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Peripheral Blood Biomarkers for Rheumatoid Arthritis–Associated Interstitial Lung Disease: A Systematic Review

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Background. Biomarkers have been proposed as tools to aid in the identification and prognostication of interstitial lung disease (ILD) in rheumatoid arthritis (RA). We performed a systematic review of studies evaluating peripheral blood biomarkers and their association with RA-ILD and its prognosis.

Methods. Medline, Embase, the Cochrane Library, and Scopus were queried for relevant studies, with the final search update on July 12, 2021. We included studies evaluating peripheral blood biomarkers for the identification and/or prognostication of RA-ILD, extracting the performance of individual biomarkers for identifying RA-ILD, and predicting prognosis. Modified versions of the Quality Assessment of Diagnostic Accuracy Studies 2 and the Quality in Prognosis Studies tools were used for quality assessment.

Results. Seventy studies met eligibility criteria. Study and patient characteristics, analytical methods, strength and consistency of associations, and study quality were heterogeneous. A total of 92 biomarkers were positively associated and 12 were negatively associated with RA-ILD among patients with RA in one or more report. Only a small number of biomarkers were evaluated in multiple cohorts using adjusted analyses. Biomarkers most strongly associated with RA-ILD overlapped with those identified for idiopathic pulmonary fibrosis. Few prognostic biomarkers of RA-ILD were identified.

Conclusion. Several peripheral blood biomarkers are associated with the presence of RA-ILD, but few have been assessed in multivariable models, have been externally validated, have discriminated RA-ILD from other lung disease, or have prognosticated the disease course. High-quality studies investigating and validating peripheral biomarkers in RA-ILD are needed before they can be employed in clinical care.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by small joint synovitis that is estimated to affect 0.3% to 1% of the global population (1,2). Extraarticular disease may occur in up to 50% of patients with RA, with pulmonary manifestations among the most common extraarticular features. Interstitial lung disease (ILD) clinically affects up to 10% of patients with RA and subclinically affects up to 40% (3–7). The pathogenesis of RA-associated ILD (RA-ILD) is complex

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and incompletely understood, with evidence supporting autoimmunity, dysregulated inflammatory and fibrotic pathways, and oxidative stress in a genetically susceptible host (8,9). RA-ILD typically presents as a usual interstitial pneumonia (UIP) or nonspecific interstitial pneumonia pattern (3,4,10–13). Diagnosis requires a thorough evaluation, including laboratory and imaging studies; pulmonary function testing (PFT); medication review; occasionally, tissue histopathology; and frequently, multidisciplinary input. Prompt recognition of RA-ILD is crucial because it warrants close monitoring and often necessitates therapeutic alterations (4,14–16). Although overall survival of patients with RA has improved over the last few decades, respiratory disease remains one of the leading causes of death, and RA-ILD is associated with a marked reduction in survival compared with RA without ILD, illustrating the need for improved diagnostic and therapeutic modalities (17–19).

Biomarkers are a promising area of investigation in RA-ILD because they have the potential to advance pathophysiologic understanding and elucidate therapeutic targets, improve disease identification and diagnostic accuracy, facilitate prognostication, and inform treatment decisions. Although imaging and histopathology have important roles that are unlikely to be replaced by biomarkers, they can be nonspecific in RA-ILD, can be impractical to obtain in certain settings, and cannot be scaled for population health efforts (8,12,14). Peripheral blood biomarkers, which are more practical in both clinical and population health settings, are of particular interest. Numerous biomarkers, including autoantibodies, cytokines, lung epithelial–related proteins (eg, surfactant proteins and mucins), and genetic polymorphisms, have been recognized as candidates for identifying and/or prognosticating RA-ILD (20,21). Although promising, the evidence supporting these biomarkers has not been rigorously assessed, which is necessary before they can be used clinically.

We aimed to perform a systematic literature review of peripheral blood biomarkers in RA-ILD. Our objectives were to synthesize the evidence concerning these biomarkers' ability to 1) differentiate RA-ILD from RA without ILD, 2) differentiate RA-ILD from other lung diseases, and 3) prognosticate RA-ILD disease course.

MATERIALS AND METHODS

We conducted a systematic literature review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (22). We registered the systematic literature review protocol with PROSPERO (identifier: CRD42019137143), an international prospective registry of systematic reviews.

Search strategy. A medical librarian (CS) searched Medline (via EBSCOhost), the Cochrane Library (via Wiley), Embase (1974-present version via embase.com), and Scopus. She also searched PubMed for recently indexed records and unindexed records because these appear in PubMed earlier than they appear in Medline via EBSCOhost. The initial searches were conducted on April 25, 2019, and several search updates were performed. The last search update took place on July 12, 2021.

Both keywords and subject headings (when available) were used for each of the following three search concepts: RA, ILD, and biomarkers. The terms used for the biomarker concept included terms (subject headings and keywords) for the general biomarker concept as well as terms for the individual potential RA-ILD-associated biomarkers that had been identified by pilot searches. A few additional biomarkers were identified by the first attempt at an exhaustive search. Terms for these biomarkers were added to the search strategies. Because no funds were available for translation, English-language filters were applied to the searches. Publication-type filters were used to remove editorials, review articles, and conference abstracts. Publication-type filters were used (when available) to separate the remaining records into three groups: 1) systematic reviews and meta-analyses, 2) case reports, and 3) other articles. Complete search strategies are included in Supplementary Material 1.

A total of 1604 records were retrieved by the initial search and search updates. This total included 34 records from the Cochrane Library, 485 records from Embase, 435 records from EBSCOhost Medline, 181 records from PubMed, and 469 records from Scopus. The RefWorks duplicate detection tool was used to identify and remove 690 duplicate records. Records for 914 unique publications remained for review. We also reviewed the reference lists of other pertinent systematic reviews and meta-analyses and identified 10 additional potentially relevant studies.

Study selection. We included the results of published literature on peripheral blood biomarkers in the English language. Case reports, case series, studies with less than 20 participants with RA-ILD, review articles, practice guidelines, systematic reviews, meta-analyses, editorials, articles not reporting results specifically for RA-ILD (eg, combining RA-ILD with other connective tissue disease–associated ILD), and articles published prior to 1990 (because of differences in the assessment of ILD during this time period) were excluded. Four authors (AE, DS, DVK, and RB) independently reviewed titles, abstracts, and full texts to determine eligibility for inclusion. Disagreements were settled by a third reviewer (BRE). Full texts of the included studies were stored in an EndNote library.

Data extraction. Three authors (DS, DVK, and RB) extracted relevant study data, including study characteristics, patient characteristics, and the performance of the biomarker(s) studied. Training in data abstraction was performed by abstracting one study in tandem and then abstracting five studies in duplicate and comparing results. Study characteristics extracted

consisted of country(ies) of study participants, study design, sample size (including the number with RA-ILD), sample handling, method of biomarker measurement, inclusion and exclusion criteria, and criteria for RA and ILD diagnosis. Patient characteristics extracted included age, sex, race and/or ethnicity, smoking status, RA and ILD disease severity, RA disease duration, and serological status. Study outcomes were collected for identification of RA-ILD compared with RA without ILD, identification of RA-ILD compared with other lung diseases, and the prognostication of RA-ILD (PFT and/or radiographic progression, respiratory events, and all-cause or respiratory-related mortality). Abstracted data were organized in an Excel spreadsheet. Performance data across studies were summarized descriptively for each biomarker. Heterogeneity in these results precluded a formal meta-analysis. When studies performed both adjusted and unadjusted analyses for a given biomarker, results of the adjusted analysis were reported. Because terminology varied across studies, we used RA-ILD to encompass RA-associated interstitial pneumonia and RA-associated pulmonary fibrosis. Because of variability between studies, the following terms were used interchangeably unless otherwise specified: titers and concentration; anti–cyclic citrullinated peptides (anti-CCPs) and anti–citrullinated protein antibodies.

Quality assessment. Study quality was assessed by three authors (DS, DVK, and RB) using a modified Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool for diagnostic studies and the Quality in Prognosis Studies (QUIPS) tool for prognostic studies (23,24). We added a statistical analysis domain to the QUADAS-2 tool to enable a more thorough assessment for risk of bias related to confounding and considered the risk of bias to be low if analyses were adjusted for appropriate confounders (eg, age, sex, smoking history, and RA disease characteristics) and high if analyses were unadjusted. Risk of bias was reported as unclear, low, or high for studies being evaluated with QUADAS-2 and as low, moderate, or high for studies being evaluated with QUIPS. Training in quality assessment was done using the same method as for training in data abstraction.

RESULTS

Study identification and study characteristics. The literature search revealed 924 articles after deduplication, with 70 meeting inclusion criteria (Supplementary Figure 1). Included studies were from 12 different countries and most often used a cross-sectional study design (Table 1). RA was typically classified using the 1987 American College of Rheumatology (ACR) criteria or the 2010 ACR/European League Against Rheumatism (EULAR) criteria. ILD assessment was variable; although many studies used chest computed tomography (CT), they differed in the number and type of assessors interpreting the CT findings, the type of CT performed, and whether other criteria were employed, such as PFTs, specialist diagnoses, multidisciplinary discussion, or review of medical records. The majority of studies analyzed serum samples, with enzyme-linked immunosorbent assay being the most common biomarker measurement method. Sample handling processes were rarely specified.

Sample sizes of individual studies ranged from 60 to 6682 overall, with the number of patients with RA-ILD ranging from 20 to 620 (Table 2). The mean age of participants was generally in the sixth or seventh decade. Patients were most frequently of White or Asian race. There was a strong female predominance among patients with RA (approximately 60%-70% female), but this was attenuated in the patients with RA-ILD (approximately 50%-60% female). The proportion of patients who had a smoking history varied across studies, but patients with RA-ILD were consistently more likely to have a history of smoking than patients with RA without ILD. RA disease duration was more than 8 years in most studies. Severity measures for RA and ILD were not consistently reported.

Peripheral biomarkers that differentiated RA-ILD from RA without ILD. From the 70 included studies, we identified 104 unique biomarkers that were able to differentiate RA-ILD from RA without ILD in at least one analysis. These included cytokines and chemokines (n = 25), autoantibodies (n = 21), genetic markers (n = 15), growth factors (n = 8), extracellular matrix proteins (n = 5), tumor markers (n = 5), lung epithelial or surfactant proteins (n = 2), and those classified as "other" (n = 23) (Table 3). Of these biomarkers, 56 were associated with the presence of RA-ILD in at least one adjusted analysis, 14 were associated with RA-ILD in two or more studies, and six were associated with RA-ILD in two or more studies with at least one being adjusted (rheumatoid factor [RF], anti-CCP, Krebs von den Lungen 6 [KL-6], surfactant protein D [SP-D], carbohydrate antigen 19-9 [CA-19-9], and matrix metalloproteinase 7 [MMP-7]). Twelve biomarkers had a negative association with RA-ILD, including human leukocyte antigen (HLA)–DR4.

RF and anti-CCP were the most frequently studied autoantibodies, with conflicting findings for both (Supplementary Table 1). Although several studies, including those with adjusted analyses, found these autoantibodies to be more prevalent or present in higher concentrations in RA-ILD, a nearly equal number of others found no association. KL-6 (a mucin-like glycoprotein also referred to as MUC1) and SP-D (a collectin expressed in pulmonary epithelia), together categorized as lung epithelial and surfactant protein biomarkers, were both associated with RA-ILD in the majority of analyses. CA-19-9 and soluble programmed death ligand 1 (sPD-L1) were the most promising tumor markers, with both having an association with RA-ILD in a multivariable analysis, though only CA-19-9 was validated in another study (25–28). Most cytokines and growth factors were evaluated in a single study using a broad multianalyte biomarker discovery approach in two independent cohorts, with modest consistency of findings

Table 1. Study characteristics

Author, year (citation)	Country	Study design	Biomarkers	Sample type/measurement method	Inclusion/exclusion criteria	ILD ascertainment
Abdel-Wahab et al, 2016 (52)	Egypt	Cross-sectional	IL-33	Serum/ELISA	1987 ACR criteria/liver disease, prior anaphylaxis or ischemia, other rheumatologic disease	HRCT
Alunno et al, 2018 (53)	Italy	Cross-sectional	Anti-CEP-1	Serum/ELISA	2010 ACR/EULAR criteria/not specified	CXR, HRCT
Alunno et al, 2018 (54)	Italy	Cross-sectional	Anti-CEP-1	Serum/ELISA	1987 ACR criteria/not specified	Clinical and radiological records
Avouac et al, 2020 (38)	France	Cross-sectional	Anti-CCP, KL-6, CCL18, SP-D	Serum/ELISA	1987 ACR or 2010 ACR/EULAR criteria/not specified	HRCT by one to two blinded investigators
Bao et al, 2021 (55)	China	Cross-sectional	CA-19-9, CA-125, CEA, CA-153, CYFRA21-1	Serum/not specified	RA, SS, SLE, IM, SSc, or MCTD/overlap syndromes, multiple autoimmune diseases, malignancy, sarcoidosis, amyloidosis, severe infection, and/or severe liver or kidney disease	HRCT by one blinded investigator
Castellanos-Moreira et al, 2020 (56)	Spain	Cross-sectional	Anti-FCS IgG, anti-Fib IgG, anti-CFFHP IgG, anti-FCS IgA, RF, anti-CCP	Serum/ELISA, nephelometry, chemiluminescent immunoassay	2010 ACR/EULAR criteria/other inflammatory arthritis or CTD	HRCT confirmation by multidisciplinary committee
Chen et al, 2015 (30)	China, USA	Cross-sectional	RF, anti-CCP, MMP-7, IP-10	Serum/ELISA	1987 ACR criteria/indeterminate CT findings	HRCT agreement between two blinded reviewers, PFT
Chen et al, 2019 (57)	China	Cross-sectional	Platelet/lymphocyte ratio, lymphocyte/monocyte ratio, neutrophil/lymphocyte ratio, ESR	Serum/automatic blood counting system	1987 ACR or 2010 ACR/EULAR criteria/cancer, severe infections, cardiovascular disease, systemic blood disease, or other diseases	HRCT
Correia et al, 2019 (58)	USA	Cross-sectional	Anti-CCP	Serum/ELISA	2010 ACR/EULAR criteria or RA diagnosed by rheumatologist/other rheumatologic disease, occupational exposure, or thoracic radiation	Clinical diagnosis by pulmonologist, CT, PFT
Darrah et al, 2018 (59)	USA	Cross-sectional	Anti-PAD2	Serum/ELISA	ESCAPE cohort, 1987 ACR criteria/not specified	MDCT by blinded radiologist
Del Angel-Pablo et al, 2020 (60)	Mexico	Case-control	Anti-HLA class II, LABScreen PRA, ESR, CRP, anti-CCP	Serum/fluorescence immunoassay	2010 ACR/EULAR criteria, ATS or ERS IIP criteria/not specified	HRCT
Doyle et al, 2015 (31)	USA	Cross-sectional	RF, anti-CCP, MMP-7, CCL18 (PARC), SP-D	Serum/ELISA, custom multiplex bead array assay	BRASS or ACR cohort, fulfilling ACR criteria/indeterminate or uninterpretable imaging	HRCT
England et al, 2019 (61)	USA	Cross-sectional	Anti-MAA antibody	Serum/ELISA	VARA registry, 1987 ACR criteria/RA-ILD development >2 years after registry enrollment	Medical record review: clinical diagnosis, imaging findings, and histopathology

(Continued)

Table 1. (*Cont'd*)

Author, year (citation)	Country	Study design	Biomarkers	Sample type/measurement method	Inclusion/exclusion criteria	ILD ascertainment
Fadda et al, 2018 (62)	Egypt	Cross-sectional	RF, anti-CCP	Serum/nephelometry, ELISA	2010 ACR/EULAR criteria/TB, hepatitis C, overlap syndromes, methotrexate pneumonitis	HRCT, PFT
Fotoh et al, 2021 (39)	USA	Case-control	KL-6, ESR, CRP	Serum/latex-enhanced immunoturbidimetric assay method, ELISA	2010 ACR criteria, age > 18 years, duration >3 years/pneumonia, multiple autoimmune diseases, heart failure, pulmonary surgery, respiratory infections, asthma, COPD, lung cancer, renal failure, and pregnancy	HRCT by same radiologist, PFT analysis according to ATS
Fu et al, 2018 (63)	China	Cross-sectional	LOXL2	Serum/ELISA	2010 ACR/EULAR criteria/other autoimmune, infectious, or neoplastic disease; lung surgery	HRCT reviewed by experienced work group
Fujita et al, 2020 (64)	Japan	Case-control	GAL-9, ACPA, RF, anti-CCP, MMP-3, ESR, CRP	Serum/ELISA	2010 ACR/EULAR criteria/ overlapping syndromes	HRCT by one blinded radiologist
Furukawa et al, 2012 (34)	Japan	Cross-sectional	RF, Anti-CCP, shared epitope	Not specified/latex agglutination, ELISA, PCR	1987 ACR criteria/other CTD, non-ILD findings on imaging	HRCT or CT reviewed by two specialized physicians
Furukawa et al, 2013 (65)	Japan	Cross-sectional	RF, LDH, CRP, KL-6, SP-D, amino acids	Plasma/not specified	1987 ACR criteria/steroid administration (≥15 mg/day prednisolone equivalent) or unavailable imaging	HRCT or CT with agreement by two specialized physicians
Furukawa et al, 2020 (66)	Japan	Case-control	Metabolomic profiles, RF, ACPA, KL-6, SP-D	Serum/nephelometry, ELISA, electrochemiluminescence immunoassay, capillary electrophoresis time-of-flight mass spectrometry	1987 ACR or 2010 ACR/EULAR criteria, CT images/not specified	CT or HRCT reviewed by two specialists in RA-ILD
Giles et al, 2014 (67)	USA	Cross-sectional	RF, anti-CCP, anti-PAD3/4XR, CRP, IL-6	Serum/custom radioimmunoassay	ESCAPE RA cohort, 1987 ACR criteria/not specified	MDCT by blinded radiologist
Giles et al, 2014 (68)	USA	Cross-sectional	RF, anti-CCP, shared epitope alleles, CRP, IL-6, specific ACPAs, anti-Fib A, anti-hsp60, anti-apolipoprotein A1, anti-apolipoprotein E	Serum/ELISA, nephelometry, custom Bio-Plex bead array	ESCAPE RA cohort, 1987 ACR criteria/not specified	HRCT by blinded pulmonary radiologist
Harlow et al, 2013 (69)	USA	Cross-sectional	Anti-cit-hsp90	Serum/ELISA	1987 ACR criteria/not specified	Radiograph, CT, PFT
Hillarby et al, 1993 (70)	UK	Cross-sectional	HLA-DQ and HLA-DR, C4 allotype	Serum, plasma/PCR, electrophoresis, immunofixation	1958 revised criteria/heart failure or pneumoconiosis	Clinical and radiographic findings
Hussein et al, 2021 (71)	Egypt	Cross-sectional	RF, anti-CCP, ESR, CRP, IL-13, KL-6, SP-D	Serum/Westergren method, ELISA, real-time quantitative PCR	2010 ACR/EULAR criteria/chronic chest disorders (asthma, COPD), TB, CHF	Pulmonologist diagnosis and two of the following three: CXR or CT, restrictive pattern PFTs, and/or lung biopsy

(Continued)

Table 1. (*Cont'd*)

Author, year (citation)	Country	Study design	Biomarkers	Sample type/measurement method	Inclusion/exclusion criteria	ILD ascertainment
Juge et al, 2018 (32)	Multinational	Cross-sectional	RF, anti-CCP, MUC5B rs35705950 promoter variant	Not specified/genotyping assay, PCR	1987 ACR or 2010 ACR/EULAR criteria/not specified	HRCT
Kass et al, 2019 (29)	USA	Cross-sectional	Numerous cytokines, growth factors, remodeling proteins	Serum/multiplex ELISA	1987 ACR criteria/not specified	Radiograph, HRCT
Kelly et al, 2014 (72)	UK	Case-control	RF, anti-CCP	Serum/not specified	2010 ACR/EULAR criteria/not specified	HRCT
Kim et al, 2020 (40)	Korea	Case-control	KL-6, RF	Plasma/latex-enhanced immunoturbidimetric assay	2010 ACR criteria, blood sample availability/not specified	HRCT, pathologic findings
Lai et al, 2019 (73)	China	Cross-sectional	RF, ACPA, ESR, CRP IgG, IgA, IgM, NK cells, T cells, B cells	Not specified/flow cytometry	1987 ACR criteria/other chronic respiratory disease, TB, lung nodules or tumors, other major organ dysfunction, heavy smoking or alcohol intake	HRCT
Lee et al, 2016 (41)	South Korea	Retrospective cohort	IL-6, IL-32, KL-6, MMP-7, SP-A	Plasma/ELISA	RA diagnosed by rheumatologist, fulfillment of revised ACR criteria/other rheumatologic disease, drug-induced lung disease, or < 1 year follow-up	Multidisciplinary team, HRCT, histopathology
Lee et al, 2019 (45)	South Korea	Cross-sectional	KL-6	Serum/immunoturbidimetry	Not specified/patients with overlapping syndromes or multiple autoimmune diseases	HRCT, PFT
Ma et al, 2019 (74)	China	Cross-sectional	RF, CXCL16	Serum/ELISA	2010 ACR/EULAR criteria/ infectious, cancer, and metabolic diseases	HRCT, PFT
Maniwa et al, 2000 (75)	Japan	Cross-sectional	IL-1a	Serum/radioimmunoassay	1987 ACR criteria/not specified	Imaging, PFT, histopathology
Matsuo et al, 2019 (76)	Japan	Cross-sectional	RF, CCP, IL-16, ANA, KL-6, MMP-3	Serum/ELISA	KURAMA cohort, 1987 ACR or 2010 ACR/EULAR criteria/not specified	CT
Matsushita et al, 2017 (77)	Japan	Cross-sectional	RF, anti-CCP, anti-aaRS antibody	Serum/latex agglutination, ELISA, line blot test kit	2010 ACR/EULAR criteria/not specified	Histopathology, CXR, HRCT
Mori et al, 2012 (78)	Japan	Cross-sectional	HLA-DRB1 alleles, RF, anti-CCP	Serum/ELISA, nephelometry, PCR	1987 ACR criteria/history of occupational exposure or thoracic radiation	HRCT
Nakajima et al, 2000 (79)	Japan	Cross-sectional	KL-6, CRP, LDH	Serum/ELISA	1987 ACR criteria/other pulmonary disease or malignancy	Clinical diagnosis, CT, PFT
Natalini et al, 2021 (80)	USA	Cross-sectional and retrospective cohort	RF, ACPA	Serum/ELISA, nephelometry	VARA registry, 1987 ACR criteria/ not specified	Provider diagnosis of ILD and CT evidence or lung biopsy
Newton et al, 2019 (37)	USA	Cross-sectional	MUC5B rs35705950, TOLLIP rs5743890, leukocyte telomere length	Peripheral blood leukocytes/ PCR, SNP genotyping assays	Rheumatologic evaluation/not specified	HRCT, histopathology

(Continued)

Table 1. (*Cont'd*)

Author, year (citation)	Country	Study design	Biomarkers	Sample type/measurement method	Inclusion/exclusion criteria	ILD ascertainment
Oka et al, 2016 (35)	Japan	Cross-sectional	RF, CCP, KL-6, HLA-DR2, HLA-DR4, shared epitope	Not specified/latex agglutination, ELISA, PCR	1987 ACR criteria, cross-sectional imaging/history of occupational exposure, thoracic radiation, or other predominant imaging finding	HRCT agreement between two specialized radiologists
Oka et al, 2017 (81)	Japan	Cross-sectional	SP-D, KL-6, miRNAs	Plasma/ELISA, RT-PCR	1987 ACR criteria/not specified	HRCT with agreement between two specialized physicians
Pulito-Cueto et al, 2020 (82)	Spain	Cross-sectional	CRP, ESR, RF, ACPA, endothelial progenitor cells (CD34+, $CD45^{low}$, CD309+, and CD133+)	Peripheral venous blood/flow cytometry	2010 ACR/EULAR criteria/not specified	HRCT by radiologist, ATS/ERS ILD criteria
Ren et al, 2021 (83)	China	Cross-sectional	ESR, CRP, IgG, IgM, IgA, CTGF	Serum/ELISA	2010 ACR/EULAR criteria or early RA criteria (defined by three of the following: morning stiffness ≥30 min, arthritis of ≥3 joints, arthritis of hands, and positive RF)	HRCT by radiologist, ATS/ERS ILD criteria
Restrepo et al, 2015 (84)	USA	Cross-sectional	RF, anti-CCP, shared epitope	Serum/ELISA, PCR	1987 ACR criteria/history of other pulmonary disease	Medical record review, clinical diagnosis, imaging, PFT, histopathology
Rocha-Muñoz et al, 2015 (85)	Mexico	Cross-sectional	RF, anti-CCP	Serum/ELISA	1987 ACR criteria/other pulmonary disease or psychiatric disorder	HRCT, PFT
Saku et al, 2021 (42)	Japan	Case-control	Monocytes, neutrophils, lymphocyte ratios, KL-6, SP-D, CRP, RF	Not specified/not specified	1987 or 2010 ACR/EULAR criteria/ other causes of pulmonary disorders	Clinical presentation, PFTs, or HRCT
Salaffi et al, 2019 (86)	Italy	Cross-sectional	ESR, CRP, ACPA, RF	Not specified	2010 ACR/EULAR criteria/ pulmonary infection, pulmonary hypertension, CHF, other significant pulmonary abnormalities on HRCT	HRCT by two experienced radiologists
Sargin et al, 2018 (26)	Turkey	Cross-sectional	RF, CA-125	Serum/not specified	2010 ACR/EULAR criteria/other connective tissue disease, TB, or pulmonary infection	Clinical diagnosis, PFT, imaging
Sargin et al, 2021 (87)	Turkey	Cross-sectional	Platelet indices, RF, anti-CCP, ESR, CRP	Not specified/Mindray BC-6800 hematology analyzer	2010 ACR/EULAR criteria/ <18 years, other autoimmune diseases, hematologic diseases, antiaggregant medication, malignancy, pulmonary infections	HRCT
Shen et al, 2019 (88)	China	Cross-sectional	Tumor markers, ESR, CRP, complement, immunoglobulins	Serum/not specified	PM/DM, SSc, CTD, MCTD, RA, SS, or SLE/other severe pulmonary disease (eg, sleep apnea, PAH)	HRCT by two blinded expert radiologists

(Continued)

Table 1. (*Cont'd*)

Author, year (citation)	Country	Study design	Biomarkers	Sample type/measurement method	Inclusion/exclusion criteria	ILD ascertainment
Sherin et al, 2019 (89)	Egypt	Cross-sectional	RF, vitamin D	Serum/latex agglutination, ELISA	2010 ACR/EULAR criteria/not specified	HRCT interpreted by radiologist and pulmonologist
Skare et al, 2011 (90)	Brazil	Cross-sectional	RF, anti-CCP, ANA	Not specified/not specified	1987 ACR criteria/COPD, TB, prior radiation, chest surgery	HRCT
Sokai et al, 2016 (46)	Japan	Cross-sectional	RF, anti-CCP, KL-6, SP-D	Not specified/not specified	1987 ACR criteria/no respiratory impedance, PFTs, or CT	HRCT evaluated by experienced radiologist
Solomon et al, 2020 (91)	USA	Cross-sectional	IgA-ACPA, IgG-ACPA	Serum/ELISA, nephelometry	RA (rheumatologist diagnosis), IPF (2018 ATS guidelines), HP (pulmonologist with expertise in ILD and multidisciplinary conference)/RA cohort (atypical mycobacterial infection); others not specified	HRCT with UIP or probable UIP evaluated by two independent expert thoracic radiologists
Wada et al, 2010 (92)	Japan	Cross-sectional	RF, ESR, CRP, ANCA	Serum/ELISA	1987 ACR criteria/not specified	HRCT evaluated by two experienced physicians
Wang et al, 2016 (27)	China	Cross-sectional	RF, CA-125, CA-15-3, CA-19-9	Not specified/not specified	1987 ACR criteria/current or prior neoplasm	HRCT with agreement by blinded radiologist and pulmonologist
Wang et al, 2019 (93)	China	Cross-sectional	TGFβ1	Serum/ELISA	1987 ACR criteria/not specified	Not specified
Wang et al, 2020 (33)	China	Retrospective cohort	ESR, RF, ACPA, MUC5B, ABCA3, SFTPC, PARN, RTEL1	Peripheral blood mononuclear cells/whole-exome sequencing	2010 ACR/EULAR criteria/ occupational or environmental exposure, drug use, other known causes of ILD	Clinical presentation, PFTs, and HRCT reviewed by radiologists and pulmonologists
Wang et al, 2021 (94)	China	Cross-sectional	IL-11	Serum/ELISA	1987 ACR or 2010 ACR/EULAR criteria/infection, malignancy, or other CTD	HRCT
Wen et al, 2018 (95)	China	Cross-sectional	LBP	Serum/ELISA	2010 ACR/EULAR criteria/not specified	Radiograph, PFT
Wu et al, 2020 (28)	China	Cross-sectional	sPD-L1, anti-CCP, RF, ESR, CRP, ferritin	Serum/ELISA	1987 ACR criteria/other ILD causes, chronic pulmonary diseases, infectious diseases, severe heart, lung, and renal dysfunction	HRCT and PFT
Xiangyang et al, 2012 (96)	China	Cross-sectional	IL-33	Serum/ELISA	1987 ACR criteria/not specified	HRCT
Xue et al, 2021 (97)	China	Retrospective cohort	DKK1, CRP	Serum/ELISA	ACR (year not specified)/not specified	2013 IIP classification (ATS/ERS criteria not specified)
Yang et al, 2019 (98)	Korea	Case-control	RF, anti-CCP, ESR, CRP	Not specified/ immunoturbidimetric assay, chemiluminescent microparticle immunoassay	1987 ACR criteria/not specified	2013 ATS/ERS IIP criteria

(Continued)

Table 1. (*Cont'd*)

Author, year (citation)	Country	Study design	Biomarkers	Sample type/measurement method	Inclusion/exclusion criteria	ILD ascertainment
Yin et al, 2014 (99)	China	Cross-sectional	RF, anti-CCP	Serum/ELISA	1987 ACR criteria/ILD prior to RA diagnosis, other chronic pulmonary disease, or incomplete medical record	HRCT by blinded radiologist
Yu et al, 2019 (36)	China	Cross-sectional	RF, CCP, anti-keratin, ESR, LDH, CRP, Wnt5a	Plasma, serum/ELISA	1987 ACR criteria, HRCT scan/ uninterpretable or indeterminate imaging, other pulmonary disease, unavailable serum, heart disease, severe heart, lung, or renal impairment	HRCT
Zhang et al, 2017 (100)	China	Retrospective cohort	RF, CCP	Not specified/not specified	1987 ACR criteria or 2010 ACR/EULAR criteria/other pulmonary disease, chronic liver or kidney disease, rheumatic heart disease, myocardial infarction, or other disease	HRCT
Zheng et al, 2021 (25)	China	Cross-sectional	KL-6, CA-19-9, CA-125, CEA, RF, anti-CCP, CRP, ESR	Serum/chemiluminescent microparticle immunoassay	1987 ACR criteria/other pulmonary disease, malignancy or diseases that affect tumor markers, recent infection of HIV, viral hepatitis	HRCT by two blinded radiologists and a respiratory surgeon
Zhou et al, 2020 (101)	China	Cross-sectional	lncRNA, RF, anti-CCP, ESR, CRP	Peripheral blood mononuclear cells/PCR, commercial lncRNA microarray	2010 ACR/EULAR criteria/male patients, elderly, smokers, other autoimmune disease, positive ANA, other respiratory disease, tumors, chronic liver or kidney disease, heart disease	Clinical, HRCT, and PFT interpreted by two physicians

Abbreviations: aaRS, aminoacyl–transfer RNA synthetase; ABCA, adenosine triphosphate-binding cassette sub-family A; ACPA, anti–citrullinated protein antibody; ACR, American College of Rheumatology; ANA, antinuclear antibody; ATS, American Thoracic Society; BRASS, Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study; CA, cancer or carbohydrate antigen; CCL, chemokine ligand; CCP, cyclic citrullinated peptide; CEA, carcinoembryonic antigen; CEP-1, citrullinated α-enolase peptide; CFFHP, chimeric fibrine/filagrine homocitrullinated peptide; CHF, congestive heart failure; cit-hsp, citrullinated heat shock protein; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, computed tomography; CTD, connective tissue disease; CTGF, connective tissue growth factor; CXCL, CXC chemokine ligand; CXR, chest radiograph; CYFRA21-1, cytokeratin 19 fragment; DKK, dickkopf; DM, dermatomyositis; ELISA, enzyme-linked immunosorbent assay; ERS, European Respiratory Society; ESCAPE, Evaluation of Subclinical Cardiovascular Disease and Predictors; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; FCS, fetal calf serum; Fib, fibrinogen; GAL, galactin; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; hsp, heat shock protein; Ig, immunoglobulin; IIP, idiopathic interstitial pneumonia; IL, interleukin; ILD, interstitial lung disease; IM, inflammatory myositis; IP, inducible protein; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen 6 glycoprotein; KURAMA, Kyoto University Rheumatoid Arthritis Management Alliance; LBP, lipopolysaccharide binding protein; LDH, lactate dehydrogenase; lncRNA, long noncoding RNA; LOXL, lysyl oxidase-like; MAA, malondialdehyde-acetaldehyde adducts; MCTD, mixed connective tissue disease; MDCT, multidetector row computed tomography; miRNA, microRNA; MMP, matrix metalloproteinases; MUC5B, mucin5B; NK, natural killer; PAD, peptidyl arginine deiminase; PAH, pulmonary arterial hypertension; PARC, pulmonary and activation-regulated chemokine; PARN, poly[A]-specific ribonuclease; PCR, polymerase chain reaction; PFT, pulmonary function test; PM, polymyositis; PRA, panel-reactive antibodies; RA, rheumatoid arthritis; RF, rheumatoid factor; RTEL1, regulator of telomere elongation helicase 1; RT-PCR, reverse transcription–polymerase chain reaction; SFTPC, surfactant protein C; SLE, systemic lupus erythematosus; SNP, single-nucleotide polymorphism; SP-A, surfactant protein-A; SP-D, lung epithelial-derived surfactant protein D; sPD-L, soluble programmed death-ligand; SS, Sjögren syndrome; SSc, systemic sclerosis; TB, tuberculosis; TGFβ1, transforming growth factor β1; TOLLIP, Toll-interacting protein; UIP, usual interstitial pneumonia; VARA, Veterans Affairs Rheumatoid Arthritis; XR, cross-reactive.

Table 2. Patient characteristics

Author, year (citation)	Sample size	Age, mean or median years	Race and ethnicity	Sex, % female	Smoking history, %	RA duration, mean or median	RA severity	ILD severity
Abdel-Wahab et al, 2016 (52)	RA: 50 Control: 30	RA: 51.5 Control: 51	Study site: Egypt	RA: 76	Not reported	RA: 11.4 y	Not reported	Not reported
Alunno et al, 2018 (53)	RA: 252 RA-ILD: 37	All RA: 61.7	Study site: Italy	All RA: 77	Not reported	RA without ILD: 12.6 y	Not reported	Not reported
Alunno et al, 2018 (54)	RA: 100 RA-ILD: 21	Total cohort: 62	Study site: Italy	Not reported	Total: 26	Not reported	Erosive disease (%) Total: 60	Not reported
Avouac et al, 2020 (38)	RA without ILD: 107 RA-ILD: 40	RA without ILD: 62 RA-ILD: 71	Study sites: France, Japan, Switzerland	RA without ILD: 75 RA-ILD: 55	RA without ILD: 26 RA-ILD: 60	RA without ILD: 12 y RA-ILD: 12 y	Erosions (%) RA without ILD: 63 RA-ILD: 50	FVC% pred RA-ILD: 15%[a] DLCO% pred RA-ILD: 79%, 61%
Bao et al, 2021 (55)	RA without ILD: 60 RA-ILD: 91 SS-ILD: 19 SLE-ILD: 13 IM-ILD: 11	CTD-ILD: 58.5 CTD alone: 56.2	Study site: Japan	CTD-ILD: 67.6 CTD alone: 65	Not reported	Not reported	Not reported	Not reported
Castellanos-Moreira et al, 2020 (56)	RA-ILD: 37 RA without ILD: 243	RA-ILD: 67.3 RA without ILD: 57.7	White (%) RA-ILD: 84 RA without ILD: 85	RA-ILD: 68 RA without ILD: 82	Current, ever RA-ILD: 19, 57 RA without ILD: 16, 44	RA-ILD: 11.6 y RA without ILD: 5.3 y	DAS28 RA-ILD: 3.7 RA without ILD: 2.7 HAQ RA-ILD: 0.69 RA without ILD: 0.31	Not reported
Chen et al, 2015 (30)	USA, Chinese Total: 86, 133 RA without ILD: 22, 50 RA-ILD: 49, 41 Indeterminate RA-ILD: 15, 42	USA, Chinese RA without ILD: 50.3, 43.4 RA-ILD: 65.3, 53.0	White (%) USA cohort RA without ILD: 71% RA-ILD: 76% Chinese cohort Not reported	USA, Chinese RA without ILD: 76, 82 RA-ILD: 37, 71	USA, Chinese RA without ILD: 42, 12 RA-ILD: 55, 12	USA, Chinese RA without ILD: 8.4 y, 4.3 y RA-ILD: 12.8 y, 5.6 y	DAS28 USA, Chinese RA-advanced ILD: 4.4, 3.3	FVC% pred USA, Chinese RA without ILD: 101.4, 83.8 RA-advanced ILD: 68.1, 72.3
Chen et al, 2019 (57)	RA without ILD: 198 RA-ILD: 103	RA without ILD: 59.8 RA-ILD: 60.9	Study site: China	RA without ILD: 80.3 RA-ILD: 76.7	Not reported	Not reported	Not reported	Not reported
Correia et al, 2019 (58)	Confirmed RA: 453 Unconfirmed RA: 1577	Confirmed RA: 59.6 Unconfirmed RA: 55.7	White: 68.1% African American: 14.2% Hispanic: 1.8% Asian: 2.0%	Confirmed RA: 80.6 Unconfirmed RA: 78.7	Not reported	Not reported	Not reported	Not reported

(Continued)

Table 2. (*Cont'd*)

Author, year (citation)	Sample size	Age, mean or median years	Race and ethnicity	Sex, % female	Smoking history, %	RA duration, mean or median	RA severity	ILD severity
Darrah et al, 2018 (59)	Total: 284 RA: 184, 55 had evidence of RA- ILD Healthy controls: 100	Anti-PAD2 (−): 61 Anti-PAD2 (+): 63	White (%) Anti-PAD2 (−): 87 Anti-PAD2 (+): 82	Anti-PAD2 (−): 55 Anti-PAD2 (+): 82	Ever, current Anti-PAD2 (−): 59, 12 Anti-PAD2 (+): 62, 6	Anti-PAD2 (−): 8 y Anti-PAD2 (+): 9.5 y	DAS28, HAQ, SHS, JSN Anti-PAD2 (−): 3.3, 0.75, 7, 5 Anti-PAD2 (+): 3.2, 1.0, 1, 8	Not reported
Del Angel-Pablo et al, 2020 (60)	RA-ILD: 65 RA without ILD: 82	RA-ILD: 61 RA without ILD: 53.50	Study site: Mexico	RA-ILD: 53 RA without ILD: 81	RA-ILD: 22 RA without ILD: 19	Age at RA diagnosis RA-ILD: 53 y RA without ILD: 45.5 y	Not reported	FVC% pred RA-ILD: 67 RA without ILD: 97
Doyle et al, 2015 (31)	BRASS, ACR RA without ILD: 29, 22 Subclinical RA-ILD: 29, 18 Clinical RA-ILD: 17, 21	BRASS, ACR RA without ILD: 53, 50 Subclinical RA-ILD: 68, 65 Clinical RA-ILD: 65, 64	Study site: USA	BRASS, ACR Clinical RA-ILD: 76, 57	BRASS, ACR RA without ILD: 41, 42 Subclinical RA-ILD: 69, 44 Clinical RA-ILD: 53, 52	Not reported	Not reported	BRASS, ACR FVC% pred Subclinical RA-ILD: 80, 82 Clinical RA-ILD: 70, 71 DLCO% pred Subclinical RA-ILD: 69, 61 Clinical RA-ILD: 57, 53
England et al, 2019 (61)	RA-ILD: 90 RA without ILD: 1439 RA-COPD: 294	RA-ILD: 67.0 RA without ILD: 62.8 RA-COPD: 65.8	White: 76.7%	Total: 9.9	Current: 26.1 Former: 53.4 Never: 13.3	RA-ILD: 13.3 y	DAS28 RA-ILD: 4.1	FVC% pred RA-ILD: 75.1
Fadda et al, 2018 (62)	RA-ILD: 6 RA without ILD: 25	RA-ILD: 50 RA without ILD: 48.4	Study site: Egypt	RA-ILD: 87.3 RA without ILD: 80	Total: 1.1	RA-ILD: 10.1 y RA without ILD: 10.4 y	CDAI by RA severity RA-ILD: mild 6, moderate 16, severe 3 RA without ILD: mild 19, moderate 30, severe 14	Not reported
Fotoh et al, 2021 (39)	RA-ILD: 75 RA without ILD: 75	RA-ILD:47.4 RA without ILD: 45.3	Not reported	RA-ILD: 46.7 RA without ILD: 48	RA-ILD: 85.3 RA without ILD: 2.7	RA-ILD: 8.4 y RA without ILD: 8.04 y	Not reported	FVC% pred RA-ILD: 52.5 RA without ILD: 93.0
Fu et al, 2018 (63)	Total: 92 RA without ILD: 43 RA-ILD: 49	RA without ILD: 61.5	Study site: China	RA without ILD: 69.8	Not reported	RA without ILD: 5 y	DAS28 RA without ILD: 5.6 Early ILD: 5.4 Established ILD: 4.9	FVC% pred Early ILD: 79.0 Established ILD: 81.5

(Continued)

Table 2. (*Cont'd*)

Author, year (citation)	Sample size	Age, mean or median years	Race and ethnicity	Sex, % female	Smoking history, %	RA duration, mean or median	RA severity	ILD severity
Fujita et al, 2020 (64)	RA without ILD: 84 RA-ILD: 31	Total: 66	Study site: Japan	Total: 71.6	Total: 37.9	Not reported	Not reported	Not reported
Furukawa et al, 2012 (34)	RA-ILD: 129 RA without ILD: 321	RA-ILD: 69.5 RA without ILD: 61.7	Japanese	RA-ILD: 67.4 RA without ILD: 85.4	RA-ILD: 32.6 RA without ILD: 27.4	RA-ILD: 17.1 y RA without ILD: 13.5 y	Steinbrocker stages III and IV (%) RA-ILD: 65.1 RA without ILD: 55.1	Not reported
Furukawa et al, 2013 (65)	RA-ILD: 26 RA without ILD: 38	RA-ILD: 67.6 RA without ILD: 59.7	Study site: Japan	RA-ILD: 61.5 RA without ILD: 84.2	Not reported	Not reported	Not reported	Not reported
Furukawa et al, 2020 (66)	RA-ILD: 100 RA without ILD: 100	RA-ILD: 67.3 RA without ILD: 66.2	Study site: Japan	RA-ILD: 76 RA without ILD: 24	RA-ILD: 38.1 RA without ILD: 32.6	Not reported	Not reported	Not reported
Giles et al, 2014 (67)	RA-ILD: 58 RA without ILD: 118	RA-ILD: 61 RA without ILD: 58	White: 86%	RA-ILD: 50 RA without ILD: 64	RA-ILD: 76 RA without ILD: 53	Total: 8 y	DAS28 RA-ILD: 3.8 RA without ILD: 3.5 HAQ RA-ILD: 0.75 RA without ILD: 0.6	PFT restriction or impaired diffusion: 21%
Giles et al, 2014 (68)	RA-ILD: 57 RA without ILD: 120	RA-ILD: 61 RA without ILD: 58	White RA-ILD: 88% RA without ILD: 86%	RA-ILD: 51 RA without ILD: 64	Current, ever RA-ILD: 23, 75 RA without ILD: 6, 53	RA-ILD: 9 y RA without ILD: 8 y	DAS28-CRP RA-ILD: 3.8 RA without ILD: 3.5	PFT restriction or low DLCO, % RA-ILD: 40 RA without ILD: 13
Harlow et al, 2013 (69)	RA-ILD: 58 RA without ILD: 27 MCTD: 41 IPF: 33	Not reported	RA-ILD citHSP90 (+): White 100% citHSP90 (−): White 88%	RA-ILD: 2.0	RA-ILD citHSP90 (+): 80 ever citHSP90 (−): 91 ever	Not reported	DAS28 RA-ILD citHSP90 (+): 3.8 citHSP90 (−): 3.6	Not reported
Hillarby et al, 1993 (70)	RA-ILD: 23 RA without ILD: 153	RA-ILD: 50.3 RA without ILD: 45.2	Study site: UK	RA-ILD: 39 RA without ILD: 73	Not reported	RA-ILD: 16.7 y RA without ILD: 9.8 y	Not reported	Not reported
Hussein et al, 2021 (71)	RA-ILD: 50 RA without ILD: 50	RA-ILD: 67.3 RA without ILD: 55.8	Study site: Egypt	RA-ILD: 70 RA without ILD: 94	RA-ILD: 10 RA without ILD: 6	RA-ILD: 16.5 y RA without ILD: 10.5 y	DAS28 RA-ILD: 4.89 RA without ILD: 3.6 HAQ RA-ILD: 1.2 RA without ILD: 0.93	Cough/dyspnea (%) RA-ILD: 16/24

(Continued)

Table 2. (*Cont'd*)

Author, year (citation)	Sample size	Age, mean or median years	Race and ethnicity	Sex, % female	Smoking history, %	RA duration, mean or median	RA severity	ILD severity
Juge et al, 2018 (32)	RA-ILD: 620 RA without ILD: 614 Control: 5448	RA-ILD: 69 RA without ILD: 60.4	Multinational	RA-ILD: 61.1 RA without ILD: 82.6	RA-ILD: 54.7 RA without ILD: 36.1	Not reported	Erosions (%) RA-ILD: 46.5 RA without ILD: 58.4	RA-ILD FVC% pred: 78.2 DLCO% pred: 57.6
Kass et al, 2019 (29)	VA, non-VA Control: NA, 36 IPF: NA, 100 RA without ILD: 17, 22 RA-ILD: 86, 49	VA, non-VA Control: NA, 65 IPF: NA, 70 RA without ILD: 57, 49 RA-ILD: 64, 65	Study site: USA	VA, non-VA Control: NA, 36 IPF: NA, 33 RA without ILD: 35, 76 RA-ILD: 5, 63	VA, non-VA Control: NA, 52 IPF: NA, 68 RA without ILD: 41,42 RA-ILD: 88, 55	VA, non-VA RA without ILD: 10 y, 8 y RA-ILD: 10 y, 13 y	VA, non-VA (DAS28) RA without ILD: 4.1, 3.4 RA-ILD: 3.7, 3.5	FVC% pred VA, non-VA IPF: NA, 71 RA without ILD: 84, 104 RA-ILD: 83, 71
Kelly et al, 2014 (72)	RA-ILD: 230 RA without ILD: 230	RA-ILD: 56	Study site: UK	RA-ILD: 52	Female, male RA-ILD: 60, 75 RA without ILD: 59, 60	RA-ILD: 9 y	Not reported	Not reported
Kim et al, 2020 (40)	RA-ILD: 84 UIP: 30	Total: 61.4 UIP: 65.8	Study site: Republic of Korea	Total: 54.8 UIP: 46.7	Total: 44 UIP: 53.3	RA-ILD: 47 mo RA-ILD, UIP: 66 mo RA-ILD, non-UIP: 37 mo	Not reported	FVC% pred Total: 74.0 UIP: 74.7 Non-UIP: 73.6
Lai et al, 2019 (73)	RA-ILD: 100 RA without ILD: 100	RA-ILD: 63.9 RA without ILD: 53.3	Study site: China	RA-ILD: 57 RA without ILD: 75	Not reported	RA-ILD: 9.87 y RA without ILD: 9.05 y	Not reported	Not reported
Lee et al, 2016 (41)	RA-ILD: 62	Total: 64	Study site: South Korea	Total: 48.4	Total: 51.6	Not reported	Not reported	Not reported
Lee et al, 2019 (45)	RA-ILD: 41 RA without ILD: 106 SSc: 74 IM: 108 Other CTD: 220	CTD-ILD (+): 56.4 CTD-ILD (−): 51.1	Study site: South Korea	CTD-ILD (+): 83.6 CTD-ILD (−): 88.5	Not reported	Not reported	Not reported	FVC% pred CTD-ILD (+): 77.2
Ma et al, 2019 (74)	RA without ILD: 45 RA-ILD: 42 Control: 49	RA without ILD: 68 RA-ILD: 58.1	Study site: China	RA without ILD: 80 RA-ILD: 69	RA without ILD: 17.8 RA-ILD: 23.8	RA without ILD: 6 y RA-ILD: 7 y	DAS28 RA without ILD: 4.9 RA-ILD: 5.0	RA-ILD DLCO Impairment Normal: 35% Slight: 38% Moderate: 23% Severe: 3.8%
Maniwa et al, 2000 (75)	RA without ILD: 38 RA-ILD: 32 Control: 40	RA without ILD: 56 RA-ILD: 63 Control: 50	Study site: Japan	RA without ILD: 73.7 RA-ILD: 53.1 Control: 37.5	Not reported	Range 3 mo to 15 y	RA without ILD, RA-ILD Lansbury Index: 55%, 46%	DLCO% pred RA without ILD: 78 RA-ILD: 45

(Continued)

Table 2. (*Cont'd*)

Author, year (citation)	Sample size	Age, mean or median years	Race and ethnicity	Sex, % female	Smoking history, %	RA duration, mean or median	RA severity	ILD severity
Matsuo et al, 2019 (76)	RA-ILD: 26 RA without ILD: 286	RA-ILD: 69.8 RA without ILD: 62.9	Study site: Japan	RA-ILD: 80.8 RA without ILD: 87.4	Former, current RA-ILD: 31, 0 RA without ILD: 30, 7	RA-ILD: 15.7 y RA without ILD: 14.8 y	DAS28 RA-ILD: 2.8 RA without ILD: 2.5 HAQ RA-ILD: 1.1 RA without ILD: 0.9	Not reported
Matsushita et al, 2017 (77)	Total: 228 RA-ILD: 56	Total: 62.9	Study site: Japan	Total: 80.7	Not reported	Not reported	Not reported	Not reported
Mori et al, 2012 (78)	RA-ILD: 24 RA without ILD: 302 RA airway disease: 30	RA-ILD: 72.5 RA without ILD: 59.0 RA airway disease: 64.5	Study site: Japan Race and ethnicity: not reported	RA-ILD: 50	RA-ILD: 45.8 RA without ILD: 20.5 RA airway disease: 10	RA-ILD: 1.5 y	Steinbroker stages III and IV (%) RA-ILD: 41.7 RA without ILD: 32.5 RA airway disease: 86.7	Respiratory symptoms (%) RA-ILD: 33.3 RA without ILD: 0 RA airway disease: 73.3
Nakajima et al, 2000 (79)	SSc: 47 PM/DM: 21 SLE: 18 RA-ILD: 22 RA without ILD: 35 SSc-IP: 24 DM/PM-IP: 14 SLE-IP: 1	All RA: 61.8 SSc: 52.4 PM/DM: 48.5 SLE: 37.0	Study site: Japan	All RA: 70.1 SSc: 87.2 PM/DM: 85.7 SLE: 83.3	Not reported	All RA: 8.4 y	Not reported	Not reported
Natalini et al, 2021 (80)	Total: 2328 Prevalent RA-ILD: 100 Incident RA-ILD: 83	Total: 64	White: 76.3% Black or African American: 14.8% Hispanic or Latino: 4.3%	Total: 10.7	Never: 21.0 Former: 25.1 Current: 54.0	Total: 8.0 y	Not reported	Not reported
Newton et al, 2019 (37)	IPF: 499 RA-ILD: 62 SSc-ILD: 74 CTD-ILD: 112	RA-ILD: 60.2	RA-ILD: 65% White	RA-ILD: 66	RA-ILD: 65	Not reported	Not reported	FVC% pred IPF: 67 CTD-ILD: 68 DLCO% pred IPF: 47 CTD-ILD: 53 ΔFVC% pred $year^{-1}$ RA-ILD: −0.59 SSc-ILD: −1.03
Oka et al, 2016 (35)	Total: 1383 UIP: 107 NSIP: 183	UIP: 69.8 NSIP: 69.6 BLAD: 68.2	Study site: Japan	UIP: 56.1 NSIP: 73.8 BLAD: 84.3	UIP: 44.2 NSIP: 45.2 BLAD: 38.8	Not reported	Steinbroker stages III and IV (%) UIP: 59.3 NSIP: 51.6	Not reported

(Continued)

Table 2. (*Cont'd*)

Author, year (citation)	Sample size	Age, mean or median years	Race and ethnicity	Sex, % female	Smoking history, %	RA duration, mean or median	RA severity	ILD severity
	BLAD: 116 BEAD: 121 Emphysema: 83 CLD (−): 773	BEAD: 66.8 Emphysema: 67.8 CLD (−): 61.3		BEAD: 85.8 Emphysema: 36.1 CLD (−): 84.8	BEAD: 38.2 Emphysema: 81.6 CLD (−): 35.6		BLAD: 64.9 BEAD: 53.3 Emphysema: 40.4 CLD (−): 48.6	
Oka et al, 2017 (81)	RA without ILD: 32 RA-ILD: 32	RA without ILD: 57.7 RA-ILD: 70.2 RA-UIP: 70.6 RA-NSIP: 69.6	Study site: Japan	RA without ILD: 93.7 RA-ILD: 34.4 RA-UIP: 50 RA-NSIP: 85.7	RA without ILD: 32.3 RA-ILD: 33.3 RA-UIP: 38.9 RA-NSIP: 25.0	RA without ILD: 10.6 y RA-ILD: 15.5 y RA-UIP: 12.8 y RA-NSIP: 18.9 y	DAS28 RA without ILD: 3.1 RA-ILD: 4.0 RA-UIP: 3.7 RA-NSIP: 4.3	Not reported
Pulito-Cueto et al, 2020 (82)	RA-ILD: 20 RA without ILD: 25 IPF: 21	RA-ILD: 66.8 RA without ILD: 60.1 IPF: 69.2	Study site: Spain	RA-ILD: 45 RA without ILD: 60 IPF: 33.3	RA-ILD: 65 RA without ILD: 52 IPF: 76.2	RA-ILD: 9.2 y RA without ILD: 4.1 y	Not reported	FVC% pred RA-ILD: 95.1 RA without ILD: 99.2 IPF: 84.9
Ren et al, 2021 (83)	Total: 348 RA-ILD: 49	RA: 59.9	Study site: China	RA: 74.4	All RA: 15.6	RA: 54 mo	Not reported	Not reported
Restrepo et al, 2015 (84)	RA without ILD: 563 RA-ILD: 69	RA without ILD: 52.9 RA-ILD: 60.2	RA-ILD: 36% White	RA-ILD: 50.7	RA without ILD: 54.5 RA-ILD: 72.4	RA without ILD: 10.2 y RA-ILD: 12.6 y	DAS28 RA without ILD: 5.3 RA-ILD: 6.0	Not reported
Rocha-Muñoz et al, 2015 (85)	RA-ILD: 39 RA without ILD: 42	RA-ILD: 51 RA without ILD: 49	Study site: Mexico	100	RA-ILD: 31 RA without ILD: 23.1	RA-ILD: 7 y RA without ILD: 6.5 y	DAS28 RA-ILD: 3.9 RA without ILD: 2.5	FVC% pred RA-ILD: 71 RA without ILD: 86
Saku et al, 2021 (42)	RA-ILD: 72	RA-ILD: 68.6	Study site: Japan	RA-ILD: 41.7	Ever: 69.5	Not reported	Not reported	FVC% pred RA-ILD: 83
Salaffi et al, 2019 (86)	RA-ILD: 29 RA without ILD: 122	RA-ILD: 66.6 RA without ILD: 54.7	Study site: Italy	Total: 70.3	RA-ILD: 34.5 RA without ILD: 21.3	RA-ILD: 7.5 y RA without ILD: 7.5 y	DAS28-ESR RA-ILD 5.8 RA without ILD: 5.7	FVC% pred, DLCO% pred RA-ILD: 69.9, 64.3 RA without ILD: 90.8, 77.3
Sargin et al, 2018 (26)	RA-ILD: 43 RA without ILD: 40	RA-ILD: 60.1 RA without ILD: 58.5	Study site: Turkey	RA-ILD: 69.8 RA without ILD: 82.5	RA-ILD: 11.6 RA without ILD: 10	Not reported	Not reported	Not reported
Sargin et al, 2021 (87)	Total: 113	RA without ILD: 57.6 RA-ILD: 62.1	Not reported	RA without ILD: 80 RA-ILD: 63.6	RA without ILD: 12 RA-ILD: 14	Total: 34.9 mo	Not reported	Not reported
Shen et al, 2019 (88)	CTD-ILD: 332 RA-ILD: 52	RA-ILD: 60.6	Study site: China	RA-ILD: 75	RA-ILD: 21	Not reported	Not reported	Symptoms (%) Exertional dyspnea: 26.9 Cough: 32.7

(Continued)

Table 2. (*Cont'd*)

Author, year (citation)	Sample size	Age, mean or median years	Race and ethnicity	Sex, % female	Smoking history, %	RA duration, mean or median	RA severity	ILD severity
Sherin et al, 2019 (89)	RA-ILD: 40	RA-ILD: 50.0	Study site: Egypt	RA-ILD: 80	RA-ILD: 10	RA-ILD: 7 y	DAS28	FVC% pred
	RA without ILD: 60	RA without ILD: 41.3		RA without ILD: 93.3	RA without ILD: 6.7	RA without ILD: 7 y	RA-ILD: 4.8	RA-ILD: 82.0
							RA without ILD: 4.2	RA without ILD: 93.6
Skare et al, 2011 (90)	Total: 71	Total: 43.9 (at RA diagnosis)	Study site: Brazil	Total: 85.9	Total: 35.8	Total: 11.8 y	Not reported	Total (%) Dyspnea: 18.4 Cough: 9.0
Sokai et al, 2016 (46)	Total: 69 RA-ILD: 23	Total: 65.5 RA-ILD: 62.5	Study site: Japan	Total: 60.8 RA-ILD: 39.1	Current, former Total: 13, 41 RA-ILD: 17, 52	Total: 12.5 y RA-ILD: 8.5 y	Not reported	FVC% pred Total: 99.9 RA-ILD: 97.9
Solomon et al, 2020 (91)	Total: 427 RA-UIP: 40	RA-UIP: 64	Study site: USA	RA-UIP: 50	RA-UIP: 62	Not reported	Not reported	FVC% pred RA-UIP: 72
Wada et al, 2010 (92)	Total: 74 RA-BD: 26 RA-ILD: 25	RA-BD: 67.5 RA-ILD: 67.1	Study site: Japan	RA-BD: 84.6 RA-ILD: 64	Not reported	RA-BD: 11.0 y RA-ILD: 12.3 y	DAS28 RA-BD: 3.3 RA-ILD: 2.7	Not reported
Wang et al, 2016 (27)	RA without ILD: 83 RA-ILD: 28	RA without ILD: 54.1 RA-ILD: 63.6	Study site: China	RA-ILD: 42.9	Never, former, current RA without ILD: 72, 17, 10 RA-ILD: 54, 25, 21	Not reported	Not reported	Not reported
Wang et al, 2019 (93)	RA-ILD: 48 RA without ILD: 50	RA-ILD: 52.8 RA without ILD: 53.4	Study site: China	RA-ILD: 50 RA without ILD: 48	Not reported	Not reported	Not reported	Not reported
Wang et al, 2020 (33)	Total: 96 RA without ILD: 51 RA-ILD: 45	Total: 55.5 RA without ILD: 46.1 RA-ILD: 59.5	Study site: China	Total: 66.6 RA without ILD: 72.6 RA-ILD: 60	Total: 16.7 RA without ILD: 12.7 RA-ILD: 20	RA without ILD: 6.0 y RA-ILD: 7.2 y	Not reported	FVC% pred RA-ILD: 79.9
Wang et al, 2021 (94)	RA-ILD: 31 RA without ILD: 75	RA-ILD: 59.84, 60.5 RA without ILD: 58.83, 56.49	Study site: China	RA-ILD: 68.4, 75RA without ILD: 87.5, 82.9	Not reported	Not reported	Not reported	Warrick score RA-ILD: 7.0
Wen et al, 2018 (95)	RA-ILD: 64 RA without ILD: 56	Total: 60.3	Study site: China	Total: 76.7	Total: 20.3	Not reported	DAS28 Total: 5.1	Not reported
Wu et al, 2020 (28)	RA-ILD: 58 RA without ILD: 29	RA-ILD: 65.7 RA without ILD: 61.8	Study site: China	RA-ILD: 62.1 RA without ILD: 86.2	RA-ILD: 25.9 RA without ILD: 3.4	RA-ILD: 5 y RA without ILD: 6 y	Not reported	FVC% pred sPD-L1(+): 79.8 sPD-L1(−): 95.3
Xiangyang et al, 2012 (96)	RA-ILD: 59 RA without ILD: 62	All RA: 51	Study site: USA	All RA: 84.3	Not reported	All RA: 47 y	DAS28 All RA: 6.7	Not reported
Xue et al, 2021 (97)	RA-ILD: 35 RA without ILD: 67	RA-ILD: 60.4	RA-ILD: 95% Chinese Han	Total: 66.67 RA-ILD: 51.4	Current RA-ILD: 55	RA-ILD: 10.1	DAS28 RA-ILD: 5.9	Not reported

(Continued)

Table 2. (*Cont'd*)

Author, year (citation)	Sample size	Age, mean or median years	Race and ethnicity	Sex, % female	Smoking history, %	RA duration, mean or median	RA severity	ILD severity
Yang et al, 2019 (98)	RA-ILD: 77 RA without ILD: 231	RA-ILD: 56.6 RA without ILD: 57.1	Study site: Japan	RA-ILD: 75.3 RA without ILD: 75.3	Former/current RA-ILD: 14.7/5.9 RA without ILD: 11.8/4.6	RA-ILD: 11.5 RA without ILD: 10.8	Erosions (%) RA-ILD: 33.3 RA without ILD: 19.5	FVC% pred RA-ILD: 81.2
Yin et al, 2014 (99)	RA without ILD: 214 RA-ILD: 71	RA without ILD: 49.5 RA-ILD: 58.3	Study site: China	RA without ILD: 75.2 RA-ILD: 70.4	RA without ILD: 19.2 RA-ILD: 25.4	RA without ILD: 4.0 RA-ILD: 9.0	DAS28 RA without ILD: 5.5 RA-ILD: 5.2	Not reported
Yu et al, 2019 (36)	RA-ILD: 40 RA without ILD: 41	RA-ILD Wnt5a (−): 60.1 Wnt5a (+): 61.1	>90% Chinese Han	RA-ILD: 52.5	RA-ILD Wnt5a (−): 44.8 Wnt5a (+): 81.8	RA-ILD Wnt5a (−): 9.2 Wnt5a (+): 12.6	RA-ILD DAS28-ESR Wnt5a (−): 5.3 Wnt5a (+): 5.5	RA-ILD Wnt5a (−)/Wnt5a (+) (%) Cough: 93.1/90.9 Dyspnea: 89.7/72.7
Zhang et al, 2017 (100)	RA-ILD: 237 RA without ILD: 313	RA-ILD: 57.6 RA without ILD: 47.7	Study site: China	RA-ILD: 63.7 RA without ILD: 64.8	RA-ILD: 40.9 RA without ILD: 4.8	RA-ILD: 2 RA without ILD: 4	Not reported	Respiratory symptoms (%) RA-ILD: 41 RA without ILD: 4.7
Zheng et al, 2021 (25)	RA without ILD: 26 RA-ILD: 24 CTD-ILD: 14	RA without ILD: 56.6 RA-ILD: 62.9 CTD-ILD: 53.1	Study site: China	RA without ILD: 76.9 RA-ILD: 41.7 CTD-ILD: 64.3	RA without ILD: 15.4 RA-ILD: 50 CTD-ILD: 21.4	RA without ILD: 3 RA-ILD: 4.5	Not reported	HRCT fibrosis score RA-ILD: 14.6
Zhou et al, 2020 (101)	RA-ILD: 20 RA without ILD: 20	RA-ILD: 57.7 RA without ILD: 52.6	Study site: China	Total: 100	Not reported	RA-ILD: 8.1 RA without ILD: 8.4	DAS28 RA-ILD: 6.3 RA without ILD: 5.9	Not reported

Abbreviations: ACR, American College of Rheumatology; BD, bronchial disease; BEAD, bronchiectatic airway disease; BLAD, bronchiolitic airway disease; BRASS, Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study; CDAI, clinical disease activity index; citHSP, citrullinated heat shock protein; CLD, chronic lung disease; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; CRP, C-reactive protein; DAS28, disease activity score in 28 joints; DLCO, diffusion capacity for carbon monoxide; DM, dermatomyositis; FVC, forced vital capacity; HAQ, health assessment questionnaire; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IM, inflammatory myositis; IP, interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; JSN, joint space narrowing; MCTD, mixed connective tissue disease; NA, not available; NSIP, nonspecific interstitial pneumonia; PAD, peptidyl arginine deiminase; PFT, pulmonary function test; PM, polymyositis; pred, predicted; RA, rheumatoid arthritis; SHS, Sharp van der Heijde score; SLE, systemic lupus erythematous; sPD-L, soluble programmed death-ligand; SS, Sjögren syndrome; SSc, systemic sclerosis; UIP, usual interstitial pneumonia; VA, Department of Veterans Affairs; y, year (s); $year^{-1}$, per year.
aValues reported for FVC% pred and DLCO% pred were inconsistent.

Table 3. Summary of peripheral blood biomarkers associated with the presence of RA-ILD

Biomarker category	Biomarkers associated with RA-ILD vs. RA without ILD
Autoantibodies	Multiple studies: rheumatoid factor,[a] anti-CCP,[a] anti-CEP-1 Single study: anti-MAA,[a] anti-IL-1a, anti-aaRS (anti-PL-7, anti-PL-12), anti-PAD2,[a,b] anti-PAD3/4XR,[a] anti-CarP,[a] anti-fibrinogen A, anti-apolipoprotein E, anti-cit-hsp90, anti-cit-fibrinogen A, anti-cit-apolipoprotein A1, anti-cit-lipoprotein E, anti-cit-vimentin, anti-cit-histone 2B, anti-cit-filaggrin, anti-cit-biglycan, anti-cit-clusterin
Lung epithelial–related proteins	Multiple studies: KL-6,[a] SP-D[a]
Tumor markers	Multiple studies: CA-125, CA-19-9[a] Single study: CA-15-3, sPD-L1,[a] Gal-9
Cytokines and chemokines	Multiple studies: IL-6, IL-33 Single study: IL-1α,[a] IL-1β,[a] IL-2,[a] IL-7,[a] IL-8,[a] IL-9,[a] IL-11, IL-12p40,[a] IL-12p70,[a] IL-13, IL-15,[a] IL-18,[a] TNF-α,[a] IFN-α2,[a] LPS-BP, CXCL10,[a] CXCL16, CCL18,[a] GRO-1,[a] MCP-3,[a] MIP-1β,[a] eotaxin,[a] fractalkine[a]
Growth factors	Single study: FGF-2,[a] FLT-3L,[a] GM-CSF,[a] TGF-α,[a] TGF-β1, VEGF,[a] DKK-1, CTGF
Extracellular matrix proteins	Multiple studies: MMP-7[a] Single study: MMP-1,[a] MMP-2,[a] MMP-9,[a] MMP-10[a]
Genetic polymorphisms	Multiple studies: HLA-DR2, HLA-DR4[b] Single study: shared epitope,[b] HLA-DQ4,[b] HLA-DQ6, HLA-DRB1*14:06, HLA-DRB1*15:02, HLA-DRB1*16:02-DQB1*05:02, MUC5B mutations, MUC5B rs35705950,[a] hsa-miR-214-5p,[a] hsa-miR-7-6p,[a] lncRNA (NR_002819, ENST00000603415, ENST00000560199[b])
Others	Multiple studies: ESR, CRP Single study: lysine, 25-OH vitamin D,[a,b] Wnt5a,[a] GGT, LDH,[a] immunoglobulins, decanoic acid,[a,b] glycerol,[a] morpholine,[a,b] dyphylline,[a] octanoic acid,[a,b] fumaric acid,[a,b] N-acetylgalactosamine-1,[a] immature platelet fraction, endothelial progenitor cells, % and absolute CD3-CD56+ NK cells,[a] % T cells,[a,b] % CD4+ T cells,[a,b] platelet/lymphocyte ratio, neutrophil/lymphocyte ratio

Abbreviations: aaRS, aminoacyl–transfer RNA synthetase; CA, cancer or carbohydrate antigen; CarP, carbamylated protein; CCL, chemokine ligand; CCP, cyclic citrullinated peptide; CEP-1, citrullinated alpha-enolase peptide; cit, citrullinated; cit-hsp, citrullinated heat shock protein; CRP, C-reactive protein; CTGF, connective tissue growth factor; CXCL, CXC chemokine ligand; DKK, dickkopf; ESR, erythrocyte sedimentation rate; FGF, fibroblast growth factor; FLT-3L, FMS-like tyrosine kinase 3 ligand; Gal, galactin; GGT, γ-glutamyl transferase; GM-CSF, granulocyte macrophage colony-stimulating factor; GRO, growth-related oncogene; HLA, human leukocyte antigen; hsa-miR, Homo sapiens microRNA; IFN, interferon; IL, interleukin; ILD, interstitial lung disease; KL, Krebs von den Lungen; LDH, lactate dehydrogenase; lncRNA, long noncoding RNA; LPS-BP, lipopolysaccharide-binding protein; MAA, malondialdehyde-acetaldehyde adducts; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; MMP, matrix metallopeptidase; MUC5B, mucin5B; NK, natural killer; NR, nucleotide result; OH, hydroxy; PAD, peptidyl arginine deiminase; PL-7, anti-threonyl-tRNA synthetase; PL-12, anti-alanyl-tRNA-synthetase; RA, rheumatoid arthritis; SP-D, lung epithelial–derived surfactant protein D; sPD-L, soluble programmed death-ligand; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF; vascular endothelial growth factor; XR, cross-reactive.
aBiomarkers were associated with RA-ILD in at least one adjusted analysis.
bBiomarkers were negatively associated with RA-ILD in at least one study.

for a specific analyte across the cohorts (29). MMP-7, an extracellular matrix protein involved in lung tissue repair, was evaluated in three separate studies that each performed adjusted analyses in two independent cohorts. MMP-7 concentration was associated with RA-ILD in all three studies but was only validated in an independent cohort in one of the studies (29–31). The mucin 5B (MUC5B) promotor variant rs35705950 and other MUC5B mutations were the genetic variants most closely associated with RA-ILD and were restricted to the UIP subset of RA-ILD (32,33). RA-associated genes in the HLA family were not consistently more prevalent among patients with RA-ILD; in fact, the shared epitope alleles, HLA-DR4 and HLA-DQ4, were negatively associated with RA-ILD in at least one study (34,35). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), commonly assessed in the management of RA, had inconsistent findings in unadjusted analyses. Neither was associated with RA-ILD in the single analysis with multivariable adjustment (36).

Peripheral biomarkers that differentiated RA-ILD from a different type of lung disease. Fourteen biomarkers were found in at least one study to differentiate RA-ILD from a different type of lung disease (Table 4). Comparator lung diseases included other RA-associated lung diseases (eg, airway disease, bronchiectasis, and chronic obstructive pulmonary disease), other connective tissue disease–related ILDs (CTD-ILDs), and idiopathic pulmonary fibrosis (IPF). None of the studies adjusted for potential confounders. The MUC5B promoter variant rs35705950 was more prevalent (minor allele frequency: RA-ILD, 34.6%; systemic sclerosis–associated ILD [SSc-ILD], 16.2%; CTD-ILD, 12.7%) and leukocyte telomere length was shorter (observed-minus-expected telomere length: RA-ILD, –0.14; SSc-ILD, –0.02; CTD-ILD, 0.00) in RA-ILD compared with SSc-ILD and a combined group of other CTD-ILDs, although these analyses did not account for differences in ILD pattern (37). Among other biomarkers evaluated in multiple studies, RF and anti-CCP did not differentiate RA-ILD from other RA-associated lung diseases. KL-6 levels were higher in RA-ILD compared with RA-associated airway disease but did not differ between RA-ILD and other CTD-ILDs. ESR and CRP level were not different in RA-ILD compared with other RA-associated lung diseases but tended to be higher in RA-ILD than in other CTD-ILDs.

Peripheral biomarkers for RA-ILD prognostication. Eight studies (five case-control studies and three retrospective

Table 4. Peripheral blood biomarker identification of RA-ILD vs. other lung disease

Biomarker (citation)	Outcome
Autoantibodies	
Anti-cit-hsp90 (69)	Single unadjusted study found more frequent positivity for anti-cit-hsp90-ß-P (P = 0.01) and anti-cit-hsp90-α (P = 0.04) but not anti-cit-hsp90-β-E (P = 0.07) in RA-ILD compared with MCTD. Additionally, positivity for anti-cit-hsp90-β-P (P = 0.002) and anti-cit-hsp90-β-E (P = 0.006) but not anti-cit-hsp90-α (P = 0.080) was more frequent in RA-ILD compared with IPF.
Anti-CCP antibody (46,78,91)	Two unadjusted studies found no difference in anti-CCP titers between RA-ILD and RA airway disease (mean concentration/titer 222.8 [RA-ILD] vs. 221.6 U/ml [RA airway disease], P = NS; LR 0.22, P = 0.64). Another unadjusted study found IgA-ACPA and/or IgG-ACPA positivity in patients with RA-UIP was more frequent than that in two IPF cohorts (P < 0.01 for all comparisons).
Anti-MAA antibody (61)	Single unadjusted analysis found higher concentrations of IgM anti-MAA antibody in RA-ILD compared with RA-COPD (P = 0.01). There was no difference in concentrations of IgG anti-MAA antibody (P = 0.09).
ANCAs (92)	Single unadjusted study found no difference in titers of BPI-ANCA (P = 0.09), cytoplasmic-ANCA (P = 0.98), or perinuclear-ANCA (P = 0.08) between RA-ILD and RA bronchial diseases.
RF (46,78,92)	Two studies found no difference in RF titer/concentration between RA-ILD and RA airway disease (mean concentration/titer 208.3 [RA-ILD] vs. 218.8 U/ml [RA airway disease], P = NS; LR 0.01, P = 0.93). Another found no difference in RF titers between RA-ILD and RA bronchial diseases (mean concentration/titer 478 [RA-ILD] vs. 190 IU/ml [RA bronchial disease]).
Lung epithelial–related proteins	
KL-6 (25,45,46)	Three studies with unadjusted analyses, one finding higher levels of KL-6 in RA-ILD compared with RA airway disease (mean concentration/titer 646 [RA-ILD] vs. 394.3 U/ml [RA airway disease], P = 0.018). Two other studies found no significant difference in KL-6 levels between RA-ILD and other CTD-ILD (mean concentration/titer 558 [RA-ILD] vs. 824.5 U/ml, P = 0.365; other effect size not reported, P = NS).
SP-D (46)	Single unadjusted study found no significant difference in SP-D levels between RA-ILD and RA airway disease (P = 0.081).
Tumor markers	
Tumor markers (25,55,88)	Three unadjusted studies. One found no difference in proportion positive for CEA, AFP, SCC, CA-15-3, CA-125, CA-19-9, CA-72-4, or CYFRA-21-1 between RA-ILD and IPF. Another found no difference in levels of CA-19-9, CA-125, CEA, CA-153, or CYFRA-21-1 between RA-ILD and other CTD-ILD. Another found greater levels of CA-19-9 in RA-ILD compared with other CTD-ILD (P < 0.001) but no difference in CA-125 or CEA levels.
Genetic polymorphisms	
C4 allotypes (70)	Single unadjusted analysis found no difference in C4A or C4B null allele between RA-ILD, RA bronchiectasis, RA nonsmokers without small airway obstruction, or RA nonsmokers with small airway obstruction.
HLA (70,78)	Two unadjusted studies. One found that HLA-DRB*15:01 (P = 0.007) and 15:02 (P = 0.0005) were more likely in RA-ILD vs. with RA airway disease. The other study evaluated numerous DQ and Dw alleles and found no difference between RA-ILD, RA bronchiectasis, RA nonsmokers without small airway obstruction, and RA nonsmokers with small airway obstruction.
MUC5B rs35705950 promoter variant (37)	Single Bonferroni-corrected analysis found higher prevalence of MUC5B promoter variant in RA-ILD compared with SSc-ILD (MAF 34.6 [95% CI: 24.4-46.3] vs. 16.6 [95% CI: 9.3-26.6], P = 0.040) and other CTD-ILD (MAF 12.7 [95% CI: 7.5-20.4], P = 0.0015). ILD pattern was not accounted for in comparisons.
TOLLIP rs5743890 (37)	Single Bonferroni-corrected analysis found no difference in minor allele frequency between RA-ILD, SSc-ILD, and other CTD-ILD (P = 0.072).
Others	
Complement (88)	Single unadjusted study found no difference in C3 or C4 levels between IPF and RA-ILD.
CRP (25,88,92)	Three unadjusted studies. One found higher CRP in RA-ILD vs. other CTD-ILD (mean concentration/titer 54.5 [RA-ILD] vs. 11.7 mg/l [CTD-ILD], P = 0.032). One found no difference in CRP between RA-ILD and RA bronchial diseases (mean concentration/titer 2.2 [RA-ILD] vs. 3.2 g/dl [RA bronchial disease], P = 0.82). Another found no difference in CRP between RA-ILD and IPF (mean concentration/titer 31.64 [RA-ILD] vs. 23.62 mg/dl [IPF], P = NS).
EPCs (82)	Single unadjusted study found greater EPC frequency in IPF compared with RA-ILD and RA-UIP (P < 0.001 for both).
ESR (88,92)	Two unadjusted studies. One found higher ESR levels in RA-ILD compared with IPF (mean concentration/titer 47.94 [RA-ILD] vs. 27.39 mm/h [IPF], P < 0.05). Another found no difference in levels between RA-ILD and RA bronchial diseases (P = 0.38) (mean concentration/titer 43.1 [RA-ILD] vs. 55.2 mm/h [RA bronchial disease], P = NS).

(Continued)

Table 4. (*Cont'd*)

Biomarker (citation)	Outcome
Ig (88)	Single unadjusted study found no difference in IgG, IgM, or IgA levels between IPF and RA-ILD.
Leukocyte telomere length (37)	Single Bonferroni-corrected analysis found shorter leukocyte telomere length in RA-ILD compared with SSc-ILD (observed expected telomere length − 0.14 vs. −0.02, $P = 0.013$) and other CTD-ILD (−0.014 vs. 0.00, $P = 0.00042$).

Abbreviations: ACPA, anti–citrullinated protein antibodies; AFP, α-fetoprotein; ANCA, antineutrophil cytoplasmic antibody; BPI-ANCA, bactericidal/permeability–increasing antineutrophilic cytoplasmic antibody; CA, cancer or carbohydrate antigen; CCP, cyclic citrullinated peptide; CEA, carcinoembryonic antigen; CI, confidence interval; cit-hsp, citrullinated heat shock protein; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CTD, connective tissue disease; CYFRA, cytokeratin 19 fragments; EPC, endothelial progenitor cell; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; Ig, immunoglobulin; ILD, interstitial lung disease; IPF, interstitial pulmonary fibrosis; KL, Krebs von den Lungen; LR, likelihood ratio; MAA, malondialdehyde-acetaldehyde adducts; MAF, minor allele frequency; MCTD, mixed connective tissue disease; ml, milliliter; MUC5B, mucin5B; NS, nonsignificant; RA, rheumatoid arthritis; RF, rheumatoid factor; SCC, squamous cell carcinoma antigen; SP-D, lung epithelial–derived surfactant protein D; SSc, systemic sclerosis; TOLLIP, Toll-interacting protein; U, unit; UIP, usual interstitial pneumonia.

cohort studies) evaluated the prognostic value of biomarkers in RA-ILD (Table 5). Study outcomes varied and included mortality, disease progression by PFTs and/or imaging, and/or ILD exacerbations. Eight biomarkers were associated with a worse prognosis in at least one study. Six of these biomarkers were prognostic in adjusted analyses, and two were associated with poor outcomes in two or more studies. KL-6 was the biomarker most consistently found to be associated with RA-ILD outcome measures. In four of five studies, including one cohort study, KL-6 was associated with increased mortality, a greater risk of ILD exacerbation, and/or more rapid disease progression (38–42). RF and anti-CCP were evaluated in multiple studies and were not associated with mortality risk, with the exception of a single case-control study performing unadjusted analysis of high-titer RF (40). Similarly, multiple studies evaluating CRP and ESR did not consistently find these biomarkers to prognosticate poor outcomes. Other biomarkers, including MUC5B mutations and MMP-7, were infrequently studied and did not appear highly prognostic.

Quality assessment. Study quality was highly variable, as assessed by the modified QUADAS-2 or QUIPS (Supplementary Table 2). Among the nonprognostic studies, risk of bias was most frequently related to a lack of, or poorly described, exclusion criteria, occurring in 51 of the 66 studies. The reference standard used for determining the presence or absence of RA-ILD introduced the potential for bias in 25 studies, typically for vaguely described diagnostic criteria or, rarely, for absence of cross-sectional imaging in the diagnostic criteria. Statistical analyses were unadjusted in 41 studies, resulting in a high risk of confounding bias.

All eight of the prognostic studies had moderate risk of bias in the study participation domain because of low sample size and/or incompletely described source population and characteristics. Six of the eight studies were at moderate or high risk of confounding bias because of incompletely measuring or defining confounders or for lack of adjustment in statistical analyses.

DISCUSSION

This systematic review has identified several candidate peripheral blood biomarkers for RA-ILD and has summarized their performance for distinguishing RA-ILD from RA without ILD or from other types of lung disease, as well as their ability to prognosticate RA-ILD disease course. Biomarkers capable of serving these roles included cytokines and chemokines, genetic polymorphisms, autoantibodies, growth factors, extracellular matrix proteins, tumor markers, lung epithelial–related proteins, and others. Despite the large number of identified biomarkers and an increase in RA-ILD biomarker research over the past decade, few biomarkers have been rigorously assessed with appropriate confounder adjustment and external validation. Thus, before adopting them for regular clinical use, these biomarkers need further evaluation in well-designed studies and in additional RA-ILD populations.

The most common study objective identified in our review was to evaluate biomarkers distinguishing RA-ILD from RA without ILD. Such biomarkers could serve a valuable clinical role by identifying patients requiring further ILD evaluation (eg, PFTs, high-resolution CT) and guiding discussions regarding treatment options and/or risk reduction (eg, smoking cessation). Biomarkers already widely used in RA diagnosis and management, including autoantibodies and acute phase reactants, were investigated in several studies. Across these studies, mixed findings were observed for RF, anti-CCP, ESR, and CRP, with a general tendency for patients with RA-ILD to be more often seropositive and have higher autoantibody and/or acute phase reactant levels. Hampering the clinical utility of these biomarkers is their limited specificity for RA-ILD, as demonstrated by the discrepancy between frequency of seropositivity (60%-80%) and the estimated prevalence of RA-ILD (10%-40%) (4–7). In agreement with our findings, a recent meta-analysis focused only on the role of RF and anti-CCP antibody in the identification of RA-ILD and found substantial heterogeneity across studies (43). Based on pooled data, authors of this report estimated higher odds of RA-ILD related to RF and anti-CCP positivity and titer, although only a minority of the studies included in this meta-

Table 5. Peripheral blood biomarker prognostication of RA-ILD

Biomarker (citations)	Outcome
Autoantibodies	
Anti-CCP (33,40,98)	Three studies, all negative. One retrospective cohort study found high titer ACPA was associated with acute exacerbations and/or all-cause mortality in univariate analysis (OR 3.949, 95% CI: 1.119-13.932, $P = 0.033$) but did not persist after multivariable adjustment (OR 0.722, 95% CI: 0.262-1.989, $P = 0.528$). Two other case-control studies with unadjusted analyses found no difference in anti-CCP positivity and/or titer between patients with RA-ILD who died vs. survived.
RF (40,42,98)	Three case-control studies performed, with two negative and one positive. One found that over a 10-year period, patients with RA-ILD who died had a greater RF titer than those who survived (774.5 vs. 345.2 IU/mL, $P = 0.001$) but no difference in proportion RF-positive (82.1% vs. 70.8%, $P = 0.161$). Multivariable logistic regression found no association between high RF titer (>3 times ULN) and mortality (OR 1.90, 95% CI: 0.56-6.43). Another found no association between RF titer and mortality (HR 1.00, 95% CI: 0.999-1.001, $P = 0.31$). Another of patients with RA-ILD found that nonsurvivors had greater mean RF titer than survivors (349 vs. 86.1 IU/ml), $P = 0.016$), with no difference between groups in RF positivity (27 [nonsurvivors] vs. 39 [survivors], $P = 0.673$). In univariate analysis, RF >88 IU/ml was associated with mortality (HR 2.246, 95% CI: 1.066-4.732, $P = 0.033$).
Lung epithelial–related proteins	
KL-6 (38-42)	Five studies, four positive, one negative. The only retrospective cohort design of the group was a study of RA-UIP in which unadjusted analysis found an association with disease progression at 1 year (OR 1.001, 95% CI: 1.000-1.002, $P = 0.008$) that was no longer significant after adjustment (OR 1.001, 95% CI: 1.000-1.003, $P = 0.077$). KL-6 levels were significantly greater during acute exacerbations compared with baseline disease (2147 vs. 794 U/ml, $P < 0.001$). Multivariate analysis revealed that high levels of KL-6 (≥933 U/ml) were an independent predictor of mortality (HR 3.035, 95% CI: 1.168-7.885, $P = 0.023$). The remaining four were case-control designs. In one study of patients with RA-ILD, KL-6 was found to be a significant predictor of death, with an optimal cutoff of 685 U/ml (C-index = 0.687, $P = 0.004$). High levels of KL-6 (>685U/ml) were associated with mortality in multivariable analysis (HR 2.984, 95% CI: 1.227-7.257, $P = 0.016$). When stratified by ILD pattern, the findings remained for the RA-UIP group, but no association with mortality was found for the non-UIP group. Another adjusted study found no association between KL-6 and mortality (HR 1.003, 95% CI: 0.999-1.006, $P = 0.068$). Other unadjusted studies found that baseline KL-6 levels were significantly higher in those who experienced disease progression (1987 vs. 799 U/ml), $P = 0.027$) or did not survive a 1-year follow-up period (OR 1.016, 95% CI: 1.01-1.02).
SP-A (41)	Single retrospective cohort study of RA-UIP. Unadjusted analysis found no association with SP-A levels and disease progression at 1 year (OR 1.004, $P = 0.418$). Levels were similar during acute exacerbations compared with baseline disease ($P = 0.265$).
SP-D (38,42)	Two case-control studies, both negative. In an adjusted analysis, there was no association with SP-D and mortality (HR 1.001, $P = 0.203$). Another unadjusted analysis found no association between SP-D concentrations and disease progression over a mean follow-up of 3 years.
Genetic polymorphisms	
MUC5B mutation (33)	Single retrospective cohort study found that MUC5B mutations (rare [MAF <0.01] and deleterious variants not including rs35705950) were associated with acute exacerbations and/or all-cause mortality in a univariate LR (OR 2.308 $P = 0.043$), though this was not statistically significant after multivariable adjustment (OR 2.312, 95% CI: 0.951-5.620, $P = 0.065$).
Cytokines and chemokines	
CCL18 (PARC) (38)	Single case-control study of RA-ILD. Unadjusted analyses found no relationship between CCL18 concentrations and disease progression at mean follow-up of 3 years. Data not reported.
IL-32 (41)	Single retrospective cohort study of RA-UIP. Unadjusted analysis found no association with IL-32 levels and disease progression at 1 year (OR 0.999, $P = 0.218$). Levels were no different during acute exacerbations compared with baseline disease ($P = 0.461$).
IL-6 (41)	Single retrospective cohort study of RA-UIP. Adjusted analysis revealed an association with IL-6 levels and disease progression at 1 year (OR 1.040, $P = 0.039$). IL-6 levels tended to be higher during acute exacerbations, though not statistically significant ($P = 0.068$).
Extracellular matrix proteins	
MMP-7 (41)	Single retrospective cohort study of RA-UIP. Unadjusted analysis found no association between MMP-7 levels and disease progression at 1 year (OR 1.099, $P = 0.394$). Levels were no different during acute exacerbations compared with baseline disease ($P = 0.580$).
Others	
CRP (40–42,97,98)	Five studies, with two positive and three negative. In a case-control study of RA-ILD, baseline CRP levels were higher in those who had died vs. those who had survived over a 10-year period (37.2 vs. 25.1 mg/l, $P = 0.009$), though multivariable regression found no association with mortality (OR 1.34, 95% CI: 0.95-1.88). In a retrospective cohort study, multivariable analysis found higher CRP concentrations were associated with fatal outcomes (OR 1.072, 95% CI: 1.000-1.150, $P = 0.049$). An adjusted case-control study found no association between CRP and mortality (HR 1.027, 95% CI: 0.954-1.094, $P = 0.458$). In a retrospective cohort study of RA-UIP, unadjusted analysis found higher CRP levels in patients whose disease progressed at 1 year compared with those whose disease did not progress (5.7 vs. 1.3 [units not reported], $P = 0.013$). Lastly, in a case-control

(Continued)

Table 5. (*Cont'd*)

Biomarker (citations)	Outcome
	study of patients with RA-ILD, there was no difference in mean CRP titers between survivors and nonsurvivors (3.9 [non-survivors] vs. 2.7 mg/dl, $P = 0.303$), and univariate analysis found no association with mortality (HR 1.030, 95% CI: 0.972-1.092, $P = 0.322$).
DKK-1 (97)	Single retrospective cohort study performed multivariable analysis, finding that DKK-1 was associated with fatal outcomes (OR 15.764, 95% CI: 1.086-228.843, $P = 0.043$). Median survival was longer for DKK-1-negative patients (5.1 vs. 2.7 years, $P = 0.041$).
ESR (41,98)	Two studies. In one case-control study of RA-ILD, baseline ESR was higher in those who had died vs. those who had survived over a 10-year period (58 vs. 42.2 mm/h, $P = 0.008$), though multivariable analysis of mortality was null (OR 1.00, 95% CI: 0.97-1.02). In another retrospective cohort study of RA-UIP, unadjusted analysis found higher ESR in patients whose disease progressed at 1 year compared with those whose disease did not progress (74 vs. 41 mm/hour, $P = 0.001$).
Leukocyte indices (42)	Single adjusted case-control study found that higher monocyte count (HR 1.020, 95% CI: 1.004-1.035, $P = 0.018$) and neutrophil count (HR 1.001, 95% CI: 1.001-1.117, $P = 0.026$) were associated with mortality in RA-ILD. No association was observed with lymphocyte count (HR 1.002, $P = 0.385$). Patients with high monocyte and neutrophil counts had worse survival than those with no ($P < 0.001$) or just one high lineage ($P = 0.001$).

Abbreviations: ACPA, anti–citrullinated protein antibody; CCL, chemokine ligand; CCP, cyclic citrullinated peptide; CI, confidence interval; CRP, C-reactive protein; DKK, dickkopf; ESR, erythrocyte sedimentation rate; HR, hazard ratio; IL, interleukin; ILD, interstitial lung disease; IU, international unit; KL, Krebs von den Lungen; LR, logistic regression; MAF, minor allele frequency; ml, milliliter; mm, millimeter; MMP, matrix metallopeptidase; MUC5B, mucin5B; OR, odds ratio; PARC, pulmonary and activation-regulated chemokine; RA, rheumatoid arthritis; RF, rheumatoid factor; SP-A, surfactant protein A; SP-D, lung epithelial–derived surfactant protein D; U, unit; UIP, usual interstitial pneumonia; ULN, upper limit of normal.

analysis performed multivariable adjustment. Moreover, findings varied based on geographic region, and there was the potential for publication bias. Based on these considerations, RF, anti-CCP, ESR, and CRP do not appear to be sufficient biomarkers for RA-ILD identification alone.

Beyond using existing RA-related biomarkers, several efforts to test biomarkers have shown promise in IPF, a disease that shares histopathologic similarities to RA-ILD in a UIP pattern (10,13). KL-6, SP-D, and MMP-7, which are lung epithelial and extracellular matrix proteins, were examined in multiple studies, including some with adjustment for potential confounders. The majority of these studies found an association between these biomarkers and RA-ILD, but additional testing of these biomarkers is needed in larger populations to adequately define their clinical application. The MUC5B rs35705950 promoter variant, the strongest known genetic risk factor for IPF, was associated with RA-ILD in a large multinational study (32,44). This association was restricted to RA-ILD in a UIP pattern resembling IPF, and the minor allele frequency was highly variable across regions. As biomarkers initially identified in IPF, they are clearly not specific to RA-ILD. Rather, they appear to be indicators of ILD, regardless of etiology (eg, IPF, RA, other CTD). For example, KL-6 levels differentiated between ILD and airway disease in RA but not between RA-ILD and other CTD-ILDs (25,45,46). In contrast, genetic variants associated with RA risk, such as shared epitope alleles, were not strongly associated with the presence of RA-ILD. At present, it does not appear that a single biomarker has adequate specificity for both RA and ILD.

The disease course of RA-ILD is variable and can be devastatingly progressive, with a median survival estimated between 3 and 8 years depending on the histopathologic and radiographic criteria used to characterize subtype and severity of disease (47,48). The ability to risk stratify patients could have significant clinical implications because treatment options such as immunomodulatory therapies and antifibrotics may reduce morbidity and preserve lung function but carry significant risks (16,49). However, few studies have evaluated the ability of biomarkers to predict the disease course. In a limited number of studies, a higher KL-6 level was associated with mortality and RA-ILD progression, though this was not universal. This observation parallels similar prognostic findings observed for KL-6 in IPF and other CTD-ILDs (50,51). Ultimately, limited conclusions can be drawn from these studies given the risk of bias related to small sample sizes and likely confounding as well as variability in assessed measures of outcomes (eg, all-cause mortality vs. PFT progression vs. acute exacerbations) and outcome timing. To advance toward a precision medicine approach of selecting therapies for patients with RA-ILD that is likely to progress, larger prospective cohort studies with sufficient follow-up, appropriate outcome assessments, and confounder adjustment are therefore required.

Although this systematic review focused on evaluating the performance of individual biomarkers, advances in multiplex biomarker assessment and big-data analytics have opened the possibility of using composite biomarker profiles consisting of multiple individual biomarkers. Data reduction techniques can inform the creation of biomarker profiles that may improve diagnostic sensitivity and specificity over individual biomarkers alone (29). Indeed, some studies included in this review evaluated a large number of biomarkers not for their individual performance but rather to inform biomarker profile development. This consideration may explain the infrequency of adjustment for potential confounders in those analyses; however, critical appraisal of multibiomarker

profiles for RA-ILD identification and prognostication was beyond the scope of this review.

A limitation of this systematic review relates to the variability in study quality for reports identified in our search. Many did not adjust for potential confounders, and few biomarkers were assessed in multiple studies or externally validated. Moreover, the criteria for RA-ILD, the composition of comparator groups, and the type and timing of prognostic outcomes were highly variable or inadequately detailed. Because of this variability, we could not perform meta-analysis and were only able to narratively summarize findings. Identifying RA-ILD biomarkers is an active area of expanding research productivity, and we were unable to include recent studies published after our search date. We focused on peripheral blood biomarkers because of their feasibility to obtain and be integrated into clinical care. Biomarkers collected from other sites (eg, bronchoalveolar lavage, sputum) may also be valuable in the assessment of RA-ILD, and their appraisal will require future work. Although we used validated quality assessment tools, we did have to adapt them to ensure appropriate assessment for risk of bias related to confounding. Despite these limitations, this is among the first efforts to comprehensively and systematically assess and appraise the performance of peripheral blood biomarkers in RA-ILD.

In conclusion, we have summarized the performance of peripheral blood biomarkers for identifying RA-ILD and predicting disease outcomes. Autoantibodies, lung epithelial and surfactant proteins, cytokines, growth factors, extracellular matrix proteins, genetic markers, and various other biomarkers are candidates for filling these roles. Biomarkers identified in IPF (MMP-7, SP-D, and KL-6) were those most closely associated with ILD among patients with RA in our review, but they appear to lack specificity for the underlying disease associated with ILD. All biomarkers considered require additional testing in larger well-designed studies before they can be integrated into regular clinical care, and additional RA-ILD biomarker discovery endeavors are encouraged.

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AUTHOR CONTRIBUTIONS

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