012) to FVC, FEV_1 and FEV_1/FVC ratio [15] and ECSC-93 to D_{LCO} [2]. The 1993 ECSC update recommend to calculate the K_{CO} predicted value as the predicted D_{LCO} to predicted TLC ratio [4], so the predicted V_A used in this study is the predicted TLC for the K_{CO} calculation according to ECSC. GLI-2017 were applied to D_{LCO}, V_A and K_{CO} [11].

Spirometric and TLC values were expressed as z-scores, D_{LCO} and V_A results as z-scores and %predicted, K_{CO} adjustment on the ECSC-1993 predicted value as %predicted only (the standard deviations required for z-scores is not available).

Groups creation

Selected PFTs came from 4 groups of patients with symptoms compatible with one of the following diseases: asthma, chronic bronchitis, cystic fibrosis, and ILD. The chronic bronchitis group included patients with symptoms compatible with chronic bronchitis (with a FEV_1/FVC ratio $\geq$ 0.7) or with chronic obstructive pulmonary disease (COPD) (with a FEV_1/FVC ratio $<$ 0.7 according to the GOLD 2021 report [16]). ILD category covers more than 150 entities such as sarcoidosis, idiopathic pulmonary fibrosis or pneumoconiosis [17]. The disease was initially filled out by the prescribing physician and recorded in the laboratory database at the time of the PFT validation. In order to ensure data quality, diagnoses were checked from

patient files in random samples of each groups (see S1 Appendix and S1 Table in S1 Appendix). Selected PFTs could have been performed at any stage of the concerned disease, from initial evaluation to advanced stage. The control group consisted of subjects complaining of dyspnea without parenchymal lung abnormalities and subjects from a health monitoring checking their work ability. Employees with professional exposures were excluded. Subject selection for this control group was performed independently from the PFT results.

Statistical analysis

Data analysis was performed using the statistical software SAS® (version 9.4; Statistical Analysis System) and R (version 3.6.1; R Foundation, www.r-project.org). Five types of ventilatory disorders were created from spirometric and TLC values: "obstruction" (FEV_1/FVC below lower limit of normal (LLN) (z-score <-1.645), TLC ≥LLN), "restriction" (TLC <LLN, FEV_1/FVC ≥LLN), "mixed" (coexistence of obstruction and restriction) [18], Preserved Ratio Impaired Spirometry (PRISm) (FEV_1/FVC and TLC ≥LLN, FEV_1 <LLN) [19], "normal" (FVC, FEV_1, FEV_1/FVC and TLC ≥LLN) and "other" (not elsewhere classified).

D_{LCO} parameters below LLN were considered altered. The ATS/ERS-2005 degrees of D_{LCO} impairment were used: "Mild" (D_{LCO}>60%predicted and <LLN), "Moderate" (D_{LCO}>40% and ≤60%predicted), "Severe" (D_{LCO}≤40%predicted) [18].

Data analysis were stratified by sex and reported by subject groups. Continuous quantitative variables were expressed as medians, 1st and 3rd quartiles; qualitative variables as absolute values and frequencies (percentages).

Non-parametric Wilcoxon and Kruskall-Wallis tests were used for data without normal distribution to compare quantitative variables between groups, Chi-squared tests to compare qualitative variables, Wilcoxon signed-rank tests to compare PFT values between equation sets. Differences in D_{LCO} and V_A alteration prevalence rates according to each equation sets were tested using McNemar's Chi-squared test.

Linear or multilinear regressions were used to study the relationship between the differences of the 2 D_{LCO} z-scores, calculated with each equation sets, and age, sex, and decrease severity.

Statistical significance was set at $p < 0.05$ for all tests.

Results

From the 15th November 2012 to the 30 May 2016, 9699 tests with spirometry and D_{LCO} measurements were performed. 4180 tests were included (representing 2898 subjects) with 2181 tests in men and 1999 in women (Fig 1).

Table 1 shows the main characteristics of our population. Ventilatory defect types are significantly different between groups (Table 1). In the control group, "normal" ventilatory profiles proportions are close to the 95% expected in a normal population.

GLI-2012 produce significantly lower median z-scores for FEV_1 ($p < 0.0001$ in both genders), FVC ($p < 0.0001$ in both genders) and FEV_1/FVC ($p < 0.0001$ in both genders) than ECSC, all groups combined, in both genders (Table 2). In control subjects, ECSC FEV_1 and FVC median z-scores are more distant from the zero expected value than GLI-2012 values.

For both equation sets, D_{LCO}, V_A and K_{CO} z-score and %predicted are statistically linked to subject groups ($p < 0.0001$ in both genders; Kruskall-Wallis tests). Median z-scores in the control group are close to the zero expected with GLI-2017 in both genders (Table 3). In this group, standard deviations are also slightly closer to zero using GLI-2017 (0.819 in women, 0.928 in men) than using ECSC (0.866 in women, 0.968 in men). Furthermore, in this group, z-score differences between the 2 equations sets are linearly correlated to age ($p < 0.0001$) and

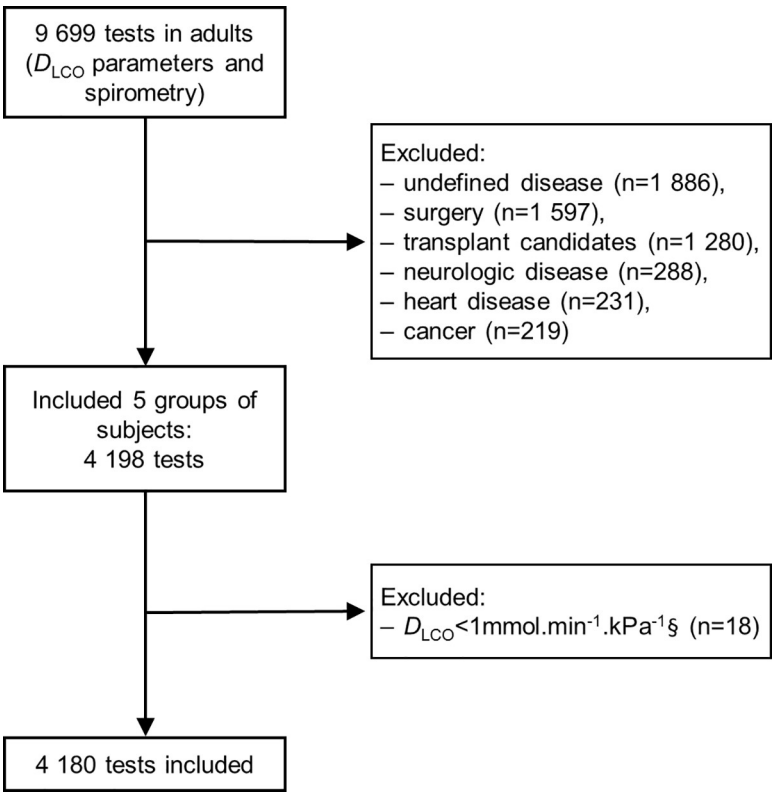

Fig 1. Study flow-chart. D_{LCO}: Diffusing capacity of the lung for carbon monoxide. §: Minimal value for the D_{LCO} predicted value calculation [6,11].

https://doi.org/10.1371/journal.pone.0245434.g001

height (p = 0.0004 in women, p = 0.0392 in men) in both genders, with a stronger trend in women. In the asthma and cystic fibrosis groups, GLI-2017 produce significantly higher D_{LCO} z-scores than ECSC in both genders (Asthma group: $p < 0.0001$ in both genders. Cystic fibrosis group: $p < 0.0001$ in both genders). In the chronic bronchitis and ILD groups, the same trends are seen only in women, with a significant difference between D_{LCO} z-scores in the ILD group only ($p < 0.0001$ in the ILD group; p = 0.27 in the chronic bronchitis group). In men with chronic bronchitis or ILD, which are the groups with the lowest D_{LCO} values, GLI-2017 generate significantly lower D_{LCO} z-scores than ECSC ($p < 0.0001$ in the chronic bronchitis group; $p < 0.0001$ in the ILD group).

For %predicted D_{LCO}, GLI-2017 results are significantly higher than ECSC values ($p < 0.0001$ in men and women). In the control group, D_{LCO} impairment prevalence rates are nearer to the expected 5% using GLI-2017 (6.5% in men, 1.4% in women) compared to ECSC (19.5% in men, 31.5% in women) (Table 4). In the other groups, D_{LCO} impairment prevalence rates are significantly lower using GLI-2017 than using ECSC with larger differences in women (in women: $p < 0.0001$ in the chronic bronchitis group, $p < 0.0001$ in the cystic fibrosis group, $p < 0.0001$ in the ILD group; in men: $p < 0.0001$ in the chronic bronchitis group, p = 0.0026 in the cystic fibrosis group, $p < 0.0001$ in the ILD group). In the asthma group, for example, the proportion of D_{LCO} measurements categorized as normal with GLI-2017 is significantly higher than using ECSC, especially in women ($p < 0.0001$ in both genders).

GLI-2017 and ECSC D_{LCO} z-scores comparison by degree of decrease in D_{LCO} according to ATS/ERS-2005 in the ILD group is shown in Fig 2. GLI-2017 D_{LCO} z-scores are -2.03, -3.39, -5.47 in men and -1.55, -3.36, -7.22 in women, in "mild", "moderate" and "severe" categories

Table 1. Characteristics of the population by sex.

Variables	Overall	Controls	Asthma	Chronic bronchitis	Cystic fibrosis	ILD	Statistics between groups p-value
	n = 4180	n = 150	n = 527	n = 732	n = 145	n = 2626	
Male							
Subjects, n	2181	77	197	534	70	1303	
Age, years	59 (47; 68)	40 (27; 51)	46 (34; 56)	59 (51; 66)	28 (24; 37)	62 (52; 70)	< 0.0001
Weight, kg	80 (70; 90)	81 (72; 91)	78 (69; 90)	75 (66; 90)	64 (57; 77)	81 (72; 91)	< 0.0001
Height, cm	173 (169; 178)	178 (174; 184)	176 (171; 180)	172 (168; 178)	171 (168; 176)	173 (168; 178)	< 0.0001
BMI, $kg.m^{-2}$	26.3 (23.2; 29.8)	25.9 (23.1; 28.1)	25.1 (22.5; 28.4)	25.3 (22.0; 29.4)	21.7 (19.9; 24.9)	27.2 (24.1; 30.4)	< 0.0001
Ventilatory defect type	2167	73	189	532	69	1300	< 0.0001
Normal	658 (30.4%)	73 (94.8%)	83 (43.9%)	80 (15.0%)	22 (31.9%)	400 (30.8%)	
Restriction	793 (36.6%)	2 (2.6%)	18 (9.5%)	36 (6.8%)	6 (8.7%)	731 (56.2%)	
Obstruction	361 (16.7%)	2 (2.6%)	55 (29.1%)	234 (44.0%)	12 (17.4%)	58 (4.5%)	
Mixed	322 (14.9%)	0	26 (13.8%)	168 (31.6%)	29 (42%)	99 (7.6%)	
PRISm	31 (1.4%)	0	7 (3.7%)	14 (2.6%)	0	10 (0.8%)	
Other	2 (0.1%)	0	0	0	0	2 (0.1%)	
Missing data‡	14	0	8	2	1	3	
Female							
Subjects, n	1999	73	330	198	75	1323	
Age, years	53 (41; 65)	43 (29; 54)	48 (34; 57)	55 (48; 65)	31 (22; 42)	56 (43; 66)	< 0.0001
Weight, kg	67 (57; 80)	63 (56; 78)	67 (58; 79)	62 (53; 76)	53 (50; 60)	68 (58; 82)	< 0.0001
Height, cm	162 (157; 167)	163 (160; 167)	162 (157; 168)	161 (157; 166)	164 (160; 167)	161 (156; 166)	0.00022
BMI, $kg.m^{-2}$	25.5 (21.8; 30.8)	23.7 (21.3; 28.9)	25.3 (21.3; 29.7)	23.4 (20.7; 28.4)	20.2 (18.7; 21.8)	26.4 (22.5; 31.5)	< 0.0001
Ventilatory defect type	1963	70	301	194	75	1323	< 0.0001
Normal	1104 (56.2%)	66 (94.3%)	173 (57.5%)	32 (16.5%)	25 (33.3%)	808 (61.1%)	
Restriction	393 (20.2%)	0	15 (5%)	6 (3.1%)	6 (8%)	366 (27.7%)	
Obstruction	294 (15.0%)	2 (2.9%)	76 (25.2%)	110 (56.7%)	20 (26.7%)	86 (6.5%)	
Mixed	118 (6.0%)	0	27 (9%)	40 (20.6%)	21 (28%)	30 (2.3%)	
PRISm	51 (2.6%)	1 (1.4%)	9 (3.0%)	6 (3.1%)	3 (4%)	32 (2.4%)	
Other	3 (0.1%)	2 (1.4%)	1 (0.3%)	0	0	1 (0.1%)	
Missing data‡	36	3	29	4	0	0	

Ventilatory defect types according to the 2005 recommendations for lung function test interpretation from the American Thoracic Society (ATS) and the European Respiratory Society (ERS): Obstruction: z-score of FEV_1/FVC ratio < -1.645 and TLC z-score ≥ -1.645; restriction: TLC z-score < -1.645 and z-score of FEV_1/FVC ratio ≥ -1.645; mixed (coexistence of obstruction and restriction); [18] PRISm (Preserved Ratio Impaired Spirometry): z-score of FEV_1/FVC ratio ≥ -1.645, TLC z-score ≥ -1.645 and FEV_1 z-score < -1.645; [19] normal: z-score of FVC, FEV_1, FEV_1/FVC ratio and TLC ≥ -1.645; other: Not elsewhere classified. ILD: Interstitial lung disease; BMI: Body mass index; FEV_1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; TLC: Total lung capacity. Data are presented as n, median (Q1; Q3) and n (%). Kruskall-Wallis tests were used to compare qualitative variables between disease groups, Chi-squared tests to compare qualitative variables between disease groups. ‡Missing data only concern TLC.

https://doi.org/10.1371/journal.pone.0245434.t001

respectively. GLI-2017 z-scores are significantly higher than ECSC z-scores in patients with no ($p < 0.0001$ in both genders) or "mild" decrease in D_{LCO} ($p < 0.0001$ in both genders), but are significantly lower in "moderate" ($p < 0.0001$ in both genders) or "severe" ($p < 0.0001$ in both genders) decrease in D_{LCO}. The multivariate analysis confirmed that the z-scores differences (ECSC vs GLI-2017 z-scores) is influenced by the DLCO severity grade (taking age in account). Multiple linear regression analysis showed, in both genders, a highly significant

Table 2. Z-scores of FVC, FEV_1, FEV_1/FVC and TLC according to ECSC-93 and GLI-2012 (except for TLC) by sex.

Variables		Overall	Controls	Asthma	Chronic bronchitis	Cystic fibrosis	ILD
		n = 4180	n = 150	n = 527	n = 732	n = 145	n = 2626
Male							
Tests, n		2181	77	197	534	70	1303
FVC	ECSC-93	-0.759 (-1.77; 0.19)	0.88 (0.08; 1.35)	-0.13 (-1.29; 0.64)	-0.94 (-1.97; 0.09)	-0.67 (-2.18; 0.09)	-0.87 (-1.80; 0.05)
	GLI-2012	-1.18 (-2.21; -0.26)	0.23 (-0.46; 0.65)	-0.58 (-1.61; 0.08)	-1.33 (-2.34; -0.40)	-1.15 (-2.62; -0.36)	-1.25 (-2.24; -0.39)
FEV_1	ECSC-93	-1.29 (-2.47; -0.33)	0.59 (-0.36; 1.17)	-1.31 (-2.47; -0.17)	-2.52 (-3.60; -1.41)	-2.19 (-4.22; -0.76)	-1.00 (-1.88; -0.21)
	GLI-2012	-1.65 (-2.73; -0.68)	0.16 (-0.77; 0.68)	-1.63 (-2.69; -0.54)	-2.79 (-3.73; -1.82)	-2.54 (-4.36; -0.89)	-1.37 (-2.24; -0.54)
FEV_1/FVC	ECSC-93	-0.685 (-2.09; 0.40)	0.002 (-0.48; 0.43)	-1.34 (-2.56; -0.32)	-2.75 (-4.42; -1.67)	-2.37 (-3.65; -0.74)	0.05 (-0.84; 0.83)
	GLI-2012	-0.910 (-2.19; 0.21)	-0.23 (-0.67; 0.38)	-1.58 (-2.56; -0.48)	-2.68 (-3.89; -1.83)	-2.55 (-3.51; -1.07)	-0.13 (-1.00; 0.58)
TLC	ECSC-93	-1.70 (-3.06; -0.50)	-0.10 (-0.53; 0.63)	-0.77 (-1.56; 0.25)	-1.14 (-2.21; -0.14)	-1.65 (-2.60; -0.58)	-2.34 (-3.48; -1.16)
	Missing data	14 (0.6%)	0	8 (4.1%)	2 (0.4%)	1 (1.4%)	3 (0.2%)
Female							
Tests, n		1999	73	330	198	75	1323
FVC	ECSC-93	-0.03 (-0.97; 0.83)	0.91 (0.01; 1.69)	0.13 (-0.75; 1.02)	-0.46 (-1.21; 0.41)	-0.99 (-2.33; 0.29)	-0.01 (-0.94; 0.80)
	GLI-2012	-0.85 (-1.81; -0.09)	-0.04 (-0.64; 0.77)	-0.70 (-1.60; 0.21)	-1.28 (-2.07; -0.51)	-1.48 (-2.55; -0.48)	-0.86 (-1.81; -0.12)
FEV_1	ECSC-93	-0.62 (-1.73; 0.23)	0.31 (-0.29; 1.08)	-0.65 (-1.81; 0.23)	-1.96 (-3.54; -1.11)	-1.92 (-4.10; -0.54)	-0.47 (-1.43; 0.30)
	GLI-2012	-1.15 (-2.24; -0.28)	-0.042 (-0.74; 0.71)	-1.18 (-2.44; -0.26)	-2.70 (-3.76; -1.77)	-1.94 (-4.21; -0.88)	-1.03 (-1.98; -0.23)
FEV_1/FVC	ECSC-93	-0.29 (-1.33; 0.55)	0.04 (-0.60; 0.60)	-0.72 (-1.99; 0.02)	-2.52 (-4.90; -1.71)	-2.00 (-3.16; -0.52)	0.03 (-0.68; 0.77)
	GLI-2012	-0.52 (-1.43; 0.26)	-0.17 (-0.82; 0.33)	-0.97 (-1.98; -0.24)	-2.32 (-3.64; -1.75)	-1.98 (-2.81; -0.75)	-0.18 (-0.88; 0.50)
TLC	ECSC-93	-0.72 (-1.68; 0.17)	0.44 (-0.25; 0.99)	-0.23 (-1.09; 0.50)	-0.72 (-1.55; 0.21)	-1.30 (-2.40; -0.20)	-0.85 (-1.90; 0.01)
	Missing data	36 (1.8%)	3 (4.1%)	29 (8.8%)	4 (2.0%)	0	0

ILD: Interstitial lung disease; FVC: Forced vital capacity; FEV_1: Forced expiratory volume in 1 s; TLC: Total lung capacity; ECSC-93: European Community for Steel and Coal 1993 reference values; [2,4] GLI-2012: Global Lung function Initiative 2012 reference values [15]. Data are presented as n, median z-score (Q1; Q3) and n (%).

https://doi.org/10.1371/journal.pone.0245434.t002

relationship between z-scores differences (ECSC vs GLI-2017) and age (as in the "control" group) ($p < 0.0001$, in both genders), the decrease in D_{LCO} severity ($p < 0.0001$, in both genders) and the interaction between age and severity ($p < 0.0001$ in both genders).

Discussion

To our knowledge, this study is the first to apply D_{LCO} measured values to the GLI-2017 reference values on a large population of patients and controls. Results in control group showed that the z-scores of the 3 D_{LCO} indices are nearer to 0 (expected value in a normal population) according to GLI-2017 than with ECSC-93. Moreover, in this control population, the proportion of tests with altered indices was near the expected 5%. GLI-2017 equations increase the proportion of tests classified as normal for D_{LCO} compared to ECSC, notably in the control and asthma groups. In the disease groups, we found a significant relationship between the severity degree of decrease in D_{LCO} and the z-scores differences between GLI-2017 and ECSC. GLI-2017 produce lower D_{LCO} z-scores for moderate to severe decrease in D_{LCO} than ECSC, notably in the ILD group. In all groups, differences between the 2 equation sets were more pronounced in women. Finally, K_{CO} results expressed as %predicted using GLI-2017 were significantly lower than using ECSC in men, but significantly higher in women.

We recruited subjects without a disease diagnosed by a physician. Ventilatory disorder types analysis showed a "normal" type proportion close to the 95% expected in a healthy population. To validate this control group, we applied the approach used to validate GLI-2012 [20,21]: z-scores close to zero, tests with a D_{LCO} below LLN proportion. In this group, GLI-

Table 3. Measured values, z-scores and %predicted for D_{LCO}, V_A and K_{CO} according to ECSC-93 and GLI-2017 by sex.

Variables		Overall	Controls	Asthma	Chronic bronchitis	Cystic fibrosis	ILD
		n = 4180	n = 150	n = 527	n = 732	n = 145	n = 2626
Male							
Subjects, n		2181	77	197	534	70	1303
D_{LCO}, mmol.min^{-1}.kPa^{-1}		5.64 (3.80; 8.13)	10.08 (8.84; 11.42)	9.01 (7.63; 10.05)	5.20 (3.74; 6.70)	9.01 (7.78; 10.46)	5.08 (3.42; 7.06)
Z-score	ECSC-93	-2.50 (-3.61; -1.41)	-0.95 (-1.48; 0.10)	-1.12 (-1.99; -0.16)	-2.67 (-3.80; -1.62)	-1.42 (-2.31; -0.55)	-2.76 (-3.83; -1.73)
	GLI-2017	-2.45 (-4.05; -1.00)	-0.45 (-1.02; 0.43)	-0.64 (-1.50; 0.27)	-2.82 (-4.23; -1.48)	-0.67 (-1.68; 0.13)	-2.86 (-4.40; -1.52)
	ECSC vs GLI	p = 0.02	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001
% pred.	ECSC-93	61.7 (43.9; 80.2)	88.5 (80.6; 101.4)	85.3 (73.4; 97.5)	57.2 (41.7; 74.0)	83.3 (71.5; 92.9)	56.7 (40.1; 73.2)
	GLI-2017	64.7 (46.1; 85.1)	93.9 (85.1; 107.2)	90.9 (78.6; 104.6)	60.0 (44.5; 78.4)	91.0 (78.4; 101.8)	59.5 (41.9; 77.4)
	ECSC vs GLI	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001
V_A, L		5.16 (4.17; 6.12)	6.65 (6.12; 7.51)	6.24 (5.37; 6.70)	5.48 (4.64; 6.15)	5.06 (4.51; 5.94)	4.75 (3.81; 5.73)
Z-score	ECSC-93	-2.21 (-3.56; -1.05)	-0.40 (-1.03; .18)	-1.21 (-1.87; -0.24)	-1.68 (-2.77; -0.74)	-2.16 (-2.97; -1.01)	-2.86 (-3.96; -1.64)
	GLI-2017	-1.26 (-2.60; -0.18)	0.25 (-0.41; 0.63)	-0.24 (-1.05; 0.51)	-0.79 (-1.77; 0.12)	-1.26 (-2.25; -0.16)	-1.91 (-3.00; -0.71)
	ECSC vs GLI	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001
% pred.	ECSC-93	76.8 (62.7; 89.2)	93.9 (89.1; 99.5)	87.8 (81.1; 97.6)	82.2 (71.2; 92.0)	76.9 (69.0; 87.8)	69.9 (58.3; 83.5)
	GLI-2017	85.1 (69.6; 97.8)	103.0 (95.4; 107.0)	97.1 (88.4; 106.0)	90.5 (79.5; 101.4)	86.3 (76.0; 98.3)	77.5 (65.2; 91.4)
	ECSC vs GLI	p < 0.0001	p = 0.00039	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001
K_{CO}, mmol.min^{-1}.kPa^{-1}.L^{-1}		1.12 (0.87; 1.40)	1.45 (1.29; 1.61)	1.43 (1.28; 1.65)	0.97 (0.72; 1.25)	1.70 (1.59; 1.91)	1.08 (0.86; 1.34)
Z-score	GLI-2017	-1.49 (-2.78; -0.44)	-0.50 (-1.03; -0.08)	-0.44 (-1.03; 0.38)	-2.23 (-3.63; -1.09)	0.15 (-0.48; 1.00)	-1.60 (-2.77; -0.59)
% pred.	ECSC-93	82.4 (64.3; 97.4)	94.3 (87.4; 100.3)	97.1 (87.3; 107.5)	71.5 (52.7; 88.2)	102.4 (94.0; 115.0)	80.9 (64.4; 96.1)
	GLI-2017	78.0 (60.7; 93.6)	93.1 (85.2; 99.0)	94.0 (85.2; 105.4)	67.6 (49.7; 84.0)	101.9 (93.8; 113.8)	75.6 (60.7; 91.2)
	ECSC vs GLI	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001
Female							
Subjects, n		1999	73	330	198	75	1323
D_{LCO}, mmol.min^{-1}.kPa^{-1}		5.44 (3.97; 6.67)	6.99 (6.57; 7.81)	6.45 (5.46; 7.41)	4.54 (2.89; 5.91)	6.40 (5.49; 7.53)	5.06 (3.60; 6.31)
Z-score	ECSC-93	-2.11 (-3.04; -1.27)	-1.27 (-1.74; -0.57)	-1.59 (-2.28; -0.87)	-2.56 (-3.64; -1.65)	-2.07 (-2.88; -1.08)	-2.27 (-3.17; -1.40)
	GLI-2017	-1.46 (-3.11; -0.41)	-0.13 (-0.72; 0.42)	-0.67 (-1.48; 0.13)	-2.19 (-5.12; -1.03)	-0.96 (-1.68; 0.12)	-1.78 (-3.60; -0.66)
	ECSC vs GLI	p < 0.0001	p < 0.0001	p < 0.0001	p = 0.27	p < 0.0001	p < 0.0001
% pred.	ECSC-93	69.0 (54.1; 81.2)	82.7 (76.9; 92.1)	77.3 (68.1; 87.0)	61.5 (40.6; 73.4)	72.7 (62.8; 85.7)	65.9 (50.4; 78.5)
	GLI-2017	79.3 (61.0; 93.6)	97.8 (88.8; 107.1)	89.6 (78.7; 102.1)	69.6 (46.0; 84.4)	86.2 (77.4; 101.8)	74.8 (56.3; 89.8)
	ECSC vs GLI	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001
V_A, L		4.12 (3.44; 4.73)	4.85 (4.50; 5.37)	4.51 (3.87; 5.02)	4.06 (3.51; 4.69)	4.13 (3.30; 4.65)	4.01 (3.28; 4.58)
Z-score	ECSC-93	-1.21 (-2.20; -0.30)	0.17 (-0.54; 0.86)	-0.67 (-1.44; 0.06)	-1.36 (-2.36; -0.23)	-1.65 (-2.51; -0.78)	-1.40 (-2.38; -0.50)
	GLI-2017	-1.04 (-2.18; -0.11)	0.09 (-0.58; 0.63)	-0.49 (-1.33; 0.23)	-1.15 (-2.33; -0.07)	-1.61 (-2.76; -0.64)	-1.23 (-2.42; -0.29)

(*Continued*)

Table 3. (Continued)

Variables		Overall	Controls	Asthma	Chronic bronchitis	Cystic fibrosis	ILD
		n = 4180	n = 150	n = 527	n = 732	n = 145	n = 2626
	ECSC vs GLI	p < 0.0001	p < 0.0001	p < 0.0001	p = 0.0031	p = 0.66	p = 0.00037
% pred.	ECSC-93	85.1 (72.6; 96.1)	98.7 (91.3; 106.1)	91.8 (81.7; 100.8)	82.5 (71.8; 96.1)	80.7 (69.3; 90.7)	82.8 (70.5; 93.7)
	GLI-2017	87.5 (75.2; 98.7)	101.1 (93.1; 108.1)	93.6 (84.8; 102.8)	85.7 (73.2; 99.1)	81.5 (71.2; 92.5)	85.0 (72.8; 96.4)
	ECSC vs GLI	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001
K_{CO}, mmol.min^{-1}.kPa^{-1}.L^{-1}		1.32 (1.09; 1.52)	1.43 (1.31; 1.60)	1.45 (1.27; 1.63)	1.11 (0.78; 1.42)	1.62 (1.38; 1.88)	1.28 (1.06; 1.47)
Z-score	GLI-2017	-0.72 (-1.78; 0.18)	-0.16 (-0.90; 0.47)	-0.25 (-0.97; 0.60)	-1.57 (-3.77; -0.16)	0.28 (-0.64; 1.22)	-0.88 (-1.96; 0.01)
% pred.	ECSC-93	80.9 (68.6; 92.6)	85.0 (77.1; 94.7)	85.6 (77.2; 96.4)	70.0 (48.1; 87.6)	90.7 (78.5; 104.0)	79.4 (67.5; 90.9)
	GLI-2017	89.8 (75.5; 102.6)	97.7 (87.3; 107.0)	96.5 (86.6; 109.0)	78.4 (52.9; 97.7)	104.0 (91.0; 119.3)	87.4 (73.5; 100.2)
	ECSC vs GLI	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001

ILD: Interstitial lung disease; D_{LCO}: Diffusing capacity of the lung for carbon monoxide; ECSC-93: European Community for Steel and Coal 1993 reference values; [2,4] GLI-2017: Global Lung function Initiative 2017 reference values; [6] % pred.: %predicted; V_A: Alveolar volume; K_{CO}: Transfer coefficient of the lung for carbon monoxide. Data are presented as n and median (Q1; Q3). Wilcoxon signed-rank tests were used. All D_{LCO}, V_A and K_{CO} values expressed as %pred. or z-scores were significantly different between groups of subjects using ECSC and GLI equations sets ($p < 0.0001$; Kruskall-Wallis tests).

https://doi.org/10.1371/journal.pone.0245434.t003

Table 4. Number of tests and prevalence rates for D_{LCO}, V_A and K_{CO} impairment according to ECSC-93 and GLI-2017, by sex.

Variables		Overall	Controls	Asthma	Chronic bronchitis	Cystic Fibrosis	ILD
		n = 4180	n = 150	n = 527	n = 732	n = 145	n = 2626
Male							
Subjects, n		2181	77	197	534	70	1303
Abnormalities in D_{LCO}‡	ECSC-93	1 507 (69.1%)	15 (19.5%)	67 (34%)	397 (74.3%)	29 (41.4%)	999 (76.7%)
	GLI-2017	1 400 (64.2%)	5 (6.5%)	46 (23.4%)	376 (70.4%)	18 (25.7%)	955 (73.3%)
	ECSC vs GLI	p < 0.0001	p = 0.0044	p < 0.0001	p < 0.0001	p = 0.0026	p < 0.0001
Abnormalities in V_A‡	ECSC-93	1 360 (62.4%)	9 (11.7%)	62 (31.5%)	271 (50.7%)	43 (61.4%)	975 (74.8%)
	GLI-2017	924 (42.4%)	0	35 (17.8%)	145 (27.1%)	31 (44.3%)	713 (54.7%)
	ECSC vs GLI	p < 0.0001	p = 0.0077	p < 0.0001	p < 0.0001	p = 0.0015	p < 0.0001
Abnormalities in K_{CO}‡	GLI-2017	1013 (46.4%)	7 (9.1%)	29 (14.7%)	334 (62.5%)	2 (2.9%)	641 (49.2%)
Female							
Subjects, n		1999	73	330	198	75	1323
Abnormalities in D_{LCO}‡	ECSC-93	1 282 (64.1%)	23 (31.5%)	152 (46.1%)	150 (75.8%)	43 (57.3%)	914 (69.1%)
	GLI-2017	912 (45.6%)	1 (1.4%)	69 (20.9%)	123 (62.1%)	19 (25.3%)	700 (52.9%)
	ECSC vs GLI	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001
Abnormalities in V_A‡	ECSC-93	758 (37.9%)	6 (8.2%)	69 (20.9%)	84 (42.4%)	38 (50.7%)	561 (42.4%)
	GLI-2017	702 (35.1%)	3 (4.1%)	65 (19.7%)	75 (37.8%)	37 (49.3%)	522 (39.5%)
	ECSC vs GLI	p < 0.0001	p = 0.25	p = 0.29	p = 0.0077	p = 1	p < 0.0001
Abnormalities in K_{CO}‡	GLI-2017	552 (27.6%)	4 (5.5%)	35 (10.6%)	97 (49.0%)	7 (9.3%)	409 (30.9%)

ILD: Interstitial lung disease; D_{LCO}: Diffusing capacity of the lung for carbon monoxide; ECSC-93: European Community for Steel and Coal 1993 reference values; [2,4] GLI-2017: Global Lung function Initiative 2017 reference values; [6] V_A: Alveolar volume; K_{CO}: Transfer coefficient of the lung for carbon monoxide. Data are presented as n (%). McNemar's tests were used.

‡Abnormalities in indices if the z-score was strictly less than -1.645.

https://doi.org/10.1371/journal.pone.0245434.t004

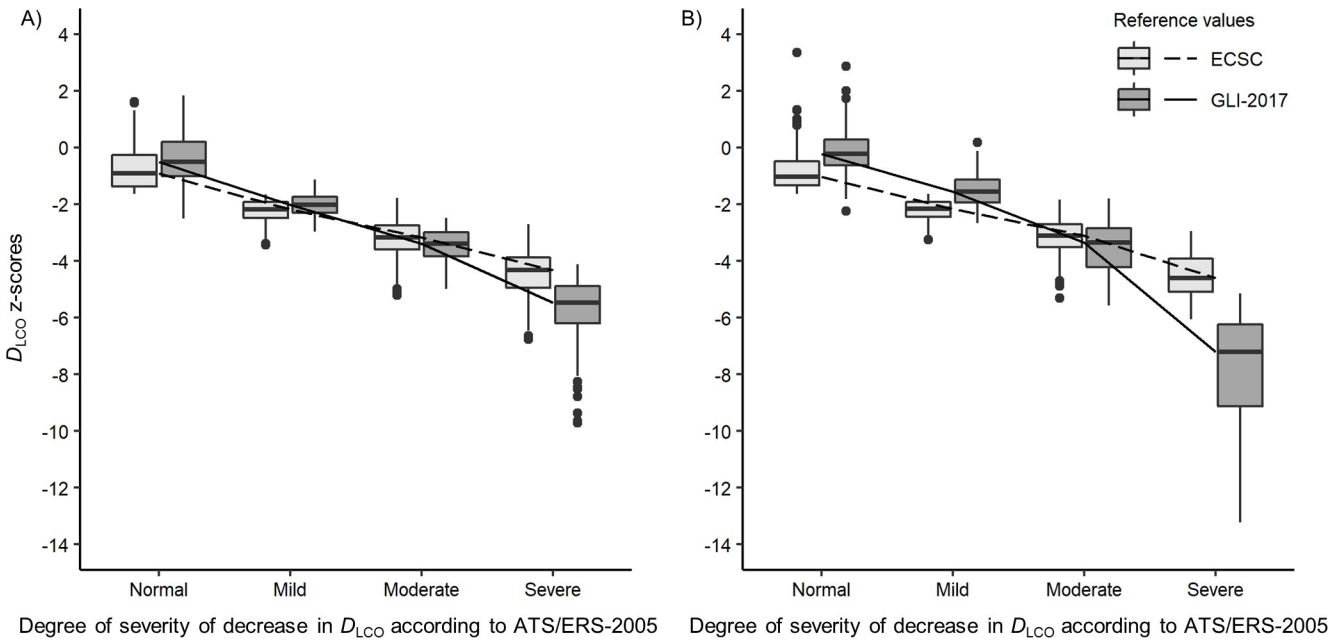

Fig 2. Box-plots of D_{LCO} ECSC-93 and GLI-2017 z-scores by degree of decrease in D_{LCO} according to ATS/ERS-2005 in (A) men and (B) women with ILD. Median values are represented by horizontal line within the boxes and interquartile ranges by box height. •: Outliers (values > 1.5 box lengths). D_{LCO} was considered normal if the z-score was equal or greater than -1.645. The 2005 ATS/ERS recommendations for lung function test interpretation were used to define the degree of severity of D_{LCO} impairment: "Mild" (D_{LCO} > 60% predicted and below lower limits of normal), "Moderate" (D_{LCO} > 40% and ≤ 60% predicted), "Severe" (D_{LCO} ≤ 40% predicted) [18]. D_{LCO}: Diffusing capacity of the lung for carbon monoxide; ECSC: European Community for Steel and Coal; GLI-2017: Global Lung function Initiative 2017 reference values; [6] ATS/ERS-2005: 2005 recommendations for lung function test interpretation from the American Thoracic Society (ATS) and the European Respiratory Society (ERS) [18].

https://doi.org/10.1371/journal.pone.0245434.g002

2017 z-scores of the 3 D_{LCO} indices are closer to zero (expected value in a normal population) than ECSC-93 z-scores and the proportion of tests with an impaired D_{LCO} is close to the expected 5%. This finding is important for clinical practice, obviating the need for additional diagnostic evaluations in females with falsely abnormal D_{LCO} when using ECSC.

Our results are consistent with recent literature. In our study, GLI-2017 produce significantly higher %predicted than ECSC for D_{LCO} and V_A in both gender (all groups combined) with larger differences in women. These findings were already reported on mathematical modelling by Oostveen et al. [22]. Similarly to our results, Brazzale et al. [10] showed that GLI-2017 tend to increase the proportion of tests classified as normal, with a larger difference in younger women, compared to ECSC-93 and that the level of agreement between GLI and ECSC-93 was lower for females than for males. Unfortunately, there is no information about the pulmonary condition of the included subjects and the analyses were limited to the use of the LLN. Finally, Wapenaar et al. [9] have compared GLI-2017 to ECSC for D_{LCO} in patient with idiopathic pulmonary fibrosis but their sample was composed of 82% of men and there was no analysis by sex.

In asthma and cystic fibrosis groups, GLI-2017 D_{LCO} z-scores were significantly higher than ECSC z-scores in both genders. Conversely, in the chronic bronchitis and ILD groups, results are discordant between women and men. D_{LCO} impairment severity seems to provide some clues. In the ILD group, Fig 2 shows an inversion of the trend for "moderate" or "severe" decrease in D_{LCO}: in "normal" D_{LCO} or "mild" decrease in D_{LCO}, GLI-2017 produce significantly higher z-scores than ECSC, whereas, in "moderate" or "severe" decrease, GLI-2017

produce significantly lower z-scores than ECSC. This observation is even more important in women. Mathematical modelling showed an inversion of the GLI/ECSC z-scores ratio when D_{LCO} is extremely decreased (see S1 Fig). These findings are consistent with recent literature [9].

One of the main strengths of our study is the size of our population. GLI-2017 were applied to 4180 tests (including 2898 subjects). To our knowledge, this is the first study to compare the GLI-2017 reference values to the ECSC using z-scores which should be favored in the interpretation of PFT results according to the ATS/ERS [1]. We also included control subjects, allowing us to applied the approach used for GLI-2012 [20,21]. To date, studies similar to ours has included patients without information about their pulmonary condition [10] or including only patients with a specific disease (e.g., idiopathic pulmonary fibrosis [9]). We have included PFTs from patients with symptoms compatible with one of four diseases (asthma, chronic bronchitis, cystic fibrosis or ILD). The chosen disease groups seemed to be the most relevant to us according to their definition and the diagnostic entities implied. It is worth noticing that patients with uncertain or associated diagnosis (e.g., a patient with asthma and chronic bronchitis) were excluded. Furthermore, all of the PFTs were performed on the same type of device, by a unique team, implying homogeneity in measurement method.

Our study also shows some weaknesses. We have compared the GLI-2017 reference values only to the ECSC in adults. The ECSC equations are currently one of the most used in European laboratories. Also, focusing on only one equation set and only on adult patients allowed us to detail different types of results (%predicted, z-scores and the 2005-ATS/ERS degrees of D_{LCO} impairment [18]) and study those results in controls and multiple categories of patients with several degrees of decrease in D_{LCO}. This retrospective study uses highly suspected diagnoses, established by the referring physician (pulmonologist or internist) prescribing the PFT, and recorded in the laboratory database. However, in order to ensure data quality, diagnoses were checked from patient files in random samples of each groups. Some PFTs from the chronic bronchitis group are classified as normal (16.5% in women and 15% in men). There are 2 main reasons. First, we included tests performed at every stage of the diseases, including patients with mild symptoms of chronic bronchitis without obstruction. Secondly, we used z-score to define obstruction according to the 2005-ATS/ERS recommendations for lung function test interpretation [18] (z-score of FEV_1/FVC ratio $<$ -1.645 and TLC z-score $\geq$ -1.645). Using the GOLD 2021 definition for COPD ($FEV_1/FVC < 0.7$) [16] could have led us to classify fewer PFTs as normal in the chronic bronchitis group in our sample due to the fact that a FEV_1/FVC ratio < 0.7 can be associated with a z-score of the FEV_1/FVC ratio $>$ -1.645. On the other hand, some PFTs in the chronic bronchitis group were classified as restrictive without obstruction (3.1% in women and 6.8% in men with chronic bronchitis). This may happen in case of chronic bronchitis evaluation in a patient with a concomitant disease which has not been clinically detected by the prescribing physician. Also, we were unable to collect ethnicity, this data collection being strictly regulated by French law. However, the majority of the laboratory patients are Caucasians. We did not take into account active tobacco consumption and hemoglobinemia (which would only have corrected D_{LCO} crude value). The aim of this study was not to assess the GLI-2017 diagnostic interest but to compare them to ECSC. Finally, our data come from a single laboratory, but it cover an area of more than 4 million people (approximately 9% of the French population) [23].

In conclusion, we showed that GLI-2017 reference values are more suitable to our sample than ECSC and that the differences between the 2 equation sets depend on the severity of D_{LCO} impairment in the Interstitial Lung Disease group. Our study shows the impact of a possible future application of these new reference values on the diagnostic criteria for several lung diseases and on the definition of their severity.

Supporting information

S1 Fig. Mathematical modelling of theorical D_{LCO} as a function of ECSC-93 and GLI-2017 z-scores and height in a 30 years old a) man and b) woman. D_{LCO}: Diffusing capacity of the lung for carbon monoxide; ECSC: European Community for Steel and Coal 1993 reference values [2,4]; GLI: Global Lung function Initiative 2017 reference values [6].
(PDF)

S1 Appendix. Quality control of the disease group classification. Contains: S1 Table. Sample sizes, number of classification errors in the random sample and estimated classification error rate on the population of the study according to the ISO 2859–1 standard [24]. ILD: interstitial lung disease. Data are presented as n or %. §Classification error rate estimated for the overall population of the study in each disease group according to the ISO 2859–1 standard [24].
(PDF)

Acknowledgments

The authors thank all of the staff of the Pulmonary Functional Tests Department for their help in this work.

Author Contributions

Conceptualization: Pierre-Marie Wardyn, Virginie de Broucker, Jean-Louis Edmé, Sébastien Hulo.

Data curation: Virginie de Broucker, Richard Van Bulck, Jean-Louis Edmé.

Formal analysis: Pierre-Marie Wardyn, Jean-Louis Edmé.

Investigation: Richard Van Bulck, Jean-Louis Edmé.

Methodology: Pierre-Marie Wardyn, Virginie de Broucker, Jean-Louis Edmé, Sébastien Hulo.

Project administration: Jean-Louis Edmé, Sébastien Hulo.

Supervision: Jean-Louis Edmé, Sébastien Hulo.

Validation: Pierre-Marie Wardyn, Virginie de Broucker, Cécile Chenivesse, Annie Sobaszek, Richard Van Bulck, Thierry Perez, Jean-Louis Edmé, Sébastien Hulo.

Writing – original draft: Pierre-Marie Wardyn, Virginie de Broucker, Jean-Louis Edmé, Sébastien Hulo.

Writing – review & editing: Pierre-Marie Wardyn, Virginie de Broucker, Cécile Chenivesse, Annie Sobaszek, Richard Van Bulck, Thierry Perez, Jean-Louis Edmé, Sébastien Hulo.

References

1. Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J. 2017; 49: 1600016. https://doi.org/10.1183/13993003.00016-2016 PMID: 28049168
2. Quanjer PH, Dalhuijsen A, Van Zoramen B. Standardized lung function testing. Report working party. Bull Eur Physiopathol Respir. 1983; 19 Suppl 5: 1–95.
3. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl. 1993; 16: 5–40. PMID: 8499054

4. Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault J-C. Standardization of the measurement of transfer factor (diffusing capacity). Eur Respir J. 1993; 6: 41–52. https://doi.org/10.1183/09041950.041s1693 PMID: 24576916

5. Polgar G, Promadhat V. Pulmonary function testing in children: techniques and standards. Philadelphia: Saunders; 1971.

6. Stanojevic S, Graham BL, Cooper BG, Thompson BR, Carter KW, Francis RW, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. Eur Respir J. 2017; 50: 1700010. https://doi.org/10.1183/13993003.00010-2017 PMID: 28893868

7. Quanjer PH, Stanojevic S. Do the Global Lung Function Initiative 2012 equations fit my population? Eur Respir J. 2016; 48: 1782–1785. https://doi.org/10.1183/13993003.01757-2016 PMID: 27811067

8. Culver BH, Graham BL, Coates AL, Wanger J, Berry CE, Clarke PK, et al. Recommendations for a Standardized Pulmonary Function Report. An Official American Thoracic Society Technical Statement. Am J Respir Crit Care Med. 2017; 196: 1463–1472. https://doi.org/10.1164/rccm.201710-1981ST PMID: 29192835

9. Wapenaar M, Miedema JR, Lammering CJ, Mertens FW, Wijsenbeek MS. The impact of the new Global Lung Function Initiative TLCO reference values on trial inclusion for patients with idiopathic pulmonary fibrosis. Eur Respir J. 2019; 53: 1801895. https://doi.org/10.1183/13993003.01895-2018 PMID: 30760543

10. Brazzale DJ, Seccombe LM, Welsh L, Lanteri CJ, Farah CS, Ruehland WR. Effects of adopting the Global Lung Function Initiative 2017 reference equations on the interpretation of carbon monoxide transfer factor. Eur Respir J. 2020; in press. https://doi.org/10.1183/13993003.01905–2019

11. Stanojevic S. Instructions for using the GLI TLCO excel sheet calculator. 2017. Available: https://erj.ersjournals.com/content/erj/50/3/1700010/DC1/embed/inline-supplementary-material-5.pdf?download=true.

12. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J. 2005; 26: 511–522. https://doi.org/10.1183/09031936.05.00035005 PMID: 16135736

13. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005; 26: 319–338. https://doi.org/10.1183/09031936.05.00034805 PMID: 16055882

14. MacIntyre N, Crapo RO, Viegi G, Johnson DC, Grinten CPM van der, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005; 26: 720–735. https://doi.org/10.1183/09031936.05.00034905 PMID: 16204605

15. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012; 40: 1324–1343. https://doi.org/10.1183/09031936.00080312 PMID: 22743675

16. Global initiative for chronic obstructive lung disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2021 report). 2020. Available: https://goldcopd.org/2021-gold-reports/.

17. Weinberger SE, Cockrill BA, Mandel J. 9—Overview of Diffuse Parenchymal Lung Diseases. In: Weinberger SE, Cockrill BA, Mandel J, editors. Principles of Pulmonary Medicine (Seventh Edition). Philadelphia: Elsevier; 2019. pp. 132–144. https://doi.org/10.1016/B978-0-323-52371-4.00012-X

18. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005; 26: 948–968. https://doi.org/10.1183/09031936.05.00035205 PMID: 16264058

19. Wan ES, Fortis S, Regan EA, Hokanson J, Han MK, Casaburi R, et al. Longitudinal Phenotypes and Mortality in Preserved Ratio Impaired Spirometry in the COPDGene Study. Am J Respir Crit Care Med. 2018; 198: 1397–1405. https://doi.org/10.1164/rccm.201804-0663OC PMID: 29874098

20. Hulo S, Broucker V de, Giovannelli J, Cherot-Kornobis N, Nève V, Sobaszek A, et al. Global Lung Function Initiative reference equations better describe a middle-aged, healthy French population than the European Community for Steel and Coal values. Eur Respir J. 2016; 48: 1779–1781. https://doi.org/10.1183/13993003.00606-2016 PMID: 27540022

21. de Broucker V, Edmé J-L, Plantier L, Hulo S. Les valeurs de référence GLI-2012 pour la spirométrie forcée décrivent fidèlement la population européenne et française. Rev Mal Respir. 2019; 36: 287–290. https://doi.org/10.1016/j.rmr.2018.12.005 PMID: 30902447

22. Oostveen E, Derom E, Vints A-M, Liistro G. Comparison of ERS'93 to the newly published GLI'17 reference values for carbon monoxide transfer factor. Respir Med. 2019; 146: 113–115. https://doi.org/10.1016/j.rmed.2018.12.005 PMID: 30665508

23. Hennebert P, Riem B, INSEE. Au 1er janvier 2016, 2 603 700 habitants dans le Nord—Insee Flash Hauts-de-France—59. 27 Dec 2018 [cited 13 May 2020]. Available: https://www.insee.fr/fr/statistiques/3680462#consulter.

24. International Organization for Standardization. ISO 2859–1—Sampling procedures for inspection by attributes—Part 1: Sampling plans indexed by acceptable quality level (AQL) for lot-by-lot inspection. 1989.