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The impact of changing to the Global Lung Function Initiative reference equations for transfer factor in paediatrics

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Introduction

The European Respiratory Society Global Lung Function Initiative TLCO Task Force published all age reference equations for the single breath transfer factor test for carbon monoxide (T_{LCO}) in 2017 [1]. These were part of the Global Lung Function Initiative (GLI) and have been endorsed by all major respiratory societies. These are now considered the gold standard reference equations for transfer factor measurements and provide all age equations from age 4.5 to 85 years old.

Prior to the development of the GLI standards, the most commonly used and widely referenced equations for T_{LCO} in paediatrics in the UK were Rosenthal [2]. These were based on 772 children and used simple regression. During puberty, lung function no longer increases proportionally to height but rather follows a more complex pattern [3] therefore arbitrary cut off points were used at a certain height for males and females that introduced a 'step' in the predicted equation. This meant that when boys reached a height of 162.6 cm, they would move into a new regression equation for the calculation of their lung function parameters and for girls it was 152.6 cm. The authors did perform pubertal staging in 64% of their subjects and acknowledged that using 2 separate linear equations may lead to spurious changes in relative lung function for longitudinal assessment. Therefore, they recommended correcting for pubertal stage to minimise this. However, paediatric respiratory laboratories do not routinely pubertally stage their patients.

Before implementing these new reference values in the UK in paediatrics, it is important to look at the impact of changing to these new reference equations in a population of children where this measurement is often of clinical importance. Stem cell transplantation (SCT) and chemotherapy can cause impairment in lung function which is often manifested by impaired alveolar gas transfer. Thus, the measurements of transfer factor of the lung for carbon monoxide (T_{Lco}), transfer coefficient (K_{CO}) and alveolar volume (V_A) are particularly important for monitoring for the onset or progression of interstitial lung disease in this group of patients [4].

In this study, we aimed to determine the impact of the switch from Rosenthal equations to the GLI equations upon interpretation of transfer factor results in patients referred from a Haematology/Oncology service.

Methods

Study design and patients

Pulmonary function results from the Royal Hospital for Children, Glasgow were reviewed from 2010 to 2018. Ethics approval was not sought as this was a retrospective review of anonymized data. All patients who had been referred from Haematology/Oncology aged <18 years with a valid T_{Lco} result according to the test meeting the criteria of the 1994 ARTP/BTS lung function guidelines [5] were included. The results contained the actual measurements and the Z score based on Rosenthal reference equations [2]. The GLI online excel calculator provided by the ERS [6] was used to convert the predicted values and Z

scores. The patient's sex, height and age were used. Height and age were taken to 1 decimal place. The Z score was then calculated using the test result data.

Statistical Analysis

The predicted values for T_{LCO}, K_{CO} and V_A were plotted against height using both reference sets for males and females. The mean difference and 95% confidence intervals between % predicted for the 2 reference ranges was calculated for all observations included in the dataset. Comparisons of Z scores for each parameter were analysed using Bland Altman plots. This is a statistical way to evaluate a bias between the mean differences, and to estimate an agreement interval, within which 95% of the differences of the second method, compared to the first one, fall [7]. The number of observations that were below the lower limit of normal for each parameter were directly compared for the 2 reference sets.

Results

There were 241 patient test results analysed – 130 male and 111 female. Of these test results, some were from the same patient on different dates as part of longitudinal follow up. Table 1 shows the subject demographics. Height, weight and BMI Z scores are calculated from the British 1990 growth reference data [8].

Variable	Mean	SD	Range
Age (yrs)	13.2	2.7	7 - 18
Height (cm)	151.5	13.6	118 - 182
Height Z score	-0.5	1.3	-5.76 - 3.29
Weight (kg)	46.3	13.8	21 - 86
Weight Z score	-0.1	1.5	-5.06 - 2.69
BMI Z score	0.2	1.5	-6.19 - 2.86

Table 1: Demographic details of children referred from Paediatric Haematology/Oncology Service for measurement of Transfer Factor

Figure 1a&b compares the predicted T_{LCO} values for Rosenthal and GLI in males and females when plotted against height. In the shorter patients, Rosenthal predicts higher values from 122cm to around 140cm with some cross-over at 140cm to 145cm. From 145cm to the pubertal breakpoint of 162.6cm as defined in the Rosenthal paper, Rosenthal predicts lower values than GLI. After the arbitrary break point, Rosenthal largely over-predicts the T_{LCO}. Overall, the predicted values using Rosenthal were higher compared to GLI such that, on average, % predicted values were underestimated by 2.3% (95% CI [2.1, 2.7]).

In females, the Rosenthal values were systematically higher for T_{Lco} as shown in figure 1b. There was no pubertal breakpoint in the T_{Lco} data for females. On average, % predicted

values were underestimated by 5.8% (95% CI [5.6, 6.0]) when compared to the GLI predicted values.

Figure 1c&d show the comparison of predicted K_{co} values. There are some striking differences for both male and female. Rosenthal values were systematically higher compared to GLI in both male and female. % predicted values were underestimated by 15.7% (95% CI [15.4, 16.1] and 20.9% (95% CI [20.4, 21.5]) in males and females, respectively.

Figure 1e&f show the comparison of predicted V_A values. The opposite effect occurs from TL_{CO} and K_{CO} with Rosenthal predicted V_A values being systematically lower in males and females. The difference in males is more marked before the arbitrary pubertal break point with % predicted values being estimated as higher by 14.5% (95% CI [14, 15.1]) and 15.2% (95% CI [14.5, 15.8]) in males and females, respectively.

Figures 2a, b & c show the Bland Altman plots for comparison of the Z scores between the two reference sets for T_{LCO}, K_{CO}, V_A. Table 2 shows the summary of the mean differences and 95% Limits of agreement.

	Rosenthal mean Z (SD)	GLI mean Z (SD)	Mean Difference (Ros -GLI) [95% CI]	95% LOA
T_{LCO} Z score	-1.33 (1.3)	-1.06 (1.2)	-0.27 [-0.3, -0.2]	-1.4; 0.9
K_{CO} Z score	-1.98 (1.1)	-0.31 (1.0)	-1.67 [-1.7, -1.6]	-2.3; -1.0
$V_{A\ Z\ score}$	0.39 (1.6)	-0.99 (1.4)	1.38 [1.3, 1.5]	0.1; 2.7

Table 2. Comparison of Z-scores using Rosenthal and GLI reference sets. The mean for each reference set is shown with the standard deviation, the mean difference between the 2 with the 95% confidence interval of the mean and the 95% limits of agreement.

Table 3 shows the difference in the % of patients that would be classed as being below the lower limit of normal using either the Rosenthal or GLI predicted set for each parameter. For T_{LCO}, 39% of patients would have abnormal results using Rosenthal and 27% using GLI. The same pattern occurred in the K_{co} but there was a much wider discrepancy. 61% were below the lower limit of normal using Rosenthal and only 10% using GLI. The opposite occurred with V_A with only 10% of patients having a result below the lower limit of normal and 26% using GLI.

Predicted set	T_{LCO}	K_{CO}	V_A
Rosenthal % < LLN	40	61	11
GLI % < LLN	27	10	27

Table 3. Percentage of patients who have a Z-score <-1.645 for each reference set.

We looked at an individual case to demonstrate the effects of the different reference equations over time as part of longitudinal follow up of patients. The patient was male and

the 1st measurement was taken post SCT when he was 12.6 years old and 158.8cm in height. The 2nd was taken 6 months later due to a relapse and prior to a repeat SCT. He was now 164.1cm therefore crossed the pubertal breakpoint in the Rosenthal equations. The results from both visits are shown in table 4a & b.

1st visit	Rosenthal Predicted	GLI Predicted	Measured	Rosenthal Z score	GLI Z score
T_{LCO}	7.13	7.50	5.23	-1.56	-2.27
K_{CO}	2.07	1.79	1.71	-1.57	-0.31
V_A	3.43	4.25	3.07	-0.95	-2.56

Table 4a. Transfer factor results from a patient on 1st visit

2nd visit	Rosenthal Predicted	GLI Predicted	Measured	Rosenthal Z score	GLI Z score
T_{LCO}	9.39	8.22	5.29	-2.51	-2.74
K_{CO}	2.1	1.78	1.50	-2.60	-1.13
V_A	4.44	4.66	3.52	-1.89	-2.26

Table 4b. Transfer factor results from a patient on 2nd visit

Looking at the patient's results using the Rosenthal reference values, the initial results show that the T_{LCO} and K_{co} are at the low end of normal and the V_A is normal. However, the follow-up results show a significant deterioration in the T_{LCO}, K_{co} and V_A with all the values being below the lower limit of normal.

Using GLI, the initial results show a reduced T_{LCO} with a preserved – but not elevated – K_{co} and a reduced V_A. The follow-up results show a deterioration in T_{LCO} and K_{co} and an improvement in V_A.

Discussion

Comparison of the Rosenthal values with the new gold standard GLI-2017 equations demonstrates several potential problems with using the Rosenthal values. Overall, Rosenthal produces higher predicted values for TL_{co} in the majority of boys and in all girls. It also produces grossly higher predicted K_{co} in all boys and girls. The opposite occurs in alveolar volume where Rosenthal produces systematically lower predicted values than GLI-2017 in boys and girls.

The difference in these predicted values for transfer factor has a significant clinical impact. Table 3 shows the differences in clinical interpretation for each parameter in our dataset. There were a greater number of patients who had a value below the lower limit of normal (a Z score < -1.645) for T_{Lco} and K_{co} when using the Rosenthal predicted equations. The biggest difference was seen in the K_{co} with the proportion of patients classed as having an 'abnormal' measurement being 61% using Rosenthal and only 10% when using GLI-2017.

The opposite occurred with V_A with a greater proportion being classed as abnormal when using GLI-2017 compared to Rosenthal.

When measuring lung function in patients undergoing cancer treatment or stem cell transplantation, the T_{Lco} is an important measurement for evaluating any potential lung damage caused by the treatment. The K_{co} measures the rate of transfer of carbon monoxide from alveolar gas to the pulmonary blood and therefore gives information on potential alveolar-capillary damage and diffusion impairment [9]. For this reason, K_{co} is an important marker of lung function in such patients. We have shown that using the Rosenthal equations will lead to a gross over diagnosis of lung dysfunction.

The results showed that the mean difference in the T_{Lco} Z scores between the Rosenthal and GLI reference values was quite small. However, there was a large mean difference in the K_{CO} and the V_A Z scores indicating that the Rosenthal values are over predicting K_{CO} and under predicting V_A in relation to the GLI predicted values. The reasons for this discrepancy can only be speculated. One possibility is the differences in equipment and gas analysis since the Rosenthal equations were published compared to the data sets used in the GLI. The GLI reference values dataset did not include the Rosenthal data because these data were collected on analysers that were made prior to 2000, which was the cut-off for contemporary data collection. The Rosenthal study used a Morgan body box. Modern systems such as rapidly responding gas analysers (RGAs) which use a different test gas and different algorithms may have contributed to the large differences seen between the 2 datasets.

Despite the Rosenthal equations being applicable across the age range from 6-18 years, in males particularly, the arbitrary break point at the height cut off of 162.4cm may cause significant misinterpretation of results when looking at patient trend data across this height cut off. We have shown this to be the case in our results. We looked at an individual subject who had transfer factor post SCT. His results using Rosenthal were within the normal range and did not look concerning. He had repeat measurements 6 months later due to SCT failure with the view to having a second transplant. He had grown by 5.3 cm in height. His results on his second test showed a significantly reduced T_{LCO} and K_{CO} with a slightly reduced V_A which would indicate a rapid decline and abnormal gas transfer. However, using GLI, his initial test results were abnormal with a significantly reduced T_{LCO}, VA and preserved K_{CO} indicating impaired gas transfer with a slight decline 6 months later. The difference in these 2 sets of results could have significantly impacted on this patient's treatment regimen. Additionally, many adolescent patients will be followed up into early adulthood and their measurements will be referenced against another reference equation when they reach 18 years of age. The GLI-2017 equations have the advantage of providing a single reference set from age 4.5-85 years old, providing uniform clinical interpretation of trend data in patients undergoing long-term follow up and avoiding any discontinuity arising from arbitrary cut-offs or changes in reference equations.

It has now been shown that linear regression has significant limitations when used for modelling lung function throughout life and more advanced statistical methods, such as the LMS method, are required to generate adequate reference ranges [10]. The major

limitations of the Rosenthal values were that only height and sex were used to develop the equations. Age was not considered, and simple additive linear regression techniques were used.

Previous research has looked at the impact of changing to GLI reference equations for spirometric parameters [11]. They showed that the discrepancies were largest in young children and adolescents. This is similar to what we have found for transfer factor. Future research should look at the impact of switching to the GLI-2017 equations in the adult population, where the measurement of transfer factor will occur more frequently.

In summary, the Rosenthal predicted equations for transfer factor are likely to lead to significant misinterpretation of the results in paediatric patients. The GLI-2017 reference equations are all age equations, developed using complex statistical methods that account for growth and development of the lungs across the transition from child to adolescent to adult with no arbitrary break points. We recommended that the GLI-2017 reference equations are adopted to improve interpretation of lung function results. When switching to these reference equations, the clinical team should be educated on the differences that are likely to be seen and made aware of the potential clinical impact. This will be particularly important when trending results. Therefore, we would recommend that all retrospective results should be re-calculated using the GLI equations before evaluating the trend report.

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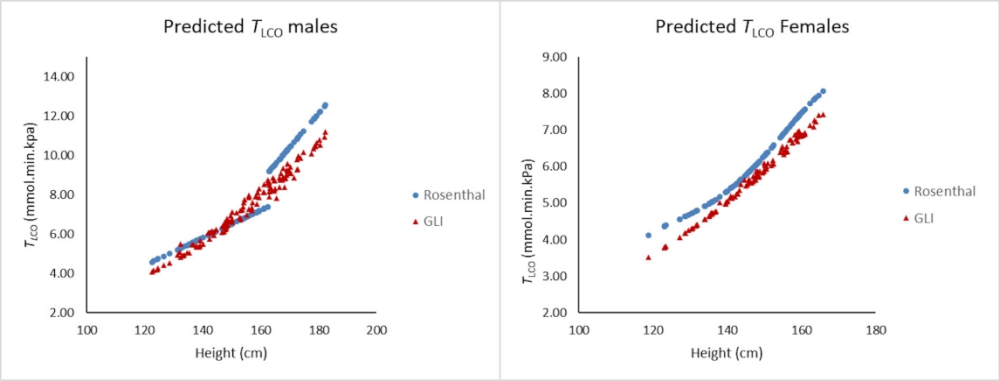

Figure1 a & b. Predicted value using Rosenthal & GLI equations plotted against height in males and females for T_{LCO}

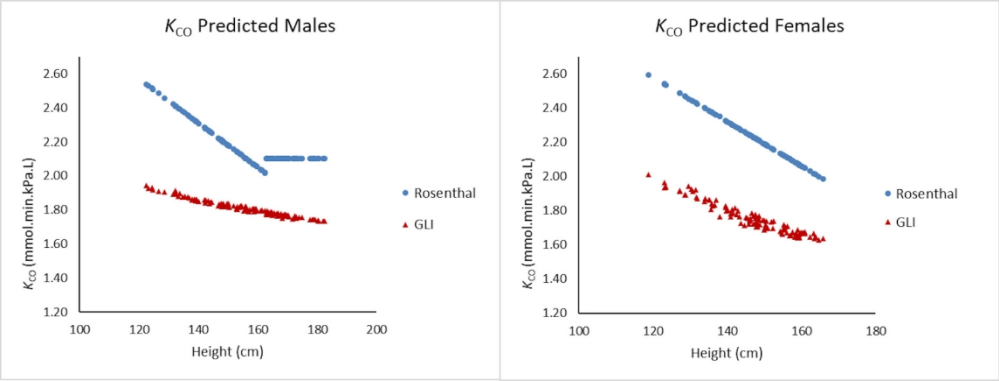

Figure 1 c & d - K_{CO}

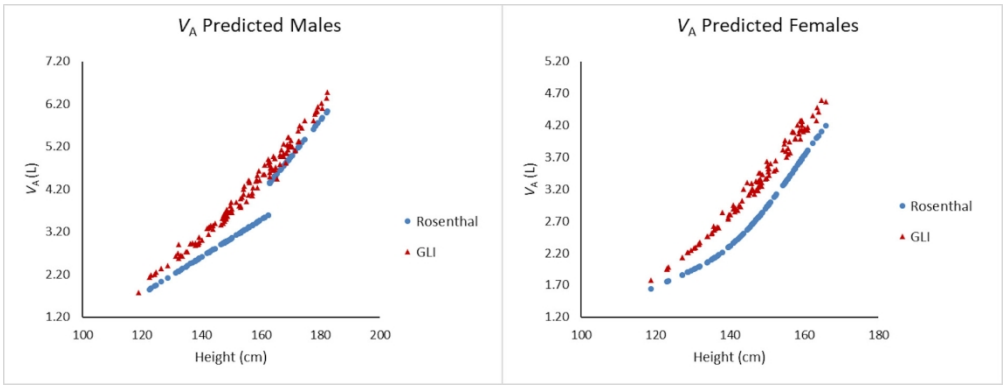

Figure 1 e & f - V_A

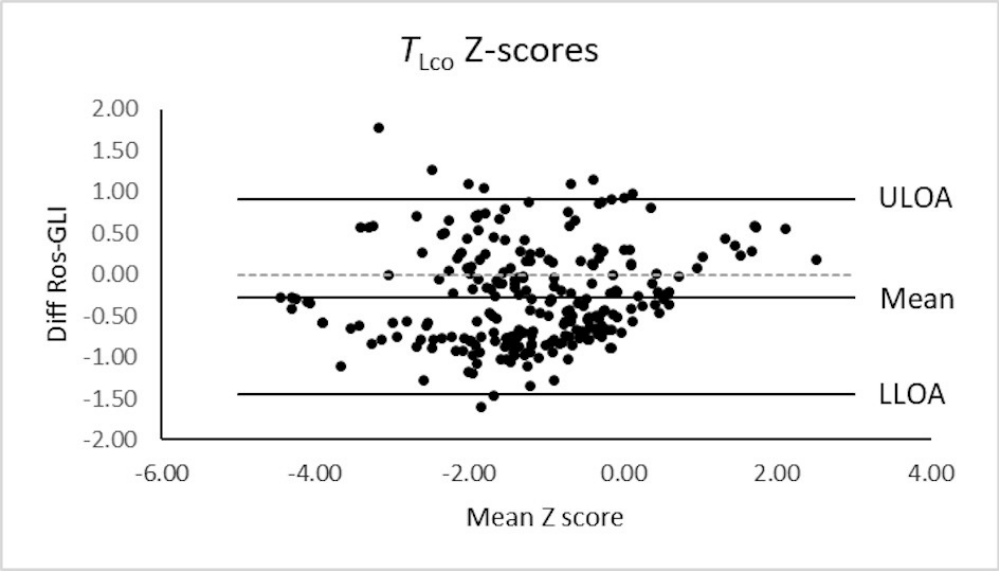

Figure 2 a. Bland Altman plot comparing Z scores using Rosenthal and GLI reference equations for T_{LCO}

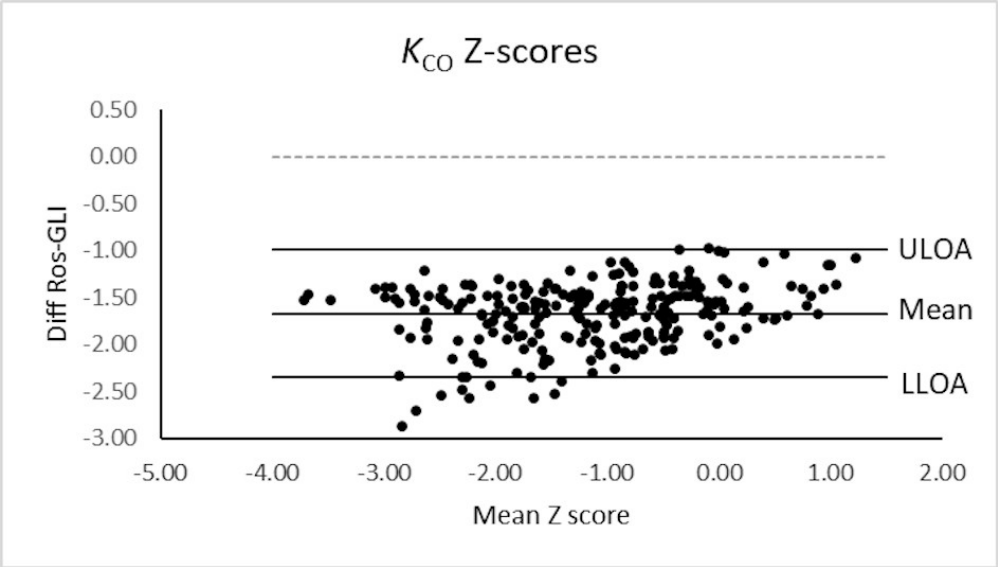

Figure 2 b - K_{CO}

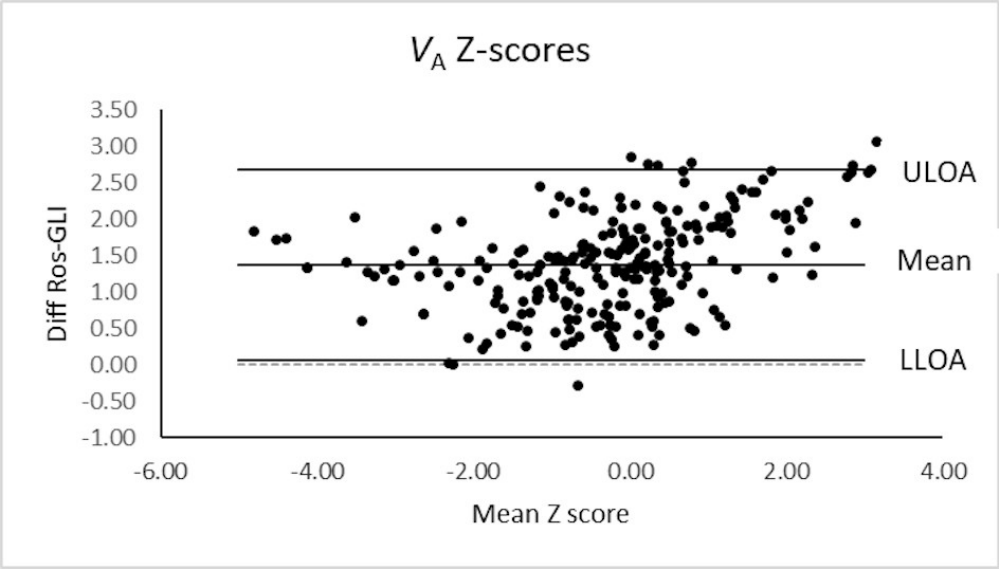
V_A Z-scores
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
-0.50
-1.00
Diff Ros-GLI
-6.00
-4.00
-2.00
0.00
2.00
4.00
Mean Z score
ULOA
Mean
LLOA

Figure 2 c - V_A