Computed Tomography Findings as Determinants of Local and Systemic Inflammation Biomarkers in Interstitial Lung Diseases: A Retrospective Cohort Study

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Abstract

Background:

Additional to high-resolution computed tomography (HRCT), peripheral blood (PBL) and broncho-alveolar lavage (BAL) could provide biomarkers to distinguish predominantly inflammatory from non-inflammatory/fibrotic interstitial lung disease (ILD) phenotypes.

Methods:

HRCT of 127 subsequent ILD-board patients were semi-quantitatively evaluated in a standardized way: Reticulation/honeycombing (RET), traction bronchiectasis (TBR) and emphysema (EMP) were classified as non-inflammatory/fibrotic; consolidations (CON), ground glass opacities (GGO), noduli (NDL) and mosaic attenuation (MOS) as active inflammatory findings. These HRCT findings were counted as present or absent in 6 distinct lung regions, resulting scores were graded as minimal (0-1 regions involved), medium (2-4) or extensive (5-6).

Associations between routinely assessed PBL/BAL biomarkers with these radiological scores were evaluated using Spearman correlation coefficients; significance of the graded HRCT scores by applying Kruskal-Wallis tests.

Results:

Blood neutrophil, lymphocyte and eosinophil fraction, neutrophil-lymphocyte ratio (NLR) and BAL lymphocyte fraction consistently showed opposite correlations for inflammatory versus non-inflammatory/fibrotic HRCT finding scores. Blood lymphocyte fraction significantly differed by graded GGO (p=0.032) and CON (p=0.027) extent, eosinophil fraction by TBR (p=0.006) and NLR by CON (p=0.009). C-reactive protein was significantly related to GGO (p=0.023) and CON (p=0.004), BAL lymphocyte fraction to GGO (p=0.017).

Conclusions:

Blood lymphocyte and eosinophil fraction, NLR, CRP and BAL lymphocyte fraction may aid to differentiate inflammatory from non-inflammatory/fibrotic ILD patterns.

Trial registration:

This evaluation was based on data from the ILD registry of Kepler University Hospital Linz, as approved by the ethics committee of the federal state of Upper-Austria (EK Nr. I-26-17).

Introduction

The efficacy of anti-fibrotic drugs in decelerating lung function decline in idiopathic pulmonary fibrosis (IPF) and progressive fibrosing interstitial lung diseases (PFILD) is well established.[1–4] Patients with

ILD susceptible to immunomodulatory therapies can experience an improvement in both radiological imaging and pulmonary function tests,[5–7] while such therapies prove no or even adverse effects in IPF.[8, 9] Importantly, also ILD with an “inflammatory” origin like SSCILD or chronic hypersensitivity pneumonitis (CHP) frequently present with a PFILD phenotype.[10] In systemic sclerosis associated ILD (SSCILD) placebo-controlled trials have provided evidence on the efficacy of immunomodulatory therapies,[6, 11] as well as of anti-fibrotic therapy.[12] It is still unclear whether an anti-fibrotic, an immunomodulatory or a combined approach may be most beneficial in such conditions. Biomarkers predicting the response to either therapeutic strategy are therefore warranted.

In current clinical practice, most biomarker information is derived from high-resolution computed tomography (HRCT) imaging, the cornerstone in the multi-disciplinary diagnosis of ILD. A radiological pattern of usual interstitial pneumonia (UIP) irrespective of the underlying bears a poorer prognosis than possible UIP or nonspecific interstitial pneumonia (NSIP).[13–19] Under certain conditions, an UIP-pattern can be diagnostic for IPF and lead to the initiation of anti-fibrotic therapy without the need of lung biopsy.[18, 19] In most ILD cases however, HRCT patterns are not uniform but rather involve several coexisting abnormalities like for example reticulation (RET), ground glass opacities (GGO) and traction bronchiectasis (TBR) in fibrotic NSIP. The relative distribution and extent of such radiological findings may depend on the underlying pathogenetic processes, the course and duration of the disease.[14]

Hypothetically, peripheral blood (PBL) and broncho-alveolar lavage (BAL) biomarkers could help to differentiate ILD cases with an inflammatory from those with a predominantly fibrotic phenotype. Knowledge on their interaction with HRCT findings could aid the development of biomarkers guiding ILD therapy in the future.

Materials & Methods

Based on a retrospective ILD registry cohort, we have evaluated routine biomarkers from PBL and BAL fluid for their association with a set of visually semi-quantified typical HRCT finding scores.

Patient data used for this analysis were retrieved from the ILD registry of Kepler University Hospital Linz, Austria. The registry as well as the present evaluation have been conducted in concordance with the Declaration of Helsinki and were approved and re-assessed on a yearly basis by the ethics committee of the Federal State of Upper Austria (Study number I-26-17). All patients enregistered were subsequently discussed by the monthly local ILD-board after they had undergone a standardized ILD evaluation program including assessment of patient history, physical examination, HRCT imaging, pulmonary function tests and laboratory analyses with standard autoimmune serologies.[19, 20] Patients, in whom ILD board discussion resulted in no diagnosis of an ILD were excluded from this study.

HRCT images were acquired according to protocols suggested by the relevant guidelines.[18, 19, 21] If clinically feasible, prone imaging was preferred in order to differ opacities in dependent lung areas from true interstitial lung abnormalities.[22]

Blood samples were analyzed with a Sysmex® XN-3000 hematology analyzer (Sysmex Europe GmbH, Norderstedt, Germany) for blood cell counts and a Cobas® 8000 modular analyzer (Roche Diagnostics International AG, Rotkreuz, Switzerland) for C-reactive protein (CRP) and lactate dehydrogenase (LDH).

Bronchoalveolar lavage was performed according to the relevant guidelines,[23, 24] when clinically indicated by the treating physician or when requested by the ILD-board. A total of 100 mL of 0,9% saline was instilled and retrieved in aliquots of 20 mL via flexible bronchoscopy under sedoanalgesia. The BAL location was a segmental bronchus of either one of the upper lobes including the lingula or the middle lobe at the discretion of the conducting physician according to the location of most active or extensive disease in HRCT. BAL samples were prepared using 100 µL of BAL fluid on a Tharmac® Cellspin I cytocentrifuge (Tharmac GmbH, Wiesbaden, Germany) at 700 rounds per minute for 5 minutes and Wright Giemsa staining. Cell counting was performed manually under 400-fold magnification, cell fractions were given as % of the total cell count, excluding epithelial cells or erythrocytes.

To allow for statistical analyses of HRCT scans, we have previously devised a semi-quantitative scoring system based on four elementary lesion types: nodular pattern (NDL), reticular abnormalities (interlobular septal and intralobular interstitial thickening and honeycombing – RET), increased lung attenuation (consolidations (CON), ground glass opacities(GGO)) and reduced lung attenuation (emphysema - EMP) findings. Besides, extent of mosaic attenuation (mosaic perfusion, air-trapping - MOS) and traction bronchi(-ol)ectasis (TBR) were assessed. [21, 25, 26]. For quantification, both lungs were separated in an upper-, middle- and lower lung area, as defined by thirds of the largest cranio-caudal diameter in the sagittal reconstructions, leading to six distinct lung areas. For each quantified pattern (RET, TBR, EMP, CON, GGO, NDL, MOS) the individual extent was calculated as the sum of all involved defined lung areas (0–6). The described HRCT scoring process was accomplished during the respective ILD-board session by a specialized ILD radiologist in a non-blinded fashion.

To evaluate the associations between the mentioned inflammation biomarkers with the standardized imaging features, correlation coefficients were calculated for each HRCT finding score and each blood and BAL biomarker. Direction, strength, and significance of these correlations were depicted in color-coded tables for visual analysis. To test for clinical relevance of the associations between HRCT finding scores and the different PBL and BAL biomarkers, groups with no or minimal involvement (0–1), medium (2–5) and extensive involvement (5–6) were compared using the Kruskal-Wallis test. All statistical analyses were performed using R (R: A Language and Environment for Statistical Computing; Version 3.6.0; https://www.R-project.org). For all tests performed, a p-value < 0.05 was regarded statistically significant.

Results

We evaluated 127 ILD patients consecutively discussed by the multidisciplinary ILD-board of Kepler University Hospital Linz, Austria between February 2017, and September 2018. Clinical and radiological patient characteristics are shown in Tables 1 and 2.

Table 1

Patient characteristics. Data are given as n (%) unless otherwise specified. SD = standard deviation, ILD = interstitial lung disease, IPAF = interstitial pneumonia with autoimmune features, IPF = idiopathic pulmonary fibrosis, CHP = chronic hypersensitivity pneumonitis, iNSIP = idiopathic non-specific interstitial pneumonia, aILD = autoimmune-associated ILD

Patient Characteristics	
Mean age (years, SD)	65 (14)
Age range (years)	18–91
Male Sex (n, %)	82 (65)
Reported onset of respiratory symptoms (years, SD)	4.1 (5.8)
Family history of ILD (n, %)	8 (6)
ILD-board diagnosis	n (%)
IPAF	26 (20)
IPF	23 (18)
CHP	17 (13)
iNSIP	16 (13)
aILD	11 (9)
Unclassified ILD	11 (9)
Other ILD	23 (18)
Smoking history	n (%)
Mean pack years (mean, SD)	19.4 (25.2)
Never smoker	52 (41)
Former smoker	50 (39)
Current smoker	17 (13)
Exclusively passive smoker	6 (5)

Table 2
Peripheral blood, BAL and HRCT characteristics. Values are given as n (%) and mean (SD) or median (range) as specified. SD = standard deviation, IQR = interquartile range, BAL = broncho-alveolar lavage, HRCT = high-resolution computed tomography

Peripheral blood biomarkers	**n (%)**	**mean (SD)**
Leukocyte count (G/L)	122 (96)	8.7 (3.4)
Neutrophil fraction (%)	121 (95)	70.9 (10.9)
Lymphocyte fraction (%)		20.5 (8.7)
Neutrophil/lymphocyte ratio		5 (4.9)
Eosinophil count (%)		0.2 (0.3)
C-reactive protein (mg/dL)	123 (97)	1.6 (2.6)
Lactate dehydrogenase (U/L)	113 (89)	247 (78.2)
BAL biomarkers	n (%)	mean (SD)
Makrophage fraction (%)	66 (52)	51.9 (29.9)
Neutrophil fraction (%)		18.5 (23.1)
Lymphocyte fraction (%)		18.5 (21.6)
Eosinophil fraction (%)		3.6 (7.9)
HRCT finding scores	n (%)	median (range)
Noduli	40 (31)	0 (0–6)
Reticulation/honeycombing	106 (83)	4 (0–6)
Honeycombing	22 (17)	0 (0–6)
Ground glass opacities	49 (39)	0 (0–6)
Consolidations	44 (35)	0 (0–6)
Emphysema	23 (18)	0 (0–6)
Traction bronchiectasis	100 (79)	2 (0–6)
Mosaic attenuation	32 (25)	0 (0–6)

A considerable fraction of patients (n = 26, 20%) fulfilled the criteria for interstitial pneumonia with autoimmune features (IPAF), and a similar proportion of the collective was diagnosed with IPF (n = 23, 18%) or chronic hypersensitivity pneumonitis (CHP; n = 17, 13%). The fraction of patients with “other ILD” (n = 23; 18%) included nine cases of organizing pneumonia (OP), six patients with sarcoidosis, three with

respiratory-bronchiolitis-ILD, two with drug-associated pneumonitis and one patient each with pulmonary Langerhans-cell histiocytosis, pleuro-parenchymal fibroelastosis and lymphangioleiomyomatosis. Eleven patients (9%) were considered “unclassified ILD”, either due to patients not willing to undergo further necessary diagnostic steps like lung biopsy or to situations, where further work-up was deemed inappropriate due to age or major comorbidities. Eleven patients (9%; ten with NSIP, one with unclassifiable ILD) were or had already been diagnosed with autoimmune disorders considered causative or causally related to ILD (rheumatoid arthritis in four patients, autoimmune-hepatitis in two patients, Sjögren’s syndrome in two patients and pauci-immune glomerulonephritis, granulomatosis with polyangiitis and SHARP-syndrome in one patient each).

HRCT, PBL and BAL characteristics according to ILD-board diagnoses are shown in Table 3.

Table 3

HRCT findings, peripheral blood and BAL characteristics according to ILD-board diagnoses. Values are given as median (range) or mean (SD) as specified. SD = standard deviation, HRCT = high-resolution computed tomography, ILD = interstitial lung disease, IPAF = interstitial pneumonia with autoimmune features, IPF = idiopathic pulmonary fibrosis, CHP = chronic hypersensitivity pneumonitis, iNSIP = idiopathic non-specific interstitial pneumonia, aILD = autoimmune-associated ILD, RET = reticulation/honeycombing, TBR = traction bronchiectasis, EMP = emphysema, GGO = ground glass opacities, CON = consolidations, NDL = noduli, MOS = mosaic attenuation, HRCT = high-resolution computed tomography, PBL = peripheral blood, LEU = absolute leukocyte count, NEU = relative neutrophil fraction, LYM = relative lymphocyte fraction, NLR = neutrophil to lymphocyte fraction, EOS = relative eosinophil count, CRP = C-reactive protein, LDH = lactate dehydrogenase, BAL = broncho-alveolar lavage, MAK = relative macrophage fraction

HRCT finding scores (median, range)	**IPAF**	**IPF**	**CHP**	**iNSIP**	**aILD**	**Unclassified ILD**	**Other ILD**
RET	5 (0–6)	6 (2–6)	6 (0–6)	6 (2–6)	4 (2–6)	4 (0–6)	0 (0–6)
TBR	2 (0–6)	4 (0–6)	4 (0–6)	3 (0–6)	2 (0–5)	3 (0–6)	1 (0–4)
EMP	0 (0–2)	0 (0–6)	0 (0–2)	0 (0–2)	0 (0–0)	0 (0–0)	0 (0–4)
GGO	0 (0–6)	0 (0–6)	2 (0–6)	0 (0–6)	0 (0–6)	0 (0–6)	0 (0–6)
NDL	0 (0–6)	0 (0–0)	2 (0–6)	0 (0–6)	0 (0–6)	0 (0–6)	1 (0–6)
CON	0.5 (0–6)	0 (0–4)	0 (0–2)	0 (0–6)	0 (0–3)	0 (0–6)	1 (0–6)
MOS	0 (0–6)	0 (0–2)	3 (0–6)	0 (0–6)	0 (0–3)	0 (0–4)	0 (0–6)
Peripheral blood biomarkers (mean, SD)	**IPAF**	**IPF**	**CHP**	**iNSIP**	**aILD**	**Unclassified ILD**	**Other ILD**
PBL LEU (G/L)	8.6 (3.0)	8.4 (2.5)	8.2 (2.3)	9.4 (3.3)	7.5 (3.7)	8.2 (3.1)	10.0 (5.0)
PBL NEU (%)	74.4 (10.2)	66.2 (10.7)	70.6 (7.5)	70.9 (11.4)	73.7 (10.8)	69.9 (11.0)	70.8 (13.5)
PBL LYM (%)	18.2 (8.4)	24.9 (8.6)	20.3 (6.6)	19.6 (8.6)	19.3 (8.0)	19.9 (8.3)	20.5 (10.7)
PBL NLR	6.2 (5.9)	3.4 (2.9)	4.0 (1.7)	4.8 (3.3)	4.8 (2.9)	4.7 (3.5)	6.4 (8.1)
PBL EOS (%)	1.4 (1.5)	2.5 (2.3)	2.3 (1.9)	2.9 (4.0)	2.0 (2.5)	3.9 (4.1)	2.0 (2.5)

HRCT finding scores (median, range)	IPAF	IPF	CHP	iNSIP	aILD	Unclassified ILD	Other ILD
PBL CRP (mg/dL)	2.1 (3.1)	1.4 (2.2)	1.3 (1.8)	0.7 (1.0)	0.6 (0.5)	2.8 (4.6)	1.7 (2.2)
PBL LDH (U/L)	243 (56.2)	230.8 (49.1)	273 .4 (101.3)	259.6 (85.7)	302.7 (126.1)	257.7 (77.8)	206.0 (51.9)
BAL biomarkers (mean, SD)	**IPAF**	**IPF**	**CHP**	**iNSIP**	**aILD**	**Unclassified ILD**	**Other ILD**
BAL MAK (%)	44.7 (28.2)	60.1 (31.9)	30.0 (21.0)	81.9 (10.2)	61.3 (39.0)	34.7 (16.3)	48.9 (31.0)
BAL NEU (%)	21.8 (23.5)	29.3 (30.5)	30.9 (34.0)	6.9 (7.7)	4.5 (4.2)	24.8 (23.9)	12.8 (13.4)
BAL EOS (%)	4.1 (3.9)	7.6 (8.2)	12.0 (19.4)	1.5 (1.3)	2.0 (2.8)	12.0 (7.0)	3.8 (1.5)
BAL LYM (%)	24.8 (27.1)	6.5 (6.3)	24.1 (24.8)	10.0 (8.2)	18 (2–89)	18.4 (9.9)	28.1 (23.1)

Correlations of peripheral blood and BAL biomarkers with HRCT finding scores are visualized in Fig. 1.

As shown in Tables 4 and 5, the categorized scores for the extent of HRCT findings were used to assess clinically meaningful implications on each peripheral blood or BAL biomarker variable.

Table 4. Peripheral blood biomarkers according to HRCT finding categories. Data are given as median (range). The p-value for statistical significance of differences ($p<0.05$) between the groups was calculated using the Kruskal-Wallis test. Significant association are shown in bold letters and blue color for positive, red for negative associations. RET=reticulation/honeycombing, TBR=traction bronchiectasis, EMP=emphysema, GGO=ground glass opacities, CON=consolidations, NDL=noduli, MOS=mosaic attenuation, HRCT=high-resolution computed tomography, LEU=absolute blood leukocyte count, NEU=relative blood neutrophil fraction, LYM=relative blood lymphocyte fraction, NLR= neutrophil to lymphocyte fraction, EOS=relative blood eosinophil count, CRP=C-reactive protein, LDH=lactate dehydrogenase

	Median in HRCT score groups (range)			p	n		
LEU (G/L)	**0 - 1**	**2 - 4**	**5 – 6**		**0 - 1**	**2 - 4**	**5 - 6**
RET	7.3 (4.8-15.9)	7.5 (3.8-25.5)	8.5 (4.5-16.1)	0.617	22	46	54
TBR	7.8 (4.6-25.5)	7.5 (3.8-19.1)	8.5 (4.8-14.6)	0.537	30	66	26
EMP	7.8 (3.8-19.1)	8.6 (4.6-25.5)	7.2 (4.8-14.6)	0.916	100	19	3
GGO	7.6 (3.8-16.1)	7.9 (4.2-14.6)	8.3 (4.8-25.5)	0.449	78	24	20
CON	7.8 (3.8-25.5)	7.4 (4.5-19.1)	9.7 (4.8-14.6)	0.811	93	21	8
NDL	7.6 (3.8-19.1)	8.3 (4.2-25.5)	9.6 (5.6-15.4)	0.117	85	24	13
MOS	7.7 (3.8-25.5)	8.4 (4.2-13.3)	7.6 (4.8-18.1)	0.839	96	18	8
NEU (%)	**0 - 1**	**2 - 4**	**5 – 6**	**p**	**0 - 1**	**2 - 4**	**5 - 6**
RET	74.5 (54.4-91.7)	72.4 (46.2-96.6)	68.8 (47.6-88.3)	0.362	22	54	54
TBR	74.3 (46.2-94.9)	69.0 (46.2-94.9)	73.1 (47.6-86.3)	0.130	30	65	26
EMP	71.3 (51.4-94.9)	69.6 (46.2-96.6)	69.8 (47.6-86.3)	0.967	99	19	3
GGO	69.7 (46.2-91.7)	71.9 (51.9-89.6)	74.8 (47.6-96.6)	0.289	78	24	19
CON	69.8 (46.2-96.6)	71.5 (51.4-86.3)	79.5 (58.2-89.6)	0.077	93	20	8
NDL	69.5 (46.2-89.6)	72.8 (54.4-96.6)	71.4 (51.9-91.7)	0.217	84	24	13
MOS	69.6 (46.2-96.6)	72.6 (51.4-90.2)	79.3 (61.0-94.9)	0.108	95	18	8
LYM (%)	**0 - 1**	**2 - 4**	**5 – 6**	**p**	**0 - 1**	**2 - 4**	**5 - 6**
RET	19.3 (4.6-37.4)	19.1 (2.6-41.9)	22.3 (4.6-38.2)	0.366	22	45	54
TBR	18.6 (2.6-37.4)	21.4 (3.4-41.9)	19.3 (5.9-38.2)	0.337	30	65	26
EMP	20.0 (3.4-38.0)	20.6 (2.6-41.9)	23.2 (5.9-38.2)	0.915	99	19	3
GGO	**22.7 (4.6-41.9)**	**16.9 (7.8-41.5)**	**17.9 (2.6-38.2)**	**0.032**	78	24	19
CON	**21.0 (2.6-41.9)**	**19.7 (5.9-34.2)**	**13.0 (7.8-21.5)**	**0.027**	93	20	8
NDL	21.1 (4.6-41.9)	18.4 (2.6-37.4)	21.8 (4.6-41.5)	0.150	84	24	13
MOS	20.9 (2.6-41.9)	18.2 (6.6-34.8)	15.6 (3.4-24.4)	0.154	95	18	8
NLR	**0 - 1**	**2 - 4**	**5 – 6**	**p**	**0 - 1**	**2 - 4**	**5 - 6**
RET	4.2 (1.5-19.9)	3.8 (1.1-37.1)	3.1 (1.2 - 19.3)	0.311	22	45	54
TBR	4.1 (1.5 -37.1)	3.2 (1.1-27.8)	3.9 (1.2-14.7)	0.160	30	65	26
EMP	3.7 (1.4 -27.8)	3.5 (1.1-37.1)	3.0 (1.2-14.7)	0.941	99	19	3
GGO	3.2 (1.1-19.9)	4.2 (1.3-11.4)	4.2 (1.2-37.1)	0.095	78	24	19
CON	**3.2 (1.1-37.1)**	**3.7 (1.5-14.7)**	**6.4 (5.1-11.4)**	**0.009**	93	20	8
NDL	3.5 (1.1-19.3)	4.0 (1.5-37.1)	3.2 (1.3-19.9)	0.172	84	24	13
MOS	3.4 (1.1-37.1)	4.1 (1.5-13.3)	5.1 (2.5-27.8)	0.156	95	18	8
EOS (%)	**0 - 1**	**2 - 4**	**5 – 6**	**p**	**0 - 1**	**2 - 4**	**5 - 6**
RET	1.0 (0.0-5.1)	1.4 (0.0-13.8)	1.8 (0.1-14.7)	0.092	21	45	52
TBR	**0.9 (0.0-4.4)**	**1.7 (0.0-13.8)**	**1.9 (0.1-14.7)**	**0.006**	30	64	24
EMP	1.5 (0.0-14.7)	1.5 (0.1-13.8)	1.8 (0.1-6.5)	0.909	96	19	3
GGO	1.5 (0.0-9.5)	1.5 (0.0-14.7)	1.4 (0.0-11.2)	0.973	75	24	19
CON	1.5 (0.0-13.8)	1.7 (0.1-14.7)	0.6 (0.1-2.5)	0.168	91	19	8
NDL	1.5 (0.0-14.7)	1.6 (0.0-13.8)	1.1 (0.0-11.2)	0.753	82	23	13
MOS	1.5 (0.0-14.7)	1.8 (0.0-8.4)	0.3 (0.0-8.6)	0.148	93	17	8
CRP (mg/dL)	**0 - 1**	**2 - 4**	**5 – 6**	**p**	**0 - 1**	**2 - 4**	**5 - 6**
RET	0.5 (0.1-7.1)	0.4 (0.1-8.4)	0.9 (0.1-15.9)	0.257	22	45	56
TBR	0.4 (0.1-7.1)	0.7 (0.1-12.3)	0.3 (0.1-15.9)	0.332	30	67	26
EMP	0.5 (0.1-15.9)	0.6 (0.1-12.3)	0.3 (0.1-5.0)	0.917	101	19	3
GGO	**0.4 (0.1-12.3)**	**1.0 (0.1-15.9)**	**0.9 (0.1-8.4)**	**0.023**	80	23	20
CON	**0.5 (0.1-12.3)**	**0.4 (0.1-15.9)**	**4.1 (0.6-8.4)**	**0.004**	93	22	8
NDL	0.4 (0.1-15.9)	0.9 (0.1-6.8)	0.7 (0.1-7.1)	0.221	87	23	13
MOS	0.5 (0.1-15.9)	0.7 (0.1-3.8)	0.9 (0.2-6.0)	0.393	98	17	8
LDH (U/L)	**0 - 1**	**2 - 4**	**5 – 6**	**p**	**0 - 1**	**2 - 4**	**5 - 6**
RET	**199 (131-372)**	**236 (113-614)**	**244 (152-426)**	**0.010**	20	42	51
TBR	**195 (125-394)**	**245 (113-614)**	**259 (188-587)**	**<0.001**	26	61	26
EMP	236 (113-614)	200 (152-306)	232 (181-340)	0.210	94	16	3
GGO	**224 (113-397)**	**244 (153-614)**	**261 (194-587)**	**0.049**	74	21	18
CON	233 (113-614)	228 (131-390)	293 (211-426)	0.115	88	19	6
NDL	232 (113-397)	231 (153-587)	266 (171-614)	0.196	90	24	13
MOS	**226 (113-614)**	**267 (167-354)**	**259 (220-587)**	**0.027**	89	16	8

Table 5. Broncho-alveolar lavage biomarkers according to HRCT finding categories. Data are given as median (range). The p-value for statistical significance of differences ($p<0.05$) between the groups was calculated using the Kruskal-Wallis test. Significant association are shown in bold letters and blue color for positive associations. RET=reticulation/honeycombing, TBR=traction bronchiectasis, EMP=emphysema, GGO=ground glass opacities, CON=consolidations, NDL=noduli, MOS=mosaic attenuation, HRCT=high-resolution computed tomography, MAK=relative BAL macrophage fraction, NEU=relative BAL neutrophil fraction, EOS=relative BAL eosinophil fraction, LYM=relative BAL lymphocyte fraction

	Median in HRCT score groups (range)			p	n		
MAK (%)	**0 - 1**	**2 - 4**	**5 - 6**		**0 - 1**	**2 - 4**	**5 - 6**
RET	37.0 (6.0-95.0)	49.5 (5.0-98.0)	62.0 (5.0-93.0)	0.694	13	18	35
TBR	25.0 (5.0-98.0)	61.0 (5.0-98.0)	67.0 (7.0-90.0)	0.327	17	35	14
EMP	61.0 (5.0-98.0)	48.5 (7.0-84.0)	7.0 (7.0-7.0)	0.308	55	10	1
GGO	57.0 (5.0-98.0)	52.5 (5.0-82.0)	34.5 (7.0-87.0)	0.565	46	10	10
CON	53.0 (5.0-98.0)	46.0 (6.0-90.0)	69.0 (19.0-87.0)	0.908	50	13	3
NDL	63.0 (6.0-98.0)	46.5 (17.0-95.0)	37.0 (5.0-85.0)	0.405	42	14	10
MOS	61.5 (5.0-98.0)	53.0 (23.0-93.0)	20.0 (5.0-66.0)	0.092	54	7	5
NEU (%)	**0 - 1**	**2 - 4**	**5 - 6**	**p**	**0 - 1**	**2 - 4**	**5 - 6**
RET	12.0 (1.0-65.0)	7.5 (0.0-89.0)	10.0 (0.0-84.0)	0.520	13	16	33
TBR	11.0 (0.0-89.0)	7.5 (0.0-84.0)	13.0 (1.0-64.0)	0.691	16	32	14
EMP	10.0 (0.0-89.0)	8.0 (0.0-66.0)	58.0 (58.0-58.0)	0.452	52	9	1
GGO	10.0 (0.0-89.0)	6.5 (0.0-24.0)	9.5 (1.0-61.0)	0.209	42	10	10
CON	9.5 (0.0-89.0)	10.0 (2.0-61.0)	7.0 (3.0-19.0)	0.873	46	13	3
NDL	10.0 (0.0-89.0)	10.5 (1.0-70.0)	10.0 (0.0-84.0)	0.914	39	14	9
MOS	9.0 (0.0-89.0)	10.0 (4.0-70.0)	12.0 (1.0-84.0)	0.739	50	7	5
EOS (%)	**0 - 1**	**2 - 4**	**5 - 6**	**p**	**0 - 1**	**2 - 4**	**5 - 6**
RET	3.0 (2.0-4.0)	4.0 (0.0-23.0)	4.0 (0.0-55.0)	0.876	4	11	21
TBR	3.5 (0.0-4.0)	3.0 (0.0-55.0)	5.0 (0.0-19.0)	0.699	6	21	9
EMP	3.0 (0.0-55.0)	6.0 (0.0-23.0)	-	0.547	29	7	-
GGO	3.0 (0.0-23.0)	4.0 (0.0-55.0)	5.0 (1.0-10.0)	0.891	26	5	5
CON	3.5 (0.0-55.0)	3.0 (1.0-19.0)	4.0 (4.0-4.0)	0.978	28	7	1
NDL	3.0 (0.0-55.0)	3.0 (0.0-13.0)	4.5 (0.0-12.0)	0.835	21	9	6
MOS	3.0 (0.0-55.0)	7.0 (0.0-13.0)	5.0 (3.0-6.0)	0.794	29	4	3
LYM (%)	**0 - 1**	**2 - 4**	**5 - 6**	**p**	**0 - 1**	**2 - 4**	**5 - 6**
RET	15.0 (2.0-68.0)	13.0 (0.0-89.0)	11.0 (0.0-88.0)	0.578	12	17	34
TBR	11.0 (0.0-88.0)	13.0 (0.0-89.0)	11.5 (4.0-74.0)	0.921	15	34	14
EMP	14.5 (1.0-89.0)	7.5 (0.0-43.0)	4.0 (4.0-4.0)	0.249	52	10	1
GGO	**7.5 (0.0-77.0)**	**21.0 (7.0-89.0)**	**17.0 (4.0-88.0)**	**0.017**	44	10	9
CON	9.5 (0.0-89.0)	17.5 (2.0-77.0)	24.0 (16.0-54.0)	0.783	48	12	3
NDL	9.0 (0.0-88.0)	16.5 (2.0-74.0)	23.0 (2.0-89.0)	0.344	41	14	8
MOS	11.0 (0.0-89.0)	15.0 (3.0-33.0)	33.0 (2.0-74.0)	0.223	51	7	5

Discussion

In synopsis, our analyses indicate that PBL lymphocyte and eosinophil fraction, neutrophil-lymphocyte ratio (NLR), CRP as well as BAL lymphocyte fraction may have clinically relevant implications in differing HRCT abnormalities indicating either active inflammation (ground glass opacities, consolidations, noduli, mosaic attenuation) or non-inflammatory/fibrotic processes (reticulation/honeycombing, traction bronchiectasis, emphysema).

Blood lymphocyte count is of known prognostic relevance in systemic disorders like SSC or malignancy.[27–29] Our finding, that lymphocyte fraction was consistently negatively correlated to HRCT findings considered “inflammatory” suggests, that similar mechanisms may be present in ILD patients with such phenotype. In BAL however, lymphocyte fraction showed the opposite behavior with distinctly higher values in the presence of GGO and CON, but also NOD and MOS. Lymphocytosis in BAL is a common finding in inflammatory ILD presenting with patterns of NSIP or OP,[5, 30, 31] and especially in ILD associated with formation of granulomas, such as sarcoidosis or hypersensitivity pneumonitis.[23] Conversely, BAL lymphocyte counts are reportedly lower with increasing fibrosis.[7, 32]

Similar to our observation of eosinophil counts in peripheral blood being positively correlated with RET and TBR, blood eosinophilia has been found to be associated with disease severity in SSCILD.[33] Slightly elevated eosinophil counts in BAL fluid have repeatedly been reported in IPF patients as well as in

fibrotic rather than in cellular NSIP.[7, 30, 32] In our patient cohort, such relationship with BAL eosinophil fraction could not be shown, possibly due to the low number of patients presenting with significant BAL eosinophilia.

The close relationship observed between CRP and GGO/CON resembles reports of commonly elevated CRP in ILD patients presenting with patterns like NSIP or OP.[5, 7, 14] In ILD in the context of autoimmune disorders, alterations to systemic inflammatory parameters like CRP have been frequently reported and also pose a risk factor for the development of pulmonary involvement in such conditions.[28, 34–36] Contrary to CRP, we found lactate dehydrogenase (LDH) significantly positively correlated with multiple non-inflammatory/fibrotic as well as inflammatory HRCT finding scores. Elevations in LDH have been reported in IPF, where they may be associated with functional impairment and have prognostic properties.[37] Our findings however suggest, that LDH may rather be a biomarker of general disease severity than of its underlying pathogenetic processes.

Our reported study has several limitations that need to be addressed: Next to its retrospective, single center approach, the sample size was limited. The reported collective represents a heterogeneous group of several different ILD entities also including a minority of patients without signs of reticulation or honeycombing (17%). The study collective was derived from patients subsequently discussed by the local ILD-board, which could have caused the increased inclusion of rather more complex ILD, while more typical ILD like for example sarcoidosis may be underrepresented. However, our reported evaluation did explicitly not focus on distinct ILD diagnoses, but on HRCT imaging findings and their association with biomarkers of systemic and local inflammation. Radiological assessment was not done in a blinded fashion but in the presence of the ILD-board, which reflects the multidisciplinary approach to ILD. Our reported scoring system has not been validated in a larger patient cohort but is simple to perform and does not require additional tools like special software. It was not our aim to create a comprehensive HRCT quantification and classification tool but rather to allow quantitative statistical analyses beyond only “present or absent”, with a semi-quantitative dimension. It is obvious that peripheral blood cell counts as well as inflammation biomarkers like CRP or LDH can be substantially altered by infections, neoplastic or hematological conditions. Also, BAL differential cell counts can be influenced by presence of infection as well as by smoking status or age.[24, 38] Additionally, BAL was only performed in approximately half of the patient collective, for it had either been done previously or it was deemed clinically unnecessary. This could have led to a selection of patients with uncommon presentation in HRCT or with rather acute than chronic ILD, as suggested by the comparably high mean lymphocyte and neutrophil counts reported. Concerning statistical methods, we acknowledge, that numerous associations have been evaluated for statistical significance, which brings up the issue of multiple testing. It was not our aim to test for significance of certain associations, but rather to apply an experimental, hypothesis-building approach aiming to extract clinically relevant biomarkers from a large, diverse dataset. Thus, we primarily used descriptive statistical evaluation like Spearman correlation coefficients and graphical presentation. We chose clinically meaningful quantification categories (no or little, medium, or abundant involvement) for HRCT findings and used the Kruskal-Wallis test due to its robustness against outliers for significance testing.

Conclusions

We conclude that blood lymphocyte and eosinophil fraction, NLR, CRP and BAL lymphocyte fraction may help to differ between non-inflammatory/fibrotic and active inflammatory ILD phenotypes. Especially in ILD with multiple coexisting HRCT abnormalities, these biomarkers could aid the decision whether to primarily initiate anti-inflammatory or antifibrotic treatment. Further prospective and larger-scale trials are warranted to evaluate the implications of such biomarkers on response to either therapeutic approach.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the federal state of Upper-Austria (EK Nr. I-26-17). It was conducted in an entirely retrospective fashion, without an experimental approach or additional patient contact. Only patient data assessed in clinical routine were analyzed. Data were collected in an anonymized fashion and securely electronically stored in a way, that only the authors had access to the data. No identifiable patient data has been or will ever be published by the authors.
According to the ethic committee approval, no patient consent was necessary for participation in this study.

Consent for publication

Not applicable as stated above.

Availability of data and materials

According to the terms imposed by the ethics committees, the full datasets analyzed during the current study cannot be made publicly available, as they contain possibly identifiable patient data. Upon reasonable request to the authors and if approved as an amendment by the responsible local ethics committee, selected anonymized data can however be shared.

Competing interests

The authors declare no competing interest.

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Authors' Contributions

All authors have approved the paper, are able to verify the validity of the results reported and meet the criteria for authorship as established by the International Committee of Medical Journal Editors.

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Figures

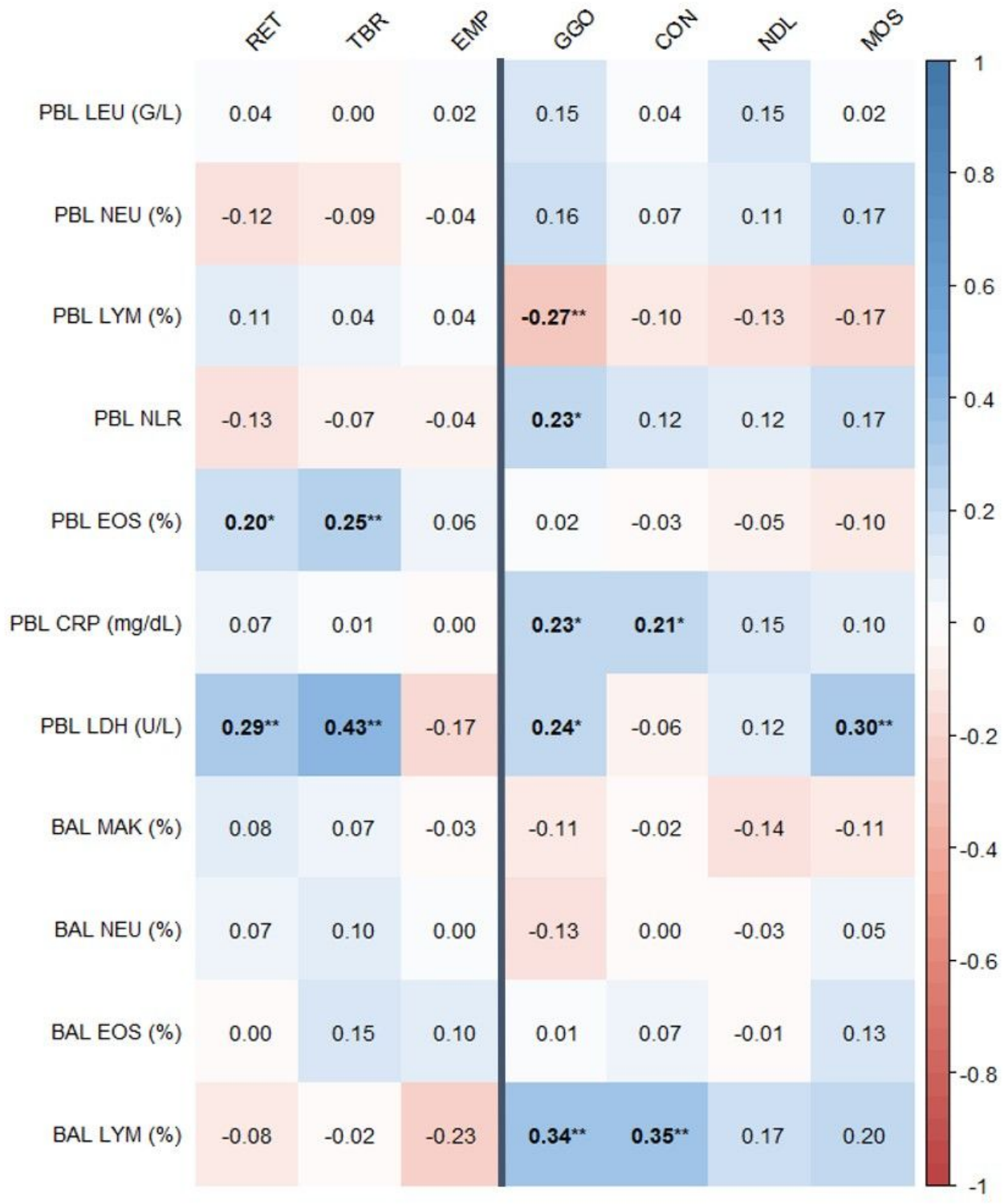

Figure 1

Correlation matrix of peripheral blood and BAL biomarkers with HRCT finding scores. Values are for Spearman correlation coefficients; colors indicate strength and direction of correlations as shown by the scale on the right side. Bold numbers are for significant correlations, *is for p<0.05, **is for p<0.01. The line between the EMP and GGO category visually separates non-inflammatory from inflammatory HRCT findings. PBL=peripheral blood, BAL=bronchoalveolar lavage, HRCT=high-resolution computed

tomography, RET=reticulation/honeycombing, TBR=traction bronchiectasis, EMP=emphysema, GGO=ground glass opacities, CON=consolidations, NDL=noduli, MOS=mosaic attenuation, LEU=absolute blood leukocyte count, NEU=relative neutrophil fraction, LYM= relative lymphocyte fraction, NLR= neutrophil to lymphocyte fraction, EOS=relative eosinophil count, CRP=C-reactive protein, LDH=lactate dehydrogenase, MAK=relative macrophage fraction