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DE DOCTEUR EN MEDECINE

Survie et facteurs pronostiques dans la sclérodermie systémique : étude d'une cohorte multicentrique incidente française, revue systématique de la littérature et méta-analyse

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AVERTISSEMENT

La Faculté n'entend donner aucune approbation aux opinions émises dans les thèses : celles-ci sont propres à leurs auteurs.

LISTE DES ABRÉVIATIONS

SSc: systemic sclerosis

ILD: interstitial lung disease

PH: pulmonary hypertension

PAP: pulmonary arterial pressure

FVC: forced vital capacity

TLC: total lung capacity

DLCO: diffusing capacity of the lung for carbon monoxide

6MWT: 6 minutes walking test

HRCT: high resolution computed tomography

RHC: right heart catheterization

RP: Raynaud phenomenon

mRSS: modified Rodnan skin score

ACA: anti-centromere antibodies

APL: antiphospholipid antibodies

GFR: glomerular filtration rate

CRP: C reactive protein

BMI: body mass index

SMR: standardized mortality ratio

HR: hazard ratio

INTRODUCTION GENERALE

La sclérodermie systémique (SSc) est une maladie auto-immune caractérisée par une activation endothéliale, des altérations des systèmes immunitaires inné et adaptatif et une fibrose de multiples organes. Une grande hétérogénéité interindividuelle des manifestations cliniques, du profil d'auto-anticorps, de la vitesse progression de la maladie et de la survie existe entre les patients sclérodermiques [(1)]. Selon l'étendue de la fibrose cutanée, les patients sont classés en deux catégories : ceux présentant une forme cutanée limitée et ceux présentant une forme cutanée diffuse. La forme cutanée diffuse est typiquement d'évolution rapide et associée à une fibrose pulmonaire et d'autres organes alors que la forme cutanée limitée présente généralement une atteinte vasculaire prédominante et une fibrose moins marquée [(2)].

Au cours des dernières décennies, nous avons assisté à une évolution des causes de décès dans la SSc grâce à l'introduction des inhibiteurs de l'enzyme de conversion de l'angiotensine, ayant permis de diminuer la mortalité liée à la crise rénale sclérodermique [(3)]. Les principales causes de décès liés à la SSc sont, aujourd'hui, d'ordre cardiopulmonaire [(3)]. Le taux de mortalité dans la SSc reste cependant toujours élevé.

Afin d'étudier l'évolution de la survie dans la SSc, il peut être intéressant de comparer, dans un centre donné, les données de survie d'une cohorte dite « historique » à celle d'une cohorte contemporaine. Ainsi, les équipes de Medsger [(3)], Pope [(4)] et Denton [(5)] ont suggéré que la survie s'était améliorée dans la SSc au cours du temps. Par exemple, la survie à 10 ans, était passée de 54% à 66% sur la période de 1972 à 2002 dans la cohorte de Pittsburgh [(3)].

Une seconde méthode, plus précise, d'étudier l'évolution de la survie dans la SSc est à travers la mesure de l'indice standardisé de mortalité (SMR). Le SMR est calculé en rapportant le nombre de décès observé au sein d'un groupe de patients sclérodermiques sur une période donnée, au nombre de décès survenus si ce groupe avait été soumis à la mortalité par âge de la population générale sur cette même période. Le SMR permet donc de prendre en compte l'amélioration de la survie de la population générale au cours du temps. Deux méta-analyses récentes [6,7] ont permis de synthétiser les résultats de SMR provenant de différentes cohortes de patients SSc et ont montré d'une part que le SMR combiné dans la SSc était dans un cas de 3,53 [6], et dans l'autre de 2,72 [7], et d'autre part, que le SMR ne s'était pas amélioré de façon statistiquement significative au cours du temps.

Un autre élément à prendre en compte dans le calcul de la mortalité est la durée d'évolution de la maladie depuis le diagnostic de la SSc ou, mieux encore, depuis le premier symptôme. En effet, les cohortes de cas prévalents, en d'autres termes, dont la durée d'évolution de la maladie est plus longue, ont tendance à sous-estimer la mortalité car l'analyse n'inclut pas les patients qui seraient décédés en début de maladie [8,9]. Nous constatons qu'une majorité des études estimant la survie dans la SSc incluent des cas prévalents.

Devant le taux de mortalité élevé dans la SSc, plusieurs études [10–26] se sont intéressées aux facteurs pronostiques de la maladie, identifiant ainsi les atteintes spécifiques d'organes, la forme cutanée diffuse et le sexe masculin comme facteurs principaux. Elhai *et al.* [27] ont récemment développé un score pronostique pouvant prédire la mortalité à 3 ans à partir de la grande base de données EUSTAR. A notre connaissance, 2 méta-analyses [7,28] étudiant les facteurs pronostiques dans la SSc ont été réalisées. Cependant,

ces méta-analyses se sont surtout intéressées aux atteintes spécifiques d'organes et n'ont pas étudié les auto-anticorps, le cancer et l'origine ethnique dans la SSc.

Les objectifs de notre étude étaient d'évaluer la survie et les facteurs pronostiques dans une cohorte multicentrique incidente française, puis de réaliser une revue systématique de la littérature et une méta-analyse sur le SMR et les facteurs pronostiques dans la SSc.

DISCUSSION GENERALE

Dans notre série de 625 patients recrutés à partir de 5 centres experts, les taux cumulés de survie globale étaient estimés à 86% à 5 ans et 72% à 10 ans et le SMR était calculé à 5,73 (IC95% 4,68 – 6,94). Cette surmortalité compte parmi les plus élevées rapportées dans d'autres séries récentes [21,23,26,29,30]. Une proportion élevée d'anti-Scl70 (35%) et une inclusion limitée aux cas incidents dans notre série peuvent, du moins en partie, rendre compte de cette différence observée. En effet, notre méta-analyse, synthétisant les données de SMR à partir de 18 études, a retrouvé une association significative entre le SMR et la proportion de forme diffuse de la maladie (P=0,0008) ainsi que la proportion d'anti-Scl70 (P = 0,0206). En revanche, notre méta-analyse n'a pas mis en évidence de différence significative entre le SMR combiné des études ayant inclus indifféremment des cas incidents ou prévalents [SMR 3,45 ; (IC95% 3,03 – 3,94)] et le SMR combiné des études ayant inclus uniquement des cas incidents [SMR 3,63 ; (IC95% 3,03 – 4,36)]. Enfin, nos résultats concordent avec ceux de Elhai *et al.* [6] en ne montrant pas d'amélioration significative du SMR au cours du temps.

Outre les facteurs pronostiques déjà bien décrits dans les études antérieures, tels que le sexe masculin, l'âge, la forme diffuse de la maladie, l'atteinte cardiopulmonaire, l'atteinte rénale, et l'inflammation, notre étude en a identifié de nouveaux grâce à une caractérisation exhaustive de notre cohorte. A notre connaissance, notre étude a décrit pour la première fois le rôle pronostique de la présence de télangiectasies, de la distance parcourue au test de marche de 6 minutes et de la présence d'une valvulopathie cardiaque. Notre méta-analyse, synthétisant les données sur les facteurs pronostiques de 33 études, a permis de calculer pour la première fois les *hazard ratios* combinés des facteurs suivants : l'origine ethnique africaine, la présence d'auto-anticorps anti-Scl70 et anti-centromère et la présence d'un cancer associé. Un probable biais de publication entraîne une potentielle surestimation du rôle pronostique des auto-anticorps anti-Scl70.

En conclusion, nos résultats confirment que la mortalité dans la SSc reste élevée à ce jour. Les facteurs pronostiques majeurs identifiés étaient un âge au diagnostic > 60 ans, une forme diffuse de la maladie, un antécédent de crise rénale sclérodermique, une capacité vitale fonctionnelle et une capacité de transfert du monoxyde de carbone < 70% de la théorique, une hypertension pulmonaire, une anémie et une CRP > 8mg/l. Des études additionnelles sont requises pour confirmer la valeur pronostique de la présence de télangiectasies, de valvulopathies cardiaques et de la distance parcourue au test de marche de 6 minutes.

SURVIVAL AND PROGNOSTIC FACTORS IN SYSTEMIC SCLEROSIS: DATA OF A FRENCH MULTICENTER COHORT OF INCIDENT PATIENTS, SYSTEMATIC REVIEW AND META-ANALYSIS OF THE LITERATURE

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ABSTRACT

Introduction

Several studies have assessed prognosis factors in systemic sclerosis (SSc), but only few have investigated extensive clinical and laboratory factors in a large, incident and well-phenotyped population. The aim of the present study was to describe survival, standardized mortality ratio (SMR) and prognostic factors in a well-phenotyped and multicenter French cohort of incident SSc patients. A systematic review and meta-analysis of cohort studies was then performed to further assess SMR and prognostic factors in SSc.

Materials and methods

Survival, SMR and prognosis factors were assessed in a cohort of SSc patients followed in five referral centers in France. A systematic review of the literature up to July 2017 was performed. Cohort studies of unselected SSc patients reporting SMR and prognostic factors were included in the meta-analysis. We calculated the pooled summary estimates of SMR and hazard ratios (HR) of prognosis factors.

Results

625 SSc patients (28.6% of diffuse SSc (dcSSc)) with recent diagnosis were included in the study. 104 deaths were recorded. Overall survival rates at 1, 3, 5 and 10 years from diagnosis were 98.0%, 92.5%, 85.9% and 71.7% respectively. Overall SMR was 5.73 (95% confidence interval (CI) 4.68 - 6.94). Age at diagnosis > 60 years, dcSSc, scleroderma renal crisis, severe dyspnea, FVC < 70%, DLCO < 70%, pulmonary hypertension (PH), telangiectases, valvular disease, malignancy, anemia, CRP > 8mg/l were associated with a poorer survival.

Eighteen articles were included in the SMR meta-analysis, representing a total population of 11,719 patients and 33 studies were included in the prognosis factors meta-analysis, representing a total of 23,145 patients. Pooled SMR was 3.45 (95%CI 3.03 – 3.94). Age at disease onset, age at diagnosis, male sex, black race, dcSSc subtype, anti-Scl70 autoantibodies, cardiac and renal involvements, interstitial lung disease, PH and malignancy were significantly associated with a worse prognosis. Presence of ACA autoantibodies was associated with a better survival.

Conclusion

Overall, our study and meta-analysis confirm a high mortality rate in SSc and previously described prognosis factors related to skin extension, autoantibody status and organ involvement while reporting new association such as telangiectases and valvular disease.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease, characterized by microvascular damage, dysregulation of both innate and adaptative immunity and fibrosis of multiple organs [1]. The causes of SSc-related deaths have changed over the last decades, with cardiac and respiratory complications currently being the leading causes of death [3,27].

Prior cohort studies comparing contemporary and historical cohort have suggested an improvement of survival rates over time [3–5]. Yet, two recent meta-analysis have reported that standardized mortality ratio (SMR) was stable over time [6,7]. Moreover, most of the observational studies investigating mortality in SSc have included prevalent cases, which may result in an underestimation of mortality due to a survivor bias [8,9].

Previous studies [10–26] have focused on risk factors for poor survival in SSc and identified male sex, diffuse cutaneous subtype and specific organ involvement as poor prognostic factors. Recently, Elhai *et al*. have developed a prognostic score from the large EUSTAR database, which accurately predicts 3-year mortality [27]. To our knowledge, two meta-analysis have combined the results of the available literature to assess prognostic factors [7,28]. However, these studies focused mainly on specific organ involvement and did not assess prognostic factors such as auto-antibody profile, race and cancer.

The aim of the present study was to fill these gaps by assessing prognostic factors in a well-characterized and multicenter French incident cohort of SSc patients. A systematic review of the literature and meta-analysis, focused on SMR and prognostic factors and including our new cohort was then performed.

METHODS

Population

The French National Scleroderma Cohort includes 42 centers. However, the present analysis was restricted to five university hospitals, Lille, Paris (two centers), Nantes and Lyon to ensure the lowest rate of missing data. Data were retrospectively collected before 2010, and then prospectively collected.

Patients were included between January 1, 2000 to December 31, 2013, if they met the following inclusion criteria: (i) to be aged over 18, (ii) to fulfil the ACR/EULAR 2013 classification criteria for SSc, (iii) to have at least one additional visit after the inclusion visit and (iv) to be incident cases, defined as patients having disease duration from time of diagnosis to enrolment in study of less than 3 years. Patients were followed-up until July 1, 2016. Patients were considered as lost to follow-up if the vital status could not be ascertained. When possible, the vital status was ascertained by querying death registers at birth town councils.

Collected data and variables definition

Data collected at the inclusion visit were patient demographics, history of Raynaud phenomenon (RP) and first non-RP symptom, SSc subtype and modified Rodnan skin score (mRSS), autoantibody profile, and organ involvement.

Disease onset was defined as the time of onset of first non-RP symptom. Interstitial lung disease was defined as the presence of pulmonary interstitial pattern on HRCT or chest x-ray. Pulmonary hypertension was suspected on doppler echocardiogram when systolic pulmonary arterial pressure (PAP) was estimated to be > 35mmHg or maximum tricuspid regurgitant jet velocity > 2,8m/s. Pulmonary hypertension was confirmed by RHC when mean PAP was found to be > 25mmHg at rest. Scleroderma renal crisis was defined as

new onset hypertension > 150/85mmHg associated with a decrease in renal function defined by a decrement of at least 10% in the estimated glomerular filtration rate. Gastrointestinal was defined by the presence of reflux, dysmotility, constipation and diarrhea, signs of bacterial overgrowth and/or malabsorption, abnormal oesophagomanometry and/or endoscopy test. Muscular involvement was defined by the presence of myalgia or muscle weakness, or elevation of CPK. Articular involvement was defined as the presence of arthralgia, synovitis and/or friction rubs. Pulmonary function tests including forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO) were collected at baseline.

Systematic review and meta-analysis

The meta-analysis was conducted according to the PRISMA statement [31]. MEDLINE database was queried by 2 of the authors (MRP and DL) using the following search terms: ((systemic sclerosis [Title]) OR (scleroderma, systemic[Title])) AND ((death) OR (mortality) OR (prognosis) OR (survival)). All records published before July 1, 2017 were included in the search. Language was restricted to English or French. Reference list of selected studies were hand-searched for additional relevant studies to be included in the meta-analysis.

Two of the authors (MRP and DL) independently screened the titles and abstracts of the retrieved records to identify eligible articles to be studied in full-text. The two reviewers then read the full-text of eligible articles for inclusion in the meta-analysis. Selected articles were compared and in case of disagreement, decisions were made by consensus.

Studies of unselected adult SSc patients assessing routine clinical and laboratory prognosis factors and SMR were included in the analysis. Studies which included patients diagnosed with SSc overlap with other connective tissue diseases were excluded from the study.

Studies from same centers were included if their respective study periods were different. If for a same center, two studies covered an overlapping study period, data from the largest cohort were kept. A study was recorded as incident according to the authors' definition or if disease duration from time of diagnosis to enrolment was ≤ 5 years.

Quality of the studies was assessed using the Quality In Prognosis Studies tool [32].

Data were extracted and entered into a predefined spreadsheet table which included the following items: country, center, study period, study design, length of follow up, definition of disease onset, disease duration, mean age of patients, sex ratio, proportions of diffuse and limited forms of SSc, SMR, organ involvement as defined by authors, adjusted, or if unavailable, unadjusted hazard ratios (HR) for each studied prognostic factor.

Data analysis

Continuous variables were expressed as means ± standard deviation (sd). Categorical variables were expressed as n (%). Comparisons between groups were conducted using Fisher's exact test for categorical variables and Wilcoxon test for continuous variables.

Survival was estimated from diagnosis using Kaplan Meier method. Prognostic factors were assessed by Cox regression analysis in the univariate analysis, and subsequently adjusted for age, sex, and SSc subtype. The assumption that hazard ratios were constant over time was verified. SMR was calculated as the ratio of observed death in the cohort to the expected number of death of an age/sex-matched population.

We calculated weighted pooled summary estimates of SMR and HR of prognostic factors. For each meta-analysis, we used the DerSimonian and Laird method. Accordingly, studies were considered to be a random sample from a population of studies. Heterogeneity was assessed using an I^2 statistic and a chi-square heterogeneity statistic. A random-effects model was used to combine data. The overall effect was estimated using a weighted average of individual effects, with weights inversely proportional to variance in observed

effects. Publication bias was evaluated with funnel plot and Egger's test. The pooled SMR and HR were estimated, with 95% confidence interval (CI). Meta-regression was used to assess the impact of mid–cohort year, the proportion of males, the proportion of diffuse forms and the prevalence of anti-Scl70 antibodies on SMR. Meta-regression was used to evaluate the impact of diagnostic by RHC on the association of pulmonary hypertension (PH) with mortality. Separate analyses were performed for: (i) SMR according to whether a given study included incident cases only, (ii) HR of PH diagnosed by either echocardiography and/or RHC and PH diagnosed by RHC.

All analyses were performed using R software with the survival and metafor packages. P values less than 0.05 were considered significant.

RESULTS

French cohort study

Baseline characteristics

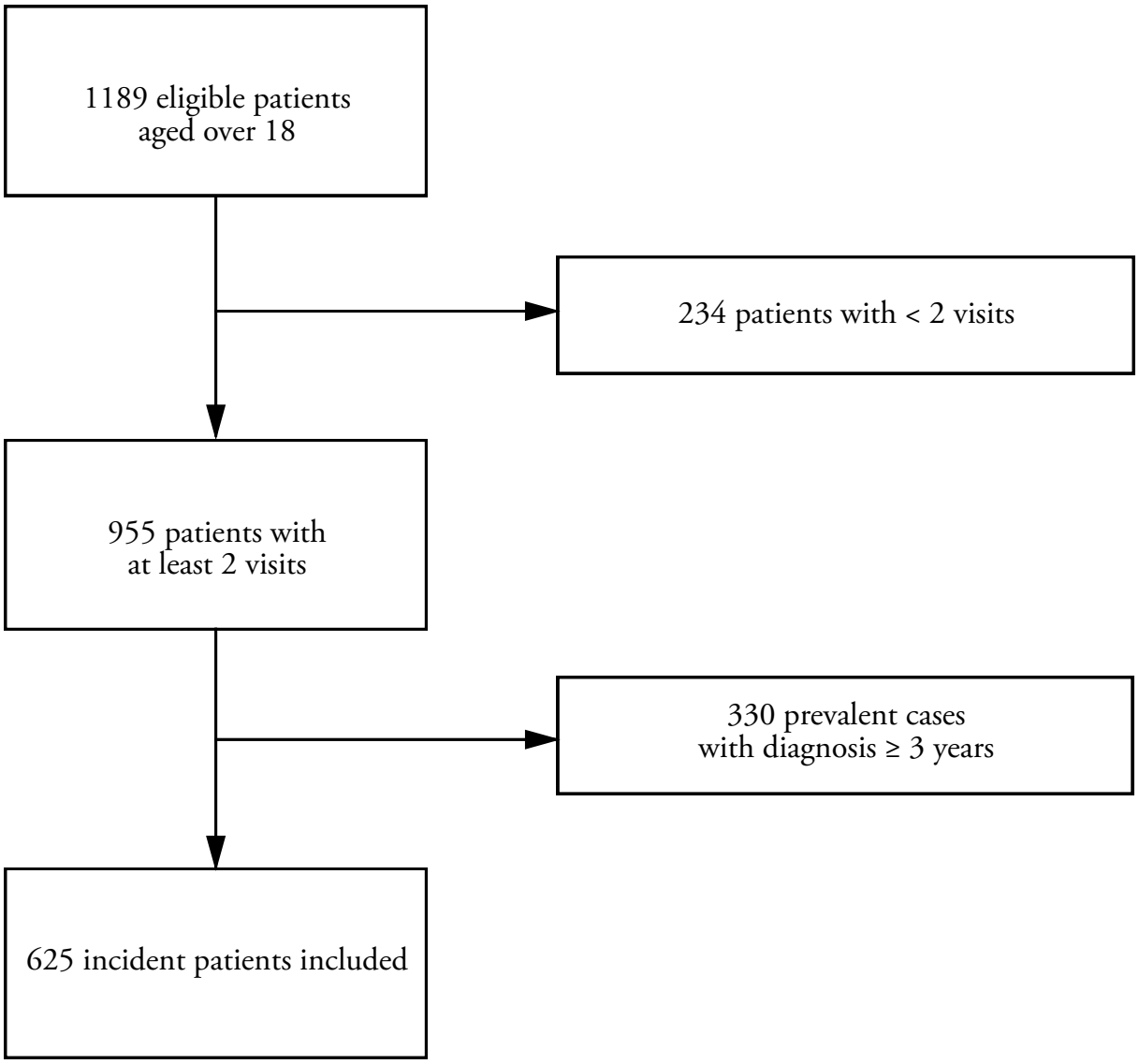

Figure 1. Flowchart of cohort study

A total of 625 patients (493 females, 443 lcSSc) were included in our study (Figure 1). Mean age at disease onset (first non-RP symptom) was 52.7 ± 14.9 years. The disease duration from disease onset was 2.2 ± 3.8 years. Mean follow-up time was 5.2 ± 3.6 years. The baseline characteristics are shown in Table 1.

Table 1. Patient demographics and clinical characteristics

	n (n for dcSSc)	Total	dcSSc	lcSSc	p
Demographics					
Female sex	625 (179)	493 (79%)	124 (69%)	369 (83%)	<0.001
Age at first Raynaud phenomenon (years)	554 (155)	45.4±15.7	45.8±15.7	45.3±15.8	0.784
Age at first non-Raynaud phenomenon (years)	502 (160)	50.6±14.5	48.5±14.4	51.5±14.4	0.025
Age at diagnosis (years)	625 (179)	52.7±14.9	49.5±14.5	53.9±14.9	<0.001
Disease duration from disease onset (years)	499 (160)	2.2±3.8	1.6±2.9	2.5±4.2	0.042
Follow up time from inclusion to death or last visit (years)	625 (179)	5.2±3.6	4.7±3.4	5.4±3.7	0.023
Caucasian	503 (147)	453 (90%)	118 (80%)	335 (94%)	<0.001
Black race	503 (147)	50 (10%)	29 (20%)	21 (6%)	<0.001
Skin involvement					
Telangiectases	572 (160)	264 (46%)	65 (41%)	199 (48%)	0.112
Calcinosis	549 (152)	64 (12%)	7 (5%)	57 (14%)	<0.001
mRSS	342 (123)	9.2±10.2	19.6±10.1	3.5±3.6	<0.001
Digital ulcers	538 (145)	161 (30%)	66 (46%)	95 (24%)	<0.001
Pulmonary involvement					
NYHA class I-II	515 (150)	425 (83%)	122 (81%)	303 (83%)	0.702
NYHA class III-IV	515 (150)	90 (17%)	28 (19%)	62 (17%)	0.702
6MWT (meters)	274 (61)	427±127	432±135	425±125	0.990
TLC < 70% predicted	472 (145)	64 (14%)	33 (23%)	31 (9%)	<0.001
FVC < 70% predicted	475 (148)	82 (17%)	44 (30%)	38 (12%)	<0.001
DLCO < 70% predicted	471 (141)	249 (53%)	102 (72%)	147 (45%)	<0.001
Interstitial lung disease (HRCT or chest x-ray)	582 (166)	262 (45%)	115 (69%)	147 (35%)	<0.001
PH (echocardiography)	547 (157)	67 (12%)	18 (11%)	49 (13%)	0.775
sPAP < 35mmHg	397 (118)	307 (77%)	89 (75%)	218 (78%)	0.004
35 < sPAP < 46mmHg	397 (118)	43 (11%)	21 (18%)	22 (8%)	0.004
sPAP > 46mmHg	397 (118)	47 (12%)	8 (7%)	39 (14%)	0.004
PH (RHC)	490 (116)	40 (8%)	4 (3%)	36 (10%)	0.033
Heart involvement					
Arrhythmia	519 (150)	17 (3%)	5 (3%)	12 (3%)	1.000
AV block	512 (146)	7 (1%)	4 (3%)	3 (1%)	0.106
BB block	479 (128)	16 (3%)	6 (5%)	10 (3%)	0.388
LVF	402 (102)	64.9±7.1	65.5±8.6	64.7±6.6	0.251
Diastolic dysfunction	423 (110)	20 (5%)	6 (5%)	14 (4%)	0.613
Pericarditis	478 (136)	32 (7%)	14 (10%)	18 (5%)	0.066
Valvular disease	430 (111)	33 (8%)	5 (5%)	28 (9%)	0.213

Renal involvement					
GFR<80ml/min	459 (136)	179 (39%)	38 (28%)	141 (44%)	0.002
Scleroderma renal crisis	428 (139)	44 (10%)	31 (22%)	13 (5%)	<0.001
Gastrointestinal involvement	611 (172)	429 (70%)	135 (78%)	294 (67%)	0.006
BMI (kg/m2)	514 (159)	24.4±5.0	23.6±4.0	24.7±5.3	0.046
Albuminemia < 35g/l	331 (108)	52 (16%)	28 (26%)	24 (11%)	<0.001
Muscular involvement	604 (172)	137 (23%)	71 (41%)	66 (15%)	<0.001
CPK > 200 IU/l	250 (82)	66 (26%)	33 (40%)	33 (20%)	<0.001
Articular involvement	598 (172)	291 (49%)	127 (74%)	164 (39%)	<0.001
Cancer	625 (179)	49 (8%)	17 (10%)	32 (7%)	0.327
Hemoglobin	559 (163)	13.0±1.6	12.5±1.6	13.1±1.5	<0.001
Anemia	559 (163)	127 (23%)	52 (32%)	75 (19%)	0.001
CRP > 8mg/l	470 (136)	118 (25%)	57 (42%)	61 (18%)	<0.001
Serologic features					
ACA	557 (151)	221 (40%)	6 (4%)	215 (53%)	<0.001
Anti-Scl70 antibodies	504 (149)	177 (35%)	90 (60%)	87 (25%)	<0.001
Anti-U1RNP antibodies	342 (63)	15 (4%)	4 (6%)	11 (4%)	0.492
Anti-RNAP3 antibodies	345 (72)	18 (5%)	13 (18%)	5 (2%)	<0.001
Anti-PMScl antibodies	343 (62)	16 (5%)	3 (5%)	13 (5%)	1.000
Anti-SSa antibodies	387 (79)	60 (16%)	20 (25%)	40 (13%)	0.014
Anti-SSb antibodies	338 (62)	327 (97%)	59 (95%)	268 (97%)	0.431
APL antibodies	441 (129)	31 (7%)	16 (12%)	15 (5%)	0.007
Low complement	482 (130)	18 (4%)	6 (5%)	12 (3%)	0.589
Smoking	572 (158)	215 (38%)	69 (44%)	146 (35%)	0.067

Results are expressed as n (%) or mean±SD.

mRSS: modified Rodnan score, GFR: glomerular filtration rate, AV block: atrioventricular block, BB block: bundle branch block, LVF: left ventricular function, PH: pulmonary hypertension, RHC: right heart catheterization, 6MWT: 6 minutes walking test, sPAP: systolic pulmonary arterial pressure, TLC: total lung capacity, FVC: forced vital capacity, DLCO: diffusing capacity of the lungs for carbon monoxide, CRP: C reactive protein, BMI: body mass index, ACA: anti-centromere antibodies, APL: antiphospholipid antibodies.

Survival and standardized mortality ratio

A total of 104 deaths (16.6%) were recorded during the study period and 133 patients were lost of follow up. Overall survival rates at 1, 3, 5, 10 and 15 years from diagnosis were 98% (95%CI 96.9% - 99.1%), 92.5% (90.4% - 94.7%), 85.9 % (82.8% - 89.1%), 71.7% (66.3% - 77.5%) and 53% (33.8% – 83.4%) respectively. Overall SMR was 5.73 (4.68 - 6.94).

Survival rates at 1, 3, 5, and 10 years in patients with lcSSc were 98.2% (96.9% – 99.4%), 94% (91.7% - 96.4%), 88.2% (84.8% - 91.7%), and 75.9% (69.7% - 82.7%), respectively. Survival rates at 1, 3, 5 and 10 years in patients with dcSSc were 97.1% (94.7% - 99.6%), 88% (83.1% - 93.3%), 78.9% (72.1% - 86.3%) and 57% (45.8% - 70.9%), respectively (Figure 2).

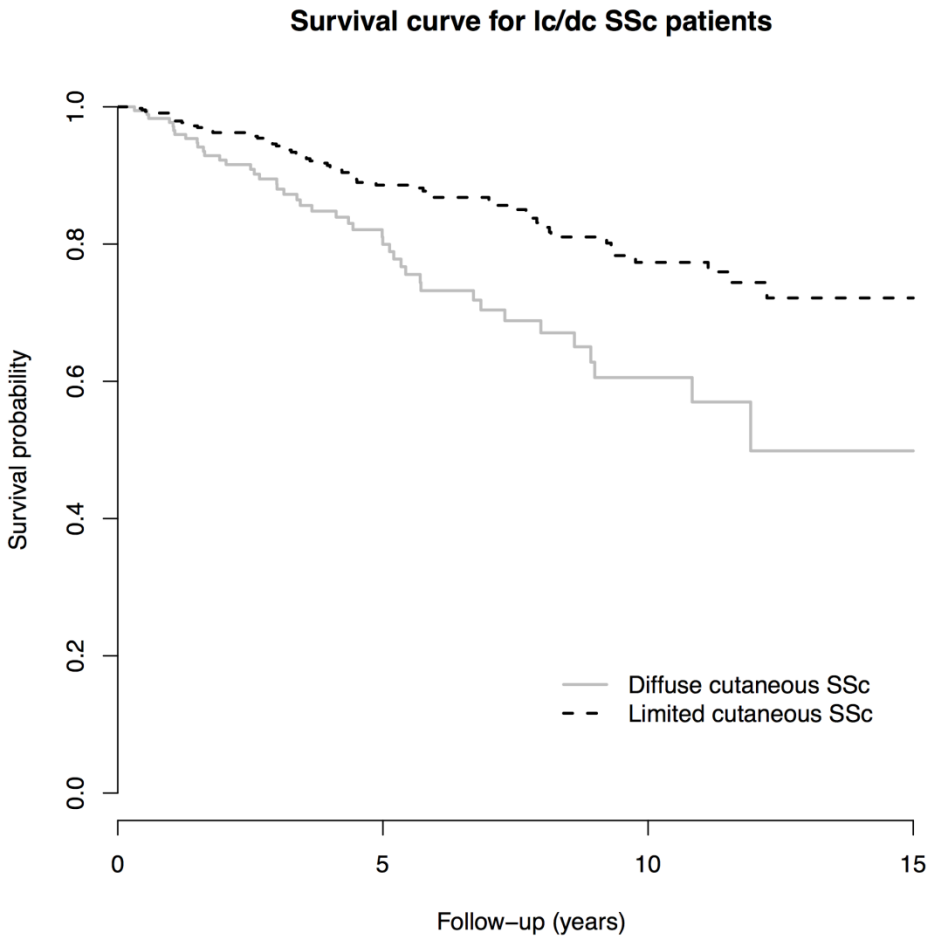

Figure 2. Survival curves for lcSSc and dcSSc patients

Prognosis factors

Age of diagnosis > 60 years, dcSSc subtype, telangiectases, scleroderma renal crisis, severe dyspnea NYHA functional class III and IV, a shorter distance at the 6MWT, FVC < 70%, DLCO < 70%, PH (doppler echocardiography and RHC), valvular disease, anemia, CRP > 8mg/l, TLC < 70%, FVC < 70%, DLCO < 70%, and cancer, were associated with a worse prognosis (Table 2).

No association were found for digital ulcers, gastrointestinal, articular, muscular involvement and specific auto-antibodies after adjustment.

Male sex showed a trend towards worse outcome, but without reaching statistical significance [HR 1.53 (95%CI 0.98 - 2.39); p = 0.06].

Table 2. Non-adjusted and adjusted analysis on age at diagnosis, sex and SSc subtype

	Non-adjusted HR	p	Adjusted HR	p
Demographics				
Male sex	2.00 (1.31-3.05)	0.001	1.53 (0.98-2.39)	0.060
Age at diagnosis (years)	1.05 (1.04-1.07)	<0.001	1.08 (1.04-1.12)	<0.001
Age at diagnostic > 60 years	4.97 (2.53-9.78)	<0.001	5.79 (2.92-11.49)	<0.001
Disease duration at time of diagnosis (years)	1.02 (0.97-1.07)	0.542	1.01 (0.96-1.06)	0.763
Black race (vs. Caucasian)	0.79 (0.38-1.62)	0.516	0.93 (0.43-2.03)	0.864
Skin involvement				
dcSSc subtype (vs. lcSSc)	2.06 (1.39-3.05)	<0.001	2.40 (1.58-3.64)	<0.001
mRSS > 5	1.24 (1.12-1.38)	<0.001	1.21 (1.03-1.43)	0.022
Past and/or active digital ulcers	1.22 (0.79-1.90)	0.371	1.29 (0.81-2.04)	0.277
Telangiectasia	1.64 (1.08-2.48)	0.019	1.55 (1.02-2.35)	0.039
Calcinosis	1.37 (0.79-2.36)	0.260	1.22 (0.69-2.16)	0.503
Lung involvement				
NYHA class II (vs. class I)	2.68 (1.46-4.92)	0.001	2.37 (1.29-4.36)	0.006
NYHA class III (vs. class I)	17.53 (3.97-14.27)	<0.001	6.74 (3.53-12.88)	<0.001
NYHA class IV (vs. class I)	25.76 (10.55-62.92)	<0.001	16.61 (6.68-41.26)	<0.001
NYHA class III-IV (vs. class I)	4.68 (3.07-7.13)	<0.001	4.33 (2.82-6.66)	<0.001
6MWT (per 100 meters)	0.46 (0.36-0.58)	<0.001	0.51 (0.39-0.67)	<0.001
TLC < 70% predicted	3.87 (2.36-6.35)	<0.001	3.38 (1.96-5.82)	<0.001

FVC < 70% predicted	3.11 (1.92-5.02)	<0.001	2.79 (1.62-4.80)	<0.001
DLCO < 70% predicted	4.01 (2.33-6.89)	<0.001	3.31 (1.87-5.88)	<0.001
Interstitial lung disease (HRCT)	1.99 (1.32-2.99)	<0.001	1.50 (0.96-2.34)	0.072
PH (Echocardiography)	5.01 (3.18-7.89)	<0.001	4.15 (2.59-6.65)	<0.001
35 <sPAP < 46mmHg (vs. sPAP< 35mmHg)	2.05 (0.98-4.28)	0.056	1.26 (0.58-2.70)	0.559
sPAP > 46mmHg (vs. sPAP < 35mmHg)	6.44 (3.69-11.22)	<0.001	5.94 (3.30-10.72)	<0.001
PH (RHC)	4.96 (2.82-8.72)	<0.001	4.39 (2.43-7.93)	<0.001
Heart involvement				
Arrhythmia	2.44 (0.98-6.02)	0.054	1.31 (0.52-3.32)	0.569
AV block	0.95 (0.13-6.80)	0.956	1.15 (0.15-8.58)	0.890
BB block	1.26 (0.31-5.15)	0.748	1.37 (0.33-5.67)	0.661
LVF < 50%	1.82 (0.25-13.24)	0.555	0.92 (0.12-6.84)	0.938
Diastolic dysfunction	1.36 (0.43-4.35)	0.603	0.97 (0.30-3.13)	0.953
Pericarditis	1.74 (0.84-3.61)	0.139	1.07 (0.50-2.26)	0.864
Valvular disease	4.64 (2.39-9.01)	<0.001	2.61 (1.32-5.17)	0.006
Renal involvement				
Scleroderma renal crisis	3.44 (2.01-5.89)	<0.001	2.95 (1.61-5.40)	<0.001
GFR < 80ml/min	1.64 (1.06-2.52)	0.025	1.37 (0.85-2.21)	0.199
Gastrointestinal involvement	1.07 (0.68-1.69)	0.756	1.02 (0.65-1.62)	0.916
BMI < 18.5kg/m2	1.10 (0.45-2.74)	0.831	1.79 (0.71-4.51)	0.220
Albuminemia < 35g/l	2.30 (1.24-4.30)	0.009	1.45 (0.75-2.82)	0.270
Muscular involvement	1.66 (1.10-2.51)	0.016	1.46 (0.92-2.31)	0.106
CPK > 200 IU/L	1.27 (0.58-2.76)	0.550	1.15 (0.50-2.64)	0.740
Articular involvement	1.22 (0.82-1.80)	0.329	1.08 (0.70-1.66)	0.720
Cancer	2.44 (1.41-4.21)	0.001	1.86 (1.07-3.26)	0.029
Anemia	2.66 (1.75-4.06)	<0.001	2.37 (1.54-3.66)	<0.001
CRP > 8mg/l	2.05 (1.28-3.27)	0.003	1.70 (1.02-2.82)	0.041
Serologic features				
ACA	0.95 (0.62-1.44)	0.795	0.85 (0.55-1.31)	0.459
Anti-Scl70 antibodies	0.87 (0.55-1.36)	0.534	0.82 (0.51-1.30)	0.390
Anti-U1RNP antibodies	1.41 (0.51-3.93)	0.506	1.32 (0.44-3.92)	0.616
Anti-RNAP3 antibodies	0.96 (0.23-3.94)	0.949	1.32 (0.44-3.92)	0.616
Anti-PMScl antibodies	0.33 (0.05-2.41)	0.277	0.49 (0.07-3.54)	0.476
APL antibodies	1.54 (0.71-3.35)	0.280	1.18 (0.53-2.63)	0.679
Low complement	2.40 (0.97-5.95)	0.059	2.38 (0.95-5.95)	0.063
Smoking	1.06 (0.69-1.62)	0.795	0.97 (0.59-1.59)	0.901

Results are expressed as hazard ratios and 95% confidence interval.

mRSS: modified Rodnan score, GFR: glomerular filtration rate, AV block: atrioventricular block, BB block: bundle branch block, LVF: left ventricular function, PH: pulmonary

hypertension, RHC: right heart catheterization, 6MWT: 6 minutes walking test, sPAP: systolic pulmonary arterial pressure, HRCT: high resolution computer tomography, TLC: total lung capacity, FVC: forced vital capacity, DLCO: diffusing capacity of the lungs for carbon monoxide, CRP: C reactive protein, BMI: body mass index, ACA: anti-centromere antibodies, APL: antiphospholipid antibodies.

Meta-analysis: study selection

A total of 1700 citations were assessed for inclusion. After screening, 226 papers were deemed potentially relevant evaluation studies and full text copies of these citations were obtained. Of these articles, 41 studies, including our cohort, were included in the meta-analysis (Figure 3). Eighteen articles were included in the SMR analysis, representing a total population of 11,719 patients. Thirty-three studies were included in the prognosis factors analysis, representing a total of 23,145 patients. No study was excluded based on poor quality. The main characteristics of the included studies are summarized in Tables 3 and 4.

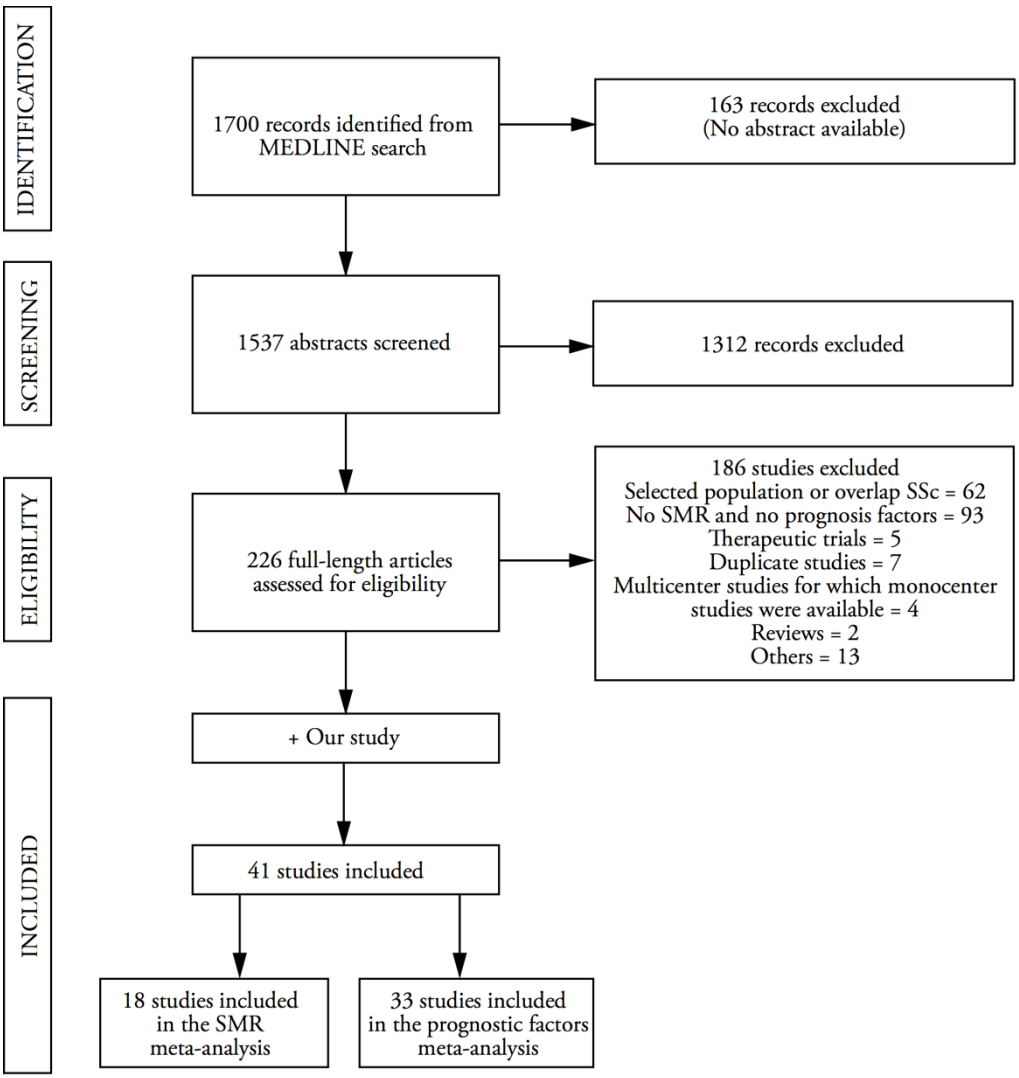

Figure 3. Flow chart showing search strategy to identify studies in the meta-analysis

Table 3. Main characteristics of studies in the SMR meta-analysis

First author	Study period	Mid-cohort year	Country	n	Inclusion of incident cases only	Study type	SMR	Males (%)	dc-SSc (%)	ACA (%)	Anti-Scl70 (%)
Abu-Shakra [33]	1979-1990	1984.5	Canada	237	No	Prospective	4.69 (3.58-6.02)	17.3	43.0	NA	NA
Alamanos [34]	1981-2002	1991.5	Greece	109	Yes	Retrospective	2.00 (1.20-2.80)	10.1	24.8	NA	NA
Alba [23]	2006-2012	2009	Spain	1037	No	Retrospective	3.80 (3.18-4.43)	12.5	26.1	43.6	22.2
Bryan [35]	1982-1992	1987	UK	283	Yes	Retrospective	4.05 (3.03-5.22)	23.0	45.9	NA	NA
Cruz-Domínguez [36]	2005-2014	2009.5	Mexico	220	No	Retrospective	4.50 (2.99-6.50)	9.5	57.3	29.1	22.3
Hao [26]	2007-2014	2010.5	Australia	389	Yes	Prospective	3.40 (2.30-4.50)	18.3	40.2	37.4	18.7
	2007-2014	2010.5	Australia	1411	No	Prospective	2.80 (2.40-3.30)	9.5	26.3	46.4	14.5
	2005-2014	2009.5	Canada	484	Yes	Prospective	5.10 (4.00-6.20)	19.2	44.0	29.5	18.2
	2005-2014	2009.5	Canada	1465	No	Prospective	3.80 (3.30-4.20)	14.1	36.2	34.5	15.2
	2000-2014	2007	Spain	197	Yes	Prospective	3.20 (2.30-4.20)	12.2	31.4	42.3	27.0
	2000-2014	2007	Spain	342	No	Prospective	4.20 (3.30-5.00)	13.7	30.4	41.9	26.9
Hesselstrand [37]	1983-1995	1989	Sweden	249	No	Prospective	4.59 (3.48-6.07)	28.5	25.3	NA	NA
Hoffmann-Vold [21]	1999-2009	2004	Norway	312	No	Retrospective	2.03 (1.40-2.60)	22.8	21.8	NA	NA
Ioannidis [38]	NA	1989	Greece	84	Yes	Retrospective	2.77 (1.33-5.87)	NA	NA	NA	NA
	NA	1989	Japan	156	Yes	Retrospective	3.20 (2.33-4.41)	NA	NA	NA	NA
	NA	1989	Nether-lands /Leiden	53	Yes	Retrospective	7.18 (4.31-11.96)	NA	NA	NA	NA
	NA	1989	Nether-lands/ Nijmegen	69	Yes	Retrospective	7.18 (4.94-10.53)	NA	NA	NA	NA

	NA	1989	USA /Mayo	105	Yes	Retrospective	1.50 (1.06-2.12)	NA	NA	NA	NA
Jacobsen [39]	1960-1996	1978	Denmark	344	Yes	Retrospective	2.90 (2.50-3.40)	19.2	34.3	NA	NA
Kuo [40]	2002-2007	2004.5	Taiwan	1479	Yes	Retrospective	3.24 (2.82-3.71)	22.0	NA	NA	NA
Mok [41]	1999-2008	2003.5	China	449	No	Retrospective	3.94 (3.20-4.68)	14.9	NA	NA	NA
Nihtyanova [25]	1995-2010	2002.5	UK	398	Yes	Retrospective	3.82 (3.13-4.52)	13.6	36.7	27.7	21.3
Pérez-Bocanegra [42]	1976-2007	1991.5	Spain	319	No	Prospective	1.90 (1.50-2.30)	NA	20.1	42.6	19.0
Pokeerbux	2000-2016	2008	France	625	Yes	Retrospective	5.73 (4.68-6.94)	21.1	28.6	39.7	35.1
Scussel-Lonzetti [12]	1984-1999	1991.5	Canada	309	No	Prospective	2.69 (2.10-3.40)	13.9	34.6	43.7	12.0
Strickland [22]	1999-2010	2004.5	UK	204	No	Retrospective	1.34 (1.00-1.75)	12.3	19.6	47.1	16.2
Zarafonetis [43]	1948-1980	1964	USA	390	No	Retrospective	5.40 (4.55-6.37)	18.5	NA	NA	NA

Table 4. Main characteristics of studies in the prognosis factors meta-analysis

First author	Study period	Mid-cohort year	Country	n	Inclusion of incident cases only	Study type	Males (%)	dcSSc (%)	ACA (%)	Anti-Scl70 (%)
Alba [23]	2006-2012	2009	Spain	1037	No	Retrospective	12.5	30.2	43.6	22.2
Al-Dhaher [4]	1994-2004	1999	Canada	185	No	Retrospective	14.6	36.8	NA	NA
Assassi [15]	1998-2005	2001.5	USA	250	Yes	Prospective	16.0	57.2	11.7	18.9
Beretta [44]	1982-2008	1995	Italia	558	No	Retrospective	10.6	26.9	34.2	43.7
Beretta [45]	1997-2005	2001	Italia	161	No	Retrospective	12.4	28.6	44.7	40.4
Codullo [46]	2006-2012	2009	Italia	299	No	Retrospective	13.0	17.1	54.8	16.4
Cottrell [24]	1976-2010	1993	USA	2205	No	Retrospective	17.0	38.9	27.5	23.0
Cruz-Dominguez [36]	2005-2014	2009.5	Mexico	220	No	Retrospective	9.5	57.3	29.1	22.3
Czirjak [13]	1983-2005	1994	Hungary	366	No	NA	13.9	27.6	13.1	36.6
Ferri [30]	2000-2011	2005.5	Italia	821	No	Retrospective	9.1	12.5	NA	NA
Ferri [11]	1955-1999	1977	Italia	1012	No	Retrospective	11.4	44.0	38.9	36.0
Hachulla [14]	2002-2005	2003.5	France	546	No	Prospective	15.9	27.5	48.1	28.0
Hao [26]	2000-2014	2007	Australia, Canada, Spain	1070	Yes	Retrospective	17.6	40.9	35.4	20.3
	2000-2014	2007	Australia, Canada, Spain	3218	No	Retrospective	13.6	32.5	40.9	16.3
Hesselstrand [47]	1983-1998	1990.5	Sweden	276	No	NA	26.1	24.6	18.5	9.4
Hinchcliff [48]	2005-2009	2007	USA	153	No	Retrospective	15.0	39.9	NA	NA
Hoffmann-Vold [21]	1999-2009	2004	Norway	312	No	Retrospective	22.8	21.8	NA	NA
Hussein [49]	1970-2013	1991.5	Canada	959	No	Retrospective	17.5	32.5	NA	NA
Ioannidis [38]	NA	1989	International	467	Yes	Retrospective	NA	NA	NA	NA
Jacobsen [39]	1960-1996	1978	Denmark	174	Yes	Retrospective	16.1	32.8	37.0	13.0

Kim [17]	1972-2007	1989.5	Korea	230	No	Retrospective	10.9	43.9	13.6	53.6
Költő [50]	2007-2012	2009.5	Hungary	120	No	Retrospective	11.7	32.5	NA	NA
Kuo [40]	2002-2007	2004.5	Taiwan	1479	Yes	Retrospective	22.0	NA	NA	NA
Lee [10]	1979-1990	1984.5	Canada	237	No	Prospective	17.3	43.0	NA	NA
Mayes [51]	1989-1991	1990	USA	706	No	Retrospective	16.3	34.9	22.1	19.6
Nihtyanova [25]	1995-2010	2002.5	UK	398	Yes	Retrospective	13.6	36.7	27.7	21.3
Pokeerbux	2000-2016	2008	France	625	Yes	Retrospective	21.1	28.6	39.7	35.1
Poormoghim [52]	1998-2012	2005	Iran	220	No	Prospective	12.7	40.0	8.4	70.2
Ruangjutipopan [53]	1987-2001	1994	Thailand	222	No	Retrospective	23.8	57.2	NA	NA
Scussel-Lonzetti [12]	1984-1999	1991.5	Canada	309	No	Prospective	14.0	34.6	43.7	12.0
Simeon [54]	1976-1996	1986	Spain	79	Yes	Retrospective	13.9	27.8	NA	NA
Simeon-Aznar [29]	2006-2008	2007	Spain	879	No	Retrospective	14.8	27.6	NA	NA
Steen [55]	1972-2007	1989.5	USA	3148	No	Prospective	19.7	43.4	21.1	17.5
Strickland [22]	1999-2010	2004.5	UK	204	No	Retrospective	12.3	19.6	47.1	16.2

SMR meta-analysis

The pooled SMR for all studies was 3.45 [(95%CI 3.03 – 3.94); I^2 = 88.8%; p(het) < 0.0001] (Figure 4) and the pooled SMR studies including only incident patients was 3.63 [(3.03 - 4.36); I^2 =85.4%; p(het) < 0.0001]. There was no funnel plot asymmetry and Egger's test failed to provide any evidence for small study effect, making publication bias unlikely. Meta-regression analysis revealed a significant association between SMR and proportion of diffuse forms (p = 0.0008) and prevalence of anti-Scl70 antibodies (p = 0.0206). There was no association with male sex (p = 0.1302). Meta-regression stratified by study type (incident or prevalent), did not show any association with SMR (p = 0.4833). There was no significant association between SMR and mid-cohort year (p = 0.461) (Supplementary Figure 1).

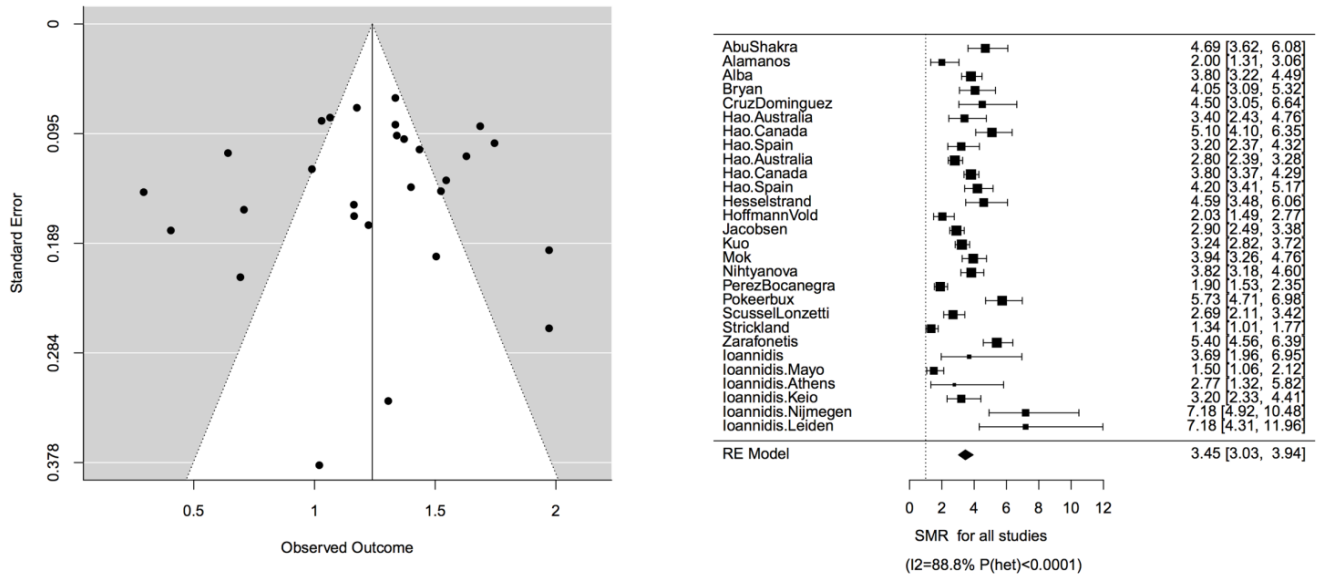

Figure 4. Funnel and forest plots of SMR in SSc cohorts

Prognostic factors meta-analysis

Table 5 shows the results of the meta-analysis of prognostic factors. Age at disease onset, age at diagnosis, male sex, black race, dcSSc, anti-Scl70 antibodies, renal involvement, scleroderma renal crisis, ILD, cardiac involvement, PH and cancer were significantly associated with a worse prognosis (Figure 5). The presence of PH, diagnosed by doppler echocardiography and/or right heart catheterization, was associated with a poor outcome [pooled HR 3.44; (95%CI 2.59 - 4.58); I^2 = 61.5%; p(het) = 0.0018]. Heterogeneity could not be fully explained by the use of either echocardiography or right-heart catheterization (RHC) alone in defining PH as revealed by meta-regression stratified by RHC-diagnosis method (p value for test for residual heterogeneity = 0.0116). Meta-analysis of the five studies with PH defined by RHC revealed an increased pooled HR for mortality of 5.27 [(2.98 - 9.31); I^2 = 63.7%; p(het) = 0.0265]. Presence of ACA antibodies was associated with a better survival while the presence of joint involvement was not associated with prognosis (Supplementary Figure 2).

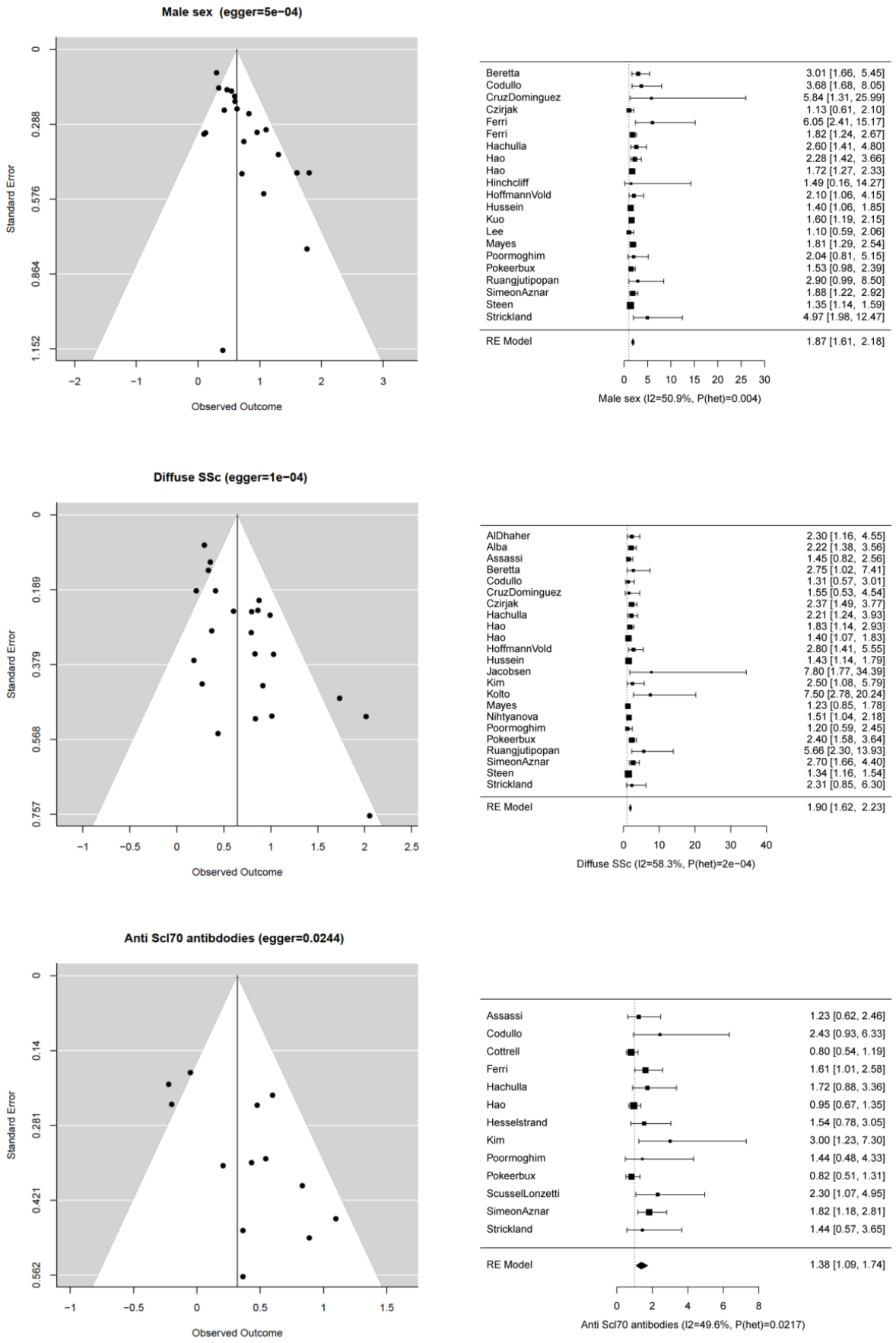

Figure 5. Funnel plots and forest plots of main prognostic factors in SSc cohorts

Table 5. Results of the meta-analysis of prognosis factors in SSc

	HR	95%CI	I^2 (%)	p(het)	Egger's test
Age at disease onset	1.05	(1.04-1.07)	68.6	0.0070	0.7826
Age at diagnosis	1.04	(1.04-1.05)	71.2	0.0077	0.0251
Male sex	1.87	(1.61-2.18)	50.9	0.0044	0.0005
Black race	1.40	(1.06-1.85)	37.9	0.1844	0.6615
dcSSc	1.90	(1.62-2.23)	58.3	0.0002	0.0001
Anti-Scl70 autoantibodies	1.38	(1.09-1.74)	49.6	0.0217	0.0244
ACA	0.62	(0.47-0.82)	54.3	0.0411	0.5897
Joint involvement	1.32	(0.82-2.12)	54.0	0.0887	0.5080
Renal involvement	2.79	(1.95-3.99)	50.9	0.0385	0.5119
Scleroderma renal crisis	3.89	(2.38-6.36)	75.6	<0.0001	0.0968
ILD	2.34	(1.78-3.08)	69.5	0.0001	0.0007
Cardiac involvement	4.92	(2.34-10.34)	91.3	<0.0001	0.0607
PH (echocardiography or RHC)	3.44	(2.59-4.58)	61.5	0.0018	0.0572
PH (RHC)	5.27	(2.98-9.31)	63.7	0.0265	0.7613
Cancer	2.02	(1.13-3.61)	76.9	0.0017	0.0310

Results are expressed as hazard ratios with 95% confidence interval. The I^2 statistics describes the percentage of variation across studies that is due to heterogeneity rather than chance. p(het) is the p-value for the $\chi 2$ test for heterogeneity. Egger's test checks for funnel plot asymmetry.

dcSSc: diffuse cutaneous systemic sclerosis, ILD: interstitial lung disease, ACA: anti-centromere antibodies, PH: pulmonary hypertension, RHC: right heart catheterization.

DISCUSSION

The main results of our study are: (i) a high risk of mortality in our cohort of incident patients, as shown by a high SMR of 5.73, (ii) the identification of age > 60 years, dcSSc, severe dyspnea, PH, low FVC, low DLCO, kidney involvement, valvular disease, cancer, telangiectases, shorter distance at 6MWT, anemia and inflammation as prognostic factors in our cohort, (iii) a high pooled SMR of 3.45 in our meta-analysis of the literature, including our new cohort, and (iv) the identification of male sex, black race, ILD, cardiac involvement and antiScl-70 antibodies as associated with worse prognosis in our meta-analysis, while ACA were associated with better prognosis.

Survival and SMR

With a mid-cohort year of 2008, our study population is the largest multicenter incident and well-phenotyped cohort study of SSc patients in France and is among the most recent published to date. In our study, overall survival rates at 5 and 10 years from diagnosis were 86% and 72% respectively, which is lower than those reported in recent cohorts [21,23,26,29,30]. In the same way, we report one of the highest SMR of 5.73 (95%CI 4.68 - 6.94). These differences can be explained by a high heterogeneity between studies as well as methodological issues such as the inclusion of prevalent cases in many studies or differences in time origin from which survival time is calculated, for example from disease onset, diagnosis or enrolment in a study. It is usually admitted that studies including patients with a prevalent disease underestimate mortality, and that better survival is observed in prevalent patients with longer disease duration prior to inclusion [8,9]. However, our meta-analysis did not show a significant difference between pooled SMR of studies that included prevalent cases of SSc [SMR 3.45; (95%CI 3.03 – 3.94)] and those restricted to incident or inception cases [SMR 3.63; (95%CI 3.03 - 4.36)]. Meta-regression showed a significant association between SMR and proportion of diffuse forms (p =

0.0008) and prevalence of anti-Scl70 antibodies (p = 0.0206). Our high SMR of 5.73 could be partly explained by the high proportion of anti-Scl70 (35%) positive patients in our population. Interestingly, there has been a debate whether or not the survival could have improved overtime in SSc. Our study did not show any improvement of SMR overtime, which is in line with Elhai *et al.* [6]. Altogether, these results suggest that SSc remains a devastating disease, which still requires a treatment to improve the mortality rate.

Prognosis factors

Prognosis factors have been assessed in many observational studies [10–26] and have been recently reviewed [56]. Overall, our systematic review and meta-analysis, as well as 2 prior meta-analysis [7,28] and a recent EUSTAR study [27] have identified the following characteristics as consistently associated with a worse prognosis : male gender, older age, dcSSc, lung and cardiac involvement, including PH and ILD, kidney involvement and inflammation. Interestingly, these robust factors are those found in a recent prognosis score [27] as well as in older ones [57,58].

Besides these well-known prognostic factors, our cohort study identifies new ones: telangiectasia, 6MWT, valvular disease and cancer. Likewise, black race, anti-Scl70/ACA autoantibodies and cancer have been identified in our meta-analysis.

Telangiectases were slightly associated with higher mortality in our study population. Interestingly, an increased number of telangiectases has been suggested to be a clinical marker of microvascular disease in SSc and is associated with an increased risk of pulmonary arterial hypertension [59,60]. In contrast, Poormoghim *et al.* [52] reported a non-significant, yet elevated HR of 1.44 [(95%CI 0.49 – 4.20); p = 0.5] in a smaller cohort of Iranian patients. Further studies are therefore needed to confirm the prognosis value of telangiectases in SSc.

The 6MWT is a simple tool used to assess submaximal functional capacity. It is influenced by various systemic manifestations during SSc and lacks organ-specificity [61,62]. While the 6MWT has been shown to be an independent predictor of mortality in idiopathic PAH [63], its prognosis value in SSc-PAH is less clear [64–66]. To our knowledge, we are the first to report a negative association of the 6MWT with survival [HR 0.51, (95%CI 0.39 - 0.67), $p < 0.001$] in SSc patients. Further studies are needed to confirm whether 6MWT is a prognosis marker in unselected SSc patients.

While cardiac involvement in SSc patients is robustly associated with a poor prognosis, conferring a nearly 5-fold increased risk of mortality in our meta-analysis, no study had yet focused on the valvular manifestations of SSc. A recent article comparing echocardiography in SSc patients and a matched control population showed a greater frequency of valvular regurgitation and valvular replacement due to regurgitation [67]. Moreover, in a large multicenter French cohort, De Groote *et al.* [68] reported 6.7% mitral regurgitation and 2.5% aortic regurgitations. To our knowledge, we are the first to describe an association between valvular disease and survival in SSc. Altogether, these data indicate that more attention should be paid to valvular disease in SSc patients and further studies are needed to confirm its prognostic significance.

An increased incidence of malignancy has been reported during SSc, especially lung and hematological cancer [69–72]. Cancer has also been described as the leading cause of non-SSc-related deaths [12,26,39,73] and a temporal relation has been reported between the onset of cancer and SSc [74,75]. In our cohort as well as in the meta-analysis, malignancy was significantly associated with shorter survival.

In our cohort, neither anti-Scl70 nor anti-centromere autoantibodies were associated with survival. Interestingly, the lack of association of anti-Scl70 antibodies with survival has been shown by numerous studies [14,15,22,24,26,76] while the protective role of anti-centromere antibodies is better established [15,21,24,26,49]. Indeed, our meta-analysis confirms that ACA have a protective role with a pooled HR of 0.58 [(95%IC 0.44 - 0.77); I^2 = 54.3%; p = 0.0411]. Moreover, our meta-analysis also suggests that the presence of anti-Scl70 antibodies could be a predictor of mortality with a pooled HR of 1.38 [(95%IC 1.09 - 1.74), I^2 = 49.6%; p = 0.0217]. Our analysis also highlights a probable publication bias. Small studies reporting negative association of anti-Scl70 antibodies with death are notably lacking. Therefore, it is difficult to draw a firm conclusion on the role of anti-Scl70 antibodies as a prognostic factor in SSc.

The major strength of our study is the availability of detailed clinical and laboratory characteristics in a multicenter cohort of incident patients. The major strengths of our meta-analysis include: (i) the very first analysis of pooled HR of anti-Scl70/ACA antibodies, (ii) the separate analysis of pooled SMR in incident cohorts of SSc, and (iii) the separate analysis of pooled HR of PH diagnosed by RHC only.

The main limitation is a proportion of loss to follow up of around 20% in our cohort, despite our attempts to collect information on participants who dropped out. These patients lost to follow-up had higher prevalence of ILD and lower prevalence of ACA at baseline, leading to potential underestimation of mortality. Because of a large number of missing values for the characteristics of patients, no multivariate analysis could be performed. Finally, our study was performed in five selected referral centers and may therefore have focused on a subset of patients with more severe disease.

In conclusion, our results show that mortality is still high in SSc even in the current era. Strong prognostic factors identified at baseline are age at diagnosis > 60 years, dcSSc subtype, scleroderma renal crisis, severe dyspnea, FVC and DLCO < 70%, PH, anemia, and CRP > 8mg/l. Our study also suggests the prognosis value of telangiectases, valvular disease and 6MWT.

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Competing Interests: none

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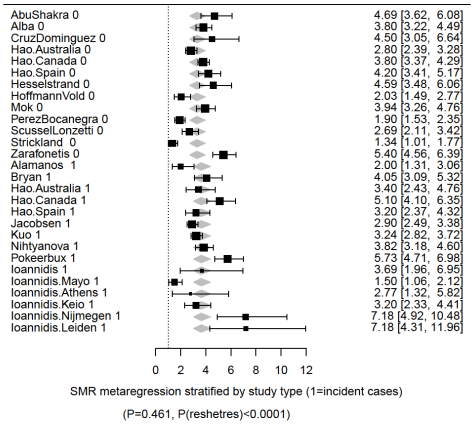
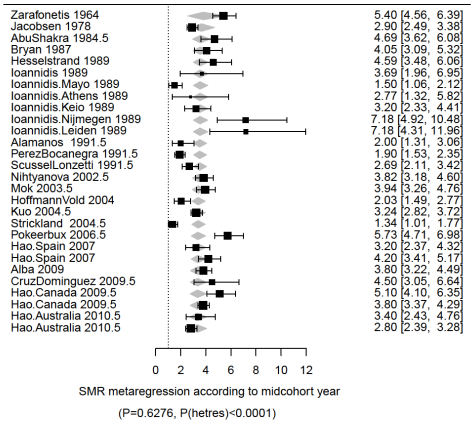
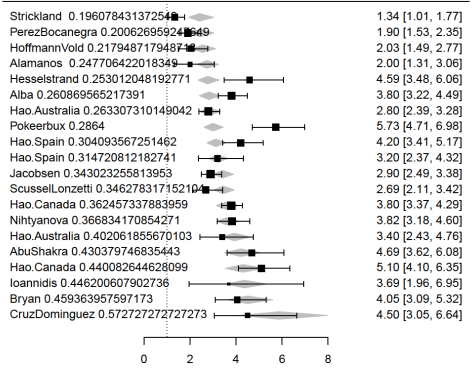
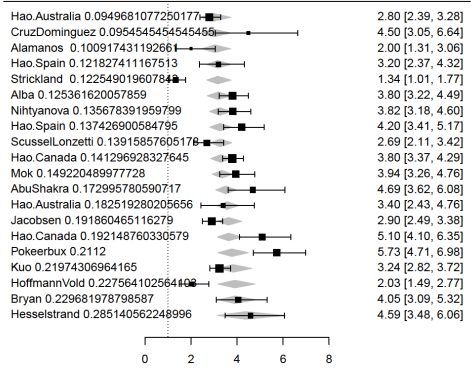
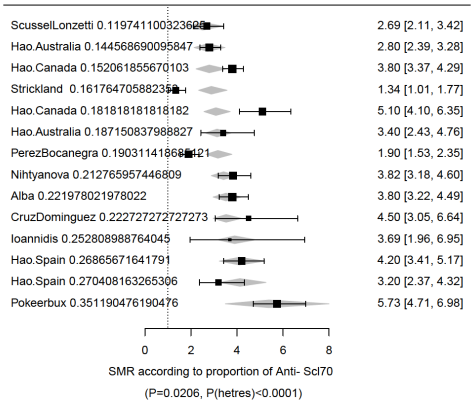
Supplementary figure 1



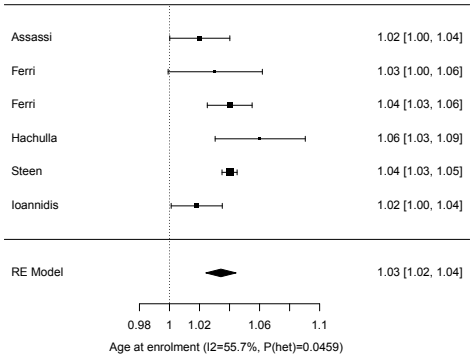


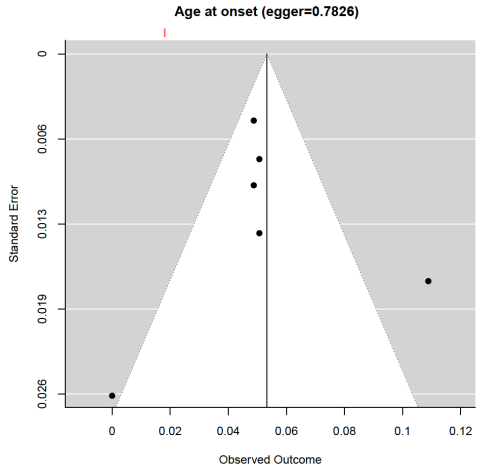


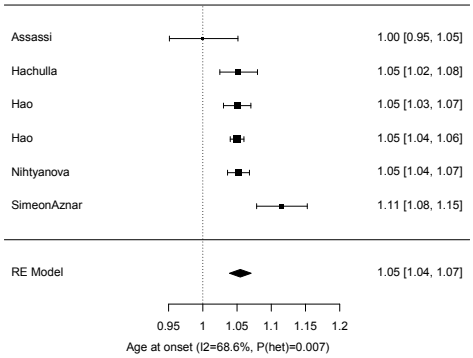


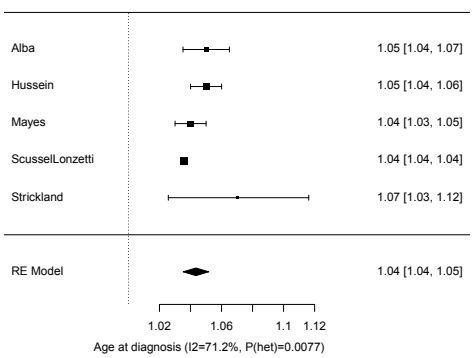


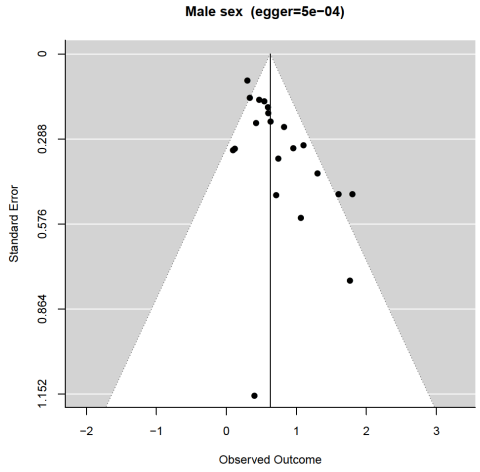
Supplementary figure 2










Male sex (egger=5e−04)
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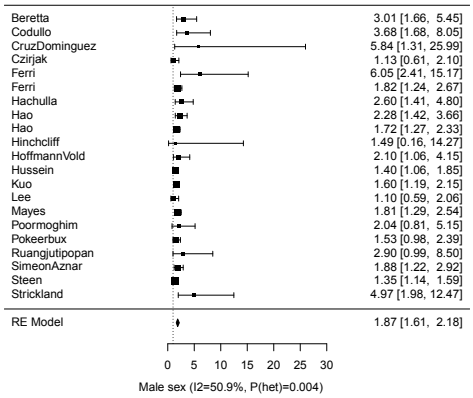
0.576
0.864
1.152
−2
−1
0
1
2
3
Observed Outcome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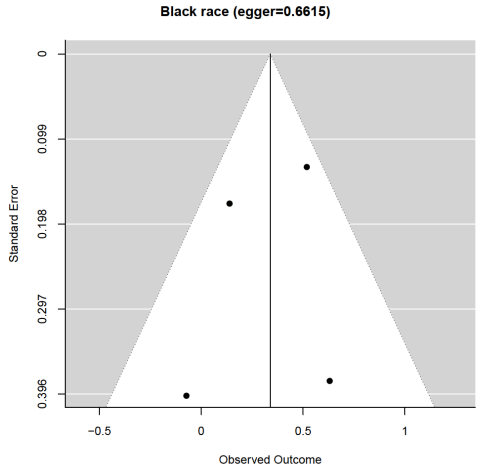
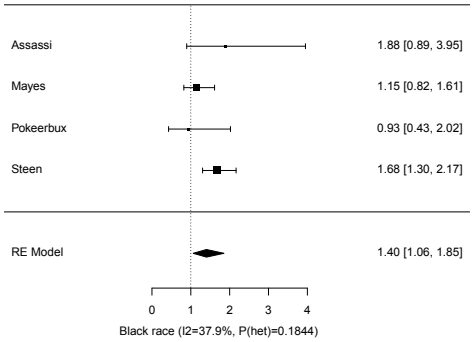
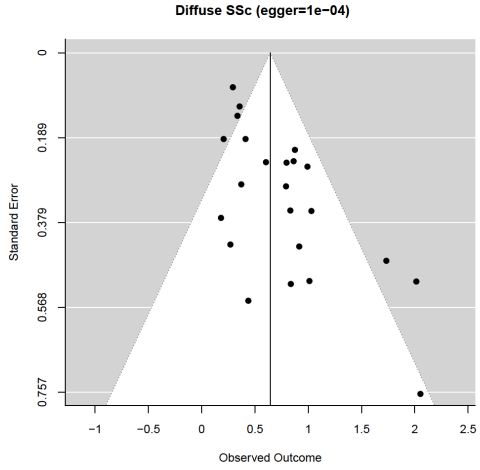
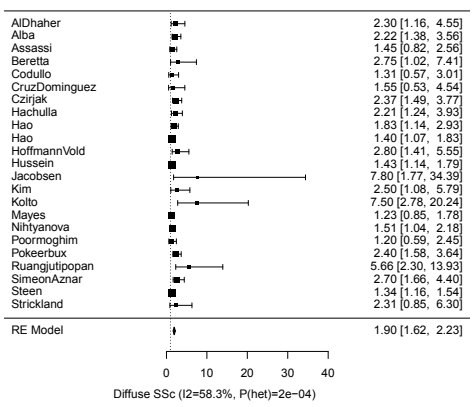
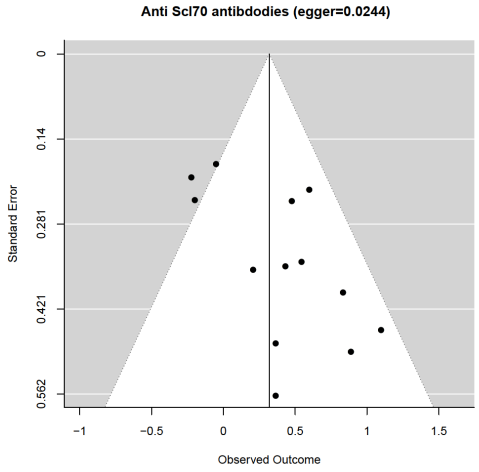
Codullo 3.68 [1.68, 8.05]
CruzDominguez 5.84 [1.31, 25.99]
Czirjak 1.13 [0.61, 2.10]
Ferri 6.05 [2.41, 15.17]
Ferri 1.82 [1.24, 2.67]
Hachulla 2.60 [1.41, 4.80]
Hao 2.28 [1.42, 3.66]
Hao 1.72 [1.27, 2.33]
Hinchcliff 1.49 [0.16, 14.27]
HoffmannVold 2.10 [1.06, 4.15]
Hussein 1.40 [1.06, 1.85]
Kuo 1.60 [1.19, 2.15]
Lee 1.10 [0.59, 2.06]
Mayes 1.81 [1.29, 2.54]
Poormoghim 2.04 [0.81, 5.15]
Pokeerbux 1.53 [0.98, 2.39]
Ruangjutipopan 2.90 [0.99, 8.50]
SimeonAznar 1.88 [1.22, 2.92]
Steen 1.35 [1.14, 1.59]
Strickland 4.97 [1.98, 12.47]
RE Model 1.87 [1.61, 2.18]
0
5
10
15
20
25
30
Male sex (I2=50.9%, P(het)=0.004)

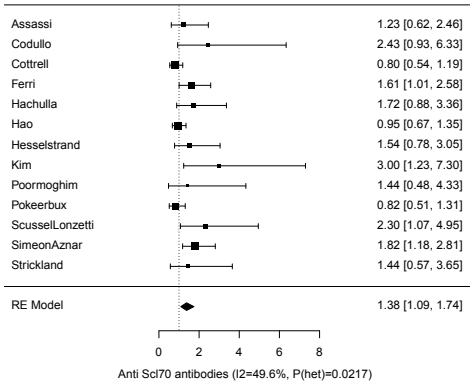

Black race (egger=0.6615)
Standard Error
0
0.099
0.198
0.297
0.396
−0.5
0
0.5
1
Observed Outcome

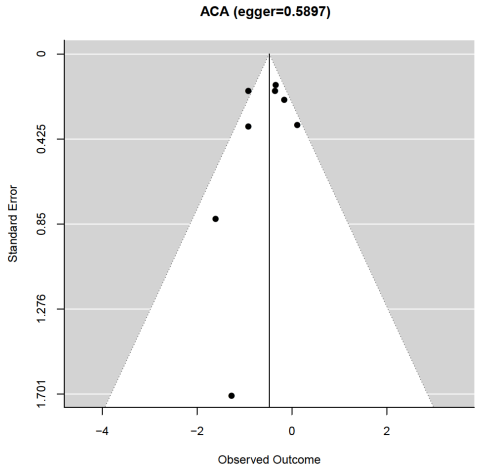

Assassi 1.88 [0.89, 3.95]
Mayes 1.15 [0.82, 1.61]
Pokeerbux 0.93 [0.43, 2.02]
Steen 1.68 [1.30, 2.17]
RE Model 1.40 [1.06, 1.85]
0
1
2
3
4
Black race (I2=37.9%, P(het)=0.1844)

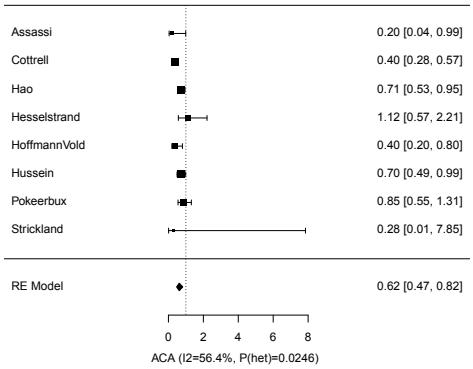

Diffuse SSc (egger=1e−04)
Standard Error
0
0.189
0.379
0.568
0.757
−1
−0.5
0
0.5
1
1.5
2
2.5
Observed Outcome

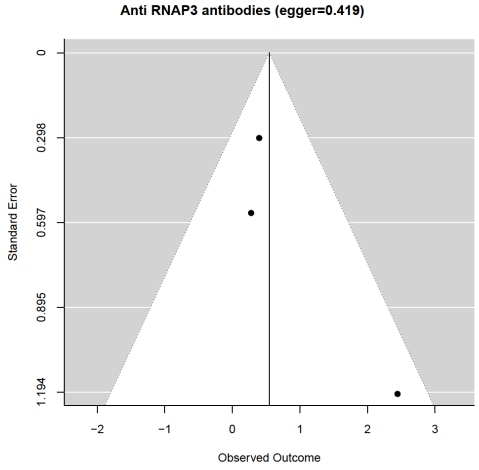

AlDhaher 2.30 [1.16, 4.55]
Alba 2.22 [1.38, 3.56]
Assassi 1.45 [0.82, 2.56]
Beretta 2.75 [1.02, 7.41]
Codullo 1.31 [0.57, 3.01]
CruzDominguez 1.55 [0.53, 4.54]
Czirjak 2.37 [1.49, 3.77]
Hachulla 2.21 [1.24, 3.93]
Hao 1.83 [1.14, 2.93]
Hao 1.40 [1.07, 1.83]
HoffmannVold 2.80 [1.41, 5.55]
Hussein 1.43 [1.14, 1.79]
Jacobsen 7.80 [1.77, 34.39]
Kim 2.50 [1.08, 5.79]
Kolto 7.50 [2.78, 20.24]
Mayes 1.23 [0.85, 1.78]
Nihtyanova 1.51 [1.04, 2.18]
Poormoghim 1.20 [0.59, 2.45]
Pokeerbux 2.40 [1.58, 3.64]
Ruangjutipopan 5.66 [2.30, 13.93]
SimeonAznar 2.70 [1.66, 4.40]
Steen 1.34 [1.16, 1.54]
Strickland 2.31 [0.85, 6.30]
RE Model 1.90 [1.62, 2.23]
0
10
20
30
40
Diffuse SSc (I2=58.3%, P(het)=2e−04)

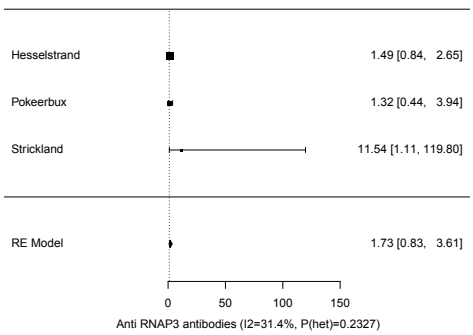

Anti Scl70 antibdodies (egger=0.0244)
Standard Error
0
0.14
0.281
0.421
0.562
−1
−0.5
0
0.5
1
1.5
Observed Outcome

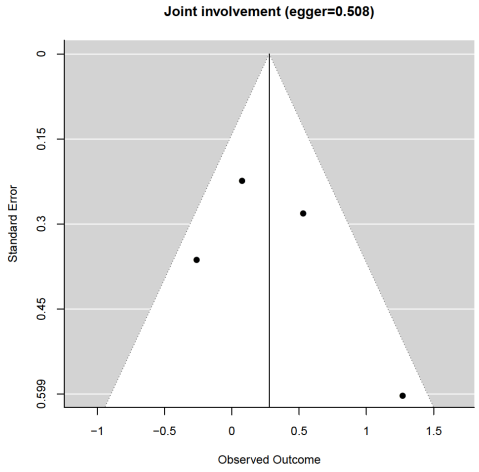

Assassi 1.23 [0.62, 2.46]
Codullo 2.43 [0.93, 6.33]
Cottrell 0.80 [0.54, 1.19]
Ferri 1.61 [1.01, 2.58]
Hachulla 1.72 [0.88, 3.36]
Hao 0.95 [0.67, 1.35]
Hesselstrand 1.54 [0.78, 3.05]
Kim 3.00 [1.23, 7.30]
Poormoghim 1.44 [0.48, 4.33]
Pokeerbux 0.82 [0.51, 1.31]
ScussellLonzetti 2.30 [1.07, 4.95]
SimeonAznar 1.82 [1.18, 2.81]
Strickland 1.44 [0.57, 3.65]
RE Model 1.38 [1.09, 1.74]
0
2
4
6
8
Anti Scl70 antibodies (I2=49.6%, P(het)=0.0217)

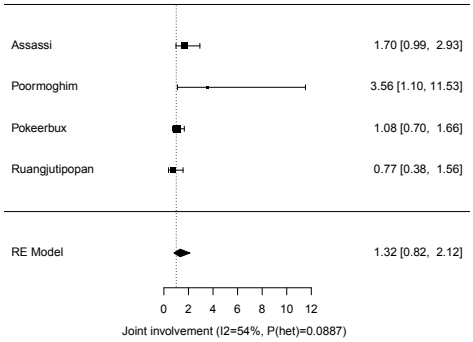

ACA (egger=0.5897)
Standard Error
0
0.425
0.85
1.276
1.701
−4
−2
0
2
Observed Outcome

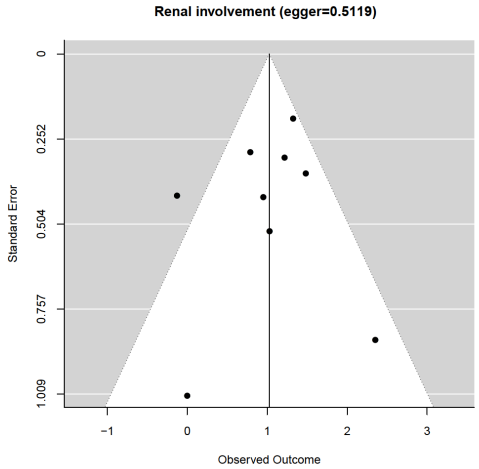

Assassi 0.20 [0.04, 0.99]
Cottrell 0.40 [0.28, 0.57]
Hao 0.71 [0.53, 0.95]
Hesselstrand 1.12 [0.57, 2.21]
HoffmannVold 0.40 [0.20, 0.80]
Hussein 0.70 [0.49, 0.99]
Pokeerbux 0.85 [0.55, 1.31]
Strickland 0.28 [0.01, 7.85]
RE Model 0.62 [0.47, 0.82]
0
2
4
6
8
ACA (I2=56.4%, P(het)=0.0246)

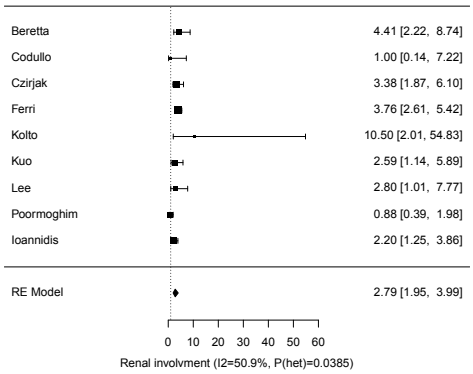

Anti RNAP3 antibodies (egger=0.419)
Standard Error
0
0.298
0.597
0.895
1.194
−2
−1
0
1
2
3
Observed Outcome

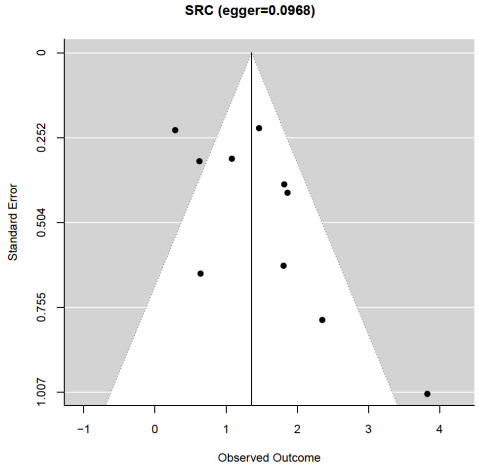

Hesselstrand 1.49 [0.84, 2.65]
Pokeerbux 1.32 [0.44, 3.94]
Strickland 11.54 [1.11, 119.80]
RE Model 1.73 [0.83, 3.61]
0
50
100
150
Anti RNAP3 antibodies (I2=31.4%, P(het)=0.2327)

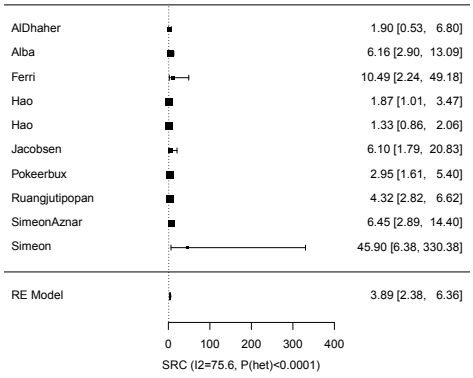

Joint involvement (egger=0.508)
Standard Error
0
0.15
0.3
0.45
0.599
−1
−0.5
0
0.5
1
1.5
Observed Outcome

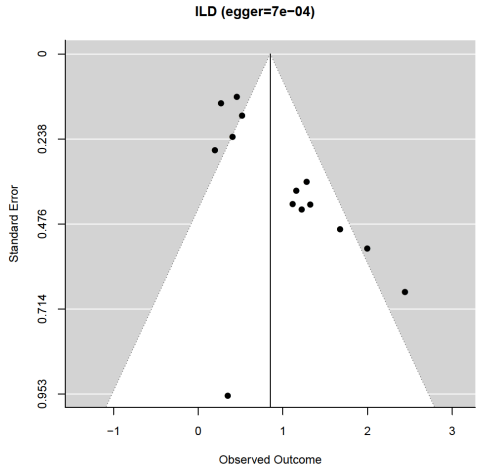

Assassi
1.70 [0.99, 2.93]
Poormoghim
3.56 [1.10, 11.53]
Pokeerbux
1.08 [0.70, 1.66]
Ruangjutipopan
0.77 [0.38, 1.56]
RE Model
1.32 [0.82, 2.12]
0
2
4
6
8
10
12
Joint involvement (I2=54%, P(het)=0.0887)

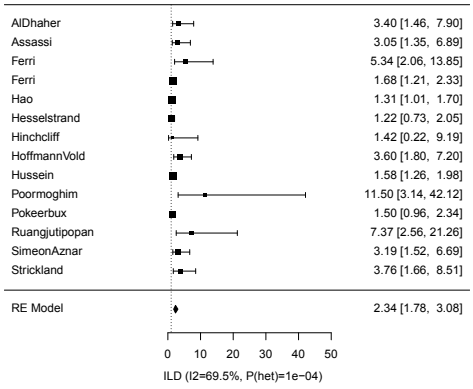

Renal involvement (egger=0.5119)
Standard Error
0
0.252
0.504
0.757
1.009
−1
0
1
2
3
Observed Outcome

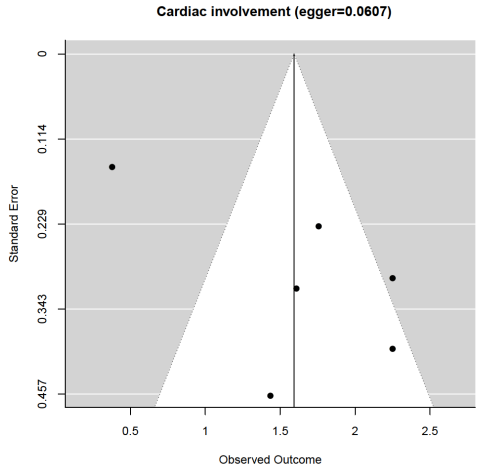

Beretta
4.41 [2.22, 8.74]
Codullo
1.00 [0.14, 7.22]
Czirjak
3.38 [1.87, 6.10]
Ferri
3.76 [2.61, 5.42]
Kolto
10.50 [2.01, 54.83]
Kuo
2.59 [1.14, 5.89]
Lee
2.80 [1.01, 7.77]
Poormoghim
0.88 [0.39, 1.98]
Ioannidis
2.20 [1.25, 3.86]
RE Model
2.79 [1.95, 3.99]
0
10
20
30
40
50
60
Renal involvment (I2=50.9%, P(het)=0.0385)

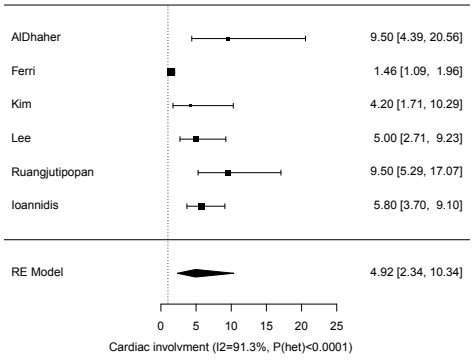

SRC (egger=0.0968)
Standard Error
0
0.252
0.504
0.755
1.007
−1
0
1
2
3
4
Observed Outcome

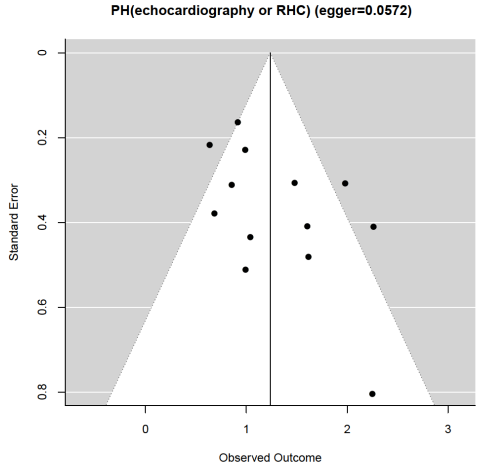

AlDhaher
1.90 [0.53, 6.80]
Alba
6.16 [2.90, 13.09]
Ferri
10.49 [2.24, 49.18]
Hao
1.87 [1.01, 3.47]
Hao
1.33 [0.86, 2.06]
Jacobsen
6.10 [1.79, 20.83]
Pokeerbux
2.95 [1.61, 5.40]
Ruangjutipopan
4.32 [2.82, 6.62]
SimeonAznar
6.45 [2.89, 14.40]
Simeon
45.90 [6.38, 330.38]
RE Model
3.89 [2.38, 6.36]
0
100
200
300
400
SRC (I2=75.6, P(het)<0.0001)

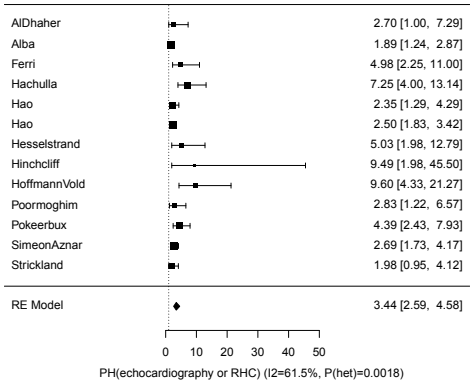

ILD (egger=7e−04)
Standard Error
0
0.238
0.476
0.714
0.953
−1
0
1
2
3
Observed Outcome

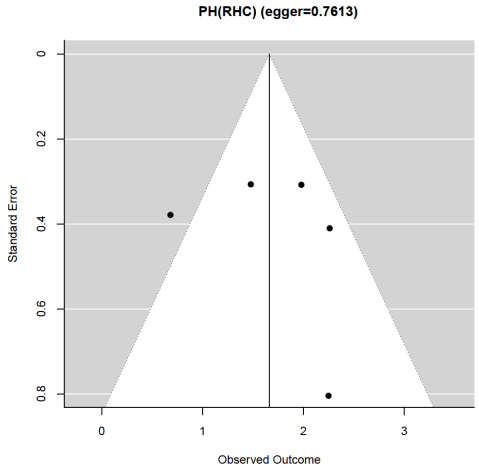

AlDhaher 3.40 [1.46, 7.90]
Assassi 3.05 [1.35, 6.89]
Ferri 5.34 [2.06, 13.85]
Ferri 1.68 [1.21, 2.33]
Hao 1.31 [1.01, 1.70]
Hesselstrand 1.22 [0.73, 2.05]
Hinchcliff 1.42 [0.22, 9.19]
HoffmannVold 3.60 [1.80, 7.20]
Hussein 1.58 [1.26, 1.98]
Poormoghim 11.50 [3.14, 42.12]
Pokeerbux 1.50 [0.96, 2.34]
Ruangjutipopan 7.37 [2.56, 21.26]
SimeonAznar 3.19 [1.52, 6.69]
Strickland 3.76 [1.66, 8.51]
RE Model 2.34 [1.78, 3.08]
0 10 20 30 40 50
ILD (I2=69.5%, P(het)=1e−04)

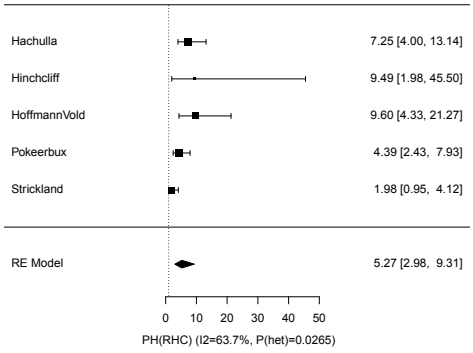

Cardiac involvement (egger=0.0607)
Standard Error
0
0.114
0.229
0.343
0.457
0.5
1
1.5
2
2.5
Observed Outcome

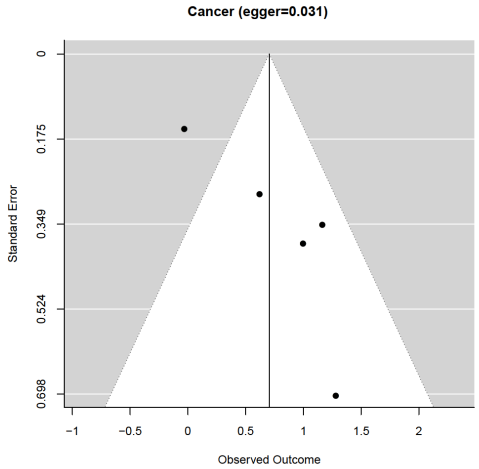

AlDhaher 9.50 [4.39, 20.56]
Ferri 1.46 [1.09, 1.96]
Kim 4.20 [1.71, 10.29]
Lee 5.00 [2.71, 9.23]
Ruangjutipopan 9.50 [5.29, 17.07]
Ioannidis 5.80 [3.70, 9.10]
RE Model 4.92 [2.34, 10.34]
0 5 10 15 20 25
Cardiac involvment (I2=91.3%, P(het)<0.0001)

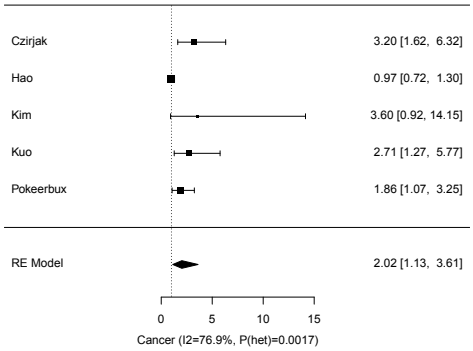

PH(echocardiography or RHC) (egger=0.0572)
Standard Error
0
0.2
0.4
0.6
0.8
0
1
2
3
Observed Outcome


AlDhaher 2.70 [1.00, 7.29]
Alba 1.89 [1.24, 2.87]
Ferri 4.98 [2.25, 11.00]
Hachulla 7.25 [4.00, 13.14]
Hao 2.35 [1.29, 4.29]
Hao 2.50 [1.83, 3.42]
Hesselstrand 5.03 [1.98, 12.79]
Hinchcliff 9.49 [1.98, 45.50]
HoffmannVold 9.60 [4.33, 21.27]
Poormoghim 2.83 [1.22, 6.57]
Pokeerbux 4.39 [2.43, 7.93]
SimeonAznar 2.69 [1.73, 4.17]
Strickland 1.98 [0.95, 4.12]
RE Model 3.44 [2.59, 4.58]
0 10 20 30 40 50
PH(echocardiography or RHC) (I2=61.5%, P(het)=0.0018)


PH(RHC) (egger=0.7613)
Standard Error
0
0.2
0.4
0.6
0.8
0
1
2
3
Observed Outcome


Hachulla
7.25 [4.00, 13.14]
Hinchcliff
9.49 [1.98, 45.50]
HoffmannVold
9.60 [4.33, 21.27]
Pokeerbux
4.39 [2.43, 7.93]
Strickland
1.98 [0.95, 4.12]
RE Model
5.27 [2.98, 9.31]
0
10
20
30
40
50
PH(RHC) (I2=63.7%, P(het)=0.0265)


Cancer (egger=0.031)
Standard Error
0
0.175
0.349
0.524
0.698
−1
−0.5
0
0.5
1
1.5
2
Observed Outcome


Czirjak
3.20 [1.62, 6.32]
Hao
0.97 [0.72, 1.30]
Kim
3.60 [0.92, 14.15]
Kuo
2.71 [1.27, 5.77]
Pokeerbux
1.86 [1.07, 3.25]
RE Model
2.02 [1.13, 3.61]
0
5
10
15
Cancer (I2=76.9%, P(het)=0.0017)

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Date de Soutenance : 11 décembre 2017

Titre de la Thèse : Survie et facteurs pronostiques dans la sclérodermie systémique : étude d'une cohorte multicentrique incidente française, revue systématique de la littérature et méta-analyse

Thèse - Médecine - Lille 2017

Cadre de classement : *Médecine*

DES + spécialité : *Médecine interne*

Mots-clés : sclérodermie systémique, survie, facteurs pronostiques

Résumé : Contexte : Parmi les études qui ont évalué les facteurs pronostiques dans la sclérodermie systémique (SSc), seules quelques-unes se sont intéressées à l'ensemble des caractéristiques cliniques et paracliniques d'une cohorte de patients. Les objectifs de notre étude étaient d'évaluer la survie et les facteurs pronostiques dans une cohorte multicentrique incidente française, puis de réaliser une revue systématique de la littérature et une méta-analyse sur l'indice de mortalité standardisé (SMR) et les facteurs pronostiques dans la SSc. **Méthodes :** Nous avons décrit les caractéristiques puis déterminé les taux de survie, le SMR et les facteurs pronostiques d'une série de cas incidents recrutés à partir de 5 centres experts. Après avoir réalisé une revue systématique de la littérature, nous avons conduit une méta-analyse et déterminé le SMR combiné et les HR combinés des facteurs pronostiques dans la SSc. **Résultats:** Six cent vingt-cinq patients, dont 132 hommes et 179 formes diffuses, ont été inclus. La durée moyenne du suivi était de 5,2 +/- 3,6 années. Cent quatre décès sont survenus. Les taux de survie globale à 1 an, 3 ans, 5 ans et 10 ans étaient de 98,0%, 92,5%, 85,9% et 71,7% respectivement. Le SMR était estimé à 5,73 [IC95 4,68 - 6,94]. Les paramètres associés à la survie étaient un âge au diagnostic > 60 ans, la forme cutanée diffuse, la crise rénale sclérodermique, l'hypertension pulmonaire, une dyspnée sévère, la présence de télangiectasies, une valvulopathie cardiaque, l'anémie, une CRP > 8mg/l et un cancer associé. Dix-huit études étaient inclues dans la méta-analyse sur le SMR et 33 études dans la méta-analyse sur les facteurs pronostiques. Le SMR combiné était de 3,45 [IC95 3,03 – 3,94]. La méta-analyse a identifié les facteurs suivants comme étant associé à une plus grande mortalité : l'âge de début de la maladie, l'âge du diagnostic, le sexe masculin, l'origine ethnique africaine, la forme cutanée diffuse, la présence d'anti-Scl70, les atteintes rénale et cardiaque, la fibrose pulmonaire, l'hypertension pulmonaire et un cancer associé. La présence d'anti-centromère était un facteur de bon pronostic. **Conclusion :** Nos résultats confirment que la mortalité dans la SSc reste élevée à ce jour. Outre l'extension cutanée, le profil d'auto-anticorps et les atteintes spécifique d'organes déjà décrits, nous rapportons de nouveaux facteurs pronostiques tels que la présence de télangiectasies et de valvulopathies cardiaques.

Composition du Jury :

Président : Monsieur le Professeur Pierre-Yves Hatron

Assesseurs : Monsieur le Professeur Eric Hachulla, Monsieur le Professeur David Launay (directeur de thèse), Monsieur le Docteur Luc Dauchet, Monsieur le Docteur Jonathan Giovanelli