GLILD
– a Nordic perspective

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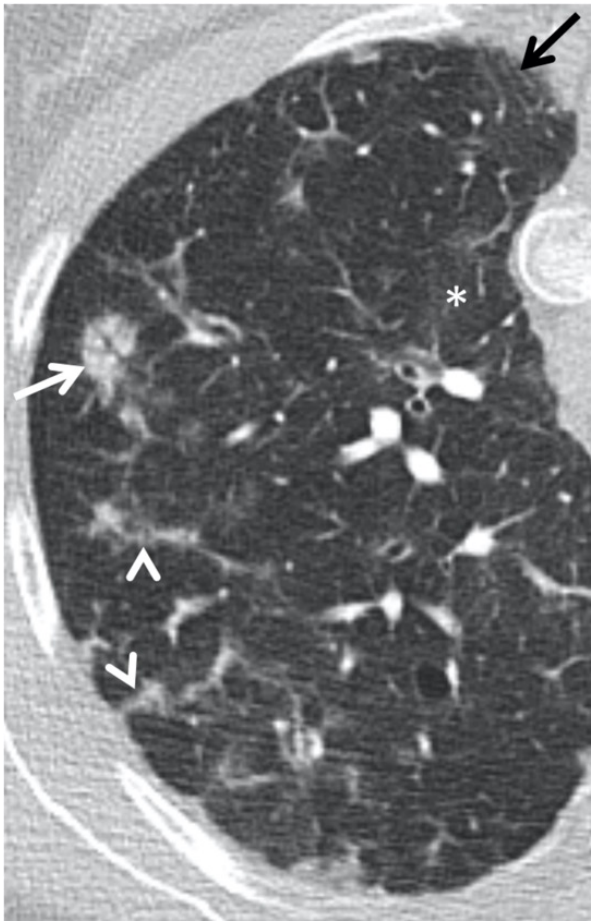
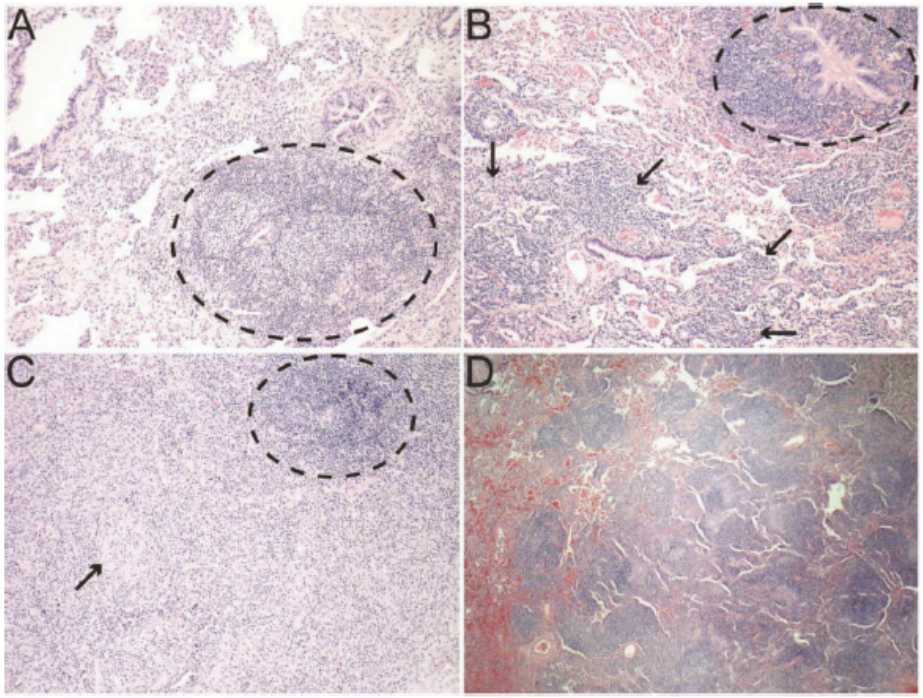


Disposition

- GLILD basics
- Oslo studies
  - Diagnosis
  - Radiology
  - Biomarkers
- Nordic GLILD initiative
  - Diagnosis
  - Treatment
  - Research

GLILD - definition



Schussler, E., et al. 2016. *JACI Pract* 4:1039-1052.

A distinct clinic-radio-pathological interstitial lung disease

- Dyspnea and chronic cough
- Fall in DLCO and FVC
- Typical radiologic features:
  - Noduli up to 3 cm
  - Patchy ground glass lesions
  - Consolidations
  - Peribronchial and perilymphatic distribution
- Lymphocytic infiltrate and/or granuloma in the lung

Bang, T.J., et al. 2018. *J Thorac Imaging* 33:377-383.
Bouvry, D., et al. 2013. *Eur Respir J* 41:115-122.
Gregersen, S., et al. 2010. *Ann allergy, asthma imm* 104:503-510.
Hurst, J.R., et al. 2017. *JACI Pract* 5:938-945.
Maglione, P.J., et al. 2014. *JACI* 133:535-542.
Maglione, P.J., et al. 2015. *JACI Pract* 3:941-950.
Mannina, A., et al. 2016.. *Ann Am Thorac Soc* 13:1042-1049.
Prasse, A., et al. 2013. *Curr Opin Pulm Med* 19:503-509.

Characteristics	CVID-GLILD ($n = 34$)	CVID Control Subjects ($n = 52$)	*P* Value
Demographics			
Age, yr	39 ± 13	45 ± 15	0.07
Female sex, n (%)	17 (50)	28 (54)	0.93
Cigarette smoking status			
Ever smoker, n (%)	5 (15)	9 (17)	0.59
Smoking history, pack-years	21 ± 20	21 ± 35	0.51
Extrapulmonary manifestations, n (%)			
Cytopenia	16 (47)	2 (4)	<0.01
Hypersplenism	26 (76)	6 (11)	<0.01
Granulomatous hepatitis	5 (14)	2 (4)	0.04
Polyarthritis	9 (26)	4 (7)	<0.01
Enteropathy	5 (15)	4 (7)	0.44
Mean duration of CVID diagnosis	8 ± 6	8 ± 10	0.19
Dyspnea score*	2 ± 3	1 ± 1	<0.01
Pulmonary function tests, % predicted			
FVC	77 ± 21	89 ± 14	0.02
FEV_1	73 ± 23	86 ± 18	0.01
FEV_1/FVC ratio	81 ± 11	82 ± 12	0.81
D_{LCO}	72 ± 23	94 ± 12	0.01
Dosage of IVIG, mg/kg/mo	608 ± 140	516 ± 154	0.01
Serum immunoglobulin level, mg/dl			
IgA	11 ± 8	93 ± 61	<0.01
IgE	11 ± 29	80 ± 64	0.02
IgG	512 ± 419	872 ± 403	<0.01
IgM	31 ± 44	60 ± 68	0.01
Peripheral blood lymphocytes, %			
CD3 T cells	74 ± 18	77 ± 13	0.89
CD4 T cells	47 ± 12	46 ± 16	0.89
CD8 T cells	28 ± 11	36 ± 53	0.77
CD4/CD8 ratio	2 ± 1.4	2 ± 2.3	0.84
CD19 B cells	12 ± 11	12 ± 13	0.96
B-cell subsets, %			
IgD^+CD27^+ B cells	8 ± 15	18 ± 18	<0.01
IgD^-CD27^+ B cells	2.8 ± 7	7.6 ± 9	<0.01
IgD^+CD27^- B cells	51 ± 43	66 ± 28	0.67

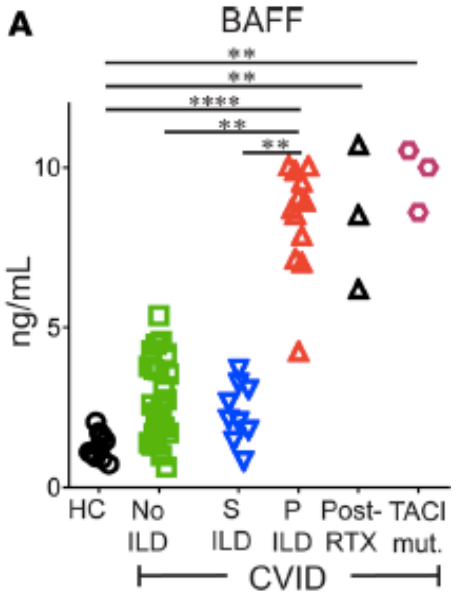
Mannina, A., et al. 2016. *Ann Am Thorac Soc* 13:1042-1049.

Clinical risk factors

- Granulomas in other tissues
- Hepatosplenomegaly
- Lymphadenopathy
- Nodular regenerative hyperplasia of liver (NRH)
- Autoimmune hemolytic anemia
- Immune thrombocytopenic purpura
- Polyarthritis

Chase, N.M., et al. 2013. *J Clin Immunol* 33:30-39.
Hartono, S., et al. 2017. *Ann allergy, asthma & imm* 118:614-620.
Mannina, et al. 2016. *Ann Am Thorac Soc* 13:1042-1049.

Immunologic and genetic risk factors

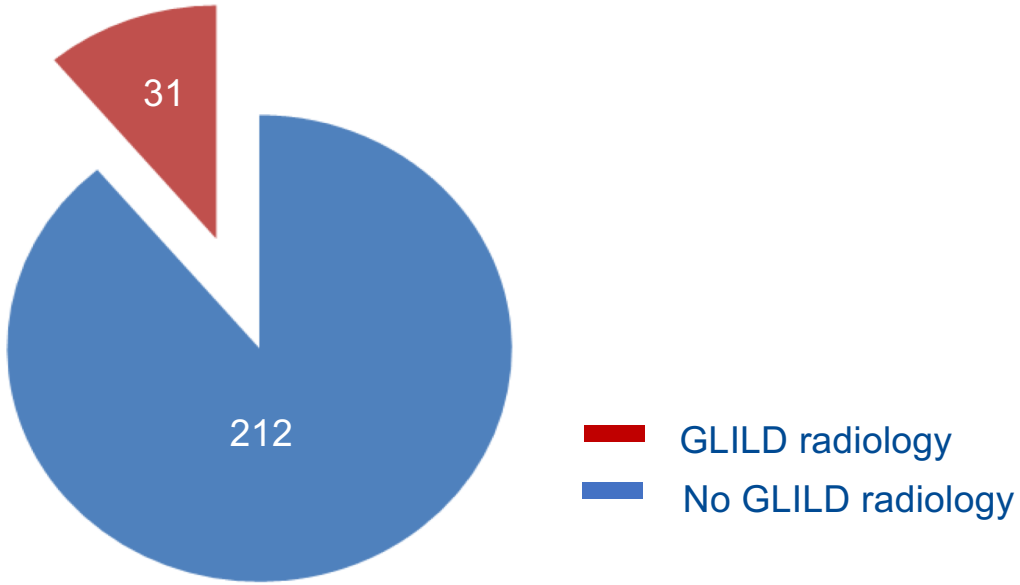


Maglione, P.J., et al. 2019. *JCI Insight* 4:5

- ⇧ TNF, INF-g, IgM, STAT1, BAFF
- ⇩ Switched-memory B cells.
- *TACI, CTLA4, LRBA, STAT3* and *PI3KD*.

Gregersen, S., et al. 2010. *Ann allergy, asthma & imm* 104:503-510.
Mannina, et al. 2016. *Ann Am Thorac Soc* 13:1042-1049.
Schussler, E., et al. 2016. *JACI Pract* 4:1039-1052.

CVID in Oslo – 243 patients in register

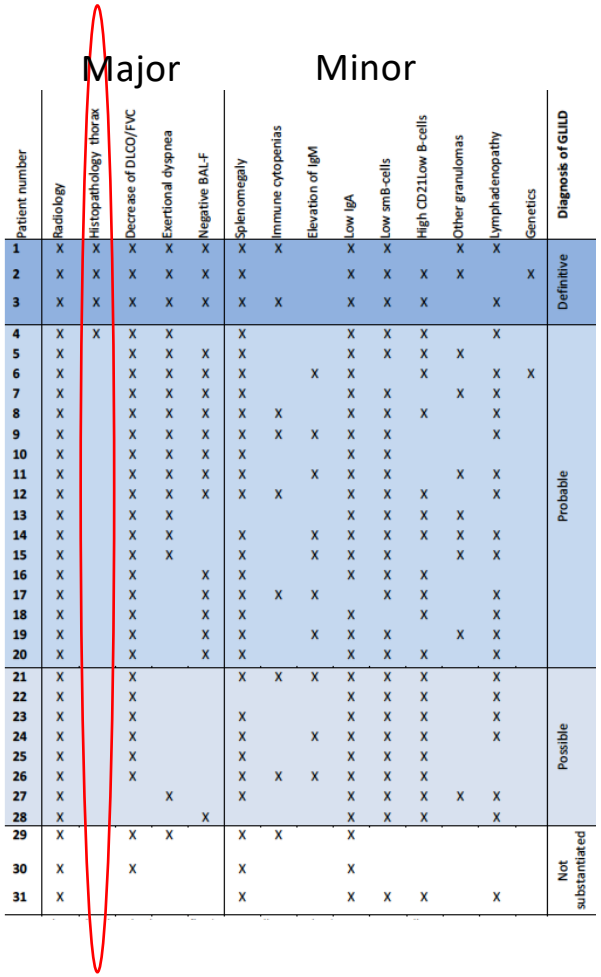


Oslo study – diagnosis

Major	
	Typical radiology
	Typical histopathology on lung biopsy/thoracic lymph node
	Reduced/decrease of DLCO/FVC
	Exertional dyspnea
	Negative microbiologic analyses of BAL-F
Minor	
	Splenomegaly
	Immune cytopenias
	Elevated IgM
	Low IgA
	Low switched memory B-cells
	Increased $CD21_{Low}$ B-cells
	Granulomatous lesions in other tissue
	Generalized lymphadenopathy
	Genetics associated with interstitial lung disease

Classification

	Major criteria	Minor criteria
Definitive	5	-
Probable	3 incl neg microbiology	≥4
Possible	2 incl neg microbiology	≥4



	Major		Minor													
Patient number	Radiology	Histopathology thorax	Decrease of DLCO/FVC	Exertional dyspnea	Negative BAL-F	Splenomegaly	Immune cytopenias	Elevation of IgM	Low IgA	Low smB-cells	High CD21Low B-cells	Other granulomas	Lymphadenopathy	Genetics	Diagnosis of GLILD
1	X	X	X	X	X	X	X		X	X		X	X		Definitive
2	X	X	X	X	X	X			X	X	X	X		X	
3	X	X	X	X	X	X	X		X	X	X		X		
4	X	X	X	X		X			X	X	X		X		Probable
5	X		X	X	X	X			X	X	X	X			
6	X		X	X	X	X		X	X		X		X	X	
7	X		X	X	X	X			X	X		X	X		
8	X		X	X	X	X	X		X	X	X		X		
9	X		X	X	X	X	X	X	X	X			X		
10	X		X	X	X	X			X	X					
11	X		X	X	X	X		X	X	X		X	X		
12	X		X	X	X	X	X		X	X	X		X		
13	X		X	X					X	X	X	X			
14	X		X	X		X		X	X	X	X	X	X		
15	X		X	X		X		X	X	X		X	X		
16	X		X		X	X			X	X	X				
17	X		X		X	X	X	X		X	X		X		
18	X		X		X	X			X		X		X		
19	X		X		X	X		X	X	X		X	X		
20	X		X		X	X			X	X	X		X		
21	X		X			X	X	X	X	X	X		X		Possible
22	X		X						X	X	X		X		
23	X		X			X			X	X	X		X		
24	X		X			X		X	X	X	X		X		
25	X		X			X			X	X	X				
26	X		X			X	X	X	X	X	X				
27	X			X		X			X	X	X	X	X		
28	X				X				X	X	X		X		
29	X		X	X		X	X		X						Not substantiated
30	X		X			X			X						
31	X					X			X	X	X		X		

Results

- 3 definitive
- 17 probable
  - 16 without biopsy
- 8 possible
  - All without biopsy
- 3 not substantiated
  - No BAL
- 14 patients >5 minor criteria

Discussion
– can we diagnose without biopsy?

FVC, % Predicted	GLILD Cases (*n* = 34)	SLBx-GLILD (*n* = 19)	Non-SLBx GLILD (*n* = 15)	*P* Value
At diagnosis	77 ± 21	76 ± 18	79 ± 24	0.24
1 yr	76 ± 22	72 ± 25	78 ± 20	0.35
5 yr	75 ± 19	69 ± 18	77 ± 20	0.17

Mannina, et al. 2016. *Ann Am Thorac Soc* 13:1042-1049

- Radiological findings not considered sufficient to avoid biopsy
- Diagnosis based on surgical biopsy vs radiology alone same course
- Several studies used radiologic diagnosis only

Hartono, S., et al. 2017. *Ann allergy, asthma & imm* 118:614-620
Hurst, J.R., et al. 2017. *JACI Pract* 5:938-945.
Maglione, P.J., et al. 2015. *JACI Pract* 3:941-950.
Limsuwat, C., et al. 2018.. *Chest* 154:e27-e30.

Oslo study – radiology and PET-CT

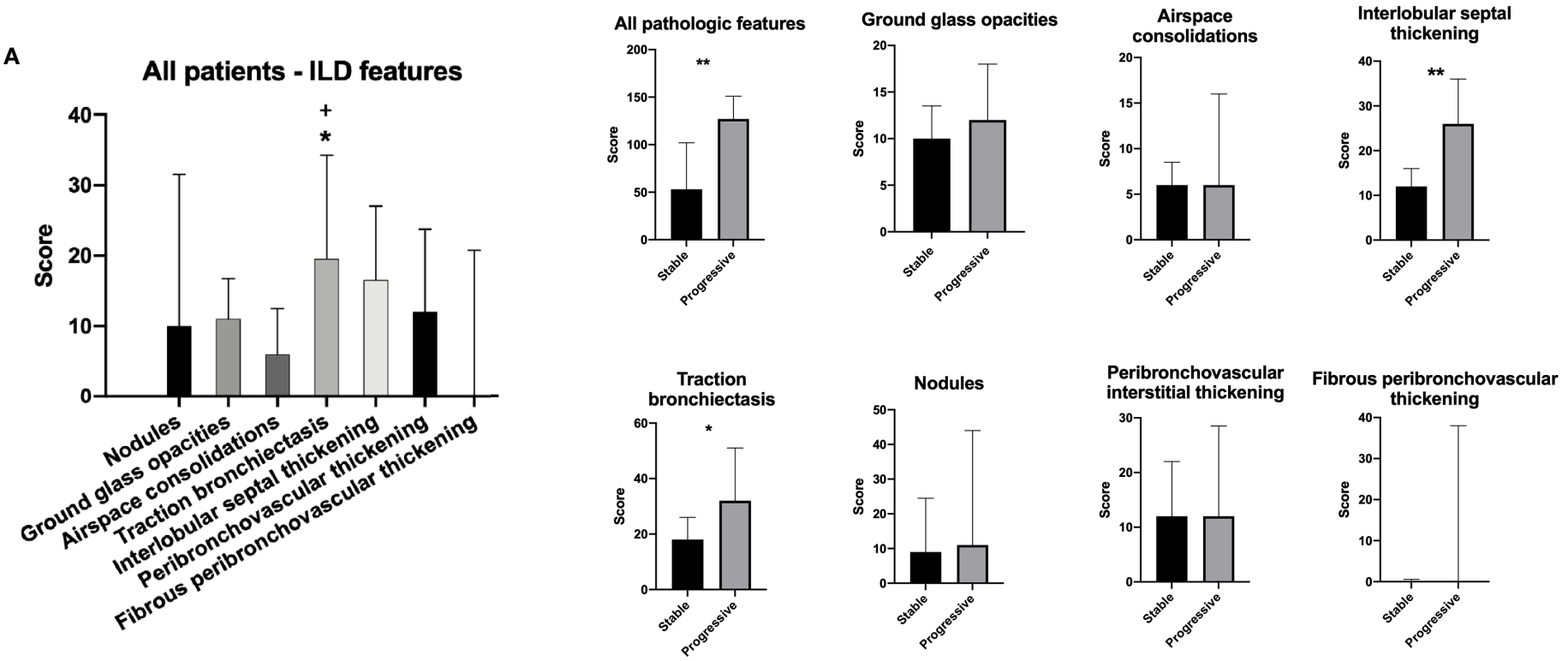
TABLE 1 | Patient characteristics.

	Stable disease (n = 13)	Progressive disease (n=19)	p-value*
Age (years)**	44 (37–56)	51 (39–61)	0.274
Female sex, n (%)	5 (39)	12 (63)	0.169
Known monogenic defect,*** n (%)	2 (15)	2 (11)	0.683
Coexisting obstructive lung disease, n (%)	1 (8)	3 (16)	0.496
History of smoking, n (%)	2 (15)	4 (21)	0.687
First DLCO at our clinic (% of predicted)**	81 (65–85)	75 (67–83)	0.828
First FVC at our clinic (% of predicted)**	99 (90–109)	82 (69–105)	0.172
Follow-up time (months)**	73 (15–74)	142 (59–157)	0.033
Other non-infectious complications			
Lymphadenopathy, n (%)	11 (85)	19 (100)	0.077
Splenomegaly, n (%)	12 (92)	17 (90)	0.787
CVID associated enteropathy, n (%)	5 (39)	9 (47)	0.618
Autoimmune cytopenia, n (%)	6 (46)	6 (32)	0.403
Granulomas in other tissue, n (%)	5 (39)	7 (37)	0.926
NRH in liver, n (%)	3 (23)	5 (26)	0.835
Immunoglobulin substitution form[§]			
IVIG, n (%)	2 (15)	9 (47)	0.061
SCIG, n (%)	7 (54)	11 (58)	0.821
fSCIG, n (%)	3 (23)	2 (11)	0.337
Immunomodulatory treatment for GLILD			
Any treatment (%)	2 (15)	10 (53)	0.033
Rituximab (%)	1 (8)	7 (37)	0.034
Corticosteroids (%)	2 (15)	6 (32)	0.300
Azathioprine (%)	0 (0)	7 (37)	0.013
Abatacept (%)	0 (0)	1 (5)	0.401
Anti TNF agents (%)	0 (0)	1 (5)	0.401
Immunomodulatory treatment, other indications			
Rituximab (%)	2 (15)	2 (11)	0.683
Corticosteroids (%)	7 (54)	8 (42)	0.513

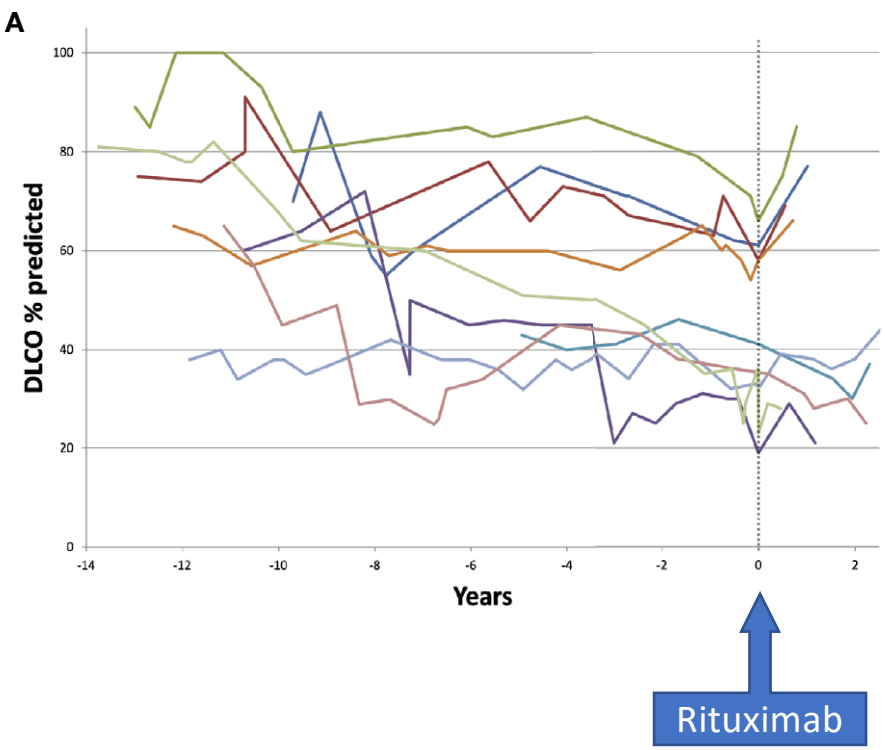
Stable and progressive disease compared.

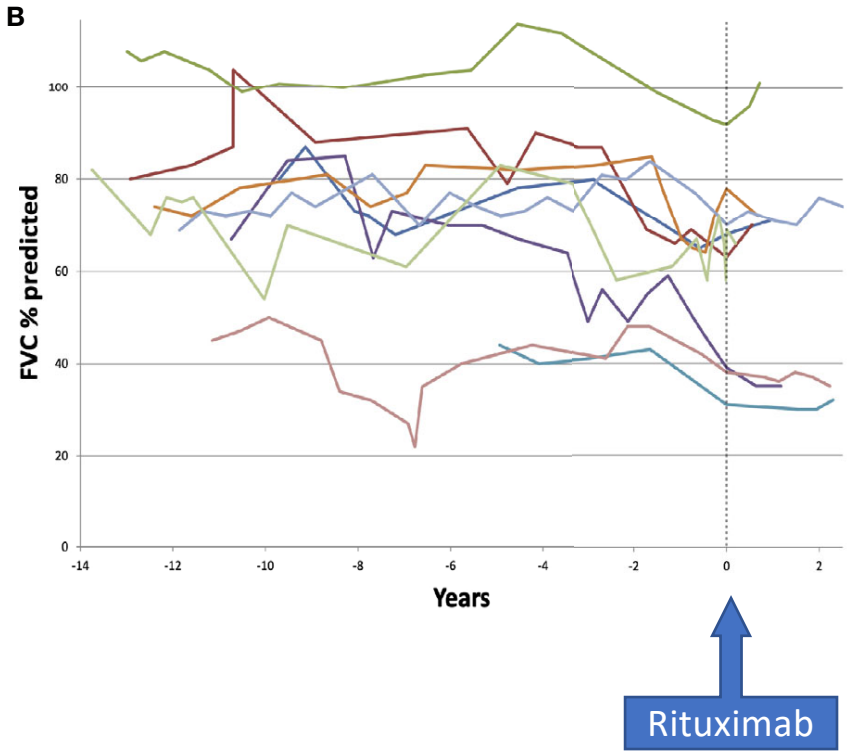
- 32 CVID patients with radiologic features of GLILD
- Stable vs progressive disease
  - Decline in FVC > 10 p.p.
  - Decline in DLCO > 15 p.p.
  - FVC <50%
  - DLCO <40%
- Effect of rituximab treatment

CT findings in stable and progressive diasease



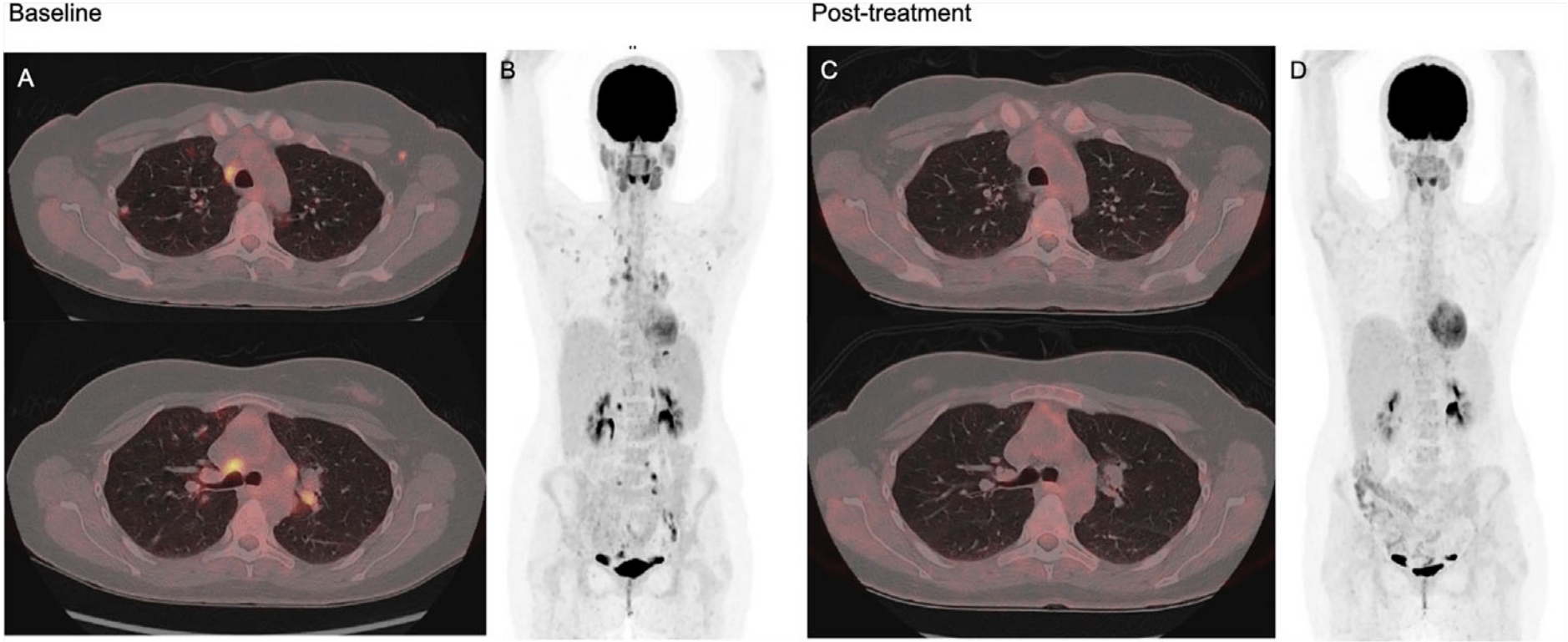
Pulmonary function



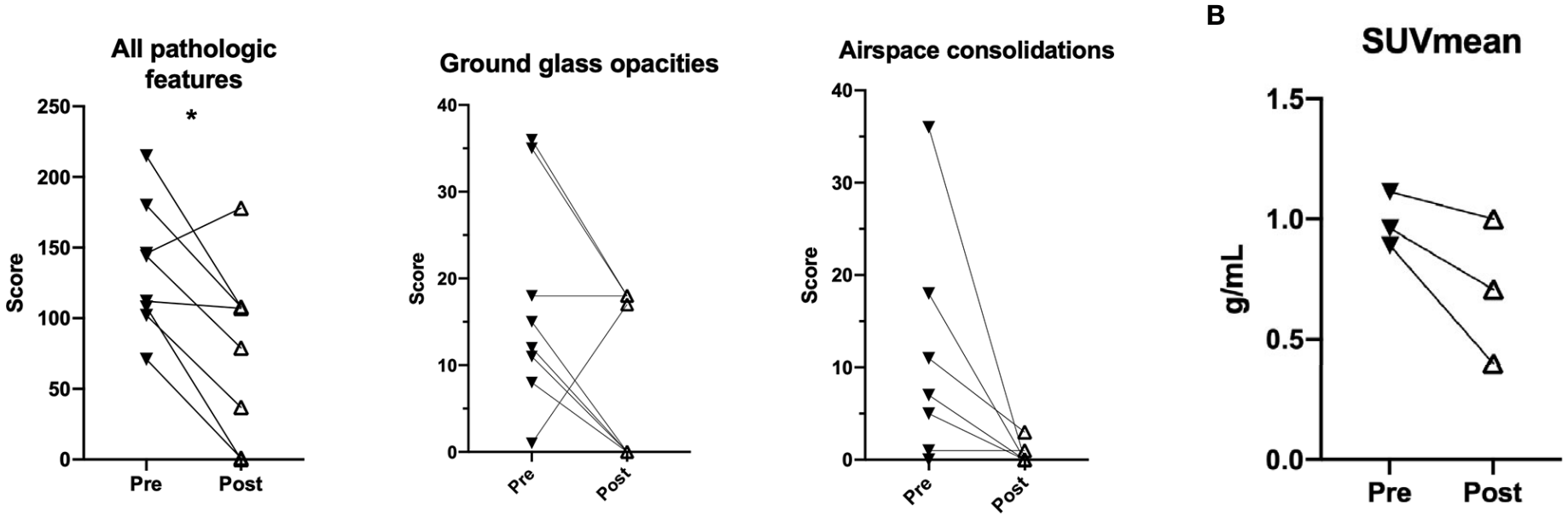


Fraz MSA, et al. Front Imm. January 2021 | Volume 11 | Article 617985

PET-CT after treatment with rituximab



CT and PET-CT scores after treatment



Nordic GLILD – participating centres

	Copenhagen	Gothenburg	Helsinki	Oslo	Oulo	Stockholm
Principal investigator	J Helweg-Larsen	V Friman	T Martelius	B Fevang	T Hautala	P Bergman
Affiliaton	Copenhagen University Hospital	Sahlgrenska University Hospital	Helsinki University Hospital	Oslo University Hospital	Oulo University Hospital	Karolinska University Hospital
CVID-patients	100	50	120	120	50	90
Clinical features, immunology, radiology	+	+	+	+	+	+
Genetic screening	(+)	(+)	+	+	+	+
Stored blood samples	(+)	+	(+)	+	+	(+)

Nordic GLILD – diagnostic checklist

	Status	Date
Imaging		
• **HRCT lung**		
• PET-CT torso		
• Echocardiography		
Bronchoscopy		
• Biopsy		
• **Lavage fluid for microbial analyses: aerob/ anaerob/ mycobacteria/ fungi cultivation, resp virus-PCR, Pneumocystis-PCR**		
• Lavage fluid for microbial analyses: Aspergillus-PCR, CMV-PCR, EBV-PCR		
• Lavage fluid for immunophenotyping		
• Lavage fluid for biobanking (supernatant/cell pellet)		
Other pulmonary tests		
• **Spirometry with gas diffusion test**		
• Exercise testing with O2-saturation		
• Body-box test		
• **Symptomatic questionnaire**		

Blood samples		
• **Regular: hemoglobin, thrombocytes, leukocytes w/diff, ALP, GT, ALAT, creatinin, imm globulins, b2-microglobulin**		
• **Inflammatory markers (CRP, ferritin, sIL2R)**		
• **Cardiac markers (pro-BNP, Trop T)**		
• **Immunophenotyping**		
• Microbiology (CMV-PCR, EBV-PCR)		
• **Serum/plasma for biobanking**		
• **Genetic testing - immunodeficiency panel**		

Strongly suggested procedures in bold, suggested procedures in normal font.

Nordic GLILD – diagnosis and indication

- Genetic testing for monogenic immunodeficiencies should be performed as some primary immunodeficiencies have a particularly high frequency of interstitial lung disease, and require specific treatment (e.g. CTLA4-haploinsufficiency and LRBA-deficiency).
- The indication for treatment of GLILD rests on the following features:
  - Clinical. Progressive decline in pulmonary function is the main factor
  - Radiological. Signs of active pulmonary inflammation with reversible parenchymal manifestations
  - Abscence of microbial infection.

- In addition the following features will support treatment
  - Optimized immunoglobulin treatment
  - Immunological characteristics and signs of systemic inflammation.

Nordic GLILD – suggested treatment

We recommend that patients with CVID where an indication for treatment of GLILD has been found receive the following treatment:

- Prednisolone 1 mg/kg/day tapered to 0,1 mg/kg/day(max 7,5 mg/day)

or

- Rituximab 1 g iv, repeat after 2 weeks, 6 months and 12 months

First line treatment should be continued for at least 6 months before changing regimen.

Patients should be evaluated with pulmonary function tests and pulmonary CT scan 3-6 months after initiating treatment.

Treatment failure is defined as continued decline in pulmonary function or active inflammatory features on pulmonary CT-scan after 6-12 months treatment

Summarizing

Acknowledgements

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