Global Lung Initiative equations for pulmonary hypertension screening in systemic sclerosis

To the Editor:

Systemic sclerosis (SSc) is a connective tissue disease characterised by widespread vasculopathy and excessive fibrosis in multiple organs, including the lungs [1]. The most frequent pulmonary involvement in SSc is interstitial lung disease (ILD), but the most harmful is pulmonary hypertension (PH), a complication found in about 10% of SSc patients [2]. In patients with SSc, early diagnosis of and prompt therapy for PH (either isolated or associated with ILD) are beneficial from a prognostic standpoint and recommendations for active screening of PH in SSc have therefore been established [3].

Pulmonary function tests (PFTs) are one of the key tools used for PH screening in SSc patients [4] and transfer factor of the lung for carbon monoxide (*T*LCO) and forced vital capacity (FVC) are the two tests most widely used for this purpose [2, 5]. As these two PFTs are expressed as percentages of predicted values (% predicted), reference equations to calculate predicted values are of critical importance for interpretation.

New reference equations for FVC and for *T*LCO, based on a large sample of normal subjects, have recently been published by the Global Lung Function Initiative (GLI) [6, 7]. By analysing a large multicentre sample of unselected patients with SSc, we aimed to compare the optimal thresholds of *T*LCO and of the FVC/*T*LCO ratio for identification of PH in these patients, using either previous reference equations [8, 9] or the latest GLI equations [6, 7].

The population analysed here has been fully described elsewhere [2]. Briefly, PFTs were carried out in SSc patients under stable conditions with standard equipment according to the latest guidelines [10, 11]. All patients underwent Doppler echocardiography at the time of the PFTs and right-heart catheterisation was performed if PH was suspected. Of the 572 SSc patients who were included, 58 had PH (35 had both ILD and PH, while 23 had PH without ILD) and 514 did not have PH (313 had no pulmonary involvement, *i.e.* neither ILD nor PH, while 201 had ILD without PH). The area under the receiver operating characteristic (ROC) curve (the AUC) was used to assess the ability of *T*LCO and of the FVC/*T*LCO ratio to discriminate between the presence and the absence of PH. As *T*LCO is modified not only by PH but also by ILD we performed two analyses, one in SSc patients without ILD (n=336) and another in SSc patients with ILD (n=236). The optimal thresholds for both analyses were assessed according to the Youden index of ROC curve analysis in order to maximise both sensitivity and specificity.

By comparison with the previous equations for *T*LCO [8] and for FVC [9] we observed that, with the GLI equations, mean values of *T*LCO (% predicted) were significantly higher (by 4 to 9%, depending on the presence of PH and/or ILD) and mean values of FVC (% predicted) were significantly lower (by 9 to 12%). Use of the GLI equations also resulted in much lower FVC (% predicted)/*T*LCO (% predicted) ratios than with the previous equations.

In SSc patients without ILD, analysis of the ROC curves regarding the probability of PH showed that the optimal threshold of *T*LCO was higher with the GLI equation (70% predicted *versus* 60% predicted) compared with the previous equation (table 1). However, optimal thresholds were similar with both the GLI equation and with the previous equation for SSc patients with ILD. The area under the ROC curve

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GLI equations provide new cut-offs for *T*LCO for detection of PH in patients with SSc, either with or without ILD http://ow.ly/aCpD30l2zch

Cite this article as: Soumagne T, Guillien A, Chambellan A, *et al*. Global Lung Initiative equations for pulmonary hypertension screening in systemic sclerosis. *Eur Respir J* 2018; 52: 1800528 [https://doi.org/10.1183/13993003.00528-2018].

TABLE 1 Performance of transfer factor of the lung for carbon monoxide (T_{LCO}) and of forced vital capacity (FVC) with different thresholds for detecting the probability of pulmonary hypertension (PH) in patients with systemic sclerosis (SSc), with or without interstitial lung disease (ILD)

	SSc patients without ILD						SSc patients with ILD					
	AUC (95% CI)	Cut-off	Se %	Sp %	PPV %	NPV %	AUC (95% CI)	Cut-off	Se %	Sp %	PPV %	NPV %
T_{LCO} % predicted (Crapo)	0.89 (0.84–0.95)	60%	78	84	26	98	0.76 (0.68–0.84)	55%	83	58	26	95
T_{LCO} % predicted (GLI)	0.91 (0.86–0.95)	70%	83	82	26	98	0.76 (0.68–0.84)	52%	74	72	32	94
T_{LCO} z-score (GLI)[#]	0.90 (0.85–0.95)	−2.02	87	79	23	99	0.74 (0.66–0.82)	−3.55	77	66	28	94
		−1.96	87	77	22	99		−1.96	91	43	22	97
		−1.64	87	72	19	99		−1.64	94	36	20	97
FVC % predicted/T_{LCO} % predicted (Quanjer/Crapo)	0.86 (0.77–0.95)	1.66	77	87	29	98	0.73 (0.65–0.81)	1.69	80	60	26	94
FVC % predicted/T_{LCO} % predicted (GLI)	0.87 (0.79–0.95)	1.50	77	87	30	98	0.73 (0.65–0.81)	1.45	71	67	27	93

AUC: area under the receiver operating characteristic curve; Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; GLI: Global Lung Initiative. [#]: a z-score = −1.96 results when 2.5% of healthy individuals will be below a cut-off identified as the lower limit of normal (LLN); a z-score = −1.64 results when 5% of healthy individuals will be below a cut-off identified as the LLN.

was significantly higher for SSc patients without ILD than for those with ILD. When T_{LCO} was expressed as a z-score, the optimal threshold value was ∼ −2.00 for SSc patients without ILD and ∼ −3.50 for SSc patients with ILD.

For the FVC/T_{LCO} ratio (FVC and T_{LCO} both being expressed as % predicted values), we identified an optimal threshold that was similar for SSc patients without ILD whatever the equations used. However, this threshold was ∼15% lower for SSc patients with ILD with the GLI equations compared with the previous equations (table 1).

As other authors have recently remarked, PFTs are used for diagnosis and monitoring at the patient level, and percentage of predicted value is the most common way to express results, to define normal status and/or to grade disease severity [12]. Consistency in interpretation of PFTs from one laboratory to another depends at least in part on the choice of reference equation used to standardise measurements [12]. The GLI was formed in 2008 with the aim of improving reference equations in order to standardise the interpretation of PFTs worldwide. The GLI reference equations have been endorsed by all major international respiratory societies and adopted as the recommended reference equations by many national respiratory societies [12]. Given the crucial role of PFTs in screening for PH in SSc, it was important to make a comprehensive evaluation of the diagnostic value of T_{LCO} and FVC/T_{LCO} with these new equations, which are likely to be the most widely used worldwide in the near future.

There are both pragmatic and pathophysiological reasons for using T_{LCO} as a screening test for PH. First, T_{LCO} is a non-invasive test widely available in pulmonary function laboratories where SSc patients are followed. Secondly, T_{LCO} is very strongly correlated with pulmonary capillary blood volume [2]. This is impaired when pulmonary vessels are remodelled, as is the case in SSc-related PH. In contrast, use of the FVC/T_{LCO} ratio is less pertinent from a pathophysiological point of view. It should be remembered that T_{LCO} is calculated by the product of the transfer coefficient of the lung for carbon monoxide (K_{CO}) and the alveolar volume (V_A) [13]. At least in part V_A is dependent on vital capacity and thus depends on FVC. Taken together, the FVC/T_{LCO} ratio, which by design inversely correlates with T_{LCO}/V_A, can be considered as a surrogate for K_{CO}. The FVC/T_{LCO} ratio has been used instead of K_{CO} mainly in order to take into consideration the fact that, in SSc, T_{LCO} can be decreased not only because of vascular involvement (*i.e.* decreased pulmonary capillary blood volume in PH) but also because of a restrictive pattern (*i.e.* decreased FVC in ILD). Nevertheless, when we took into consideration the presence of ILD, information that is in many cases available in patients with SSc, we found that the FVC/T_{LCO} ratio did not have a better diagnostic power for PH than T_{LCO} alone. As such, the usefulness of measuring FVC in this context is therefore unclear.

In conclusion, we provide here cut-off values obtained with the latest GLI prediction equations for the screening of PH. For this purpose, we suggest taking into account T_{LCO} only (and not the FVC/T_{LCO} ratio) with a cut-off of 70% predicted (or a z-score of −2.00) in SSc subjects without ILD and of 50% predicted (or a z-score of −3.50) in SSc patients with ILD.

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Received: March 16 2018 | Accepted after revision: July 15 2018

Conflict of interest: None declared.

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