5ο ΠΑΝΕΛΛΗΝΙΟ ΣΥΝΕΔΡΙΟ ΝΟΣΗΜΑΤΩΝ ΘΩΡΑΚΟΣ

Πρόληψη και Πρώιμη Διάγνωση στα Σύγχρονα Αναπνευστικά Νοσήματα

12-14 ΜΑΪΟΥ 2022

ΔΙΑΜΕΣΑ ΝΟΣΗΜΑΤΑ

Προεδρείο: **Σ. Παπίρης, Δ. Παπακώστα**

Ιδιοπαθής πνευμονική ίνωση
Δ. Μπούρος

Οξεία Παρόξυνση Ιδιοπαθούς πνευμονικής ίνωσης
Σ. Παπίρης

Κληρονομούμενη πνευμονική ίνωση
Ε. Μάναλη

Μικροβίωμα και ιδιοπαθής πνευμονική ίνωση
Ζ. Δανιήλ

Ιδιοπαθής Πνευμονική Ίνωση: με στόχο την Πρώιμη Διάγνωση
Αικ. Αντωνίου

Katerina M. Antoniou, MD, PhD

ERS Assembly 12 Head

Professor in Respiratory Medicine

Faculty of Medicine, University of Crete

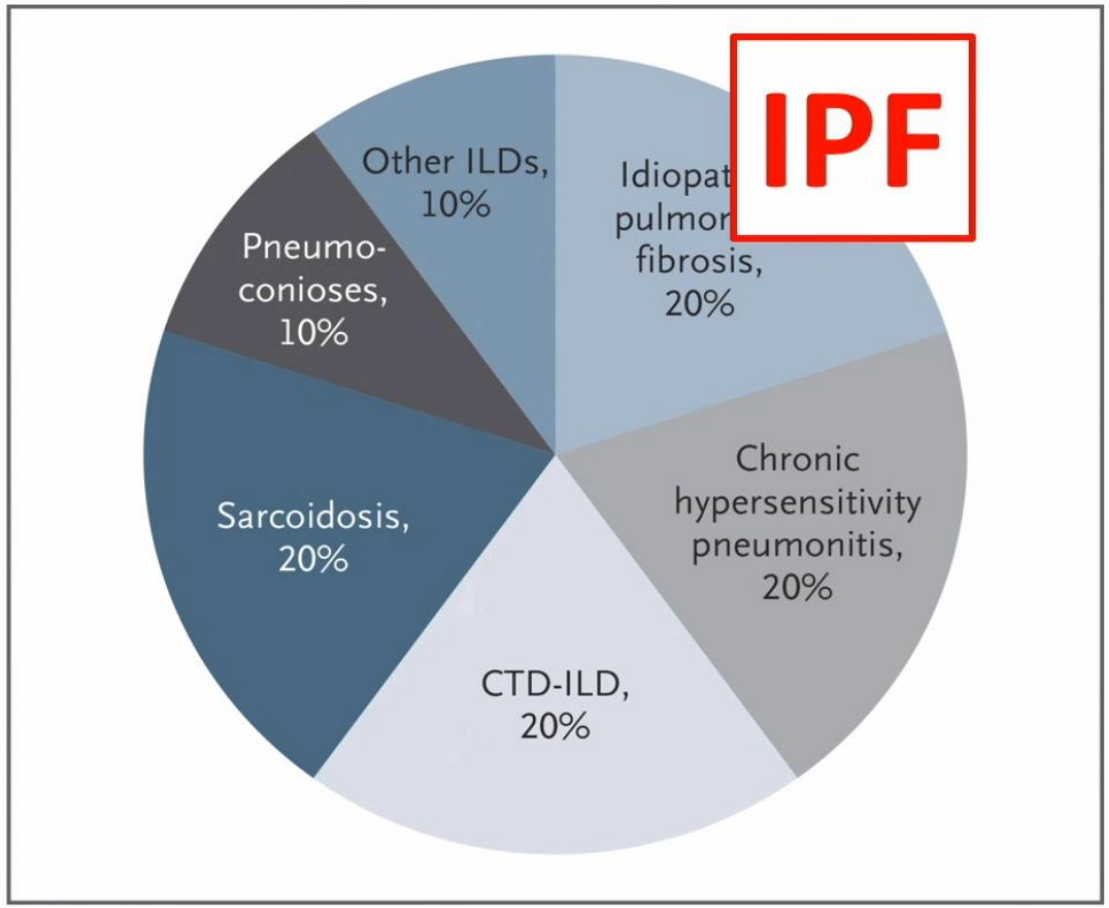
ERS EUROPEAN RESPIRATORY SOCIETY every breath counts

WASOG

Outline of the talk

- New Guidelines and the concept of PFP
- The IPF algorithm
- The primary care involvement
- ILAs
- The Lung ultrasound

Pulmonary fibrosis is not only IPF – 70-80% have different ILD



Lederer D and Martinez F. N Engl J Med.;379(8):797-798

AMERICAN THORACIC SOCIETY DOCUMENTS

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

This official clinical practice guideline was approved by the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax February 2022

Definition of Progressive Pulmonary Fibrosis

Definition of PPF

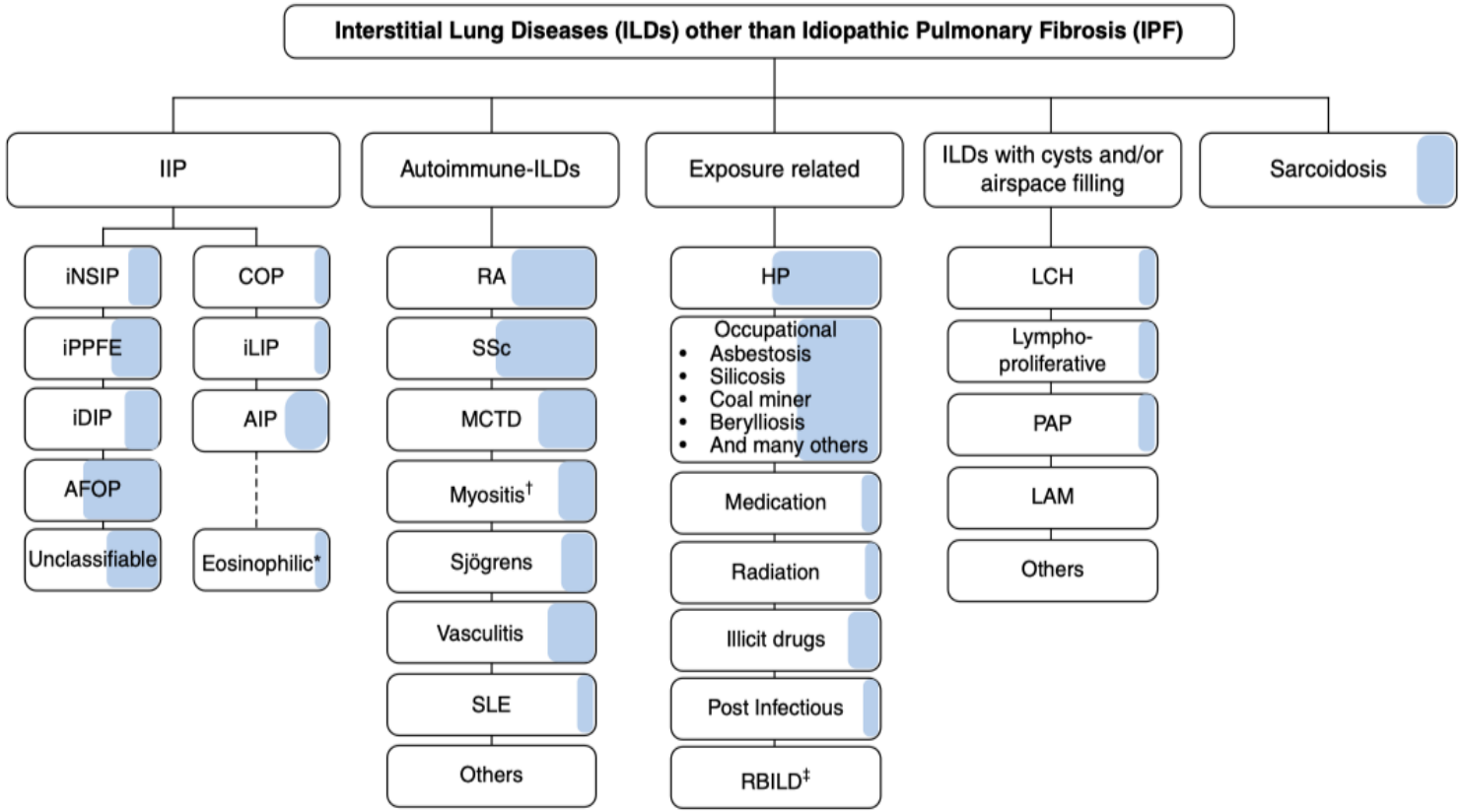
In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation*:

1 Worsening respiratory symptoms

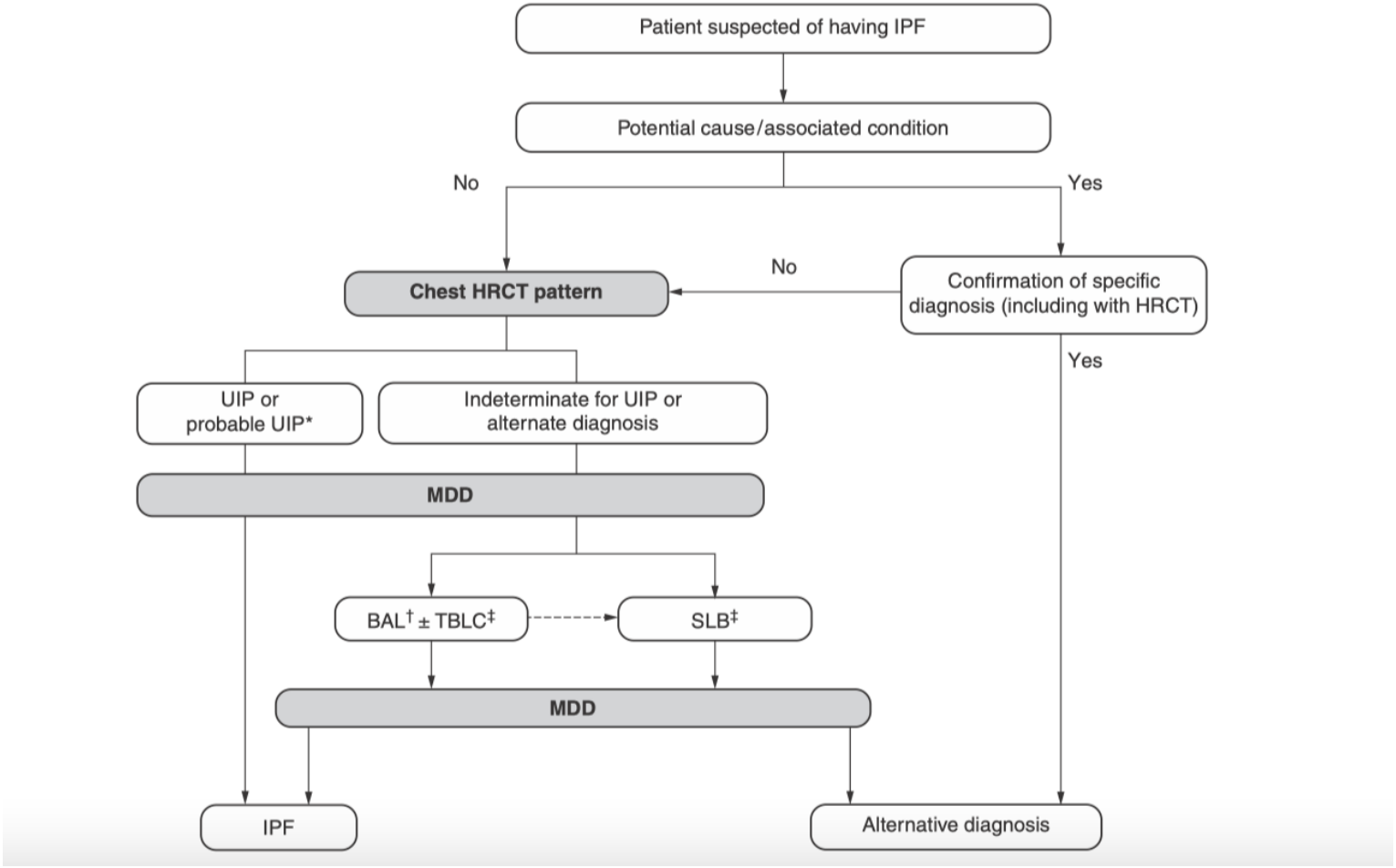
2 Physiological evidence of disease progression (either of the following):
- a. Absolute decline in FVC ⩾5% predicted within 1 yr of follow-up
- b. Absolute decline in D_{LCO} (corrected for Hb) ⩾10% predicted within 1 yr of follow-up

3 Radiological evidence of disease progression (one or more of the following):
- a. Increased extent or severity of traction bronchiectasis and bronchiolectasis
- b. New ground-glass opacity with traction bronchiectasis
- c. New fine reticulation
- d. Increased extent or increased coarseness of reticular abnormality
- e. New or increased honeycombing
- f. Increased lobar volume loss

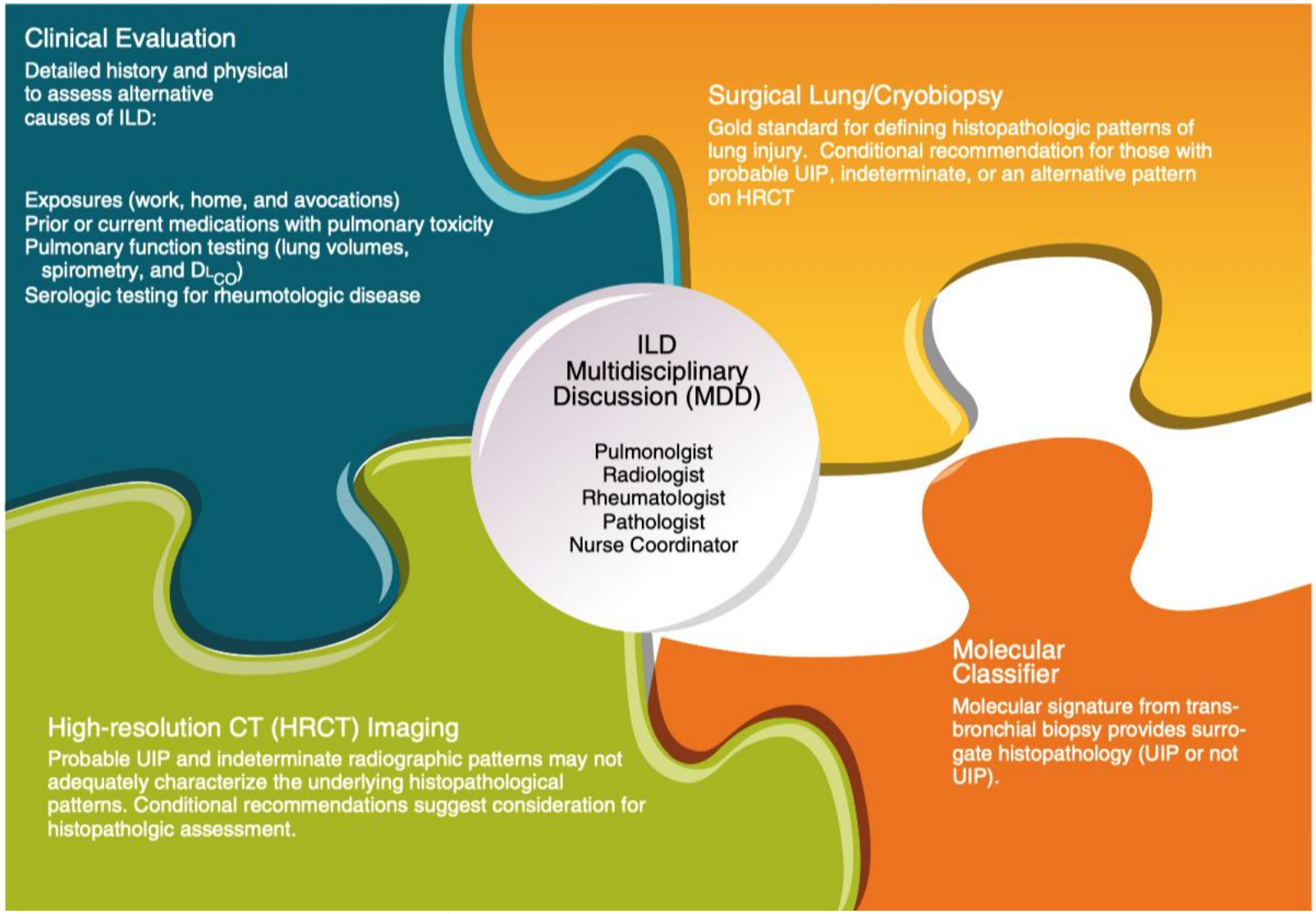
Interstitial lung diseases (ILDs) manifesting progressive pulmonary fibrosis (PPF), developed ***using consensus by discussion.***



Diagnostic algorithm for idiopathic pulmonary fibrosis (IPF)



A New Piece to Help Solve the Interstitial Lung Disease Diagnostic Puzzle



American Journal of Respiratory and Critical Care Medicine
Volume 203 Number 2 | January 15 2021

Primary Health Care

THE RCN COMMUNITY HEALTH NURSING JOURNAL
Primary Health Care

Palliative and end of life care in idiopathic pulmonary fibrosis

The three Rs of IPF in primary care

- **Recognise**
- **Refer**
- **Review**

NHS RightCare

Pathway for IPF

NHS RightCare Pathways. Available at: https://www.england.nhs.uk/rightcare/products/pathways/;
Newell K, et al. *Primary Health Care*. 2018;28:doi: 10.7748/phc.2018.e1387

Key points

After reading this article, you should be able to describe:

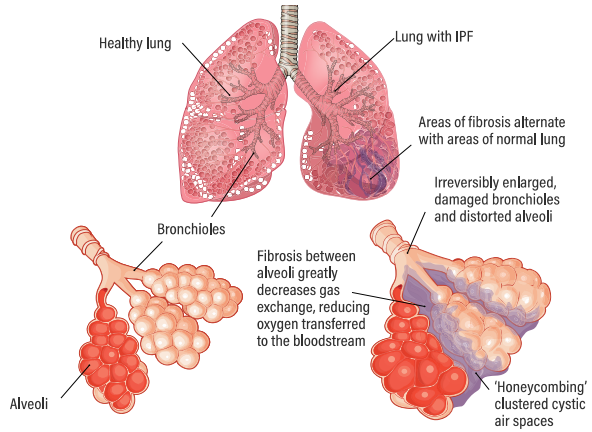
- What idiopathic pulmonary fibrosis (IPF) is
- How it is recognised
- How it is diagnosed
- How it is treated
- How it is managed
- How to optimise living well and dying well with IPF

TABLE 1. Comparison of clinical signs in restrictive versus obstructive lung conditions

Physical signs	Interstitial lung disease	Chronic obstructive pulmonary disease
Inspiratory crackles	Yes	No
Wheeze	No	Yes
Finger clubbing	Often	Occasionally
Spirometry	Normal/restrictive	Obstructed
Reduces transfer factor for carbon monoxide	Yes	With emphysema
Reduced FEV_1/ FVC	No	Yes
Response to bronchodilators	No	Yes
Chest X-ray	Often normal	Largely abnormal

FEV_1 = Forced expiratory volume in one second; FVC = Forced vital capacity

Figure 2. Comparison of healthy lung and lung with idiopathic pulmonary fibrosis (IPF)



Peter Lamb

If the patient is symptomatic – but has a normal or even obstructed spirometry in primary care – referral to secondary care for full pulmonary function test is indicated. Smoking status impacts spirometry and in patients with concomitant emphysema or dual diagnosis of IPF and COPD it is difficult to interpret spirometry correctly. Radiological examination should include a high-resolution

BOX 1. Red flags

Clinical features of idiopathic pulmonary fibrosis
- Persistent breathlessness on exertion
- Persistent cough
- Bilateral inspiratory crackles when listening to the chest
- Usually basal and can be more pronounced unilaterally
- Clubbing of the fingers

(NICE 2013a, 2013b)

THE LANCET
Respiratory Medicine

Early diagnosis of IPF: time for a primary-care case-finding initiative?

Idiopathic pulmonary fibrosis (IPF) is a seriously under recognised problem for public health. It is not widely appreciated that, if classified as a malignancy, IPF would rank as the eighth most prevalent cancer worldwide. By the time diagnosis is made, average survival is little better than that for inoperable lung cancer. Indirect evidence suggests that early expert evaluation is important. After the onset of exertional dyspnoea, delayed referral to a tertiary care centre is associated with increased mortality, independent of disease severity.[1] In the placebo groups of recent treatment trials, in which lung cancer might expedite diagnosis in some cases,[4] but is not applicable to all patients or in all health services. In reality, earlier diagnosis will be achieved only if primary care physicians take note of the presence of inspiratory velcro-like crackles on auscultation and restrictive ventilatory patterns on spirometry. Our view is that either of these findings should prompt further evaluation, including high-resolution CT screening.

A stand-alone IPF programme will not be viable because of cost-efficiency grounds and low prevalence of the disease. Therefore, efforts to diagnose IPF earlier in a community setting can only be successful if linked to a COPD case-detection strategy. The logic of this strategy lies in the fact that the two disease processes become

IPF is a neglected topic in educational activities for general practice. With the extension of spirometry in primary care to include the detection of restrictive lung disease in current and former smokers, it can reasonably be hoped that primary care practitioners will, in time, become more aware of IPF in older patients. ←

We declare that we have no conflicts of interest.

*Katerina M Antoniou, Emmanouil K Symvoulakis, George A Margaritopoulos, Christos Lionis, Athol U Wells
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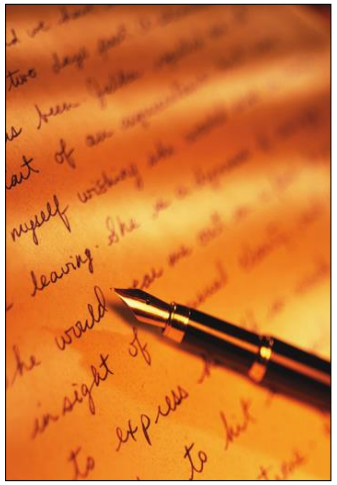
Department of Thoracic Medicine & Laboratory of Cellular and Molecular Pneumonology, Medical School, University of Crete, Heraklion, 71110 Crete, Greece (KMA, GAM); Clinic of Social and Family Medicine, Medical School, University of Crete, Heraklion, Greece (EKS, CL); and Interstitial Lung Disease Unit, Royal Brompton Hospital, London, UK (AUW)



See 2013 Research Highlights page 17

Hoyer *et al. Respiratory Research* (2019) 20:103
https://doi.org/10.1186/s12931-019-1076-0

Respiratory Research

RESEARCH Open Access

Risk factors for diagnostic delay in idiopathic pulmonary fibrosis

Nils Hoyer[1*], Thomas Skovhus Prior[2], Elisabeth Bendstrup[2], Torgny Wilcke[1] and Saher Burhan Shaker[1]

Abstract

Background: Surveys and retrospective studies of patients with idiopathic pulmonary fibrosis (IPF) have shown a significant diagnostic delay. However, the causes and risk factors for this delay are not known.

Methods: Dates at six time points before the IPF diagnosis (onset of symptoms, first contact to a general practitioner, first hospital contact, referral to an interstitial lung disease (ILD) centre, first visit at an ILD centre, and final diagnosis) were recorded in a multicentre cohort of 204 incident IPF patients. Based on these dates, the delay was divided into specific patient-related and healthcare-related delays. Demographic and clinical data were used to determine risk factors for a prolonged delay, using multivariate negative binomial regression analysis.

Results: The median diagnostic delay was 2.1 years (IQR: 0.9–5.0), mainly attributable to the patients, general practitioners and community hospitals. Male sex was a risk factor for patient delay (IRR: 3.84, 95% CI: 1.17–11.36, $p = 0.006$) and old age was a risk factor for healthcare delay (IRR: 1.03, 95% CI: 1.01–1.06, $p = 0.004$). The total delay was prolonged in previous users of inhalation therapy (IRR: 1.99, 95% CI: 1.40–2.88, $p < 0.0001$) but not in patients with airway obstruction. Misdiagnosis of respiratory symptoms was reported by 41% of all patients.

Conclusion: Despite increased awareness of IPF, the diagnostic delay is still 2.1 years. Male sex, older age and treatment attempts for alternative diagnoses are risk factors for a delayed diagnosis of IPF. Efforts to reduce the diagnostic delay should focus on these risk factors.

Trial registration: This study was registered at http://clinicaltrials.gov (NCT02772549) on May 10, 2016.

Keywords: IPF, Diagnosis, Delay, Cohort, Observational

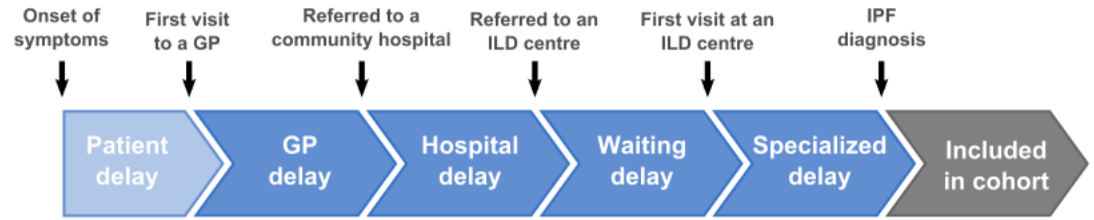


Fig. 1 Diagnostic delay from patients' awareness of symptoms until an IPF diagnosis is made. The total delay is divided into patient delay and healthcare delay (GP delay, hospital delay, waiting delay and specialized delay combined)

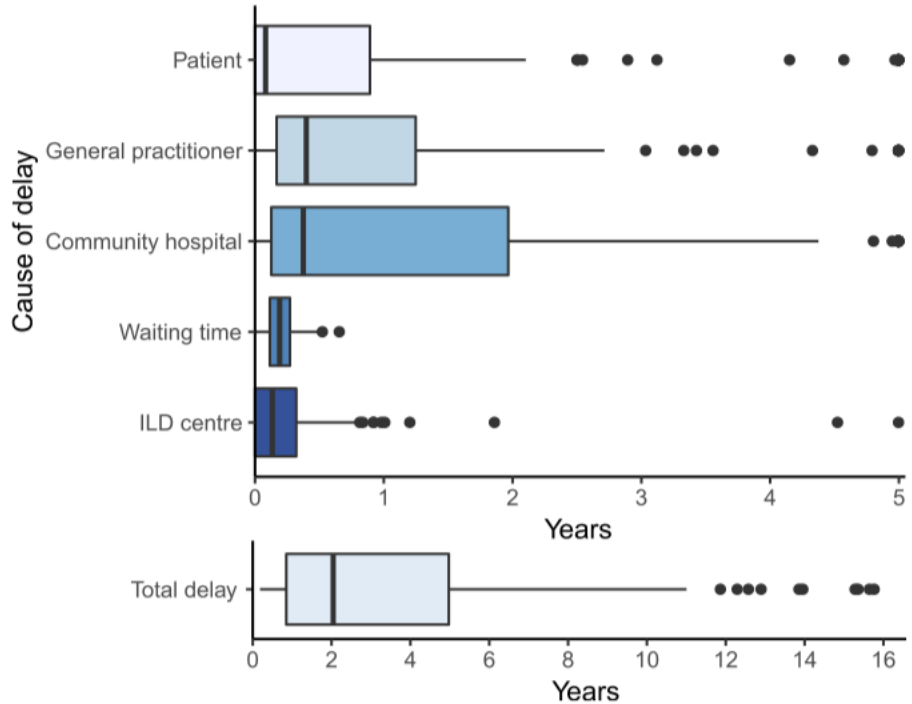


Fig. 2 Duration (median, IQR) of total and specific delays due to patient, general practitioner, community hospitals, waiting time and ILD centres. Time periods of the specialized delays are truncated at 5 years to increase legibility. Note different time scales

Barriers to timely diagnosis of interstitial lung disease in the real world: the INTENSITY survey

Gregory P. Cosgrove[1,2*], Pauline Bianchi[3], Sherry Danese[4] and David J. Lederer[2,5]

Abstract

Background: The diagnosis of idiopathic pulmonary fibrosis (IPF) and other interstitial lung diseases (ILD) presents significant clinical challenges. To gain insights regarding the diagnostic experience of patients with ILD and to identify potential barriers to a timely and accurate diagnosis, we developed an online questionnaire and conducted a national survey of adults with a self-reported diagnosis of ILD.

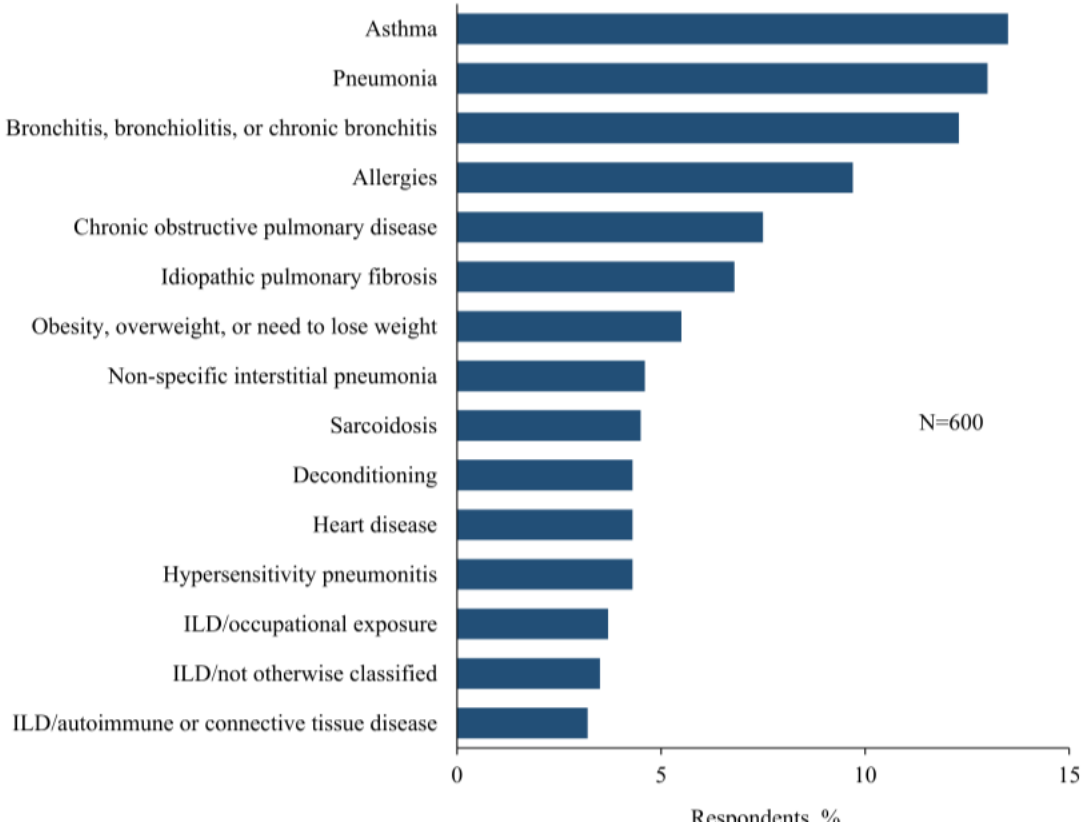
Methods: A pre-specified total of 600 subjects were recruited to participate in a 40-question online survey. E-mail invitations containing a link to the survey were sent to 16427 registered members of the Pulmonary Fibrosis Foundation. Additionally, an open invitation was posted on an online forum for patients and caregivers (www.inspire.com). The recruitment and screening period was closed once the pre-defined target number of respondents was reached. Eligible participants were adult U.S. residents with a diagnosis of IPF or a non-IPF ILD.

Results: A total of 600 eligible respondents met the eligibility criteria and completed the survey. Of these, 55% reported ≥ 1 misdiagnosis and 38% reported ≥ 2 misdiagnoses prior to the current diagnosis. The most common misdiagnoses were asthma (13.5%), pneumonia (13.0%), and bronchitis (12.3%). The median time from symptom onset to current diagnosis was 7 months (range, 0–252 months), with 43% of respondents reporting a delay of ≥ 1 year and 19% reporting a delay of ≥ 3 years. Sixty-one percent of respondents underwent at least one invasive diagnostic procedure.

Conclusions: While a minority of patients with ILD will experience an appropriate and expedient diagnosis, the more typical diagnostic experience for individuals with ILD is characterized by considerable delays, frequent misdiagnosis, exposure to costly and invasive diagnostic procedures, and substantial use of healthcare resources. These findings suggest a need for physician education, development of clinical practice recommendations, and improved diagnostic tools aimed at improving diagnostic accuracy in patients with ILD.

Cosgrove et al. BMC Pulmonary Medicine (2018) 18:9

Most commonly reported misdiagnoses



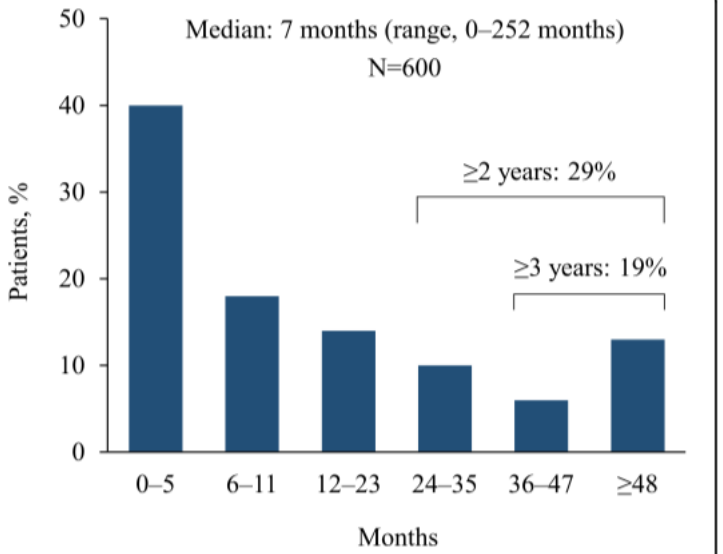


Fig. 4 Time from initial onset of symptoms to final diagnosis

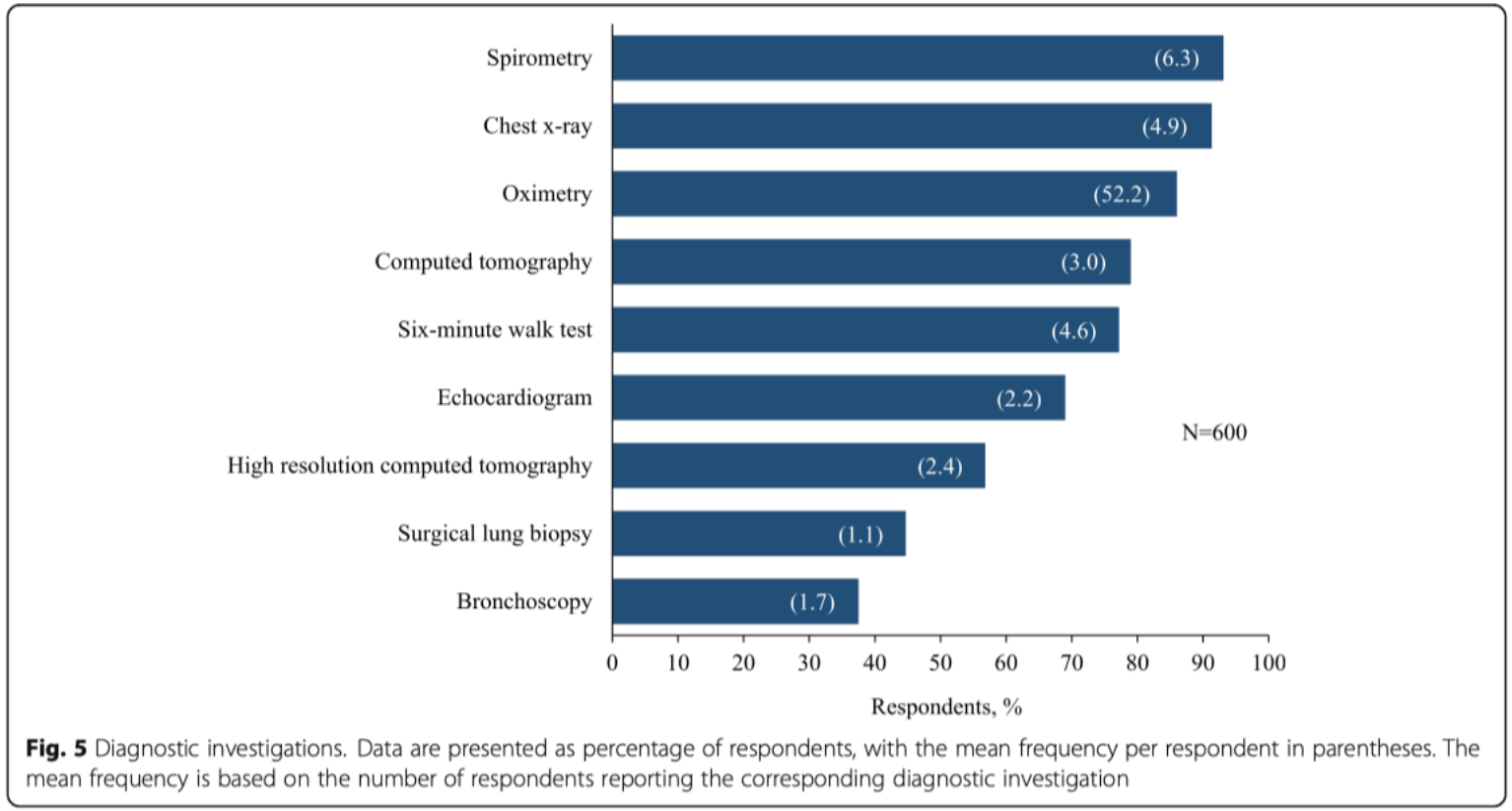


Fig. 5 Diagnostic investigations. Data are presented as percentage of respondents, with the mean frequency per respondent in parentheses. The mean frequency is based on the number of respondents reporting the corresponding diagnostic investigation

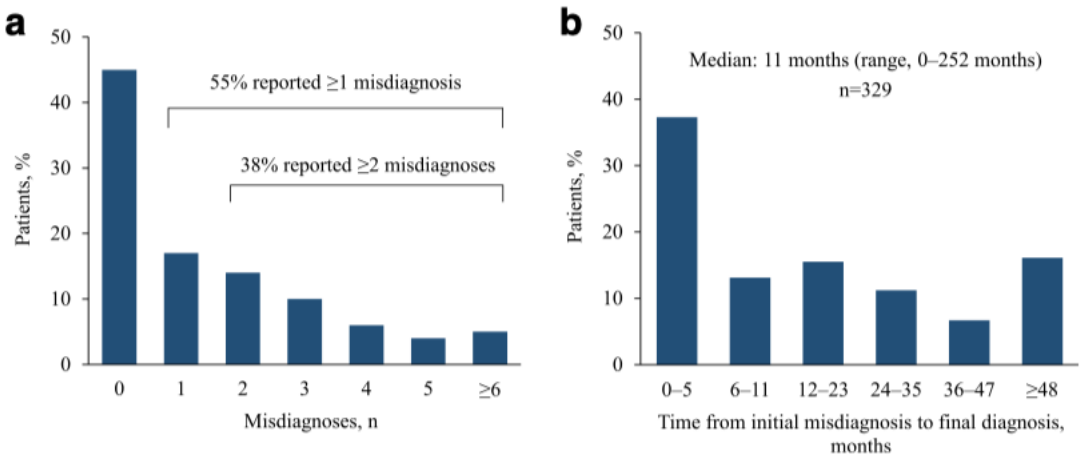


Fig. 2 Reported frequency of misdiagnosis (**a**) and time from initial misdiagnosis to final diagnosis (**b**)

- The median time from symptom onset to current diagnosis was 7 months (range, 0–252 months)
- 43% of respondents reporting a delay of ≥ 1 year and 19% reporting a delay of ≥ 3 years.
- 61% of respondents underwent at least one invasive diagnostic procedure.

BMJ Open Respiratory Research

Time to diagnosis of idiopathic pulmonary fibrosis in the IPF-PRO Registry

2020

Laurie D Snyder [1,2] Christopher Mosher [2] Colin H Holtze,[3] Lisa H Lancaster [4] Kevin R Flaherty,[3] Imre Noth,[5] Megan L Neely,[1,2] Anne S Hellkamp,[1,2] Shaun Bender,[6] Craig S Conoscenti,[6] Joao A de Andrade,[4] Timothy PM Whelan[7]

- In patients with IPF, the time from symptom onset to diagnosis remains over 1 year in about half of the patients, but once imaging evidence of pulmonary fibrosis is obtained, most patients receive a diagnosis within 1 year.
- Cardiac conditions and gastro-oesophageal disorders were reported more frequently in patients with a longer (>1 year) versus shorter time to diagnosis of IPF.
- There was no significant difference between the longer (>1 year) versus shorter time to diagnosis groups in a combined endpoint of risk of death or lung transplant.

Key messages

- How long does it take from onset of symptoms and from first imaging evidence of pulmonary fibrosis to diagnosis of idiopathic pulmonary fibrosis (IPF)?
- Among patients who received their first diagnosis of IPF at an enrolling centre in the IPF-PRO (Idiopathic Pulmonary Fibrosis Prospective Outcomes) Registry, approximately 50% were diagnosed more than 1 year after symptom onset, while approximately 80% were diagnosed within 1 year of imaging evidence of pulmonary fibrosis.
- Our results show that despite improved awareness of IPF, there remains a long period from symptom onset to diagnosis in a large proportion of patients and certain comorbidities are associated with a longer time to diagnosis.

SCREENING FOR FIBROTIC ILD – WHO TO SCREEN

Familiar Interstitial Lung Disease

Connective tissue disease

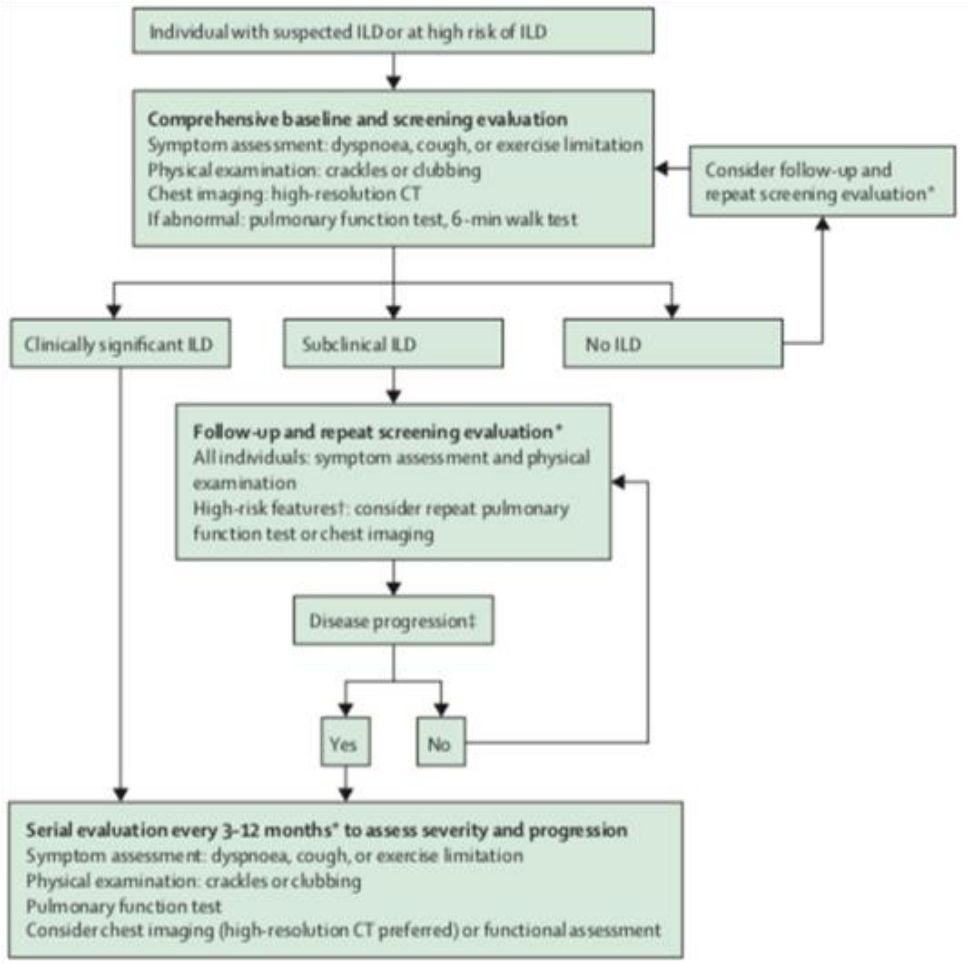
***Rheumatoid arthritis*: male gender, older age, cigarette smoking, RF and anti-CCP positivity, *MUC5B* genotype**

***Systemic sclerosis*: anti-Scl70 antibodies**

***Polymyositis/dermatomyositis*: anti-synthetase, anti-PM-Scl and anti-MDA-5 antibodies**

Occupational exposure (i.e., metal and wood dusts and asbestos)

SCREENING FOR FIBROTIC ILD – HOW TO SCREEN



Spagnolo P et, *Lancet Respir Med* 2021. Published Online July 28, 2021 https://doi.org/10.1016/ S2213-2600(21)00017-5

POTENTIAL SOLUTIONS TO DIAGNOSTIC DELAYS

Greater awareness of clinical manifestations of fibrotic ILD

Finger clubbing

Incidental identification of ILD on imaging

Interstitial lung abnormalities (ILA)

Thickett D et al. *BMJ Open* 2020;10:e034428

Eur Respir J 2012; 40: 519–521
DOI: 10.1183/09031936.00001612

EDITORIAL

Velcro crackles: the key for early diagnosis of idiopathic pulmonary fibrosis?

Vincent Cottin and Jean-François Cordier

Pulmonologists should educate students and general physicians to recognize the characteristic sound of fine Velcro crackles and be aware of their diagnostic relevance.

If present throughout the inspiratory time and persisting after several deep breaths, and if remaining present on several occasions several weeks apart in a subject aged ≥ 60 yrs, bilateral fine crackles should raise the suspicion of IPF and should lead to consideration of a chest radiograph and/or high resolution computed tomography of the chest (more sensitive than the chest radiograph, which may falsely reassure the patient).

It is time that the stethoscope draped around the neck of physicians, which tends to be used for identification purposes rather than for medical diagnosis, be also the (presently only) genuine tool for an earlier diagnosis of IPF, the prerequisite for earlier treatment, and maybe for improvement of the long-term clinical outcome of this dreadful disease.

Sgalla et al. BMC Pulmonary Medicine (2018) 18:103
https://doi.org/10.1186/s12890-018-0670-0

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

"Velcro-type" crackles predict specific radiologic features of fibrotic interstitial lung disease

Giacomo Sgalla[1,4*], Simon L. F. Walsh[2], Nicola Sverzellati[3], Sophie Fletcher[4], Stefania Cerri[5], Borislav Dimitrov[6^], Dragana Nikolic[7], Anna Barney[7], Fabrizio Pancaldi[8], Luca Larcher[8], Fabrizio Luppi[5], Mark G. Jones[4], Donna Davies[4] and Luca Richeldi[1,4]

Abstract

Background: "Velcro-type" crackles on chest auscultation are considered a typical acoustic finding of Fibrotic Interstitial Lung Disease (FILD), however whether they may have a role in the early detection of these disorders has been unknown. This study investigated how "Velcro-type" crackles correlate with the presence of distinct patterns of FILD and individual radiologic features of pulmonary fibrosis on High Resolution Computed Tomography (HRCT).

Methods: Lung sounds were digitally recorded from subjects immediately prior to undergoing clinically indicated chest HRCT. Audio files were independently assessed by two chest physicians and both full volume and single HRCT sections corresponding to the recording sites were extracted. The relationships between audible "Velcro-type" crackles and radiologic HRCT patterns and individual features of pulmonary fibrosis were investigated using multivariate regression models.

Results: 148 subjects were enrolled: bilateral "Velcro-type" crackles predicted the presence of FILD at HRCT (OR 13.46, 95% CI 5.85–30.96, $p < 0.001$) and most strongly the Usual Interstitial Pneumonia (UIP) pattern (OR 19.8, 95% CI 5.28–74.25, $p < 0.001$). Extent of isolated reticulation (OR 2.04, 95% CI 1.62–2.57, $p < 0.001$), honeycombing (OR 1.88, 95% CI 1.24–2.83, < 0.01), ground glass opacities (OR 1.74, 95% CI 1.29–2.32, $p < 0.001$) and traction bronchiectasis (OR 1.55, 95% CI 1.03–2.32, $p < 0.05$) were all independently associated with the presence of "Velcro-type" crackles.

Conclusions: "Velcro-type" crackles predict the presence of FILD and directly correlate with the extent of distinct radiologic features of pulmonary fibrosis. Such evidence provides grounds for further investigation of lung sounds as an early identification tool in FILD.

Keywords: Fibrotic interstitial lung disease, Idiopathic pulmonary fibrosis, Velcro crackles, Lung sounds, Breath sounds

DIGITALLY RECORDED LUNG SOUNDS

HRCT pattern	Bilateral "Velcro-type" crackles		Unilateral "Velcro-type" crackles	
	OR (CI 95%)	p	OR (CI 95%)	p
FILD*	13.46 (5.71–29.182)	< 0.001	0.58 (0.29–1.16)	0.12
Definite UIP	19.8 (5.28–74.25)	< 0.001	0.49 (0.14–1.66)	0.25
Possible UIP	13.09 (4.87–35.2)	< 0.001	0.55 (0.23–1.34)	0.19
Inconsistent with UIP	10.8 (3.85–32.85)	< 0.001	0.75 (0.26–2)	0.53

Sgalla G et al. *BMC Pulm Med* 2018;18:103

Integrating Clinical Probability into the Diagnostic Approach to Idiopathic Pulmonary Fibrosis: An International Working Group Perspective.

Cottin V, Tomassetti S, Valenzuela C, Walsh S, Antoniou K, Bonella F, Brown KK, Collard HR, Corte TJ, Flaherty K, Johannson KA, Kolb M, Kreuter M, Inoue Y, Jenkins G, Lee JS, Lynch DA, Maher TM, Martinez FJ, Molina-Molina M, Myers J, Nathan SD, Poletti V, Quadrelli S, Raghu G, Rajan SK, Ravaglia C, Remy-Jardin M, Renzoni E, Richeldi L, Spagnolo P, Troy L, Wijsenbeek M, Wilson KC, Wuyts W, Wells AU, Ryerson C.

Background: When considering the diagnosis of idiopathic pulmonary fibrosis (IPF), experienced clinicians integrate clinical features that help to differentiate IPF from other fibrosing interstitial lung diseases, thus generating a "pre-test" probability of IPF. The aim of this international working group perspective was to summarize these features using a tabulated approach similar to chest HRCT and histopathologic patterns reported in the international guidelines for the diagnosis of IPF, and to help formally incorporate these clinical likelihoods into diagnostic reasoning to facilitate the diagnosis of IPF.

Methods: The committee group identified factors that influence the clinical likelihood of a diagnosis of IPF, which was categorized as a pre-test clinical probability of IPF into "high" (70-100%), "intermediate" (30-70%), or "low" (0-30%). After integration of radiological and histopathological features, the post-test probability of diagnosis was categorized into "definite" (90-100%), "high confidence" (70-89%), "low confidence" (51-69%), or "low" (0-50%) probability of IPF.

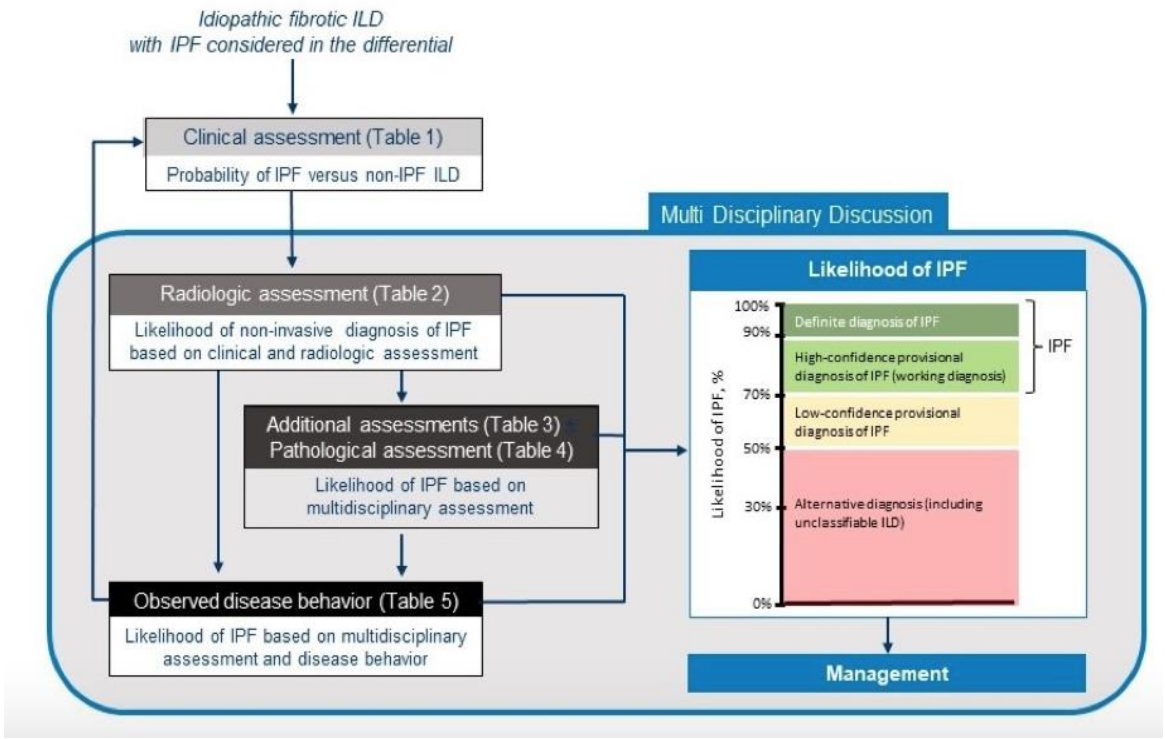
Am J Respir Crit Care Med. 2022 Mar 30.

	Clinical likelihood of IPF		
	Likelihood decreased if present		**Likelihood increased if present**
Sex	Female sex		Male sex
Age	< 50 years		> 60 years
Tobacco history	Never smoker		Ex-smoker (or current smoker)
Auscultation	Absence of crackles Presence of squeaks or wheezing		Velcro crackles
Clubbing	Absent		Present
Exposure to significant antigens that may cause hypersensitivity pneumonitis	Present		Absent
Autoimmune features*	Present		Absent
Plausible differential diagnosis	Yes		No
Familial aggregation of fibrotic ILD	No		Yes
Lung function	Airflow obstruction or mixed physiology not ascribable to emphysema		Restrictive physiology
Onset	Acute or subacute onset		Chronic onset

IPF diagnostic confidence categories based on their assigned diagnostic likelihood can be estimated as follows: “high” diagnostic likelihood (70-100%), “intermediate” diagnostic likelihood (30-70%), or “low” diagnostic likelihood (0-30%) of IPF.

Clinical probability of IPF based on additional assessment, when available. When assessed, items listed may increase or decrease the probability of IPF. This evaluation would typically take place after the clinic-radiological assessment.

	Likelihood of IPF		
	Likelihood decreased if present		**Likelihood increased if present**
Pre-diagnostic disease behavior*	Long-term stability over years		Progression over months-years despite treatment
Pre-diagnostic short-term response to glucocorticoids or immunosuppression*	Present		Absent
Bronchoalveolar lavage if performed	Lymphocyte count increased (>30%)		Lymphocyte count not increased (<15%)
Genetics if performed	Absent		*Single nucleotide polymorphisms (e.g. MUC5B)* *Pathogenic gene variants related to surfactant metabolism and telomere maintenance.* Syndromic ILD (e.g. short telomere syndrome)
Molecular classifier on transbronchial lung biopsy	Molecular classifier « Not UIP »		Molecular classifier « UIP »



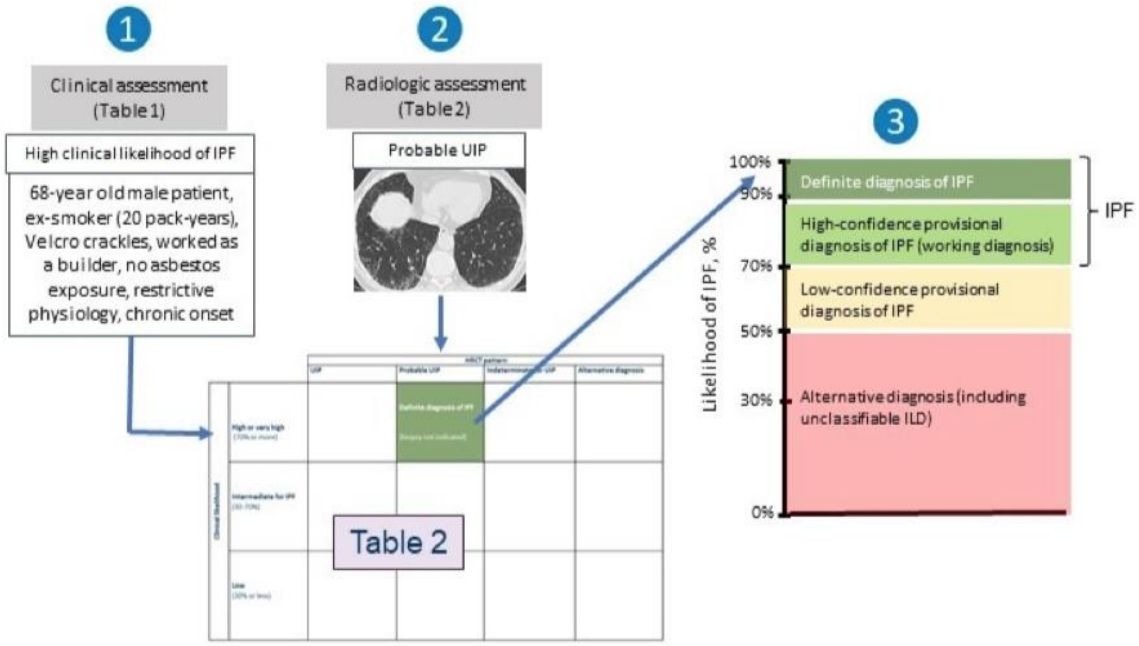


Figure 2. Schematic representation of probability of diagnosis at each step of the evaluation.
Figure 2a. Example 1: patient with high clinical likelihood of IPF and probable UIP at HRCT. A high-confidence diagnosis of IPF was made; biopsy was not necessary.

THE LANCET
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COMMENT | VOLUME 7, ISSUE 5, P376-378, MAY 01, 2019

Interstitial lung abnormalities: *ignotum per ignotius*

Katerina M Antoniou • Vasilios Tzilas • Eirini Vasarmidi • Emmanouil K Symvoulakis • Argyris Tzouvelekis • Demosthenes Bouros

Published: March 29, 2019 • DOI: https://doi.org/10.1016/S2213-2600(19)30052-9 •

The widespread use of multiple-detector computed tomography and the increased vigilance of the medical community regarding interstitial lung diseases have led to the recognition of interstitial lung abnormalities in subclinical settings, which presents an opportunity for early diagnosis of idiopathic pulmonary fibrosis and the subsequent timely initiation of antifibrotic therapy. Interstitial lung abnormalities, however, should not a priori be considered evidence of clinically relevant disease. They are frequently observed with advanced age and are associated with smoking and environmental pollution. The difficulty in defining the appearance of normal lung on imaging, especially in people aged 80 years and over, further adds to the problem of identifying potentially clinically important changes in lung tissue. [1] However, interstitial lung

INTERSTITIAL LUNG ABNORMALITIES

The term interstitial lung abnormalities (ILAs) refers to the presence of CT findings *compatible* with ILD but without previous suspicion of ILD

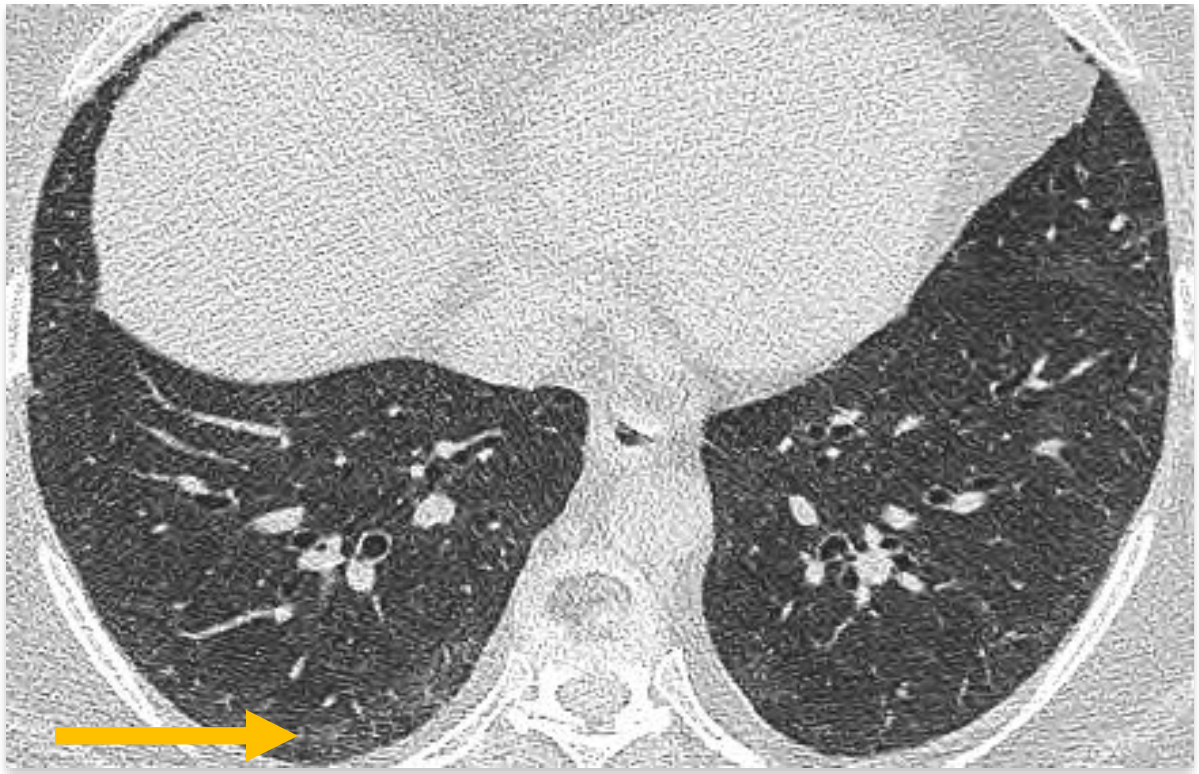
When associated with respiratory signs, symptoms, or functional impairment, ILAs are likely to represent mild ILD rather than subclinical abnormalities

ILAs are often associated with respiratory symptoms, functional impairment, risk of progression and increased all-cause mortality, hence their clinical relevance

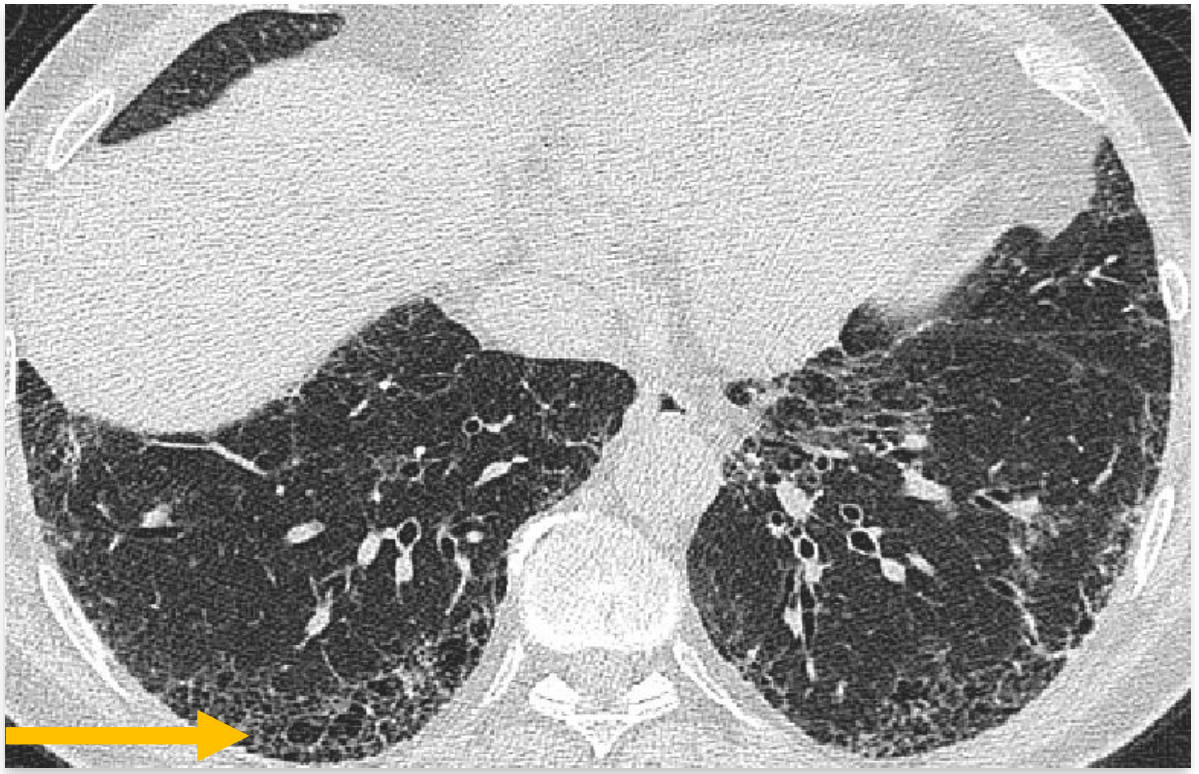
Hatabu H et al. *Lancet Respir Med* 2020;8:726-37

The disease spectrum

Interstitial lung abnormalities



Fibrosis



Incidental discovery of interstitial lung disease: diagnostic approach, surveillance and perspectives

Sara Tomassetti [1,2], Venerino Poletti[3], Claudia Ravaglia[3], Nicola Sverzellati[4], Sara Piciucchi [5], Diletta Cozzi[6], Valentina Luzzi[2], Camilla Comin[1] and Athol U. Wells[7,8]

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Shareable abstract (@ERSpublications)
In patients with interstitial lung abnormalities (ILA), monitoring of those at risk of progression is currently recommended, and pulmonary physicians should pursue an early diagnosis when ILA become clinically significant to facilitate timely treatment https://bit.ly/3HKOQc8

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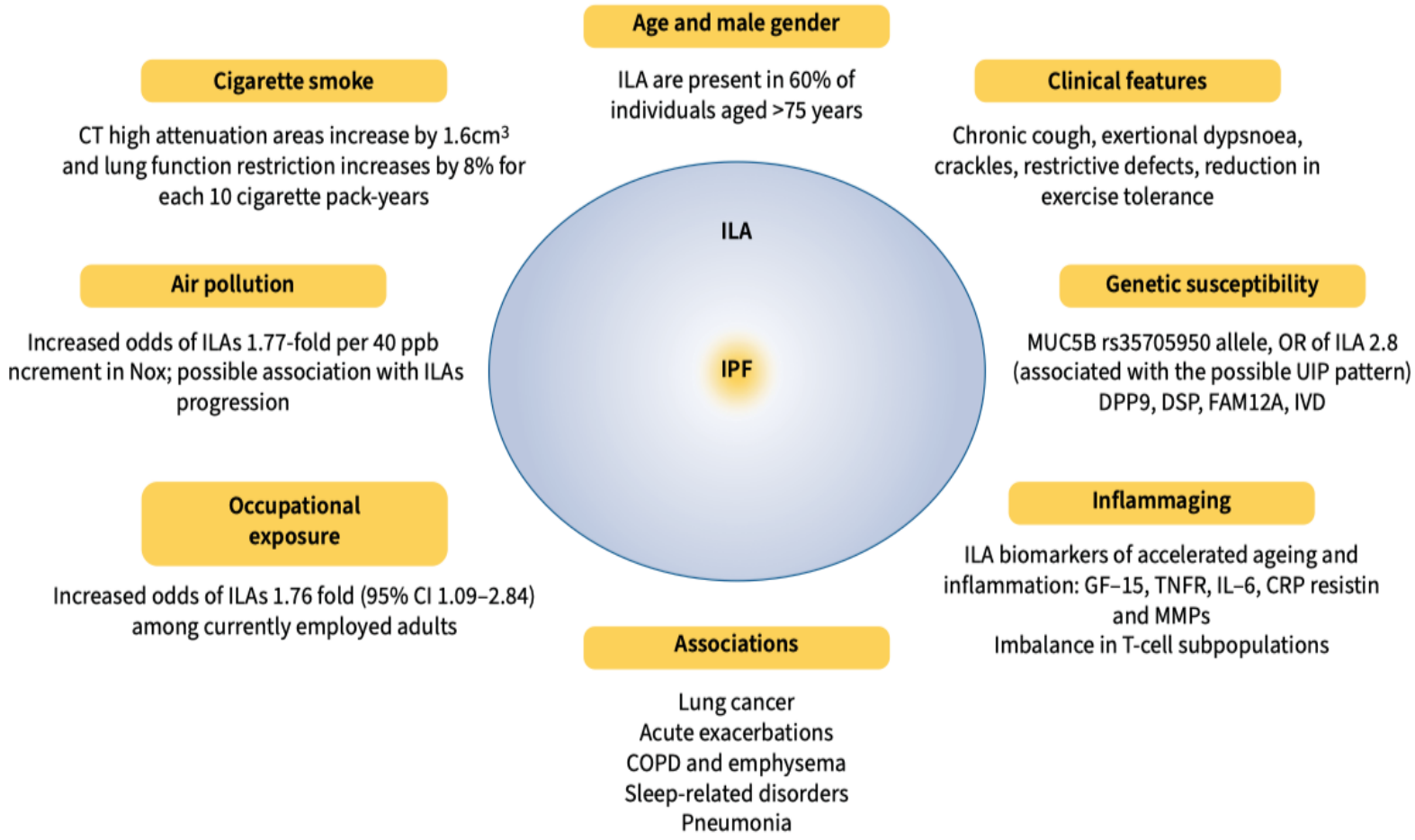
TABLE 1 Simplified definitions

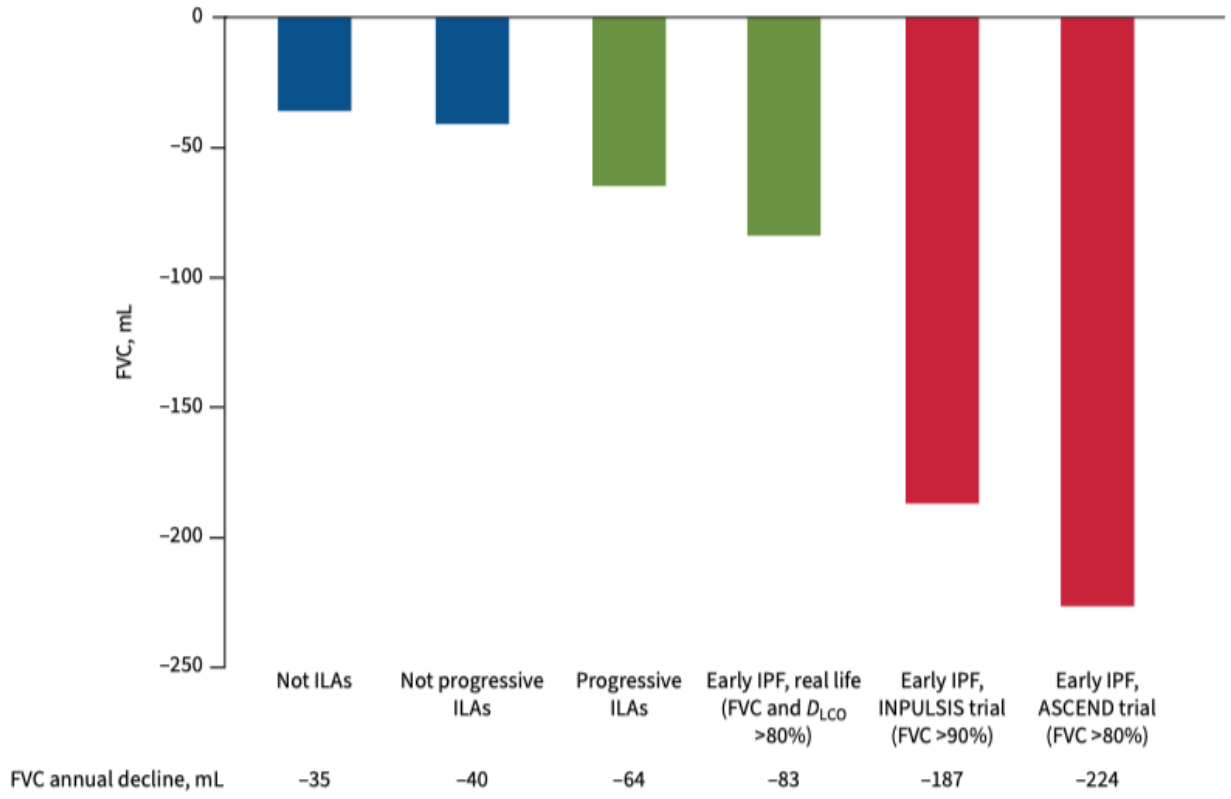
Entity	Population	Diagnostic criteria	Definition
ILA	Only individuals without known or suspected ILD[#]	Clinical-radiological entity	Incidental finding of CT abnormalities affecting more than 5% of any lung zone
Pre-clinical ILD	Individuals at risk for ILD	Clinical-radiological-pathological entity	Any ILD in asymptomatic patients with preserved lung function
Subclinical ILD	Individuals NOT at risk for ILD	Clinical-radiological-pathological entity	Any ILD in asymptomatic patients with preserved lung function
Early ILD	All individuals	Clinical-radiological-pathological entity	Any ILD in asymptomatic patients with preserved lung function
Mild ILD	All individuals	Clinical-radiological-pathological entity	Any clinically significant ILD with minor symptoms and/or trivial PFT abnormalities

ILA: interstitial lung abnormalities; ILD: interstitial lung disease; CT: computed tomography; PFT: pulmonary function test. [#]: abnormalities identified during screening for ILD in high-risk groups (*e.g.* those with rheumatoid arthritis, systemic sclerosis or familial ILD) are not considered as ILA because they are not incidental.

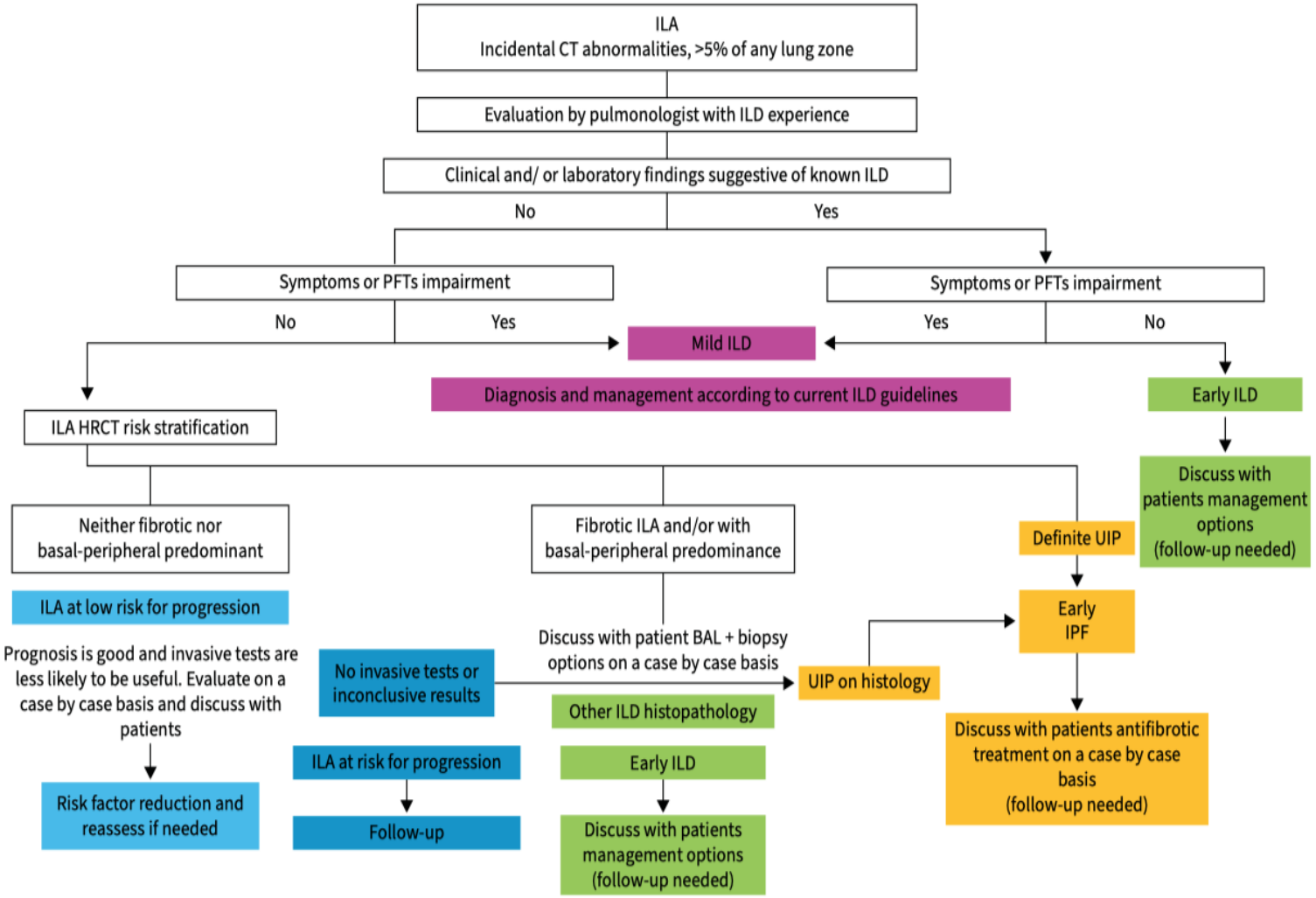
Summary of shared features between interstitial lung abnormalities (ILA) and idiopathic pulmonary fibrosis (IPF)



Forced vital capacity (FVC) annual trends of early idiopathic pulmonary fibrosis (IPF) and interstitial lung abnormalities (ILA)



Proposed algorithm for diagnosis and management of interstitial lung abnormalities (ILA)



Soldati et al. Multidisciplinary Respiratory Medicine (2017) 12:15
DOI 10.1186/s40248-017-0098-z

Multidisciplinary
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STATE OF THE ART Open Access

Novel aspects in diagnostic approach to respiratory patients: is it the time for a new semiotics?

Gino Soldati[1], Andrea Smargiassi[2*], Alberto A. Mariani[1] and Riccardo Inchingolo[2]

Abstract

Medical approach to patients is a fundamental step to get the correct diagnosis. The aim of this paper is to analyze some aspects of the reasoning process inherent in medical diagnosis in our era. Pathologic signs (anamnestic data, symptoms, semiotics, laboratory and strumental findings) represent informative phenomena to be integrated for inferring a diagnosis. Thus, diagnosis begins with "signs" and finishes in a probability of disease. The abductive reasoning process is the generation of a hypothesis to explain one or more observations (signs) in order to decide between alternative explanations searching the best one. This process is iterative during the diagnostic activity while collecting further observations and it could be creative generating new knowledge about what has not been experienced before. In the clinical setting the abductive process is not only theoretical, conversely the physical exploitation of the patient (palpation, percussion, auscultation) is always crucial. Through this manipulative abduction, new and still unexpressed information is discovered and evaluated and physicians are able "to think through doing" to get the correct diagnosis. Abductive inferential path originates with an emotional reaction (discovery of the signs), step by step explanations are formed and it ends with another emotional reaction (diagnosis). Few bedside instruments are allowed to physicians to amplify their ability to search for signs. Stethoscope is an example. Similarities between ultrasound exploration and percussion can be found. Bedside ultrasonography can be considered an external amplifier of signs, a particular kind of percussion and represents a valid example of abductive manipulation. In this searching for signs doctors act like detectives and sometimes the discovering of a strategic, unsuspected sign during abductive manipulation could represent the key point for the correct diagnosis. This condition is called serendipity. Ultrasound is a powerful tool for detecting soft, hidden, unexpected and strategic signs.

Keywords: Abduction, Chest ultrasonography, Diagnostic approach, Lung, Semiotics, Ultrasound

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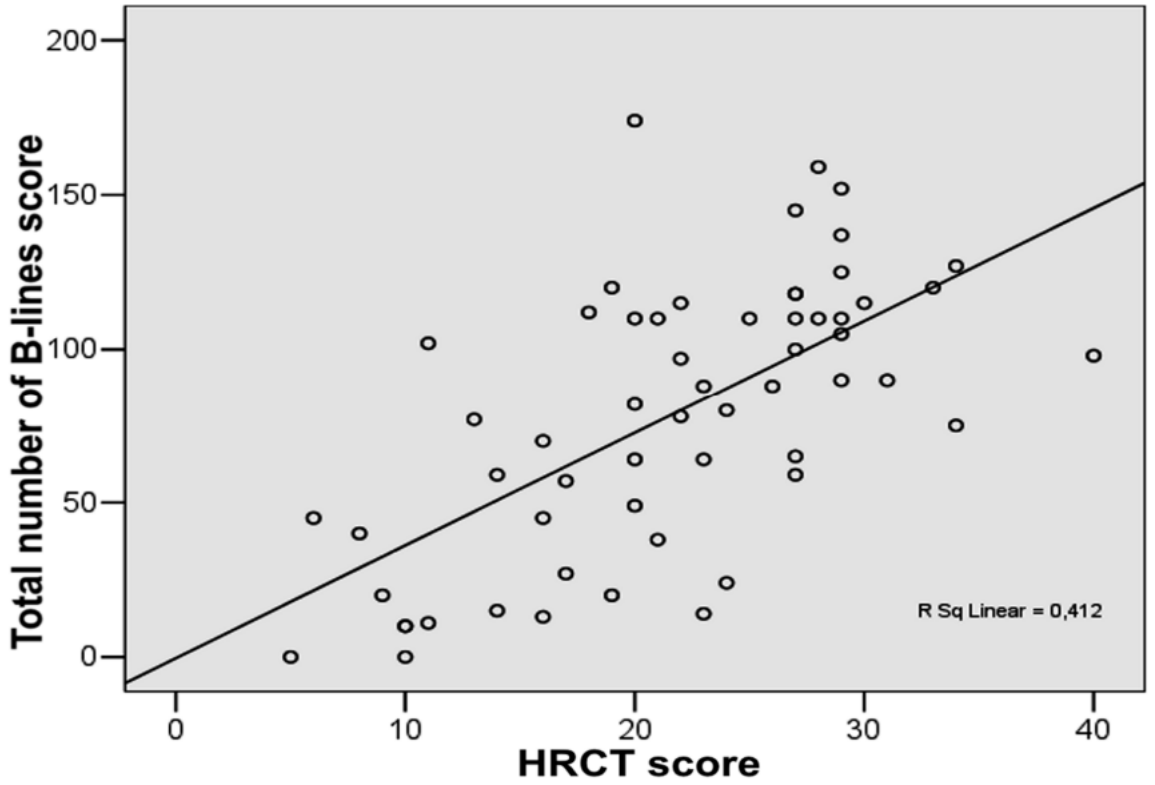
Article

Correlation between Transthoracic Lung Ultrasound Score and HRCT Features in Patients with Interstitial Lung Diseases

Milena Adina Man [1,†], Elena Dantes [2,†], Bianca Domokos Hancu [1,*], Cosmina Ioana Bondor [1], Alina Ruscovan [3], Adriana Parau [3], Nicoleta Stefania Motoc [1] and Monica Marc [4]

J. Clin. Med. 2019



JSRD Journal of Scleroderma and Related Disorders

Review

The role of ultrasound in systemic sclerosis: On the cutting edge to foster clinical and research advancement

Journal of Scleroderma and Related Disorders
1–10

DOI: 10.1177/2397198320970394
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Michael Hughes[1], Cosimo Bruni[2], Giovanna Cuomo[3], Andrea Delle Sedie[4], Luna Gargani[5], Marwin Gutierrez[6,7], Gemma Lepri[2], Barbara Ruaro[8], Tania Santiago[9,10], Yossra Suliman[11], Shinji Watanabe[12], Annamaria Iagnocco[13], Daniel Furst[2,14,15] and Silvia Bellando-Randone[2,16]

Table 1. The potential uses and measurements of US for MSK, DU, lung disease and skin disease in SSc.

MSK	Synovitis
	Tenosynovitis
	Non-inflammatory arthropathy
	Enthesitis
	Nerves
DU	DU dimensions – width and depth
	Doppler signal – infection and correlation with pain
	Associated pathology (e.g. calcinosis)
Lung	Pleural line alterations
	B-lines
Skin	Skin US – skin thickness, echogenicity
	US elastography

MSK: musculoskeletal; DU: digital ulcer.

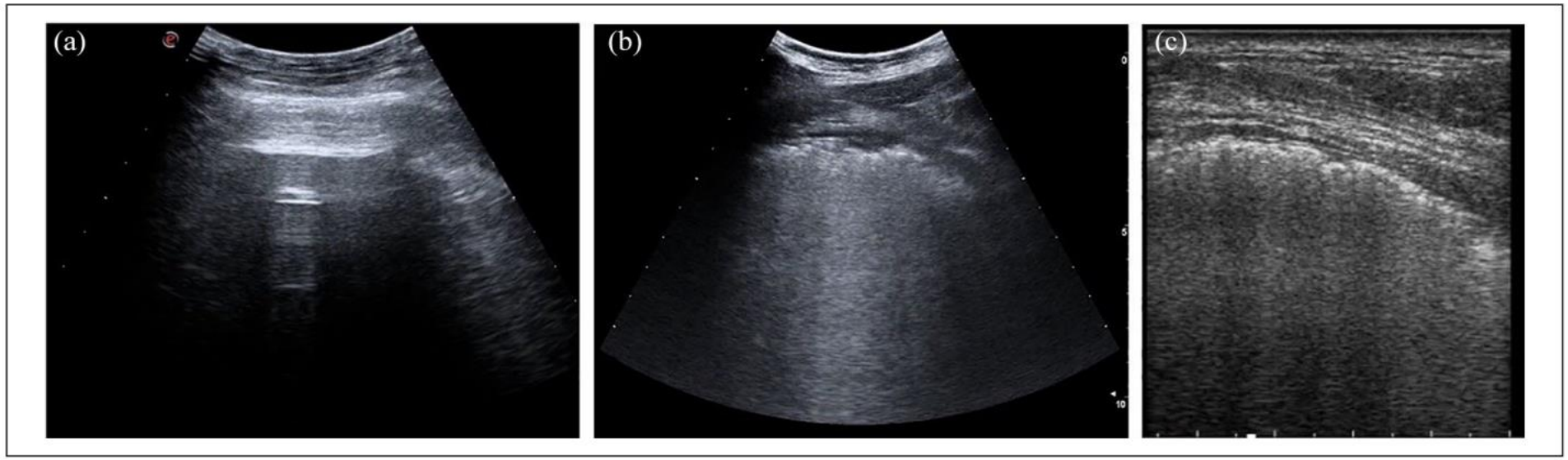

Figure 3. LUS in SSc. (a) Normal LUS. Advanced ILD (B-lines and pleural line alterations) using (b) convex and (c) linear probes.

Clinical Interventions in Aging

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REVIEW

The reliability of lung ultrasound in assessment of idiopathic pulmonary fibrosis

This article was published in the following Dove Press journal:
Clinical Interventions in Aging

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Abstract: Idiopathic pulmonary fibrosis (IPF) is the severest form of idiopathic interstitial pneumonia, with a median survival time estimated at 2–5 years from the time of diagnosis. It occurs mainly in elderly adults, suggesting a strong link between the fibrosis process and aging. Although chest high-resolution computed tomography (HRCT) is currently the method of choice in IPF assessment, diagnostic imaging with typical usual interstitial pneumonia (UIP) provides definitive results in only 55%, requiring an invasive surgical procedure such as lung biopsy or cryobiopsy for the final diagnostic analysis. Lung ultrasound (LUS) as a noninvasive, non-radiating examination is very sensitive to detect subtle changes in the subpleural space. The evidence of diffuse, multiple B-lines defined as vertical, hyperechoic artifacts is the hallmark of interstitial syndrome. A thick, irregular, fragmented pleura line is associated with subpleural fibrotic scars. The total numbers of B-lines are correlated with the extension of pulmonary fibrosis on HRCT, being an LUS marker of severity. The average distance between two adjacent B-lines is an indicator of a particular pattern on HRCT. It is used to appreciate a pure reticular fibrotic pattern as in IPF compared with a predominant ground glass pattern seen in fibrotic nonspecific interstitial pattern. The distribution of the LUS artifacts has a diagnostic value. An upper predominance of multiple B-lines associated with the thickening of pleura line is an LUS feature of an inconsistent UIP pattern, excluding the IPF diagnosis. LUS is a repeatable, totally radiation-free procedure, well tolerated by patients, very sensitive in detecting early changes of fibrotic lung, and therefore a useful imaging technique in monitoring disease progression in the natural course or after initiation of treatment.

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Figure 1 The physical and anatomic basis of echo lung comets.

Notes: (**A**) Normally aerated lung with A-lines artifact as reflection of pleura line. (**B**) Reflections of the ultrasound beam by the thickened interlobular septa proved comet-tail artifact (B-lines) in patients with IPF. Modified from *Am J Cardiol*, 93(10), Jambrik Z, Monti S, Coppola V, et al, Usefulness of ultrasound lung comets as a nonradiologic sign of extravascular lung water, 1265–1270, Copyrgiht (2004), with permission from Elsevier.[29]

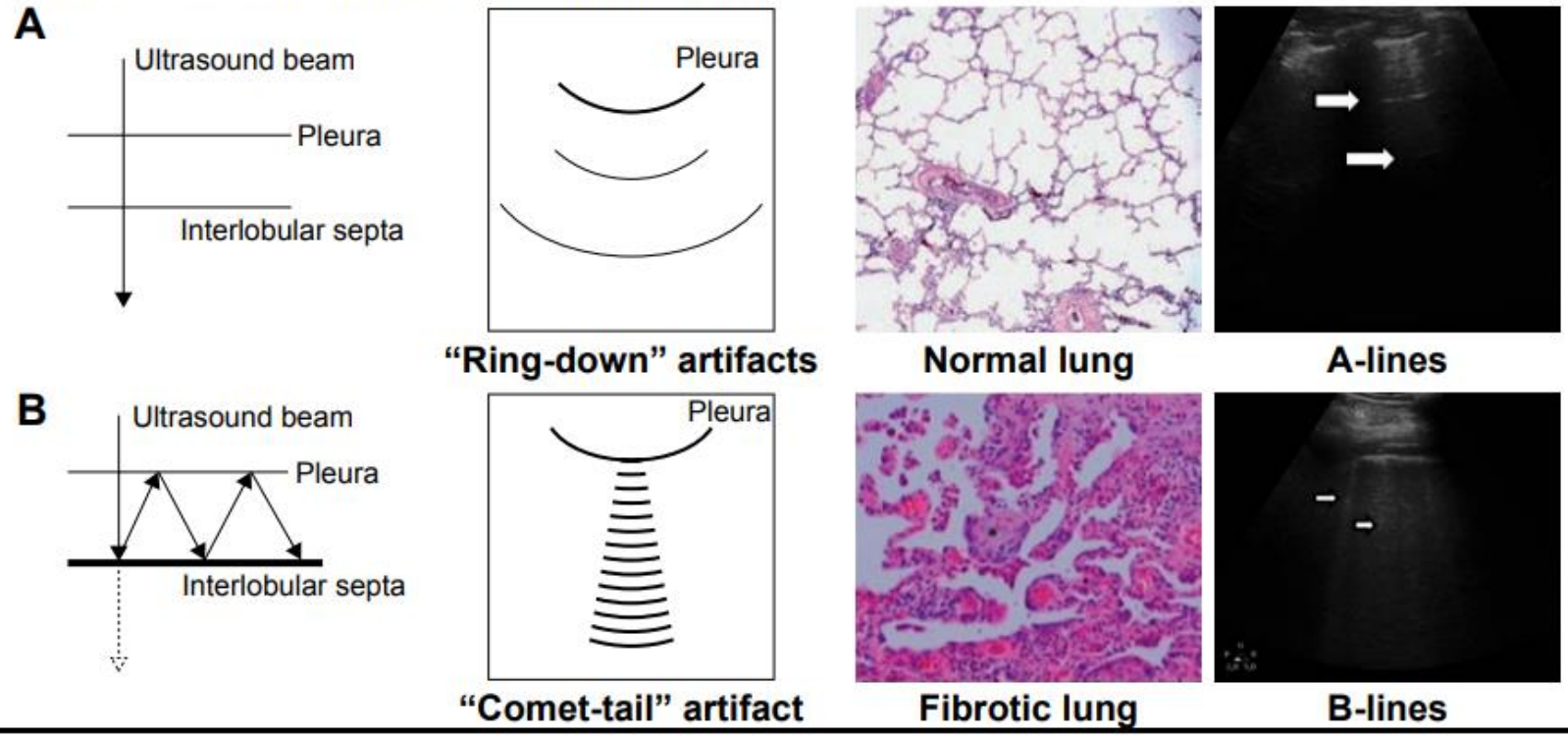
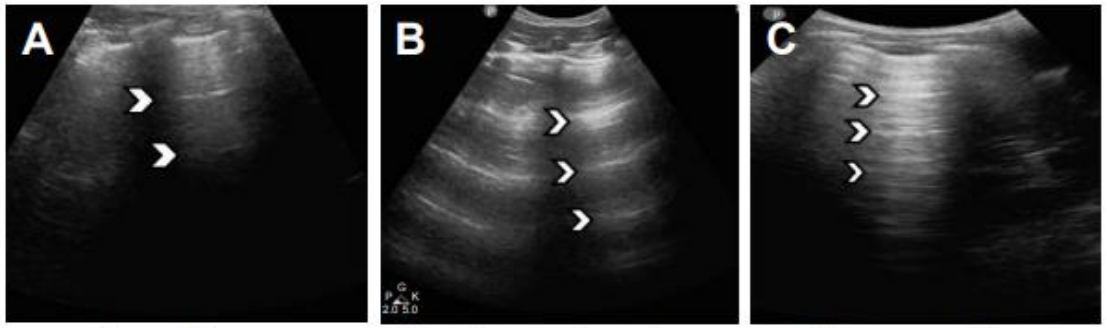


Figure 2 Aspect of A-lines (arrows) in (**A**) normal lung, (**B**) emphysematous lung, and (**C**) IPF with honeycombing.



Manolescu, Diana et al. "The reliability of lung ultrasound in assessment of idiopathic pulmonary fibrosis." *Clinical interventions in aging* vol. 13 437-449. 22 Mar. 2018, doi:10.2147/CIA.S156615

Performance of Lung Ultrasound for Monitoring Interstitial Lung Disease

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The authors of this manuscript have no conflicts of interest to disclose.

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Objectives—In this study, we sought to assess the validity of lung ultrasound (LUS) during the follow-up of patients with a wide spectrum of interstitial lung diseases (ILDs).

Methods—Twenty-four patients (13 males, 11 females; mean age ± SD, 65.4 ± 14.3 years; age range, 40–84 years) with a diagnosis of ILDs who were admitted to the Interstitial Lung Disease Unit were prospectively enrolled. Patients were examined with a 56-lung intercostal space LUS protocol in lateral decubitus position, at baseline, 6-months, and 1-year. The LUS score was defined as the sum of B-lines counted in each intercostal space. All patients underwent complete pulmonary function tests at baseline and follow-up time-points. High-resolution computed tomography (HRCT) was performed at baseline and during follow-up, according to personalized patients' needs. All HRCT studies were graded according to the Warrick scoring system (WS).

Results—Pooled data analysis showed a significant correlation between WS and LUS scores ($P < .001$). For separate time-point analysis, a significant correlation between LUS scores and WS was found at baseline ($P < .001$) and 1 year ($P = .005$). LUS scores negatively correlated with alveolar volume (VA) ($P < .046$) and diffusing capacity for carbon monoxide (DLCO) ($P < .001$) at 6 months and with transfer coefficient of the lung for carbon monoxide (KCO) ($P < .031$) and DLCO ($P = .002$) at 12-months. A multivariate regression model showed DLCO to be an independent predictor of LUS score at 1 year ($P = .026$).

Conclusions—Our results highlight the validity and potential applicability of LUS for disease monitoring in a wide spectrum of ILDs.

Key Words—disease monitoring; high-resolution tomography, X-ray computed; HRCT; interstitial lung disease; ultrasound

KEY MESSAGES

Early identification of individuals with fibrotic ILD poses a number of challenges

Many occupational/environmental exposures as well as a family history of the disease are associated with increased risk of preclinical and overt fibrotic ILD

Screening programmes are currently realistic only in selected populations at high risk of developing the disease


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