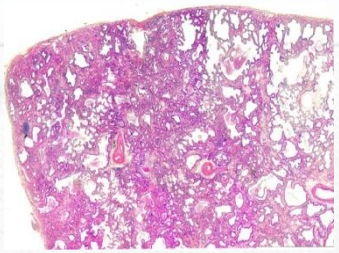
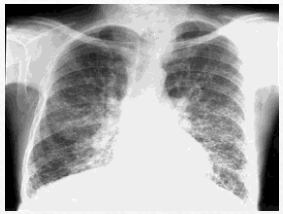
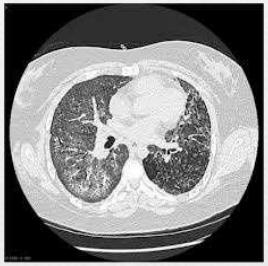




Fibrotic NSIP



Αθηνά Γόγαλη

Πνευμονολόγος

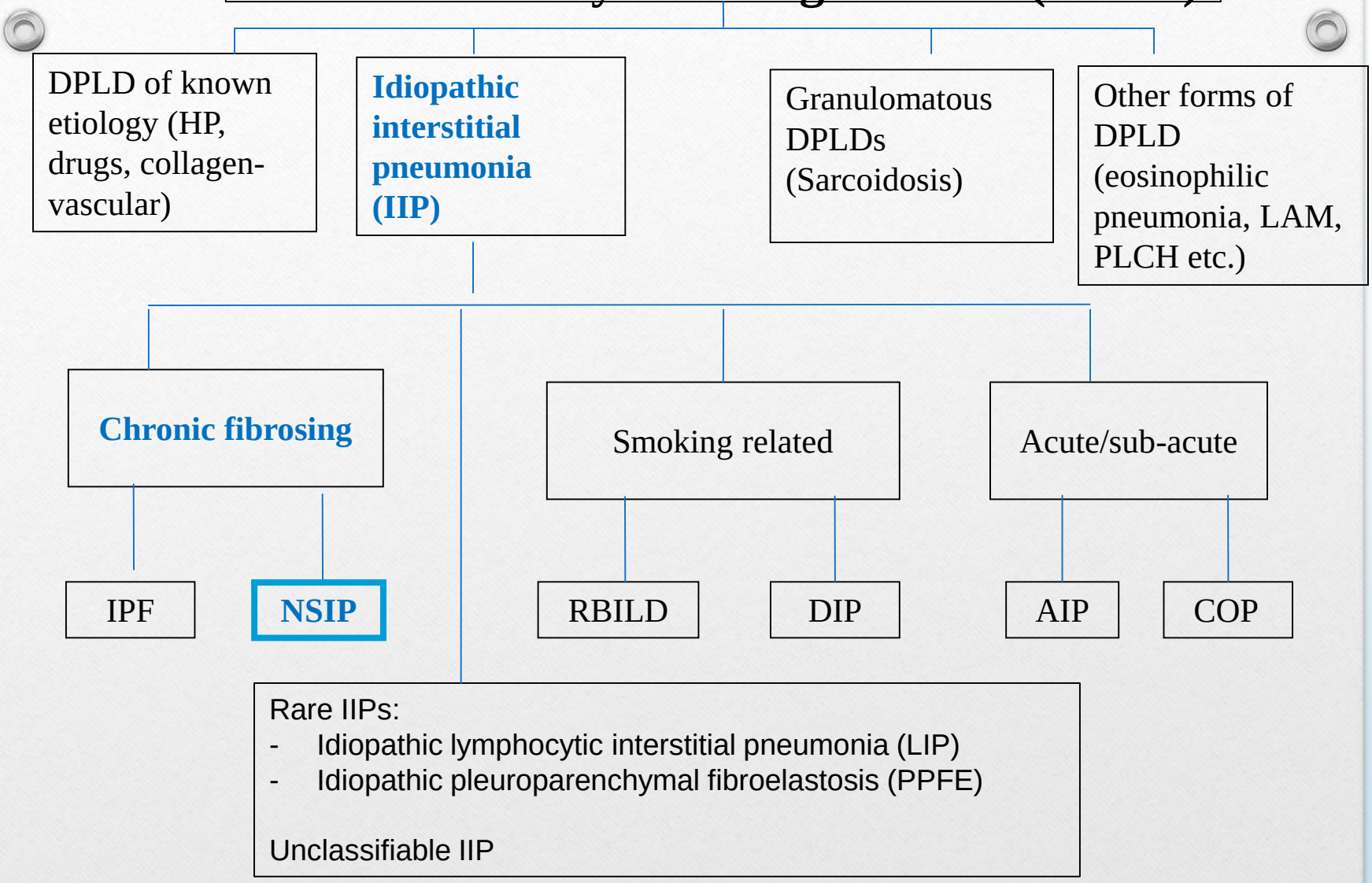
ΕΠ Α' ΠΓΝΙ

NSIP *history*

- 1994: Katzenstein & Fiorelli: NSIP defined as a (*wastebasket)* histopathologic presentation which does not fit Liebow's classification of IIP
- 1998 : A reevaluation of biopsies of IIPs diagnosed before led to 14% of previous IPF/UIP diagnoses being reclassified as NSIP (Bjoraker et al.)
- 2002: ATS/ERS international consensus panel
  - Accepted as a provisional entity
- 2008: ATS project report: idiopathic NSIP is a distinct clinical entity with a better survival than IPF
- 2013: ATS/ERS: update of the multidisciplinary classification of IIP
  - Idiopathic NSIP confirmed as a distinct clinical entity
  - NSIP occurs as:
    - Idiopathic (one of the two fibrosing IIP with IPF)
    - Diverse settings: CVD; HP; drug toxicity; familial pulmonary fibrosis
    - Usefulness of MDD

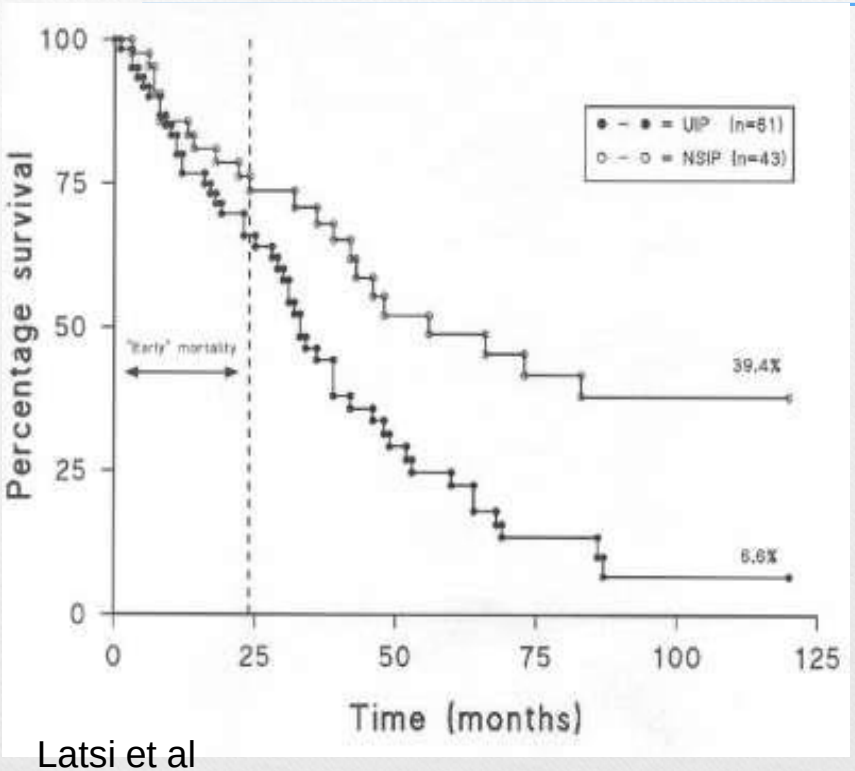
Travis AJRCCM 2008; Poletti & Chilosi SRCCM 2012; Travis AJRCCM 2013

Diffuse Parenchymal Lung Diseases (DPLD)

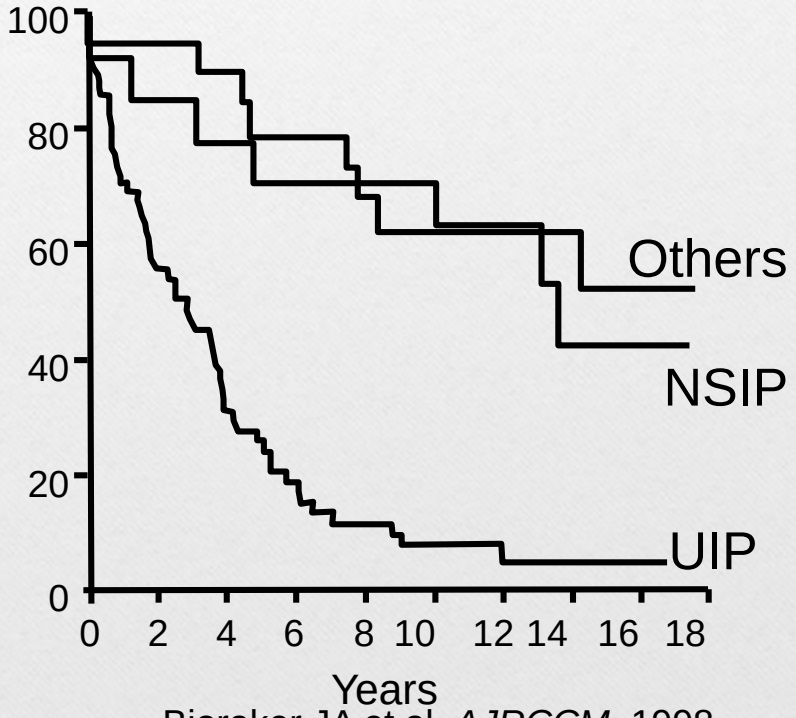


Spagnolo P. et al. Multidiscip Respir Med 2012;7(1):42
American Thoracic Society. Am J Respir Cnt Care Med. 2002;165(2):277-304
Travis WD, et al. Am J Respir Cnt Care Med 2013; 188 (6); 733-748

Is there a clinical meaning? YES: IPF and NSIP have different prognosis



Latsi et al



Bjoraker JA et al. *AJRCCM.* 1998

Are there any differences in etiopathogenesis in IPF and NSIP?

- **Nonspecific reactions of lung tissue to both external and internal injury**

Progressive Remodeling (IPF), Resolution and Healing (NSIP)

- **NSIP: More inflammation, Th1 dominant**

- **Neovascularization is substantially greater in IPF** than in NSIP
  - accompanied by greater expression of VEGF-A mRNA and MMP-2 mRNA

Takahashi et al., Pathol Int 2013

- **Proteomic analysis - UIP vs. NSIP**

Involves different subtypes of vimentin *Ohara et al., Histol Histopathol 2013*

Clinical associations of NSIP

Exclusion diagnosis !!!

Idiopathic NSIP

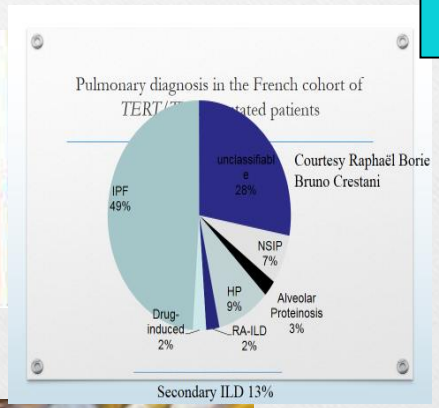
CTD's

HP

Drugs

HIV

the NSIP pattern more common than the UIP



Familiar NSIP

Immunodeficiency

IgG4 autoimmune disease
hypo and dysgammaglobulinemia – CVID

Clinical presentation of iNSIP

- Younger age (40-50 years), more often in women, non-smokers
- Insidious onset of dyspnea and dry cough
- Systemic signs and symptoms
- Digital clubbing and crackles are less frequent

REVISED HISTOLOGIC FEATURES OF NONSPECIFIC INTERSTITIAL PNEUMONIA

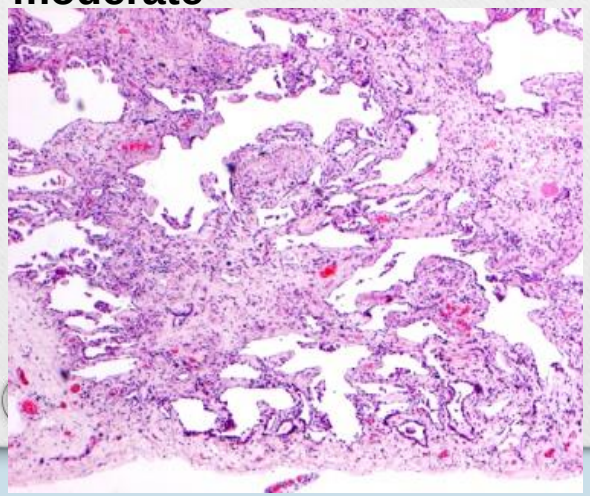
Key Features

Fibrosing Pattern*

Dense or loose interstitial fibrosis *with uniform appearance*.

Lung architecture is frequently preserved

Interstitial chronic inflammation—mild or moderate



Pertinent Negative Findings

Fibrosing Pattern

Temporal heterogeneity pattern: fibroblastic foci with dense fibrosis are inconspicuous or absent – this is especially important in cases with patchy involvement and subpleural or paraseptal distribution

Honeycombing inconspicuous or absent

(Enlarged fibrotic airspaces may be present)

Both Patterns

Acute lung injury pattern, especially hyaline membranes: absent

Eosinophils: inconspicuous or absent

Granulomas: absent

Lack of viral inclusions and organisms on special stains for organisms

Dominant airway disease such as extensive peribronchiolar metaplasia

American Journal of Respiratory and Critical Care Medicine **Vol 177. pp. 1338-1347 (2008)**

Diagnosis …..

HRCT? BAL? Biopsy?

HRCT & NSIP

Non Specific Interstitial Pneumonia CT features

IDIOPATHIC NONSPECIFIC INTERSTITIAL PNEUMONIA: HIGH-RESOLUTION COMPUTED TOMOGRAPHY FEATURES IN 61 CASES

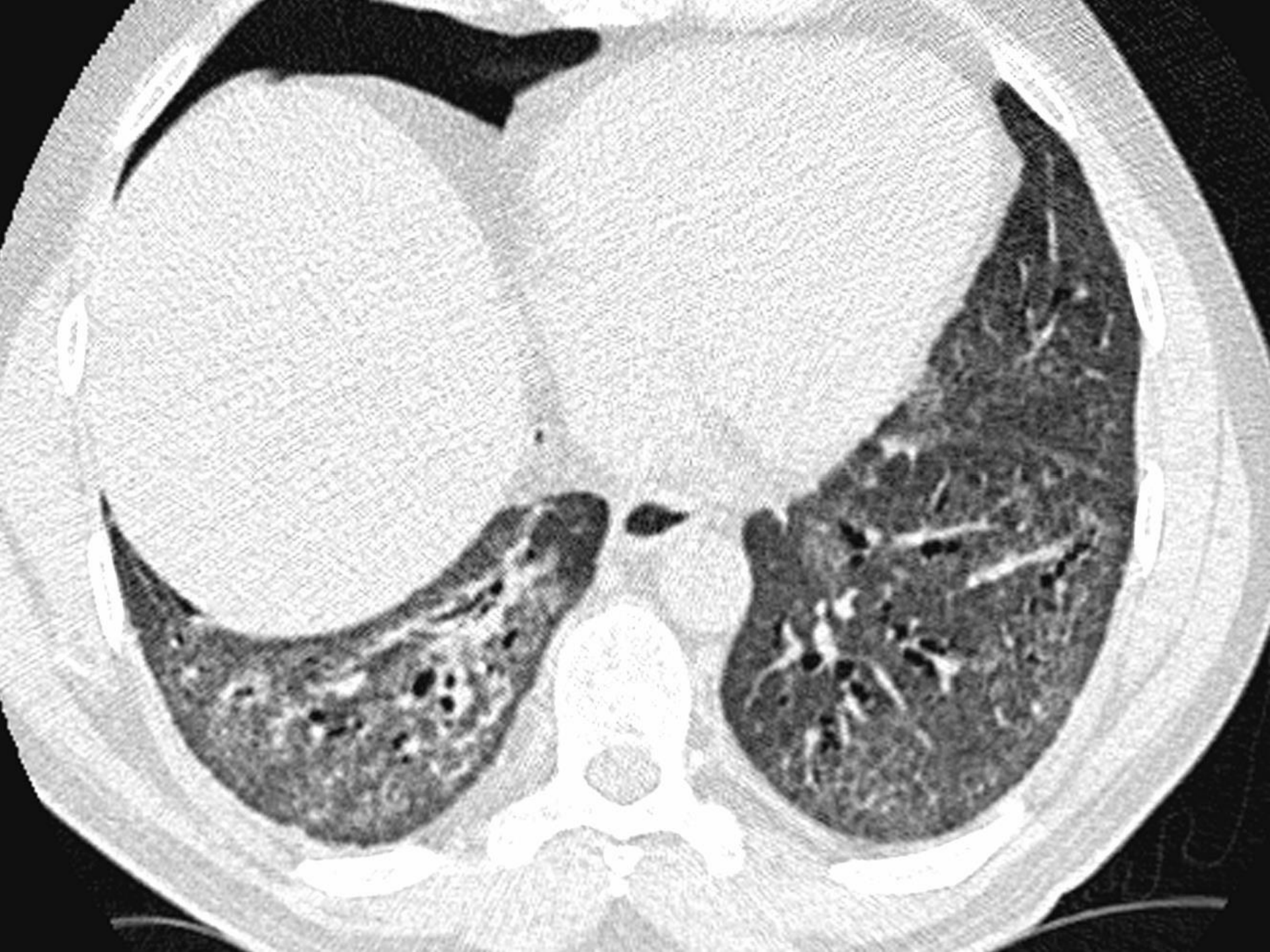
Radiologic Feature	Number (*n* = *61*)	Percent	95% CI
Craniocaudal Distribution			
Lower	**56**	**92**	**82–96**
Diffuse	**5**	**8**	**4–18**
Upper	**0**	**0**	**0–6**
CT axial distribution			
Diffuse	**29**	**47**	**36–60**
Peripheral	**28**	**46**	**34–58**
Central	**4**	**7**	**3–16**

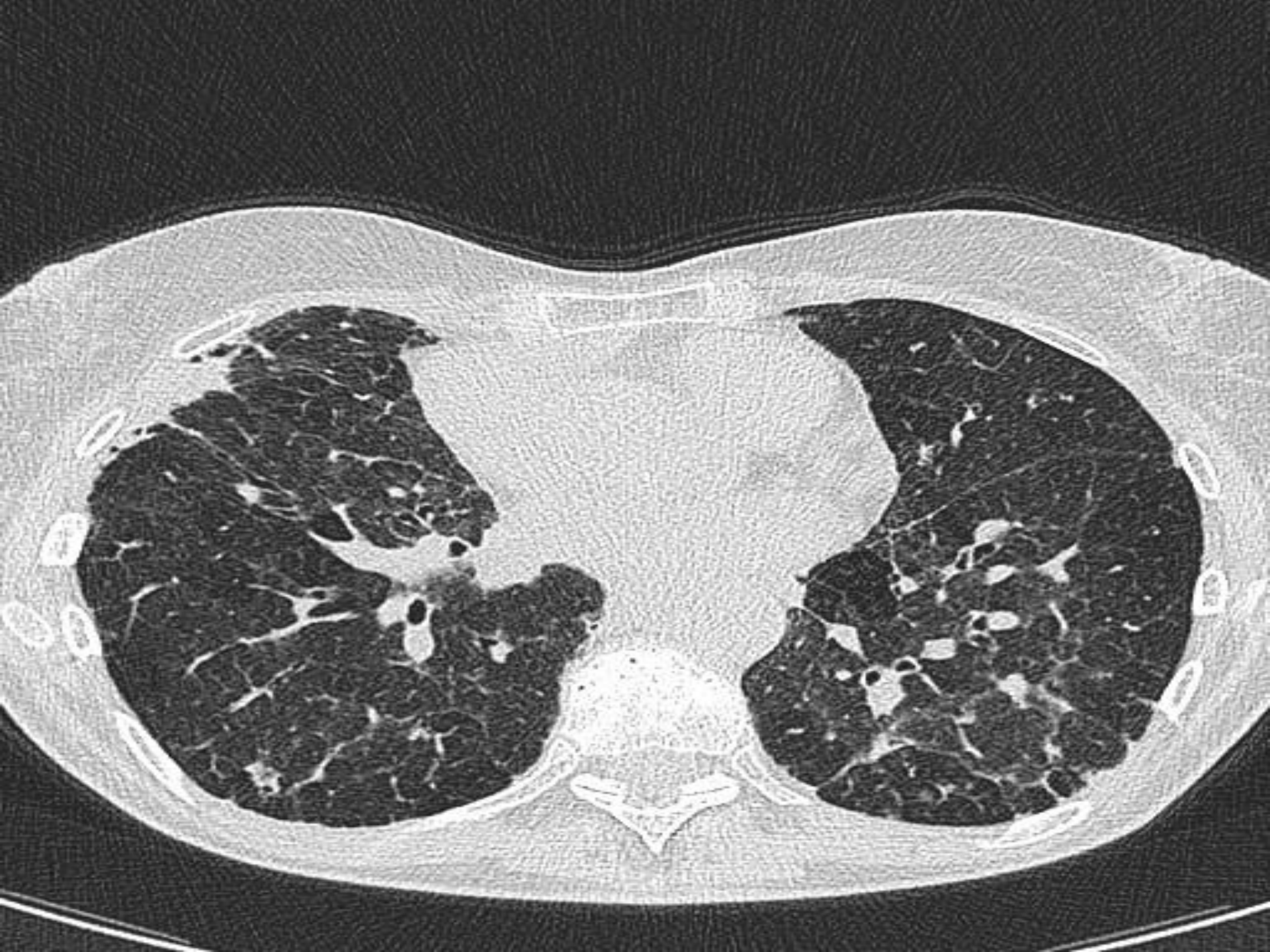
American Journal of Respiratory and Critical Care Medicine Vol 177. pp. 1338-1347, (2008)

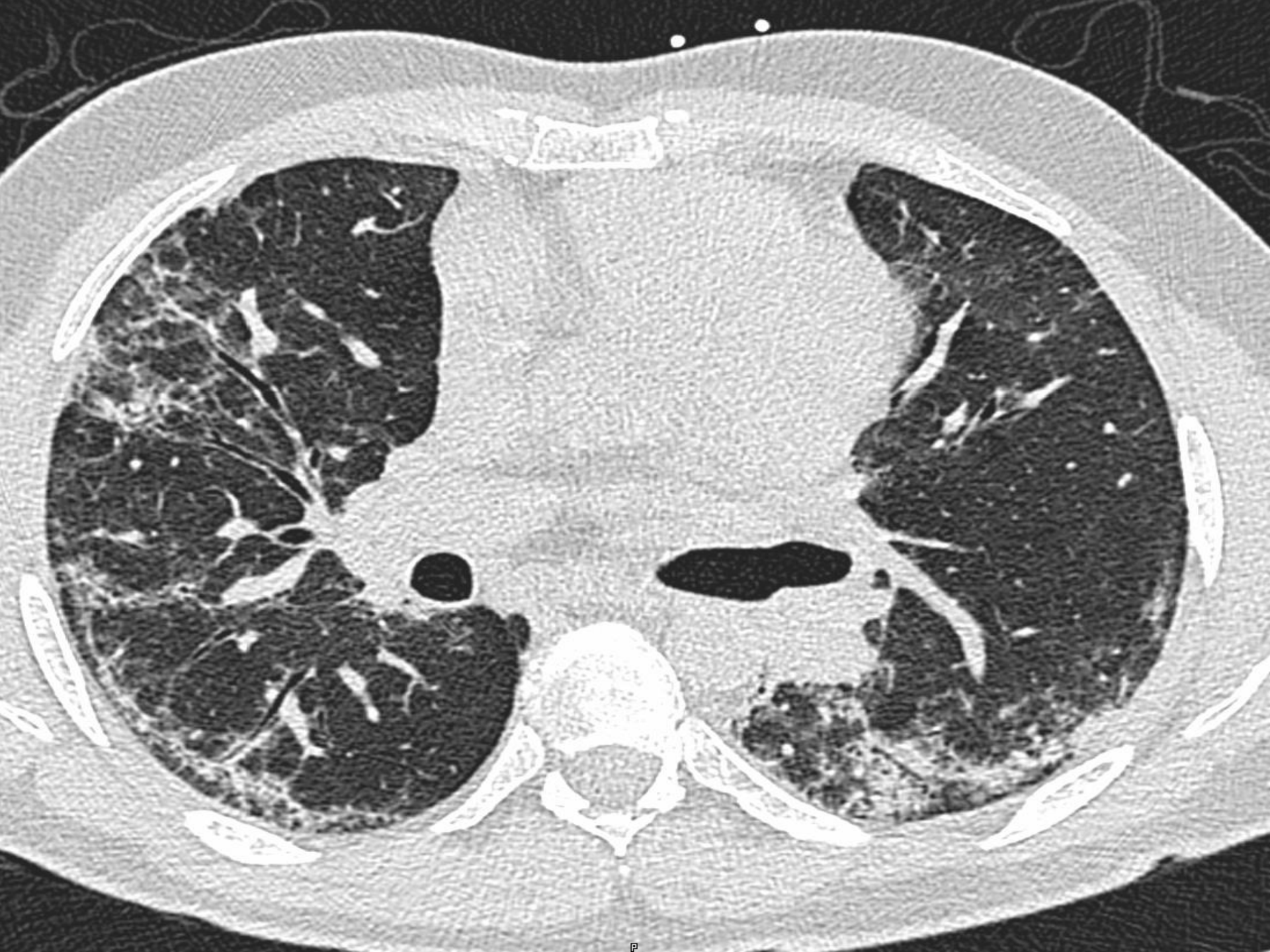
Non Specific Interstitial Pneumonia CT features

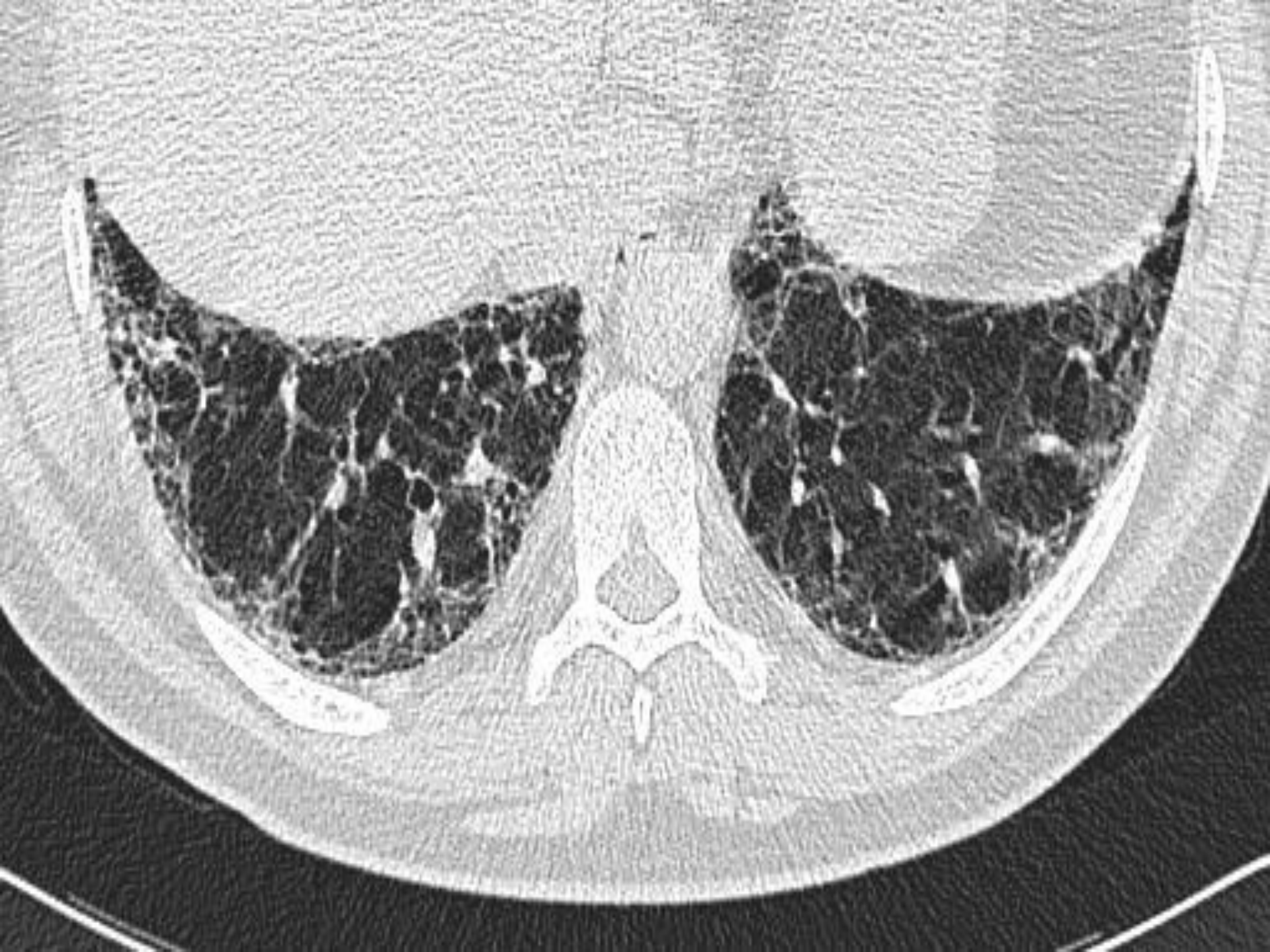
Reticulation	53	87	76–93
Traction bronchiectasis	50	82	71–90
Lobar volume loss	47	77	65–86
Ground-glass attenuation	27	44	33–57
Subpleural sparing	13	21	13–33
Emphysema/cysts	7	12	6–22
Consolidation	8	13	7–24
Peribronchial thickening	4	7	3–16
Substantial micronodules	2	3	1–11
Honeycombing	3	5	2–13

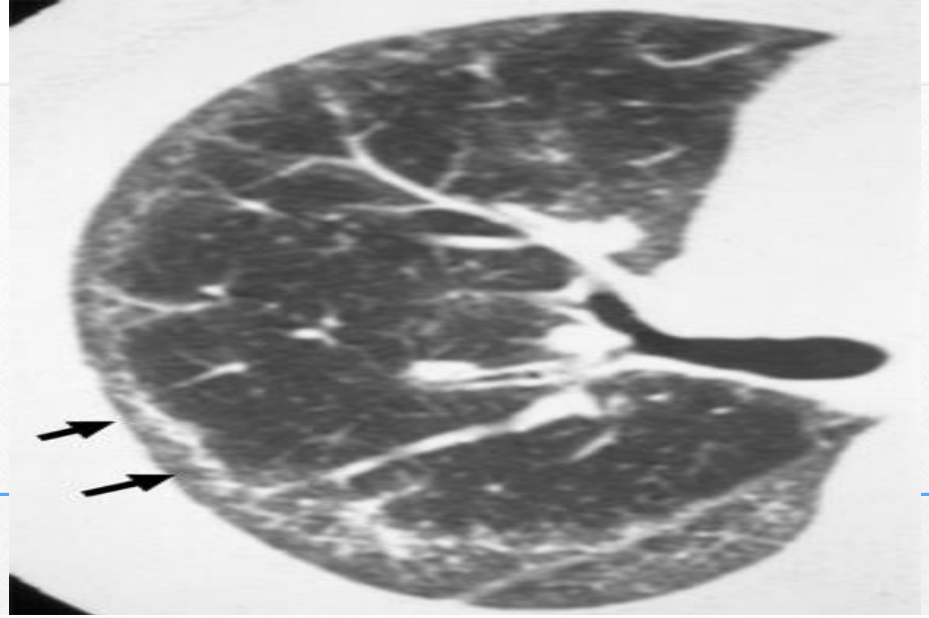
American Journal of Respiratory and Critical Care Medicine Vol 177. pp. 1338-1347, (2008)

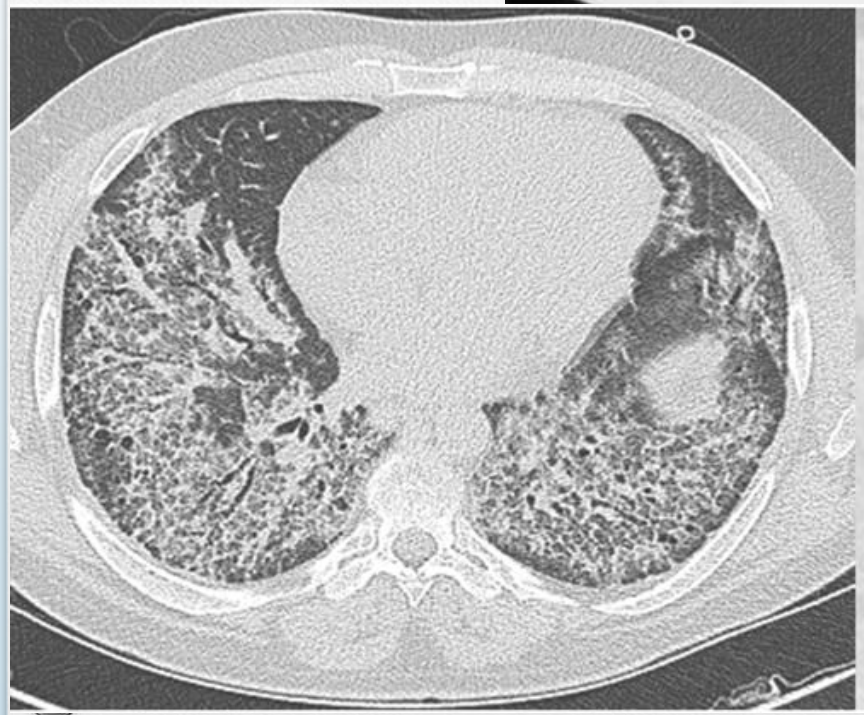


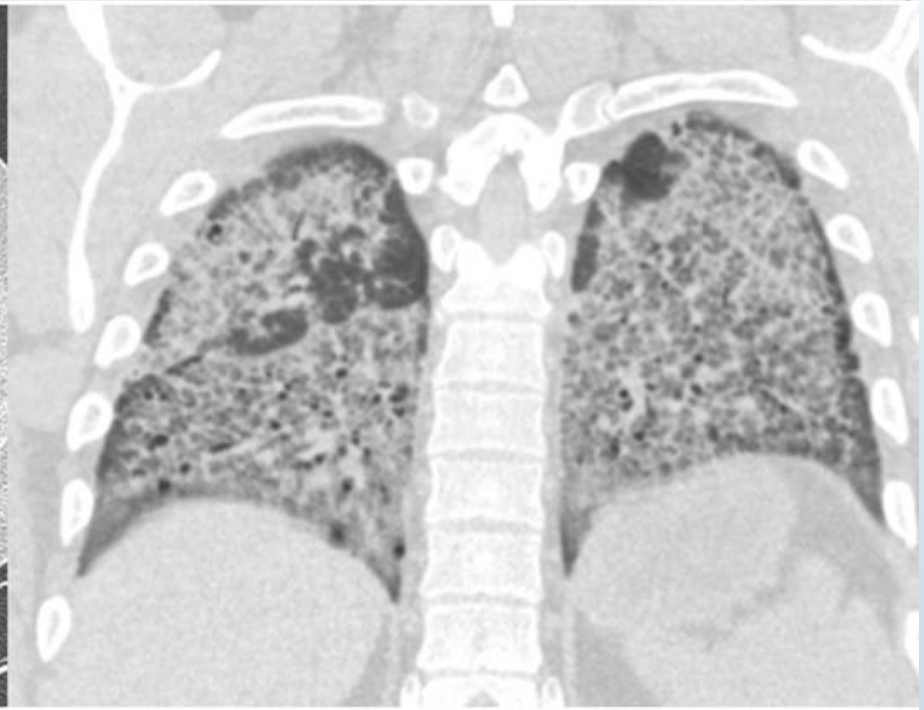


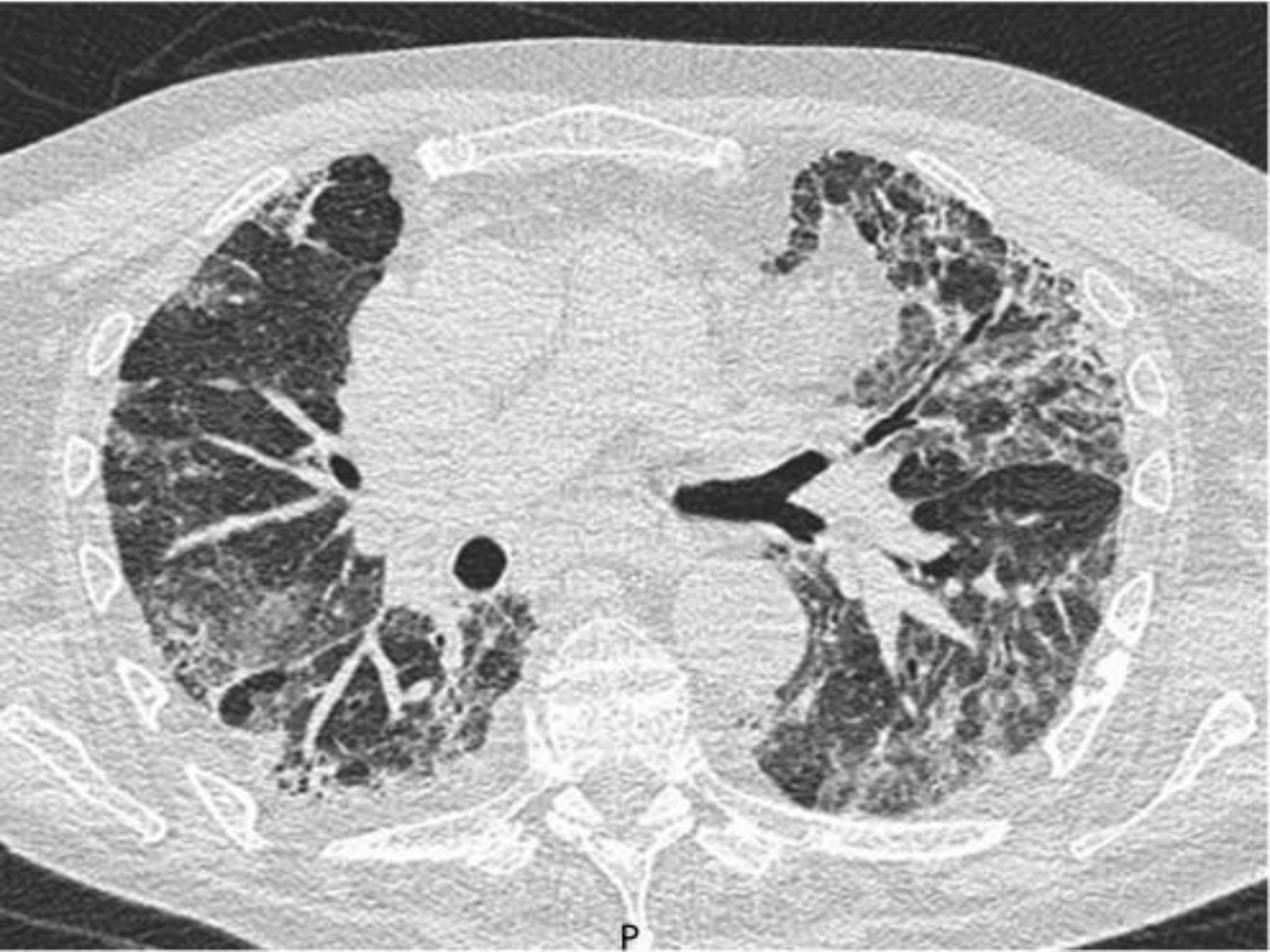











P

MacDonald SLS. Radiology 2001; 221:600-605

	NSIP	UIP	p value
Extent	37.1 ± 22.7	44.0 ± 23.0	NS
Proportion GGO	47.4 ± 27.2	26.7 ± 22.5	<0.005
Coarseness	6.0 ± 3.1	8.3 ± 2.9	0.01
Subpleural	50/84	91/128	NS
Basal	52/84	89/128	NS
Bronchocentric	4/84	11/128	NS

Is HRCT diagnostic ? PPV < 50%

Thoracic Imaging

Idiopathic Interstitial Pneumonias: Diagnostic Accuracy of Thin-Section CT in 129 Patients[1]

PURPOSE: To determine whether idiopathic interstitial pneumonias can be differentiated on the basis of the pattern and distribution of abnormalities at thin-section computed tomography (CT).

Radiology

HRCT remarkably inaccurate in NSIP (9%)

Thomas E. Hartman, MD
Stephen J. Swensen, MD
David M. Hansell, MD
Thomas V. Colby, MD
Jeffrey L. Myers, MD
Henry D. Tazelaar, MD
Andrew G. Nicholson, MD
Athol U. Wells, MD
Jay H. Ryu, MD
David E. Midthun, MD
Roland M. du Bois, MD
Nestor L. Müller, MD

Nonspecific Interstitial Pneumonia: Variable Appearance at High-Resolution Chest CT[1]

PURPOSE: To describe the computed tomographic (CT) findings in patients with nonspecific interstitial pneumonia (NSIP) and to compare these with the CT findings of other chronic infiltrative lung diseases.

HRCT: a wide variety in NSIP. Findings ressembling HP, UIP, OP

Diagnosis …..

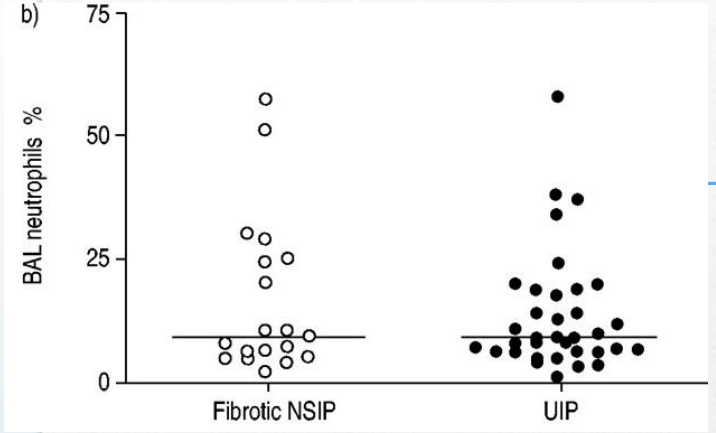
HRCT? BAL? Biopsy?

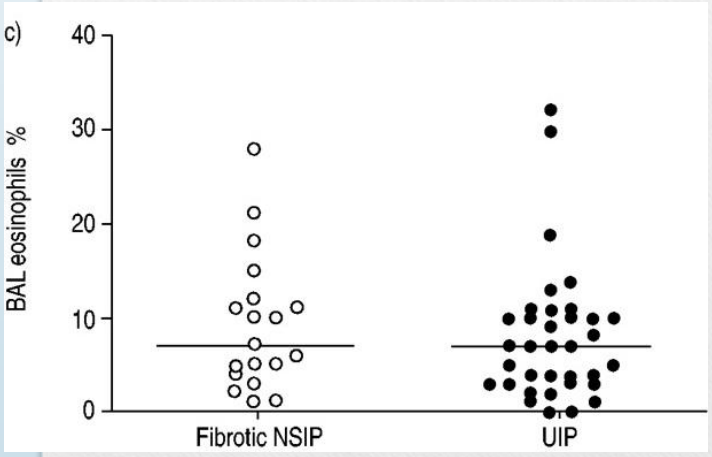
BAL & NSIP

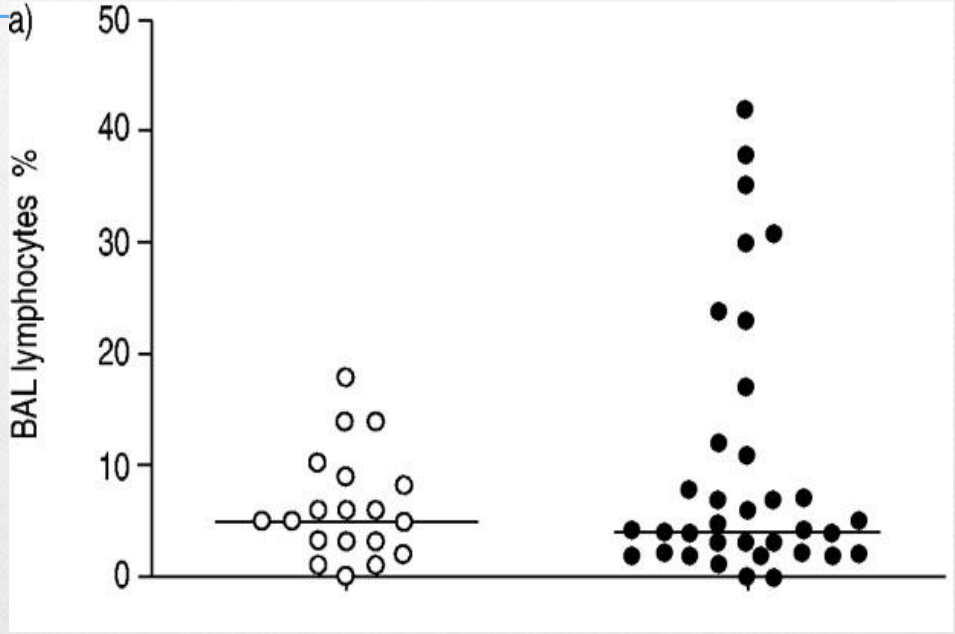
Nagai SR et al. Eur Respir J 1998; 12:1010-1019

	NSIP	COP	IPF
Lymph	37.3%	44.4%	7.2%
Neut	8.0%	6.4%	5.0%
Eos	5.5%	2.2%	3.3%

BAL compared between IPF and NSIP







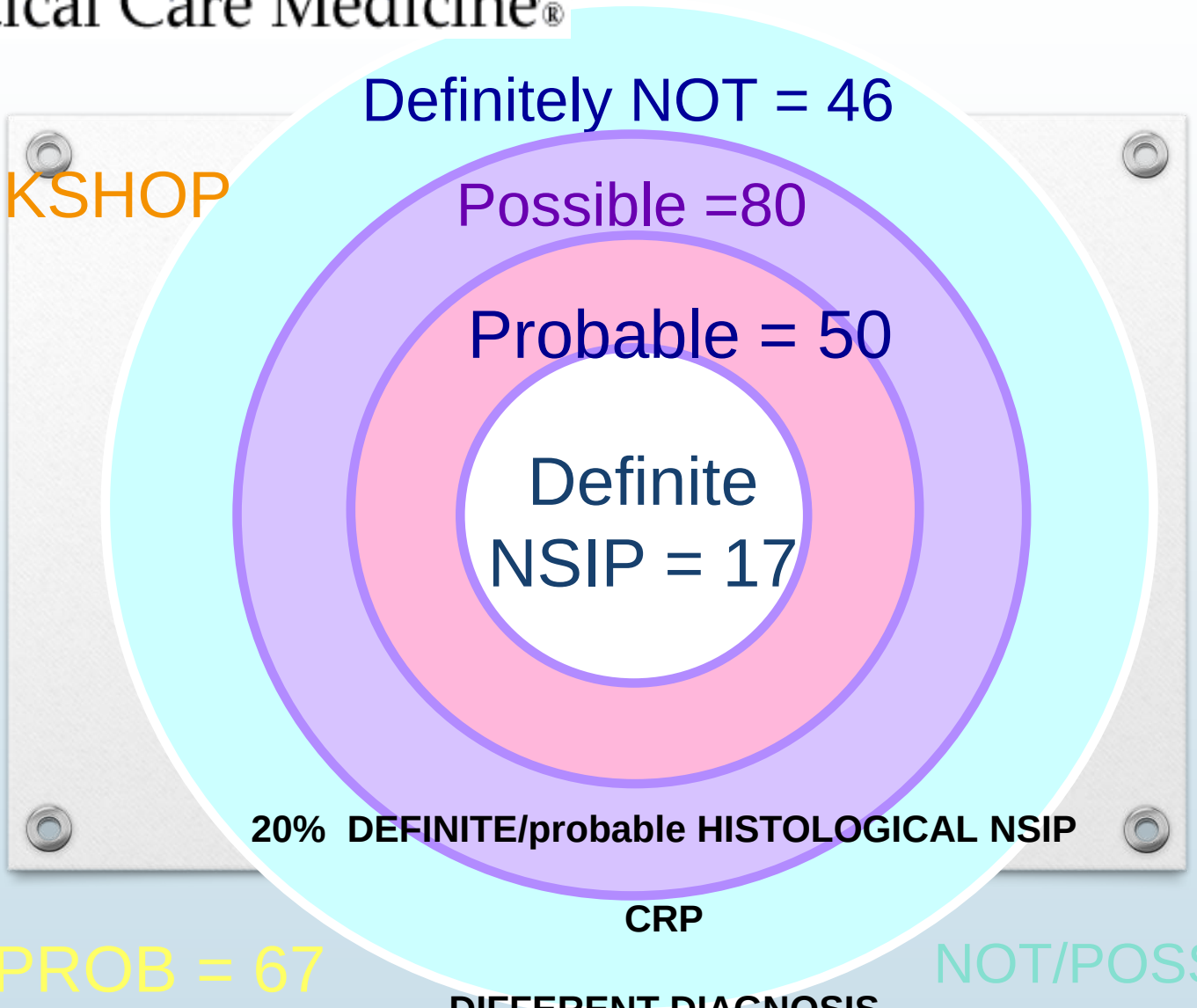
Veeraraghavan S et al. Eur Respir J 2003; 22:239-244

Is NSIP simply a histological diagnosis?

AMERICAN JOURNAL OF
Respiratory and
Critical Care Medicine®

TOTAL CASES = 193

NSIP
WORKSHOP



DEF/PROB = 67

NOT/POSS = 126

THE LANCET
Respiratory Medicine

Online First Current Issue All Issues Multimedia About the Journal Advisory Board

Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study

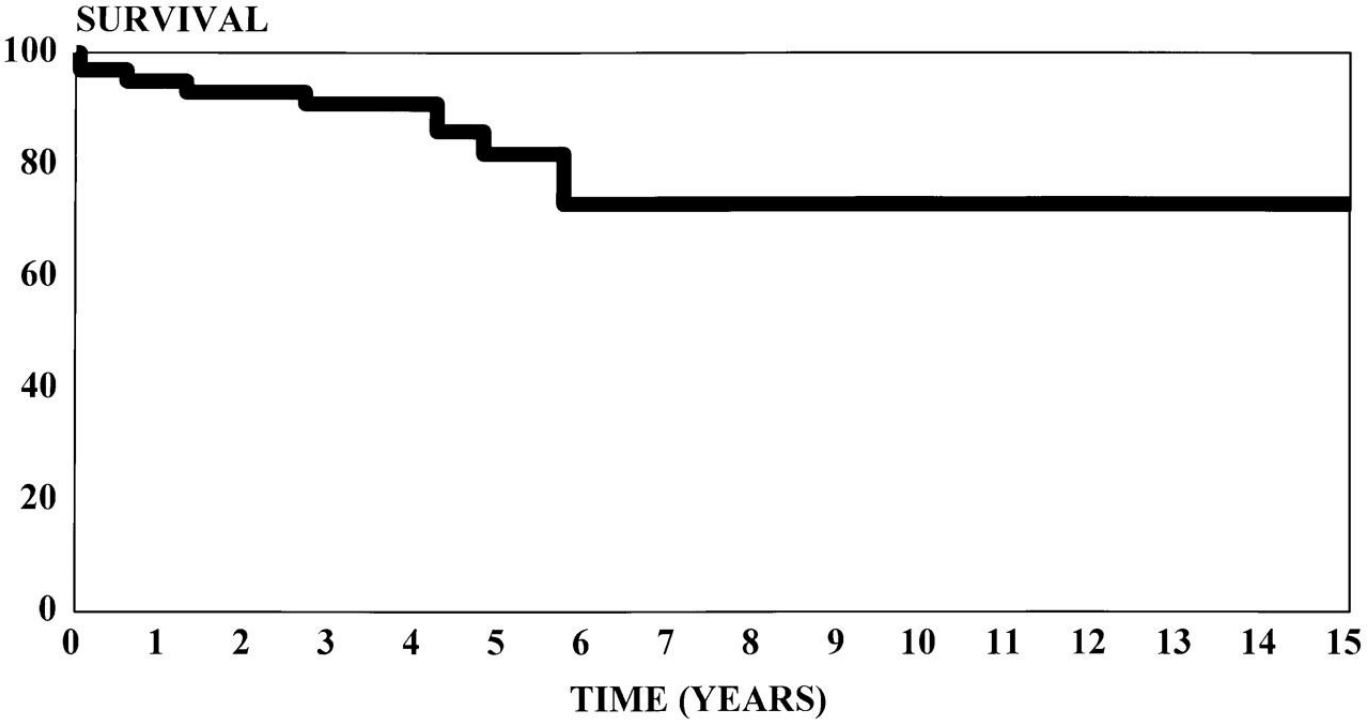
Dr Simon L F Walsh, MD, Prof Athol U Wells, MD, Sujal R Desai, MD, Prof Venerino Poletti, MD, Sara Piciucchi, MD, Alessandra Dubini, MD, Prof Hilario Nunes, MD, Prof Dominique Valeyre, MD, Prof Pierre Y Brillet, MD, Marianne Kambouchner, MD, Prof António Morais, MD, José M Pereira, MD, Conceição Souto Moura, MD, Prof Jan C Grutters, MD, Daniel A van den Heuvel, MD, Hendrik W van Es, MD, Matthijs F van Oosterhout, MD, Cornelis A Seldenrijk, MD, Elisabeth

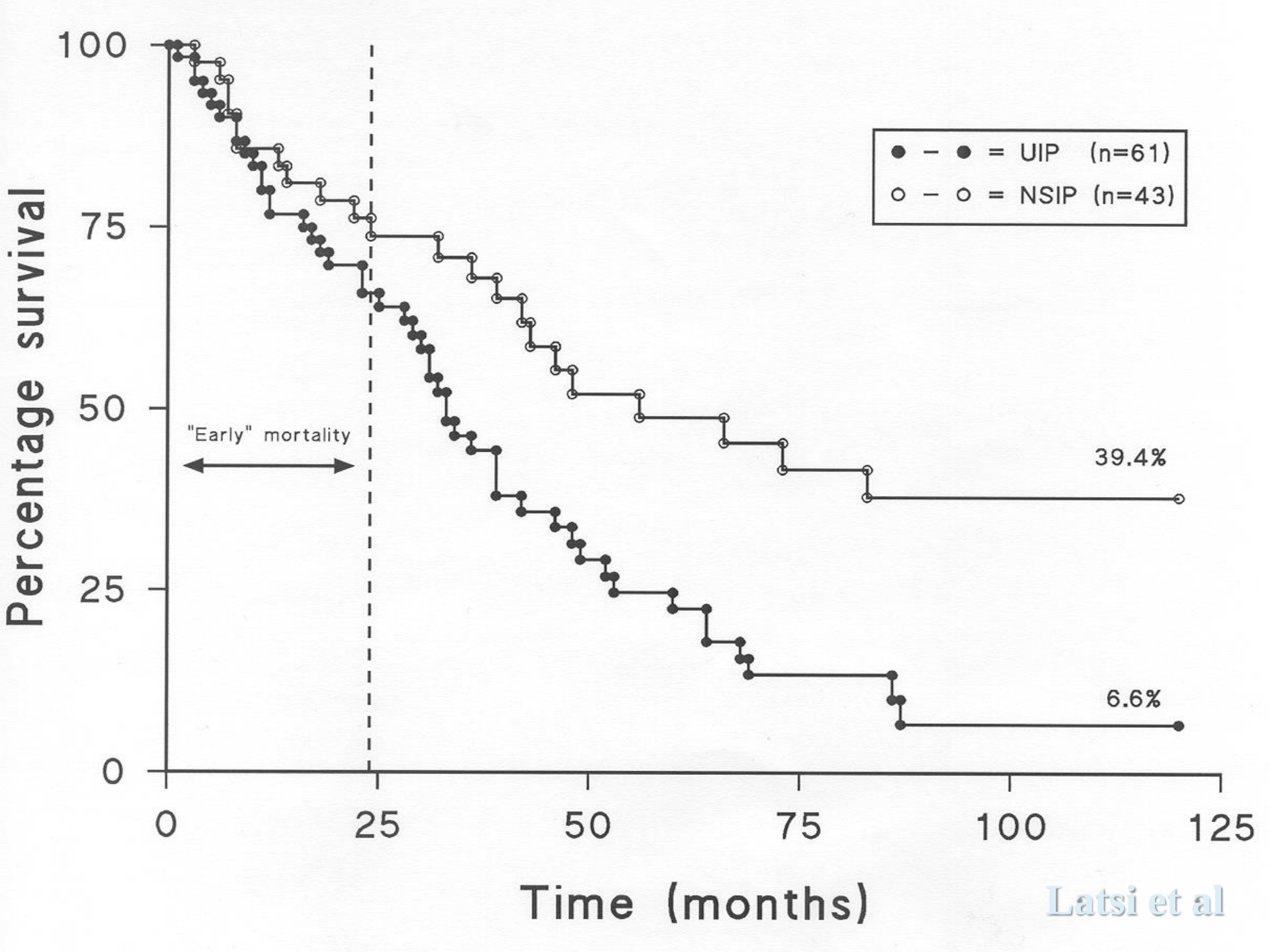
Inter-MDTM agreement on diagnostic likelihoods was good for IPF (κw=0·71 [IQR 0·64–0·77]) and connective tissue disease-related interstitial lung disease (κw=0·73 [0·68–0·78]); moderate for non-specific interstitial pneumonia (NSIP; κw=0·42 [0·37–0·49]);and fair for hypersensitivity pneumonitis (κw=0·29 [0·24–0·40])

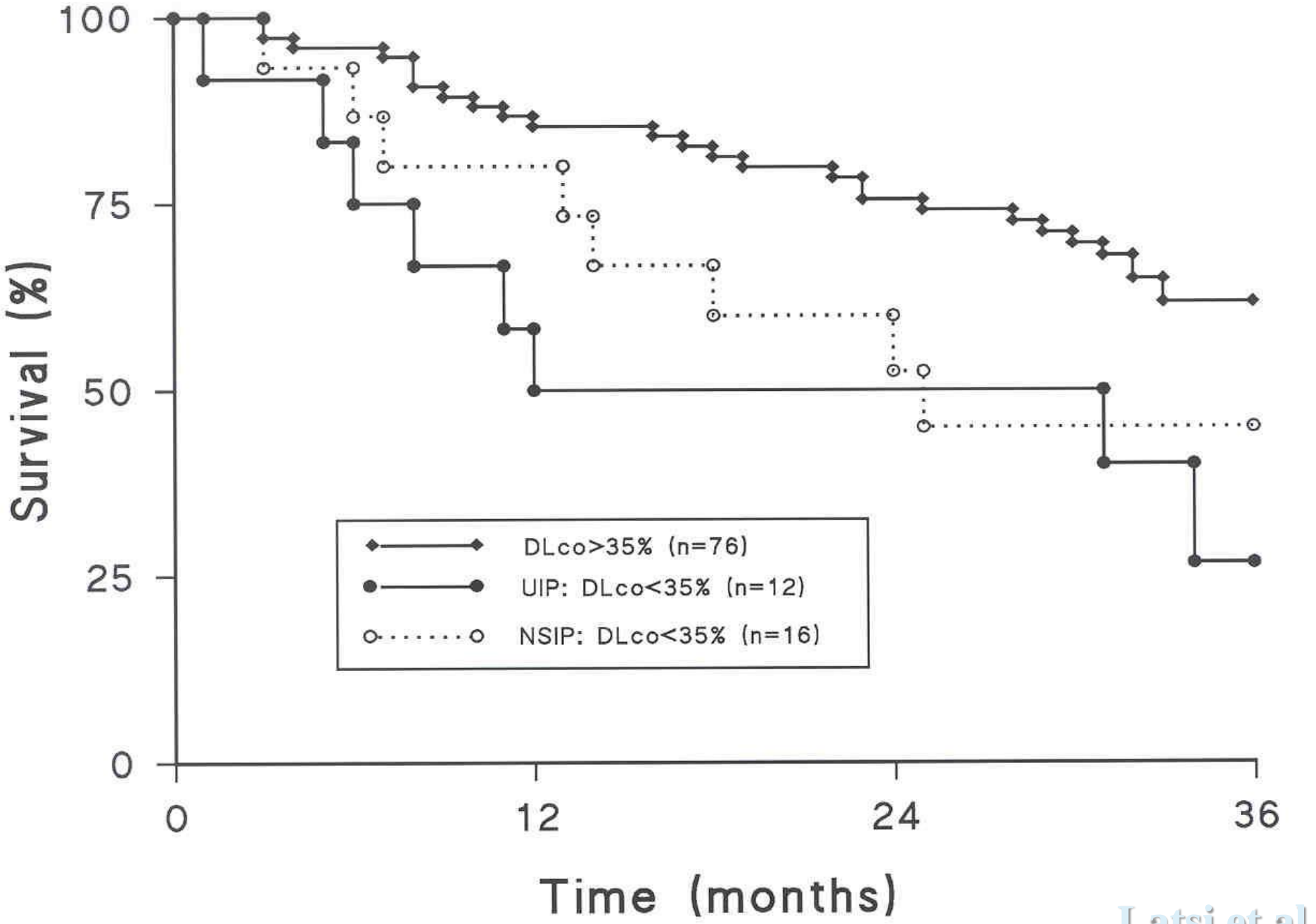
Poor levels of inter-MDTM agreement were demonstrated for NSIP

Prognosis…

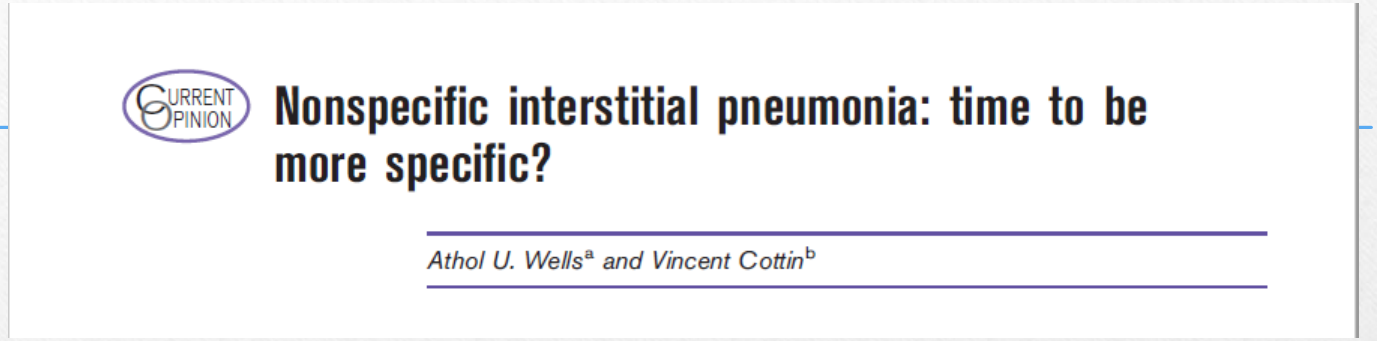
American Journal of Respiratory and Critical Care Medicine Vol 177. pp. 1338-1347, (2008)




100
75
50
25
0
Percentage survival
"Early" mortality
● – ● = UIP (n=61)
○ – ○ = NSIP (n=43)
39.4%
6.6%
0
25
50
75
100
125
Time (months)
Latsi et al


100
75
50
25
0
Survival (%)
0
12
24
36
Time (months)
DLco>35% (n=76)
UIP: DLco<35% (n=12)
NSIP: DLco<35% (n=16)

It is obvious that NSIP cannot be considered as a uniform entity



Two major idiopathic NSIP subgroups

(i.e. isolated NSIP and an NSIP/OP overlap)

FIBROTIC NSIP

sub-groups

- ‘chronic NSIP’ (isolated NSIP)
- ‘subacute NSIP’ (organizing pneumonia/NSIP overlap)

Taniguchi H

- ‘systemic sclerosis-type NSIP’ (isolated NSIP)
- ‘inflammatory myopathy-type NSIP’ (organizing pneumonia/NSIP overlap)

Poletti V

Histopathology

Histopathology 2016, 68, 347–355. DOI: 10.1111/his.12761

Organizing pneumonia components in non-specific interstitial pneumonia (NSIP): a clinicopathological study of 33 NSIP cases

Zhen Huo, Ji Li, Shanqing Li,[1] Haibo Zhang,[2] Zhengyu Jin,[2] Junyi Pang, Hongrui Liu, Juhong Shi[3] & Ruie Feng

Department of Pathology, [1]Department of Thoracic Surgery, [2]Department of Radiology, and [3]Department of Respiratory Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Date of submission 9 February 2015
Accepted for publication 18 June 2015
Published online Article Accepted 22 June 2015

Huo Z, Li J, Li S, Zhang H, Jin Z, Pang J, Liu H, Shi J & Feng R

(2016) *Histopathology* 68, 347–355. DOI: 10.1111/his.12761

Organizing pneumonia components in non-specific interstitial pneumonia (NSIP): a clinicopathological study of 33 NSIP cases

Aims: To review the clinical, radiological and pathological features of non-specific interstitial pneumonia (NSIP), mainly to characterise organizing pneumonia (OP) components in NSIP.

Methods and results: Lung biopsy samples from 33 NSIP patients were collected over a period of 10 years. Microscopic analysis revealed that 13 cases showed a cellular pattern and 20 showed a mixed/fibrosing pattern. OP components were detected in 26 cases (13 with a cellular pattern; 13 with a mixed/fibrosing pattern), and were found to constitute a median proportion of 9% (range, 1–40%) of the affected tissues. In nine cellular and four mixed/fibrosing NSIP cases, the OP components accounted for ≥10%. A proportion of ≥20% was found in only five cellular pattern cases. Twenty-nine patients were followed up: 17 showed improvements, five were stabilised, and seven showed progression.

Conclusions: OP components are common basic lesions in NSIP cases, although their proportion in cellular and mixed/fibrosing pattern cases varies substantially between patients. OP components do not impact on prognosis, even when they constitute ≥20% of the affected tissue. Thus, a high level of OP components does not exclude a diagnosis of NSIP in cases that otherwise show pathological and radiological findings characteristic of NSIP.

Keywords: high-resolution computed tomography scan, lung biopsy, non-specific interstitial pneumonia, organizing pneumonia components, pathology

Nonspecific Interstitial Pneumonia: What Is the Optimal Approach to Management?

Sara Tomassetti, MD[1] Jay H. Ryu, MD[2] Sara Piciucchi, MD[3] Marco Chilosi, MD[4] Venerino Poletti, MD[1]

[1] Department of Diseases of the Thorax, GB Morgagni Hospital, Forlì, Italy
[2] Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota
[3] Department of Radiology, GB Morgagni Hospital, Forlì, Italy
[4] Department of Pathology, University of Verona, Verona, Italy

Address for correspondence Sara Tomassetti, MD, Department of Diseases of the Thorax, GB Morgagni Hospital, via C Forlanini 34, 47121 Forlì (FC), Italy (e-mail: s.tomassetti@gmail.com).

Semin Respir Crit Care Med 2016;37:378–394.

- First, the "inflammatory type" characterized by prominent lymphocytic inflammation both on biopsy and bronchoalveolar lavage (BAL), and high-resolution computed tomography (HRCT) with mixed NSIP/organizing pneumonia pattern that tends to have a better response to corticosteroid and immunosuppressive treatment.

- Second, the "highly fibrotic" subgroup that shows prominent reticular changes and traction bronchiectasis by HRCT, high fibrotic background on biopsy, and no lymphocytosis on BAL. The latter fibrotic NSIP is the subgroup with less potential to respond to immunosuppressive treatment and a marginal risk to evolve into "full-blown idiopathic pulmonary fibrosis." The management of patients with fibrotic, progressive, and immunosuppressive treatment, refractory NSIP remains uncertain, and further studies are needed to address the role of antifibrotic drug in this settings.

American Thoracic Society Documents

Clinical Behavior	Treatment Goal	Monitoring Strategy
Reversible and self-limited (e.g., many cases of RB-ILD)	Remove possible cause	Short-term (3- to 6-mo) observation to confirm disease regression
Reversible disease with risk of progression (e.g., cellular NSIP and some fibrotic NSIP, DIP, COP)	Initially achieve response and then rationalize longer term therapy	Short-term observation to confirm treatment response. Long-term observation to ensure that gains are preserved
Stable with residual disease (e.g., some fibrotic NSIP)	Maintain status	Long-term observation to assess disease course
Progressive, irreversible disease with potential for stabilization (e.g., some fibrotic NSIP)	Stabilize	Long-term observation to assess disease course
Progressive, irreversible disease despite therapy (e.g., IPF, some fibrotic NSIP)	Slow progression	Long-term observation to assess disease course and need for transplant or effective palliation

EUROPEAN RESPIRATORY *journal*

OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

ERS/ATS TASK FORCE
INTERSTITIAL LUNG DISEASE

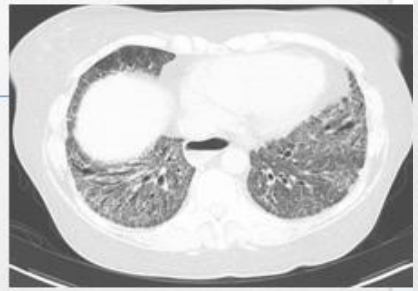
An official European Respiratory Society/ American Thoracic Society research statement: interstitial pneumonia with autoimmune features

Aryeh Fischer[1,17,18], Katerina M. Antoniou[2], Kevin K. Brown[3], Jacques Cadranel[4],

C. Morphologic domain

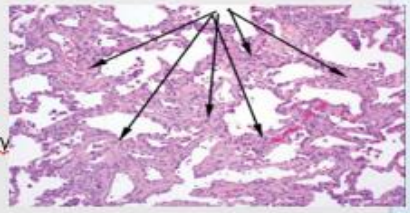
Suggestive radiology patterns by HRCT

- a. **NSIP**
- b. OP
- c. **NSIP with OP overlap**
- d. LIP



Histopathology patterns or features by surgical lung biopsy:

- a. **NSIP**
- b. OP
- c. **NSIP with OP overlap**
- d. LIP
- e. Interstitial lymphoid aggregates with germinal centres
- f. Diffuse lymphoplasmacytic infiltration (with or without ly



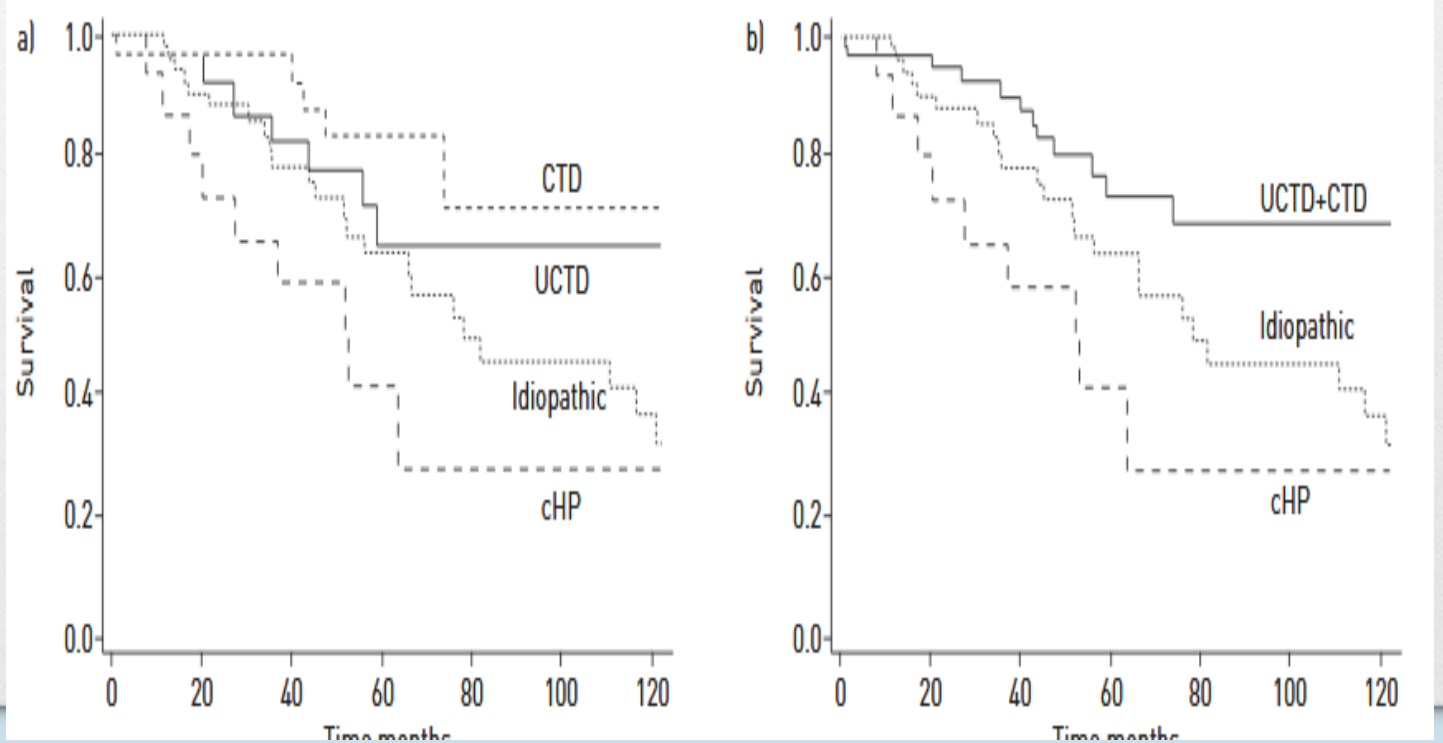
Nonspecific interstitial pneumonia: survival is influenced by the underlying cause

Hilario Nunes[1,2], Kirsten Schubel[2], Diane Piver[3], Eline Magois[4], Séverine Feuillet[5], Yurdagul Uzunhan[1,2], Zohra Carton[2], Abdellatif Tazi[5], Pierre Levy[6], Pierre-Yves Brillet[3], Andrew G. Nicholson[7], Marianne Kambouchner[8] and Dominique Valeyre[1,2]

This retrospective study included 127 biopsy-proven NSIP patients (65 women, mean±SD age 55±12 years). Survivals were estimated using a Kaplan–Meier curve and compared using the log-rank test. Multivariate analyses were based on a Cox model.

15 (11.8%) patients had cHP, 29 (22.8%) had CTD, 32 (25.2%) satisfied the Kinder criteria for UCTD and 51 (40.1%) had idiopathic NSIP. At the end of follow-up (mean±SD 64±54 months), a difference in survival was observed between aetiological groups (p=0.002). Survival was better for UCTD than for idiopathic NSIP (p=0.020) and similar to that observed for CTD. cHP survival tended to be poorer than that of idiopathic NSIP (p=0.087) and was an independent predictor of mortality (hazard ratio 2.17, 95% CI 1.05–4.47; p=0.035).

NSIP outcome is influenced by its cause. cHP exhibits the highest mortality. UCTD does not differ from CTD supporting the concept of autoimmune NSIP, with a prognosis that is better than that of idiopathic NSIP.



Contents lists available at ScienceDirect

Respiratory Medicine

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Nonspecific interstitial pneumonia preceding diagnosis of collagen vascular disease

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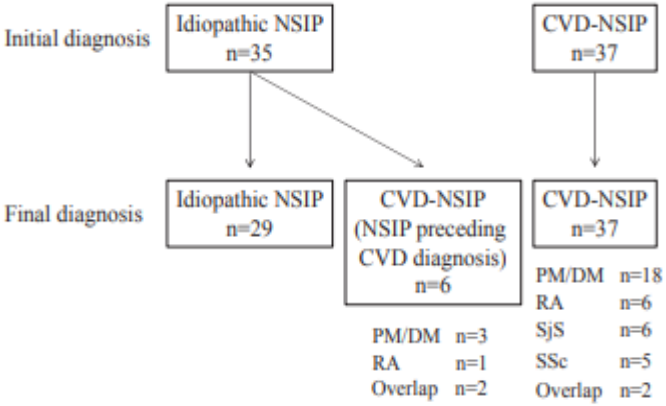
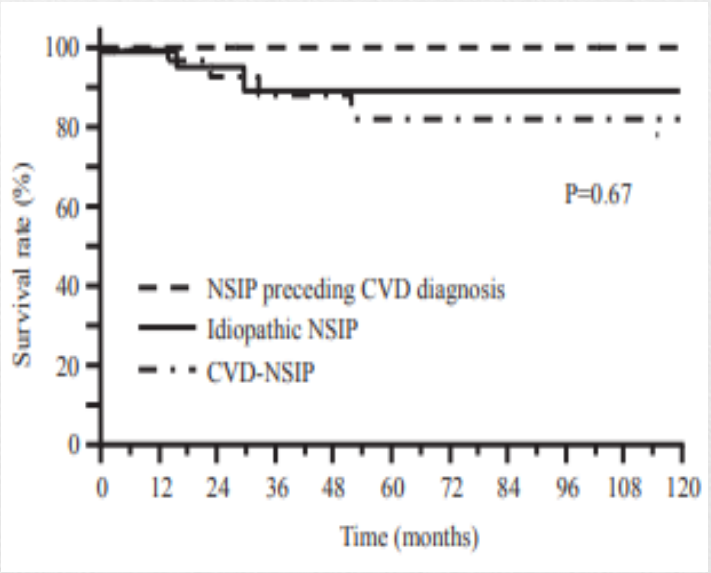


Fig. 1. The algorithm for the diagnosis of NSIP among enrolled patients. All 72 patients were initially diagnosed with idiopathic NSIP (n = 35) or CVD-NSIP (n = 37). Six patients (17.1%) initially diagnosed with NSIP developed CVD during the follow-up period.

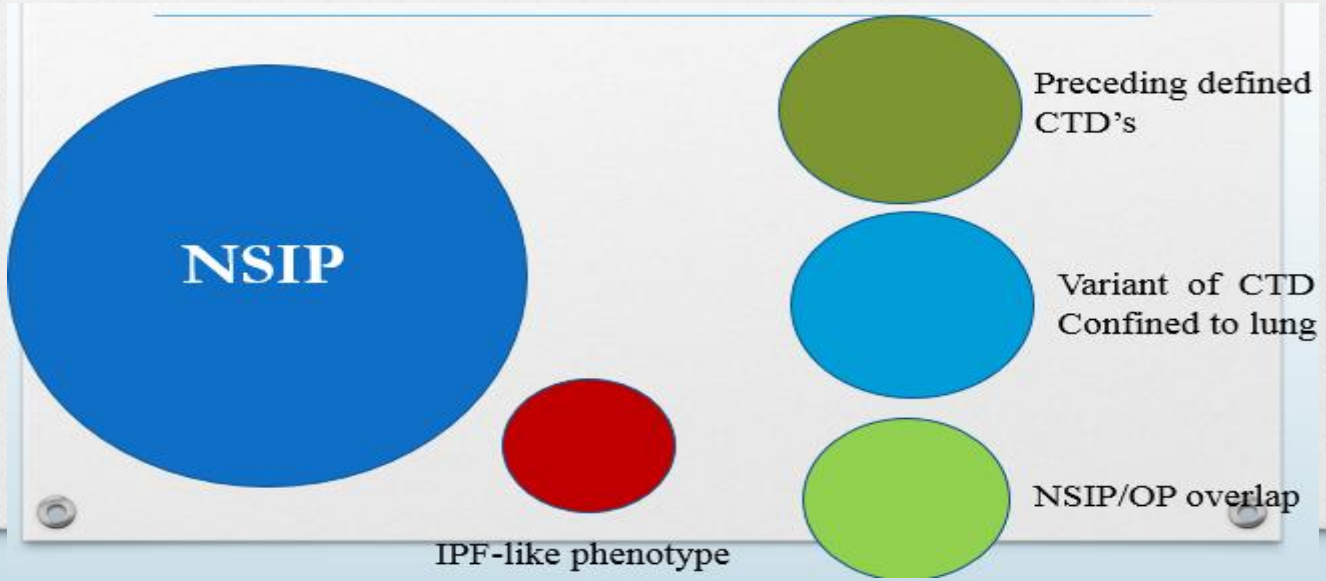


Unanswered questions

- Incidence? Prevalence?

- Is NSIP an unrecognized autoimmune disease?

- Can fibrotic NSIP be treated by anti-fibrotic treatment?



NSIP

A MDT DIAGNOSIS