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DOCTORAL PROGRAM IN CLINICAL AND EXPERIMENTAL BIOMEDICAL SCIENCES

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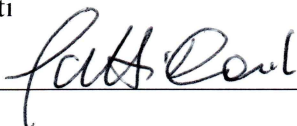
TITLE OF THE DOCTORAL THESIS

THE IMPACT OF VERTEBRAL FRACTURES ON PULMONARY FUNCTION TESTS IN
PATIENTS WITH INTERSTITIAL LUNG DISEASE. A CROSS-SECTIONAL STUDY

S.S.D. MED/16

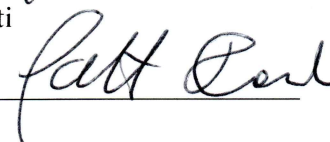
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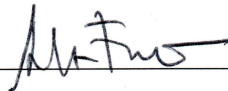
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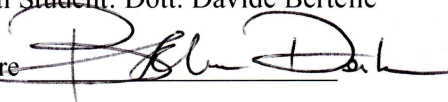
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To my mom

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Abstract

Introduction

Multiple studies have shown that vertebral fractures are associated with a reduction in pulmonary function. The degree of restrictive ventilatory defect generally correlated with the number and severity of spinal deformity, estimated as spinal deformity index (SDI). Few data are actually available on impact of spinal deformities on lung function in patients affected by interstitial lung diseases (ILDs).

Aim of the study

To investigate the association between vertebral deformities, quantified through SDI, and lung functional parameters, independently of underlying high resolution computed tomography (HRCT) pattern, radiographic linear morphometric indices of pulmonary restriction and spinal osteoarthritis (OA)/diffuse idiopathic skeletal hyperostosis (DISH)

Material and Methods

We conducted a cross-sectional study, including adult subjects diagnosed with ILD. HRCT scan and pulmonary function tests (PFTs) were performed, including percent predicted and absolute forced vital capacity (FVC), total lung capacity (TLC), forced expiratory volume in 1 second (FEV1) and diffusing capacity of carbon monoxide (DLCO). SDI was assessed from T4 to T12, and presence of severe spinal OA and/or DISH, aortosternal distance (AOST), right oblique fissure posterior retraction distance (ROFPRD) and the left oblique fissure posterior retraction distance (LOFPRD) were measured on HRCT scans. The required sample size, estimated a priori, was N = 200.

Results

A total of 200 patients were included, 76 idiopathic pulmonary fibrosis (IPF), 31 idiopathic inflammatory myopathies (IIM)-ILD, 65 systemic sclerosis (SSc)-ILD and 28 other forms of ILD. Sagittal HRCT reconstruction showed at least one mild thoracic vertebral fracture in 46 (23%) subjects. Each additional one-point increase in the SDI was associated with an estimated reduction of 2.9% in the ppFVC ($p < 0.01$) and 2.7% in

the ppTLC ($p < 0.01$), while for ppDLCO the reduction was non-statistically significant (1.45%, $p = 0.087$). The models predicting the absolute lung parameters was statistically significant for absolute FVC (adjusted $R^2 = 0.57$, $p < 0.001$) and absolute TLC (adjusted $R^2 = 0.43$, $p < 0.001$). Each additional one-point increase in the SDI was associated with an estimated reduction of 95.64 ml in FVC ($p < 0.05$) and of 199.46 ml in TLC ($p < 0.05$). Regarding ppFEV1, the overall model fit was also statistically significant (adjusted $R^2 = 0.14$, $p < 0.001$). 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

Conclusion

Vertebral deformities quantified by the SDI 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

Background

Respiratory mechanism and pathophysiology

Respiration is the physiological process by which oxygen is taken up from the atmosphere and delivered to tissues, while carbon dioxide produced by cellular metabolism is removed from the body. The mechanisms and pathophysiology of respiration involve several integrated systems:

1. **Mechanical aspects:** ventilation is achieved by the coordinated contraction of the diaphragm and intercostal muscles, which expand the thoracic cavity – constituted by ribs and spinal vertebrae – and create negative intrathoracic pressure, allowing air to flow into the lungs. Expiration is typically passive at rest but becomes active during increased ventilatory demand [1].
2. **Lung performance and gas exchange:** oxygen and carbon dioxide exchange occurs across the alveolar-capillary membrane via passive diffusion, driven by partial pressure gradients. Oxygen binds to hemoglobin for transport, while CO₂ is carried dissolved, as bicarbonate, or bound to proteins [2].
3. **Neural control:** central respiratory rhythm is generated by complex neuronal networks. Neural centers in the brain, medulla and pons coordinate the timing and pattern of inspiration and expiration, integrating inputs from peripheral and central chemoreceptors [3]. Higher brain structures, including the hypothalamus, modulate breathing in response to behavioral and homeostatic demands [4].
4. **Pathophysiology:** disruption at any level – thoracic anatomy, lung physiology and gas exchange, neural control and muscle function – can lead to progressive decline in lung function even to respiratory failure [5].

Interstitial lung diseases (ILDs) and skeletal deformities can act synergistically, by altering lung performance and respiratory mechanics respectively, causing a significant progressive reduction in respiratory function.

Interstitial Lung Diseases

ILDs are a heterogeneous group of disorders characterized by inflammation, fibrosis, or both, affecting the lung interstitium. This process impairs gas exchange, leading to symptoms such as progressive dyspnea, cough, and, in advanced cases, respiratory failure and death [6].

ILDs include more than 200 distinct entities, with different etiologies, clinical and radiological presentation, and prognoses, with an approximately global prevalence of 58 case for 100.000 people [7], which however varies widely depending on geographic region, case definitions and ILDs subtypes [8].

From an etiological point of view, ILDs can be broadly classified [9] as:

- **Idiopathic:** idiopathic pulmonary fibrosis (IPF)
- **Autoimmune-related:** systemic autoimmune rheumatic diseases (SARD), such as systemic sclerosis (SSc), idiopathic inflammatory myopathies (IIM), rheumatoid arthritis (RA), and Sjogren disease (SjD)
- **Exposure-related:** fibrotic hypersensitivity pneumonitis (fHP) and drug-induced ILD
- **Granulomatous diseases:** sarcoidosis,
- **Other ILDs** rare forms, for example lymphangioleiomyomatosis

The most common subtypes are idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, and connective tissue disease-associated ILD [6,10].

ILDs are also classified based on the radiological features detect by High Resolution Computed Tomography (HRCT), which is considered the key diagnostic test and the reference standard for the initial diagnosis of ILDs [11]. HRCT highlight specific patterns correlating to underlying histopathology, driving diagnostic iter and clinical management. ILD subtypes classified by HRCT patterns [12] include:

- **Usual interstitial pneumonia (UIP):** UIP can be caused by numerous causes (e.g., rheumatoid arthritis), but the most common scenario is idiopathic UIP, in which the term IPF can be used. IPF is most common in older white male individuals with a history of smoking. UIP pattern is characterized by bilateral subpleural lower lobe predominant reticulation, honeycombing, traction

bronchiectasis, and architectural distortion with volume loss (**figure 1, panel A**). In 2018, the Fleischner Society updated the categorization of UIP into one of four predefined categories: typical UIP, probable UIP, indeterminate for UIP, and features most consistent with a non-IPF diagnosis [13].

- **Non-specific interstitial pneumonia (NSIP):** NSIP is the second most common fibrotic lung disease accounting for 14% to 35% of all interstitial pneumonias [12]. Unlike UIP, most cases of NSIP are not idiopathic, but rather secondary to CTD [14] and drug-related. The primary HRCT findings of NSIP are reticulation (87%), traction bronchiectasis (82%), lower lobe volume loss (77%), and ground glass opacities (GGOs, 44%) (**figure 1, panel B**). Upper lobe predominant parenchymal abnormalities are very unlikely with NSIP [15].
- **Interstitial lung abnormalities (ILAs):** ILAs are incidental CT scan findings that may suggest early ILD in patients without clinical suspicion for ILD. ILAs are defined as nondependent imaging findings affecting > 5% of any lung zone and include ground glass or reticulation, architectural distortion, nonemphysematous cysts, honeycombing, and/or traction bronchiectasis [16] (**figure 1, panel C**).

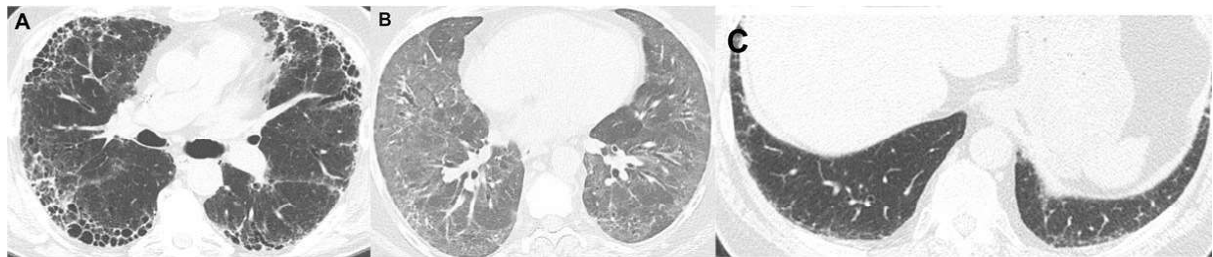


Figure 1. HRCT typical findings of UIP, NSIP and ILA. **Panel A:** Usual Interstitial Pneumonia, demonstrating basilar predominant, subpleural reticulation with traction bronchiectasis and honeycombing; **Panel B:** Mixed cellular/fibrotic Non-Specific Interstitial Pneumonia; **Panel C:** Subpleural nonfibrotic ILA, with presence of mild subpleural reticulation without fibrosis [12]

Finally, from a functional point of view, ILDs typically present on pulmonary function tests (PFT) with a restrictive ventilatory defect and impaired gas exchange [6], even if in early or mild ILD pulmonary function tests may be normal. The hallmark findings are:

- **Reduced forced vital capacity (FVC) and reduced total lung capacity (TLC)**, reflecting restriction due to parenchymal fibrosis or inflammation [17]
- **Decreased diffusing capacity for carbon monoxide (DLCO)**, often the earliest abnormality [18]
- The **forced expiratory volume in 1 second (FEV₁)/FVC ratio** is usually **normal or increased**, distinguishing restriction from obstruction [17]

Integration of HRCT findings with clinical, functional, serologic data - and sometimes histopathological findings - in multidisciplinary discussion is essential for accurate diagnosis and management of ILD [11]. The clinical course and prognosis vary widely among ILD subtypes, with some forms associated with progressive fibrosis and poor survival (e.g. IPF), while others, particularly those driven by inflammation, may respond well to therapy [6].

Effects of spinal deformities on lung function

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 [19]. However, until now the relationship between vertebral deformity and pulmonary function has been indagated primarily in osteoporotic subjects [20,21], in which vertebral fractures produced a decrease in FVC and FEV1. In these patients the degree of impairment correlated with the number and severity of spinal deformity estimated as spinal deformity index (SDI) [22,23], 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), asthma and ILDs, vertebral fractures further exacerbate pulmonary function decline and are associated with increased morbidity and mortality [24]. 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 IPF [25], without considering other ILD subtypes and without a systematic assessment of overall burden in vertebral deformity [26].

Spinal Deformity Index

The SDI is a semiquantitative tool that quantifies the overall burden of vertebral fractures by summing the severity grades of each vertebra from the fourth thoracic vertebra (T4) to fourth lumbar vertebra (L4), where each vertebra is assigned a grade: 0 (no fracture), 1 (mild fracture), 2 (moderate fracture), or 3 (severe fracture), as described by Genant et al [27]. The total SDI score reflects both the number and severity of vertebral deformities, providing a cumulative measure of spinal deformity [22].

Through its role of cumulative morphometric index of vertebral fracture burden, the SDI becomes very relevant from a clinical perspective. Higher SDI scores are strongly associated with increased risk of future vertebral fractures, independent of bone mineral density. The SDI is validated as a prognostic tool for incident vertebral fractures and is

actually used to stratify patients for treatment prioritization in osteoporosis management [23].

Secondary Osteoporosis

Secondary osteoporosis is defined as osteoporosis resulting from an identifiable underlying medical condition, therapies, or lifestyle factor other than aging or postmenopausal status [28]. Chronic glucocorticoid therapy, which remains a cornerstone in induction and treatment of several rheumatic diseases and ILDs, is recognized as one of the most common cause of secondary osteoporosis [29]. Moreover, glucocorticoid requiring diseases pose a risk themselves for fracture independently from glucocorticoid use, particularly in patients affected by connective tissue diseases (CTD), rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), inflammatory bowel diseases (IBD), haematological and neurological conditions [28,30].

As result of this, the risk of fragility fractures and consequent progressive spinal deformity is particularly increased in these patients.

Aim of the study

The primary aim of this study was to investigate the association between vertebral deformities (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.

Material and methods

Study design

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

Inclusion and exclusion criteria

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 pattern other than NSIP or UIP, including the presence of significant pulmonary emphysema ($\geq 10\%$), nonfibrotic ILD abnormalities (i.e. acute or chronic infection, pulmonary oedema, pleural effusion) or interstitial lung abnormalities (ILAs) not classifiable within one of the above mentioned CT patterns [16].

Ethics

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 [31,32], including measurements of percent predicted FVC (ppFVC), percent predicted TLC (ppTLC), percent predicted DLCO (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).

High Resolution Computed Tomography and thoracic morphometry indices assessment

HRCT were performed in all patients in accordance to the most updated indications [33]. 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 [34]. 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 [35].

Vertebral deformity was assessed from T4 to T12 at the mid-sagittal slice of each vertebra using the methodology introduced by Genant et al. [36], and the SDI [23] was applied to the sagittal reconstructions of the HRCT and applied from the T4 to the T12 vertebrae. The total SDI was determined by summing the grade of vertebral

deformity of each vertebra from T4 to T12 according to the presence and severity of the vertebral deformity (normal = 0, mild = 1, moderate = 2, severe = 3).

Presence of severe spinal OA and/or DISH were also assessed and established based on Resnik criteria [37].

Sample Size

Sample size was estimated a priori using G*Power 3.1 [38] 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 [39]. 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) 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 (ie. CT linear morphometric indices) were explored through visual inspection of the bivariate scatter dots

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 R Studio (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.

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 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.

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).

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

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

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 **Figure 2**.

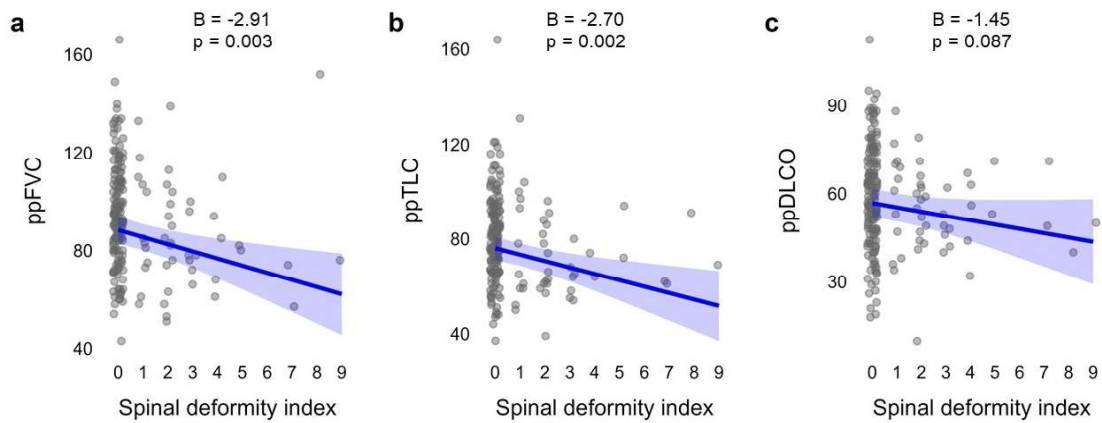


Figure 2: Marginal effect of spinal deformity index (SDI) on pulmonary function. Each panel shows the adjusted association between SDI (x-axis) and a PFT parameter (y-axis) from the reduced multiple linear regression models, with the blue line representing the model-predicted mean and the shaded band 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.

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 (**figure 3, panel a**), as well as reduced absolute values of FVC and TLC (**figure 3, 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.

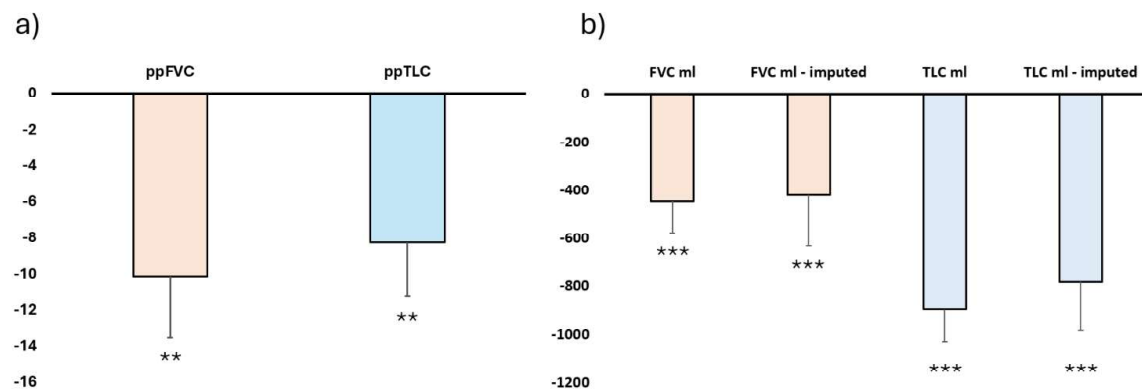


Figure 3: estimated volume losses associated with the presence of at least one vertebral fracture. **Panel a:** estimated differences in ppFVC and ppTLC. **Panel b:** Estimated differences in absolute FVC and TLC values, including results after multiple imputation. Models are adjusted for HRCT pattern, DISH/OA, Age, Sex, and the radiographic mobility indices (AOST, ROFPRD, LOFPRD) as specified in the Methods. Error bars show standard errors. ** $p < 0.01$, *** $p < 0.001$.

Discussion

In this cross-sectional study of patients with interstitial lung diseases we demonstrated that vertebral deformities, 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 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 deformities, 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 [20,21,39], 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 both in IPF and sarcoidosis patients, but in these work cumulative SDI was considered only in association with DLCO [40], or not considered [26]. 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 [35], 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 deformity, 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 [41]. For example, in patients with severe emphysema was observed that DLCO correlates best with total tissue volume, supporting the hypothesis that pulmonary capillary blood volume is the main determinant of DLCO in the human lung [42].

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 [29,43]. 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 [44]. 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 [45]. 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 [46,47], probably due to these patients were at high risk of osteoporosis with adverse outcome, considering underlying comorbidities and pharmacological exposure. 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 [48–50] and, among other adverse outcomes, with a higher risk of pulmonary complications and respiratory failure [50–52]. Similar associations have also been reported in patients with COPD [24]. 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 [53,54], 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 [55] and FIBRONEER-PPF [56]. Furthermore, data from the Scleroderma Lung Study I and II [57] 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 and emphasizing the importance of a multidisciplinary approach in the management and follow-up of these patients. Moreover, in subjects 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 [58]. 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 [59]; moreover, regarding specifically rehabilitation interventions in patients with vertebral fractures, a 2019 Cochrane systematic review showed that exercise programs may improve physical performance measures - like the Timed Up and Go test - but on the other hand the evidence for improvements in pain, function, and quality of life was very low quality with inconsistent findings across studies, even if this review did not specifically assess pulmonary function as an outcome [60]. 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

[61], 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 deformity 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 [62] in response to profibrotic cytokines such as TGF- β and IL-13 [63]. 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 [62], also applying as possible biomarker for both disease activity and treatment response in recent *ex vivo* models [63].

Our study has limitations. The cross-sectional design precludes causal inference and does not capture the longitudinal impact of vertebral deformity progression on pulmonary function decline. The single centre nature of the study sample, although representative of a tertiary ILD cohort, may limit generalizability. Despite adjustment for several relevant covariates, residual confounding cannot be fully excluded due to data lacking on other comorbidities and therapies, such as in particular data on chronic glucocorticoids use and dosage - which may be associated with more severe ILD phenotypes and increased prevalence of fragility fractures – and prior exposure of anti-resorptive treatments. Secondly, 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.

Moreover, bone mineral density data from dual-energy X-ray absorptiometry were not available, preventing a comprehensive assessment of densitometric osteoporosis and overall skeletal health in this cohort, and not allowing the stratification of patients with

a higher fractures risk. This limitation is particularly relevant given the substantial prevalence of thoracic vertebral fractures (23%) detected on HRCT, which likely underestimates the true burden of bone fragility in these patients.

Finally, we did not perform a subgroup analysis among different diseases groups, as such analyses would have been underpowered based on the sample size calculation.

Prospective longitudinal studies are needed to confirm these findings, assess whether vertebral deformity progression predicts accelerated respiratory decline, and determine whether interventions to prevent or treat vertebral fractures may translate into measurable respiratory benefits.

Conclusion

In conclusion, vertebral deformities 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.

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Supplementary table

FVC, milliliters			
Variable	Estimate (β)	95% CI	p-value
Intercept	713.84	[-156.49; 1584.17]	0.10
SDI	-95.64	[-171.20; -20.08]	0.013
HRCT pattern: UIP/UIP-like	Ref	Ref	
HRCT pattern: NSIP	219.22	[-40.82; 497.27]	0.097
HRCT pattern: Other	210.03	[-316.70; 736.75]	0.43
DISH/OA (present)	-26.53	[-256.75; 203.68]	0.82
Age	-4.27	[-13.69; 5.14]	0.37
Sex (Male)	904.23	[650.03; 1158.43]	<0.001
AOST (mm)	12.34	[1.34; 23.33]	0.028
ROFPRD (mm)	8.96	[3.79; 14.13]	<0.001
LOFPRD (mm)	4.06	[-0.89; 9.02]	0.10
TLC, milliliters			
Variable	Estimate (β)	95% CI	p-value
Intercept	59.39	[-1352.01; 1471.08]	0.933
SDI	-199.46	[-332.35; -76.57]	0.001
HRCT pattern: UIP/UIP-like	Ref.	Ref.	
HRCT pattern: NSIP	511.56	[95.45; 927.67]	0.016
HRCT pattern: Other	165.37	[-667.36; 1000.10]	0.69
DISH/OA	-114.83	[-491.66; 261.98]	0.54
Age	7.31	[-7.77; 22.41]	0.40
Sex (Male)	1069.60	[655.33; 1483.85]	<0.001
AOST (mm)	7.71	[-10.47; 25.89]	0.40
ROFPRD (mm)	14.52	[6.00; 23.04]	<0.001
LOFPRD (mm)	10.76	[2.177; 19.35]	0.14
ppFEV1			
Variable	Estimate (β)	95% CI	p-value
Intercept	31.41	[6.84; 55.98]	0.12
SDI	-0.57	[-2.67; 1.52]	0.59
HRCT pattern: UIP/UIP-like	Ref.	Ref.	
HRCT pattern: NSIP	0.11	[-7.11; 7.34]	0.97
HRCT pattern: Other	0.46	[-12.75; 13.68]	0.94
DISH/OA	-1.22	[-7.60; 5.15]	0.70
Age	0.59	[0.33; 0.86]	<0.001
Sex (Male)	-12.32	[-19.56; -5.11]	<0.001
AOST (mm)	-0.02	[-0.34; 0.29]	0.089
ROFPRD (mm)	0.19	[0.04; 0.34]	0.01
LOFPRD (mm)	0.07	[-0.07; 0.21]	0.34

Supplementary table 1. 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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Intellectual and publication statements

The candidate confirms that the work submitted is his own, except where work that has formed part of jointly authored publications has been included.

The contribution of the candidate and the other authors to this work has been explicitly indicated below.

The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Authors' contributions:

The candidate confirms that the work submitted is his own, except where work that has formed part of jointly authored publications has been included. In particular, I confirm I am the sole author of the writing of the present thesis.

The present thesis is based on data collected during my PhD course period at the Rheumatology Unit of University of Verona, under the supervision of Prof. Davide Gatti, Prof. Maurizio Rossini and Dott. Angelo Fassio, that led the multidisciplinary investigation team which include Dr Francesco Pollastri, Dr Matteo Appoloni, Dr Giovanni Adami, Prof. Marco Sebastiani (Rheumatology Unit), Dr.ssa Susanna Baltieri, Dr.ssa Angela Ventura (Radiology Unit) and Dr.ssa Loredana Carobene, Prof. Claudio Micheletto (Pulmonology Unit).

I conceptualised the research work's aims and methodology under the precious input of Dr. Angelo Fassio. The data analysis was reviewed by Prof. Davide Gatti, Prof. Maurizio Rossini, Prof. Claudio Micheletto and Prof. Marco Sebastiani.

The results of the present study have not been previously published in a journal before the thesis submission. However, at the time of writing this thesis, part of this data are under consideration for submission for publication in peer-reviewed journals.

Additionally, parts of this thesis have been published as abstracts and presented as posters at the following conferences: SIR National Congress 2025 (Italy)