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Clinical characteristics and survival in systemic sclerosis-mixed connective tissue disease and systemic sclerosis-overlap syndrome

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- JF: study design, data analysis, interpretation of results, preparation of manuscript (Criterion 1a, 1c, 2 and 3)
- DH: data analysis, interpretation of results, preparation of manuscript (Criterion 1c, 2 and 3)
- SP: data collection, interpretation of results, preparation of manuscript (Criterion 1a, 1c, 2 and 3)
- MW: data collection, interpretation of results, preparation of manuscript (Criterion 1a, 1c, 2 and 3)

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Abstract

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Objectives: To describe the clinical characteristics and outcomes of systemic sclerosis -mixed connective tissue disease (SSc-MCTD) and SSc-overlap.

Methods: We included patients from the Australian Scleroderma Cohort Study who met ACR/EULAR criteria for SSc. Three mutually exclusive groups were created: SSc-MCTD, SSc-overlap and SSc-only. Univariate comparison of clinical features was performed by ANOVA or chi-square. Survival analysis was performed using Kaplan-Meier (KM) curves and Cox regression.

Results: Of 1728 patients, 97 (5.6%) had SSc-MCTD and 126 (7.3%) SSc-overlap. Those with MCTD-SSc were more commonly Asian (18.3% vs 10.1% in SSc-overlap and 3.6% in SSc-only, p<0.0001) and younger at disease onset (38.4 years versus 46.5 or 46.8 years, p<0.0001). Those with SSc-MCTD or SSc-overlap were more likely to have limited SSc. All three groups had similar frequency of interstitial lung disease (ILD), although pulmonary arterial hypertension (PAH) was less common in

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SSc-overlap. Synovitis and myositis were more common in SSc-overlap and SSc-MCTD than in SSc-only. KM curves showed better survival in SSc-MCTD than SSc-overlap or SSc-only (p=0.011), but this was not significant after adjustment for sex and age at disease onset. SSc-specific antibodies were survival prognostic markers, with ANA-centromere or anti-RNP conferring better survival than anti-Scl-70 or anti-RNA polymerase 3 (p=0.005). SSc-MCTD and SSc-overlap had lower mortality following diagnosis of ILD and PAH than patients with SSc-only.

Conclusion: This study provides insights into the clinical characteristics of patients with SSc-MCTD, SSc-overlap and SSc-only and shows that anti-RNP antibodies are associated with better survival than anti-Scl-70 and anti-RNA polymerase III antibodies.

Keywords (up to 10): Scleroderma, mixed connective tissue disease, scleroderma overlap syndromes, clinical features

Significance and Innovations:

1. There are some significant differences in clinical features of SSc-MCTD and SSc-overlap compared with SSc-only
2. Antibodies may be more accurate at predicting prognosis than classification according to these disease groups
3. While development of interstitial lung disease or pulmonary arterial hypertension were poor prognostic factors, patients with SSc-MCTD and SSc-overlap had lower mortality following diagnosis of ILD and PAH than patients with SSc-only

Introduction

Mixed connective tissue disease (MCTD) is a heterogeneous clinical syndrome first described in 1972(1). It is characterised by overlapping features of multiple connective tissue diseases, including systemic sclerosis (SSc), systemic lupus erythematosus (SLE), polymyositis (PM) and rheumatoid arthritis (RA)(1, 2). Features may include synovitis, myositis, finger swelling, Raynaud phenomenon and acrosclerosis(1, 3). Antibody to the extractable nuclear antigen U1 ribonucleoprotein complex (U1RNP) is the serologic hallmark of MCTD(2). Multiple diagnostic criteria exist, with the most sensitive and specific being those described by Alargon-Sergovia and Kahn(3). These criteria require positive anti-U1RNP antibodies (titre ≥1:1600) in combination with 3 or more of swollen hands, synovitis, myositis, Raynaud phenomenon and acrosclerosis(3).

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By definition, MCTD shares many features with other connective tissue diseases (2, 4). Accordingly, there are some patients with MCTD who will fulfil diagnostic criteria for both MCTD and another connective tissue disease. Of interest is the overlap between patients who meet diagnostic criteria for MCTD and SSc simultaneously.

Patients who have both SSc and clinical features of another connective tissue disease such as SLE, RA, PM or Sjogren syndrome are often classified as having 'SSc-overlap' syndromes(2, 4). The wider literature suggests that these patients have a different disease course and organ involvement from those who purely meet criteria for limited or diffuse SSc(2). Thus arguably, they should be considered a distinct subgroup.

Our study aims to describe the clinical phenotype of patients in the Australian Scleroderma Cohort Study (ASCS) who are recorded as having MCTD or SSc-overlap syndromes. We aim to compare these groups with the remainder of the cohort in terms of clinical manifestations and outcome.

Patients and Methods

Patients

Patients were recruited from the ASCS. The ASCS is a multicentre study across 13 participating Australian Centres, to investigate risk and prognostic factors in SSc. The ASCS has been approved by all human research ethics committees of participating sites, with St Vincent's Hospital Melbourne Human Research Ethics committee acting as the coordinating site. Written informed consent was obtained from all patients at recruitment.

Selection of patient groups

We included only those patients who met ACR/EULAR criteria for SSc (5). We divided patients into three mutually exclusive groups for analysis: those with SSc and MCTD (SSc-MCTD), those with SSc overlap syndromes (SSc-overlap) and those with SSc only. SSc-MCTD was defined as positive anti-RNP antibodies, and at least 3 of the following clinical features synovitis, myositis, finger swelling, Raynaud phenomenon and acrosclerosis in accordance with accepted diagnostic criteria (1, 3). Patients who were positive for anti-RNP but did not have at least 3 clinical features of MCTD as above were not included in the SSc-MCTD group, but as SSc-only or SSc-overlap depending on other clinical features recorded in the database and classification according to the treating physician. SSc-overlap was designated by the treating physician if there were clinical features of another connective tissue disease present e.g. SLE, RA, PM or Sjogren syndrome, although it was not mandated that patients independently fulfilled diagnostic criteria for these conditions. In those that were classified as having SSc-overlap, physicians were offered the option of nominating the

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connective tissue disease that patients shared features with, but this was not compulsory. The physician could also nominate more than one overlap condition. Patients who were listed in the database as having both MCTD and an overlap syndrome were included in the SSc-MCTD group. Patients who did not meet criteria for SSc-MCTD or SSc-overlap were included in the SSc-only group.

Autoantibody testing

Indirect immunofluorescence was used to detect anti-nuclear antibody (ANA). Antibodies to extractable nuclear antigens (ENA) and antibodies to RNA-polymerase 3 were detected by ELISA, immunoblot, or a combination of these using local laboratory commercial test kits. ELISA was used to determine anti-double stranded DNA (dsDNA) antibody in most laboratories, with the Farr radioimmunoassay used by two laboratories. Autoantibody positivity was defined by a positive result according to the local laboratory protocol.

Data collection

Demographic and disease data were prospectively collected at baseline and annual reviews thereafter in a standardised fashion as part of the ASCS. All disease data or antibody results were defined as present if they had ever been reported from time of diagnosis. Disease onset and duration was defined as time from the first non-Raynaud's manifestation. The LeRoy criteria were used to determine disease subtype (diffuse or limited)(6). Pulmonary arterial hypertension (PAH) was diagnosed by right heart catheterisation, using a mean pulmonary artery pressure ≥25mmHg in association with a pulmonary arterial wedge pressure ≤15mmHg. High-resolution-computed tomography (HRCT) of the chest was used to diagnose interstitial lung disease (ILD), usually performed in response to clinical examination findings (chest crepitations) or abnormal respiratory function testing. Severity of ILD was defined by extent of involvement on HRCT (mild <20%, moderate 20-30%, severe >30%). In the absence of symptoms suggestive of PAH or ILD, patients within the ASCS were screened annually with both transthoracic echocardiography and pulmonary function testing. Definitive diagnostic testing as discussed above was arranged if these were abnormal. Scleroderma renal crisis was diagnosed in the presence of two of three criteria: new-onset hypertension with no alternate cause, unexplained rise in serum creatinine or microangiopathic haemolytic anaemia. Small intestinal bacterial overgrowth (SIBO) was diagnosed by concurrent diarrhoea and use of cyclical antibiotics. Endoscopy was used to diagnose gastric antral vascular ectasia (GAVE), reflux oesophagitis and oesophageal strictures. Hospitalisation data were collected annually based on patient-reported admissions of greater than 24 hours. Malignancy was defined by presence of melanoma, solid organ or haematological malignancy.

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Statistical Analysis

Characteristics of patients in the study are presented as mean (standard deviation (SD)) for continuous variables or number (percentage) for categorical variables. We compared continuous variables among the three groups using one-way analysis of variance. Discrete variables were compared using the chi-squared test. All-cause mortality was used for survival analysis. Kaplan-Meier curves and the Wilcoxon test were used to estimate survival from SSc onset, PAH diagnosis, and ILD diagnosis according to disease group and antibody status. Cox proportional hazards regression analysis was used to determine multivariable predictors of mortality. Patient characteristics that were clinically significant were considered for multivariate analysis of survival including gender, age at disease onset and one of either disease group or autoantibody status. In the antibody model, any patient that had multiple antibodies (among ANA centromere, Anti RNP, Anti Scl-70, and Anti RNA Polymerase 3) was excluded from the analysis. Any patients that did not have any of these antibodies were included in the 'no antibody' category. Characteristics with a p-value ≤ 0.05 that did not violate the proportional hazards assumption were included in the multivariate model. Due to collinearity between disease groups and SSc-specific antibodies, these variables were each included in separate multivariable models. The results were reported as hazard ratios (HR) with accompanying 95% confidence intervals. All statistical analyses were performed using STATA 15.1 (Statacorp LP, College Station, TX, USA).

Results

Description of whole cohort

One thousand seven hundred and twenty-eight patients fulfilled the inclusion criteria for this study. The characteristics of this cohort are summarised in Table 1. Of the 1728 patients included, 1489 (86%) were female, 1285 (74%) had limited and 442 (26%) diffuse disease. Ninety-seven (5.6%) patients were identified as having both SSc and MCTD (SSc-MCTD), while 126 (7.3%) were identified as having SSc-overlap syndrome. Patients with SSc-MCTD or SSc-overlap were more likely to have limited SSc than patients with SSc-only (84.5% and 83.3% versus 73%). Most patients were Caucasian (92%) followed by Asian ethnicity (4.9%). Ethnicity was similar between SSc-only and SSc-overlap, although in the SSc-MCTD group Asian background was significantly more common (18.3% versus 10.1% (SSc-overlap) and 3.6% (SSc only), $p<0.0001$). Patients with SSc-MCTD were younger at disease onset (38.4 years versus 46.5 or 46.8 years, $p<0.0001$). Mean duration of follow up was similar between groups at around 4.5 years.

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Among those that had SSc-overlap, 49 (38.9%) were listed as overlap with RA, 17 (13.5%) with SLE, 22 (17.5%) with polymyositis, 3 (2.4%) with dermatomyositis, 43 (34.1%) with Sjogren syndrome, and in 2 (1.6%), the overlap condition was not specified.

Autoantibody profile of the three disease groups

The autoantibody profile of the cohort is summarised in Table 1. In accordance with our definition of MCTD, antibodies to RNP were positive in all patients with SSc-MCTD. Anti-RNP was positive in 2.4% of patients with SSc-overlap and 0.3% with SSc-only. These RNP-positive patients did not otherwise meet diagnostic criteria for MCTD. Anti-Scl-70 was more commonly positive in patients with SSc-only (15.0%) or SSc-overlap (20.2%) than those with SSc-MCTD (7.5%). There was a higher frequency of anti-RNA polymerase 3 positivity in SSc-only (14.6%) compared with the other two groups (SSc-overlap 8.0%, SSc-MCTD 2.1%, p=0.0135). Anti-Jo-1 positivity was more common in patients with SSc-overlap (1.7%) or SSc-MCTD (2.1%) than SSc-only (0.3%, p=0.0073). Anti-Ro and anti-La were both more common in SSc-MCTD (26.3% and 5.3% respectively) and SSc-overlap (28.8% and 4.2% respectively) than SSc-only (6.6% and 1.3% respectively) (p<0.0001 and p=0.0023 respectively). Anti-Smith positivity was significantly more common in SSc-MCTD (25.8%) than SSc-overlap (3.4%) or SSc-only (0.3%, p<0.0001).

Anti-nuclear cytoplasmic antibodies (ANCA) were more common in patients with SSc-MCTD (25.0%) or SSc-overlap (25.2%) than SSc-only (13.2%, p=0.0001), although with no significant differences in frequency of anti-MPO or anti-PR3 positivity. Anti-CCP antibody was most common in SSc-overlap (9.4%), followed by SSc-MCTD (7.1%) and SSc-only (2.8%, p=0.0451), without significant difference in frequency of rheumatoid factor positivity. Anti-dsDNA antibody was significantly more common in SSc-MCTD (19.8%) and SSc-overlap (15.0%) than SSc-only (5.9%, p<0.0001).

Clinical characteristics and organ involvement

The clinical characteristics of patients is presented in Table 2.

Regarding cardiopulmonary involvement, PAH was more common in those with SSc-MCTD (12.4%) and SSc-only (11.1%) than in patients with SSc-overlap (4.8%), although this was not statistically significant (p=0.0751). There was no significant difference in mean pulmonary artery pressure at PAH diagnosis among groups. No significant differences existed for frequency of ILD between groups. No difference existed in frequency of pericardial or myocardial disease.

In terms of gastrointestinal involvement, patients with SSc-overlap were significantly more likely to have experienced dysphagia (60.3% vs. SSc-MCTD 45.4%, SSc-only 45.5%, p=0.0006) than those with SSc-only or SSc-MCTD. There was a higher frequency of oesophageal strictures in this group (SSc-

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overlap 24.6% vs. SSc-MCTD 23.7% and SSc-only 16.7%, p=0.0221). Lowest recorded body mass index (BMI) was within normal range in all groups, although lower in those with SSc-MCTD (23.6 versus SSc-only 25.0 and SSc-overlap 24.4, p=0.0260).

In terms of musculoskeletal and mucocutaneous manifestations, patients with SSc-MCTD were less likely to experience non-hand skin ulcers (SSc-only 8.8% vs. SSc-overlap 7.9%, SSc-MCTD 4.1%, p=0.0018), calcinosis (SSc-MCTD 21.6% vs. SSc-only 41.3%, SSc-overlap 37.3%; p=0.0011), and joint contractures than other groups (SSc-MCTD 25.8% vs. SSc-only 39.7%, SSc-overlap 42.9%; p=0.0344). There was no difference in frequency of sclerodactyly. Highest recorded Rodnan skin scores were greater in those with SSc-only (11.9 +/- 9.6) rather than SSc-MCTD (8.8 +/- 7.8) or SSc-overlap (9.4 +/- 7.9, p=0.0003). Sicca symptoms were more common in those with SSc-overlap than SSc-only or SSc-MCTD (dry eyes 79.4% versus SSc-MCTD 66.0% and SSc-only 62.5%, p=0.0056; dry mouth 87.3% versus SSc-only 72.1% and SSc-MCTD 69.1%, p=0.0048). Synovitis was equally common in SSc-MCTD and SSc-overlap groups (57.7% and 58.7% respectively) compared with SSc-only (35.9%, p<0.0001), as was myositis (SSc-MCTD 18.6% and SSc-overlap 22.2% versus SSc-only 4.3%, p<0.0001). Puffy digits were more common in patients with SSc-MCTD (82.5%) than those with SSc-only (69.2%) or SSc-overlap (66.7%, p=0.0522).

No significant differences in the frequency of renal crisis or vascular manifestations existed between groups, with the exception of telangiectasia, more commonly seen in SSc-only (86.4%) or SSc-MCTD (84.5%) than SSc-overlap (76.2%, p=0.0094).

In terms of biochemical and laboratory parameters, patients with SSc-overlap were more likely to have had a low C3 reading (27.0% vs. SSc-MCTD 22.8% and SSc-only 17.6%, p=0.0260), while patients with SSc-MCTD were more likely to have had a low C4 reading (33.7% vs. SSc-overlap 26.1% and SSc-only 17.3%, p=0.0001). Highest recorded erythrocyte sedimentation rate (ESR) was greater in those with SSc-MCTD (34.6) than those with SSc-overlap (30.5) or SSc-only (24.7, p=0.0145).

Patients with SSc-MCTD and SSc-overlap recorded similar mean peak creatine kinase (CK) levels (209.1 and 199.7, respectively), significantly higher than those with SSc-only (132.6, p<0.0001). Other parameters were similar between groups.

Treatment data

Exposure to immunosuppressive or immunomodulatory treatment was generally much more common in those with SSc-MCTD or SSc-overlap than SSc-only (Table 2). Patients with SSc-overlap were more likely than those with SSc-MCTD to have been exposed to biologic medications including abatacept, rituximab and anti-tumour necrosis factor (TNF)-alpha agents, as well as azathioprine and

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intravenous immune globulin (IVIG) (p<0.01 for all). Both groups were equally likely to have been exposed to synthetic disease-modifying antirheumatic drugs (DMARDs) including hydroxychloroquine, leflunomide and methotrexate, as well as prednisolone, than those with SSc-only (p<0.0001 for all). Hydroxychloroquine and methotrexate were the most commonly used DMARDs in our population, both significantly more common in those with SSc-MCTD and SSc-overlap than SSc-only. All three groups were equally exposed to cyclophosphamide, mycophenolate, calcineurin inhibitors and tocilizumab.

Patients with ILD were more likely to be treated with rituximab, azathioprine, cyclophosphamide, mycophenolate and prednisolone than those without ILD (Supplementary Table S1). Patients with PAH were more likely to be treated with cyclophosphamide (Supplementary Table S2). Frequency of immunosuppressive therapies in SSc-overlap patients by overlap condition is presented in Supplementary Table S3.

There was no difference between groups in exposure to antihypertensives, vasodilators or anticoagulants, or therapies targeting gastrointestinal manifestations (Supplementary Table S4). No major differences existed in frequency of PAH treatments.

Survival and risk factors for mortality

Comparing survival by diagnosis, in KM analysis, patients with SSc-MCTD had a better prognosis than those with SSc-only (p=0.011) (Figure 1(a)). Those with SSc-MCTD also had better survival than patients with SSc-overlap (p=0.037). However, in multivariable Cox proportional hazard models, after adjusting for sex and age at disease onset, there was no significant difference in survival among the three groups (Table 3).

Compared to KM analysis of survival according to disease group, in KM analysis according to antibody positivity, differences were more pronounced (Figure 1(b)). Those who were ANA centromere positive had a similar survival to anti-RNP positive patients (Figure 1(b)). Patients with anti-Scl-70 or anti-RNA polymerase 3 positivity had a worse survival than ANA centromere or anti-RNP positive patients. In a multivariate cox proportional hazard model of survival according to antibody status (using ANA centromere as a reference category), anti-Scl-70 positivity conferred a significantly worse prognosis (HR 2.75, 95% CI 1.88 to 4.04, p<0.001), as did anti-RNA Polymerase 3 positivity (HR 1.79, 95% CI 1.11-2.89, p=0.018) and absence of any positive SSc-specific antibody (HR 1.85, 95% CI 1.38 to 2.47, p<0.001). There was no significant difference in survival between ANA centromere and anti-RNP positive patients (Table 3). Male gender (HR 2.20, 95% CI 1.62-2.97,

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p<0.001) and older age at disease onset (HR 1.10, 95% CI 1.09-1.11, p<0.001) were predictors of mortality, independently of disease groups (Table 3).

Patients with SSc-MCTD and SSc-overlap had lower all-cause mortality following diagnosis of ILD than those with SSc-only (p=0.024)(Figure 2(a)). A similar pattern was seen in all-cause mortality following diagnosis of PAH, but this was not statistically significant (p=0.058) (Figure 2(b)). However, when SSc-MCTD and SSc-overlap patients were combined, they had a significantly better survival than those with SSc-only (p=0.019) (Figure 2(c)). SSc myocardial disease or history of renal crisis did not predict increased mortality in this cohort.

Discussion

In this large cohort of patients with SSc, 5.6% of patients were identified as having SSc-MCTD and 7.3% had SSc-overlap. Compared with SSc-MCTD, patients with SSc-overlap or SSc-only were more likely to have positive SSc-specific antibodies, including ANA centromere, anti-Scl-70 and anti-RNA Polyermase 3. SSc-overlap patients were more likely to have positive anti-CCP antibodies than those with SSc-MCTD. SSc-MCTD patients were more likely to be positive for anti-Smith and anti-dsDNA. Patients with SSc-MCTD or SSc-overlap were more likely than those with SSc-only to have a number of other positive autoantibodies (anti-Ro, anti-La, anti-Jo1 and ANCA).

Clinically, both groups had similar frequency of ILD and PAH. Patients with SSc-overlap had higher frequency of multiple gastrointestinal manifestations and cutaneous than those with SSc-only or SSc-MCTD. Synovitis was equally common in SSc-overlap and SSc-MCTD groups, although puffy digits were more common in those with SSc-MCTD. Myositis was equally common in those with SSc-MCTD and SSc-overlap. Patients with SSc-overlap or SSc-MCTD were significantly more likely to be exposed to a range of immunosuppressive medications including prednisolone, than those with SSc-only, with the most commonly used DMARDs being hydroxychloroquine and methotrexate. This increased frequency of immunomodulatory and immunosuppressive therapies likely reflects a greater frequency of “inflammatory” manifestations (e.g. synovitis and myositis) in SSc-MCTD and SSc-overlap groups than SSc-only.

In terms of survival, scleroderma-specific antibodies were a more reliable indicator of survival than disease groups. ANA centromere or anti-RNP conferred consistently better survival than anti-Scl-70 or anti-RNA polymerase 3, while disease groups were not associated with consistent differences in survival. Despite no difference in prognosis between groups in a multivariable model accounting for younger age of patients with SSc-MCTD, anti-RNP positivity continued to confer a survival benefit. Furthermore, absence of any SSc-specific antibody was associated with worse prognosis than ANA

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centromere or RNP positivity. Despite similar severity of ILD, SSc-MCTD and SSc-overlap had consistently lower all-cause mortality following diagnosis of PAH or ILD than patients with SSc-only. It may be that this difference is related to lower frequency of diffuse disease in those with SSc-overlap and SSc-MCTD, or a protective effect of particular antibodies e.g. anti-RNP or ANA centromere. Other potential explanations include different pathogenic mechanisms, or greater exposure to immunosuppressive medications.

In the wider literature, there are infrequent data about disease features of SSc-overlap, often lacking consistency, and there is a paucity of data about patients with SSc-MCTD. While one study supports our finding that patients with SSc-overlap, in addition to SSc-MCTD, were more likely to have limited skin involvement (2), another showed those with SSc and myositis overlap were more likely to have diffuse skin disease (7). We identified similar frequency of PAH and ILD in those with SSc-MCTD and SSc-overlap. Other data support similar frequency of PAH in those with SSc-overlap and limited SSc (2), albeit with a higher risk of ILD in SSc-overlap than in limited SSc (2) or SSc in general (7). Data in the wider literature consistently report higher rates of myositis (2) and arthritis/synovitis (7, 8) in those with SSc-overlap than SSc-only, as was the case in our study. Furthermore, multiple studies in patients with SSc-overlap (2, 7) support our findings that patients with SSc-overlap and SSc-MCTD are more likely to have more than one detectable autoantibody compared to those with SSc-only.

Multiple studies have shown lower mortality in SSc patients with ANA centromere antibody positivity compared to those with anti-Scl-70(9, 10). In another cohort of patients with SSc, improved survival was demonstrated in those with anti-RNP or anti-centromere antibody than those with anti-Scl-70(11). Interestingly, unlike in our study, this study did not demonstrate significantly worse survival in those with anti-RNA Polymerase 3 positivity(11). Once ILD or PAH was diagnosed, patients with SSc-MCTD or SSc-overlap had a better prognosis than those with SSc-only, despite similar severity of ILD. In the wider literature, disease subtype has not been shown to impact survival in those with PAH, suggesting that PAH is the most important factor(12). However, in our data, patients with SSc-MCTD had a lower all-cause mortality following ILD diagnosis.

MCTD is a controversial entity that some argue is a disease defined by an antibody(13). Among those who fulfil classification criteria for SSc, the diagnostic label of MCTD has limited usefulness beyond prognostic significance of anti-RNP relative to other SSc-specific antibodies. We would suggest the most important step is identifying anti-RNP positivity, rather than in making an additional diagnosis of MCTD. Not all patients with anti-RNP positivity meet criteria for MCTD; we have identified a small number of patients in our cohort with SSc who are anti-RNP positive but did not fulfil criteria for MCTD.

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To our knowledge, this is the largest study to investigate clinical features of patients with both SSc-MCTD and SSc-overlap. Our study includes a comprehensive analysis of disease features, serological profile and survival, using prospectively collected data. However, our study does have limitations. We did not have scope within our study to investigate patients with MCTD who do not fulfil criteria for SSc, as our database includes only those with SSc. Furthermore, on average, patients in our study were recruited more than 10 years after diagnosis of their disease, which may mean there is a degree of "survivor bias", as those with more aggressive disease and early mortality are less likely to have survived to be recruited into our study. This is likely to underestimate differences in survival between patients with SSc-MCTD and SSc-only. While data were collected prospectively, analysis was performed retrospectively. Furthermore, while the study overall included a large number of patients, SSc-MCTD was relatively uncommon leading to small numbers in some subgroup analyses.

Conclusions

This study reveals significant differences between patients with SSc-MCTD, SSc-overlap and SSc-only. We have identified a number of similarities between patients with SSc-overlap and SSc-MCTD, including prognosis, and frequency of PAH, ILD, myositis, synovitis, and autoantibody positivity. Furthermore, this study highlights the critical importance of antibody profile in determining prognosis, with greater accuracy than disease group. Patients with anti-RNP positivity display better long-term survival than those with anti-Scl-70 or anti-RNA polymerase 3 positivity. Furthermore, patients with SSc-MCTD and SSc-overlap had better survival following ILD or PAH diagnosis, despite similar severity. These data suggest that testing for antibody to RNP is a valuable prognostic tool in patients with SSc. Whether a 'diagnostic label' of SSc-MCTD or SSc-RNP is more appropriate in this setting is a point of contention. Regardless, this group of patients has a distinct phenotypic profile. While we did not have a consensus *a priori* definition of SSc-overlap, it was clear that treating physicians were indeed able to identify a group of patients with SSc with 'overlap' features who also had distinct clinical features and outcomes that differed significantly from those with SSc-only. Furthermore, it may assist with determining risk of specific organ manifestations in patients with SSc, particularly if an overlap syndrome is suspected. Further data are required to better understand these patients.

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Tables and Figures

Table 1: Demographic and autoantibody profile of study participants

Variable	Value	SSc Only	SSc-MCTD	SSc-overlap	p
Gender	Female	1293 (85.9%)	83 (85.6%)	113 (89.7%)	0.4924
	Male	212 (14.1%)	14 (14.4%)	13 (10.3%)	.
Disease subtype	Diffuse	406 (27.0%)	15 (15.5%)	21 (16.7%)	0.0024
	Limited	1098 (73.0%)	82 (84.5%)	105 (83.3%)	.
Race	Aboriginal-Islander	16 (1.1%)	1 (1.1%)	1 (0.8%)	<0.0001
	Asian	52 (3.6%)	17 (18.3%)	12 (10.1%)	
	Caucasian	1341 (93.3%)	71 (76.3%)	105 (88.2%)	
	Hispanic	12 (0.8%)	1 (1.1%)	0 (0.0%)	
	Other	16 (1.1%)	3 (3.2%)	1 (0.8%)	
Age at recruitment		57.6 (12.50)	49.9 (13.67)	57.5 (12.4)	<0.0001
Age at onset of SSc		46.8 (14.1)	38.4 (14.4)	46.5 (15.2)	<0.0001
Follow up in ASCS (years)		4.5 (3.33)	4.6 (2.98)	4.4 (3.0)	0.8699
Ever smoked		742 (49.3%)	50 (51.5%)	64 (50.8%)	0.9885
Autoantibody profile					
	ANA positive	1395 (95.4%)	94 (96.9%)	114 (92.7%)	0.2884
	ANA centromere	717 (49.6%)	11 (11.6%)	51 (42.1%)	<0.0001
	ANA homogenous	278 (19.5%)	17 (18.1%)	28 (23.5%)	0.5293
	ANA nucleolar	329 (22.9%)	8 (8.5%)	25 (21.0%)	0.0045
	ANA speckled	352 (24.6%)	76 (79.2%)	34 (28.1%)	<0.0001

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	Anti-RNA polymerase 3	141 (14.6%)	1 (2.1%)	7 (8.0%)	0.0135
	Anti-RNP	5 (0.3%)	97 (100.0%)	3 (2.4%)	<0.0001
	Anti-Jo-1	4 (0.3%)	2 (2.1%)	2 (1.7%)	0.0073
	Anti-La	19 (1.3%)	5 (5.3%)	5 (4.2%)	0.0023
	Anti-Ro*	93 (6.6%)	25 (26.3%)	34 (28.8%)	<0.0001
	Anti-Scl-70	214 (15.0%)	7 (7.5%)	24 (20.2%)	0.0374
	Anti-Sm	4 (0.3%)	24 (25.8%)	4 (3.4%)	<0.0001
	ANCA	175 (13.2%)	21 (25.0%)	27 (25.2%)	0.0001
	Anti-MPO	19 (1.4%)	2 (2.4%)	3 (2.8%)	0.4558
	Anti-PR3	24 (1.8%)	3 (3.6%)	4 (3.7%)	0.2340
	Anti-dsDNA	70 (5.9%)	17 (19.8%)	17 (15.0%)	<0.0001
	Anti-CCP	11 (2.8%)	2 (7.1%)	5 (9.3%)	0.0451
	Rheumatoid Factor	391 (28.9%)	31 (34.1%)	38 (33.3%)	0.3769
	Anti-PM-Scl	21 (1.5%)	1 (1.1%)	2 (1.7%)	0.9312
	No SSc-specific antibody**	376 (27.9%)	71 (81.6%)	42 (36.2%)	<0.0001

Abbreviations: SSc (Systemic Sclerosis), ASCS (Australian Scleroderma Cohort Study), MCTD (mixed connective tissue disease), SSc-only (Scleroderma only group), SSc-MCTD (scleroderma and mixed connective tissue disease overlap group), SSc-overlap (scleroderma overlap group), ENA (extractable nuclear antigen), Sm (Smith), RNP (ribonucleoprotein), ANCA (anti-neutrophil cytoplasmic antibodies), MPO (myeloperoxidase), PR3 (proteinase-3), IgG (immunoglobulin G), IgM (Immunoglobulin M), dsDNA (double stranded deoxyribonucleic acid), CCP (cyclic citrullinated peptide), RNA (ribonucleic acid)

*Anti-Ro60 antibody

**This refers to the absence of Scleroderma-specific antibodies, i.e. none of ANA centromere, anti-RNP, anti-Scl70, anti-RNA polymerase 3.

Table 2: Organ involvement and immunosuppressive treatment in study participants*

Variable	SSc Only	SSc-MCTD	SSc-overlap	p
Cardiopulmonary				
PAH*	167 (11.1%)	12 (12.4%)	6 (4.8%)	0.0751
Mean pulmonary artery	35.4 (10.1)	38.8 (13.0)	29.3 (5.2)	0.1742

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Pressure at PAH diagnosis (mmHg)				
ILD (on HRCT)*	393 (66.4%)	25 (61.0%)	34 (70.8%)	0.6178
Severity of ILD[#]				
Mild(<20%)	212 (56.5%)	17 (70.8%)	17 (53.1%)	0.6317
Moderate(20-30%)	111 (29.6%)	4 (16.7%)	11 (34.4%)	.
Severe(>30%)	52 (13.9%)	3 (12.5%)	4 (12.5%)	.
Lowest FVC (%)*	89.3 (22.1)	81.5 (19.5)	87.7 (21.6)	0.0029
Pericardial effusion*	126 (8.5%)	7 (7.3%)	7 (5.7%)	0.5396
Myocardial disease*	114 (7.6%)	6 (6.2%)	10 (7.9%)	0.8667
Gastrointestinal				
Malabsorption*	56 (3.7%)	7 (7.2%)	9 (7.1%)	0.0549
Rectal prolapse*	30 (2.0%)	0 (0.0%)	5 (4.0%)	0.1103
GAVE*	169 (11.2%)	5 (5.2%)	10 (7.9%)	0.1010
Oesophageal stricture*	251 (16.7%)	23 (23.7%)	31 (24.6%)	0.0221
Faecal incontinence*	439 (29.2%)	16 (16.5%)	34 (27.0%)	0.0577
Dysphagia*	685 (45.5%)	44 (45.4%)	76 (60.3%)	0.0006
Reflux oesophagitis*	1248 (82.9%)	80 (82.5%)	107 (84.9%)	0.8382
Vomiting*	320 (21.3%)	18 (18.6%)	45 (35.7%)	0.0044
Lowest BMI score*	25.0 (5.4)	23.6 (4.8)	24.4 (5.0)	0.0260
Musculoskeletal and mucocutaneous				
SSc skin changes present*	1365 (93.0%)	81 (85.3%)	111 (89.5%)	0.0115
Skin ulcers (non-hand)*	132 (8.8%)	4 (4.1%)	10 (7.9%)	0.0018
Highest Rodnan score*	11.9 (9.6)	8.8 (7.8)	9.4 (7.9)	0.0003
Synovitis*	541 (35.9%)	56 (57.7%)	74 (58.7%)	<0.0001
Myositis*	64 (4.3%)	18 (18.6%)	28 (22.2%)	<0.0001
Calcinosis*	622 (41.3%)	21 (21.6%)	47 (37.3%)	0.0011
Joint contractures	597 (39.7%)	25 (25.8%)	54 (42.9%)	0.0344
Large joint contractures	54 (3.6%)	1 (1.0%)	7 (5.6%)	0.0074
Small joint contractures	268 (17.8%)	7 (7.2%)	31 (24.6%)	0.0159
Puffy digits/ scleredaema*	1041 (69.2%)	80 (82.5%)	84 (66.7%)	0.0522
Sclerodactyly*	1337 (88.8%)	84 (86.6%)	114 (90.5%)	0.7123

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Dry eyes*	941 (62.5%)	64 (66.0%)	100 (79.4%)	0.0056
Dry mouth*	1085 (72.1%)	67 (69.1%)	110 (87.3%)	0.0048
Tendon friction rubs*	130 (8.6%)	8 (8.2%)	12 (9.5%)	0.9810
Renal				
Renal Crisis*	55 (3.7%)	0 (0.0%)	5 (4.0%)	0.1548
Glomerular Filtration Rate (lowest*)				
<30	40 (2.8%)	1 (1.1%)	5 (4.1%)	0.1545
30-60	347 (24.4%)	14 (14.9%)	29 (24.0%)	
>60	1036 (72.8%)	79 (84.0%)	87 (71.9%)	
Vascular				
Raynaud Phenomenon*	1494 (99.3%)	97 (100.0%)	126 (100.0%)	0.4404
Digital gangrene/ amputation*	199 (13.2%)	11 (11.3%)	10 (7.9%)	0.4191
Digital ulcers*	777 (51.6%)	42 (43.3%)	56 (44.4%)	0.2876
Telangiectasia*	1300 (86.4%)	82 (84.5%)	96 (76.2%)	0.0094
Malignancy				
All malignancies[1]	314 (20.9%)	15 (15.5%)	26 (20.6%)	0.4430
Biochemistry/laboratory parameters				
Low C3*	238 (17.6%)	21 (22.8%)	31 (27.0%)	0.0260
Low C4*	234 (17.3%)	31 (33.7%)	30 (26.1%)	0.0001
Highest ESR*	27.5 (24.7)	34.6 (25.7)	30.5 (23.6)	0.0145
Highest CK*	132.6 (134.9)	209.1 (403.7)	199.7 (378.1)	<0.0001
Lowest haemoglobin*	123.6 (17.2)	120.8 (14.2)	123.1 (17.3)	0.2650
Lowest albumin*	37.5 (4.5)	37.1 (5.6)	37.0 (4.2)	0.4580
Lowest platelet count*	244.3 (71.0)	225.7 (69.9)	246.7 (64.4)	0.0869
Immunomodulatory/immunosuppressive treatments				
Abatacept	2 (0.1%)	0 (0.0%)	2 (1.6%)	0.0044
Rituximab/Anti-CD20	10 (0.7%)	5 (5.2%)	9 (7.2%)	<0.0001
Azathioprine	106 (7.1%)	14 (14.4%)	23 (18.4%)	<0.0001
Calcineurin inhibitor	21 (1.4%)	4 (4.1%)	2 (1.6%)	0.1116
Cyclophosphamide	135 (9.0%)	9 (9.3%)	12 (9.6%)	0.9715

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Hydroxychloroquine	262 (17.5%)	48 (49.5%)	54 (43.2%)	<0.0001
Leflunomide	10 (0.7%)	4 (4.1%)	5 (4.0%)	<0.0001
Methotrexate	292 (19.4%)	43 (44.3%)	61 (48.8%)	<0.0001
Mycophenolate	152 (10.1%)	11 (11.3%)	16 (12.8%)	0.6109
Penicillamine	119 (7.9%)	2 (2.1%)	8 (6.4%)	0.0927
Prednisolone	646 (43.0%)	63 (64.9%)	79 (63.2%)	<0.0001
TNF-Alpha inhibitors	6 (0.4%)	3 (3.1%)	6 (4.8%)	<0.0001
Tocilizumab	5 (0.3%)	1 (1.0%)	1 (0.8%)	0.4488
Intravenous immunoglobulin	4 (0.3%)	0 (0.0%)	6 (4.8%)	<0.0001

* ever during follow-up/from SSc diagnosis

[#]ILD severity based on extent (%) of lung involvement on high-resolution CT lung (HRCT)

[1]Recorded malignancies included bowel, breast, haematological, lung, melanoma and non-melanoma skin cancers.

Abbreviations: SSc (Systemic Sclerosis), MCTD (mixed connective tissue disease), SSc-only (Scleroderma only group), SSc-MCTD (scleroderma and mixed connective tissue disease overlap group), SSc-overlap (scleroderma overlap group), PAH (pulmonary arterial hypertension), ILD (interstitial lung disease), FVC (forced vital capacity), GAVE (Gastric antral vascular ectasia), BMI (Body mass index), ESR (erythrocyte sedimentation rate), CK (creatine kinase), C3 (C3 complement), C4 (C4 complement), CD20 (B-lymphocyte antigen CD20), TNF (tumour necrosis factor), IVIG (intravenous immune globulin), ACE (angiotensin converting enzyme), SIBO (small intestinal bacterial overgrowth), H2 (histamine receptor H2), PEG (percutaneous endoscopic gastrostomy)

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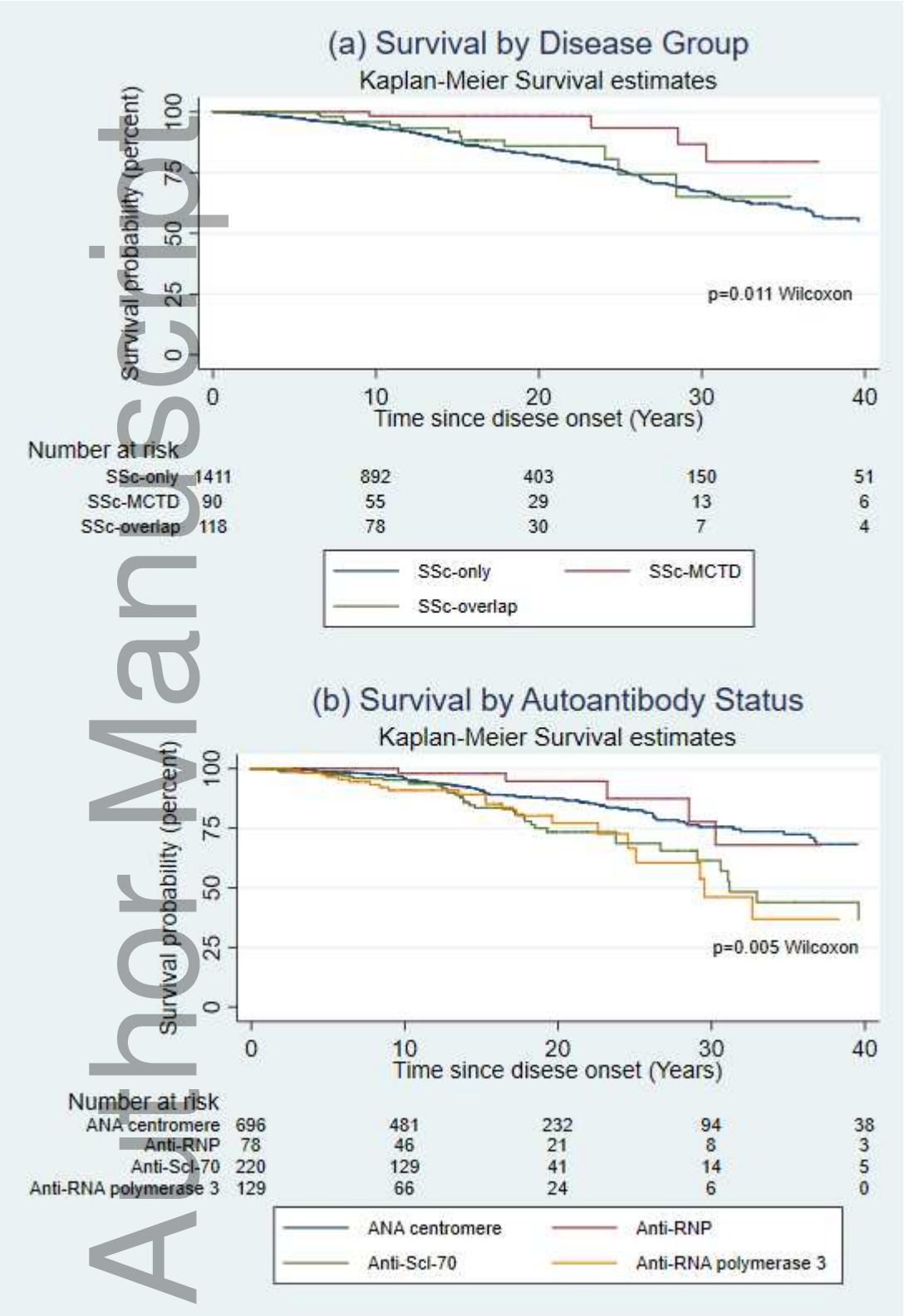
Figure 1: Survival by disease group and autoantibody status



Abbreviations: SSc (Systemic Sclerosis), MCTD (mixed connective tissue disease), SSc-only (Scleroderma only group), SSc-MCTD (scleroderma and mixed connective tissue disease overlap group), SSc-overlap (scleroderma overlap group), ANA (anti-nuclear antibody), ENA (extractable nuclear antigen), RNP (ribonucleoprotein), RNA (ribonucleic acid)

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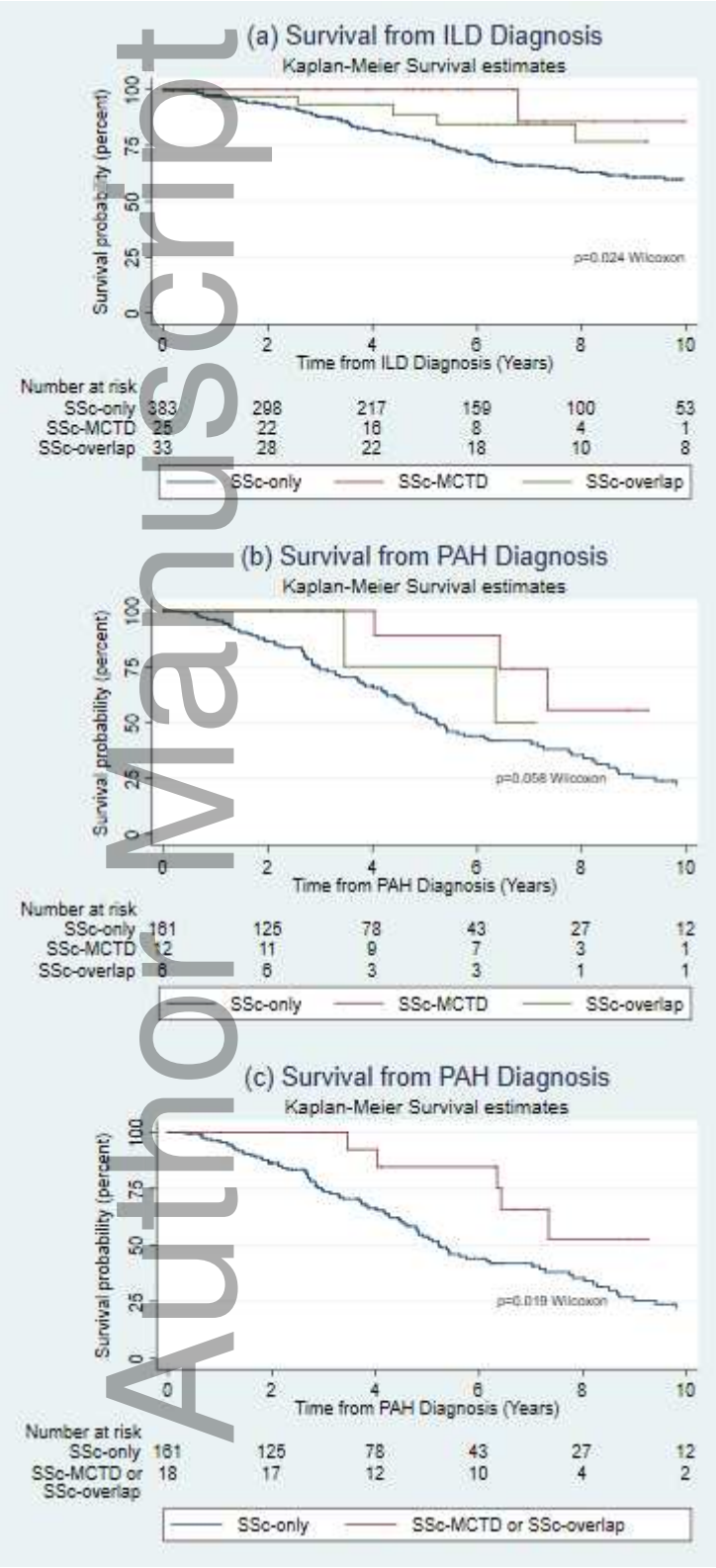
Figure 2: Survival from diagnosis of PAH or ILD (years)



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Abbreviations: SSc (Systemic Sclerosis), MCTD (mixed connective tissue disease), SSc-only (Scleroderma only group), SSc-MCTD (scleroderma and mixed connective tissue disease overlap group), SSc-overlap (scleroderma overlap group)

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Table 3: Multivariable hazard models for mortality

	Model with disease group (n=1555)	**Model with autoantibodies (n=1,094)**

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Variable	HR	p-value (95% CI)	HR	p-value (95% CI)
Gender				
Female	1	-	1	-
Male	1.85	<0.001 (1.33 to 2.56)	1.72	0.018 (1.10 to 2.68)
Age of disease onset	1.10	<0.001 (1.09 to 1.11)	1.12	<0.001 (1.10 to 1.14)
Disease group				
SSc-only	1	-		
SSc-MCTD	0.42	0.090 (0.15 to 1.14)		
SSc-overlap	0.89	0.718 (0.47 to 1.69)		
Antibody				
ANA centromere			1	-
Anti-RNP			0.85	0.740 (0.33 to 2.19)
Anti-Scl-70			2.16	0.004 (1.28 to 3.65)
Anti-RNA polymerase 3			1.22	0.529 (0.66 to 2.25)
Interstitial Lung Disease				
No	1	-	1	-
Mild/Moderate	1.66	0.001 (1.25 to 2.22)	1.39	0.132 (0.91 to 2.14)
Severe	5.23	<0.001 (3.47 to 7.89)	4.14	<0.001 (2.16 to 7.95)
Pulmonary Arterial Hypertension				
No	1	-	1	-
Yes	2.99	<0.001 (2.26 to 3.94)	3.26	<0.001 (2.30 to 4.63)
Renal Crisis				
No	1	-	1	-

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Yes	1.42	0.237 (0.79 to 2.54)	1.14	0.775 (0.45 to 2.93)
Myocardial Involvement				
No	1	-	1	-
Yes	1.08	0.696 (0.72 to 1.63)	1.36	0.234 (0.82 to 2.27)

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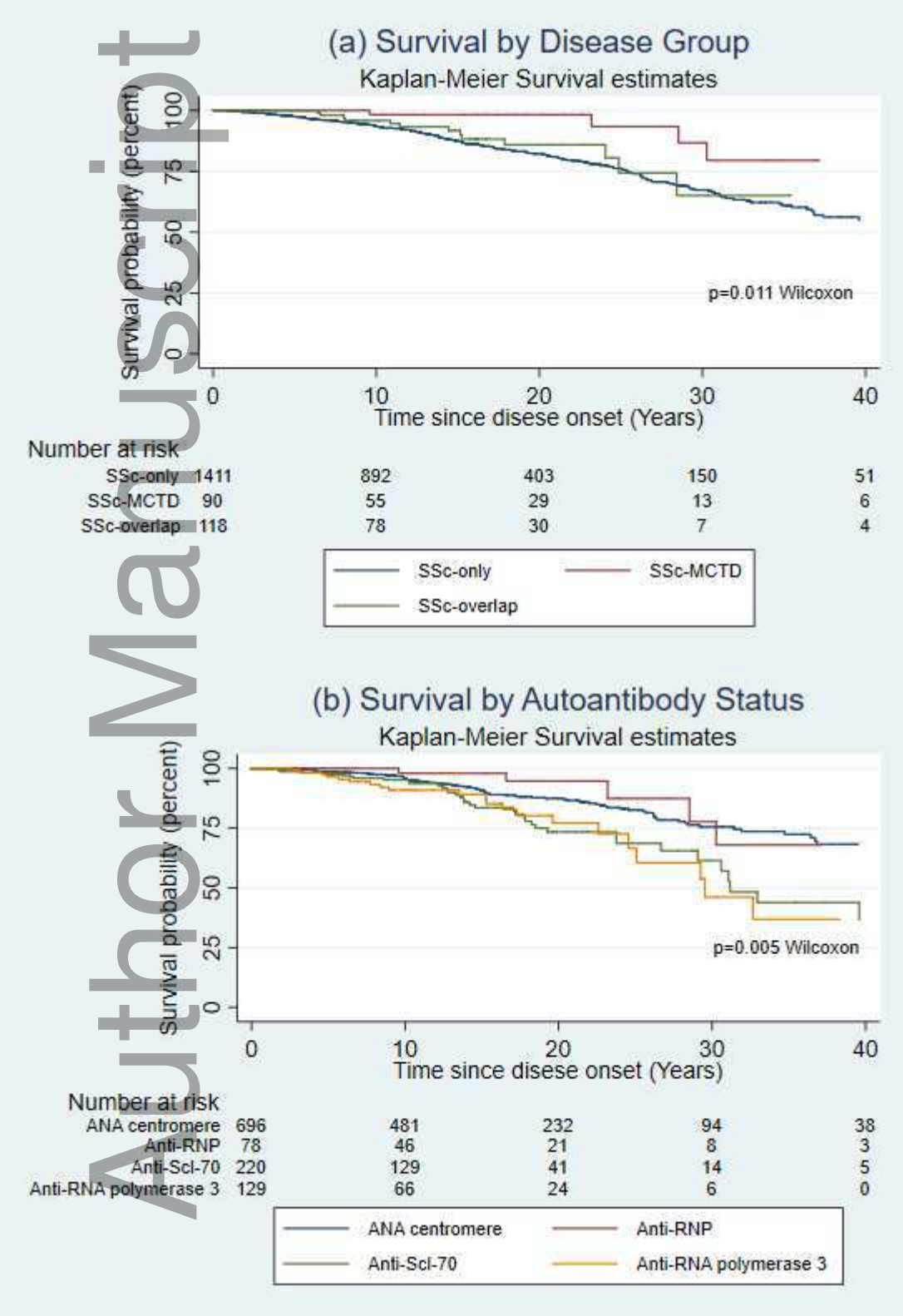
Tables and Figures

Figure 1: Survival by disease group and autoantibody status



Abbreviations: SSc (Systemic Sclerosis), MCTD (mixed connective tissue disease), SSc-only (Scleroderma only group), SSc-MCTD (scleroderma and mixed connective tissue disease overlap group), SSc-overlap (scleroderma overlap group), ANA (anti-nuclear antibody), ENA (extractable nuclear antigen), RNP (ribonucleoprotein), RNA (ribonucleic acid)

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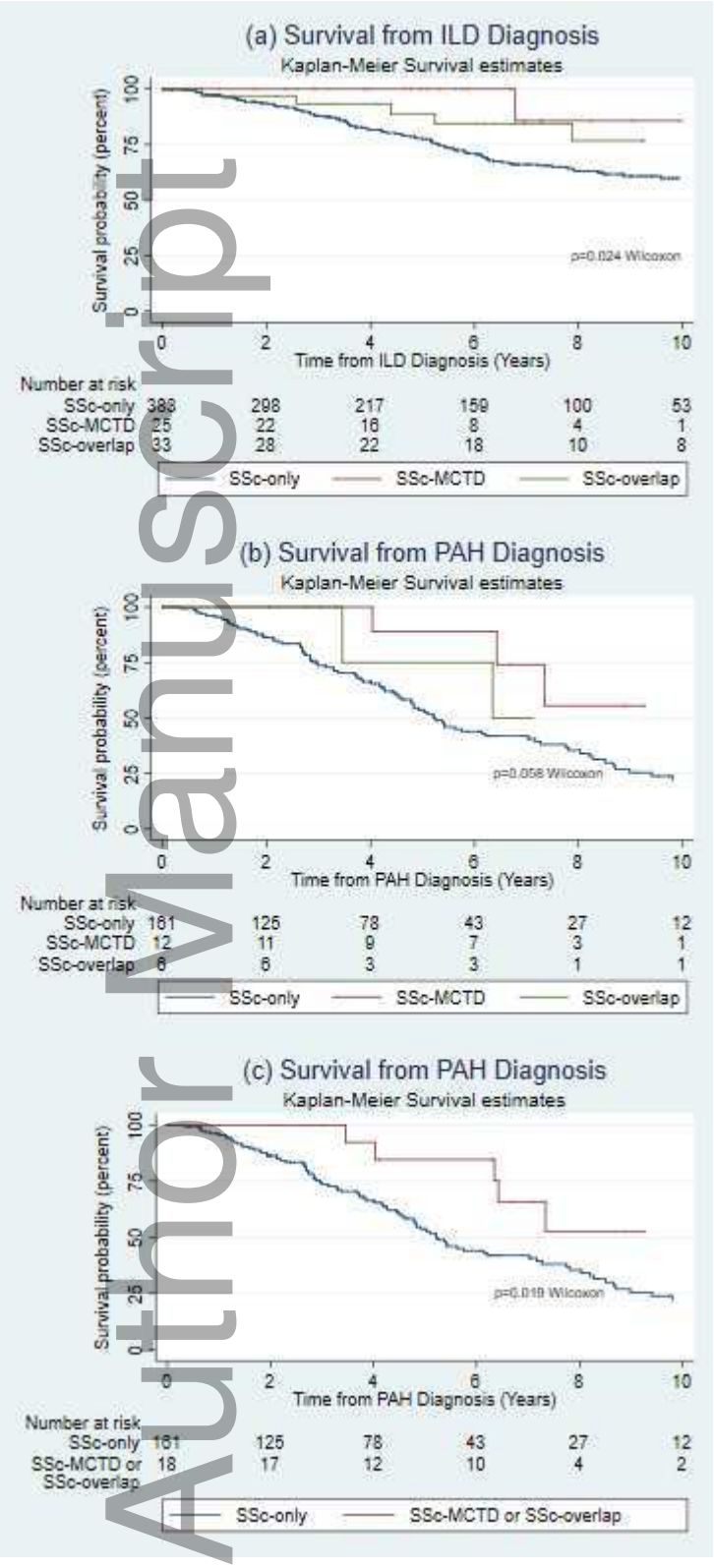
Figure 2: Survival from diagnosis of PAH or ILD (years)



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Abbreviations: SSc (Systemic Sclerosis), MCTD (mixed connective tissue disease), SSc-only (Scleroderma only group), SSc-MCTD (scleroderma and mixed connective tissue disease overlap group), SSc-overlap (scleroderma overlap group)

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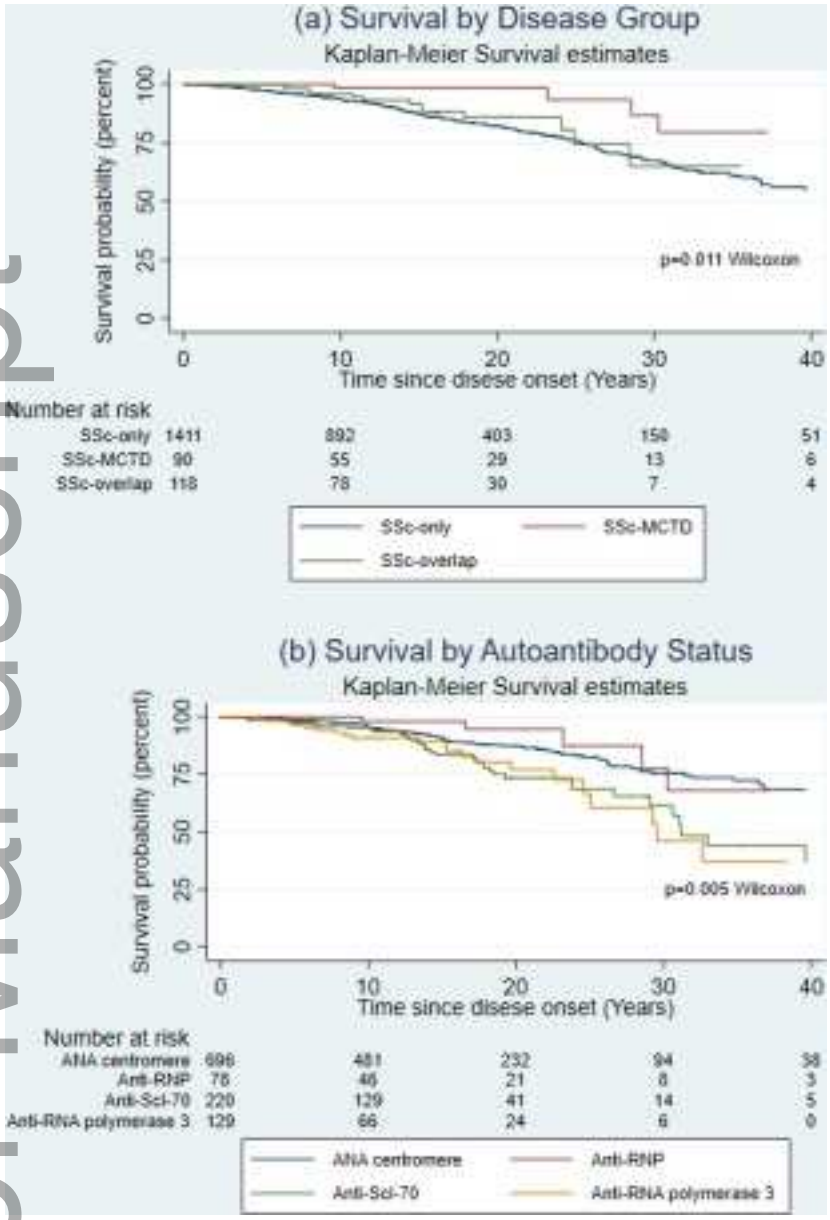

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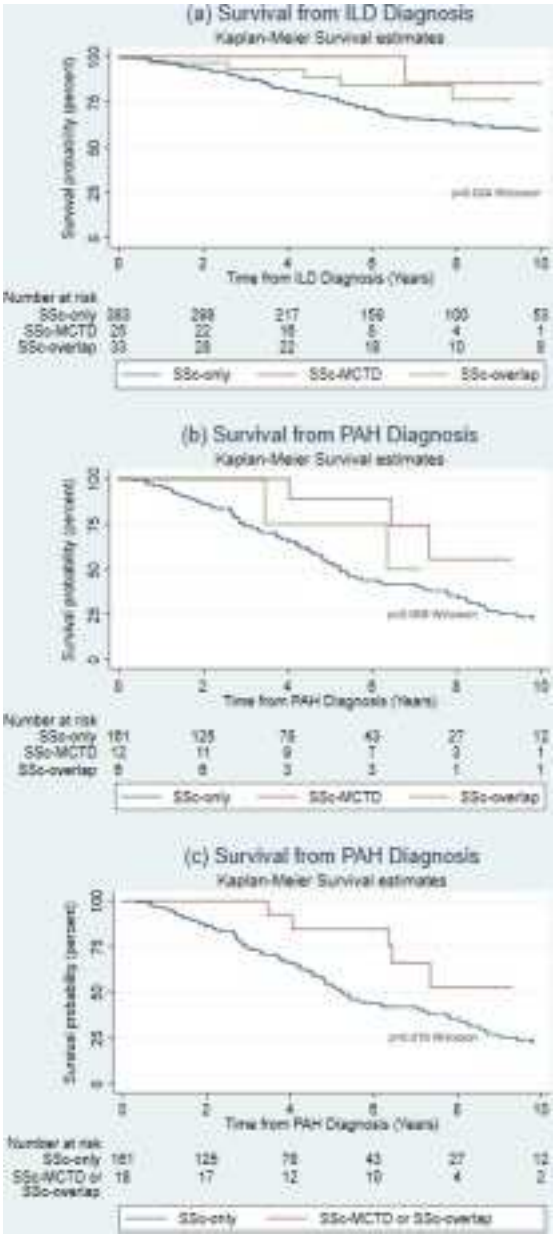

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