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Assessing feasibility of targeted primary care referrals for patients with clinical suspicion of interstitial lung disease using lung ultrasound: A prospective case finding study. The potential benefits of LUS utilization

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Abstract. *Background:* In Primary Health Care (PHC) many interstitial lung disease (ILD) cases may remain at diagnostic delay, due to their challenging presentation and the limited experience of general practitioners (GPs) in recognizing their early symptoms. *Objective:* We have designed a feasibility study to investigate early ILD case-finding competency between PHC and tertiary care. *Methods:* A cross-sectional prospective case-finding study was launched at two private health care centers of Heraklion, Crete, Greece, with a 1:1 patient recruitment ratio during nine months (2021-2022). After clinical assessment by GP, PHC attenders, who agreed to participate in the study, were referred to the Respiratory Medicine Department, University Hospital of Heraklion, Crete, underwent Lung Ultrasound (LUS) and those with an overall suspicion for ILDs underwent high resolution computed tomography (HRCT) scan. Descriptive statistics and chi-square tests were used. Multiple Poisson regression analysis was performed to explain positive LUS and HRCT decision with selected variables. *Results:* One hundred and nine patients out of 183 were finally included (54.1% females; mean age 61, SD: 8.3 years). Thirty-five (32.1%) were current smokers. Overall, two out of ten cases were assessed to need HRCT due to a moderate or high suspicion (19.3%; 95%CI 12.7, 27.4). However, in those who had dyspnea in relation to counterparts, a significantly higher percentage of patients with LUS findings (57.9% vs. 34.0%, p=0.013) was found, as in those who had crackles (100.0% vs. 44.2%, p= 0.005). Detected possible ILD provisional labelling cases were 6 and most importantly, 5 of those cases were considered highly suspicious for further evaluation based on LUS findings. *Conclusions:* This is a feasibility study exploring potentials by combining data of medical history, basic auscultation skills, as crackles detection, and inexpensive and radiation-free imaging technique, such as LUS. Cases of ILD labeling may be hidden within PHC, sometimes, much before any clinical manifestation.

Key words: pulmonary fibrosis, interstitial lung disease, lung ultrasound, screening, primary health care

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Introduction

Interstitial Lung Diseases (ILDs) are a group of typically chronic and diffuse parenchymal lung disorders, gradually progressive, characterized by damage to the lung parenchyma with varying patterns of inflammation and fibrosis (1). ILDs are roughly grouped into disorders of known and unknown

etiology. Idiopathic pulmonary fibrosis (IPF) is the prototype of idiopathic interstitial pneumonias, as it is the most common and the most well-studied (2,3). Despite a major and acknowledged limitation to estimate the global incidence of ILDs due to their wide heterogeneity, epidemiological data present an increasing incidence rate over the years (4,5). Many studies on IPF epidemiology show incidence variation, depending on various factors such as geographic distribution, with higher frequencies in Europe and North America (3-9 cases per 100.000 person-years) than in Asia and South America (less than 4 cases per 100.000 person-years), gender, as it is more common in men than women, and age, while older age groups are more vulnerable to the disease than younger age groups (6,7). Given the poor prognosis of patients with IPF, the early diagnosis is considered crucial, while a variety of factors, including the delayed access to tertiary health care have been correlated with worse prognosis (8,9). During the last decade, much attention has been given to recognize IPF patients, as two antifibrotic drugs, nintedanib and pirfenidone, are currently available and show to slow down disease progression, thus improving survival (10,11).

However, ILDs remain an unclear and sibylic topic for general practitioners (GPs), being often underdiagnosed (12, 13). The main reason for that seems to be the rarity of the disease, in combination with the limited experience of the GPs in distinguishing its initial clinical manifestations, as the symptoms are non-specific (13). Many times, the only notion for many physicians about ILDs is recalled from their undergraduate theoretical knowledge without any clinical experience or involvement with ILD sufferers (8). At a primary care level, the fundamental diagnostic tool is the physical examination in combination with a detailed personal and family history (14). Inspiratory velcro-like crackles on auscultation, chronic dry cough, and exertional dyspnea in elderly patients should aware physicians (14). Affected lungs show restrictive ventilatory patterns on spirometry, as the disease increases lung stiffness, resulting in the reduction of Total Lung Capacity (TLC) (15). Additional spirometric parameters such as reduction of Forced Vital Capacity (FVC) and Diffusing Capacity of the lung for carbon monoxide (DLco) should amplify the suspicion of ILD (15). At tertiary centers, established protocols based on the combination of clinical, functional, imaging and if needed, histological data, such as ATS/ERS/JRS/ALAT clinical practice guideline and Fleischner white paper consensus statement are undoubtedly used for final diagnosis (3,16–18). Although chest high resolution computed tomography (HRCT) is considered the gold-standard for the radiological evaluation of ILDs, its use is hampered by its cost, availability, and the risks associated with ionizing radiation (19). These factors imply that HRCT is a debatable screening tool to identify ILD in the general population.

Lung ultrasound (LUS) constitutes an imaging procedure of the lung parenchyma using the physical principles of sound waves, and it may represent a promptly available technique in comparison to HRCT for ILD evaluation (20). It is non-invasive, radiation-free, prompt, and easily repeatable, resulting in its significant everyday clinical role (21). B-lines correspond to the sonographic hallmark of pulmonary interstitial syndrome and their presence is attributed to partial lung deaeration and extension of the interstitial space, either due to fluid accumulation or collagen deposition (22). This sign demonstrates high diagnostic accuracy, with the number of B-lines showing a strong association with the extent of the fibrotic lung pattern on HRCT and the disease severity based on pulmonary function tests (PFTs) (23,24). Irregular/fragmented and thickened (by more than 3mm) pleural line, represents also an ultrasound finding of interstitial syndrome, and is considered to differentiate it from cardiogenic pulmonary congestion (25).

This study aims to explore the interface between primary and tertiary care potentials, to assess ILD early case-finding capacity, and to overall interconnect knowledge of similar future research initiatives in terms of feasibility. This conceptual approach may offer information on how to increase diagnostic likelihood and clinical suspicion, expedite evidence-based referrals, and consequently facilitate access to appropriate care, by earlier improvement of the cooperation between GPs and chest physicians to jointly share skills and competency for patients' benefit.

Methods

Study design

We conducted a cross-sectional prospective case finding study to collect data from patients at

an urban location of Heraklion, Crete, Greece. The main purpose was to attempt ILD cases' eventual identification among the targeted population group. Two private primary health centers enrolled patients with a recruitment ratio 1:1, during two weekly sessions, regardless of prior visits and by using inclusion criteria, as described below. According to the GPs clinical assessment, all the patients who accepted, after written informed consent, were referred to the unique tertiary hospital of the island of Crete for further evaluation. Lung ultrasound (LUS) was performed to all of them and HRCT to the most suspicious cases for ILD. The overall recruitment and referral period was 9 months between 2021 and 2022. The Department of Respiratory Medicine of the tertiary hospital involved has a major clinical and research interest, with international recognition in ILDs and primary health care field, which is well established with much contribution to community health for decades, through the Clinic of Social and Family Medicine, University of Crete (http://old.fammed.uoc.gr/).

Inclusion and exclusion criteria

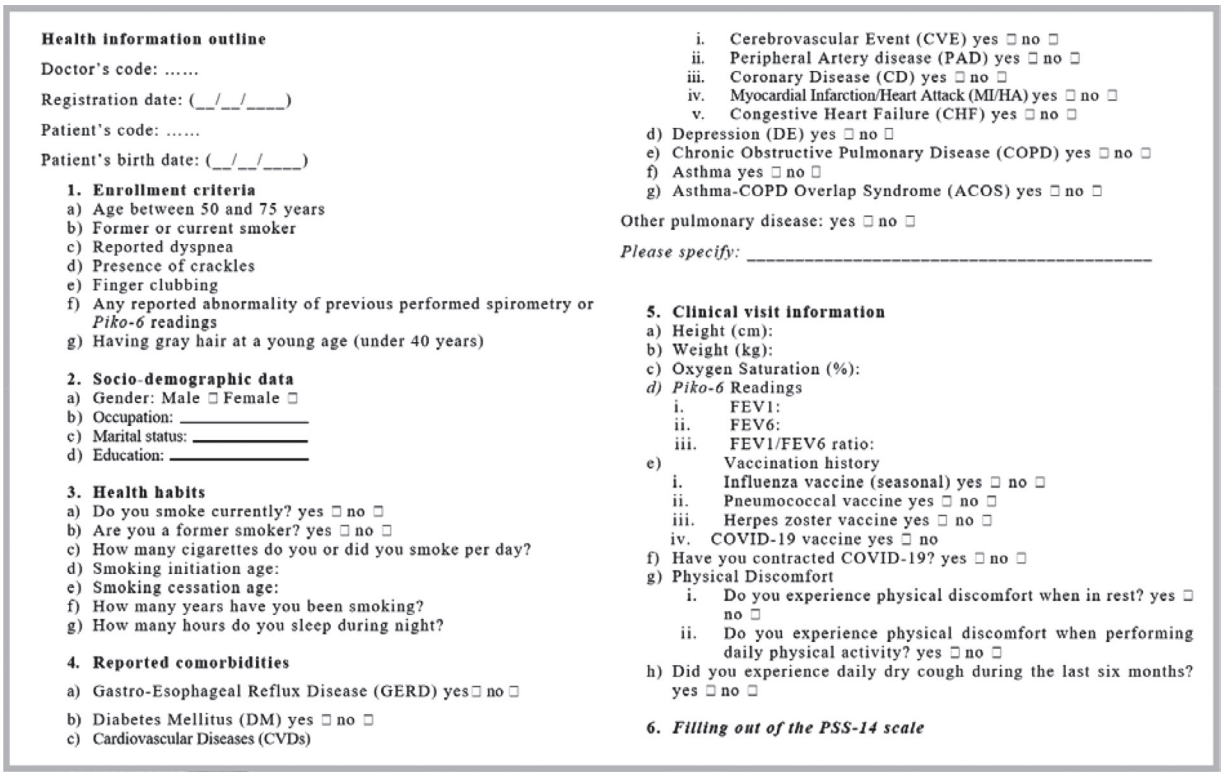
Approached patients were 281, and the main age target group was between 45 and 75 years old. Patients' selection was carried out by trained and adequately informed GPs, with at least 15 years of clinical activity after the end of their formal specialization. Patients were invited to be enrolled in the study if they had met predefined inclusion criteria. The first criterion was age as described above with a two-tail extension of five years in case of more than two other co-existing of the following criteria. Namely, previous or current smoking habit, self-reporting dyspnea at current visit, detection of bilateral crackle sounds, and/or of finger clubbing. All participants were asked if able to comply with the study requirements. Criteria to exclude patients were: a) request of urgent care, b) current history of low respiratory tract infection, c) having severe mental or physical problems. Once assurance with emphasis on privacy had been provided, written informed consent was obtained. Through a face-to-face interview, the GP registered responses. Patients' information was uploaded in an electronic platform with an encoded ID in order to guarantee personal data protection and safe storage. Processing and analysis of information was strictly performed in order to avoid any tracing of individual participants. Patients who have been recruited were 225. Patients who were able by fulfilling criteria and agreed to participate were 183.

Measures and evaluation tools

We developed a questionnaire sheet to collect information on several variables such as sociodemographic characteristics, patients' health profile, and physical examination findings, as seen in Figure 1. The clinical profile was drawn from the presence of previously reported or confirmed respiratory diseases, known risk factors for pulmonary morbidity such as smoking habit, night-time sleep duration, body mass index, daily activity discomfort, dry cough during the last 6 months and comorbidities. The clinical examination focused on the detection of crackle sounds, Piko-6 readings, oxygen saturation and the assessment of Perceived Stress Scale (PSS-14) (26,27). Piko-6 was used as an easy method to assess FEV1 (Forced Expiratory Volume in the first second) and FEV6 (Forced Expiratory Volume in 6 seconds) abnormal readings, awareness for obstructive lung disease was increased (28). The second part of the study procedure included patients' referrals to the tertiary hospital for additional evaluation, by respiratory medicine specialists within the ILD outpatient clinic. LUS was performed, and in case of medium and high suspicion (orange and red flag cases), then a chest HRCT was performed to confirm a diagnosis of ILD in the mentioned cases. After LUS and HRCT request in the selected patients, they were invited for further consultation and a provisional diagnosis was labeled.

Lung ultrasound

A senior consultant pulmonologist with 10 years of experience in LUS performed all ultrasound examinations, using an M7 diagnostic ultrasound system (Mindray) equipped with a 5-8-MHz micro-convex transducer. Imaging parameters were manually adjusted to ensure maximal contrast between the examined structures. LUS was performed by placing the transducer on the examined lung intercostal space, while moving along anatomic reference lines, yielding a 14-lung intercostal space US assessment of the anterior and posterior chest, as previously described (23). A B-line is defined as a vertical, hyperechoic, wedge-shaped signal that originates from the pleural



Health information outline

Doctor's code: .....

Registration date: (__/__/____)

Patient's code: .....

Patient's birth date: (__/__/____)

1. Enrollment criteria
a) Age between 50 and 75 years
b) Former or current smoker
c) Reported dyspnea
d) Presence of crackles
e) Finger clubbing
f) Any reported abnormality of previous performed spirometry or *Piko-6* readings
g) Having gray hair at a young age (under 40 years)

2. Socio-demographic data
a) Gender: Male ☐ Female ☐
b) Occupation: _____
c) Marital status: _____
d) Education: _____

3. Health habits
a) Do you smoke currently? yes ☐ no ☐
b) Are you a former smoker? yes ☐ no ☐
c) How many cigarettes do you or did you smoke per day?
d) Smoking initiation age:
e) Smoking cessation age:
f) How many years have you been smoking?
g) How many hours do you sleep during night?

4. Reported comorbidities
a) Gastro-Esophageal Reflux Disease (GERD) yes ☐ no ☐
b) Diabetes Mellitus (DM) yes ☐ no ☐
c) Cardiovascular Diseases (CVDs)
i. Cerebrovascular Event (CVE) yes ☐ no ☐
ii. Peripheral Artery disease (PAD) yes ☐ no ☐
iii. Coronary Disease (CD) yes ☐ no ☐
iv. Myocardial Infarction/Heart Attack (MI/HA) yes ☐ no ☐
v. Congestive Heart Failure (CHF) yes ☐ no ☐
d) Depression (DE) yes ☐ no ☐
e) Chronic Obstructive Pulmonary Disease (COPD) yes ☐ no ☐
f) Asthma yes ☐ no ☐
g) Asthma-COPD Overlap Syndrome (ACOS) yes ☐ no ☐

Other pulmonary disease: yes ☐ no ☐

Please specify: _____

5. Clinical visit information
a) Height (cm):
b) Weight (kg):
c) Oxygen Saturation (%):
d) Piko-6 Readings
i. FEV1:
ii. FEV6:
iii. FEV1/FEV6 ratio:
e) Vaccination history
i. Influenza vaccine (seasonal) yes ☐ no ☐
ii. Pneumococcal vaccine yes ☐ no ☐
iii. Herpes zoster vaccine yes ☐ no ☐
iv. COVID-19 vaccine yes ☐ no
f) Have you contracted COVID-19? yes ☐ no ☐
g) Physical Discomfort
i. Do you experience physical discomfort when in rest? yes ☐ no ☐
ii. Do you experience physical discomfort when performing daily physical activity? yes ☐ no ☐
h) Did you experience daily dry cough during the last six months? yes ☐ no ☐

6. *Filling out of the PSS-14 scale*

Fig. 1. Clinical information sheet within primary care consultation.

line, extends deeply to the edge of the screen and moves synchronously with the pleural line during the breathing cycle (29). Alveolar interstitial syndrome is suspected by the presence of more than 3 B-lines in at least 1 intercostal space (30). This finding, adding the presence of irregular/fragmented or thickened (more than 3mm) pleural line, defined the medium suspicion for ILD in our study. High suspicion was noted when more than 3 B-lines were described in at least 2 intercostal spaces, along with the aforementioned pleural abnormalities in those spaces. These findings cleared the decision for further diagnostic procedures, which were of higher cost and more technically demanding such as chest HRCT.

Ethical considerations

Informed verbal and written consent were obtained from all participants before data collection. All diagnostic examinations were carried out in the context of the involved clinical setting, according to defined medical ethics. Ethical approval has been received from the Research Ethics Committee of University of Crete (REC-UoC) (30.11.2020/205) and executive clearance for hospital outpatient service facility was granted through a patient registry permission (16.12.2020/18117). Involved physicians and researchers signed confidentiality forms. The research was completed in compliance with the Helsinki Declaration.

Statistical analysis

The analysis of data was performed using SPSS software (IBM Corp. Released 2021, IBM SPSS Statistics for Windows, v.28.0, Armonk, NY: IBM Corp.). Frequency distributions of the specific features of the attendees within PHC facilities were calculated. For reasons of direct comparison of distributions, 95% confidence intervals (95% CIs) were calculated. The Perceived Stress Scale (PSS-14) was tested for reliability using the Cronbach-alpha coefficient. Chi-square tests were also followed for assessing the relationship of the health assessment information, clinical and bio-metric data of the patients-visitors with the revealed findings of lung ultrasound imaging (*absence of any findings* versus *with any present finding*). Highly suspicious LUS

findings were specified within result tabulation. Regressed correlations between lung ultrasound findings (*no/yes*), a posterior overall rating from chest physician about low, medium or high suspicion for ILDs and the consequent referral for HRCT (*no/yes*), for the cases with medium and high suspicion, in relation to the clinical history and relevant data, were assessed with the Poisson regression (estimation of unstandardized β coefficients through Generalized Linear Modeling), with an assessment of variable main effects. The critical value was set at 0.05.

Results

Primary health care assessment

The number of patients who initiated and concluded both study phases were 109 from 183 enrolled at primary care facilities. Table 1 shows patients' features recorded in the private PHC settings. Among them, most were women 54.1% and 45.9% were men. One hundred and five participants were older than 50 years. The distribution of the smoking habits among attendees was as follows: 52 were ex-smokers, accounting for 47.7%, 35 were currently smokers (32.1%) and 22 were non-smokers (20.2%). The mean night-time sleep hours reported were 6.4 (SD: 1.2). Most patients-attendees were either overweight or obese, representing 47.7% and 37.6% respectively. The mean oxygen saturation was 96.6% (SD: 1.6), while 22 patients had readings lower or equal to 95 (20.6%). Lung function readings obtained by piko-6 uncovered mean spirometry values of FEV1 and FEV6 being 2.20 (SD: 0.64) and 2.64 (SD: 0.63) respectively, while the FEV1/FEV6 ratio counted for 0.83 (SD: 0.11). Thirty-nine cases were associated with a Perceived Stress Scale (PSS-14) score indicating a medium/high stress level (PSS-14 score: 22-56), accounting for 35.8% (Table 1).

The health profile of the 109 patients of the PHC setting is shown in Table 2. Presence of co-morbidities was described, including Chronic Obstructive Pulmonary Disease (COPD), Asthma, Asthma-COPD Overlap Syndrome (ACOS), Gastroesophageal reflux disease (GERD), cardiovascular disease (CVD), Depression (DE), Diabetes Mellitus (DM), Cerebrovascular Event (CVE) and Peripheral Artery Disease (PAD). Thirty-one individuals (28.4%) had one of the selected co-morbidities, 23 had two co-morbidities (21.1%), 14 had more than three co-morbidities (23%) and 30 had none (27.5%).

A chronic respiratory disease (CRD) history was observed in 34.8% of patients, 25.7% self-reported dyspnea as inclusion criterion. Physical discomfort was also self-reportedly registered, with 70 out of 109 patients declaring having none (64.2%). Furthermore, 22.4% reported having daily dry cough during the last 6 months before their examination.

Chest physician evaluation in the tertiary center

The flow chart of the study population is presented in Figure 2. Information retrieved from chest physician consultation is shown in Table 3. Any recent recalled experience of dyspnea was reported admittedly by 57 participants, representing a percentage of 53.3% (95%, CI 43.8, 62.5). Crackles were detected in 7 patients (6.9%), whereas finger clubbing was not found in any patient. ILD clinical suspicion was classified as low, moderate or high, by the respiratory physician, based on clinical assessment, including all the aforementioned factors, and the findings of LUS. Thirteen patients were considered at medium risk (11.9%) and 9 at high risk for ILDs presence (8.3%). A medium risk patient's findings were consistent with post-COVID lesions; thus, another follow-up pathway was proposed (Fig. 2). Eight out of ten patients were found to have low ILD suspicion (79.8%), while two out of ten cases were assessed to have moderate or high ILD suspicion (19.3%) based on clinical and LUS assessment. Interestingly, in those who had dyspnea in relation to counterparts, a significantly higher percentage of patients with LUS findings (n=33, 57.9% vs. n=17, 34.0%, p=0.013) was found, as in those who had crackles (n=7, 100.0% vs. n=42, 44.2%, p= 0.005), as shown in Figure 3. Following this evaluation, an HRCT scan was deemed necessary for 21 participants representing a percentage of 19.3%.

Without findings: low risk, with findings: medium and high risk for ILD.

The multiple Poisson regression analysis suggested that current smoking habit is significantly associated with the need for HRCT (β=1.00, p=0.041, 95% CI) when compared to other determinants. Furthermore, significant interaction between the detection of crackle sounds and the need for HRCT was found (β=1.45, p=0.039) (Table 4). No other significant associations were identified between the selected variables and LUS findings or the need for HRCT.

Table 1. Features of 109 patients-attendees within primary care setting.

		n	%	mean	st. dev.	min, max
Gender	*male*	50	45.9			
	female	59	54.1			
Age, *years*	*50+*	105	96.3	61.0	8.3	39, 88
Smoking	*Non-smoker*	22	20.2			
	Ex-smoker	52	47.7			
	Currently smoker	35	32.1			
Packyears		86		35.4	29.8	0.1, 172.0
Night-time sleep hours	*<6.0*	18	16.5	6.4	1.2	3.0, 10.0
Body Mass Index, (*kg/m²*)	*normal*	16	14.7	29.5	5.3	19.4, 50.6
	overweight	52	47.7			
	obese	41	37.6			
Oxygen saturation (%)		107		96.6	1.6	
	≤95	22	20.6			
FEV1 (Lt)		86		2.20	0.64	
FEV6 (Lt)		86		2.64	0.63	
FEV1/FEV6 ratio		86		0.83	0.11	
Perceived stress (PSS Scale)	*22-56 ή medium/high stress level*	39	35.8	20.0	7.0	3, 40

The PSS Scale (4th, 10th or 14th form) is not a diagnostic tool and therefore does not involve cut-offs. Indicatively, the current sample shows the limits 22-56 as moderate / high levels of stress and correspond to 14-40 of the 10th form (moderate / high perceived stress, https://das.nh.gov/wellness/docs/percieved%20stress % 20scale.pdf). Its reliability was found with Cronbach α=0.790.

Table 2. Health profile of 109 patients-attendees within primary care setting.

		n	%
Co-morbidity (COPD, Asthma, ACOS, GERD, CVD, DE, DM, CVE, PAD) (see in text)	*None*	30	27.5
	1	31	28.4
	2	23	21.1
	3+	14	23.0
Chronic respiratory disease (CRD) history	*yes*	38	34.8
Self-reported dyspnea (as recruitment criterion)	*yes*	28	25.7
Physical discomfort during activities (Rest, Daily Physical Activity)	*None*	70	64.2
	In one	26	23.9
	In two	13	11.9
Presence of daily dry cough during the last 6 months (n=107)	*yes*	24	22.4

Further evaluation and provisional diagnosis of the identified cases

In Table 5, a case finding list and a provisional outpatient clinic diagnosis are provided. All cases presented in this Table were classified either as medium or high risk, given that their LUS unveiled abnormal findings, based on the mentioned criteria. Six cases of possible ILD provisional labelling are listed, comprising an untreated Sarcoidosis case, with usual interstitial pneumonia (UIP) pattern, two cases of mediastinal lymphadenopathy and micronodules, likely to be Sarcoidosis, one case of ground glass opacities/drug-induced ILD, one case

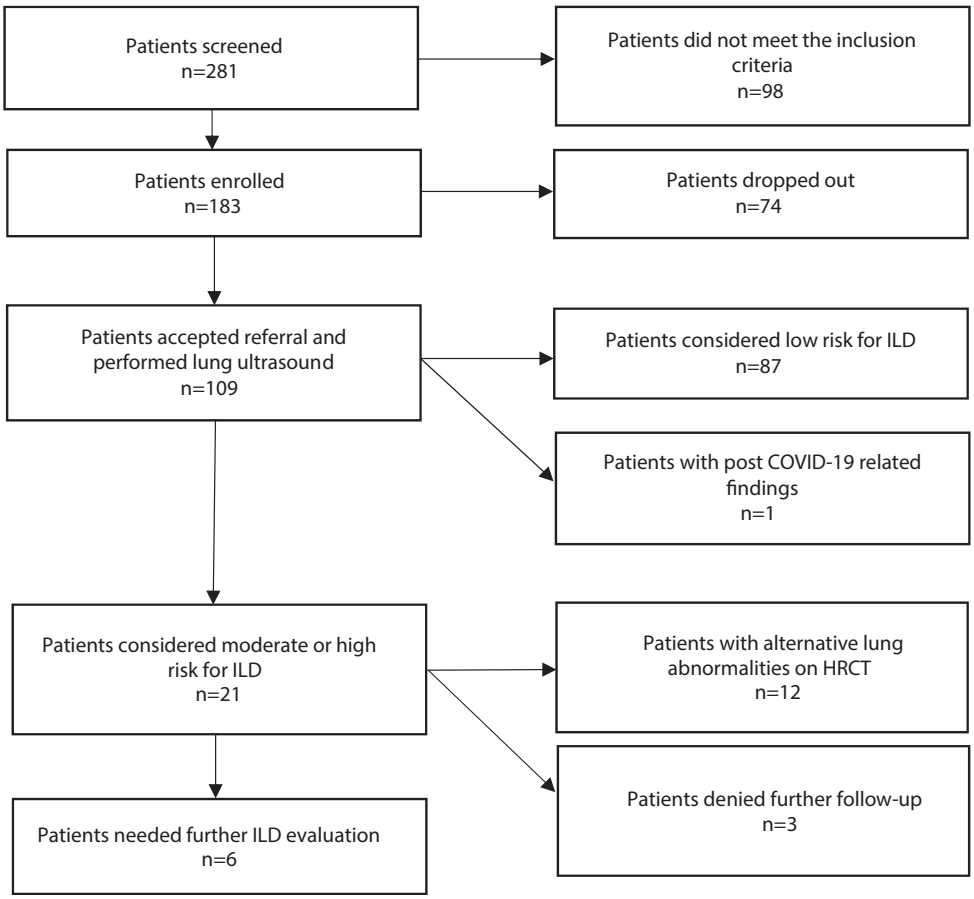


Fig. 2. Flow chart of the study population.

Table 3. Relevant clinical and lung ultrasound information from chest physician consultation of 109 patients-attendees.

		n	%	95%CI
Crackles (n=102)	*yes*	7	6.9	3.1, 13.0
Finger clubbing (n=107)	*yes*	0	0%	
Dyspnea (any experience) (n=107)	*yes*	57	53.3	43.8, 62.5
ILD suspicion	*low*	87	79.8	71.6, 86.5
	medium	13	11.9	6.9, 19.0
	high	9	8.3	4.2, 14.5
Need for HRCT*	*yes*	21	19.3	12.7, 27.4

*One patient was excluded from count due to post-COVID lung manifestations.

of interstitial lung abnormalities, and one case of possible interstitial pneumonitis with autoimmune features. Importantly, we realized that five from six cases that needed further ILD labeling attention were considered in the high-risk group based on the LUS findings.

Discussion

Our main finding is that current smoking habit and crackles (Table 4) mainly explain the overall decision for requesting a chest HRCT. Although positive findings with LUS have not been correlated with

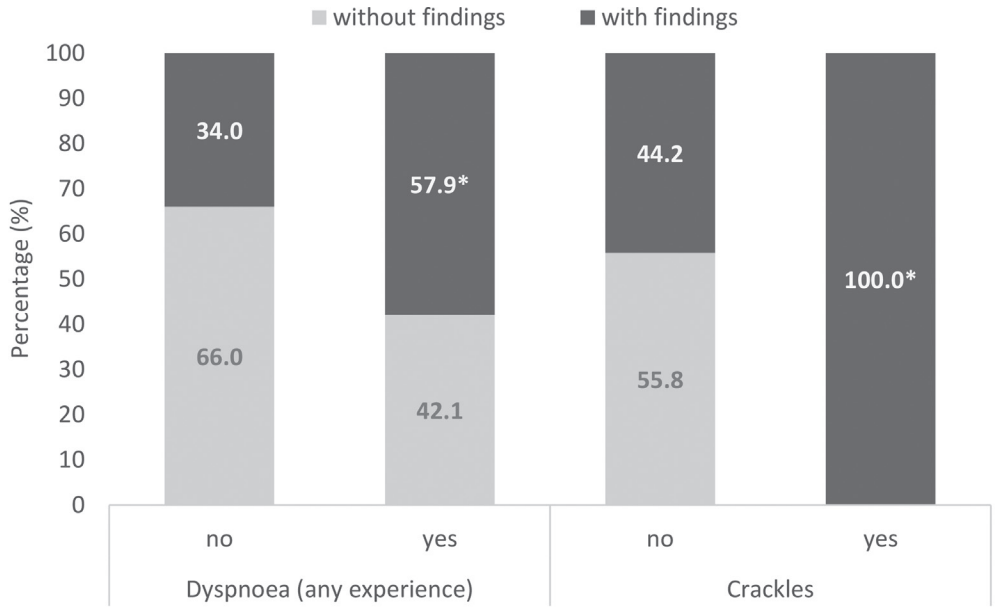


Fig. 3. Lung ultrasound information from chest physician consultation of 109 patients-attendees.

Table 4. Multiple Poisson regression analysis of lung ultrasound findings and referrals for HRCT among 99 patient-attendees.

		Lung ultrasound findings (yes *vs.* no)		Need for HRCT (yes *vs.* no)	
Prognostic factors		**β (95%CI)**	**p-value**	**β (95%CI)**	**p-value**
Primary Health Care	**Gender** (1:male, 2:female)	-0.02 (-0.72, 0.67)	0.952	0.05 (-1.20, 1.30)	0.941
	Age (years)	-0.02 (-0.06, 0.02)	0.300	-0.04 (-0.11, 0.03)	0.268
	Smoking habit (1: non smoker, ex smoker, 2:currently smoker)	0.19 (-0.42, 0.79)	0.546	**1.00** (0.04, 1.96)	0.041
	Co-morbidity	0.07 (-0.17, 0.32)	0.564	-0.06 (-0.47, 0.35)	0.779
	Physical discomfort (Number in two activities)	-0.07 (-0.55, 0.40)	0.756	0.06 (-0.68, 0.80)	0.877
	Covid-19 contraction (1:no, 2:yes)	-0.65 (-1.71, 0.41)	0.226	-0.81 (-2.91, 1.28)	0.446
	Presence of daily dry cough during the last 6 months (1:no, 2: yes)	0.13 (-0.60, 0.85)	0.732	0.23 (-0.86, 1.32)	0.683
Tertiary care	**Dyspnea (any recent recalled experience)** (1:no, 2:yes)	0.36 (-0.32, 1.05)	0.298	0.78 (-0.49, 2.06)	0.228
	Crackles (1:no, 2:yes)	0.63 (-0.32, 1.57)	0.197	**1.45** (0.07, 2.82)	0.039
	CRD history (1:no, 2: yes)	-0.01 (-0.73, 0.71)	0.972	0.30 (-0.89, 1.50)	0.619

Generalized linear modeling: Poisson regression (log link function).
β, unstandardized regression coefficient; 95%CI, 95% confidence interval

Table 5. Case finding list* and provisional outpatient clinic diagnosis.

Patient code	Gender	Age	Smoking Habit	Pack years	BMI	Cough last 6 months	Comorbidities	PSS-14 score	LUS findings	ILD on HRCT (parenchymal lesions)	HRCT Findings / Provisional outpatient clinic diagnosis
NK030	M	72	smoker	100	27.8	+	1	17	++	-	Airway disease – bronchiectasis / COPD
NK045	F	65	smoker	60	29.4	+	1	11	++	-	Airway disease – bronchiectasis / COPD
XP051	F	51	smoker	30	30	_	1	36	+	-	Airway disease - air trapping / COPD
XP053	M	60	ex smoker	40	27.9	+	0	20	++	+	**UIP pattern / Untreated Sarcoidosis**
NK056	F	62	non smoker	0	27.6	+	1	30	+	-	Airway disease – air trapping / asthma or airway disease in the context of Rheumatoid Arthritis
XP001	M	62	ex smoker	35	26	_	0	10	++	-	**Mediastinal lymphadenopathy and micronodules / Sarcoidosis**
NK016	M	56	smoker	60	23.4	+	0	21	+	-	Airway disease – emphysema / COPD
NK044	M	71	ex smoker	30	31	+	1	3	+	-	Airway disease - tree in bud /Asthma
XP084	M	76	smoker	60	27.4	_	0	23	++	-	Bronchiectasis – linear atelectasis / COPD
NK071	M	53	smoker	60	22.1	+	0	15	++	-	**Mediastinal lymphadenopathy and micronodules /Sarcoidosis**
NK061	M	76	ex smoker	60	26	_	1	24	++	+	**Ground glass opacities / Drug induced-interstitial lung disease**
NK046	F	65	smoker	80	33.3	_	1	35	+	-	Mild ground glass opacities -linear atelectasis /COPD
XP060	M	61	smoker	60	28.1	+	0	22	+	-	Airway disease / COPD
XP052	M	55	smoker	80	22.4	_	0	20	++	-	Airway disease / COPD
XP100	M	62	non smoker	0	33.59	_	1	23	+	-	Airway disease / Asthma
XP032	F	67	non smoker	0	27.4	_	2	13	++	+	**Interstitial lung abnormalities - early reticulation / Interstitial lung disease under investigation**
NK036	F	40	smoker	16	30.8	_	1	27	+	-	Airway disease / Asthma
NK070	F	48	smoker	23	27.9	_	0	23	+	+	**Bronchiolitis/ Possible interstitial pneumonitis with autoimmune features**

*3 patients denied further consultation having a free for ILD imaging suspicion within HRCT and did not wish to include their data for publication purposes at the final study phase.
For LUS findings:
+: any LUS finding
++: highly suspicious LUS findings, as described in the text

any of the tested variables in the Poisson model, it appears that, from primary care information extraction, current smoking habit significantly correlates with the overall clinical decision for a chest HRCT, then taken by chest physicians. Additionally, in regard to crackles, it appears to well correlate with such demand by specialized chest physicians. Any recent experience of dyspnea and crackles are strongly related with LUS findings. In that manner, we showed that LUS findings well correlate with dyspnea and crackles; but only crackles significantly continue to explain chest physician's decision for requesting a chest HRCT, in the multilinear model adopted. This finding is in accordance with many studies which highlight the importance of detection of velcro type crackles as a prodromic indicator of ILDs (14,31). We can likely think that if current smoking, crackles detection and LUS were simultaneously ticked, as information add-on, from the same physician's hand during a first or early contact, the benefits in terms of prompt and targeted referrals would be synergistic.

This is a feasibility study which revealed that flows from primary to tertiary care referrals are possible and plausible. We showed that about one third of approached patients did not agree to follow a research invitation that aims to establish a preclinical diagnosis, but we also proved that the connection between primary and tertiary care share a viability trend of more than 50% if well assisted. Current literature emphasizes the need for a well-articulated, integrative and co-operative approach in the context of collaboration between health care providers (32). In a recent study in Italy, opportunities for improvement were identified in the definition of criteria that justify the decisions of GPs to refer a patient with suspected symptoms to a specialized pulmonologist and then to an ILD center (33). Moreover, in a recent published survey (34), performed in both GPs and pulmonologists, both respondent sources were likely to cite testing prior to diagnosis and limited primary care physician (PCP) knowledge about IPF as factors driving delays. Although pulmonologists cited limited knowledge about IPF among PCPs as a factor contributing to delays, they also referenced imaging/testing issues as sources of delay, making a diagnosis without adequate testing and the absence of HRCT (31). They were also more likely than PCPs to indicate that allowing symptoms to persist for 6 to 8 weeks without imaging is a factor contributing to delays (31). Furthermore, in the INTENSITY survey, about 28% of respondents were referred to a specialist after the first visit to a PCP, but roughly 30% reported four or more visits to a PCP prior to being referred to a specialist (35). Last but not least, in a US study, in more than one-third of the beneficiaries, the first pulmonologist evaluation occurred more than three years before IPF diagnosis, whereas an increase in the number of pulmonologist visits occurred just before diagnosis (36). Similarly novel was the finding that almost one-third of the beneficiaries had their first CT scans more than three years before IPF diagnosis (33).

In our study, we found six overall cases of possible ILD provisional labelling (where one untreated denied previous diagnosis of sarcoidosis, two earlier-stage ones and three cases that deserve further consultation to gain ILD diagnostic clarity in the near future). Importantly, five of six cases were listed as highly suspicious for further evaluation based on LUS findings (Table 5). The rest of the eighteen cases listed mainly showed a provisional diagnosis of lung chronic disease towards obstructive patterns, as shown in Table 5. This fact proves the hypothesis that if referrals are guided, the diagnostic likelihood increases. If we consider that frequencies of the disorders searched are low, it is clear that likelihood of numbered provisional diagnoses is summed up in the pool of patients selected with the imaging and clinical algorithm adopted.

In the study by Bellou et al. (37), the effects of tobacco use and the intensity of smoking habit were described as an independent factor causing IPF. In addition, Moran-Medoza et al. (38) showed a high prevalence of crackles sounds in patients with ILD, being present on chest auscultation, even in 98% of the patients who suffer from IPF. However, there are limited data in the literature concerning the benefits of LUS utilization by GPs in order to enhance the clinical possibility of earlier suspicion of ILD cases (39). LUS remains an inaccessible diagnostic tool for PCPs and an underutilized skill for many chest physicians. This fact seems to play a neglected role in the delaying of any first or early diagnostic contact among care users. Therefore, the present study, by combining those two clinical characteristics with LUS findings, proved the feasibility of an evidence guided referral for advanced evaluation. In our study, most patients-participants (96%) were over fifty years old indicating a potential vulnerability, as ILDs occurrence increases from such age and greater, a finding

that is plausibly described by López-Muñiz Ballesteros et al. (40). It is also common for the patients with ILDs to present various comorbidities that may synergistically affect the diagnosis and prognosis. Series of studies (41–45) cite certain co-morbidities that frequently accompany ILDs, including COPD, cardiovascular disease, diabetes mellitus, obesity, gastroesophageal reflux, and depression. In our study, any association with co-morbidity was not detected and may require a much larger sampling to emerge.

Strengths and limitations

This is a feasibility study exploring potentials of information flow from a larger primary care patient pool to a narrower tertiary care patient group, by triangulating data of medical history, inexpensive and radiation-free imaging technique, such as LUS, and basic auscultation skills as crackles detection. One can think that a control group among LUS negative patients would be interesting. The answer is that the study purpose was not LUS diagnostic efficiency. It was attempted to run an investigational route, by changing 'the baton between runners', from GPs to chest physicians, with a handling information progressive manner. LUS, even for chest physicians, mostly remains a technical skill for a few having a major research orientation. Multidisciplinary collaboration should allow LUS to be a clinically used option within community care physicians, regardless if they are GPs or chest physicians who work at a community-based facility. At a community level with the large number of patients, the everyday gained experience of LUS technique and after a certified articulated training, could create promising diagnostic opportunities for research data networks and clinical support (46,47).

One of the limitations of this study is that crackles were not detected from the GP in any of the cases identified from the chest physician. This fact shows the need for basic skill acquisition from GPs by 'translating' capacity from colleagues or audio sourced material, in order to become familiar with crackles sounds. This process of course starts from undergraduate training and continues with life-long professional education. Self-reported dyspnea, as recruitment criterion, appeared with a lower frequency in comparison to the more accurate information from chest physician on any recent recalled experience of dyspnea. When a question is used as criterion for study participation, it may lose some meaning. Some patients at the primary care facilities, described self-reported dyspnea as a feeling at the moment of their recruitment, as we perceived later on.

Another important limitation of this study is that the whole recruitment period, referrals and outpatient consultations took place during pandemic. Many patients denied to attend due to their perceived risk of hospital visit and their underestimation of a preclinical testing with eventual benefit, when their real preoccupation was to not get sick from COVID-19, which was spreading outdoors. Additionally, due to e-delivered medical prescriptions, visits at a primary care facility were significantly reduced for more demanding reasons, when necessary. This led to a further refusal of participation for some.

A last important observation is that with the help of a liaison researcher and a mobile help desk, the connection between GPs and chest physicians was mostly uneventful in terms of cancelled consultations, delays, lack of coordination, loss of information and patients' limited satisfaction.

Conclusion

This is a feasibility, prospective, study building on mixed clinical information, from primary to tertiary care settings, in order to challenge and sum-up potentials for earlier case finding procedures within ILD morbidity. Frequencies of the targeted disorders were expectingly low. However, a few provisional diagnoses of ILD labeling emerged across the patients who followed the route from primary care to tertiary hospital unit. To this end, it was proved that the connection between primary and tertiary care may be limited by a non-adherence rate of less than 50% if well supported, and in conditions of access or fear limitations due to the pandemic. Our study explored ways from a more expanded primary care patient group to a tighter tertiary care patient pool, by triangulating data of medical history, inexpensive and radiation free imaging technique, such as LUS and basic auscultation skills like crackles detection. Not all LUS findings generate clinical suspicion for ILDs hidden morbidity, but in one out of five cases within our study, LUS findings are of a notable consideration. Furthermore, six patients revealed the need for further ILD evaluation, while five out of them were stratified as highly suspicious based on the evaluation by the respiratory physician, including LUS

findings. No crackles were detected from the GPs, although crackles occurrence accounted for 7% of the cases seen by chest physicians. The need of HRCT was driven by the overall clinical assessment of the respiratory medicine experts, yet the information on smoking habit effect comes from primary care and it appears enough to explain some of this decision made later. At a community level, the everyday gained experience from inexpensive and repeatable diagnostic skill resources, combined with a certified articulated clinical and communicational training, could create promising investigational opportunities for research data networks and clinical impact.

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