International Doctoral School
Medical University of Lodz

Biomarkers

as predictors
of lung fibrosis progression
in patients with

interstitial pneumonia with autoimmune features (IPAF)

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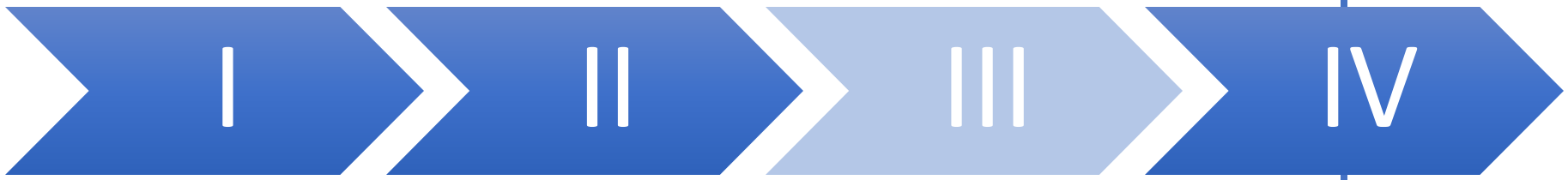
I
II
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IV

Maternity leave

I II III IV V

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], Tamera J. Corte[5,18], Roland M. du Bois[6], Joyce S. Lee[7,18], Kevin O. Leslie[8], David A. Lynch[9], Eric L. Matteson[10], Marta Mosca[11], Imre Noth[12], Luca Richeldi[13], Mary E. Strek[12,18], Jeffrey J. Swigris[3,18], Athol U. Wells[14], Sterling G. West[15], Harold R. Collard[7,18,19] and Vincent Cottin[16,18,19], on behalf of the "ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD"

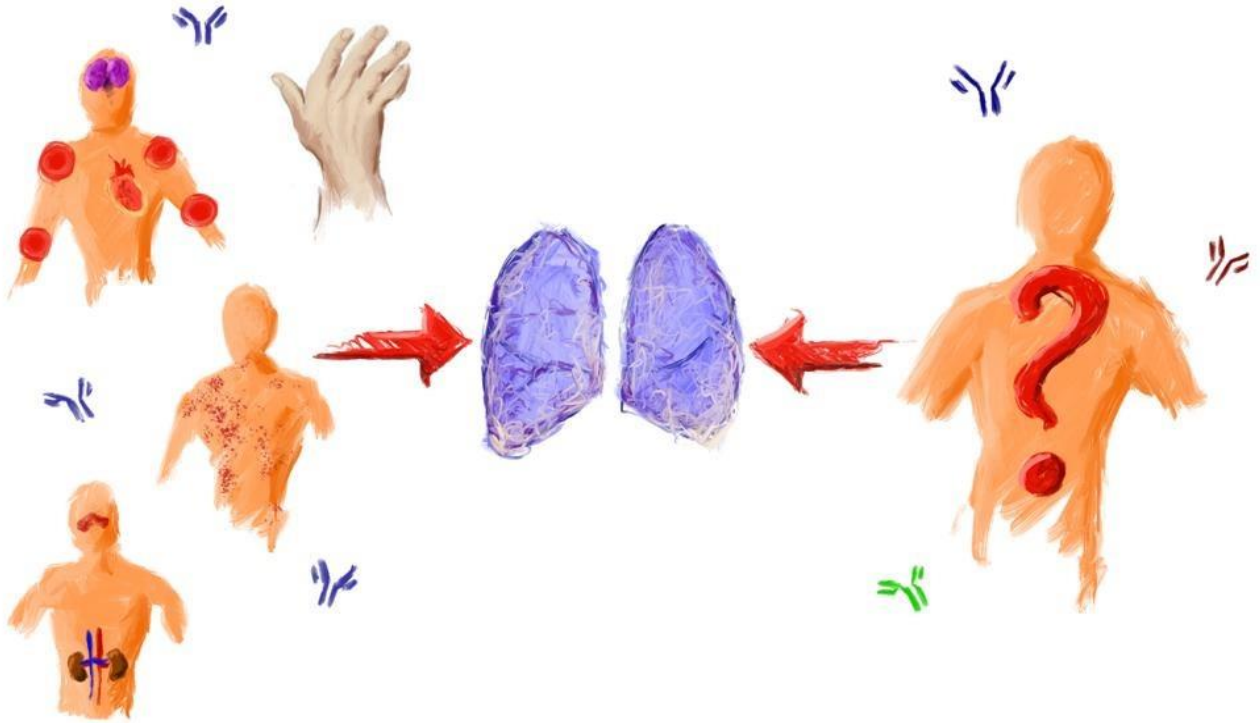


TABLE 1 Classification criteria for "interstitial pneumonia with autoimmune features"

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) *and*,
2. Exclusion of alternative aetiologies *and*,
3. Does not meet criteria of a defined connective tissue disease *and*,
4. At least one feature from at least two of these domains:
   A. Clinical domain
   B. Serologic domain
   C. Morphologic domain

A. Clinical domain

1. Distal digital fissuring (*i.e.* "mechanic hands")
2. Distal digital tip ulceration
3. Inflammatory arthritis *or* polyarticular morning joint stiffness ⩾60 min
4. Palmar telangiectasia
5. Raynaud's phenomenon
6. Unexplained digital oedema
7. Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)

B. Serologic domain

1. ANA ⩾1:320 titre, diffuse, speckled, homogeneous patterns *or*
   a. ANA nucleolar pattern (any titre) *or*
   b. ANA centromere pattern (any titre)
2. Rheumatoid factor ⩾2× upper limit of normal
3. Anti-CCP
4. Anti-dsDNA
5. Anti-Ro (SS-A)
6. Anti-La (SS-B)
7. Anti-ribonucleoprotein
8. Anti-Smith
9. Anti-topoisomerase (Scl-70)
10. Anti-tRNA synthetase (*e.g.* Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)
11. Anti-PM-Scl
12. Anti-MDA-5

C. Morphologic domain

1. Suggestive radiology patterns by HRCT (see text for descriptions):
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
2. 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 lymphoid follicles)
3. Multi-compartment involvement (in addition to interstitial pneumonia):
   a. Unexplained pleural effusion or thickening
   b. Unexplained pericardial effusion or thickening
   c. Unexplained intrinsic airways disease[#] (by PFT, imaging or pathology)
   d. Unexplained pulmonary vasculopathy

- **Hypothesis 1:** There are biomarkers of lung fibrosis in IPAF which can be used in everyday clinical practice

- Can KL-6, SP-D, TGF-β serve as biomarkers of lung fibrosis in IPAF?

- Do these biomarkers share similar roles as it is in pathobiological pathways of CTD-ILD?

- Do these biomarkers have any predictive value in the assessment of the progression of pulmonary fibrosis in patients with IPAF?

- Are there any relationships between the biomarkers and clinical, functional and radiological features of proven predictive importance?

- **Hypothesis 2:** Conversion to CTD in patients with IPAF has an impact on prognosis

- How many patients will develop a specific CTD-ILD?

- Does conversion change the natural history of IPAF?

- What is the impact of IPAF preceding the manifestation of CTD-ILD?

IPAF
n=31

Follow up: n=31

CANCER — n=1

DEATH (unrelated to cancer) — n=4

LUNG TRANSPLANTATION — n=0

CONVERSION TO CTD — n=2

CTD-ILD
n=38

Follow up: n=32

n=1

n=3

n=1

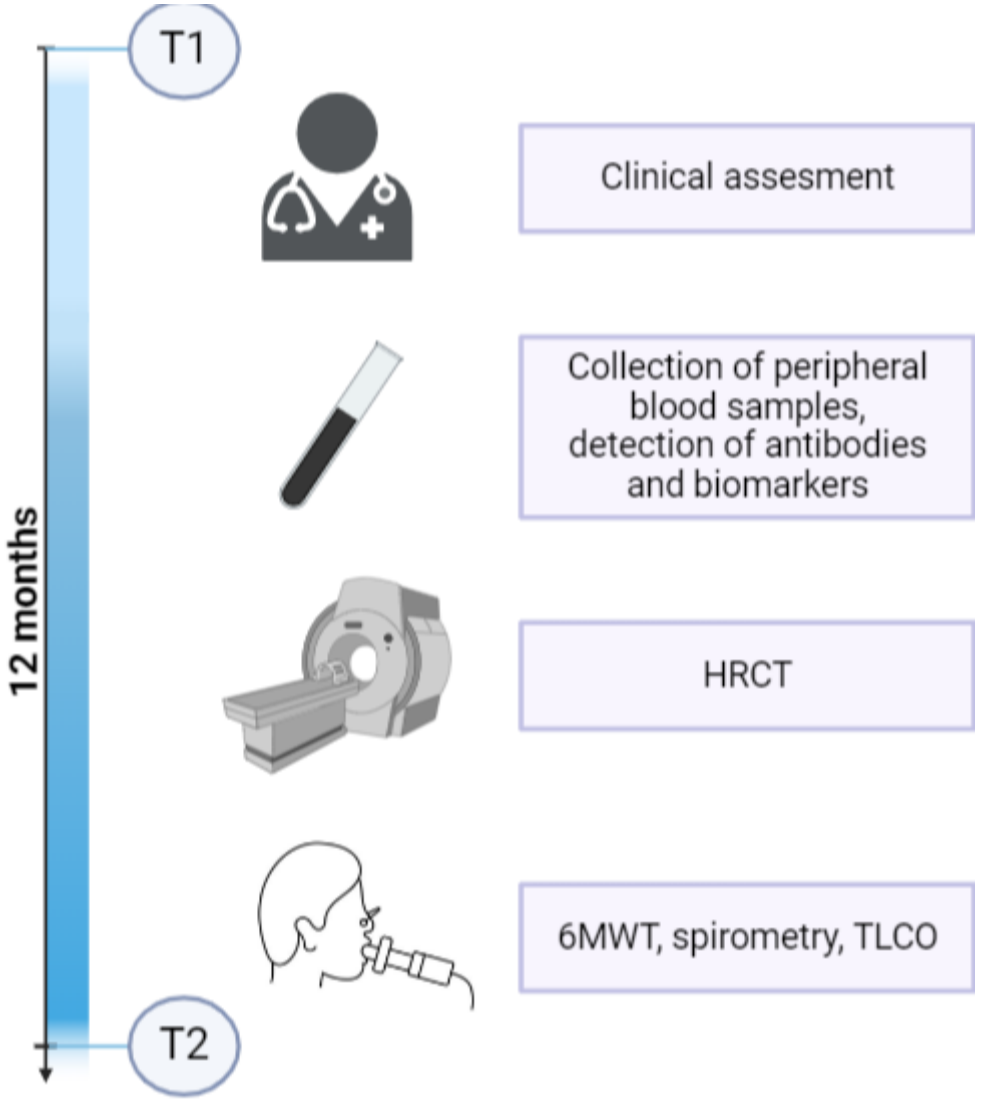
CTD
n=30

Follow up: n=24

n=0

n=0

n=0



Biomarkers:

- KL-6
- SP-D
- TGF-β

- **Progression of interstitial lung disease – 5 definitions:**

- FVC ≥ 5% decline
- FVC ≥ 10% decline
- INBUILD criteria
- 2022 ATS guidelines
- Polish Respiratory Society guidelines

- + death/lung transplantation

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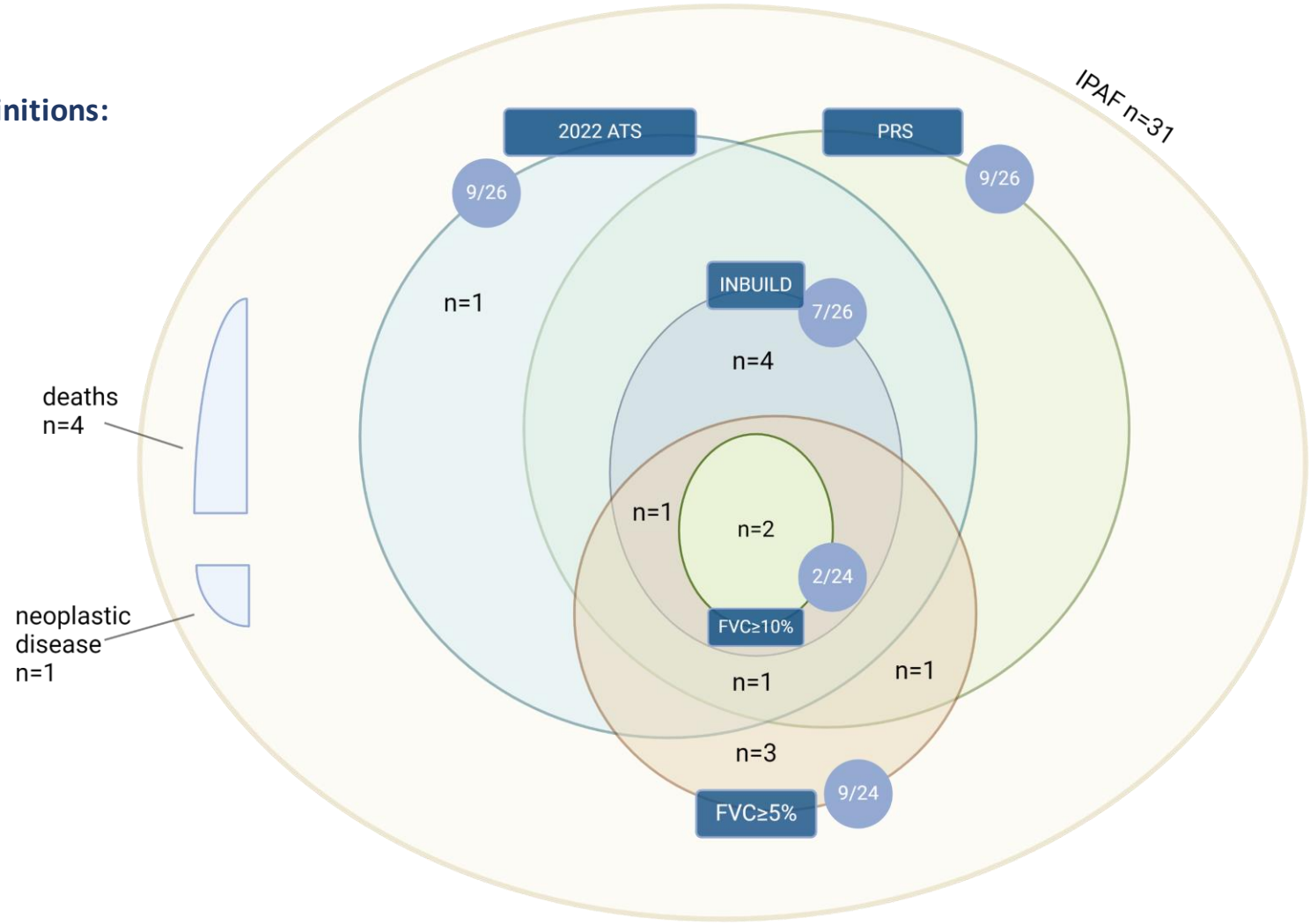
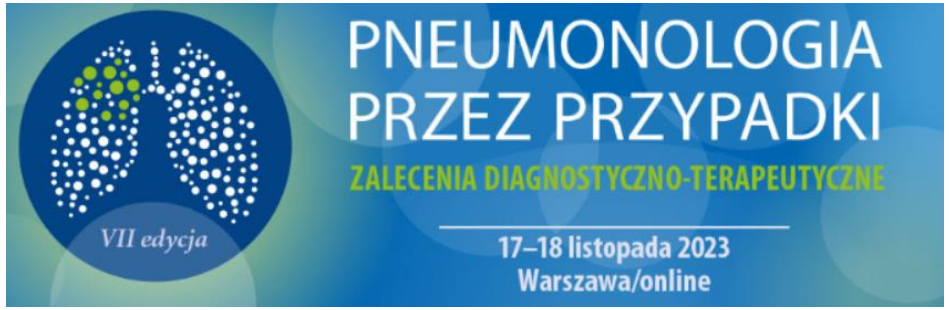


STATISTICAL ANALYSIS

This year…

Active participation in conferences - Poland



„A po nocy przychodzi dzień – leczenie SSc-ILD”
[*After the night comes the day - treatment of SSc-ILD*]

„Dostępność do panelu badań reumatologicznych w diagnostyce chorób śródmiąższowych płuc – czy potrzebna?”
[*Accessibility to autoantybodies diagnosic panel in the diagnosis of interstitial lung diseases - is it necessary?]*

Member of the organizing committee of the conference

Active participation in conferences - Poland

"Interstitial pneumonia with autoimmune features (IPAF)"

MEDYCYNA
po Dyplomie

Manifestacje chorób tkanki łącznej w obrębie układu oddechowego

- Charakterystyka wzorców radiologicznych zmian widocznych w płucach w tomografii komputerowej wysokiej rozdzielczości
- Badania wykorzystywane w diagnostyce i monitorowaniu zmian (m.in. badania obrazowe, czynnościowe, BAL)
- Możliwe opcje leczenia z uwzględnieniem farmakoterapii (w tym programów lekowych) i postępowania zabiegowego

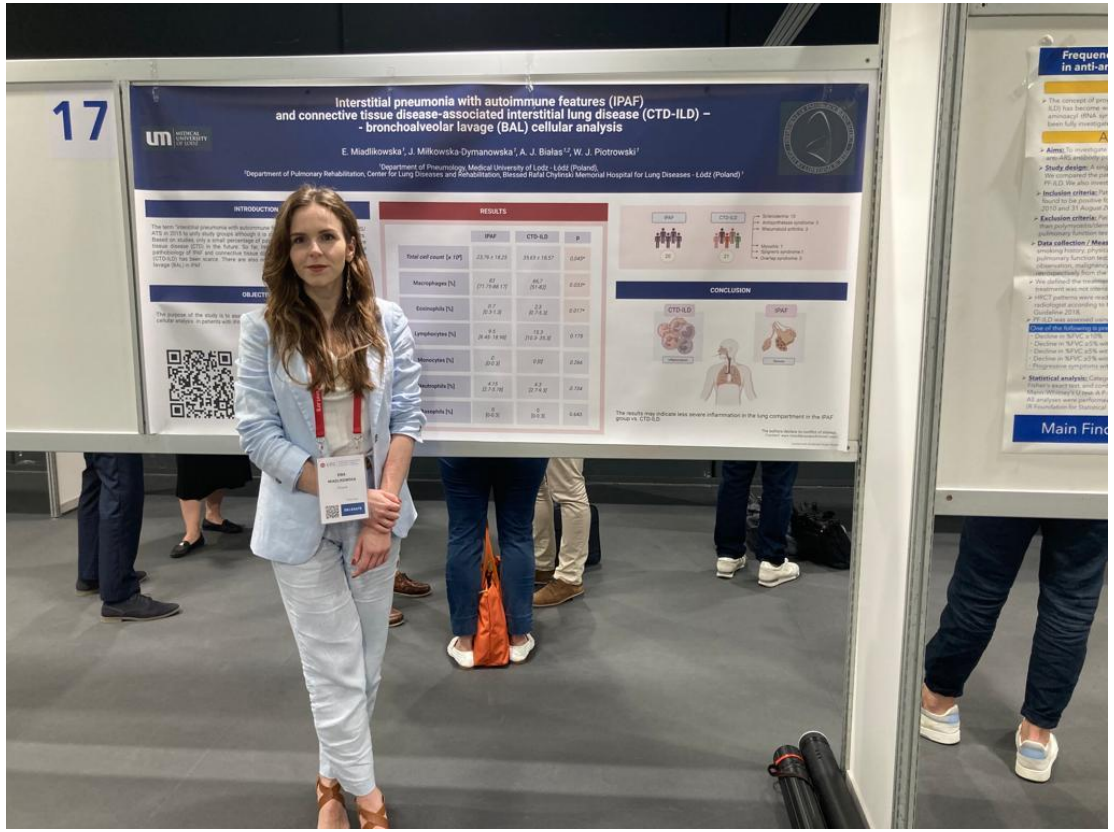
lek.
Ewa Miądlikowska

dr n. med. Joanna
Miłkowska-Dymanowska

prof. dr hab. n. med.
Wojciech Jerzy Piotrowski

Miądlikowska E., Miłkowska-Dymanowska J., Piotrowski W.J. Manifestacje chorób tkanki łącznej w obrębie układu oddechowego [Pulmonary manifestations of connective tissue diseases]. Medycyna po Dyplomie 7-8, 102–109 (2023).

The Polish Respiratory Society awarded me a grant for
Young Pneumologists
to attend
the European Respiratory Society Congress 2023 in Milan



Miadlikowska E., Miłkowska-Dymanowska J., Białas A. J. & Piotrowski W. J. Interstitial pneumonia with autoimmune features (IPAF) and connective tissue disease-associated interstitial lung disease (CTD-ILD) – differences in parameters measured in bronchoalveolar lavage (BAL). European Respiratory Journal vol.62 PA1167 (2023).

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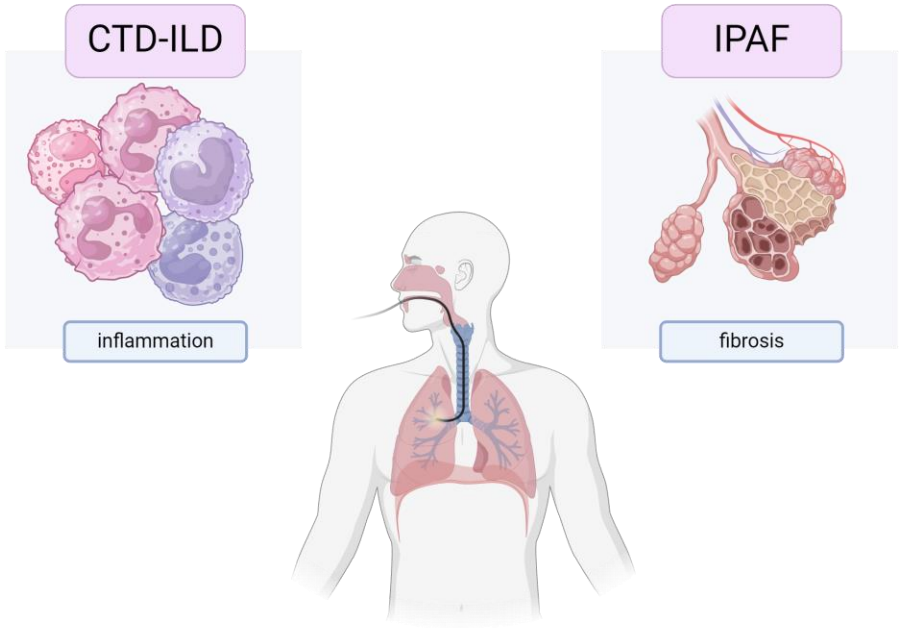
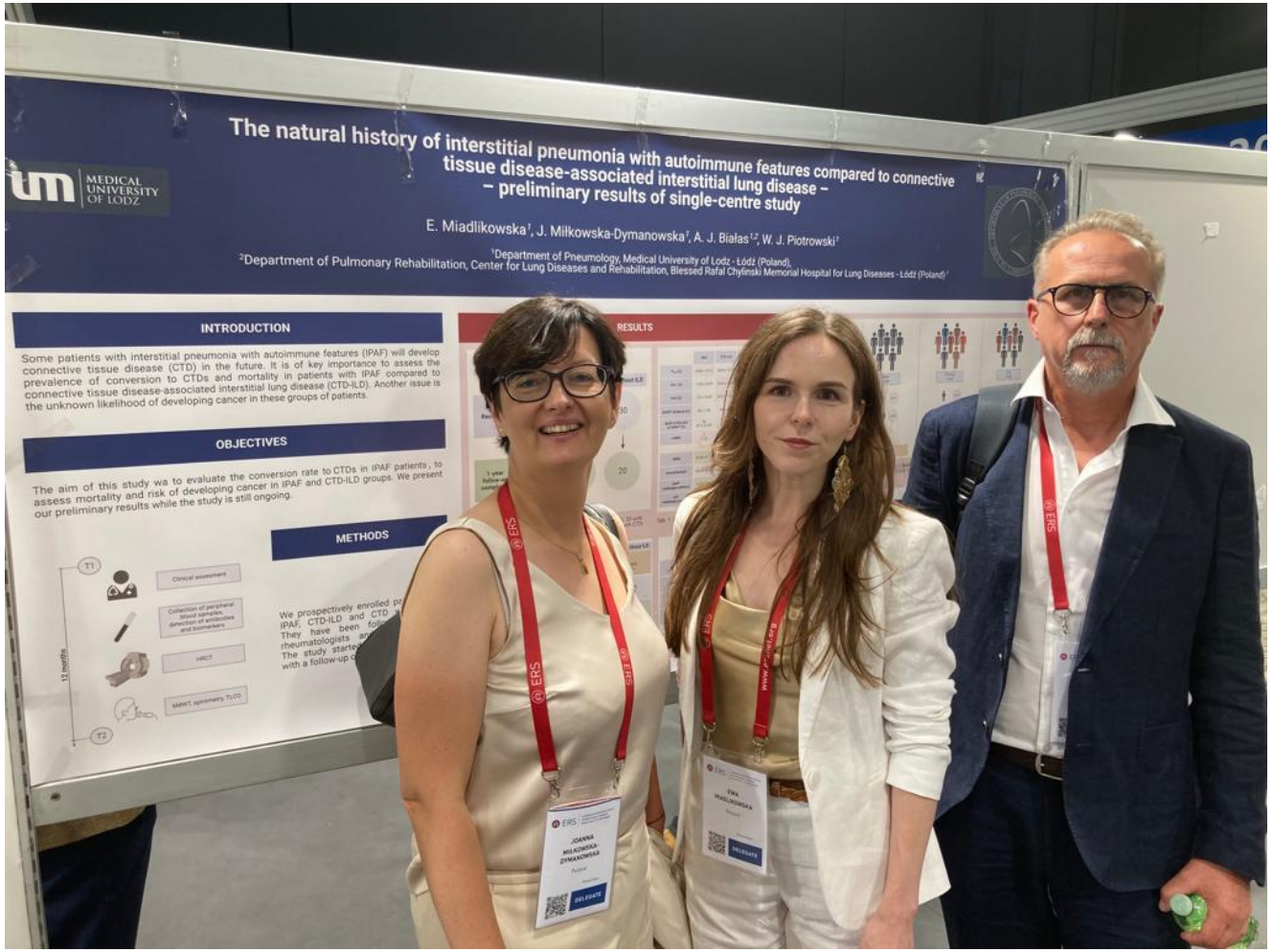
	IPAF	CTD-ILD	p
Total cell count [x 10^6]	*23,76 ± 18,25*	*35,65 ± 18,57*	*0,045*
Macrophages [%]	*83 [71.75-88.17]*	*66,7 [51-82]*	*0.033*
Eosinophils [%]	*0.7 [0.3-1.3]*	*2,3 [0.7-5.3]*	*0.017*
Lymphocytes [%]	*9.5 [8.45- 18.98]*	*15.3 [10.3- 35.3]*	*0.175*
Monocytes [%]	*0 [0-0.3]*	*0 [0]*	*0.266*
Neutrophils [%]	*4.15 [2.7-5.78]*	*4.3 [2.7-9.3]*	*0.734*
Basophils [%]	0 [0-0.3]	0 [0-0.3]	0.643



Miadlikowska E., Miłkowska-Dymanowska J., Białas A. J. & Piotrowski W. J. Interstitial pneumonia with autoimmune features (IPAF) and connective tissue disease-associated interstitial lung disease (CTD-ILD) – differences in parameters measured in bronchoalveolar lavage (BAL). European Respiratory Journal vol.62 PA1167 (2023).



Miadlikowska E., Miłkowska-Dymanowska J., Białas A. J. & Piotrowski W. J. The natural history of interstitial pneumonia with autoimmune features compared to connective tissue disease-associated interstitial lung disease – prospective single-centre study preliminary results. European Respiratory Journal vol. 62 PA3482 (2023).

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The natural history of interstitial pneumonia with autoimmune features compared to connective tissue disease-associated interstitial lung disease – – preliminary results of single-centre study

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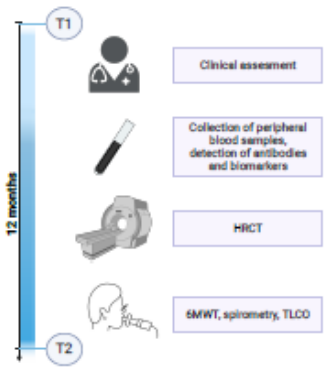
[2]Department of Pulmonary Rehabilitation, Center for Lung Diseases and Rehabilitation, Blessed Rafal Chylinski Memorial Hospital for Lung Diseases - Łódź (Poland)[1]

INTRODUCTION

Some patients with interstitial pneumonia with autoimmune features (IPAF) will develop connective tissue disease (CTD) in the future. It is of key importance to assess the prevalence of conversion to CTDs and mortality in patients with IPAF compared to connective tissue disease-associated interstitial lung disease (CTD-ILD). Another issue is the unknown likelihood of developing cancer in these groups of patients.

OBJECTIVES

The aim of this study wa to evaluate the conversion rate to CTDs in IPAF patients , to assess mortality and risk of developing cancer in IPAF and CTD-ILD groups. We present our preliminary results while the study is still ongoing.



METHODS

We prospectively enrolled patients with IPAF, CTD-ILD and CTD without ILD. They have been followed by both rheumatologists and pulmonologists. The study started in December 2020, with a follow-up of 12 months.

RESULTS

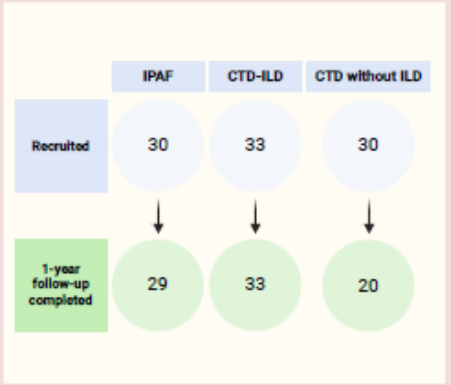


Fig. 1. We recruited 30 patients with IPAF and CTD without ILD; 33 with CTD-ILD. We completed follow-up in 29 patients with IPAF, 33 with CTD-ILD and 20 with CTD without ILD.

	IPAF	CTD-ILD	CTD without ILD	p
TL_{CO} [%]	63,69 ± 23,12	66,69 ± 16,17	86,72 ± 14,58	<0,001*
FEV$_1$ [%]	71,83 ± 20,99	68,84 ± 19,62	83,83 ± 20,09	0,009*
FVC [%]	72,2 ± 24,59	69,25 ± 17,24	85,25 ± 19,57	0,002*
6MWT distance [m]	421 ± 124	405 ± 113	496 ± 99	0,04*
SpO2 at the end of 6MWT [%]	89 [87,0; 91,25]	91 [86,5; 93]	97 [94,5; 98]	0,02*
mMRC	2 [1-3]	1 [1-2]	0 [0-1]	<0,001*
GERD	10/29 (33,7%)	13/29 (31,7%)	2/19 (10,6%)	0,04*
bronchiectasis	23/25 (92%)	25/29 (86,7%)		0,07*
NSIP (radiologic pattern)	8/25 (32%)	12/29 (41,4%)		
UIP (radiologic pattern)	8/25 (24%)	12/29 (41,4%)		

Tab. 1. Initial differences between groups.

		IPAF	CTD-ILD	CTD without ILD
PROGRESSION	absolute FVC decline ≥5% or TLCO ≥10%	48% 13/28	45% 15/33	26% 5/19
STABILIZATION	absolute FVC difference <5% or TLCO <10%	12% 3/28	24% 7/33	37% 7/19
IMPROVEMENT	absolute FVC increase ≥5% or TLCO ≥10%	40% 10/28	31% 9/29	37% 7/19
				p=0,24

Tab. 2. Annual assessment of the course of the disease.

	IPAF	CTD-ILD	CTD without ILD	p
ΔTL_{CO} [%]	2 [-12; 6]	-1,5 [-10,5; 6,25]	-6,5 [-11,25 – 8,5]	0,65
ΔFEV_1 [%]	-2 [-8; 5]	-2 [-10,5; 5,75]	0 [-1; 4,25]	0,48
ΔFVC [%]	0 [-5; 6]	-2,5 [-8,75; 5,5]	2,5 [-1; 10]	0,23
Δ6MWT distance [m]	10 [-15; 105]	-2 [-107; 99]	-7,5 [-71; 30]	0,42

Tab. 3. Annual assessment of patients - differences between T1 and T2.

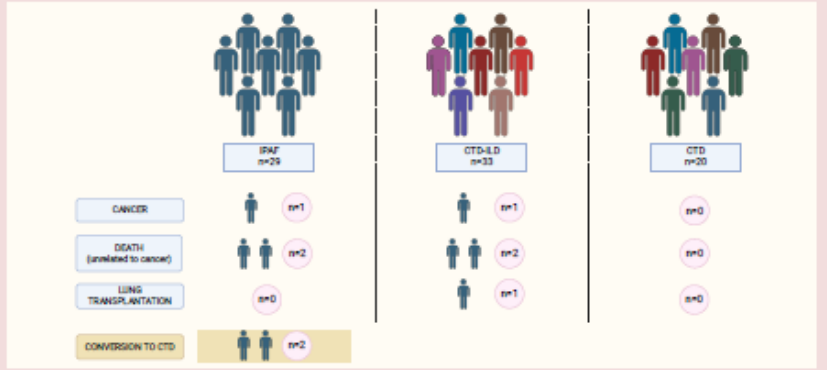


Fig. 2. In patients with IPAF and CTD-ILD we noted 2 deaths (unrelated to cancer) in each group. 1 patient in both groups developed a neoplastic process (IPAF: pancreatic cancer, CTD-ILD: lung cancer). 2 patients with IPAF met the criteria for CTD during follow-up (1 Sjögren syndrome, 1 polymyositis).

CONCLUSION

Only a small percentage of patients with IPAF developed CTD during follow-up. Mortality and the likelihood of developing cancer in IPAF and CTD-ILD patients seems to be high.
There are no signifficant differences in the annual assessment between the groups in terms of pulmonary function tests.

QR

The authors declare no conflict of interest.
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A retrospective study based on cluster analysis aiming to identify subgroups of IPAF patients with different clinical profiles and prognoses

SEMMELWEIS UNIVERSITY 1769

Alexandra Nagy MD, PhD

Prof. Veronika Müller MD, PhD

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ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

ERS International Congress 2023: highlights from the Interstitial Lung Diseases Assembly

Laura Fabbri[1,2], Julien Guiot[3,4], Marie Vermant[5], Ewa Miądlikowska[6], Deborah Estrella[7], Marlies S. Wijsenbeek[8], Wim Wuyts[5], Elena Bargagli[9], Antoine Froidure[10], Paolo Spagnolo[11], Marcel Veltkamp[12,13], Maria Molina-Molina[14], Cormac McCarthy[15], Katerina Antoniou[16], Michael Kreuter[17] and Catharina C. Moor[8]

Fabbri L, Guiot J, Vermant M, Miądlikowska E, Estrella D, Wijsenbeek MS, Wuyts W, Bargagli E, Froidure A, Spagnolo P, Veltkamp M, Molina-Molina M, McCarthy C, Antoniou K, Kreuter M, Moor C, ERS International Congress 2023: highlights from the Interstitial Lung Diseases Assembly. ERJ Open Res 10: 00839-2023 (2024)

I received a grant from the Count Jakub Potocki Foundation, which main statutory goal is to fight cancer and lung diseases, for a 3-month internship abroad at UZ Leuven in Leuven, Belgium.

February 1st – April 30th 2024

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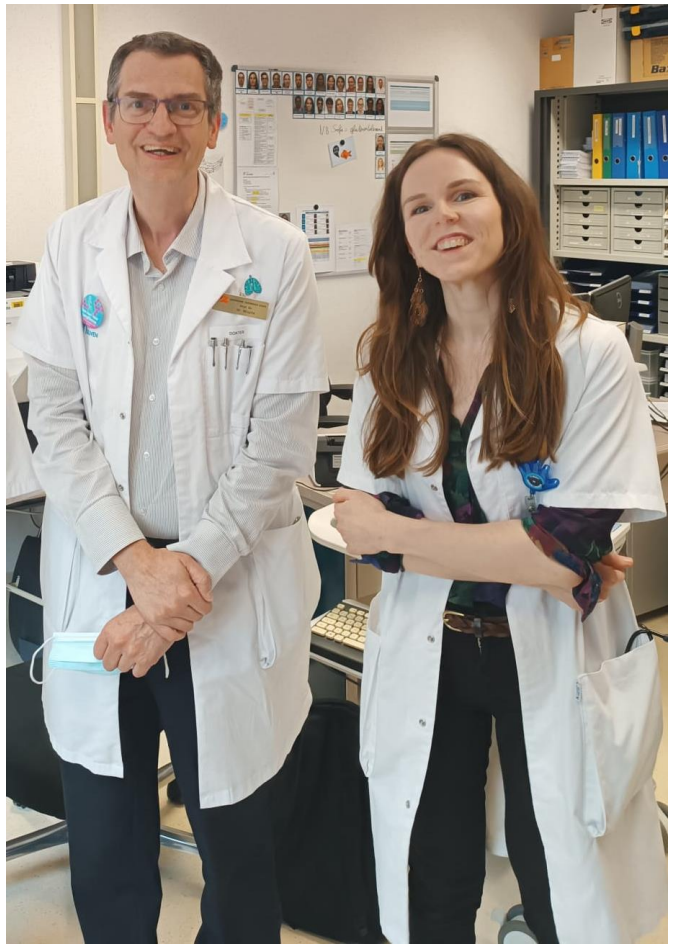

Prof. Wim Wuyts MD, PhD

UZ LEUVEN

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During the intership in Leuven I started working on 2 research projects with:

Francesca Lalla MD

Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Ran Tenzin Rangdol

UZ LEUVEN







Thank you for your attention!