EUROPEAN CLINICAL RESPIRATORY JOURNAL
2025, VOL. 12, , No. 1, 2470002
https://doi.org/10.1080/20018525.2025.2470002

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RESEARCH ARTICLE

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Can the single-breath alveolar volume be adjusted to estimate true total lung capacity?

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ABSTRACT

Background: Total lung capacity (TLC) measured with single-breath gas diffusion (TLCsb) is systematically lower than TLC measured with whole-body plethysmography (TLCwbp) especially in patients with obstructive defects. We aimed to develop and validate a regression correction equation to reduce the discrepancy between the two measurements of TLC. Second, we compared the ability to detect restriction (reduced TLC) from adjusted TLC measured by single-breath ($TLCsb_{adj}$) with gold standard TLCwbp.

Methods: Lung function data from 800 consecutive patients were analysed with multivariable linear regression. A group of 530 were included for model development, and 270 were used for model validation.

Results: TLCsb was found to be on average 1.1 L lower than TLCwbp ($p < 0.001$). This difference increased with degree of airway obstruction. After adjustment $TLCsb_{adj}$ did not significantly differ from TLCwbp in obstructive and mixed obstructive-restrictive subjects. $TLCsb_{adj}$ had a sensitivity of 70% and a specificity of 99% to predict restriction on an individual basis, with a 95% confidence interval (CI) of [−19.6%; 17.7%] percentage when comparing adjusted values of TLCsb with the true TLCwbp value.

Conclusions: After adjustment TLCsb was no longer significantly underestimated in obstructive and mixed restrictive-obstructive groups compared to TLCwbp. The adjustment can be used on individual subjects to estimate restriction via the TLCsb, thereby making the single-breath gas diffusion method a more valid alternative than without adjustment, when compared with the gold standard whole-body plethysmography to measure TLC.

ARTICLE HISTORY
Received 24 April 2024
Accepted 17 February 2025

KEYWORDS
Total lung capacity; static lung volumes; bodybox; whole-body plethysmography; single breath gas diffusion capacity; predicted value; linear regression; correction equation

Introduction

Pulmonary function tests (PFT) are important tools for diagnosing ventilatory defects. The forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), FEV_1/FVC and total lung capacity (TLC) are used to identify and characterize the presence of a ventilatory defect in a patient [1]. Ventilatory defects are categorized according to the European Respiratory Society (ERS) and American Thoracic Society (ATS) as follows: a value below the fifth percentile (z-score ≤-1.65) of its predicted value may be either *a) obstructive* when FEV_1/FVC is reduced, *b) restrictive* when TLC is reduced, *c) mixed obstructive-restrictive* when both are reduced and *d) non-specific* when both are normal, but FEV_1 and/or FVC are reduced [2,3].

Although spirometry measurement of FEV_1/FVC alone identifies an obstructive defect, measurements of TLC help clarify degree of disease and underlying conditions such as emphysema and lung hyperinflation. Attempts to identify restrictive defects with just spirometry have a low positive predictive value of <60% [4]. TLC measurement is, therefore, required for a proper diagnosis. TLC is likewise needed to diagnose a mixed or non-specific defect. Thus, spirometry is often supplemented with measurements of the static lung volumes, TLC and residual volume (RV), in addition to measurement of pulmonary diffusion capacity. Static lung volumes may be measured with different methods such as imaging, gas dilution and nitrogen washout [5], yet whole body plethysmography (WBP)

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/20018525.2025.2470002

is considered the gold standard and hence most often used.

The common method of testing diffusion capacity is the single-breath (SB) diffusing capacity for carbon monoxide (DLco), using either helium or methane as inert gas for simultaneous measurement of alveolar volume (V_A) [6]. Adding dead space to V_A gives an indication of effective TLC. TLC measured this way (TLCsb) is known to be systematically lower than TLC measured with WBP (TLCwbp), especially in patients with obstructive defects [3,7]. This discrepancy is believed to be caused by air trapping, maldistribution and poor gas mixing [3]. Yet, SB is easy and quick to perform, and requires less hygienic measures than WBP; hence during the COVID-19 pandemic use of WBP has been avoided or restricted. Regression equations have been developed earlier to adjust for the discrepancy and predict TLC when comparing SB to multiple-breath helium dilution [8] and WBP [9,10]. Multiple-breath helium dilution takes longer to perform but is more accurate than the SB method. However, both underestimate TLC compared to WBP [11]. Previous attempts to estimate TLCwbp from TLCsb have focused on obstructive patients only.

The purpose of this study was to compare TLC measurements made by SB and WBP in a broad spectra of patients, and to develop and validate a correction equation based on TLCsb to predict TLCwbp, and the ability to detect restriction.

Methods

Participants

This study included anonymized data on consecutive PFTs from routine diagnostic work-up on 800 Caucasian adults at Rigshospitalet, Copenhagen, Denmark and was approved by Institutional review board (kf-532_22). Patients informed consent was not required. A total of 800 PFTs were chosen for inclusion, so that the study had a larger sample size than similar studies [9,10]. Data was included retrospectively on PFTs performed with Jaeger Masterlab from the 22/2–2022 to the 15/7–2022. The first 270 PFTs were included in the validation group and last 530 in the development group. Spirometry, WBP and DLco were performed according to ATS/ERS guidelines [1,5,6]. Exclusion criteria were PFTs in which either WBP or SB were not performed, and tests not performed adequately with regards to repeatability and quality criteria according to ERS/ATS [1,5,6]. In addition, subjects whose PFTs had large discrepancies between FVC and vital capacity (VC) measured as part of spirometry, SB and WBP, respectively, were excluded to reduce intra-test inconsistency. The study used complete case analysis with regard to missing data, and subjects without all relevant parameters for study were excluded and in turn replaced by subjects with complete PFT data.

Pulmonary function interpretation

PFTs were categorized according to ERS/ATS guidelines as normal, obstructive, restrictive, mixed, or non-specific ventilatory defects [3] (see introduction). FEV_1, FVC, FEV_1/FVC and TLC values were compared with reference values [12]. Severity was graded as mild, moderate and severe based on z-scores <-1.645, <-2.5 and <-4, respectively [3]. The lowest of FEV_1, FVC, or TLC was used for grading ventilatory defects.

Outcome

The primary aim was to develop a correction equation to predict TLCwbp from TLCsb.

The secondary aim was to diagnose restriction (reduced TLC) from adjusted TLCsb compared with true TLCwbp.

Statistical analysis

Statistical analysis was performed using SPSS statistics software version 28.0. Multiple linear regression models were used to predict TLCwbp. The variables used for the regression models were sex, age (years), height (cm), weight (kg), TLCsb (L), FEV_1 (L), FVC (L), FEV_1/FVC (%), degree of obstruction (mild, moderate or severe) and TLCwbp (L). The equations were first developed on a group of 530 subjects and subsequently tested on the validation group of 270.

Correlations with variables and the models were tested with Pearsons r. A final model ($TLCsb_{adj}$) was developed including sex, age, height, weight, FEV_1/FVC, TLCsb and degree of obstruction. The absolute error (MAE) and root mean squared error (RMSE) were calculated to evaluate performance.

A probability value of $p < 0.05$ was considered statistically significant. Wilcoxon Signed Rank Tests were used to compare means between different methods.

Adjusted values of TLCsb were converted into z-scores and used to predict restriction, which was then compared with true WBP measurements of TLC in 2×2 tables for the calculation of diagnostic values.

Results

Participants

Anthropometric data, test values and categorization into abnormality groups of the 800 subjects are shown in Table 1 (in median values). Forty-four percent had normal ventilatory function, 52% were females, mean age was 57 ± 14.8 years and average BMI 26.8 ± 5.2 kg/m^2. TLCsb was on average 1.1 L lower than TLCwbp (5.01 ± 1.34 L vs 6.11 ± 1.59 L) ($p < 0.001$).

TLCsb was significantly lower in the development group than in the validation group ($p = 0.012$). Likewise, restriction was unevenly distributed when including mixed abnormality, with 17.1% compared to 11% in the development and validation group, respectively. Obstruction was more evenly distributed at 31% and 32.4%. Severity of lung function reduction was more evenly distributed in obstructive subjects than in restrictive subjects, which had fewer cases of moderate restriction in the validation group. Additionally, the validation group had fewer subjects in the moderate non-specified and mixed groups. Out of all the subgroups, severe restrictive and severe non-specified had the fewest subjects, with a total of 4 and 5, respectively.

Model development and specification

The spirometry parameters FEV_1, FVC and FEV_1/FVC used for categorisation and determination of degree of airflow severity were correlated with differences in TLC. TLCsb was subtracted from TLCwbp (ΔTLC)

Table 1. Anthropometric data and PFT parameters in 800 subjects.

Variable	Total	Development	Validation
	N = 800	N = 530	N = 270
Anthropometric data			
Female (%)	416 (52%)	279 (52.6%)	137 (50.7%)
Male (%)	384 (48%)	251 (47.4%)	133 (49.3%)
Height, cm	170.2 (163.4–177.3)	169.9 (163–177)	170.7 (163.4–177.9)
Weight, kg	77.2 (65.5–89.3)	76.7 (65–89.1)	79.4 (67.3–89.5)
Age, years	59 (48–69)	59 (47–68)	60 (48.8–69.3)
BMI, kg/m [2]	26.2 (23.1–29.9)	26.0 (22.8–29.9)	26.4 (23.3–30.1)
ERS/ATS Classification:			
Normal Ventilation	352 (44%)	220 (41.5%)	132 (48.9%)
Obstruction			
Mild OLD	96 (12%)	58 (11%)	38 (14%)
Moderate OLD	71 (8.9%)	42 (7.9%)	29 (10.7%)
Severe OLD	70 (8.8%)	51 (9.6%)	19 (7%)
Total OLD	237 (29.7%)	151 (28.5%)	86 (31.7%)
Restriction			
Mild RLD	73 (9.1%)	50 (9.5%)	23 (8.5%)
Moderate RLD	28 (3.5%)	25 (4.7%)	3 (1.1%)
Severe RLD	4 (0.5%)	2 (0.4%)	2 (0.7%)
Total RLD	105 (13.1%)	77 (14.6%)	28 (10.3%)
Mixed	15 (1.9%)	13 (2.5%)	2 (0.7%)
Non-specified			
Mild non-specified	56 (7%)	41 (7.7%)	15 (5.6%)
Moderate non-specified	30 (3.8%)	25 (4.7%)	5 (1.9%)
Severe non-specified	5 (0.6%)	3 (0.6%)	2 (0.7%)
Total non-specified	91 (11.4%)	69 (13%)	22 (8.2%)
Test values:			
FEV_1, L	2.42 (1.66–3.21)	2.37 (1.61–3.22)	2.49 (1.82–3.20)
FEV_1%P	89.4 (64.4–108.1)	87.8 (61.3–107.3)	91.2 (70.1–109.5)
FEV_1, Z-score	−0.703 (−2.239–0.539)	−0.862 (−2.395–0.487)	−0.566 (−2.012–0.632)
FVC, L	3.45 (2.27–4.36)	3.42 (2.65–4.33)	3.53 (2.81–4.53)
FVC%P	100.8 (84.1–117.9)	99.1 (82.1–116.3)	106.4 (89.0–119.8)
FVC, Z-score	0.056 (−1.084–1.258)	−0.073 (−1.24–1.185)	0.454 (−0.766–1.396)
FEV_1/FVC, %	73 (61–80)	72.78 (61.43–79.80)	72.96 (61.52–79.45)
FEV_1/FVC%P	94.0 (81.0–101.7)	94.0 (81.2–101.7)	94.0 (80.8–101.8)
FEV_1/FVC, Z-score	−0.682 (−2.116–0.19)	−0.686 (−2.091–0.194)	−0.675 (−2.237–0.189)
TLCwbp, L	5.99 (4.95–7.07)	5.85 (4.95–6.98)	6.28 (4.95–7.31)
TLCwbp%P	101.6 (89.1–113.5)	100.6 (87.5–112.8)	103.7 (92.6–114.6)
TLCwbp, Z-score	0.136 (−1.027–1.235)	0.052 (−1.198–1.188)	0.306 (−0.683–1.326)
TLCsb [1], L	4.9 (4.03–5.85)	4.84 (3.93–5.73)	5.06 (4.21–6.09)
TLCsb%P	84.0 (72.7–94.9)	82.6 (70.1–93.6)	85.9 (76.7–96.5)
TLCsb, Z-score	−1.467 (−2.517- −0.44)	−1.595 (−2.712- −0.573)	−1.317 (−2.177- −0.317)
ΔTLC, L	0.75 (0.49–1.31)	0.77 (0.51–1.34)	0.73 (0.47–1.20)

Data presented as median listed with interquartile range of 25–75% in parentheses. ERS/ATS, European Respiratory Society/American Thoracic Society; FEV1, forced expiratory volume in the 1st second; FVC, forced vital capacity; TLC, total lung capacity; WBP, whole-body plethysmography; SB, single-breath gas diffusion; ΔTLC, the difference between total lung capacity measured by whole-body plethysmography and single-breath gas dilution.

1: TLCsb was significantly different (p=0.012) between development and validation groups.

and compared to FEV_1 % predicted, which showed a moderate negative correlation ($r = -0.67$, $p < 0.001$, Figure 1a). Likewise, FVC % predicted and FEV_1/FVC showed low and moderate negative correlations, respectively, with ΔTLC (Fig. S2a,b in supplementum). ΔTLC increased with severity of abnormality and was most pronounced in obstructive subjects, while only marginal increases with severity were found in non-obstructive subjects. TLCsb was moderately positive correlated with TLCwbp ($r = 0.76$, $p < 0.001$, Figure 1b). After adjustment, the correlations between TLCwbp and $TLCsb_{adj}$ ($r = 0.92$, $p < 0.001$, Figure 1c) were stronger.

A multiple linear regression model was developed based on subjects from the development group (Table 2). This model initially included sex, age, weight, height, FEV_1/FVC, TLCsb as well as degree of obstruction. Sex and mild obstruction were found to be

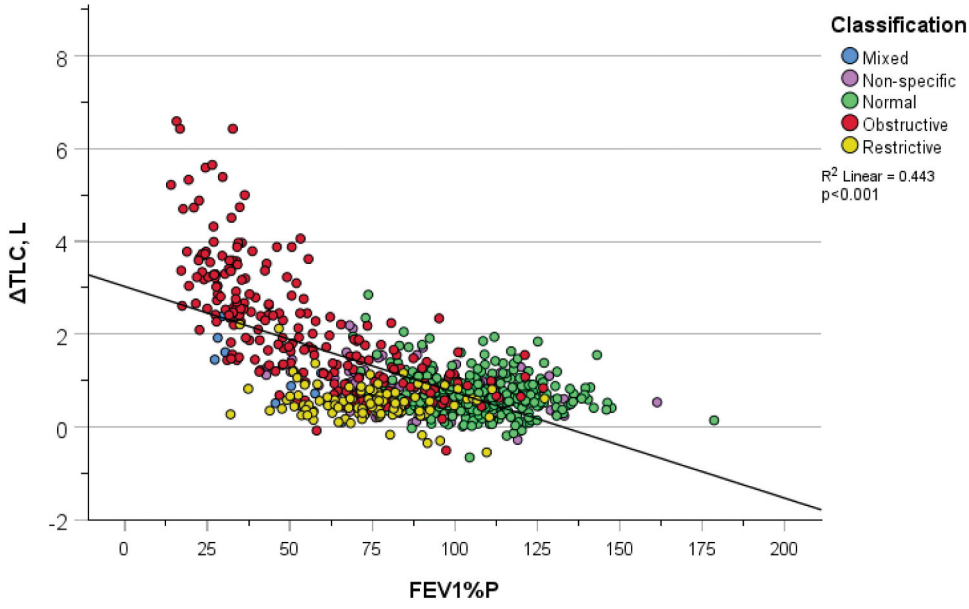

Figure 1. A. Correlation between difference in total lung capacity (Δ TLC) measured with plethysmography (TLCwbp) and single breath gas diffusion (TLCsb) and forced expiratory volume in the first second in percentage of predicted value (FEV_1%P) ($r = -0.67$, $p < 0.001$) in all subjects.

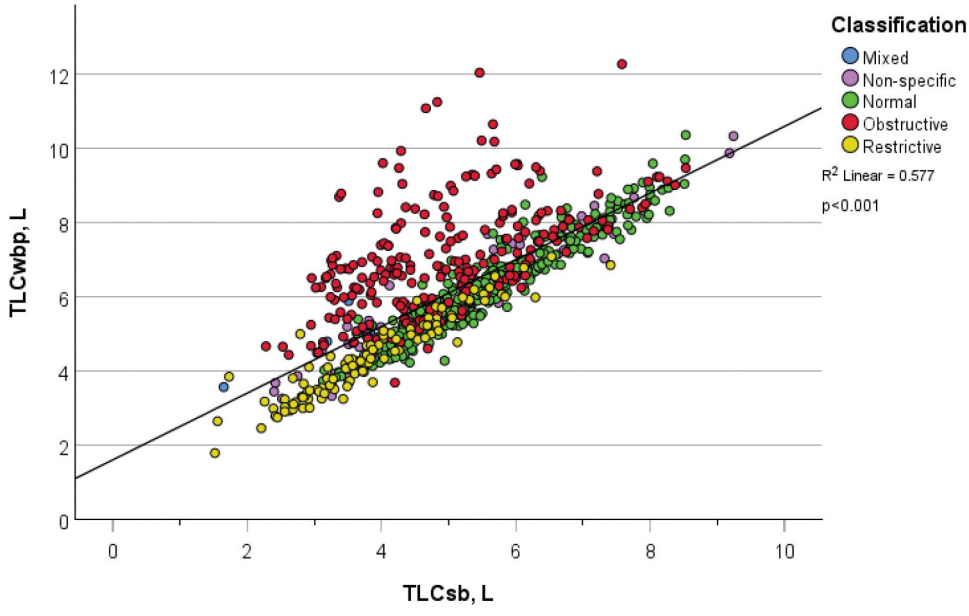

Figure 1. B. Correlation between total lung capacity (TLC) measured with plethysmography (TLCwbp) and single breath gas diffusion (TLCsb) ($r = 0.76$, $p < 0.001$) in all subjects.

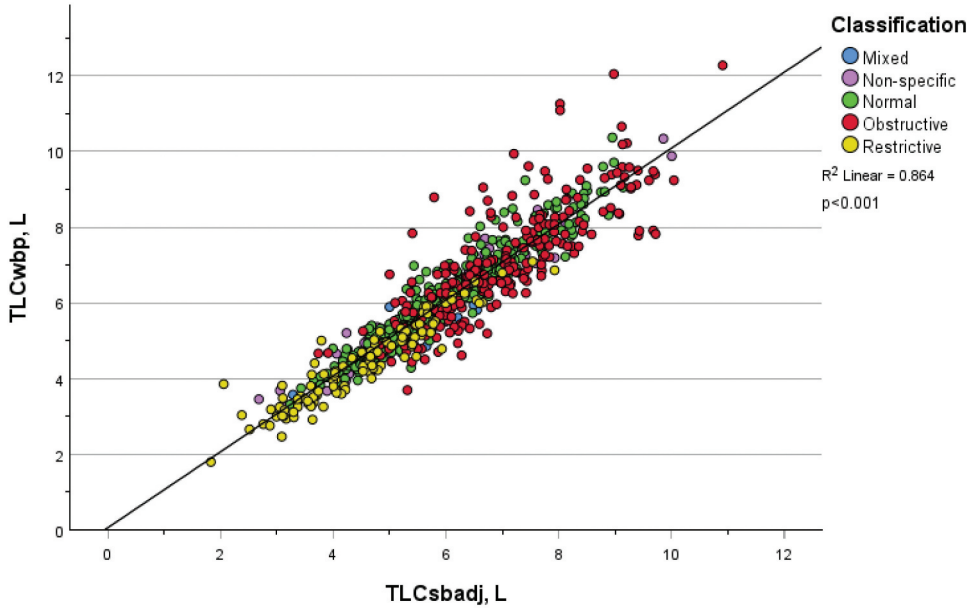

Figure 1. C. Correlation between total lung capacity (TLC) measured with plethysmography (TLCwbp) and adjusted single breath gas diffusion TLC ($TLCsb_{adj}$) ($r = 0.93$, $p < 0.001$) in all subjects.

Table 2. Final model for adjustment of single-breath total lung capacity ($TLCsb_{adj}$) using age, height, weight, FEV_1/FVC, TLCsb and degree of obstruction as independent variables.

Predictor	Value
B	0.249
Age (years)	0.006
Height (cm)	0.017
Weight (kg)	−0.004
FEV_1/FVC %	−0.028
TLCsb (L)	0.919
Mild obstruction [1]	0.071
Moderate obstruction [1]	0.463
Severe obstruction [1]	1.204

1: 0 for no and 1 for yes for obstruction.
Example of calculation for e.g. 70 y-o-m, 180 cm, 80 kg, FEV1/FVC 60%, mild obstruction (FEV1 z-score −2.2) and TLCsb 3.0 L. Adjusted TLC (TLCsbadj) = 4.56 L (95% CI: 3.66–5.36 L).

insignificant. Sex was excluded from the model, but it was decided to keep mild obstruction due to the apparent influence of obstruction on TLC. The equation was then used to adjust TLCsb ($TLCsb_{adj}$). Assumptions of linear regression were tested for the model and were not found to be violated (Fig. S3a–c and Table S6 in supplementum).

TLCsb was found to systematically underestimate TLC in all types of subjects. As severity progressed, so did the discrepancy between TLCsb and TLCwbp. In contrast, $TLCsb_{adj}$ was closer to TLCwbp, with slight underestimation in the normal, severe obstructive, severe restrictive and severe mixed/non-specific (mixed/NS) groups, and a slight overestimation in the mild and moderate restrictive groups (Figure 2).

The effects of adjustment were then compared on the validation group. Six subgroups were created based on abnormality: Mixed and non-specific, restrictive, normal and three degrees of obstruction. TLCsb was consistently significantly different from TLCwbp ($p < 0.001$). With $TLCsb_{adj}$, however, there was no significant difference in obstructive groups ($p = 0.23$ to 0.70) and the mixed and non-specific groups ($p = 0.98$), while the normal and restrictive groups ($p < 0.001$) remained significantly different, with the restrictive group now being overestimated rather than underestimated (Table S1 supplementum), especially so in subjects with mild restriction compared with moderate and severe restriction (Fig. S4 supplementum).

Model performance

The adjusted R^2 [2] of $TLCsb_{adj}$ was 0.87, MAE was 0.42 and RMSE was 0.63, showing an improvement in prediction over TLCsb which had an adjusted R^2 of 0.59, MAE of 1.01 and RMSE of 1.52. $TLCsb_{adj}$ was compared with TLCwbp, as a percentage difference and in litres, per FEV_1/FVC percentage (Figure 3 and Fig. S1 supplementum). ΔTLC was generally no longer systematically underestimated but was about evenly over-and underestimated. The model thus has an improved capability to predict TLC in obstructive subjects, but at the cost of only being marginally better at prediction in non-obstructive subjects compared to TLCsb. When comparing percentage difference from TLCwbp, $TLCsb_{adj}$ had a mean difference of −1.0% with a 95% CI [−19.6%; 17.7%].

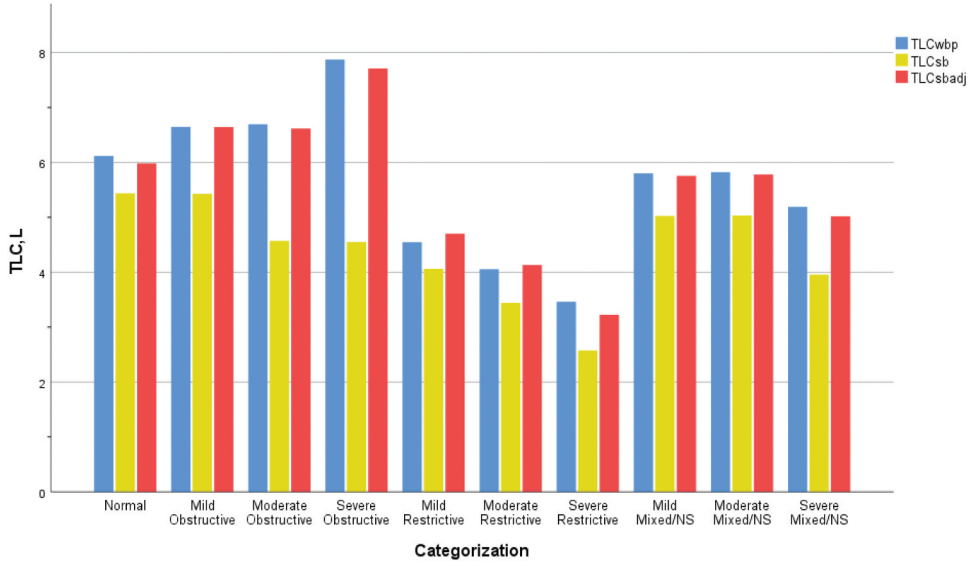

Figure 2. Comparison of the different methods of TLC measurement at different severities of abnormality in all subjects.

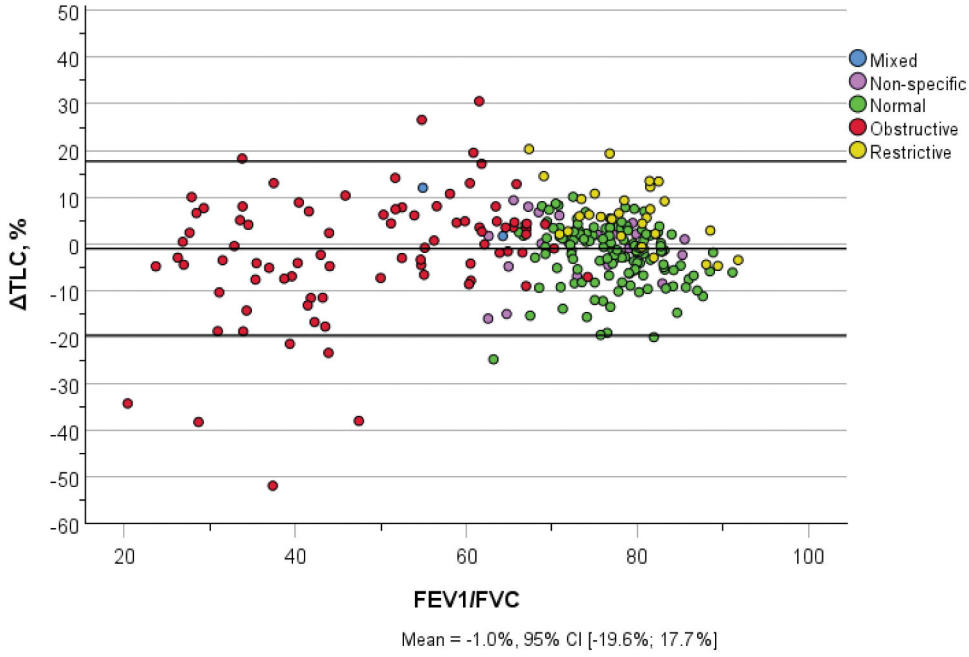

Figure 3. Differences in percentage between total lung capacity (TLC) measured with plethysmography (TLCwbp) and adjusted single breath gas diffusion TLC ($TLCsb_{adj}$) related to FEV_1/FVC in the validation group.

Z-scores of adjusted TLC-measurements ($TLCsb_{adj}$) were used to predict restriction (TLC z-score < −1.645), and compared to 'true' restriction based on TLCwbp (Table 3). $TLCsb_{adj}$ was found to have a sensitivity of 70% and specificity of 99.2%. In comparison, TLCsb had a sensitivity of 93%, specificity of 70% and a precision of 28%, thus greatly overestimating restriction (Table 4d and Table 5 supplementum).

Table 3. Diagnostic values of adjusted single breath gas diffusion total lung capacity ($TLCsb_{adj}$) in the development and validation group.

	Accuracy	Misclassification	Precision	Sensitivity	Specificity
$TLCsb_{adj}$ Development	95.7%	4.3%	86.8%	87.8%	97.3%
$TLCsb_{adj}$ Validation	95.9%	4.1%	91.3%	70%	99.2%

With the adjusted model's confidence interval (CI), and with a specificity of 99.2%, a measured TLCsb value can be adjusted and applied on an individual level. If a $TLCsb_{adj}$ value remains in the normal range after subtracting 18.6% (or adding 18.7%), then it is highly likely that the 'true' value of TLCwbp would be within the normal range. In such cases, measurement of TLCwbp would be unnecessary for rejecting restriction.

Discussion

We found that TLCsb significantly underestimated TLCwbp in every subgroup. This underestimation increased with degree of obstruction. It was possible to adjust TLCsb by the correction equation to predict TLCwbp. Prediction of restriction could be made for individuals by converting $TLCsb_{adj}$ into z-scores and compare diagnostic outcomes with gold standard TLCwbp.

Gas dilution methods such as multiple-breath and SB are known to underestimate TLC in obstructive subjects [3,11]. As obstruction progresses, so do pathological changes resulting in loss of lung elastic recoil, increased resistance of the small airways and airflow limitation [13–15]. As FEV_1/FVC ratio is reduced, air gets trapped in the lungs, RV increases and VC decreases and TLC may increase as the lungs hyperinflate due to the trapped air and emphysema [16,17]. Areas of the lung with trapped air and gas maldistribution hinder the gas dilution in SB and multiple-breath methods, causing underestimation of measured TLCsb, whereas WBP is unaffected by non-communicating airways.

While SB is known to generally underestimate TLC, research suggests that WBP in some circumstances may overestimate TLC [7]. In one study by O'Donnel *et al.* WBP was found to overestimate TLC, especially in severely obstructive subjects, compared with multiple-breath helium dilution and CT-scans [18]. A study by Garfield *et al.* comparing WBP and CT found that WBP overestimated TLC as RV% and FRV% increased, showing that gas trapping predicted the overestimation in WBP compared to CT [19]. In contrast to these findings, Tantucci et al. found that when comparing multiple-breath helium dilution, CT and WBP there was no overestimation when using WBP [20]. These findings may be explained by the influence of panting frequency during WBP measurements, as frequencies >1 hz are known to cause overestimation and <1 hz result in more accurate measurements in obstructive subjects [5,11,21,22]. During panting in WBP, the pressure changes in the alveolar regions during inspiratory and expiratory attempts should be transmitted through the open airways into the mouth, where similar pressure changes ought to be measured. However, if the central airways are unstable in obstructive disease, during panting mouth pressure changes may be reduced, and intrathoracic gas volumes overestimated and hence also TLC.

In this study, different patterns emerged depending on type of abnormality, with obstruction having the biggest impact on the underestimation of TLC by SB. The correction equation was developed on all types of subjects, so it generalizes the changes of all included subjects, thus lacking nuance with regards to specific subgroups. While the model is applicable regardless of abnormality, specialized models developed for specific subgroups based on the abnormality types may have better predictive power.

A limitation of the study may be the higher representation of obstructive compared to restrictive subjects, especially the relatively smaller moderate and severe restrictive subgroups, thereby limiting their impact on model development. This may be an important factor in $TLCsb_{adj}$ overestimating TLC in restrictive subjects and the 30% false negatives of $TLCsb_{adj}$ when predicting restriction. Additionally, the validation group contained five subgroups with five of fewer subjects, including moderate and severe restrictive subgroups, thereby making the performance of $TLCsb_{adj}$ on these subgroups uncertain.

Interpretation

The correction equation presented in this study is based on our experiences from preliminary attempts at developing correction equations for TLCsb (supplementum). These attempts were based on the same 800 PFTs as $TLCsb_{adj}$, and they consisted of two simpler models ($TLCsb_{sim}$ and $TLCsb_{adv}$) that did not take degree of obstruction into account, and whose metrics had worse performance than the presented model. Likewise, predictions did not improve upon the presented model in attempts with degree of obstruction incorporated as an interaction term. The presented final model ($TLCsb_{adj}$), with its incorporation of obstruction, proved to have an overall better performance over the others, with its sensitivity of 70%, specificity of 99% and precision of 91%.

Studies comparing TLCsb and TLCwbp have been presented earlier. Coertjens et al. found that SB helium dilution underestimated TLC in normal, restrictive and obstructive patients [10]. They developed a correction equation for obstructive patients only, and they had a small sample size of 169, no validation group and their regression had a low

adjusted R^2 of 0.32. Liu et al. predicted WBP TLC from SB in obstructive patients with a larger sample size of 628, a validation group and found an adjusted R^2 of 0.751 for their correction [9], which was a smaller sample size and smaller R^2 than ours of 800 and 0.87, respectively. They found that after correction, the means of TLCsb no longer significantly differed from TLCwbp when stratifying for degree of obstruction. Unlike our study, neither of these two studies investigated predictive outcomes on an individual level.

Applications and conclusions

An important contribution of this study is the regression equation and its ability to adjust TLCsb. If (unadjusted) TLCsb is in the reference range a restriction may be ruled out, but it cannot be ruled in if TLCsb is low. However, one may use the correction equation to estimate restriction. If $TLCsb_{adj}$ is still within the normal range after subtracting 18.6%, the true TLCwbp value would likely be as well, and restriction may therefore be rejected. Additionally, using the upper and lower 95% CI, an estimated TLC can be used for donor-recipient matching before lung transplantation if WBP cannot be performed. In PFTs where SB is performed but not WBP, the adjustment allows for better estimation and monitoring of TLC when compared to the unadjusted SB.

In conclusion, the adjusted SB makes it possible to forego the accuracy of WBP in favour of fewer expenses, less time, hygienic measures and simpler instrumentation. Further validation is needed to test the performance of the model in different settings and populations.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request in anonymized form.

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