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Circulating interferon–α and soluble CD25 are associated with distinct pulmonary phenotypes in untreated early rheumatoid arthritis

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Keywords: Rheumatoid arthritis, Airway abnormalities, Interstitial lung abnormalities, Parenchymal nodules, Interferon–alpha, Soluble CD25

Abstract

Background Pulmonary abnormalities (PA) of airways and parenchyma are prevalent in rheumatoid arthritis (RA), and interstitial lung disease (ILD) is a severe extra-articular manifestation affecting up to 10% of patients. Yet, the immune mechanisms underlying the different forms of pulmonary involvement and the relationships between them remain incompletely understood. We investigated whether distinct pulmonary phenotypes in untreated patients with newly diagnosed RA are associated with specific systemic immune profiles.

Methods This cross-sectional study included 55 consecutive treatment-naïve patients with newly diagnosed autoantibody-positive RA who underwent high-resolution computed tomography of the lungs. Presence of bronchiectasis, bronchial wall thickening, air trapping, reticulations, ground-glass opacities, traction bronchiectasis, honeycombing, pleural effusion and parenchymal nodules was evaluated by thoracic radiologists in consensus. Serum cytokines, chemokines and growth factors were quantified using a 48-plex immunoassay, neutrophil elastase by ELISA, and interferon α (IFN–α) by Single molecule array (Simoa) ultra-sensitive immunoassay. A type I interferon gene score was determined by RT-PCR based on the mean gene expression of *IFI6*, *IFI44L*, *ISG15*, *MX1* and *OAS1*. Multivariate data analyses were followed by predefined univariate validation of the five highest-ranked variables associated with 1) parenchymal nodules, 2) interstitial lung abnormalities (ILA) and 3) airway abnormalities. Sensitivity analyses and correlations with clinical parameters were performed.

Results Pulmonary abnormalities were identified in 78% of the untreated early (ue) RA patients. Despite substantial overlap between the pulmonary phenotypes, both airway abnormalities and parenchymal nodules were present as isolated phenotypes. A presence of any PA was strongly associated with rheumatoid factor IgM and systemic inflammation. Higher levels of soluble CD25

were associated with parenchymal nodules, whereas ILA was associated with increased IFN–α levels and higher Disease Activity Score in 28 joints. The most significant markers of airway abnormalities were increased CRP and shorter symptom duration.

Conclusions Pulmonary phenotypes in ueRA are associated with different inflammatory and immune activation profiles and suggest IFN–α as a candidate biomarker for ILD development. Whether the lungs represent a primary site of autoimmune events during the development of RA or an extra-articular site of RA-related inflammation remains to be determined.

Background

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily affects the synovial joints and leads to synovial inflammation and progressive cartilage and bone destruction [1, 2]. The lung is a common site of extra-articular involvement, and about 60% of RA patients are estimated to develop a lung manifestation during disease course [3]. Pulmonary involvement encompasses a broad spectrum of manifestations, including interstitial lung abnormalities (ILA), interstitial lung disease (ILD), pulmonary nodules, airway disease (i.e., bronchiectasis and bronchiolitis), and pleural disease (i.e., pleuritis) [3, 4]. Although pulmonary phenotypes often develop after the onset of articular symptoms, they may precede clinically apparent arthritis by several years [3]. Consequently, RA-associated lung disease is increasingly regarded as an integral component of RA pathogenesis rather than merely a late extra-articular complication. Despite substantial improvements in RA treatment, pulmonary disease remains a major unmet clinical challenge [4, 5].

ILA are defined as bilateral and non-dependent ground-glass opacities, reticular abnormalities, traction bronchiectasis, lung distortion and/or honeycombing affecting at least 5% of a lung zone on high-resolution computed tomography (HRCT) in individuals without clinically suspected ILD. In patients with RA, ILA is considered to be a preclinical stage of RA-associated ILD (RA-ILD) [6]. In contrast to clinically manifest RA-ILD, patients with ILA typically lack clinically significant respiratory symptoms and pulmonary function impairment at the time of HRCT detection [6, 7]. Accordingly, in this study, the term ILA is used to describe early interstitial HRCT abnormalities in patients without clinically established RA-ILD.

Both innate and adaptive immune mechanisms contribute to RA pathogenesis [1]. Anti-citrullinated protein antibodies (ACPA) and/or rheumatoid factor (RF) are present in the majority

of patients with RA and appear long before any signs of inflammation emerge in the joint, suggesting that the initiation of autoimmunity occurs outside the joints [8]. The lungs have been suggested as a possible site where autoimmunity is triggered and RA initiated [9, 10]. This is supported by an enrichment of ACPAs in bronchoalveolar lavage fluid compared with peripheral blood from individuals at risk of RA and patients with early RA [11]. Local immune activation and inflammation have also been demonstrated in bronchial biopsies from untreated early (ue) RA patients [12]. High-titre of RF and ACPA, high levels of systemic inflammation, smoking and older age have consistently been associated with RA-ILD [5]. Clinically manifest RA-ILD is a severe complication of RA, affecting approximately 5–17% of patients and associated with a median survival of 3–8 years after diagnosis [3, 13]. Identifying patients at risk of developing RA-ILD, or of progressing from RA-associated ILA to clinically manifest disease, remains challenging due to non-specific symptoms and the lack of reliable methods for early detection and validated biomarkers. This is further complicated by an incomplete understanding of the mechanisms underlying early pulmonary involvement in RA. Most biomarker studies in RA have focused on clinical RA-ILD, whereas considerably less is known about the systemic immune profiles associated with the earliest HRCT-defined pulmonary phenotypes present at the time of RA diagnosis [14, 15].

Hence, there is an urgent need to identify biomarkers and improve our understanding of the underlying pathogenic mechanisms of RA-associated lung disease in order to facilitate earlier diagnosis, risk stratification and targeted therapeutic approaches. In the present study, serum protein profiles were analysed in relation to chest HRCT-defined pulmonary phenotypes in patients with ueRA before the initiation of glucocorticoids or disease modifying anti-rheumatic drugs (DMARDs). Unsupervised multivariate data modelling followed by predefined univariate

validation identified candidate biomarkers of distinct pulmonary phenotypes, including soluble CD25 (sCD25), also known as soluble interleukin-2 receptor alpha (IL–2Rα), for parenchymal nodules, and interferon α (IFN–α) for ILA in ueRA.

Patients and Methods

Study design and participants

PULMORA is a 5-year prospective observational study of lungs and joints in early RA at Sahlgrenska University Hospital, Gothenburg, Sweden. The present cross-sectional study of baseline data includes 55 adult patients with untreated RA enrolled at the time of diagnosis.

All patients in PULMORA fulfil the 2010 ACR/EULAR classification criteria and are positive for RF IgM and/or ACPA IgG. The study is approved by the Swedish Ethical Review Authority, and all participants provide written informed consent prior to inclusion. The study protocol includes demographics (age and sex), medical history, presence of respiratory symptoms, self-reported history of pulmonary disease, current medication, clinical RA disease assessments, chest HRCT, radiography of the hands and feet, blood sampling and smoking status. Smoking status is classified as current smoker if having smoked ≥100 cigarettes during their lifetime and currently smoking, former smoker if having smoked ≥100 cigarettes during their lifetime but not during the preceding 12 months, and never smoker if having smoked <100 cigarettes during their lifetime. All data is collected within one week of diagnosis and before initiation of DMARDs or oral glucocorticoids. The use of non-steroidal anti-inflammatory drugs (NSAIDs) is allowed. Exclusion criteria include current inflammatory joint disease other than RA, a history of malignancy within the previous 5 years, primary or secondary immunodeficiency, and active infection requiring antibiotics/anti-viral therapy within 2 weeks before inclusion.

RA disease activity assessments

Disease activity was assessed by swollen and tender joint counts of 28 joints (SJC28 and TJC28, respectively), physician's global assessment of disease activity (PhGA), patient global assessment

of disease activity (PGA), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). PhGA and PGA were recorded using 100-mm visual analogue scales (VAS). Disease Activity Score in 28 joints (DAS28) and the Clinical Disease Activity Index (CDAI) were calculated according to standard definitions. Structural joint damage, including presence of bone erosions and joint space narrowing, was assessed on conventional radiographs of the hands and feet using the Sharp/van der Heijde (SvH) score and expressed as the total SvH score (0–448).

High-resolution computed tomography

Chest HRCT was performed using a Siemens SOMATOM Force scanner (Siemens Healthineers, Germany). Volumetric CT scans were obtained during maximal inspiration and expiration using a low-dose protocol, as described previously [16]. Pseudonymized image series were independently evaluated by two experienced thoracic radiologists, with the final judgement and score established by consensus. The chest HRCT findings were classified according to published guidelines from The Fleischner Society and The American Thoracic Society [6, 17]. For this study, we defined "Airway abnormalities" as a presence of bronchial wall thickening, air trapping, and/or bronchiectasis. "ILA" was defined as bilateral non-dependent reticular abnormalities, ground-glass opacities, traction bronchiectasis and/or honeycombing affecting ≥5% of a lung zone. ILA severity was graded as mild, moderate, or severe. "Parenchymal nodules" included nodules (≥6 mm and <30 mm) and micronodules (<6 mm). Patients with incidental lung nodules were subjected to clinical follow-up according to the Swedish national guidelines for lung cancer. None of the included patients were diagnosed with lung cancer during the one-year follow-up after the study HRCT.

Serum protein analyses

Serum cytokines, chemokines and growth factors were quantified using the Bio-Plex Pro Human Cytokine Screening Panel, 48-Plex (Bio-Rad Laboratories, Hercules, CA, USA; catalogue no. 12007283) according to the manufacturer's instructions. Protein concentrations were calculated using Bio-Plex Manager software and are presented as pg/mL. Because circulating IFN–α concentrations were frequently below the detection range in the multiplex assay, serum IFN–α was quantified using an ultra-sensitive bead-based Single molecule array (Simoa) immunoassay (Quanterix, Billerica, MA, USA) as previously described and presented as fg/mL [18]. Serum concentrations of human neutrophil elastase (HNE) were quantified using a sandwich enzyme-linked immunosorbent assay (IDK® PMN-Elastase ELISA, Immundiagnostik AG, Bensheim, Germany; catalogue no. K 6841) according to the manufacturer's instructions. HNE concentrations are reported as ng/mL. Values below the lower limit of detection (LOD) were assigned a value of LOD/2. Among the analytes retained for multivariate analysis, nine had samples with values below LOD, with the following proportions: IL-1Ra and MIF (2.4% each), IL-12p40 (26.2%), IL-13 and MCP-3 (42.9% each), IL-6 (47.6%), GM-CSF (71.4%), IL-10 (73.8%) and IL-12p70 (83.3%).

Interferon gene expression analysis

Total RNA was isolated from PAXgene Blood RNA tubes using the PAXgene Blood RNA Kit (PreAnalytiX) according to the manufacturer's instructions. RNA concentration was determined using a NanoDrop spectrophotometer. cDNA was generated from 500 ng RNA using the High-Capacity cDNA Reverse Transcription Kit (Cat no 4374966, Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions. Gene expression was quantified by TaqMan real-time PCR using a QuantStudio 3 System (Applied Biosystems). TaqMan gene expression

assays (Applied Biosystems) were used for *IFI6* (assay ID Hs00242571_m1), *IFI44L* (Hs00915292_m1), *ISG15* (Hs01921425_s1), *MX1* (Hs00895608_m1), and *OAS1* (Hs00973635_m1), with *GAPDH* (Hs99999905_m1) used as the reference gene. Relative gene expression was calculated using the 2^−ΔCt method, where Ct denotes the cycle threshold and ΔCt was defined as the difference between the Ct value of each target gene and that of the reference gene, *GAPDH*. The type I interferon gene score (IGS) was calculated as the mean relative expression of the five interferon-stimulated genes (*IFI6, IFI44L, ISG15, MX1,* and *OAS1*) according to Cooles *et al.* [19].

Autoantibodies and markers of inflammation

Serum rheumatoid factor IgM (RF IgM) and anti-cyclic citrullinated peptide antibodies (ACPA IgG) were quantified at clinical laboratories within 4 weeks of inclusion using fluoroenzyme immunoassay (FEIA) on a Phadia 250 instrument (Thermo Fisher Scientific, Uppsala, Sweden) and chemiluminescent microparticle immunoassay (CMIA) on an Alinity i instrument (Abbott Laboratories, Abbott Park, IL, USA), respectively. CRP concentrations and ESR were determined according to clinical laboratory procedures.

Statistical analysis

The multivariate dataset included age, demographic binary variables (female sex, current smoker, former smoker and never smoker), continuous clinical variables (symptom duration, SJC28, TJC28, ESR, DAS28, CDAI and CRP), total SvH score, autoantibody levels (RF IgM and ACPA IgG) and levels of 49 serum proteins (including HNE), as well as binary radiographic data on the presence and subtype of PA. Four HRCT-defined pulmonary phenotypes were identified in this ueRA cohort: (i) no PA, (ii) parenchymal nodules, (iii) ILA, and (iv) airway abnormalities. “Any

PA" was defined as the presence of (ii), (iii) and/or (iv). Before multivariate modelling, all continuous variables were log-transformed, whereas binary variables were left untransformed. Data were mean-centred and unit variance (UV)-scaled prior to model construction. All 55 patients were retained in the multivariate analyses. Missing values were not imputed prior to multivariate modelling but were handled internally by SIMCA (SIMCA-P+, version 18.0.0; Umetrics, Umeå, Sweden) during model construction, allowing available observations to be retained in the analyses. Prior to multivariate modelling, cytokines showing high collinearity or near-zero variance were excluded to reduce redundancy and improve model stability. Unsupervised principal component analysis (PCA) was used to explore and visualize the overall relationships among variables. Orthogonal partial least squares (OPLS)-discriminant analysis (DA) was applied to compare patients with "any PA" and "no PA". Variables were ranked according to their Variable Importance in Projection (VIP) values derived from the corresponding multivariate model. Subsequently, phenotype-specific supervised multivariate models using OPLS for airway abnormalities, parenchymal nodules and ILA were generated. Supervised model performance was assessed by R2X, indicating the proportion of variation in the X variables explained by the model; R2Y, indicating the proportion of variation in the Y variable explained by the model; and Q2, reflecting the cross-validated predictive ability of the model. To provide a focused, predefined validation strategy, the five highest-ranked VIP variables were selected a priori for subsequent univariate validation. Subsequent univariate analyses were performed using GraphPad Prism version 11.0.2 (GraphPad Software, San Diego, CA, USA). Differences between groups were analysed using two-tailed Mann–Whitney U tests, and correlations were assessed using Spearman's rank correlation coefficient. A two-sided p-value <0.05 was considered statistically significant.

Results

Prevalence and overlap of pulmonary phenotypes in ueRA

Clinical and demographic characteristics of the study participants are presented in Table 1. The median age was 59 years (interquartile range [IQR], 52–65 years). Seventy-nine percent of the patients were female. Fifty-two percent were ever smokers. The median duration of RA symptoms before diagnosis was 6 months (IQR, 4–11). Eighty-two percent of patients were positive for RF IgM, 84% for ACPA IgG, and 71% for both autoantibodies. Disease activity was moderate (median DAS28 = 4.7 and median CDAI = 21.2). Erosive disease was present in 23% of patients, with a median total SvH score of 8 (IQR, 2–22).

PA were identified on HRCT in 43 of 55 patients (78%), Figure 1. Airway abnormalities and parenchymal nodules were the most common pulmonary phenotypes, each present in 30 patients (55%), whereas ILA was identified in six patients (11%). All ILA cases were graded as mild, and no honeycombing was present. Thirteen patients had isolated airway abnormalities and 12 had isolated parenchymal nodules. All patients with ILA had concomitant airway abnormalities and/or parenchymal nodules. Most parenchymal nodules were peripheral/subpleural. No pleural effusions were observed.

Presence of pulmonary abnormalities in ueRA is associated with systemic inflammation

Unsupervised PCA was performed to visualize the overall relationships among the included demographic, clinical, serological and cytokine variables in 2D in patients with and without any PA (Figure 2A). Subsequently, OPLS-DA was performed to identify variables associated with any PA (Figure 2B and Supplementary Figure S1A; see Additional file 1). Compared with patients without PA, patients with any PA had significantly higher levels of markers of systemic

inflammation including CRP ($p < 0.001$), ESR ($p = 0.005$) and IL-6 ($p = 0.01$; Figure 2C-E). IL-6 correlated with CRP, as expected, and with the number of swollen joints (SJC28), but not with total SvH score (Supplementary Figure S2A–C).

Moreover, in line with our previous report on neutrophil activation in the first 30 consecutive patients of this cohort [16], RF IgM levels were significantly higher in patients with any PA ($p < 0.0001$; Figure 2F) compared to no PA. Interestingly, sCD25, a marker of immune activation and commonly associated with T-cell activation [20], was higher in patients with PA compared with patients without PA ($p = 0.04$; Figure 2G) and correlated with CRP but not with SJC28 or total SvH score (Supplementary Figure S3A–C).

Parenchymal nodules and ILA are associated with distinct markers of immune activation

The overall relationships among the included demographic, clinical, serological and cytokine variables in relation to the separate pulmonary phenotypes are illustrated in Figure 3A. OPLS was then performed to identify variables associated with parenchymal nodules, ILA and airway abnormalities respectively (Figures 3B, 4A and 5A, and Supplementary Figure S1B–D). Patients with parenchymal nodules had significantly higher sCD25 levels than patients without parenchymal nodules (Figure 3C; $p = 0.03$). In addition, the upstream drivers of sCD25, IFN–γ and IL-12p70, showed trends towards higher levels ($p = 0.06$ and $p = 0.07$, respectively), whereas MCP–3 and GM-CSF did not differ significantly between the groups (Figure 3D–G).

Patients with ILA had significantly higher DAS28 compared with patients without ILA (Figure 4B; $p = 0.03$), whereas ESR, SJC28 and CDAI did not differ significantly between groups (Figure 4C–E). Despite the small ILA subgroup, IFN–α levels were significantly higher in patients with ILA than in patients without ILA (Figure 4F; $p = 0.01$). IFN–α levels correlated with clinical

disease activity measures, as reported earlier [21] but not with total SvH score (Supplementary Figure S4A–C). An interferon gene signature of five genes (*IFI6, IFI44L, ISG15, MX1,* and *OAS1*) has been suggested to mirror IFN–α activity in blood [21]. However, this interferon gene score (IGS) did not differ between patients with and without ILA ($p = 0.52$), and no correlation was observed between serum IFN–α levels and IGS ($r = -0.17$, $p = 0.25$; Supplementary Figure S5A–B).

Airway abnormalities are associated with systemic inflammation and shorter symptom duration in ueRA

Compared with patients without airway abnormalities, patients with airway abnormalities showed a trend towards higher levels of the T-cell chemokine CTACK ($p = 0.05$; Figure 5B) and had significantly higher CRP levels ($p = 0.03$; Figure 5C), whereas RF IgM, ACPA IgG and sCD25 did not differ significantly between groups (Figure 5D–F). Notably, in the OPLS model, symptom duration was inversely associated with this pulmonary phenotype. Univariate analysis confirmed that patients with airway abnormalities had shorter symptom duration than patients without (median 5 vs 9 months; $p = 0.01$; Supplementary Figure S6).

To determine whether the observed associations reflected specific pulmonary phenotypes rather than overlapping HRCT abnormalities, additional analyses were performed in patients with isolated airway abnormalities and isolated parenchymal nodules. Sensitivity analyses supported the main findings: higher sCD25 levels remained associated with isolated parenchymal nodules, whereas IFN–α did not differ between isolated parenchymal nodules and patients without pulmonary abnormalities. Similarly, higher CRP levels remained associated with isolated airway

abnormalities, whereas CTACK showed no significant association (Supplementary Figure S7A–B).

Discussion

In this study of treatment-naïve patients with newly diagnosed RA, pulmonary abnormalities were common already at the time of diagnosis and comprised partly overlapping HRCT-defined phenotypes. Importantly, the pulmonary phenotypes were associated with different systemic inflammatory and immune profiles. Parenchymal nodules were associated with higher circulating sCD25 levels, whereas ILA was associated with increased IFN–α. In contrast, airway abnormalities were primarily associated with systemic inflammation. The high prevalence of pulmonary involvement is consistent with findings from the Swedish Lung Investigation in Newly Diagnosed RA (LURA) study of untreated early RA, in which HRCT-defined airway and parenchymal abnormalities were present in 66% and 54% of patients, respectively [9]. Together, these findings suggest that pulmonary involvement is present early in the course of RA and that different pulmonary phenotypes may reflect partly distinct underlying biological processes.

Among the phenotype-associated immune markers identified in the present study, higher circulating sCD25 levels were associated with HRCT-defined parenchymal nodules. Notably, although sCD25 levels were within the normal reference range, the potential biological relevance of this association is supported by the fact that both IFN–γ and IL-12p70, key activators of the sCD25 pathway, were among the top five variables in the OPLS analysis. sCD25 represents the soluble form of the IL-2 receptor α-chain and is released predominantly from activated T cells [22]. It is clinically used for diagnosis and monitoring of hemophagocytic lymphohistiocytosis and in support for sarcoidosis [20]. Furthermore, sCD25 was associated with disease persistence in a Dutch RA cohort [23]. Our findings extend those reported by Cao *et al*., who reported increased serum sCD25 in patients with RA-associated ILD [15]. However, whereas their study evaluated patients with established RA and patterns of ILD on HRCT, our cohort consisted exclusively of

treatment-naïve patients at RA diagnosis and analysed HRCT-defined pulmonary phenotypes separately.

A second notable finding was the association between increased circulating IFN–α and HRCT-defined ILA. IFN–α belongs to the family of type I interferons, which bridge innate and adaptive immunity by promoting dendritic cell activation and antigen presentation. Type I interferons have also long been implicated in the initiation of systemic autoimmunity [24]. Increased type I interferon activity has previously been associated with early untreated RA and in particular for the transition to manifest disease [19, 21, 25]. To our knowledge, increased circulating IFN–α levels have not previously been reported in patients with HRCT-defined ILA in untreated early RA. Whether circulating IFN–α mirrors activities originating in the lungs or represents RA disease activity in general warrants further investigation. Notably, serum IFN–α levels did not correlate with the IGS in the present study, in contrast to findings by Cooles *et al.* [21]. This discrepancy might be explained by differences in study population, sample processing, kinetics of gene expression and by the fact that Cooles *et al.* quantified serum IFN–α using a more sensitive Simoa assay based on high affinity autoantibodies from patients with autoimmune polyendocrine syndrome type 1. Thus, the lack of a corresponding IGS signal should not be interpreted as evidence of absent type I interferon signalling in RA-associated ILA.

Unlike parenchymal nodules and ILA, airway abnormalities were early findings and predominantly associated with systemic inflammation rather than a distinct immune profile. In our previous report on neutrophil status in early RA, airway abnormalities were associated with an activated peripheral neutrophil phenotype [16]. This supports a role for innate immunity in the lungs early in RA disease development.

Finally, when considering parenchymal nodules, ILA and/or airway abnormalities collectively as any pulmonary abnormality, IL-6 was strongly associated with pulmonary involvement. However, IL-6 also correlated with CRP, ESR and swollen joint count, indicating that circulating IL-6 might reflect systemic and synovial inflammatory burden rather than pulmonary-specific immune activation.

The major strengths of this study include a comprehensive collection of radiographic pulmonary data of treatment-naïve RA patients. All participants underwent standardized HRCT assessed by experienced thoracic radiologists using a predefined imaging protocol. Furthermore, the combination of serum protein profiling and multivariate analyses followed by predefined univariate validation provided a comprehensive and structured analytical approach for identifying phenotype-specific immune signatures. However, the study also has limitations. Several cytokines showed circulating concentrations close to or below the detection range of the multiplex assay and should therefore be interpreted with caution. In addition, the cross-sectional design and relatively small cohort, particularly the ILA subgroup, warrant further validation in larger cohorts.

Conclusions

In conclusion, airway abnormalities in untreated early RA were associated with systemic inflammation, while higher circulating sCD25 and IFN–α levels were associated with parenchymal nodules and ILA, respectively. These findings suggest that different HRCT-defined pulmonary phenotypes may reflect partly distinct underlying biological processes and indicate that analysing these pulmonary phenotypes separately may improve our understanding of the development of lung disease in RA. Validation in larger prospective cohorts will be important to determine the clinical relevance of these phenotype-specific immune profiles.

Abbreviations

ACPA, anti-citrullinated protein antibodies; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; CTACK, cutaneous T-cell-attracting chemokine; DAS28, Disease Activity Score in 28 joints; DAS28–CRP, Disease Activity Score in 28 joints based on C-reactive protein; ELISA, enzyme-linked immunosorbent assay; ESR, erythrocyte sedimentation rate; GM-CSF, granulocyte-macrophage colony-stimulating factor; HNE, human neutrophil elastase; HRCT, high-resolution computed tomography; IFN–α, interferon alpha; IFN–γ, interferon gamma; ILA, interstitial lung abnormalities; ILD, interstitial lung disease; MCP–3, monocyte chemoattractant protein-3; OPLS, orthogonal partial least squares; OPLS-DA, orthogonal partial least squares discriminant analysis; PCA, principal component analysis; PGA, patient global assessment; PhGA, physician global assessment; RA, rheumatoid arthritis; RF, rheumatoid factor; sCD25, soluble CD25 (soluble interleukin-2 receptor alpha); SDAI, Simplified Disease Activity Index; SJC28, swollen joint count (28 joints); Simoa, single molecule array; SvH, Sharp/van der Heijde score; TJC28, tender joint count (28 joints); ueRA, untreated early rheumatoid arthritis; VIP, variable importance in projection

Additional file

Additional file 1 (.pdf): Supplementary Figures S1–S7. Supplementary multivariate, correlation and sensitivity analyses.

Declarations

Ethics approval and consent to participate

The present study was reviewed and approved by the Swedish Ethical Review Authority (Dnr. 2019-05725) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients included in the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

AKHE has received consulting fees from AbbVie, scientific advisory board fees from Pfizer and AbbVie, speaker honoraria from Boehringer Ingelheim, and a research grant from Aqilion. DG has served on advisory boards for AbbVie and UCB, received speaker fees from UCB, Lilly and Amgen, and acted as a consultant for Janssen and AbbVie, all outside the submitted work. HZ has served on scientific advisory boards and/or as a consultant for AbbVie, Acumen, Alamar, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Bioventix, Cognitact, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, Johnson & Johnson, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, Neurocode, New Amsterdam, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix Biochemica AB, Roche, and WebMD; is a co-founder

of Brain Biomarker Solutions in Gothenburg AB (BBS), which is part of the GU Ventures Incubator Program; and is a shareholder of CERimmune Therapeutics (outside the submitted work). The remaining authors declare that they have no competing interests.

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Authors' contributions

Conceptualisation: AR, IG, ACL, AKHE; Methodology: MS, ÅJ, ACL, AKHE; Investigation: MS, JB, ÅJ, FA, BB, TS, DG, AKHE; Resources: AR, IG, ACL, AKHE, HZ; Formal analysis: MS, SK, MLA, ACL, AKHE; Visualisation: MS, ACL, AKHE; Writing – Original draft: MS, SK, AKHE; Writing – Review & Editing: All authors; Project Administration: AKHE; Funding

acquisition: AKHE, MS, HZ; Guarantor: AKHE. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Table 1. Clinical characteristics of the included RA patients

Characteristic	All RA patients (n = 55)
Demographics and categorical variables, n (%)	
Female sex	44 (79)
Current smoker	13 (23)
Former smoker	16 (29)
Never smoker	26 (46)
Erosive disease	13 (23)
RF positive[a]	46 (82)
ACPA positive[b]	47 (84)
RF and ACPA positive	39 (71)
Continuous variables, median (IQR)	
Age (years)	59 (52 – 65)
RA symptom duration (months)	6 (4 – 11)
SJC28	7 (4 – 10)
TJC28	6 (3 – 9)
DAS28	4.7 (4.2 – 5.9)
DAS28-CRP	4.5 (3.9 – 5.4)
CDAI	21.2 (15.4 – 30.9)
SDAI	21.6 (17.0 – 32.1)
PhGA	40 (23 – 57)
PGA	56 (30 – 68)
Total SvH score	8 (2 – 22)
ESR (mm/h)	24 (12 – 48)
CRP (mg/L)	9 (4 – 28)

Abbreviations: ACPA, anti-citrullinated protein antibody; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score 28; DAS28-CRP, DAS28 based on CRP; ESR, erythrocyte sedimentation rate; IQR, interquartile range; PGA, patient global assessment of disease activity; PhGA, physician global assessment of disease activity; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; SJC28, swollen joint count (28 joints); SvH, Sharp/van der Heijde score; TJC28, tender joint count (28 joints). Missing data: PhGA (n = 1); DAS28, DAS28-CRP, PGA, SDAI and total SvH score (n = 2); CDAI (n = 3).

[a] RF positivity defined as RF IgM >5 kIU/L

[b] ACPA positivity defined as ACPA IgG >5 U/mL

FIGURE LEGENDS

Figure 1. **Overlap of pulmonary abnormalities in untreated early rheumatoid arthritis.** Venn diagram illustrating the overlap between HRCT-defined pulmonary abnormalities in patients with untreated early rheumatoid arthritis (n = 55). Numbers indicate the number of patients in each unique or overlapping pulmonary phenotype.

Figure 2. Associations of serum proteins and pulmonary abnormalities in untreated early rheumatoid arthritis. (**A**) Principal component analysis (PCA) illustrating the overall relationships of clinical, serological and cytokine variables in relation to any pulmonary abnormalities (PA) and no PA. (**B**) Orthogonal partial least squares discriminant analysis (OPLS-DA) loading plot showing the 20 highest-ranked variables according to their Variable Importance in Projection (VIP) values associated with any PA compared with no PA. Model parameters are shown as R2X, R2Y and Q2. (**C**–**G**) Univariate validation of the five highest-ranked variables: CRP (C), ESR (D), IL-6 (E), RF IgM (F), and sCD25 (G). Data are shown as individual data points with horizontal lines representing the median. For (E), the y-axis is broken between 75 and 150 pg/mL to improve visualization. Statistical analysis was performed using two-tailed Mann–Whitney U tests. *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$.

Figure 3. Multivariate and univariate analyses of parenchymal nodules in untreated early rheumatoid arthritis. (**A**) Principal component analysis (PCA) illustrating the overall relationships among clinical, serological and cytokine variables in relation to airway abnormalities, parenchymal nodules and interstitial lung abnormalities (ILA). (**B**) Orthogonal partial least squares (OPLS) loading plot showing the 20 highest-ranked variables according to their Variable Importance in Projection (VIP) values associated with parenchymal nodules. Model parameters are shown as R2X, R2Y and Q2. (**C**–**G**) Univariate validation of the five highest-ranked VIP

variables: sCD25 (C), MCP–3 (D), IFN–γ (E), IL–12p70 (F), and GM-CSF (G). Data are shown as individual data points with horizontal lines representing the median. Patients with isolated parenchymal nodules (without concomitant airway abnormalities or ILA) are indicated by filled squares. To improve visualization, the y-axis is broken between 90 and 100 pg/mL in (E) and between 40 and 100 pg/mL in (G). Statistical analysis was performed using two-tailed Mann–Whitney U tests. *$p < 0.05$.

Figure 4. Multivariate and univariate analyses of interstitial lung abnormalities (ILA) in untreated early rheumatoid arthritis. (**A**) Orthogonal partial least squares (OPLS) loading plot showing the 20 highest-ranked variables according to their Variable Importance in Projection (VIP) values associated with ILA. Model parameters are shown as R2X, R2Y and Q2. (**B–F**) Univariate validation of the five highest-ranked VIP variables: DAS28 (B), ESR (C), SJC28 (D), CDAI (E), and IFN–α (F). Data are shown as individual data points with horizontal lines representing the median. For (F), the y-axis is broken between 500 and 800 fg/mL to improve visualization. Statistical analysis was performed using two-tailed Mann–Whitney U tests. *$p < 0.05$.

Figure 5. Multivariate and univariate analyses of airway abnormalities in untreated early rheumatoid arthritis. (**A**) Orthogonal partial least squares (OPLS) loading plot showing the 20 highest-ranked variables according to their Variable Importance in Projection (VIP) values associated with airway abnormalities. Model parameters are shown as R2X, R2Y and Q2. (**B–F**) Univariate validation of the five highest-ranked VIP variables: CTACK (B), CRP (C), RF IgM (D), ACPA IgG (E), and sCD25 (F). Data are shown as individual data points with horizontal lines representing the median. Patients with isolated airway abnormalities (without concomitant

parenchymal nodules or interstitial lung abnormalities) are indicated by filled squares. Statistical analysis was performed using two-tailed Mann–Whitney U tests. *$p < 0.05$.

Figure 1

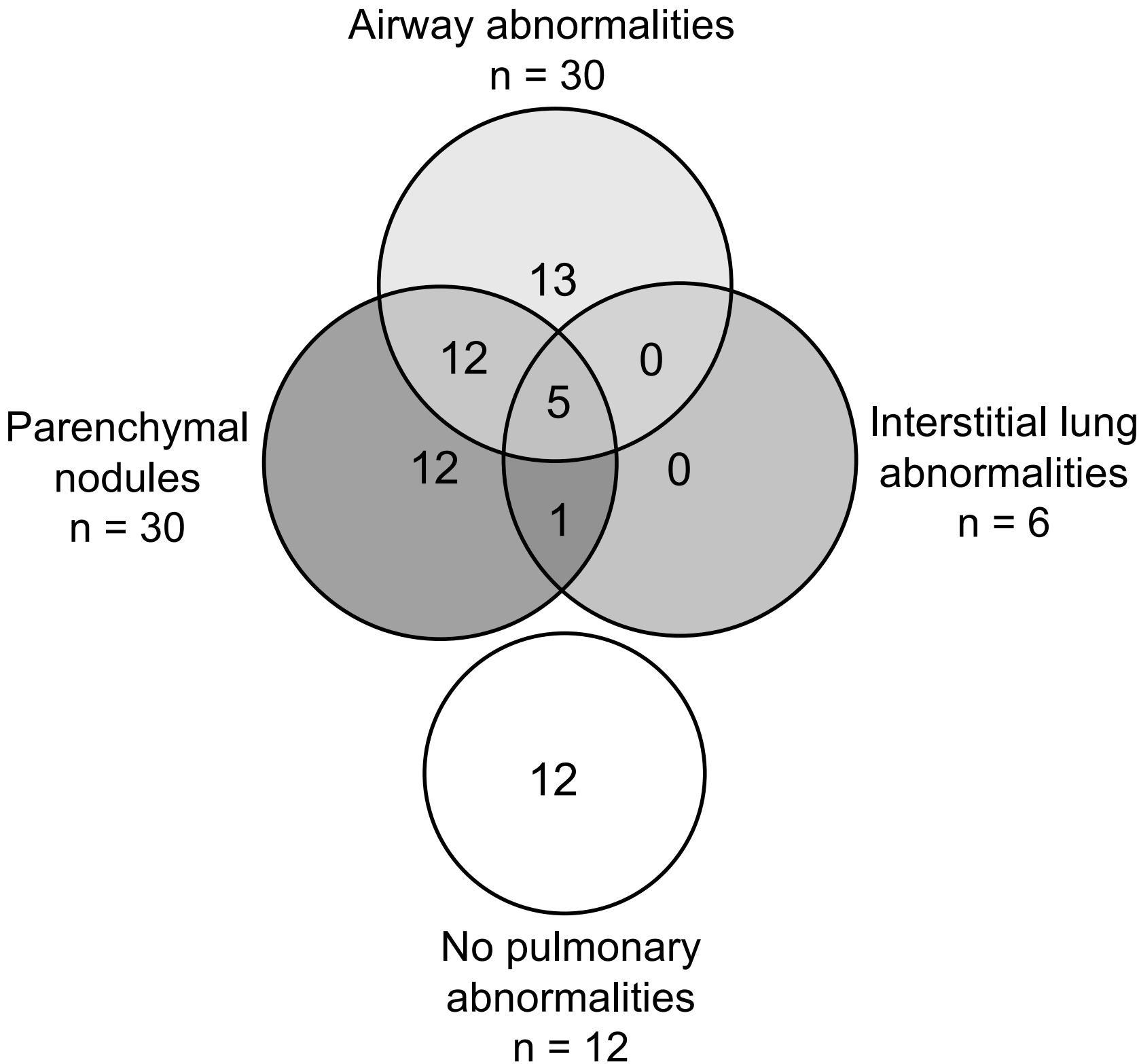
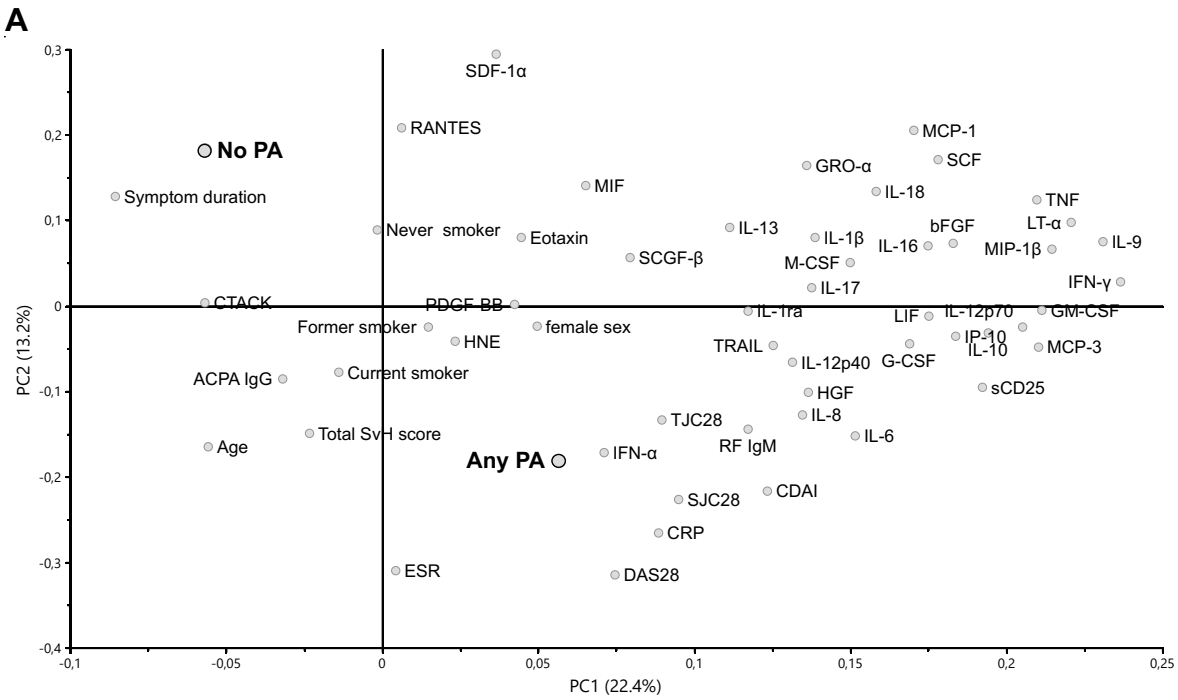
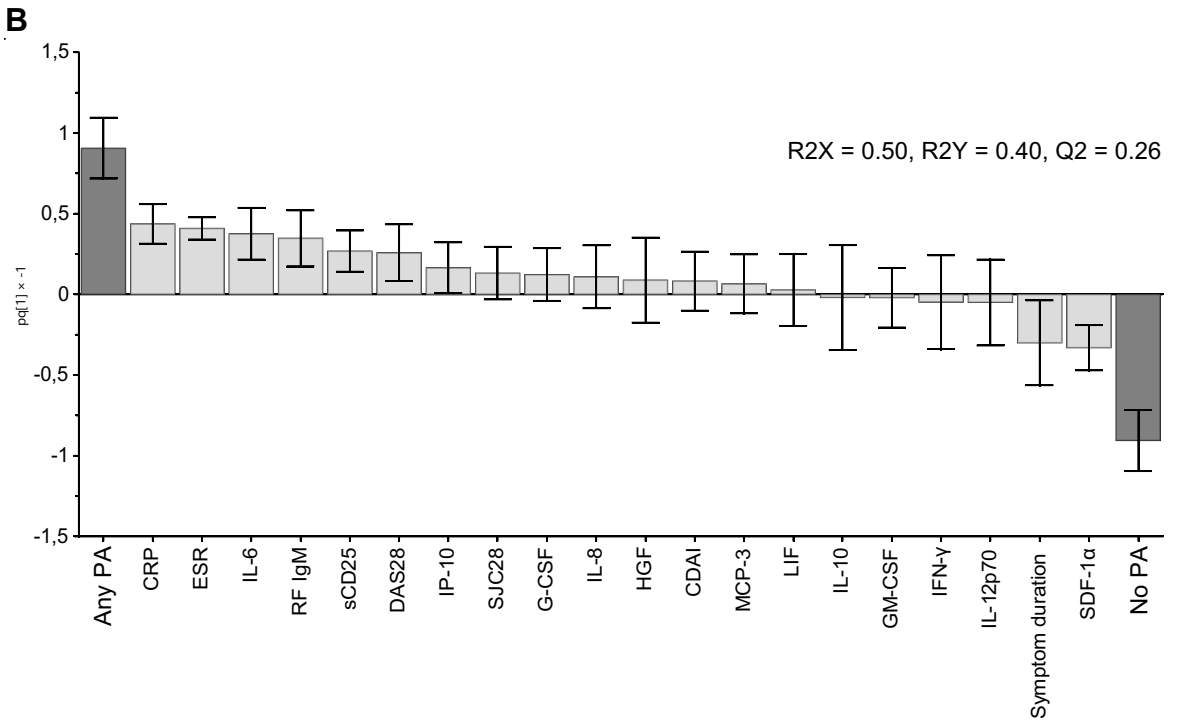

Airway abnormalities
n = 30
13
12
0
5
Parenchymal
nodules
n = 30
12
0
1
Interstitial lung
abnormalities
n = 6
12
No pulmonary
abnormalities
n = 12

Figure 2


A
SDF-1α
RANTES
MCP-1
No PA
SCF
GRO-α
MIF
IL-18
Symptom duration
TNF
IL-13
bFGF
LT-α
Never smoker
Eotaxin
IL-1β
IL-16
IL-9
SCGF-β
MIP-1β
M-CSF
IFN-γ
IL-17
CTACK
PDGF-BB
IL-1ra
LIF
IL-12p70
GM-CSF
Former smoker
female sex
IP-10
HNE
TRAIL
IL-10
MCP-3
IL-12p40
G-CSF
ACPA IgG
Current smoker
HGF
sCD25
TJC28
IL-8
Total SvH score
RF IgM
IL-6
Age
Any PA
IFN-α
SJC28
CDAI
CRP
ESR
DAS28
PC2 (13.2%)
PC1 (22.4%)


B
R2X = 0.50, R2Y = 0.40, Q2 = 0.26
p[1] × -1
Any PA
CRP
ESR
IL-6
RF IgM
sCD25
DAS28
IP-10
SJC28
G-CSF
IL-8
HGF
CDAI
MCP-3
LIF
IL-10
GM-CSF
IFN-γ
IL-12p70
Symptom duration
SDF-1α
No PA

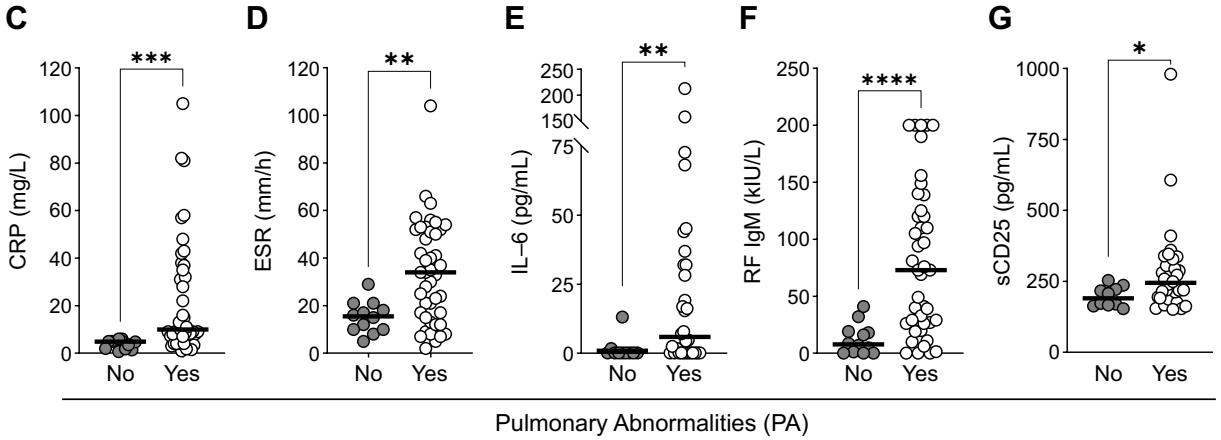
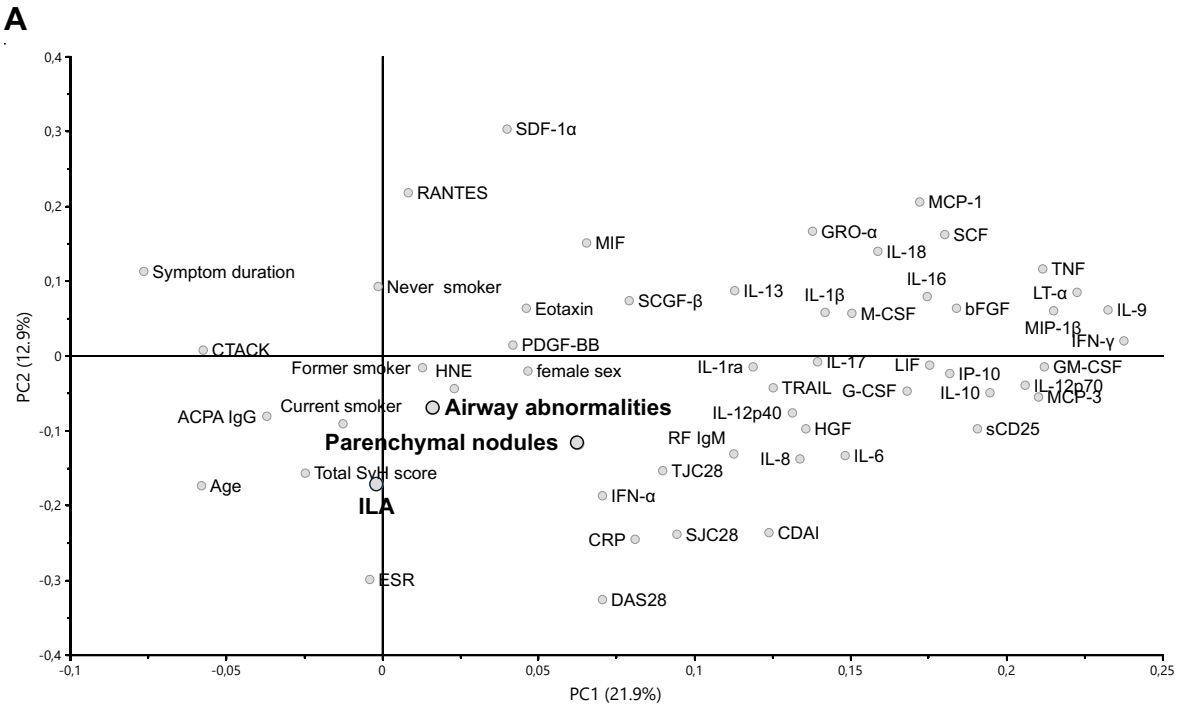
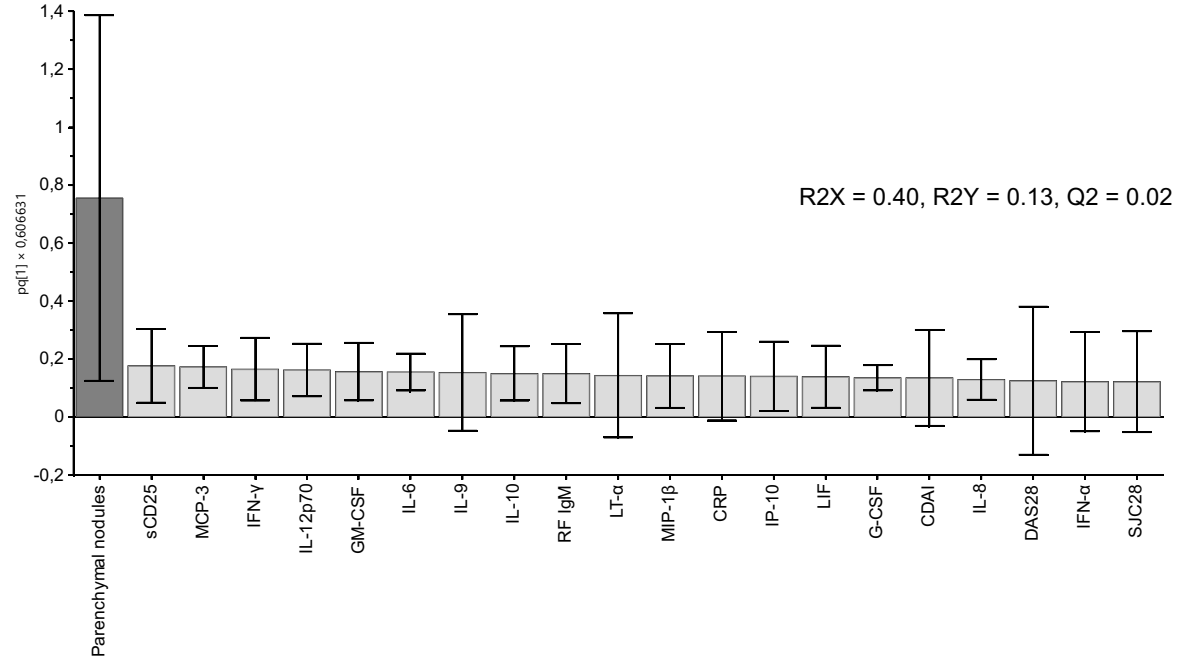

C
CRP (mg/L)
***
No
Yes
D
ESR (mm/h)
**
No
Yes
E
IL-6 (pg/mL)
**
No
Yes
F
RF IgM (kIU/L)
****
No
Yes
G
sCD25 (pg/mL)
*
No
Yes
Pulmonary Abnormalities (PA)

Figure 3


A
PC2 (12.9%)
PC1 (21.9%)
SDF-1α
RANTES
MCP-1
MIF
GRO-α
SCF
IL-18
Symptom duration
Never smoker
IL-16
TNF
IL-13
IL-1β
LT-α
Eotaxin
SCGF-β
M-CSF
bFGF
IL-9
MIP-1β
IFN-γ
CTACK
PDGF-BB
Former smoker
HNE
female sex
IL-1ra
IL-17
LIF
IP-10
GM-CSF
TRAIL
G-CSF
IL-10
IL-12p70
MCP-3
ACPA IgG
Current smoker
Airway abnormalities
IL-12p40
HGF
sCD25
Parenchymal nodules
RF IgM
IL-8
IL-6
Total SvH score
TJC28
Age
IFN-α
ILA
CRP
SJC28
CDAI
ESR
DAS28


B
R2X = 0.40, R2Y = 0.13, Q2 = 0.02
pq[1] × 0,606631
Parenchymal nodules
sCD25
MCP-3
IFN-γ
IL-12p70
GM-CSF
IL-6
IL-9
IL-10
RF IgM
LT-α
MIP-1β
CRP
IP-10
LIF
G-CSF
CDAI
IL-8
DAS28
IFN-α
SJC28

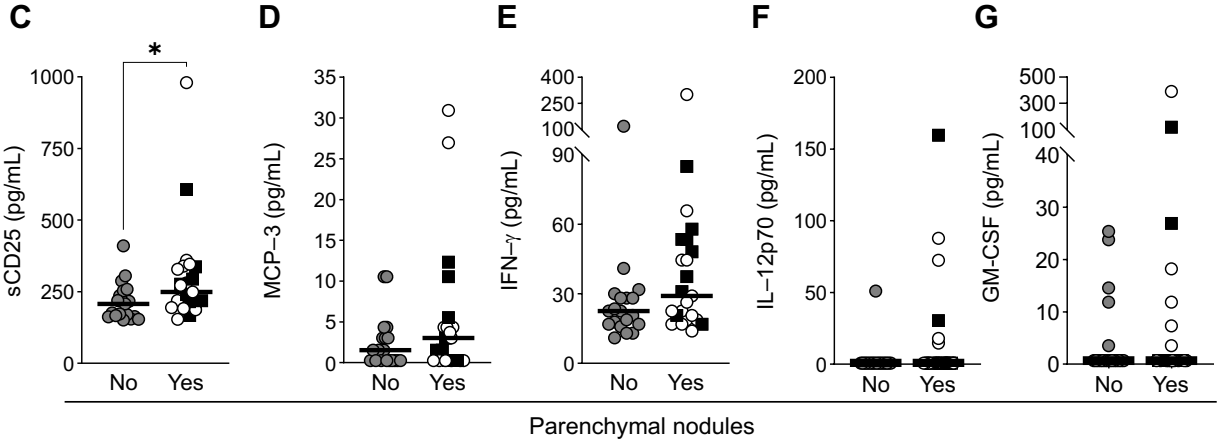

C
sCD25 (pg/mL)
*
No
Yes
D
MCP–3 (pg/mL)
E
IFN–γ (pg/mL)
F
IL–12p70 (pg/mL)
G
GM-CSF (pg/mL)
Parenchymal nodules

Figure 4

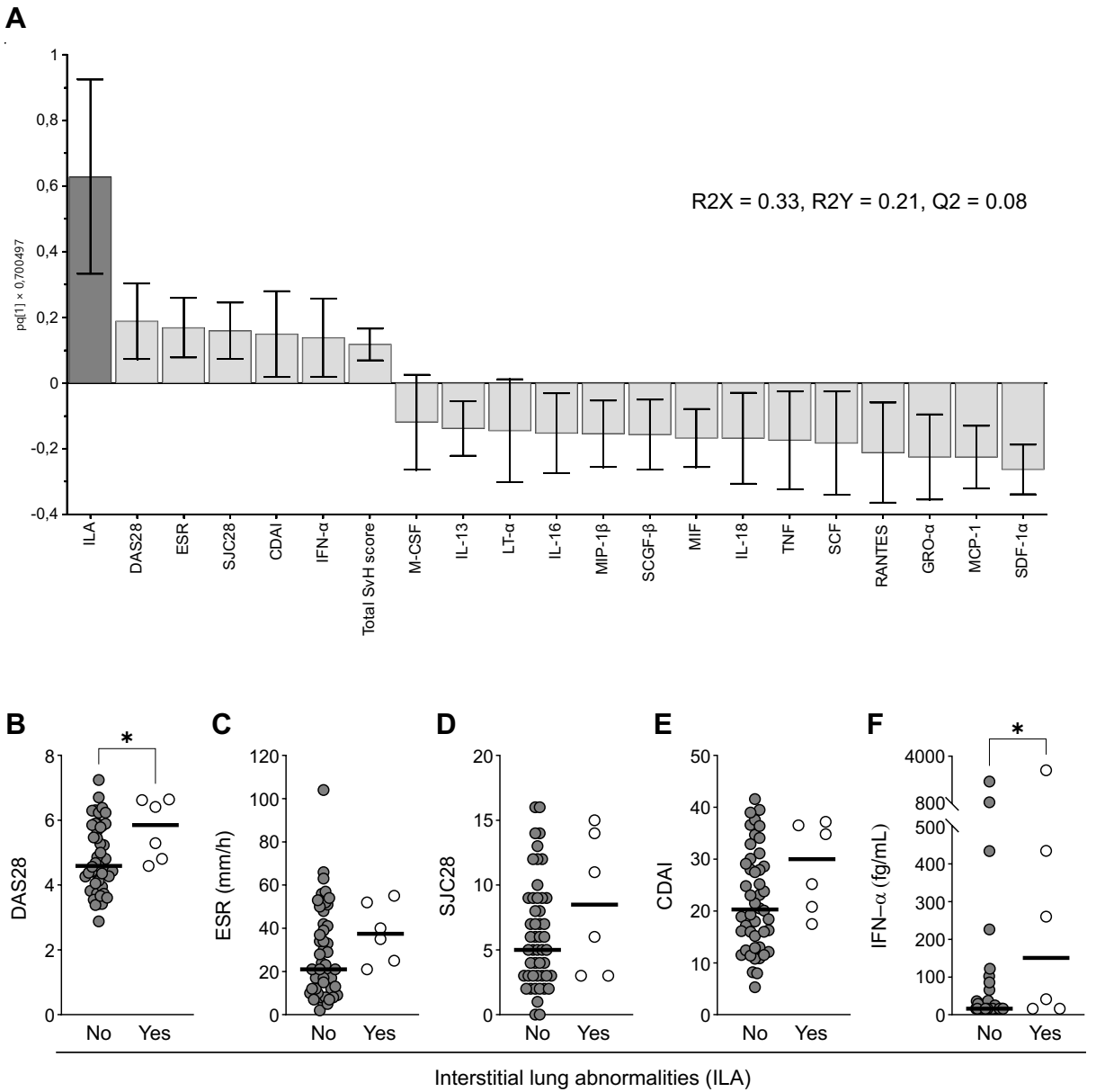
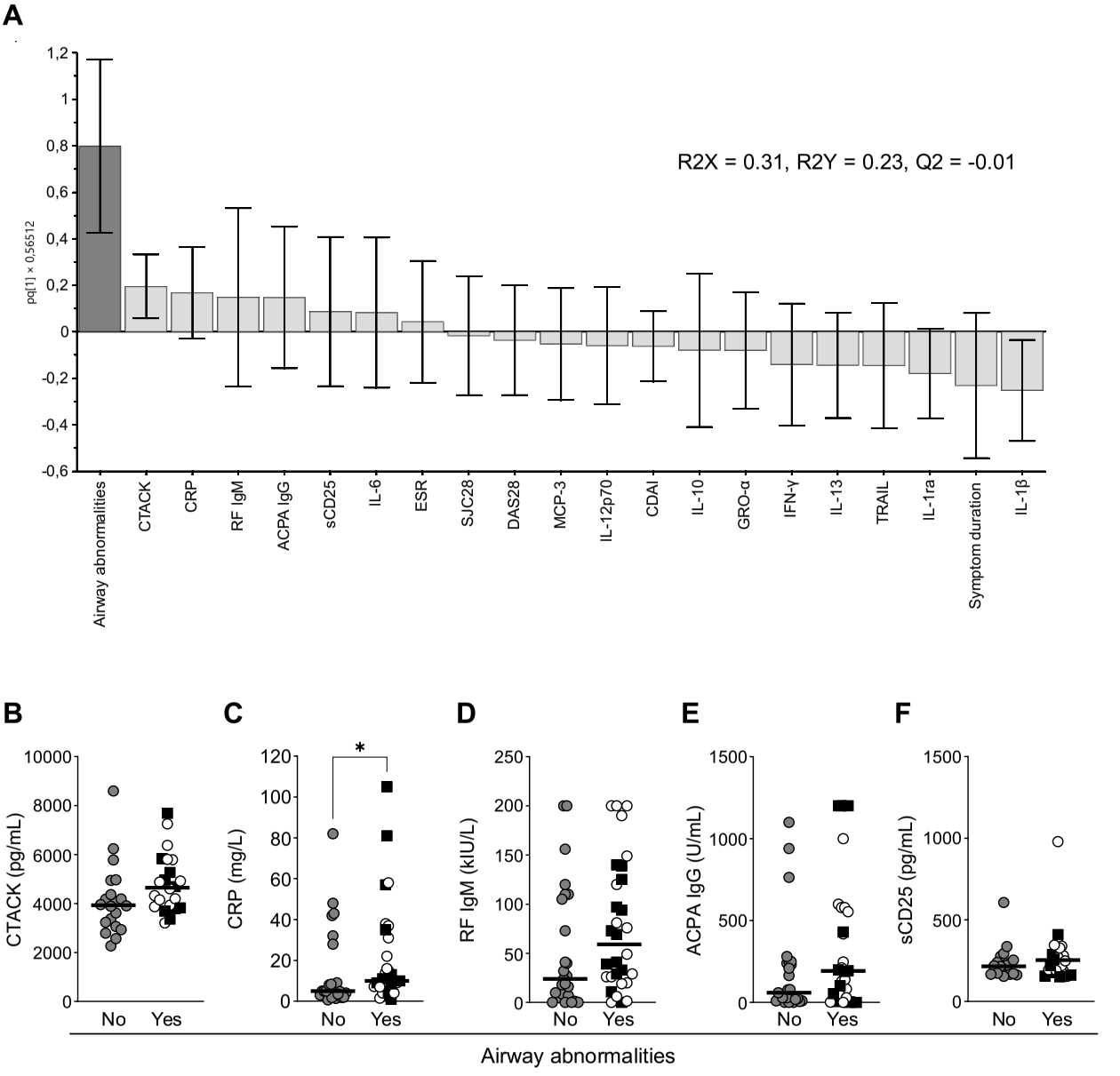

A
R2X = 0.33, R2Y = 0.21, Q2 = 0.08
pq[1] × 0.700497
ILA
DAS28
ESR
SJC28
CDAI
IFN-α
Total SvH score
M-CSF
IL-13
LT-α
IL-16
MIP-1β
SCGF-β
MIF
IL-18
TNF
SCF
RANTES
GRO-α
MCP-1
SDF-1α
B
DAS28
C
ESR (mm/h)
D
SJC28
E
CDAI
F
IFN–α (fg/mL)
No
Yes
Interstitial lung abnormalities (ILA)

Figure 5


A
R2X = 0.31, R2Y = 0.23, Q2 = -0.01
pq[1] × 0,56512
1,2
1
0,8
0,6
0,4
0,2
0
-0,2
-0,4
-0,6
Airway abnormalities
CTACK
CRP
RF IgM
ACPA IgG
sCD25
IL-6
ESR
SJC28
DAS28
MCP-3
IL-12p70
CDAI
IL-10
GRO-α
IFN-γ
IL-13
TRAIL
IL-1ra
Symptom duration
IL-1β
B
CTACK (pg/mL)
10000
8000
6000
4000
2000
0
No
Yes
C
CRP (mg/L)
120
100
80
60
40
20
0
*
No
Yes
D
RF IgM (kIU/L)
250
200
150
100
50
0
No
Yes
E
ACPA IgG (U/mL)
1500
1000
500
0
No
Yes
F
sCD25 (pg/mL)
1500
1000
500
0
No
Yes
Airway abnormalities

Supplementary Files

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