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Original article

The impact of disease severity measures on survival in U.S. veterans with rheumatoid arthritis-associated interstitial lung disease

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Abstract

Objectives. To determine whether RA and interstitial lung disease (ILD) severity measures are associated with survival in patients with RA-ILD.

Methods. We studied US veterans with RA-ILD participating in a multicentre, prospective RA cohort study. RA disease activity (28-joint DAS [DAS28-ESR]) and functional status (multidimensional HAQ [MDHAQ]) were collected longitudinally while pulmonary function tests (forced vital capacity [FVC], diffusing capacity for carbon monoxide) were obtained from medical records. Vital status and cause of death were determined from the National Death Index and administrative data. Predictors of death were assessed using multivariable Cox regression models adjusting for age, sex, smoking status, ILD duration, comorbidity burden and medications.

Results. We followed 227 RA-ILD participants (93% male and mean age of 69 years) over 1073 person-years. Median survival after RA-ILD diagnosis was 8.5 years. Respiratory diseases (28%) were the leading cause of death, with ILD accounting for 58% of respiratory deaths. Time-varying DAS28-ESR (adjusted hazard ratio [aHR] 1.21; 95% CI: 1.03, 1.41) and MDHAQ (aHR 1.85; 95% CI: 1.29, 2.65) were separately associated with mortality independent of FVC and other confounders. Modelled together, the presence of either uncontrolled disease activity (moderate/high DAS28-ESR) or FVC impairment (<80% predicted) was significantly associated with mortality risk. Those with a combination of moderate/high disease activity and FVC <80% predicted had the highest risk of death (aHR 4.43; 95% CI: 1.70, 11.55).

Conclusion. Both RA and ILD disease severity measures are independent predictors of survival in RA-ILD. These findings demonstrate the prognostic value of monitoring the systemic features of RA-ILD.

Key words: RA, interstitial lung disease, disease activity, mortality

Rheumatology key messages

- Few modifiable determinants of mortality risk have been identified in rheumatoid arthritis-associated interstitial lung disease (RA-ILD).
- RA disease activity and functional status measures were independently predictive of mortality in RA-ILD.
- The management of RA-ILD should include comprehensive monitoring and treatment of systemic disease manifestations.

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CLINICAL SCIENCE

Introduction

One in ten patients with RA develops clinically significant interstitial lung disease (ILD) [1–4], and subclinical interstitial lung abnormalities occur in another 30–50% of patients [5, 6]. ILD is among the most severe extra-articular manifestations of RA due to its dramatic impact on survival [1, 7, 8], with the median survival estimated to be as low as 3 years [1, 3, 9]. In the limited studies conducted to date, which often have a modest number of RA-ILD patients, the primary determinants of survival in RA-ILD have included older age [3, 10–12], male sex [13, 14], baseline pulmonary physiologic impairment [15, 16] and the extent of parenchymal involvement on lung imaging [14]. There are conflicting findings regarding whether ILD pattern such as usual interstitial pneumonia (UIP) impacts survival following a diagnosis of RA-ILD [17], though such studies have further established pulmonary function as a crucial predictor of mortality in RA-ILD [15].

While greater RA disease activity is associated with the risk of incident RA-ILD [18], it is unclear whether ongoing RA disease activity contributes to RA-ILD prognosis. RA disease activity is associated with overall survival in RA irrespective of lung disease [19], but it has not been evaluated as an independent prognostic factor for survival in patients with RA-ILD. Poorer functional status has similarly been tied to reduced survival in RA [20], but the impact on survival in patients with RA-ILD is uncertain. Understanding whether these RA disease severity measures are associated with RA-ILD survival could inform disease monitoring strategies in this population as well as the selection and use of DMARDs. This knowledge is highly relevant to clinical care since the therapeutic roles of DMARDs and anti-fibrotic agents in RA-ILD are still being defined.

The objective of this study was to examine whether RA disease activity and functional status, conventional measures of RA disease severity, following ILD onset were associated with mortality risk in this population independent of ILD severity as assessed by pulmonary function testing. We hypothesized that RA disease severity measures, 28-joint Disease Activity Score with ESR (DAS28-ESR) and multidimensional HAQ (MDHAQ), would be associated with reduced survival in RA-ILD independent of pulmonary function (forced vital capacity [FVC]), and other known RA-ILD prognostic factors.

Methods

Study design

We conducted a cohort study of RA-ILD patients from the Veteran Affairs RA (VARA) registry, a multicentre, prospective cohort study of US veterans with rheumatologist-diagnosed RA who fulfilled the 1987 ACR classification criteria [21]. Demographics and RA disease features were collected at registry enrolment while RA disease activity measures and functional status were collected longitudinally per routine care. Linkages between the registry and Veterans Affairs (VA) electronic health record and administrative data in the VA Corporate Data Warehouse (CDW) allowed for robust capture of comorbidities and medications [22]. All participants provided written informed consent, and each participating site received Institutional Review Board approval. This study was approved by the VA Nebraska–Western Iowa Health Care System Institutional Review Board.

RA-ILD identification and validation

RA-ILD identification and classification in the registry has previously been described [23–25]. Briefly, to identify participants with RA-ILD, we first screened all registry participants for $\geq$2 International Classification of Diseases (ICD)-9/10 codes for ILD or $\geq$1 ICD-9/10 code and $\geq$1 CT scan of the chest using national VA data in the CDW. Subsequently, a board-certified rheumatologist validated ILD diagnoses through standardized medical record review and recorded the date of the first clinical ILD diagnosis. RA-ILD cases were deemed valid if patients had a provider diagnosis of RA-ILD and had either imaging findings (CT of the chest [>96% of cases] or chest radiography) or lung biopsy consistent with RA-ILD. The patients who did not meet the RA-ILD validation criteria were excluded from this study.

Primary exposures

The primary exposures assessed were RA disease activity, functional status and pulmonary function. RA disease activity and functional status measures were obtained from the VARA registry and considered time-varying (values updated at each follow-up observation) in all analyses. RA disease activity was measured using the DAS28-ESR in the primary analyses and categorized according to defined thresholds (remission, low, moderate and high) [26]. The DAS28 with CRP was used in secondary analyses [26], as were individual disease activity components (patient global assessment [PtGA, 0–100 mm], provider global assessment [PrGA, 0–100 mm], swollen joint count [SJC], tender joint count [TJC], ESR [mm/h] and CRP [mg/dl]). Functional status was measured with the MDHAQ (range 0–3) [27] and categorized into approximately equally sized groups as follows: 0–0.49, 0.50–0.99, 1.00–1.49 and $\geq$1.50.

Pulmonary function test (PFT) results were collected from the medical records and considered time-invariant. Percentage predicted forced vital capacity (FVC % predicted) and diffusing capacity for carbon monoxide (DLCO % predicted) were from the PFT closest to the start of follow-up (i.e. index date, defined below). This included data prior to the index date or within 2 years after the index date. FVC and DLCO % predicted were categorized as $\geq$80%, 50–80%, 30–50% and <30%, analogous to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity criteria for chronic obstructive pulmonary disease (COPD) [28].

Study covariates and descriptive variables

Demographic and health behaviour data were collected from patients at registry enrolment and included age, sex, race, education level and self-reported smoking status (modelled as ever *vs* never use). BMI (kg/m^2) was calculated from weight measurements and the modal height, which were extracted from the VA CDW as previously reported [29, 30]. The Rheumatic Disease Comorbidity Index (RDCI) score without lung disease was calculated from comorbidities collected from linked administrative data in the CDW [31].

RA disease duration was obtained from the registry. Anti-CCP antibody and RF were measured using banked serum collected at registry enrolment with positivity defined using established thresholds [32]. RA treatments were obtained from pharmacy dispensing data within the CDW at the index date and included prednisone, methotrexate, other conventional synthetic DMARDs (csDMARDs: leflunomide, sulfasalazine, hydroxychloroquine, azathioprine), biologic and targeted-synthetic (bDMARDs and tsDMARDs, respectively: TNF inhibitors [TNFi], abatacept, tocilizumab, sarilumab, rituximab, and Janus kinase inhibitors [JAKi]).

ILD imaging features and the presence of a clinical diagnosis of comorbid COPD were both collected by standardized medical record review. Usual interstitial pneumonia (UIP) or non-UIP pattern was obtained from chest CT reports, when available. Supplemental oxygen use at the index date was obtained from the CDW.

Study outcome

The primary outcome in this study was all-cause mortality. Vital status was determined using the National Death Index (NDI) as well as vital status data maintained by the VA in CDW [22]. NDI data were available through 31 December 2017, while CDW death data were available through the end of the study period (31 December 2019). Cause of death was obtained from ICD-10 codes in the NDI and categorized according to Centers for Disease Control and Prevention (CDC) chapters [33].

Statistical analysis

An index date was assigned to patients based on the latest of either VARA enrolment or diagnosis of RA-ILD, to prevent immortal time bias occurring after RA-ILD diagnosis and before VARA enrolment [34]. Participants were followed from the index date until the date of death or the end of the study period. Mortality rate per 1000 person-years was calculated.

Associations of the primary exposures (time-updated disease activity and functional status, time-invariant PFT parameters) with survival were evaluated in three models with variable adjustment in order to separately assess confounding from specific covariates. Initially, these measures were evaluated in age-adjusted Cox proportional hazards regression models. RA disease activity (DAS28-ESR), functional status (MDHAQ) and PFT parameters (FVC % predicted and DLCO % predicted) were then assessed as predictors of survival in separate multivariable Cox models. The pre-hypothesized covariates that were examined in multivariable models included age, sex, smoking status, ILD duration, RDCI score and DMARDs (all time-invariant), which were selected for their potential to confound the association between disease severity measures and mortality based on prior literature [13, 15]. Adjusted survival curves were generated from these models.

We then evaluated whether RA disease activity and functional status measures were associated with survival independent of PFT values. We constructed separate multivariable Cox models for disease activity (DAS28-ESR) and functional status (MDHAQ) measures, adjusting for FVC % predicted in addition to the aforementioned covariates. FVC % predicted was selected for these models over DLCO % predicted due to a greater number of FVC measurements being available. Secondarily, we assessed the DAS28-CRP and components of the DAS28-ESR/CRP in a similar manner. Sensitivity analyses were performed categorizing smoking status into three categories (current, former and never) and, to assess for potential reverse causation, incorporating a 180-day lag in updating RA disease activity and functional status measures. Results from these sensitivity analyses were unchanged from the primary analyses (data not shown).

Finally, to assess the combined association of disease activity and PFT measures with mortality, we categorized patients by the combination of DAS28-ESR (remission or low *vs* moderate or high) and FVC % predicted ($\geq$80% *vs* $<$80%). These Cox models were adjusted for the aforementioned covariates and adjusted survival curves were generated.

Complete case analysis was performed such that individuals with missing predictor variables (e.g. PFT components) were excluded from models that included those variables. The proportional hazards assumption was assessed through log-log plots and testing of Schoenfeld residuals, which did not suggest violation of the proportional hazards assumption. All analyses were completed using Stata v15 (StataCorp; College Station, TX, USA) within the VA Informatics and Computing Infrastructure (VINCI) environment.

Results

Baseline patient characteristics

We identified 227 participants from the registry with RA-ILD. Our study cohort was predominantly male (92.5%), primarily white (74.4%) and had a mean age of 68.7 years (Table 1). Approximately 85% of the cohort had a smoking history, and 45% of the cohort had a concurrent diagnosis of COPD. Participants had a mean RA disease duration at the index date of 14.6 years (12.4 years at registry enrolment). Most participants were seropositive for anti-CCP antibody (84.5%) and/or RF (87.9%). Participants had a baseline mean (S.D.) DAS28-ESR score

Table 1 Baseline characteristics of patients with RA-ILD ($n = 227$)

Characteristic	Value
Demographics and health behaviours	
Age, mean (S.D.), years	68.7 (9.2)
Male sex, %	92.5
White race, %	74.4
≥ High-school education, %	86.4
Ever smoker, %	85.3
Body mass index, mean (S.D.), kg/m^2	28.4 (5.8)
Chronic obstructive pulmonary disease, %	44.9
RDCI score (no lung disease), mean (S.D.)	2.3 (1.3)
RA-related factors	
RA duration, mean (S.D.), years	14.6 (12.2)
Anti-CCP positive, %	84.5
RF positive, %	87.9
DAS28-ESR, mean (S.D.)	4.0 (1.3)
DAS28-CRP, mean (S.D.)	3.5 (1.3)
MDHAQ, mean (S.D.)	1.0 (0.6)
DMARDs (hierarchical), %	
None	14.1
Non-methotrexate csDMARDs	33.0
Methotrexate	20.3
b/tsDMARDs	25.6
b/tsDMARDs + methotrexate	7.1
Prednisone, %	45.8
ILD-related factors	
ILD duration, mean (S.D.), years	1.7 (3.3)
UIP pattern, %	65.0
Supplemental oxygen use, %	21.2
FVC % predicted, mean (S.D.)	77.2 (17.9)
DLCO % predicted, mean (S.D.)	60.2 (21.9)

Missing: high school education, $n = 21$; smoking status, $n = 3$; BMI, $n = 6$; RA duration, $n = 3$; anti-CCP antibody, $n = 20$; RF, $n = 20$; Rheumatoid nodules, $n = 40$; DAS28-CRP, $n = 9$; DAS28-ESR, $n = 6$; MDHAQ, $n = 4$; UIP pattern, $n = 130$; FVC % predicted, $n = 52$; DLCO % predicted, $n = 62$. Anti-CCP: anti-CCP antibody; b/tsDMARD: biologic or target synthetic DMARD; csDMARD: conventional synthetic DMARD; DAS28-CRP; DAS-28 with CRP; DAS28-ESR: DAS-28 with ESR; DLCO: diffusing capacity for carbon monoxide; FVC: forced vital capacity; ILD: interstitial lung disease; MDHAQ: multi-dimensional HAQ; RDCI: Rheumatic Disease Comorbidity Index; UIP: usual interstitial pneumonia.

of 4.0 (1.3) and MDHAQ score of 1.0 (0.6). Non-methotrexate csDMARDs (33.0%), b/tsDMARDs (25.6%) and methotrexate (20.3%) were the most commonly used DMARDs at the index date. While radiographic patterns of ILD were available for only a portion of the cohort ($n = 97$), UIP pattern was the most frequently reported pattern (65.0%). Mean (S.D.) FVC % predicted was 77.2 (17.9) and DLCO % predicted was 60.2 (21.9).

Mortality rates and causes of death

Over 1073 person-years of follow-up (mean follow-up 4.7 years), 108 deaths occurred. The crude mortality rate was 100.7 (95% CI: 83.4, 121.6) deaths per 1000 person-years, and the median survival after the index date was 6.7 years. Using the RA-ILD diagnosis date as the start of follow-up, median survival after diagnosis was 8.5 years.

Cause of death was available for 94 of the 108 total deaths and is listed in Table 2. Respiratory-related deaths were the leading cause of death (27.7%), with 57.7% of respiratory deaths attributed to ILD. Other common causes of death were diseases of the circulatory system (23.4%), neoplasms (18.1%) and diseases of the musculoskeletal system (11.7%). Lung cancers accounted for 70.6% of the deaths related to neoplasms.

Age-adjusted associations with survival

Age-adjusted associations between exposures of interest and survival among individuals with RA-ILD are presented in Table 3. Higher RA disease activity and lower functional status over time were significantly associated with worse survival when modelled as continuous or categorical variables. Relative to those in remission, those with a DAS28-ESR in high disease activity had a >4-fold higher risk of death (HR 4.87; 95% CI: 2.02, 11.71). Results were similar using the DAS28-CRP. Individual disease activity components associated with mortality risk included PtGA (per 10 mm, HR 1.16; 95% CI: 1.08, 1.25), PrGA (per 10 mm, HR 1.14; 95% CI: 1.05, 1.24), ESR (per 10 mm/h, HR 1.15; 95% CI: 1.02, 1.17) and CRP (per 1 mg/dl, HR 1.12; 95% CI: 1.06, 1.18). Compared with those with preserved physical function (MDHAQ <0.5), RA-ILD patients with a MDHAQ >1.5 had a 3-fold increased risk of death (HR 3.19; 95% CI: 1.60, 6.39). Lower DLCO % predicted was significantly associated with poorer survival (HR 1.16 per 5% decrease; 95% CI: 1.08, 1.25). While not statistically significant, there were trends towards poorer survival with lower FVC % predicted values.

Multivariable associations of disease activity, functional status, and PFTs with survival

In separate multivariable models, DAS28-ESR, MDHAQ, FVC and DLCO were all independently associated with survival (Fig. 1A–D). Patients with high disease activity had a >4-fold higher mortality risk compared with those in remission. Similarly, those with the poorest functional status (MDHAQ >1.5) had a >3-fold increase in mortality risk compared with those with preserved physical function (MDHAQ 0–0.49) (Fig. 1A and B). Patients with FVC and DLCO % predicted values below 80% also demonstrated an increased mortality risk (Fig. 1C and D).

Associations of disease activity and functional status with survival adjusted for FVC

Associations of RA disease activity and functional status with survival persisted after adjusting for FVC % predicted (Table 4). For each 1-unit increase of DAS28-ESR, there was a 22% increase in mortality (HR 1.21;

Table 2 Causes of death among participants with RA-ILD

ICD-10 Chapter	Percentage of deaths
Diseases of respiratory system	27.7 ($n = 26$)
Interstitial lung disease ($n = 15$, 57.7%[a])	
Chronic obstructive pulmonary disease ($n = 7$, 26.9%[a])	
Pneumonia ($n = 2$, 7.7%[a])	
Other ($n = 2$, 7.7%[a])	
Diseases of the circulatory system	23.4 ($n = 22$)
Neoplasms	18.1 ($n = 17$)[b]
Diseases of musculoskeletal system	11.7 ($n = 11$)
Certain infection and parasitic diseases	5.3 ($n = 5$)
Diseases of nervous system	3.2 ($n = 3$)
Diseases of digestive system	2.1 ($n = 2$)
Diseases of genitourinary system	2.1 ($n = 2$)
Symptoms, signs, and abnormal clinical and laboratory findings not classified elsewhere	2.1 ($n = 2$)
Other	4.3 ($n = 4$)[c]
Total number of deaths with available cause of death	94[d]

[a]Percentage of respiratory deaths. [b]$n = 12$ lung cancers. [c]Other includes $n = 1$ each of endocrine, nutritional and metabolic diseases; external causes of morbidity and mortality; mental and behavioural disorders; diseases of skin and subcutaneous tissue. [d]Cause of death was unavailable for 14 patients (deaths occurred after 31 December 2017, data from National Death Index not available after this date). ICD-10: international classification of diseases—10th revision; ILD: interstitial lung disease.

95% CI: 1.03, 1.41). Relative to those in remission, those with high disease activity had a >4-fold higher risk of death. Sensitivity analyses using the DAS28-CRP produced similar results. Mortality risk increased by 85% for each 1-unit increase in MDHAQ (HR 1.85; 95% CI: 1.29, 2.65), independent of FVC % predicted and other covariates. MDHAQ values >1.5 were associated with a >2.4-fold increase in mortality.

When evaluating the different RA disease activity components as predictors of death in RA-ILD, the PtGA (HR 1.19 per 10 mm; 95% CI: 1.08, 1.31), PrGA (HR 1.16; 95% CI: 1.05, 1.29), ESR (HR 1.14 per 10 mm; 95% CI: 1.05, 1.23) and CRP (HR 1.11; 95% CI: 1.03, 1.20) were each significantly associated with higher mortality risk. In contrast, neither SJC (HR 1.02; 95% CI: 0.96, 1.08) nor TJC (HR 1.00; 95% CI: 0.96, 1.04) was associated with mortality risk.

Survival by combined disease activity and FVC categorization

To assess the combined contribution of disease activity and pulmonary severity to mortality in RA-ILD, we categorized patients into four groups by the combination of RA disease activity (DAS28-ESR remission or low *vs* moderate or high) and/or FVC % predicted (≥80% *vs* <80%). The presence of either uncontrolled RA disease activity (HR 3.00; 95% CI: 1.13, 7.97) or FVC impairment (HR 3.07; 95% CI: 1.03, 9.19) alone was significantly associated with reduced survival (Fig. 2). The poorest survival was for those who had both uncontrolled RA disease activity and impaired FVC (HR 4.43; 95% CI: 1.70, 11.55).

Discussion

ILD dramatically impacts survival in RA [1, 3, 9], yet the prognostic factors in RA-ILD are poorly understood. In this study, we aimed to determine whether RA and ILD disease severity measures were independently associated with survival following the diagnosis of RA-ILD. Utilizing one of the largest RA-ILD cohorts to date to evaluate prognostic factors as well as linkage to robust medical and death records, we found that RA disease activity, functional status and PFT measures were independently predictive of survival in RA-ILD. The risk of death was >3-fold higher for RA-ILD patients who had either high composite RA disease activity or FVC impairment and nearly 4.5-fold higher for patients with both. Recognizing the independent contributions of disease activity, functional status and pulmonary disease severity on survival, our results demonstrate the value of comprehensively monitoring patients with RA-ILD, a systemic disease. Moreover, it is possible that utilizing treatment strategies guided by these measures could meaningfully improve long-term outcomes for patients with RA-ILD.

We tested and confirmed our hypothesis that routinely assessed measures of RA disease activity and functional status were associated with poorer survival in RA-ILD. Moreover, RA disease activity and functional status were predictive of mortality independent of the severity of pulmonary disease, as measured by FVC % predicted. Notably, the magnitude of the observed associations between RA disease severity measures and mortality was as strong or stronger in this RA-ILD population compared with a broader RA population from the same registry in prior work [35, 36]. Periodic assessment

TABLE 3 Age-adjusted associations of primary exposures with survival in RA-ILD

Variable	*n*	HR (95% CI)	*P*-value
Disease activity measures			
DAS28-ESR (per 1 unit)	221	1.27 (1.11, 1.44)	<0.001
DAS28-ESR categories	221		
Remission		Referent	—
Low		2.16 (0.84, 5.60)	0.11
Moderate		3.32 (1.43, 7.72)	0.005
High		4.87 (2.02, 11.71)	<0.001
DAS28-CRP (per 1 unit)	216	1.22 (1.06, 1.40)	0.005
DAS28-CRP categories	216		
Remission		Referent	
Low		2.56 (1.39, 4.72)	0.002
Moderate		2.19 (1.30, 3.70)	0.003
High		2.99 (1.55, 5.77)	0.001
Patient global assessment (per 10 mm)	224	1.16 (1.08, 1.25)	<0.001
Provider global assessment (per 10 mm)	213	1.14 (1.05, 1.24)	0.003
Swollen joint count	226	1.01 (0.96, 1.07)	0.60
Tender joint count	226	1.01 (0.98, 1.04)	0.65
ESR (per 10 mm/h)	222	1.15 (1.08, 1.23)	<0.001
CRP (per 1 mg/dl)	218	1.12 (1.06, 1.18)	<0.001
Functional status measures			
MDHAQ (per 1 unit)	223	2.01 (1.49, 2.70)	<0.001
MDHAQ categories	223		
0.00–0.49		Referent	—
0.50–0.99		1.57 (0.75, 3.30)	0.23
1.00–1.49		2.12 (1.04, 4.34)	0.04
1.50–3.00		3.19 (1.60, 6.39)	0.001
PFT measures			
FVC % predicted (per 5% decrease)	175	1.05 (0.99, 1.12)	0.10
DLCO % predicted (per 5% decrease)	165	1.16 (1.08, 1.25)	<0.001

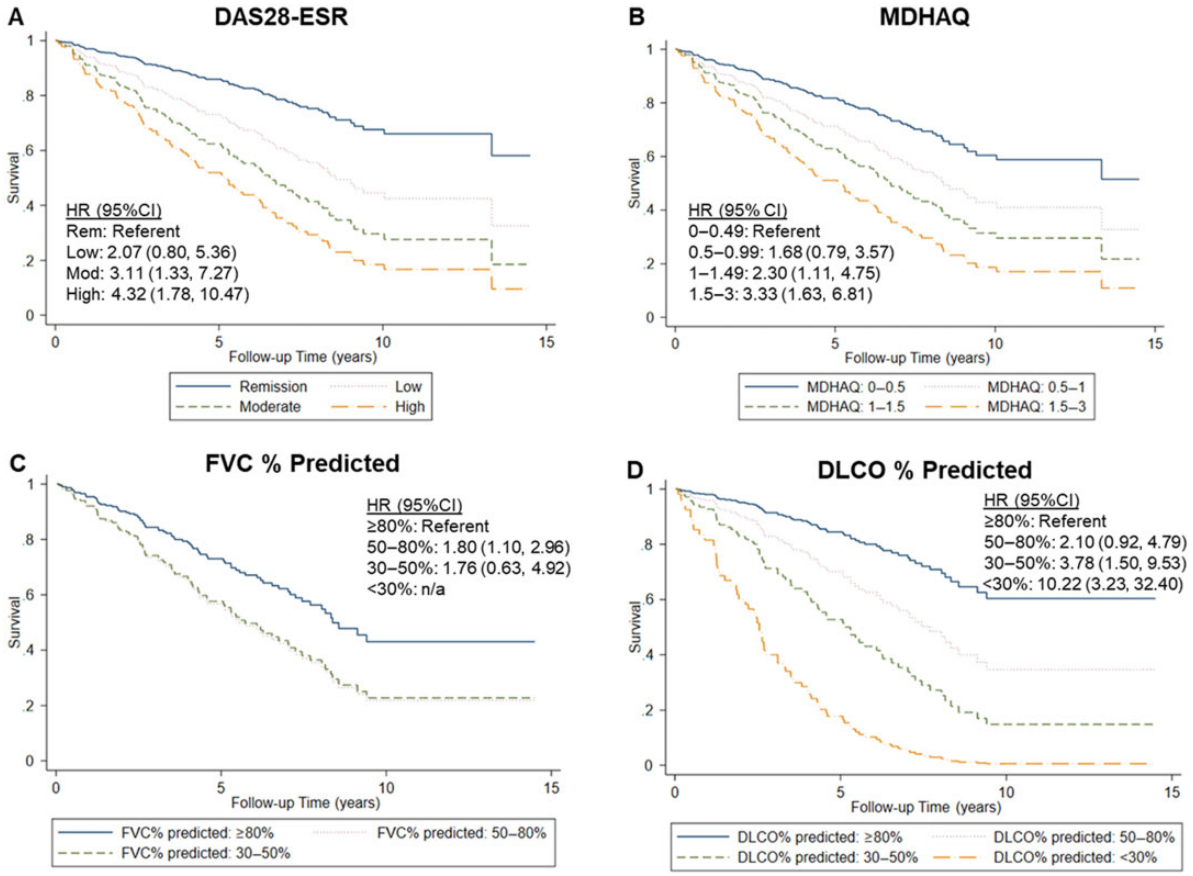
DAS28-CRP: disease activity score-28 with CRP; DAS28-ESR: disease activity score-28 with ESR; DLCO: diffusing capacity for carbon monoxide; FVC: forced vital capacity; HR: hazard ratio; ILD: interstitial lung disease; MDHAQ: multidimensional HAQ; PFT: pulmonary function test.

of RA disease activity and functional status as quality metrics for RA care in the US is part of the Merit-based Incentive Payment System (https://qpp.cms.gov/mips/quality-requirements). Our findings support the collection and utilization of these measures after a diagnosis of ILD given their ongoing prognostic value. Whether altering management based on these measures can improve RA-ILD longevity and outcomes will require future study. Importantly, an improving trend in mortality in RA patients compared with the general population has been reported during recent treatment periods characterized by early diagnosis, treat-to-target strategies and increasing availability of DMARDs [37]. Anti-fibrotic agents such as nintedanib and pirfenidone also appear to slow progression in progressive fibrotic lung disease [38], but it is unclear if anti-fibrotic agents can improve survival or have any efficacy for systemic features, in RA-ILD. The roles of these therapies alone and together in RA-ILD management remain an important question.

It is theorized that the inflammatory processes in the synovium and resultant systemic inflammatory responses that are central to RA pathogenesis contribute to the local production of pro-inflammatory and pro-fibrotic mediators within the lungs that are responsible for the development of ILD [39]. With disease activity being associated with poorer survival among RA-ILD patients, it could be speculated that ongoing articular and systemic inflammation are negatively affecting pulmonary status. To investigate this, we performed analyses of individual components of RA disease activity measures. Neither SJC nor TJC was predictive of mortality. Rather, associations of disease activity with mortality were driven by patient and provider global assessments as well as acute phase reactants. While this analysis does not support a direct role for articular disease activity in driving mortality risk, it may suggest that systemic features of RA not adequately captured by joint counts contribute to survival. Alternatively, we may be detecting the adverse influence of ILD itself on these components of RA disease activity. If so, then clinicians must consider the impact of ILD on RA disease activity measures when following a treat-to-target management approach of RA in patients with RA-ILD. Subsequent studies with longitudinal PFTs, imaging and RA disease activity measurements are needed to elucidate these answers.

Consistent with prior studies in RA-ILD [15, 16, 40], physiological measures of ILD severity were strongly predictive of survival in our study. Both lower FVC and

FIG. 1 Adjusted survival curves in RA-ILD by RA disease activity, functional status, and pulmonary function test severity



All models adjusted for age, sex, smoking history, ILD duration, RDCI score, and DMARDs

Survival curves depict the associations of disease activity levels (**A**), functional status (**B**), forced vital capacity % predicted (**C**), and diffusing capacity for carbon monoxide % predicted (**D**) with mortality in separate models. All survival curves were adjusted for age, sex, smoking history, ILD duration, Rheumatic Disease Comorbidity Index score and DMARDs. DAS28-ESR: 28-joint DAS with ESR; DLCO: diffusing capacity for carbon monoxide; FVC: forced vital capacity; HR: hazard ratio; ILD: interstitial lung disease; MDHAQ: multi-dimensional HAQ; Mod: moderate; RDCI: Rheumatic Disease Comorbidity Index; Rem: remission.

lower DLCO values were independent predictors of reduced survival. A clear dose-dependent relationship between more severe DLCO impairment and survival was observed with those having DLCO values <30% of predicted at a near 9-fold higher risk of death (Fig. 1D). Such findings were not seen in our study with FVC (Fig. 1C), which may be related to the infrequency of more severe FVC impairment in our cohort. While FVC values are obtained from spirometry, a routinely obtained PFT component, the strong influence of DLCO on survival as well as its value in assessing ILD progression suggests that patients with RA-ILD should also undergo regular DLCO monitoring for optimal disease prognostication [16].

While survival in RA-ILD was previously estimated to be as short as <3 years [1], ours and other more recent studies have estimated a median survival of 7–8 years [13, 15, 41]. Differences in the methods of classifying ILD, with our study predominantly capturing clinically significant ILD, as well as broader inclusion of RA-ILD patients at various stages and with various patterns, earlier detection due to increased chest imaging or growing awareness, and improved survival overall in RA may explain these discrepancies. As expected, diseases of the respiratory system were the leading cause of death among patients with RA-ILD, similar to a recent large study using Medicare claims data [42]. Cancer deaths were also elevated in RA-ILD patients in the aforementioned study. These findings were validated in our study and related specifically to lung cancer. The increased frequency of lung cancers in patients with RA-ILD may be related to shared risk factors such as

TABLE 4 Associations of disease activity and functional status measures with survival in RA-ILD after adjusting for forced vital capacity[a]

	n	HR (95% CI)	*P*-value
Primary analyses			
Disease activity measures			
DAS28-ESR (per 1 unit)	169	1.21 (1.03, 1.41)	0.02
DAS28-ESR categories	169		
Remission		Referent	—
Low		2.20 (0.70, 6.90)	0.18
Moderate		2.70 (0.95, 7.67)	0.06
High		4.14 (1.41, 12.12)	0.009
Functional status measures			
MDHAQ (per 1 unit)	170	1.85 (1.29, 2.65)	0.001
MDHAQ categories	170		
0.00–0.49		Referent	—
0.50–0.99		1.12 (0.45, 2.76)	0.81
1.00–1.49		1.88 (0.80, 4.42)	0.15
1.50–3.00		2.42 (1.07, 5.50)	0.03
Secondary analyses			
DAS28-CRP (per 1 unit)	165	1.18 (1.00, 1.39)	0.06
DAS28-CRP categories	165		
Remission		Referent	—
Low		2.78 (1.31, 5.87)	0.008
Moderate		2.04 (1.08, 3.87)	0.03
High		2.75 (1.29, 5.88)	0.009
Patient global assessment (per 10 mm)	170	1.19 (1.08, 1.31)	<0.001
Provider global assessment (per 10 mm)	164	1.16 (1.05, 1.29)	0.004
Swollen joint count	172	1.02 (0.96, 1.08)	0.49
Tender joint count	172	1.00 (0.96, 1.04)	0.99
ESR (per 10 mm/h)	170	1.14 (1.05, 1.23)	0.002
CRP (per 1 mg/dl)	167	1.11 (1.03, 1.20)	0.008

[a]Disease activity and functional status measures assessed in separate models adjusting for FVC % predicted, age, sex, ever smoking history, ILD duration, RDCI score and DMARDs. DAS28-CRP: DAS-28 with CRP; DAS28-ESR, disease activity score-28 with ESR; DLCO: carbon monoxide diffusing capacity; FVC: forced vital capacity; HR: hazard ratio; ILD: interstitial lung disease; MDHAQ: multidimensional HAQ; PFT: pulmonary function test; RDCI: Rheumatic Disease Comorbidity Index.

smoking, the disease itself and/or increased surveillance with chest imaging. Additional studies are needed to test whether ILD represents an independent risk factor for the development of lung cancer in RA.

Limitations to the study include the predominantly male cohort, which could impact generalizability. However, men more frequently develop extra-articular manifestations in RA, including ILD [43]. The classification and assessment of ILD was retrospective, which prohibited multidisciplinary discussion for RA-ILD diagnosis, resulted in missing PFT values, and prevented assessment of ILD pattern as a predictor of survival because of limited availability. Additionally, clinical indications for chest imaging and 6-min walk test results were not available. Cause of death was only available for NDI identified deaths, though this source captured 87% of deaths. Median survival estimates may be affected by left censoring related to patients being required to survive until the time of registry enrolment if they had previously developed RA-ILD. Causal inferences regarding DMARDs and their impact on survival cannot be drawn from this study, in part because only baseline medications were evaluated. Alternative study designs will be needed to evaluate the effects of DMARDs, as well as anti-fibrotic agents, on survival in RA-ILD. Finally, as with any observational study, there may be residual and/or unmeasured confounding. For example, smoking pack-years data were not available in the registry.

In summary, RA disease severity measures were prognostic of poorer survival in RA-ILD, independent of the severity of ILD. Monitoring patients with this systemic disorder should include the regular assessment of disease activity, functional status and pulmonary function to guide patient education and management. Tailoring the treatment of patients with RA-ILD to optimize each of these measures may offer a means to preserve longevity and reduce the morbidity that frequently accompanies RA-ILD.

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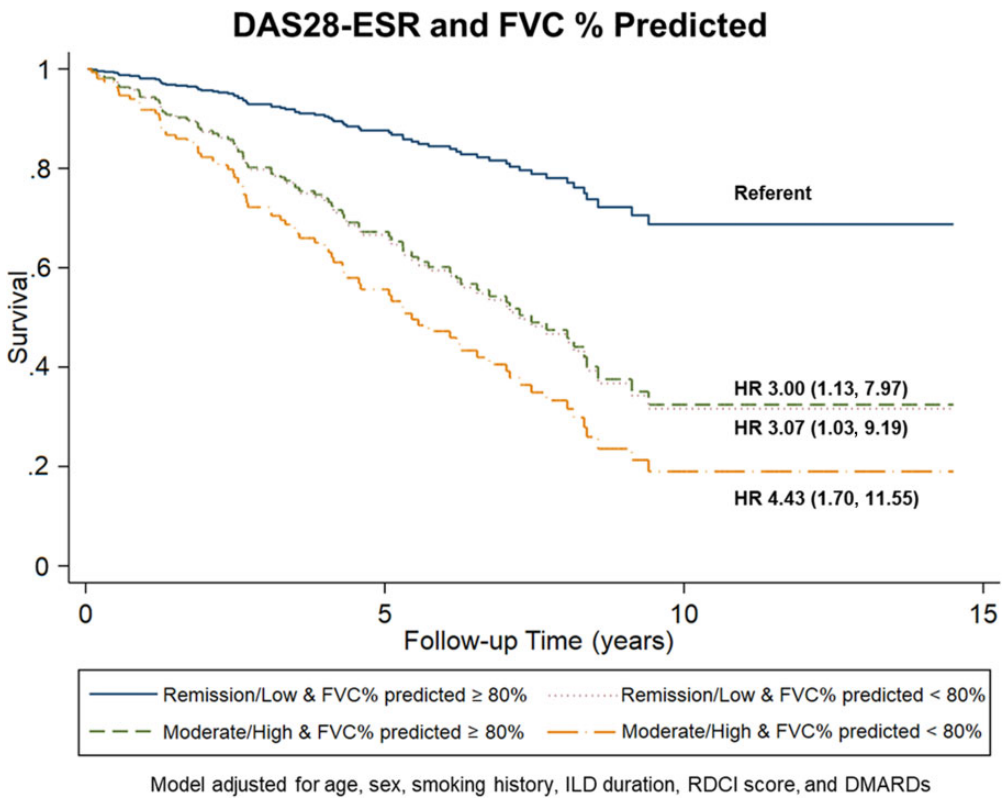
Fig. 2 Survival in RA-ILD by combined RA disease activity and forced vital capacity classification



Adjusted survival curves for patients with RA-ILD categorized by both disease activity (DAS28-ESR) and forced vital capacity (FVC). DAS28-ESR classified as either remission/low disease activity or moderate/high disease activity using established thresholds while FVC was dichotomized at 80% predicted. Remission/low disease activity and FVC % predicted $\geq$80% served as the reference group. All survival curves were adjusted for age, sex, smoking history, ILD duration, Rheumatic Disease Comorbidity Index score and DMARDs. DAS28-ESR, 28-joint DAS with ESR; FVC: forced vital capacity; HR: hazard ratio; ILD: interstitial lung disease; RDCI: Rheumatic Disease Comorbidity Index.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author and obtainment of necessary regulatory approvals.

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