70 ANNI DI REUMATOLOGIA ALLE MOLINETTE

IL POLMONE REUMATOIDE

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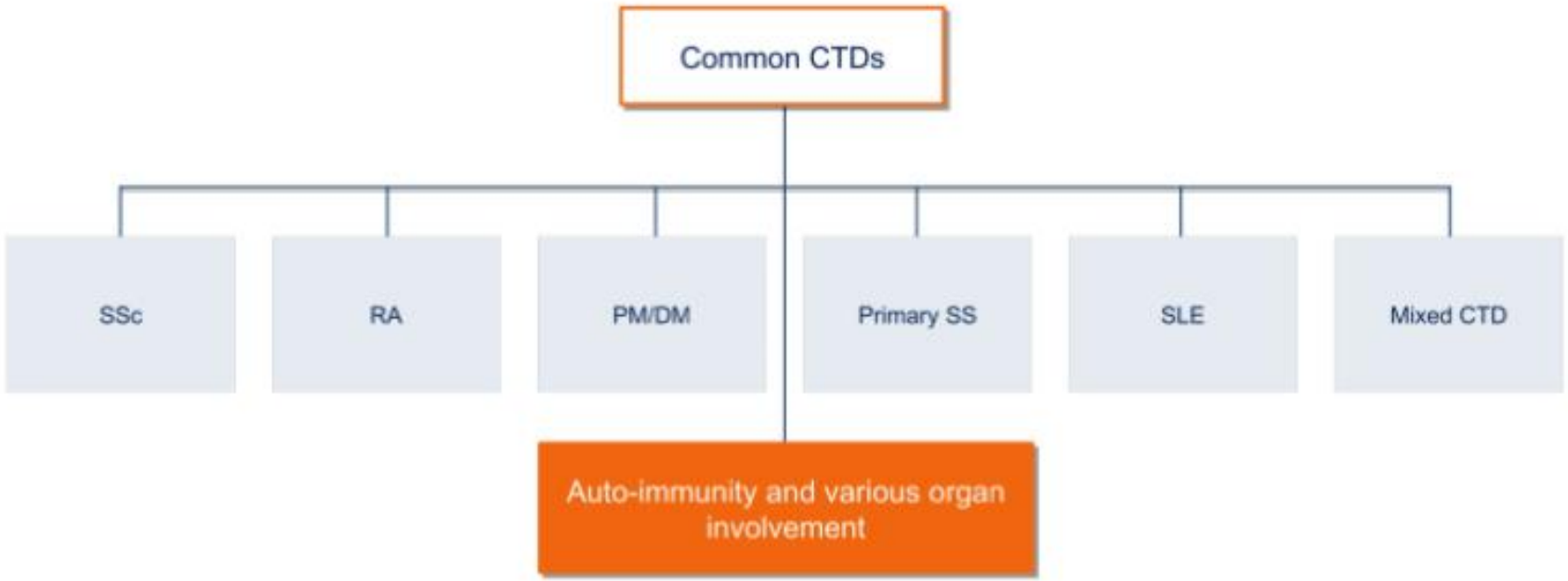
CTDs are a heterogeneous group of systemic disorders



Pulmonary complications, including ILD, are common in CTDs and are associated with significant morbidity and mortality

COINVOLGIMENTO POLMONARE NELL'AR

- ***30-40% dei pazienti con artrite reumatoide***
- ***Nel 10-20% è la prima manifestazione della malattia***
- ***Responsabile del 10-20% della mortalità***
- ***Spesso riscontro occasionale durante lo screening***
- ***Possibile individuazione nel follow-up***
- ***Può precedere o seguire le manifestazioni articolari***

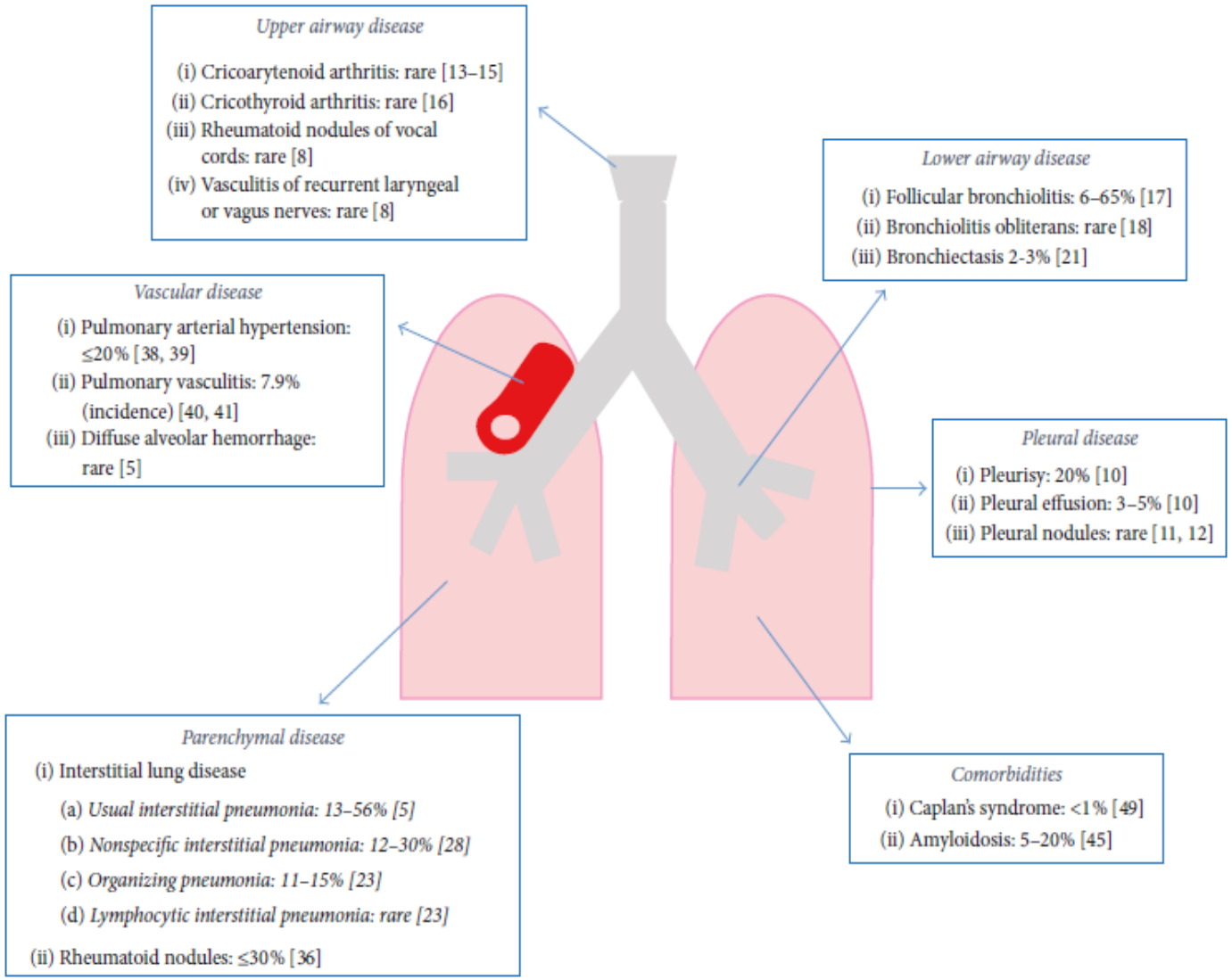
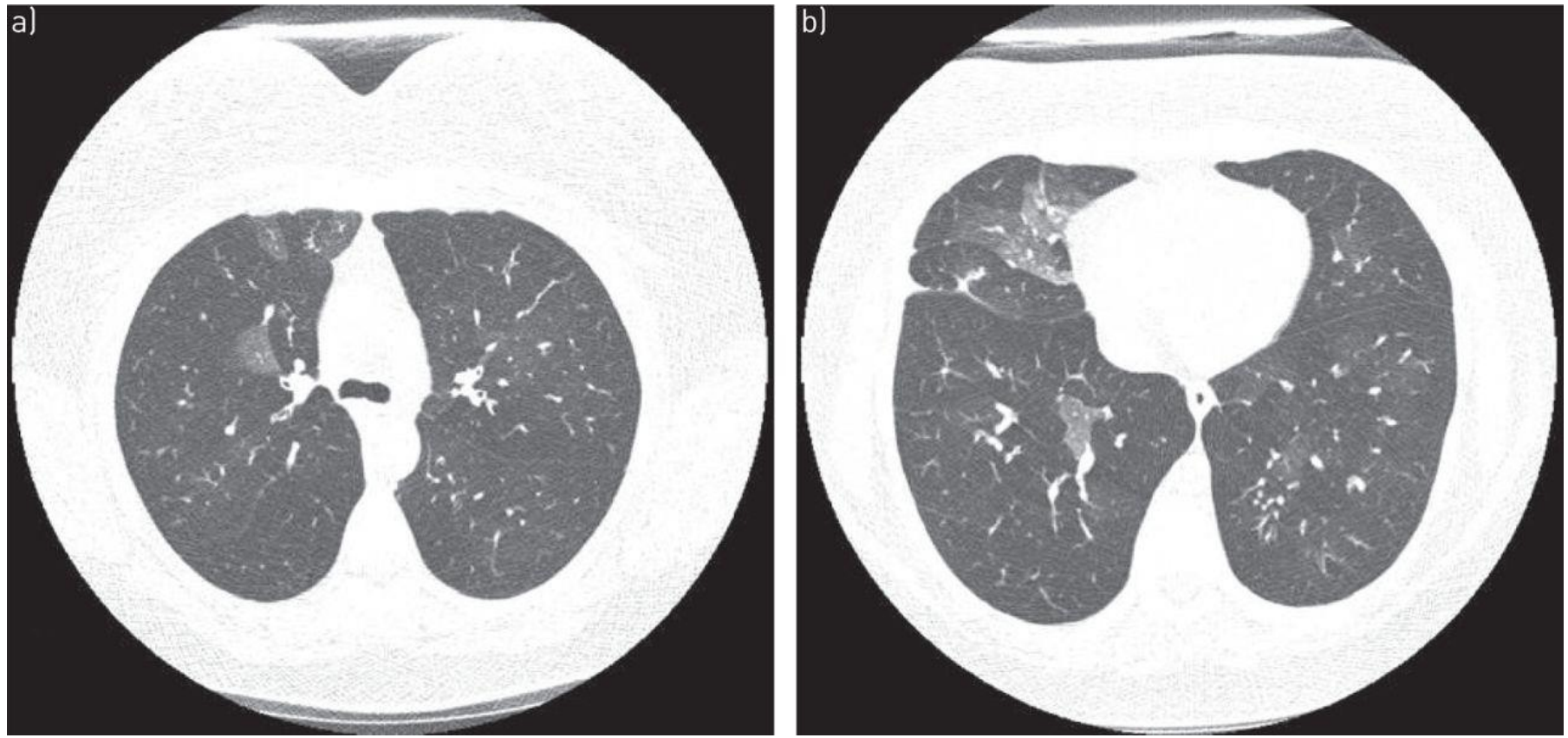


FIGURE 1: Respiratory manifestations in rheumatoid arthritis. Percentages indicate disease prevalence unless otherwise stated. Numbers in round brackets indicate the corresponding reference.

VIE AEREE INFERIORI

- bronchiolite costrittiva obliterante
- bronchiolite follicolare
- bronchiectasie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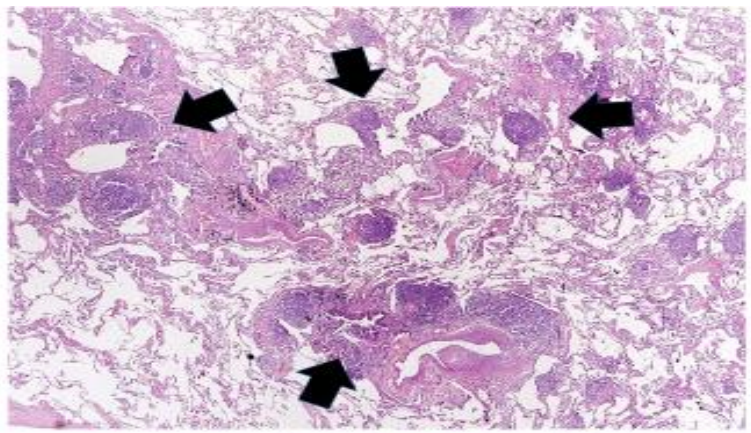


Figure 2. Photomicrograph showing highly cellulated interstitial pneumonia with several aggregates of nodular lymphoid tissue (**arrows**) around bronchi and bronchioles in a patient with rheumatoid arthritis. Hematoxylin and eosin stained; original magnification × 40.

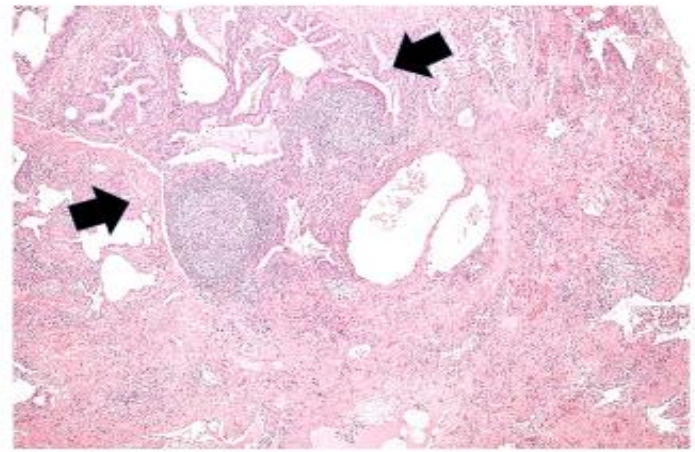


Figure 3. Photomicrograph showing interstitial lung disease with a usual interstitial pneumonia pattern and scattered follicular bronchiolitis (**arrows**) secondary to rheumatoid arthritis. Hematoxylin and eosin stained; original magnification × 100.

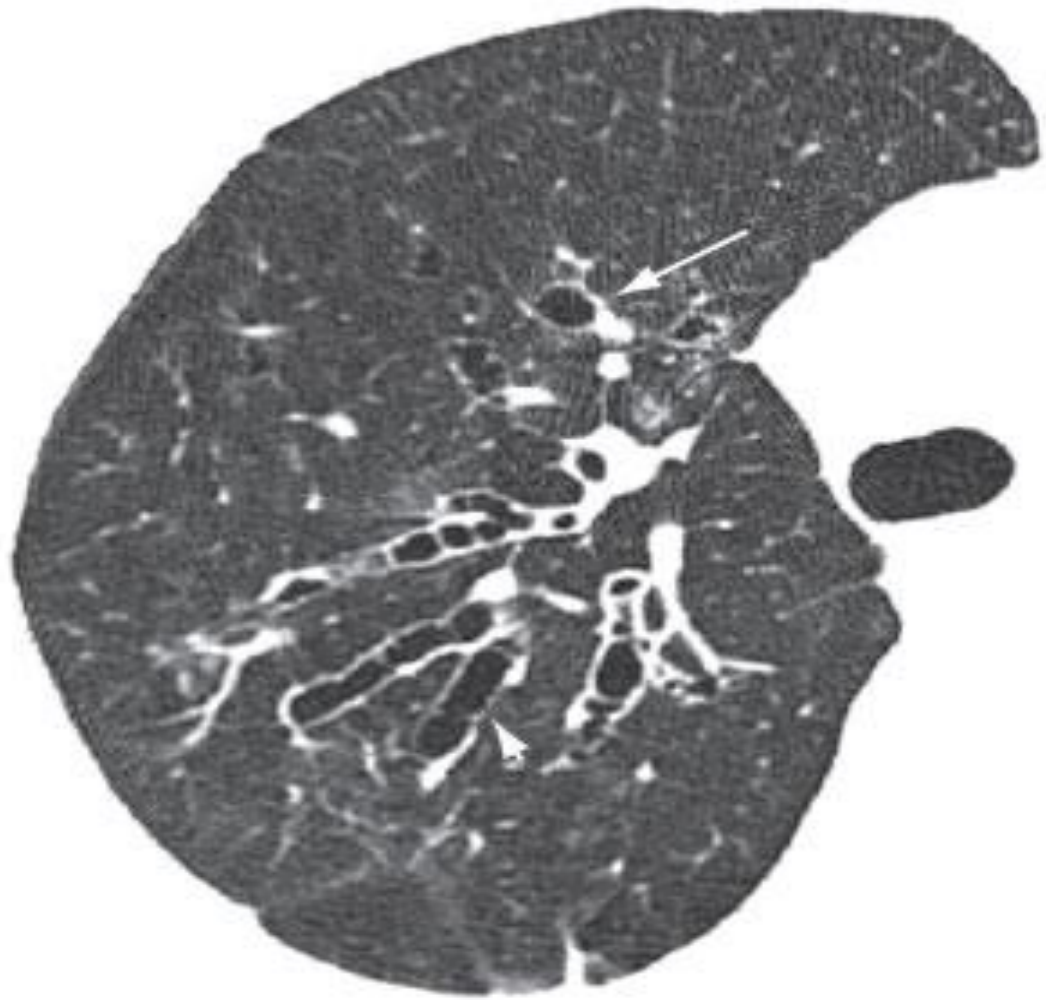
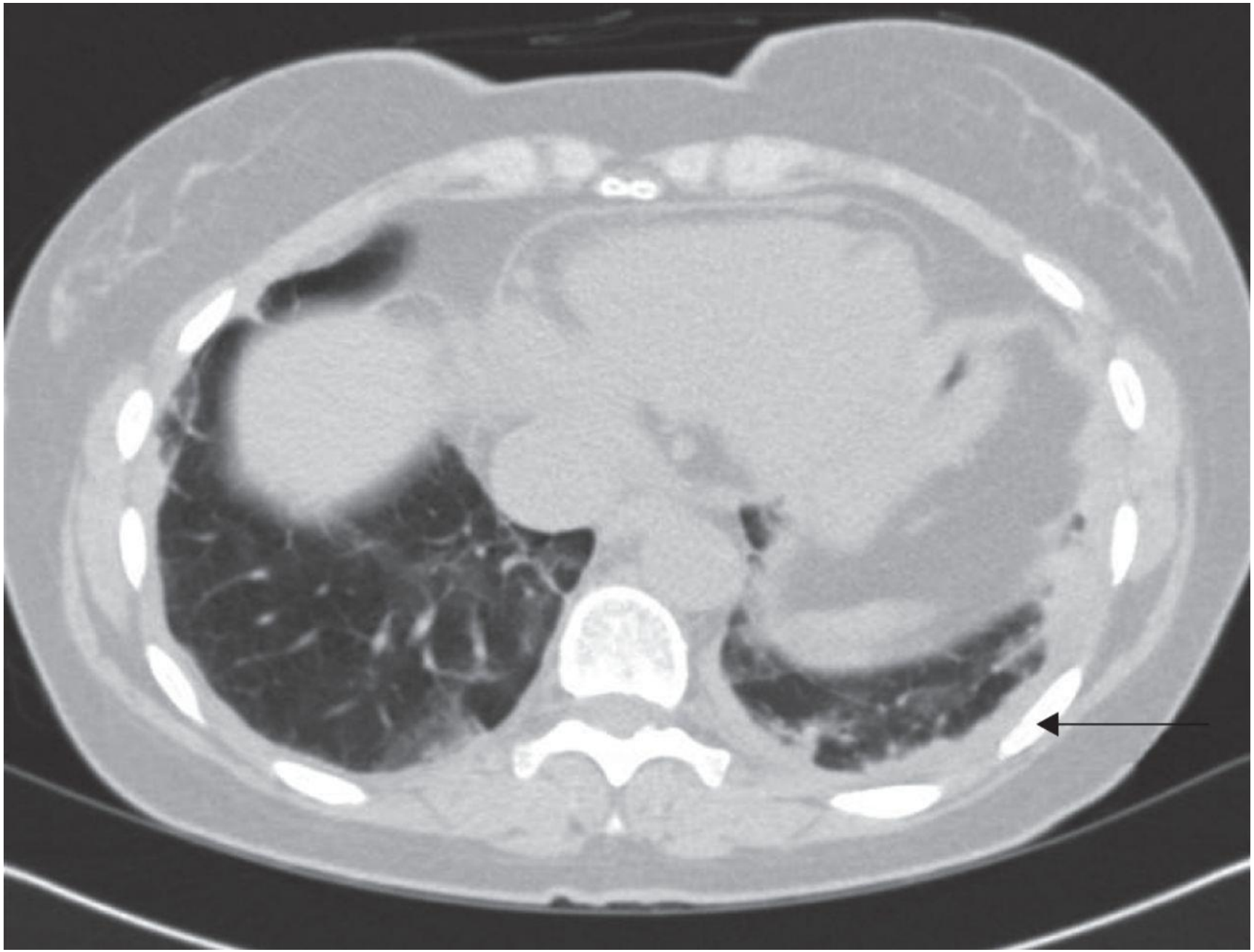


Figure 12 - Bronchiectasis characterized by the "signet-ring sign" (long arrow) and "tram tracks" appearance (short arrow).

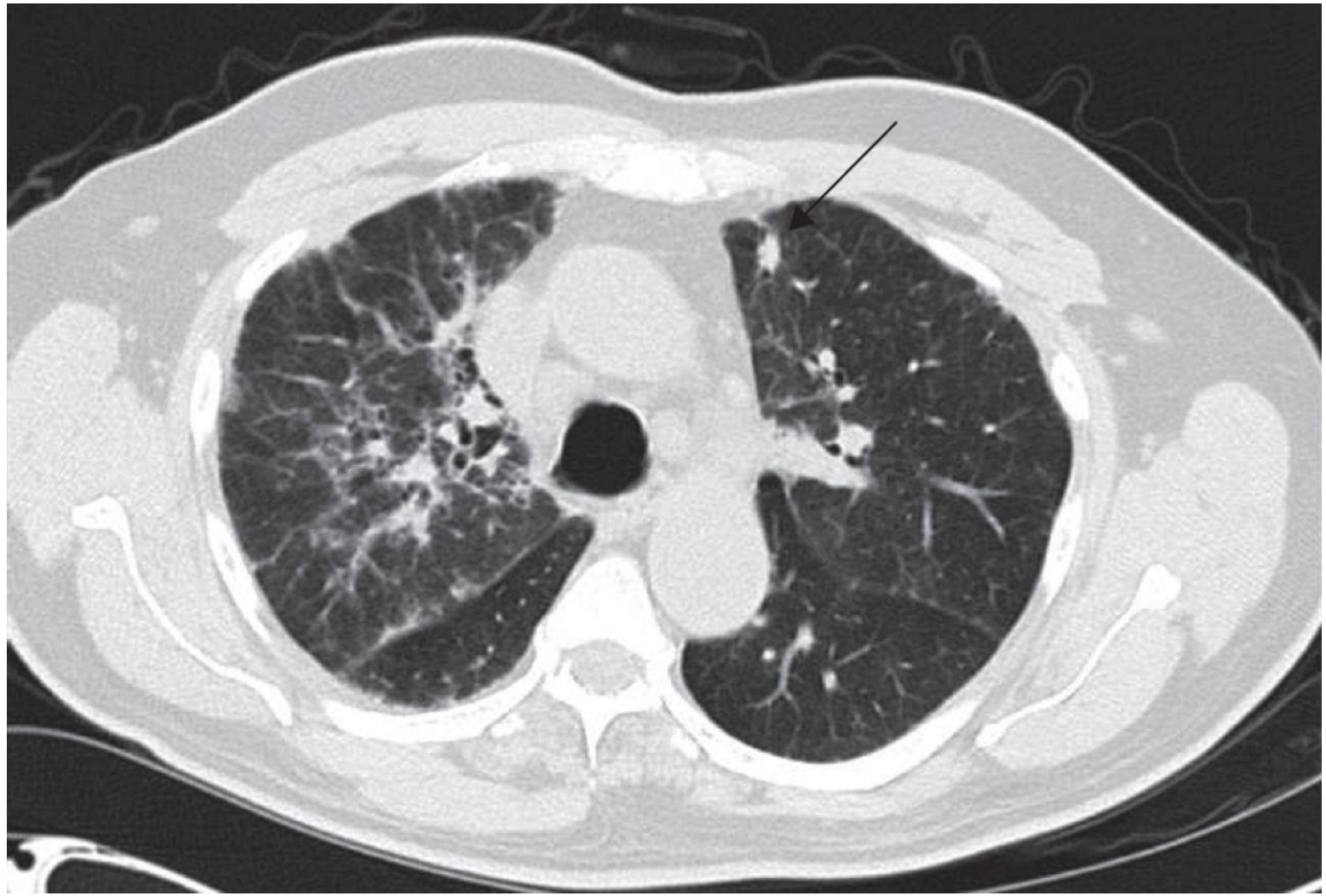
MALATTIA PLEURICA

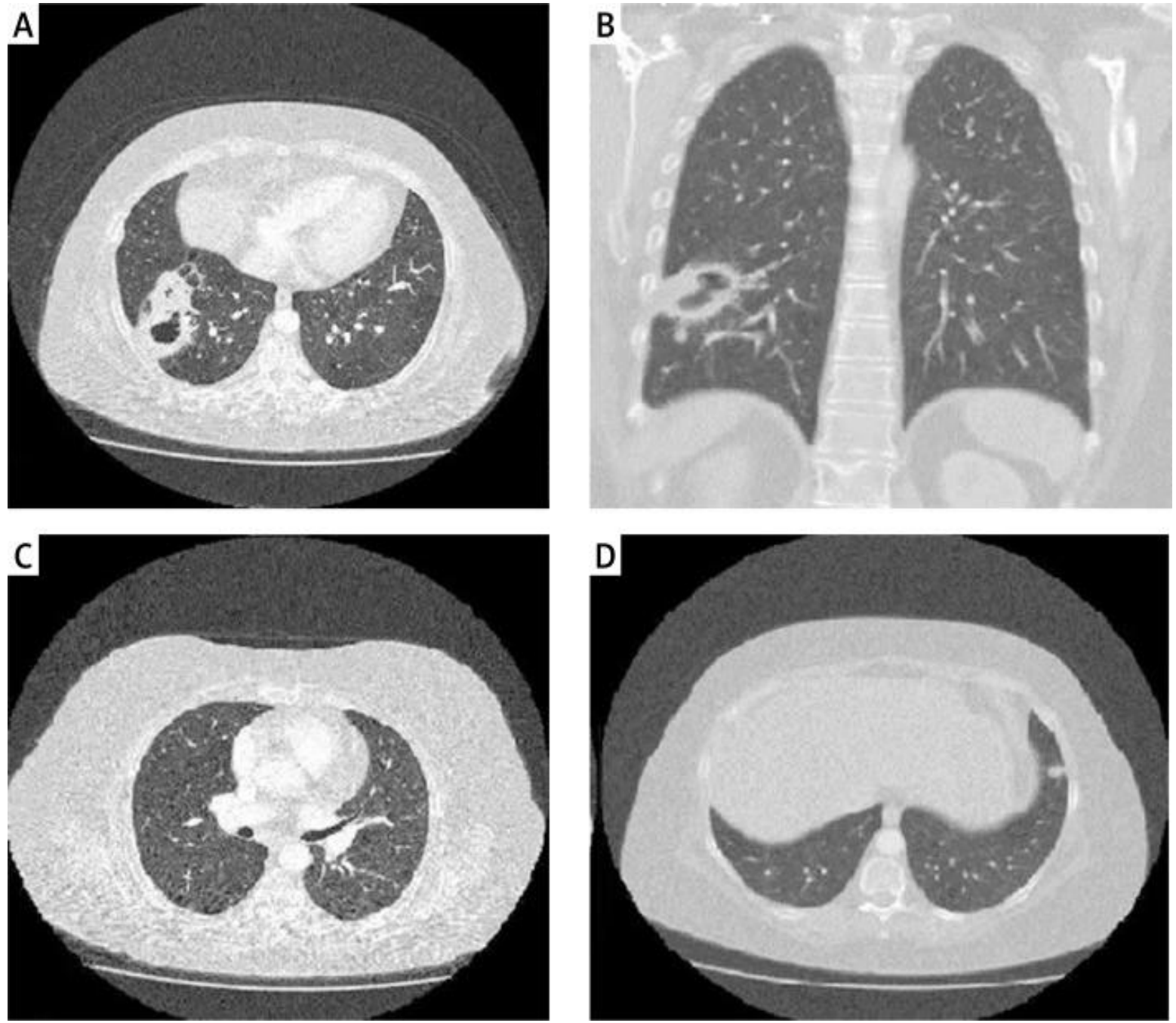
- ***Nel 50-70% degli studi autoptici***
- ***Prevalente nei maschi***
- ***Se elevato titolo di FR***
- ***Spesso manifestazione tardiva***
- ***Ispessimenti pleurici (+ frequente 20%)***
- ***Versamento pleurico (3-5%)***
- ***Noduli (rari)***



Noduli reumatoidi

- Tipici dei pazienti con sierologia positiva
- Malattia di lunga durata
- Associati ai noduli sottocutanei
- Da pochi mm a diversi cm nei setti interlobulari e regioni subpleuriche
- Asintomatici se non si complicano
- Nel 30% dei pz con AR
- Di solito PET negativi o a bassa captazione




A
B
C
D

Malattia vascolare polmonare

- Ipertensione polmonare (20%)
- Interessamento dei piccoli vasi (vasculite) (8%)
- Emorragia alveolare diffusa (rara)

Tossicità da farmaco

- Methotrexate :esacerbazione della manifestazione polmonare ;peggioramento noduli reumatoidi
- Leflunomide : EAD
- Inibitori TNF infez micobatteri; tocilizumab (anti IL-6) esacerbazione di ILD
- Abatacept : esacerbazione bpco
- Rituximab: polmoniti da pneumococco e OP, polmonite interstiziale cellulare
- Azatioprina e tacrolimus: accentuazione dell'interstiziopatia
- Sulfalazina e penicillamina: OP

Comorbidità

- Amiloidosi : amiloide reattiva AA associata a AR (< 1%)

- Sindrome di Caplan noduli che tendono alla cavitazione

The prevalence of ILD varies by CTD type

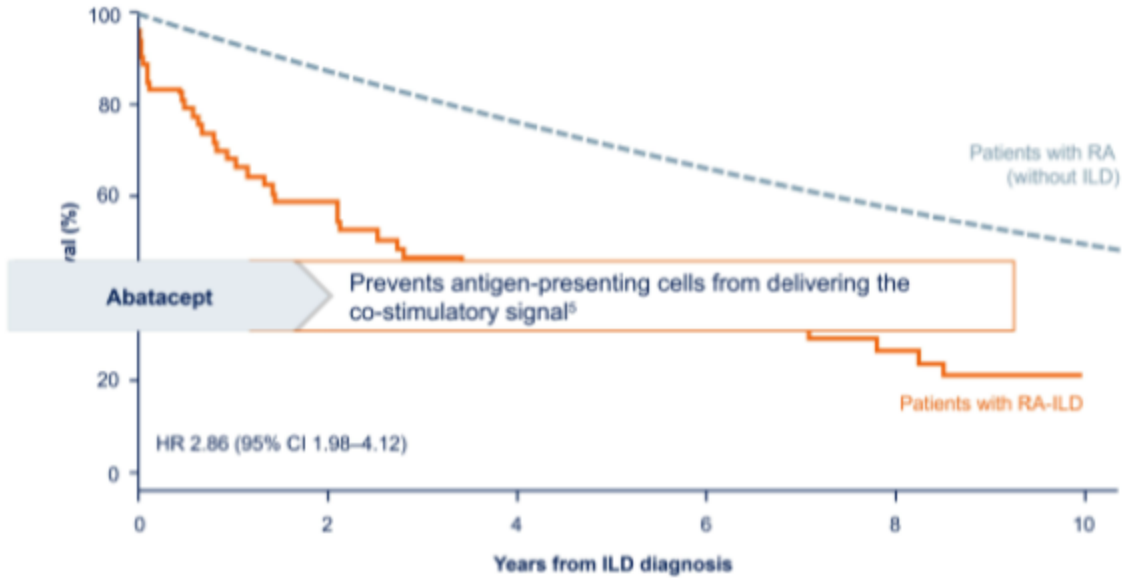
CTD-ILD	Prevalence of CTD[1]	Prevalence of ILD[2]
SSc	26*	70–90%
RA	0.5–2%†	4–68%
SS	3%‡	10–30%
Mixed CTD	3.8*	20–85%
PM/DM	Unknown	15–70%
SLE	15–50*	2–10%

Clinical outcomes for patients with CTD-ILD are poor[1]

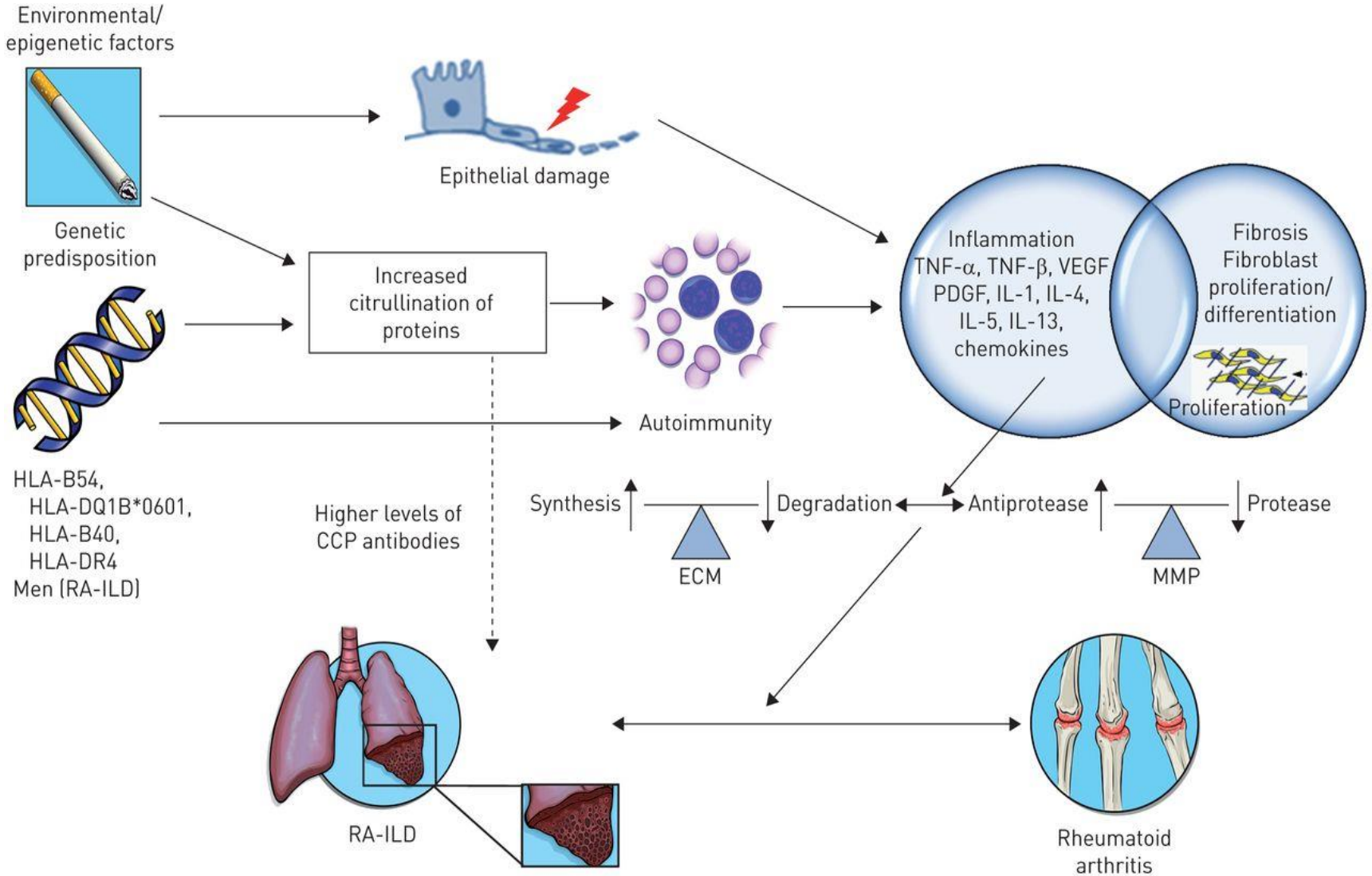
	SSc	RA	SS	Mixed CTD	PM/DM	SLE
Clinical ILD*	≤45%	7.7%	11–15%	54%	15–78%	11%
ILD-cause mortality	Unknown[1] (but leading cause of death in SSc)[2]	10–20%	5-year survival: 84%	Unknown	From subclinical to rapidly progressive and fatal	50%

Pulmonary involvement is now one of the leading causes of morbidity and mortality in CTD[3]

Patients with RA-ILD have been reported to have significantly lower survival than patients with RA only



"Development of better strategies for the treatment of ILD could significantly lower the excess mortality of individuals with RA"

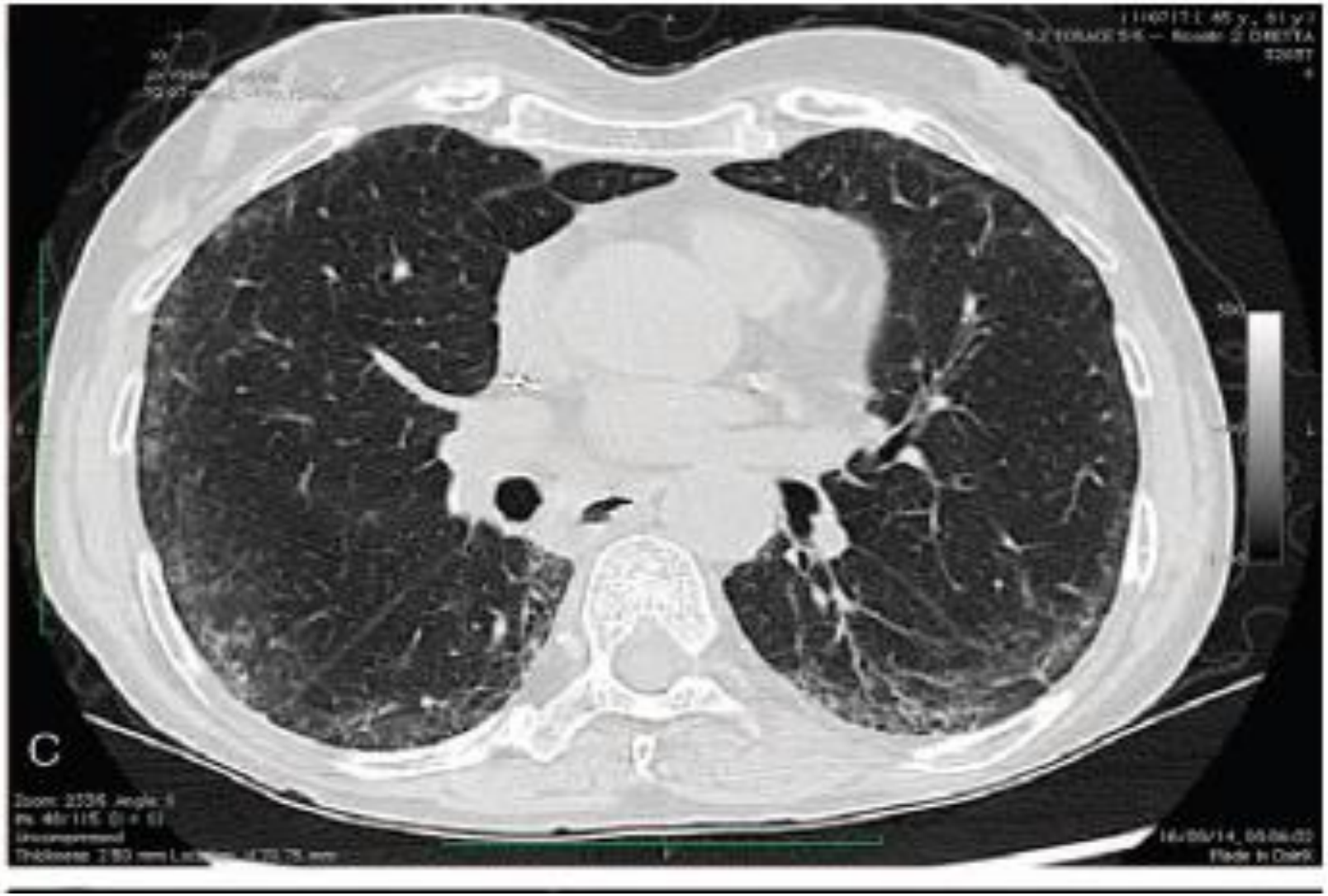

Environmental/
epigenetic factors
Genetic
predisposition
Epithelial damage
Increased
citrullination of
proteins
Autoimmunity
Inflammation
TNF-α, TNF-β, VEGF
PDGF, IL-1, IL-4,
IL-5, IL-13,
chemokines
Fibrosis
Fibroblast
proliferation/
differentiation
Proliferation
HLA-B54,
HLA-DQ1B*0601,
HLA-B40,
HLA-DR4
Men (RA-ILD)
Higher levels of
CCP antibodies
Synthesis
Degradation
ECM
Antiprotease
Protease
MMP
RA-ILD
Rheumatoid
arthritis

Malattie parenchimali

Più alta prevalenza fumatori, maschi e con marker elevati e età avanzata

Pattern:

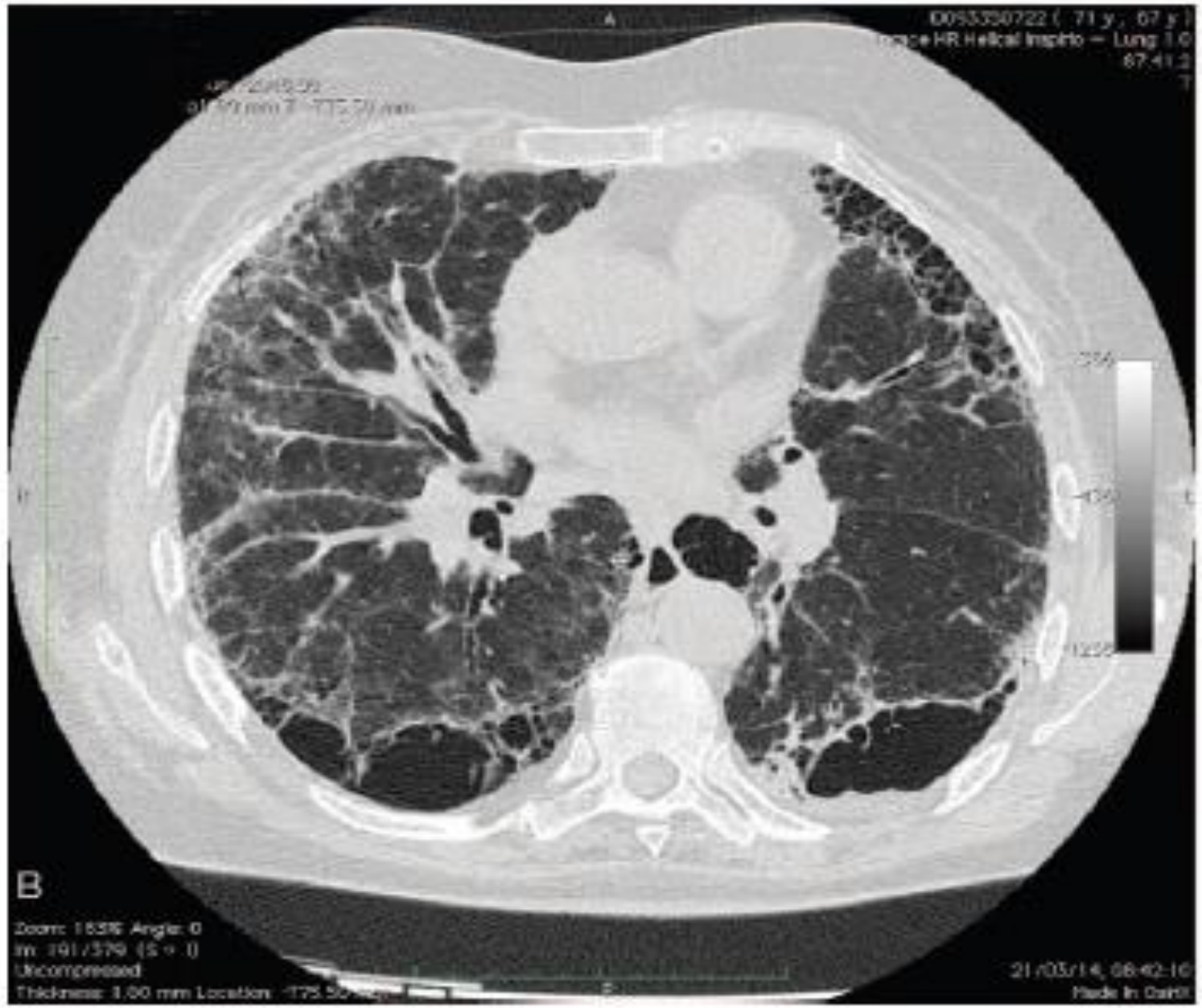
- UIP (40-60%dei casi)
- NSIP 11-32%
- OP(10%)
- LIP (rara)
- Prognosi migliore rispetto alle forme idiopatiche
- I migliori predittori di sopravvivenza sono le PFR e la rapida progressione di malattia
- Esacerbazione acuta : > UIP pattern , età avanzata e uso methotrexate



High-resolution computed tomography of the lung in patients with rheumatoid arthritis

Prevalence of interstitial lung disease involvement and determinants of abnormalities

Fausto Salaffi, MD, PhD[a], Marina Carotti, MD[b], Marco Di Carlo, MD[a], Marika Tardella, MD[a,*], Andrea Giovagnoni, MD[b]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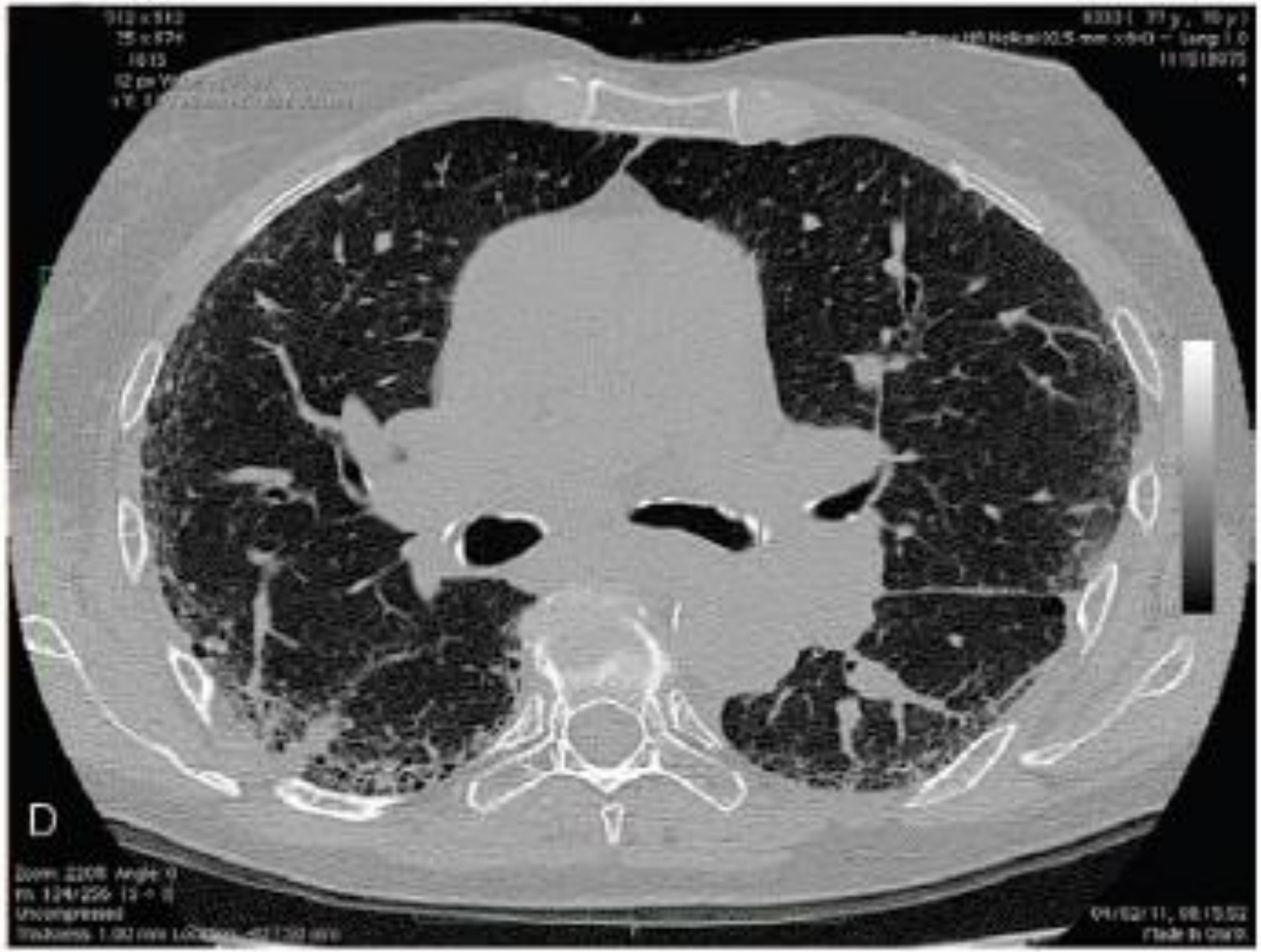
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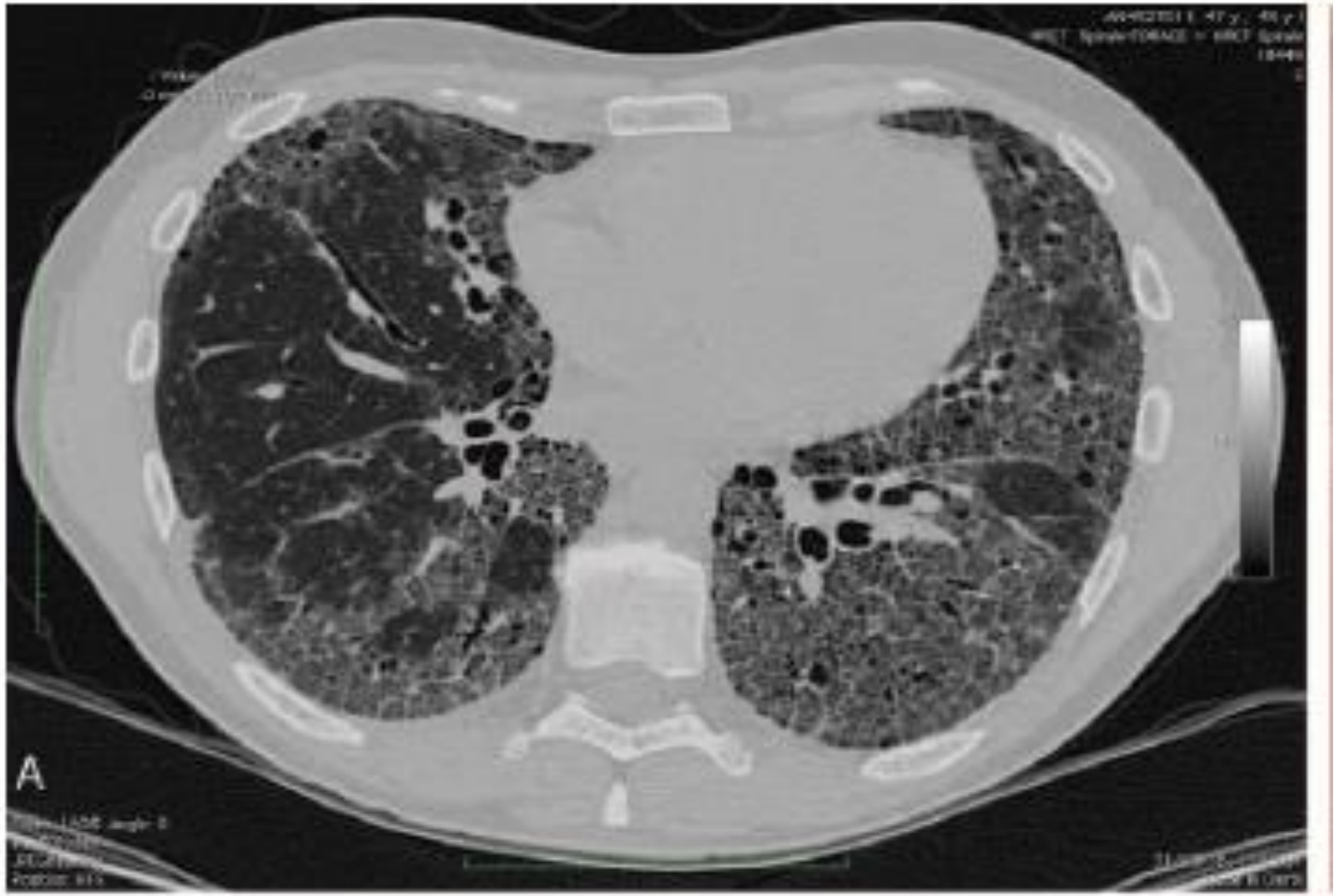
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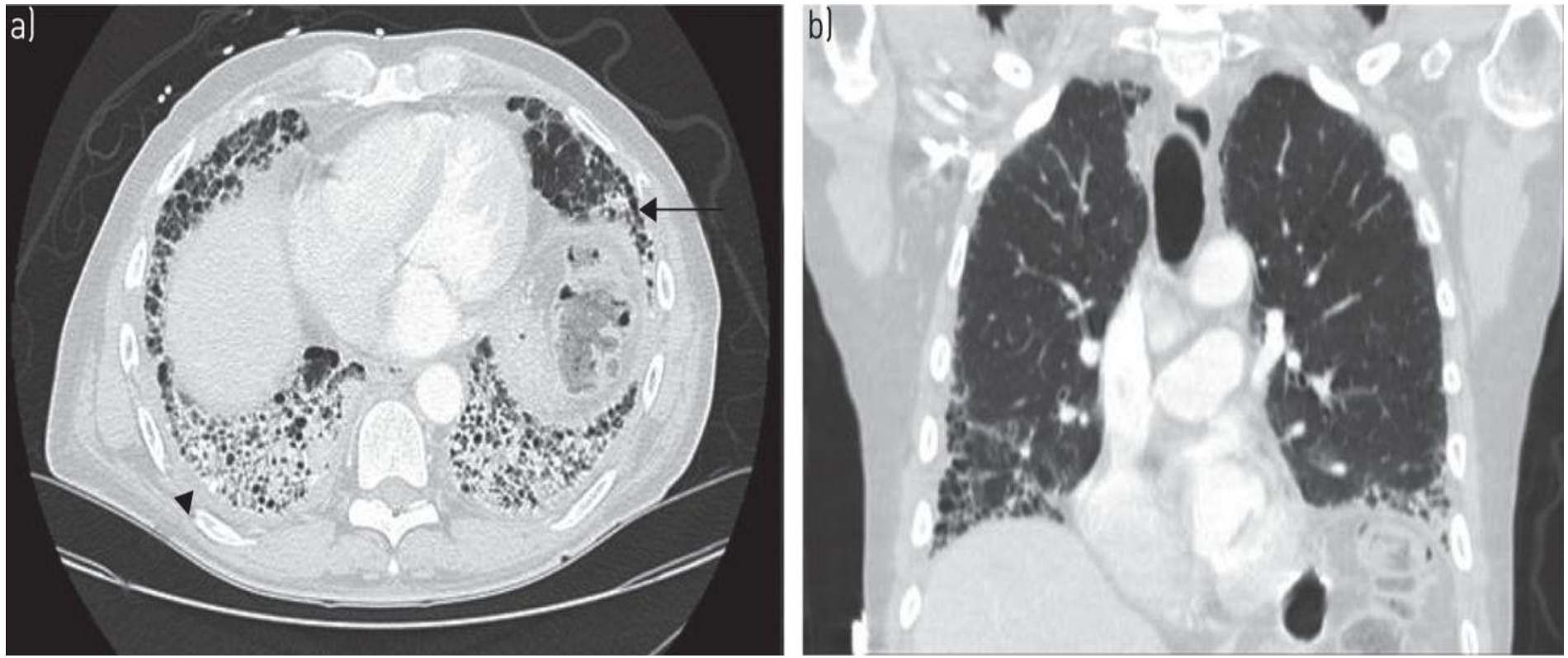
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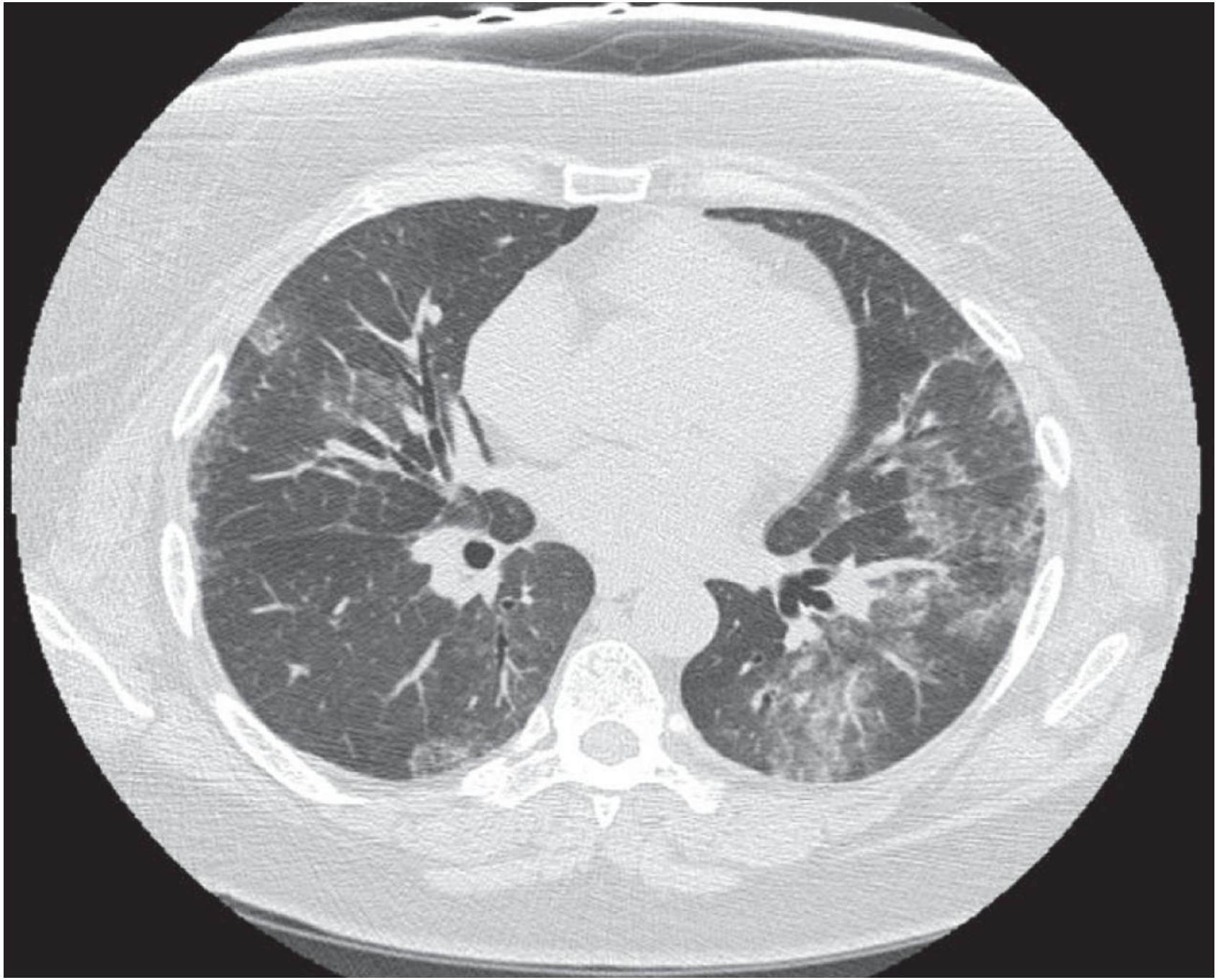
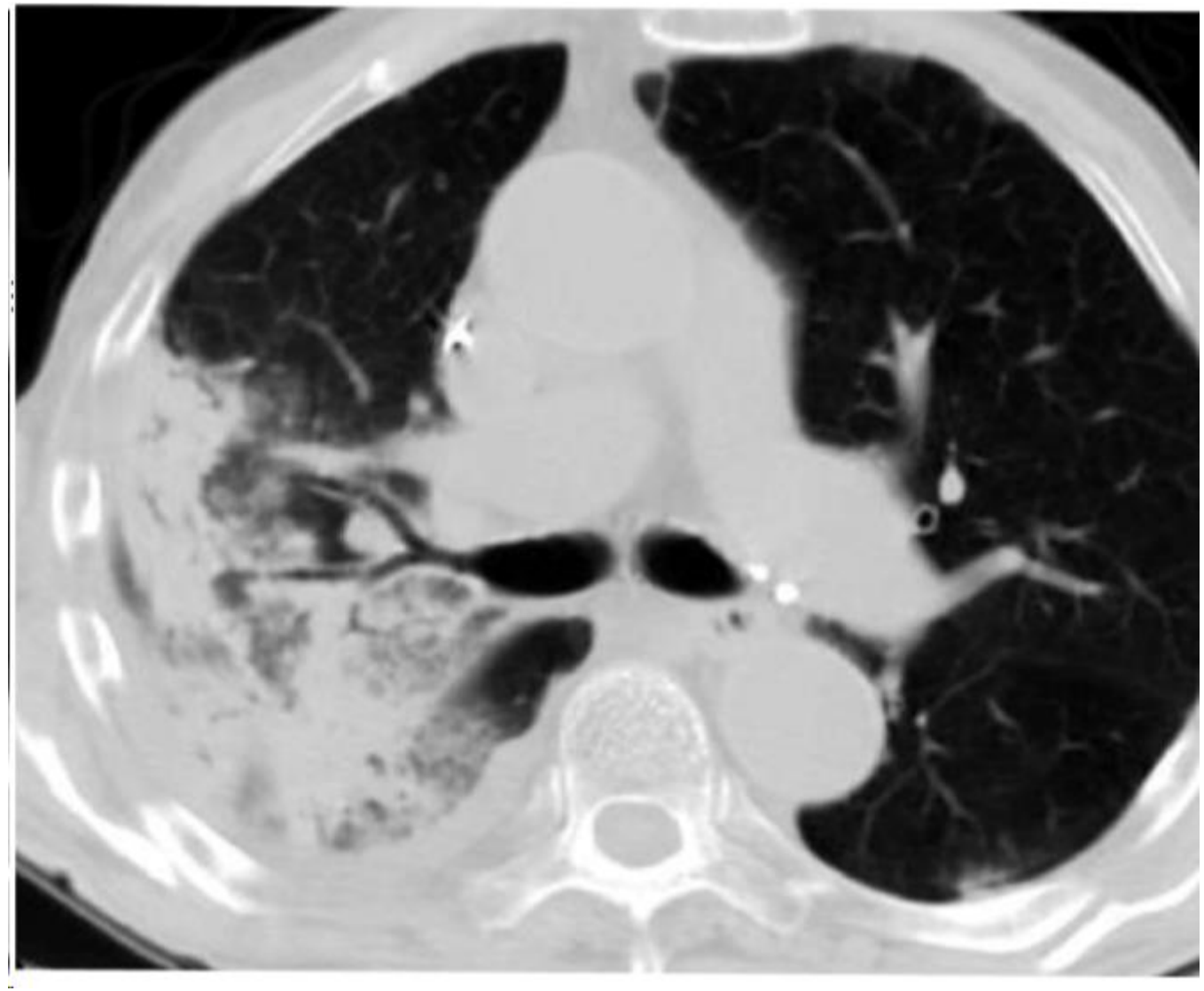




CLINICA

- Inizialmente asintomatici nonostante significative anomalie radiologiche
- Dispnea
- Tosse
- Tachipnea
- Crepitii bibasali velcro-like
- Sfregamenti pleurici
- Segni di ipertensione polmonare
- Clubbing

FUNZIONALITA' RESPIRATORIA

- PFR: pattern restrittivo

- Dlco: la sua riduzione è marker predittivo di malattia parenchimale (prevalenza di PAH bassa)

Terapia

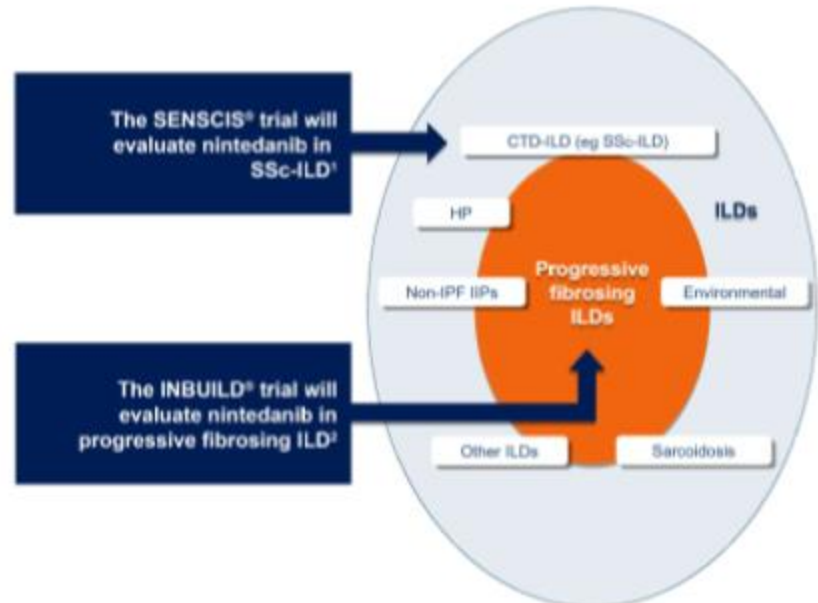
- Non esisto dati che evidenziino un trattamento ottimale
- Bisogna valutare l' entità della malattia e i fattori di relativi al paziente
- I dati della letteratura suggeriscono un trattamento(sterodi + is) in caso di NSIP, OP, LIP mentre per la UIP non dati di efficacia
- Steroide 0.5 mg /kg die e graduale tapering
- Micofenolato mofetile o azatioprina
- No methotrexate se coinvolgimento polmonare
- Rituximab se preso nelle fasi iniziali
- Farmaci antifibrosanti
- Tx polmonare

Trial identifier	Trial characteristics				
	Intervention	Condition	Phase	Primary end point	Status
NCT02808871	Pirfenidone vs. placebo	RA-related ILD	II	Progression-free survival	Not yet recruiting
EudraCT no. 2014-000861-32	Pirfenidone vs. placebo	Progressive non-IPF lung fibrosis[b]	II	Change in FVC	Recruiting
NCT02999178	Nintedanib vs. placebo	Progressive fibrosing ILD[b]	III	Annual rate of decline in FVC	Recruiting
NCT03084419	Abatacept	RA-related ILD	II (open-label)	Change in FVC	Not yet recruiting

[a] RA = rheumatoid arthritis; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; FVC = forced vital capacity.

[b] The study population may include patients with RA-related ILD.

Nintedanib is a targeted agent being evaluated in SSc-ILD (SENSCIS®) and progressive fibrosing ILD (INBUILD®)



Key eligibility criteria

- Physician-diagnosed ILD other than IPF
- Features of diffuse fibrosing lung disease (reticular abnormality with traction bronchiectasis, with or without honeycombing) of >10% extent on HRCT performed ≤12 months prior to screening, confirmed by central review
- FVC ≥45% predicted
- DLco ≥30%–<80% predicted

Primary and main secondary endpoints[1]

Primary endpoint:

- Annual rate of decline in FVC (mL/year) assessed over 52 weeks

Main secondary endpoints:

- Absolute change from baseline in K-BILD questionnaire[2] total score at week 52
- Time to first acute exacerbation of ILD or death over 52 weeks
- Time to death over 52 weeks

Summary

•In patients with progressive fibrosing ILDs other than IPF:

–Nintedanib slowed the progression of ILD, as demonstrated by a lower rate of decline in FVC, with a consistent effect between patients with a UIP-like fibrotic pattern and other fibrotic patterns on HRCT

–Using data up to first database lock, nintedanib was associated with a numerically reduced risk of acute exacerbation of ILD or death, and of death

–Changes in health-related quality of life measured using the K-BILD questionnaire were small, with no meaningful difference between treatment groups

–The adverse event profile of nintedanib was consistent with that observed in patients with IPF