

Pain is a common problem in patients with ILD

Qinxue Shen

Second Xiangya Hospital

Ting Guo

Second Xiangya Hospital

Min Song

Second Xiangya Hospital

Wei Guo

Second Xiangya Hospital

Yi Zhang

Second Xiangya Hospital

Wang Duan

Second Xiangya Hospital

Yating Peng

Second Xiangya Hospital

Shanshan Ni

Second Xiangya Hospital

Xiaoli Ouyang

Second Xiangya Hospital

Hong Peng (✉ penghong66@csu.edu.cn)

Second Xiangya Hospital <https://orcid.org/0000-0003-3235-3348>

Research

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Abstract

Background Less is known about the prevalence and characteristics of pain in interstitial lung disease (ILD) patients. To determine the characteristics of pain in ILD patients.

Methods Participants with ILD and age, gender-matched, healthy controls completed short form McGill Pain Questionnaire (SF-MPQ) and part of the Brief Pain Inventory short form(BPI) to elicit pain characteristics. ILD patients also had assessments of pulmonary function test, six minutes walking test (6MWT), modified medical research council dyspnea scale (mMRC) for state of the illness and measured health-related quality of life(HRQoL) by short form-36(SF-36)and psychological associations by hospital anxiety and depression scale(HADS).

Results A total of 63 participants with ILD and 63 healthy controls(HC) were recruited in our study. The prevalence of pain was 61.9% in ILDs versus 25.3% in HC ($p = 0.005$) and the median score of pain rank index (PRI) in ILDs was higher than in HC ($P = 0.014$). Chest(46.1%) accounted for the highest of overall pain locations in participants with ILD. Associated clinical factors for pain intensity in ILD patients included younger age (< 60 years), exposure history of ILD risk factors, longer distance of 6MWD(≥ 250 m), higher mMRC score(2–4) and lower DLCo, % predicted($\leq 45\%$). ILD patients with pain are more likely to suffer impaired HRQoL($P = 0.0014$) and psychological problems($P = 0.0017, P = 0.044$).

Conclusion Pain is common in those with ILD and the pain intensity is associated with age, exposure history, 6MWD, mMRC score and DLCo, % predicted. ILD patients with pain have more possible to suffer depression, anxiety and impaired HRQoL.

Backgrounds

Interstitial lung disease (ILD) refers to a complex and large group of diseases that are typically characterized by the pathological basic changes of diffuse lung parenchyma, alveolar inflammation, and interstitial fibrosis (1,2), which are somewhat challenging due to their unknown cause. Patients with ILD are suffered from distressing dyspnea, progressive deterioration in exercise tolerance and reduced life expectancy, leading to impaired health related quality of life (HRQoL) in many patients life domains, there are some correlation between the physical and mental components of HRQoL (3,4).

In addition, there is some evidence that ILD patients with impaired HRQoL also frequently experience pain(5–7). In 2020, The current International Association for the Study of Pain (IASP) definition of pain as “An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”(8). Depressive symptoms in ILD were reported independently correlated with pain(9). Pain was also the most common symptoms in end-of-life stage patients with ILD(10,11). It is reported that higher pain intensity in chronic obstructive pulmonary disease (COPD) is associated with more dyspnea, depression, anxiety and poor quality of life(12). However, less is known about the prevalence and determinants of pain in ILD,the location and mechanism of the pain in ILD have not been reported clearly yet. Given the limited treatment options available to sufferers of ILD, it is

important that coexisting conditions are accurately identified and optimally managed. A better understanding of the characteristics of pain and its influence on symptoms and physical activity will help inform approaches for managing pain in ILD. We hypothesized that pain would be common among people with ILD and would be determined by features independent of the underlying disease.

The goals of this study was to determine the characteristics of pain (prevalence, intensity, location, pain sensory) in patients with ILD compared to healthy, age and gender-matched control participants and explore the association between pain, dyspnea, physiology function, psychological symptoms and quality of life.

Materials And Methods

Study overview

This cross-sectional study used routinely collected data from the Second Xiangya hospital of central south university, a tertiary hospital in Changsha, Hunan province of China, between January of 2019 and January of 2020. This study was approved by the Medical Ethical Committee of the Second Xiangya Hospital of Central South University(Approved Number KL-2014-S009), and all participants gave written informed consent.

Study population

The ILD patients were sequentially selected from among those under hospitalization and treatments at the Second Xiangya Hospital, included in the study if he or she 1)met the diagnosis criterion of ILD(the diagnosis of ILD were made by certified respiratory physicians with extensive experience with the management of ILD and according to standardized criteria(13) (14), 2) was able to offer informed consent and medical chart, 3) was a local resident aged 40–85 years, 4) was able to complete the questionnaire interview. Patients with serious or unstable conditions and advanced illness, such as cardiovascular, neurological, musculoskeletal diseases and cancer, who needed to be treated as inpatients, were excluded from the research. Healthy, age-matched control participants were recruited from Health management center of the Second Xiangya Hospital, included in the study if he or she 1) was a local resident aged 40–85 years ,2) with no respiratory or musculoskeletal history and other advanced diseases according to the medical examination report. Subjects with cognitive impairment and mobility limitation were also excluded.

Procedures

All participants attended for 1 visit, at which time the following measures were undertaken:

Information recorded in the registry include demographic details(gender, age, BMI,diagnosis, smoking history,commodities, use of supplemental oxygen).Pain assessment by the short form McGill Pain Questionnaire (SF-MPQ) and part of the Brief Pain Inventory short form(BPI): SF-MPQ was used to evaluated the pain intensity of participants, scores of different parts of SF-MPQ were calculated to

characterize the pain problems(15–17). SF-MPQ is composed of 15 representative items of MPQ, 11 of which are feelings and 4 of which are emotions. For each description, patients were asked to rank the intensity level: 0-none, 1-mild, 2-moderate, 3-discomfort, 4-worse. Considering we have used SF-MPQ to measure the pain intensity, we only use BPI for participants to locate the pain from the body chart which were determined by standardized body regions based on 45 anatomical areas(18,19).

Participants with ILD also completed the following measures:

Whether there was a history of exposure to risk factors related to ILD. The pulmonary function test (PFT) to investigate the lung volume compartment and pulmonary diffusing capacity, according to standard criteria(20–22). Six minutes walking test (6MWT) to conducted without supplemental oxygen according to ATS guidelines in a 30-meter corridor at the pulmonary unit within the hospital(23), heart rate and oxygen saturation, as measured by pulse oximetry (SpO₂) were recorded at the start and end of minute of the test. Modified Medical Research Council Dyspnea Scale (MMRC) to rate their level of dyspnea during daily life, a self-measuring tool that is associated with survival in people with IPF(24) and is responsive to changes with therapy in ILD(25). Hospital Anxiety and Depression Scale (HADS) to measure the severity of anxiety and depression from 14 statements, with a higher score indicating greater anxiety or depression(26). Short Form-36(SF-36) to evaluate HRQoL, which was made up of eight dimensions, 36 projects and the sum of 8 dimension scores is SFTotal score, the higher the score, the less damage the function is(27).

Statistical Analysis

Continuous variables were described as mean (SD) if they are normally distributed or median (IQR) if they are not, and categorical variables as count and percentages (%). Comparisons between groups (ILD and control; ILD with or without pain; key variables) for continuous measurements were analyzed using paired t-tests, independent t-test or Kruskal-Wallis H test, with categorical data analyzed using Chi Square test. The statistical analyses were conducted using SPSS (version.25) software(Chicago, IL, USA). $P \leq 0.05$ was considered statistically significant.

Results

From January 2019 to December 2019, a total of 141 potential participants with ILD and 100 healthy controls were approached (Fig. 1). A total of 63 participants with ILD and 63 healthy control participants were recruited, with no difference in age, gender or BMI between groups. 49 patients with ILD completed physical functions and 40 patients with ILD completed 6 minute walking test. Other participants with ILD were unable to undertake the measurement due to their poor healthy situation. All participants and healthy controls completed all questionnaires independent.

Comparisons Between Ild And Healthy Control Groups

The average age in all participants was 62 ± 9 years (Table1). The average pack years of participants with ILD was 16.68 years which was a much larger number to healthy controls whose average pack years was only 4.2 years ($P < 0.0001$). According to SF-MPQ, the prevalence of pain was 39(61.9%) in ILD group versus 16(25.3%) in control participants ($p = 0.005$) and the median score of pain rank index(PRI) was 2.5(IQR 1.0–5.0) in ILD versus 2.0(IQR,1.0–2.0) in HC ($P = 0.014$). The median scores of PRI affective dimension was 2.0(IQR 0–3.0) in ILD and 0 in HC ($P < 0.0001$). But the visual an analogue scales (VAS) score and present pain intensity (PPI) rank didn't show obvious differences.

Table 1
Demographic and pain characteristics measured by SF-MPQ of participants

Demographic	All patients N = 126	ILD N = 63	Control N = 63	P value
Age(years)	62 ± 9	61 ± 10	63 ± 8	0.730
> 65	77(61.1%)	40(63.5%)	37(58.7%)	0.714
Gender(Male)	77(61.1%)	38(60.3%)	39(61.9%)	0.828
BMI(kg/m ²)	24.8 ± 3.5	25.1 ± 3.6	24.4 ± 3.4	0.327
Pack years(years)	10.8 ± 17.7	16.6 ± 21.8	4.2 ± 7.1	< 0.0001
Pain	55(43.6%)	39(61.9%)	16(25.3%)	0.005
Pain Intensity				
PRI score	2.0(1.0–4.0)	2.5(1.0–5.0)	2.0(1.0–2.0)	0.014
Sensory	2.0(1.0–2.0)	2.0(2.0–3.0)	2.0(1.0–2.0)	0.053
Affective	1.0(0–2.0)	2.0(0–3.0)	0	< 0.0001
VAS score	4.0(2.7-6.0)	4.5(2.8-6.0)	4.0(2.3–5.8)	0.163
PPI rank				
No pain(n%)	19(34.5%)	11(28.2%)	8(50.0%)	0.107
Mild discomfort(n%)	29(52.7%)	21(53.8%)	8(50.0%)	
Discomfort or worse(n%)	7(12.7%)	7(17.9%)	0	
Note: For comparison, χ^2 test was used for binary variables, and Student's t-test or Wilcoxon nonparametric test was employed for continuous variables; the bold P-values indicate statistical significance.				
Abbreviations: BMI, body mass index; PRI, pain rank index; VAS, visual an analogue scales; PPI, present pain intensity.				

The proportion of pain location in participants with HC group and ILD group showed significant difference in Fig. 2. In HC group, pain locations were more evenly distributed, however, chest(46.1%) accounted for the highest of overall pain duration in participants with ILD, other locations were joint(23.1%), limb(15.3%), back(10.3%), abdomen(2.6%), head and lumbar vertebra(2.6%). Most participants with pain problem experienced aching(25.6% in ILD group, 16.7% in HC group), heavy(33.3% in ILD group, 27.8% in HC group), shooting(33.3% in ILD group,22.2% in HC group) in pain sensory. In HC group, participants with pain also suffered hot-burning(11.1%) and cramping (11.1%).

ILD Only: Pain Versus No Pain

In the ILD group (Table 2), 39 (61.9%) participants were older than 60 years, 38(60.3%) were male, and the average BMI was $25.1 \pm 3.5 \text{ kg/m}^2$, which were no difference between the pain and the no-pain group. Among the 39(61.9%) ILD patients with pain, 14(35.9%) was diagnosed as IPF, 22(56.4%) was CTD-ILD and 3(7.7%) were other ILD (two patients with NSIP and one patient with IIP). The pain location in 14 IPF patients distributed in chest(57.1%), joint(21.4%), back(14.3%) and limb(7.1%) and in 25 non-IPF patients distributed in chest (40.0%), joint (24.0%), limb(20.0%), back(8.0%), abdomen(4.0%) and other parts (4.0%) including head and lumbar vertebra(Fig. 2). ILD patients with pain have more comorbidities than ILD patients without pain ($P = 0.040$). More ILD patients with pain had DLCo % of predicted $< 45\%$ than ILD patients with no-pain ($P = 0.022$). There was no obvious difference in FVC % of predicted and 6MWT in ILD patients with or without pain. When it comes to dyspnea, the mMRC score of 32(82.1%) ILD patients with pain was 2–4, higher than 13(54.2%) ILD patients without pain ($p = 0.023$). Besides, ILD participants with pain showed more anxious and depression according to the HADS, in anxious dimension 23(59.0%) patients with pain and 21(87.5%) patients without pain were assessed for no case, 16(41.0%) patients with pain and 3(12.5%) patients without pain were assessed for borderline or case ($P = 0.017$); in depression dimension 23(59.0%) with pain vs 20(83.3%) without pain were assessed for no case, 16(41.0%) with pain vs 4(16.7%) without pain were assessed for borderline or case ($P = 0.044$). From the different dimensions of HRQL measured by RAND-36, HRQL were significantly impaired in ILD participants with pain which can be found in SF Total score(93.0 ± 20.0 in ILD with pain, 107.5 ± 24.6 in ILD without pain, $P = 0.014$), and also performed in mental health ($p = 0.029$), bodily pain ($P = 0.049$), vitality($P = 0.043$), role emotional dimension ($P = 0.006$).

Table 2
Clinical characteristics and symptom burden of ILD patients with pain and no pain

	All patients N = 63	Pain N = 39	No-pain N = 24	<i>P value</i>
Age	61 ± 10	62 ± 10	61 ± 11	0.437
> 60 years	39(61.9%)	23(59.0%)	16(66.7%)	0.601
Gender(Male)	38(60.3%)	24(63.2%)	14(58.3%)	0.801
BMI(kg/m ²)	25.1 ± 3.5	25.4 ± 3.8	24.6 ± 2.8	0.093
Diagnosis				
IPF	24(38.1%)	14(35.9%)	10(41.7%)	0.882
CTD-ILD	34(54.0%)	22(56.4%)	12(50.0%)	
Others	5(7.9%)	3(7.7%)	2(8.3%)	
Smoker	28(44.4%)	19(48.7%)	9(37.5%)	0.441
Exposure history	23(36.5%)	17(43.6%)	6(25.0%)	0.181
Comorbidity	34(53.9%)	25(64.1%)	9(37.5%)	0.040
FVC, % predicted	74.5 ± 21.8	70.8 ± 15.8	80.3 ± 28.3	0.195
⊗80	32(65.3%)	22(73.3%)	10(52.6%)	0.138
≥ 80	17(34.7%)	8(26.7%)	9(47.4%)	
DLCO, % predicted	45.2 ± 14.2	44.1 ± 12.8	46.8 ± 16.5	0.525
⊗45	23(48.9%)	18(62.1%)	5(27.8%)	0.022
≥ 45	24(51.1%)	11(37.9%)	13(72.2%)	
6MWT	333.2 ± 112.2	329.7 ± 100.7	338.5 ± 129.0	0.801
6MWD < 250 m	9(14.2%)	5(55.6%)	4(44.4%)	0.893
6MWD ≥ 250 m	31(49.2%)	18(58.1%)	13(41.9%)	
6MWT SpO ₂ ,before(%)	94.5 ± 3.8	94.7 ± 3.4	94.1 ± 4.4	0.654
6MWT SpO ₂ ,later(%)	88.7 ± 8.4	89.9 ± 8.5	88.2 ± 8.5	0.809

Note: For comparison, χ^2 test was used for binary variables, and Student's t-test or Wilcoxon nonparametric test was employed for continuous variables; the bold P-values indicate statistical significance.

Abbreviations: 6MWT, Six minutes walking test; MMRC, Modified Medical Research Council Dyspnea Scale; HADS, Hospital Anxiety and Depression Scale; SF-36, Short Form-36

	All patients N = 63	Pain N = 39	No-pain N = 24	<i>P value</i>
mMRC score				
0–1(n%)	24(38.1%)	7(17.9%)	11(45.8%)	0.023
2–4(n%)	39(61.9%)	32(82.1%)	13(54.2%)	
HAD anxious				
No case(n%)	43(68.2%)	23(59.0%)	21(87.5%)	0.017
Borderline and case(n%)	19(30.2%)	16(41.0%)	3(12.5%)	
HAD depression				
No case(%)	43(68.2%)	23(59.0%)	20(83.3%)	0.044
Borderline and case(%)	20(31.7%)	16(41.0%)	4(16.7%)	
SF-36				
Social functioning	7.7 ± 2.5	7.3 ± 2.4	8.1 ± 2.4	0.265
Mental health	20.1 ± 5.8	18.9 ± 5.3	33.0 ± 6.1	0.029
Bodily pain	10.4 ± 4.3	9.5 ± 4.1	11.7 ± 4.2	0.049
Vitality	14.4 ± 5.6	13.2 ± 5.6	16.2 ± 5.5	0.043
Role emotional	3.8 ± 1.3	3.4 ± 1.1	4.3 ± 1.3	0.006
Physical functioning	17.1 ± 8.4	16.2 ± 8.1	18.6 ± 9.1	0.294
General health	16.3 ± 3.6	16.1 ± 3.5	16.8 ± 3.8	0.474
Role physical	6.2 ± 4.0	5.7 ± 3.7	7.0 ± 4.4	0.218
Health Transition	2.5 ± 1.1	2.4 ± 1.1	2.5 ± 1.2	0.661
SF Total score	98.7 ± 22.9	93.0 ± 20.0	107.5 ± 24.6	0.014
Note: For comparison, χ^2 test was used for binary variables, and Student's t-test or Wilcoxon nonparametric test was employed for continuous variables;the bold P-values indicate statistical significance.				
Abbreviations: 6MWT,Six minutes walking test; mMRC, Modified Medical Research Council Dyspnea Scale; HADS, Hospital Anxiety and Depression Scale; SF-36,Short Form-36				

Pain Characteristics Measured By Sf-mpq

Table 3 presents pain characteristics from SF-MPQ according to key variables. Patients aged < 60 years had a significantly higher score in PPI rank compared with older patients (P = 0.018). Patients with a

history of exposure to risk factors related to ILD had a significantly higher score in the sensory dimension ($P = 0.010$). Patients with higher mMRC score (range 2–4) showed greater pain intensity indicated by sensory dimension ($P = 0.014$), affective dimension ($P = 0.037$), PRI ($P = 0.006$). Patients whose 6MWD ≥ 250 m had a significantly higher score of pain in PPI rank than patients who has 6MWD < 250 m ($P = 0.001$). DLCo % of predicted $< 45\%$ had a significantly higher score in PPI rank ($P = 0.046$) than those whose DLCo % of predicted $\geq 45\%$. ILD patients assessed by HADS on no case showed lower pain intensity than patients assessed on borderline or case both in anxious dimension indicated by sensory dimension ($P = 0.002$), affective dimension ($P = 0.001$), PRI ($P = 0.001$), VAS ($P = 0.017$) or PPI ($P = 0.014$) and in depression dimension indicated by sensory dimension ($P = 0.002$), affective dimension ($P = 0.001$), PRI ($P < 0.0001$), VAS ($P = 0.013$) or PPI ($P = 0.046$).

Table 3
Pain characteristics from SF-MPQ according to key variables

	PRI score			VAS	PPI rank(N%)		
	Sensory	Affective	Total	Score	No pain	Mild discomfort	Discomfort or worse
Age							
≤60 years	1.5(0–3.0)	0(0–2.0)	2.5(0–5.0)	3.0(0–5.7)	14(38.9)	16(44.4)	6(16.7)
≥60 years	1.0(0–2.0)	0(0–2.0)	2.0(0–4.0)	3.0(0–5.0)	20(74.1)	6(22.2)	1(3.7)
<i>P-value</i>	0.308	0.828	0.607	0.456	0.018		
Gender							
Male	2.0(0–3.0)	0(0–2.25)	2.0(0–5.0)	3.0(0–6.0)	2(57.9)	10(26.3)	6(15.8)
Female	1.0(0–2.0)	0(0–2.0)	2.0(0–4.0)	3.0(0–4.5)	12(48.0)	12(54.5)	1(14.3)
<i>P-value</i>	0.344	0.969	0.541	0.906	0.124		
Exposure history							
No	0.5(0–2.0)	0(0–2.0)	1.0(0–4.0)	3.0(0–3.8)	22(55.0)	14(35.0)	4(10.0)
Yes	2.0(0–3.0)	1.0(0–4.0)	3.0(0–6.0)	5.0(0–6.0)	12(35.3)	8(34.8)	3(13.0)
<i>P-value</i>	0.010	0.057	0.505	0.143	0.931		
6MWD							
≤250 m	0.5(0–2.0)	0(0–2.0)	1.0(0–4.0)	3.0(0–3.8)	8(88.9)	1(11.1)	0
≥250 m	2.0(0–3.0)	1.0(0–4.0)	3.0(0–6.0)	5.0(0–6.0)	15(48.4)	15(48.4)	1(3.2)
<i>P-value</i>	0.849	0.633	0.406	0.824	0.001		
mMRC score							

Note: For comparison, χ^2 test was used for binary variables (*Fisher's test) and Student's t-test or Wilcoxon nonparametric test was employed for comparisons of two independent groups of continuous variables;

	PRI score			VAS	PPI rank(N%)		
	Sensory	Affective	Total	Score	No pain	Mild discomfort	Discomfort or worse
0-1	0(0-1.0)	0(0-0.5)	0(0-1.5)	0(0-3.4)	13(72.2)	4(22.2)	1(5.6)
2-4	2.0(0-2.0)	1.0(0-2.0)	3.0(1.0-5.0)	3.0(0-5.3)	21(46.7)	18(40.0)	6(13.3)
<i>P-value</i>	0.014	0.037	0.006	0.104	0.181		
FVC, % predicted							
⊗80	1.0(0-2.0)	0(0-2.0)	2.0(0-5.0)	3.0(0-5.0)	26(50.0)	12(37.5)	4(12.5)
≥ 80	1.5(0-2.0)	0(0-2.0)	2.0(0-4.3)	3.0(0-5.3)	20(38.5)	7(36.8)	0
<i>P-value</i>	0.728	0.908	0.955	0.605	0.395		
DLCO, % predicted							
⊗45	2.0(0-2.5)	0(0-2.5)	3.0(1.0-5.0)	3.0(0-5.3)	9(22.2)	10(55.6)	4(22.2)
≥ 45	1.0(0-2.0)	0(0-2.0)	1.0(0-4.0)	3.0(0-5.0)	16(66.7)	8(33.3)	0
<i>P-value</i>	0.231	0.517	0.099	0.333	0.046		
Note: For comparison, χ^2 test was used for binary variables (*Fisher's test) and Student's t-test or Wilcoxon nonparametric test was employed for comparisons of two independent groups of continuous variables;							

Discussion

Pain problems were prevalent in ILD patients but only few studies were carried out this problem. It is the first time that study were carried on to measure pain problem in ILD patients by SF-MPQ and a healthy control group, persons of similar age and gender without lung disease, was set in order to explore the characteristics of pain in ILD patients. In our present study, these findings indicate that pain problem is more prevalent in ILD patients. The main pain location in ILD patients was chest, joint and limb. The intensity of pain may be related to age, exposure history, mMRC score and DLCo, % of predicted. Compared to ILD patients with no-pain, patients with pain also experienced impaired healthy statues both physically and mentally, which might be predominantly caused by more limitations in daily functional.

Significant pain is not considered a typical feature of ILD. However, pain was common in both IPF and non-IPF ILDs, and the prevalence of this deficit was higher compared to the rates found in healthy controls. ILD group experienced higher pain intensity than HC group both in feeling and emotion dimension. Prevalence of pain was found higher in ILD compared to the general population(28,29). As was showed in our study more than half ILD patients(39/63) suffered pain in their daily life. We also noted that in the ILD individuals, the main pain locations were chest (46.2%) and joint (23.1%) among all ILD patients with pain. 57.1% IPF patients with pain declared having chest pain, which was higher than non-IPF(40.0%). Kaisa's study (7) also found that 31.2% (79/253) IPF patients experienced chest pain. But a British study (30) about 111 patients with fibrotic ILD found that most frequently reported painful areas of this subjects were the back (34%) and lower limbs (25%), and they were similar comparing IPF and non-IPF patients. According to literatures about pulmonary disease, the causes of chest pain remain unclear which can be related to pulmonary loss of elasticity of the parietal pleura, pathological bronchial fibrosis, thoracic vertebral deformity, costotransverse, intervertebral arthropathy and activities related to breathing and postural dysfunction (31,32). The incidence of joint pain in patients with CTD-ILD was higher than patients with IPF in our study, which was in line with the previous studies(33). It was reported that the prevalence of joint pain in CTD-ILD patients could be explained by the high anti-cyclic citrullinated peptide antibody (anti-CCP) positivity in patients(34). Further studies with larger sample sizes are required to confirm these findings.

Higher intensity of pain in ILD patients was also associated with many factors in our study, included younger age (< 60 years), exposure history of ILD risk factors, longer distance of 6MWD(≥ 250 m), higher mMRC score(2–4) and lower DLCo, % predicted, impaired SF-36 and HAD score. When undergoing severe dyspnea, patients normally gave an extra worse result of pulmonary function test, especially FVC, % predicted and DLCo, % predicted, and unsatisfied 6WMT, a practical and reliable measure of exercise tolerance that is widely used to assess the functional status of patients with IPF(35), which show the severity of the patient's current condition and reflect the current quality of life(36–38). It was reported in previous studies that the association between dyspnea severity in mMRC score and intensity of pain was reported in the previous studies(7,10), and the prevalence of chest pain in IPF patients had a positive linear relationship to increased mMRC score (7). In our study, compared to ILD patients without pain, the ILDs with pain did have lower DLCo pred % and higher mMRC score. Moreover, according to the results of MPQ, the pain intensity in ILD patients was greatly infected by the DLCo, % predicted and dyspnea severity. But we didn't see the relationship of pain intensity in ILD patients with the 6MWT SpO₂ and FVC, % predicted. The apparent paradoxical relationship between pain and lung function was also reported in lots of pain studies in COPD studies(12,39,40). This inverse relationship, probably also caused by selection bias, also can be interpreted that other symptoms like dyspnea were more distressing than pain, leading to more focus on dyspnea and less on pain, also causing patients to be reluctant to spontaneously report pain(41–43).

ILD Patients with pain also suffer worse quality of life and psychological deficits, like symptoms of anxiety and depression[44], [45]. The impaired HRQoL, according to results of SF-36, except for the poor total score, mainly performed on mental health, bodily pain, vitality and role emotional, which was

reflected in the results of SF-MPQ and HADs. We further found the pain intensity related to the degree of depression and anxiety. In addition to increasing dyspnea, many of the ILDs, such as sarcoidosis and connective tissue disease ILDs, are associated with extrapulmonary manifestations that may also lead to pain and add tremendous burden on HRQoL and mental health. Ryerson et al(9) reported the novel finding that baseline pain severity was associated with baseline depression score and particularly in the non-idiopathic pulmonary fibrosis population. Therefore, those indicated the need for healthcare providers, clinicians, and patients to pay greater attention to ILD patients with pain and consider strategies to minimize their impact on patients' quality of life, healthcare utilization, and prognosis.

□To our knowledge, this is the first study to investigate pain in patients with ILD including the intensity, location, type and associated factors. However, generalizability beyond this specific group and setting is limited, as only 126 participants from one hospital were included. There are some limits in our study results to a single time-point and does not allow us to describe the changes in pain or symptoms over time. Our study may be subjected to some selection bias and, as some patients at a very advanced stage of the disease or close to death were likely to be lost from the cohort. Possibilities of false negative due to small sample size and false positive due to multiple testing. Another limitation is that the score of those questionnaire may be mixed with subjective feeling ,especially the VAS score, and effected by individual verbal comprehension. The last but not the least, what were the accurate causes of pain in ILD patients couldn't be completely sure in our study. In the future, a larger sample of cross- sectional or cohort studies may be conducted on factors related to pain intensity to further verify these results.

Conclusion

In conclusion, pain is common in ILD patients and the pain intensity is associated with age, exposure history, 6MWD, mMRC score and DLCo, % predicted. ILD patients with pain have more possible to suffer depression, anxiety and impaired HRQoL. Knowledge of pain in ILD and intervention measures should be developed for both patients and clinicians about the pain management to improve the health-related quality of life at early stages of ILD .

List Of Abbreviations

ILD: interstitial lung disease, IPF: idiopathic pulmonary fibrosis, HRQoL: health related quality of life, SF-MPQ: McGill Pain Questionnaire, BPI: the Brief Pain Inventory short form, PFT: the pulmonary function test, 6MWT: six minutes walking test, SpO₂: pulse oximetry, MMRC: modified medical research council dyspnea scale, HADS: hospital anxiety and depression scale, SF-36: short form-36, PRI: pain rank index, VSA: visual an analogue scales, PPI: present pain intensity

Declarations

Ethics approval and consent to participate: This study was approved by the Medical Ethical Committee of the Second Xiangya Hospital of Central South University(Approved Number KL-2014-S009), and all

participants gave written informed consent.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: SQX contributed to the design of study, the acquisition, analysis and interpretation of data, the draft and revision of the manuscript. GT contributed to the design of study, the revision of the manuscript. All authors read and approved the final manuscript. SM, GW, ZY, DW and PYT contributed to the design of study, the revision of the manuscript. NSS and OYXL contributed to the acquisition, analysis and interpretation of data, revision of the manuscript. PH contributed to the conception and design of study, acquisition of data, revision and final approval for the publication of the manuscript. All authors have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

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Figures

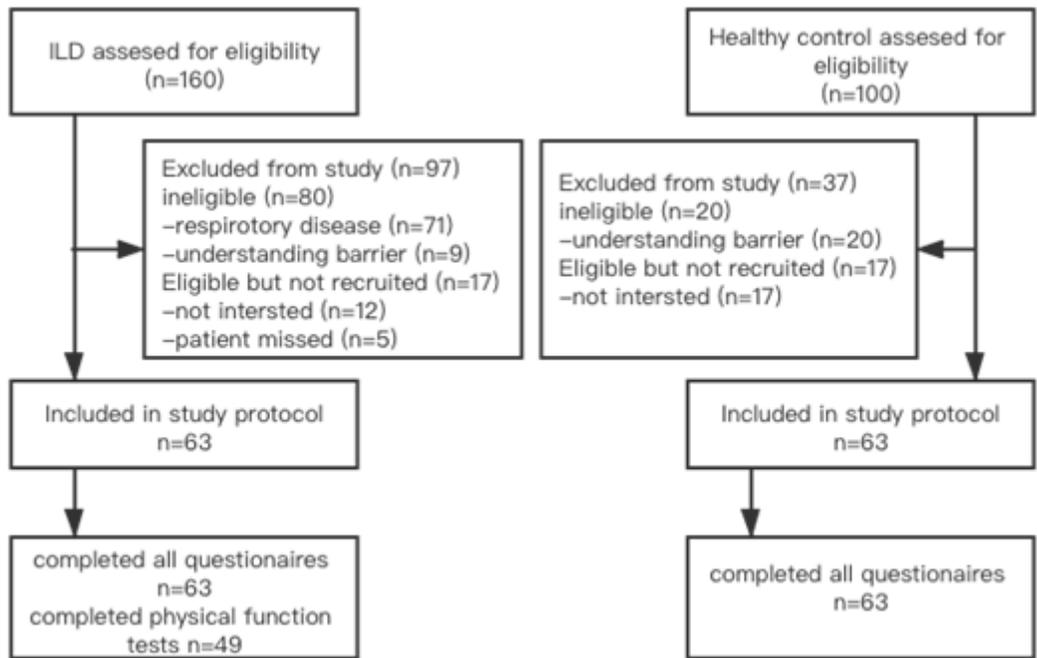


Figure 1

Flow diagram of study participants

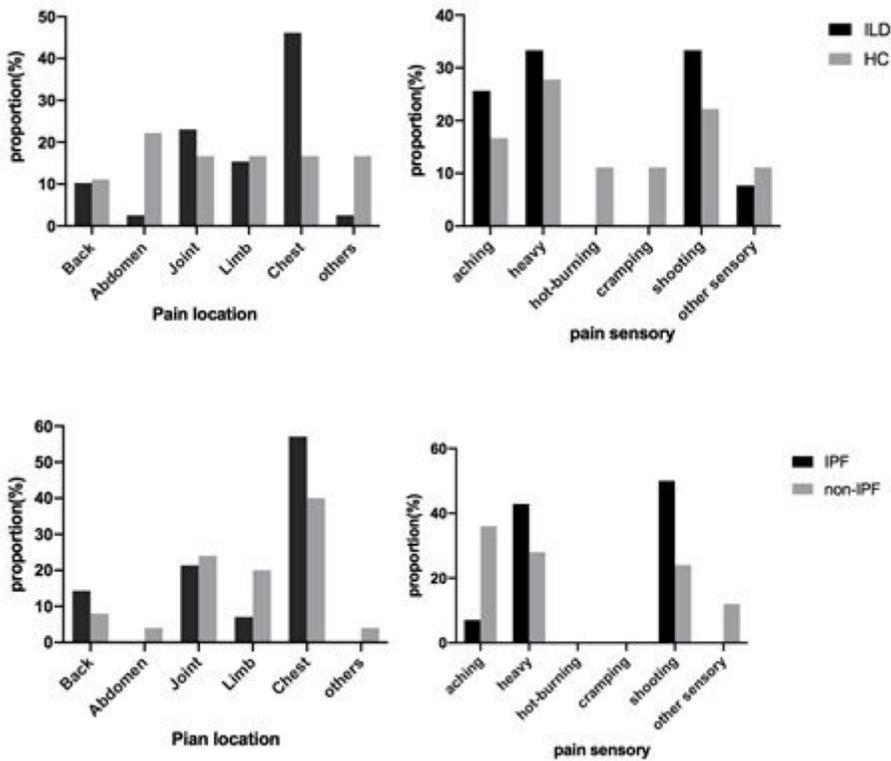


Figure 2

Pain location and sensory in all participants Notes: Other pain locations include head, lumbar vertebra. Other sensory include throbbing, tender, stabbing.