

Prevalence and quantification of thoracic pain (TP) through quantitative sensory testing (QST) in patients with chronic interstitial lung disease (cILD)

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Abstract

Background

Prevalence and predisposing factors for the development of thoracic pain in patients with chronic interstitial lung disease are largely unknown. Underestimation and insufficient therapy of pain can lead to worsened ventilatory function. Quantitative sensory testing is an established tool for characterization of chronic pain and its neuropathic components. We investigated frequency and intensity of TP in cILD patients and the potential association with lung function and quality of life.

Methods

We prospectively investigated patients with chronic interstitial lung disease to analyze risk factors for the development of thoracic pain and quantify thoracic pain through quantitative sensory testing. In addition, we studied the relationship between pain sensitivity and lung function impairment.

Results

78 patients with chronic interstitial lung disease and 36 healthy controls were included. Thoracic pain occurred in 38 of 78 patients (49%), most frequently in 13 of 18 (72%) in pulmonary sarcoidosis. The occurrence was mostly spontaneous and not related to thoracic surgical interventions (76%). Patients with thoracic pain showed a significant impairment of mental well-being. A higher sensitivity to pinprick stimulation during QST can be observed in patients with thoracic pain. Steroid treatment was associated with lower sensitivity within thermal and pressure pain testing. We observed a significant correlation between total lung capacity and thermal or pressure pain sensitivity.

Conclusion

This study was performed to investigate prevalence, risk factors and thoracic pain in patients with chronic interstitial lung disease. Thoracic pain mostly occurs spontaneous as a frequent symptom, and seems to be an underestimated symptom in patients with chronic interstitial lung disease, especially those with pulmonary sarcoidosis. Identifying thoracic pain at early stage may allow starting palliation of symptoms earlier.

Clinical Trial Registration

Deutsches Register Klinischer Studien (DRKS) https://www.drks.de/drks_web/ DRKS00022978

1. Background

Interstitial lung diseases (ILDs) are chronic diseases characterized by diffuse inflammation and/or fibrosis of the lung parenchyma, leading to restrictive ventilatory impairment, progressive dyspnea and respiratory insufficiency[1]. The diagnosis is mainly based on clinical and high resolution computed

tomography (HRCT) findings[1]. Quality of life in IPF/ILD patients is impaired, especially due to cough and shortness of breath [2–5].

Although the exact frequency is unknown, a subgroup of IPF/ILD patients develops thoracic pain (TP), sometimes migrating, sometimes localized, which is difficult to classify especially in absence of a history of thoracotomy or any other thoracic intervention, and is often not associated with cough [6]. Inadequate recognition and management of TP could lead to inspiration limitation, contraction of expiratory muscles, and consecutively to enhanced restriction, aggravating hypoxemia in advanced stage of disease [7].

Quantitative sensory testing (QST), developed within the framework of the German Research Network "Pain" and used worldwide since 2002 as a routine tool to assess pain [8], is a validated tool to assess sensory and nociceptive perception, as well as identifying neuropathic components of pain [9, 10]. Patient responses to different physiological stimuli are recorded to quantify and qualify somatosensory integrity and pain sensitivity [11].

Aim of this study was to investigate frequency and intensity of thoracic pain in cILD patients and how thoracic pain affects lung function and quality of life in patients with cILD.

2. Methods

2.1 Study subjects

The study prospectively investigated patients with cILD and a control group of healthy controls (HCs). Study participants were consecutively recruited among patients with cILD followed at the Ruhrlandklinik between April 2017 and November 2019.

Inclusion criteria were an interstitial lung disease diagnosed according to American Thoracic Society (ATS)/ European Respiratory Society (ERS) criteria 2013 [12]. Patients with unclassifiable ILD, incomplete data set or acute thoracic pain caused by any recent events (embolism, pneumothorax) or surgical interventions (including open lung biopsy) during the past six month, were excluded.

As a control group, we investigated HCs with age > 18 years, no pre-existing lung diseases, no chronic pain syndromes, no pre-existing analgesic medication or neurological conditions such as polyneuropathy. The study was approved by the local ethics committee of the Medical Faculty of the University Duisburg-Essen (16-7028-BO), and registered in the German register of clinical studies (DRKS00022978). Written informed consent was obtained from all participants.

2.2 Questionnaires

All questionnaires were collected prior to performing QST. The Short Form 12 (SF-12) questionnaire was employed for assessing health-related QoL regarding physical and mental well-being [13]. The painDETECT questionnaire was used to evaluate potential neuropathic pain [14]. The painDETECT total score ranges between 0-38 and denotes the possibility of a neuropathic pain component being present

(<13 very unlikely, 13-18 likely, >19 certainly). The number of pain areas was recorded by the body scheme of the painDETECT questionnaire.

2.3 Thoracic pain definition and quantitative sensory testing

TP was defined as persistent or intermittent pain ≥ 1 in the numeric rating scale (NRS), the most frequently used pain assessment scale [15].

QST is an established psychophysical test protocol for the quantitative evaluation of somatosensory function [16]. The test is based on standardized somatosensory stimuli for which participant responses are recorded. 13 parameters can be obtained from seven separate test procedures involving nociceptive and non-nociceptive sensations [8]. The same calibrated thermal and mechanical stimuli are always set in the same test sequence. For the present study, the following 10 QST-parameters were obtained in the given order: cold detection threshold (CDT), warm detection threshold (WDT), cold pain threshold (CPT), heat pain threshold (HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA), wind-up ratio (WUR), and pressure pain threshold (PPT) (Extensive description in Supporting information). The correlation of the scores with impairment of sensitivity and pain perception can vary, for some scores being positive (WDT, HPT, MDT, MPS, DMA, WUR) and for others negative (CDT, CPT, MPT, PPT).

QST was performed by two trained examiners. Participants were trained in QST procedures by performing all tests on one hand, once. Subsequently, QST measurements were performed on both sides of the thorax. Patients were instructed not to look at the test area.

2.3.1 Thermal measurement

Thermal measurement was performed with a Medoc TSA 2001-II device (Medoc, Israel) [17, 18]. The contact area of the thermode was 30x30mm. Baseline temperature was 32°C for skin adaption. The subject was requested to stop the stimulus with linearly increasing intensity (1°C/s) immediately when perceiving the onset of cooling (CDT), warming (WDT), or the additional sensation of burning, stinging, drilling or pulling (CPT, HPT). The measurement was terminated by the patient through pressing a button, or when reaching the cut-off temperatures of 0°C and 50°C. Each temperature threshold was obtained three times per target area. Thresholds were calculated as the arithmetic mean temperature of the three consecutive measurements [16].

2.3.2 Mechanical detection threshold (MDT)

MDT was measured with modified von Frey filaments made of optic glass fibres (OptiHair2-Set, Marstock Nervtest, Germany) that exert forces between 0.25 and 512mN increasing by a factor of two from filament to filament [19, 20]. The contact area of the filaments was a small epoxy beat with a diameter of 0.30-0.45mm. Participants were asked to close their eyes, so that they could not observe the application

of filaments, and were instructed to immediately report any perceived touch sensation within the target area. The force of the filaments was incrementally increased until the participant reported the first touch sensation. The force of the last filament used was noted as the first suprathreshold value. After this, filaments were applied in incrementally decreasing force until the patient did not report a touch perception. The force of the last filament was noted as the first infrathreshold value [21]. This procedure was repeated five times per target area. The threshold was determined as the geometric mean of five supra- and infrathreshold values [16].

2.3.3 Mechanical pain threshold (MPT)

MPT was measured with a PinPrick-Set (MRC Systems GmbH, Germany) that exert forces between 8 and 512mN increasing by a factor of two from pinprick to pinprick [22]. The contact area of the pinpricks is 0.2mm diameter. The sensation of pinpricks is produced by the weight of the needle resting on the skin of patient. Patients were instructed to report whether the touch of a pinprick evoked the sensation sharpness, or not. In increasing forces, the force of the first pinprick described as sharp had to be noted as the first suprathreshold value, followed by descending stimuli until the first pinprick is only a touch, noted as infrathreshold value. As for the MDT, five ascending and descending series of stimuli were performed per target area. The MPT was calculated as the geometric mean of five infra- and suprathreshold values [16].

2.3.4 Mechanical pain sensitivity (MPS)/ Dynamic mechanical allodynia (DMA)

Using needle stimulators of different intensities, a stimulus-response curve of MPS was generated [21]. Seven different stimulus intensities were applied in a randomized sequence including each stimulus intensity five times per area. The patient evaluated the individual pain intensities directly after each individual stimulus according to a numeric rating scale between 0 and 100. DMA was examined according to the same test scheme as described for MPS. A moving touch stimulus (cotton swab, Q-tip, brush), which normally does not lead to painful perception, was applied between the needle stimuli. Each of these three non-noxious stimuli was applied five times per area. A total of 50 stimuli (touch and needle stimulus) were applied on both sides of the thorax and the painfulness was recorded numerically. As a measure for the sensitivity to pain, the geometric mean value of pain ratings for needle (MPS) and touch (DMA) stimuli was calculated [16].

2.3.5 Wind-up ratio (WUR)

WUR was determined with a pinprick of 128mN. A single stimulus alternated with a train of ten pinprick stimuli (1/s) within an area of 1cm². The single stimulus and the stimulus train were rated by the patient on a numeric rating scale between 0 and 100, separately. The procedure was repeated five times. The

wind-up ratio was calculated as the arithmetic mean pain rating of the five trains divided by the arithmetic mean pain rating of the five single stimuli [16].

2.3.6 Pressure pain threshold (PPT)

PPT was measured using a pressure gauge device (FDN 200, Wagner Instruments, USA) with a contact area of 1cm² and pressure limit of 20kg/cm², equivalent to 2000kPa. The algometer was applied to the thenar of the respective test side, as testing on the chest is not possible due to the insufficiently large contact area to the muscles in the intercostal space. The application was made manually, with an increasing force of 50kPa/s, corresponding to 0.5kg/cm²/s. Participants were asked to indicate the onset of a burning, stinging, drilling or pulling sensation. Application of pressure was stopped on feedback and the force reached was recorded as the threshold [23, 24]. The procedure was repeated three times per target area. Pressure pain threshold was calculated as the arithmetic mean of these three measurements [16].

2.4 Pulmonary function tests and blood gas analysis

Measurements including FVC, forced expiratory volume in 1s (FEV1), TLC, DLCO, arterial oxygen tension, arterial carbon dioxide tension, arterial oxygen saturation, and alveolar-arterial oxygen tension difference were performed at the time of QST.

2.5 Statistics

Variables distribution was calculated by using Kolmogorov-Smirnov test. Descriptive statistics (frequency, mean ± standard deviation) were performed.

Sample size was calculated based on a number of 360 patients with a new diagnosis of ILD per year at our institution and the fact that up to 10% of them are expected to have TP not dependent on surgical procedures (estimated population size 36). The minimum sample size of ILD patients with TP is 33 with a confidence level of 95% (95%CI) and a margin of error of 5%.

Comparison between cILD patients and HCs were tested using the Mann-Whitney U-test or Student's t-test for continuous variables and chi-square test for categorical variables. Correlations between continuous variables were calculated by using Pearson or Spearman correlation tests. We considered $p < 0.05$ to be statistically significant. Statistical analysis was performed with SPSS 27.0 (SPSS Inc., Chicago, USA).

3. Results

3.1 Studied subjects

Between April 2017 and November 2019 81 consecutive patients with cILD and 36 HCs were enrolled in the study. Three patients were excluded from testing because QST or lung function were not completed.

cILD patients and HCs differed significantly in percentage of women, age, pack/years and alcohol units per week (Table 1).

Table 1: Demographic data of patients with chronic interstitial lung disease and healthy controls.

Group:	Patients with chronic interstitial lung disease (N=78)	Healthy controls (N=36)	p-value
women	25 (32.1%)	20 (55.6%)	0.017
age [year]	65.0 ± 13.0	45.8 ± 14.9	<0.001
smoking years (pack years)	18.0 ± 23.8	3.6 ± 5.8	0.002
alcohol units per week	4.3 ± 10.6	4.4 ± 6.2	0.001
respiratory comorbidities:			
• COPD	5 (6.4%)	_a	-
• Asthma	7 (9.0%)	_a	-
pre-existing treatments with analgesic or potential analgesic effect			
• non-opioid analgesics	36 (46%)	_b	-
• opioids	24 (30.8%)	_b	-
	12 (15.4%)	_b	-

^a pre-existing pulmonary disease was an exclusion criterion for healthy controls.

^b the intake of analgesic medication was an exclusion criterion for healthy controls.

3.2 Frequency of thoracic pain and correlation with demographics and clinical characteristics

TP occurred in 38 (48.7%) of 78 examined patients with cILD (Table 2). Time since initial diagnosis of cILD did not differ between patients with and without thoracic pain (Table 2). TP occurred more frequently in patients with pulmonary sarcoidosis (72%) (p=0.02) than in those with other cILDs (47%), and less frequently in patients with EAA (29%) (p=0.07). TP was spontaneous in 76% of cases, related to previous thorax interventions in 5%, and of unknown origin (not indicated by the patients) in 19% of cases.

There were no differences according to gender, age, pack/years or alcohol units per week between cILD patients with (TP+) and without thoracic pain (TP-). The intake of non-opioid analgesics was higher in

TP+ compared to TP- patients (17 vs 7, $p=0.009$), the intake of opioids did not differ between the groups. Furthermore, we did not detect any difference in frequency of previous interventions between TP+ and TP- (Table 2).

Table 2: Demographic data of patients with chronic interstitial lung disease with and without thoracic pain.

Group:	ILD patients with thoracic pain	ILD patients without thoracic pain	p- value
patients	38 (48.7%)	40 (51.3%)	
women	15 (39.5%)	10 (25.0%)	0.17
age [year]	64.0 ± 12.8	65.9 ± 13.3	0.37
smoking years [pack years]	17.5 ± 26.1	18.5 ± 21.7	0.47
alcohol units per week	3.7 ± 10.3	5.0 ± 10.9	0.47
ILD disease duration prior to QST [month]	30 ± 70	28 ± 42	0.07
diagnosis			
• IPF	11 (28.9%)	12 (30.0%)	0.92
• NSIP	4 (10.5%)	2 (5.0%)	0.36
• EAA	5 (13.2%)	12 (30.0%)	0.07
• DIP	2 (5.3%)	1 (2.5%)	0.53
• sarcoidosis	13 (34.2%)	5 (12.5%)	0.02
• other ILD	3 (7.9%)	8 (20.0%)	0.13
respiratory comorbidities:			
• COPD	3 (7.9%)	2 (5.0%)	0.60
• Asthma	4 (10.5%)	3 (7.5%)	0.64
lung function testing			
• oxygen dependency [l/min]	2.7 ± 1.0	3.5 ± 1.4	0.34
• TLC [l]	5.2 ± 1.3	5.0 ± 1.5	0.49
• TLC [%]	82.1 ± 16.7	74.8 ± 16.9	0.06
• FEV1 [%]	69.9 ± 19.6	73.1 ± 18.4	0.60
• IVC [l]	2.9 ± 1.2	2.9 ± 1.1	1.00
• IVC [%]	75.5 ± 17.9	73.8 ± 20.6	0.62
• Tiffeneau index [%]	98.9 ± 14.5	107.6 ± 13.2	0.015
• DLCO [%]	49.3 ± 17.5	41.5 ± 17.7	0.11
• paO ₂	73.1 ± 14.8	70.8 ± 10.9	0.12
previous interventions			

• no intervention	15 (39.5%)	19 (47.5%)	0.48
• transbronchial biopsy	15 (39.5%)	17 (42.5%)	0.79
• surgical lung biopsy	8 (21.1%)	4 (10.0%)	0.18
SF-12			
• physical health summary scale	31.7 ± 8.9	36.6 ± 12.8	0.11
• mental health summary scale	44.7 ± 12.8	53.2 ± 9.3	0.004
painDETECT	8.1 ± 6.4	2.8 ± 4.6	<0.001
areas of pain	2.6 ± 1.6	1.4 ± 1.8	<0.001
pre-existing treatments with analgesic or potential analgesic effect			
• non-opioid analgesics	17 (44.7%)	7 (17.5%) ^a	0.009
• opioids	7 (18.4%)	5 (12.5%) ^a	0.47
• steroids	15 (39.5%)	17 (42.5%)	0.79
• tricyclics	2	1	0.59
onset of pain symptoms			
• spontaneously	29 (76.3%)		
• after intervention	2 (5.3%)		
• statement not possible	7 (18.4%)		

^a treatment with analgesic medication in patients without thoracic pain was because of other reasons like back pain, rheumatoid arthritis and arthrosis.

IPF = idiopathic pulmonary fibrosis, NSIP = nonspecific interstitial pneumonia, EAA = exogenous allergic alveolitis, DIP = desquamative interstitial pneumonia, ILD = interstitial lung disease, COPD = chronic obstructive pulmonary disease, TLC = total lung capacity, FEV₁ = forced expiratory volume in one second, IVC = inspiratory vital capacity, DLCO = diffusing capacity for carbon monoxide, paO₂ = oxygen partial pressure

3.3 Questionnaires

In the physical health summary scale, we did not observe any difference between TP+ and TP- patients, whereas mental health score was significantly more impaired in TP+ compared to TP-patients (Table 2). The total score of the pain detect questionnaire was significantly higher in TP+ patients, but did not reach values that are indicative of neuropathic pain. The number of pain areas was significantly higher in TP+ patients ranging from 0 to 7 pain areas without differences in localization of pain.

3.4 Quantitative sensory testing

TP+ patients had higher MPS compared to TP- on both body sides and a significant difference in MPT and DMA on the left body side reflecting a higher sensitivity to pinprick stimulation (Table 3).

Measurements of CDT, WDT, CPT, HPT, MDT, WUR and PPT did not differ between TP + and TP- patients.

Patients under corticosteroid treatment had lower sensitivity within thermal testing and pressure pain testing compared to patients without steroids. Differences in HPT were significant on the right side ($46.6 \pm 4.6^{\circ}\text{C}$ vs. $44.9 \pm 4.8^{\circ}\text{C}$, $p=0.034$) and left side ($46.4 \pm 3.9^{\circ}\text{C}$ vs. $44.5 \pm 4.0^{\circ}\text{C}$, $p=0.032$) of the body, while CPT was only significant on the right side ($9.7 \pm 11.8^{\circ}\text{C}$ vs. $13.9 \pm 11.2^{\circ}\text{C}$, $p=0.032$) and PPT only significant on the left side ($7.1 \pm 1.9\text{kg}/\text{cm}^2$ vs. $6.3 \pm 2.1\text{kg}/\text{cm}^2$, $p=0.046$).

Table 3: Comparison of quantitative sensory testing in patients with cILD with and without thoracic pain.

Group:	ILD patients with thoracic pain	ILD patients without thoracic pain	p-value
<u>right body side</u>			
CDT (Cold Detection Threshold) [°C]	26.5 ± 6.4	27.6 ± 5.2	0.61
WDT (Warm Detection Threshold) [°C]	38.3 ± 4.3	37.6 ± 4.4	0.31
CPT (Cold Pain Threshold) [°C]	13.4 ± 10.5	11.0 ± 12.5	0.31
HPT (Heat Pain Threshold) [°C]	45.3 ± 4.6	45.9 ± 4.9	0.54
MDT (Mechanical Detection Threshold) [mN]	21.8 ± 45.0	23.3 ± 69.7	0.13
MPT (Mechanical Pain Threshold) [mN]	46.4 ± 54.1	98.4 ± 150.4	0.09
MPS (Mechanical Pain Sensitivity)	12.2 ± 10.0	4.3 ± 5.3	<0.001
DMA (Dynamic Mechanical Allodynia)	1.2 ± 3.0	0.2 ± 0.7	0.21
WUR (Wind-Up Ratio)	0.4 ± 0.3	0.3 ± 0.2	0.06
PPT (Pressure Pain Threshold) [kg/cm ²]	6.5 ± 2.1	7.1 ± 2.1	0.25
<u>left body side</u>			
CDT (Cold Detection Threshold) [°C]	28.3 ± 3.2	28.2 ± 3.7	0.91
WDT (Warm Detection Threshold) [°C]	37.8 ± 3.6	37.0 ± 3.4	0.22
CPT (Cold Pain Threshold) [°C]	16.3 ± 10.7	12.0 ± 12.2	0.10
HPT (Heat Pain Threshold) [°C]	44.9 ± 4.2	45.6 ± 4.0	0.58
MDT (Mechanical Detection Threshold) [mN]	12.7 ± 15.4	21.8 ± 70.0	0.66
MPT (Mechanical Pain Threshold) [mN]	45.6 ± 76.0	112.8 ± 175.2	0.008
MPS (Mechanical Pain Sensitivity)	11.5 ± 9.1	3.7 ± 4.9	<0.001
DMA (Dynamic Mechanical Allodynia)	1.1 ± 3.6	0.1 ± 0.2	0.012
WUR (Wind-Up Ratio)	0.4 ± 0.2	0.4 ± 0.3	0.38
PPT (Pressure Pain Threshold) [kg/cm ²]	6.4 ± 2.1	6.8 ± 2.1	0.45

3.5 Correlation with lung function impairment

A significant direct correlation between total lung capacity (TLC) and PPT on the right side of the body in cILD patients was found, independent from the presence or absence of TP (e-Figure 1). In TP+ patients, TLC directly correlated with CDT and PPT on both sides of the body, meaning that the higher are the

values of TLC, the better was cold sensitivity and the lower was the pressure pain sensitivity (e-Figure 2 and 3).

3.6 Comparison to healthy controls

Significant differences between cILD patients with thoracic pain (TP+) and HCs could be observed in CDT, MPS, DMA and PPT on both body sides and in HPT only on the left body side (Table 4). TP+ patients showed lower sensitivity within thermal testing, increased values on numeric rating scale during pinprick stimulation and higher sensitivity to pressure pain. Between cILD patients without thoracic pain (TP-) and HCs we found significant differences in HPT and MPT on both sides and in CDT, CPT and MPS on the left side of the body (Table 5). TP- patients showed lower sensitivity within thermal testing, delayed sensation of sharpness and decreased values on numeric rating scale during pinprick stimulation compared to HCs.

Table 4: Comparison of quantitative sensory testing in patients with cILD with thoracic pain and healthy controls.

Group:	ILD patients with thoracic pain	Healthy controls	p-value
<u>right body side</u>			
CDT (Cold Detection Threshold) [°C]	26.5 ± 6.4	28.9 ± 3.4	0.021
WDT (Warm Detection Threshold) [°C]	38.3 ± 4.3	36.5 ± 2.6	0.056
CPT (Cold Pain Threshold) [°C]	13.4 ± 10.5	16.8 ± 10.2	0.16
HPT (Heat Pain Threshold) [°C]	45.3 ± 4.6	44.1 ± 4.4	0.15
MDT (Mechanical Detection Threshold) [mN]	21.8 ± 45.0	12.3 ± 19.1	0.31
MPT (Mechanical Pain Threshold) [mN]	46.4 ± 54.1	33.3 ± 50.7	0.16
MPS (Mechanical Pain Sensitivity)	12.2 ± 10.0	5.7 ± 5.1	0.001
DMA (Dynamic Mechanical Allodynia)	1.2 ± 3.0	0.0 ± 0.02	0.006
WUR (Wind-Up Ratio)	0.4 ± 0.3	0.4 ± 0.3	0.59
PPT (Pressure Pain Threshold) [kg/cm ²]	6.5 ± 2.1	7.8 ± 1.9	0.007
<u>left body side</u>			
CDT (Cold Detection Threshold) [°C]	28.3 ± 3.2	29.9 ± 1.3	0.002
WDT (Warm Detection Threshold) [°C]	37.8 ± 3.6	36.3 ± 1.5	0.09
CPT (Cold Pain Threshold) [°C]	16.3 ± 10.7	20.5 ± 9.6	0.12
HPT (Heat Pain Threshold) [°C]	44.9 ± 4.2	43.2 ± 3.9	0.045
MDT (Mechanical Detection Threshold) [mN]	12.7 ± 15.4	11.7 ± 17.2	0.66
MPT (Mechanical Pain Threshold) [mN]	45.6 ± 76.0	34.9 ± 62.7	0.23
MPS (Mechanical Pain Sensitivity)	11.5 ± 9.1	5.8 ± 5.9	0.002
DMA (Dynamic Mechanical Allodynia)	1.1 ± 3.6	0.2 ± 0.9	0.003
WUR (Wind-Up Ratio)	0.4 ± 0.2	0.4 ± 0.2	0.19
PPT (Pressure Pain Threshold) [kg/cm ²]	6.4 ± 2.1	7.3 ± 2.3	0.047

Table 5: Comparison of quantitative sensory testing in patients with cILD without thoracic pain and healthy controls.

Group:	ILD patients without thoracic pain	Healthy controls	p-value
<u>right body side</u>			
CDT (Cold Detection Threshold) [°C]	27.6 ± 5.2	28.9 ± 3.4	0.07
WDT (Warm Detection Threshold) [°C]	37.6 ± 4.4	36.5 ± 2.6	0.41
CPT (Cold Pain Threshold) [°C]	11.0 ± 12.5	16.8 ± 10.2	0.052
HPT (Heat Pain Threshold) [°C]	45.9 ± 4.9	44.1 ± 4.4	0.025
MDT (Mechanical Detection Threshold) [mN]	23.3 ± 69.7	12.3 ± 19.1	0.66
MPT (Mechanical Pain Threshold) [mN]	98.4 ± 150.4	33.3 ± 50.7	0.001
MPS (Mechanical Pain Sensitivity)	4.3 ± 5.3	5.7 ± 5.1	0.058
DMA (Dynamic Mechanical Allodynia)	0.2 ± 0.7	0.0 ± 0.02	0.054
WUR (Wind-Up Ratio)	0.3 ± 0.2	0.4 ± 0.3	0.051
PPT (Pressure Pain Threshold) [kg/cm ²]	7.1 ± 2.1	7.8 ± 1.9	0.10
<u>left body side</u>			
CDT (Cold Detection Threshold) [°C]	28.2 ± 3.7	29.9 ± 1.3	0.005
WDT (Warm Detection Threshold) [°C]	37.0 ± 3.4	36.3 ± 1.5	0.93
CPT (Cold Pain Threshold) [°C]	12.0 ± 12.2	20.5 ± 9.6	0.009
HPT (Heat Pain Threshold) [°C]	45.6 ± 4.0	43.2 ± 3.9	0.005
MDT (Mechanical Detection Threshold) [mN]	21.8 ± 70.0	11.7 ± 17.2	0.79
MPT (Mechanical Pain Threshold) [mN]	112.8 ± 175.2	34.9 ± 62.7	<0.001
MPS (Mechanical Pain Sensitivity)	3.7 ± 4.9	5.8 ± 5.9	0.017
DMA (Dynamic Mechanical Allodynia)	0.1 ± 0.2	0.2 ± 0.9	0.34
WUR (Wind-Up Ratio)	0.4 ± 0.3	0.4 ± 0.2	0.68
PPT (Pressure Pain Threshold) [kg/cm ²]	6.8 ± 2.1	7.3 ± 2.3	0.17

4. Discussion

This is the first study specifically investigating thoracic pain in patients with chronic interstitial lung disease. Thoracic pain occurred in 48.7% of patients with chronic interstitial lung disease, most frequently in those with pulmonary sarcoidosis. Moreover, we found an association of thoracic pain with

lung function and quality of life. Pain intensity did not differ between patients with pulmonary sarcoidosis and the other patients with chronic interstitial lung disease.

Thoracic pain seems to be an underestimated symptom in patients with chronic interstitial lung disease and, in general, knowledge on thoracic pain in patients with interstitial lung disease is scarce. A recent study reported that the prevalence of pain in ILD patients was 62% compared to 25% in healthy controls, with thoracic pain being the most frequent form (46%), followed by joint and limb pain [25]. In that study, the occurrence of chest pain was higher in patients with idiopathic pulmonary fibrosis than those with CTD-ILD. Moreover, an association was found between intensity of pain, dyspnea, and quality of life.

In our study, pain usually occurred spontaneously, and appeared to be related to the disease itself rather than to previous interventions. It is likely that this kind of pain is associated with the fibrotic involvement and consequent thickening of the pleura, especially in idiopathic pulmonary fibrosis, where the fibrotic changes are predominantly localized in the subpleural area. In patients with pulmonary sarcoidosis, on the other side, thoracic pain may be related to an involvement of small nerve fibers. It has been reported that small fiber neuropathy occurs in 30–50% of sarcoidosis patients, with pain and paresthesia being the most common symptoms [26, 27]. Further studies are needed to elucidate the origin of thoracic pain in ILD patients.

With regard to pain characterization, significant signals in specific tests among the whole quantitative sensory testing were observed in cILD patients. Comparing cILD patients with thoracic pain and healthy controls, the observed significant differences in cold detection threshold, heat pain threshold, dynamic mechanical allodynia and pressure pain threshold mean a lower sensitivity to thermal testing and increased sensibility to pressure at the thenar. In addition, the lower values in cold detection threshold and cold pain threshold, and higher values in heat pain threshold in patients without thoracic pain compared to healthy controls underline the lower sensitivity to thermal stimuli of cILD patients. In contrast, patients without thoracic pain point out higher values in mechanical pain threshold as well as lower values in numeric rating scale in mechanical pain sensitivity compared to healthy controls, which discloses a lower sensitivity against pinprick stimulation and contrasts with the higher sensitivity to pinpricks in patients with thoracic pain. In summary, thoracic pain in ILD compared to healthy controls seems to be characterized by decreased perception and pain sensitivity in response to thermal stimuli. Moreover, patients with thoracic pain compared to healthy controls showed an increased sensitivity to pinprick stimuli and pressure pain.

We observed an influence of corticosteroid therapy on the sensitivity to thermal testing and pressure pain testing in cILD patients. Subjects under long-term corticosteroid treatment had a lower sensitivity to temperature and pressure during quantitative sensory testing. This can be explained by the analgesic effect of corticosteroids [28].

Similarly to the study by Shen et al. [25], we did not find a correlation between lung function tests and the intensity of thoracic pain. Nevertheless, positive correlations between total lung capacity and sensitivity to stimuli, i.e. cold detection threshold as well as pressure pain threshold in all cILD patients (not only

those with thoracic pain) were found. The positive correlation between total lung capacity and cold detection threshold shows that patients with mild or no ventilatory restriction can perceive coldness similarly to healthy subjects, whereas a more pronounced restriction in patients with advanced ILD seems to be associated with a pathologically reduced perception of coldness. This may indicate that the fibrotic changes of the lung tissue affect neural pathways of the thorax. An impairment of the sensory nervous system in advanced ILD might explain both, changes in quantitative sensory testing and the development of thoracic pain in patients with ILD.

The positive correlation between total lung capacity and pressure pain threshold indicates that higher pressure on the thenar is necessary to trigger a painful sensation in patients with better values in total lung capacity. This means that patients with more pronounced restriction have a hypersensitivity to pressure at the thenar. In patients with thoracic pain, especially in sarcoidosis, the hypersensitivity at the thenar could possibly be explained by a generalized sensitivity to pain in other parts of the body caused by a chronic pain syndrome.

Thoracic pain seems to cause a limitation of mental well-being in patients with thoracic pain. An association between pain in patients with ILD and impaired quality of life was observed by Shen et al. [25]. Our study confirms recent investigations in patients with pulmonary sarcoidosis, in whom the loss of mental well-being and concentration impairment have been reported with high frequency [29]. Similar to the observations of Shen et al. [25], by using the painDETECT questionnaire we could detect more pain areas in patients with thoracic pain than in patients without thoracic pain. This was reflected by the significantly higher consumption of non-opioid analgesics in patients with thoracic compared to those without. Since medication burden is an important factor impacting patients quality of life, early pain identification and management could lead to a better preservation of quality of life in ILD patients.

This study has several limitations. First, we did not include patients with lung diseases other than ILDs as a control group. This may lead to overestimation of thoracic pain as symptom in ILD, as the prevalence of pain in patients with chronic obstructive pulmonary disease is reported with 32 to 60% [30]. Furthermore, the lack of a matched control group may lead to biased results due to the fact that the controls are younger and more likely to be female. Second, subgroups of ILD were too small to find significant differences between ILD patients. Third, the cross-sectional study design does not allow drawing any conclusion about long-term consequences of thoracic pain on lung function, quality of life, or disease course. Moreover, we were not able to analyse the temporal relation with onset of ILD symptoms, since data on duration of thoracic pain were not available. Fourth, previous treatment with corticosteroids and analgesics could have led to underestimation of thoracic pain in our patients' population. Finally, in quantitative sensory testing it is difficult to distinguish between faked and true loss or gain of sensation as well as central and peripheral abnormalities can lead to the same deficit in measurement.

5. Conclusion

This study was performed to investigate prevalence, risk factors and thoracic pain in patients with chronic interstitial lung disease. Thoracic pain mostly occurs spontaneous as a frequent symptom in chronic interstitial lung disease patients, especially in pulmonary sarcoidosis. Identifying risk factors for thoracic pain may allow earlier palliation of symptoms.

Abbreviations

CDT – cold detection threshold

COPD – chronic obstructive pulmonary disease

CPT – cold pain threshold

cILD – chronic interstitial lung disease

DIP – desquamative interstitial pneumonia

DLCO – diffusing capacity for carbon monoxide

DMA – dynamic mechanical allodynia

EAA – exogenous allergic alveolitis

FEV₁ – forced expiratory volume in one second

HCS – healthy controls

HP – hypersensitivity pneumonitis

HPT – heat pain threshold

HRCT – high resolution computed tomography

IIP – idiopathic interstitial pneumonias

ILD – interstitial lung disease

IPF – idiopathic pulmonary fibrosis

IVC – inspiratory vital capacity

MDT – mechanical detection threshold

MPS – mechanical pain sensitivity

MPT – mechanical pain threshold

NRS – numerical rating scale

NSIP – nonspecific interstitial pneumonia

paO₂ – oxygen partial pressure

PAP – pulmonary alveolar proteinosis

PPT – pressure pain threshold

QoL – quality of life

QST – quantitative sensory testing

RBILD – respiratory bronchiolitis

TLC – total lung capacity

TP – thoracic pain

TP+ – patients with thoracic pain

TP- – patients without thoracic pain

WDT – warm detection threshold

WUR – wind-up ratio

Declarations

Ethics Approval and consent to participate

The study was approved by the local ethics committee of the Medical Faculty of the University Duisburg-Essen (16-7028-BO), and written informed consent was obtained from all participants.

Consent for Publication

Not applicable.

Availability of data and materials

Dr. Manuela J. Scherer and Dr. Francesco Bonella had full access to the datasets used and analyzed during the current study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Dr. Manuela J. Scherer and PD Dr. Dr. Francesco Bonella are responsible for all content of the manuscript.

MS contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

SK contributed substantially to the study design, and the writing of the manuscript.

JF-B contributed substantially to the data analysis, and the writing of the manuscript.

GW contributed substantially to the study design, data analysis, and the writing of the manuscript.

UC contributed substantially to the data interpretation, and the writing of the manuscript.

FB contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

All authors read and approved the final manuscript.

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Figures

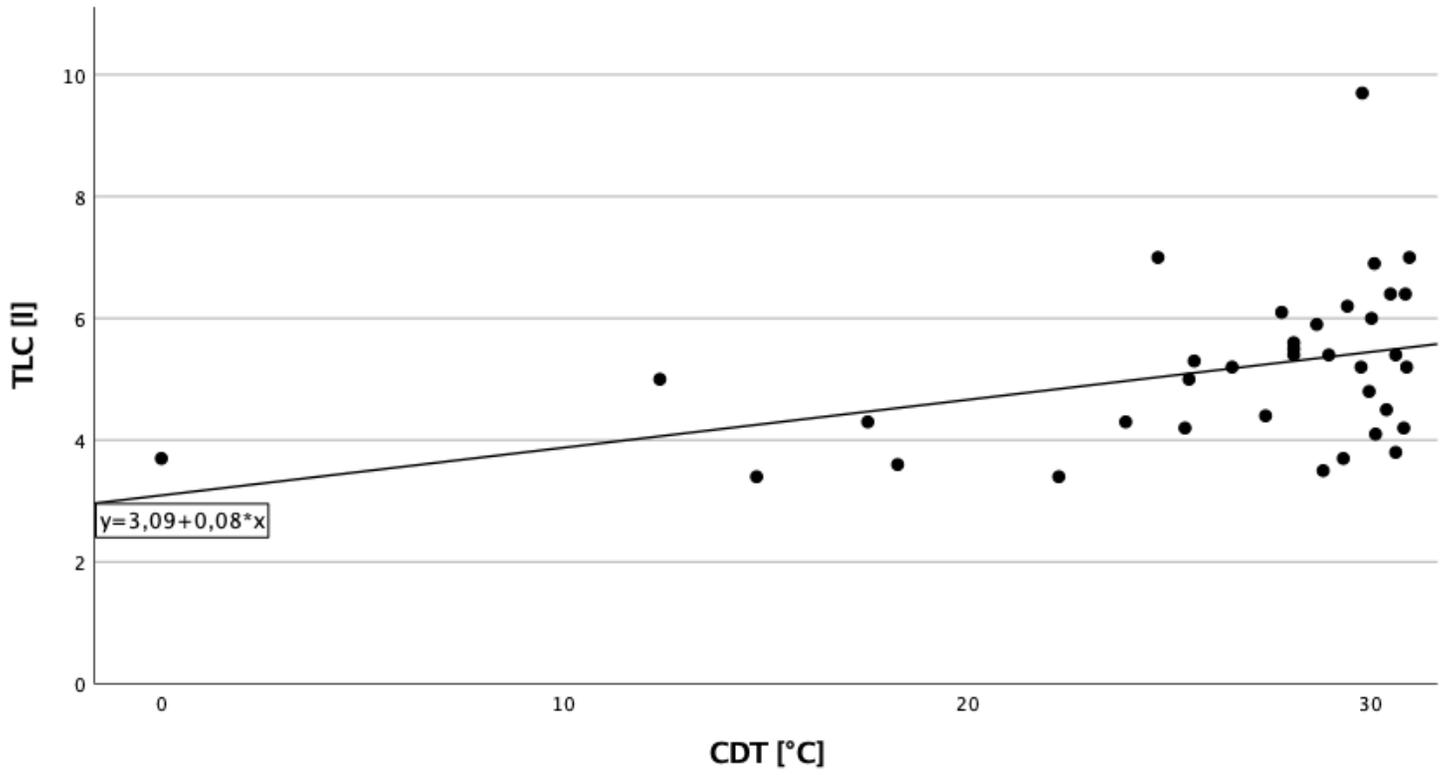


Figure 1

Total lung capacity and pressure pain threshold cILD-patients on the right side of the body

Figure 2a: on the right side of the body

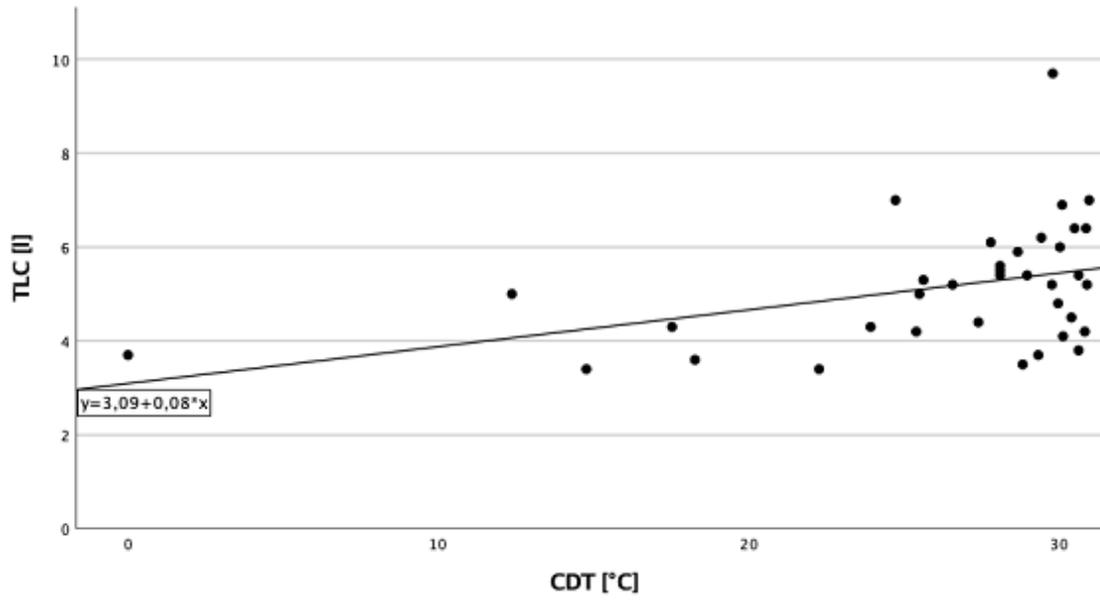


Figure 2b: on the left side of the body

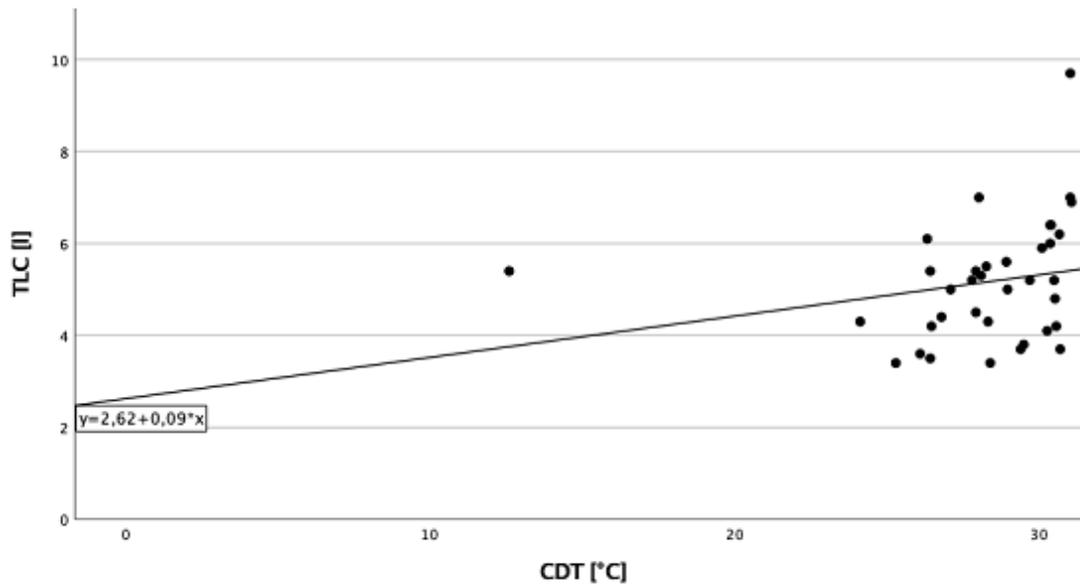


Figure 2

Total lung capacity and cold detection threshold in patients with thoracic pain

Figure 3a: right side of the body

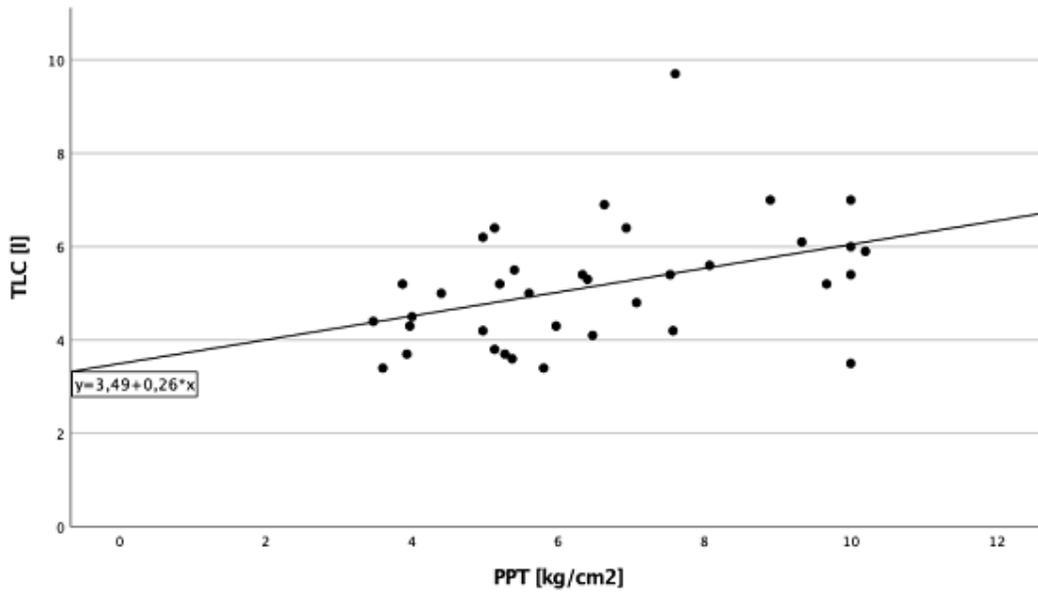


Figure 3b: left side of the body

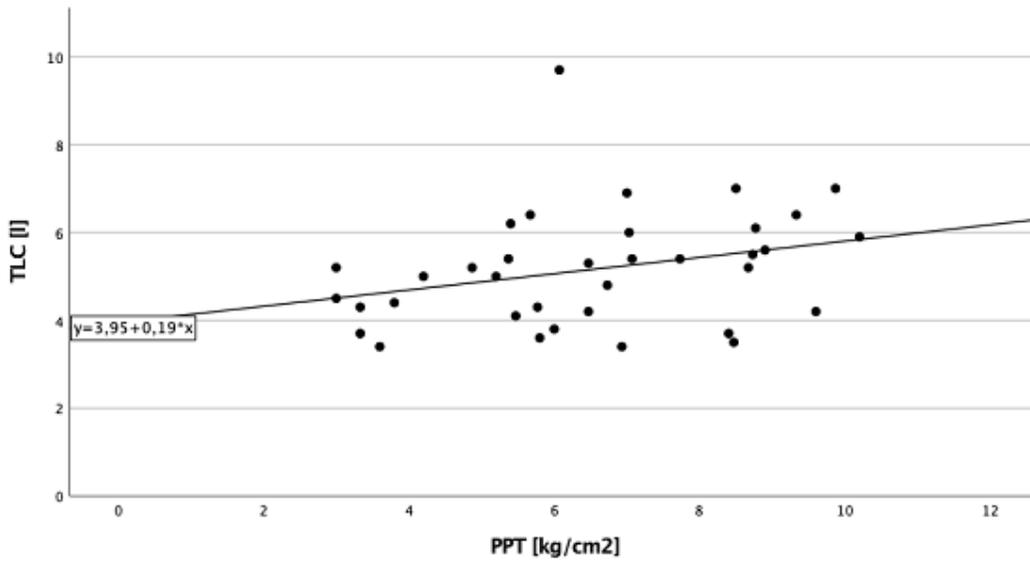


Figure 3

Total lung capacity and pressure pain threshold in patients with thoracic pain