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Clinical characteristics, physiological progression and survival in rheumatoid arthritis-associated interstitial lung disease: a retrospective multicentre cohort study in Malaysia

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Abstract

Background

Rheumatoid arthritis-associated interstitial lung disease (RA-ILD) is a major cause of morbidity and mortality in rheumatoid arthritis, but long-term multicentre data from Southeast Asia are limited. We described the clinical characteristics and outcomes of RA-ILD in a Malaysian cohort and explored factors associated with physiological progression and overall survival.

Methods

This retrospective cohort study included adults with RA-ILD attending three Malaysian tertiary centres between January 2024 and June 2026, irrespective of diagnosis date. Physiological progression (relative FVC decline ≥ 10%, absolute FVC decline ≥ 5% predicted, or absolute DLCO decline ≥ 10% predicted, at least six months from baseline) was assessed in patients with baseline and follow-up lung function. Progression-free and overall survival were estimated by Kaplan–Meier analysis, and factors associated with progression by univariable Cox regression.

Results

Of 115 patients, 87.0% were female; median age at RA-ILD diagnosis was 59.0 years (IQR 53.0–64.0) and median follow-up 8.3 years. Definite or probable usual interstitial pneumonia (UIP) was present in 57.4%, and median baseline FVC was 66.5% predicted. Forty-five patients (39.1%) had 73 hospitalisations, of which 35 (47.9%) were respiratory-related, mostly infections. Among 75 evaluable patients, 16 (21.3%) progressed, at a median of 2.0 years. Older age (HR 1.06 per year, 95% CI 1.02–1.10) and male sex (HR 3.30, 95% CI 1.06–10.30) were associated with progression, whereas UIP was associated with a lower hazard (HR 0.35, 95% CI 0.13–0.97). Seven patients (6.1%) died, five from lung infection. Overall survival was poorer in men (log-rank p = 0.008) but did not differ by HRCT pattern (p = 0.230).

Conclusions

Physiological progression occurred in about one in five evaluable Malaysian patients with RA-ILD and was associated with older age and male sex. The lower hazard with UIP was unexpected and may reflect survivor bias from left truncation and fluctuating lung function in non-UIP inflammatory phenotypes. Respiratory infection was the leading cause of respiratory hospitalisation and death, supporting long-term multidisciplinary surveillance with attention to infection prevention.

Background

Interstitial lung disease (ILD) is among the most clinically significant extra-articular manifestations of rheumatoid arthritis (RA) and contributes substantially to morbidity and mortality [1]. Its reported prevalence varies with study population, screening strategy and diagnostic criteria [2–4]; a 2024 meta-analysis of more than 11,000 patients estimated a pooled prevalence of approximately 18.7% [1]. The clinical course of RA-associated ILD (RA-ILD) is heterogeneous, ranging from stable disease to progressive pulmonary fibrosis, acute exacerbation, respiratory failure and death [5]. Usual interstitial pneumonia (UIP) is a commonly recognised pattern on high-resolution computed tomography (HRCT), although non-specific interstitial pneumonia (NSIP), organising pneumonia (OP) and other patterns also occur [6, 7].

Lower baseline forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO), greater fibrotic extent and a UIP pattern have been associated with progression and poorer survival [5, 8–12], and older age, male sex and smoking with increased mortality [11, 13, 14]. A meta-analysis of 78 studies reported median survival ranging from 2 to 14 years, with pooled cumulative mortality of approximately 9% in the first year, 30.2% at 3–5 years and 49.1% at 5–10 years [15]. Acute exacerbations carry a particularly poor prognosis, with 90-day mortality approaching 50% in some cohorts [16–18]. Nonetheless, predicting the course of an individual patient remains difficult [19], and definitions of progression vary widely between studies, limiting comparison between cohorts.

Treatment is guided largely by observational data and expert consensus. The 2023 American College of Rheumatology/American College of Chest Physicians guideline conditionally recommends mycophenolate mofetil, azathioprine, rituximab and cyclophosphamide as first-line options for ILD in systemic autoimmune rheumatic diseases, with antifibrotic therapy for progressive disease [20], and rituximab has been associated with stabilisation of lung function in observational cohorts [21, 22].

Most evidence on RA-ILD progression and survival comes from Western and East Asian populations [23, 24]. Differences in ethnicity, disease severity, healthcare practice and treatment may limit its applicability to Southeast Asia. A Malaysian study has described the clinical and radiological features of RA-ILD [25], but long-term multicentre data on progression, hospitalisation and survival in Malaysia's multi-ethnic population are lacking. We therefore aimed to describe the clinical characteristics and long-term outcomes of patients with RA-ILD managed at three Malaysian tertiary referral centres, to explore factors associated with physiological progression, and to compare overall survival by sex and baseline HRCT pattern.

Methods

Study design and setting

This retrospective multicentre cohort study was conducted at three tertiary referral centres in Malaysia: Hospital Canselor Tuanku Muhriz (HCTM), Kuala Lumpur; Hospital Sultan Idris Shah (HSIS), Serdang; and Hospital Putrajaya (HPJ). Adults with RA-ILD who attended the rheumatology, respiratory or ILD clinics of

these centres between 1 January 2024 and 30 June 2026 were identified, irrespective of the date of RA-ILD diagnosis, and their records were reviewed from RA-ILD diagnosis to the end of follow-up. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (Additional file 2).

Participants

Patients with RA were identified through rheumatology, respiratory and ILD clinic registries, departmental census and medical records, including electronic medical records, the Hospital Electronic Information System, case files and laboratory databases (Fig. 1). Eligible patients were aged 18 years or older at diagnosis, fulfilled the 1987 American College of Rheumatology (ACR) [26] or 2010 ACR/European League Against Rheumatism (EULAR) [27] classification criteria for RA, and had ILD attributed to RA on HRCT, with or without multidisciplinary team consensus. Patients were excluded if ILD was attributed to another aetiology or if a coexisting primary pulmonary disease made it impossible to distinguish its effect on symptoms, lung function or HRCT from that of RA-ILD.

Data collection

Baseline data, obtained at or closest to RA-ILD diagnosis, comprised demographics (age, sex, ethnicity and smoking status), comorbidities, rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and RA-directed treatment received before ILD diagnosis (glucocorticoids and conventional synthetic, targeted synthetic and biologic disease-modifying antirheumatic drugs [csDMARDs, tsDMARDs and bDMARDs]). RA disease activity, measured by the Disease Activity Score in 28 joints using ESR (DAS28-ESR), FVC, DLCO and HRCT were taken from assessments within three months of RA-ILD diagnosis. DAS28-ESR was classified as remission (< 2.6), low (2.6–3.2), moderate (> 3.2–5.1) or high (> 5.1) activity. ESR was classified using the age- and sex-adjusted upper limit proposed by Miller et al. [28], and CRP according to each laboratory's reference range.

HRCT features were recorded individually (ground-glass opacity, reticulation, consolidation, traction bronchiectasis, centrilobular nodules, mosaic attenuation, honeycombing and pleural effusion), and the overall pattern was classified as UIP, probable UIP, indeterminate for UIP, NSIP, OP or NSIP–OP overlap [29, 30]. Follow-up data comprised serial FVC and DLCO measurements, ILD-directed therapy (immunosuppressants, glucocorticoids or antifibrotics initiated or escalated with the documented intention of treating ILD), complications, hospitalisations and vital status.

Definitions and outcomes

The date of RA-ILD diagnosis was the date of the first HRCT showing ILD. The outcomes were physiological progression, hospitalisation and all-cause mortality. Physiological progression was

defined, using study-specific criteria, as a relative decline of ≥ 10% in FVC % predicted [11], an absolute decline of ≥ 5 percentage points in FVC % predicted, or an absolute decline of ≥ 10 percentage points in DLCO % predicted [29], relative to baseline, at any assessment at least six months after baseline. This definition was adapted from, but is not equivalent to, the physiological criteria for progressive pulmonary fibrosis (PPF) in the 2022 ATS/ERS/JRS/ALAT guideline [29]. Progression was assessed only in evaluable patients, defined as those with a baseline FVC or DLCO measurement and at least one follow-up measurement of the same parameter at least six months later.

Hospitalisation was defined as any inpatient admission after RA-ILD diagnosis, including elective admissions, with each admission counted separately; emergency department visits without admission were excluded. Respiratory infection was defined as a physician-documented respiratory tract infection requiring treatment, supported by compatible clinical, radiological or microbiological findings where available. Hospitalisation and mortality were assessed in all patients.

Sample size

The sample size was based on estimating 5-year all-cause mortality, the most consistently reported outcome in RA-ILD [15, 31]. Using the formula for a single proportion, $n = Z^2p(1 - p)/d^2$ [32], with an expected 5-year mortality of 39.0% from a Danish population-based cohort [31], 95% confidence ($Z = 1.96$) and a precision of 10% ($d = 0.10$), 92 patients were required. Allowing for 20% of patients being censored before five years of follow-up [33], the target sample size was 115.

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as mean (standard deviation, SD) or median (interquartile range, IQR) according to distribution, assessed by the Shapiro–Wilk test and visual inspection. Physiological progression-free survival (PFS) was measured from RA-ILD diagnosis to the first lung function test meeting the progression criteria; patients without progression were censored at their last evaluable test. Overall survival (OS) was measured from RA-ILD diagnosis to death from any cause, with censoring at the date last known alive. PFS and OS were estimated using the Kaplan–Meier method and compared using the log-rank test: PFS by sex, baseline HRCT pattern (definite or probable UIP vs non-UIP) and DAS28-ESR category (remission or low vs moderate or high), and OS by sex and HRCT pattern. Cumulative mortality at 1, 5, 10 and 15 years was derived as one minus the Kaplan–Meier survival estimate.

Candidate factors for physiological progression were examined using univariable Cox proportional hazards regression in the evaluable subgroup. Given the small number of events, multivariable modelling was not performed, and all regression analyses were considered exploratory and hypothesis-generating. Missing data were not imputed; analyses used all available observations under a missing-at-random assumption, and denominators are reported for each variable. Hospitalisations were summarised

descriptively. Analyses were performed using IBM SPSS Statistics version 30.0 (IBM Corp., Armonk, NY, USA), and a two-sided $p < 0.05$ was considered statistically significant.

Results

Study population

Of 542 patients with RA identified, 427 were excluded (415 did not fulfil the diagnostic criteria for ILD and 12 had ILD of another aetiology or a coexisting primary pulmonary disease), leaving 115 patients with RA-ILD (Fig. 1): 65 (56.5%) from HPJ, 27 (23.5%) from HCTM and 23 (20.0%) from HSIS. All 115 were included in the analyses of hospitalisation and mortality, and 75 patients with baseline and follow-up lung function measurements at least six months apart formed the physiological progression subgroup.

Baseline characteristics

Baseline characteristics are shown in Table 1. The cohort was predominantly female (n = 100, 87.0%) and never-smokers (n = 106, 92.2%); 63 patients (54.8%) were Malay, 33 (28.7%) Indian, 18 (15.7%) Chinese and one (0.9%) of another ethnicity. Mean age at RA diagnosis was 51.8 years (SD 11.2), and median age at RA-ILD diagnosis was 59.0 years (IQR 53.0–64.0). The median interval from RA to ILD diagnosis was 4.7 years (IQR 1.3–10.9); ILD preceded RA in six patients (5.2%) and was diagnosed concurrently in 16 (13.9%). Median follow-up from RA-ILD diagnosis was 8.3 years (IQR 5.1–12.3). Hypertension (n = 76, 66.1%) and dyslipidaemia (n = 58, 50.4%) were the most common comorbidities.

At RA-ILD diagnosis, DAS28-ESR indicated high disease activity in 23 patients (20.0%), moderate in 49 (42.6%), low in 18 (15.7%) and remission in 17 (14.8%), and was not recorded in eight (7.0%). Median FVC was 66.5% predicted (IQR 51.0–80.0; n = 111) and median DLCO 67.0% predicted (IQR 56.3–83.3; n = 29). A definite or probable UIP pattern was present in 66 patients (57.4%; definite 30 [26.1%], probable 36 [31.3%]); the remainder had indeterminate UIP (n = 22, 19.1%), NSIP (n = 18, 15.7%), NSIP–OP overlap (n = 5, 4.3%) or OP (n = 4, 3.5%).

All patients had received systemic glucocorticoids and 108 (93.9%) had received csDMARDs before RA-ILD diagnosis, most commonly methotrexate (n = 91, 79.1%); 12 (10.4%) had received tsDMARDs and 28 (24.3%) bDMARDs. After diagnosis, 20 patients (17.4%) received ILD-directed therapy, most often mycophenolate mofetil (n = 14, 12.2%) or rituximab (n = 5, 4.3%), and seven (6.1%) received the antifibrotic nintedanib. During follow-up, osteopenia or osteoporosis was found in 64 of the 82 patients (78.0%) who underwent bone densitometry, and malignancy and pulmonary hypertension were each documented in three patients (2.6%).

Hospitalisation

Outcomes are summarised in Table 2. Forty-five patients (39.1%) were hospitalised at least once, accounting for 73 admissions, of which 35 (47.9%) were respiratory-related. Respiratory infection

accounted for 32 admissions (43.8% of all admissions). Three admissions were due to RA-ILD itself: one for acute exacerbation and two for disease progression.

Physiological progression

Among the 75 evaluable patients, 16 (21.3%) met the criteria for physiological progression, at a median of 2.0 years (IQR 1.0–3.0) from RA-ILD diagnosis. Mean PFS was shorter in men than in women (6.4 [SE 1.59] vs 15.8 [SE 0.84] years; log-rank p = 0.027; Fig. 2). Mean PFS was longer in patients with a definite or probable UIP pattern than in those with non-UIP patterns (16.7 [SE 0.89] vs 10.1 [SE 1.16] years; p = 0.032), and in those with moderate or high DAS28-ESR activity than in those in remission or with low activity (15.9 [SE 0.64] vs 11.4 [SE 1.65] years; p < 0.001) (Table 3).

On univariable Cox regression (Table 4), older age at RA-ILD diagnosis (HR 1.06 per year, 95% CI 1.02–1.10; p = 0.002) and male sex (HR 3.30, 95% CI 1.06–10.30; p = 0.040) were associated with a higher hazard of progression, whereas a definite or probable UIP pattern was associated with a lower hazard (HR 0.35, 95% CI 0.13–0.97; p = 0.044). Baseline FVC was not associated with progression (HR 1.01 per 1% predicted, 95% CI 0.99–1.04; p = 0.237).

ILD-directed therapy was documented more often in progressors than in non-progressors (43.8% vs 16.9%; Additional file 1: Table S1). ILD-directed rituximab was given to two progressors (12.5%) and three non-progressors (5.1%), and exposure to Janus kinase inhibitors (JAKi) was similar between groups (12.5% vs 10.2%).

Mortality and overall survival

Seven patients (6.1%) died during follow-up, at a median of 6.17 years (IQR 2.92–6.25) after RA-ILD diagnosis (Additional file 1: Table S2). Lung infection caused five deaths, and one each was due to myocardial infarction and to ILD progression. Four of the seven patients had physiological progression before death, three had received mycophenolate mofetil-based ILD-directed therapy, and none had received antifibrotic therapy. Kaplan–Meier cumulative mortality was 0% at 1 year, 2.9% at 5 years, 6.5% at 10 years and 10.8% at 15 years (Fig. 3). OS was poorer in men than in women (deaths 3/15 [20.0%] vs 4/100 [4.0%]; mean survival 14.96 [SE 2.04] vs 19.49 [SE 0.46] years; log-rank p = 0.008; Fig. 4) but did not differ by HRCT pattern (deaths 6/66 [9.1%] with UIP vs 1/49 [2.0%] with non-UIP; p = 0.230) (Table 5). Median OS was not reached.

Discussion

In this multicentre Malaysian cohort followed for a median of 8.3 years, physiological progression occurred in about one in five evaluable patients and was associated with older age and male sex, whereas a UIP pattern was unexpectedly associated with a lower hazard of progression. All-cause mortality was low, and respiratory infection, rather than ILD progression, was the leading cause of respiratory hospitalisation and death.

Our cohort resembled the earlier Malaysian cohort of Ong et al. [25] in being predominantly female, with a similar age at diagnosis and moderately impaired lung function (median FVC 66.5% vs mean 62.4% predicted). However, the interval from RA to ILD diagnosis was longer (4.7 vs 3.5 years), and definite or probable UIP predominated (57.4%), whereas NSIP was the commonest pattern (44.4%) in that study. The longer follow-up in our cohort (median 8.3 vs 3.2 years) allowed more extended assessment of outcomes. This phenotypic heterogeneity, even within one country, is consistent with observations from multicentre cohorts in the United Kingdom [8, 9] and a hospital-based cohort in Sri Lanka [34].

The proportion with physiological progression (21.3%) was comparable to the 19.8% over five years reported in the prospective multicentre study of Mena-Vázquez et al. [35], but lower than the approximately 35% over three years in the prospective KORAIL cohort [36]. Such comparisons are limited by differences in progression definitions, frequency of lung function testing and duration of follow-up. Our definition used physiological criteria only and should not be equated with PPF, as symptomatic and radiological domains were not included [29]. The limited availability of serial DLCO measurements probably also led to under-detection of DLCO-defined progression. Zamora-Legoff et al. reported that 21.6% and 39.7% of patients reached severe FVC and DLCO impairment, respectively, within five years of diagnosis [37], and longitudinal FVC trajectories have been shown to be heterogeneous and prognostically informative [38–41]. Risk factors for progressive fibrosis in connective tissue disease-related ILD overlap with those explored here [19, 42–44].

Male sex was associated with shorter PFS and a higher hazard of progression, although this estimate is unadjusted and imprecise, being based on four events among nine evaluable men. Each additional year of age at diagnosis conferred a 6% higher hazard, equivalent to approximately 1.8-fold per decade, consistent with previous reports and with age-related decline in lung repair capacity and physiological reserve [19, 45, 46]. Patients in remission or with low disease activity at RA-ILD diagnosis had shorter PFS than those with moderate or high activity. This was unexpected, as higher articular disease activity has been associated with both incident RA-ILD and progression of established disease [47, 48], and it may reflect differences in background immunosuppression at ILD diagnosis rather than a direct effect of articular disease activity.

The longer PFS and lower hazard of progression with a definite or probable UIP pattern also contrast with previous studies, in which UIP has generally been associated with worse outcomes [7, 11, 14, 19]. Several explanations are possible. First, the non-UIP group included OP and NSIP–OP patterns, which are prone to fluctuating lung function [30, 49]; these patterns accounted for five of the 16 progressors despite comprising only eight evaluable patients, and such fluctuations may have been captured as progression under our definition. Second, the findings may reflect survivor bias from left truncation [50]. Patients were identified among those attending the centres during the study period, whereas follow-up was measured from RA-ILD diagnosis, which often preceded study entry; patients with rapidly progressive or fatal disease, particularly those with UIP, may therefore have died or left follow-up before they could be included [11]. Third, differences in surveillance and treatment between phenotypes may

have influenced when decline was detected. This finding should therefore be regarded as hypothesis-generating.

The more frequent use of ILD-directed rituximab among progressors probably reflects confounding by indication, as rituximab was preferentially introduced in patients with more active or progressive lung disease. Conversely, six of the eight rituximab-exposed patients did not progress, in keeping with observational data suggesting a stabilising effect of rituximab in RA-ILD [21, 22]. JAKi exposure was similar between progressors and non-progressors and, in both exposed progressors, preceded documented progression. This differs from retrospective data in which most JAKi-treated patients had stable or improved fibrosis on HRCT [51], but it rests on only two exposed progressors, and prospective studies are required to determine whether these agents modify lung function decline in RA-ILD.

Overall mortality was low, with cumulative mortality of 2.9% at five years and 10.8% at 15 years. This is lower than in several previous cohorts: Nieto et al. reported 16 deaths among 47 patients (34%), with a median survival of 8.3 years [52], and a Danish nationwide cohort reported mortality of 13.9% at one year, 39.0% at five years and 60.1% at ten years [31]. Besides differences in patient characteristics, disease severity, treatment and outcome ascertainment, our estimate was probably lowered by left truncation, and by incomplete capture of deaths among the six patients (5.2%) lost to follow-up or occurring outside the participating centres.

Survival was poorer in men than in women, consistent with a meta-analysis of 23 studies that found an association between male sex and mortality in RA-ILD (pooled HR 1.44, 95% CI 1.21–1.73) [13]. However, in the study by Nieto et al., this association was no longer significant after multivariable adjustment [52], and the small number of deaths in our cohort precluded adjustment for other risk factors. Survival did not differ between UIP and non-UIP patterns, in contrast to cohorts reporting higher mortality with UIP than with NSIP after adjustment for confounders [7, 14].

Lung infection caused five of the seven deaths and respiratory infection was the main cause of respiratory hospitalisation, whereas only one death was attributed to ILD progression. A similar pattern was reported in the Korean prospective cohort of Song et al., in which infection accounted for 9 of 15 deaths and ILD progression for one [24], and the adverse impact of infection has been reported in other RA-ILD cohorts [53, 54]. Infection-related deaths occurred both in patients who had received ILD-directed immunosuppression (two of three) and in those who had not (three of four), suggesting that ILD-directed therapy alone does not explain this risk; concurrent RA treatment, structural lung damage and reduced respiratory reserve may also contribute. Acute exacerbation was the primary cause of only one hospitalisation, which may reflect under-recognition or misclassification when acute deterioration was attributed to infection without excluding an exacerbation [16–18]. These findings support vaccination, infection prevention and early treatment of infection alongside regular surveillance for ILD progression [53].

Strengths and limitations

This study provides long-term, real-world data on RA-ILD from three centres in a multi-ethnic Southeast Asian population, with detailed clinical, pulmonary function and HRCT data and time-to-event analyses over a median follow-up of 8.3 years. It has several limitations. The retrospective design resulted in incomplete data, particularly for DLCO. Physiological progression was defined using study-specific criteria without symptomatic or radiological domains and is not equivalent to guideline-defined PPF. Inclusion of prevalent patients attending clinic during the study period, with follow-up measured from diagnosis, introduces left truncation and survivor bias, which may have underestimated mortality and progression among patients with UIP. The small numbers of progression events (n = 16) and deaths (n = 7) limited statistical power and precluded multivariable analysis, so the associations reported are unadjusted. Censoring of deaths in the progression analysis may have introduced competing-risk effects, and heterogeneity in treatment and follow-up over the long observation period may have influenced outcomes.

Conclusions

In this multicentre Malaysian cohort, physiological progression occurred in about one in five evaluable patients with RA-ILD and was associated with older age and male sex, and men also had poorer overall survival. The lower hazard of progression with a UIP pattern was unexpected and may reflect survivor bias and the fluctuating course of non-UIP inflammatory phenotypes. Respiratory infection was the leading cause of respiratory hospitalisation and death. These findings support multidisciplinary management with serial lung function monitoring and infection prevention.

Abbreviations

ACPA: Anti-citrullinated protein antibody; ACR: American College of Rheumatology; bDMARD: Biologic disease-modifying antirheumatic drug; CI: Confidence interval; CRP: C-reactive protein; csDMARD: Conventional synthetic disease-modifying antirheumatic drug; DAS28-ESR: Disease Activity Score in 28 joints using erythrocyte sedimentation rate; DLCO: Diffusing capacity of the lung for carbon monoxide; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; FVC: Forced vital capacity; HCTM: Hospital Canselor Tuanku Muhriz; HPJ: Hospital Putrajaya; HR: Hazard ratio; HRCT: High-resolution computed tomography; HSIS: Hospital Sultan Idris Shah; ILD: Interstitial lung disease; IQR: Interquartile range; JAKi: Janus kinase inhibitor; NSIP: Non-specific interstitial pneumonia; OP: Organising pneumonia; OS: Overall survival; PFS: Progression-free survival; PPF: Progressive pulmonary fibrosis; RA: Rheumatoid arthritis; RA-ILD: Rheumatoid arthritis-associated interstitial lung disease; RF: Rheumatoid factor; SD: Standard deviation; SE: Standard error; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; tsDMARD: Targeted synthetic disease-modifying antirheumatic drug; UIP: Usual interstitial pneumonia

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and the Malaysian Guideline for Good Clinical Practice. It was approved by the Research Ethics Committee of Universiti Kebangsaan Malaysia (JEP-2025-1198) and the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID-26-02553-PK7), with permission from the hospital director and Clinical Research Centre of each site. The requirement for informed consent was waived by Sekretariat Etika Penyelidikan Universiti Kebangsaan Malaysia (SEPUKM) and Medical Research Ethics Committee (MREC) because of the retrospective design using existing medical records. Data were de-identified before analysis.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study are not publicly available because of patient confidentiality and institutional restrictions, but are available from the corresponding author on reasonable request, subject to approval by the relevant ethics committees

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' contributions

FH: conceptualisation, data collection, formal analysis, writing – original draft. NNNA, ABYL and NBH: conceptualisation, supervision, writing – review and editing. MSMS and MIA: conceptualisation, interpretation of hrct, multidisciplinary meeting and radioconference, supervision. NAM and NSS: data collection at site, proof reading. SAS and YSQ: methodology, formal analysis, writing – review and editing. All authors read and approved the final manuscript.

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Tables

Table 1 Baseline characteristics of patients with RA-ILD (N = 115)

Characteristics	n (%)
DEMOGRAPHIC CHARACTERISTICS	
Age at RA diagnosis (years), mean (SD)	51.8 (11.23)
Age at RA-ILD diagnosis (years), median (IQR)	59.0 (53.0–64.0)
Sex, n (%)	
Female	100 (87.0)
Male	15 (13.0)
Smoking status, n (%)	
Ever smoke	9 (7.8)
Never smoke	106 (92.2)
Ethnicity, n (%)	
Malay	63 (54.8)
Chinese	18 (15.7)
Indian	33 (28.7)
Others	1 (0.9)
Comorbidities at RA-ILD diagnosis, n (%)[§]	
Hypertension	76 (66.1)
Dyslipidaemia	58 (50.4)
Diabetes Mellitus	23 (20.0)
Cardiovascular Disease (Cardiac and Peripheral)	10 (8.7)
Chronic Kidney Disease	7 (6.1)
Cerebrovascular disease	2 (1.7)
Other Respiratory Diseases, n (%)	
Bronchial Asthma	10 (8.7)
Chronic Obstructive Pulmonary Disease	1 (0.9)
DISEASE STATUS	
Time from RA diagnosis to ILD diagnosis (years), median (IQR)	4.7 (1.3–10.9)
Duration of follow up from RA-ILD diagnosis (years), median (IQR)	8.3 (5.1–12.3)
CRP level at RA-ILD diagnosis (mg/L), median (IQR)[a]	8.7 (5.0–19.2)

ESR level at RA-ILD diagnosis (mm/hr), median (IQR)[b]	69.0 (40.0–89.0)
RA disease activity according to DAS-28 ESR, n (%)	
Remission,	17 (14.8)
Low disease activity,	18 (15.7)
Moderate disease activity,	49 (42.6)
High disease activity,	23 (20.0)
DAS-28 ESR not available	8 (7.0)
BASELINE PULMONARY FUNCTION	
FVC, % predicted, median (IQR)[c]	66.5 (51.0-80.0)
DLCO, % predicted, median (IQR)[d]	67.0 (56.3–83.3)
RADIOLOGICAL PATTERN ON BASELINE HRCT, n=115	
UIP	30 (26.1)
Probable UIP	36 (31.3)
Indeterminate UIP	22 (19.1)
NSIP	18 (15.7)
NSIP-OP overlap	5 (4.3)
OP	4 (3.5)
TREATMENT SUMMARY, n=115	
Systemic Corticosteroids	115 (100.0)
PRIOR EXPOSURE TO CONVENTIONAL SYNTHETIC DMARDs (csDMARDs) [§]	
Any csDMARD, n (%)	108 (93.9)
Methotrexate	91 (79.1)
Sulfasalazine	75 (65.2)
Leflunomide	73 (63.5)
Hydroxychloroquine	56 (48.7)
Cyclosporin	12 (10.4)
PRIOR EXPOSURE TO BIOLOGIC DMARDs (bDMARDs)[§]	
Any bDMARD, n (%)	28 (24.3)
Tocilizumab	15 (13.0)

Adalimumab	10 (8.7)
Infliximab	3 (2.6)
Golimumab	4 (3.5)
Etanercept	8 (7.0)
Rituximab	6 (5.2)
PRIOR EXPOSURE TO TARGETED SYNTHETIC DMARDs (tsDMARDs) §	
Any tsDMARD, n (%)	12 (10.4)
Tofacitinib	11 (9.6)
Baricitinib	3 (2.6)
Upadacitinib	0 (0.0)
COMORBIDITIES AND COMPLICATIONS IDENTIFIED DURING FOLLOW UP§	
Incident comorbidities,	
Metabolic Bone Disease (Osteoporosis/Osteopenia)[e]	64 (78.0)
Malignancy	3 (2.6)
Cardiovascular disease	19 (16.5)
Other cardiac-related disease	3 (2.6)
Cerebrovascular disease	11 (9.6)
Chronic Kidney Disease	3 (2.6)
Complications,	
Total Infection (respiratory and non respiratory)[f]	32 (27.8)
Pulmonary hypertension	3 (2.6)

RA = rheumatoid arthritis, RA-ILD = RA related interstitial lung disease, FVC = forced vital capacity, DLCO = diffusing lung capacity for carbon monoxide, UIP = usual interstitial pneumonia, NSIP = non specific interstitial pneumonia, OP = organising pneumonia, csDMARDs = conventional synthetic disease-modifying anti-rheumatic drugs; tsDMARDs = targeted synthetic DMARDs; bDMARDs = biologic DMARDs

"Prior exposure" indicates the patient had ever received the agent for RA (not necessarily at RA-ILD diagnosis or currently); categories are not mutually exclusive, as patients may have received more than one agent. ILD-directed treatment rows likewise are not mutually exclusive.

§ n are not mutually exclusive to each groups, therefore cumulative percentages may exceed 100%

a CRP level (mg/L) at ILD diagnosis, n = 112.

b ESR level (mm/hr) at ILD diagnosis, n = 111.

c Baseline Forced Vital Capacity (FVC) (%), n = 111.

d Baseline Diffusing Lung Capacity for Carbon Monoxide (DLCO) (%), n = 29.

e Total number underwent bone mineral densitometry (BMD) assessment, n = 82
f Inclusive of infections in outpatient and inpatient setting

Table 2 Clinical outcomes of patients with RA-ILD during follow-up (N = 115)

CLINICAL OUTCOME	n (%)
HOSPITALISATION, n=115	
Hospitalised during follow up	45 (39.1)
Not hospitalised during follow up	70 (60.9)
PRIMARY CAUSES OF HOSPITALISATION, n (%)[$]	
Respiratory related causes, n (%)	35 (47.9)
Respiratory infection	32 (43.8)
Acute exacerbation of RA-ILD	1 (1.4)
Progression of RA-ILD	2 (2.7)
Non respiratory causes, n (%)	38 (52.1)
Non-respiratory infection	19 (26.0)
Cardiovascular event	8 (11.0)
Malignancy	2 (2.7)
Others	9 (12.3)
PHYSIOLOGICAL PROGRESSION[a], n=75	
Physiological progression	16 (21.3)
No physiological progression	59 (78.7)
Time from RA-ILD diagnosis to physiological progression in years, median (IQR)	2.00 (1.00-3.00)
STATUS AT STUDY COMPLETION	
Alive and under follow up	102 (88.7)
Died	7 (6.1)
Lost to follow-up	6 (5.2)
Time from RA-ILD diagnosis to death in years, median (IQR)	6.17 (2.92–6.25)
CAUSE OF DEATH	
Respiratory infection	5 (71.4)
Progression of RA-ILD	1 (14.3)
Cardiovascular event	1 (14.3)

RA-ILD = rheumatoid arthritis related ILD, HRCT = high resolution computed tomography, UIP = usual interstitial pneumonia

§ n represent events and are not mutually exclusive to each groups.

$ n are number of events, with % represent percentage out of total events.

a Evaluable patients for physiological progression, n = 75

Table 3 Kaplan–Meier analysis of physiological progression-free survival by sex, HRCT pattern and disease activity

Groups	Total, n (%)	Physiological progression events, n (%)	Mean PFS, years (SE)	Median PFS	p value
Sex					
Male	9	4 (44.4)	6.43 (1.59)	NR	0.027
Female	66	12 (18.2)	15.84 (0.84)	NR	
Baseline HRCT Pattern					
UIP	44	6 (13.6)	16.74 (0.89)	NR	0.032
Others	31	10 (32.3)	10.05 (1.16)	NR	
DAS28 Level					
Moderate/High	46	4 (8.7)	15.91 (0.64)	NR	<0.001
Remission/Low	29	12 (41.4)	11.44 (1.65)	NR	

PFS = physiological progression-free survival, HRCT = high resolution computed tomography, UIP = usual interstitial pneumonia, DAS-28 ESR = disease activity score – 28 joints using erythrocyte sedimentation rate, SE = standard error, NR = not reached.

Table 4 Univariable Cox regression of factors associated with physiological progression (n = 75)

Factors	Analysed, N (events)	Crude HR(95% CI)	p value
Age at RA-ILD diagnosis, per 1 year increase	75 (16)	1.06 (1.02–1.10)	0.002
Male	75 (16)	3.30 (1.06–10.30)	0.040
Baseline FVC (%), per 1% point increase	73 (14)	1.01 (0.99–1.04)	0.237
UIP on baseline HRCT (reference: non-UIP)	75 (16)	0.35 (0.13–0.97)	0.044

HR = hazard ratio, CI = confidence interval, RA-ILD = rheumatoid arthritis associated interstitial lung disease, FVC = forced vital capacity, UIP = usual interstitial pneumonia, HRCT = high-resolution computed tomography. Sample sizes varied according to the availability of data for individual variables.

Table 5 Kaplan–Meier analysis of overall survival by sex and baseline HRCT pattern

Group	Total, n	Censored, n	Deaths, n (%)	Mean survival, years (SE)	p value
Sex					
Male	15	12	3 (20.0)	14.96 (2.04)	
Female	100	96	4 (4.0)	19.49 (0.46)	0.008
Overall	115	108	7 (6.1)	19.11 (0.49)	
Baseline HRCT Pattern					
UIP	66	60	6 (9.1)	18.72 (0.65)	
Non-UIP	49	48	1 (2.0)	18.07 (0.35)	0.230
Overall	115	108	7 (6.1)	19.11 (0.49)	

HRCT = high resolution computed tomography, UIP = usual interstitial pneumonia, SE = standard error.

Figures

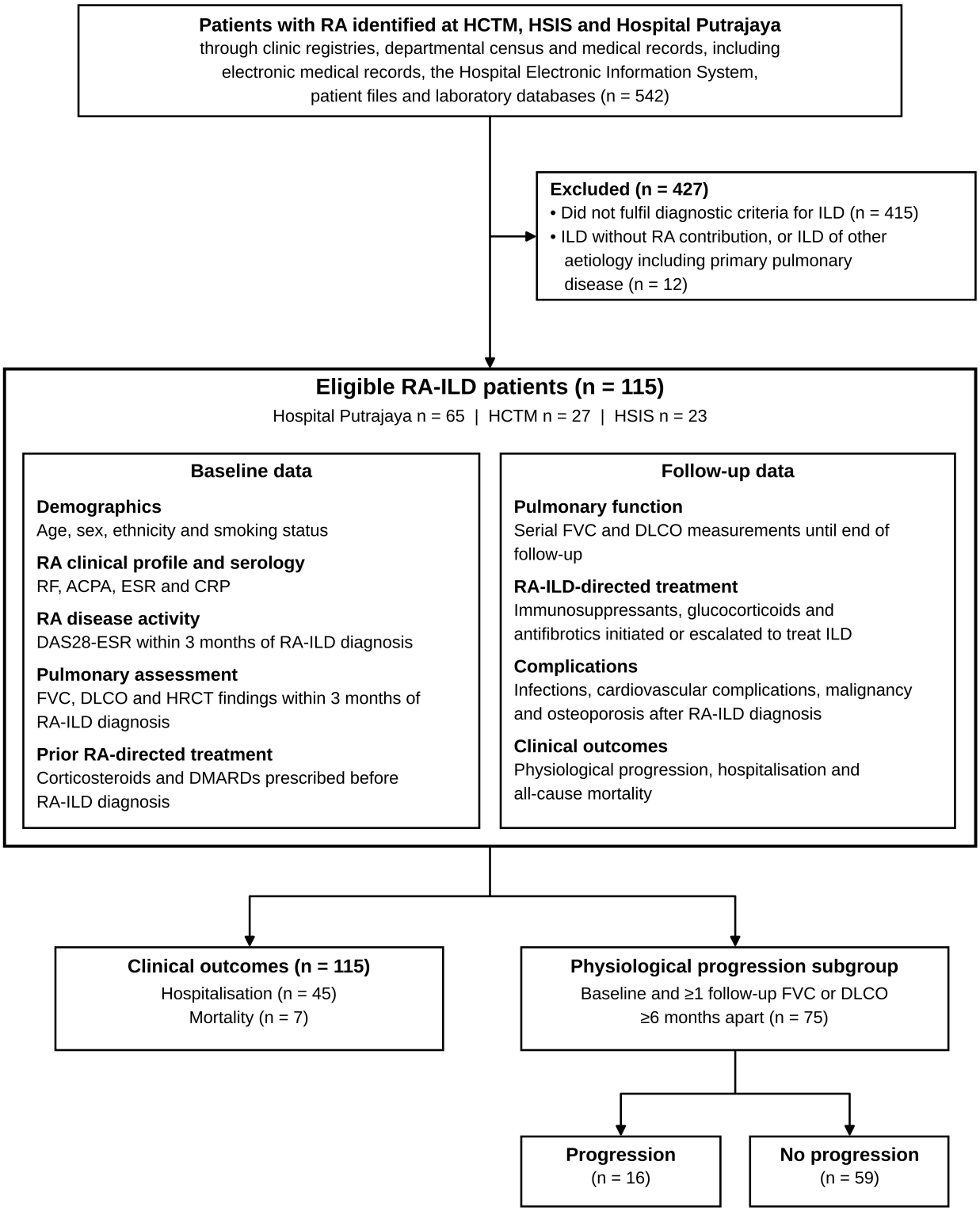


Figure 1

Study flow diagram

Identification, screening and inclusion of patients with RA-ILD at the three participating centres. HCTM, Hospital Canselor Tuanku Muhriz; HSIS, Hospital Sultan Idris Shah; RA, rheumatoid arthritis; ILD, interstitial lung disease; FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide.

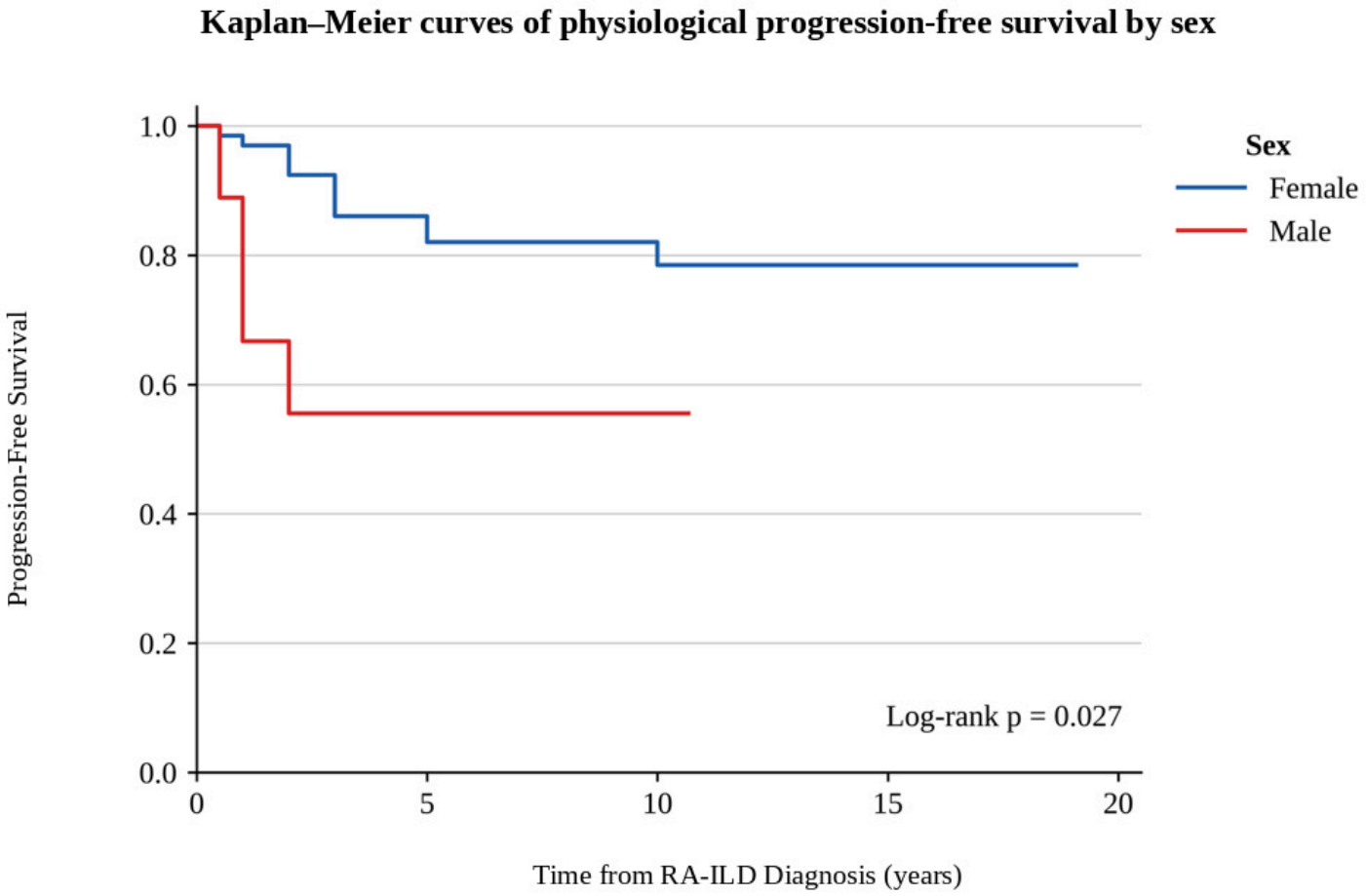


Figure 2

Kaplan–Meier curves of physiological progression-free survival by sex

Evaluable patients with baseline and follow-up lung function at least six months apart (n = 75). Physiological progression-free survival was shorter in men than in women (log-rank p = 0.027).

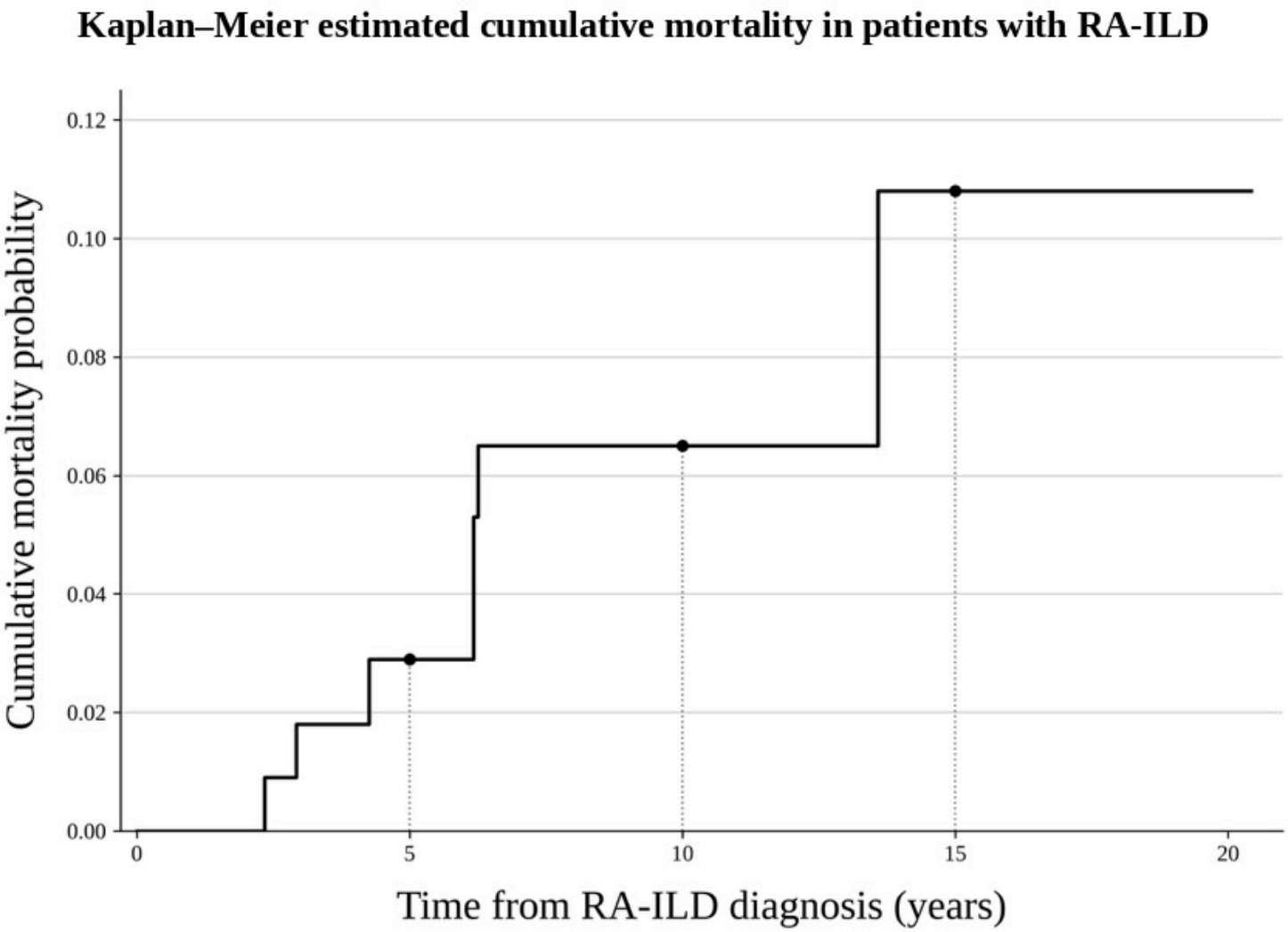


Figure 3

Kaplan–Meier estimated cumulative mortality in patients with RA-ILD

All patients (N = 115). Cumulative mortality was 0% at 1 year, 2.9% at 5 years, 6.5% at 10 years and 10.8% at 15 years after RA-ILD diagnosis.

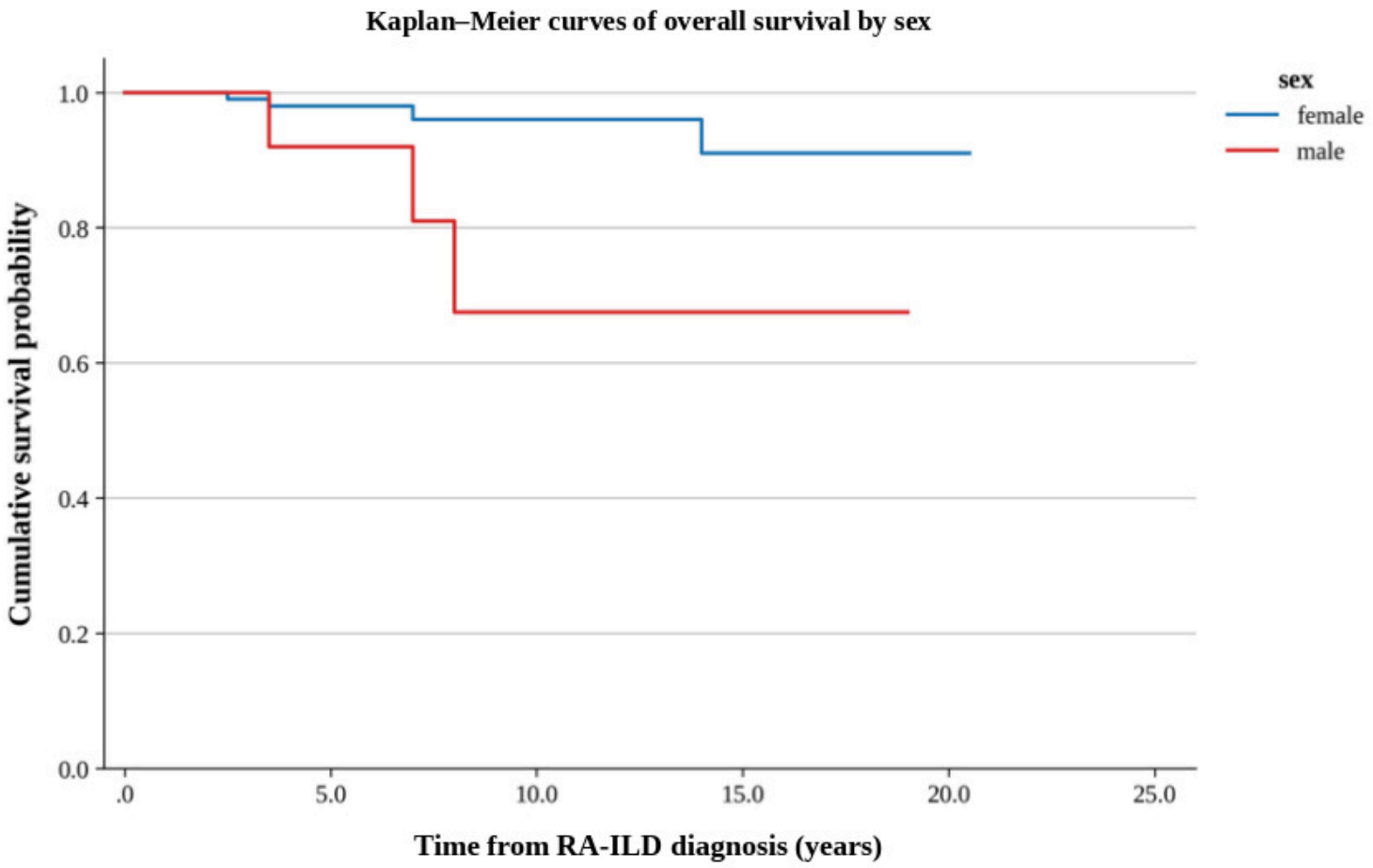


Figure 4

Kaplan–Meier curves of overall survival by sex

All patients (N = 115). Overall survival was poorer in men than in women (log-rank p = 0.008).

Supplementary Files

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