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JOURNAL CLUB

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ARTICLE

The Impact of Disease Severity Measures on Survival in U.S. Veterans with Rheumatoid Arthritis-Associated Interstitial Lung Disease. Rebecca Brooks et al. Rheumatology (Oxford). 2022 Apr 4:keac208. doi: 10.1093/rheumatology/keac208. Epub ahead of print. PMID: 35377443.

CLINICAL QUESTION

When it comes to improving survival in patients with Rheumatoid Arthritis (RA) who have a diagnosis of associated interstitial lung disease (ILD), should we focus solely on managing the ILD, or should we also aim for minimal disease activity (MDA)? *In other words, will patients with RA-ILD have any benefit in survival if we also treat their joint disease?*

SUMMARY

RA-ILD is one of the most severe extra-articular manifestations of RA and affects 10% of patients, while it is present at least subclinically in up to 50% of them. Patients with RA-ILD have a much worse survival rate than patients without ILD, with the median survival of patients with RA-ILD estimated to be as low as 3 years. The primary determinants of survival in RA-ILD have included older age, male sex, baseline pulmonary physiologic impairment and the extent of parenchymal involvement on lung imaging.

The risk of incident RA-ILD is greater with RA disease activity. RA disease activity is also associated with overall survival in RA irrespective of lung disease. However, it is unclear if RA disease activity contributes to RA-ILD prognosis, and it has not been evaluated as an independent prognostic factor for survival in patients with RA-ILD.

Treatments for RA-ILD are still being defined as new therapeutic agents are available and focus on the fibrotic lung disease. Understanding whether 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 study evaluated **patients** from the Veterans Affairs RA (VARA) registry, which follows a prospective cohort of **US veterans with RA**, with RA-ILD (n=227). The **primary outcome** was all cause mortality. RA disease activity (28-joint DAS [DAS28-ESR]) and functional status (multidimensional HAQ [MDHAQ]) were collected, as well as the pulmonary function tests (forced vital capacity [FVC], diffusing capacity for carbon monoxide).

Analyses:
Predictors of death were assessed using multivariable Cox regression models adjusting for age, sex, smoking status, ILD duration, comorbidity burden and medications.

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Results:
A total of 227 RA-ILD participants (**93% male** and mean age of 69 years) over 1073 person-years were followed.

- Median survival after RA-ILD diagnosis was 8.5 years.
- Respiratory diseases (28%) were the leading cause of death.
    - Cause of death was available for 94 of the 108 total deaths.
    - Respiratory-related deaths were the leading cause of death (27.7%).
        - 58% of respiratory deaths were attributed to ILD.
    - Other common causes of death were:
        - Diseases of the circulatory system (23%);
        - Neoplasms (18%), with lung cancers accounting for 71% of them;
        - Diseases of the musculoskeletal system (12%).

- RA disease activity and functional status were each associated with mortality, independently of FVC and other confounders:
    - Time-varying DAS28-ESR (adjusted hazard ratio [aHR] 1.21; 95% CI: 1.03, 1.41)
    - MDHAQ (aHR 1.85; 95% CI: 1.29, 2.65).

- Modelled together, the presence of **either** uncontrolled disease activity (moderate/high DAS28-ESR) or FVC impairment (<80% predicted) was significantly associated with mortality risk.
    - The highest risk of death was seen in those with a combination of moderate/high disease activity and FVC <80% predicted (aHR 4.43; 95% CI: 1.70, 11.55).

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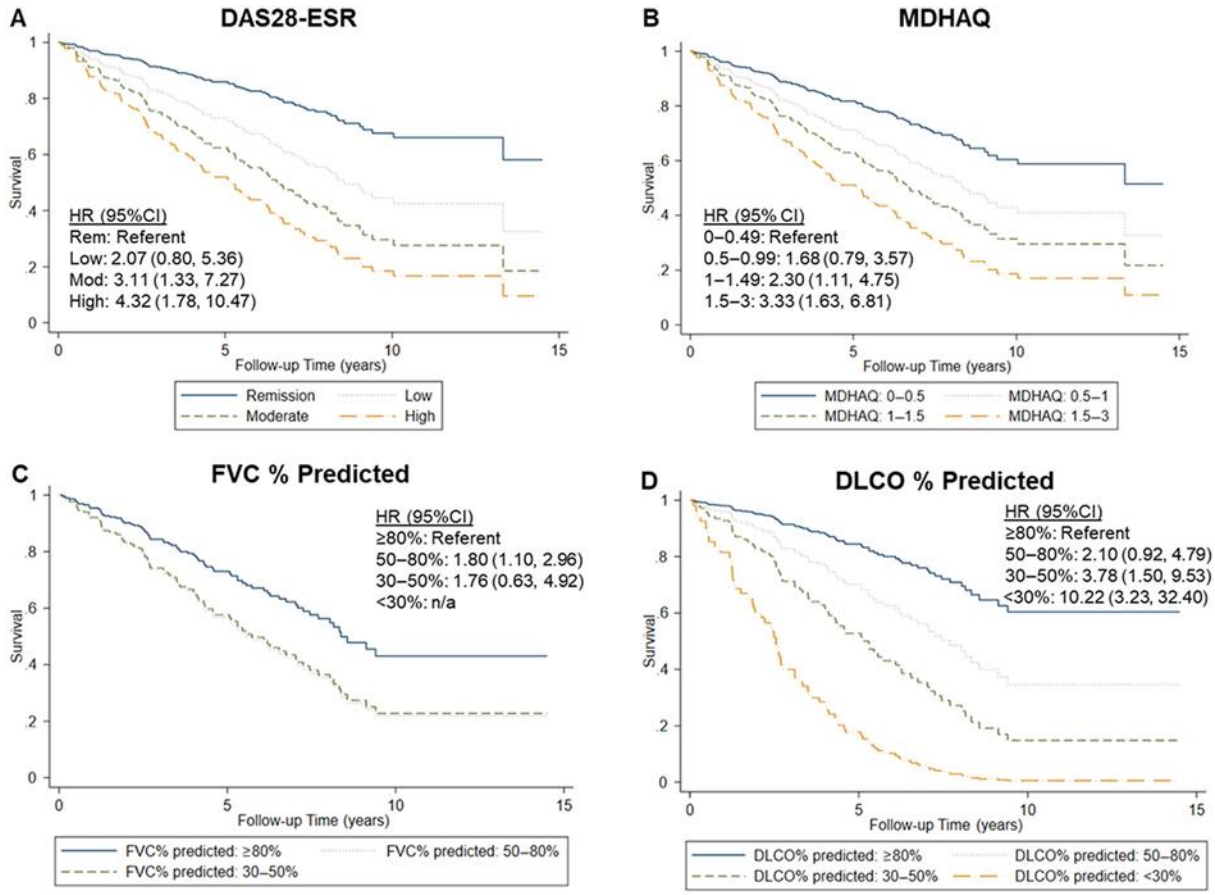

All models adjusted for age, sex, smoking history, ILD duration, RDCI score, and DMARDs

Conclusion:
Both RA and ILD disease severity measures were independent predictors of survival in RA-ILD. In patients with RA-ILD systemic features of RA, including RA disease activity, need to be monitored and managed.

Limitations:
This is a fairly large cohort, however, this cohort may not be representative of the general population, as it mostly involves men (Veterans) and follows a cohort of patients managed by the Veterans Affairs systems.

The analyses did not include patients who may have died with RA-ILD but never developed joint symptoms consistent with RA, as patients were required to survive until the time of registry enrollment.

Because of its observational nature, this study may still have residual and/or unmeasured confounding.

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GROUP OPINION

RA-ILD is one of the most severe extra-articular manifestations of RA and affects 10% of patients, while it is present at least subclinically in up to 50% of them. Patients with RA-ILD have a much worse survival rate than patients without ILD. We knew that the risk of incident RA-ILD is greater with RA disease activity. We also knew that RA disease activity is associated with overall survival in RA irrespective of lung disease. What we did not know was if RA disease activity contributed to RA-ILD survival prognosis.

This work by Brooks et al. helps us answer this question and found that both RA and ILD disease severity measures were independent predictors of survival in RA-ILD. The presence of either uncontrolled disease activity or FVC impairment was significantly associated with mortality risk. Not surprisingly, the highest risk of death was seen in those with a combination of moderate/high disease activity and FVC <80% predicted.

While this study may not be representative of the general population as it is a VA cohort study, it does bring an important point that all clinicians who care for patients with RA-ILD should consider. Managing RA disease activity is not only important for the quality of life of our patients with RA-ILD, but may also improve their survival rate overall.

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