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Title: Prevalence of diaphragm dysfunction in patients with Interstitial Lung Disease (ILD): the role of diaphragmatic ultrasound

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ABSTRACT (count: 250)

Background: Diaphragm ultrasound (DUS) has been extensively used in critically ill patients while data on outpatients with interstitial lung disease (ILD) are limited. We hypothesized that diaphragm function, assessed by ultrasound, could be impaired in patients with ILD, considering both Idiopathic Pulmonary Fibrosis (IPF) and Connective Tissue Disease (CTD-ILD), compared to healthy subjects. Moreover, this impairment could impact clinical and functional parameters.

Methods: All consecutive CTD-ILD and IPF patients followed in our center (March-October 2020) were screened. Diaphragm displacement (DD), inspiratory thickness (Ti), expiratory thickness (Te), thickening fraction (TF), and respiratory functional parameters were collected. The prevalence of diaphragmatic dysfunction (TF <30%) was then recorded.

Results: Eighty-two consecutive patients (41 CTD-ILD, 41 IPF) and 15 age- and sex-matched controls were enrolled. In the overall population, 24 out of 82 (29%) presented diaphragmatic dysfunction. In CTD-ILD, DD and Ti were lower as compared to IPF (p=0.021 and p=0.036, respectively); while diaphragmatic dysfunction was more prevalent compared to controls (37% vs 7%, p=0.043). TF positively correlated to patients' functional parameters in the CTD-ILD group (FVC%pred: p=0.003; r=0.45), while not in the IPF group. Diaphragmatic dysfunction was associated with moderate/severe dyspnea in both CTD-ILD and IPF (p=0.021).

Conclusion: The prevalence of diaphragmatic dysfunction was 29% in patients with ILD and was associated with moderate/severe dyspnea. CTD-ILD presented lower DD compared with IPF and a higher prevalence of diaphragmatic dysfunction (TF<30%) compared with controls. TF was associated with lung function only in CTD-ILD patients, suggesting its potential role in the comprehensive patient assessment.

Keywords: diaphragm ultrasound, interstitial lung disease, idiopathic pulmonary fibrosis, connective tissue disease.

INTRODUCTION

In the last few decades, the use of ultrasound techniques has constantly increased in clinical practice [1-2]. Owing to its safety and feasibility, ultrasound evaluation could be easily performed at the patient's bedside and repeated over time during follow-up. Recent, several pieces of evidence have suggested that ultrasound assessment of diaphragm function might be helpful in the evaluation of a spectrum of lung diseases, especially in critically ill patients receiving mechanical ventilation [3-4].

Of note, some authors have assessed the role of diaphragmatic function as a predictor of weaning outcomes, length of hospitalization, mortality, and other adverse events in intensive care unit (ICU) settings [5-6]. In neuromuscular diseases, especially amyotrophic lateral sclerosis (ALS) [7] and Duchenne syndrome [8], the utility of diaphragm ultrasound (DUS) has been widely investigated. I n ALS patients, diaphragmatic mobility assessed by ultrasound differs significantly from that of healthy subjects and correlates with several parameters of respiratory function [7]. The role of DUS has also been investigated in other chronic lung diseases such as asthma [9], chronic obstructive pulmonary disease (COPD) [10], bronchiectasis [11], and cystic fibrosis [12]. Among patients with COPD, a positive correlation was observed between diaphragmatic mobility and 6-minute walk distance (6MWD) while a negative correlation was found with dyspnea [13]. In another study that included patients with COPD, pulmonary fibrosis associated with emphysema (CPFE), and idiopathic pulmonary fibrosis (IPF), the presence of emphysema but not fibrosis was associated with limited diaphragmatic motion recorded by M-mode [14].

Studies of diaphragmatic function in patients with Interstitial Lung Diseases (ILD), including Connective Tissue Disease-associated ILD (CTD-ILD) and IPF, are scarce. In one such study in patients with fibrotic interstitial lung disease (F-ILD), an association between decreased diaphragmatic mobility during deep breathing and reduced lung volumes has been found [15]. Moreover, in a subsequent study conducted on patients with IPF and healthy subjects, no differences were observed in the respiratory excursions during spontaneous breathing [16]. Finally, Santana and coauthors showed an association between lower diaphragmatic activity and dyspnea and lower exercise tolerance in F-ILD patients [17]. Based on these assumptions, our aims were to investigate the diaphragmatic function, as assessed by ultrasound, in ILD patients. Then, we investigated whether the TF is related to patients' lung function and, if a TF < 30% is a predictor of dyspnea.

MATERIALS AND METHODS

In this observational study, 41 adult patients with CTD-ILD and 41 with IPF were consecutively enrolled between March 2020 and October 2020 at the ILD-Unit of the University Hospital of Padova. The diagnosis of IPF was made based on the ATS/ERS/JRS/ALAT guidelines [18-19]. Similarly, the diagnosis of CTD-ILD was made in accordance with current guidelines [20-26]. All cases were discussed by a multidisciplinary team (MDT) and revised according to guidelines [18-19]. High-Resolution Computed Tomography (HRCT) was evaluated by an expert thoracic radiologist (C.G.). Fifteen sex- and age-matched healthy subjects served as controls and were recruited as volunteers in our hospital by word of mouth or leaflets.

Exclusion criteria were the presence of emphysema/COPD, active infection, both past, and recent abdominal/thoracic surgery, oral prednisone equivalent or more than 25 mg/day, and neuromuscular disease. Pulmonary function tests, including FVC (forced vital capacity), FEV1 (forced expiratory volume in 1 second), TLC (total lung capacity), DLCO (diffusion lung carbon monoxide), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP), were performed with CareFusion MasterScreen™ PFT, at the same time as DUS and according to the ATS/ERS guidelines [27-28]. The presence of dyspnea was evaluated with the modified British Medical Research Council Questionnaire (mMRC) [29]. A score of 0 – 1 indicated mild dyspnea, a score of 2 – 3 indicated moderate dyspnea while a score of 4 – 5 indicated severe dyspnea. Demographics and clinical and radiological data were also collected for all CTD-ILD and IPF patients.

Ultrasound measurement and analysis

A portable ultrasound unit (Sonosite M-Turbo©, Fujifilm, Amsterdam, Netherlands) was used to measure, during quiet breathing, right diaphragm displacement (DD), right diaphragm inspiratory thickness (Ti), and right expiratory thickness (Te) at baseline and follow-up visits. The thickening fraction (TF) was calculated as previously described and expressed as a percentage: [(Ti – Te) / Te] x 100 [30], as reported in Figure 1. There is no standardized approach in the measurement of diaphragm thickening fraction in the literature. However, as a first study, we decided to evaluate

only quiet breathing. As the resting diaphragm thickening fraction in healthy subjects is about 30-40% [3], we considered a TF<30% as a cut-off for diaphragmatic dysfunction in our analyses. All ultrasound evaluations were conducted in a semi-recumbent position (40° head-up). For each parameter (Ti, Te, and DD), we used the mean of three consecutive measurements, and the values were reported in centimeters. A convex array (model C60xi – 2-5MHz) was used to measure right diaphragm displacement (DD) and the convex probe was positioned dorso-cranially in the right anterior to mid-clavicular line. Diaphragm and respiratory excursions were then evaluated in M-mode. Measurements, in patients and controls, were performed after freezing the image of the diaphragmatic curve during the respiratory cycle and measuring the distance from the base of the curve to the apex, as previously described [30 - 31]. A linear probe (model HFL38x – 6-13MHz) was used for the measurements of both right diaphragm inspiratory thickness (Ti) and right expiratory thickness (Te). The linear array was positioned in the right mid-axillary line, perpendicular to the diaphragm (approximately at the 8th - 10th intercostal spaces, as appropriate). Ti and Te were obtained with M-mode imaging revealing the variation in diaphragm thickness over time. For demonstrative purposes, we measured the left diaphragmatic function (Figure S1) with the same method used for the right hemidiaphragm (DD, Ti, and Te). We reached acceptable measurements only in 61 patients, due to the loss of the hepatic acoustic window on this side. The agreement between the first 12 ultrasonographic measurements, collected by two different observers (N.B. and A.B.), was assessed through the intraclass correlation coefficient (ICC) using a two-way random effect model (good agreement = 0.75-0.90, excellent agreement > 0.90), as reported in supplementary material, Table S2. The remaining measurements were made by a single trained pneumologist (N.B.) who was blinded to the medical condition of the subject examined.

Statistical analysis

Categorical variables were described as absolute (n) and relative (%) values. Continuous variables were reported as median and range. The two groups were compared with the Mann-Whitney U test

or Fisher's exact test, as appropriate. A comparison between the three groups was made using the Kruskal-Wallis test. Then, we performed a multivariable logistic regression analysis considering, for the latter analysis, only parameters with a p-value ≥ 0.05 in the univariable analysis. Intraclass correlation coefficient (ICC) was used for agreement between the two DUS operators. Finally, Spearman's rank method was used for correlation analysis. All data were analyzed using SPSS Software version 25.0 (New York, NY, US: IBM Corp. USA). Graphs were created using GraphpadPrism 5 (Graphpad Software Inc., La Jolla California USA). We considered statistically significant a p-value < 0.05.

RESULTS

Clinical and demographic features of the study population

The demographics and clinical characteristics of the study population are shown in Table 1. CTD-ILD patients were less frequently male [8 (20%) vs. 32 (78%); p=<0.0001] and younger than patients with IPF [61 (28 – 78) vs. 74 (59 – 83) years; p=<0.0001]. Details of the CTD-ILD population are given in the supplementary material (Table S1). Former smokers were less prevalent in the CTD-ILD group compared with the IPF group [12 (29%) vs. 25 (61%); p=0.008]. Antifibrotic therapies (pirfenidone or nintedanib) were equally distributed between groups, while 23 (56%) CTD-ILD patients were on low-dose corticosteroids at the time of ultrasound evaluation. Cardiovascular and metabolic diseases were less frequent in CTD-ILD patients than in IPF patients [10 (24%) vs. 30 (73%) p=<0.0001 and 2 (5%) vs. 9 (22%) p=0.045] while the prevalence of gastroesophageal reflux disease (GERD) was similar in both groups.

Diaphragm assessment, lung function, and radiologic evaluation

The incidence of diaphragmatic dysfunction was 37% in the CTD-ILD group, 22% in IPF, and 7% in the control group. Compared to the IPF group, CTD-ILD patients recorded the following ultrasound and functional respiratory parameters: *i)* lower DD and Ti [1.4 (0.6 – 2.8) vs. 1.8 (0.9 – 2.6) cm,

p=0.021 and 0.17 (0.08 – 0.27) vs. 0.19 (0.11 – 0.34) cm, p=0.036; respectively] (Table 1); *ii)* greater functional parameters (TLC%pred and DLCO%) [75 (42 – 112) vs. 63 (38 – 100), p=0.014 and 69 (27 – 115) vs. 52 (23 – 88), p=0.0006; respectively] (Table 1); and *iii)* lower MIP [57 (14 – 103) vs. 77 (37 – 134) cmH_2O; p=0.0009] (Table 1).

While comparing CTD-ILD with healthy subjects, Ti was lower [0.17 (0.08 – 0.27) vs. 0.19 (0.12 – 0.24) cm; p=0.039] and diaphragmatic dysfunction was more frequent [15 (37%) vs. 1 (7%); p=0.043], as reported in Table S3. No differences were observed between IPF and healthy subjects. Considering the whole population, the multivariable model (Table 2) showed as a TF <30% was an independent predictor of moderate/severe dyspnea (mMRC ≥2) (OR 3.8, 95%CI [1.39 – 10.39]; p=0.009 and OR 6.3, 95%CI [1.3 – 29]; p=0.021; respectively), as well GERD (OR 8.4, 95% CI [1.8 – 39.3], p=0.007).

Correlation analysis between diaphragm evaluation and lung function

In the CTD-ILD group, we found a positive correlation between TF and FVC%pred. (r=0.45, p=0.003), TLC%pred. (r=0.42, p=0.006), FEV1 (L) (r=0.39, p=0.011) and DLCO% (r=0.48, p=0.001) (Figure 2). Conversely, in the IPF group, no correlation was found between TF and all functional parameters assessed (data not shown), such as FVC%pred (r=0.29, p=0.058), and TLC%pred. (r=0.25, p=0.101), and DLCO% (r=-0.01, p=0.915).

DISCUSSION

Our study showed that the prevalence of diaphragmatic function was nearly 30% in ILD patients. Moreover, TF<30% was more prevalent in CTD-ILD compared with healthy subjects and correlated to patients' respiratory functional parameters, while not in IPF patients. A TF value<30% was correlated to moderate/severe dyspnea considering the overall ILD population. Conversely, diaphragmatic displacement during quiet breathing was similar between IPF and controls.

This is in agreement with a previous study, which found similar results during quiet breathing in a smaller group of patients with IPF [16]. When the authors investigated diaphragmatic displacement during deep breathing, they observed decreased values in IPF patients compared with healthy controls. Moreover, this is in line with Santana et al. who studied 16 patients with fibrotic ILD and showed limited diaphragmatic motility only during deep breathing [15], suggesting that diaphragmatic dysfunction may become evident only during deep breathing.

Differently from previous studies, we assessed for the first-time diaphragm function both in CTD-ILD, in IPF patients, and in healthy subjects. Interestingly, we showed that CTD-ILD patients had lower DD and Ti, as compared to the IPF group; lower Ti and more diaphragmatic dysfunction (TF <30%), as opposed to controls. To note, in the CTD-ILD group, a lower diaphragmatic displacement and thickening fraction probably reflect a "global" muscle dysfunction and deconditioning, which is less prevalent in IPF patients. Being a systemic condition, connective tissue disease could reduce muscle strength (diaphragm and expiratory muscles), limiting the overall respiratory function; on the contrary, IPF is a chronic disease limited to the lung, and muscle strength seems to be more preserved. Despite a higher diaphragm dysfunction, CTD-ILD patients had a better-preserved lung function, in terms of both lung volumes and diffusing capacity. CTD-ILD patients were younger, but previous studies suggested that age did not affect diaphragmatic function [32]. Only CTD-ILD patients showed positive results in this regard to the correlation between TF and respiratory functional parameters (as FVC%pred, TLC%pred, and DLCO%). In fact, pulmonary function tests, especially FVC and FEV1, are potentially influenced by respiratory muscle strength. Our study showed that muscle dysfunction, which is probably affected by the patient's respiratory workload, resulted more prevalent in CTD-ILD than in controls and IPF. In addition, as confirmed by Santana et al. [17], TF was negatively correlated with the MRC scale, SpO2 desaturation at the end of 6MWD and BORG dyspnea, but positively associated with FVC%pred and DLCO%pred.

In the overall population (CTD-ILD and IPF patients), a TF value lower than 30%, a valid index of limited muscle strength, was an independent predictor of dyspnea. However, several variables might

have influenced this result, such as malnutrition, sarcopenia, and physical deconditioning and a real-time ultrasound assessment of diaphragmatic motility might represent an easy and inexpensive method for evaluating patients' weakness during pulmonary and muscle rehabilitation [33].

Despite the novelty of our findings, some limitations need to be declared: *i)* the monocentric design; *II)*; the inability to control the breathing workload due to the setting of measurements (outpatient clinic vs ICU or in-hospital), which limits the complete evaluation of diaphragmatic strength; and *III)* the relatively small sample size. However, all the patients enrolled in the study were deeply characterized to avoid missing data and they are still under evaluation in our clinic allowing further longitudinal assessment in a further study.

As expected, the number of males was higher in the IPF group while the number of females was higher in the CTD-ILD group. This may potentially represent a limitation because the diaphragmatic function is influenced by gender with higher augmentation in males than females which may alter the results of DD [31; 34]. However, in our study, gender was not an independent predictor of dyspnea according to a pre-designed multivariable model.

In addition, dyspnea is a very complex sensation with multiple factors involved, other variables that we have not evaluated may interplay in dyspnea sensation.

Finally, intrinsic limitations of the measurement of TF and DD must be mentioned: *i)* the measurement of DD is angle-dependent; *II)* DD has not been validated as an index of diaphragmatic dysfunction because is dependent on multiple factors; *III)* previous studies have used variable definitions for diaphragmatic dysfunction, ranging from 10-30% TF. For this reason, the prevalence may change according to each definition. In our study, 29% of prevalence could be probably overestimated using 30% as a cutoff; *IV)* TF is susceptible to the "small number effect", as it is measured in millimeters off of the US screen machine with a cursor that has itself a certain thickness and from a tracing that may not be perfectly outlined.

In conclusion, we found a prevalence of 29% of diaphragmatic dysfunction in outpatients with Interstitial Lung Disease. Moreover, a TF<30% was related to moderate/severe dyspnea and

positively correlates with CTD-ILD patients' lung function. The ultrasound assessment of diaphragmatic function represents a non-invasive and reliable tool that could contribute, in combination with respiratory function tests, to the evaluation of ILD patients.

Abbreviations:

IPF: Idiopathic pulmonary fibrosis; CTD-ILD: Connective Tissue Disease-associated ILD; DUS: Diaphragm ultrasound; FVC: Forced vital capacity; ILD: Interstitial lung disease; UIP: Usual interstitial pneumonia; DD: Diaphragm displacement; Ti: Right diaphragm inspiratory thickness; Te: Right expiratory thickness; TF: Thickening fraction; FEV1: Forced expiratory volume in 1 second; TLC: Total lung capacity; DLCO: Diffusion lung carbon monoxide; MIP: Maximal inspiratory pressure; MEP: Maximal expiratory pressure; COPD: Chronic obstructive pulmonary disease; 6MWD: 6-minute walk distance; mMRC: British Medical Research Council Questionnaire; CPFE: Pulmonary fibrosis associated with emphysema; ALS: Amyotrophic lateral sclerosis; GERD: gastroesophageal reflux disease; ICC: Intraclass correlation coefficient.

Declarations

Ethics approval and consent to participate

The present study was conducted between May 2020 to January 2021, in line with the declaration of Helsinki and approved by the Ethics Committee of the University Hospital of Padua (4280/AO/17). All subjects signed informed consent.

Consent for publication

Not applicable

Availability of data and material: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

N.B. received personal fees from Chiesi Farmaceutici. P.S. has received personal fees and non-financial support from Roche, Boehringer-Ingelheim, and PPM Services, and personal fees from Galapagos, Pieris, Lupin, Chiesi, and Santhera outside the submitted work. E.Z. received personal fees from Boehringer-Ingelheim, Janssen Pharmaceutica, and GSK. P.N. research lab received grants/research equipment from Draeger, Intersurgical SPA, and Gilead. P.N. receives royalties from Intersurgical SPA for Helmet Next invention. He also received speaking fees from Getinge, Intersurgical SPA, Gilead, MSD, Draeger, and Medicair. E.B. has received personal fees from Roche and Boehringer-Ingelheim. M.S. has received research grants for the Department (not personal) to her Institution from Takeda Ltd., Chiesi Farmaceutici, and Laboratori Guidotti SpA. These funds were not used to support this project.

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Figure 1: Ultrasound measurement and analysis

Panel I: M-mode window obtained by convex probe, displaying a normal right hemidiaphragmatic exclusion during quiet breathing. A and B points represent diaphragm displacement measurement. Panel I: M-mode window obtained by linear probe, showing thickening fraction analysis of the right hemidiaphragm. B and B represent thickness at inspiration (Ti) while A and A represent thickness at expiration (Te). TF% was calculated as (Ti - Te)/Te.

Figure 2: correlation between respiratory functional parameters and TF (%) during quiet breathing

in patients with CTD-ILD.

Legend: FVC: forced vital capacity, DLCO: diffusion lung carbon monoxide, TLC: total lung capacity, FEV1: forced expiratory volume in 1 second.

Table 1: demographics, clinical characteristics, respiratory function parameters and diaphragm measurements during quiet breathing of the overall population and of patients with CTD-ILD, IPF and healthy subjects.

	Overall population (n=82)	Healthy subjects (n=15)	P value	CTD-ILD (n=41)	IPF (n=41)	P value
Age (years)	70 (28 – 83)	54 (45 – 63)	**<0.0001**	61 (28 – 78)	74 (59 – 83)	**<0.0001**
Male - n (%)	40 (49%)	7 (47%)	0.999	8 (20%)	32 (78%)	**<0.0001**
Smoke history						
● **Current - n (%)**	3 (4%%)	1 (7%)	0.495	2 (5%)	1 (2%)	0.999
● **Former smokers - n (%)**	37 (45%)	1 (7%)	**0.004**	12 (29%)	25 (61%)	**0.008**
Pack/years	0 (0 – 80)	0 (0 – 5)	**0.006**	0 (0 – 30)	8 (0 – 80)	**0.001**
BMI (Kg/m^2)	27 (16.8 – 41)	25 (22.1 – 42.4)	0.321	26 (16.8 – 41)	28 (22.3 – 36.6)	0.109
Steroid therapy - n (%)	23 (28%)	-	-	23 (56%)	-	-
Antifibrotic therapy - n (%)	41 (50%)	-	-	-	41 (100%)	-
Nintedanib - n (%)	23 (28%)	-	-	-	23 (56%)	-
Pirfenidone - n (%)	18 (22%)	-	-	-	18 (44%)	-
Oxygen on effort - n (%)	13 (16%)	-	-	2 (5%)	11 (27%)	**0.013**
mMRC ≥ 2 – n (%)	36 (44%)	-	-	19 (46%)	17 (41%)	0.824
Months from diagnosis	35 (0 – 229)	-	-	43 (6 – 229)	30 (0 – 113)	**0.018**
Comorbidities			-			
Cardiovascular - n (%)	40 (49%)	-	-	10 (24%)	30 (73%)	**<0.0001**
GERD - n (%)	43 (52%)	-	-	24 (58%)	19 (46%)	0.377
Diabetes - n (%)	11 (13%)	-	-	2 (5%)	9 (22%)	**0.045**
Diaphragm measurements						
Ti dx (cm)	0.17 (0.08 – 0.34)	0.19 (0.12 – 0.24)	0.216	0.17 (0.08 – 0.27)	0.19 (0.11 – 0.34)	**0.036**
Te dx (cm)	0.12 (0.06 – 0.27)	0.14 (0.08 – 0.17)	0.591	0.12 (0.06 – 0.2)	0.14 (0.07 – 0.27)	0.087
TF (%)	40 (10 – 83)	44 (25 - 54)	0.303	36 (10 – 83)	42 (14 – 80)	0.447
TF < 30 %	24 (29%)	1 (7%)	0.105	15 (37%)	9 (22%)	0.219
DD dx (cm)	1.6 (0.6 – 2.8)	1.5 (1.1 – 2.4)	0.927	1.4 (0.6 – 2.8)	1.8 (0.9 – 2.6)	**0.021**
Respiratory function						
FVC (L)	2.5 (1.1 – 4.7)	-	-	2.4 (1.1 – 4.7)	2.6 (1.24 – 4.09)	0.386
FVC (%)	88 (43 – 152)	-	-	89 (43 – 152)	79 (47 – 139)	0.282
TLC (L)	3.8 (1.8 – 7.5)	-	-	3.6 (1.9 – 7.5)	3.9 (1.8 – 5.9)	0.575
TLC (%)	68 (38 – 112)	-	-	75 (42 – 112)	63 (38 – 100)	**0.014**
DLCO (%)	3.8 (1.8 – 7.5)	-	-	69 (27 – 115)	52 (23 – 88)	**0.0006**
MIP (cmH2O)	69 (14– 134)	-	-	57 (14 – 103)	77 (37 – 134)	**0.0009**
MEP (cmH2O)	80 (22 – 128)	-	-	77 (22 – 124)	89 (27 – 128)	0.075

CTD-ILD: connective tissue disease-associated interstitial lung disease, IPF: idiopathic pulmonary fibrosis, GERD: gastroesophageal reflux disease, BMI: body mass index, mMRC: Modified British Medical Research Council Questionnaire, TF: thickening fraction, Ti: inspiratory thickness, Te: expiratory thickness, DD: diaphragmatic

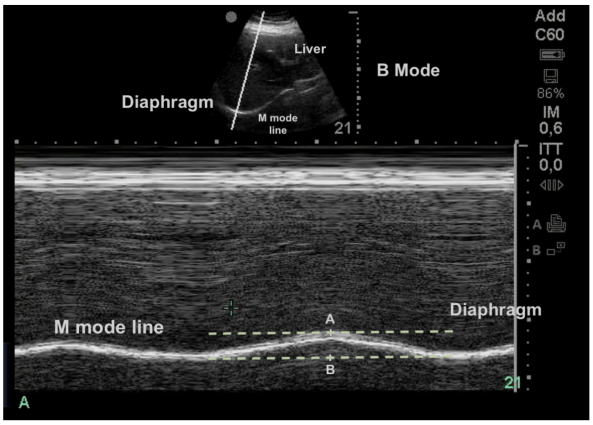
displacement, FVC: forced vital capacity, DLCO: diffusion lung carbon monoxide, TLC: total lung capacity, FEV1: forced expiratory volume in 1 second, MEP: maximum expiratory pressure, MIP: maximum inspiratory pressure. Values are expressed as numbers and (%) or median and range, as appropriate. Chi-square test, Fisher's t-test (n < 5) for categorical variables, and Mann–Whitney t-test for continuous variables was used.

Table 2: predictors of dyspnea (mMRC ≥ 2 at the follow-up visit) in the overall population

		Univariable Analysis		**Multivariable Analysis**	
		OR (95% IC)	**P value**	**OR (95% IC)**	**P value**
Age (years)		0.99 (0.95 – 1.02)	0.501	-	-
BMI (Kg/m^2)		**1.1 (1.02 – 1.3)**	**0.023**	1.1 (0.97 – 1.36)	0.095
DD (cm)		0.62 (0.26 – 1.5)	0.280	-	-
TF dx (%)	**< 30%**	**3.8 (1.38 – 10.3)**	**0.009**	**6.3 (1.3 – 29)**	**0.021**
Sex	**Male**	1.7 (0.69 – 4.02)	0.256	-	-
Diagnosis	**IPF**	0.82 (0.34 – 1.96)	0.656	-	-
	CTD-ILD	-	-	-	-
Smoke history	**Yes**	0.89 (0.37 – 2.14)	0.803	-	-
Steroid use	**Yes**	1.25 (0.47 – 3.28)	0.655	-	-
GERD	**Yes**	**2.84 (1.14 – 7.05)**	**0.024**	**8.4 (1.8 – 39.3)**	**0.007**
Cardiovascular disease - yes		1.09 (0.46 – 2.6)	0.845	-	-
Disease duration (months)		0.99 (0.98 – 1.00)	0.632	-	-
FVC (%)		**0.96 (0.93 – 0.98)**	**0.001**	0.98 (0.95 – 1.01)	0.287
DLCO (%)		**0.93 (0.89 – 0.96)**	**0.0001**	0.96 (0.92 – 1.01)	0.139
Oxygen therapy (on effort) - yes		**22 (2.7 – 183.1)**	**0.004**	12.6 (0.86 – 185.4)	0.065

FVC: forced vital capacity, GERD: gastroesophageal reflux disease, TF: thickening fraction, BMI: body mass index, CTD-ILD: connective tissue disease-associated interstitial lung disease, DD, diaphragmatic displacement, DLCO: diffusion lung carbon monoxide, mMRC: Modified British Medical Research Council Questionnaire.

I



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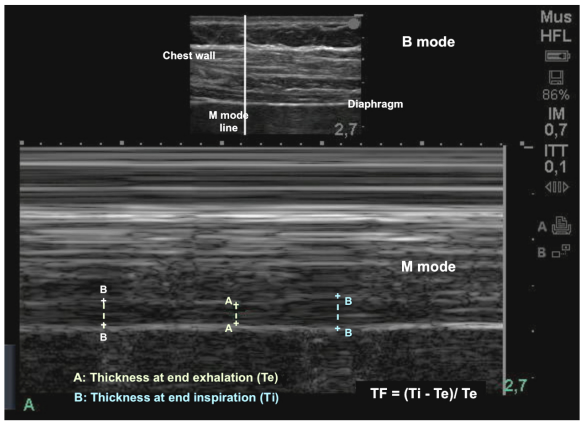

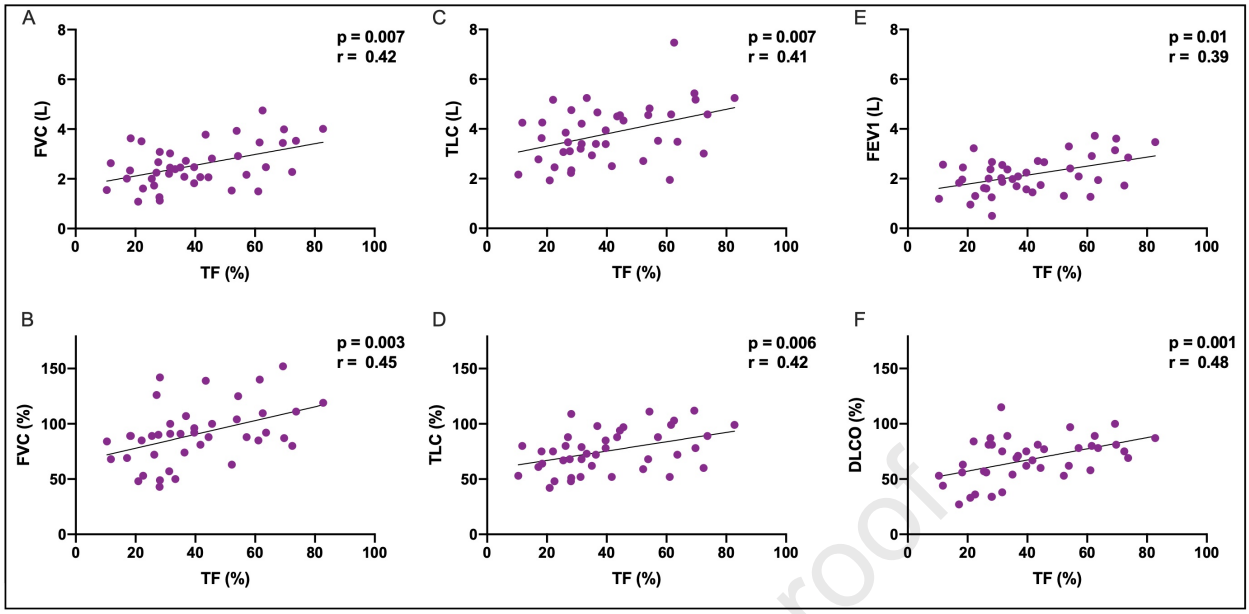

Ethical Disclosures

Ethics approval and consent to participate

The present study was conducted between May 2020 to January 2021, in line with the declaration of Helsinki and approved by the Ethics Committee of the University Hospital of Padua (4280/AO/17). All subjects signed informed consent.

Competing interests

N.B. received personal fees from Chiesi Farmaceutici. P.S. has received personal fees and non-financial support from Roche, Boehringer-Ingelheim, and PPM Services, and personal fees from Galapagos, Pieris, Lupin, Chiesi, and Santhera outside the submitted work. E.Z. received personal fees from Boehringer-Ingelheim, Janssen Pharmaceutica, and GSK. P.N. research lab received grants/research equipment from Draeger, Intersurgical SPA, and Gilead. P.N. receives royalties from Intersurgical SPA for Helmet Next invention. He also received speaking fees from Getinge, Intersurgical SPA, Gilead, MSD, Draeger, and Medicair. E.B. has received personal fees from Roche and Boehringer-Ingelheim. M.S. has received research grants for the Department (not personal) to her Institution from Takeda Ltd., Chiesi Farmaceutici, and Laboratori Guidotti SpA. These funds were not used to support this project.

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