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The impact of vertebral fractures on pulmonary function tests in patients with interstitial lung disease: a cross-sectional study

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Abstract

Background Data on the impact of vertebral fractures on lung function in interstitial lung diseases (ILDs) are limited. This study aimed to evaluate the association between vertebral fractures, quantified by the spinal deformity index (SDI), and pulmonary function parameters, independently of ILD pattern and thoracic morphometric indices.

Methods This cross-sectional study included adult patients diagnosed with ILD who underwent high-resolution computed tomography (HRCT) and pulmonary function tests (PFTs). PFTs included absolute and percent predicted values of forced vital capacity (ppFVC), absolute and percent predicted total lung capacity (ppTLC), forced expiratory volume in one second (FEV_1), and percent predicted diffusing capacity of carbon monoxide (ppDLCO). The SDI was calculated from T4 to T12 on sagittal HRCT reconstructions.

Results A total of 200 patients were analyzed: 76 with idiopathic pulmonary fibrosis (IPF), 65 with systemic sclerosis–associated ILD (SSc-ILD), 31 with idiopathic inflammatory myopathy–associated ILD, and 28 with other ILDs. At least one mild thoracic vertebral fracture was detected in 46 subjects (23%). Each one-point increase in SDI was associated with a 2.9% reduction in ppFVC ($p < 0.01$), a 2.7% reduction in ppTLC ($p < 0.01$). Absolute FVC and TLC declined by 95.6 mL ($p < 0.05$) and 199.5 mL ($p < 0.05$) per SDI point, respectively, with consistent results after multiple imputation.

Conclusions Vertebral fractures quantified by SDI are independently associated with reduced lung volumes in ILD patients, beyond fibrotic pattern and thoracic morphometry. These findings reveal a novel bone–lung interaction and support the inclusion of vertebral assessment in the comprehensive evaluation of ILD.

Keywords Interstitial lung disease, Vertebral fractures, Spinal deformity index, Pulmonary function test

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Introduction

Respiratory function is determined by a complex interaction between anatomical, physiological, genetical and environmental factors. Alterations in each component of the physiological respiratory mechanisms may modulate and reduce lung function, especially in older adults with pulmonary comorbidities [1]. Multiple studies have demonstrated that vertebral fractures are associated with a reduction in pulmonary function, most notably manifesting as a restrictive ventilatory defect on pulmonary function test, primarily due to increased thoracic kyphosis and spinal deformity, which reduce chest wall compliance and lung volumes [2]. However, until now the relationship between vertebral fractures and pulmonary function has been indagated primarily in osteoporotic subjects [3, 4], in which vertebral fractures produced a decrease in forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1). In these patients the degree of impairment correlated with the number and severity of spinal fractures estimated as spinal deformity index (SDI) [5, 6], a semiquantitative radiographic tool used to assess overall vertebral fracture burden.

Moreover, in patients with underlying respiratory disease, such as chronic obstructive pulmonary disease (COPD) and asthma, vertebral fractures further exacerbate pulmonary function decline and are associated with increased morbidity and mortality [7]. Nevertheless, few data are actually available on impact of spinal deformities on lung function in patients affected by interstitial lung diseases (ILDs), and they are generally limited to idiopathic pulmonary fibrosis (IPF) without considering other ILD subtypes [8], such as connective tissue disease-associated ILDs (CTD-ILDs) and fibrotic hypersensitivity pneumonitis (fHP), and without a systematic assessment of overall burden in verterbral deformity.

The primary aim of this study was to explore the association between vertebral fractures and percent-predicted forced vital capacity (ppFVC) in patients with ILDs. Specifically, we sought to determine whether higher SDI scores were related to reduced ppFVC, independently of underlying HRCT pattern, vertebral pathological osteoproliferation - such as spinal osteoarthritis (OA) and diffuse idiopathic skeletal hyperostosis (DISH) - and radiographic linear morphometric indices of pulmonary restriction. In addition, as secondary aims, we sought to explore the same relationships with the other functional test parameters (percent-predicted and absolute), including percent predicted carbon-monoxide diffusion.

Materials and methods

Study design

This cross-sectional study was conducted at the Rheumatology Unit in collaboration with the Pulmonology and Radiology Units of the University of Verona (Verona, Italy).

We included adult subjects (≥18 years) diagnosed with ILD attending our multidisciplinary Rheumatology Clinic at the University of Verona, with a HRCT scan and pulmonary function tests (PFTs) performed within three months of each other. Included ILDs were: IPF, Systemic Autoimmune Rheumatic Diseases (SARD-ILDs) - including systemic sclerosis (SSc), Idiopathic Inflammatory Myopathies (IIM), rheumatoid arthritis (RA), and Sjogren Disease (SjD) - and other ILDs, including fHP, Combined Pulmonary Fibrosis and Emphysema (CPFE), undetermined ILD, and Interstitial Pneumonia with Autoimmune Features (IPAF).

Both HRCT and PFTs were performed at our center. Clinical data were obtained from patients' electronic medical records.

Exclusion criteria included a current or past history of malignancy, other known pulmonary diseases such as established diagnosis of asthma, COPD, bronchiectasis (unrelated to ILD; traction bronchiectasis were not an exclusion criteria), severe pulmonary hypertension (established or suspected through echocardiography), previous pulmonary lobectomy or pneumonectomy, inability to perform PFTs or HRCT, and HRCT patter other than NSIP or UIP, including the presence of significant pulmonary emphysema (≥ 10%), nonfibrotic ILD abnormalities (i.e. acute or chronic infection, pulmonary edema, pleural effusion) or interstitial lung abnormalities (ILAs) not classifiable within one of the above mentioned CT patterns [9].

The study was conducted under protocol 1483CESC, approved by the local Ethics Committee, in accordance with the 1964 Declaration of Helsinki and its subsequent amendments or equivalent ethical standards. The clinical and research activities reported herein are consistent with the principles outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism". Written informed consent was obtained from all participants.

Pulmonary function tests

Pulmonary function tests (PFTs) were performed in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [10, 11], including measurements of percent predicted FVC (ppFVC), percent predicted total lung capacity (ppTLC), percent predicted diffusing capacity of carbon monoxide (ppDLCO), absolute values of FVC (expressed as millilitres), absolute values of TLC (expressed as millilitres), and percent predicted measurements of percent-predicted forced expiratory volume in one second (ppFEV1).

Computed tomography assessment

HRCT were performed in all patients in accordance to the most updated indications [12]. HRCT images were acquired without intravenous contrast using multidetector CT scanners (64-slice Philips, 128-slice Siemens, or 256-slice Philips), with patients in the supine position during full inspiration. Images were reconstructed with a slice thickness of 1–1.25 mm using high spatial resolution algorithms.

The scans were visually evaluated by experienced radiologists (S.B and A.V.) to assess the presence or absence of ILD and to classify the radiological pattern in each patient as follows: NSIP, UIP/UIP-like, or other, according to the current definitions [13]. HRCT scans compromised by motion artifacts due to poor breath-holding, acute inflammatory changes, pulmonary emphysema, lung carcinoma, ILAs, or other technical issues were excluded.

Additionally, the aortosternal distance (AOST), the right oblique fissure posterior retraction distance (ROFPRD) and the left oblique fissure posterior retraction distance (LOFPRD) were measured on HRCT scans as described by Robbie et al. in IPF patients [14].

Vertebral fractures were assessed from T4 to T12 at the mid-sagittal slice of each vertebra using the methodology introduced by Genant et al. [15], and the SDI [6] was applied to the sagittal reconstructions of the HRCT ad applied from the T4 to the T12 vertebrae. The total SDI was the determined by summating the grade of vertebral fracture of each vertebra from T4 to T12 according to the presence and severity of the vertebral fracture (normal = 0, mild = 1, moderate = 2, severe = 3). Vertebral deformities unrelated to fracture, such as those associated with Scheuermann's disease, osteoarthritis, and short vertebral heights were excluded from the grading.

Presence of severe spinal OA and/or DISH were also assessed and established based on Resnik criteria [16].

Sample size

Sample size was estimated a priori using G*Power 3.1 [17] for the incremental effect of SDI in a multiple linear regression predicting our primary outcome of interest (ppFVC). We used the option "F test: Linear multiple regression, fixed model, R^2 increase", with one tested predictor (SDI) and nine total predictors (including also: age, sex, HRCT pattern, DISH/OA, and CT linear morphometric indices). We assumed a small-to-moderate effect size ($f^2 = 0.05$), corresponding to an incremental variance explained (ΔR^2) of approximately 0.04. This conservative assumption is supported by previous findings in osteoporotic cohorts [18]. With alpha = 0.05 and target power = 0.9, the required sample size was $N = 200$.

Statistical analysis

Group comparisons across ILD subtypes (IPF, IIM-ILD, RA-ILD, SSc-ILD, and Other ILDs) were performed using the Kruskal–Wallis test for continuous variables and the Pearson χ^2 test (or Fisher's exact test when appropriate) for categorical variables. When relevant, pairwise comparisons were conducted using the Wilcoxon rank-sum test.

Associations between the SDI and pulmonary function parameters were examined using multiple linear regression models. Separate analyses were conducted with percent predicted forced vital capacity (ppFVC), percent predicted total lung capacity (ppTLC), and percent predicted diffusing capacity of the lung for carbon monoxide (ppDLCO), and absolute values of FVC and TLC as dependent variables.

For each outcome, we first specified a reduced model including SDI, CT pattern (UIP/UIP-like, NSIP or other), presence of DISH/OA, age, sex, and CT linear morphometric indices (AOST, ROFPRD, LOFPRD) as covariates. Visual inspection of residual distributions, spread-location plots, residual dependence plots, and partial residual plots was used to identify potential interactions among independent variables. Significant collinearity among variables (i.e. CT linear morphometric indices) were explored through visual inspection of the bivariate scatter dots.

Similarly, the same models were applied to ppFVC, ppTLC, and the absolute values of FVC and TLC as dependent variables, replacing SDI with the presence of vertebral fractures (present/absent) while keeping all other covariates unchanged.

Sensitivity analysis with multiple imputation

To assess the potential impact of missing data (> 10% for absolute FVC, absolute TLC, and ppFEV1), we conducted a sensitivity analysis using multiple imputation by chained equations (MICE). Fifty imputed datasets were generated under a Missing at Random assumption, including all variables used in the regression models. Continuous variables were imputed using predictive mean matching, and categorical variables using logistic or polytomous regression as appropriate. The same linear regression models were fitted within each imputed dataset, and results were pooled using Rubin's rules. Estimates were consistent with the complete-case analyses.

A p-value < 0.05 was considered statistically significant. All analyses were performed using RStudio (version 2024.09.1).

Results

A total of 200 patients were included, 76 IPF, 31 IIM-ILD, 65 SSc-ILD and 28 other forms of ILD. The characteristics of the enrolled sample, in which we observed

a cumulative slight male predominance (51.5%) and an overall mean age of 66.4 years, is reported in Table 1. Sagittal CT reconstruction showed at least one mild thoracic vertebral fracture in 46 (23%) subjects, similarly, distributed along the four different ILD subgroups. The three linear models predicting respectively ppFVC, ppTLC and ppDLCO are reported in Table 2. Overall model fit was statistically significant for ppFVC (adjusted R^2 = 0.197, $p < 0.001$) and ppTLC (adjusted R^2 = 0.23, $p < 0.001$, 14 missing observations), whereas the model predicting ppDLCO showed only a weak explanatory power (adjusted R^2 = 0.042, $p = 0.049$, 7 missing observations).

Each additional one-point increase in the SDI was associated with an estimated reduction of 2.9% in the ppFVC and 2.7% in the ppTLC ($p < 0.01$ for both), and for ppDLCO a non-statistically significant reduction of 1.45 ($p = 0.087$).

The marginal effect plots depicting the adjusted association between SDI and pulmonary function parameters, with the fitted line representing the predicted mean values derived from the multivariable regression models, are reported in Fig. 1.

The models predicting the absolute FVC values (millilitres) and TLC (millilitres) are reported in supplementary Table 1. Overall model fit was statistically significant for absolute FVC (adjusted R^2 = 0.57, $p < 0.001$, with 40 missing observations) and absolute TLC (adjusted R^2 = 0.43, $p < 0.001$, with 52 missing observations). Each additional one-point increase in the SDI was associated with an estimated reduction of 95.64 ml in FVC and of 199.46 ml in TLC ($p < 0.05$ for both).

For ppFEV1, the overall model fit was also statistically significant (adjusted R^2 = 0.14, $p < 0.001$, with 22 missing observations), however SDI was not observed to significantly predict ppFEV1 (supplementary Table 1).

After multiple imputation, the estimates for SDI remained stable: -88.6 (95%CI -169.34; -7.86, p-value 0.032) for absolute FVC, -182.40 (95%CI -301.46; -63.38, p-value < 0.001) for absolute TLC and −0.79 (95%CI -2.92; 1.34, p-value 0.47) for ppFEV1.

When vertebral fractures (present vs. absent) were included as the main predictor in place of SDI, significantly lower values of ppFVC and ppTLC were observed (Fig. 2, panel a), as well as reduced absolute values of FVC and TLC (Fig. 2, panel b). Similar results were obtained for absolute FVC and TLC values after multiple imputation, with estimates remaining stable and consistent with those of the complete-case analysis.

Discussion

In this cross-sectional study of patients with interstitial lung diseases we demonstrated that vertebral fractures, quantified through the SDI on HRCT, are independently associated with worse pulmonary function. Each one-point increase in SDI (corresponding to one mild vertebral fracture) corresponded to an approximately 2.9% decline in ppFVC and 2.7% in ppTLC, while the effect on ppDLCO was weaker. Consistently, when the

Table 1 Characteristics of the overall sample. Data expressed as absolute numbers or mean (standard deviation). SDI: spinal deformity Index, HRCT: high resolution computed Tomography, UIP: usual interstitial Pneumonia, NSIP: Non-Specific interstitial Pneumonia, AOST: AOrto-STernal distance, LOFPRD: left oblique fissure posterior Retraction Distance, ROFPRD: right oblique fissure posterior Retraction Distance, ppfvc: percent predicted forced vital Capacity, pptlc: percent predicted total lung Capacity, ppdlco: percent predicted diffusing capacity of the lung for carbon mOnoxide, ppFEV1: percent predicted forced expiratory volume in one second

Variable	Missing *N*	IIM-ILD (*N* = 31)	IPF (*N* = 76)	Other ILD (*N* = 28)	SSc-ILD (*N* = 65)	*p*-value
Age	0	63.3 (12.3)	71.5 (7.39)	68.8 (16.4)	60.8 (9.37)	< 0.01
Sex (male)	0	11/31	64/76	14/28	14/65	< 0.01
Subjects with at least one mild fracture	0	9/31	20/76	8/28	9/65	0.20
Subjects with at least one moderate or severe fracture	0	4/31	11/76	4/28	3/65	0.25
Subjects with multiple fractures	0	6/31	4/76	3/28	1/65	0.01
SDI (range)	0	0–7	0–7	0–9	0–8	0.14
HRCT pattern: UIP/UIP-like	0	7/31	72/76	17/28	16/65	< 0.01
HRCT pattern: NSIP	0	23/31	2/76	7/28	46/65	
HRCT pattern: Other	0	1/31	2/76	4/28	3/65	
AOST (mm)	0	26.6 (9.71)	26.6 (9.94)	23.5 (11.8)	24.9 (9.37)	0.49
LOFPRD (mm)	0	105 (23.3)	116 (26.1)	125 (28.4)	105 (26.0)	< 0.01
ROFPRD (mm)	0	113 (22.5)	12 (18.4)	130 (60.4)	118 (26.1)	0.18
ppFVC	0	91.4 (24.9)	87.2 (16.9)	93.6 (19.3)	98.4 (24.6)	0.05
ppTLC	14	78.2 (17.1)	71.4 (14.4)	79.0 (16.8)	86.5 (21.0)	< 0.01
ppDLCO	7	59.4 (14.2)	56.1 (15.6)	55.1 (17.1)	60.9 (19.7)	0.41
FVC (ml)	42	2700 (857)	2940 (831)	2730 (853)	2690 (907)	0.24
TLC (ml)	54	4070 (1230)	4430 (1200)	4300 (1490)	4530 (1440)	0.29
ppFEV1	22	97.7 (24.3)	92.3 (18.0)	84.2 (21.2)	94.7 (23.6)	0.69

Table 2 Multiple linear regression models examining the association between the spinal deformity index (SDI) and pulmonary function parameters. Separate models were fitted for percent-predicted forced vital capacity (ppFVC), percent-predicted total lung capacity (ppTLC), and percent-predicted diffusing capacity of the lung for carbon monoxide (ppDLCO). Estimates are reported as regression coefficients (β) with 95% confidence intervals (CI) and corresponding p-values. SDI: spinal deformity Index, HRCT: high resolution computed Tomography, UIP: usual interstitial Pneumonia, NSIP: Non-Specific interstitial Pneumonia, DISH: diffuse idiopathic skeletal hyperostosis, OA: Osteo-Arthritis, AOST: AOrto-STernal distance, LOFPRD: left oblique fissure posterior Retraction distance, ROFPRD: right oblique fissure posterior Retraction distance

ppFVC			
Variable	**Estimate (β)**	**95% CI**	***p*-value**
Intercept	23.08	[-0.27; 46.43]	0.052
SDI	**-2.92**	**[-4.88; -0.99]**	**0.0030**
HRCT pattern: UIP/UIP-like	Ref.	Ref.	
HRCT pattern: NSIP	2.61	[-3.94; 9.17]	0.43
HRCT pattern: Other	2.81	[-10.15; 15.79]	0.67
DISH/OA (present)	-3.36	[-9.27; 2.53]	0.26
Age	**0.51**	**[0.25; 0.76]**	**< 0.001**
Sex (Male)	**-13.80**	**[-20.37; -7.22]**	**< 0.001**
AOST (mm)	0.17	[-0.11; 0.46]	0.23
ROFPRD (mm)	**0.25**	**[0.10; 0.39]**	**< 0.001**
LOFPRD (mm)	0.09	[-0.04; 0.22]	0.179
ppTLC			
Variable	**Estimate (β)**	**95% CI**	**p-value**
Intercept	27.07	[7.12; 47.03]	0.008
SDI	**-2.70**	**[-4.41; -0.99]**	**0.002**
HRCT pattern: UIP/UIP-like	Ref.	Ref.	
HRCT pattern: NSIP	**7.88**	**[2.55; 13.51]**	**0.006**
HRCT pattern: Other	3.63	[-7.89; 15.15]	0.53
DISH/OA	-4.41	[-9.56; 0.73]	0.09
Age	0.16	[-0.04; 0.38]	0.12
Sex (Male)	**-5.84**	**[-11.48; -0.19]**	**0.04**
AOST (mm)	0.06	[-0.18; 0.32]	0.59
ROFPRD (mm)	**0.21**	**[0.08; 0.34]**	**0.001**
LOFPRD (mm)	**0.144**	**[0.023; 0.266]**	**0.019**
ppDLCO			
Variable	**Estimate (β)**	**95% CI**	**p-value**
Intercept	36.18	[15.62; 56.74	$p < 0.001$
SDI	-1.45	[-3.13; 0.21]	0.087
HRCT pattern: UIP/UIP-like	Ref.	Ref.	
HRCT pattern: NSIP	3.25	[-2.43; 8.93]	0.26
HRCT pattern: Other	5.39	[-7.68; 18.47]	0.41
DISH/OA	1.13	[-3.99; 6.27]	0.66
Age	-0.01	[-0.23; 0.21]	0.91
Sex (Male)	-0.06	[-6.35; 5.14]	0.83
AOST (mm)	-0.05	[-0.30; 0.20]	0.70
ROFPRD (mm)	0.12	[-0.004; 0.25]	0.057
LOFPRD (mm)	0.07	[-0.40; 0.19]	0.20

analysis was repeated using a binary classification of vertebral fractures (present vs. absent), similar results were observed. Patients with at least one vertebral fracture showed remarkably lower ppFVC (-10.11%) and ppTLC (-8.23%) estimated values, as well as reduced absolute FVC (-447 ml) and TLC (-895 ml) estimated values.

To our knowledge, this is the first study to investigate the association between cumulative vertebral fractures, estimated by SDI, and pulmonary function in different ILD subtypes. While previous work in osteoporotic cohorts has shown that vertebral fracture burden negatively impacts lung volumes and ventilatory mechanics [3, 4, 18], no prior study had directly addressed this association in a wide ILD cohort. Previous studies of Caffarelli et al. show a positive correlation between bone mineral density (BMD), fractures and lung parameters

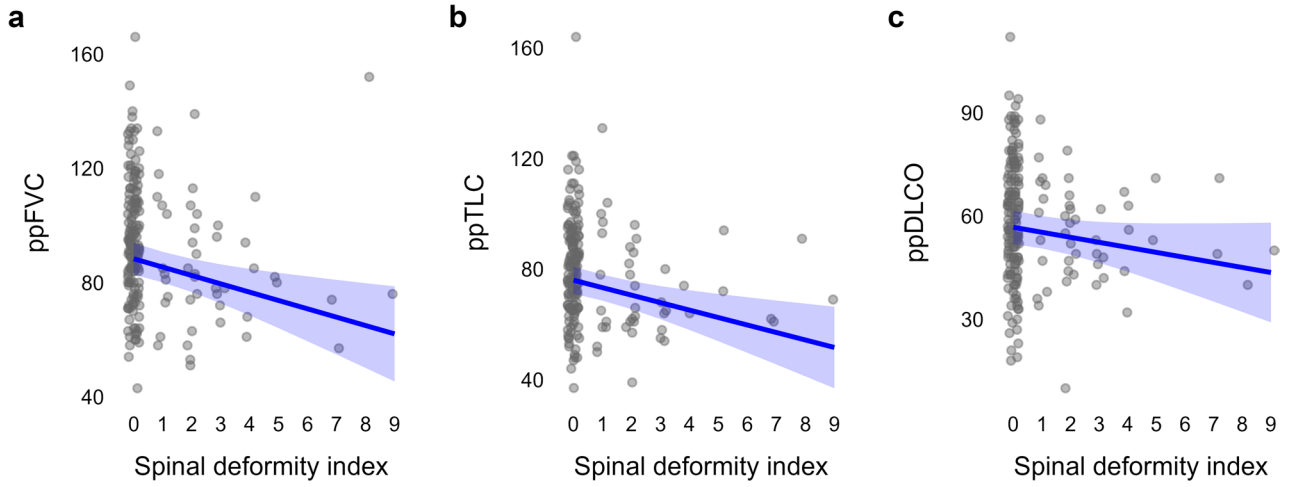

Fig. 1 Marginal effect of spinal deformity index (SDI) on pulmonary function. Each panel shows the adjusted association between SDI (x-axis) and a PFT parameter (y-axis) from the reduced multiple linear regression models, with the blue line representing the model-predicted mean and the shaded band the 95% confidence interval. Semi-transparent gray points depict individual observed values. **a** ppFVC vs. SDI. **b** ppTLC vs. SDI. **c** ppDLCO vs. SDI. Axes are scaled to integer SDI values. Models are adjusted for HRCT pattern, DISH/OA, Age, Sex, and the radiographic mobility indices (AOST, ROFPRD, LOFPRD) as specified in the Methods

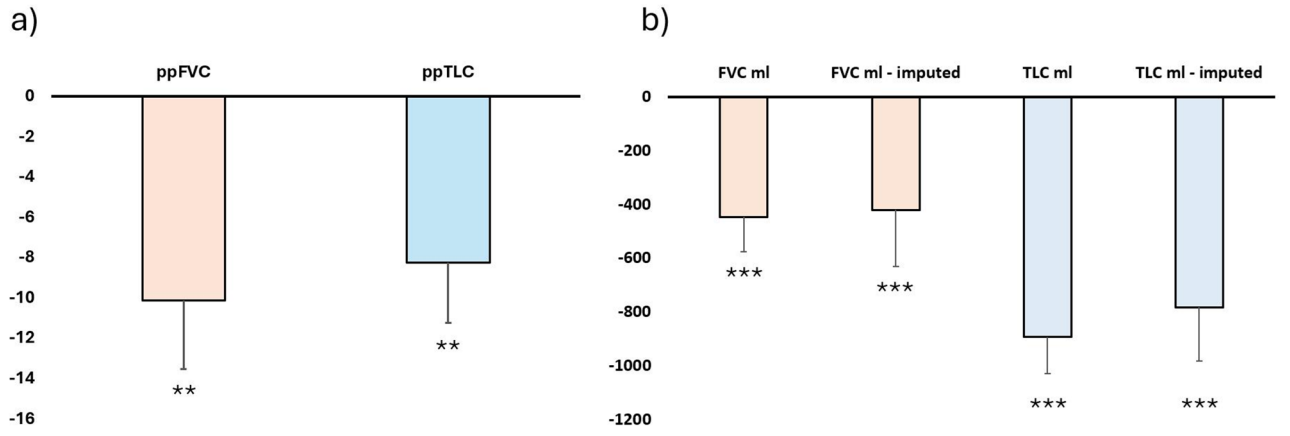

Fig. 2 estimated volume losses associated with the presence of at least one vertebral fracture. Panel **a**: estimated differences in ppFVC and ppTLC. Panel **b**: Estimated differences in absolute FVC and TLC values, including results after multiple imputation. Models are adjusted for HRCT pattern, DISH/OA, Age, Sex, and the radiographic mobility indices (AOST, ROFPRD, LOFPRD) as specified in the Methods. Error bars show standard errors. $^{**}p < 0.01$, $^{***}p < 0.001$

both in IPF and sarcoidosis patients, but in these works cumulative SDI was considered only in association with DLCO [8], or not considered at all [19]. Similarly, imaging studies in IPF and related conditions have validated thoracic morphometric indices such as the aorto-sternal distance and fissure retraction as surrogates of restrictive impairment [14], but these approaches did not incorporate vertebral deformity assessment. By integrating the SDI (or other assessments of vertebral fracture burden) into the evaluation of ILD patients, our findings highlight a novel skeletal determinant of respiratory restriction that is independent of fibrotic parenchymal involvement and thoracic morphometry.

The inverse association between SDI and lung volumes observed in our cohort is indeed biologically plausible. Progressive vertebral fractures, particularly in the thoracic spine, reduces the anteroposterior chest diameter, limits diaphragmatic excursion, and alters rib mechanics. In ILD, where fibrotic remodelling already compromises compliance, these skeletal changes may further amplify the restrictive physiology. The weaker association with DLCO likely reflects the multifactorial determinants of gas transfer, including vascular abnormalities and alveolar-capillary surface area, which are less directly affected by thoracic geometry [20].

From a clinical perspective, our results emphasize the importance of bone health in the multidisciplinary care of ILD patients. Osteoporosis and fragility fractures are common in this population due to systemic inflammation, chronic glucocorticoid use, and reduced physical activity [21, 22]. Moreover, vitamin D deficiency, which is not uncommon in ILD patients, is also associated with

increased risk, prevalence, and severity of both osteoporosis and ILD [23], particularly in the context of CTD-ILD, and may contribute to disease progression and poorer lung function [24].

Furthermore, vertebral fractures can be occult or hidden. Up two-thirds of vertebral fractures are not recognized clinically when they occur and are often asymptomatic or present with nonspecific symptoms [25]. As a results, these fractures are frequently identified incidentally on imaging performed for other reason, and while severe fracture can appear clearly as vertebral collapse or a wedge shape, milder deformities can be difficult to identify with a plan radiographic image [26]. In our cohort we observed at least one mild thoracic vertebral fracture in 46 subjects, with an overall prevalence of 23%. This rate fractures appear major respect with other studies in the general population, which shown a prevalence of 12.2% in men and 12.0% in women aged 50 to 79 years [27, 28], probably due to these patients were at high risk of osteoporosis with adverse outcome, considering underlying comorbidities and pharmacological exposure. Osteoporosis and fragility fracture risk moreover increase with age and are substantially higher in women than men [29], and the lifetime risk of any osteoporotic fracture after age 50 is about 1 in 3 for women and 1 in 5 for men [25], and must be considered that our cohort include 48.5% of female subjects, with a major prevalence in SSc-ILD and IIM-ILD groups, and a population that tends to be elderly, especially in IFP group. Furthermore, our rate fractures appear to be underestimated, considering that the HRCT images in this study detect fractures only in the thoracic spine, which reflect negatively on respiratory mechanism, thus not detecting those at the lumbar spine.

There is an increasing body of evidence in the general population showing that incident osteoporotic vertebral fractures are associated with a substantial increase in all-cause mortality [30–32] and, among other adverse outcomes, with a higher risk of pulmonary complications and respiratory failure [32–34]. Similar associations have also been reported in patients with COPD [7]. To date, similar data are lacking in interstitial lung disease; therefore, PFTs represent a pragmatic surrogate to contextualize the clinical relevance of our findings. In this context, the magnitude of the observed association appears clinically meaningful when interpreted in light of the existing ILD literature. A reduction in percent-predicted FVC of approximately 3% associated with a single mild vertebral fracture is comparable to the annual between-group differences reported in pivotal randomized controlled trials of antifibrotic therapies. In the INPULSIS and INBUILD trials [35, 36], which supported the approval of nintedanib for idiopathic pulmonary fibrosis and progressive pulmonary fibrosis, the difference-in-differences in percent-predicted FVC between the active treatment and placebo arms at one year was approximately 3%, corresponding to about 100–110 mL in absolute terms. Similar effect sizes have been reported in more recent trials such as FIBRONEER-IPF [37] and FIBRONEER-PPF [38]. Furthermore, data from the Scleroderma Lung Study I and II [39] identified a minimal clinically important difference for worsening in percent-predicted FVC ranging from – 3.0% to – 3.3%, supporting the clinical relevance of changes of this magnitude. When extrapolated to moderate or severe vertebral fractures, the cumulative reduction in lung volumes observed in our study (approximately 6% and 9%, respectively) would therefore exceed commonly accepted thresholds for clinically meaningful functional decline. Taken together, these considerations suggest that vertebral deformities may represent a non-negligible contributor to respiratory impairment in ILD and provide a strong rationale for future longitudinal studies specifically addressing the impact of incident vertebral fractures on pulmonary function trajectories.For clinicians therefore become essential that radiologists consider routine assessment of vertebral shape and underline any spinal deformities - leveraging opportunistic HRCT-based SDI scoring - that may provide additional prognostic information and may identify patients at higher risk of pulmonary functional decline, highlighting even more the potential value of preventive strategies aimed at preserving skeletal integrity. Moreover, in patients with fragility fractures, surgical intervention such as percutaneous vertebroplasty may improve chest mobility and maximal voluntary ventilation in the short term, but this approach does not fully restore pulmonary function [40]. Similarly, non-pharmacological intervention such as physiotherapy and exercise sessions do not prevent further decline in pulmonary function. Physical therapy seems to provide short-term improvements in physical performance, but these changes do not persist long-term [41]. Contrariwise, pharmacologic agents for osteoporosis, including antiresorptive and anabolic therapy, which have demonstrated effectiveness in reducing risk of new vertebral fractures in patients with osteoporosis [42], may contribute on prevention in decline of pulmonary function by helping the preservation of thoracic structure in these patients. However, currently there is no direct evidence that pharmacological therapy for osteoporosis prevents reduction in lung volumes. The benefit is inferred from fractures reduction, which are a major contributor to kyphosis and pulmonary compromise, highlighting the importance of preventing vertebral fractures and considering the bone health in the multidisciplinary care of patients affected by ILDs. These considerations can also be translated into the molecular and physiopathological fields of the bone-lung interaction. The receptor activator of nuclear factor kappa-B/osteoprotegerin (RANK/

RANKL/OPG) pathway, indeed, may play a modulatory role in the pathogenesis of ILD. OPG, a soluble decoy receptor for RANKL, is produced by lung fibroblasts and is upregulated in fibrotic lung tissue [43] in response to profibrotic cytokines such as TGF-B and IL-13 [44]. Elevated OPG levels correlate with increased collagen deposition and disease progression in IPF, and higher serum OPG is associated with reduced diffusing capacity and worse prognosis [43], also applying as possible biomarker for both disease activity and treatment response in recent ex vivo models [44].

Our study has several limitations. First, the cross-sectional design precludes causal inference and does not allow evaluation of the longitudinal impact of vertebral deformity progression on pulmonary function decline, nor of its potential prognostic implications. In particular, it remains unclear whether the observed reductions in FVC and TLC represent early markers of subsequent functional deterioration or stable, non-progressive impairments that persist over time in the absence of further vertebral injury. Second, the single-centre nature of the study, although representative of a tertiary referral ILD cohort, may limit the generalizability of our findings to other clinical settings. Despite adjustment for multiple relevant covariates, residual confounding cannot be entirely excluded. In particular, chronic glucocorticoid exposure was not systematically quantified and may be associated both with more severe ILD phenotypes and with an increased prevalence of fragility fractures.

Moreover, bone mineral density data assessed by dual-energy X-ray absorptiometry (DXA) were not available, preventing a comprehensive evaluation of densitometric osteoporosis and overall skeletal health in this cohort. This limitation is especially relevant given the substantial prevalence of thoracic vertebral fractures detected on HRCT (23%), which likely underestimates the true burden of skeletal fragility, as fractures outside the thoracic spine were not captured. Finally, no variables assessing patient symptoms or functional status, such as dyspnoea scores (e.g. mMRC), functional class (e.g. NYHA), or health-related quality of life measures, were available. Therefore, the clinical relevance of the observed reductions in lung volumes cannot be directly inferred, as lower FVC and TLC may or may not translate into a measurable impact on symptoms or daily functioning.

Prospective longitudinal studies are warranted to confirm these findings, to assess whether progression of vertebral fractures predicts accelerated respiratory decline, and to determine whether interventions aimed at preventing or treating vertebral fractures may translate into meaningful functional and patient-centred outcomes.

Finally, future studies may explore the role of alternative strategies for vertebral fracture screening in ILD, such as DXA-based vertebral fracture assessment or, in selected clinical settings, spine MRI. These approaches may provide complementary information, but their added value over opportunistic HRCT-based assessment, in terms of feasibility, cost-effectiveness (especially for MRI), and clinical impact, remains to be explored in the ILD setting.

Conclusion

In conclusion, vertebral fractures quantified by the spinal deformity index are independently associated with reduced lung volumes in patients with ILD, beyond the effects of fibrotic pattern and thoracic morphometry. These findings provide novel evidence of bone–lung interactions in fibrosing lung disease and support the integration of vertebral assessment into the comprehensive evaluation of ILD patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-026-03552-2.

Supplementary Material 1: Table S1. Multiple linear regression models examining the association between the spinal deformity index (SDI) and pulmonary function parameters. Separate models were fitted for absolute forced vital capacity (FVC), absolute total lung capacity (TLC) and percent-predicted Forced expiratory volume (FEV1). Estimates are reported as regression coefficients (β) with 95% confidence intervals (CI) and corresponding p-values.

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Authors' contributions

Conceptualization: A.F., G.A., M.R., D.G.; methodology: A.F., F.P., M.A., S.B., A.V., M.R., L.C., C.M., G.A., M.S., D.B., S.N., D.G.; formal analysis: A.F., F.P., M.A., D.B., G.A.; investigation: A.F., F.P., M.A., S.B., A.V., L.C., C.M., M.S., S.N.; data curation: A.F., F.P., L.C., D.B.; resources: M.R., C.M., M.S., D.G.; writing – original draft: A.F., F.P., M.A., G.A., D.B.; writing – review & editing: A.F., S.B., A.V., M.R., L.C., C.M., G.A., M.S., S.N., D.G.; visualization: F.P., M.A., D.B.; supervision: M.R., D.G., M.S.; project administration: A.F., M.R., D.G.

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Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by our local Ethics Committee of Verona (Italy) and the study was conducted within the protocol 1483CESC, in accordance with the 1964 Declaration of Helsinki and its subsequent amendments or equivalent ethical standards. The clinical and research activities reported herein are consistent with the principles outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism". All subjects provided written informed consent prior to their participation.

Consent for publication

Not applicable.

Competing interests
DG has received advisory board honoraria, consultancy fees, and/or speaker fees from Amgen, Celgene, Eli-Lilly, MSD-Italia, Organon, and UCB. MR has received advisory board honoraria, consultancy fees and/or speaker fees from Abbvie, Eli-Lilly, Italfarmaco, Neopharmed-Gentili, Theramex, and UCB.

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