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Sex differences in clinical outcomes and biological profiles in systemic sclerosis-associated interstitial lung disease: a post-hoc analysis of two randomised controlled trials

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Summary

Background—Observational studies have shown that men with systemic sclerosis have an increased risk of interstitial lung disease (ILD) and mortality compared with women. However, previous studies have not controlled for treatment effect or evaluated the biological mechanism or mechanisms underlying this sex difference. We aimed to compare ILD progression and long-term morbidity and mortality outcomes in male and female participants of two randomised controlled trials for systemic sclerosis-associated ILD.

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See Online for appendix

Methods—For this post-hoc analysis, data from all participants in the Scleroderma Lung Study (SLS) I and SLS II were analysed. The primary objective was to explore the effect of sex on the course of the percentage predicted forced vital capacity (FVC) during and after active treatment over the 24-month study periods. In SLS I, 158 participants (111 women, 47 men) were randomly assigned to receive oral cyclophosphamide (cyclophosphamide; 2 mg/kg daily) or placebo; in SLS II, 142 participants (105 women, 37 men) were randomly assigned to receive oral mycophenolate mofetil (1500 mg twice daily) or oral cyclophosphamide (2 mg/kg daily). Sex (ie, male or female) was self-reported in both studies by the participants. Changes in radiographic fibrosis and time to death and respiratory failure were secondary outcomes of the present analysis. Baseline levels of biomarkers implicated in the pathobiology of systemic sclerosis-associated ILD were measured in bronchoalveolar lavage fluid in SLS I.

Findings—In the SLS I placebo group, the rate of decline in percentage predicted FVC from 3 months to 12 months was greater in men than in women, but the difference was not significant (estimated effect −0·29 [95% CI −0·67 to 0·10]; p=0·14). In SLS II, the rate of decline in percentage predicted FVC from 3 months to 12 months was significantly worse in men treated with either cyclophosphamide (estimated effect −0·72; [95% CI −1·14 to −0·31]; p=0·00060) or mycophenolate mofetil (estimated effect −0·34 [−0·58 to −0·10]; p=0·0051) than in women. A greater proportion of men had a decline in percentage predicted FVC of 10% or greater compared with women for the pooled active treatment groups from SLS I and SLS II and the placebo group of SLS I. Men had worse radiographic outcomes at 2 years than women in SLS II, even after adjusting for baseline disease severity and treatment arm assignment. Long-term survival was worse in men in SLS I (log-rank test p=0·080) and SLS II (log-rank test p=0·030). In SLS II, male sex was independently associated with increased mortality (hazard ratio 2·42 [95% CI 1·16 to 5·04]; p=0·018). In bronchoalveolar lavage fluid, men had increased concentrations of pro-fibrotic mediators (eg, matrix metalloproteinase-13 and tissue inhibitor of metallopeptidase 1), whereas women had increased pro-inflammatory mediators (eg, interleukin [IL]-12, IL-7, and granulocyte-colony stimulating factor).

Interpretation—In two randomised controlled trials, men with systemic sclerosis-associated ILD had a less favourable course of ILD both with and without active treatment, as well as worse long-term survival. Sex differences in pro-fibrotic or inflammatory mediators of disease might account for these differences and warrant future study.

Introduction

Although systemic sclerosis disproportionately affects women compared with men (with an estimated sex ratio of 4:1),[1] observational studies have shown that men are more likely to present with diffuse cutaneous disease,[2] interstitial lung disease (ILD),[2–5] and cardiac involvement.[3] Observational studies have also reported that men have worse survival outcomes than women,[5] with an estimated 10-year survival rate of 45% in men compared with 62% in women.[3]

The reasons for these differences are unclear, and both sex (a biological phenomenon based on chromosomes and hormones) and gender (a social construct) might play important roles. Occupational exposures linked to the pathogenesis of systemic sclerosis, such as silica, are typically increased in men compared with women.[6] Hormonal factors might also play a role, as higher serum oestradiol is associated with worse survival in men older than 50 years with diffuse cutaneous systemic sclerosis.[7] It is also conceivable that men might seek medical attention for symptoms related to systemic sclerosis at a later point in the disease course, as many studies have shown sex and gender disparities in health-care system utilisation.[8] Delayed presentation to a systemic sclerosis specialist might lead to missed opportunities for early therapeutic intervention. Finally, existing therapeutics for systemic sclerosis might have differential effects in men versus women.

Randomised controlled trials represent a unique platform for studying sex differences because all patients, regardless of sex or gender, are treated in a uniform manner and receive standard therapy. To the best of our knowledge, no studies have systematically examined whether the course of ILD varies between male and female patients with systemic sclerosis-associated ILD undergoing treatment with immunosuppression. We aimed to compare ILD progression and long-term morbidity and mortality outcomes in male and female participants of two randomised controlled trials for systemic sclerosis-associated ILD: the Scleroderma Lung Study (SLS) I[9] and SLS II.[10] As a post-hoc analysis of SLS I and SLS II, the present study investigated sex differences in known mediators of systemic sclerosis-associated ILD pathogenesis through the measurement of biomarkers in bronchoalveolar lavage fluid. Based on existing knowledge and our clinical experience, we hypothesised that women would show improved ILD outcomes in both trials and better long-term survival than men.

Methods

Study design and participants

All participants enrolled in SLS I (ClinicalTrials.gov; NCT00004563 and NCT01762449)[9] and SLS II (NCT00883129)[10] were included in this post-hoc analysis. SLS I and II were randomised controlled trials investigating the treatment of active systemic sclerosis-associated ILD. Both studies were done at multiple Scleroderma Centers for Excellence across the USA (13 sites for SLS I and 14 sites for SLS II) and included a racially and ethnically diverse population of female and male patients with systemic sclerosis-associated ILD. Eligibility criteria for these trials were similar, as previously reported.[9,10] Common inclusion criteria included age 18 years and older, disease duration that was 7 years or less from onset of the first non-Raynaud's symptom of systemic sclerosis, predicted forced vital capacity (FVC) 40–85% (SLS I) or 40–80% (SLS II), haemoglobin-adjusted single-breath predicted diffusing capacity for carbon monoxide (DLCO) of 40% or greater (or 30–39% if no evidence of clinically significant pulmonary hypertension), and evidence of any ground glass opacity on high-resolution CT (HRCT; SLS II) or evidence of any ground glass opacity on HRCT or inflammation on bronchoalveolar lavage fluid (defined as neutrophilia of 3%, eosinophilia of 2%, or both [in SLS I]). Key exclusion criteria included clinically significant pulmonary vascular disease and smoking within the previous 6 months.

In SLS I, 158 participants were randomly assigned to receive oral cyclophosphamide (cyclophosphamide; 2 mg/kg daily) or placebo for 12 months and were followed up for an additional 12 months off therapy.[9] In SLS II, 142 patients were randomly assigned to receive oral mycophenolate mofetil (1500 mg twice daily) for 24 months or oral cyclophosphamide (2 mg/kg daily) for 12 months followed by an additional 12 months of placebo.[10]

The placebo-controlled design of SLS I allowed us to study a population of patients with systemic sclerosis-associated ILD who were followed up over time without receiving active drug therapy. This provided insight into the natural history of disease progression. Sex (ie, male or female) was self-reported in both studies by the participants. Data on gender were not collected. The institutional review board of each site approved the primary studies and long-term follow-up. Written informed consent was obtained from all participants.

Study assessments

The percentage predicted FVC (the primary endpoint of SLS I and II) was measured every 3 months during the 24-month study periods. HRCT thoracic imaging was obtained at baseline and at the conclusion of active treatment in both trials (ie, at 12 months in SLS I and at 24 months in SLS II). A computer assisted diagnosis scoring system[11,12] was used to calculate the quantitative ILD and quantitative lung fibrosis score for the whole lung and zone of maximum involvement at baseline and follow-up (appendix p 1). The quantitative ILD score included the sum of all abnormally classified scores, including fibrosis (eg, reticular opacity with architectural distortion), ground glass opacity (eg, increased parenchymal attenuation through which normal lung markings are visible), and honeycombing (eg, clustered air-filled cysts with dense walls).

The frequency of protocol-defined adverse events of special interest, study withdrawals, treatment failures, and deaths were collected for both sexes. Treatment failure, mandating withdrawal from active study treatment, was defined as an absolute decrease from a baseline predicted FVC of 15% or greater occurring 3 or more months after randomisation and lasting for 1 month or longer.

Long-term follow-up

Long-term morbidity and mortality outcomes were assessed up to 12 years after the first patient was randomly assigned in SLS I and up to 8 years after the first patient was randomly assigned in SLS II. If survival status was unknown, survival time (in months) was censored at the date when the participant was last known to be alive. The methodology for the long-term follow-up studies of SLS I and SLS II has been previously published.[13] We defined long-term morbidity and mortality outcomes as those occurring any time after the 24-month study period until the conclusion of the follow-up period. The morbidity outcome of interest was time to respiratory failure, which was defined as the need for supplemental oxygen or lung transplantation, or both.

Biomarker analysis

SLS I participants underwent bronchoscopy as part of the screening protocol for the study, and bronchoalveolar lavage fluid was recovered from the right middle lobe. All investigators

viewed a bronchoalveolar lavage training video on the procedure and specimen processing to ensure standardisation across study sites. Four 60 mL aliquots of room temperature saline were serially instilled and manually aspirated from the right middle lobe and passed through a 100 μm filter to remove mucous and particulates. Bronchoalveolar lavage samples were lyophilised, stored at −80°C, and reconstituted before assay at 10% of the original volume in 2·5 mM Tris buffer with 0·25% ASB-14 (Sigma-Aldrich, St Louis, MO, USA). Samples were analysed in duplicate on either a Luminex-100 system (Luminex Corp, Austin, TX, USA) with multiplexed fluorescent bead arrays from Linco Research (St Charles, MO, USA), Bio-Rad Laboratories (Hercules, CA, USA), and R&D Systems (Minneapolis, MN, USA), a SearchLight Protein Array (Aushon Biosystems, Burlington, MA, USA), or commercial ELISA kit to measure 68 different proteins (appendix p 2). Technicians doing the assays were blinded to the treatment group and outcome data.

Statistical analysis

A descriptive analysis was done for baseline characteristics. A two-sample *t* test or Wilcoxon rank-sum test was used to compare continuous variables, and a χ^2 test or Fisher's exact test were used to compare categorical variables.

For the biomarker analysis, measured values were log-transformed to remove skewness where necessary. Where more than 80% of participants had unmeasurable values for a specific bronchoalveolar lavage protein (ie, below the lower limit of detection), this bronchoalveolar lavage protein was dichotomised as detectable versus undetectable. No corrections for multiple comparisons were done for this exploratory assessment.

For the primary outcome, a joint model analysis was used to compare the course of the percentage predicted FVC between men and women during and after active treatment over the 24-month study periods. The joint model (as in the original SLS II analysis)[10] adjusts for non-ignorable missing data due to treatment failure, death, and dropouts.[14] The longitudinal model of the joint analysis included the following covariates: sex, baseline percentage predicted FVC, baseline quantitative lung fibrosis score for the zone of maximum involvement, a linear spline time trend with knots at 12 months and 18 months for SLS I and at 12 months and 21 months for SLS II, and the interaction between sex and these time trends. The inflection points (knots) for the time trends were determined by examining the changes in the slopes of the percentage predicted FVC from 3 months to 24 months.[14] Since participants randomly assigned to cyclophosphamide in SLS I and II only received active treatment for the first 12 months, the time interval of 3–12 months was the time interval of central interest for this analysis, as this is when participants in both trials had the greatest rate of increase in the percentage predicted FVC.[9,10] After 12 months, with cessation of cyclophosphamide, the slope of the percentage predicted FVC changed. Providing data for the slope of the percentage predicted FVC at these different time intervals provides a more accurate depiction of how this parameter evolves during and after active treatment in these trials. The quantitative lung fibrosis score for the zone of maximum involvement was included as a baseline covariate, as our previous study found that the maximum fibrosis score (measured semi-quantitatively in this previous study) was an independent predictor of treatment response in SLS I.[15]

A pooled analysis was also done to evaluate the change in percentage predicted FVC at 12 and 24 months (combining all treatment groups of SLS I and SLS II) to determine the proportion of men and women who had a decline in percentage predicted FVC of 10% or greater.

For the secondary outcome, linear regression models were created to evaluate the change in the quantitative ILD and quantitative lung fibrosis scores from baseline to 12 months (SLS I) or baseline to 24 months (SLS II). The covariates for these models were baseline quantitative lung fibrosis score, baseline quantitative lung fibrosis score for the whole lung and zone of maximum involvement, sex, and treatment group. Data were not pooled for the secondary outcome of changes in radiographic fibrosis, because follow-up HRCTs were obtained at different time intervals in SLS I and SLS II.

The Kaplan-Meier estimate was used to generate survival curves, and the log-rank test was used to compare survival between groups. Cox proportional hazards models were created to evaluate time to death and time to respiratory failure. Based on our previous publication of long-term outcomes in SLS I and SLS II,[13] the following covariates were included in these models: age, baseline modified Rodnan Skin Score (mRSS), and baseline percentage predicted FVC. The covariate of sex was added to the models to assess the relationship between sex and time to death or respiratory failure. Treatment group was not included as a covariate since our previous publication found no relationship between treatment group and long-term survival in SLS I or SLS II.[13] Data were not pooled for the long-term outcomes, since follow up periods were substantially longer in SLS I compared with SLS II.

All tests were two-sided. The joint analyses were done with the R package JMbayes, and all other analyses were done in SAS (version 9.4).

Role of the funding source

Results

158 participants were included in the SLS I trial and 142 participants were included in the SLS II trial. In SLS I, 79 participants were randomly assigned to cyclophosphamide and 79 were randomly assigned to placebo. In SLS II, 73 participants were randomly assigned to cyclophosphamide and 69 were randomly assigned to mycophenolate mofetil. Complete details of participant disposition have been previously published for both trials.[9,10] The majority of patients in both trials were female (111 [70%] of 158 in SLS I and 105 [74%] of 142 in SLS II). In SLS I, male (n=47) participants had a lower baseline percentage predicted

FVC, lower percentage predicted DLCO, and lower percentage predicted total lung capacity than female participants (n=111; table 1). In SLS II, male participants (n=37) had a lower baseline percentage predicted DLCO compared with female participants. No sex differences were observed for age, disease duration, prevalence of diffuse cutaneous disease, extent of radiographic ILD, or mRSS. The majority of male participants from SLS I were White, whereas a greater percentage of female participants from SLS I were anti-RNA polymerase III antibody positive.

After adjustment for baseline ILD severity (baseline percentage predicted FVC and quantitative lung fibrosis score for the zone of maximum involvement from HRCT imaging), male participants of SLS I randomly assigned to placebo had an accelerated rate of decline in percentage predicted FVC from 3 months to 12 months compared with female participants (estimated effect −0·29; [95% CI −0·67 to 0·10]; p=0·14; figure 1A; appendix p 3). Additionally, for the placebo group, four (17%) of 24 male participants versus eight (17%) of 46 female participants had a decline in percentage predicted FVC of 10% or greater at 12 months; four (24%) of 17 male participants versus four (10%) of 39 female participants had a decline in percentage predicted FVC of 10% or greater at 24 months. There were no sex differences in the rate of improvement in the course of the percentage predicted FVC from 3 months to 12 months in the cyclophosphamide group of SLS I (estimated effect −0·06 [95% CI −0·62 to 0·50]; p=0·84; figure 1B; appendix p 4).

In SLS II, which did not have a placebo group, all patients were randomly assigned to active treatment with either cyclophosphamide or mycophenolate mofetil. After adjustment for baseline ILD severity, male participants in SLS II randomly assigned to cyclophosphamide had a decline in the course of percentage predicted FVC from 3 months to 12 months, whereas female participants had an improvement in the course of the percentage predicted FVC (estimated effect −0·72 [95% CI −1·14 to −0·31]; p=0·00060; figure 2A; appendix p 5). Among SLS II participants randomly assigned to mycophenolate mofetil, the rate of improvement in percentage predicted FVC from 3 months to 12 months was lower in male participants than in female participants (estimated effect −0·34 [95% CI −0·58 to −0·10]; p=0·0051; figure 2B; appendix p 6).

In the pooled treatment group analysis (the cyclophosphamide groups of SLS I and II, and the mycophenolate mofetil group of SLS II), five (10%) of 48 male participants versus seven (5%) of 134 female participants had a decline in percentage predicted FVC of 10% or greater at 12 months. At 24 months, five (12%) of 41 male participants and 12 (10%) of 120 female participants had a decline in percentage predicted FVC of 10% or greater.

After adjustment for baseline ILD severity and treatment group, there were no sex differences in the change in quantitative lung fibrosis and quantitative ILD scores for both the whole lung and for the zone of maximum involvement from baseline to 12 months in SLS I (appendix p 7). After adjustment for baseline ILD severity and treatment group, male participants in SLS II had increased radiographic progression of ILD at 24 months based on the quantitative lung fibrosis and quantitative ILD scores for both the whole lung and for the zone of maximum involvement, whereas female participants had decreased radiographic progression (ie, an improvement; table 2).

Protocol-defined adverse events of special interest were similar for male and female participants in SLS I (appendix p 8) and SLS II (appendix p 9), with the exception of a greater frequency of anaemia in women. However, compared with women, a higher proportion of men dropped out (18 [38%] of 47 *vs* 26 [23%] of 111), had treatment failure (five [11%] of 47 *vs* six [5%] of 111), or died (three [6%] of 47) *vs* one [1%] of 111) in SLS I (appendix p 10). In SLS II, no appreciable sex differences were observed in rates of dropout, treatment failures, or deaths, although the number of patients fulfilling the criteria for treatment failure was extremely low (one male participant; appendix p 11).

The median follow-up time for all SLS I participants was 8 years. During this time, 66 participants died (23 men and 43 women). The leading cause of death in SLS I for both male and female participants was respiratory failure due to ILD.[13] In SLS I, male participants had worse long-term survival than women (log-rank test p=0·080; figure 3A). After controlling for baseline disease severity (FVC and modified Rodnan Skin Score) and age, male sex was not independently associated with survival (hazard ratio [HR] 1·14 [95% CI 0·67–1·96]; p=0·63; appendix p 12). There was also no association between male sex and time to respiratory failure in the univariate and multivariable analyses (appendix pp 13, 16).

The median follow-up time for all SLS II participants was 4 years. During this time, 30 participants died (13 men and 17 women). The leading cause of death in SLS II for both male and female participants was respiratory failure due to ILD.[13] In SLS II, male participants had worse long-term survival than women (log-rank test p=0·030; figure 3B). Male sex remained associated with worse survival, even after controlling for baseline disease severity (FVC and mRSS) and age (HR 2·42 [95% CI 1·16–5·04]; p=0·018; appendix p 14). Male sex was also associated with a more rapid onset of respiratory failure in the univariate and multivariable analyses (p=0·13 for log-rank test; multivariable analysis: HR 2·61 [95% CI 0·94–7·22]; p=0·065; appendix pp 15, 17).

Among all SLS I participants, 103 (76 women and 27 men) had bronchoalveolar lavage specimens suitable for multiplex analysis. Among the 68 bronchoalveolar lavage proteins investigated, female participants in SLS I had higher concentrations of, or a higher frequency of detectable concentrations of, bronchoalveolar lavage proteins involved in the immune response and inflammation, including interleukin (IL)-12 (detectable in 59 [78%] of 76 women *vs* 14 [52%] of 27 men; p=0·011), IL-7 (detectable in 69 [91%] of 76 women *vs* 17 [63%] of 27 men; p=0·0019), granulocyte colony-stimulating factor (G-CSF; mean concentration of 342·37 [SD 297·32] in women and 225·72 [263·52] in men; p=0·015; based on log-transformed values; figure 4). By contrast, male participants of SLS I had higher concentrations of, or a higher frequency of detectable concentrations of, bronchoalveolar lavage proteins involved in matrix remodelling and fibrosis, including matrix metalloproteinase (MMP)-13 (detectable in 15 [56%] of 27 men *vs* 23 [30%] of 76 women; p=0·019) and tissue inhibitor of metallopeptidase (TIMP)-1 (mean concentration of 58 579·60 [SD 31 779·05] in men vs 45 072·65 [33 777·18] in women; p=0·0057, based on log-transformed values; figure 4).

Discussion

In a post-hoc analysis of the SLS I and SLS II studies, we identified sex differences in various important outcomes of systemic sclerosis-associated ILD. In SLS II, for example, women responded more favourably than men to treatment with cyclophosphamide and mycophenolate mofetil, with greater improvements observed in the percentage predicted FVC and the radiographic extent of ILD. Even after adjusting for potentially confounding factors, women in SLS II had improved long-term survival. The analysis of bronchoalveolar lavage fluid recovered from the lungs of SLS I study participants at baseline also identified an imbalance in several measured proteins, supporting the notion that women might have a more pro-inflammatory immune signature, whereas men might have a more pro-fibrotic immune signature. As such, biological factors might contribute to sex differences in outcomes of systemic sclerosis-associated ILD.

The SLS I and SLS II study databases include data collected prospectively from randomly assigned patients meeting uniform criteria for active systemic sclerosis-associated ILD. Although the analyses presented here are post-hoc, they represent a unique opportunity to evaluate the potential influence of sex on the natural course of systemic sclerosis-associated ILD (from the placebo group of SLS I) and the response to immunosuppressive therapies, including cyclophosphamide (SLS I and SLS II) and mycophenolate mofetil (SLS II). In both studies, it is noteworthy that female patients represented the overwhelming majority of participants, consistent with the marked predominance of systemic sclerosis in women.[1] Although various baseline disease features were similar between men and women in SLS I (eg, age, proportion of participants with diffuse cutaneous disease, disease duration, education, mRSS, and patient-reported outcomes), male participants had signs of more advanced disease or fibrotic disease, or both, at baseline, with worse scores for FVC, total lung capacity, DLCO, and numerically higher quantitative lung fibrosis scores for the zone of maximum involvement. Previous observational studies have reported that men have a more severe ILD phenotype than women.[3] Some of these trends were observed in SLS II, with a worse DLCO and quantitative lung fibrosis score for the zone of maximum involvement, but overall, male and female participants appeared to be more closely matched at baseline in the SLS II cohort.

Among those assigned to the placebo group of SLS I, no sex differences in the course of percentage predicted FVC were observed, although the loss of lung function was numerically greater in men. Our analysis might have been underpowered to detect statistical significance since only 28 male participants were randomly assigned to placebo in SLS I. We did observe, however, that more male participants had a decline in percentage predicted FVC of 10% or greater at 24 months than did female participants.

This study also identified sex differences in the course of percentage predicted FVC and changes in the radiographic extent of ILD in patients receiving treatment with immunosuppression. Previous observational studies reporting sex differences in systemic sclerosis-associated ILD outcomes did not report differences in treatment regimens or in treatment response, increasing the likelihood of confounding bias.[3–5] One retrospective study of 959 patients with systemic sclerosis, 332 of whom had ILD, found that

male sex was associated with increased mortality in an adjusted model that included immunosuppressive use.[4] However, the duration and type of immunosuppression used was not reported.

The present study found that female participants with systemic sclerosis-associated ILD had a more favourable course of percentage predicted FVC during the period of active treatment with cyclophosphamide than did male participants, even after controlling for baseline ILD severity, particularly in SLS II where men had a decline in FVC, whereas women had an improvement in FVC over time. In SLS I, no sex differences were observed in the rate of improvement in FVC during active treatment with cyclophosphamide. Possible explanations for this discrepancy might include the fact that female participants in SLS II had a shorter disease duration, less radiographic extent of ILD, and a higher percentage predicted total lung capacity and percentage predicted DLCO at baseline compared with female participants in SLS I. It is conceivable that intervention with cyclophosphamide at an earlier disease stage might lead to better outcomes. Additionally, fewer sex-related differences in baseline characteristics were observed in SLS II compared with SLS I, and this might have also influenced study outcomes.

Although both male and female participants responded favourably to treatment with mycophenolate mofetil, the rate of improvement in FVC was greater in women. It is unclear why men with systemic sclerosis-associated ILD appeared to respond better to mycophenolate mofetil than cyclophosphamide in SLS II. One possibility is that mycophenolate mofetil possesses more anti-fibrotic properties than cyclophosphamide. Animal and human studies have shown that mycophenolate mofetil both prevents and inhibits fibrosis.[16–18] Additionally, studies have found that mycophenolate mofetil affects the expression of genes involved in lung development and the endovascular system.[19]

In the pooled analysis (all active treatment groups), men were more likely to have a loss of lung function (percentage predicted FVC 10%) associated in previous studies with a higher risk of mortality[13,20] than women, particularly after the first year of treatment. This finding highlights the importance of monitoring lung function within the first year of treatment.

Sex differences in the radiographic progression of ILD paralleled the FVC findings. In the multivariable model, male sex was associated with increased radiographic progression of ILD in SLS II, but not in SLS I. It is unknown why a sex association for changes in radiographic fibrosis was observed in SLS II, but not in SLS I. One possibility is that the radiographic analysis in SLS I was underpowered to detect statistical significance since fewer patients in SLS I had follow-up HRCT scans at 12 months (82 [52%] of 158), compared with SLS II (97 [68%] of 142). Additionally, since the HRCT was obtained at 24 months in SLS II and at 12 months in SLS I, it is possible that sex differences in radiographic progression of ILD become more pronounced over time. Future studies are needed to investigate this hypothesis, with serial quantitative radiographic ILD assessment.

Consistent with previous observational studies,[3,4] survival was also worse in men than in women. In SLS II, but not in SLS I, male sex was independently associated with worse survival in the multivariable model. More participants were lost to follow-up in SLS I than

in SLS II, which might have affected this outcome.[13] A survival bias might also exist. Nearly half (49%) of all men had died during the long-term follow up period for SLS I, whereas 35% had died during the long-term follow up period for SLS II. With so few male survivors in SLS I (n=19), our analyses might have been underpowered to detect statistical significance.

In a preliminary and exploratory analysis, the present study sought to investigate the biology of sex differences in systemic sclerosis-associated ILD through a comprehensive evaluation of cytokines, chemokines, and growth factors measured in bronchoalveolar lavage fluid. Proteins measured in bronchoalveolar lavage fluid might potentially represent a more direct assessment of lung pathobiology than proteins measured in circulation. Few studies have investigated bronchoalveolar lavage proteins in systemic sclerosis,[21] and among these studies, none has explored sex differences. The present study found that more male patients with systemic sclerosis-associated ILD in SLS I had detectable proteins involved in matrix remodelling and fibrosis, whereas more female patients with systemic sclerosis-associated ILD had detectable proteins involved in the immune response in inflammation. Although these findings should be considered exploratory in nature, the difference in bronchoalveolar lavage immune profiles could signify a more advanced fibrotic ILD present in men at baseline, or could suggest a difference in the pathobiology of ILD between men and women (ie, a more fibrotic disease in men *vs* a more inflammatory disease in women that portends less of an improvement in FVC in response to treatment with cyclophosphamide in men than in women).

A post-hoc analysis of the SENSCIS trial (nintedanib *vs* placebo for systemic sclerosis-associated ILD),[22] showed that men and women had a similar treatment response to the anti-fibrotic drug nintedanib.[23] Treatment with nintedanib was associated with a relative reduction in the adjusted annual rate of decline in FVC of 42% in women and 46% in men (treatment-by-time-by-sex interaction p=0·59). Notably, in the SENSCIS trial (433 women and 143 men), 47·1% of female participants and 54·5% of male participants had been taking a stable dose of mycophenolate mofetil for at least 6 months at the time of enrolment.[23] Future studies are needed to assess whether early intervention with anti-fibrotic therapy could lead to improved outcomes in men with systemic sclerosis-associated ILD. Results from the forthcoming SLS III trial (mycophenolate *vs* mycophenolate plus pirfenidone for systemic sclerosis-associated ILD), might shed further light on this question.

The findings of the present study should be interpreted in the context of certain limitations. First, both SLS I and II enrolled a disproportionate number of female patients. Although this is a reflection of the higher prevalence of systemic sclerosis among women and is consistent with other clinical trials in this area,[22,24] this limitation could represent a source of selection bias. It is also possible that men with systemic sclerosis-associated ILD who participate in clinical trials might have increased disease severity compared with men who do not participate in clinical trials. However, one could reason that the same could be said for women with systemic sclerosis-associated ILD who participate in clinical trials. It is also conceivable that some of the variables that differed between men and women in these studies (eg, ethnicity and autoantibody profiles) could have accounted for the observed sex differences, and this warrants future study in larger cohorts. Another limitation was that the

bronchoalveolar lavage analysis was only done on 103 of 158 SLS I participants and not on any SLS II participants. Reassuringly, however, there were no differences in the baseline characteristics of patients with suitable bronchoalveolar lavage specimens compared with those without such specimens in SLS I. Given that the sample size for men was small, the analyses were likely to be underpowered for detecting statistically significant sex differences in bronchoalveolar lavage proteins. There is a risk of both type I and II error in the present analyses, which did not adjust for multiple comparisons.

The present study also had several strengths. First, this study used two valid measures to define ILD progression (FVC and radiographic fibrosis), and both measures were collected at standard intervals for all patients following a uniform protocol. Second, the follow-up period for assessing survival was longer than most follow-up periods for randomised controlled trials for systemic sclerosis-associated ILD, increasing the likelihood that our findings are not due to chance alone. Third, the joint model adjusts for dropouts, treatment failures, and deaths, minimising the potential confounding effects of these variables on the outcomes of interest. Finally, this study measured a comprehensive suite of proteins involved in fibrosis and inflammation in bronchoalveolar lavage fluid in a population of patients who were treatment naive. This represents a unique feature of the present study as it offers insight into the pathobiology of ILD before therapeutic intervention.

In summary, data from two independent randomised controlled trials showed that men with systemic sclerosis-associated ILD appear to have a more severe phenotype of ILD than women, even when treated with immunosuppression. These sex differences might be due to sex-related variations in the pathobiology of systemic sclerosis-associated ILD and might contribute to increased mortality rates among men with systemic sclerosis-associated ILD. This study also highlights the importance of exploring sex differences in treatment response in patients enrolled in clinical trials for systemic sclerosis.[25] Future studies are needed to investigate whether combining an anti-fibrotic drug with an immunosuppressive agent could potentially improve outcomes for men with systemic sclerosis-associated ILD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Declaration of interests

support received for performing systemic sclerosis studies for Boehringer Ingelheim outside of the submitted work. SA reports the following financial relationships outside of the submitted work on SLS I and SLS II outcomes: consulting (Boehringer Ingelheim, Corbus, Novartis, CSL Behring, AbbVie, and AstraZeneca); payment or honoraria for lectures or presentations (Integrity CE and the North Carolina Rheumatology Association); institutional support received for doing systemic sclerosis studies for Momenta, Boehringer Ingelhim, Janssen, Scleroderma Research Foundation, the US Department of Defense and the NIH; and a leadership role (unpaid volunteer) for the Scleroderma Clinical Trial Consortium and the Scleroderma Foundation Medical Advisory Board. GHK reports being a research consultant for MedQIA and has a patent issued on the radiographic quantification of ILD (UC-2015-0324982-A1). JG is the founder of MedQIA. MDR reports receiving institutional support from Genentech for leading an investigator-initiated clinical trial in systemic sclerosis-associated ILD outside of the SLS I and SLS II studies reported here. All other authors declare no competing interests outside of the submitted work.

Data sharing

Data collected for the study, including de-identified, individual participant data and a data dictionary defining each field, will be made available to investigators at academic institutions for non-commercial research upon request, following the peer-reviewed publications of these data and execution of the negotiated standard institutional agreement. We will also provide study protocols and published data upon request. The institutional agreement should include the recipient investigators' written assurance that the data will be used solely in accord with their local research committee review, including the protection of human subject research committee. Requests for data can be made via email to the corresponding author. As per our agreement with the US National Heart, Lung, and Blood Institute, we will not distribute any data that are not in the public domain for use for commercial purposes.

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Research in context

Evidence before this study

We searched PubMed on Jan 7, 2021, using the search terms "systemic sclerosis" AND "sex" OR "gender" for studies published from database inception to Jan 7, 2021, and identified 938 articles published in English with potential information on sex and gender differences in systemic sclerosis. Among the retrieved articles, we identified several single-centre studies reporting sex differences in systemic sclerosis-related outcomes, including interstitial lung disease (ILD). We found no prospective or randomised controlled trials that evaluated the impact of sex on systemic sclerosis-related ILD treatment outcomes or long-term mortality. Moreover, we found no information as to whether men and women with systemic sclerosis-associated ILD have different concentrations of biomarkers in the lungs. Thus, there is an unmet need to understand whether treatment modifies the relationship between sex and outcomes of systemic sclerosis-associated ILD and to investigate whether men and women with systemic sclerosis-associated ILD have distinct pulmonary biological signatures.

Added value of this study

To the best of our knowledge, this is the first study to examine sex differences in two independent cohorts with systemic sclerosis-associated ILD, in which all patients received standard treatment and long-term follow-up. In this post-hoc analysis of data from two clinical trials, women generally showed better treatment responses to immunosuppression compared with men. This is also the first study to identify sex differences in biomarkers measured in the bronchoalveolar lavage fluid of patients with systemic sclerosis-associated ILD. Women had increased pro-inflammatory pulmonary biomarkers (eg, interleukin [IL]-12, IL-7, and granulocyte-colony stimulating factor), while men had increased pro-fibrotic pulmonary biomarkers (eg, matrix metalloproteinase-13 and tissue inhibitor of metalloproteinase 1). Since these two trials examined the effectiveness of therapies aimed at decreasing inflammation, the analyses of bronchoalveolar lavage fluid could help explain why women had improved outcomes after treatment with mycophenolate mofetil and cyclophosphamide.

Implications of all the available evidence

The present findings suggest that men with systemic sclerosis-associated ILD have a more severe phenotype than women, which affects both treatment response and long-term mortality. The sex differences in biological mediators of disease pathogenesis found in this study might explain why men had a more limited treatment response to immunosuppression than did women, who had a more pro-inflammatory immune signature, and suggest that the biology of systemic sclerosis-associated ILD might vary between men and women. An improved understanding of these sex differences could help to advance personalised medicine in this field. These pulmonary biomarkers could potentially be used for prognostic and predictive enrichment of clinical trials and as novel treatment targets.
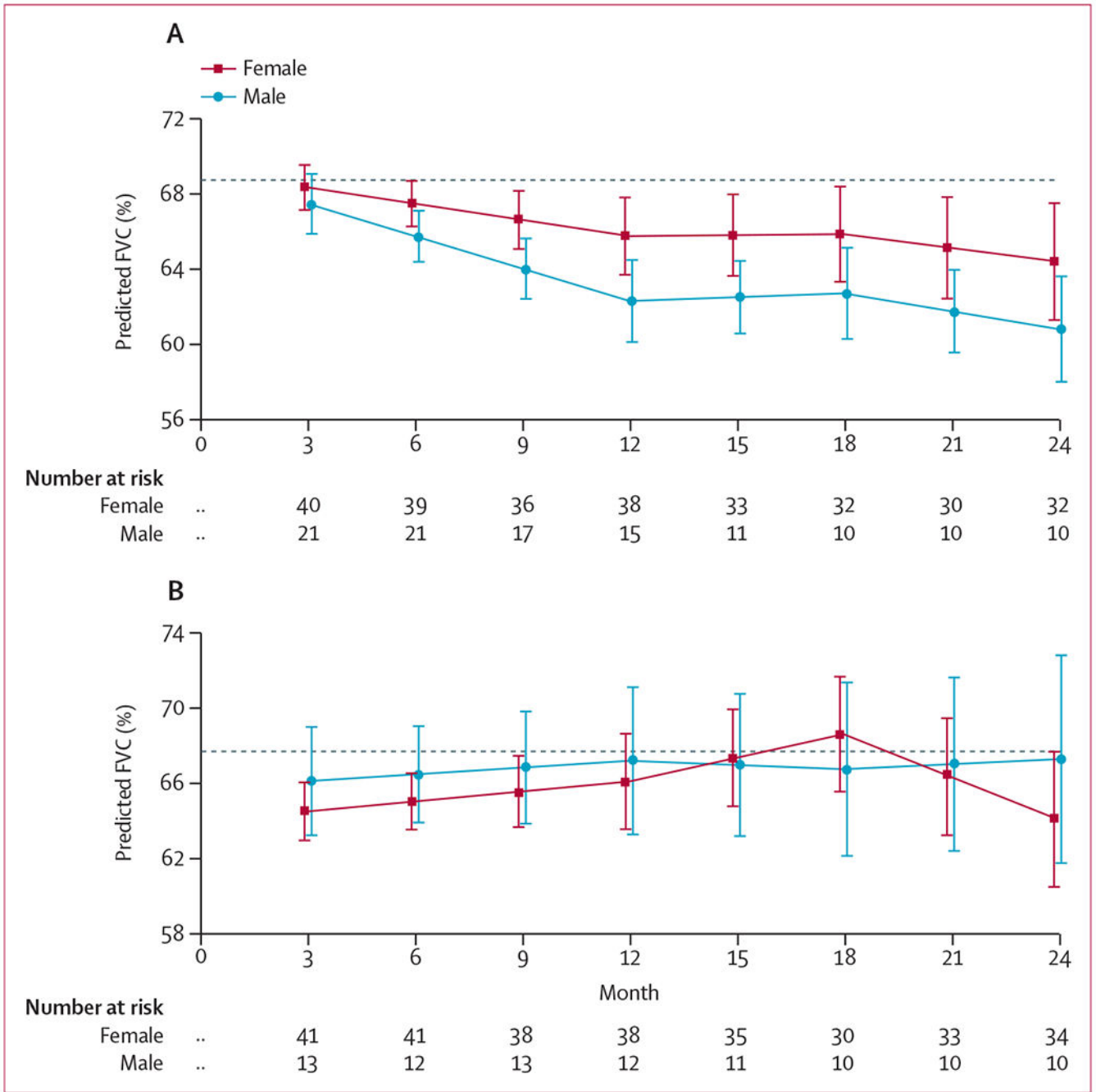
Figure 1: Course of percentage predicted FVC from 3 months to 24 months in male and female participants assigned to placebo (A) and cyclophosphamide (B) in SLS I by use of a joint model analysis

Pre-specified covariates for these models included the baseline percentage predicted FVC, baseline quantitative lung fibrosis score for the zone of maximum involvement, sex, time trends (3–12 months, 12–18 months, and 18–24 months), and interactions between sex and the time trends. The dotted line denotes the mean baseline percentage predicted FVC for both groups. FVC=forced vital capacity. SLS I=Scleroderma Lung Study I.
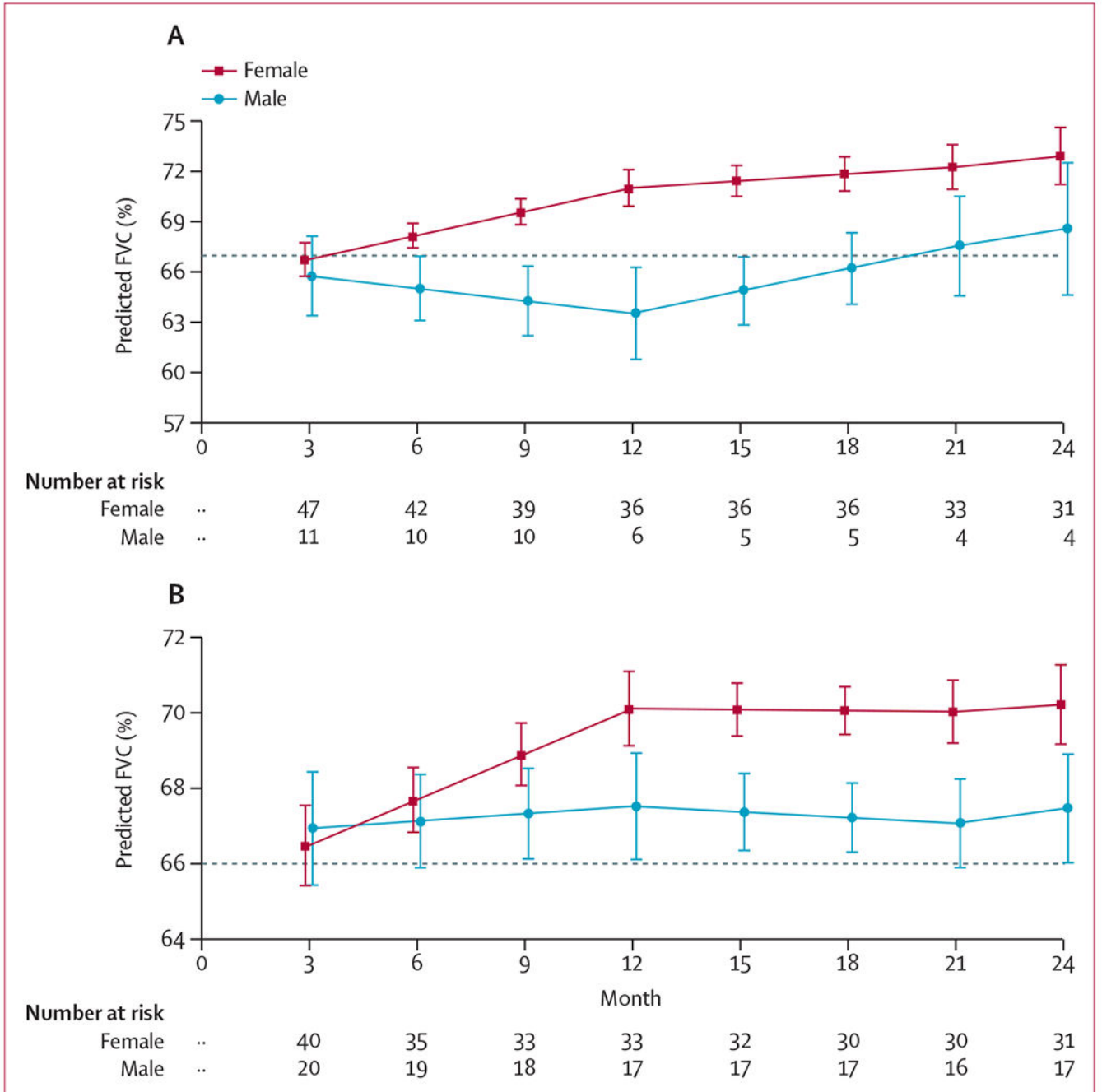
Figure 2: Course of percentage predicted FVC from 3 months to 24 months in male and female participants assigned to cyclophosphamide (A) and mycophenolate mofetil (B) in SLS II by use of a joint model analysis

Pre-specified covariates for this model included the baseline percentage predicted FVC, baseline quantitative lung fibrosis score for the zone of maximum involvement, sex, time trends (3–12 months, 12–21 months, and 21–24 months), and interactions between sex and the time trends. The dotted line denotes the mean baseline percentage predicted FVC for both groups. FVC=forced vital capacity. SLS II=Scleroderma Lung Study II.

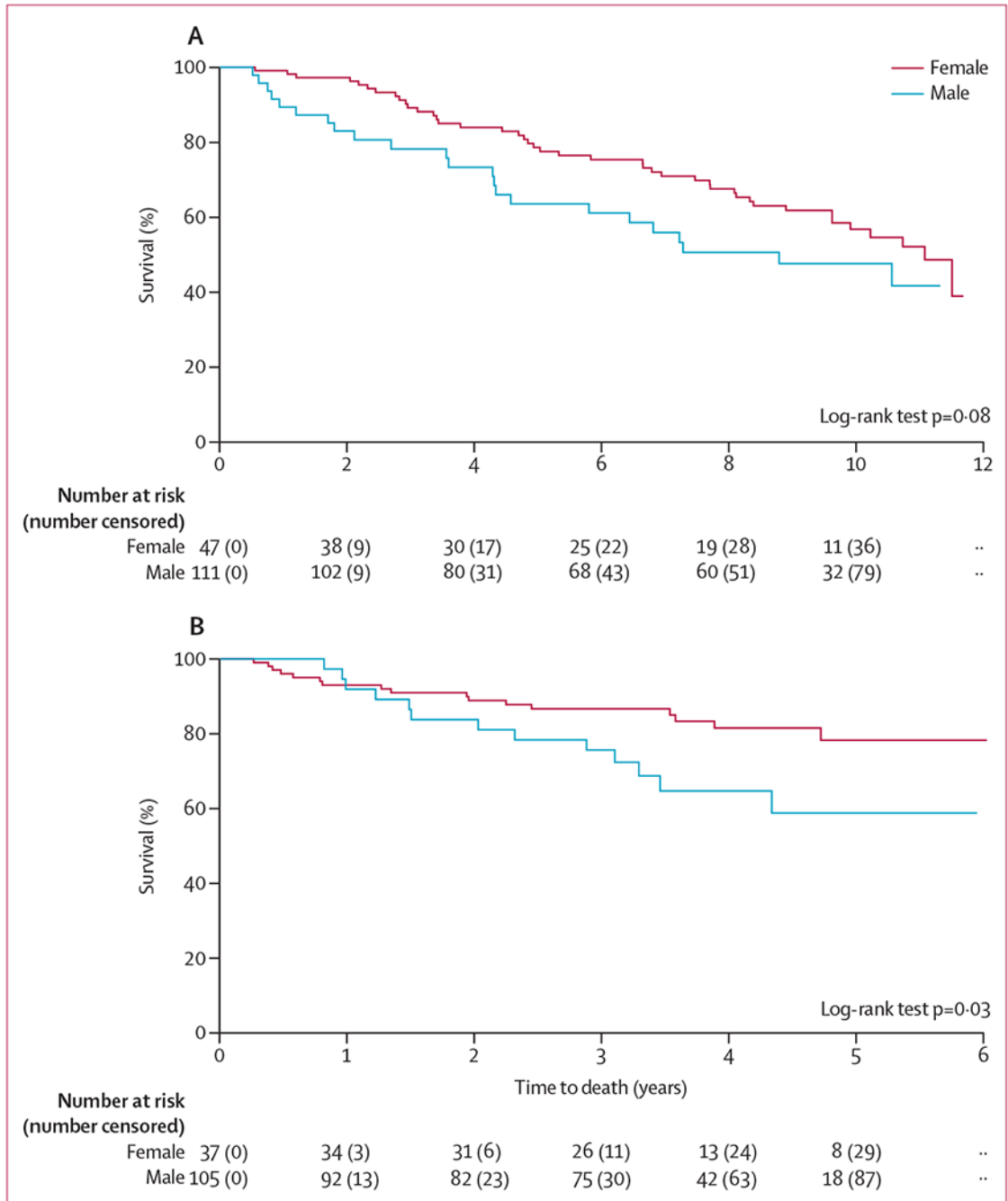**Figure 3: Time to death in male versus female participants from the time of randomisation in SLS I (A) and SLS II (B)**

SLS=Scleroderma Lung Study. Numbers censored shown in parentheses include participants who died.
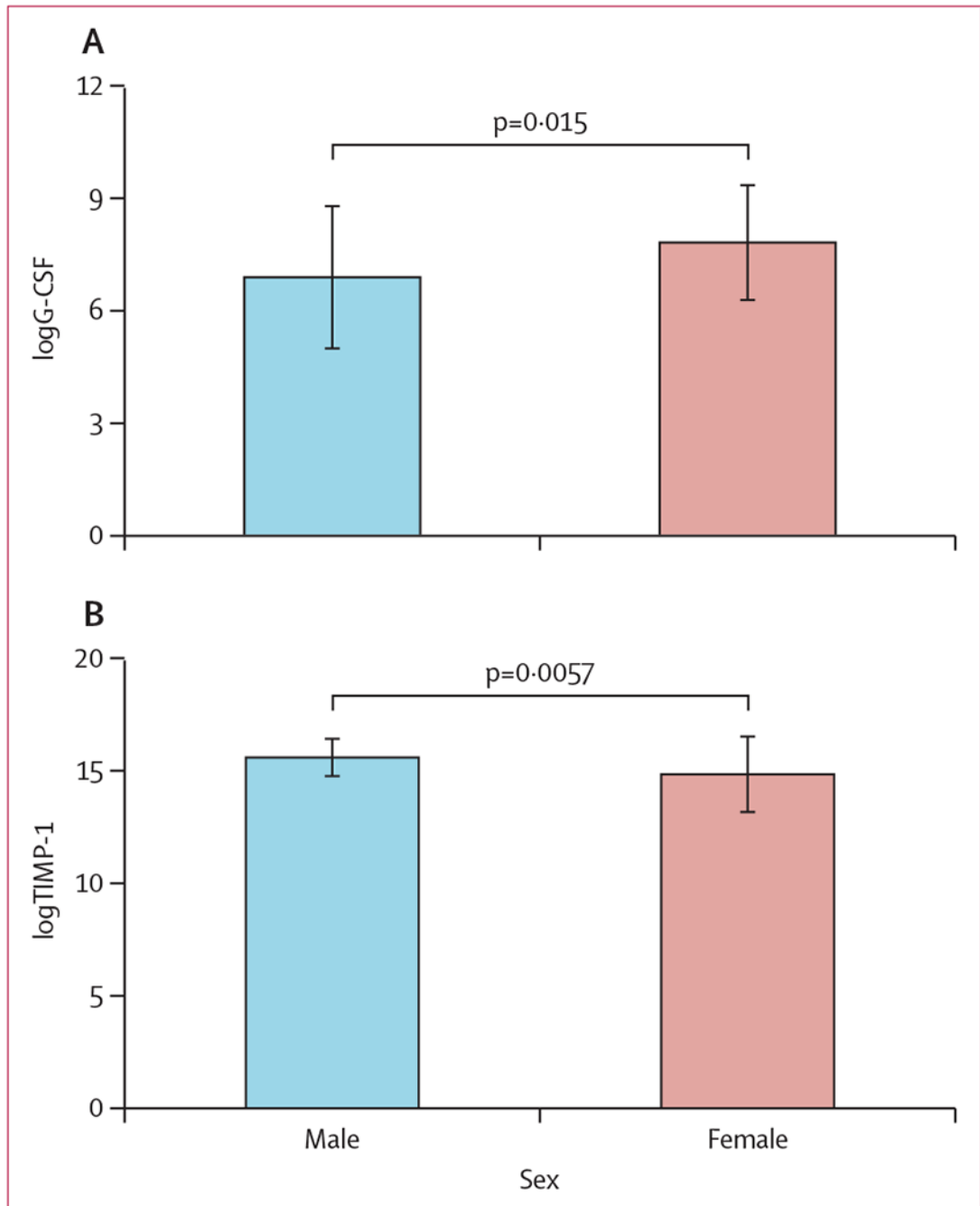
Figure 4: Example of sex differences in bronchoalveolar lavage protein concentrations
G-CSF=granulocyte colony-stimulating factor. TIMP-1=tissue inhibitor of metallopeptidase 1.

Table 1:

Baseline characteristics in SLS I and SLS II participants

	SLS I cohort (n=158)		SLS II cohort (n=142)	
	Male (n=47)	**Female (n=111)**	**Male (n=37)**	**Female (n=105)**
Treatment group, cyclophosphamide	19/47 (40%)	60/111 (54%)	16/37 (43%)	57/105 (54%)
Age, years [*]	51·0 (14·0)	47·4 (11·5)	52·1 (8·8)	52·3 (10·1)
Race [*†]				
White	37/47 (79%)	64/111 (58%)	28/37 (76%)	69/105 (66%)
Black	7/47 (15%)	19/111 (17%)	7/37 (19%)	26/105 (25%)
Asian	2/47 (4%)	10/111 (9%)	1/37 (3%)	8/105 (8%)
Other	1/47 (2%)	18/111 (16%)	1/37 (3%)	2/105 (2%)
Education [*‡]				
Eighth grade or less	1/47 (2%)	2/109 (2%)	0/37 (0%)	4/105 (4%)
Some high school	5/47 (11%)	4/109 (4%)	2/37 (5%)	1/105 (1%)
High school graduate	9/47 (19%)	27/109 (25%)	8/37 (22%)	23/105 (22%)
Trade school or some college	1/47 (2%)	10/109 (9%)	8/37 (22%)	29/105 (28%)
Received bachelor's degree	14/47 (30%)	32/109 (29%)	14/37 (38%)	31/105 (30%)
Graduate or professional degree	13/47 (28%)	20/109 (18%)	5/37 (14%)	17/105 (16%)
Other	4/47 (9%)	14/109 (13%)	0/37 (0%)	0/105 (0%)
Diffuse cutaneous disease	31/47 (66%)	63/110 (57%)	23/37 (62%)	60/105 (57%)
Disease duration, years [*]	2·8 (2·0)	3·3 (2·1)	2·5 (1·6)	2·6 (1·8)
Predicted FVC [†]	65·1% (13·5)	69·4 (11·3)	65·5 (8·7)	66·9 (9·3)
FEV1/FVC	81·6% (8·0)	83·3 (8·0)	82·4 (7·0)	82·7 (5·0)
Predicted TLC [*†]	66·1% (14·6)	71·1 (12·1)	65·4 (10·8)	66·0 (11·3)
Predicted DLCO [*†‡§]	41·8% (11·9)	48·7 (12·8)	49·2 (9·3)	55·7 (13·3)
BDI (focal score; 0–12) [*]	6·0 (2·2)	5·6 (1·7)	6·5 (2·4)	7·4 (2·1)
HAQ-DI (score 1–3)	0·8 (0·7)	0·9 (0·7)	0·6 (0·5)	0·8 (0·7)
Modified Rodnan Skin Score (0–51)	16·6 (10·5)	14·1 (11·1)	15·9 (10·8)	14·2 (10·4)
Quantitative lung fibrosis score, whole lung	10·7% (9·1)	10·0% (10·9)	8·8% (6·1)	8·5% (7·2)
Quantitative lung fibrosis score, worst zone of maximum involvement	28·3% (21·8)	25·8% (22·0)	25·6% (20·0)	21·9% (19·5)
Quantitative ILD score, percentage of whole lung [*‡]	36·5% (15·2)	35·2% (17·7)	28·8% (11·8)	29·7% (14·7)
Quantitative ILD score, percentage of zone of maximum involvement [*]	60·1% (19·5)	57·2% (22·6)	53·3% (19·3)	50·5% (20·7)

	SLS I cohort (n=158)		SLS II cohort (n=142)	
	Male (n=47)	**Female (n=111)**	**Male (n=37)**	**Female (n=105)**
Anti-Scl-70 antibody	9/28 (32%)	27/78 (35%)	13/36 (36%)	48/98 (49%)
Anti-centromere antibody	0/28 (0%)	3/78 (4%)	2/36 (6%)	1/98 (1%)
Anti-RNA polymerase III	2/28 (7%)	15/78 (19%)	4/36 (11%)	14/98 (14%)

Data are n/N (%) or mean (SD). FVC=forced vital capacity. FEV=forced expiratory volume. TLC=total lung capacity. DLCO=diffusing capacity for carbon monoxide. BDI=Baseline Dyspnea Index. HAQ-DI=health assessment disability questionnaire. ILD=interstitial lung disease.

[*] p<0·05 comparing female particpants in SLS I with female participants in SLS II.

[†] p<0·05 comparing male participants with female participants in SLS I.

[‡] p<0·05 comparing male versus female participants in SLS II.

[§] p<0·05 comparing male participants in SLS I with male participants in SLS II.

Table 2:

Linear regression analysis for change in quantitative radiographic fibrosis or ILD scores at 24 months in the SLS II cohort

	Estimated effect	p value
Quantitative lung fibrosis score for the zone of maximum involvement at 24 months		
Baseline quantitative lung fibrosis score for the zone of maximum involvement [*]	0·94 (0·05)	<0·0001
Male sex [†]	7·13 (2·43)	0·0043
Cyclophosphamide group[‡]	0·16 (2·12)	0·94
Quantitative lung fibrosis score for the whole lung at 24 months		
Baseline quantitative lung fibrosis score for the whole lung [*]	0·81 (0·06)	<0·0001
Male sex [†]	2·41 (0·94)	0·012
Cyclophosphamide group[‡]	0·14 (0·82)	0·87
Quantitative ILD score for the zone of maximum involvement at 24 months		
Baseline quantitative ILD score for the zone of maximum involvement [*]	0·95 (0·06)	<0·0001
Male sex [†]	7·46 (2·79)	0·0088
Cyclophosphamide group[‡]	0·42 (2·42)	0·86
Quantitative ILD score for the whole lung at 24 months		
Baseline quantitative ILD score for the whole lung [*]	0·78 (0·06)	<0·0001
Male sex [†]	4·80 (1·99)	0·018
Cyclophosphamide group[‡]	1·44 (1·76)	0·42

Data are estimated effect (SE). Data are shown for 97 participants (25 male and 72 female participants). ILD=interstitial lung disease.

[*] Increased baseline radiographic extent of quantitative lung fibrosis or quantitative ILD score associated with significant increase (worsening) in quantitative lung fibrosis or quantitative ILD score.

[†] Male sex associated with significant increase (worsening) in quantitative lung fibrosis or quantitative ILD score.

[‡] No significant difference in change in quantitative lung fibrosis or quantitative ILD score between patients randomly assigned to cyclophosphamide versus mycophenolate mofetil.