Therapeutic Advances in Musculoskeletal Disease

Review

Biomarkers for interstitial lung disease and acute-onset diffuse interstitial lung disease in rheumatoid arthritis

Hiroshi Furukawa, Shomi Oka, Takashi Higuchi, Kota Shimada, Atsushi Hashimoto, Toshihiro Matsui and Shigeto Tohma

Ther Adv Musculoskel Dis

2021, Vol. 13: 1–12

DOI: 10.1177/1759720X211022506

***Abstract*:** Interstitial lung disease (ILD) is frequently a complication of rheumatoid arthritis (RA) as an extra-articular manifestation which has a poor prognosis. Acute-onset diffuse ILD (AoDILD) occasionally occurs in RA and includes acute exacerbation of ILD, drug-induced ILD, and *Pneumocystis* pneumonia. AoDILD also confers a poor prognosis in RA. Previously-established biomarkers for ILD include Krebs von den lungen-6 and surfactant protein-D originally defined in patients with idiopathic pulmonary fibrosis; the sensitivity of these markers for RA-associated ILD (RA-ILD) is low. Although many studies on ILD markers have been performed in idiopathic pulmonary fibrosis, only a few validation studies in RA-ILD or AoDILD have been reported. Biomarkers for RA-ILD and AoDILD are thus still required. Recently, genomic, cytokine, antibody, and metabolomic profiles of RA-ILD or AoDILD have been investigated with the aim of improving biomarkers. In this review, we summarize current preliminary data on these potential biomarkers for RA-ILD or AoDILD. The development of biomarkers on RA-ILD has only just begun. When validated, such candidate biomarkers will provide valuable information on pathogenesis, prognosis, and drug responses in RA-ILD in future.

Keywords: biomarker, rheumatoid arthritis, interstitial lung disease, acute-onset diffuse interstitial lung disease

Received: 26 January 2021; revised manuscript accepted: 11 May 2021.

Correspondence to:
Hiroshi Furukawa
Department of Rheumatology, National Hospital Organization Tokyo National Hospital, 3-1-1 Takeoka, Kiyose 204-8585, Japan

Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital, Minami-ku, Sagamihara, Japan
furukawa-tky@umin.org

Shomi Oka
Shigeto Tohma
Department of Rheumatology, National Hospital Organization Tokyo National Hospital, Kiyose, Japan

Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital, Minami-ku, Sagamihara, Japan

Toshihiro Matsui
Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital, Minami-ku, Sagamihara, Japan

Department of Rheumatology, National Hospital Organization Sagamihara National Hospital, Minami-ku, Sagamihara, Japan

Takashi Higuchi
Department of Rheumatology, National Hospital Organization Tokyo National Hospital, Kiyose, Japan

Department of Nephrology, Ushiku Aiwa General Hospital, Ushiku, Japan

Kota Shimada
Department of Rheumatology, National Hospital Organization Sagamihara National Hospital, Minami-ku, Sagamihara, Japan

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease of unknown etiology with a prevalence of 0.5–1.0%. Genetic, environmental, and stochastic factors are thought to be involved in its pathogenesis.[1] The synovial joints are destroyed in RA but extra-articular manifestations are also frequent complications, namely, serositis, Felty's syndrome, rheumatoid vasculitis, lymphoproliferative disease, and interstitial lung disease (ILD). The last is characterized by interstitial inflammation of the lung as a complication in 10–70% of RA patients.[2–6] Such RA-associated ILD (RA-ILD) confers a dismal prognosis.[7–9] RA patients may exhibit usual interstitial pneumonia (UIP) showing honeycombing and irregular linear opacities on chest computed tomography, or non-specific interstitial pneumonia (NSIP) with bilateral ground-glass attenuation patterns observed in subpleural and basal regions of the lung,[10] with the prognosis of the former being worse.[11]

Acute-onset diffuse ILD (AoDILD) is an acute onset ILD, progresses within 1 month, and occurs in RA patients with or without underlying pre-existing ILD.[12,13] Acute exacerbation of ILD, drug-induced ILD, and *Pneumocystis* pneumonia are included in the AoDILD category. Because these three conditions sometimes overlap, it is difficult to distinguish one from the other. Methotrexate is a first-line drug for the treatment of RA[14,15] and may cause methotrexate-induced ILD, as one type of AoDILD.[16,17] Recent studies indicate that treatment with methotrexate does not increase the risk of chronic ILD in RA.[18–20]

Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, Fuchu, Japan

Atsushi Hashimoto
Department of Rheumatology, National Hospital Organization Sagamihara National Hospital, Minami-ku, Sagamihara, Japan

Department of Internal Medicine, Sagami Seikyou Hospital, Minami-ku, Sagamihara, Japan

The pathogenesis of AoDILD is believed to involve "immune reconstitution inflammatory syndrome" caused by infection by pathogens including *Pneumocystis jirovecii*.[21] Patients with collagen disease treated with immunosuppressive drugs may be affected by immune reconstitution inflammatory syndrome.[22,23] It was reported that AoDILD occurring in RA patients confers a poor prognosis.[11,12]

Krebs von den lungen-6 (KL-6) and surfactant protein-D (SP-D) are currently used as biomarkers for ILD. The cutoff levels for KL-6 and SP-D were set to distinguish both idiopathic pulmonary fibrosis (IPF) and collagen vascular disease-associated ILD from healthy controls and patients with bacterial pneumonia.[24,25] These markers have been validated in RA patients with ILD or AoDILD but their sensitivity is not acceptable.[26,27] KL-6 levels fluctuate during RA treatments with methotrexate or biological disease-modifying anti-rheumatic drugs under no clinical events.[28,29] Serum KL-6 levels were normal in about 30% of the RA patients with biological disease-modifying anti-rheumatic drug-induced ILD.[30,31] However, the efficacy of KL-6 for diagnosis of ILD in RA has been investigated.[32–35] Risk factors for ILD in RA are age, male sex, and smoking status.[10,36,37] Risk factors for AoDILD in RA are age at diagnosis of ILD, methotrexate use, and UIP pattern,[38] whereas risk factors for drug-induced ILD in RA are older age, disease-modifying anti-rheumatic drug use, existing ILD, hypoalbuminemia, and diabetes.[16] Prognostic factors for RA-ILD are age, male sex, forced vital capacity, history of AoDILD, and UIP pattern.[39–43] Although KL-6 could be a prognostic marker for RA-ILD, it was not better than other factors.[44] KL-6 might be a predictive biomarker for AoDILD in RA patients.[45] KL-6 levels in RA-ILD patients were reported to be reduced by baricitinib therapy.[46] Many studies of ILD markers were performed in IPF, but only a few validation studies on RA-ILD or AoDILD were reported. Thus, biomarkers for RA-ILD and AoDILD are required (Table 1).

Antibody biomarkers for RA-ILD or AoDILD

Rheumatoid factors (RFs) are autoantibodies against denatured Fc fragments of immunoglobulin (Ig) G which are present in the sera of 80% of RA patients. Most RF are IgM antibodies, high levels of which are associated with ILD in RA patients.[10,11,47] IgA RFs were also reported to be associated with ILD in RA patients.[48,49] Anti-citrullinated protein antibodies (ACPAs) are specific for proteins in which the arginine residues have been modified by peptidylarginine deiminases; they are detected in the sera of 70–80% of RA patients. It is known that the specificity of ACPAs for RA is higher than RFs. High levels of ACPAs in RA are also associated with ILD.[47,49,50] It was reported that IPF is associated with the production of IgA-ACPAs,[48,51] although this was not associated with ILD as a complication of RA. It was also reported that circulating secretory IgA-ACPAs were associated with RA with ILD.[52] ACPAs were detected in the sera of ILD patients without RA who were former or current smokers.[53,54] Citrullinated peptides found in the lung of RA-ILD patients could be generated by smoking[55] and thus contribute to the pathogenesis of RA.[56] Anti-carbamylated protein antibodies are auto-antibodies against homocitrullinated proteins (in which lysine residues are modified by a non-enzymatic post-translational mechanism); these are also increased in RA with ILD.[57] Anti-citrullinated alpha-enolase peptide-1 antibodies are included in the ACPA grouping and are also associated with RA with ILD.[58,59] It was also reported that other autoantibodies, including anti-citrullinated heat shock protein 90 antibodies or anti-malondialdehyde-acetaldehyde antibodies, can be detected in sera from RA patients with ILD.[60,61]

It has also been reported that anti-melanoma differentiation-associated gene 5 (MDA5)-specific antibodies are found in the sera of clinically amyopathic dermatomyositis patients and are biomarkers for AoDILD in Japanese dermatomyositis patients.[62] Anti-aminoacyl-tRNA synthetase antibodies are also frequently detected in polymyositis/dermatomyositis patients with ILD.[63] Anti-MDA5 antibodies or anti-aminoacyl-tRNA synthetase antibodies are usually absent in RA patient sera.[64,65] Acute respiratory distress syndrome associated with blood transfusion, designated "transfusion-related acute lung injury" is caused by anti-human leukocyte antigen (HLA) antibodies or anti-granulocyte antibodies in transfused blood.[66,67] Thus, some autoantibodies are biomarkers for collagen vascular disease-associated ILD or AoDILD. Similarly, anti-major histocompatibility complex class I chain-related gene A antibodies in RA are associated with ILD.[68] We ourselves have also extensively investigated autoantibody profiles of ILD and AoDILD in RA patients using a protein array method, Protoarray (Thermo Fisher Scientific Inc., Waltham, MA, USA; unpublished results). This protein array allows for screening autoantibodies in sera from RA patients with ILD or without

Table 1. Candidate biomarkers for RA-ILD or AoDILD.

RA-ILD	AoDILD	References
Antibody biomarkers		
Rheumatoid factors		Oka *et al.*,[10] Kakutani *et al.*,[11] and Mori *et al.*[47]
IgA rheumatoid factors		Bernstein *et al.*[48] and Joshua *et al.*[49]
Anti-citrullinated protein antibodies		Mori *et al.*,[47] Joshua *et al.*,[49] and Zhu *et al.*[50]
Circulating secretory IgA anti-citrullinated protein antibodies		Roos Ljungberg *et al.*[52]
Anti-carbamylated protein antibodies		Castellanos-Moreira *et al.*[57]
Anti-citrullinated alpha-enolase peptide-1 antibodies		Alunno *et al.*[58] and Liu *et al.*[59]
Anti-citrullinated heat shock protein 90 antibodies		Harlow *et al.*[60]
Anti-malondialdehyde-acetaldehyde antibodies		England *et al.*[61]
Anti-major histocompatibility complex class I chain-related gene A antibodies		Furukawa *et al.*[68]
Genetic biomarkers		
rs35705950 in *MUC5B* gene		Juge *et al.*[72]
rs12702634 in the *RPA3-UMAD1* gene		Shirai *et al.*[76]
Rare variants in the genes responsible for IPF		Juge *et al.*[72]
Rare variants of the *MUC5B* gene		Wang *et al.*[78]
Rare variants in the genes upregulated in acute exacerbation of IPF		Furukawa *et al.*[80]
HLA DR2 alleles		Furukawa *et al.*,[4] Oka *et al.*,[10] Mori *et al.*,[47] and Migita *et al.*[87]
Shared epitope alleles (protective)		Furukawa *et al.*,[4] Mori *et al.*,[47] Migita *et al.*,[87] and Turesson *et al.*[88]
	*HLA-A*31:01*	Furukawa *et al.*[90]
hsa-miR-214-5p and hsa-miR-7-5p		Oka *et al.*[97]
Long non-coding RNAs		Zhou *et al.*[98]
Krebs von den lungen-6		Ohnishi *et al.*[24] and Nakajima *et al.*[25]
Surfactant protein-D		Ohnishi *et al.*[24]
Protein biomarkers		
Matrix metalloproteinase7, C-C motif chemokine ligand 18		Doyle *et al.*[105]

(continued)

Table 1. (continued)

RA-ILD	AoDILD	References
Matrix metalloproteinase7, C-X-C motif chemokine ligand 10		Chen *et al*.[106]
Interleukin-18		Matsuo *et al*.[107]
Interleukin-13		Hussein *et al*.[109]
Soluble programmed death-ligand 1		Wu *et al*.[108]
	Matrix metalloproteinase-1, tissue inhibitors of metalloproteinases-1, osteopontin, soluble interleukin-2 receptor α, and interleukin-1 receptor antagonist	Oka *et al*.[13]
Other biomarkers		
Amino acid		Furukawa *et al*.[26]
Decanoic acid, morpholine, and glycerol		Furukawa *et al*.[118]
	Mannosamine, alliin, kynurenine, and 2-hydroxybutyric acid	Furukawa *et al*.[27]
Platelet/lymphocyte ratio		Chen *et al*.[119]

AoDILD, acute-onset diffuse interstitial lung disease; HLA, human leukocyte antigen; IPF, idiopathic pulmonary fibrosis; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis-associated interstitial lung disease.

chronic lung diseases; our data suggested KIAA0174, RPS19, PCDHA4, and ANKRD45 as four candidate target autoantigens in this case. In contrast, this approach suggested six candidate autoantigens, FGF12, MGC21881, MTHFD2, RBM22, PPIL2, and XAGE1D, when screening sera from RA patients before and after an AoDILD episode. Additionally, anti-MDA5 antibodies were detected in one RA patient with AoDILD. It was attempted to validate these candidate antigens by the Protoplex method (Thermo Fisher Scientific Inc.), a multiplex flow-cytometric microsphere-based immunoassay, but the results could not be confirmed. These candidate antigens were also analyzed by glutathione S-transferase-capture enzyme-linked immunosorbent assay[69] for validation of the results of protein arrays, but again the results could not be confirmed. Thus, comprehensive exploration of auto-antibody biomarkers for RA-ILD has been conducted, but with inconclusive results. Thus, the exploration of antibody biomarkers for RA-ILD or AoDILD has been conducted.

Genetic biomarkers for RA-ILD or AoDILD

Although genetic risk factors for RA or IPF have been sought, only a few reports on genetic associations with ILD in RA have been published. A single nucleotide variant (SNV) rs35705950 in the promoter region of the *MUC5B* gene was found to be associated with familial and sporadic IPF[70,71] and an association between RA-ILD and this SNV was confirmed,[72] although rs35705950 was not associated with ILD in systemic sclerosis (SSc) patients.[73] This risk allele increases the expression of the *MUC5B* gene,[74] which encodes a secretory mucin expressed on submucosal gland cells in the lung. An excess of MUC5B could impair alveolar repair. However, this risk allele was paradoxically associated with better survival of IPF patients,[75] suggesting its importance in mild IPF. Genome-wide association studies (GWASs) have been conducted to determine the role of common variants on disease predisposition; a Japanese GWAS was performed for ILD in RA with the result that a significant association with SNV rs12702634 in the *RPA3-UMAD1*

gene was found.[76] Deleterious rare variants including loss of function variants and deleterious missense variants are causative in some diseases.[77] A role for rare variants in the genes responsible for IPF was reported in European RA patients with ILD.[72] A role for rare variants of the *MUC5B* gene was also reported in Chinese RA patients with ILD.[78] Genes upregulated in acute exacerbation of IPF have been reported as well[79] and the frequency of rare deleterious alleles of these candidate genes was increased in AoDILD.[80]

HLA molecules present antigens to T-cell receptors, and for this reason *HLA* alleles are associated with many diseases. Thus, *HLA-B*15*, *B*40*, HLA-DR2 (*DRB1*15* and *DRB1*16*), and *MICA*001* are associated with IPF.[81–85] *HLA-DRB1*04:01*, **04:04*, **04:05*, **01:01*, and **10:01* are associated with RA. Because these RA risk alleles share amino acid sequences at positions 70–74 of the HLA-DRβ protein (QKRAA, RRRAA, or QRRAA), they are designated "shared epitope" (SE) alleles.[86] DR2 alleles were reported to predispose to ILD in RA,[4,10,47,87] whereas SE alleles were protective against ILD in RA.[4,47,87,88] Although SE alleles were strongly associated with ACPA-positive RA,[89] frequencies of these alleles are relatively lower in RA patients with ILD. An association of *HLA-A*31:01* with methotrexate-induced ILD in RA patients was reported.[90] A GWAS was conducted on methotrexate-induced ILD, but no significant associations were detected.[91]

Micro RNAs (miRNAs) are small non-coding RNAs of approximately 22 nucleotides in length. They modulate the expression of protein-coding genes at the post-transcriptional level. Circulating miRNAs can be used as disease biomarkers.[92] Some circulating miRNAs are also dysregulated in RA[93,94] or IPF.[95,96] Plasma levels of miRNAs were also investigated in RA with ILD and hsa-miR-214-5p and hsa-miR-7-5p were reported to be increased.[97] Long non-coding RNAs are transcripts >200 nucleotides in length which are not translated into protein. The levels of some of these long non-coding RNAs were also reported to be increased in peripheral blood mononuclear cells from RA-ILD patients.[98] Thus, genetic biomarkers for RA-ILD or AoDILD have been investigated.

Protein biomarkers for RA-ILD or AoDILD

Cytokines, chemokines, matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs) are involved in the pathogenesis of IPF;[99–104] MMP7 was frequently reported to be increased in IPF. The role of these proteins in RA-ILD was also investigated in several studies. Increased levels of MMP7, C-X-C motif chemokine ligand 10, C-C motif chemokine ligand 18, soluble programmed death-ligand 1, interleukin (IL)-18, and IL-13 have all been detected in sera from RA-ILD patients.[105–109] Disparate results on serum cytokine levels have been obtained in different cohorts, suggesting heterogeneity of RA-ILD.[110] Increased levels of MMP7 were also detected in idiopathic inflammatory myopathy and in systemic sclerosis patients with ILD.[111,112] Cytokine, chemokine, MMP, and TIMP profiles have all been investigated in AoDILD.[13] Serum MMP-1, TIMP-1, osteopontin, soluble IL-2 receptor α, and IL-1 receptor antagonist levels are increased, but MMP-3, TIMP-2, and eotaxin 2 are decreased in AoDILD. Serum MMP-1, MMP-3, MMP-8, MMP-9, TIMP-2, TIMP-3, osteopontin, and soluble IL-2 receptor α levels could be prognostic biomarkers in AoDILD. Thus, protein biomarkers for RA-ILD or AoDILD have been extensively analyzed.

Other biomarkers for RA-ILD or AoDILD

Low molecular weight metabolites are determined in order to elucidate altered metabolic states under pathological conditions, and to identify biomarkers.[113] Some metabolomic analyses have been conducted separately for RA[114] or IPF.[115–117] Plasma amino acid levels were analyzed in RA patients with ILD or without chronic lung diseases.[26] A complex biomarker constellation was assembled from amino acid profiles, but did not perform better than KL-6. Serum metabolomic profiles of ILD in RA have been systematically analyzed.[118] Serum levels of decanoic acid and morpholine were decreased in RA with ILD, and glycerol was increased. Serum levels of these metabolites in RA with UIP or RA with NSIP were similarly changed. The partial least squares-discriminant analysis (PLS-DA) model using these three metabolites could distinguish ILD in RA. Serum metabolomic profiles of AoDILD in RA were also investigated.[27] PLS-DA was conducted to create a complex biomarker cluster with four metabolites (mannosamine, alliin, kynurenine, and 2-hydroxybutyric acid); this was able to distinguish between AoDILD and stable states. It was also reported that the platelet/lymphocyte ratio was increased in RA-ILD.[119] Thus, other biomarkers for ILD in RA have also been investigated in recent studies.

Conclusions

Several candidate biomarkers for RA-ILD have been reported over the last few years and the number of studies on these biomarkers is increasing. The development of biomarkers on RA-ILD has only just begun and the utility for diagnosis and the prediction efficacy of severity and prognosis were not well validated for almost all of the biomarkers reported. Additionally, sensitivity and specificity of these markers were not compared. The treatment of RA-ILD was not established, but some new drugs have been developed. Thus, the important roles of these new biomarkers for decision of appropriate therapies would be validated in future. Although these serological and genetic biomarkers seem promising, validation needs to be undertaken in comparing RA-ILD with IPF, RA-ILD with RA patients having emphysema or airway diseases, RA-ILD with pulmonary tuberculosis, RA-ILD with non-tuberculous mycobacterial pulmonary disease, and, finally, RA-ILD with healthy controls. Longitudinal studies of these markers should be conducted for the assessment of correlations with clinical course. ILD in RA is of NSIP and UIP type, and is pathogenically heterogeneous. Predictive markers to distinguish NSIP from UIP would be a useful application of these biomarkers. Stratified analyses for biomarkers may reveal differences in the pathogenesis of disease subtypes and might provide an explanation for the pathogenic heterogeneity of RA-ILD. Glucocorticoid or other immunosuppressive agents are used for RA with the NSIP pattern whereas anti-fibrotic agents would be used for RA-ILD in the near future. Treatment response needs to be predicted with sufficient improved accuracy by recently-identified biomarker candidates for RA-ILD. Because the prognosis of RA patients with the complication of ILD is worse,[7–9] new biomarkers for ILD in RA may predict the prognosis. AoDILD is an acute hypersensitivity pneumonitis conferring a poor prognosis in RA[11,12]; novel biomarkers would facilitate early detection and treatment of AoDILD and improve the prognosis. Thus, extensive recent studies have aimed to establish robust new specific biomarkers for RA-ILD and to develop many applications. The future prospects of the biomarkers for RA-ILD would be splendid.

Acknowledgements

The members of the RA-ILD Study Consortium are: Akira Okamoto (NHO Himeji Medical Center), Norie Yoshikawa and Koichiro Saisho (NHO Miyakonojo Medical Center), Kiyoshi Migita (NHO Nagasaki Medical Center, Fukushima Medical University), Masao Katayama (NHO Nagoya Medical Center), Naoshi Fukui, Akiko Komiya, Atsushi Hashimoto, and Toshihiro Matsui (NHO Sagamihara National Hospital), Hiroshi Furukawa and Shigeto Tohma (NHO Sagamihara National Hospital, NHO Tokyo National Hospital), Kota Shimada (NHO Sagamihara National Hospital, Tokyo Metropolitan Tama Medical Center).

Author contributions

HF and ST conceived and designed the experiments. HF, SO, and TH performed the experiments. HF analyzed the data. HF, KS, AH, TM, and ST contributed reagents/materials/analysis tools. HF, KS, AH, TM, and ST wrote the manuscript.

Conflict of interest statement

HF has the following conflicts, and the following funders are supported wholly or in part by the indicated pharmaceutical companies. The Japan Research Foundation for Clinical Pharmacology is run by Daiichi Sankyo, the Takeda Science Foundation is supported by an endowment from Takeda Pharmaceutical Company and the Nakatomi Foundation was established by Hisamitsu Pharmaceutical Co., Inc. The Daiwa Securities Health Foundation was established by Daiwa Securities Group Inc. and Mitsui Sumitomo Insurance Welfare Foundation was established by Mitsui Sumitomo Insurance Co., Ltd. HF was supported by research grants from Bristol-Myers-Squibb Co. HF received honoraria from Ajinomoto Co., Inc., Daiichi Sankyo Co., Ltd, Dainippon Sumitomo Pharma Co., Ltd, Pfizer Japan Inc., and Takeda Pharmaceutical Company. ST was supported by research grants from nine pharmaceutical companies: Abbott Japan Co., Ltd, Astellas Pharma Inc., Chugai Pharmaceutical Co., Ltd, Eisai Co., Ltd, Mitsubishi Tanabe Pharma Corporation, Merck Sharp and Dohme Inc., Pfizer Japan Inc., Takeda Pharmaceutical Company Limited, Teijin Pharma Limited. ST received honoraria from Asahi Kasei Pharma Corporation, Astellas Pharma Inc., AbbVie GK., Chugai Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd, Mitsubishi Tanabe Pharma Corporation, Pfizer Japan Inc. The other authors declare no financial or commercial conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study at Sagamihara Hospital was supported by Grants-in-Aid for Scientific Research (B) (26293123) from the Japan Society for the Promotion of Science, Health and Labor Science Research Grants from the Ministry of Health, Labor, and Welfare of Japan, Grants-in-Aid for Clinical Research from National Hospital Organization, Research Grants from Daiwa Securities Health Foundation, Research Grants from Japan Research Foundation for Clinical Pharmacology, Research Grants from The Nakatomi Foundation, Research Grants from Takeda Science Foundation, Research Grants from Mitsui Sumitomo Insurance Welfare Foundation, and research grants from the following pharmaceutical companies: Abbott Japan Co., Ltd, Astellas Pharma Inc., Bristol-Myers-Squibb Co., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd, Mitsuibishi Tanabe Pharma Corporation, Merck Sharp and Dohme Inc., Pfizer Japan Inc., Takeda Pharmaceutical Company Limited, Teijin Pharma Limited. The funders had no role in study design, data collection and analysis, decision to publish, or preparing the manuscript.

Data availability statement

All datasets presented in this study are included in the article.

Ethics statement and informed consent

This study protocol was reviewed and approved by the NHO central Institutional Review Board. Written informed consents were obtained from all the participants. The study was performed in accordance with the principles expressed in the Declaration of Helsinki.

ORCID iD

Hiroshi Furukawa https://orcid.org/0000-0003-1353-8056

References

1. Perricone C, Ceccarelli F and Valesini G. An overview on the genetic of rheumatoid arthritis: a never-ending story. *Autoimmun Rev* 2011; 10: 599–608.
2. Dawson JK, Fewins HE, Desmond J, *et al.* Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography, and pulmonary function tests. *Thorax* 2001; 56: 622–627.
3. Mori S, Cho I, Koga Y, *et al.* Comparison of pulmonary abnormalities on high-resolution computed tomography in patients with early versus longstanding rheumatoid arthritis. *J Rheumatol* 2008; 35: 1513–1521.
4. Furukawa H, Oka S, Shimada K, *et al.* Association of human leukocyte antigen with interstitial lung disease in rheumatoid arthritis: a protective role for shared epitope. *PLoS One* 2012; 7: e33133.
5. Spagnolo P, Lee JS, Sverzellati N, *et al.* The lung in rheumatoid arthritis: focus on interstitial lung disease. *Arthritis Rheumatol* 2018; 70: 1544–1554.
6. Dai Y, Wang W, Yu Y, *et al.* Rheumatoid arthritis-associated interstitial lung disease: an overview of epidemiology, pathogenesis and management. *Clin Rheumatol* 2020; 40: 1211–1220.
7. Hakala M. Poor prognosis in patients with rheumatoid arthritis hospitalized for interstitial lung fibrosis. *Chest* 1988; 93: 114–118.
8. Turesson C and Jacobsson LT. Epidemiology of extra-articular manifestations in rheumatoid arthritis. *Scand J Rheumatol* 2004; 33: 65–72.
9. Koduri G, Norton S, Young A, *et al.* Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. *Rheumatology* 2010; 49: 1483–1489.
10. Oka S, Furukawa H, Shimada K, *et al.* Association of human leukocyte antigen alleles with chronic lung diseases in rheumatoid arthritis. *Rheumatology (Oxford)* 2016; 55: 1301–1307.
11. Kakutani T, Hashimoto A, Tominaga A, *et al.* Related factors, increased mortality and causes of death in patients with rheumatoid arthritis-associated interstitial lung disease. *Mod Rheumatol* 2020; 30: 458–464.
12. Kameda H, Tokuda H, Sakai F, *et al.* Clinical and radiological features of acute-onset diffuse interstitial lung diseases in patients with rheumatoid arthritis receiving treatment with biological agents: importance of Pneumocystis pneumonia in Japan revealed by a multicenter study. *Intern Med* 2011; 50: 305–313.
13. Oka S, Furukawa H, Shimada K, *et al.* Serum biomarker analysis of collagen disease patients with acute-onset diffuse interstitial lung disease. *BMC Immunol* 2013; 14: 9.
14. Smolen JS, Landewé R, Bijlsma J, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological

disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2016; 76: 960–977.

15. Singh JA, Saag KG, Bridges SL Jr, *et al*. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2016; 68: 1–26.
16. Alarcon GS, Kremer JM, Macaluso M, *et al*. Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis. A multicenter, case-control study. Methotrexate-Lung Study Group. *Ann Intern Med* 1997; 127: 356–364.
17. Sathi N, Chikura B, Kaushik VV, *et al*. How common is methotrexate pneumonitis? A large prospective study investigates. *Clin Rheumatol* 2012; 31: 79–83.
18. Conway R, Low C, Coughlan RJ, *et al*. Methotrexate and lung disease in rheumatoid arthritis: a meta-analysis of randomized controlled trials. *Arthritis Rheumatol* 2014; 66: 803–812.
19. Kiely P, Busby AD, Nikiphorou E, *et al*. Is incident rheumatoid arthritis interstitial lung disease associated with methotrexate treatment? Results from a multivariate analysis in the ERAS and ERAN inception cohorts. *BMJ Open* 2019; 9: e028466.
20. Juge PA, Lee JS, Lau J, *et al*. Methotrexate and rheumatoid arthritis associated interstitial lung disease. *Eur Respir J* 2021; 57: 2000337.
21. Novak RM, Richardson JT, Buchacz K, *et al*. Immune reconstitution inflammatory syndrome: incidence and implications for mortality. *AIDS* 2012; 26: 721–730.
22. Szerszen A, Gupta S, Seminara D, *et al*. Peritoneal tuberculosis complicated by immune reconstitution inflammatory syndrome in a patient treated with infliximab?: a case for adjuvant immunosuppressive therapy. *J Clin Rheumatol* 2009; 15: 417–418.
23. Tanaka T, Sekine A, Tsunoda Y, *et al*. Central nervous system manifestations of tuberculosis-associated immune reconstitution inflammatory syndrome during adalimumab therapy: a case report and review of the literature. *Intern Med* 2015; 54: 847–851.
24. Ohnishi H, Yokoyama A, Kondo K, *et al*. Comparative study of KL-6, surfactant protein-A, surfactant protein-D, and monocyte chemoattractant protein-1 as serum markers for interstitial lung diseases. *Am J Respir Crit Care Med* 2002; 165: 378–381.
25. Nakajima H, Harigai M, Hara M, *et al*. KL-6 as a novel serum marker for interstitial pneumonia associated with collagen diseases. *J Rheumatol* 2000; 27: 1164–1170.
26. Furukawa H, Oka S, Takehana K, *et al*. Plasma amino acid profiles in collagen disease patients with interstitial lung disease. *Immunome Res* 2013; 9: 1000064.
27. Furukawa H, Oka S, Shimada K, *et al*. Serum metabolomic profiles of rheumatoid arthritis patients with acute-onset diffuse interstitial lung disease. *Biomark Insights* 2019; 14: 1177271919870472.
28. Takamura A, Hirata S, Nagasawa H, *et al*. A retrospective study of serum KL-6 levels during treatment with biological disease-modifying antirheumatic drugs in rheumatoid arthritis patients: a report from the Ad Hoc Committee for Safety of Biological DMARDs of the Japan College of Rheumatology. *Mod Rheumatol* 2013; 23: 297–303.
29. Harigai M, Takamura A, Atsumi T, *et al*. Elevation of KL-6 serum levels in clinical trials of tumor necrosis factor inhibitors in patients with rheumatoid arthritis: a report from the Japan College of Rheumatology Ad Hoc Committee for Safety of Biological DMARDs. *Mod Rheumatol* 2013; 23: 284–296.
30. Suda T and Tokuda H. [Series: diagnosis at a glance]. *Nihon Naika Gakkai Zasshi* 2016; 105: 1414–1421.
31. Tokuda H, Harigai M, Kameda H, *et al*. *Consensus statements for medical practice: biological agents and lung disease*. Tokyo: The Japanese Respiratory Society, 2014, pp.81–87.
32. Zheng M, Lou A, Zhang H, *et al*. Serum KL-6, CA19-9, CA125 and CEA are diagnostic biomarkers for rheumatoid arthritis-associated interstitial lung disease in the Chinese population. *Rheumatol Ther* 2021; 81: 517–527.
33. Fotoh DS, Helal A, Rizk MS, *et al*. Serum Krebs von den Lungen-6 and lung ultrasound B lines as potential diagnostic and prognostic factors for rheumatoid arthritis-associated interstitial lung disease. *Clin Rheumatol*. Epub ahead of print 21 January 2021. DOI: 10.1007/s10067-021-05585-y.
34. Avouac J, Cauvet A, Steelandt A, *et al*. Improving risk-stratification of rheumatoid arthritis patients for interstitial lung disease. *PLoS One* 2020; 15: e0232978.
35. Mochizuki T, Ikari K, Yano K, *et al*. Long-term deterioration of interstitial lung disease in patients with rheumatoid arthritis treated with abatacept. *Mod Rheumatol* 2019; 29: 413–417.

36. Bongartz T, Nannini C, Medina-Velasquez YF, *et al.* Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 2010; 62: 1583–1591.
37. Gochuico BR, Avila NA, Chow CK, *et al.* Progressive preclinical interstitial lung disease in rheumatoid arthritis. *Arch Intern Med* 2008; 168: 159–166.
38. Hozumi H, Nakamura Y, Johkoh T, *et al.* Acute exacerbation in rheumatoid arthritis-associated interstitial lung disease: a retrospective case control study. *BMJ Open* 2013; 3: e003132.
39. Kim EJ, Elicker BM, Maldonado F, *et al.* Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J* 2010; 35: 1322–1328.
40. Nurmi HM, Purokivi MK, Kärkkäinen MS, *et al.* Are risk predicting models useful for estimating survival of patients with rheumatoid arthritis-associated interstitial lung disease? *BMC Pulm Med* 2017; 17: 16.
41. Nurmi HM, Kettunen HP, Suoranta SK, *et al.* Several high-resolution computed tomography findings associate with survival and clinical features in rheumatoid arthritis-associated interstitial lung disease. *Respir Med* 2018; 134: 24–30.
42. Yamakawa H, Sato S, Tsumiyama E, *et al.* Predictive factors of mortality in rheumatoid arthritis-associated interstitial lung disease analysed by modified HRCT classification of idiopathic pulmonary fibrosis according to the 2018 ATS/ERS/JRS/ALAT criteria. *J Thorac Dis* 2019; 11: 5247–5257.
43. Kim HC, Lee JS, Lee EY, *et al.* Risk prediction model in rheumatoid arthritis-associated interstitial lung disease. *Respirology* 2020; 25: 1257–1264.
44. Kim HC, Choi KH, Jacob J, *et al.* Prognostic role of blood KL-6 in rheumatoid arthritis-associated interstitial lung disease. *PLoS One* 2020; 15: e0229997.
45. Tanaka N, Nishimura K, Waki D, *et al.* Annual variation rate of KL-6 for predicting acute exacerbation in patients with rheumatoid arthritis-associated interstitial lung disease. *Mod Rheumatol* 2021; 25: 1–12.
46. d'Alessandro M, Perillo F, Metella Refini R, *et al.* Efficacy of baricitinib in treating rheumatoid arthritis: modulatory effects on fibrotic and inflammatory biomarkers in a real-life setting. *Int Immunopharmacol* 2020; 86: 106748.
47. Mori S, Koga Y and Sugimoto M. Different risk factors between interstitial lung disease and airway disease in rheumatoid arthritis. *Respir Med* 2012; 106: 1591–1599.
48. Bernstein EJ, Barr RG, Austin JHM, *et al.* Rheumatoid arthritis-associated autoantibodies and subclinical interstitial lung disease: the multi-ethnic study of atherosclerosis. *Thorax* 2016; 71: 1082–1090.
49. Joshua V, Hensvold AH, Reynisdottir G, *et al.* Association between number and type of different ACPA fine specificities with lung abnormalities in early, untreated rheumatoid arthritis. *RMD Open* 2020; 6: e001278.
50. Zhu J, Zhou Y, Chen X, *et al.* A metaanalysis of the increased risk of rheumatoid arthritis-related pulmonary disease as a result of serum anticitrullinated protein antibody positivity. *J Rheumatol* 2014; 41: 1282–1289.
51. Solomon JJ, Matson S, Kelmenson LB, *et al.* IgA antibodies directed against citrullinated protein antigens are elevated in patients with idiopathic pulmonary fibrosis. *Chest* 2020; 157: 1513–1521.
52. Roos Ljungberg K, Joshua V, Skogh T, *et al.* Secretory anti-citrullinated protein antibodies in serum associate with lung involvement in early rheumatoid arthritis. *Rheumatology (Oxford)* 2020; 59: 852–859.
53. Fischer A, Solomon JJ, du Bois RM, *et al.* Lung disease with anti-CCP antibodies but not rheumatoid arthritis or connective tissue disease. *Respir Med* 2012; 106: 1040–1047.
54. Gizinski AM, Mascolo M, Loucks JL, *et al.* Rheumatoid arthritis (RA)-specific autoantibodies in patients with interstitial lung disease and absence of clinically apparent articular RA. *Clin Rheumatol* 2009; 28: 611–613.
55. Bongartz T, Cantaert T, Atkins SR, *et al.* Citrullination in extra-articular manifestations of rheumatoid arthritis. *Rheumatology (Oxford)* 2007; 46: 70–75.
56. Klareskog L, Malmstrom V, Lundberg K, *et al.* Smoking, citrullination and genetic variability in the immunopathogenesis of rheumatoid arthritis. *Semin Immunol* 2011; 23: 92–98.
57. Castellanos-Moreira R, Rodríguez-García SC, Gomara MJ, *et al.* Anti-carbamylated proteins antibody repertoire in rheumatoid arthritis: evidence of a new autoantibody linked to interstitial lung disease. *Ann Rheum Dis* 2020; 79: 587–594.
58. Alunno A, Bistoni O, Pratesi F, *et al.* Anti-citrullinated alpha enolase antibodies, interstitial lung disease and bone erosion in rheumatoid

arthritis. *Rheumatology (Oxford)* 2018; 57: 850–855.

59. Liu Y, Liu C, Li L, *et al*. High levels of antibodies to citrullinated α-enolase peptide-1 (CEP-1) identify erosions and interstitial lung disease (ILD) in a Chinese rheumatoid arthritis cohort. *Clin Immunol* 2019; 200: 10–15.
60. Harlow L, Rosas IO, Gochuico BR, *et al*. Identification of citrullinated hsp90 isoforms as novel autoantigens in rheumatoid arthritis-associated interstitial lung disease. *Arthritis Rheum* 2013; 65: 869–879.
61. England BR, Duryee MJ, Roul P, *et al*. Malondialdehyde-acetaldehyde adducts and antibody responses in rheumatoid arthritis-associated interstitial lung disease. *Arthritis Rheumatol* 2019; 71: 1483–1493.
62. Koga T, Fujikawa K, Horai Y, *et al*. The diagnostic utility of anti-melanoma differentiation-associated gene 5 antibody testing for predicting the prognosis of Japanese patients with DM. *Rheumatology (Oxford)* 2012; 51: 1278–1284.
63. Hamaguchi Y, Fujimoto M, Matsushita T, *et al*. Common and distinct clinical features in adult patients with anti-aminoacyl-tRNA synthetase antibodies: heterogeneity within the syndrome. *PLoS One* 2013; 8: e60442.
64. Sato S, Hoshino K, Satoh T, *et al*. RNA helicase encoded by melanoma differentiation-associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: association with rapidly progressive interstitial lung disease. *Arthritis Rheum* 2009; 60: 2193–2200.
65. Matsushita T, Hasegawa M, Fujimoto M, *et al*. Clinical evaluation of anti-aminoacyl tRNA synthetase antibodies in Japanese patients with dermatomyositis. *J Rheumatol* 2007; 34: 1012–1018.
66. Popovsky MA and Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. *Transfusion* 1985; 25: 573–577.
67. Silliman CC, Ambruso DR and Boshkov LK. Transfusion-related acute lung injury. *Blood* 2005; 105: 2266–2273.
68. Furukawa H, Oka S, Shimada K, *et al*. Autoantibody profiles in collagen disease patients with interstitial lung disease (ILD): antibodies to major histocompatibility complex class I-related chain A (MICA) as markers of ILD. *Biomark Insights* 2015; 10: 63–73.
69. Tanaka Y, Komori H, Mori S, *et al*. Evaluating the role of rheumatoid factors for the development of rheumatoid arthritis in a mouse model with a newly established ELISA system. *Tohoku J Exp Med* 2010; 220: 199–206.
70. Seibold MA, Wise AL, Speer MC, *et al*. A common MUC5B promoter polymorphism and pulmonary fibrosis. *N Engl J Med* 2011; 364: 1503–1512.
71. Putman RK, Rosas IO and Hunninghake GM. Genetics and early detection in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2014; 189: 770–778.
72. Juge PA, Borie R, Kannengiesser C, *et al*. Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis. *Eur Respir J* 2017; 49: 1602314.
73. Stock CJ, Sato H, Fonseca C, *et al*. Mucin 5B promoter polymorphism is associated with idiopathic pulmonary fibrosis but not with development of lung fibrosis in systemic sclerosis or sarcoidosis. *Thorax* 2013; 68: 436–441.
74. Helling BA, Gerber AN, Kadiyala V, *et al*. Regulation of MUC5B expression in idiopathic pulmonary fibrosis. *Am J Respir Cell Mol Biol* 2017; 57: 91–99.
75. Peljto AL, Zhang Y, Fingerlin TE, *et al*. Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. *JAMA* 2013; 309: 2232–2239.
76. Shirai Y, Honda S, Ikari K, *et al*. Association of the RPA3-UMAD1 locus with interstitial lung diseases complicated with rheumatoid arthritis in Japanese. *Ann Rheum Dis* 2020; 79: 1305–1309.
77. Cohen JC, Kiss RS, Pertsemlidis A, *et al*. Multiple rare alleles contribute to low plasma levels of HDL cholesterol. *Science* 2004; 305: 869–872.
78. Wang N, Zhang Q, Jing X, *et al*. The association between MUC5B mutations and clinical outcome in patients with rheumatoid arthritis-associated interstitial lung disease: a retrospective exploratory study in China. *Med Sci Monit* 2019; 26: e920137.
79. Konishi K, Gibson KF, Lindell KO, *et al*. Gene expression profiles of acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009; 180: 167–175.
80. Furukawa H, Oka S, Shimada K, *et al*. Role of deleterious rare alleles for acute-onset diffuse interstitial lung disease in collagen diseases. *Clin Med Insights Circ Respir Pulm Med*. Epub ahead of print 30 July 2019. DOI: 10.1177/1179548419866443.

81. Varpela E, Tiilikainen A, Varpela M, *et al*. High prevalences of HLA-B15 and HLA-Dw6 in patients with cryptogenic fibrosing alveolitis. *Tissue Antigens* 1979; 14: 68–71.

82. Charles PJ, Sweatman MC, Markwick JR, *et al*. HLA-B40: a marker for susceptibility to lung disease in rheumatoid arthritis. *Dis Markers* 1991; 9: 97–101.

83. Libby DM, Gibofsky A, Fotino M, *et al*. Immunogenetic and clinical findings in idiopathic pulmonary fibrosis. Association with the B-cell alloantigen HLA-DR2. *Am Rev Respir Dis* 1983; 127: 618–622.

84. Xue J, Gochuico BR, Alawad AS, *et al*. The HLA class II Allele DRB1*1501 is over-represented in patients with idiopathic pulmonary fibrosis. *PLoS One* 2011; 6: e14715.

85. Aquino-Galvez A, Perez-Rodriguez M, Camarena A, *et al*. MICA polymorphisms and decreased expression of the MICA receptor NKG2D contribute to idiopathic pulmonary fibrosis susceptibility. *Hum Genet* 2009; 125: 639–648.

86. Gregersen PK, Silver J and Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum* 1987; 30: 1205–1213.

87. Migita K, Nakamura T, Koga T, *et al*. HLA-DRB1 alleles and rheumatoid arthritis-related pulmonary fibrosis. *J Rheumatol* 2010; 37: 205–207.

88. Turesson C, Schaid DJ, Weyand CM, *et al*. The impact of HLA-DRB1 genes on extra-articular disease manifestations in rheumatoid arthritis. *Arthritis Res Ther* 2005; 7: R1386–R1393.

89. Oka S, Furukawa H, Kawasaki A, *et al*. Protective effect of the *HLA-DRB1*13:02* allele in Japanese rheumatoid arthritis patients. *PLoS One* 2014; 9: e99453.

90. Furukawa H, Oka S, Shimada K, *et al*. HLA-A*31:01 and methotrexate-induced interstitial lung disease in Japanese rheumatoid arthritis patients: a multi-drug hypersensitivity marker? *Ann Rheum Dis* 2013; 72: 153–155.

91. Bluett J, Owens S, Massey J, *et al*. HLA-A 31:01 is not associated with the development of methotrexate pneumonitis in the UK population: results from a genome wide association study. *Ann Rheum Dis* 2017; 76: e51.

92. Schetter AJ, Okayama H and Harris CC. The role of microRNAs in colorectal cancer. *Cancer J* 2012; 18: 244–252.

93. Duroux-Richard I, Jorgensen C and Apparailly F. What do microRNAs mean for rheumatoid arthritis? *Arthritis Rheum* 2012; 64: 11–20.

94. Murata K, Furu M, Yoshitomi H, *et al*. Comprehensive microRNA analysis identifies miR-24 and miR-125a-5p as plasma biomarkers for rheumatoid arthritis. *PLoS One* 2013; 8: e69118.

95. Li P, Li J, Chen T, *et al*. Expression analysis of serum microRNAs in idiopathic pulmonary fibrosis. *Int J Mol Med* 2014; 33: 1554–1562.

96. Yang G, Yang L, Wang W, *et al*. Discovery and validation of extracellular/circulating microRNAs during idiopathic pulmonary fibrosis disease progression. *Gene* 2015; 562: 138–144.

97. Oka S, Furukawa H, Shimada K, *et al*. Plasma miRNA expression profiles in rheumatoid arthritis associated interstitial lung disease. *BMC Musculoskelet Disord* 2017; 18: 21.

98. Zhou W, Zheng J, Yuan M, *et al*. Differentially expressed lncRNAs in peripheral blood mononuclear cells from middle-aged female patients with rheumatoid arthritis-associated interstitial lung disease. *Clin Rheumatol* 2020; 39: 2281–2289.

99. Ricou B, Nicod L, Lacraz S, *et al*. Matrix metalloproteinases and TIMP in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; 154: 346–352.

100. Suga M, Iyonaga K, Okamoto T, *et al*. Characteristic elevation of matrix metalloproteinase activity in idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2000; 162: 1949–1956.

101. Ohbayashi H. Matrix metalloproteinases in lung diseases. *Curr Protein Pept Sci* 2002; 3: 409–421.

102. Rosas IO, Richards TJ, Konishi K, *et al*. MMP1 and MMP7 as potential peripheral blood biomarkers in idiopathic pulmonary fibrosis. *PLoS Med* 2008; 5: e93.

103. Fujishima S, Shiomi T, Yamashita S, *et al*. Production and activation of matrix metalloproteinase 7 (matrilysin 1) in the lungs of patients with idiopathic pulmonary fibrosis. *Arch Pathol Lab Med* 2010; 134: 1136–1142.

104. Richards TJ, Kaminski N, Baribaud F, *et al*. Peripheral blood proteins predict mortality in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2012; 185: 67–76.

105. Doyle TJ, Patel AS, Hatabu H, *et al*. Detection of rheumatoid arthritis-interstitial lung disease is

enhanced by serum biomarkers. *Am J Respir Crit Care Med* 2015; 191: 1403–1412.

106. Chen J, Doyle TJ, Liu Y, *et al*. Biomarkers of rheumatoid arthritis-associated interstitial lung disease. *Arthritis Rheumatol* 2015; 67: 28–38.

107. Matsuo T, Hashimoto M, Ito I, *et al*. Interleukin-18 is associated with the presence of interstitial lung disease in rheumatoid arthritis: a cross-sectional study. *Scand J Rheumatol* 2019; 48: 87–94.

108. Wu X, Xu L, Cheng Q, *et al*. Increased serum soluble programmed death ligand 1(sPD-L1) is associated with the presence of interstitial lung disease in rheumatoid arthritis: a monocentric cross-sectional study. *Respir Med* 2020; 166: 105948.

109. Hussein MS, El-Barbary AM, Nada DW, *et al*. Identification of serum interleukin-13 and interleukin-13 receptor subunit expressions: rheumatoid arthritis-associated interstitial lung disease. *Int J Rheum Dis* 2021; 24: 591–598.

110. Kass DJ, Nouraie M, Glassberg MK, *et al*. Comparative profiling of serum protein biomarkers in rheumatoid arthritis-associated interstitial lung disease and idiopathic pulmonary fibrosis. *Arthritis Rheumatol* 2020; 72: 409–419.

111. Nakatsuka Y, Handa T, Nakashima R, *et al*. Serum matrix metalloproteinase levels in polymyositis/dermatomyositis patients with interstitial lung disease. *Rheumatology (Oxford)*. Epub ahead of print 8 March 2019. DOI: 10.1093/rheumatology/kez065.

112. Moinzadeh P, Krieg T, Hellmich M, *et al*. Elevated MMP-7 levels in patients with systemic sclerosis: correlation with pulmonary involvement. *Exp Dermatol* 2011; 20: 770–773.

113. Nishiumi S, Kobayashi T, Ikeda A, *et al*. A novel serum metabolomics-based diagnostic approach for colorectal cancer. *PLoS One* 2012; 7: e40459.

114. Coras R, Murillo-Saich JD and Guma M. Circulating pro- and anti-inflammatory metabolites and its potential role in rheumatoid arthritis pathogenesis. *Cells* 2020; 9: 827.

115. Zhao YD, Yin L, Archer S, *et al*. Metabolic heterogeneity of idiopathic pulmonary fibrosis: a metabolomic study. *BMJ Open Respir Res* 2017; 4: e000183.

116. Kang YP, Lee SB, Lee JM, *et al*. Metabolic profiling regarding pathogenesis of idiopathic pulmonary fibrosis. *J Proteome Res* 2016; 15: 1717–1724.

117. Rindlisbacher B, Schmid C, Geiser T, *et al*. Serum metabolic profiling identified a distinct metabolic signature in patients with idiopathic pulmonary fibrosis – a potential biomarker role for LysoPC. *Respir Res* 2018; 19: 7.

118. Furukawa H, Oka S, Shimada K, *et al*. Serum metabolomic profiling in rheumatoid arthritis patients with interstitial lung disease: a case-control study. *Front Med (Lausanne)* 2020; 7: 599794.

119. Chen Q, Chen DY, Xu XZ, *et al*. Platelet/lymphocyte, lymphocyte/monocyte, and neutrophil/lymphocyte ratios as biomarkers in patients with rheumatoid arthritis and rheumatoid arthritis-associated interstitial lung disease. *Med Sci Monit* 2019; 25: 6474–6481.